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Simulating Alzheimer's disease with a brainsphere model

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Nowadays, there are different medical imaging techniques to collect data about the progression of Alzheimer's disease in a patient's brain. These data describe different phenomena which are still not understood from a biological point of view. How can these data sets be combined in a mathematical model to simulate the evolution of such a neurodegenerative disease in a computer? In this snapshot, we present one possible approach to address this task with the help of graph theory and partial differential equations.

1 Introduction

Alzheimer's disease is a slowly progressing neurodegenerative disease causing the brain to shrink and brain cells to die. Much progress has been made in

[1] The presented model was developed in joint work with Prof. Dr. Alexander Drzezga and Prof. Dr. Yaping Shao as part of the project "Neurodegeneration Forecasting – A Computational Brainsphere Model for the Simulation of Alzheimer's Disease", supported by the Excellence Initiative of the University of Cologne, Germany, 2017–2019.

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investigating the course and certain biomarkers of the disease. The perhaps largest attention is currently focused on two proteins that behave conspicuously in the brain of an Alzheimer's patient: On the one hand, *beta-amyloid peptides* aggregate in the surrounding area of the neuronal network in the brain as plaques [8]. On the other hand, there are abnormally folded *tau proteins* which accumulate in the neurons (nerve cells) in the form of tangles and are believed to affect their functioning and, finally, to cause their death [9].

In the past, it was only possible to examine the brains of dead Alzheimer's patients. The development of modern medical imaging techniques made it possible to visualize protein plaques in the brains of living patients as well (*in-vivo data*). PET scanners measure accumulations of tau and beta-amyloid, and functional MRI as well as DTI scanners provide indications of the structure and functioning of a human brain. Central goal of subsequent studies is the behavior of tau and beta-amyloid as well as the connectivity patterns in the brain.

A relatively new model for tau propagation is the transneuronal spread hypothesis. *Transneuronal* means that tangles travel from neuron to neuron, inducing tangles in neighboring neurons in a prion-like fashion. The word *prion* is a combination of "protein" and "infection", indicating that misfolded proteins can infect others. According to this hypothesis, the connectivity of neurons is a driver for tau pathology, that is, highly interconnected neurons are more likely to get infected [7].

On the other hand, it is also believed that aggregated tau proteins affect the functioning of neurons and their connections to other neurons in the brain. Additionally, the presence of beta-amyloid plaques in the surrounding of a neuron could influence its tendency to aggregate tau.

Having discussed only a fraction of the possible interactions and factors of the disease process, we already realize that it quickly becomes complicated to adequately describe such a complex interplay. The crucial challenge is to analyze and combine the in-vivo data within a mathematical framework. We propose a *computational brainsphere model for the simulation of Alzheimer's disease* which consists of three interacting parts:

1. A *brain network model* to represent the human brain as a dynamical network, or, in mathematical terms, as a "graph", and to investigate the effects of tau pathology on the connectivity patterns;
2. A *tau distribution model* to simulate the spreading of tau proteins across the brain network;
3. A *beta-amyloid model* to model the dispersion of beta-amyloid in the environment of the brain network.

In the following, we give a brief introduction to the brain network and the tau distribution model. These have, as described above, a reciprocal dependency,

meaning that the network structure influences the propagation of tau and the presence of tau influences the structure of the network.

2 Graph theory

One major tool in the analysis of networks is a mathematical branch called *graph theory*. It provides a formalization of a network as well as characteristics and algorithms to investigate its structure.

A *graph* G consists of *vertices* $v_1, \ldots, v_n$ and *edges* $e_1, \ldots, e_n$. Each edge connects two vertices, which are then called *neighbors*. An edge is *incident* to a vertex v if the edge is attached to v. A first example of a graph is given in Figure 1. Here, G has five vertices $v_1, \ldots, v_5$ and six edges $e_1, \ldots, e_6$. The neighbors of the vertex v_1 are v_2, v_3, and v_4, and the edge e_1 is incident to v_1 and v_2.

Besides the number of vertices n and the number of edges m, an important characteristic of a graph is the degree. The *degree* d_v of a vertex v is defined as the number of neighbors of a vertex, which is the same as the number of incident edges. In Figure 1, the degree of v_1 is $d_{v_1} = 3$.

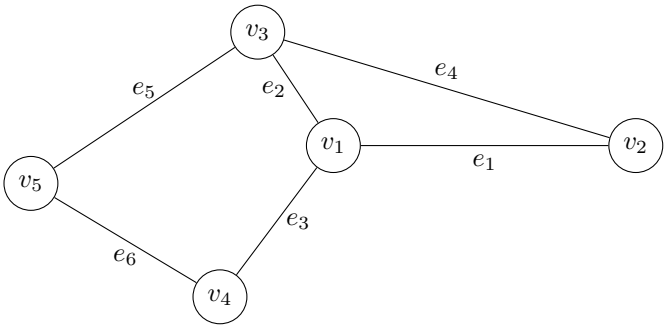


Figure 1: Example of a graph G with vertices v_1, v_2, v_3, v_4, v_5 and edges $e_1, e_2, e_3, e_4, e_5, e_6$.

Another example: Imagine the vertices of a graph to be houses on an island. Several houses are connected by streets, hence, the streets are the edges of our graph. Along the streets, houses can exchange things with each other, such as agricultural products, information, etc. As shown in Figure 2, we might identify groups of houses on the island that are more densely connected to each other than to other houses; we could speak of villages. In graph-theoretical terms, such densely interconnected sets of vertices are called *communities*. To

investigate whether a graph is organized in community structures, we can use, for example, the "Louvain community detection algorithm".

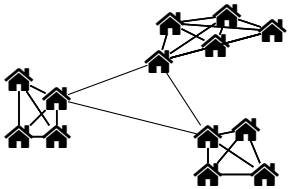


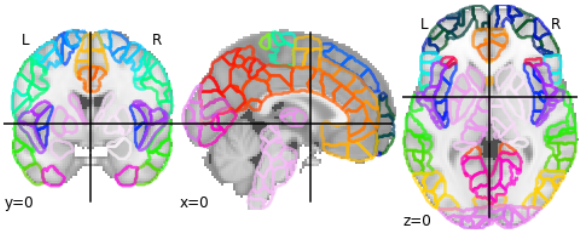
Figure 2: Houses as an example of communities in a graph.

3 Brain network model

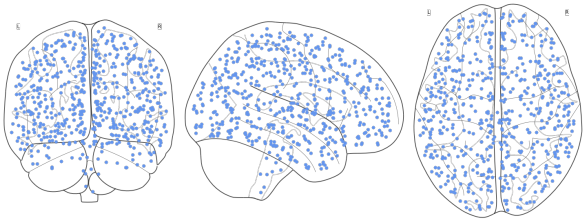
The first idea for our model is to represent the human brain as a graph with neurons as vertices and synapses as edges. Unfortunately, the resolution of common MRI scanners is not high enough to render the extremely small neurons. Instead, a common approach is to consider groups of neurons that are close to each other as *brain regions*. For the brain as a three-dimensional object, a definition of these brain regions may be achieved by a partitioning into neighboring regions that have approximately the same size and shape. In our model, this resulted in the parcellation displayed in Figure 3a with 571 regions having an approximate volume of 2 ml [11]. Each of these regions now serves as a vertex in our graph, where we position the vertex in the middle of the brain region, see Figure 3b.

The resulting groups of neurons can be structurally or functionally connected. A *structural connection* is a physical connection through fibres in the brain. A *functional connection* is more likely to refer to the collaboration of different regions. If two areas in the brain are often active at the same time, for instance, to perform a task, they are said to be functionally connected. Whether one considers structural or functional connections depends on the context and the way connectivity is defined. In both cases, the brain regions form the vertex set of our graph. The edges connecting the vertices are either the structural or functional connections (see Figure 3c for an example of a brain network with functional connections).

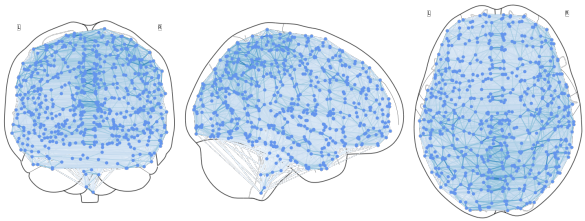
Modeling the brain as a graph enables us to apply new methods for analyzing its structure and organizing principles. A variety of algorithms from graph theory can now be applied to identify regions with particularly strong connections, to determine shortest paths, or to find communities. Several authors have



(a) Brain atlas with 571 brain regions.



(b) Vertices of the brain network.



(c) Vertices and edges of the brain network.

Figure 3: Construction of the brain network model.

performed graph-theoretical analysis of the brain network. For example, it was found that healthy brain networks are generally organized respecting economic principles of minimizing wiring costs and maximizing global efficiency (see, for example, [6] and the references therein).

If every two houses on our imaginary island were to be connected by a street, this would cause massive construction costs. An economic trade-off would be a high connectivity in local communities (villages), where wiring costs are comparably low, combined with only a few expensive long-distance roads (expressways) to more remote communities. This connection pattern is characterized by high modularity (a measure to which extent a community is present) and is a particular kind of a *small-world* network architecture allowing highly efficient information transfer with low wiring costs [5].

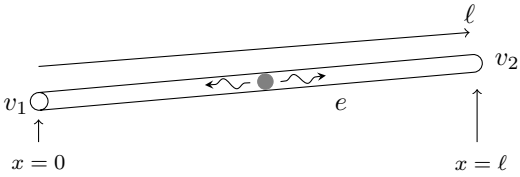


Figure 4: Diffusion across a single isolated edge.

By contrast, in many neurological disorders, peculiarities in the brain network have been noticed, for example, weakened connectivity or modified organizational structures. In [11], the community formation in brain networks of a group of healthy adults were compared to a group of Alzheimer's patients. The results of this study suggest that the community structures in the Alzheimer's group have a significantly lower modularity than the healthy control group. This decrease of modularity in Alzheimer's patients compared with both young and senior controls indicates a loss of efficiency of information transfer across the whole brain.

4 Spreading of tau proteins

The second important part of the computational brainsphere model is the tau distribution model which aims to simulate the spreading of tau proteins across the brain network. To simulate such processes, we use *partial differential equations* (PDEs). A partial differential equation relates a function in several dimensions to its partial derivatives, and the aim is to find this function from this equation.

In our first mathematical model, the two dimensions of our function are time and space. We want to simulate how the concentration of tau at position x in the network changes over time t. Following the transneuronal spread hypothesis, we suppose that tau proteins can only spread along the edges of the brain network. Here, we will model this spreading as a diffusion process.[3]

To explain this, consider first only a single isolated edge of the network, for example, the edge $e = (v_1, v_2)$ between vertex v_1 and vertex v_2. Physically, we imagine the edge to be a thin tube with length ℓ, see Figure 4. Vertex v_1 is at position $x = 0$ and v_2 at position $x = \ell$ of the edge. The concentration of tau at any position x of the edge at time t is given by a function denoted by $\tau = \tau(x, t)$ which describes the amount of tau per unit volume.

[3] *Diffusion* refers to the movement of particles from higher to lower concentrations.

Fick's first law tells us that the concentration τ can be related to the flux F by the equation

$$F = -D \cdot \frac{\partial \tau}{\partial x}. \tag{1}$$

By *flux*, we mean how much of a substance flows through a given area in a certain amount of time. D is the *diffusion coefficient*, which influences the strength of the flow. The expression $\frac{\partial \tau}{\partial x}$ stands for the first partial derivative of τ with respect to x. It describes how the concentration changes with respect to the space coordinate. If $\frac{\partial \tau}{\partial x}$ is large, the concentration rises along the edge, causing a flux in the opposite direction.

Using this relation and respecting mass conservation (the principle that the total amount of substance remains constant), we can derive an equation that tells us how diffusion causes the concentration to change with respect to time. This equation is *Fick's second law* and reads

$$\frac{\partial \tau}{\partial t} = D \cdot \frac{\partial^2 \tau}{\partial x^2}. \tag{2}$$

Here $\frac{\partial \tau}{\partial t}$ denotes the first partial derivative of τ with respect to time and $\frac{\partial^2 \tau}{\partial x^2}$ denotes the second partial derivative with respect to x. Equation (2) is a partial differential equation as it involves derivatives of τ with respect to both time and space. Solving this PDEs tells us how the concentration of τ at any position x on an edge changes with respect to time t.

Now that we elaborated how we can describe the diffusion process on a single edge, we can attend to the generalization to the whole network. Consider Figure 5, where we illustrate as an example one vertex v with three incident edges e_1, e_2, and e_3. In general, a vertex v has d_v incident edges $e_1, \ldots, e_{d_v}$, as explained in section 2. For each of these edges, we now need a separate function to describe the concentration along the coordinates of the edge. We will, therefore, denote the function for edge e_i by τ_i.

For ease of notation, we suppose that the vertex v lies at position $x = 0$ for every attached edge e_i. This means that the concentration of tau at vertex v is given by $\tau(v) = \tau_i(0)$. For this definition to make sense, we have to assume $\tau_1(0) = \tau_2(0) = \ldots = \tau_d(0)$ (*continuity condition*).

On every edge attached to vertex v, the diffusion can be described by equation (2), but what happens at the vertex v itself? According to Fick's first law (1), the rate at which tau leaves node v along an edge e_i can be modelled as

$$F_{e_i}(t) = -D \cdot \frac{\partial \tau_i}{\partial x}\Big|_{x=0},$$

where we evaluate the derivative at the point $x = 0$ since we agreed that the vertex is at position $x = 0$ on every attached edge. Hence, the total flux out

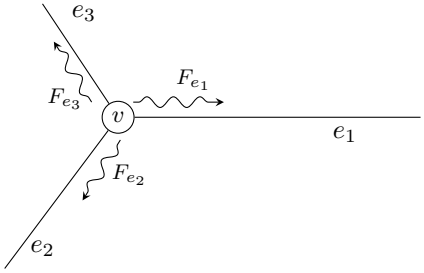


Figure 5: Diffusion at a vertex v with three incident edges e_1, e_2, e_3.

of vertex v along all incident edges $e_1, \dots, e_{d_v}$ is given by the sum of the flows over the single edges, that is,

$$F_v(t) = -D \cdot \left(\frac{\partial \tau_1}{\partial x} + \cdots + \frac{\partial \tau_{d_v}}{\partial x} \right) \Bigg|_{x=0}.$$

If we assume that no substance is produced or lost in the vertices, the total flux out of vertex v must be 0 as everything that flows in must flow out again. This is also known as *conservation of currents* and provides us with the *Neumann-Kirchhoff vertex condition*. It couples the diffusion equations on the different edges at the vertices [4]. Together, we arrive at a coupled system of partial differential equations that describes a diffusion process on a network. This system is given by

$$\left.\begin{aligned} &\frac{\partial \tau_i}{\partial t} = D \, \frac{\partial^2 \tau_i}{\partial x^2} && \text{for all edges } e_i = e_1, \dots, e_m, \\ &\tau(v) = \tau_i(0) \\ &\left(\tfrac{\partial \tau_1}{\partial x} + \cdots + \tfrac{\partial \tau_{d_v}}{\partial x} \right) \Big|_{x=0} = 0 \end{aligned} \right\} \quad \begin{aligned} &\text{for all vertices } v \text{ with incident} \\ &\text{edges } e_i = e_1, \dots, e_{d_v}. \end{aligned} \tag{3}$$

5 Numerical simulations

The goal of a numerical simulation is to predict patterns of future tau accumulation, given an initial tau pattern that was actually measured in the brain of a patient. In other words, given the initial tau distribution at time $t = 0$, we want to solve system (3) to obtain the tau concentration $\tau_i(x, t)$ for a future time point $t > 0$ and at each position x. This can be achieved by certain numerical methods redesigned for graphs, see, for example, [1, 2, 10, 12].

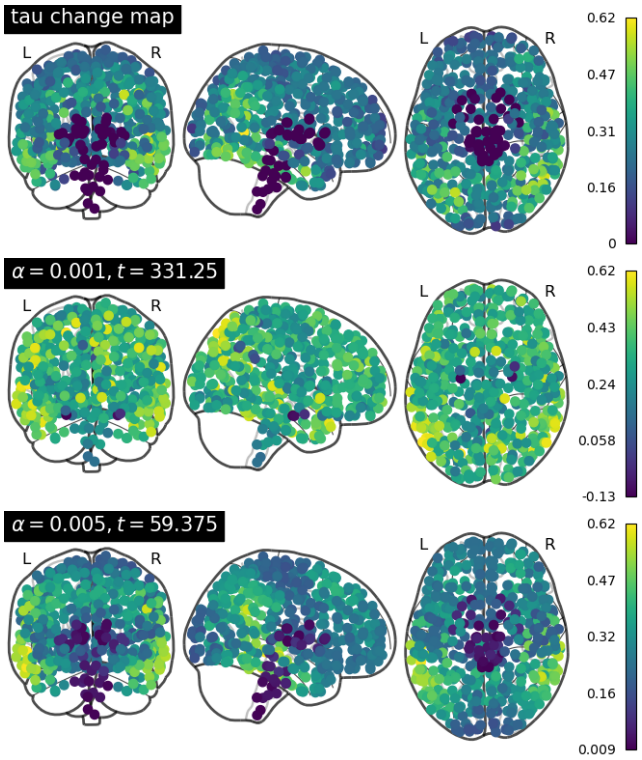


Figure 6: Observed tau changes across the brain network (top) and model predictions from the reaction-diffusion equation for $\alpha = 0.001$ (center) and $\alpha = 0.005$ (bottom). Graphical representation using `nilearn` in python [10].

In fact, equation (3) is only a very simple attempt to describe the spread of tau proteins across the brain network. In a more realistic model, other processes such as chemical reactions with the network environment are important. This leads to *reaction-diffusion equations*

$$\frac{\partial \tau_i}{\partial t} = D\,\frac{\partial^2 \tau_i}{\partial x^2} + \alpha \tau_i \qquad \text{for all edges } e_i = e_1, \ldots, e_m,$$

where α is some given constant representing all chemical reactions that affect the spread of tau proteins along each neural connection. To solve these equations, we compute the predicted change in tau distribution from the initial condition in each brain region and compare the result to the actual change measured approximately one year after the initial scan.

Figure 6 compares the observed changes in tau distribution to two model predictions for $\alpha = 0.001$ and $\alpha = 0.005$, which were obtained using a "finite element discretization"; the exact discretization details and a description of the selected data can be found in [10, 12]. For each value of α, the simulation time t was chosen such that the overall amount of predicted tau change matched the change observed in the data. While a small reaction term ($\alpha = 0.001$) required a long simulation time and still produced a tau pattern that differed markedly from the data, a larger reaction term ($\alpha = 0.005$) reached the same overall change much faster and yielded a distribution closely resembling the observed tau patterns. These results suggest that the reaction term plays an important role in the prediction of tau patterns.

Image credits

Figure 3 Own representation using data presented in [11] and the python nilearn package.

Figure 6 Simulation results from [10].

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