Chapter 5: The Troubled Brain:

Ageing and Dementia

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5.1 “I have lost myself"

At first, the signs were subtle. Only a life of intimacy allowed his wife to notice. At age 57, he had difficulty tying his neck tie, he could not properly handle the house finance and seemed withdrawn. Maybe it was a mild form of depression? As these early lapses worsened, Mr U, now aged 61, was sent for a general neurological examination which appeared normal. However, a basic psychological test showed delayed recall and problems with episodic memory. Mr U was sent for further tests. A magnetic resonance imaging scan revealed broad cerebral atrophy and together with advanced psychological tests, the devastating diagnosis of probable Alzheimer’s disease was reached. From then on, Mr U experienced a well-known pattern of decline: abstract reasoning became difficult, memory functions and word retrieval were affected, and he could not properly visualize the world around him. At age 65, he showed a global deterioration in his cognitive abilities with verbal memory, language, motor control, face recognition, and executive skills all affected. A MRI scan confirmed extended bilateral cerebral atrophy. Bouts of apathy, psychoses, and violent outbursts became more frequent.

The story of Mr U is not unique. For instance, Alois Alzheimer’s very first patient, Auguste Deter, once described her own similar conditions in these dramatic terms: “I have lost myself". As much as this tragic loss of identity and abilities are highly personal to the patient and the people close to them, the overall pattern of degeneration in Alzheimer patients is fairly homogeneous and systematic. The disease affects more than 50 million people worldwide and is found in about 1 in 9 people age 65 and older. Unlike cancer and many viral and bacterial diseases, Alzheimer’s disease, in its most common occurrence, presents itself in stages that have been codified and are found in most patients. We also know that this cognitive staging is associated with a systematic invasion in the brain of two key toxic proteins that were already identified by Alois Alzheimer in 1905. The first one is the well-known amyloid beta, an extracellular protein whose natural functions are not well understood but is known to form plaques in elderly humans. The second one is the group of tau proteins that normally stabilize microtubules in axons. However, they can misfold. It is believed that a misfolded version of tau acts as a template for healthy tau proteins and promotes the formation of oligomers of increasing sizes, eventually leading to large aggregates, known as neurofibrillary tangles, that can be observed in brain tissues after death [7].

While most drug trials focus on amyloid beta, it is the presence of toxic tau proteins that is most correlated to brain atrophy and to cognitive symptoms. The typical pattern of tau evolution obtained through histological staining is known as the Braak & Braak staging after the neuroanatomists Eva and Heiko Braak who first proposed it in 1991 [4]. It describes the evolution of the disease in six stages starting in the entorhinal cortex and evolving through the hippocampal region (associated with memory), the temporal lobe, the occipital lobe, and all regions of the neocortex, with lesions in each region worsening in time.

More generally, the prion-like hypothesis broadly postulates that neurodegenerative diseases result from an accumulation of abnormally misfolded proteins such amyloid beta and tau protein, which aggregate and contribute to tissue death, causing associated neurodegenerative pathology and cognitive decline [7]. In this process, certain disease-specific misfolded proteins can influence healthy proteins, forming extensive chains that can be transported through the brain along axonal pathways. Given that aggregates of differing sizes exhibit unique transport characteristics and varying levels of toxicity, it is crucial to independently monitor their spatial and temporal evolution.

Viewed from a modeling perspective, Alzheimer's disease is rather intimidating and when we first looked at it with my friend and colleague Ellen Kuhl in Stanford, we were told that it is the most complicated disease invading the most complicated organ with no known cure or treatment. It was, by all accounts, beyond any possible modeling. Yet, the systematic pattern of invasion through the brain and the multiple cognitive effects suggest to the curious mind that there may be some simple underlying features of the brain responsible for its spatio-temporal pattern. The challenge was therefore to obtain minimal mathematical models based on clear principles that can capture, at the brain level, the staging as well as other characteristics of the disease such as brain atrophy and changes in the overall brain dynamics.

5.2 A continuum model

From a phenomenological point of view, there are three processes to consider: *(transport)* toxic proteins are transported in the brain mostly along axonal bundles (connecting different parts of the brain and acting as information highways); *(expansion)* the aggregation process is autocatalytic and lead to an initial exponential increase of small toxic populations; *(saturation)* each region can only support a certain level of toxic proteins. A canonical model for such a process in a continuum medium is the celebrated Fisher–Kolmogorov–Petrovsky–Piskunov equation (Fisher-KPP). We define $c(x,t) \in [0,1]$ to be the scaled concentration of a toxic protein defined for $x \in \mathcal{B} \subset \mathbb{R}^3$, the brain and for time $t > 0$. Then the Fisher-KPP equation reads:

$$\frac{\partial c}{\partial t} = \rho \nabla \cdot (\mathbf{D} \nabla c) + \alpha\, c\,(1-c), \tag{5.1}$$

where **D** is a transversely anisotropic diffusion tensor with a strong preferential direction along the axonal bundle, $\rho > 0$ defines the strength of the diffusion, and $\alpha > 0$ is the growth rate. Remarkably, this model can be obtained, under generic conditions, as a normal form of the full aggregation-fragmentation equations that tracks the evolution of oligomers of different sizes [11]. Hence the parameters can be directly related to the aggregation and clearance rates at the microscopic level.

Modern brain imaging techniques are now well developed and it is relatively routine to use medical resonance imaging to obtain both the full brain geometry as well as the direction of axonal bundles. Then, starting with an initial seed of toxic proteins in the entorhinal cortex, we simulated the evolution of the field in the brain as shown in the top two rows of Fig. 5.1. The

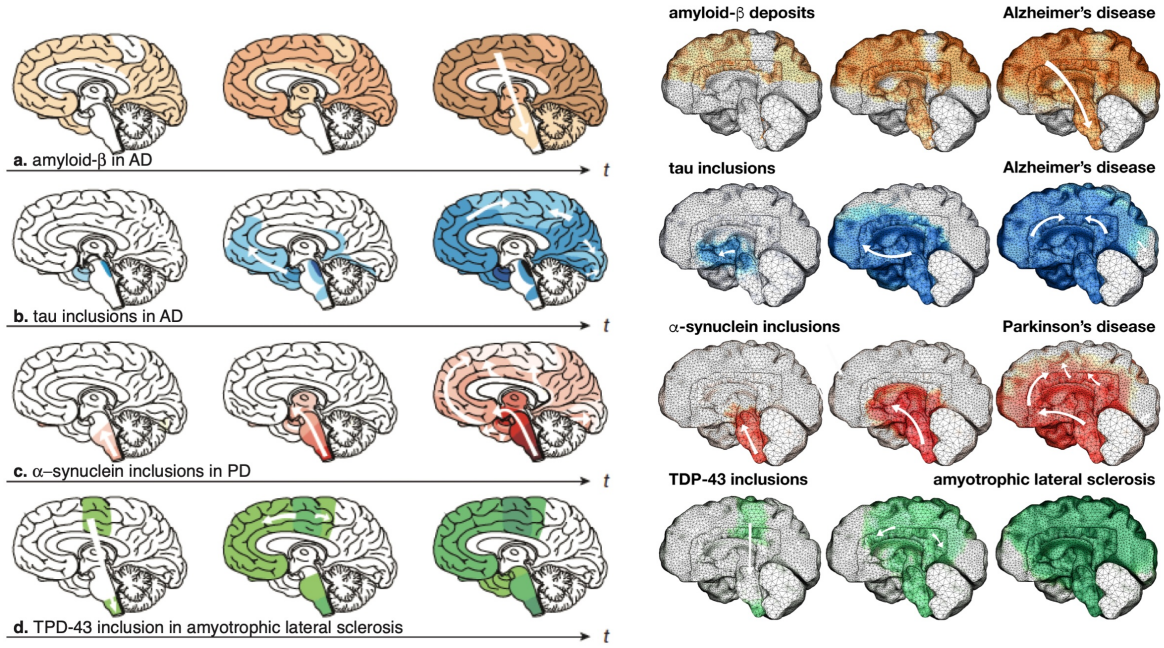


Figure 5.1: Progression of toxic tau proteins in the brain predicted from the Fisher-KPP model .

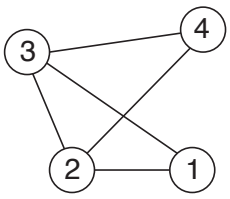
results were striking. Without any other ingredients, the dynamics obtained from this minimal model recovered the basic dynamics of the disease in great detail [12]. Further, the same model applied to other neurodegenerative diseases associated with other toxic proteins such as α-synuclein for Parkinson's or TDP-43 for amyotrophic lateral sclerosis also reproduces their basic spatio-temporal patterns as well as the atrophy patterns that can be obtained, post-processing, from finite-element simulations; the only difference being the region and extent of seeding as shown in Fig. 5.1. Despite the complexity and diversity of these diseases, universal features of progression emerge from the combination of an autocatalytic process and transport in an anisotropic medium. What is going on here?

5.3 Networks

When such strong universal patterns appear, a natural question emerges: what are the essential features responsible for the invasion pattern? Since the autocatalytic dynamics cannot be further simplified, we looked into the transport term and decided to test the hypothesis that the observed patterns are a consequence of the strong transport anisotropy along the axonal bundles. These bundles are not only information highways, they could also carry efficiently toxic proteins across the brain.

A simple way to test this idea is to coarse grain the brain by considering multiple regions and the connection between them. The full brain is then replaced by a network, *the connectome*, where each node is a region and an edge represents the possible connections between regions. This approach is the basis for a large field of neuroscience and various groups have successfully used the connectome to look at the effect of protein diffusion in the brain [9].

The natural discretization of the diffusion operator on a network is the weighted graph Laplacian $\mathbf{L}$. Given the adjacency matrix of a network (See Chapter 3 for an introduction to Brain Networks), the graph Laplacian is given by



$$A = \begin{bmatrix} 0 & 1 & 1 & 0 \\ 1 & 0 & 1 & 1 \\ 1 & 1 & 0 & 1 \\ 0 & 1 & 1 & 0 \end{bmatrix} \quad L = \begin{bmatrix} 2 & -1 & -1 & 0 \\ -1 & 3 & -1 & -1 \\ -1 & -1 & 3 & -1 \\ 0 & -1 & -1 & 2 \end{bmatrix}$$

Figure 5.2: A simple example of an undirected unweighted graph with its adjacency and Laplacian matrix.

$$\mathbf{L} = \mathbf{D} - \mathbf{A}, \tag{5.2}$$

where $\mathbf{D} = \mathrm{diag}(\mathbf{d})$ is the *degree matrix*, a diagonal matrix with diagonal elements $\mathbf{d} = \mathbf{A} \cdot \mathbf{1}$, each element on the diagonal is the sum of the weights in the corresponding row. In particular, in the unweighted case, the weight is taken to be $a_{ij} = 1$ whenever an edge is present between i and j as shown in an example in Fig. 5.2.

For the brain, we have extra information and we take the weights to be proportional to the number of connection and inversely proportional to the distance between nodes (ballistic weights) as shown in Fig. 5.3.

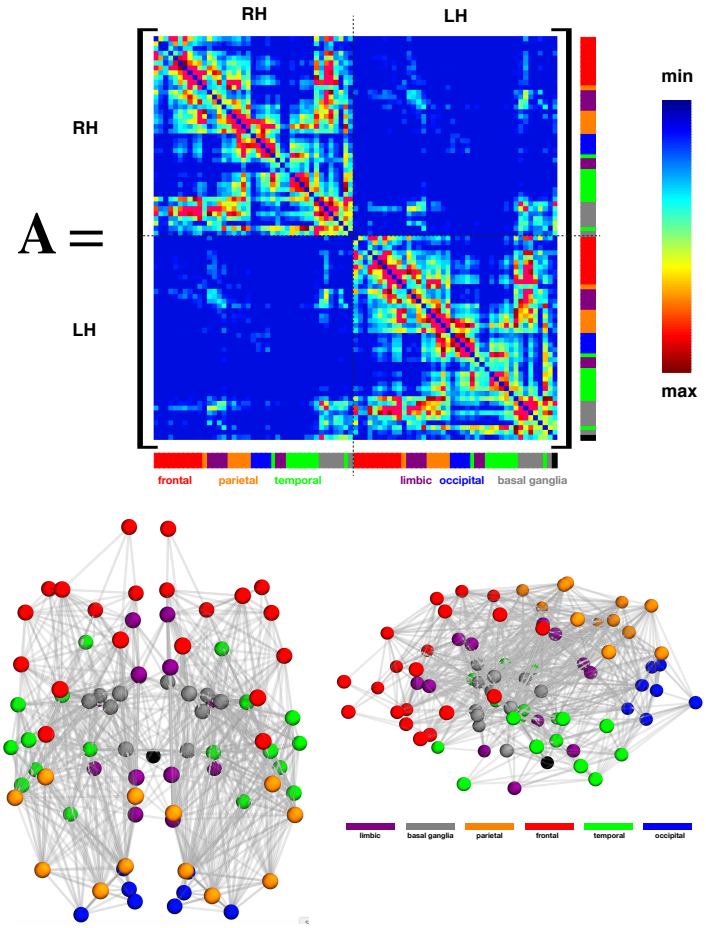


Figure 5.3: The average weighted-adjacency of 418 brain connectomes with $n = 83$ nodes and ballistic weights, together with the node position in the brain and the lobes they belong to.

Then, defining $c_i(t)$ to be the concentration of toxic proteins at node i, the discrete Fisher-KPP

equation reads:

$$\dot{c}_i = -\rho \sum_{j=1}^{N} L_{ij} c_j + \alpha c_i (1 - c_i), \quad i = 1, \ldots, N. \tag{5.3}$$

This system of nonlinear of ordinary differential equations turns out to be an excellent approximation of the dynamics generated by the full nonlinear partial differential equations that we started with [10]. Mathematically, there are two regimes of interest depending on the ratio ρ/α. In the diffusion dominated regime ($\rho/\alpha \ll 1$) the system behaves mostly homogeneously with the concentration of toxic proteins increasing in all regions uniformly as found for instance in the propagation of amyloid beta. However, a systematic study of data available from open database (the Alzheimer's Disease Neuroimaging Initiative) using hierarchical Bayesian parameter inference taught us that the evolution of tau proteins is in the growth-dominated regime ($\rho/\alpha \ll 1$) where each region is invaded in turn from the primary seed. In that regime, a systematic nonlinear perturbation method can be implemented to obtain an approximation of the solution as shown in Fig. 5.4. It is also possible to attach a metric to the graph based on the dynamics. This metric provides a natural notion of propagation times between different regions [8]. Therefore, by combining analytical and computational results we learned that the dynamics is strongly constrained by the brain topology in the early stages of the disease followed by a balance between protein kinetic and geometry in the latter stages. Topology and dynamics go hand in hand.

Despite its simplicity, this network model is a very good match for disease progression and for the more computationally demanding continuum model as shown in Fig. 5.5. This simpler framework can be used as a basic starting point to study many different aspects of the disease and test possible mechanisms. In more recent work, we have considered local variations in parameters associated with brain inhomogeneity, studied the coupling between amyloid-beta and tau proteins, the role of clearance in the initiation and dynamics of the disease [6], the interactions between the microvasculature and toxic proteins [1], the study of different treatments [5] and identified topological signatures of the disease in graph space. We have also studied the perplexing dynamics in brain activity observed in patients who typically show periods of hyperactivity followed by hypoactivity and a shift in brain wave frequencies. The same model coupled to so-called *neuronal mass models* for brain activity allowed us to test multiple hypotheses and conclude that local damage of particular groups of neuronal cells is the most likely mechanism responsible for these observations [2, 3].

5.4 Why modelling matters

Mathematicians take for granted that mathematical modelling is important. In the case of neurodegenerative diseases it is not obvious that models can be helpful and, indeed, many medical researchers will probably find them irrelevant. Yet, the direct approach based on clinical and experimental studies also has not been successful in identifying treatments. The difficulty of the disease comes from its combination of effects at different scales, from proteins to the brain over decades of interactions in a highly complex environment. This is exactly the playground of modern applied mathematics. Models help us test hypotheses and identify key mechanisms leading to possible therapeutic targets. In particular, progression models can be matched to imaging data at the macroscopic level, to the parameters that enter aggregation-fragmentation models at the microscopic level, and to clearance rates at the cellular level. A good model for progression will allow us to classify different disease trajectories and identify the best cohorts for drug trials. Unveiling these multiscale, multiphysics, interactions is key to understanding and, hence, treating the disease. At the mathematical level, it represents a formidable and exciting intellectual challenge that brings together many fields such as nonlinear partial differential

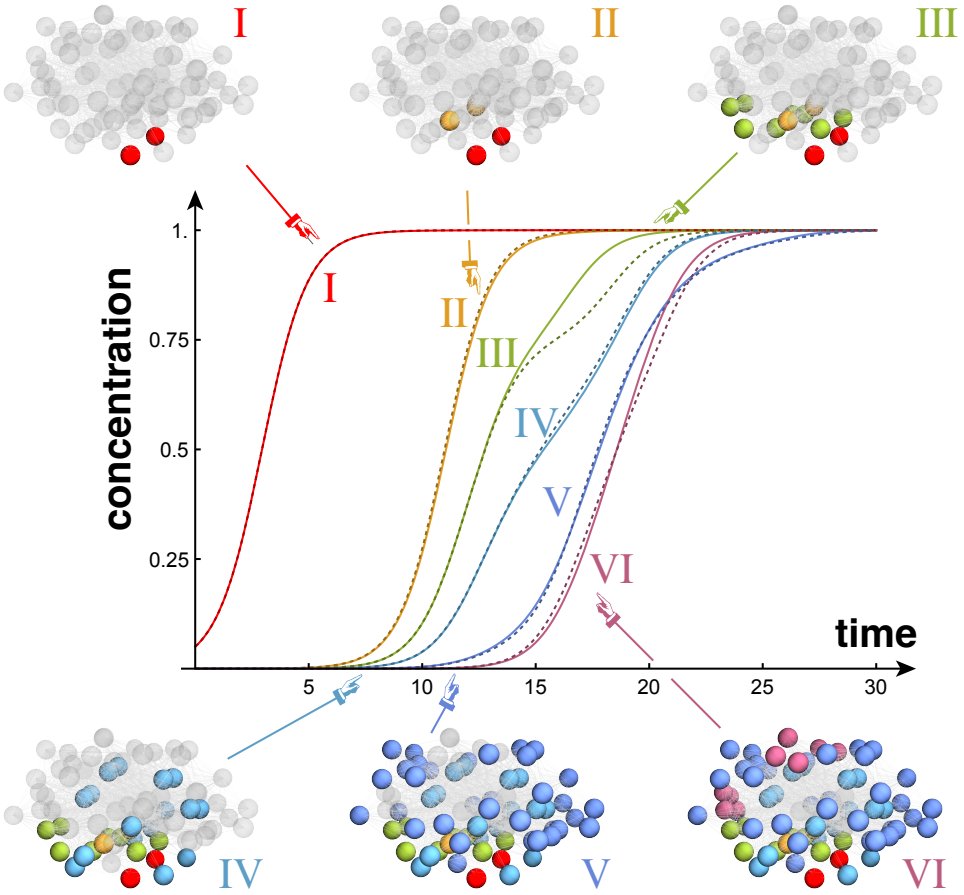


Figure 5.4: Average concentration of toxic proteins in each Braak region. The solid curves are the numerical solutions and the dashed curves are their approximations obtained from a nonlinear perturbation expansion. Initial conditions are chosen so that the total concentration in the entorhinal cortex nodes is 1/10 (Braak I) and zero for all other nodes (parameters $N = 83, \alpha = 0.5$/year, $\rho = 0.01$/year. (adapted from [8]).

equations, networks, dynamical systems, continuum mechanics, mathematical neuroscience, and topological data analysis.

At age 70 Mr U was a pale shadow of the man he once was. His wife could not manage his condition anymore and he was admitted to a nursing home. He died three years later from pneumonia.

References and Further Reading

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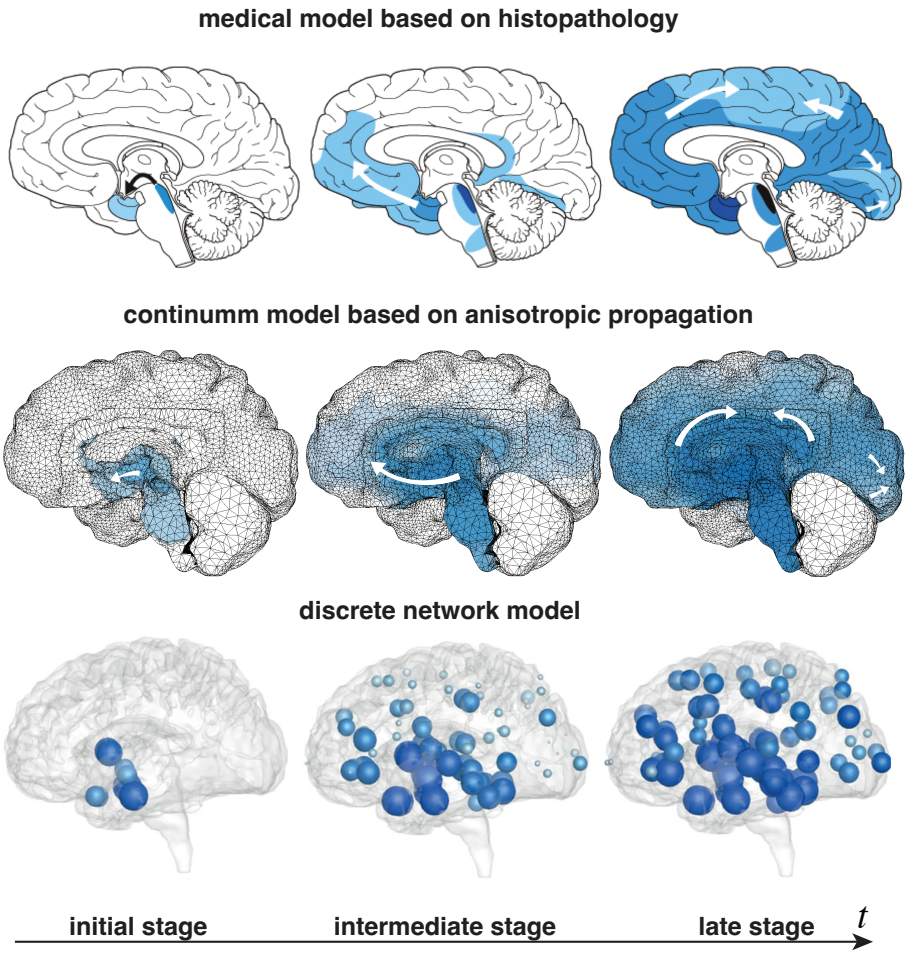

Figure 5.5: Progression of toxic tau proteins in the brain. Top: medical staging based on histopathology (the analysis of post-mortem brain slices). Middle: Simulation of the anisotropic Fisher-KPP model with initial value in the entorhinal cortex. Bottom: Simulation of the network Fisher-KPP model with initial seeding at the entorhinal node (adapted from [10]).

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