Chapter 2

Mathematical Models of Alzheimer's Disease

Given the relatively homogeneity of disease presentation, AD lends itself to mathematical modelling. Minimally, one would hope to be able to use models of AD to make predictions about patient progression. In addition to disease prediction, mathematical models provide an opportunity to gain a mechanistic understanding of the factors underlying AD that could inform pharmacologists and clinicians about potential intervention targets. Mathematical modelling of AD has becoming a fertile research programme over the past year, producing models that describe disease mechanisms and making valuable predictions about patient trajectories. In particular, network models of neurodegeneration have become increasingly popular due to the desirable balance of complexity and expressiveness. Here, I will describe the basis for network mathematical models of AD and some popular models used in the literature and throughout this report.

2.1 Dynamical Models

Typically, mathematical models of neurodegeneration have focussed on modelling the spread and aggregation of toxic protein species τP and Aβ. While there have been numerous contributions focussing on continuum dynamics [101, 31], as well as probabilistic network models [97], I will here focus on dynamical system models on networks (where network refers to a collection of vertices and edges). The use of such network models can be justified with experimental results showing that τP and to a lesser extent Aβ, preferentially travel across axonal fibres [22, 25]. An additional benefit is that solutions to ordinary differential equations (ODEs) on graphs are computationally less expensive to obtain than their partial differential equation

counterparts. As mentioned in Section 1.4, network models of AD protein pathology should aim to describe at least transport across axons and growth via an autocatalytic process akin to prion-like templating.

2.1.1 Transport and the Graph Laplacian

As highlighted in Sections 1.1 and 1.4, the graph Laplacian is the central object used to describe transport along axonal fibres. The topology of axonal pathways can be obtained through the analysis of diffusion weighted MRI data, such as those available from the Human Connectome Project (HCP). The output of this analysis is a graph $G = (V, E)$, where V is the enumeration of vertices in the graph, $v_1, v_2, ...v_n$ and E the edges between them. The transport of protein concentration between regions of the brains, vertices V, can be effectively modelled using the graph Laplacian, defined as:

$$\mathbf{L} = \mathbf{D} - \mathbf{A}, \tag{2.1}$$

where $\mathbf{A}$ is the weighted adjacency matrix encoding the connectivity between regions, weighted by the number of connections, n, and the length of connections, l,

$$A_{ij} = \begin{cases} \frac{n}{l^2} & \text{if an edge connects } v_i \text{ to } v_j \\ 0 & \text{otherwise} \end{cases}, \tag{2.2}$$

and $\mathbf{D}$ is the degree matrix, containing the total number of edges associated with a given vertex,

$$D_{ij} = \delta_{ij} \sum_{j=1}^{N} A_{ij}. \tag{2.3}$$

The Laplacian matrix is equivalent to a second order discretisation of the negative Laplace operator on a unit grid. The Laplace operator is used in a continuous setting to describe diffusive processes, in the simplest case this is the heat equation. The Laplacian matrix is therefore an adequate substitution for modelling diffusion across axonal pathways represented as a network.

The transport of protein diffusion on a graph is given by the network heat equation:

$$\frac{d\,\mathbf{p}}{d\,t} = -\kappa \mathbf{L}\mathbf{p}. \tag{2.4}$$

This model has been widely validated against data using regression studies [82, 83] and Bayesian inference [87]. However, there is a wealth of evidence to suggest that this model is not an accurate description of the prion-like process underlying AD, since it does not account for growth coming from the prion-like templating process [52, 32].

2.1.2 Protein Proliferation

To augment the network heat equation with appropriate production and clearance terms, consider the rate-reaction diagram shown in Figure 2.1, describing Pruisner's model of prion-like propagation through templating [78, 79].

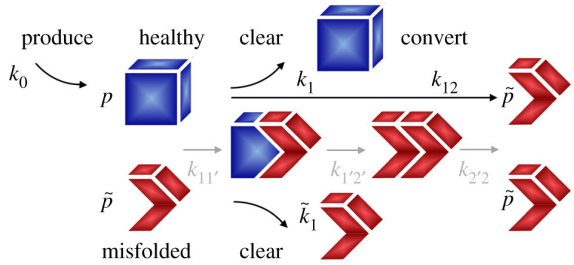

Figure 2.1: **Reaction kinetics of the heterodimer model.** Adapted from [32].

Figure 2.1 shows the process of prion templating. There is a healthy protein concentration p and toxic protein species $\hat{p}$. The toxic protein binds the healthy protein with rate $k_{11'}$ and induces a conformational change into the healthy protein, turning it into a toxic protein with rate $k_{1'2'}$, before separating into two toxic monomers with rate $k_{2'2}$, collectively summarised as rate k_{12}. Both healthy and toxic protein species are cleared with a natural clearance rate of k_1 and $\hat{k}_1$, respectively. More compactly, this can be written as a pair of coupled ODEs:

$$\frac{dp_i}{dt} = -\kappa \sum_{j=1}^{N} L_{ij} p_j + k_0 - k_1 p_i - k_{12} p_i \hat{p}_i, \tag{2.5}$$

$$\frac{d\hat{p}_i}{dt} = -\hat{\kappa} \sum_{j=1}^{N} L_{ij} \hat{p}_j - \hat{k}_1 \hat{p}_i + k_{12} p_i \hat{p}_i. \tag{2.6}$$

for $i = 1, .., N$ nodes of the graph. Here, Pruisner's kinetic model has been paired with the network diffusion equation, providing a mechanistic description of AD in terms of protein transport and growth. However, the physical insight obtained comes at the cost of an increased number of parameters. For simulation purposes, this does not pose any issues, however, it may prove problematic when validating the model against data. Given the temporal sparsity of data, it will be challenging to identify many parameters that produce complex dynamics. The heterodimer model can be reduced into one with fewer parameters. First, assume the initial healthy protein concentration is much greater than the misfolded protein concentration, $p \gg \hat{p}$. This implies a negligible change in protein concentration, $\frac{dp_i}{dt} \approx 0$, and diffusion,

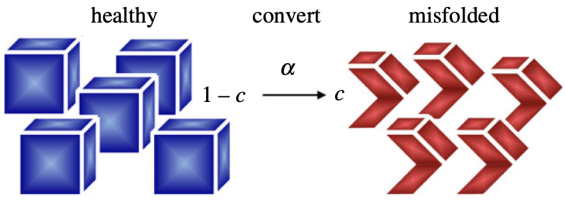

Figure 2.2: **Reaction kinetics of the FKPP model.** Adapted from [32].

$-\kappa \sum_{j=1}^{N} L_{ij} p_j \approx 0, \text{for } i = 1, ..., N$. Then, using a Taylor series to approximate p and re-parametrising in terms of the misfolded protein concentration,

$$p = \frac{\hat{p}}{\hat{p}^{max}} \tag{2.7}$$

$$\hat{p}^{max} = \frac{k_1}{k_1 2} - \frac{k_1^2}{k_{12}^2 \hat{k}_1 / k_0} \tag{2.8}$$

we arrive at the following:

$$\frac{d\hat{p}_i}{dt} = -\kappa \sum_{j=1}^{N} L_{ij} p_j + \alpha p_i \left(1 - p_i\right), \tag{2.9}$$

$$\alpha = k_{12} \frac{k_0}{k_1} - \hat{k}_1. \tag{2.10}$$

for $i = 1, ..., N$ nodes. This is the well known Fisher-Kolmogorov–Petrovsky–Piskunov (FKPP), widely used in mathematical biology. The kinetics implied by such a model are seen in Figure 2.2 and an example of dynamics and staging are shown in Figure 2.3. The FKPP model has a single parameter for the growth rate of toxic protein species. While this greatly reduces the complexity of the model, it comes at a cost of interpretability. The growth parameter α has some physical interpretation given by its parametrisation in Equation 2.10, however, in practice it would not be possible to determine the contributions of its individual terms and thus its physical interpretation is limited.

2.1.3 Models of Brain Atrophy

Alzheimer's disease is characterized by several biomarkers, including alterations in normal Aβ and τP levels, Braak staging of τP neurofibrillary tangles and distinct patterns of atrophy progression [29, 76, 65]. Early mathematical models of proteopathy have already taken steps to track atrophy progression using both a simple network model [83], founded on basic network diffusion (2.4), and a continuum model [101]

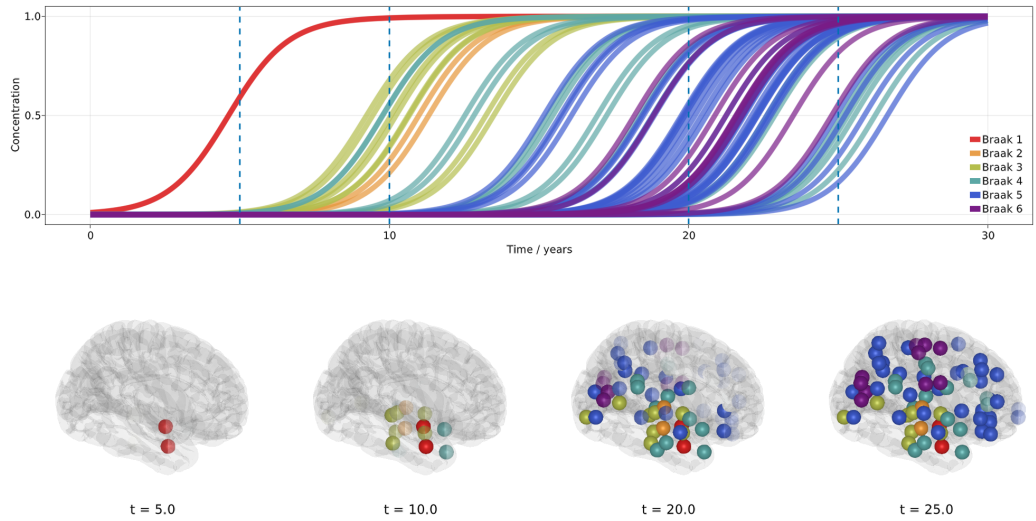

Figure 2.3: **FKPP dynamics coloured by Braak regions.** Simulation results using synthetic parameters. The entorhinal cortex was seeded with an initial concentration of 0.01. The model parameters were: $\kappa = 0.01$ and $\alpha = 1.0$.

using an FKPP model with local non-linear deformations based on the presence of the toxic protein concentration. As discussed in Section 1.2.1, atrophy is closely correlated with the typical progression of toxic τP, thus one can consider a coupled model in which regional atrophy is a function of toxic protein concentration:

$$\frac{dq_i}{dt} = G_c p_i (1 - q_i), \tag{2.11}$$

for $i = 1, .., N$ nodes, where q_i and p_i corresponds to brain volumes and toxic protein concentrations at the $i-th$ region of the connectome, respectively, and G_c is a global rate coefficient for atrophy. This is a simple logistic model of atrophy that bounds that level of atrophy such that a region can not deteriorate without constraint.

At least one benefit of extending the models to describe tissue atrophy, aside from the added descriptiveness, is that it is amenable to comparison to structural MRI data, which is manifestly more abundant than protein PET tracer data.

2.2 Identifying Uncertainty

So far, we have discussed how different models may account for AD. In practice, one would want to use the models for prediction. In this case, the model requires calibration to find the most likely parameter values. In a system of ODEs, the trajectory is uniquely determined by the initial conditions and the parameters. The process