to AD, most notably the Alzheimer's Disease Neuroimaging Initiative (ADNI). Additionally, there are a number of community standard software libraries for the analysis of brain images. Particular software that are utilised throughout the work presented here are FreeSurfer, SPM and FSL. The combination of publicly available data and analysis software ease the burden on modellers for finding and processing observational data.

Since its inception, neuroimaging has proved a valuable tool for investigating AD in humans. Without such methods, it would be near impossible to practically analyse AD pathology in-vivo in human brains. The recent advent of τP PET tracer, AV1451, has allowed for identification of distinct patterns of spread validating Braak and Braak [13, 102]. These data have been used extensively by modellers for parameter calibration and validation [97, 87, 88]. Similarly, studies using structural MRI have shown how atrophy progresses during AD [65], highlighting the relationship between atrophy and τP, but not Aβ [75, 89, 64]. As yet, few studies, have used structural MRI as observations to fit models [82, 83], however, their relative abundance compared to PET data make them a valuable resource for modelling, especially if they can be usefully combined for multimodal inference. Overall, neuroimaging has provided a wealth of knowledge and data that has advanced AD research in its own right, and has also facilitated modelling studies probing disease mechanism.

1.4 Dynamical Models of AD

Network models of neurodegeneration have been used extensively to study the progression of toxic proteins during AD but come with a number of challenges, some inherent with dynamical systems models and some particular to the modelling domain, i.e. network neuroscience. The basic mechanisms these models describe are transport across axons and growth via an autocatalytic prion-like process. The first model, describing only transport across axons, was provided by [82] and laid the foundation for other groups to expand on this with more expressive models that describe growth [32, 31, 101]. The general form of these models is a system of ordinary differential equations on a graph.

$$\frac{d\mathbf{u}}{dt} = \mathbf{f}(\mathbf{u}, t; \mathbf{p}, \mathbf{L}), \tag{1.1}$$

where $\mathbf{f}$ is a vector valued function in time, with state vector $\mathbf{u} \in \mathbb{R}^N$, additionally depending on parameters, $\mathbf{p} \in \mathbb{R}^p$, and a $N \times N$ graph Laplacian, $\mathbf{L}$, derived from a graph used to define the domain of the system. Representing the system in this way

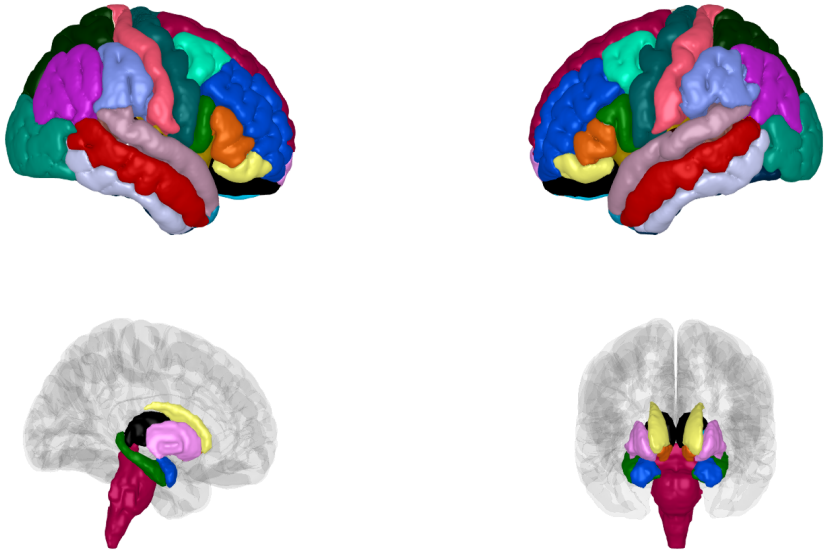


Figure 1.2: **The DKT parcellation**. The standard FreeSurfer DKT parcellation shown on a MNI brain. Top: 68 cortical regions for left and right hemispheres. Bottom: 15 subcortical regions, including the brainstem

makes it easier to identify challenges present in the modelling process: each element of the system brings its own form of uncertainty that requires quantification and rectification.

First, there is uncertainty about the nature of the function $\mathbf{f}$, principally due to our limited understanding of AD pathology. Several models have been presented in the literature, including the simple network diffusion model [82, 83], the epidemic spreading model [97] and a host of reaction-diffusion equations [32, 31]. Each of these models imbue different processes and assumptions into a model of AD pathology and at present there is little evidence to choose one over another. Thus it is important to be able to identify which of these models is most appropriate given the available domain knowledge.

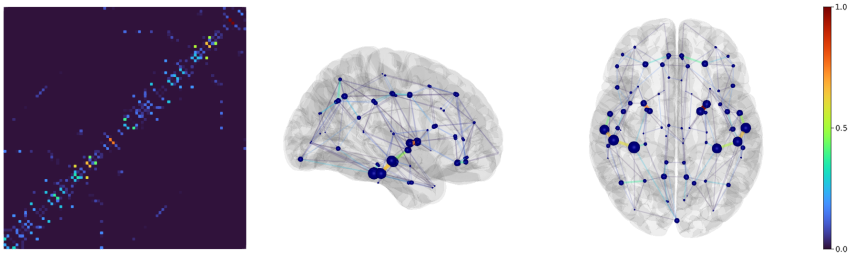
Second, there is considerable uncertainty associated with the graph used to define the dynamical system. The graph not only defines the state vector ,$\mathbf{u}$, but the transport between its elements, and therefore its properties can have a large effect on the dynamics produced by the system. The process of generating a graph, referred to in network neuroscience as a connectome, can be broadly separated into two processes: 1) parcellating the brain; 2) performing tractography. Each of these two processes are active areas of research in imaging neuroscience and there is no canonical choice

for either, leading to sources of uncertainty stemming from both.

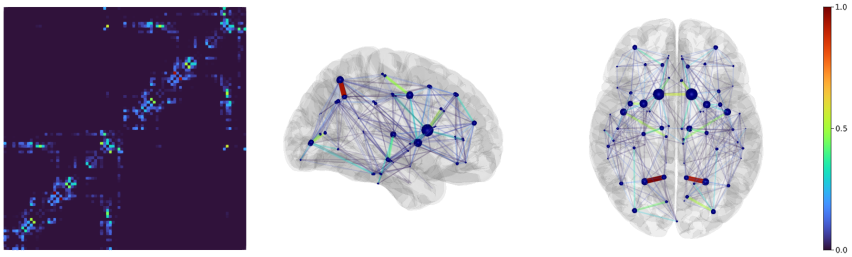
For the current work, we generate connectomes using the Lausanne multi-scale parcellation [19], built on the Desikan-Killiany-Tourville (DKT) atlas used as standard in the FreeSurfer software package [30, 57]. The standard atlas is visualised in Figure 1.2. However, there are many alternative parcellation choices, each of which characterise different features of brain, e.g. anatomy, functional connectivity, size of regions, gyrification, among others [60, 69]. It is not yet known whether some parcellations are better suited than others for marco-scale connectome modelling.

Tractography is a process of reconstructing the neuronal connections between brain regions from diffusion weighted MRI imaging. There are two broad families of tractography methods, deterministic and probabilistic, each defined by their own sets of parameters. The output of tractography is an adjacency matrix that defines a graph representing connections between regions of a given parcellation. Connectomes generated using different procedures are shown in Figure 1.3. Figure 1.3a shows a connectome generated with probabilistic tractography using FSL, while Figure 1.3b shows one generated using deterministic tractography [93, 56], distributed by the PIT group through `www.braingraph.org`. Differences in network topology, such as those shown between Figure 1.3a and 1.3b, can have significant effects on the dynamics exhibited on those networks [80]. Together with the lack of consensus about how to generate connectomes, this creates a large source of uncertainty in the modelling process.

Third, there is parametric uncertainty associated with the parameter vector, $\mathbf{p}$. For any given dynamical system, variations in parameters can lead to different results during simulation. In general, it is difficult to determine from observations alone the parameters of the dynamical system, a problem that is made more intractable in the presence of observation noise. Popular methods for determining parameter values include least squares regression, maximum likelihood estimation and maximum a posteriori estimation and have been used in the network neurodegeneration literature for model validation [82, 83]. For ill-posed problems with sparse and noisy observations, however, these methods are unsuitable since they do not account for potentially significant uncertainty around parameter estimates. Such variations of parameters and the effects on dynamics has been shown by [80]. Recent work has incorporated Bayesian analysis into the validation pipeline, which allows for the quantification of uncertainty [87, 88]. The results highlight that there can be considerable variation in parameters between individuals and groups for a given set of observations. A framework for han-



(a) Probabilistic connectome with diffusive weights



(b) Deterministic connectome with diffusive weights

Figure 1.3: **Connectomes made with different tractography procedures**. Both connectomes are made using the DKT atlas to define regions of interest. Left: Shown are weighted adjacency matrices normalised to the maximum values. Right: networks visualised on the brain; edges coloured by weight and and vertices sized by degree. Networks have been filtered using a naive threshold of 0.01. **(a)** Made using FSL probabilistic tractography [9, 8]. **(b)** Made using MRtrix deterministic tractography and distributed by the PIT group through www.braingraph.org [56].

dling sources of uncertainty has been the focus of this project thus far and will be discussed at length in Chapter 2, with example applications in Chapter 4.

1.5 Research Aims and Report Overview

1.5.1 Research Aims

My aim is to establish a mathematical and software framework for validating dynamical models of AD with human neuroimaging data. My objectives are to:

1. Investigate the theoretical conditions necessary for robust uncertainty quantification of dynamical models of AD.

2. Develop the a unified software framework that simplifies dynamical modelling of AD and inference with patient data.