InFoMM
Industrially Focused
Mathematical Modelling

UNIVERSITY OF
OXFORD

Clearance paradigms for network models of prion-like proteopathy development throughout the brain

Georgia Brennan

Neurodegenerative diseases such as Alzheimer's disease (AD) are characterised by the accumulation of toxic proteins. In particular, in AD we see heightened levels of misfolded Amyloid-β (Aβ) and tau proteins in the brain. It is thought that the disease starts in the brain decades before a person experiences the forgetfulness primarily associated with AD, during which time the two proteins enhance each other's activity. The **prion hypothesis** states that these trademark proteins spread through the brain in a prion-like manner, which describes a cascade of proteins reminiscent of a game of hide and seek, where tagged players join the team of seeker proteins. In a healthy brain, Aβ and tau are cleared from the brain through a number of interconnected protein clearance pathways, such as being transported into the cerebrospinal fluid which is hypothesized to flow in annular spaces along the outside of larger blood vessels.

Just as toxic proteins behave like seekers breaking into a region of the brain, we can imagine clearance mechanisms as different types of barriers blocking their entry and removing proteins, or at least making it more difficult to move through a region. It is thought that an imbalance between protein production and clearance triggers the spread of toxic proteins which ultimately leads to the irreversible death of brain cells. Simula Research Laboratory are interested in understanding how toxic protein concentration and clearance are linked through damage to clearance pathways. Such insights could inform strategies to restore the healthy elimination of protein deposits, and potentially produce treatments for AD.

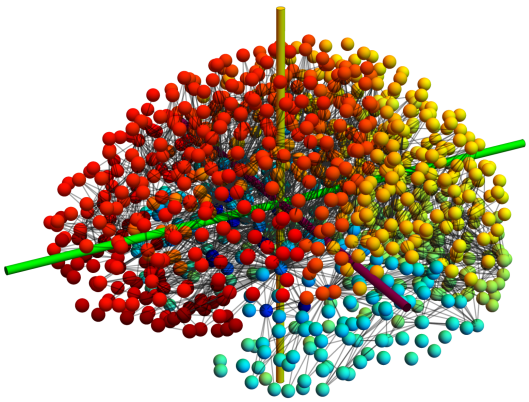

Figure 1 – Network model of the human brain constructed using the data from 418 healthy brains.

The brain consists of functionally specific groups of cells called neurons which are connected by bridges called axons. These highly clustered regions connect physically distant areas with relatively few paths so the brain is organised as a **small world network**, similar to that of a social network. Imaging studies have shown that toxic proteins travel along the axonal bridges rather than by proximity. Previous studies have extracted a brain network from the images of over 400 healthy brains in which the nodes correspond to regions of interest of the brain, with an edge between regions if bundles of axons are present (figure 1). Our aim is to capture the essence of the game of hide and seek that AD plays as our brain ages by studying a mathematical model on this network which connects the evolution of clearance with the spreading of toxic proteins throughout the brain.

UKRI Engineering and Physical Sciences Research Council

Previous studies have revealed the existence of a critical balance of clearance. This value represents the minimum number of barriers necessary to keep the toxic seeker proteins at bay. If clearance levels are above this critical value, we say that the clearance is healthy. However, we expect that there is a limit to the number of seekers these barriers can prevent from passing. Indeed, analysis of our model reveals a critical toxic load, above which the clearance barriers fail and the brain region becomes overrun with toxic seekers, tending towards a state of saturation of misfolded proteins. We conclude that a healthy number of barriers does not mean that the brain is safe, rather that it is safer for longer.

Given a brain with healthy initial clearance barriers, we use Oxford's BrainNet software to simulate an event in which toxic proteins are placed in the posterior cingulate region of the brain and refer to this region as the seeding node. We refine our model using a **perfusion hypothesis**. This hypothesis states that clearance in the brain is directly related to blood flow, so we use regional cerebral blood flow data to inform some quantities in our model. We seed a toxic load at time $t = 0$ of a concentration greater than the critical toxic load of the network. In figure 2 we display the resulting spread of toxic proteins through the brain. In subfigures 2(a)-(c), we show the initial stages of the disease. The initially healthy clearance fights to clear the toxic proteins, but is overpowered with proteins soon driving clearance below the local critical value. Following a regrowth of the protein population in the seeding node, the cascade of toxic proteins spreads through the network as seen in figures 2(d)-(f). As previously reported in the literature, we are able to simulate the spread of AD over decades in a matter of seconds through network modelling and successfully replicate the results of imaging studies. Furthermore, having built upon previous models to include the dynamics of clearance we observe a more refined timescale for proteopathy.

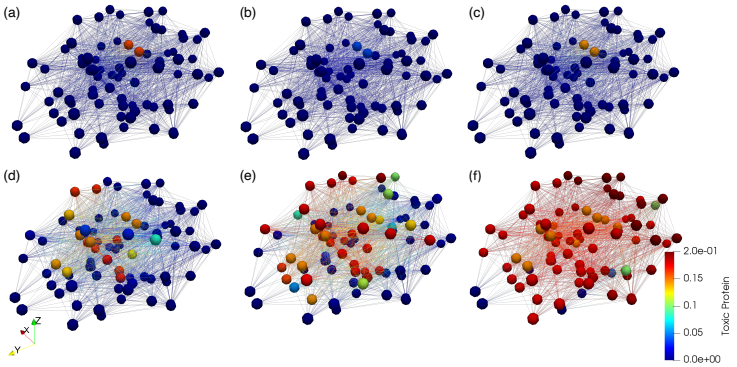

Figure 2 – The spread of toxic proteins through the connectome, displaying the initial stages of the disease (a)-(c) and the cascade of toxic proteins (d)-(f) leading the network to saturation.

In summary, we have built a model for the spread of AD across the brain's connectome which incorporates the relationship between protein accumulation and clearance. We use our model to provide intuition about the dynamics of the disease without the need for autopsies or lengthy animal/human testing. Our future aims include using the perfusion hypothesis to simulate interesting events such as chronic stroke and studying how reduced blood flow in this case can pave the way for AD. In coupling clearance to the toxic protein concentrations, we lay the groundwork for a model which can be extended to differentiate between the different modalities of clearance and explore how these mechanisms might interact. Such models give insights into the early stages of the disease, which is a vital period for medical intervention to take place, and a stage of the disease for which data is scarce since patients often present with AD symptoms years after onset.

Dr Marie Rognes, Chief Research Scientist and Research Professor at Simula said:

> *At Simula Research Laboratory, we aim to create knowledge about fundamental scientific challenges that are of genuine value for society. One of our current fundamental research goals is to use modelling and simulation to better understand and predict the flow of fluid and solutes through brain tissue. These physiological mechanisms are crucial for the well-being of the brain. In spite of their importance, our understanding is limited.*
> *Georgia's work is a ground-breaking first step in the direction of linking brain clearance pathways and neurodegeneration. Her exciting findings have allowed us to form new hypotheses on the development of neurological disorders such as e.g. Alzheimer's disease. Further, the knowledge transfer between Oxford and Simula Scientific Computing has been extremely valuable, and we very much look forward to continuing the joint research.*