Mathematical models of proteopathy in Alzheimer's disease

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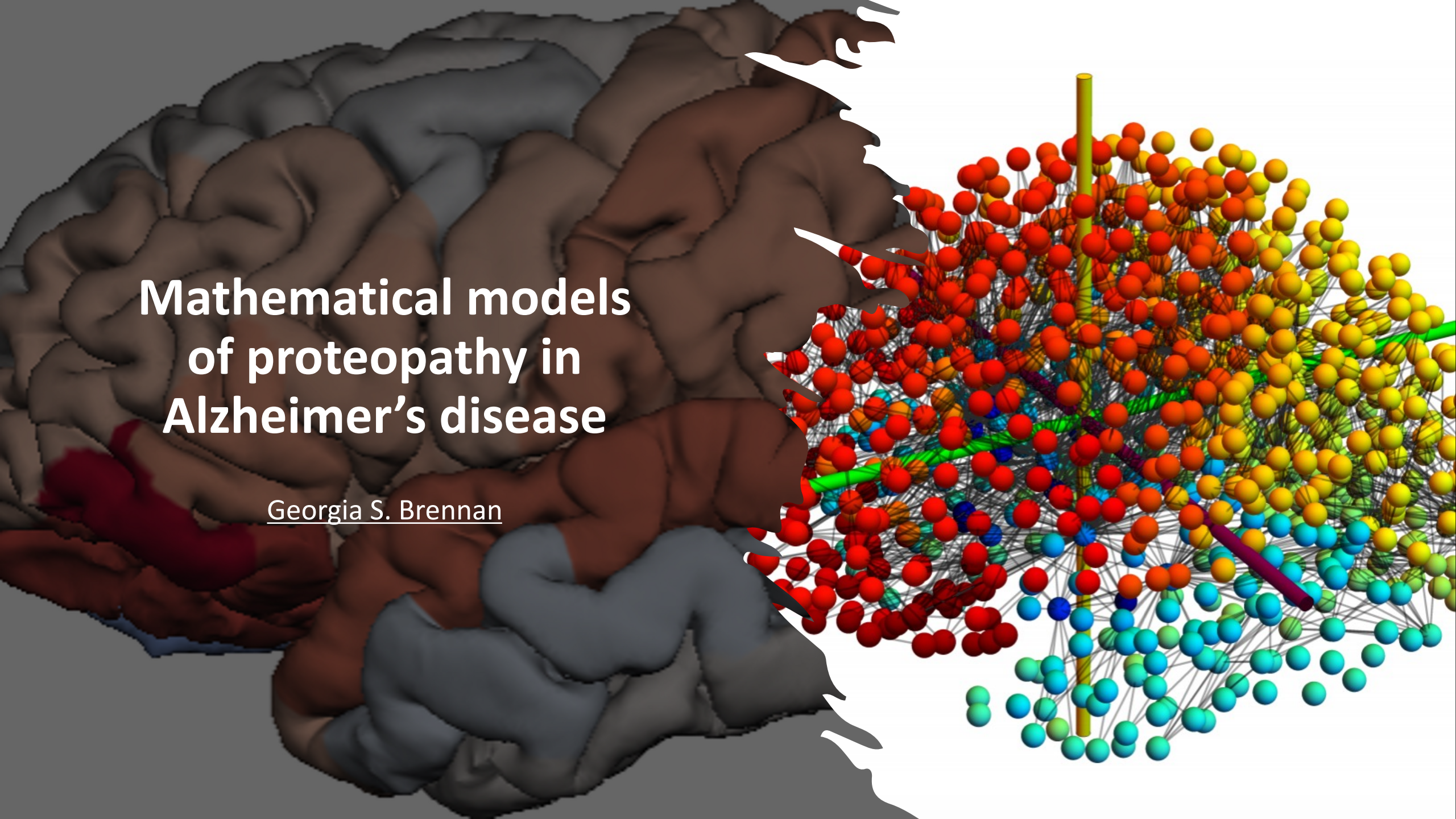

Alzheimer's disease

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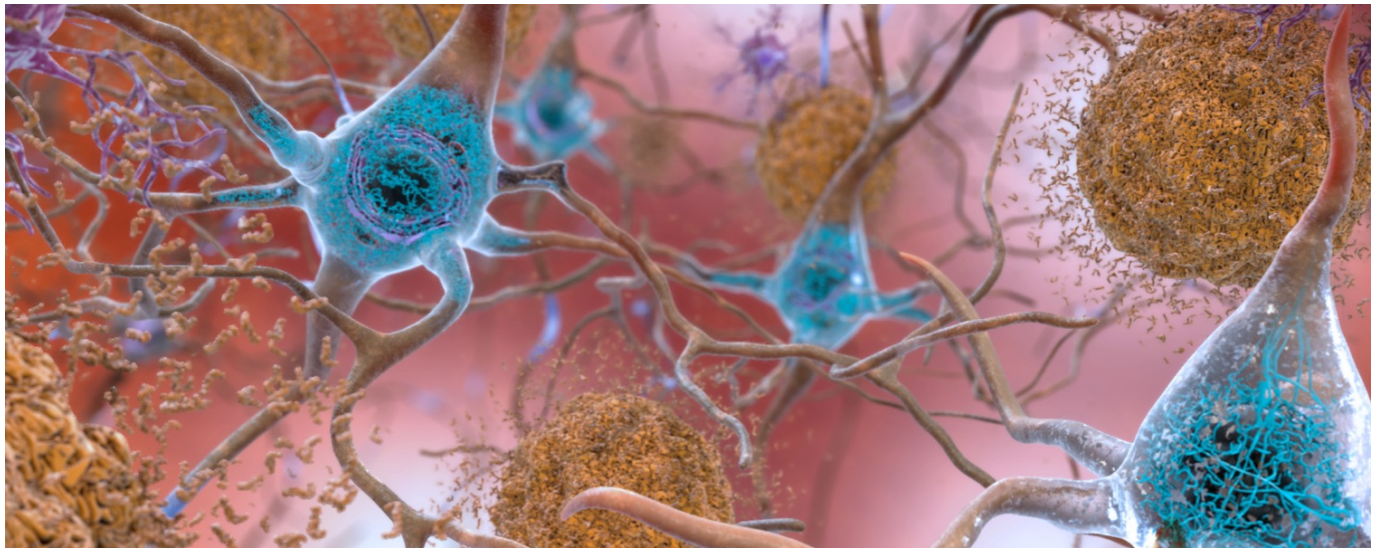
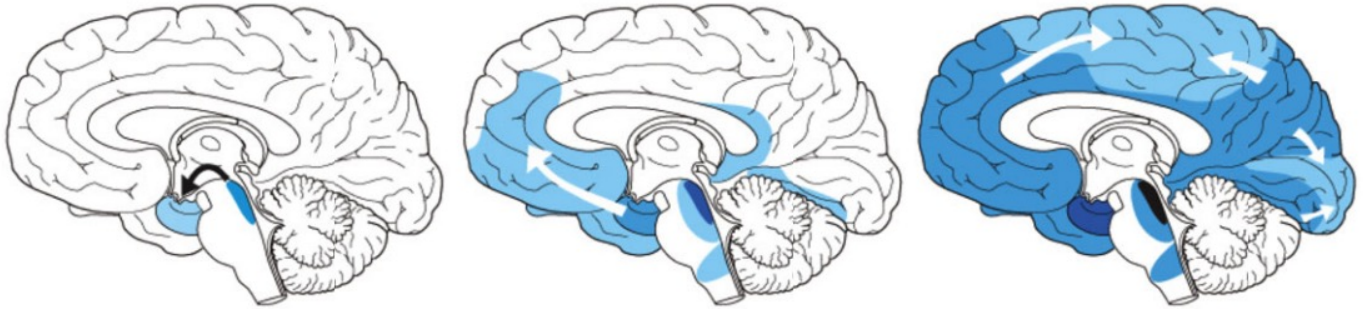
Alzheimer's disease is a neurodegenerative disease which is characterised by the accumulation of misfolded Amyloid-β (Aβ) and tau proteins.

How do the driving factors interact?



Why do neurodegenerative diseases progress so slowly?

Why such distinct spreading patterns?

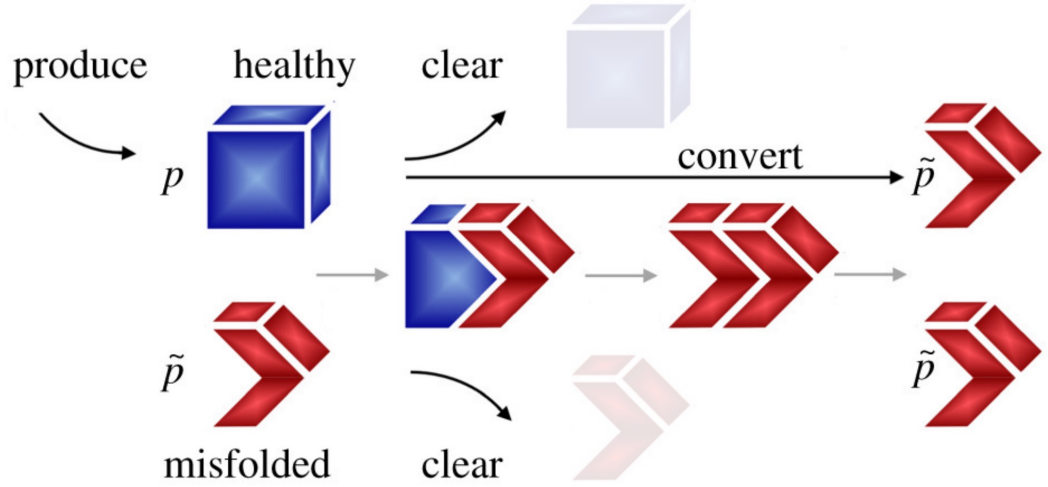


Can we interfere in the spreading?

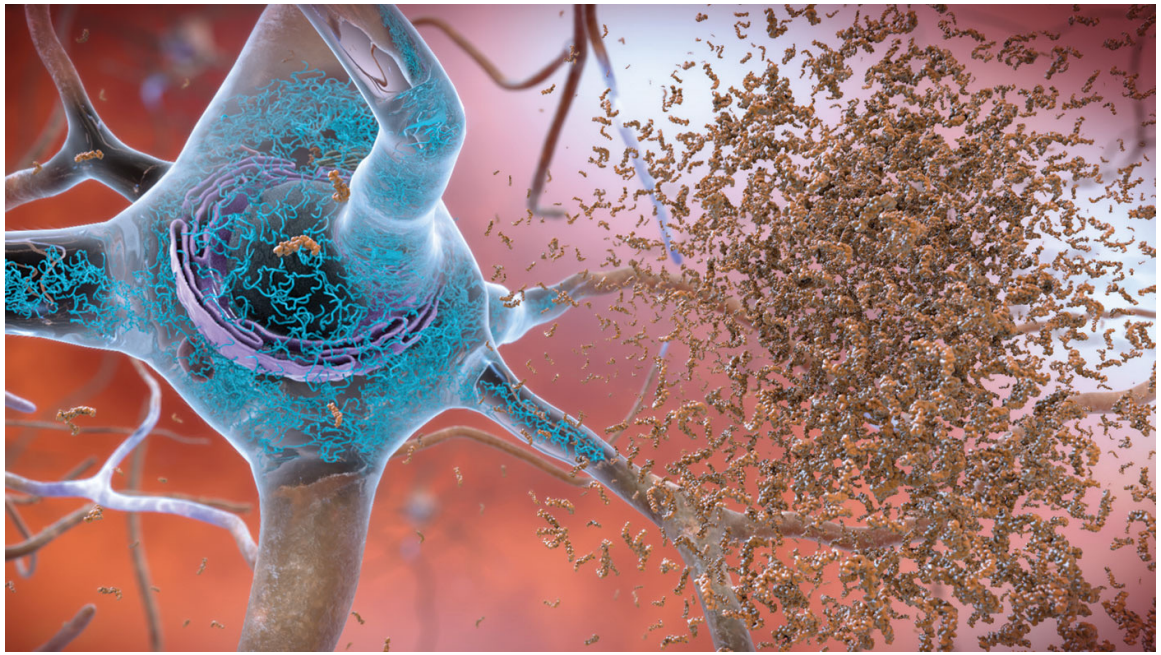
We do not understand the fundamental mechanisms driving the disease

AD Hypotheses

The Prion hypothesis



The Amyloid hypothesis (debated)



AD Hypotheses

Neurodegenerative diseases propagate along axonal fibre pathways.

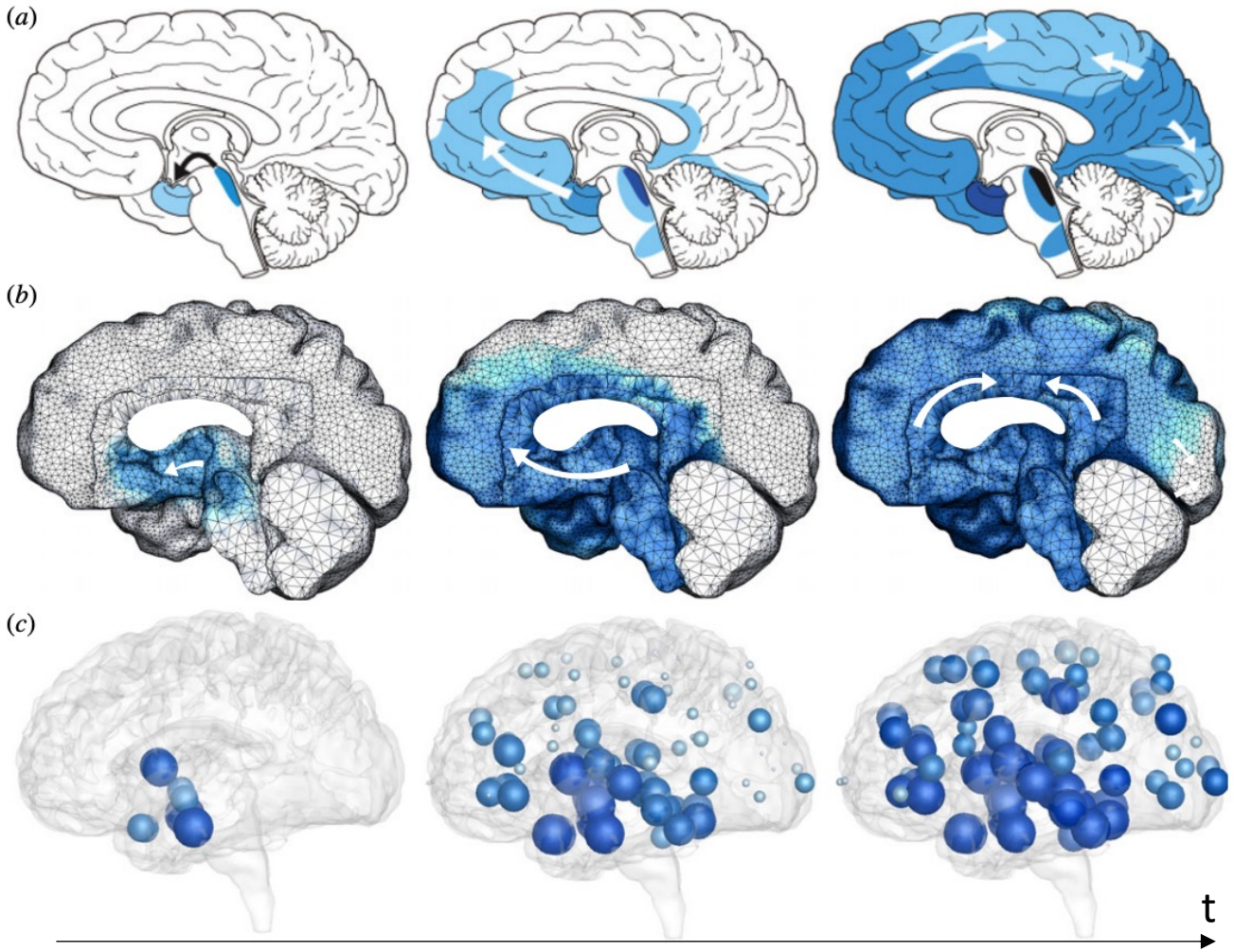
The brain as a network

Brain network models can predict the histopathological patterns of Alzheimer's disease.

Clinical observation:

Continuum model results:

Network model results:



Weickenmeier et al (2019)

Fornari et al (2019)

The brain as a network

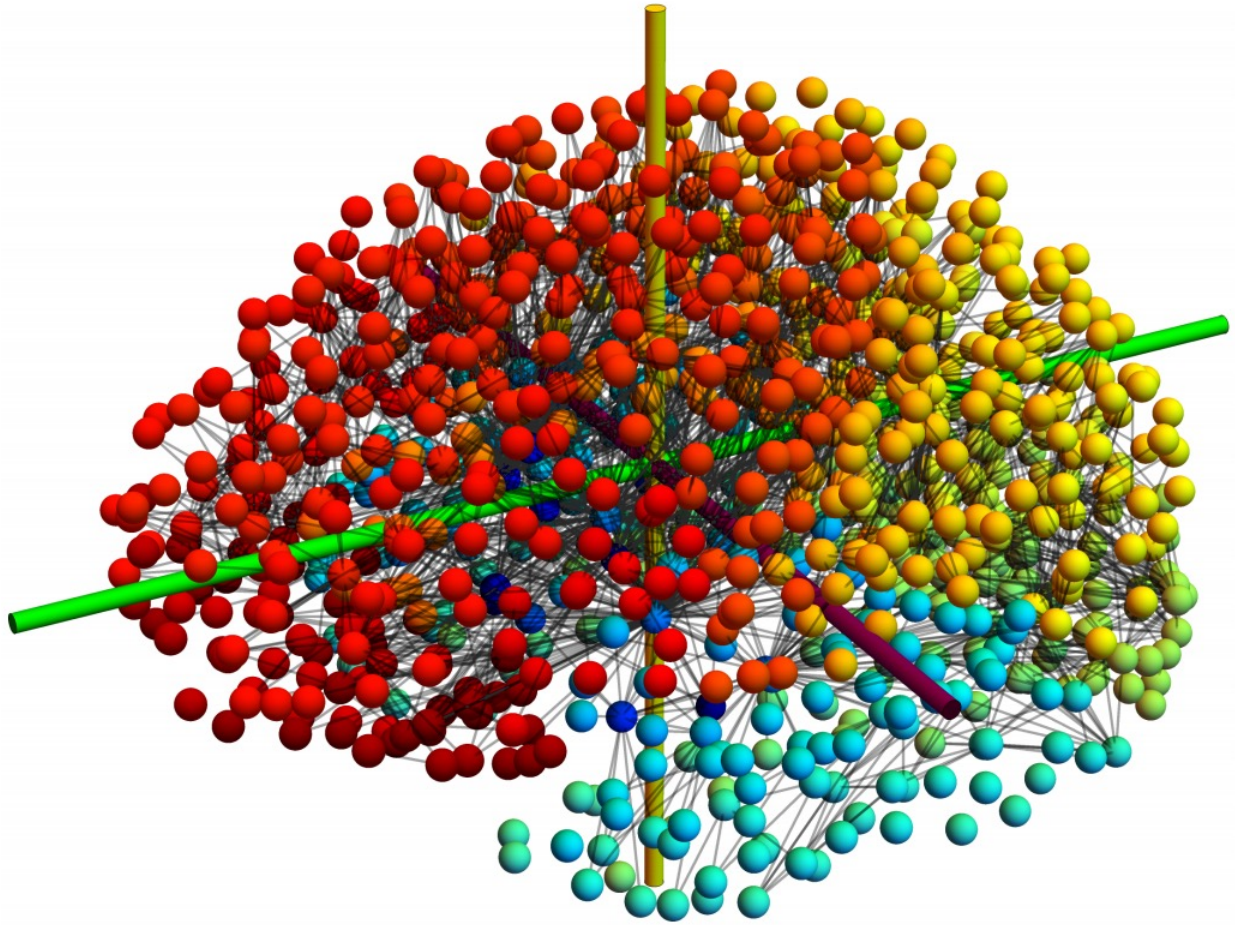
Neurodegeneration: a reaction-diffusion process on the brain network.

$$\mathcal{L} = \underbrace{\mathbf{D}}_{\text{degree matrix}} - \underbrace{\mathbf{W}}_{\text{weighted adjacency matrix}}$$

$$\mathbf{W}_{ij} = \frac{n_{ij}}{\ell_{ij}^2}, \qquad \mathbf{D}_{ii} = \sum_{j=1}^{|V|} \mathbf{W}_{ij}$$

n_{ij}, number of fibres along the axonal tract
ℓ_{ij}, average fibre length

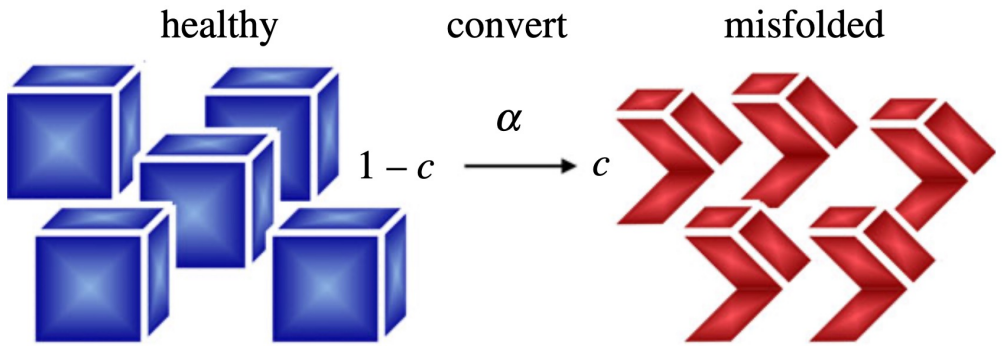
Network extracted from data of 418 healthy brains:

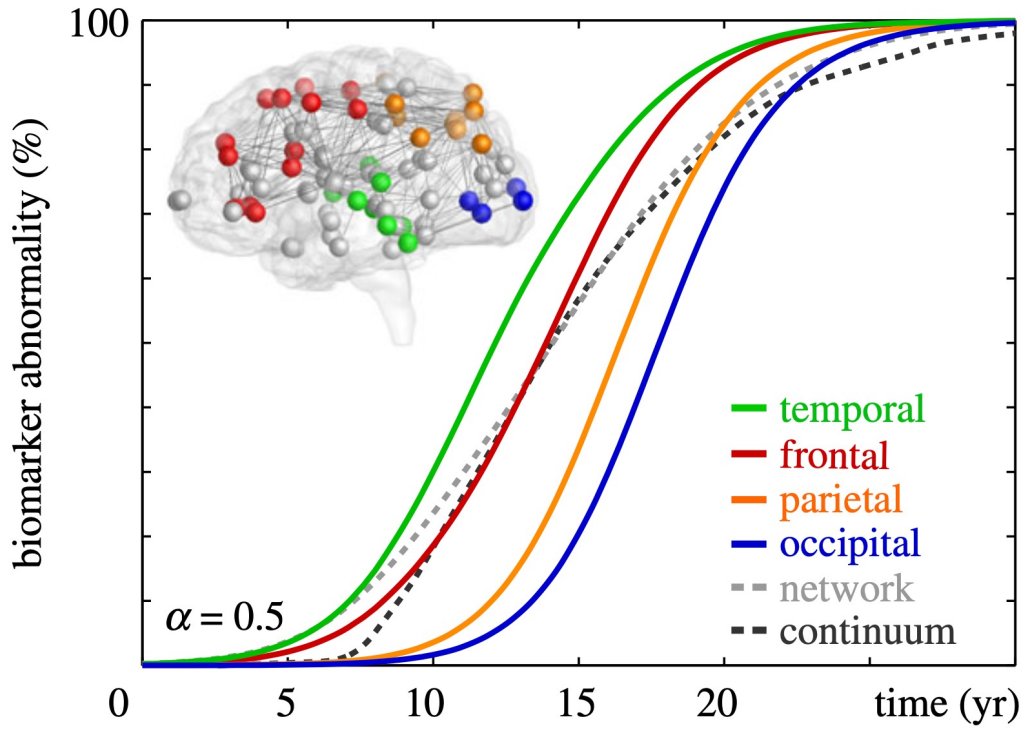


Macroscale models

Recent work has focused on the autocatalytic nature of protein dynamics in agreement with the prion-like hypothesis and captures the spatio-temporal spreading well.

The Fisher–Kolmogorov model : $$\frac{\mathrm{d}c_I}{\mathrm{d}t} = -\sum_{J=1}^{N} L_{IJ} c_J + \alpha c_I [1 - c_I]$$





Fornari et al (2019)

This model can be extended to include aggregation kinetics and clearance

Network simulations

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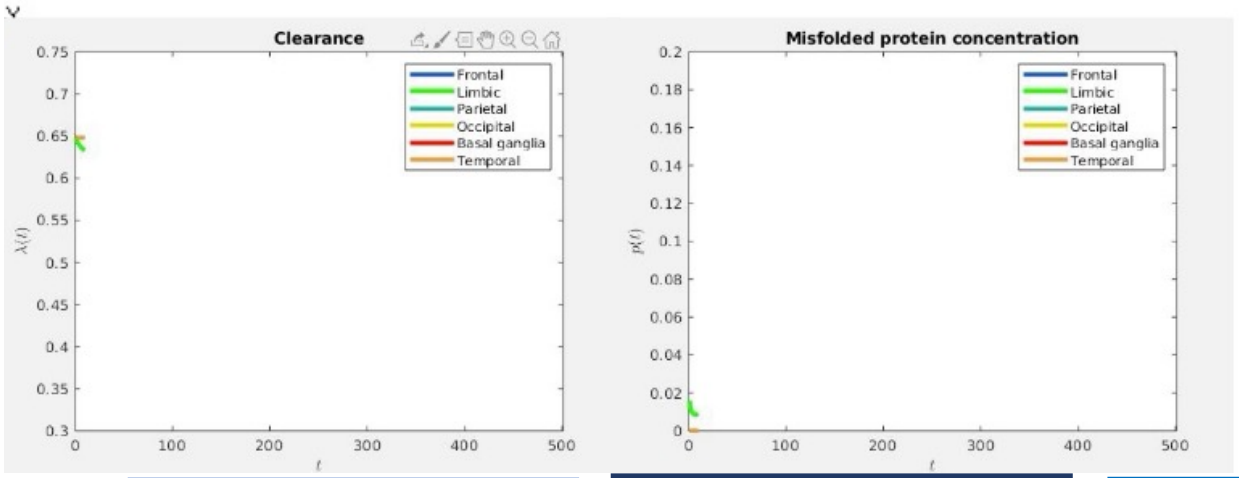
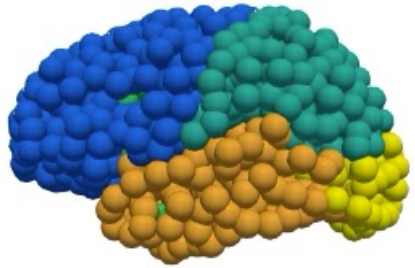
We can investigate the full model at the organ level by direct simulation.

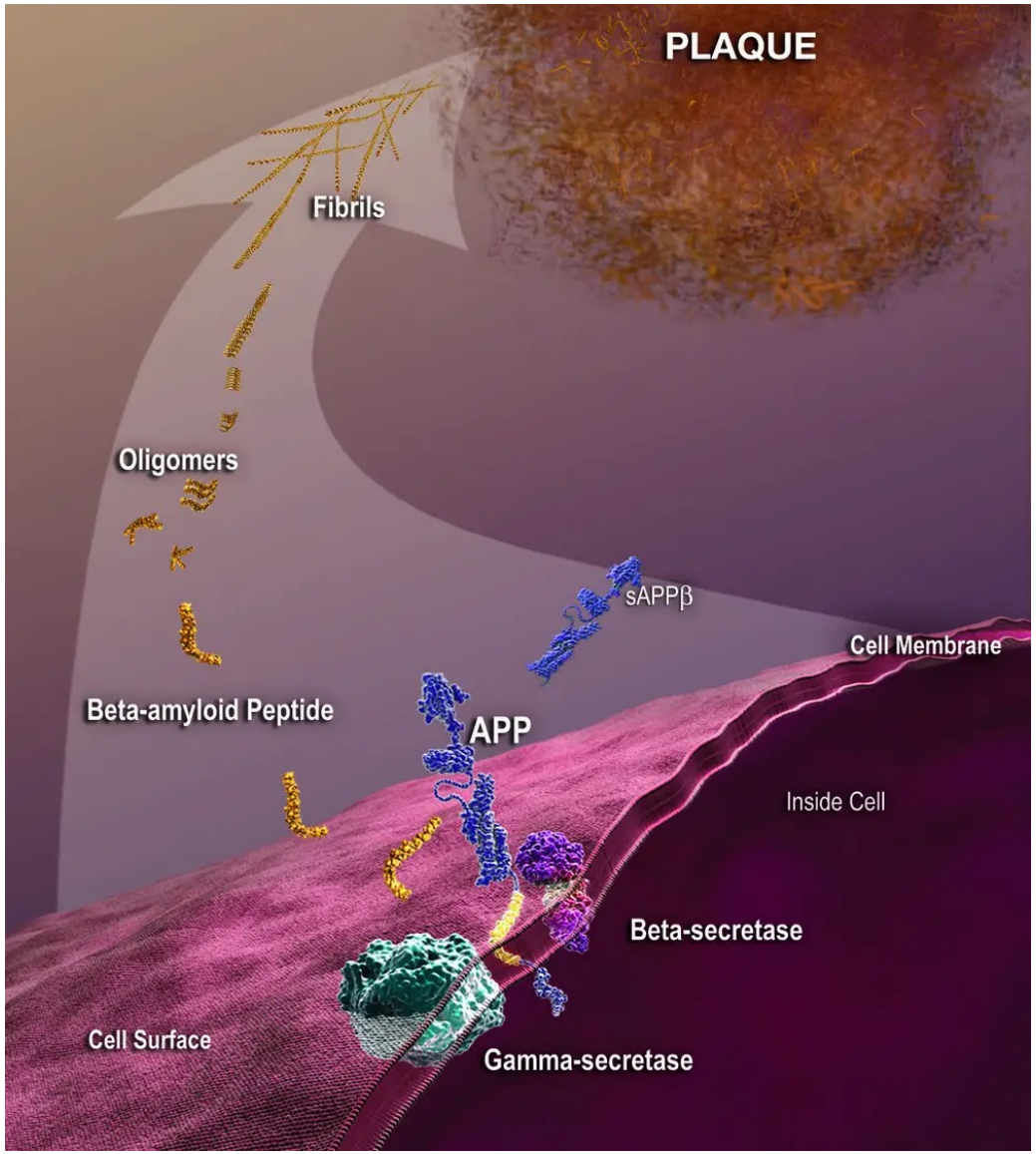




Aggregation models

We also need to know more about aggregate dynamics in the brain environment and at the brains scale

- Varying toxicity
- Varying transport properties
- Important in drug modelling



Aggregation models

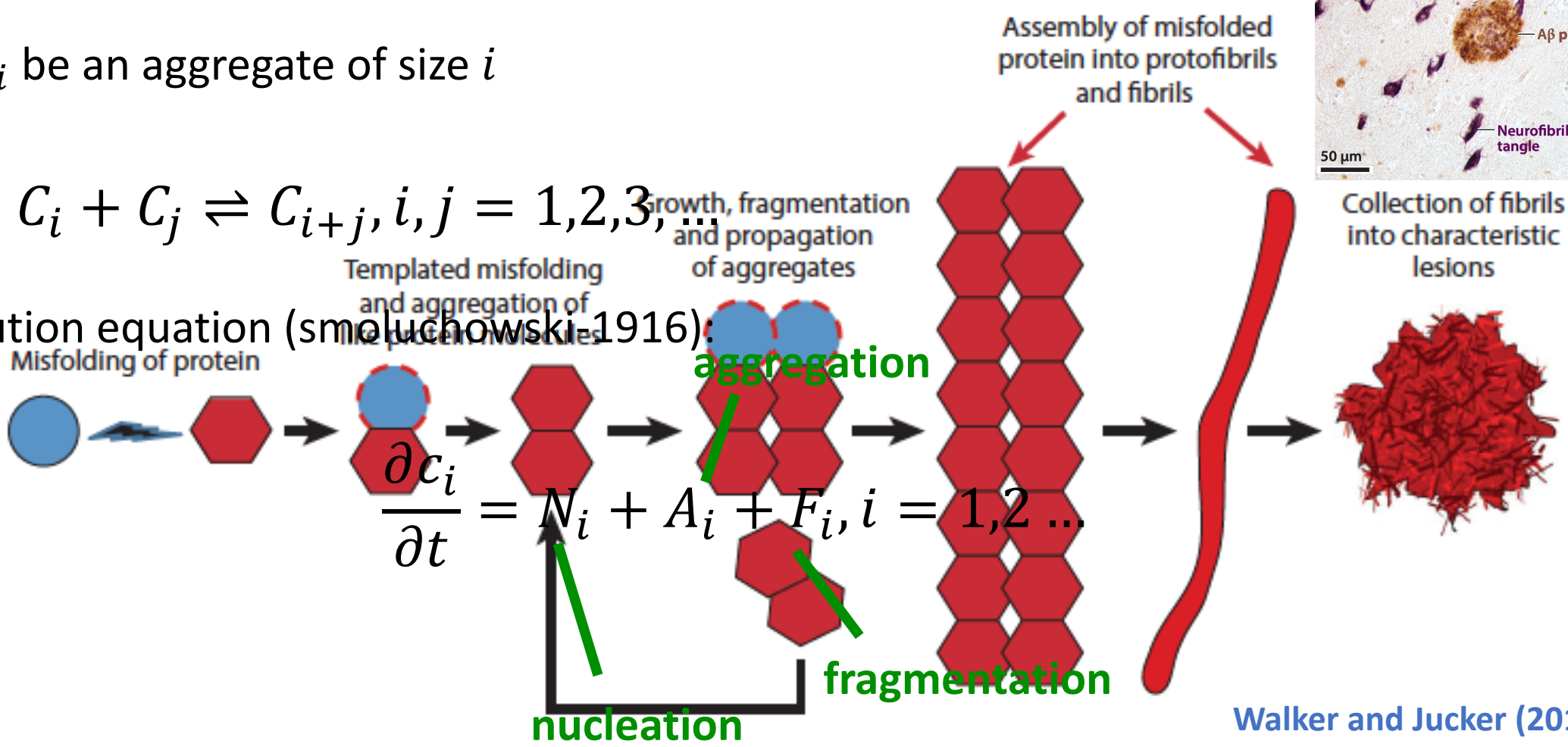
Smoluchowski's theory of aggregation:

Let C_i be an aggregate of size i

$$C_i + C_j \rightleftharpoons C_{i+j}, i, j = 1,2,3, \dots$$

Evolution equation (smoluchowski-1916):

$$\frac{\partial c_i}{\partial t} = N_i + A_i + F_i, i = 1,2 \dots$$

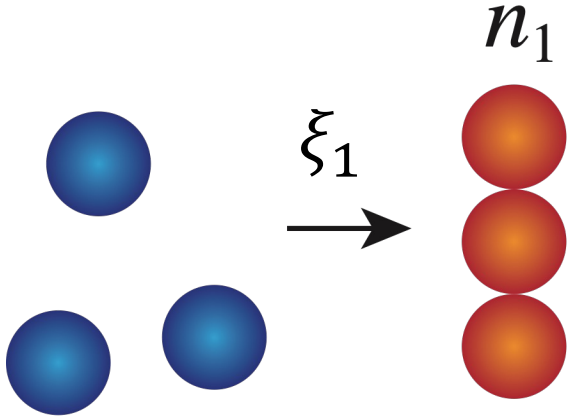


Walker and Jucker (2015)

Aggregation models

Nucleation:

$$\frac{\partial c_i}{\partial t} = N_i + A_i + F_i, i = 1,2 \ldots$$



primary nucleation

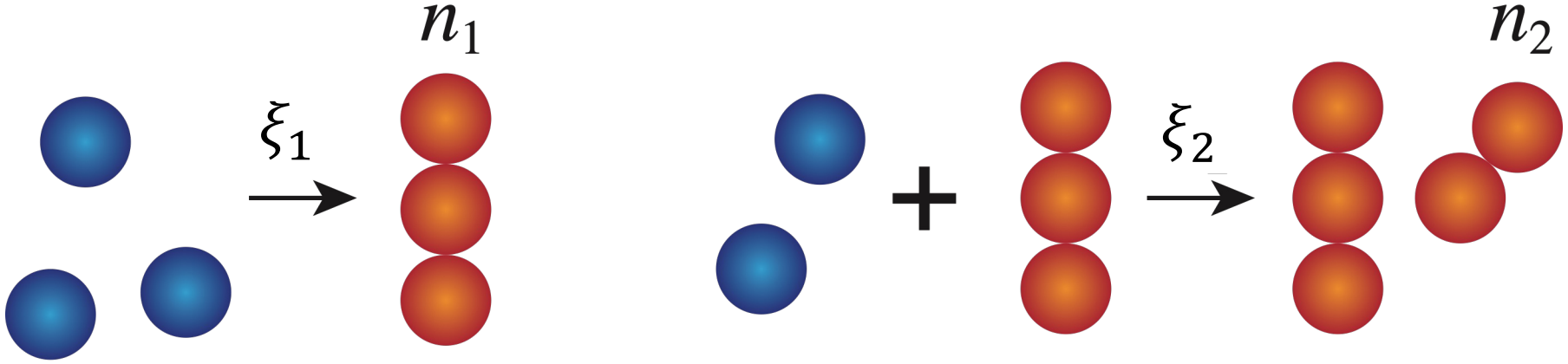
$$C_1 + \cdots + C_1 \xrightarrow{\xi_1} C_{n_1}$$

n_1 times

Aggregation models

Nucleation:

$$\frac{\partial c_i}{\partial t} = N_i + A_i + F_i, i = 1,2 \ldots$$



primary nucleation

$$C_1 + \cdots + C_1 \xrightarrow{\xi_1} C_{n_1}$$

n_1 times

secondary nucleation

$$C_i + C_1 + \cdots + C_1 \xrightarrow{\xi_2} C_i + C_{n_2}$$

n_2 times

Aggregation models

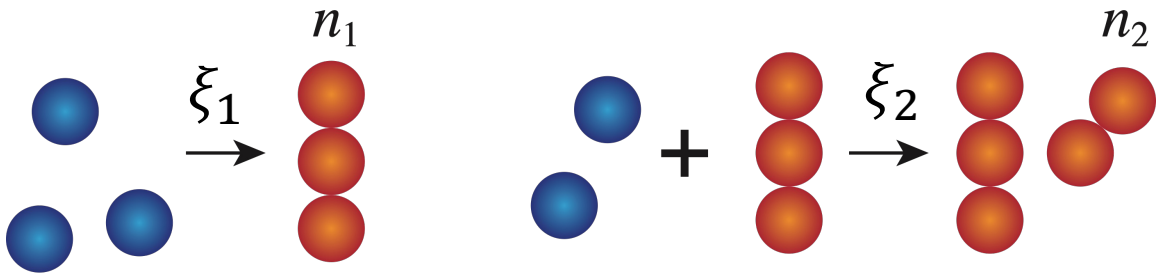
Nucleation:

$$\frac{\partial c_i}{\partial t} = N_i + A_i + F_i, i = 1,2 \ldots$$

$$\frac{\partial c_i}{\partial t} =$$

$$- \quad n_1 \xi_1 \delta_{i,1} c_1^{n_1} - n_2 \xi_2 \delta_{i,1} c_1^{n_2} \sum_{j=2}^{\infty} j c_j$$

$$+ \quad \xi_1 \delta_{i,n_1} c_1^{n_1} + \xi_2 \delta_{i,n_2} c_1^{n_2} \sum_{j=2}^{\infty} j c_j$$



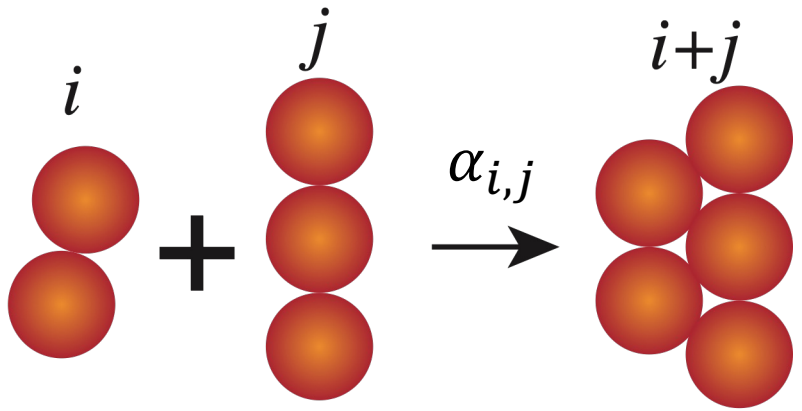
primary nucleation

secondary nucleation

Aggregation models

Aggregation:

$$\frac{\partial c_i}{\partial t} = N_i + A_i + F_i, i = 1,2 \ldots$$

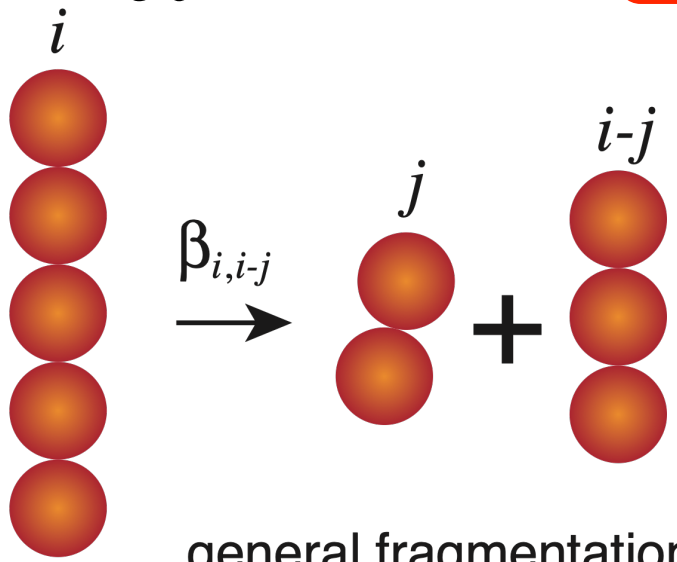


$$C_i + C_j \xrightarrow{\alpha_{i,j}} C_{i+j}$$

Aggregation models

Fragmentation:

$$\frac{\partial c_i}{\partial t} = N_i + A_i + F_i \quad i = 1,2 \ldots$$



general fragmentation

$$C_i \xrightarrow{\beta_{j,i-j}} C_j + C_{i-j}$$

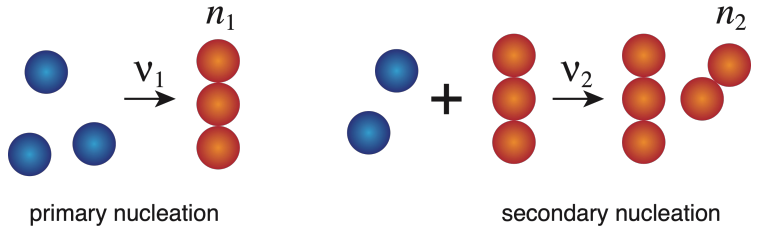
Aggregation models

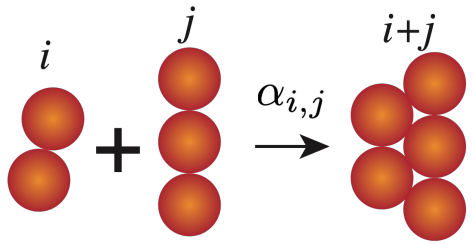
Smoluchowski equations :

$$\frac{\partial c_i}{\partial t} =$$

$$- \quad n_1 \xi_1 \delta_{i,1} c_1^{n_1} - n_2 \xi_2 \delta_{i,1} c_1^{n_2} \sum_{j=2}^{\infty} j c_j$$

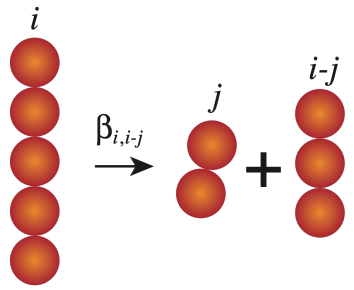
$$+ \quad \xi_1 \delta_{i,n_1} c_1^{n_1} + \xi_2 \delta_{i,n_2} c_1^{n_2} \sum_{j=2}^{\infty} j c_j$$





$$+ \quad \frac{1}{2} \sum_{j=1}^{i-1} \left(\alpha_{j,i-j} c_j c_{i-j} - \beta_{j,i-j} c_i \right)$$

$$- \quad \sum_{j=1}^{\infty} \left(\alpha_{i,j} c_i c_j - \beta_{i,j} c_{i+j} \right), \qquad i = 1, 2, \ldots$$



Project goals and objectives

1. ***Brief overview of hypotheses/ experimental observations that network models of neurodegeneration are based on***
2. ***Start by analysing macroscale reaction-diffusion network models like the FKPP***
3. ***Simulations and analysis***
   - ***Computational:*** *Run brain scale simulations including transport across a network representative of the brain's connectome. Compute average toxic mass evolution in the Braak regions and produce biomarker curves.*
   - ***Network analysis:*** *How does the brain's architecture influence pathology? Try different graph Laplacians. Try different connectome weights.*
4. ***Extend to couple important effects like clearance in the model and analyse.***
   - ***Asymptotics:*** *Fixed point analysis. What is the role of clearance in your model?*
5. ***Further work: Aggregation models.***

Example result:

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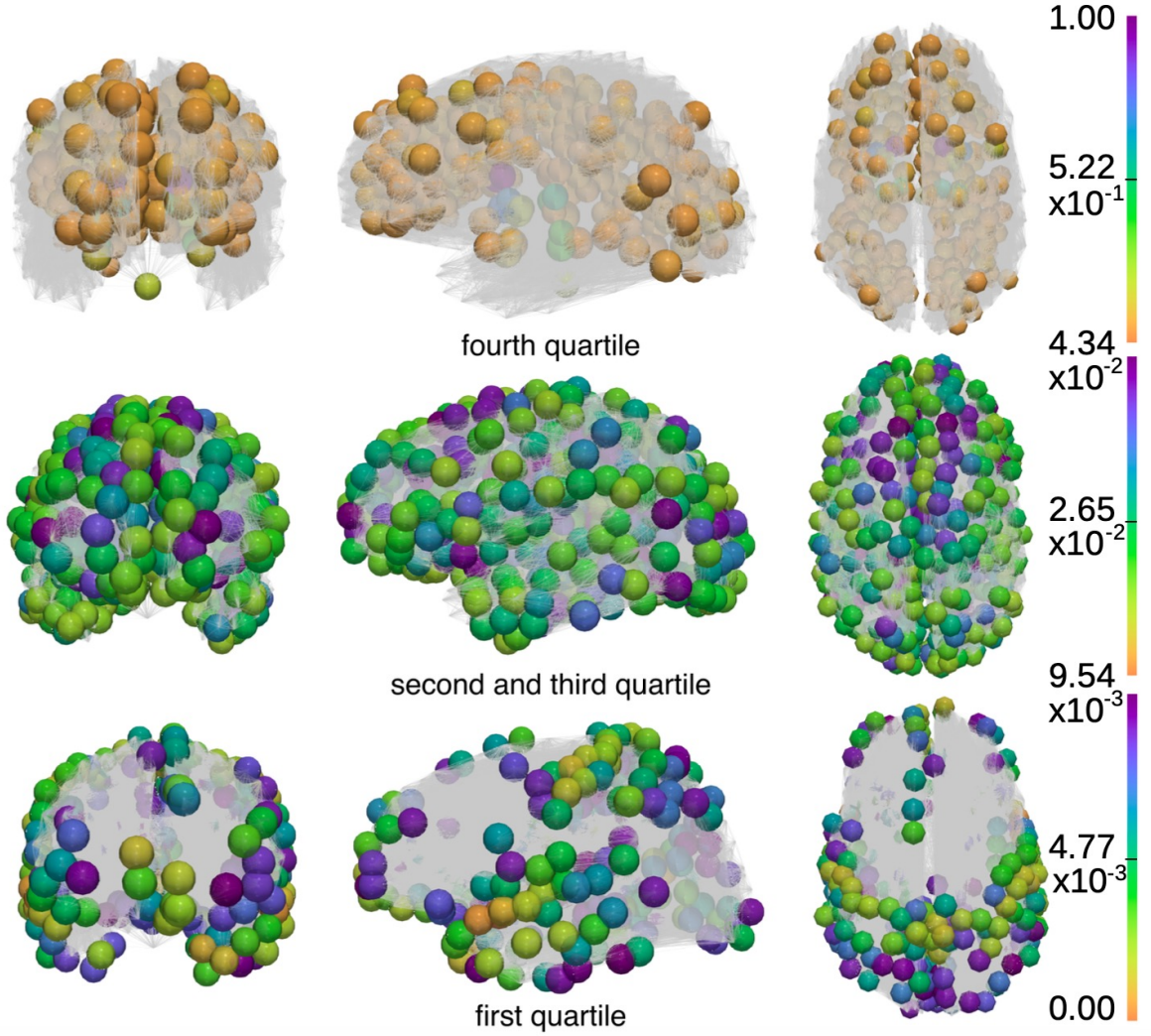
Connectivity is a source of resilience



What is the order of node activation?

The entorhinal cortex is amongst the most poorly connected regions...

Contact

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Thank you

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