Mathematical models of Alzheimer's disease treatments

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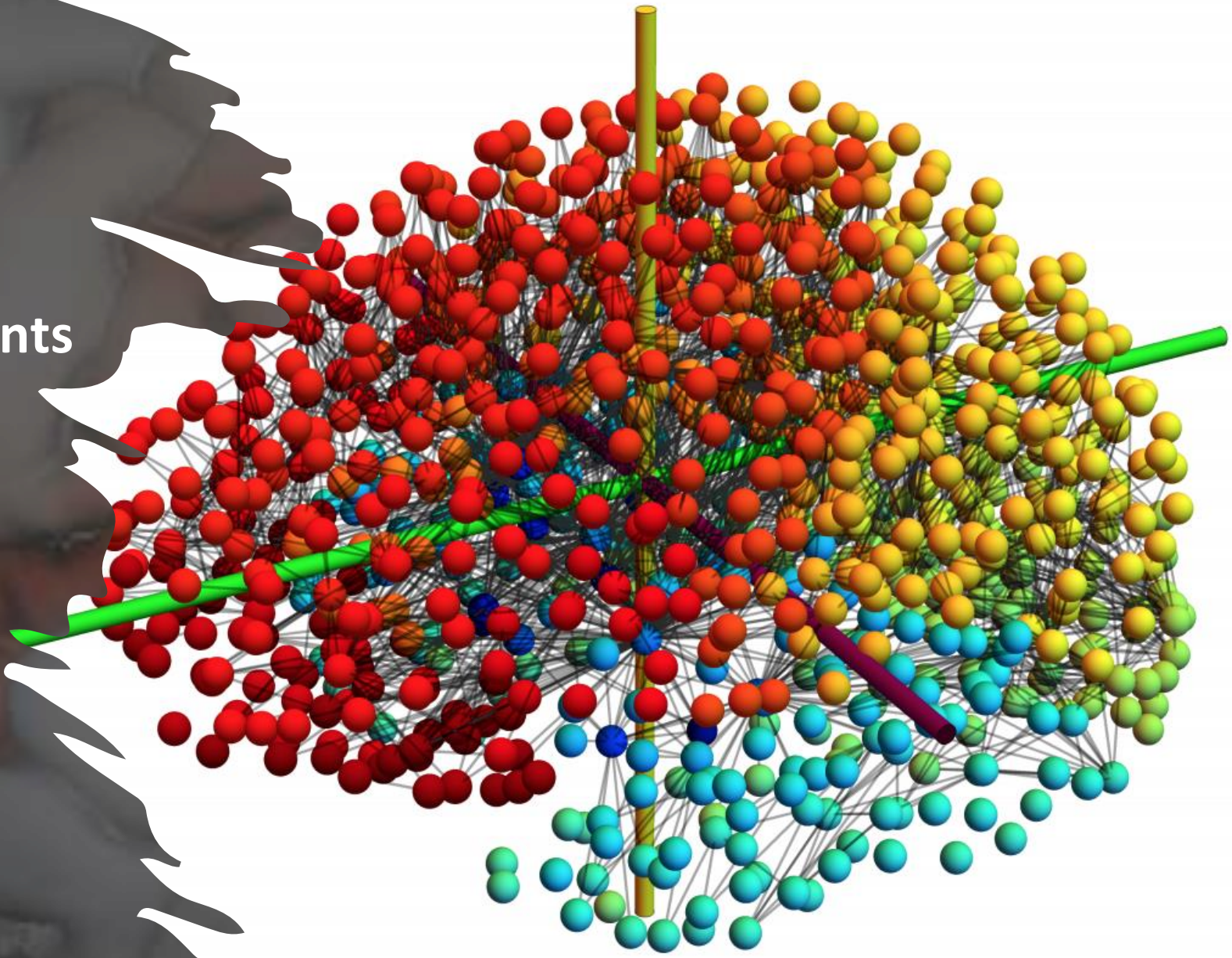
MMSC case study 2025



Alzheimer's disease

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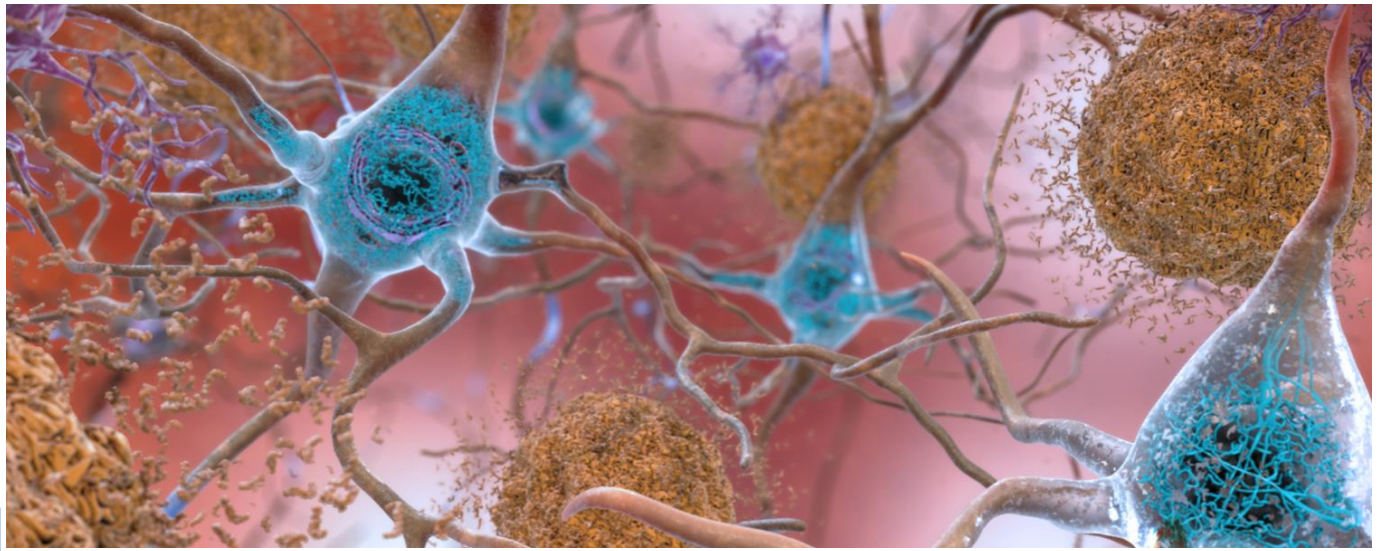
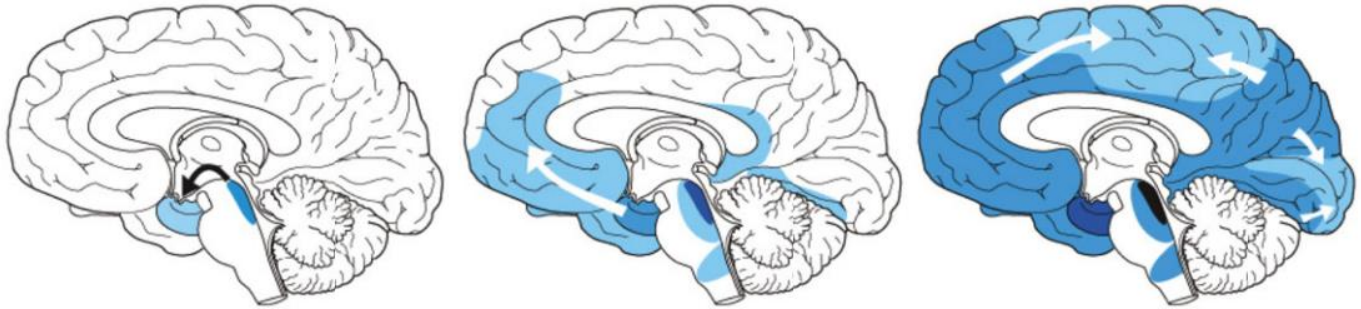
Alzheimer's disease is a neurodegenerative disease which is characterised by the accumulation of misfolded Amyloid-β (Aβ) and tau proteins.

How do the driving factors interact?



Why do neurodegenerative diseases progress so slowly?

Why such distinct spreading patterns?

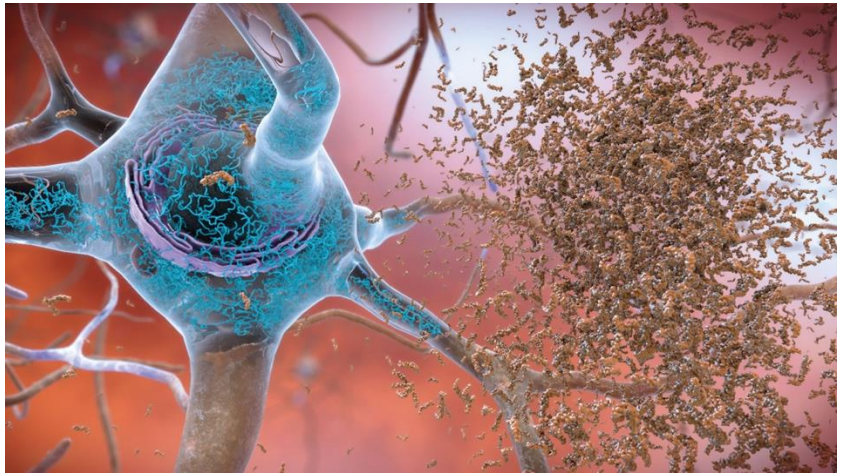


Can we interfere in the spreading?

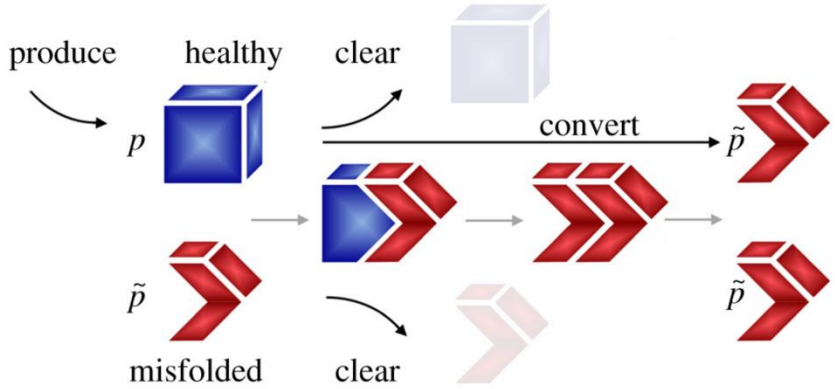
We do not understand the fundamental mechanisms driving the disease.

Alzheimer's disease hypotheses

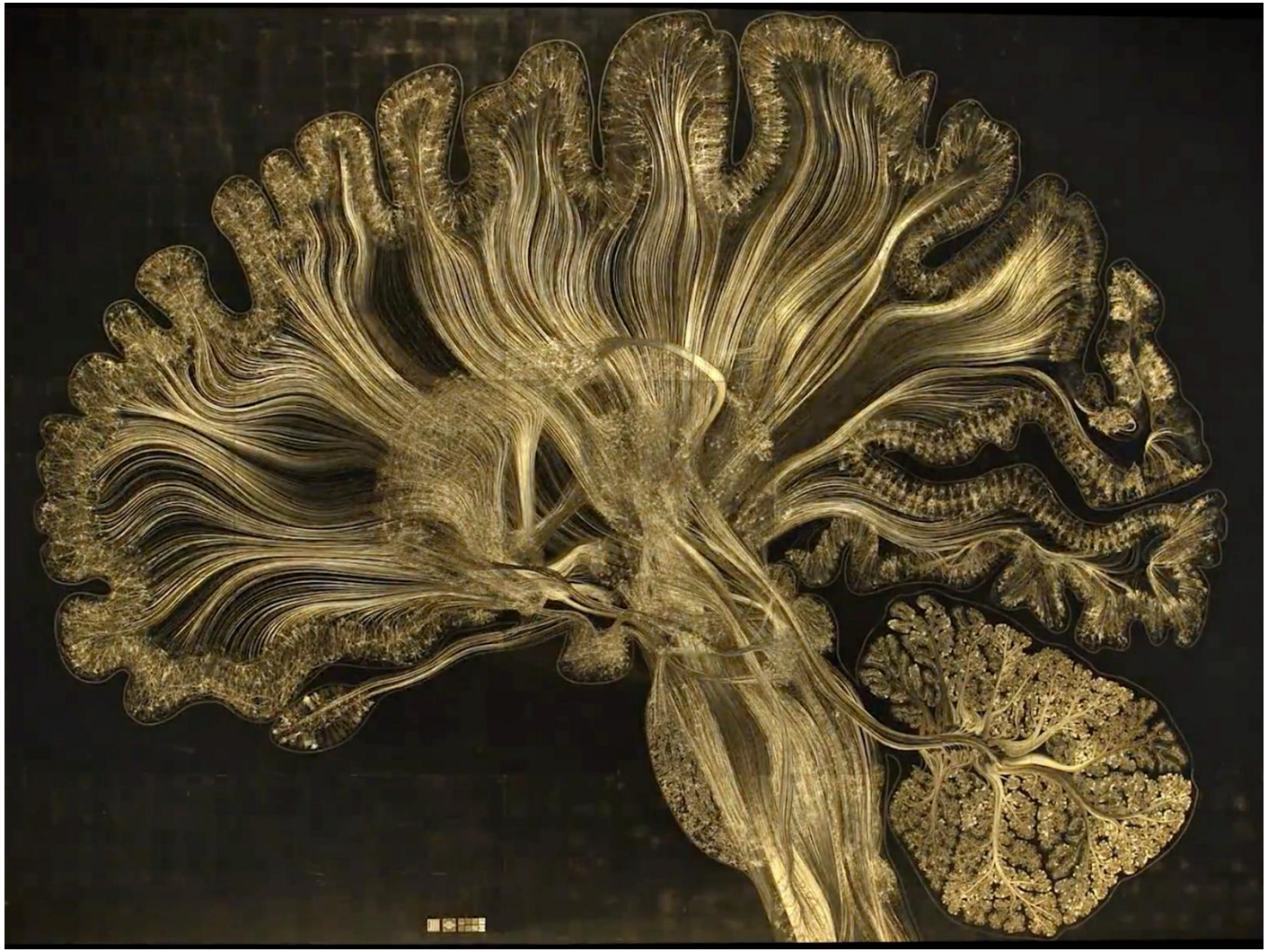
The Amyloid hypothesis



The Prion hypothesis



Toxic proteins propagate along axonal fibre bundles



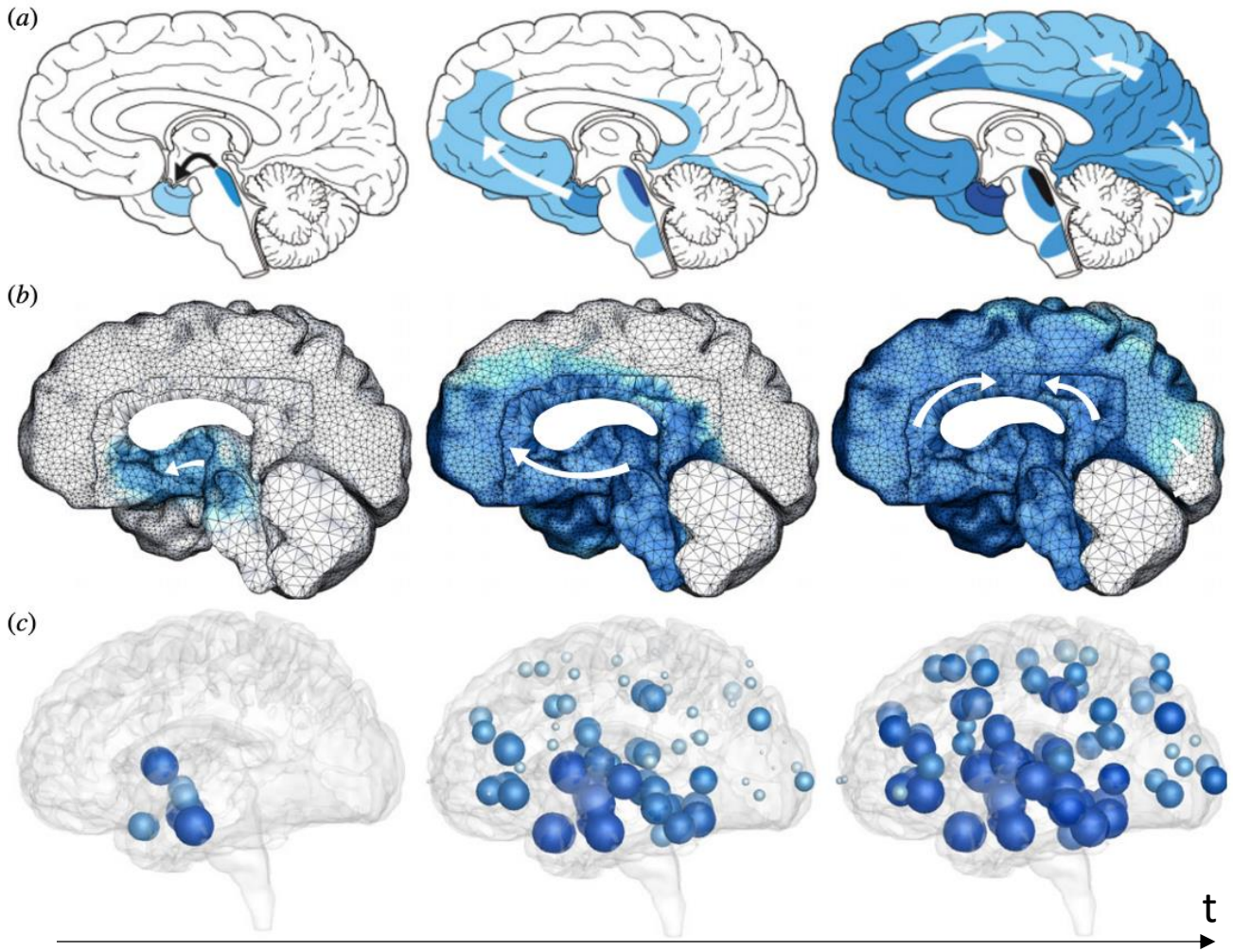
The brain as a network

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

Clinical observation:
Jucker and Walker (2013)

Continuum model results:
Weickenmeier *et al.* (2019)

Network model results:
Fornari *et al.* (2019)



The brain as a network

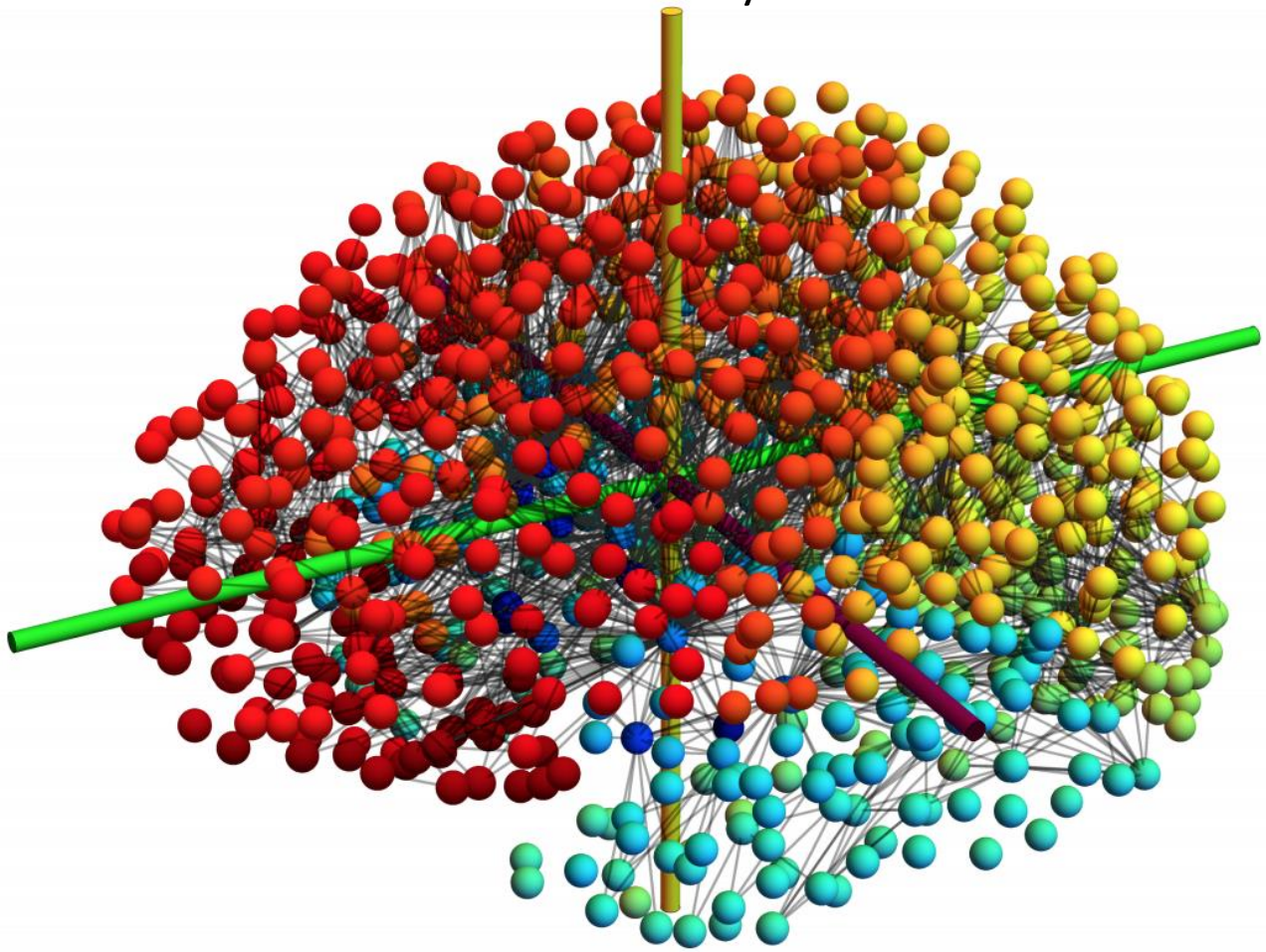
Neurodegeneration: a reaction-diffusion process on the brain network.

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

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

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

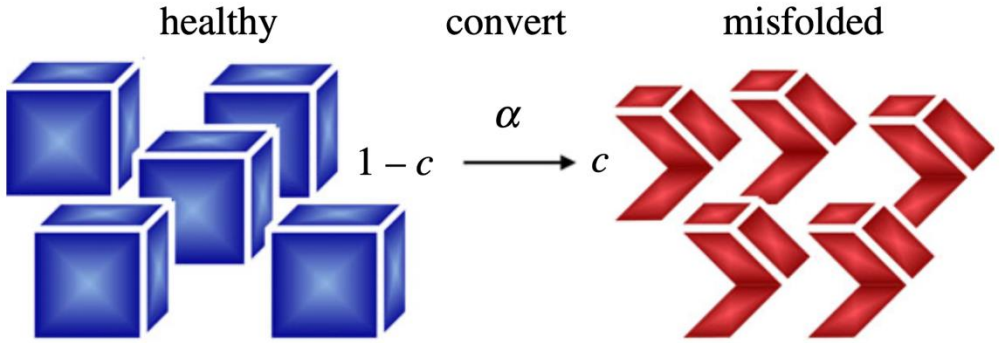
Network extracted from data of 418 healthy brains:

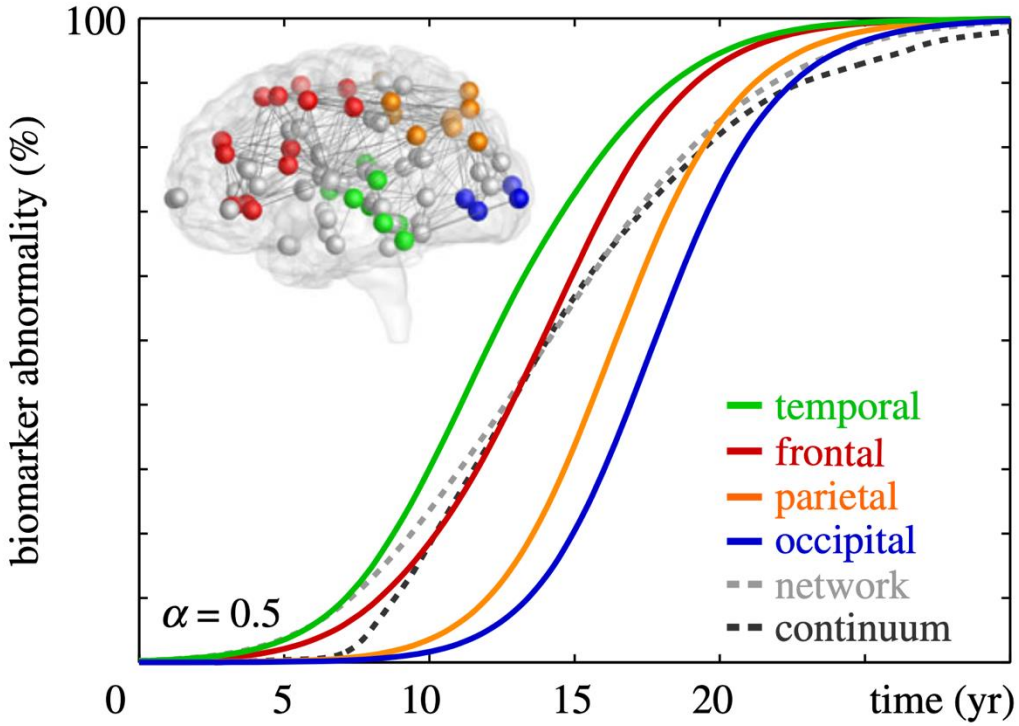


Brain network neurodegeneration models

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





This model can be extended to include aggregation kinetics and clearance

Fornari *et al.* (2019)

Brain network neurodegeneration models

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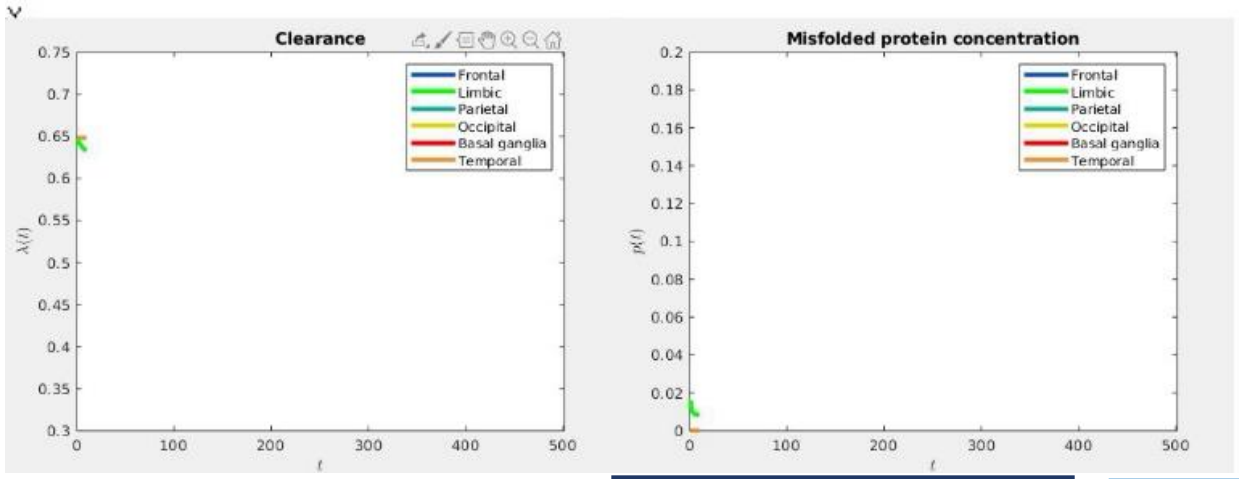
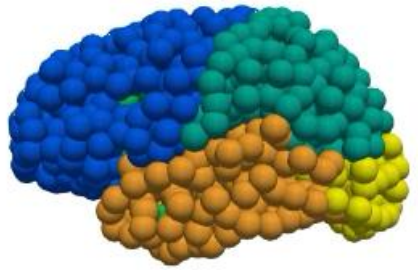
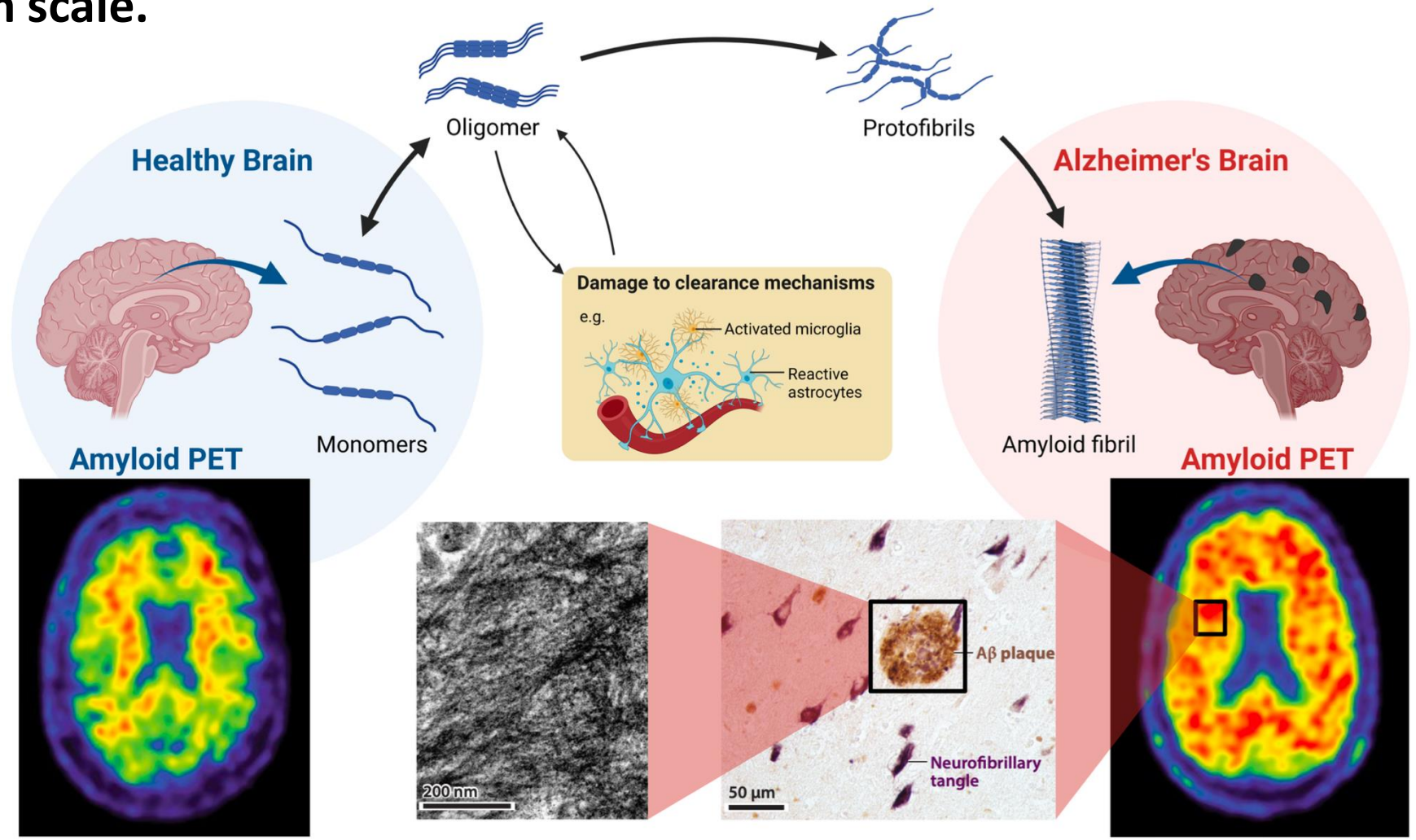
We can investigate the model at the organ level by direct simulation.





Developing an *in vivo* aggregation model

We need to further understanding of aggregate dynamics in the brain environment and at the brain scale.



Developing an *in vivo* aggregation model

Smoluchowski's theory of aggregation:

Let P_i be an aggregate of size i

$$P_i + P_j \rightleftharpoons P_{i+j}, i, j = 1,2,3, \ldots$$

Evolution equation (smoluchowski-1916):

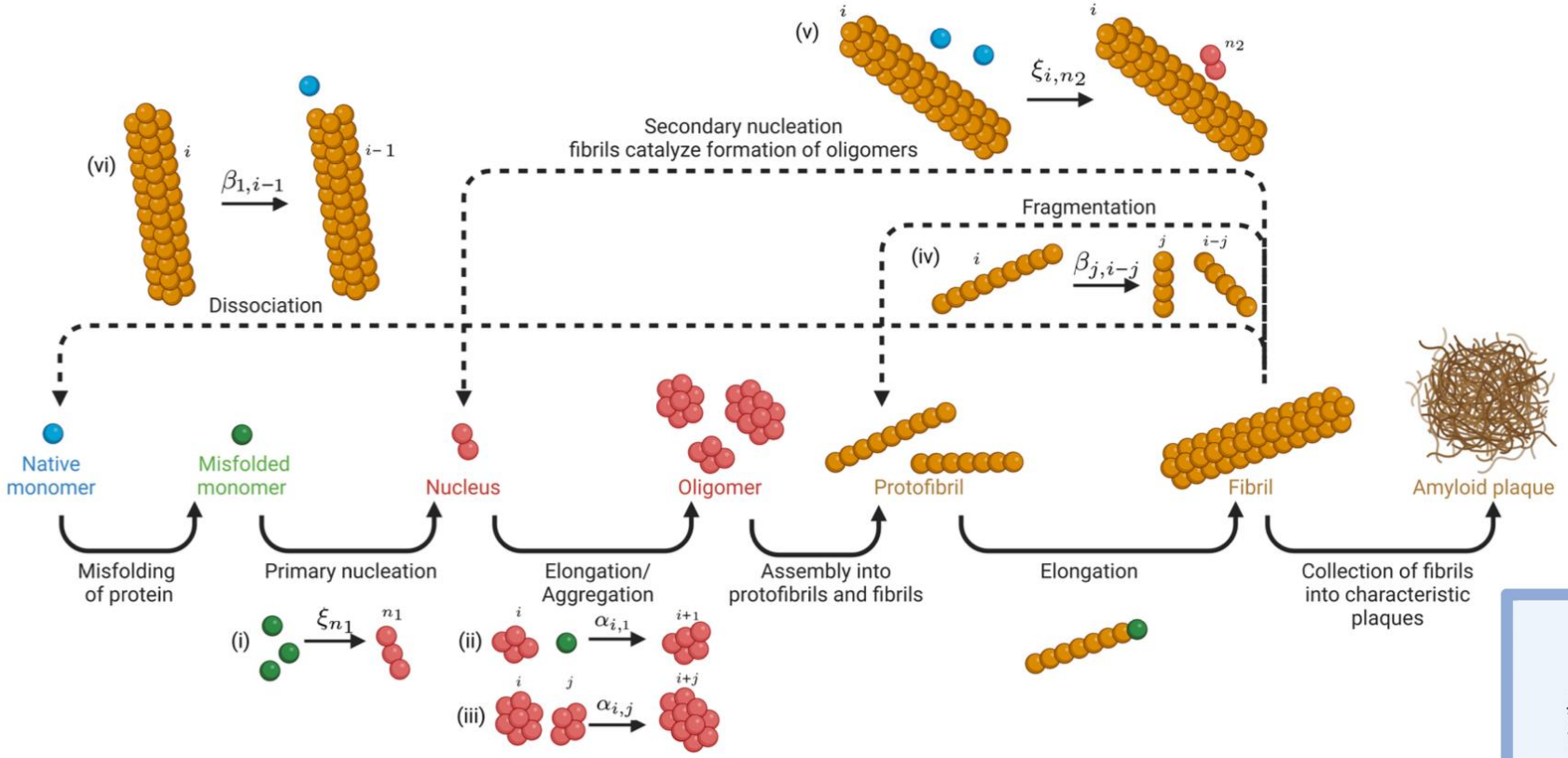
$$\frac{\partial p_i}{\partial t} = k_{0,i} - k_{1,i}p_i + N_i + A_i + F_i, i = 1,2 \ldots$$

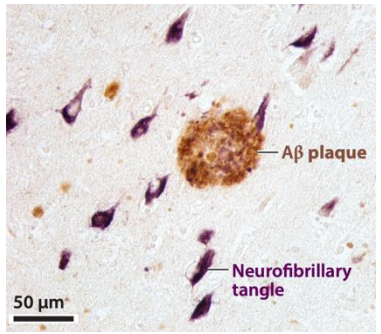
aggregation

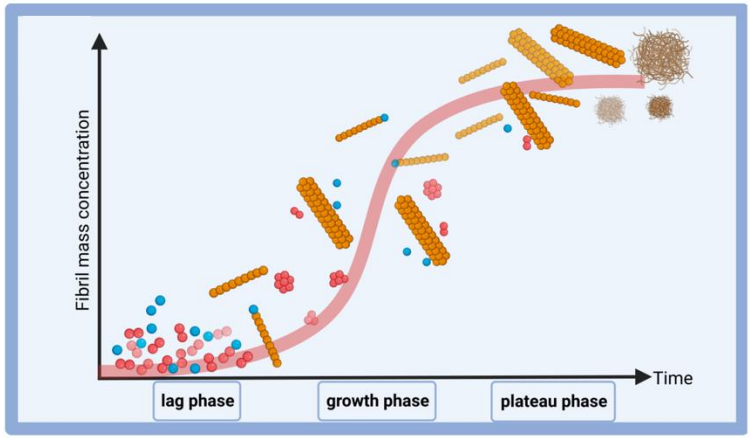
production clearance nucleation fragmentation

Developing an *in vivo* aggregation model

Smoluchowski's theory of aggregation:







Developing an *in vivo* aggregation model

Smoluchowski equations:

$$\frac{dm}{dt} = \underbrace{k_{0,1} - \lambda_1 m}_{\text{production and clearance}} - \underbrace{\rho(m) k_{h,n_1} n_1}_{\text{loss to heterogeneous nucleation}} - \underbrace{\xi_{n_1} n_1 m^{n_1}}_{\text{loss to primary homogeneous nucleation}} \underbrace{- \sigma(m) n_2 m^{n_2} \sum_{j=2}^{\infty} \xi_{j,n_2} j p_j}_{\text{loss to secondary nucleation}} + \underbrace{\beta_{i,1} m \sum_{i=2}^{\infty} p_i}_{\text{addition from disassociation}} - \underbrace{\alpha_{i,1} m \sum_{i=2}^{\infty} p_i}_{\text{loss to elongation}},$$

$$\frac{dp_i}{dt} = \underbrace{k_{0,i} - \lambda_i p_i}_{\text{production and clearance}} + \underbrace{\delta_{i,n_1} \rho(m) k_{h,n_1}}_{\text{heterogeneous nucleation}} + \underbrace{\delta_{i,n_1} \xi_{n_1} m^{n_1}}_{\text{primary nucleation}} + \underbrace{\delta_{i,n_2} \sigma(m) m^{n_2} \sum_{j=2}^{\infty} \xi_{j,n_2} j p_j}_{\text{secondary nucleation}} + \underbrace{\frac{1}{2}(1-\delta_{i,2})(1-\delta_{i,3}) \sum_{j=2}^{i-2} \left(\alpha_{j,i-j} p_j p_{i-j} - \beta_{j,i-j} p_i\right)}_{\text{addition from aggregation, and loss to fragmentation}} + \underbrace{\sum_{j=2}^{\infty} \beta_{i,j} p_{i+j}}_{\text{addition from fragmentation}} - \underbrace{\sum_{j=2}^{\infty} \alpha_{i,j} p_i p_j}_{\text{loss of oligomers to aggregation}} - \underbrace{2\beta_{1,i-1} m p_i}_{\text{loss to disassociation}} + \underbrace{(1-\delta_{i,2}) 2\alpha_{i,1} m (p_{i-1} - p_i)}_{\text{addition and loss from elongation}} - \underbrace{\delta_{i,2} 2\alpha_{i,1} m p_i}_{\text{loss of dimer from elongation}},$$

Developing an *in vivo* aggregation model

Minimal microscopic system:

$$\frac{\mathrm{d}m}{\mathrm{d}t} = -2k_n - 2k_+ mP - 2k_2\sigma(m)m^2M,$$
$$\frac{\mathrm{d}p_2}{\mathrm{d}t} = k_n - 2k_+ mp_2 + k_2\sigma(m)m^2M,$$
$$\frac{\mathrm{d}p_i}{\mathrm{d}t} = 2k_+ m(p_{i-1} - p_i), \quad i > 2$$

$$\sigma(m) = \frac{K_m}{K_m + m^2}, \quad P = \sum_{i=2}^{\infty} p_i, \quad M = \sum_{i=2}^{\infty} ip_i$$

number (toxic)

mass (toxic)

Physiological modelling assumptions:

- Production of monomers/ constant monomer concentration
- Saturation of secondary nucleation with toxic mass
- Clearance of aggregates
- Superparticle dynamics
- Transport across the connectome

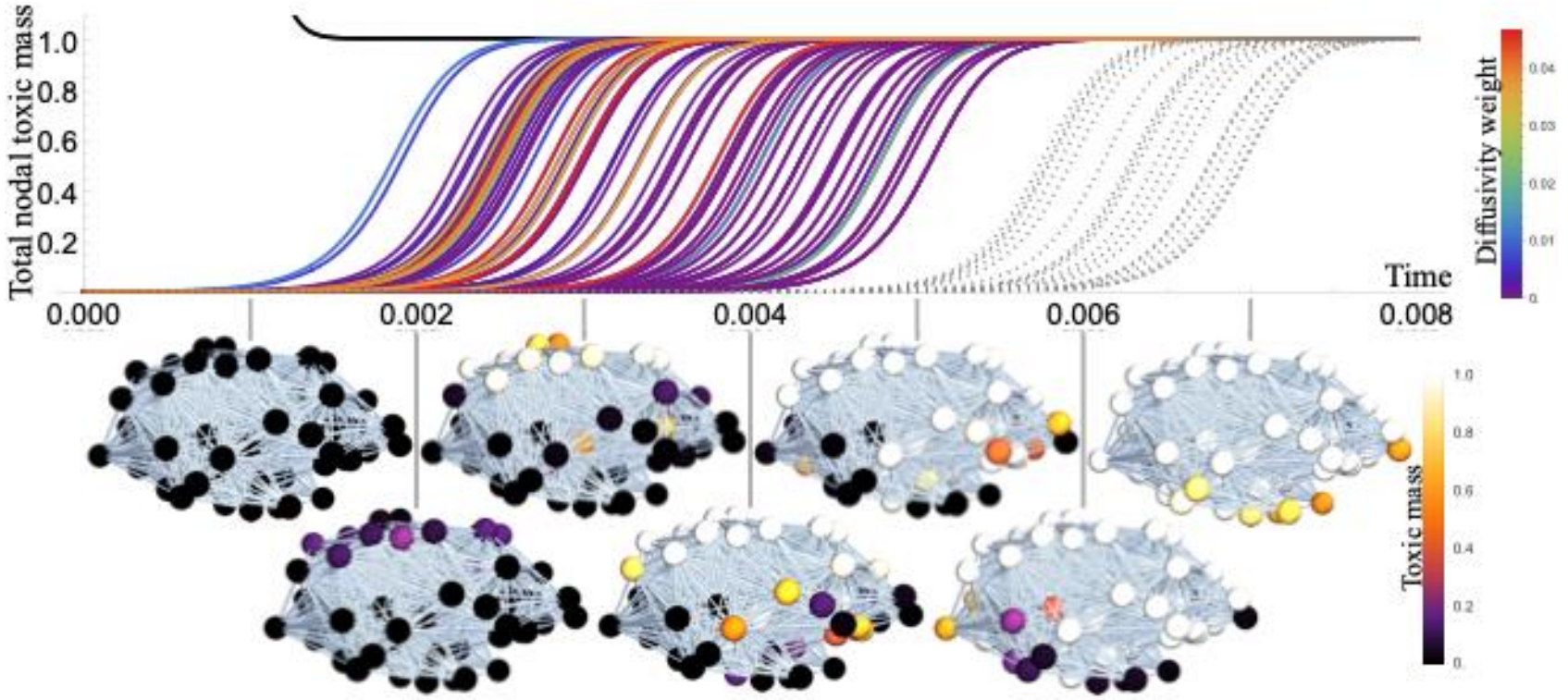
The task is to develop an *in vivo* aggregation model, and use it for therapeutic modelling.

A brain-wide aggregation model

Transport across the connectome reveals the importance of nuclei.

$$\frac{\mathrm{d}M_j}{\mathrm{d}t} = -\sum_{i=2}^{\infty} \lambda_{i,j} i p_{i,j} - \rho_j \sum_{k=1}^{V} L_{jk} M_k + 2k_n m_j^2 + 2k_+ m_j P_j + 2k_2 \sigma(M_j) m_j^2 M_j,$$

$$\frac{\mathrm{d}P_j}{\mathrm{d}t} = -\sum_{i=2}^{\infty} \lambda_{i,j} p_{i,j} - \rho_j \sum_{k=1}^{V} L_{jk} P_k + k_n m_j^2 + k_2 \sigma(M_j) m_j^2 M_j.$$



Applications in therapeutic modelling

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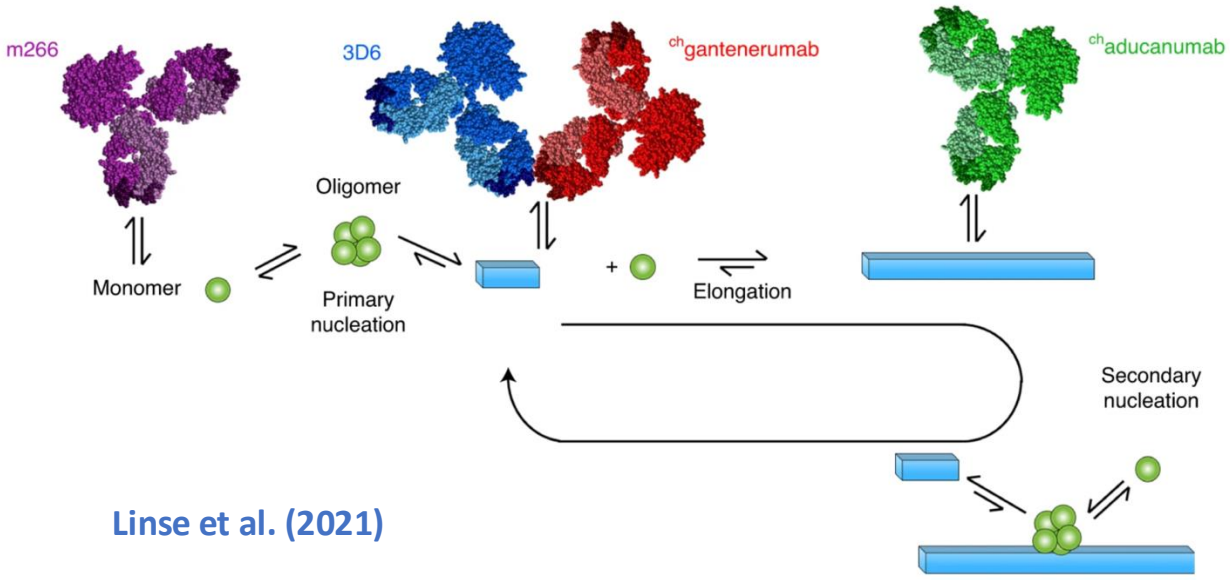
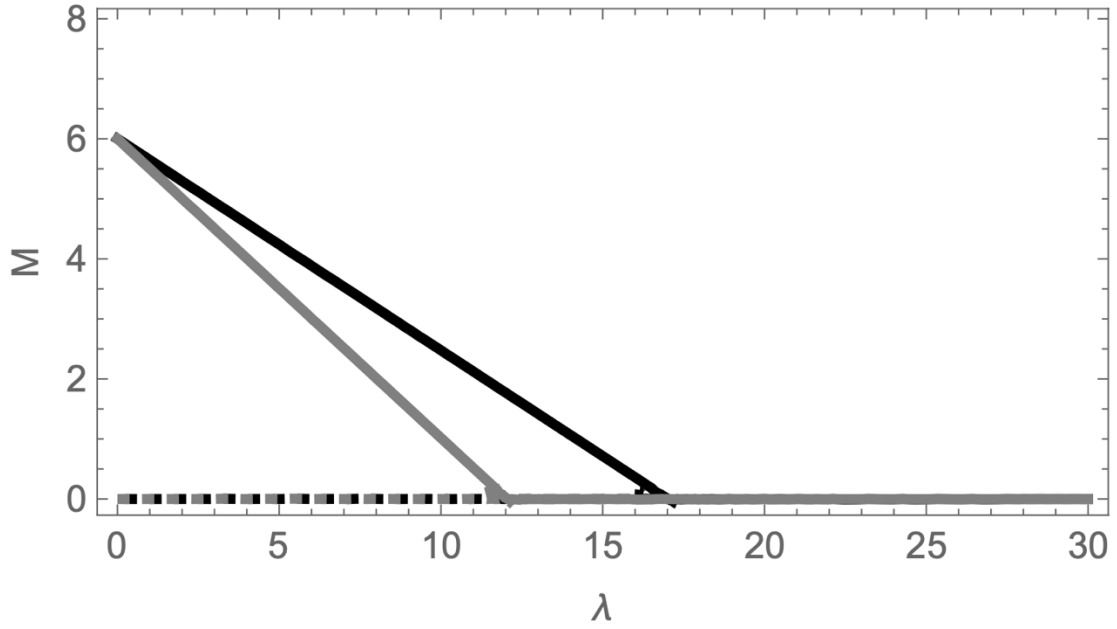
Bridging the gap from kinetic fingerprints to brain-wide dynamics:



Linse et al. (2021)



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. ***Aggregation models for exploring potential treatments***
4. ***Simulations and analysis***
   - ***Asymptotics:*** *Fixed point analysis**.** What is the role of clearance in your model?*
   - ***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.*