Mathematical Modelling of Neurodegenerative Disorders

Numerical Analysis for Partial Differential Equations

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Alzheimer Disease

Alzheimer Disease

- **Neurodegenerative disorders**: progressive damage of the neuronal tissue.
- *Degenerative*: nerve cells do not replicate, no possibility of being replaced $\implies$ **irreversible** damage to neurons.
- Focus on **Alzheimer's Disease (AD)**: formation of plaques containing β-amyloid and neurofibrillary tangles containing the τ protein.
- Loss of synapses: inability of living neurons to maintain functional axons and dendrites or the **death of neurons**.

Mathematical Model

The Fisher-Kolmogorov Model

- Single unknown $c \in [0, 1]$ - the dimensionless misfolded protein concentration.
- Conversion rate: $0 \leq \alpha \leq 1$.

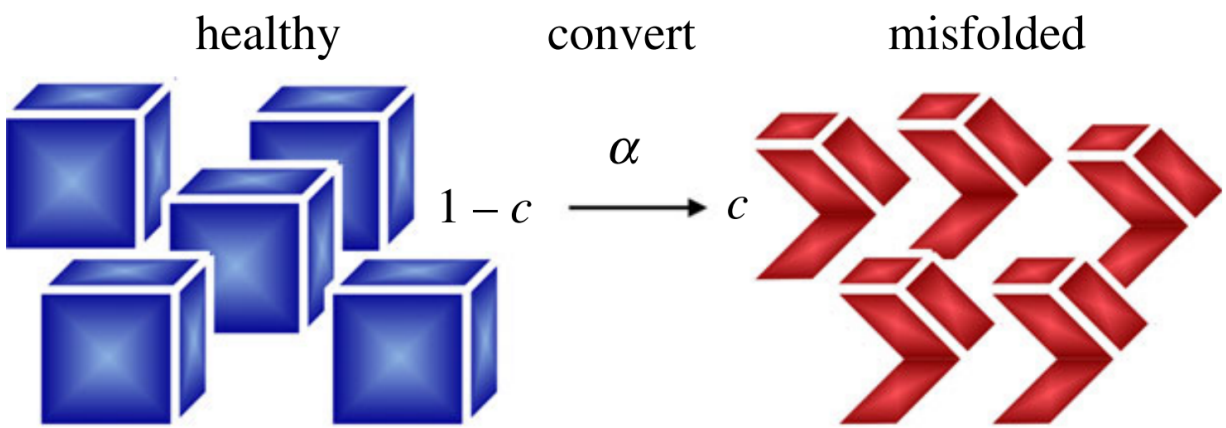


Figure: The Prion's Hypothesis[1]: from healthy to misfolded proteins.

[1] Fornari, Sveva, Amelie Schäfer, Mathias Jucker, Alain Goriely, and Ellen Kuhl. "Prion-like spreading of Alzheimer's disease within the brain's connectome". *Journal of the Royal Society Interface* 16.159 (2019), p. 20190356

The Fisher-Kolmogorov Model

- FK model widely used in population dynamics processes.
- Spreading of AD described by means of the diffusion tensor $\boldsymbol{D}$ and the reaction term α:

$$\begin{cases} \dfrac{dc}{dt} = \nabla \cdot (\boldsymbol{D}\nabla c) + \alpha c\,(1-c) & \forall (\boldsymbol{x}, t) \in \Omega \times (0, T] \\ c(\boldsymbol{x}, 0) = c_0(\boldsymbol{x}) & \forall \boldsymbol{x} \in \Omega \\ \dfrac{\partial c}{\partial n} = 0 & \forall \boldsymbol{x} \in \partial\Omega \end{cases} \tag{1}$$

- Continuous representation of the brain domain in 3D, solvable only by means of numerical methods.
- Complex structure of the brain $\implies$ finite elements discretization very **complex** and computationally **heavy**.

The Graph Laplacian

- Graph $\boldsymbol{G} := (\boldsymbol{V}, \boldsymbol{E})$, where $\boldsymbol{V} := \{v_1, v_2, \ldots, v_N\}$ is the set of nodes/vertices and $\boldsymbol{E} := \{e_1, e_2, \ldots, e_m\}$ is the set of edges.
- Adjacency (or connectivity) matrix $\boldsymbol{A} \in R^{N \times N}$ and Degree (diagonal) matrix $\mathcal{D} \in R^{N \times N}$.

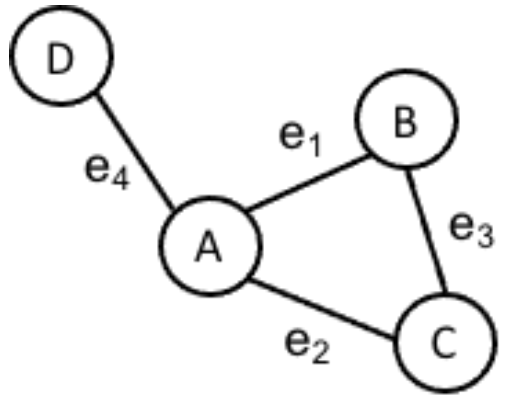


Figure: Example of graph
(source: The graph Laplacian. https://mbernste.github.io/posts/laplacian_matrix/. 2020).

  - Adjacency matrix $\boldsymbol{A}$ can be weighted or unweighted (binary), represents the link between different nodes in the brain.
  - Laplacian Graph $\boldsymbol{L} \in R^{N \times N}$ defined (by construction) as: $\boldsymbol{L} := \mathcal{D} - \boldsymbol{A}$.
  - $\boldsymbol{L}$ obtained using a gradient and a divergence discrete operators $\Longrightarrow$ representation of the Laplacian discrete operator in a graph.

Brain Network Models

- Discretized spatial domain by dividing it into a finite number of nodes N.
- Connections between nodes represented using a graph.
- System of N nonlinear ordinary differential equations to describe the dynamics of proteins in the nodes.
- Continuous Laplacian operator $\boldsymbol{D}$ replaced with the Graph Laplacian $\boldsymbol{L}$.

$$\begin{cases} \dfrac{d\boldsymbol{c}(t)}{dt} = -\boldsymbol{L}\boldsymbol{c}(t) + \alpha \boldsymbol{c}(t)\left(1 - \boldsymbol{c}(t)\right) & \forall t \in (0, T] \\ \boldsymbol{c}(0) = \boldsymbol{c_0} \end{cases} \tag{2}$$

Diffusion MRI Analysis and Graph Generation

Fiber Tracking and Graph Generation

- *DSI studio*[2]: DTI-MRIs $\Longrightarrow$ map brain connections.
- **Fiber Tracking**: generate a tractography $\Longrightarrow$ quantitative description of the connections between different brain areas.
- **Graph generation**: different atlases with different properties (number of nodes, diameter, density and clustering).
- *Brainnectome*, *CerebrA*, *FreeSurferSeg* and *HCP-MMP*.

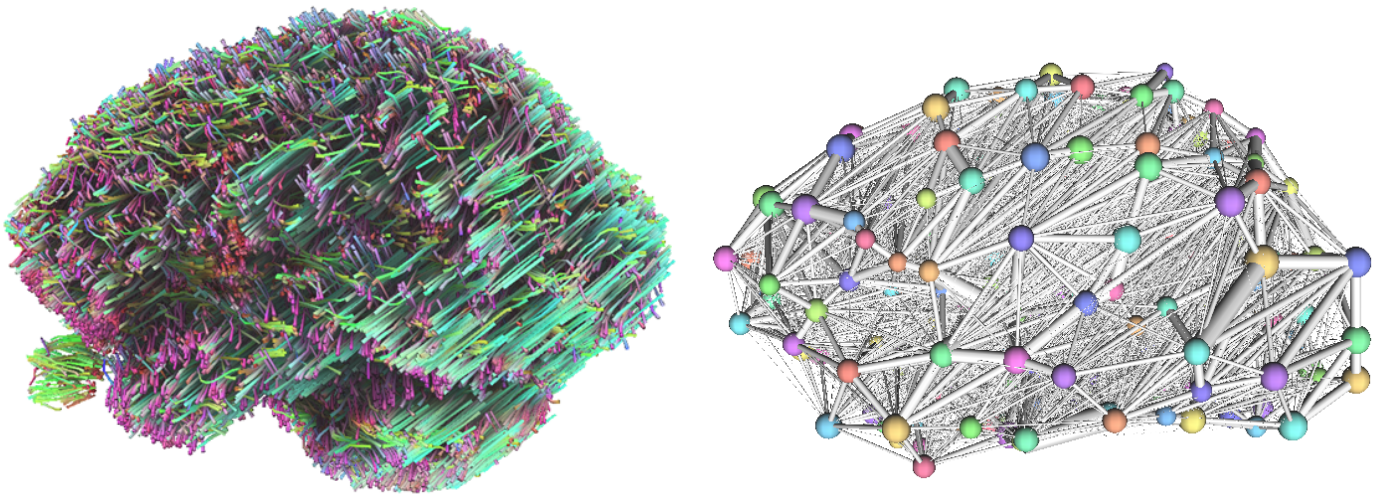


Figure: Tractography (left) and Brainnectome Graph (right)

[2] https://dsi-studio.labsolver.org/

Setting the initial condition

- The neurodegenerative process begins in the entorhinal cortex.
- The nodes referring to the entorhinal cortex are explicitly tagged in the *CerebrA* atlas.
- Assumption: same regions, on different atlases, should have almost the same coordinates.
- Computation of the barycenters: for the other atlases find the two nodes closer to the entorhinal cortex and set to 0.5 the concentration.

```
26      # extract neighbours
27      neighbours = np.argmin(distances, axis = 0)
28      neighbours2 = np.argmin(distances2, axis = 0)
29      neighbours3 = np.argmin(distances3, axis = 0)
```

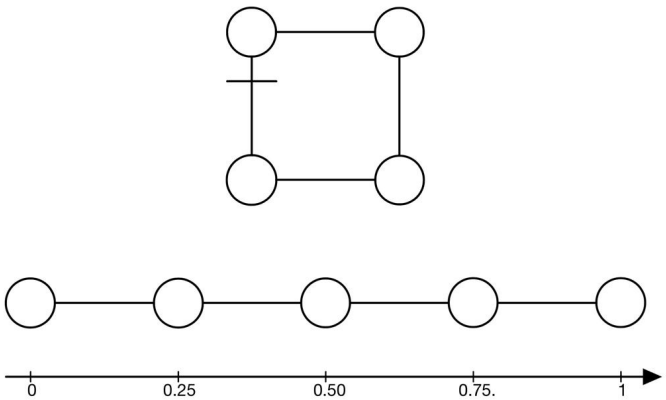
Figure: Extract of the `Python` code to find the closest nodes

Numerical Discretization

Validation

Space Discretization

- From the Graph to 1D Finite Elements



- Periodicity in space
- Tridiagonal II order derivatives matrix to discretize diffusion
- θ Method

Time Discretization

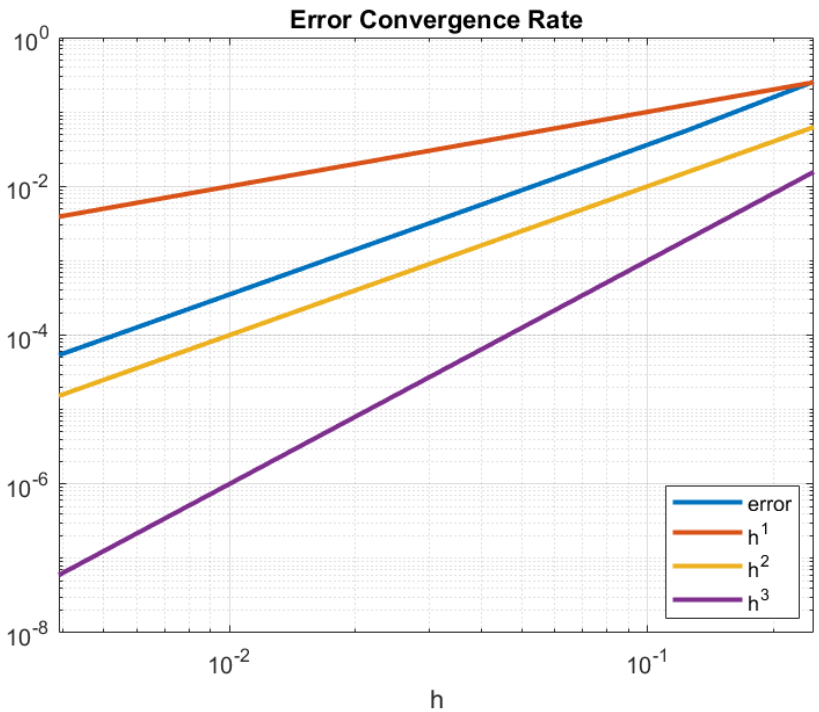
- Graph of 4 nodes, circularly connected
- System of 4 nonlinear ODEs, since the Laplacian matrix is a datum of the problem
- Semi-Implicit Treatment of the nonlinear term with II order extrapolation:

$$c_i^{k+1} \simeq \frac{3}{2} c_i^k - \frac{1}{2} c_i^{k-1}$$

- θ Method

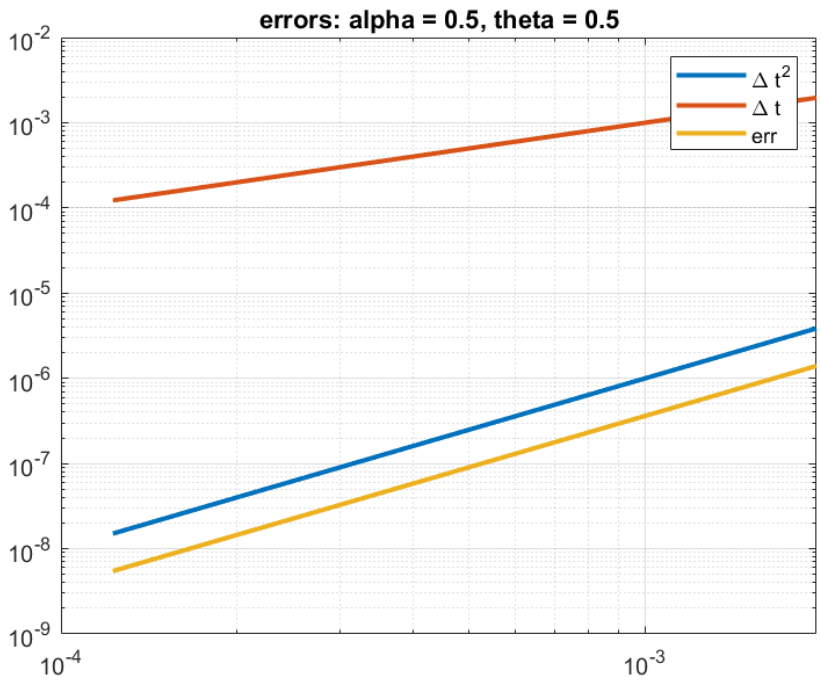
Order of Convergence

Space Discretization



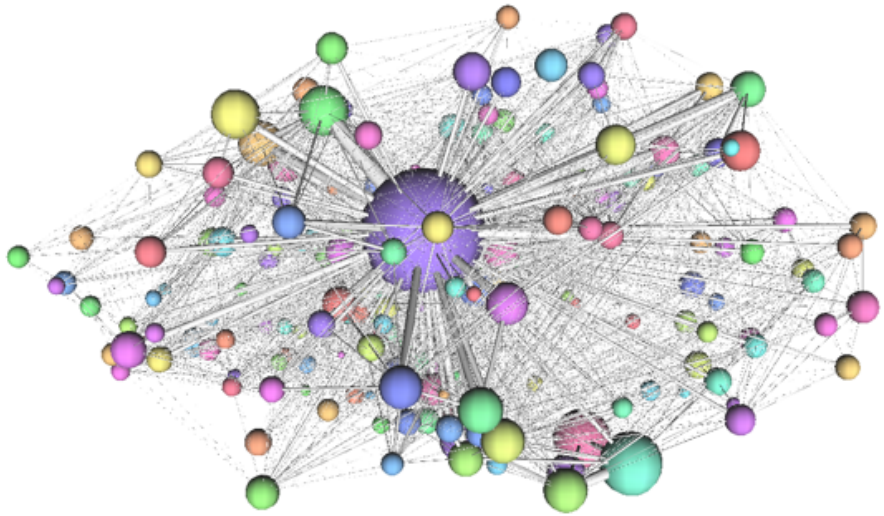
$$\|\mathbf{c} - \mathbf{c}_h\|_\infty \sim O(h^2)$$

Time Discretization



$$\|\mathbf{c} - \mathbf{c}_h\|_\infty \sim O(\Delta t^2)$$

Continuous Problem



Much more complicated domain:

Continuous-time network model:
Let N be the number of nodes of the graph, $\boldsymbol{c} : [0, T] \to [0, 1]^N$ the concentration of misfolded proteins and $\boldsymbol{c_0} : \{x_1, \ldots, x_N\} \to [0, 1]^N$ the initial concentration. The continuous-time problem is

$$\begin{cases} \dfrac{d\boldsymbol{c}(t)}{dt} = -\boldsymbol{L}\boldsymbol{c}(t) + \alpha \boldsymbol{c}(t)\left(1 - \boldsymbol{c}(t)\right) \quad \forall t \in (0, T] \\ \boldsymbol{c}(0) = \boldsymbol{c_0} \end{cases} \tag{3}$$

Discretization on patient-specific graphs

Then, the discretization method exploits:

- finite forward differences for time discretization
- semi-implicit treatment of the nonlinear term with II order extrapolation to recover an order of convergence of $O(\Delta t^2)$ with respect to the time step in case of $\theta = 0.5$

It results in the following discrete problem: $\forall i = 1, 2, 3, 4 \quad \forall k = 1, ..., K$

$$\begin{cases} \dfrac{c_i^{k+1} - c_i^k}{\Delta t} = -(1-\theta)\boldsymbol{L}_i c_i^k - \theta \boldsymbol{L}_i c_i^{k+1} + \\ \qquad\qquad +\alpha \left[(1-\theta)c_i^k + \theta c_i^{k+1}\right] \left[1 - \left(\frac{3}{2}c_i^k - \frac{1}{2}c_i^{k-1}\right)\right] \\ c_i^0 = c_i(0) \\ c_i^1 = c_i(\Delta t) \end{cases} \tag{4}$$

where Δt is the time step, K the total number of time intervals, $c_i^k \simeq c_i(k\Delta t)$ and $f_i^k = f_i(k\Delta t)$.

Simulations and Results

A preliminary simulation

- 42-year-old healthy patient
- *CerebrA* atlas
- $\alpha = 0.5$, $\theta = 0.5$
- T $= 50$ years

Initial concentration different from 0 only on the two nodes associated with the entorhinal cortex.

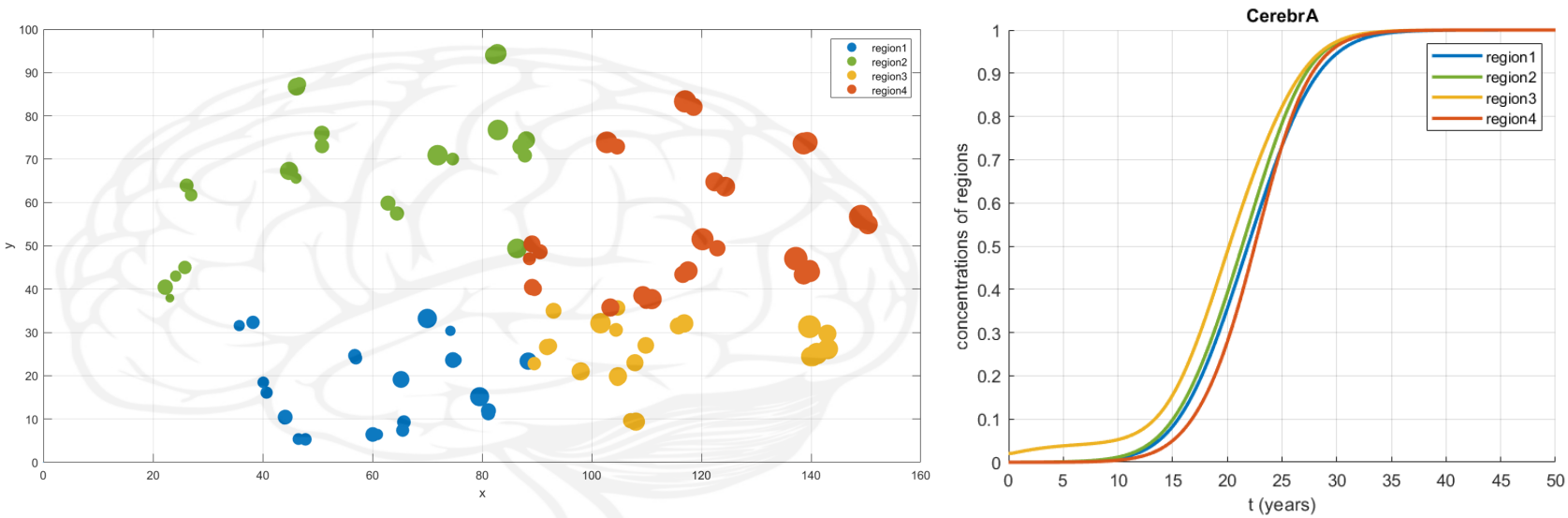


Figure: Subdivision of the brain into four different regions (left) and evolution of the concentration of misfolded proteins in each of the four regions (right).

Literature comparison

The simulation is coherent with the results presented by Fornari[3], with a saturation time of nearly 35 years.

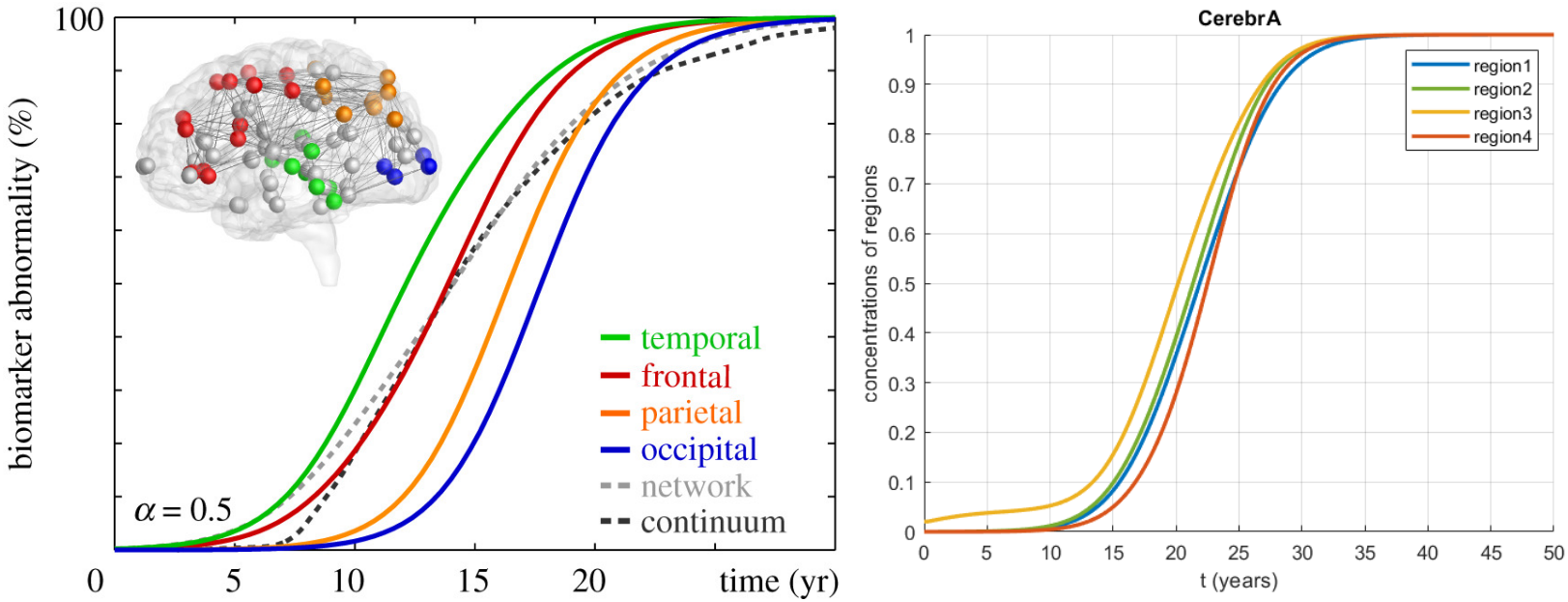
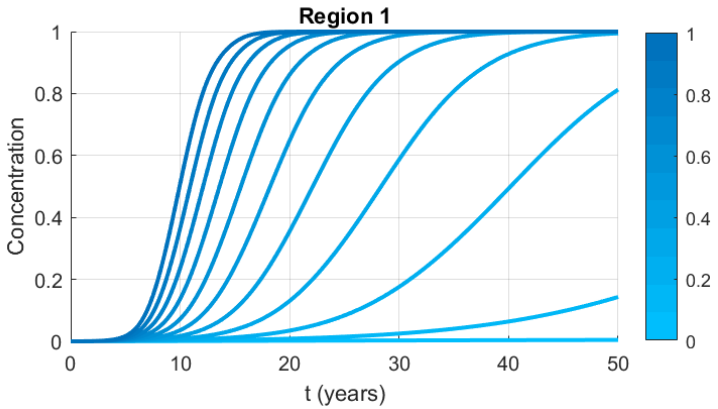


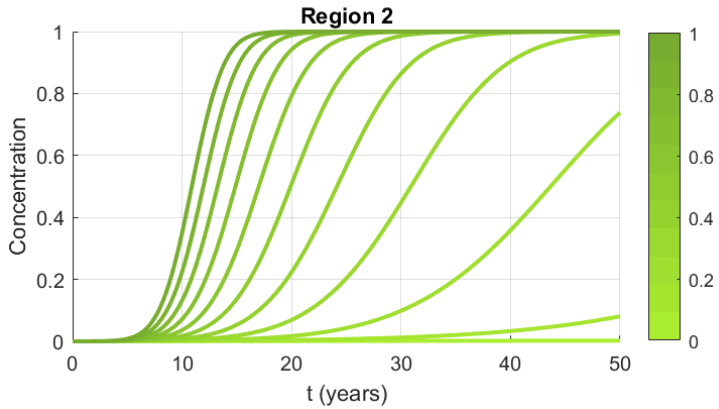
Figure: Evolution of the concentration in Fornari[3] simulation (left) and in our simulation (right).

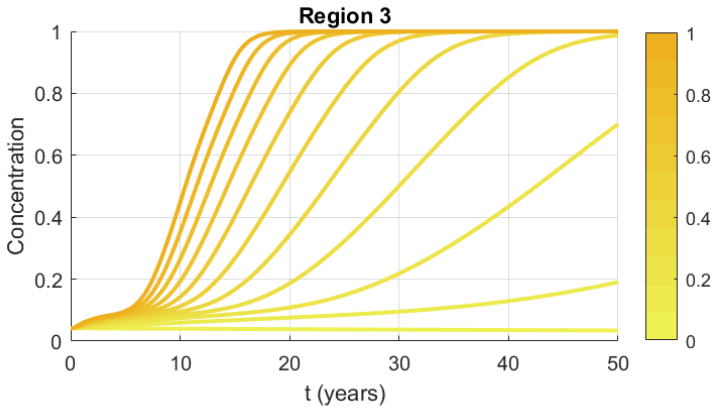
[3] Fornari, Sveva, Amelie Schäfer, Mathias Jucker, Alain Goriely, and Ellen Kuhl. "Prion-like spreading of Alzheimer's disease within the brain's connectome". *Journal of the Royal Society Interface* 16.159 (2019), p. 20190356

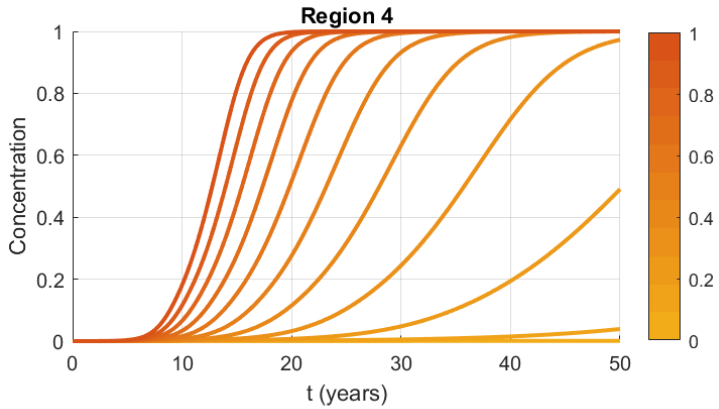
Simulation for different α

Same framework as before, but now α varies between 0 and 1.
Since α is the conversion rate, for larger values the growth of misfolded proteins' concentration is faster.





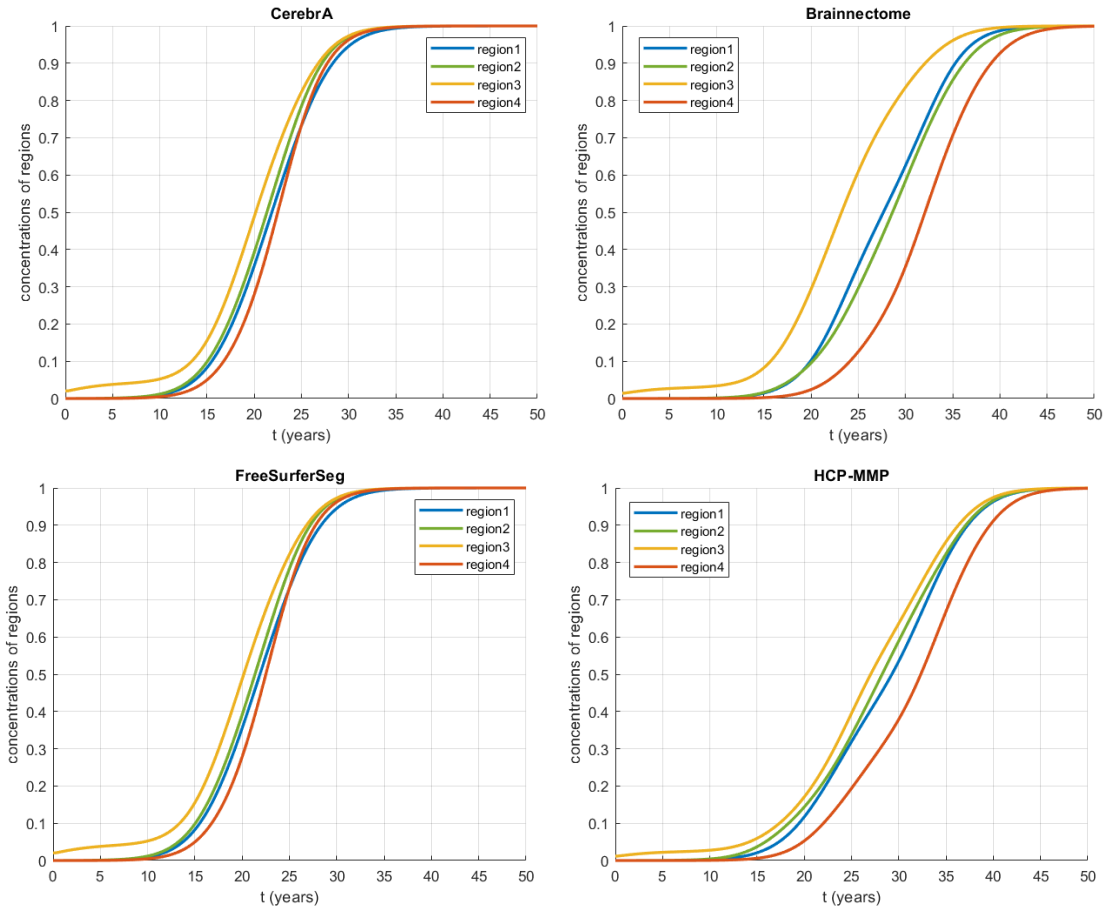




Different atlases comparison

- 42-year-old healthy patient
- $\alpha = 0.5$
- $\theta = 0.5$
- T $= 50$ years

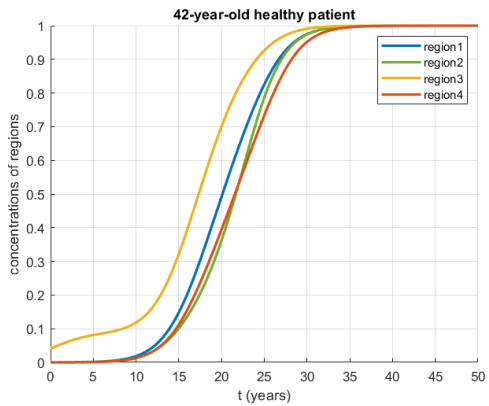
Same simulation on four graphs associated with four different atlases.

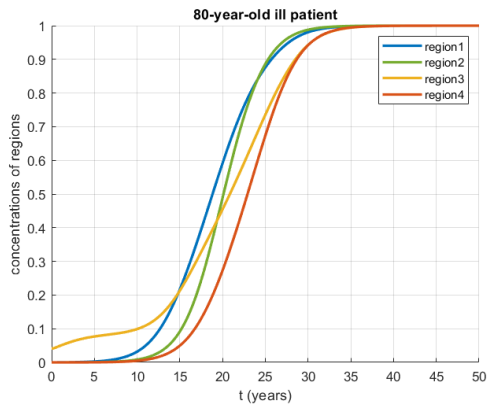


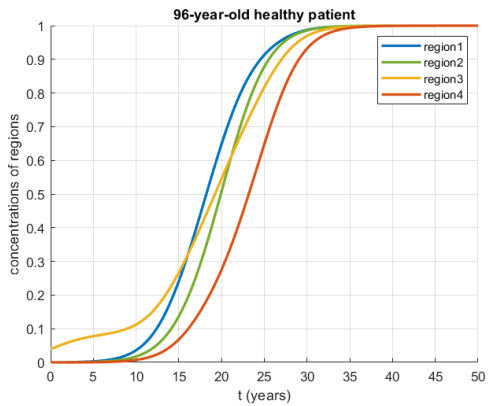
Analysis of the three patients

- *CerebrA* atlas
- $\alpha = 0.5$
- $\theta = 0.5$
- T $= 50$ years

Simulation of the diffusion process for three different patients.







The three simulations lead to an evolution of the concentration that is similar in each case, thus highlighting the robustness of the implemented numerical methods while changing the connectivity matrix, i.e. by considering different patients.

Conclusions and future work

Further investigations

- Expanding the study to more complex models of competition between populations, like **Heterodimer** and **Smoluchowski**.

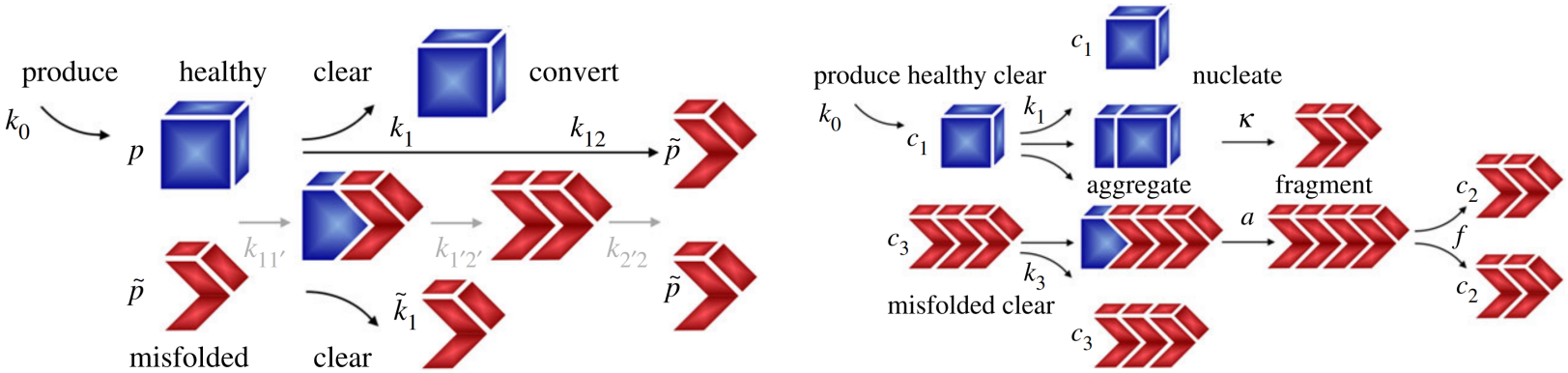


Figure: Heterodimer (left) and Smoluchoski (right) models

source: Fornari, Sveva, Amelie Schäfer, Mathias Jucker, Alain Goriely, and Ellen Kuhl. "Prion-like spreading of Alzheimer's disease within the brain's connectome". *Journal of the Royal Society Interface* 16.159 (2019), p. 20190356

- Introduction of a non-negligible factor of neurodegenerative diseases, to **model the changes in the brain graphs of patients over time**. Mathematically, this coincides with the treatment of a **time-varying domain**.

References

[1] George S Bloom. "Amyloid-β and tau: the trigger and bullet in Alzheimer disease pathogenesis". In: *JAMA neurology* 71.4 (2014), pp. 505–508.

[2] *DSI Studio*. https://dsi-studio.labsolver.org/.

[3] Sveva Fornari, Amelie Schäfer, Mathias Jucker, Alain Goriely, and Ellen Kuhl. "Prion-like spreading of Alzheimer's disease within the brain's connectome". In: *Journal of the Royal Society Interface* 16.159 (2019), p. 20190356.

[4] David S Knopman, Helene Amieva, Ronald C Petersen, Gäel Chételat, David M Holtzman, Bradley T Hyman, Ralph A Nixon, and David T Jones. "Alzheimer disease". In: *Nature reviews Disease primers* 7.1 (2021), pp. 1–21.

[5] *Multiscale Modeling of Dementia: From Proteins to Brain Dynamics*. 2022.

[6] Wieke M. van Oostveen and Elizabeth C. M. de Lange. "Imaging Techniques in Alzheimer's Disease: A Review of Applications in Early Diagnosis and Longitudinal Monitoring". In: *International Journal of Molecular Sciences* 22.4 (2021). ISSN: 1422-0067.

[7] *The graph Laplacian*. https://mbernste.github.io/posts/laplacian_matrix/. 2020.

[8] Johannes Weickenmeier, Mathias Jucker, Alain Goriely, and Ellen Kuhl. "A physics-based model explains the prion-like features of neurodegeneration in Alzheimer's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis". In: *Journal of the Mechanics and Physics of Solids* 124 (2019), pp. 264–281.

Questions?