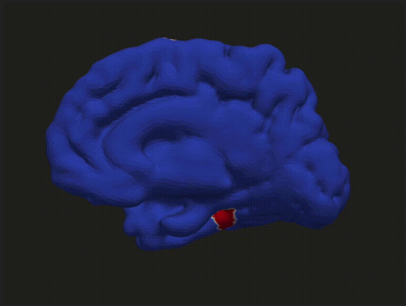
Fisher-Kolmogorov Equation

Modeling Protein Diffusion in Neurodegenerative Diseases



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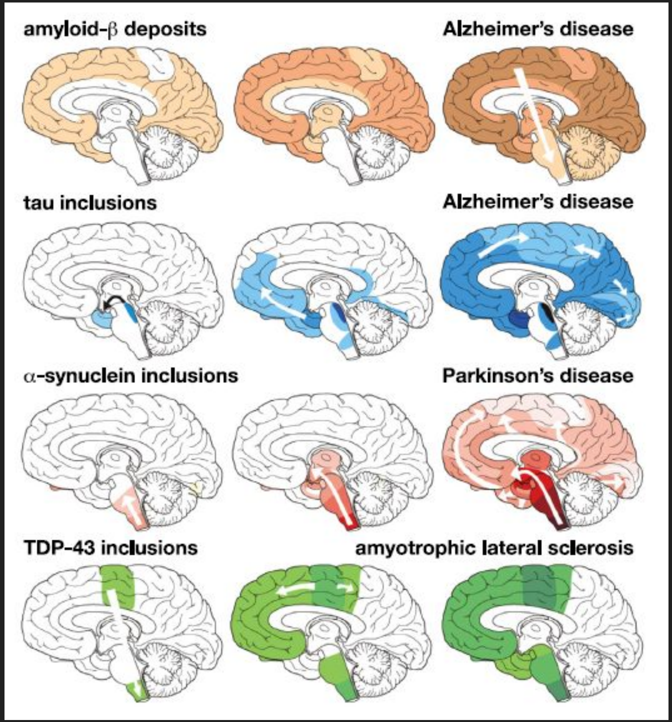
Neurodegenerative Diseases

Alzheimer's, Parkinson's, ALS are different disorders with shared features:

- Disease progression is inevitable after initial seeding.
- Duration of the incubation period depends on both the initial seeding concentration and the rate of diffusion.
- Characterized by a long, clinically silent incubation period during which prions grow and spread, followed by a brief and invariably fatal clinical disease.



Prion Disease Modelization

$$p + \tilde{p} \xrightarrow{k_{11'}} p\tilde{p}$$

$$p\tilde{p} \xrightarrow{k_{1'2'}} \tilde{p}\tilde{p}$$

$$\tilde{p}\tilde{p} \xrightarrow{k_{2'2}} \tilde{p} + \tilde{p}$$

$$\begin{aligned} \frac{\partial p}{\partial t} &= \nabla \cdot (D_p \nabla p) + k_0 - k_1 p - k_{12} p\tilde{p} \\ \frac{\partial \tilde{p}}{\partial t} &= \nabla \cdot (D_{\tilde{p}} \nabla \tilde{p}) - \tilde{k}_1 \tilde{p} + k_{12} p\tilde{p} \end{aligned}$$

Assume Healthy State and spatially homogeneous state

$$p = \frac{k_0}{k_1 + k_{12}\tilde{p}} = \frac{k_0}{k_1}\frac{1}{(1 + \tilde{p}\frac{k_{12}}{k_1})} \approx \frac{k_0}{k_1}(1 - \tilde{p}\frac{k_{12}}{k_1})$$

$$\begin{aligned}\rightarrow \frac{\partial \tilde{p}}{\partial t} &\approx \nabla \cdot (D_{\tilde{p}} \nabla \tilde{p}) - \tilde{k}_1 \tilde{p} + k_{12}\tilde{p}\frac{k_0}{k_1}\left(1 - \frac{k_{12}}{k_1}\tilde{p}\right) \\ &= \nabla \cdot (D_{\tilde{p}} \nabla \tilde{p}) + \left(\frac{k_0 k_{12}}{k_1} - \tilde{k}_1\right)\tilde{p} - \frac{k_0 k_{12}^2}{k_1^2}\tilde{p}^2\end{aligned}$$

Assume unhealthy and spatially homogeneous state

$$\tilde{p}_{\max} = \frac{k_1^2}{k_0 k_{12}^2}\left(\frac{k_{12}k_0}{k_1} - \tilde{k}_1\right) \quad \longrightarrow \quad c = \frac{\tilde{p}}{\tilde{p}_{max}}$$

$$\to \frac{\partial \tilde{p}}{\partial t} \approx \nabla \cdot (D_{\tilde{p}} \nabla(\tilde{p}_{\max} c)) + \left(\frac{k_0 k_{12}}{k_1} - \tilde{k}_1\right)(\tilde{p}_{\max} c) - \frac{k_0 k_{12}^2}{k_1^2}(\tilde{p}_{\max}^2 c^2)$$

$$= \tilde{p}_{\max}\frac{\partial c}{\partial t} = D_{\tilde{p}}\tilde{p}_{\max}\nabla^2 c + \left(\frac{k_0 k_{12}}{k_1} - \tilde{k}_1\right)\tilde{p}_{\max} c - \frac{k_0 k_{12}^2}{k_1^2}\tilde{p}_{\max}^2 c^2$$

$$\to \frac{\partial c}{\partial t} = D_{\tilde{p}}\nabla^2 c + \left(\frac{k_0 k_{12}}{k_1} - \tilde{k}_1\right) c - \frac{k_0 k_{12}^2}{k_1^2}\tilde{p}_{\max} c^2$$

$$= D_{\tilde{p}}\nabla^2 c + \left(\frac{k_0 k_{12}}{k_1} - \tilde{k}_1\right) c - \left(\frac{k_{12} k_0}{k_1} - \tilde{k}_1\right) c^2$$

Fisher-Kolmogorov Equation

$$\frac{\partial c}{\partial t} = \nabla \cdot (D \nabla c) + \alpha c(1-c), \quad \text{with} \quad \alpha = \frac{k_{12} k_0}{k_1} - \tilde{k}_1$$

$$D \nabla c \cdot n = 0 \quad \text{on } \partial\Omega$$

$$c(x,0) = c_0(x), \quad \text{for } x \in \Omega$$

Weak Formulation

Let V := $H^1(\Omega)$ be the Sobolev space of square-integrable functions with square-integrable weak derivatives. The weak formulation reads:

$$?\ c(x,t) \in V \ s.t. \quad \int_\Omega \frac{\partial c}{\partial t} v \, dx + \int_\Omega D \nabla c \cdot \nabla v \, dx = \int_\Omega \alpha c(1-c) \, v \, dx \,, \quad \begin{array}{l} \forall v \in V \\ t \in (0,T] \end{array}$$

Galerkin Formulation

Let T_h be a conforming triangulation of Ω, and let V_h be a finite-dimensional subspace of V. The discrete problem reads:

$$? \; c_h(x,t) \in V_h \;\; s.t. \;\; \int_\Omega \frac{\partial c_h}{\partial t} v_h \, dx + \int_\Omega D \nabla c_h \cdot \nabla v_h \, dx = \int_\Omega \alpha c_h (1 - c_h) \, v_h \, dx, \qquad \forall v_h \in V_h \;\; t \in (0, T]$$

Time Discretization

Let $\{t^n\}^N_{n=0}$ be a uniform partition of the time interval $[0, T]$. We denote $c_h^n \approx c_h(t^n)$. By applying theta method we get:

$$\int_\Omega \frac{c_h^{n+1} - c_h^n}{\Delta t} v_h \, dx + \int_\Omega D \nabla \left(\theta c_h^{n+1} + (1 - \theta) c_h^n \right) \cdot \nabla v_h \, dx =$$

$$\int_\Omega \alpha \left(\theta c_h^{n+1} (1 - c_h^{n+1}) + (1 - \theta) c_h^n (1 - c_h^n) \right) v_h \, dx$$

Residual Definition

We define the time-discrete residual functional as:

$$\mathcal{R}(c_h^{n+1})(v_h) := \int_\Omega \frac{c_h^{n+1} - c_h^n}{\Delta t} v_h \, dx + \int_\Omega D\nabla \left(\theta c_h^{n+1} + (1-\theta)c_h^n\right) \cdot \nabla v_h \, dx$$
$$- \int_\Omega \alpha \left(\theta c_h^{n+1}(1 - c_h^{n+1}) + (1-\theta)c_h^n(1 - c_h^n)\right) v_h \, dx$$

Fréchet Derivative

We compute the Fréchet derivative of the residual in the direction of a perturbation δ_h in V_h

$$a(c_h^{n+1})(\delta_h, v_h) := \int_\Omega \frac{\delta_h}{\Delta t} v_h \, dx + \int_\Omega D\theta \nabla \delta_h \cdot \nabla v_h \, dx - \int_\Omega \alpha\theta(1 - 2c_h^{n+1})\delta_h \, v_h \, dx$$

Newton iteration

To solve the nonlinear problem arising at each time step from the θ-method discretization, we apply Newton's method:

$$a\left(c_h^{n+1,(k)}\right)(\delta_h, v_h) = -\mathcal{R}\left(c_h^{n+1,(k)}\right)(v_h) \qquad \forall v_h \in V_h$$

The new iterate is then updated as:

$$c_h^{n+1,(k+1)} = c_h^{n+1,(k)} + \delta_h$$

Lax-Milgram Theorem for Linearized Newton subproblems

Why? Lax-Milgram Theorem requires a bilinear form, but the weak formulation contains the nonlinear reaction term, which depends nonlinearly on the unknown solution c.

$$\int_\Omega \frac{\delta_h}{\Delta t} v_h \, dx + \theta \int_\Omega D\nabla\delta_h \cdot \nabla v_h \, dx - \theta\alpha \int_\Omega (1 - 2c_h^{(k)})\delta_h \, v_h \, dx = -\mathcal{R}^{(k)}(v_h) \quad \forall v_h \in V_h.$$

But after discretization in time and Newton linearization, we obtain the subproblem above:

- Linear variational problem with bilinear form B(-,-)
- Linear functional F(k)

$$B(w,v) = \int_\Omega \tfrac{1}{\Delta t} \, w \, v \, dx + \theta \int_\Omega D\nabla w \cdot \nabla v \, dx - \theta\alpha \int_\Omega (1 - 2c_h^{(k)}) \, w \, v \, dx$$

$$F^{(k)}(v_h) = -\mathcal{R}^{(k)}(v_h) = -\int_\Omega \frac{c_h^{n+1,(k)} - c_h^n}{\Delta t} v_h \, dx - \int_\Omega D\,\nabla(\theta c_h^{n+1,(k)} + (1-\theta)c_h^n) \cdot \nabla v_h \, dx + \int_\Omega \alpha\big[\theta\, c_h^{n+1,(k)}(1 - c_h^{n+1,(k)}) + (1-\theta)c_h^n(1 - c_h^n)\big] v_h \, dx$$

Standing Assumptions

$$\Omega \subset \mathbb{R}^d \ \text{ Lipschitz}, \quad D \in L^\infty(\Omega; \mathbb{R}^{d\times d}) \text{ symmetric, uniformly elliptic}: \quad \exists\, \underline{D} > 0: \ \xi^\top D(x)\,\xi \ \geq \ \underline{D}\,|\xi|^2, \quad \forall \xi \in \mathbb{R}^d, \text{ a.e. } x \in \Omega$$

$$\alpha \geq 0, \quad \Delta t > 0, \ \theta \in [0,1], \qquad c_h^{(k)} \in V_h \subset H^1(\Omega), \ 0 \leq c_h^{(k)} \leq 1 \text{ a.e.} \qquad \|D\|_{L^\infty(\Omega)} = \operatorname*{ess\,sup}_{x\in\Omega} \|D(x)\|_{\mathrm{op}} = \sup_{x\in\Omega} \lambda_{\max}(D(x))$$

- **Continuity** ✔️

$$
\begin{aligned}
|B(w,v)| &\le \tfrac{1}{\Delta t}\|w\|_{L^2(\Omega)}\|v\|_{L^2(\Omega)} + \theta\|D\|_{L^\infty(\Omega)}\|\nabla w\|_{L^2(\Omega)}\|\nabla v\|_{L^2(\Omega)} + \theta\alpha\|w\|_{L^2(\Omega)}\|v\|_{L^2(\Omega)} \\
&\le \left(\tfrac{1}{\Delta t} + \theta\alpha\right)\|w\|_{L^2(\Omega)}\|v\|_{L^2(\Omega)} + \theta\|D\|_{L^\infty(\Omega)}\|\nabla w\|_{L^2(\Omega)}\|\nabla v\|_{L^2(\Omega)} \\
&\le\ C\,\|w\|_{H^1(\Omega)}\|v\|_{H^1(\Omega)}, \qquad\qquad C := \sqrt{\left(\tfrac{1}{\Delta t} + \theta\alpha\right)^2 + \left(\theta\|D\|_{L^\infty(\Omega)}\right)^2}.
\end{aligned}
$$

- **Coercivity** $\boxed{\frac{1}{\Delta t} > \theta\alpha}$

$$
\begin{aligned}
B(w,w) &= \tfrac{1}{\Delta t}\|w\|^2_{L^2(\Omega)} + \theta\int_\Omega D\nabla w\cdot\nabla w\,dx - \theta\alpha\int_\Omega (1-2c_h^{(k)})\,w^2\,dx \\
&\ge \left(\tfrac{1}{\Delta t} - \theta\alpha\right)\|w\|^2_{L^2(\Omega)} + \theta\,\underline{D}\,\|\nabla w\|^2_{L^2(\Omega)} \\
&\ge m\left(\|w\|^2_{L^2(\Omega)} + \|\nabla w\|^2_{L^2(\Omega)}\right) = m\,\|w\|^2_{H^1(\Omega)}, \qquad m := \min\left\{\tfrac{1}{\Delta t} - \theta\alpha,\ \theta\underline{D}\right\} > 0.
\end{aligned}
$$

- **Weak Coercivity** ✔️

$$
\begin{aligned}
B(w,w) + \lambda\|w\|^2_{L^2(\Omega)} &= \tfrac{1}{\Delta t}\|w\|^2_{L^2(\Omega)} + \theta\int_\Omega D\nabla w\cdot\nabla w\,dx \qquad\qquad \lambda := \theta\alpha\,\|1-2c_h^{(k)}\|_{L^\infty(\Omega)}\ \le\ \theta\alpha \\
&\ge \tfrac{1}{\Delta t}\|w\|^2_{L^2(\Omega)} + \theta\,\underline{D}\,\|\nabla w\|^2_{L^2(\Omega)} \\
&\ge \alpha_0\,\|w\|^2_{H^1(\Omega)}, \qquad \alpha_0 := \min\left\{\tfrac{1}{\Delta t},\ \theta\underline{D}\right\}.
\end{aligned}
$$

- **Continuity r.h.s.** ✔️

$$
\begin{aligned}
|F^{(k)}(v_h)| \leq \tfrac{1}{\Delta t}\|c_h^{n+1,(k)} - c_h^n\|_{L^2}\|v_h\|_{L^2} + \|D\|_{L^\infty}\big(\theta\|\nabla c_h^{n+1,(k)}\|_{L^2} + (1-\theta)\|\nabla c_h^n\|_{L^2}\big)\|\nabla v_h\|_{L^2} \\
+ \alpha\big(\theta\|c_h^{n+1,(k)}(1-c_h^{n+1,(k)})\|_{L^2} + (1-\theta)\|c_h^n(1-c_h^n)\|_{L^2}\big)\|v_h\|_{L^2} \\
\leq a\|v_h\|_{L^2} + b\|\nabla v_h\|_{L^2} \ \leq \ \sqrt{a^2+b^2}\,\|v_h\|_{H^1}, \\
a := \tfrac{1}{\Delta t}\|c_h^{n+1,(k)} - c_h^n\|_{L^2} + \alpha\big(\theta\|c_h^{n+1,(k)}(1-c_h^{n+1,(k)})\|_{L^2} + (1-\theta)\|c_h^n(1-c_h^n)\|_{L^2}\big), \\
b := \|D\|_{L^\infty}\big(\theta\|\nabla c_h^{n+1,(k)}\|_{L^2} + (1-\theta)\|\nabla c_h^n\|_{L^2}\big).
\end{aligned}
$$

Application of Lax-Milgram Theorem

$$
\boxed{\frac{1}{\Delta t} > \theta\alpha} \quad \Rightarrow \quad
\begin{aligned}
\exists!\ \delta_h \in V_h :\ \ B(\delta_h, v_h) = F^{(k)}(v_h) \ \ \forall v_h \in V_h, \\
\|\delta_h\|_{H^1(\Omega)} \ \leq \ C\,\|F^{(k)}\|_{(H^1(\Omega))}
\end{aligned}
$$

Energy Stability

$$v_h = c_h \;\Rightarrow\; \int_\Omega \frac{\partial c_h}{\partial t}\, c_h\, dx + \int_\Omega D|\nabla c_h|^2\, dx = \alpha \int_\Omega c_h^2(1 - c_h)\, dx$$

$$\tfrac{1}{2}\frac{d}{dt}\|c_h\|^2_{L^2(\Omega)} + \int_\Omega D|\nabla c_h|^2\, dx \;\le\; \alpha\,\|c_h\|^2_{L^2(\Omega)} \qquad (0 \le c_h \le 1)$$

$$\text{Ellipticity:}\quad \int_\Omega D|\nabla c_h|^2\, dx \;\ge\; \underline{D}\,\|\nabla c_h\|^2_{L^2(\Omega)}$$

$$y(t) := \|c_h\|^2_{L^2(\Omega)} \;\Rightarrow\; \tfrac{1}{2}\, y'(t) + \underline{D}\,\|\nabla c_h\|^2_{L^2(\Omega)} \;\le\; \alpha\, y(t).$$

$$\textbf{Gronwall (differential form):}\quad u'(t) \le \beta(t)\, u(t) \;\Rightarrow\; u(t) \le u(a)\exp\left(\int_a^t \beta(s)\, ds\right).$$

$$\textbf{Apply to } y:\; \tfrac{1}{2}y'(t) \le \alpha\, y(t) \;\Rightarrow\; y(t) \le e^{2\alpha(t-a)}\, y(a).$$

$$\textbf{With } a = 0:\quad \boxed{\|c_h(t)\|^2_{L^2(\Omega)} \le e^{2\alpha t}\,\|c_h(0)\|^2_{L^2(\Omega)}} \qquad (t \in [0, T]).$$

Energy Stability

$$\tfrac{1}{2}\, y'(t) + \underline{D}\, \|\nabla c_h\|_{L^2}^2 \;\le\; \alpha\, y(t), \qquad y(t) = \|c_h\|_{L^2}^2$$

$$\int_0^T (\cdot)\, dt: \quad \tfrac{1}{2}\,(y(T) - y(0)) + \underline{D} \int_0^T \|\nabla c_h\|_{L^2}^2\, dt \;\le\; \alpha \int_0^T y(t)\, dt$$

$$\Rightarrow \;\underline{D} \int_0^T \|\nabla c_h\|_{L^2(\Omega)}^2\, dt \;\le\; \alpha \int_0^T y(t)\, dt + \tfrac{1}{2}\, y(0)$$

$$y(t) \le e^{2\alpha t} y(0) \;\Rightarrow\; \alpha \int_0^T y(t)\, dt \;\le\; \alpha\, y(0) \int_0^T e^{2\alpha t} dt = \tfrac{e^{2\alpha T} - 1}{2}\, y(0)$$

$$\boxed{\underline{D} \int_0^T \|\nabla c_h\|_{L^2(\Omega)}^2\, dt \;\le\; \tfrac{e^{2\alpha T}}{2}\, \|c_h(0)\|_{L^2(\Omega)}^2} \qquad \Rightarrow \qquad c_h \in L^\infty(0, T; L^2(\Omega)) \cap L^2(0, T; H^1(\Omega)).$$

Empirical testing of solvers and preconditioners

Benchmark testing demonstrated the overwhelming efficiency of both the Minimum Residual (MINRES) and Conjugate Gradient (CG) solvers alongside the Incomplete LU factorization as preconditioner.

ILU breaks symmetry and is less robust so the final implementation uses MINRES with an Algebraic Multigrid (AMG) preconditioner.

Pair tested	Newton Iteration	Time step	Total time
GMRES + SSOR	7.30	21.92	175.38
GMRES + ILU	2.56	11.20	89.60
GMRES + AMG	1.51	12.51	100.06
MINRES + SSOR	5.70	15.55	124.40
MINRES + ILU	2.17	10.24	81.90
MINRES + AMG	1.79	10.77	86.22
CG + SSOR	5.32	15.33	122.68
CG + ILU	1.90	10.32	82.61
CG + AMG	1.86	11.20	89.62

Average elapsed time (s) for different solver-preconditioner pairs.

Simulation setup: Initial Conditions and Matter Types

Initial seedings were given as areas of the brain with concentration greater than zero depending on the protein.

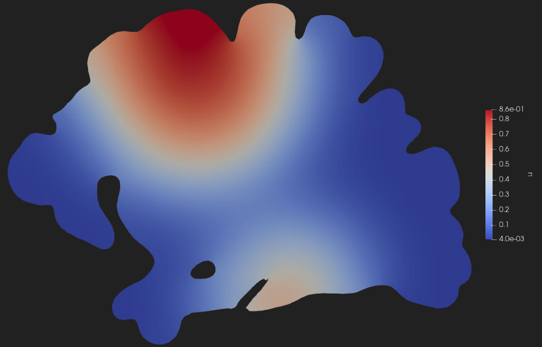
The subdivision of the brain into White and Gray matter was obtained assigning a material ID to cells close to the boundary.

Amyloid-β deposits

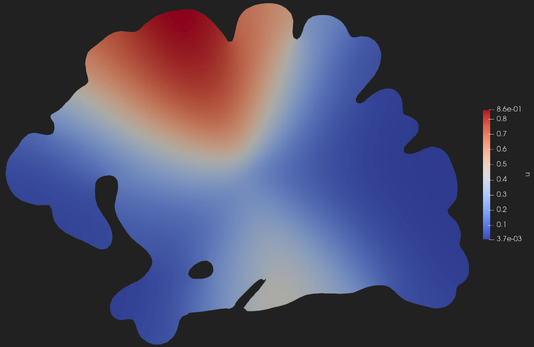
TDP-43 inclusions

White-Gray Partitioning

Simulation setup: Axonal Directions

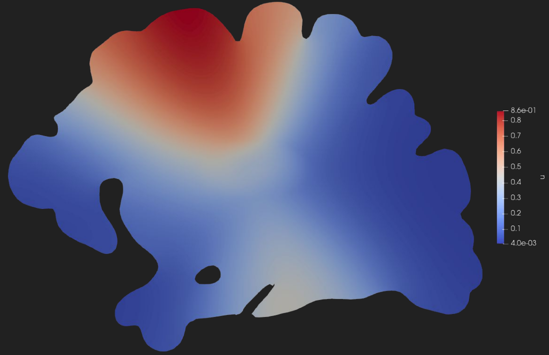


Isotropic



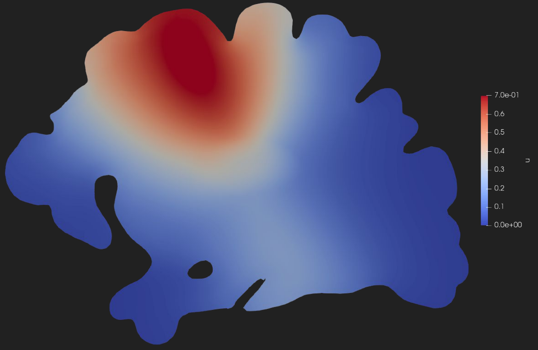
Radial

Circular

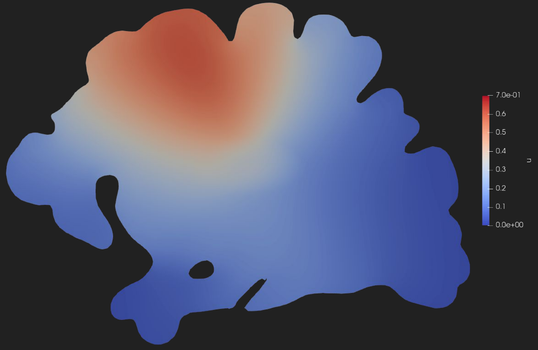


Axon-Based

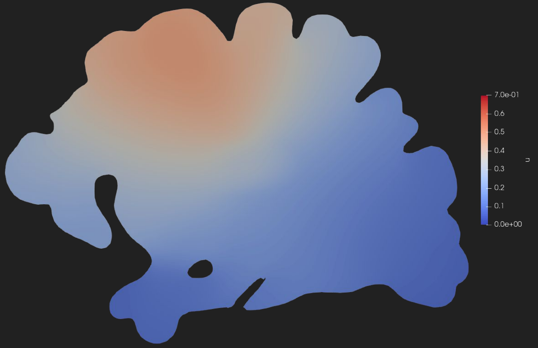
Validating the simulation: Diffusion Coefficient [mm^2/year]



d_axn=10, d_ext=5



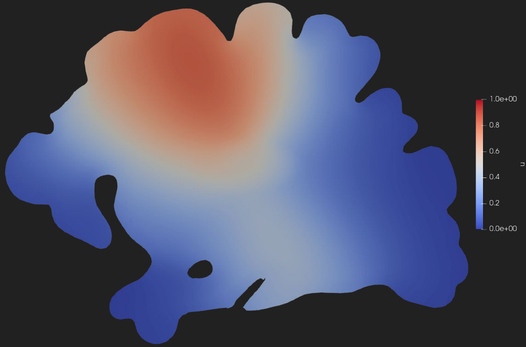
d_axn=20, d_ext=10



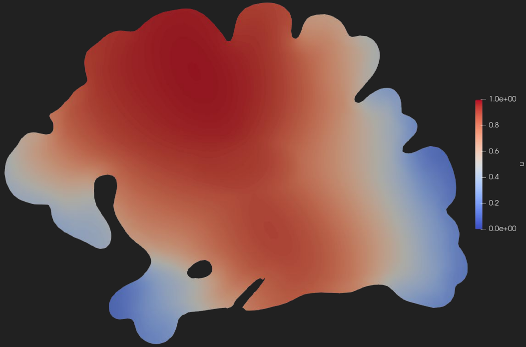
d_axn=40, d_ext=20

d_axn=80, d_ext=40

Validating the simulation: Growth Rate



α=0.3 / year

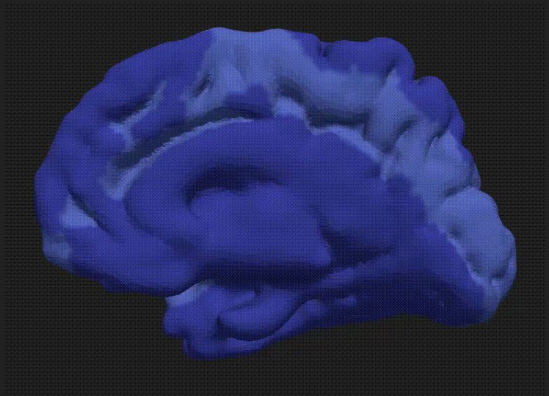


α=0.45 / year

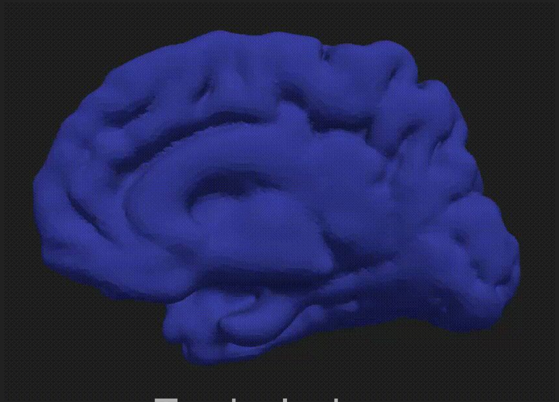
α=0.6 / year

α=1.2 / year

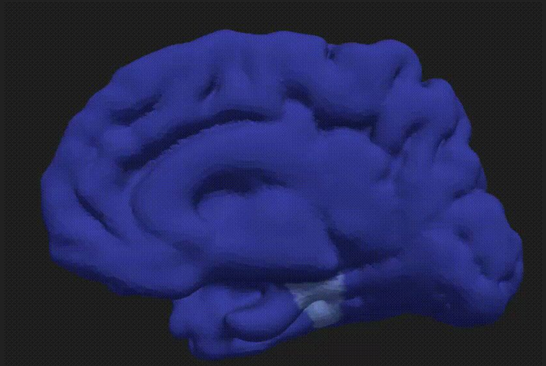
Simulation for T=50 years



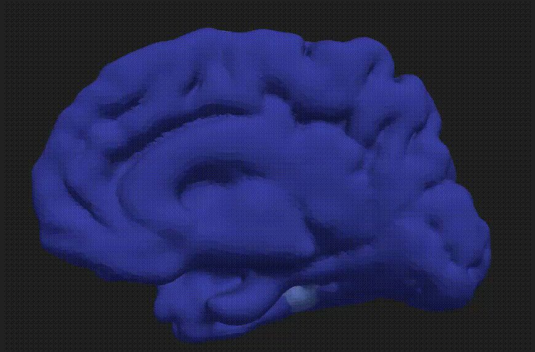
Amyloid-β deposits



Tau inclusions



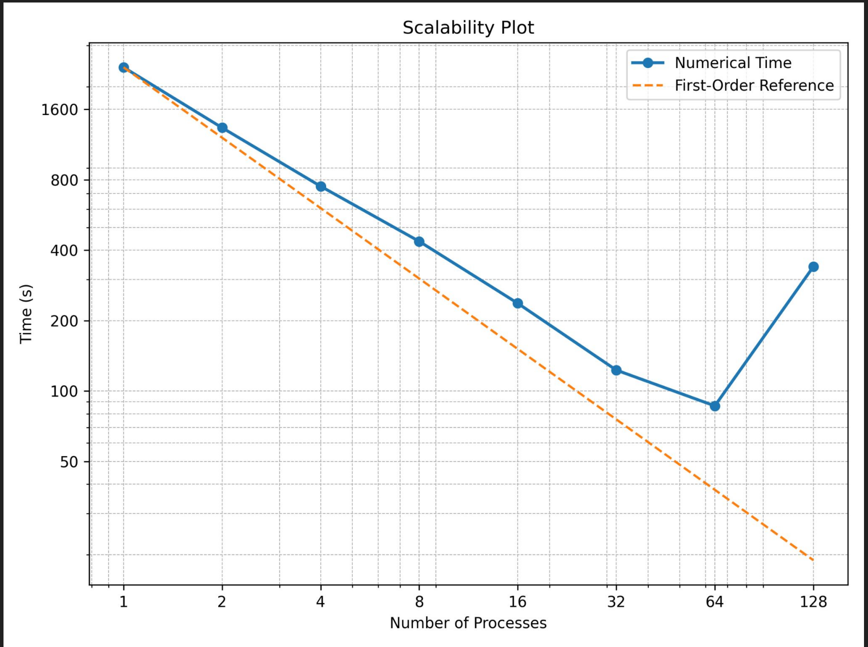
α-synuclein inclusions

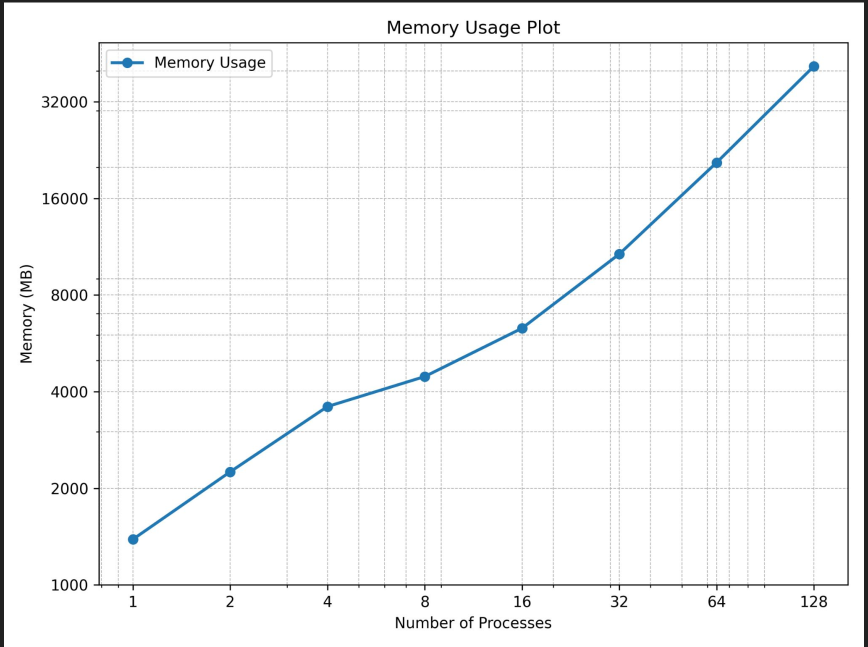


TDP-43 inclusions

Strong Scalability on MeluXina Supercomputer

- **Execution Time**: decreases nearly ideally up to 64 processes
- **Memory Usage**: grows almost linearly with the number of processes, becoming significant beyond 64.





Strong Scalability on MeluXina Supercomputer

Processes	Execution time [s]	TotalCPU [h:mm:ss]	AveRSS [MB]	MaxRSS [MB]
1	2422.912	00:40:23	1386.785	3036.592
2	1336.381	00:54:16	2250.618	3504.412
4	751.122	01:00:53	3594.989	5425.112
8	436.718	01:12:50	4458.447	5691.932
16	237.379	01:20:50	6304.562	7554.640
32	122.979	01:32:03	10738.000	13276.768
64	86.459	02:21:33	20697.175	25657.416
128	340.400	06:28:47	41313.585	46238.548

Strong scalability results on MeluXina (1 node up to 64 processes, 2 nodes for 128 processes).
CPU Hardware used: 2x AMD EPYC Rome 7452 (32 cores, 64 threads each), 512 GB RAM.

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Thank you!