Demonstration of an open-source toolbox for network spreading models: regional amyloid burden promotes tau production in Alzheimer's disease

Elinor Thompson[1], Anna Schroder[1], Tiantian He[1], Antoine Legouhy[1], Xin Zhao[2,3], James H. Cole[1,4], Neil P. Oxtoby[1], Daniel C. Alexander[1] for the Alzheimer's Disease Neuroimaging Initiative

1. UCL Centre for Medical Image Computing, Department of Computer Science, University College London, UK 2. UCL Centre for Medical Image Computing, Department of Medical Physics and Biomedical Engineering, University College London, UK 3. MRC Unit for Lifelong Health and Ageing, Department of Population Science and Experimental Medicine, University College London, UK 4. Dementia Research Centre, UCL Queen Square Institute of Neurology, University College London, UK

AIC-340 / Monday-475

Background

Connectome-based models of disease propagation are used to probe mechanisms of pathology spread in neurodegenerative disease.

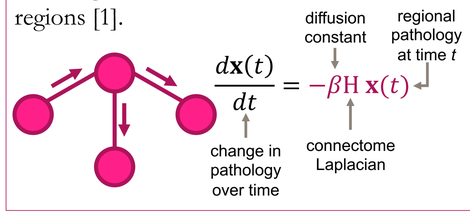
We present our open-source **network spreading model toolbox** that allows the user to compare model fits across different models and parameters.

We use the toolbox to model the influence of amyloid on tau accumulation.

Models

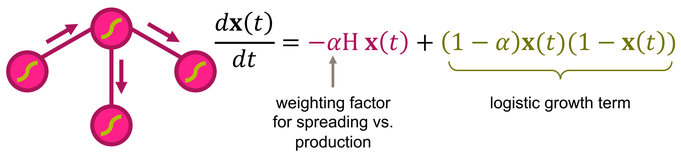
Network diffusion model (NDM)

Pathology diffuses between connected brain regions [1].



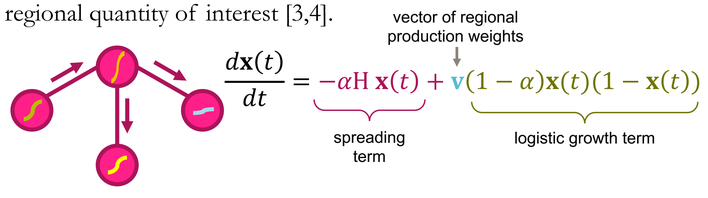
Fisher-Kolmogorov-Petrovsky-Piscounov (FKPP)

Network spreading plus uniform production of pathology at each node [2].



Weighted FKPP

Spreading plus differing levels of production at each node, weighted by a regional quantity of interest [3,4].



Application of the toolbox: modelling the effect of regional amyloid on tau production

Data

- We used tau-PET and amyloid-PET SUVRs from the Alzheimer's Disease Neuroimaging Initiative (ADNI).
- Subjects were separated into AT(~~N~~) groups: amyloid-negative, tau-negative; amyloid-positive, tau-negative; amyloid-positive, tau-positive.
- Positivity thresholds were defined using Gaussian mixture modelling.
- We used a template structural connectome, a group average across 50 young, healthy individuals from the MICA-MICs dataset [5].

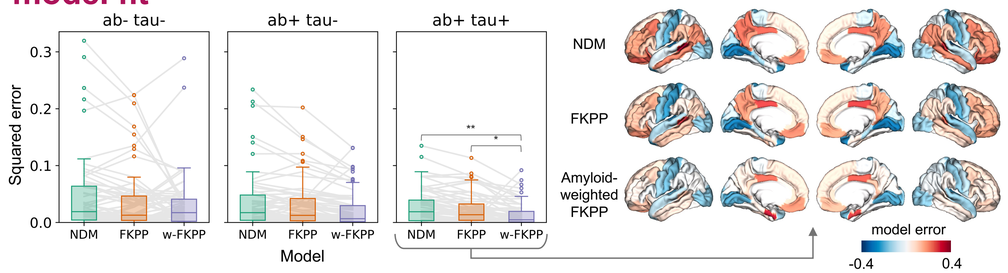
Biomarker	AT(~~N~~) disease stage	N	Age (years)	Gender (Male%)	Education (years)	Diagnosis (%) CN	MCI	AD
Tau PET	A-T-	373	73.6 ± 9.2	50.1	16.5 ± 2.5	67.5	29.4	2.7
Tau PET	A+T-	162	77.2 ± 8.5	50.0	16.5 ± 2.5	61.7	29.0	9.3
Tau PET	A+T+	242	77.2 ± 8.4	46.3	16.1 ± 2.4	26.9	41.3	31.4
Amyloid PET	A-T-	372	73.7 ± 9.1	50.0	16.5 ± 2.5	68.3	28.5	3.0
Amyloid PET	A+T-	163	77.6 ± 8.5	50.3	16.5 ± 2.5	61.9	28.2	9.8
Amyloid PET	A+T+	241	77.3 ± 8.2	46.0	16.1 ± 2.4	28.2	39.4	32.0

Table 1. Subject demographics across the biomarkers and disease stage groups

Methods

- Data were averaged within groups to produce stage-specific maps. We compared the ability of the three models to reproduce the tau pattern of each group.
- For the "weighted-FKPP" model, we used the amyloid maps from the corresponding stage as the production weights. This models a contributory role of amyloid in the tau production process.
- Models were initialised with unity pathology in a bilateral seed region, zero elsewhere.
- Free parameters were fitted using Gaussian processes optimisation .
- We benchmarked the performance of the amyloid-weighted FKPP model with a null distribution of 100 reshuffled amyloid maps, to test the significance of the amyloid maps as drivers of model performance.

Results: Weighting tau production by amyloid levels improves model fit

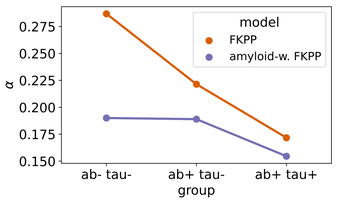


- The amyloid-weighted FKPP model significantly reduced prediction error compared to the NDM ($p = 0.001$) and FKPP ($p = 0.032$), in the amyloid+ tau+ group.
- Amyloid-weighted FKPP had the best model fit for all groups (Table 2).
- **This supports the hypothesis that amyloid promotes tau aggregation.**

	amyloid-, tau-		amyloid+, tau-		amyloid+, tau+	
model	r	AICc weight	r	AICc weight	r	AICc weight
network diffusion	0.61	1.0×10^{-5}	0.70	2.0×10^{-5}	0.75	2.6×10^{-10}
FKPP	0.61	1.7×10^{-3}	0.71	1.0×10^{4}	0.78	1.1×10^{-7}
amyloid-weighted FKPP	**0.68**	**1.0**	**0.78**	**1.0**	**0.87**	**1.0**

Table 2. Model fits. r: Pearson's correlation between the model output and tau-PET. AICc: Corrected Akaike information criterion. The highest weight corresponds to the best model, accounting for model complexity.

The FKPP weighted with amyloid significantly improved model fit compared to the reshuffled amyloid maps ($p < 1 \times 10^{-10}$). This shows the spatial significance of the amyloid patterns.



The spreading weight, α, decreased with disease stage. This suggests that tau spread is more prominent in early stages, followed by a local production phase [6].

Further application: investigating the role of neurotransmitter receptors

Poster Monday-910: Effects of regional neurotransmitter receptor densities on modelling amyloid and tau accumulation in Alzheimer's disease with network spreading models

References

1. Raj, A., Kuceyeski, A., & Weiner, M. W. (2012). A Network Diffusion Model of Disease Progression in Dementia. Neuron, 73(6), 1204–1215. https://doi.org/10.1016/j.neuron.2011.12.040

2. Weickenmeier, J., Jucker, M., Goriely, A., & Kuhl, E. (2019). A physics-based model explains the prion-like features of neurodegeneration in Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Journal of The Mechanics and Physics of Solids, 124, 264–281. https://doi.org/10.1016/j.jmps.2018.10.013

3. He, T., Schroder, A., Thompson, E., Oxtoby, N. P., Abdulaal, A., Barkhof, F., & Alexander, D. C. (2023). Coupled pathology appearance and propagation models of neurodegeneration. The Organization for Human Brain Mapping (OHBM) 2023 Annual Meeting, [Oral Presentation]

4. He, T., Thompson, E., Schroder, A., Oxtoby, N. P., Abdulaal, A., Barkhof, F., & Alexander, D. C. (2023, October). A coupled-mechanisms modelling framework for neurodegeneration. In International Conference on Medical Image Computing and Computer-Assisted Intervention (pp. 459-469).

5. Royer, J., Rodríguez-Cruces, R., Tavakol, S., Larivière, S., Herholz, P., … & Bernhardt, B. C. (2022). An Open MRI Dataset For Multiscale Neuroscience. Scientific Data, 9(1), Article 1. https://doi.org/10.1038/s41597-022-01682-y

6. Chaggar, P., Vogel, J. W., Pichet-Binette, A., Thompson, T. B., Strandberg, O. B., Stomrud, E., ... & Goriely, A. (2023). Personalised Regional Modelling Predicts Tau Progression in the Human Brain. bioRxiv, 2023-09.

Try it out for yourself:

https://github.com/ucl-pond/network_spreading_models

elinor.thompson@ucl.ac.uk

@e_thompson93