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Alzheimer's Disease: A Mathematical Model for Onset and Progression

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Original Authors: Bertsch, Franchi, Marcello, Tesi and Tosin 2016 [1]

Advanced Topics in Biomathematics

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Table of Contents

1 Introduction

2 Mathematical Model

3 Problem Setting and Discretization

4 Numerical Results and Simulations

5 Conclusions

Introduction

Introduction

- Alzheimer's Disease is one of the most common late life dementia
- Causes: still not totally clear, but experimental evidence suggest it is linked to the diffusion of "amyloid-β" peptide (**amyloid cascade hypothesis**) and the *tau* protein
- We will focus on Aβ_{42} isomer

Biological Model

- Monomeric Aβ peptides are naturally produced and removed by neurons
- For unknown reasons some neurons (**damaged neurons**) do not remove all this toxic protein
- Monomeric Aβ diffuses through the brain and agglomerates to form long, insoluble fibrils (**senile plaques**)
- Neural damage spreads in a neuron-to-neuron prion-like propagation (**prionid hypothesis**)

Mathematical Model

General Setting

- Ω: portion of the cerebral tissue, with $x \in \Omega$ generic (space) point
- Time-scales:
  - Fast s-scale (hours): diffusion of Aβ
  - Slow t-scale (months): progression of disease

$$\Delta t = \varepsilon \Delta s, \quad \varepsilon << 1$$

- Variables:
  - $u_m(x, s)$: molar concentration of soluble Aβ polymers of length m at time s for $m = 1, \ldots, N-1$
  - $u_N(x, s)$: cluster of polymers of length $\geq N$, assumed to not move

Schmoluchowski Equation

Model for m-polymers, for $m = 1, \ldots, N-1$:

$$\partial_s u_m = d_m \Delta u_m + \left[\frac{1}{2} \sum_{j=1}^{m-1} a_{j,m-j} u_j u_{m-j} - u_m \sum_{j=1}^{N} a_{m,j} u_j \right] - \sigma_m u_m$$

From experimental evidence and simplifications:

$$a_{i,j} = \alpha \frac{1}{ij}, \qquad \alpha > 0, \qquad a_{N,N} = 0$$

For the monomers u_1 we add a source term $\mathcal{F}$:

$$\partial_s u_1 = d_1 \Delta u_1 - u_1 \sum_{j=1}^{N} a_{1,j} u_j + \mathcal{F}$$

Large fibrils do not move (no diffusion):

$$\partial_s u_N = \frac{1}{2} \sum_{\substack{j+k \geq N \\ k,j<N}} a_{j,k} u_j u_k$$

Degree of Neuron Malfunctioning

Degree of neuron malfunctioning: $a \in [0, 1]$:

- $a \simeq 0$: healthy neuron
- $a \simeq 1$: dead neuron

Fraction of neurons close to x with degree of malfunctioning at time t (slow-scale) between a and $a + da$ is:

$$f(x, a, t)da$$

Introduce the deterioration rate $\nu = \nu(x, a, t)$ as

$$\nu[f] = \int \int_{\Omega \times [0,1]} \mathcal{K}(x, a, y, b) f(y, b, t) dy db + \mathcal{S}\left(x, a, u_1(x, s), \ldots, u_{N-1}(x, s)\right)$$

We can write an equation for f:

$$\partial_t f + \partial_a (f \nu[f]) = J[f]$$

The source term can be modeled in terms of f:

$$\mathcal{F} = \mathcal{F}[f] = C_{\mathcal{F}} \int_0^1 (\mu_0 + a)(1 - a) f(x, a, t) da$$

Deterioration rate

Typical assumption:

$$\mathcal{K}(x,a,y,b) = \mathcal{G}(x,a,b)H(x,y)$$

$$\mathcal{G}(x,a,b) = C_{\mathcal{G}}(b-a)^{+}, \qquad H(x,y) = h(|x-y|)$$

Assume that $\int_{|y|<r_0} h(|y|)dy = 1$. When $r_0 \to 0$

$$\nu[f] = \int_0^1 \mathcal{G}(x,a,b)f(x,b,t)db + \mathcal{S}(x,a,u_1,\ldots,u_{N-1})$$

Final assumption:

$$\mathcal{S} = C_{\mathcal{S}}(1-a)\left(\sum_{m=1}^{N-1} m u_m(x,s) - \bar{U}\right)^{+}$$

Final model

Final Model

$$
\begin{cases}
\partial_t f + \partial_a(f\nu[f]) = J[f] \\
\varepsilon\partial_t u_1 = d_1\Delta u_1 - u_1\sum_{j=1}^{N} a_{1,j}u_j + \mathcal{F}[f] - \sigma_1 u_1 \\
\varepsilon\partial_t u_m = d_m\Delta u_m + \frac{1}{2}\sum_{j=1}^{m-1} a_{j,m-j}u_j u_{m-j} \\
\qquad\qquad -u_m\sum_{j=1}^{N} a_{m,j}u_j - \sigma_m u_m \qquad\qquad 2 \le m < N \\
\varepsilon\partial_t u_N = \frac{1}{2}\sum_{\substack{j+k\ge N \\ k,j<N}} a_{j,k}u_j u_k
\end{cases}
$$

Problem Setting and Discretization

Physical Domain and Boundary Conditions

- Two-dimensional tranverse section of the brain

$$\Omega = [0, L_x] \times [0, L_y]$$

- Two inner holes for the cerebral ventricles
- Two small circles for the hippocampus

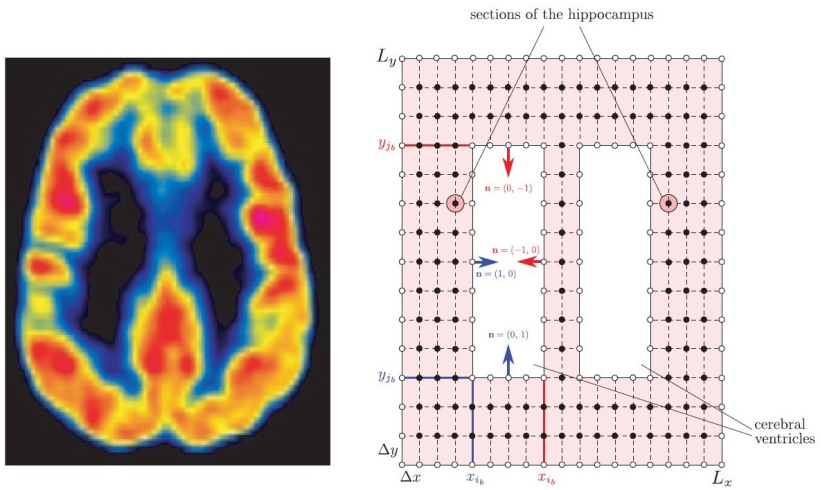

Figure: Real transverse section and numerical schematization of the brain.

Boundary Conditions

- **Outer Boundary**: vanishing polymer flow, i.e., homogeneous Neumann condition

$$-\frac{d_m}{\varepsilon}\nabla u_m \cdot \mathbf{n} = 0 \qquad \text{on } \partial\Omega_{\text{out}} \quad m = 1, \ldots, N-1$$

- **Inner Boundary** (ventricles): removal by the cerebrospinal fluid (CSF), i.e., Robin boundary condition

$$-\frac{d_m}{\varepsilon}\nabla u_m \cdot \mathbf{n} = \beta u_m \qquad \text{in } \partial\Omega_{\text{out}} \quad m = 1, \ldots, N-1$$

Physiological Indicators

- Macroscopic distribution of Neuron Malfunctioning:

$$A(x,t) = \int_0^1 af(x,a,t)da$$

- Local brain atrophy:

$$\Phi(x,t) = \max\left\{0, \frac{A(x,t) - A_0}{1 - A_0}\right\}$$

- Global Brain Atrophy:

$$\Phi(t) = \frac{1}{|\Omega|}\int_\Omega \Phi(x,t)dx$$

- Total Concentration of Soluble Amyloid in the Brain Occipital Region

$$U_S(t) = \frac{1}{|\hat{\Omega}|} \int_{\hat{\Omega}} \sum_{m=1}^{N-1} m u_m(x,t) dx$$

- Average quantity of AB deposits:

$$U_N(t) = \frac{1}{|\Omega|} \int_{\Omega} N u_N(x,t) dx$$

Numerical Results and Simulations

Simulation

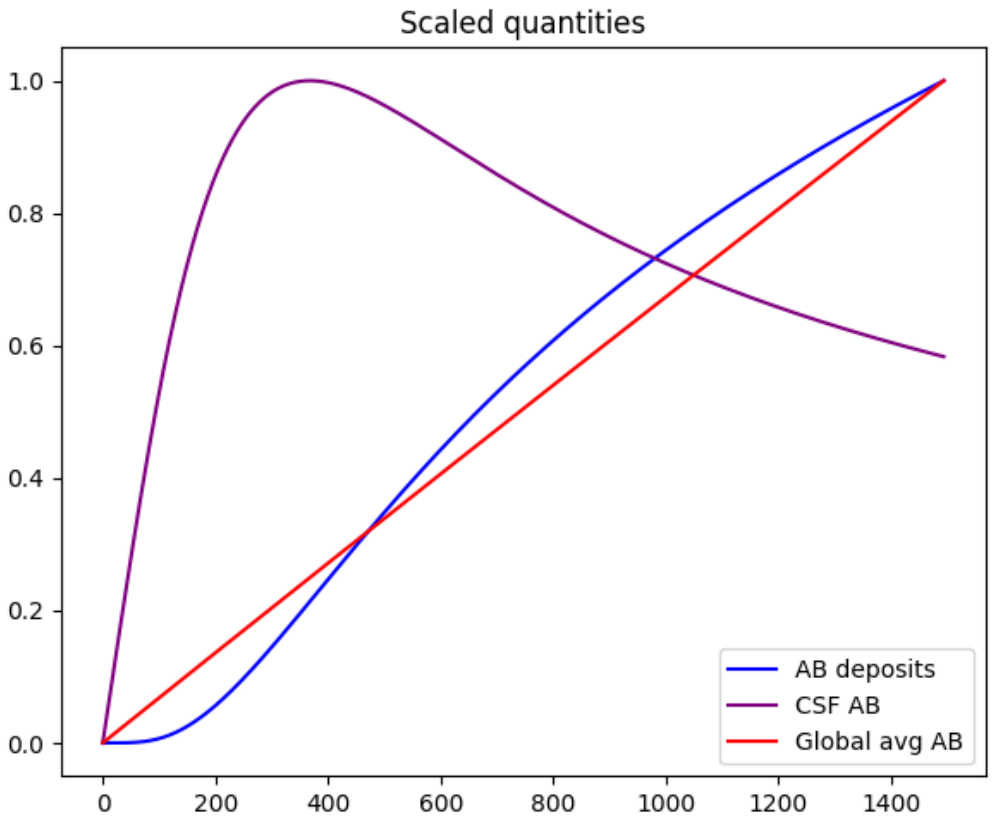

Figure: Plot of the (normalized) CSF Aβ, the Aβ deposits and the global average quantity with $\beta = 100$ and $N = 5$ isomers

Comparison with different β

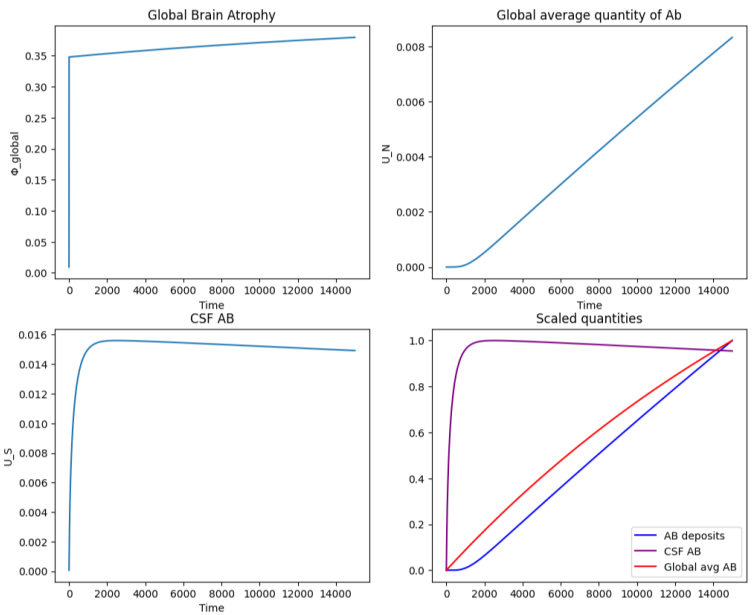

Figure: Simulation with $\beta = 100$ and $N = 10$ isomers

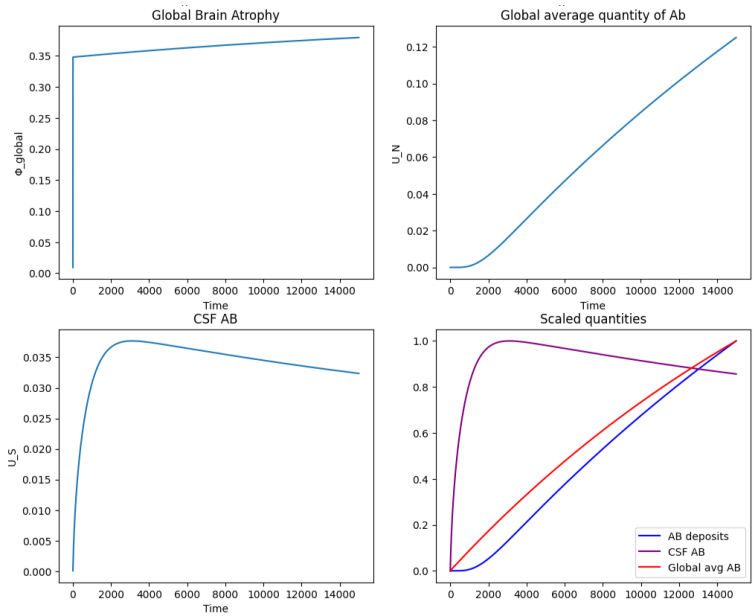

Figure: Simulation with $\beta = 0.0001$ and $N = 10$ isomers

Simulation of Neuron Malfunctioning

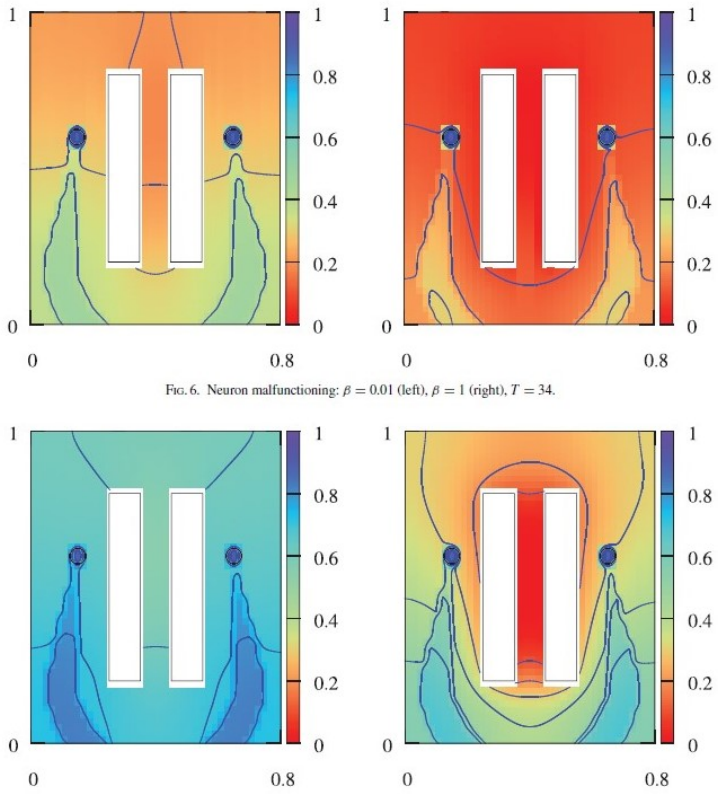

FIG. 6. Neuron malfunctioning: $\beta = 0.01$ (left), $\beta = 1$ (right), $T = 34$.

Figure: Plot of f from the paper.

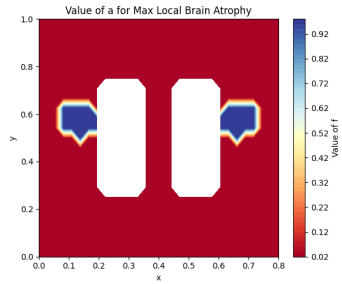

Figure: Plot of f from our simulation at $t = 1000$

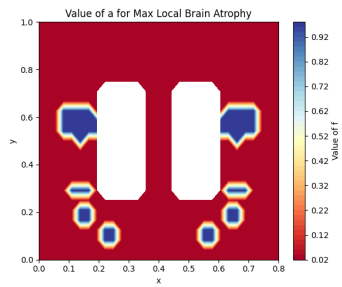

Figure: Plot of f from our simulation at $t = 15000$

Clinical Data

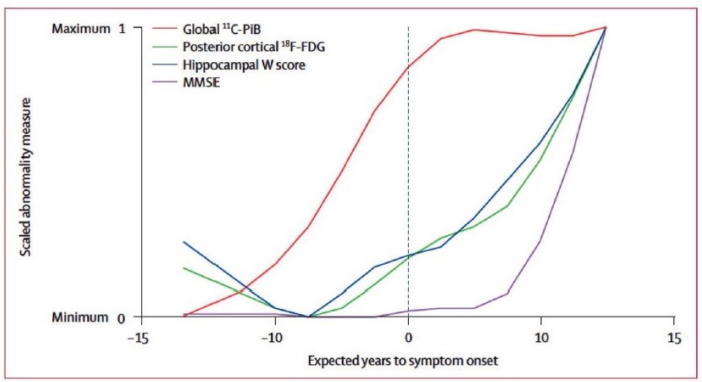

Figure: Clinical data

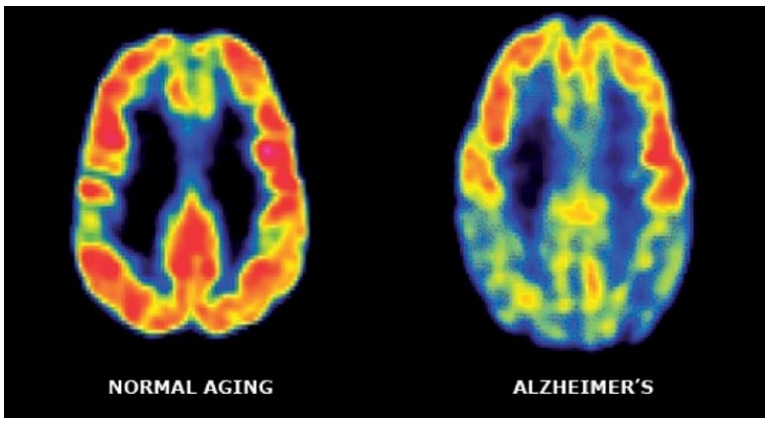

Figure: Comparison of PET images of an healthy and an ill brain

Conclusions

Discussion and future reasearch directions

Pros:

- High level of flexibility
- Simulations comparable with clinical data
- Potentially useful to study new drugs

Cons:

- Preferential diffusion of the disease in the occipital region not captured
- Parameter estimation
- Removal process not well captured

Bibliography

Michiel Bertsch, Bruno Franchi, Norina Marcello, Maria Carla Tesi, and Andrea Tosin.

Alzheimer's disease: a mathematical model for onset and progression.

Mathematical Medicine and Biology A Journal of the IMA, 4 2016.

Thank you for the attention!

Figure: QR code to the GitHub repository with the presentation, the paper and the notebooks