An elementary qualitative model for diffusion and aggregation of β-amyloid in Alzheimer's disease

Maria Carla Tesi (University of Bologna)

Connections for Women: Discrete Lattice Models in Mathematics, Physics and Computing
January 12-13, 2012 at MSRI, Berkeley, California

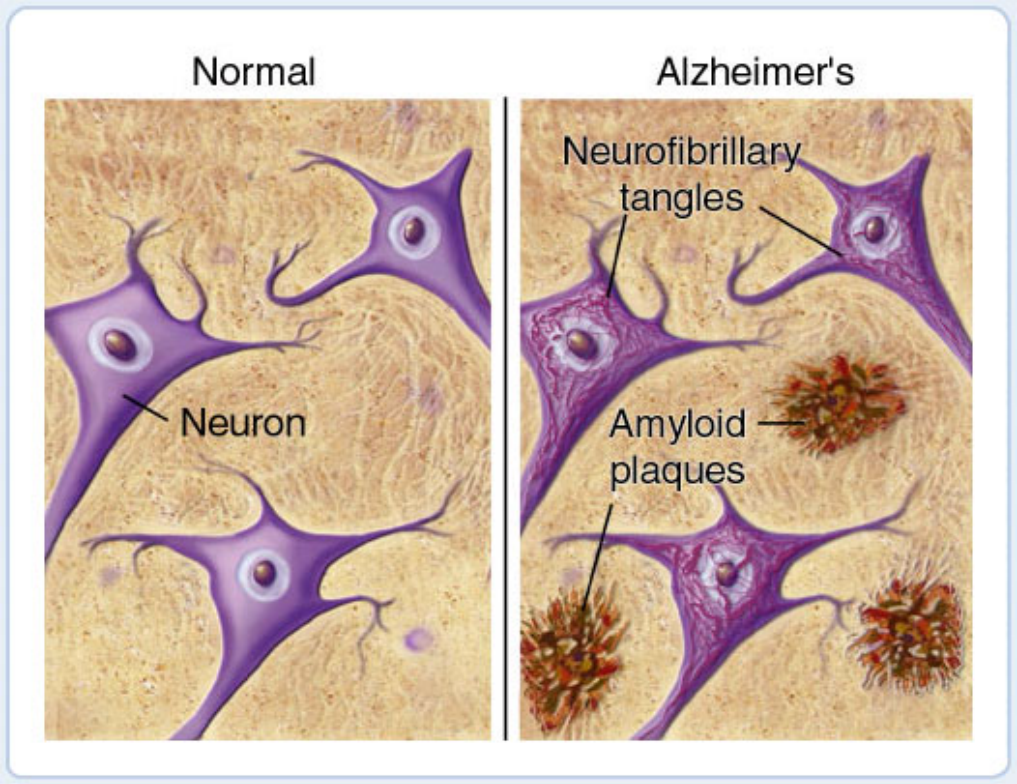
In this talk I present an elementary mathematical model of the diffusion and agglomeration of the β-amyloid (Aβ from now on) in the brain affected by Alzheimer's disease (AD).

The model is based on the classical Smoluchowski equation with diffusion.

I will also show some numerical results from a numerical scheme we implemented for the approximation of the solution. These results are in good agreement with clinical evidence.

The connection with the topics presented in this workshop is not immediate...

Amyloid is a general term for protein fragments that the body produces normally. Aβ is a protein fragment snipped from an amyloid precursor protein (APP). In a healthy brain, these protein fragments are broken down and eliminated. In Alzheimer's disease, the fragments accumulate to form hard, insoluble plaques.



Spatial scale for our description of the phenomena:

- we consider a portion of the hippocampus or of the cerebral cortex (the regions of the brain mainly affected by AD) of size comparable to a multiple of the size of the soma of a neuron.

  We discard:

Spatial scale for our description of the phenomena:

- we consider a portion of the hippocampus or of the cerebral cortex (the regions of the brain mainly affected by AD) of size comparable to a multiple of the size of the soma of a neuron.

We discard:

- the description of intracellular phenomena,

Spatial scale for our description of the phenomena:

- we consider a portion of the hippocampus or of the cerebral cortex (the regions of the brain mainly affected by AD) of size comparable to a multiple of the size of the soma of a neuron.

We discard:

- the description of intracellular phenomena,
- the description of the clinical manifestations of the disease at a macroscopic scale.

The portion of cerebral tissue considered is represented by a bounded connected smooth open region $\Omega_0 \subset \mathbb{R}^3$ (or $\Omega_0 \subset \mathbb{R}^2$), whereas the neurons are represented by a family of M smooth connected open sets Ω_h such that:

- $\overline{\Omega}_h \subset \Omega_0$ for $h = 1, \ldots, M$;

The portion of cerebral tissue considered is represented by a bounded connected smooth open region $\Omega_0 \subset \mathbb{R}^3$ (or $\Omega_0 \subset \mathbb{R}^2$), whereas the neurons are represented by a family of M smooth connected open sets Ω_h such that:

- $\overline{\Omega}_h \subset \Omega_0$ for $h = 1, \ldots, M$;
- $\overline{\Omega}_k \cap \overline{\Omega}_h = \emptyset$ if $k \neq h$.

Our model is meant to describe the evolution of AD *in vivo*.

Thefore the essential features that we want to describe are the following:

- agglomeration phenomena: by means of the so-called Smoluchowski equation;

Our model is meant to describe the evolution of AD *in vivo*.

Thefore the essential features that we want to describe are the following:

- agglomeration phenomena: by means of the so-called Smoluchowski equation;
- uniform (reasonable at our scale) diffusion: by the usual Fourier diffusion equation;

Our model is meant to describe the evolution of AD *in vivo*.

Thefore the essential features that we want to describe are the following:

- agglomeration phenomena: by means of the so-called Smoluchowski equation;
- uniform (reasonable at our scale) diffusion: by the usual Fourier diffusion equation;
- production of Aβ, in the monomeric form, at the level of the neuron's membrane: by a non-homogeneous Neumann condition on $\partial\Omega_h$, $h = 1, \ldots, M$;

Our model is meant to describe the evolution of AD *in vivo*.

Thefore the essential features that we want to describe are the following:

- agglomeration phenomena: by means of the so-called Smoluchowski equation;
- uniform (reasonable at our scale) diffusion: by the usual Fourier diffusion equation;
- production of Aβ, in the monomeric form, at the level of the neuron's membrane: by a non-homogeneous Neumann condition on $\partial\Omega_h$, $h = 1, \ldots, M$;
- isolate our portion of tissue from the environment: by an homogeneous Neumann condition on $\partial\Omega_0$.

Given $t \in \mathbb{R}$, $t \geq 0$ (the time), and $x \in \Omega := \Omega_0 \setminus \bigcup_{h=1}^{M} \overline{\Omega}_h$ (the space), we denote by $u_m = u_m(t, x)$ the(molar) concentration at time t and at point x of an Aβ assembly of m monomers, with $1 \leq m < N - 1$.

Moreover, we denote by u_N the molar concentration of assemblies of more than $N - 1$ monomers (therefore u_N is, by its own nature, slightly different from the others u_m's).

Thus, we are lead to the following Cauchy-Neumann problem for monomers ($m = 1$):

$$\begin{cases} \frac{\partial}{\partial t} u_1 = d_1 \Delta_x u_1 - u_1 \sum_{j=1}^{N} a_{1,j} u_j \\ \qquad \frac{\partial u_1}{\partial \nu} = 0 \quad \text{on } \partial\Omega_0 \\ \frac{\partial u_1}{\partial \nu} = \psi_h \quad \text{on } \partial\Omega_h, h = 1, \ldots, M \\ \qquad u_1(x, 0) = U_1(x) \geq 0, \end{cases} \tag{1}$$

where $0 \leq \psi_h \leq 1$ is a smooth function for $h = 1, \ldots, M$, describing the production of the amyloid near the membrane of the neuron. We only take into account neurons affected by the disease, i.e. we assume $\psi_h \not\equiv 0$ for $h = 1, \ldots, M$.

For oligomers $(1 < m < N-1)$ we have:

$$\begin{cases} \frac{\partial}{\partial t}u_m = d_m \Delta_x u_m - u_m \sum_{j=1}^{N} a_{m,j} u_j + \frac{1}{2} \sum_{j=1}^{m-1} a_{j,m-j} u_j u_{m-j}. \\ \dfrac{\partial u_m}{\partial \nu} = 0 \quad \text{on } \partial\Omega_0 \\ \dfrac{\partial u_m}{\partial \nu} = 0 \quad \text{on } \partial\Omega_h, h = 1, \ldots, M \\ u_m(x, 0) = 0, \end{cases} \tag{2}$$

where $d_m > 0$, $m = 1, \ldots, N-1$ and $a_{i,j} = a_{j,i} > 0$, $i, j = 1, \ldots, N-1$.

Finally for non soluble fibrils ($m = N$) we have:

$$\begin{cases} \frac{\partial}{\partial t} u_N = d_N \Delta_x u_N + \frac{1}{2} \sum_{j+k \geq N, k<N, j<N} a_{j,k} u_j u_k. \\ \frac{\partial u_N}{\partial \nu} = 0 \quad \text{on } \partial\Omega_0 \\ \frac{\partial u_N}{\partial \nu} = 0 \quad \text{on } \partial\Omega_h, h = 1, \ldots, M \\ u_N(x, 0) = 0, \end{cases} \tag{3}$$

where $d_N > 0$ and $a_{i,j} = a_{j,i} > 0$, $i, j = 1, \ldots, N$ (but $a_{N,N} = 0$).

Concerning the last term in the equation, notice that:

$$\frac{1}{2} \sum_{j+k \geq N, k<N, j<N} a_{j,k} u_j u_k = \frac{1}{2} \sum_{j+k \geq N} a_{j,k} u_j u_k - u_N \sum_{j=1}^{N} a_{N,j} u_j. \tag{4}$$

Since u_N describes the sum of the densities of all the "large" assemblies, we assume that:

1) large assemblies exhibit all the same coagulation properties;

2) large assemblies do not coagulate with other large assemblies ($a_{N,N} = 0$).

This last assumption is meant to prevent blow-up phenomena for solutions at a finite time, but is also coherent with experimental data.

Peculiarity of this model:

The non-homogeneous Neumann boundary conditions for monomers implies that we do not have mass conservation; due to this lack some estimates provided in the literature in the homogeneous case fail to hold.

We have therefore to adapt some classical techniques to our situation, relying on a repeated use of the classical parabolic maximum principle.

Results:

To avoid technicalities, we assume $U_1 \in \mathbf{C}^{2+\alpha}(\bar{\Omega})$ for some $\alpha \in (0,1)$, and $\frac{\partial U_1}{\partial \nu} = \psi_h$ on $\partial\Omega_h$, $h = 0, \ldots, M$.

We have (local existence):

Proposition

If $u = (u_1, \ldots, u_N)$, *there exists* $\tau_{\max} > 0$ *such that problem* (1)-(3) *has a local classical maximal solution* $u \in \mathbf{C}^{2+\alpha,1+\alpha/2}(\bar{\Omega} \times [0,\tau])$ *for every* $\tau \in (0, \tau_{\max})$.

Proposition

If $u = (u_1, \ldots, u_N)$ *is a solution of problems* (1)-(3), *then* $u_m > 0$ *in* $\bar{\Omega} \times (0, \tau_{\max},)$ *for* $m = 1, \ldots, N$.

Proposition

We have $\tau_{\max} = +\infty$.

The proof uses (repeatedly) the parabolic maximum principle.

Proposition

For any $T > 0$ we have

$$\lambda_T := \inf_{\Omega \times (T,\infty)} u_N > 0. \tag{5}$$

Moreover

$$\phi_N(t) := \fint_\Omega u_N(t,x)\,dx \to \infty \quad as\ t \to \infty. \tag{6}$$

Since $u_N(t,\cdot)$ describes the plaques, (5) states basically that plaques form extraordinarily quickly (this corresponds to the experimental evidences); while (6) states that the average of the insoluble fibrillar form grows and we eventually obtain thick plaques.

Another estimate on the asymptotic behaviour of the concentration of soluble (short) fibrils is the following:

Proposition

If we set

$$\Phi(t) := \sum_{m=1}^{N-1} \fint_{\Omega} m u_m(t,x)\, dx,$$

then there exists $a > 0$ *such that for* $t > 1$ *we have*

$$\Phi(t) \leq e^{-a\lambda_1(t-1)}\Phi(1) + \frac{d_1 \sum_{h=1}^{M} \int_{\partial\Omega_h} \psi_h \, d\mathcal{H}^{n-1}}{a\lambda_1 |\Omega|}(1 - e^{-a\lambda_1(t-1)}). \tag{7}$$

Our numerical simulations suggest that the estimate (7) can be considered asymptotically optimal, in the sense that the numerical experiments show that there exist positive constants $\ell_1, \ldots, \ell_{N-1}$ such that

$$\fint_\Omega m u_m(t,x)\,dx \to \ell_m \quad \text{as } t \to \infty,$$

for $m = 1, \ldots, N-1$.

In other words, the concentration of soluble oligomers stabilizes, whereas we have seen before that the average of the insoluble fibrillar form grows (see (6)) and we eventually obtain thick plaques.

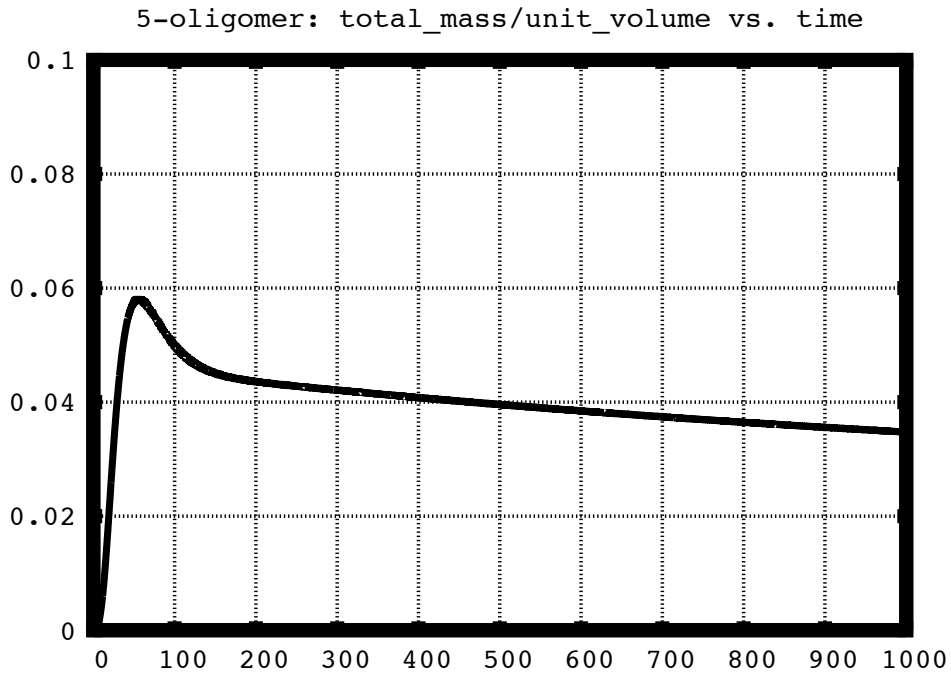


Figure: Total mass of 5-oligomers with $N = 16$, $\alpha = 10$, $U_1 \equiv 0$, $\psi = 0.5$.

The production of the amyloid does not stop ($\psi = 0.5$), but the total mass stabilizes around a positive value. The slope of the graph is very small, since only very small production of monomers prevents the death of neurons.

Numerical simulation

In the numerical simulation presented, we have not been interested in the precise quantitative matching of our results with clinical data (that is far from our current reach), but rather in producing qualitative outputs that stress interesting features of the phenomena and asymptotic behaviors in particular.

Therefore, for sake of simplicity, we assume that Ω_0 is a square in the plane, and that the neurons are periodically distributed in Ω_0. We then look for periodic solutions $u_m(t, \cdot)$.
Eventually, without loss of generality, we replace the periodic problem by a problem in a single cell perforated by a single disk, with periodic lateral conditions.

Another simplification of our numerical simulation consists in taking the same diffusion coefficient up to N_1-polymers (i.e. assuming $d_1 = d_2 = \cdots = d_{N_1} := 1$), whereas, for sake of simplicity, we choose $d_m = 0$ for $m > N_1$.

Concerning the coagulation rates (the coefficients $a_{i,j}$) we use the following form:

$$a_{i,j} = \alpha \, \frac{1}{ij} \quad \text{where } \alpha > 0, \tag{8}$$

consistent with our assumption that big assemblies do not aggregate with other big assemblies.

Plaque grown near a neuron. The picture has been obtained by taking the higher level sets of $u_N(t,\cdot)$; that is we identify senile plaques with the sets $\{x \ : u_N(t,x) > c > 0\}$.

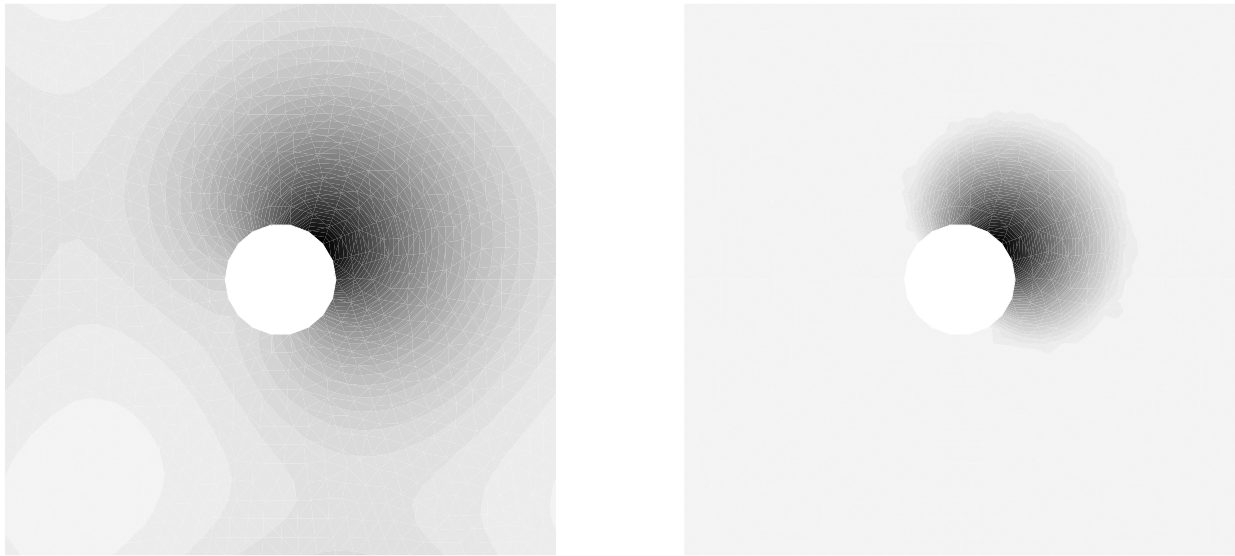


Figure: Plaque generated with $N = 16$, $\alpha = 10$, $U_1 \equiv 0$, $\psi = 0.5$. Left: full plot. Right: only the set $u_N > 0.3$ is presented, to show the shape of the senile plaque.

Recent experimental results have suggested that the plaque counting is a poor measure of the severity of the AD, and that levels of soluble Aβ correlate much better with the presence and degree of cognitive deficits than do simple plaque counts.

Even more, "the idea that large aggregates of a disease causing protein can actually be inert or even protective to neurons has been supported by work on other protein folding disorders".

To closely fit these clinical evidences, we have have slightly modified the numerical simulation of the model by assuming the existence of a threshold $\kappa > 0$ such that, as long as the global amount of soluble amyloid remains below κ, then the production of Aβ from the neuronal membrane is positive, but, when this amount exceeds κ, the neuron dies and consequently the production stops.

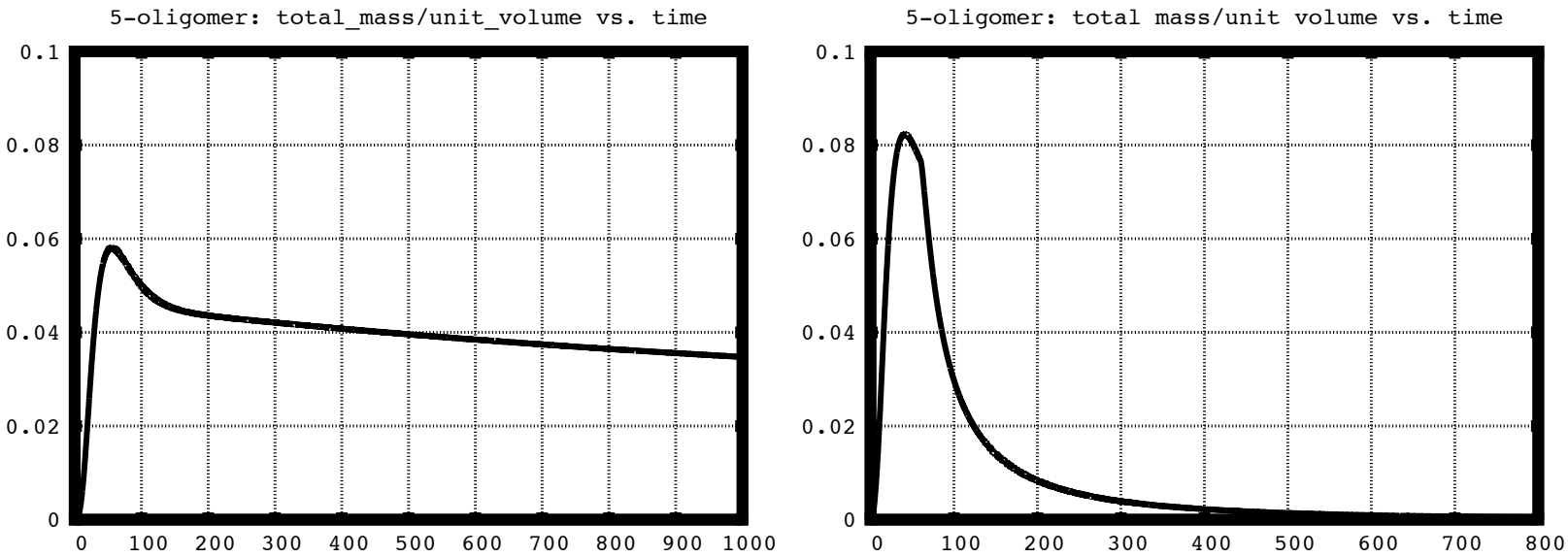


Figure: Total mass of 5-oligomers with $N = 16$, $\alpha = 10$, $U_1 \equiv 0$, $\kappa = 0.7$. Left: $\psi = 0.5$. Right: $\psi = 1.0$.

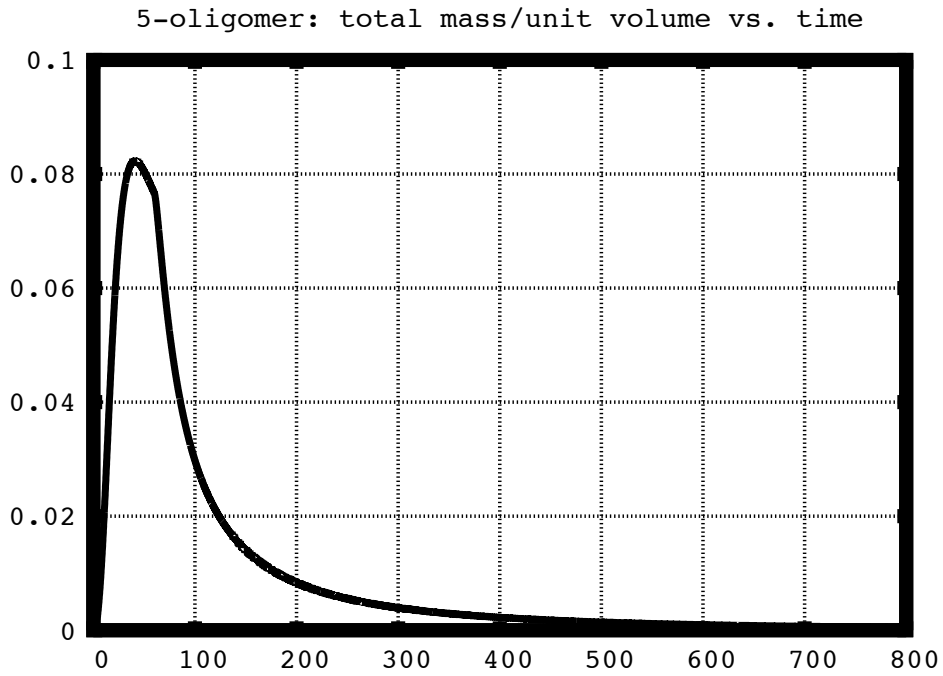


Figure: Total mass of 5-oligomers with $N = 16$, $\alpha = 10$, $U_1 \equiv 0$, $\psi = 1.0$, $\kappa = 0.7$.

Due to the higher (with respect to the threshold) production of monomers ($\psi = 1.0$), the neuron dies and quickly the total mass of soluble oligomers vanishes. This corresponds to the clinical experience of advanced AD.

In this model we deliberately ignored the action of astrocytes and microglia on the agglomeration and diffusion of Aβ amyloid, on the neuronal death and on the formation of plaques.

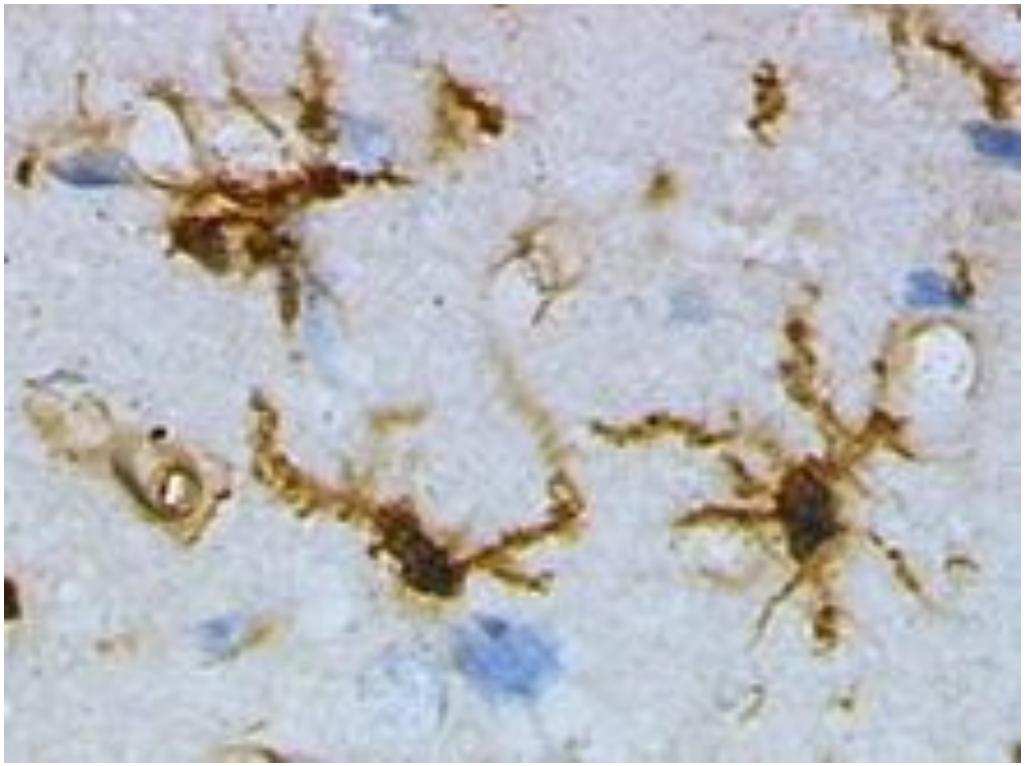


Figure: Microglia's cells

Future goal: try to incorporate in the model, in some appropriate way, these factors...