Sorbonne Université

Rapport de stage

main 5

Numerical simulations on the Smoluchowski equations

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Contents

1 Introduction

The Smoluchowski equation is a system of partial differential equations which describes the evolving densities of diffusing particles that are prone to coagulate in pairs. Here, we consider a set of Smoluchowski's discrete diffusion–coagulation equations to describe the aggregation and diffusion of β-amyloid peptide ($A\beta$), a process associated with the development of Alzheimer's disease.
It is well known that $A\beta$ peptide plays an important role in the process leading to neuronal death. The presence of $A\beta$ in the cerebral tissue is normal but by unknown reasons we can observe in some neurons an imbalance between production and clearance of $A\beta$ during aging. At elevated levels, it produces pathological aggregates : an accumulation of deposits known as senile plaques.
The mathematical model considered comes from ref paper. The model presented describes the aggregation and diffusion of β-amyloid in the brain affected by Alzheimer's disease at a micrcoscopic scale (the size of a single neuron) and at the early stage of the disease when small amyloid fibrils are free to move and to coalesce.

In this work we perform numerical simulations on this model in order to better understand the evolution of Alzheimer's disease in the brain. The difficulty of the work rests on the method used for the time discretisation since we have a set of time dependent nonlinear coupled equations.

the report is organised as follows : ...

2 Mathematical model for the aggregation and diffusion of β-amyloid peptide

2.1 Smoluchowski equation in polymerisation

The Smoluchowski coagulation equation models various kinds of phenomena as, for example: the evolution of a system of solid or liquid particles In view of our subsequent applications, we present the appearance of the Smoluchowski equation in polymerisation.
Let P_k for $k \in N$ denote a polymer of size k : a set of k identical particles (monomers). With time, if two polymers are very close, they are likely to merge creating a new polymer. By convention we consider only binary reactions. This phenomenon is called coalescence and we write the coalescence of a polymer of size k with polymer of size j :

$$P_k + P_j \rightarrow P_{k+j}$$

Restrictions of the model studied:
We assume that the aggregation results only from Brownian movement or diffusion (ther-

mal coagulation). We neglect other effects such as multiple coagulation, condensation, fragmentation...
Under theses assumptions we can introduce the discrete diffusive coagulation equations :

$$\frac{\partial u_i}{\partial t}(t,x) - d_i \triangle_x u_i(t,x) = Q_i(u) \quad \text{in } [0,T] \text{ x } \Omega \tag{1}$$

where :

- $u_i(t,x) \geq 0$ (for $i \geq 1$) : is the variable representing the concentration of i-clusters : clusters with i identical elementary particles
- $d_i > 0$ (for $i \geq 1$) : denotes the diffusion coefficient of an i-cluster
- $Q_i(u) \quad i \geq 1$: is the coagulation term where $u = (u_i)_{i \geq 1}$, it equals :

$$Q_i(u) = Q_{g,i}(u) - Q_{l,i}(u) \tag{2}$$

  - where the gain term $\quad Q_{g,i} = \frac{1}{2} \sum_{j=1}^{i-1} a_{i-j,j} u_{i-j} u_j$

    describes the creation of polymers of size i by coagulation of polymers of size j and $i-j$ (clusters of size $\leq i-1$).
  - and the loss term $\quad Q_{l,i} = u_i \sum_{j=1}^{\infty} a_{i,j} u_j$

    describes the depletion (reduction) of polymers of size i after coalescence with other polymers.
  - At last, the coagulation rates $a_{i,j}$ are non nonnegative constants such that $a_{i,j} = a_{j,i}$. $a_{i,j}$ is a kinetic coefficient that represents the reaction in which an $(i+j)$-cluster is formed from an i and a j-cluster.

2.2 Mathematical model studied

2.2.1 Parameters of the microscopic model

In the mathematical model presented in ref paper the authors consider a portion of the hippocampus or of the cerebral cortex (the regions of the brain mainly affected by the disease) whose size is comparable of the size of a neuron. With this choice of scale, it is coherent to consider that the diffusion is uniform. Moreover, it is assumed that 'large' assemblies do not aggregate with each other (which is consistent with experimental data). In the following we consider a perforated domain Ω which represents a portion of cerebral tissue where the neurons are represented by holes such that :

- $\Omega_0 \subset \mathbb{R}^3$: is a smooth bounded domain representing a portion of **cerebral tissue**
- $\overline{\Omega}_j \subset \Omega_0$ with $j = 1...N$: are regular regions representing N **neurons**
- $\overline{\Omega}_i \cap \overline{\Omega}_j = \emptyset$ if $i \neq j$: condition imposing that two neurons cannot intersect

$$\Omega := \Omega_0 \setminus \cup_{j=1}^{N} \overline{\Omega}_j$$

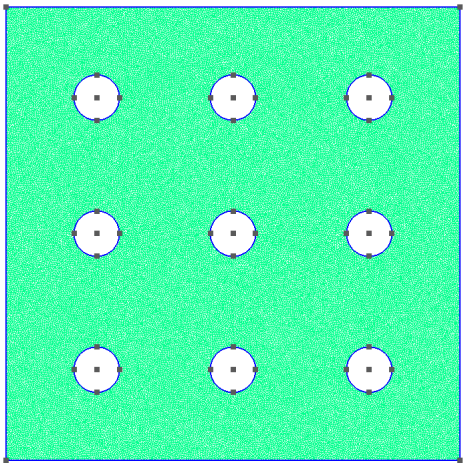

Figure 2: Representation in $\mathbb{R}^2$ for N=9 neurons

We consider a vector valued function $u = (u_1, ..., u_M$ where $M \in \mathbb{N}$ and $u_j = u_j(t, x), t \in \mathbb{R}, x \in \Omega$.

- If $1 \leq j \leq M - 1$: $u_j(t, x)$ is the molar concentration at point x and time t of an $A\beta$ assembly of j monomers.
- u_M : takes into account aggregations of more than $M - 1$ monomers ('large' assemblies)

2.2.2 The microscopic model

$A\beta$'s concentration in monomeric form

In the model we consider that $A\beta$ is produced only in monomeric form at the level of neuron membranes. This production is modeled by a non-homogeneous Neumann condition on the boundary of each neuron Ω_j : $\partial\Omega_j$ for $j = 1, ..., N$.
We also impose an homogeneous Neumann conditon on $\partial\Omega_0$ to artificially isolate the portion of cerebral tissue from its environment.
Finally at time $t = 0$, we consider that there can be an initial concentration of $A\beta$ monomers.

Thus, the following Cauchy-Neumann problem can be defined :

$$\begin{cases} \frac{\partial u_1}{\partial t}(t,x) - d_1 \triangle_x u_1(t,x) - Q_{l,1}(u) = 0 & \\ \nabla_x u_1.n = 0 & \text{on } \partial\Omega_0 \\ \nabla_x u_1.n = \Psi_j & \text{on } \partial\Omega_j,\ j = 1...N \\ u_1(0,x) = U_1 \geq 0 & \end{cases} \tag{3}$$

where $0 \leq \psi_j \leq 1$ is a smooth function for $j = 1...N$ describing the production of the amyloid near the neuron membrane j . The production of $A\beta$ is not uniform over the neuronal cells, the distribution is defined by the choice of the functions ψ_j. Moreover, only neurons affected by the disease are taken into account, i.e, $\psi_j \neq 0$.
We also have $Q_1(u) = -Q_{l,1}(u) = u_1 \sum_{j=1}^{M} a_{i,j} u_j$. There is only loss since we cannot create monomers by coagulation.

$A\beta$'s concentration in assemblies

For assemblies of size $1 < m < M$,

$$\begin{cases} \frac{\partial u_m}{\partial t}(t,x) - d_m \triangle_x u_m(t,x) + Q_{l,m}(u) = Q_{g,m}(u) & \\ \nabla_x u_m.n = 0 & \text{on } \partial\Omega_0 \\ \nabla_x u_m.n = 0 & \text{on } \partial\Omega_j,\ j = 1...N \\ u_m(0,x) = 0 & \end{cases} \tag{4}$$

where $Q_m(u) = Q_{g,m}(u) - Q_{l,m}(u) = \frac{1}{2} \sum_{j=1}^{i-1} a_{i-j,j} u_{i-j} u_j - u_i \sum_{j=1}^{M} a_{i,j} u_j$.

And,

$$\begin{cases} \frac{\partial u_M}{\partial t}(t,x) - d_M \triangle_x u_M(t,x) = Q_{g,M}(u) & \\ \nabla_x u_M.n = 0 & \text{on } \partial\Omega_0 \\ \nabla_x u_M.n = 0 & \text{on } \partial\Omega_j,\ j = 1...N \\ u_M(0,x) = 0 & \end{cases} \tag{5}$$

where $Q_M(u) = Q_{g,M}(u) = \frac{1}{2} \sum_{\substack{j+k \geq M \\ k<M \\ j<M}} a_{j,k} u_j u_k$

The meaning of u_M differs from that of u_m, $m < M$, since it describes the sum of the densities of all the 'large' assemblies. It is assumed that large assemblies exhibit all the same coagulation properties and do not coagulate with each other. That is why the expression of the coagulation term differs from the other assemblies : there is no loss and the gain term takes also into the aggregation of assemblies $< M$ creating assemblies of size M and greater than M.
The existence of a solution is given by the following theorem obtained in ref book in article bnuro franchi :

Theorem For all $T > 0$ the Neumann-Cauchy problem (3), (4), (5) has a unique classical positive solution $u \in C^{1+\alpha/2,2+\alpha}([0,T]\text{x}\overline{\Omega})$ alpha from coagulation rates.

3 Numerical method

3.1 Variational formulation

Let V be a Sobolev space and $v \in V$ a test function. Let's multiply by v the coagulation diffusion equation and integrate on Ω. For all u_i with $i = 1...M$:

$$\int_\Omega \frac{\partial u_i}{\partial t} \cdot v - d_i \int_\Omega \Delta u_i \cdot v = \int_\Omega Q_i v \quad \text{on } \Omega$$

Then applying the Green theorem we have :
For $i = 1$ (a non-homogeneous Neumann condition around the neurons):

$$\int_\Omega \Delta u_1 \cdot v = -\int_\Omega \nabla u_1 \nabla v + \int_{\partial\Omega} \underbrace{(\partial_n u_1)}_{=\Psi_j \text{ on } \partial\Omega_j} \quad v \quad \text{on } \Omega$$

$$\implies \int_\Omega \frac{\partial u_1}{\partial t} \cdot v + d_1 \int_\Omega \nabla u_1 \cdot \nabla v = \int_\Omega Q_1(u)v + \sum_{j=1}^{N} \int_{\partial\Omega_j} \Psi_j v \quad \text{on } \Omega \tag{6}$$

For $i > 1$, $i = 2...M$ (only homogeneous Neumann conditions) :

$$\int_\Omega \frac{\partial u_m}{\partial t} \cdot v + d_m \int_\Omega \nabla u_m \cdot \nabla v = \int_\Omega Q_m(u)v \quad \text{on } \Omega \tag{7}$$

We define the usual L^2-inner product $(u,v) = \int_\Omega uvdx \ \forall u, v \in L^2(\Omega)$ and the elliptic bilinear form $a(u,v) = \int_\Omega \nabla u \cdot \nabla v$.

The variational formulation reads as follows :

$$\forall v \in V \quad \frac{\partial}{\partial t}(u_m, v) + d_m a(u_m, v) = \begin{cases} (Q_1(u), v) + \int_{\partial\Omega_{j=1...N}} \Psi_j v, & \text{if } m = 1 \\ (Q_m(u), v) & \text{otherwise} \end{cases} \tag{8}$$

3.2 Space discretisation

The system ref system ?? is first discretised in space by the finite element method. In this work we will consider a space Ω of dimension 2. Let T_h be a triangulation of Ω having maximal diameter h and V_h be an associated conforming finite element space. In this work, we will consider $\mathbb{P}_1$-Lagrangian finite elements. We define a finite element basis $(\phi_i)_{i=1..N_s}$ of V_h such that u_m for $m = 1..M$ is approximated by $u_{h,m} = \sum_{i=1}^{N_s} x_m(s_i)\phi_i$.

Appearance mass matrix + stiffness matrix

Rewrite variational formulation with M + D

Space definition

In order to define V_h we first define the space of $\mathbb{P}_1$-Lagrangian functions that is a space of dimension 3 with degree 1 polynomials on ω ($\omega \subset \mathbb{R}^2$) :

$$\mathbb{P}_1(\omega) = \{p|_\omega \quad |\exists a, b, c \in \mathbb{R} \quad |\forall (x, y) \in \omega, p(x, y) = ax + by + c\}$$

We can now construct the space of $\mathbb{P}_1$-Lagrangian functions of functions locally $\mathbb{P}_1$ on each triangle. The space V_h of $\mathbb{P}_1$-Lagrangian functions associated to the triangulation T_h is defined by :

$$V_h = \{v \in C^0(\overline{\Omega}) \quad | \quad v|_K \in \mathbb{P}_1(K) \text{ for all triangle } K \in T_h\}$$

Properties of the basis $(\phi_i)_{i=1..N_s}$:

$$\forall i, j = 1, \dots N_s, \quad \phi j(s_i) = \delta_{i,j} = \begin{cases} 1 & \text{if } i = j \\ 0 & \text{otherwise.} \end{cases} \tag{9}$$

Discretising the coagulation term

$Q(u)$ is a non linear term. It is a sum of terms t_z ($z \in \mathbb{N}$) of the form $t_z = a_{i,j} u_i * u_j$ with $1 \leq i, j \leq M$. Replacing u_i and u_j by $u_{h,i} = \sum_k x_k \phi_k$ and $u_{h,j} = \sum_l x_l \phi_l$, we obtain :

$$t_z(x, y) = \sum_{k=1}^{N_s} \sum_{l=1}^{N_s} x_i(s_k) x_j(s_l) * \phi_k(x, y) \phi_l(x, y)$$

Thanks to propriety (9) we know that on the nodes s_y ($y = 1...N_s$) of the triangulation T_h, t_z simply equals :

$$t_z(s_y) = a_{i,j} x_i(s_y) * x_j(s_y) \tag{10}$$

So if we project the function t_z on V_h we have :

$$t_{h,z}(x, y) = \sum_{y=1}^{N_s} a_{i,j} x_i(s_y) x_j(s_y) \phi_y(x, y)$$

Therefore, to calculate the function Q(u) easily we approximate its value by its projection on V_h. It will be seen further on that choosing an appropriate integration quadrature formula will still lead to on an exact result for $\mathbb{P}_1$ elements.

Choice quadrature formula :
quadrature formula on a triangle : Mass lumped matrix -> exact for P1
quadrature formula on an edge : utile ?? -> exact for P1

3.3 Time discretisation

3.3.1 Euler implicit scheme

3.3.2 Cranck-Nicholson scheme

3.3.3 Picard iteration

4 Conclusion