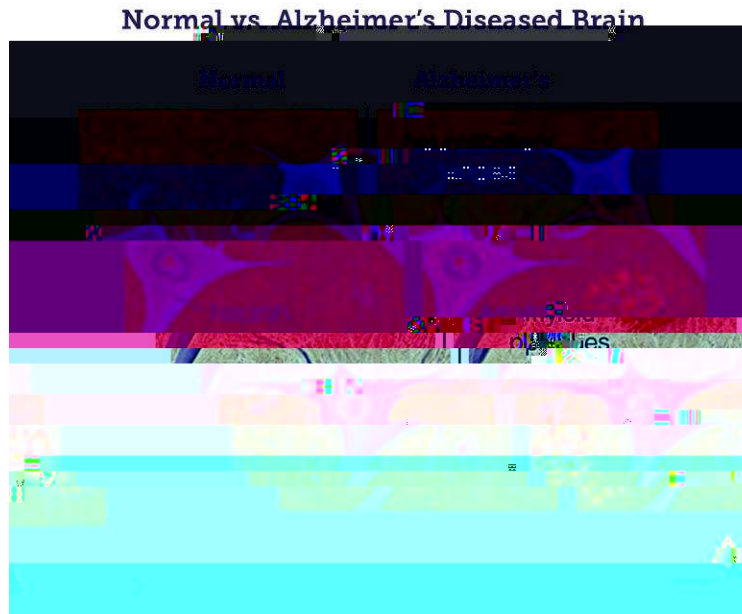


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Alzheimer Disease (AD)



Alzheimer disease is characterized pathologically by the formation of senile plaques composed of β -amyloid peptide (A β). A β is naturally present in the brain and cerebrospinal fluid of humans throughout life. By unknown reasons (partially genetic), some neurons start to present an imbalance between production and clearance of A β amyloid during aging. **Therefore, neuronal injury is the result of ordered A β self-association.**

Under these assumptions, the discrete diffusive coagulation equations read

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

where Q is the spatial domain and $[0, T]$ a time interval.

The variable $u_i(t, x)$ is the concentration of particles of size i at time t and position x .

A Mathematical Model for the Aggregation and Diffusion

of β -Amyloid Peptide

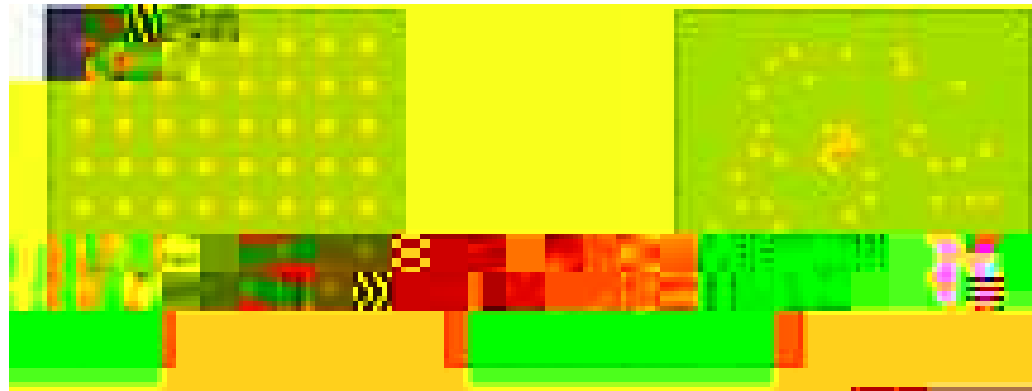


Figure 1: Periodically (left) and randomly (right) perforated domains.

In the present work, we account for the non-periodic cellular structure of the brain.

The distribution of neurons is modeled in the following way: there exists a family of predominantly genetic causes, not wholly deterministic, which influences the position of neurons and the microscopic structure of the parenchyma in a portion of the brain tissue Q .

We consider **non-periodic random diffusion coefficients** and a **random production of A** in the monomeric form at the level of neuronal membranes.

This together defines **a probability space** $(\Omega, \mathcal{F}, \mathbb{P})$.

Denoting by ω the random variable in our model, the set of random holes in \mathbb{R}^d (representing the neurons) is labeled by $G(\omega)$.

The production of β -amyloid at the boundary $\partial G(\omega)$ of $G(\omega)$

if $1 < s < M$

$$\frac{\mathbf{u}_s}{t} - \operatorname{div}(\mathbf{D}_s(\mathbf{t}, \mathbf{x}, \nabla_x \mathbf{u}_s) + \mathbf{u}_s \sum_{j=1}^M \mathbf{a}_{s j} \mathbf{u}_j) = \frac{1}{2} \sum_{j=1}^{s-1} \mathbf{a}_{j s-j} \mathbf{u}_j \mathbf{u}_{s-j} \quad \text{in } [0, T] \times Q$$

$$[\mathbf{D}_s(\mathbf{t}, \mathbf{x}, \nabla_x \mathbf{u}_s)] \cdot \mathbf{n} = 0 \quad \text{on } [0, T] \times \partial Q$$

$$[\mathbf{D}_s(\mathbf{t}, \mathbf{x}, \nabla_x \mathbf{u}_s)] \cdot \boldsymbol{\nu}_{\Gamma_Q} = 0 \quad \text{on } [0, T] \times \Gamma_Q$$

$$\mathbf{u}_s(0, \mathbf{x})$$

We assume that the movement of clusters results only from a **diffusion process** described by a **stationary ergodic random matrix**

$$d_{i,j}^s(\mathbf{t}, \mathbf{x}, \underline{x})_{i,j=1}^M =: \mathbf{D}_s(\mathbf{t}, \mathbf{x}, \underline{x}) \quad 1 \leq s \leq M$$

where $(\mathbf{t}, \mathbf{x}) \in [0, T] \times Q$.

The production of β -amyloid peptide by the malfunctioning neurons is described imposing a non-homogeneous Neumann condition on the boundary of the holes, randomly selected within our domain.

To this end, we consider on Q a **stationary ergodic random function**

$$: [0, T] \times \overline{Q} \times [0, 1] \quad (8)$$

where the value '0' is assigned to 'healthy' neurons while all the other values in $]0, 1]$ indicate different degrees of malfunctioning.

Moreover, we assume that is an increasing function of time, since once the neuron has become 'ill', it can no longer regain its original state of health.

Stationary ergodic dynamical systems

Definition 1 (**Dynamical system**). Let $(X, \mathcal{F}, \mathbb{P})$ be a probability space. An **invariant dynamical system** is defined as a family of measurable bijective mappings $T_x : X \rightarrow X$ satisfying the following conditions

(1) **Group property** $T_0 = \text{id}$ and $T_x T_y = T_{x+y}$ for $x, y \in \mathbb{R}$
 (2) **Stationarity** the mappings T_x preserve the measure \mathbb{P} on \mathcal{F} for every $x \in \mathbb{R}$
 and every \mathcal{F} -measurable set $A \in \mathcal{F}$ we have $\mathbb{P}(T_x^{-1}A) = \mathbb{P}(A)$

(3) **Product space** (X, \mathcal{F}) is measurable for the standard Borel σ -algebra on \mathbb{R} where \mathbb{R} is equipped with the Borel σ -algebra.

Definition 2 (**Ergodicity**). A dynamical system is called **ergodic** if one of the following equivalent conditions is fulfilled

(1) **Trivial invariant functions** given a measurable and invariant function $f : X \rightarrow \mathbb{R}$ it holds that

$$f(T_x \omega) = f(\omega) \quad \text{for } \mathbb{P}\text{-a.e. } \omega \in X$$

almost everywhere then

$$f(\omega) = \text{const} \quad \text{for } \mathbb{P}\text{-a.e. } \omega \in X$$

(2) **0-1 Law** $f : X \rightarrow \mathbb{R}$ is measurable and invariant then $\mathbb{P}(f = 0) = 0$ or $\mathbb{P}(f = 1) = 1$

Definition 3 (**Stationarity**). Given a probability space $(\Omega, \mathcal{F}, \mathbb{P})$ a real valued process is a measurable function $\mathbf{f} : \mathbb{R} \times \Omega \rightarrow \mathbb{R}$ we say \mathbf{f} is stationary if the distribution of $\mathbf{f}(t, \cdot) : \Omega \rightarrow \mathbb{R}$

Let $L^p(\Omega, \mathcal{F}, \mathbb{P})$ ($1 \leq p < \infty$) denote the space formed by (the equivalence classes of) measurable functions that are \mathbb{P} -integrable with exponent p and L .

One important property of random measures is the following generalization of the Birkhoff ergodic theorem

Concerning the random geometries, we make the assumptions listed below.

Definition 4. An open set $G \subset \mathbb{R}^d$ is said to be *minimally smooth* w.r.t. constants (ϵ, N, M) if we may cover G by a countable sequence of open sets $(U_i)_{i \in \mathbb{N}}$ such that

- (i) Each $x \in \mathbb{R}^d$ is contained in at most N of the open sets U_i .
- (ii) For any $x \in \mathbb{R}^d$ the ball $B_\epsilon(x)$ is contained in at least one U_i .
- (iii) For any i the portion of the boundary inside U_i admits in some Cartesian system of coordinates, with the help of a Lipschitz function whose Lipschitz constant is at most M .

Let Q be a bounded domain in \mathbb{R}^d . For given constants (ϵ, N, M) , we consider $G(\cdot)$ a random open set which is a.s. *minimally smooth* with constants (ϵ, N, M) (uniformly minimally smooth).

We furthermore assume that $G(\cdot) := \bigcup_{i \in \mathbb{N}} G_i(\cdot)$ is a countable union of disjoint open balls $G_i(\cdot)$ with a maximal diameter d_0 .

We consider $G(\cdot) := G(\cdot)$ and

$$Q(\cdot) := Q \setminus$$

Stochastic two-scale convergence

Definition 5. Let $(\varphi_i)_{i \in \mathbb{N}}$ be a countable dense family of $\mathbf{C}_b(\cdot)$ functions
 $\mathcal{Q} = (\varphi_i)_{i \in \mathbb{N}}$ be a countable dense subset of $\mathbf{C}(\overline{Q})$, Ψ set of measures, and
 $\mathbf{u} \in \mathbf{L}^2(0, T; \mathbf{L}^2(Q))$ for a $\delta > 0$

we say that \mathbf{u}

Domains with holes

Lemma 7. Let $\mathbf{u} \in L^2(Q)$ be a sequence of functions such that $\sup_0 \|\mathbf{u}\|_{L^2(Q)} < \infty$. If $(\mathbf{u}^{j_k})_{k \in \mathbb{N}}$ is a subsequence such that $\mathbf{u}^{j_k} \rightharpoonup^* \mathbf{u}$ for some $\mathbf{u} \in L^2(Q; L^2(\Omega))$ then $\mathbf{u} \in G^0 \mathbf{u}^{2s}$.

Lemma 8. Let $\mathbf{u} \in L^2(0, T; H^1(Q(\cdot)))$ be a sequence of functions such that

$$\sup_0 \|\mathbf{u}\|_{L^2(0, T; H^1(Q(\cdot)))} + \|\mathbf{u}\|_{L^2(0, T; L^2(Q(\cdot)))} < \infty.$$

then there exist functions $\mathbf{u} \in L^2(0, T; H^1(Q))$ with $\|\mathbf{u}\|_{L^2(0, T; L^2(Q))} < \infty$ and $\mathbf{v} \in L^2(0, T; L^2(Q; L^2_{\text{pot}}(\Omega)))$ such that $\mathbf{u} \rightharpoonup^* \mathbf{u}$ weakly in $L^2(0, T; H^1(Q))$ and $\mathbf{E} \mathbf{u} \rightharpoonup^* \mathbf{u}$ strongly in $L^2(0, T; L^2(Q))$ as well as

$$\mathbf{u}^{2s} \in G^0 \mathbf{u}, \quad \|\mathbf{u}^{2s}\|_{G^0} \leq \|\mathbf{u}\|_{G^0}, \quad \text{and} \quad \mathbf{u}^{2s} \in G^0 \mathbf{u} + G^0 \mathbf{v}.$$

Homogenization

We obtain the following “deterministic” (i.e. for fixed ϵ) existence and regularity result.

Theorem 2. Suppose a \bar{u} satisfies the assumptions on our random data and $\epsilon > 0$. Then for \mathbb{P} -a.e. ω and for any $\epsilon > 0$ the system (\bar{u}, ϵ) admits a unique axisymmetric solution

$$\mathbf{u} = (\mathbf{u}_1, \dots, \mathbf{u}_M)$$

such that

ϵ there exists $(0, 1)$ depending on ϵ

In the sequel we shall rely on the fact that statements that hold \mathbb{P} -a.e. can be seen as deterministic assertions, since they hold whenever Q

Main statement

Theorem 5. Let $\underline{u}_s(\mathbf{t}, \mathbf{x})$ $1 \leq s \leq M_i$ be a family of nonnegative continuous functions to the system $(\mathcal{I}, \mathcal{P}_i)$

Denote by a time extension by zero outside Q (and let G^0 represent the characteristic function of the random set G^0 where G^0 is the complement of G represent the set of random nodes $n \in \mathbb{R}_i$

then the sequences \underline{u}_s $\widetilde{x \underline{u}_s}$ and $\widetilde{t \underline{u}_s}$ $1 \leq s \leq M_i$ stochastic processes converge to $[G^0 \underline{u}_s(\mathbf{t}, \mathbf{x})]$ $[G^0(\underline{x \underline{u}_s(\mathbf{t}, \mathbf{x}) + \mathbf{v}_s(\mathbf{t}, \mathbf{x})}]$ $[G^0 t \underline{u}_s(\mathbf{t}, \mathbf{x})]$ $1 \leq s \leq M_i$ respectively

and the functions $[(\mathbf{t}, \mathbf{x})$

If $s = 1$:

$$\begin{aligned} & -\frac{\mathbf{u}_1}{t}(\mathbf{t}, \mathbf{x}) - \operatorname{div}_x \mathbf{D}_1(\mathbf{t}, \mathbf{x}) \mathbf{u}_1(\mathbf{t}, \mathbf{x}) \\ + \mathbf{u}_1(\mathbf{t}, \mathbf{x}) \sum_{j=1}^M \mathbf{a}_{1j} \mathbf{u}_j(\mathbf{t}, \mathbf{x}) &= \int_{\Omega} \Gamma_{\mathbb{G}\mathbb{E}}(\mathbf{t}, \mathbf{x}, \cdot) d\mu_{\Gamma, \mathcal{P}}(\cdot) \quad \text{in } [0, T] \times Q \\ [\mathbf{D}_1(\mathbf{t}, \mathbf{x}) \mathbf{u}_1 & \end{aligned}$$

Proof of the main Theorem.

In view of the previous Theorems, the sequences

$\{\widetilde{\mathbf{u}}_s\}_0$, $\{\widetilde{x\mathbf{u}}_s\}_0$ and $\{\frac{\widetilde{\mathbf{u}}_s}{t}\}_0$ ($1 \leq s \leq M$) are bounded in $L^2([0, T])$

In the case when $s = 1$, let us multiply the first equation of (5) by the test function φ . Integrating, the divergence theorem yields

$$\int_0^T \int_{\Omega} \frac{u_1}{t} (\mathbf{t}, \mathbf{x}, \mathbf{dx dt}) + \int_0^T \int_{\Omega} \mathbf{D}_1(\mathbf{t}, \mathbf{x}, \mathbf{x} u_1, \mathbf{dx dt}) + \int_0^T \int_{\Omega} \mathbf{u}_1 \sum_{j=1}^M \mathbf{a}_{1j} \mathbf{u}_j (\mathbf{t}, \mathbf{x}, \mathbf{dx dt}) = \int_0^T \int_{\Gamma_{\Omega}} (\mathbf{t}, \mathbf{x}, \mathbf{x} \mathbf{dH}) - \int_0^T \int_{\Omega} \mathbf{dH} - \int_0^T \int_{\Omega} \mathbf{EQ} \mathbf{q}$$

The term on the right-hand side of (28) follows from the lemma

Lemma 9. Let $(g_i)_{i \in \mathbb{N}}$ be a countable family in $L^1(Q \times \mathbb{L}; \mu_{\Gamma, \mathcal{P}})$. Then there exists a set of full measure Ψ such that for almost every $\omega \in \Psi$, every $i \in \mathbb{N}$, every $t \in \mathbb{R}$ and every $\phi \in C_b(\overline{Q})$ it follows that

$$\lim_{Q \rightarrow 0} \int_Q g_i(x, \omega) \phi(x) dx = \int_Q g_i(x, \omega) \phi(x) d\mu_{\Gamma, \mathcal{P}}(\omega, dx).$$

The last term on the left-hand side of (28) has been obtained by

An integration by parts shows that (28) can be put in the strong form associated with the following homogenized system:

$$-\operatorname{div} [\mathbf{D}_1(\mathbf{t}, \mathbf{x}, \quad (\quad_x \mathbf{u}_1(\mathbf{t}, \mathbf{x}) + \mathbf{v}_1(\mathbf{t}, \mathbf{x}, \quad)] = 0 \quad \text{in } [0, T] \times Q \times \mathbf{G}^{\mathbb{C}} \quad (29)$$

$$[\mathbf{D}_1(\mathbf{t}, \mathbf{x}, \quad (\quad_x \mathbf{u}_1(\mathbf{t}, \mathbf{x}) + \mathbf{v}_1(\mathbf{t}, \mathbf{x}, \quad)] \cdot \boldsymbol{\nu}_{\Gamma_{\mathbf{G}^{\mathbb{C}}}} = 0 \quad \text{on } [0, T] \times Q \times \Gamma_{\mathbf{G}^{\mathbb{C}}} \quad (30)$$

$$\begin{aligned} & \frac{\mathbf{u}_1}{\mathbf{t}}(\mathbf{t}, \mathbf{x}) - \operatorname{div}_x \int_{\Omega} \int_{\mathbf{G}^{\mathbb{C}}} \mathbf{D}_1(\mathbf{t}, \mathbf{x}, \quad (\quad_x \mathbf{u}_1(\mathbf{t}, \mathbf{x}) + \mathbf{v}_1(\mathbf{t}, \mathbf{x}, \quad) \, d\mathbb{P}(\quad) \\ & + \int_{j=1}^M \mathbf{u}_1(\mathbf{t}, \mathbf{x}) \mathbf{a}_{1j} \mathbf{u}_j(\mathbf{t}, \mathbf{x}) - \int_{\Omega} \int_{\Gamma_{\mathbf{G}^{\mathbb{C}}}} (\mathbf{t}, \mathbf{x}, \quad) \, d\boldsymbol{\mu}_{\Gamma_{\mathcal{P}}}(\quad) = 0 \quad \text{in } [0, T] \times Q \end{aligned} \quad (31)$$

$$\int_{\Omega} \int_{\mathbf{G}^{\mathbb{C}}} \mathbf{D}_1(\mathbf{t}, \mathbf{x}, \quad (\quad_x \mathbf{u}_1(\mathbf{t}, \mathbf{x}) + \mathbf{v}_1(\mathbf{t}, \mathbf{x}, \quad) \, d\mathbb{P}(\quad) \cdot \mathbf{n} = 0 \quad \text{on } [0, T] \times Q. \quad (32)$$

By using the relation (33) in Eqs.(31) and (32), we get

$$\begin{aligned}
 & \frac{\mathbf{u}_1}{t}(\mathbf{t}, \mathbf{x}) - \operatorname{div}_x \mathbf{D}_1(\mathbf{t}, \mathbf{x}) \mathbf{x} \mathbf{u}_1(\mathbf{t}, \mathbf{x}) + \mathbf{u}_1(\mathbf{t}, \mathbf{x}) \sum_{j=1}^M \mathbf{a}_{1j} \mathbf{u}_j(\mathbf{t}, \mathbf{x}) \\
 & - \int_{\Omega} \Gamma_{G^0}(\mathbf{t}, \mathbf{x}, \mathbf{d}\mu_{\Gamma \mathcal{P}}) = 0 \quad \text{in } [0, T] \times Q
 \end{aligned}
 \tag{35}$$

$$[\mathbf{D}_1 \mathbf{x} \mathbf{u}_1(\mathbf{t}, \mathbf{x})] \cdot \mathbf{n} = 0 \quad \text{on } [0, T] \times Q
 \tag{36}$$

where the entries of the matrix \mathbf{D}_1 (called "effective diffusivity") are given by

$$(\mathbf{D}_1)_{ij}(\mathbf{t}, \mathbf{x}) = \int_{\Omega} G^0 \mathbf{D}_1(\mathbf{t}, \mathbf{x}, [\mathbf{w}_i(\mathbf{t}, \mathbf{x}) + \hat{\cdot}$$

References

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