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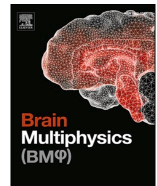

Macroscopic modelling of Alzheimer's disease: difficulties and challenges

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ABSTRACT

In the context of Alzheimer's disease (AD), *in silico* research aims at giving complementary and better insight into the complex mechanisms which determine the development of AD. One of its important aspects is the construction of macroscopic mathematical models which are the basis for numerical simulations. In this paper we discuss some of the general and fundamental difficulties of macroscopic modelling of AD. In addition we formulate a mathematical model in the case of a specific problem in an early stage of AD, namely the propagation of pathological τ protein from the entorhinal cortex to the hippocampal region. The main feature of this model consists in the representation of the brain through two superposed finite graphs, which have the same vertices (that, roughly speaking, can be thought as parcels of a brain atlas), but different edges. We call these graphs "proximity graph" and "connectivity graph", respectively. The edges of the first graph take into account the distances of the vertices and the heterogeneity of the cerebral parenchyma, whereas the edges of the second graph represent the connections by white-matter fiber pathways between different structures. The diffusion of the proteins Aβ and τ are described through the Laplace operators on the graphs, whereas the phenomenon of aggregation of the proteins leading ultimately to senile plaques and neuro-fibrillar tangles (as already observed by A. Alzheimer in 1907) is modelled by means of the classical Smoluchowski aggregation system.

STATEMENT OF SIGNIFICANCE

Alzheimer's disease is a neurodegenerative disease leading to dementia with huge economic and social costs. Despite a fast growing amount of clinical data, there is no widely accepted medical treatment to stop or slow down AD. It is generally accepted that two proteins, beta amyloid and tau, play a key role in the progression of the disease, and the edge of the current biomedical research focuses on the interactions of the two proteins also in the perspective of the production of new effective drugs. In this context, flexible mathematical models may give better and deeper insight by testing different clinical hypotheses.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disease leading to dementia, through a progressive decline in memory and other cognitive functions. Presently there are more than 50 million people suffering of AD and related disorders and by 2050 this figure is expected to increase to 150 million.

Despite a fast growing amount of clinical data, there is no medical treatment to stop or slow down AD and many questions on the causes of AD remain unanswered. In this context macroscopic mathematical modelling and numerical simulation (so-called *in silico* research) are natural tools to provide additional insight, for example by simulating specific therapies or modelling hypotheses. Recently several such models were proposed. An exhaustive review of existing mathematical models for AD up to 2018 can be found in [12], and among more recent contributions to macroscopic modeling we mention [3,4,21,23,29,38, 57,58,65,66,70] and references therein. Some of these models were successfully implemented to provide realistic simulations about the temporal and spatial evolution of AD.

AD is one of the neurodegenerative diseases involving more than one

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neurotoxic protein: beta-amyloid (Aβ) and pathological tau (τ). In his famous experimental post-mortem observations in 1907, Alois Alzheimer discovered *extracellular plaques* and *intracellular neurofibrillary tangles* (NFTs). By now we know that plaques contain Aβ and NFTs consist of pathological τ. There has been (and there still is) a lot of scientific debate on the role of the two proteins in AD and up to date Aβ and τ remain the major therapeutic targets for the treatment of the disease. Recent literature suggests that the interplay between the two proteins, as well as its timing, might be crucial for the development of the disease and should be taken into account when developing new therapies (see e. g. [11,22,35,37,43,55] and also the current debate on the perspectives of the use of aducanumab [56]).

In Section 2 we provide a brief review of the most significant properties of Aβ and τ. In Section 3 we discuss general but crucial difficulties when aiming to produce a macroscopic mathematical model of AD. Whenever feasible, we indicate possible strategies to overcome these difficulties.

Then, the core of the paper consists of Sections 4 and 5, where we discuss the propagation of τ from the entorhinal cortex to different areas of the brain and present a flexible mathematical model, taking into account the recent biomedical literature on the subject.

2. Beta amyloid and tau protein

Microscopically, monomeric Aβ peptides originate from the proteolytic cleavage of a transmembrane glycoprotein, the amyloid precursor protein, at the neuronal membrane. In healthy brains monomeric production and clearance yield an equilibrium state, while in AD, for unknown reasons, there is an imbalance between produced and cleared Aβ. In addition, the level of the neural activity plays a role in the Aβ production (see, e.g., [11,13,17]).

Monomeric Aβ diffuses within the cerebral parenchyma. In addition, aggregation and fragmentation processes lead to the formation of toxic soluble oligomers and, eventually, long, insoluble amyloid fibrils which accumulate in senile plaques (those observed by Alzheimer). Plaques are initially deposited in the neocortex, particularly in medial prefrontal and medial parietal regions. Cortical plaques are widespread many years before clinical symptoms emerge, and both autopsies and Aβ positron emission tomography (PET) suggest that up to 40% of cognitively normal individuals have profuse plaque deposition in the brain [11].

Endogenous τ protein is mainly found within axons where it stabilizes microtubules, but is also present in smaller amounts in dendrites and in the extracellular space [77]. In AD and other tauopathies the τ protein becomes pathological due to two transformations, hyperphosphorylation and misfolding (see e.g. [28]). In the disease state, the amount of hyperphosphorylated τ is at least three times higher than that in normal brains [34]. Hyperphosphorylation of τ negatively regulates the binding of τ to microtubules, compromises microtubule stabilization and axonal transport, and enhances the capacity of τ to self-assemble and form aggregates from oligomers to fibrils, eventually leading to its deposition as NFTs [27]. After 60 years of age, tau aggregates are commonly found in the entorhinal cortex (EC). From there it may propagate first to the hippocampus (HC) and then to limbic and association areas. During this process AD changes from an asymptomatic and preclinical phase to that of a devastating dementia. It is known that excess intracellular τ aggregates can be released into the extracellular space and uptaken by surrounding neurons. They induce the fibrillization of endogenous τ, which suggests a role for τ-seeding in neurodegeneration [30]. In the sequel we shall ignore that pathological τ appears in several isoforms, with different molecular structures, since this would pertain to a space scale that is not the one we are interested in.

In AD both soluble Aβ oligomers and pathological τ oligomers are neurotoxic and cause synaptic dysfunction, NFT mediated neuron loss and behavioral deficits. The precise role of Aβ and τ in this process is still not well understood, but in the literature various synergetic actions of Aβ and τ were suggested. For example, it is well-known that Aβ drives tau-pathology by causing hyperphosphorylation of endogenous τ [35], but in general there are many other possible interactions between Aβ and τ (for a recent and exhaustive review we refer to [11]).

3. Modelling: a first list of difficulties and challenges

Let $\Omega \subset \mathbb{R}^3$ represent a part of gray matter of the brain. The natural variables to build a mathematical model are the *molar concentrations* of the several monomers and oligomers, which are functions of the position $x \in \Omega$ and time t. In particular we introduce

- $u_1, \cdots, u_M : \Omega \times (0, T] \to \mathbb{R}$, the molar concentrations of Aβ oligomers; u_1 refers to monomers, $u_2, \cdots, u_N$ to soluble oligomers, and $u_{N+1}, \cdots u_M$ to insoluble Aβ oligomers, often contained in amyloid plaques (subscripts refer to the "length" of the oligomer);
- $w_1, \cdots, w_{\widetilde{M}} : \Omega \times (0, T] \to \mathbb{R}$, the molar concentrations of *extracellular* pathological τ oligomers; w_1 refers to monomers, $w_2, \cdots, w_{\widetilde{N}}$ to soluble oligomers, and $w_{\widetilde{N}+1}, \cdots, w_{\widetilde{M}}$ to insoluble pathological τ aggregates;
- $W_1, \cdots, W_{\widetilde{M}} : \Omega \times (0, T] \to \mathbb{R}$, the molar concentrations of *intracellular* pathological τ oligomers; W_1 refers to monomers, $W_2, \cdots, W_{\widetilde{N}}$ to soluble oligomers, and $W_{\widetilde{N}+1}, \cdots, W_{\widetilde{M}}$ to the insoluble oligomers, often contained in NFTs.

The idea of a *macroscopic* model is to write a *system of reaction diffusion equations* for the concentrations, where diffusion refers to spatial spreading of the proteins in the brain and the reaction terms represent specific processes such as aggregation, fragmentation, protein production, clearance etc. If necessary, equations for additional variables may be added to the system, such as the concentrations of intracellular Aβ [61] and endogenous tau.

In the present section we describe some of the major difficulties encountered in AD modelling.

3.1. Parameter identification

Reaction diffusion equations with many equations contain many parameters. On one hand, it is necessary to identify them in order to have reliable numerical simulations. On the other hand, too many parameters enhance the danger of overfitting.

For instance, in a future paper dedicated to numerical simulations of the mathematical model presented in Section 5, we shall deal with the problem of parameter identification. Here we limit ourselves to some preliminary remarks.

The maximal length of soluble Aβ oligomers (N) is an example of a parameter for which an approximate value is known: N is usually taken between 50 and 60 [49]. As for $\widetilde{N}$, the number maximal length of soluble pathological τ oligomers, the approximate value is under debate: using atomic force microscopy Maeda et al. report that filamentous τ is typically constituted of about 40 monomer weights [44], but the identification of $\widetilde{N}$ is not straightforward (see,e.g. [31]).

The choice of the values of M and $\widetilde{M}$ is less critical: we simply assume that plaques and NFTs do not contain Aβ and τ oligomers longer than some finite number (M, $\widetilde{M}$).

Once we have established approximate values of N, $\widetilde{N}$, M and $\widetilde{M}$, we should model nucleation-elongation-fragmentation mechanisms for both Aβ and τ (here nucleation means that the concentration of monomers must be large enough to trigger the aggregation from monomers into oligomers, the so-called elongation phase). These are quite complicated processes since they involve a variety of chemical protein structures, but even if we simplify them and use the so-called Smoluchovski equations to model aggregation and fragmentation, we end up

with a system which contains lots of parameters, namely all aggregation and fragmentation rates which express the probability that oligomers of length k and m combine to form an oligomer of length $k+m$ or viceversa. They can be estimated from experimental data (see for example [41,48,52,57,66,67,74]). It remains unclear whether experimental data from in vitro studies can be readily applied to in vivo scenarios, where the kinetic rates might plausibly be functions of the brain's cerebral milieu, neural activity and other physiological neural processes.

Of course the problem of parameters identification is far more general than the few examples given above, and below we shall encounter many other parameters. If it is not possible to obtain precise values or reliable approximations, it will be of great importance to estimate at least their order of magnitude. and consider the robustness of numerical simulations inside the given parameter range.

3.2. The health state of neurons

Certain processes in AD depend on the local health state of the neurons. For example, the imbalance between production and clearance of Aβ monomers increases when the neurons are damaged. In most existing models this problem is not addressed. In [4] a mathematical artifact was introduced to deal with it: let $a \in [0,1]$ be the *degree of malfunctioning* of a neuron and let, roughly speaking, $f(x,a,t)$ be the probability density of the degree of malfunctioning $a \in [0,1]$ of neurons located at a point x at time t, i.e. $f(x,a,t)\,da$ represents the fraction density of neurons at a point x and time t with degree of malfunctioning between a and $a+da$ (see [5] for a precise formulation in terms of probability measures). We assume that a close to 0 stands for "the neuron is healthy" whereas a close to 1 stands for "the neuron is dead". The parameter a, although introduced as an abstract mathematical artifact, can be directly compared with and related to medical images from Fluorodeoxyglucose PET [47].

The introduction of f leads to an additional equation in the system, a first order conservation law in a and t:

$$\partial_t f + \partial_a (vf) = 0.$$

Here $v = v(x,a,t) \geq 0$ is the *deterioration rate*, which, as we shall see below, is used to model the effect of neurotoxic processes (needless to say that this will lead to new parameters......).

3.3. Temporal multiscales

There are at least two different time scales in AD:

- a short time scale (hours) for protein agglomeration (e.g. amyloid plaques are formed within 48 h, see e.g., [46]), spatial protein spreading in the extracellular space, and many other physical processes;
- a long time scale (months) for the evolution of the disease.

Dealing correctly with this problem is a fundamental questions in AD modelling. For instance, on one hand the spatial spreading of Aβ in the extracellular space occurs in the fast time scale (the cerebral liquid in the extracellular space is renewed several times a day) while, on the other hand, the deposition of amyloid plaques is known to be strongly localized in the brain. So it seems that toxic Aβ oligomers, despite the short time scale of their spreading, do not rapidly reach other parts of the brain. What is the explanation of this apparent contradiction?

It would be possible to use parameter fitting to impose a slow spreading of oligomers. However, we are interested in "answers from first principles", hoping that they give more insight in some of the fundamental processes in AD and their interaction. One possibility is the introduction of a threshold phenomenon: it could very well be that soluble Aβ oligomers become toxic when their molar concentration exceeds a positive threshold value. So if the Aβ concentration exceeds in a small region the threshold value, after a little spatial spreading its value will go below threshold again. In addition clearance phenomena could enhance the tendency to turn below threshold. One could also assume that the aggregation of monomers requires a critical monomer concentration (the so-called nucleation phenomenon, see e.g. [49], [13]).

Of course these are only possible explanations, and we believe that a better understanding and correct treatment of the temporal multiscales is an important challenge in AD modelling.

3.4. Spatial multiscales

Aβ usually first appears in frontal regions and subsequently spreads to allocortical, diencephalic, brainstem, striatal and basal forebrain regions [72]. Neurofibrillary tangles appear first in locus coeruleus, then entorhinal cortex, then spreads into hippocampus, amygdala, temporal lobe, basal forebrain and association areas, in order [9,10,72]. Disease factors can directly propagate along neural connections, underpinned by prion-like protein aggregation followed by their trans-synaptic transmission [14,25,36]. After initial seeding and local aggregation, misfolded τ might then propagate through neuronal pathways, transmit trans-synaptically and thus spread throughout the brain [79]. Based on emerging bench science, it is clear that spatial diffusion alone might not be the most appropriate means of capturing protein spread along fibers, since active axonal transport is commonly expected to be the dominant manner for the intra-axonal movement of tau and amyloid prior to their transsynaptic transmission [16,53]. Under this mode, the process of spread will most likely involve the strength of interregional connectivity rather than its distance along fiber projections. A recent study mathematically modeled these processes in a closed axonal system and found that the microscope processes of aggregation, diffusion and axonal transport occur at relatively faster timescales (days) compared to overall disease progression [73].

Thus there are at least two different spatial scales: the typical scale of the extracellular space where Aβ and extracellular τ spread, and a much smaller scale corresponding to the typical thickness of neurons where the intracellular τ spreads. Since extra- and intracellular proteins interact, we must decide how to combine these different spatial scales.

There are two ways to proceed. The first one is to use the concentrations u_k, w_k and W_k as functions of the continuous variable $x \in \Omega$, and work with the resulting system of reaction diffusion equations. There are at least two contraindications to do so. The first one is the way in which intracellular τ spreads through the neural network, characterised by the connectivity of different regions by neural bundles rather than their physical distance. In the context of a continuous spatial variable this requires the use of nonlocal operators. The second (and more important) one is the well-known fact that numerical simulations of PDE systems with many equations in 3D is computationally very expensive.

The second way to proceed is adopted in most computational models. As the starting point we consider the neural network in which intracellular τ spreads [1] and we introduce a *parcellation* of the brain, i.e. a subdivision $\{\Omega_i,\, i = 1, \cdots n\}$ of the human cerebral cortex into a patchwork of anatomically and functionally distinct areas, known as cortical areas. Following the approach proposed in [59], we associate with the parcellation a network of white-matter fiber pathways connecting the cortical areas. As in [24,29,57,59] we identify this network with a finite weighted graph $G = \{V, E\}$. Here V is a set of vertices, $\{x_1, \cdots, x_n\}$, where $x_i \in \Omega_i$ represents the ith cortical or subcortical gray matter structure (i.e. the ith parcel). The edges $e_{ij} \in E$ represent the connections by white-matter fiber pathways between the ith and the jth structure. Coherently, we introduce a family of coefficients π_{ij} that measure how much the ith cortical area is connected with the jth cortical area. The coefficients π_{ij} are called the *connectivity weights* of the graph G. In this way we build a brain network in which the vertices x_i come from the parcellation of brain MRI and the connectivities π_{ij} are measured by fiber tractography. We call G the *connectivity graph*, which will be used to

describe the spreading of intracellular τ hrough the neural network.

Considering x_i as a discretization of the continuous variable x, the next step is natural: we use x_i to discretize the PDEs for u_k and w_k. In this way we obtain discretized equations for u_k and w_k on a second graph, $\Gamma = \{V,F\}$, with the same vertices as G but with a new family F of edges that take into account the distances of the vertices and the heterogeneity of the cerebral parenchyma. We assume that, roughly speaking, two vertices are adjacent if they are "close enough" and call Γ the *proximity graph*, and we associate to Γ a family of *proximity weights*, $\widetilde{\pi}_{ij}$.

As in [21,57,59], the map of "connectomes" can be extracted from a dataset of the MRI of a cohort of healthy subjects and diffusion-weighted MRI (dMRI) scans acquired previously and processed with a custom pre-processing connectomics pipeline. The proximity graph Γ too can be readily inferred from structural MR images of the brain, followed by simple morphological operations that yield the distance between parcels, whether in terms of Euclidean distance, or distance along the cortical ribbon. For the sake of simplicity, we assume that both G and Γ are simple graphs, i.e. there are no loops or multiple edges connecting two nodes. We say that two vertices x_m, x_j are adjacent in G (in Γ) if they are connected by one edge in E (in F, respectively), and write $x_j \sim_E x_m$ ($x_j \sim_F x_m$, respectively).

Finally, we observe that the discretization in x eliminates from the system almost all PDEs: only the conservation law for $f(x_i,a,t)$, where x_i is simply a parameter, remains. Here $f(x_i,a,t)da$ represents the fraction of neurons in the ith parcel which at time t have a degree of malfunctioning between a and $a + da$.

4. A specific modelling problem

The difficulties described in the previous section are very general and must be dealt with before considering more specific problems. In this section we give an example of a specific macroscopic model and gradually discuss the additional questions and difficulties which arise.

The specific problem we have in mind is the following. According to Braak's staging system I–VI [8], the entorhinal cortex (EC) is the first region in the human brain where tau aggregates appear. This commonly occurs after the age of 60, and if tau remains confined to the EC and does not spread to other regions, the disease does not develop. However, in AD misfolded tau propagates slowly (i.e. in the long timescale) from the EC to the hippocampal region (HC). Microglia are positively correlated with tau pathology, but their involvement in tau propagation is unknown [11]. On the basis of an experiment on mice, Asai et al. [2] suggested that depleting microglia dramatically suppresses the propagation of tau from EC to HC. They also showed that microglia spread tau via exosome secretion, and that inhibiting exosome synthesis significantly reduces tau propagation in vitro and in vivo.

Summarizing, the specific problem is to see if mathematical modelling and numerical simulation can shed some light on the question concerning which processes drive tau propagation from the entorhinal cortex to the hippocampal region.

In the following subsections we introduce the major modelling questions of the problem. In Section 5 we present and briefly discuss a mathematical system to describe the model. In Section 6 we draw some first conclusions and discuss possible future computational studies.

4.1. Microglia

The first thing to be done is including microglia in the model. Glial cells (astrocytes, microglia etc.) are the primary phagocytes in the brain and play a fundamental role in clearance processes. They phagocytose dying cells, debris and protein aggregates, but also living neurons or synapses. They move in the extracellular space towards sites containing soluble or aggregated oligomers of Aβ or tau, thereby causing inflammation.

We denote by $\omega(x,t)$ the density of activated microglia. It would be possible to construct a differential equation for ω, but for the sake of simplicity we assume that ω depends instantaneously on the molar concentrations of Aβ and tau oligomers:

$$\omega = \omega\left(u_2, \cdots, u_M, w_2, \cdots, w_{\widetilde{M}}, W_2, \cdots, W_{\widetilde{M}}\right)$$

The simplest choice is a linear dependence ω on these quantities, $\omega = \sum_{i=2}^{M} \lambda_i u_i + \sum_{i=2}^{\widetilde{M}} (\mu_i w_i + \widetilde{\mu}_i W_i)$, where the coefficients λ_i, μ_i and $\widetilde{\mu}_i$ are parameters which need to be identified. To fix the ideas we could take $\mu = \widetilde{\mu} = 0$ and assume that glial cells are mainly activated by soluble neurotoxic Aβ oligomers and, indirectly, by Aβ aggregates through the release of cytokines by senescent oligodendrocytes near plaques [80]:

$$\omega = \sum_{i=2}^{M} \lambda_i u_i. \tag{1}$$

The phagocytic activity of microglia is represented by a clearance term in the equations for soluble oligomers, proportional to the molar density of the oligomer with a proportionality factor depending on ω.

The paper by Asai et al. suggests that microglia might enhance tau propagation. Citing [2], "the evolution of Braak staging, which shows lateral propagation of tau pathology in neurons that are not connected by synapses, such as those from the transentorhinal cortex to higher order sensory association areas of the occipitotemporal gyrus in Braak III stage Alzheimer's disease." This means that tau spreading does not occur only along the connectivity graph, but also along the proximity graph. This leads to another question: how does extracellular tau contribute to tau propagation? A key role could be played by the so-called processes of "seeding, release and uptake", combined with glial activity.

4.2. Seeding, release and uptake

Pathological tau proteins, in particular short fibrils, are seed competent, i.e. able to induce misfolding to endogenous tau monomers. This so-called seeding process is known to occur inside neurons, and is often referred to as prion-like propagation of tau pathology [27]. Prion-like does not only concern synaptic transmission of tau pathology. Indeed, experimental evidence suggests that excess pathological tau protein is released from neurons into extracellular space, spreads between cells, and is uptaken by neighbouring neurons where it recruits and misfolds endogenous tau monomers [19]. Since we are interested in lateral propagation of tau pathology in neurons which are not connected by synapses, we are particularly interested in this second type of propagation which involves extracellular tau, i.e. propagation based on a combination of seeding, release and uptake. Observe that we did not include endogenous tau in the model (although this would be possible). For the sake of simplicity we assume that endogenous tau is relatively abundant with respect to pathological tau, whence we may neglect the dependence of the seeding process on the amount of available endogenous tau. It is challenging to understand if seeding also occurs in the extracellular space, but the mathematical model is flexible enough to include this possibility.

Before proposing a precise mathematical model, we discuss some possible mechanisms which play a potential role in the problem we have posed in this section. The list of mechanisms is certainly not exhaustive. For example, it could very well be that individual and partially genetic factors decide whether tau propagation from EC to HC occurs or does not.

As we have already discussed in Section 4.1, the experiments on mice by Asai and his collaborators suggest that microglia mediate tau-propagation in the extracellular space [2,11]. Following Bushe and Hyman [11], microglia migrate toward tau-positive neurons and cluster around tangles. They can uptake seed-competent tau [7], but are not always able to decompose it effectively [32] and therefore they may release tau in a more bioactive form Busche and Hyman [11]. Activated microglia may also package tau into exosomes, and, when near to tau-containing neurons, may form somatic junctions with neurons through which tau might be transmitted between cells [15]. In addition, microglia enhance tau phosphorylation through cytokine signaling [6, 45].

Another potentially important mechanism for enhanced tau-propagation is the fragmentation of tau aggregates combined with seeding. Since relatively short soluble tau oligomers are the most toxic ones, this process causes an important amplification of seed-competent tau and strongly enhances toxicity [26,41,63,74–76]. Even a moderate increase in fragmentation rate can have important consequences for the amount of seed-competent tau [39].

The flow of cerebral fluid plays an important role in the clearance of toxic substances from the brain, in addition to the glial cells discussed before. The cerebral fluid is constantly refreshed, and therefore toxic proteins contained in the liquid are eliminated from the brain. It is generally accepted that clearance is age-dependent, which at least partially explains why sporadic AD occurs more frequently in elder people. Not all proteins are eliminated in the same way. For instance, it was observed [18] that tau is more stable in the presence of Aβ and therefore extracellular soluble toxic τ-oligomers have a substantially longer half-life time than toxic Aβ oligomers. In addition, the cerebral fluid cannot clear everything. For example, amyloid plaques are not soluble and cannot be removed by it. The easiest way to model clearance by cerebral fluid is the introduction of a sink term in the equations. Otherwise one should face the challenge to model the fluid flow itself, a far from trivial issue. We refer for instance to [69] and the references therein, as well as [40]. In particular there is a lot of debate, in the context of the so-called *glymphatic system* [33,71], about the character of the flow: is it mainly diffusive or convective?

Finally, we discuss possible synergistic actions of Aβ in tau propagation, which seem to be particularly important in the early phase of AD [11]. Soluble Aβ causes neuronal hyperexcitability, which increases the steady-state levels of extracellular tau in vivo [50], in particular the attenuation of entorhinal cortex hyperactivity reduces Aβ and tau pathology, and chronic chemogenetic attenuation of Aβ-associated hyperactivity reduces pathological tau spread into downstream hippocampus [60]. Indeed tau can be secreted into the extracellular space from neurons independently from cell death and the elevation of tau in cerebrospinal fluid is associated with AD and is linked to Aβ deposition [78]. Tau release occurs within hours in response to neuronal activity, but the elimination rate of tau from the extracellular compartment and the brain is slow (half-life of about 11 days). This slow turnover will delay the elimination of extracellular tau and, as a consequence, it may affect its aggregation and synaptic transmission of tau pathology. Finally, we note that Aβ can also directly seed tau [42, 68].

5. The mathematical system

In this section we transform the problem described in the previous section in a system of equations. We recall that we have introduced the weighted connectivity graph G and weighted proximity graph Γ with vertices $V = \{x_i \in \Omega; i = 1, \cdots, n\}$. Their edges are characterized by a family of coefficients π_{ij} (respectively $\widetilde{\pi}_{ij}$) which determine a weighted Laplacian on the graph, Δ_G (respectively Δ_Γ) (see [57,59,65]).

More precisely, If x_m is a vertex of V, we set

$$\pi_m = \pi(x_m) := \sum_{x_j \sim_E x_m} \pi_{m,j} > 0 \qquad \text{and} \qquad \widetilde{\pi}_m = \widetilde{\pi}(x_m) := \sum_{x_j \sim_F x_m} \widetilde{\pi}_{m,j} > 0.$$

We define the so-called graph Laplacian operator, Δ_G as follows. Let $g(x)$ be any function defined over the vertices of the graph. Then, for any m, j with $1 \le m, j \le n$:

$$\Delta_G g(x_m) = \frac{1}{\pi_m} \sum_{x_j \sim_E x_m} \big(g(x_m) - g(x_j)\big)\pi_{m,j}\,. \tag{2}$$

The graph Laplacian Δ_Γ is defined analogously.

The progression of AD is determined by the deterioration rate v (see (6) below), which is contained in the differential equation for f:

$$\partial_t f + \partial_a(vf) = 0 \qquad \text{in } V \times [0,1] \times (0,T]. \tag{3}$$

With the notations of Section 3, below we shall discuss the following two *coupled* systems in $V \times (0,T]$ for Aβ and τ concencention: the first system deals with extracellular protein concentrations (here H is the Heaviside function and δ_u, is the nucleation threshold for extracellular Aβ).

$$\begin{cases}
\varepsilon\partial_t u_1 - d_{1,A\beta}\Delta_\Gamma u_1 = -a_{1,1}u_1^2 H(u_1-\delta_u) - u_1\sum_{j=2}^{M-1}\alpha_{1,j}u_j - \sigma_{1,A\beta}u_1 + \mathscr{F}(f) \quad (4a)\\
\varepsilon\partial_t u_2 - d_{2,A\beta}\Delta_\Gamma u_2 = \frac{1}{2}a_{1,1}u_1^2 H(u_1-\delta_u) - u_2\sum_{j=1}^{M-2}\alpha_{2,j}u_j - \frac{1}{2}b_{1,1}u_2\\
+\sum_{j=1}^{M-2} b_{2,j}u_{2+j} - \sigma_{2,A\beta}u_2 \quad (4b)\\
\varepsilon\partial_t u_m - d_{m,A\beta}\Delta_\Gamma u_m = \frac{1}{2}\sum_{j=1}^{m-1}\alpha_{j,m-j}u_j u_{m-j} - u_m\sum_{j=1}^{M-m}\alpha_{m,j}u_j - \frac{1}{2}\sum_{j=1}^{m-1} b_{m-j,j}u_m\\
+\sum_{j=1}^{M-m} b_{m,j}u_{m+j} - \sigma_{m,A\beta}u_m \,(2 \le m \le N) \quad (4c)\\
\varepsilon\partial_t u_m = \frac{1}{2}\sum_{j=1}^{m-1}\alpha_{j,m-j}u_j u_{m-j} - u_m\sum_{j=1}^{\min\{N,M-m\}}\alpha_{m,j}u_j - \frac{1}{2}\sum_{j=1}^{m-1} b_{m-j,j}u_m\\
\min\{j,m-j\} \le N\\
+\sum_{j=1}^{M-m} b_{m,j}u_{m+j} \,(N < m \le M) \quad (4d)\\
\varepsilon\partial_t w_1 - d_{1,\tau\text{ext}}\Delta_\Gamma w_1 = -\sigma_{1,\tau\text{ext}}w_1 + \kappa_{1,r}W_1 - \kappa_{1,u}w_1 + \sum_{j=2}^{\widetilde{N}}\nu_{j,\text{ext}}(\omega)w_j \quad (4e)\\
\varepsilon\partial_t w_m - d_{m,\tau\text{ext}}\Delta_\Gamma w_m = -\sigma_{m,\tau\text{ext}}w_m + \kappa_{m,r}W_m - \kappa_{m,u}w_m \left(2 \le m \le \widetilde{N}\right) \quad (4f)\\
\varepsilon\partial_t w_m = -\sigma_{m,\tau\text{ext}}w_m + \kappa_{m,r}W_m \left(\widetilde{N} < m \le \widetilde{M}\right) \quad (4g)
\end{cases}$$

The second system deals with the concentration of the intracellular τ-protein (here δ_W is the nucleation threshold for intracellular τ).

$$\left\{\begin{aligned}
&\varepsilon\partial_t W_1-\varepsilon d_{1,\tau}\Delta_G W_1=-\widetilde{\alpha}_{1,1}W_1^2H(W_1-\delta_W)-\sum_{j=2}^{\widetilde{M}-1}\widetilde{\alpha}_{1,j}W_j\\
&+\sum_{j=1}^{\widetilde{M}-1}\widetilde{b}_{1,j}W_{1+j}-\sigma_{1,\tau\,\mathrm{int}}W_1-\kappa_{1,r}W_1+\kappa_{1,u}w_1+\sum_{j=2}^{\widetilde{N}}\nu_{j,\mathrm{int}}W_j\\
&+C_W\sum_{j=2}^{N}\sum_{d_G(x_k,x_i)<R}\left(u_j(x_k,t)-\overline{U}_j\right)^+ \qquad \text{(5a)}\\
&\varepsilon\partial_t W_2-\varepsilon d_{2,\tau}\Delta_G W_2=\frac{1}{2}\widetilde{\alpha}_{1,1}W_1^2H(W_1-\delta_W)-W_2\sum_{j=1}^{\widetilde{M}-2}\widetilde{\alpha}_{2,j}W_j-\frac{1}{2}\widetilde{b}_{1,1}W_2\\
&+\sum_{j=1}^{\widetilde{M}-2}\widetilde{b}_{2,j}W_{2+j}-\sigma_{2,\tau\,\mathrm{int}}W_2-\kappa_{2,r}W_2+\kappa_{2,u}w_2 \qquad \text{(5b)}\\
&\varepsilon\partial_t W_m-\varepsilon d_{m,\tau}\Delta_G W_m=\frac{1}{2}\sum_{j=1}^{m-1}\widetilde{\alpha}_{j,m-j}W_jW_{m-j}-W_m\sum_{j=1}^{\widetilde{M}-m}\widetilde{\alpha}_{m,j}W_j\\
&-\frac{1}{2}\sum_{j=1}^{m-1}\widetilde{b}_{m-j,j}W_m+\sum_{j=1}^{\widetilde{M}-m}\widetilde{b}_{m,j}W_{m+j}\\
&-\sigma_{m,\tau\,\mathrm{int}}W_m-\kappa_{m,r}W_m+\kappa_{m,u}w_m \quad \left(2\le m\le\widetilde{N}\right) \qquad \text{(5c)}\\
&\varepsilon\partial_t W_m=\frac{1}{2}\sum_{\substack{j=1\\ \min\{j,m-j\}\le\widetilde{N}}}^{m-1}\widetilde{\alpha}_{j,m-j}W_jW_{m-j}-W_m\sum_{j=1}^{\min\{\widetilde{N},\widetilde{M}-m\}}\widetilde{\alpha}_{m,j}W_j\\
&-\frac{1}{2}\sum_{j=1}^{m-1}\widetilde{b}_{m-j,j}W_m\\
&+\sum_{j=1}^{\widetilde{M}-m}\widetilde{b}_{m,j}W_{m+j}-\sigma_{m,\tau\,\mathrm{int}}W_m-\kappa_{m,r}W_m \quad \left(\widetilde{N}<m\le\widetilde{M}\right) \qquad \text{(5d)}
\end{aligned}\right.$$

(here the transition rates $\alpha_{i,j}$, $\widetilde{\alpha}_{i,j}$, $b_{i,j}$, $\widetilde{b}_{i,j}$ are symmetric in i and j).

We associate with the system constitutive relations for the deterioration rate v, the production of Aβ monomers $\mathscr{F}$ and the glial density ω at the vertices $x_i \in V$, $i = 1,\cdots,n$. Simple choices lead to

$$v = \quad v(x_i,a,t)=C_{\mathscr{G}}\int_0^1(b-a)^+f(x_i,b,t)\,db+C_{\mathscr{S}}(1-a)\left\{\left(\sum_{j=2}^{M}p_ju_j(x_i,t)-\overline{U}\right)^+ +\sum_{j=2}^{\widetilde{N}}\widetilde{p}_jW_j(x_i,t)+\left(\sum_{j=2}^{M}p_ju_j-\overline{U}\right)^+\sum_{j=2}^{\widetilde{N}}\widetilde{p}_jW_j(x_i,t)\right\}, \tag{6}$$

where $p_j,\widetilde{p}_j > 0$ are toxicity coefficients and $\overline{U}$ is a positive threshold value,

$$\mathscr{F}(f)=\mathscr{F}(x_i,t)=C_{\mathscr{F}}\int_0^1(1-a)f(x_i,a,t)\,da. \tag{7}$$

In the remainder of this section we discuss the equations and the constitutive relations.

The differential equations contain many coefficients. They are not necessarily constants and may depend nonlinearly on the various variables. Such dependencies should be motivated by biomedical observations and data, in addition they can be modified to test numerically different modelling hypotheses. In the discussion below we mention some examples of such dependencies.

- The variable t describes the slow time scale. The equations which also describe processes occurring in the fast time scale contain a small coefficient ε, the proportion between the two time scales. So on the left hand side of the equations one find the *variation of the concentrations with respect to time*. The terms which contain the Laplacian, on each of the graphs, describe the *spatial spreading of soluble monomers and oligomers*. Observe that within the neural network τ undergoes diffusion processes in the slow time scale ([62]), while extracellular τ diffuses quickly. The diffusion rates $d_{m,A\beta}$ $d_{m,\tau\,\mathrm{ext}}$ are assumed to be constant for $m = 1, \cdots, N$. The diffusion rates of intracellular τ need special attention: on one hand, the transport of misfolded τ inside single neurons is probably faster than the slow timescale corresponding to the evolution of AD; on the other hand, the transition from one neuron to another could be much slower and cause a sort of bottleneck effect yielding effective diffusion rates which are definitely smaller. Finally, since the transition velocities between neurons may be enhanced by the presence of microglia and toxic Aβ, and may also be influenced by the average health state of neurons, the effective diffusion rates of intracellular τ might strongly depend on f and the concentrations of microglia and toxic Aβ.
- The Smoluchowski terms (with aggregation and fragmentation rates as coefficients) describe the *polymerization and depolymerization of proteins*. The role of fragmentation should not be underestimated in the propagation of the disease; for example, the fragmentation of a solid Aβ aggregate in two soluble oligomers strongly enhances toxicity [41,75]. In () and () the function H indicates the Heaviside function and the factors $H(u_1 - \delta_u)$ and $H(W_1 - \delta_W)$ describe the nucleation phenomenon, [49] where δ_u and δ_W are positive threshold values. Extracellular tau is assumed to be so diluted that we may neglect its (de)polymerization. It was observed in [41] that in case of the tau protein, fragmentation rates are much smaller than aggregation rates.
- The sink terms with coefficients σ describe *clearance mechanisms*. We assume that soluble Aβ and extracellular and intracellular τ undergo various clearance processes. Quoting Tang et al. [64]: "Overall, it is clear that tau is degraded by multiple mechanisms and that many factors determine which route is taken. In addition, pathological conditions such as AD, likely have altered degradative pathways and, hence, altered tau clearance. Decreased efficiency of any of these clearance pathways is likely to have detrimental effects on tau turnover, potentially enhancing tau accumulation and pathology." We already mentioned the important role of microglia in clearance processes.

  In addition, cerebral flow contributes to clearance in the extracellular space. The clearance occurs in the fast time scale, though the clearance of w_2 seems to occur in a slightly slower time scale. Generically the coefficients σ will depend on the glial density ω. We recall [18] that, in the presence of Aβ, extracellular soluble toxic tau-oligomers have a substantially longer half-life time than toxic Aβ oligomers, whence their clearance coefficients are smaller and Aβ dependent.
- The terms with coefficients κ describe *release and uptake* of tau, i.e. the exchange of extra and intracellular tau. The release coefficient κ depends on f, but does not vanish for $f = 0$. Indeed, Pilliod et al. [54]

write: "the presence of tau in the interstitial fluid in the absence of neurodegeneration was demonstrated by microdialysis in tau transgenic mouse brain showing that tau was released by neurons in vivo [...] Tau secretion seems to occur in both physiological and pathological conditions. Indeed, tau is found in the CSF of control individuals but at lower levels than in AD indicating that extracellular tau could have a physiological role [...] On the other hand, secretion of aggregated proteins could act as a clearance mechanism to prevent their intracellular accumulation."

As for the diffusion coefficients for intraneural τ, the coefficients κ depend on f, ω and the concentration of toxic Aβ.

- The terms with coefficients ν describe the *seeding* phenomenon of tau, i.e. the misfolding of intra and extracellular endogenous tau monomers. We recall that the extracellular seeding is enhanced by microglia which are activated due to the inflammatory effect of extracellular τ and Aβ. These phenomena occur in the fast time scale. However, due to the low concentration of extracellular monomeric tau, the relevance of extracellular seeding is questionable. We will further comment on this in Section 6.
- The term $C_W \sum_{j=2}^{N} \sum_{d_G(x_k,x_i)<R} (u_j(x_k,t) - \overline{U}_j)^+$ in Eq. () describes the production of intracellular misfolded monomers, mediated by toxic Aβ oligomers.
- (6), (7) and (1) are simple examples of constitutive relations. The expression (7) for ω was already discussed in the previous section, while (7) describes the production of Aβ monomers depending on the degree of malfunctioning of the neurons. Finally, we discuss the constitutive relations for the deterioration rate v. The first term on the right hand side of (6) describes the effect of the presence of other damaged neurons. The next three terms describe the toxic effect of, respectively, soluble Aβ oligomers, tau oligomers, and their neurotoxic interaction. The weights p_j and $\widetilde{p}_j$ express the toxicity of oligomers of length j. For example we could assume that $p_j = \phi(j)$ and $\widetilde{p}_j = \widetilde{\phi}(j)$, where ϕ is an increasing function in $[2,P]$ ($[2,\widetilde{P}]$) and decreasing in $[P,M]$, with $\phi(M) = 0$. Analogously, $\widetilde{\phi}$ is an increasing function on $[2,\widetilde{P}]$, decreasing on $[\widetilde{P},\widetilde{N}]$, with $\phi(\widetilde{N}) > 0$. This expresses the fact that relatively small soluble oligomers are the most toxic ones and Aβ plaques are not toxic (see [26,41,51,63,74–76]). Finally, we assume that a minimal amount of Aβ toxicity, expressed by $\overline{U}$, is needed to damage neurons.

6. Discussion

In the fist part of the paper we have discussed some general difficulties concerning macroscopic mathematical modelling of Alzheimer's disease. Among the most challenging ones we mention the existence of different timescales (hardly mentioned and coped with in the existing literature), the inclusion in the model of a quantification of the health state of damaged neurons, parameter identification and, more in general, the containment of the number of parameters. The existence of multiple spatial scales is less challenging and can be solved rather easily by the use of graphs and spatial discretization, reducing considerably computational costs.

In the second part, we focus on an important specific problem in Alzheimer's disease, namely the question concerning which mechanisms regulate the propagation of toxic tau oligomers from the entorhinal cortex to the hippocampal region. The answer to this question is not known and we wonder whether *in silico* research can give some further insight in the problem. In this context we have discussed relevant clinical data from *in vitro* and *in vivo* research which are the basis of several working hypotheses. Finally, we have transformed the biomedical input in a mathematical formulation of a model.

What remains to be done is to carefully design and carry out suitable computational tests which give insight in the role of the various mechanisms we have discussed. This programme goes far beyond the scope of the present note and requires a substantial amount of work. Large amounts of parameters and their nonlinear dependance on relevant quantities need to be treated correctly, preferably in collaboration with a biomedical scientist. Various modelling hypotheses should be tested and compared. In addition it is of great importance the comparison of numerical simulations with biomedical data, possibly in the context of human brains, but at least with tests on mice as those by Asai et al. [2].

The choice of the parcellation is not a minor issue from the numerical point of view. Indeed, the upper bound for the number of parcels is determined by the available datasets, i.e. by the resolution of the medical imaging. This may considerably limit the use of the connectome approach to specific problems in those parts of the brain which are "too small", i.e. where the required datasets are finer than the existing ones (think for instance of the hippocampus). In human brains the typical values for the number of parcels range from 100 to 1000 (in order of magnitude). We refer for instance to [20,57,58,65] for a discussion of different facets of brain parcellation.

All this is work in progress and will be the subject of a future computational paper. However, we stress that our model is, by its own structure, highly flexible and can implement with increasing success without modifications provided more refined parcellation atlases are available. It is also worth stressing that the flexibility of the system makes it possible to use it as a toy model, testing different hypotheses than are currently on the edge of clinical research, simply by removing or enhancing terms.

Finally, we stress that the list of challenges presented in this paper is far from exhaustive. We have made a first choice, but various other phenomena could be important to deal with. For example we did not consider either the role of atrophy [29], which even in the early stages of AD could be important in localised parts of the brain, neither that of the vascular system [11]. In addition we did not address the question if, and by which mechanisms, Aβ arrives in the entorhinal cortex before tau starts to propagate towards the hippocampal region.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Z. Ahmed, J. Cooper, T.K. Murray, et al., A novel in vivo model of tau propagation with rapid and progressive neurofibrillary tangle pathology: the pattern of spread is determined by connectivity, not proximity, Acta Neuropathol. 127 (2014) 667–683.

[2] H. Asai, S. Ikezu, S. Tsunoda, M. Medalla, J. Luebke, T. Haydar, B. Wolozin, O. Butovsky, S. Kügler, T. Ikezu, Depletion of microglia and inhibition of exosome synthesis halt tau propagation, Nat. Neurosci. 18 (11) (2015) 1584–1593.

[3] M. Bertsch, B. Franchi, L. Meacci, M. Primicerio, M.C. Tesi, The amyloid cascade hypothesis and Alzheimer's disease: a mathematical model, Eur. J. Appl. Math. (2020) 1–20.

[4] M. Bertsch, B. Franchi, V. Meschini, M.C. Tesi, A. Tosin, A sensitivity analysis of a mathematical model for the synergistic interplay of amyloid beta and tau on the dynamics of Alzheimers disease, Brain Multiphys. 2 (2021) 100020.
[5] M. Bertsch, B. Franchi, M.C. Tesi, A. Tosin, Well-posedness of a mathematical model for Alzheimer's disease, SIAM J. Math. Anal. 50 (3) (2018) 2362–2388.
[6] K. Bhaskar, et al., Regulation of tau pathology by the microglial fractalkine receptor, Neuron 68 (2010) 19–31.
[7] M. Bolós, et al., Direct evidence of internalization of tau by microglia in vitro and in vivo, J. Alzheimers Dis. 50 (2016) 7–87.
[8] H. Braak, E. Braak, Neuropathological stageing of Alzheimer-related changes, Acta Neuropathol. 82 (1991) 239–259.
[9] H. Braak, E. Braak, Supplementum, Evolution of the neuropathology of Alzheimers disease, Acta Neurol. Scand. 165 (1996) 312.
[10] H. Braak, K.D. Tredici, Where, when, and in what form does sporadic Alzheimers disease begin? Curr. Opin. Neurol. 25 (6) (2012) 708714.
[11] M.A. Busche, B.T. Hyman, Synergy between amyloid-β and tau in Alzheimers disease, Nat. Neurosci. 23 (2020) 1183–1193.
[12] F. Carbonell, Y. Iturria, A. Evans, Mathematical modeling of protein misfolding mechanisms in neurological diseases: a historical overview, Front. Neurol. 9 (2018).
[13] J.R. Cirrito, et al., Endocytosis is required for synaptic activity-dependent release of amyloid-β in vivo, Neuron 58 (2018) 42–51.
[14] F. Clavaguera, et al., Transmission and spreading of tauopathy in transgenic mouse brain, Nat. Cell Biol. 11 (7) (2009) 909913.
[15] C. Cserp, et al., Microglia monitor and protect neuronal function through specialized somatic purinergic junctions, Science 367 (2020) 528–537.
[16] A.d. Calignon, et al., Propagation of tau pathology in a model of early Alzheimers disease, Neuron 73 (4) (2012) 685697.
[17] W. de Haan, Activity dependent degeneration explains hub vulnerability in Alzheimer's disease, PLoS Comput. Biol. 8 (8) (2012) 1–14.
[18] S.L. De, Tau reduction in the presence of amyloid-β prevents tau pathology and neuronal death in vivo, Brain 141 (2018) 2194–2212.
[19] S.L. De, Synaptic tau seeding precedes tau pathology in human Alzheimer's disease brain, Front. Neurosci. 12 (2018).
[20] S.B. Eickhoff, B.T.T. Yeo, S. Genon, Imaging-based parcellations of the human brain, Nat. Rev. Neurosci. 19 (2018) 672–686.
[21] S. Fornari, A. Schäfer, M. Juncker, A. Goriely, E. Kuhl, Prion-like spreading of Alzheimers disease within the brain's connectome, J. R. Soc. Interface 16 (2019) 20190356.
[22] S. Fornari, A. Schfer, E. Kuhl, A. Goriely, Spatially-extended nucleation-aggregation-fragmentation models for the dynamics of prion-like neurodegenerative protein-spreading in the brain and its connectome, J. Theor. Biol. 486 (2020) 110102.
[23] B. Franchi, M. Heida, S. Lorenzani, A mathematical model for Alzheimer's disease: an approach via stochastic homogenization of the Smoluchowski equation, Commun. Math. Sci. 18 (4) (2020) 1105–1134.
[24] B. Franchi, M.A. Herrero, V. Tora, Dynamics of a polymerization model on a graph preprin, 2021.
[25] B. Frost, R.L. Jacks, M.I. Diamond, Propagation of tau misfolding from the outside to the inside of a cell, J. Biol. Chem. 284 (19) (2009) 12845–12852.
[26] J.E. Gillam, C.E. MacPhee, Modelling amyloid fibril formation kinetics: mechanisms of nucleation and growth, J. Phys. 25 (37) (2013) 373101.IOPScience
[27] M. Goedert, M.G. Spillantini, Propagation of tau aggregates, Mol. Brain 10 (18) (2017).
[28] M. Goedert, M.G. Spillantini, Ordered assembly of tau protein and neurodegeneration, 2019, Tau Biol. Adv. Exp. Med. Biol. 11843–22.
[29] A. Goriely, E. Kuhl, C. Bick, Neuronal oscillations on evolving networks: dynamics, damage, degradation, decline, dementia, and death, Phys. Rev. Lett. 125 (12) (2020) 128102.
[30] J.L. Guo, V.M. Lee, Seeding of normal tau by pathological tau conformers drives pathogenesis of Alzheimer-like tangles, J. Biol. Chem. 286 (17) (2011) 15317–15331.
[31] D.P. Hanger, G.M. Gibb, R. de Silva, A. Boutajangout, J.P. Brion, T. Revesz, A. J. Lees, B.H. Anderton, The complex relationship between soluble and insoluble tau in tauopathies revealed by efficient dephosphorylation and specific antibodies, FEBS Lett. 531 (2002) 538–542.
[32] S.C. Hopp, et al., The role of microglia in processing and spreading of bioactive tau seeds in Alzheimers disease, J. Neuroinflammation 15 (2018) 269.
[33] J.J. Iliff, A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β, Sci. Transl. Med 4 (147) (2012) 147ra111.
[34] K. Iqbal, F. Liu, C. Gong, I. Grundke-Iqbal, Tau in alzheimer disease and related tauopathies, Curr. Alzheimer Res. 7 (8) (2010) 656–664.
[35] L.M. Ittner, J. Götz, Amyloid-*beta* and tau–a toxic pas de deux in Alzheimer's disease, Nat. Rev. Neurosci. 12 (2) (2011) 65–72.
[36] M. Jucker, L.C. Walker, Self-propagation of pathogenic protein aggregates in neurodegenerative diseases, Nature 501 (7465) (2013) 4551.
[37] E. Kara, J.D. Marks, A. Aguzzi, Toxic protein spread in neurodegeneration: reality versus fantasy, Trends Mol. Med. 24 (12) (2018) 1007–1020.
[38] P.G. Kevrekidis, T.B. Thompson, A. Goriely, Anisotropic diffusion and traveling waves of toxic proteins in neurodegenerative diseases, Phys. Lett. A 384 (36) (2020) 126935.
[39] T.P.J. Knowles, et al., An analytical solution to the kinetics of breakable filament assembly, Science 326 (2009) 1533.
[40] S. Koundal, et al., Optimal mass transport with lagrangian workflow reveals advective and diffusion driven solute transport in the glymphatic system, Sci. Rep. 10 (1) (2020) 1990.
[41] F. Kundel, et al., Measurement of tau filament fragmentation provides insights into prion-like spreading, ACS Chem. Neurosci. 9 (2018) 1276–1282.
[42] C.A. Lasagna-Reeves, D.L. Castillo-Carranza, M.J. Guerrero-Muoz, G.R. Jackson, R. Kayed, Preparation and characterization of neurotoxic tau oligomers, Biochemistry 49 (2010) 10039–10041.
[43] J. Lewis, et al., Enhanced neurofibrillary degeneration in transgenic mice expressing mutant tau and APP, Science 293 (5534) (2001) 1487–1491.
[44] S. Maeda, et al., Granular tau oligomers as intermediates of tau filaments, Biochemistry 46 (12) (2007) 3856–3861.
[45] N. Maphis, et al., Reactive microglia drive tau pathology and contribute to the spreading of pathological tau in the brain, Brain 138 (2015) 1738–1755.
[46] M. Meyer-Luehmann, T.L. Spires-Jones, C. Prada, M. Garcia-Alloza, A. De Calignon, A. Rozkalne, J. Koenigsknecht-Talboo, D.M. Holtzman, B.J. Bacskai, B.T. Hyman, Rapid appearance and local toxicity of amyloid-β plaques in a mouse model of Alzheimer's disease, Nature 451 (7179) (2008) 720–724.
[47] L. Mosconi, V. Berti, L. Glodzik, A. Pupi, S. De, M.J. Santi, de Leon, Pre-clinical detection of Alzheimer's disease using FDG-PET, with or without amyloid imaging, J. Alzheimer's Dis. 20 (3) (2010) 843–854.
[48] R.M. Murphy, M.M. Pallitto, Probing the kinetics of β-amyloid self-association, Biophys. J. 130 (2–3) (2000) 109–122.
[49] J. Nasica-Labouze, et al., Amyloid β protein and Alzheimers disease: when computer simulations complement experimental studies, Chem. Rev. 115 (2015) 3518–3563.
[50] R.M. Nisbet, J.-C. Polanco, L.M. Ittner, J. Götz, Tau aggregation and its interplay with amyloid-β, Acta Neuropathol. 129 (2) (2015) 20–220.
[51] K. Ono, .M.M. Condron, D.B. Teplow, Structure–neurotoxicity relationships of amyloid–β protein oligomers, PNAS 106 (35) (2009) 1474–14750.
[52] M.M. Pallitto, R.M. Murphy, Mathematical model of the kinetics of beta-amyloid fibril growth from the denatured state, Biophys. J. 81 (3) (2001) 109–122.
[53] G. Pigino, et al., Disruption of fast axonal transport is a pathogenic mechanism for intraneuronal amyloid beta, Proc. Natl. Acad. Sci. U.S.A. 106 (14) (2009) 59075912.
[54] J. Pilliod, A. Desjardins, C. Pernègre, H. Jamann, C. Larochelle, E.A. Fon, N. Leclerc, Clearance of intracellular tau protein from neuronal cells via VAMP8-induced secretion, 2020, J. Biol. Chem., 295, 51, 17827–1784.
[55] A.M. Pooler, et al., Amyloid accelerates tau propagation and toxicity in a model of early Alzheimer's disease, Acta Neuropathol. Commun. 3 (1) (2015) 14.
[56] G.D. Rabinovici, Controversy and progress in alzheimers disease FDA approval of aducanumab, N. Engl. J. Med. (2021), https://doi.org/10.1056/NEJMp2111320.
[57] A. Raj, V. Tora, H. Cho, J.Y. Choi, Y.H. Ryu, C.H. Lyoo, B. Franchi, Combined model of aggregation and network diffusion recapitulates Alzheimer's regional tau-PET, Brain Connect. (2021).(to appear)
[58] A. Raj, Graph models of pathology spread in Alzheimer's disease: an alternative to conventional graph theoretic analysis, Brain Connect. (2021).
[59] A. Raj, A. Kuceyeski, M. Weiner, A network diffusion model of disease progression in dementia, Neuron 73 (2012) 1204–1215.
[60] G.A. Rodriguez, et al., Attenuation of entorhinal cortex hyperactivity reduces aβ and tau pathology, 2019, BioRxiv preprint. 10.1101/487405.
[61] M. Sakono, T. Zako, Amyloid oligomers: formation and toxicity of aβ oligomers, FEBS J. 277 (2010) 1348–1358.
[62] T. Scholz, E. Mandelkow, Transport and diffusion of tau protein in neurons, Cell. Mol. Life Sci. 71 (2014) 3139–3150.
[63] U. Sengupta, A.N. Nilson, R. Kayed, The role of amyloid β oligomers in toxicity, propagation and immunotherapy, EBioMedicine 6 (2016) 42–49.
[64] M. Tang, J. Harrison, C.A. Deaton, G.C.C. Johnson, Tau clearance mechanisms, in: A. Takashima, B. Wolozin, L. Buee (Eds.), Tau Biology, Advances in Experimental Medicine and Biology, vol. 1184, Springer, 2019.
[65] T.B. Thompson, P. Chaggar, E. Kuhl, A. Goriely, Protein-protein interactions in neurodegenerative diseases: a conspiracy theory, PLoS Comput. Biol. 16 (10) (2020) E1008267.
[66] T.B. Thompson, G. Meisl, T.P.J. Knowles, A. Goriely, The role of clearance mechanisms in the kinetics of pathological protein aggregation involved in neurodegenerative diseases, J. Chem. Phys. 154 (2021) 125101.
[67] T.T.M. Thu, N.T. Co, L.A. Tu, M.S. Li, Aggregation rate of amyloid beta peptide is controlled by beta-content in monomeric state, J. Chem. Phys. 150 (2019) 225101.
[68] B. Vasconcelos, et al., Heterotypic seeding of tau fibrillization by pre-aggregated aβ beta provides potent seeds for prion-like seeding and propagation of tau-pathology in vivo, Acta Neuropathol. 131 (2016) 549–569.
[69] V. Vinje, E.N. Bakker, M.E. Rognes, Brain solute transport is more rapid in periarterial than perivenous spaces, 10.1101/2021.03.23.436588.
[70] J. Weickenmeier, M. Jucker, A. Goriely, E. Kuhl, A physics-based model explains the prion-like features of neurodegeneration in Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, J. Mech. Phys. Solids 124 (2019) 264–281.
[71] L. Xie, et al., Sleep drives metabolite clearance from the adult brain, Science 342 (6156) (2013) 373–377.
[72] D.R. Thal, U. Rüb, M. Orantes, H. Braak, Phases of a beta-deposition in the human brain and its relevance for the development of AD, Neurology 58 (12) (2002) 17911800.
[73] J. Torok, et al., Emergence of directional bias in tau deposition from axonal transport dynamics, PLoS Comput. Biol. 17 (7) (2021) E1009258.

[74] W.-F. Xue, S. Homans, S.E. Radford, Systematic analysis of nucleation-dependent polymerization reveals new insights into the mechanism of amyloid self-assembly, Proc. Natl. Acad. Sci. U.S.A. 105 (2008) 8926–8931.
[75] W.-F. Xue, A.L. Hellewell, W.S. Gosal, S.W. Homans, E.W. Hewitt, Fibril fragmentation enhances amyloid cytotoxicity, J. Biol. Chem. 284 (49) (2009) 34272–34282.
[76] W.-F. Xue, A.L. Hellewell, E.W. Hewitt, S.E. Radford, Fibril fragmentation in amyloid assembly and cytotoxicity, Prion 4 (1) (2010) 20–25.
[77] K. Yamada, Extracellular tau and its potential role in the propagation of tau pathology, Front. Neurosci. 11 (2017) 667.
[78] K. Yamada, et al., Neuronal activity regulates extracellular tau in vivo, J. Exp. Med. 211 (3) (2014) 387–393.
[79] L.C. Walker, Mechanisms of protein seeding in neurodegenerative diseases, JAMA Neurol. 70 (3) (2013) 304310.
[80] P. Zhang, et al., Senolytic therapy alleviates a β-associated oligodendrocyte progenitor cell senescence and cognitive deficits in an Alzheimers disease model, Nat. Neurosci. 22 (2019) 719–728.