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Local and nonlocal integro-differential reaction-diffusion models for protein dynamics in Alzheimer's disease

Tesi di Laurea Magistrale in Analisi Matematica

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Introduzione

Alla base di un qualsiasi progresso scientifico c'è la collaborazione tra campi totalmente differenti al fine di perseguire un obiettivo comune. La matematica non fa eccezione e anch'essa può dare un contributo determinante, anche se ai più questo fatto non è noto. E' purtroppo convinzione comune che la matematica sia distante dalla vita di tutti i giorni e che rimanga essenzialmente un campo teorico. Approfondendo gli studi in ambito matematico però si può osservare come siano presenti, oltre ad ambiti di studio prettamente teorici, anche campi della matematica fortemente applicativi, mirati a dare risposte a problemi e interrogativi della vita ordinaria.
L'obiettivo di questo elaborato, frutto degli ultimi mesi di lavoro del mio percorso universitario, è riassumere ed esporre un esempio di come la matematica possa cooperare con la biologia e la medicina al fine di prevedere sviluppi di malattie. In particolare si vuole mostrare come, mediante sistemi di PDEs, si possano descrivere quelli che sono alcuni degli elementi principali della malattia d'Alzheimer.
Perchè proprio questa patologia? Secondo l'Organizzazione Mondiale della Sanità attualmente nel mondo sono presenti più di 55 milioni di persone affette da demenza, di cui all'incirca il $60 - 70\%$ presentano in particolare la malattia d'Alzheimer. Numeri di questo genere portano la demenza ad essere la settima causa di morte a livello mondiale [33]. La patologia d'Alzheimer colpisce principalmente persone di età superiore ai 60 anni e si ha un andamento crescente dell'incidenza con il progredire dell'età. Pertanto, a causa dell'aumento dell'età media della popolazione mondiale, si stima che le persone affette da demenza saranno circa 78 milioni nel 2030 e 139 milioni nel 2050.
A seguito di questi numeri importanti la comunità scientifica si sta concentrando molto sulla ricerca che abbia come focus la malattia d'Alzheimer, in particolare su quelle che sono le cause biologiche e in generale il processo che porta alla progressione della malattia al fine di trovare, se non una cura per la stessa, un protocollo per garantire una diagnosi il più precoce possibile ed il rallentamento del progredire della malattia.
La matematica contribuisce in questo processo elaborando modelli che permettano di fare previsioni mediante simulazioni e confrontare i risultati di queste ultime con quelli che sono i dati sperimentali. Tutto questo con il fine

di verificare quali delle dinamiche considerate siano corrette, quali ancora da migliorare, quali introdurre e quali accantonare.
In questo elaborato si procede quindi alla costruzione di modelli che descrivano l'evoluzione temporale e spaziale di due dei principali attori della malattia d'Alzheimer, ossia la proteina β-amiloide e la proteina τ nelle loro versioni sane e mal ripiegate. In particolare dopo aver descritto da un punto di vista fisiologico le dinamiche principali delle due proteine, si costruisce un modello locale partendo dal modello eterodimero. Infatti questo modello descrive l'interazione base tra proteine e lo si modifica andando ad integrare osservazioni sui funzionali di Holling, relative a modelli che descrivono le dinamiche di popolazione nel caso preda-predatore. Si passa successivamente allo studio di modelli non locali che permettono una descrizione più fine delle dinamiche interne principalmente per quanto riguarda le interazioni tra proteine, ponendo particolare attenzione alle scelte matematiche fatte, soprattutto riguardanti i kernel di convoluzione utilizzati. Dopo un breve paragrafo che presenti le caratteristiche generali dei modelli non locali e le proprietà favorevoli o meno all'utilizzo di tali modelli, si passa all'analisi di due ulteriori modelli non locali in cui viene però considerata, rispettivamente, una crescita di popolazione logistica ed una curva di crescita di Gompertz.
Per tutti i modelli esposti si procede sia alla determinazione dei punti di equilibrio e allo studio della loro stabilità, facendo riferimenti a come questi rappresentino o meno stati con significato medico e non solo matematico, sia allo studio delle disuguaglianze di clearance, ossia l'elemento matematico che serve a descrivere l'inizio dello sviluppo della malattia a seconda del valore dei parametri in gioco nel modello.
Nell'ultimo capitolo viene infine esposto come questi modelli continui possano essere trasformati in modelli discreti su un grafo al fine di poter sviluppare simulazioni e verificare la compatibilità dei modelli con i dati sperimentali a disposizione. Mentre per l'operatore Laplaciano sul grafo vengono date solamente le nozioni base per la sua introduzione, in quanto già presenti in letteratura molti testi a riguardo, per l'operazione di convoluzione sul grafo ci si sofferma in maniera più dettagliata. Questo perchè prima di tutto la convoluzione è lo strumento fondamentale che permette la distinzione del modello non locale da quello locale e secondariamente perchè la strada seguita per ottenere la convoluzione nel modello discreto non risulta essere quella standard indicata dalla teoria matematica.
Per concludere il nostro studio terminiamo con alcune osservazioni ottenute mediante simulazioni dei modelli esposti sul grafo.

Introduction

The basis of any scientific progress is the collaboration among totally different fields in order to pursue a common goal. Mathematics is no exception and can also make a decisive contribution, even if this fact is not widely known. Unfortunately, it is a common belief that mathematics is distant from everyday life and remains essentially a theoretical field. If one delves deeper into mathematical studies, however, it can be seen that, in addition to purely theoretical fields of study, there are also fields of mathematics that are strongly applied, aimed at providing answers to problems and questions from everyday life.

The aim of this thesis, which is the fruit of the last few months of my academic path, is to summarise and present an example of how mathematics can cooperate with biology and medicine in order to predict diseases developments. In particular, we want to show how, by means of PDEs systems, we can describe some of the main elements of Alzheimer's disease.

Why this disease? According to the World Health Organization, there are currently more than 55 million people in the world suffering from dementia, of which approximately $60 - 70\%$ have Alzheimer's disease. Such numbers bring dementia to be the seventh leading cause of death worldwide [33]. Alzheimer's disease mainly affects people over 60 years of age and there is an increasing trend in incidence with advancing age. Therefore, due to the increasing average age of the world population, it is estimated that there will be about 78 million people with dementia in 2030 and 139 million in 2050.

As a result of these large numbers, the scientific community is focusing heavily on research that has Alzheimer's disease as its target, in particular on its biological causes and on the process that leads to the disease progression in order to find, if not a cure for it, at least a protocol to ensure the earliest possible diagnosis and to slow down the disease progress.

Mathematics contributes to this process by developing models that allow to make predictions through simulations and to compare the results of these with experimental data. All of this with the aim to check which of the dynamics considered are correct, compared to those that still need to be improved, to be introduced and to be set aside.

In this work, models are built to describe the temporal and spatial evolu-

tion of two major players in Alzheimer's disease, namely β-amyloid protein and τ protein in their healthy and misfolded versions. In particular, after describing from a physiological point of view the main dynamics of the two proteins, a local model is constructed from the heterodimer model. Indeed this model describes the basic protein-protein interactions and it is then modified by adding remarks on Holling's functionals, obtained from models describing population dynamics in the prey-predator case. We then move on to the study of nonlocal models that allow a finer description of the internal dynamics, especially regarding protein interactions, paying particular attention to the mathematical choices made, and especially focusing on the convolution kernels used. After a brief paragraph presenting the general features of nonlocal models and the characteristics that are favorable or unfavorable to the use of such models, we move further by analyzing two other different nonlocal models in which either a logistic population growth or a Gompertz's curve of growth are taken into account.
For all the models exhibited, we proceed both to the determination of the equilibrium points and with the study of their stability, making reference to whether or not they represent states with medical and not only mathematical meaning, and to the study of clearance inequalities, i.e. the mathematical element that aims to describe the onset of the disease development depending on the value of the parameters involved in the model.
In the last chapter, it is finally explained how these continuous models can be transformed into discrete models on a graph in order to develop simulations and verify the compatibility of the models with the available experimental data. Whilst for the Laplacian operator on the graph only the basics are given for its introduction, as there are already many texts on the subject in the literature, for the convolution operation on the graph we go into more detail. This is because, on one hand, convolution is the fundamental instrument that allow the distinction between the local and the nonlocal model, on the other hand, because the path followed to obtain the convolution in the discrete model is not the standard one indicated by the mathematical theory.
To conclude our study, we end with some remarks obtained through simulations of the exposed models on the graph .

Contents

Chapter 1

Construction and analysis of a local model

In order to build a mathematical model that is consistent with reality, it is necessary to bear in mind the main players in Alzheimer's disease (AD for short) that we will take into account: the β-amyloid protein and the τ protein.
The β-amyloid protein, more simply called $A\beta$, is a protein that is naturally present in the parenchyma and under healthy conditions there is a balance between its production, from the transmembrane protein APP, and its clearance. However, under altered conditions, the $A\beta$ protein may begin to accumulate, giving rise to more complex structures known as senile plaques (as described in [42]). According to the amyloid cascade hypothesis, which was the main theory for the development of Alzheimer's disease until the early 2000s, these plaques were the cause of a succession of cascading events that ended with the symptoms of AD. However, recently it has become clear that these plaques cannot be considered the sole origin of the disease but rather we must also consider the fundamental role of the protein τ, as noted in [7].
This protein can be naturally found within axons and normally plays a stabilizing role for axons by constructing ordered structures called microtubules. As for the $A\beta$ protein, there is a process of production and clearance of the protein under healthy conditions. Due to reasons that are yet unclear, the clearance process of the protein may fail totally or partially, thus initiating a phase of protein accumulation with the subsequent creation of fibrils. According to recent studies, the abnormal presence of $A\beta$ protein induces a toxic character in the τ proteins, and the latter in turn enhances the presence of the former. There is therefore, as remarked by Busche and Hyman in [7], a synergistic effect on the toxicity of the two proteins. Another factor to be taken into account is that toxicity in the case of both proteins may be in a certain sense "transmitted", that is coming into contact with toxic $A\beta$

or τ proteins leads proteins of the same type to become toxic (misfolded). For this reason, currently developed models for modeling Alzheimer's disease consider the prions contribution ([18]) or they are often based, as mentioned in [40] and [21], on the prion-like hypothesis: neurodegenerative diseases, in which the cause lies mainly in proteins, are characterized by the progressive spread and self-induced amplification of misfolded protein assemblies via axon channels. In the case of Alzheimer's disease, following [40], both the $A\beta$ and τ proteins reflect this behavior typical of prions (hence the name of the hypothesis), i.e. the ability to transmit the misfolded form to normal variants of the protein with a resulting formation of deposits. Now, having these basic dynamics in mind, we can begin to elaborate the model.

1.1 Construction of the model

We want to construct a model at the macroscopic level that is capable of accurately describing the trend of the concentrations of the proteins involved, namely $A\beta$ and τP, in their healthy and toxic versions. Therefore, we first introduce the following notation, common to all models that will be set out: we will work in a spatial domain Ω of $\mathbb{R}^3$. For $x \in \Omega$ and for a time $t \in \mathbb{R}^+$, let $u = u(x,t)$ and $\tilde{u} = \tilde{u}(x,t)$ be the healthy and toxic concentrations of protein $A\beta$, respectively. Similarly, let us denote by $v = v(x,t)$ and $\tilde{v} = \tilde{v}(x,t)$ the healthy and toxic concentrations of τP.
The basic model that links the concentrations of healthy and toxic proteins is called the heterodimer model (referring to the medical term that emphasizes the different chemical nature of the misfolded protein and the normal variant) and was developed to model prion interactions. Since, as mentioned above, both the $A\beta$ and τ proteins have similar behavior, we use the heterodimer model as a starting point for the development of more complex models. In the case of the $A\beta$ protein, the heterodimer model can be expressed, following [24], as below

$$\begin{cases} \frac{\partial u}{\partial t} = a_0 - a_1 u - a_2 u\tilde{u} \\ \frac{\partial \tilde{u}}{\partial t} = -\tilde{a}_1 \tilde{u} + a_2 u\tilde{u} \end{cases}$$

where a_0 is the average rate of production of healthy $A\beta$ protein, a_1 and $\tilde{a}_1$ the rates of average clearance of healthy and toxic $A\beta$, respectively. On the other hand, a_2 corresponds to the average conversion rate of a healthy protein into a toxic one when they interact. For this reason the term governed by a_2 is present in both equations with opposite sign. We note that since there is no production of toxic $A\beta$ proteins in our bodies, there is no production term in the second equation.
These proteins, however, do not remain fixed at one point in space, rather

they are transported within the parenchyma or through the network of axonal channels and so we will have to introduce a diffusive term within the model to consider this behavior, obtaining:

$$\begin{cases} \frac{\partial u}{\partial t} = \nabla \cdot (D_1 \nabla u) + a_0 - a_1 u - a_2 u\tilde{u} \\ \frac{\partial \tilde{u}}{\partial t} = \nabla \cdot (\tilde{D}_1 \nabla \tilde{u}) - \tilde{a}_1 \tilde{u} + a_2 u\tilde{u} \end{cases}$$

where D_1 e $\tilde{D}_1$ are diffusion tensors that characterize diffusion of each relevant protein. For example, in the case of the τ protein, for which an entirely analogous system holds, we will have that the directions given by the axons will be favored over others. Therefore, following what was observed in [43], one could consider $\tilde{D}_1 = d_\perp \mathbf{1} + (d_\parallel - d_\perp)\gamma \otimes \gamma$ where $\gamma = \gamma(x,t)$ is a unit vector characterizing the direction of the axonal bundle, $d_\perp$ is the diffusion coefficient of the orthogonal direction to the direction of the axons and $d_\parallel \gg d_\perp$ is the diffusion coefficient along the axons. Instead, if isotropic diffusion, meaning without preferential directions, is to be considered we will have that the tensors D_1 and $\tilde{D}_1$ will be multiples of the identity and thus we will get the usual Laplacian operator: e.g. in the case of the healthy $A\beta$ protein, assuming $D_1 = d_1 \mathbb{1}$ we will obtain $\nabla \cdot (D_1 \nabla u) = d_1 \Delta u$.
Similarly, it is also possible to derive analogous equations for the protein τ, with parameters denoted by $b_0, b_1, \tilde{b}_1, b_2$ of equal meaning. The resulting global system is the following:

$$\begin{cases} \frac{\partial u}{\partial t} = \nabla \cdot (D_1 \nabla u) + a_0 - a_1 u - a_2 u\tilde{u} \\ \frac{\partial \tilde{u}}{\partial t} = \nabla \cdot (\tilde{D}_1 \nabla \tilde{u}) - \tilde{a}_1 \tilde{u} + a_2 u\tilde{u} \\ \frac{\partial v}{\partial t} = \nabla \cdot (D_2 \nabla v) + b_0 - b_1 v - b_2 v\tilde{v} \\ \frac{\partial \tilde{v}}{\partial t} = \nabla \cdot (\tilde{D}_2 \nabla \tilde{v}) - \tilde{b}_1 \tilde{v} + b_2 v\tilde{v} \end{cases} \tag{1.1}$$

However, in this way we would have two pairs of equations with no connection between the two protein families $A\beta$ and τ, i.e. the equations are uncoupled, which is not realistic from the physiological point of view.
As expressed in [40], three main components must be taken into account when modeling interactions:

- action of the $A\beta$ protein on τ: the creation of new toxic τP from healthy τP is enhanced by the presence of toxic $A\beta$
- action of the τ protein on $A\beta$: the toxicity of $A\beta$ depends on the presence of τP, as explained in [20]
- $A\beta$ and τP enhance each other's toxicity, as reported in [20]

In order to introduce a model that takes the first point into account, we insert a term into the diffusive heterodimer model for the protein τP, dependent on a parameter b_3, that governs the interaction between the toxic $A\beta$ protein

and the τP according to the relationship set out in the first point. We thus obtain the following system of coupled PDEs

$$\begin{cases} \frac{\partial u}{\partial t} = \nabla \cdot (D_1 \nabla u) + a_0 - a_1 u - a_2 u\tilde{u} \\ \frac{\partial \tilde{u}}{\partial t} = \nabla \cdot (\tilde{D}_1 \nabla \tilde{u}) - \tilde{a}_1 \tilde{u} + a_2 u\tilde{u} \\ \frac{\partial v}{\partial t} = \nabla \cdot (D_2 \nabla v) + b_0 - b_1 v - b_2 v\tilde{v} - b_3 \tilde{u} v\tilde{v} \\ \frac{\partial \tilde{v}}{\partial t} = \nabla \cdot (\tilde{D}_2 \nabla \tilde{v}) - \tilde{b}_1 \tilde{v} + b_2 v\tilde{v} + b_3 \tilde{u} v\tilde{v} \end{cases} \tag{1.2}$$

Nevertheless, we must now take into account also the other two interactions. The precise dynamics by which these proteins influence each other are unclear: what is certain, however, is that their interaction leads to the creation of aggregates of toxic proteins that damage the neuronal region. It is therefore necessary to introduce a function $q(x,t) \in [0,1]$ measuring the neuronal damage at point x at time instant t. In the case where $q(x,t) = 0$ this will mean that the neurons located at point x are healthy, whereas if it takes the value 1, the neurons at x are irreparably damaged (this includes both the case in which they are already dead and the case in which they have reached such damage that they undergo apoptosis). The evolution of the damage will then be described by the equation

$$\frac{\partial q}{\partial t} = (k_1 \tilde{u} + k_2 \tilde{v} + k_3 \tilde{u}\tilde{v} + k_4 \mathcal{A}(q))(1 - q) \tag{1.3}$$

with the initial condition $q(x,0) = 0$ since we assume to start from a healthy condition at each point of Ω. In this expression, k_1 and k_2 express the contribution of the toxic proteins $A\beta$ and τP to the neurological damage at point x as a result of the toxic aggregates (senile plaques and fibrils) being formed. As for what concerns k_3, this allows the damage caused by the interaction of both these toxic proteins to be taken into account, i.e. it allows the other two interaction hypotheses set out above to be considered. Concerning the last term of the RHS, for the moment, we limit ourselves to say that it allows us to model the damage that occurs in x as a result of contributions due to nonlocal factors, as stated in [40], and it will be analyzed in detail later. We observe that in the RHS there is the multiplication by the factor $1 - q$ because in the case where $q(x,t) = 1$, namely the damage is irreparable and has already reached its maximum value, this value must remain constant for future times and therefore its derivative with respect to time must be zero.

However, the system 1.2 can be made even more precise. For example, let us consider the case of the $A\beta$ protein (it will be analogous for τP). The interaction between the healthy and toxic protein can be schematized, as observed in [15], by means of the following three steps:

$$u + \tilde{u} \xrightarrow{t_1} u\tilde{u} \xrightarrow{t_2} \tilde{u}\tilde{u} \xrightarrow{t_3} \tilde{u} + \tilde{u}$$

That is, when the healthy protein is approached, a time t_1 is needed for its binding to the toxic protein, then a time t_2 is necessary in order to induce misfolding and thus for the healthy protein to be converted into a toxic one, and finally a time t_3 is needed for the toxic proteins to separate again. We have so far considered these three distinct processes as a single step by introducing the coefficients a_2 and b_2, not considering these transition times in practice. In other words, in the model presented so far, we are assuming that the probability of the encounter between toxic and healthy proteins in a fixed spatial region in a time interval T_t depends linearly on the density of the healthy protein. Indeed, the relationship we assume is

$$Y = aT_s u$$

where Y is the density of healthy protein consumed by a unit of toxic protein, T_s is the time for contact to occur and a is a constant of proportionality, also known as the rate of discovery. A phenomenology similar to this was studied by Holling in the context of predator-prey models, as described in [10]. In the case in which $T_s = T_t$, where no time is needed for the toxic protein to change the nature of the healthy protein, Holling speaks of a type I response and this is exactly what we have supposed for the moment: assuming that each toxic protein acts independently from the others, in a time T_t we will have that the density of healthy protein will have decreased by $aT_t u\tilde{u}$ and $\tilde{u}$ will have increased by the same amount. As suggested in [30], it can be assumed that each healthy protein requires a reaction time $t_2 = h$ to be converted to toxic (considering instead the binding and division processes as instantaneous, i.e. $t_1 = t_3 = 0$). Thus, following the construction of the type II Holling's functional described in [10], we will have that the time available for contact between the proteins to occur, maintaining the notation that Y represents the amount of healthy protein attached/consumed, is $T_s = T_t - hY$. Consequently, the density of healthy protein consumed by a unit of toxic protein will be given by $Y = a(T_t - hY)u$, from which $Y = \frac{aT_t u}{1+ahu}$ (Holling's functional of type II). Assuming again that each toxic protein acts independently from the others, we will obtain that in a time T_t the density of healthy protein will be decreased by $\frac{aT_t u}{1+ahu}\tilde{u}$. The exact same reasoning can be made for τP. So if in our model we denote $a_2 = a_\beta T_t$, $b_2 = a_\tau T_t$, $c_u = a_\beta h_\beta$ and $c_v = a_\tau h_\tau$, we obtain the following system

$$\begin{cases} \frac{\partial u}{\partial t} = \nabla \cdot (D_1 \nabla u) + a_0 - a_1 u - \frac{a_2 u}{1+c_u u}\tilde{u} \\ \frac{\partial \tilde{u}}{\partial t} = \nabla \cdot (\tilde{D}_1 \nabla \tilde{u}) - \tilde{a}_1 \tilde{u} + \frac{a_2 u}{1+c_u u}\tilde{u} \\ \frac{\partial v}{\partial t} = \nabla \cdot (D_2 \nabla v) + b_0 - b_1 v - \frac{b_2 v}{1+c_v v}\tilde{v} - b_3 \tilde{u} v \tilde{v} \\ \frac{\partial \tilde{v}}{\partial t} = \nabla \cdot (\tilde{D}_2 \nabla \tilde{v}) - \tilde{b}_1 \tilde{v} + \frac{b_2 v}{1+c_v v}\tilde{v} + b_3 \tilde{u} v \tilde{v} \end{cases} \tag{1.4}$$

Due to this modification, we have that the conversion rate of healthy to toxic proteins increases as the density of the former increases, but not in

uncontrolled manner. Indeed, we will reach a point where this conversion rate will become saturated and thus will start to tend towards a constant.

Remark 1.1. The model 1.4, proposed in [30] and taken up in [31], ignores the times t_1 and t_3 of the process. Following what is described in [19] we observe that it is possible to include them in the model using similar procedures. Suppose, for example, that we wish to consider not only time t_2 but also time t_1. Assuming that each toxic protein takes a time t_1 to bind and a time t_2 to introduce misfolding, we will have that the time available for the contact is $T_s = T_t - (t_1 + t_2)Y$. It follows, with similar reasoning to the previous case and always assuming that the toxic proteins act independently, that the density of healthy protein will be decreased by the factor $\frac{aT_t u}{1+a(t_1+t_2)u}\tilde{u}$.

1.2 Equilibrium points analysis

Having a complete reaction-diffusion model at this point we can move forward to the study of the temporal dynamics. In particular, we begin by studying its equilibrium points and relative stability. Being purely temporal dynamics, to do this we do not consider the terms that contribute solely with the spatial dynamics, i.e. the diffusive terms, obtaining the following system of ODEs

$$\begin{cases} \frac{du}{dt} = a_0 - a_1 u - \frac{a_2 u}{1+c_u u}\tilde{u} \\ \frac{d\tilde{u}}{dt} = -\tilde{a}_1\tilde{u} + \frac{a_2 u}{1+c_u u}\tilde{u} \\ \frac{dv}{dt} = b_0 - b_1 v - b_3\tilde{u}v\tilde{v} - \frac{b_2 v}{1+c_v v}\tilde{v} \\ \frac{d\tilde{v}}{dt} = -\tilde{b}_1\tilde{v} + b_3\tilde{u}v\tilde{v} + \frac{b_2 v}{1+c_v v}\tilde{v} \end{cases} \tag{1.5}$$

with non-zero initial conditions.
Let us first denote $(u, \tilde{u}, v, \tilde{v})$ the coordinates of the equilibrium points .
In order to determine them, we decide to proceed in the following way: we first determine the axial equilibrium points, that is those in which at least one of the components is null, and then those in which none of the components is null. Remember that, in order for these to be stationary points, the following system must be solved for each parameter value

$$\begin{cases} a_0 - a_1 u - \dfrac{a_2 u}{1 + c_u u}\tilde{u} = 0 & \text{(1.6a)} \\ -\tilde{a}_1\tilde{u} + \dfrac{a_2 u}{1 + c_u u}\tilde{u} = 0 & \text{(1.6b)} \\ b_0 - b_1 v - b_3\tilde{u}v\tilde{v} - \dfrac{b_2 v}{1 + c_v v}\tilde{v} = 0 & \text{(1.6c)} \\ -\tilde{b}_1\tilde{v} + b_3\tilde{u}v\tilde{v} + \dfrac{b_2 v}{1 + c_v v}\tilde{v} = 0 & \text{(1.6d)} \end{cases}$$

Let us therefore begin by analyzing the various cases:

- by placing $u = 0$ we obtain from the equation 1.6a that $a_0 = 0$. So in general we will not have stationary points with zero first component, since $a_0 > 0$.
- by posing $\tilde{u} = 0$ we have that the equation 1.6b is satisfied for every value of the parameters, so we proceed by substituting in the other equations:

$$\begin{cases} u = \frac{a_0}{a_1} \\ \tilde{u} = 0 \\ b_0 - b_1 v - \frac{b_2 v}{1+c_v v}\tilde{v} = 0 \\ -\tilde{b}_1 \tilde{v} + \frac{b_2 v}{1+c_v v}\tilde{v} = 0 \end{cases} \Rightarrow \begin{cases} u = \frac{a_0}{a_1} \\ \tilde{u} = 0 \\ \tilde{v} = \frac{b_0 - b_1 v}{\tilde{b}_1} \\ (b_0 - b_1 v)(-1 + \frac{b_2 v}{\tilde{b}_1(1+c_v v)}) = 0 \end{cases}$$

Continuing the case-by-case analysis we obtain as a first solution

$$E_1 = (\frac{a_0}{a_1}, 0, \frac{b_0}{b_1}, 0)$$

and as a second solution

$$\begin{cases} u = \frac{a_0}{a_1} \\ \tilde{u} = 0 \\ \tilde{v} = \frac{b_0 - b_1 v}{\tilde{b}_1} \\ -1 + \frac{b_2 v}{\tilde{b}_1(1+c_v v)} = 0 \end{cases} \Rightarrow \begin{cases} u = \frac{a_0}{a_1} \\ \tilde{u} = 0 \\ \tilde{v} = \frac{b_0 - b_1 v}{\tilde{b}_1} \\ v = \frac{\tilde{b}_1}{b_2 - c_v \tilde{b}_1} \end{cases}$$

that is, written in a compact way:

$$E_2 = (\frac{a_0}{a_1}, 0, \frac{\tilde{b}_1}{b_2 - \tilde{b}_1 c_v}, \frac{b_0(b_2 - \tilde{b}_1 c_v) - b_1 \tilde{b}_1}{\tilde{b}_1(b_2 - c_v \tilde{b}_1)})$$

- if $v = 0$ the equation 1.6c would lead to $b_0 = 0$ so in general we will not have stationary points with zero component v, since $b_0 > 0$.
- by posing $\tilde{v} = 0$ we obtain that the equation 1.6d is satisfied for all parameter values. Continuing with the calculations and substituting, we get

$$\begin{cases} a_0 - a_1 u - \frac{a_2 u}{1+c_u u}\tilde{u} = 0 \\ -\tilde{a}_1 \tilde{u} + \frac{a_2 u}{1+c_u u}\tilde{u} = 0 \\ v = \frac{b_0}{b_1} \\ \tilde{v} = 0 \end{cases} \Rightarrow \begin{cases} (a_0 - a_1 u)(-1 + \frac{a_2 u}{\tilde{a}_1(1+c_u u)}) = 0 \\ \tilde{u} = \frac{a_0 - a_1 u}{\tilde{a}_1} \\ v = \frac{b_0}{b_1} \\ \tilde{v} = 0 \end{cases}$$

So the first solution we find is given by

$$E_1 = (\frac{a_0}{a_1}, 0, \frac{b_0}{b_1}, 0)$$

which was already found, while the second solves the system

$$\begin{cases} -1 + \frac{a_2 u}{\tilde{a}_1(1+c_u u)} = 0 \\ \tilde{u} = \frac{a_0 - a_1 u}{\tilde{a}_1} \\ v = \frac{b_0}{b_1} \\ \tilde{v} = 0 \end{cases}$$

and then is given by

$$E_3 = (\frac{\tilde{a}_1}{a_2 - \tilde{a}_1 c_u}, \frac{a_0(a_2 - \tilde{a}_1 c_u) - a_1 \tilde{a}_1}{\tilde{a}_1(a_2 - \tilde{a}_1 c_u)}, \frac{b_0}{b_1}, 0)$$

Let us now look for stationary points that have all non-zero components. We therefore proceed to solve the following system

$$\begin{cases} a_0 - a_1 u - \frac{a_2 u}{1+c_u u}\tilde{u} = 0 \\ -\tilde{a}_1 \tilde{u} + \frac{a_2 u}{1+c_u u}\tilde{u} = 0 \\ b_0 - b_1 v - b_3 \tilde{u} v \tilde{v} - \frac{b_2 v}{1+c_v v}\tilde{v} = 0 \\ -\tilde{b}_1 \tilde{v} + b_3 \tilde{u} v \tilde{v} + \frac{b_2 v}{1+c_v v}\tilde{v} = 0 \end{cases} \Rightarrow \begin{cases} a_0 - a_1 u - \tilde{a}_1 \tilde{u} = 0 \\ -\tilde{a}_1 \tilde{u} + \frac{a_2 u}{1+c_u u}\tilde{u} = 0 \\ b_0 - b_1 v - \tilde{b}_1 \tilde{v} = 0 \\ -\tilde{b}_1 \tilde{v} + \frac{b_2 v}{1+c_v v}\tilde{v} + b_3 \tilde{u} v \tilde{v} = 0 \end{cases}$$

$$\Rightarrow \begin{cases} \tilde{u} = \frac{a_0 - a_1 u}{\tilde{a}_1} \\ -a_0 + a_1 u + \frac{a_2 u}{1+c_u u}\frac{a_0 - a_1 u}{\tilde{a}_1} = 0 \\ \tilde{v} = \frac{b_0 - b_1 v}{\tilde{b}_1} \\ -b_0 + b_1 v + \frac{b_2 v}{1+c_v v}\frac{b_0 - b_1 v}{\tilde{b}_1} + b_3 \frac{a_0 - a_1 u}{\tilde{a}_1} v \frac{b_0 - b_1 v}{\tilde{b}_1} = 0 \end{cases}$$

From which we obtain the following system to be studied by cases:

$$\begin{cases} \tilde{u} = \dfrac{a_0 - a_1 u}{\tilde{a}_1} & \text{(1.7a)} \\ (a_0 - a_1 u)(-1 + \dfrac{a_2 u}{\tilde{a}_1(1 + c_u u)}) = 0 & \text{(1.7b)} \\ \tilde{v} = \dfrac{b_0 - b_1 v}{\tilde{b}_1} & \text{(1.7c)} \\ (b_0 - b_1 v)(-1 + \dfrac{b_2 v}{\tilde{b}_1(1 + c_v v)} + b_3 \dfrac{(a_0 - a_1 u)v}{\tilde{a}_1 \tilde{b}_1}) = 0 & \text{(1.7d)} \end{cases}$$

We proceed by distinguishing the two cases arising from 1.7b. However, we do not report the results obtained for $u = \frac{a_0}{a_1}$ since they lead to $\tilde{u} = 0$ and therefore to a state with at least one zero component. The case we are interested in is therefore:

$$\begin{cases} u = \frac{\tilde{a}_1}{a_2 - \tilde{a}_1 c_u} \\ \tilde{u} = \frac{a_0(a_2 - \tilde{a}_1 c_u) - a_1 \tilde{a}_1}{\tilde{a}_1(a_2 - \tilde{a}_1 c_u)} \\ (b_0 - b_1 v)(-1 + \frac{b_2 v}{\tilde{b}_1(1+c_v v)} + \frac{b_3}{\tilde{b}_1}\tilde{u} v) = 0 \\ \tilde{v} = \frac{b_0 - b_1 v}{\tilde{b}_1} \end{cases}$$

from which, analyzing further by cases and excluding $v = \frac{b_0}{b_1}$ since it would lead to a null component, we get:

$$\begin{cases} u = \frac{\tilde{a}_1}{a_2 - \tilde{a}_1 c_u} \\ \tilde{u} = \frac{a_0(a_2 - \tilde{a}_1 c_u) - a_1 \tilde{a}_1}{\tilde{a}_1(a_2 - \tilde{a}_1 c_u)} \\ \tilde{v} = \frac{b_0 - b_1 v}{\tilde{b}_1} \\ -(1 + c_v v)\tilde{b}_1 + b_2 v + (1 + c_v v) b_3 \tilde{u} v = 0 \end{cases}$$

We observe that the equation that must satisfy v is simply the last equation of the initial system written in a different form (calculating the common denominator and dividing by $\tilde{v}$, since it is assumed to be different from zero). We then get

$$\begin{cases} u = \frac{\tilde{a}_1}{a_2 - \tilde{a}_1 c_u} \\ \tilde{u} = \frac{a_0(a_2 - \tilde{a}_1 c_u) - a_1 \tilde{a}_1}{\tilde{a}_1(a_2 - \tilde{a}_1 c_u)} \\ \tilde{v} = \frac{b_0 - b_1 v}{\tilde{b}_1} \\ b_3 c_v \tilde{u} v^2 + (b_3 \tilde{u} - c_v \tilde{b}_1 + b_2) v - \tilde{b}_1 = 0 \end{cases}$$

Consequently, we can summarize the model's steady states by

$$\begin{aligned} E_1 &= (\frac{a_0}{a_1}, 0, \frac{b_0}{b_1}, 0) \\ E_2 &= (\frac{a_0}{a_1}, 0, \frac{\tilde{b}_1}{b_2 - \tilde{b}_1 c_v}, \frac{b_0(b_2 - \tilde{b}_1 c_v) - b_1 \tilde{b}_1}{\tilde{b}_1(b_2 - c_v \tilde{b}_1)}) \\ E_3 &= (\frac{\tilde{a}_1}{a_2 - \tilde{a}_1 c_u}, \frac{a_0(a_2 - \tilde{a}_1 c_u) - a_1 \tilde{a}_1}{\tilde{a}_1(a_2 - \tilde{a}_1 c_u)}, \frac{b_0}{b_1}, 0) \\ E_* &= (\frac{\tilde{a}_1}{a_2 - \tilde{a}_1 c_u}, \frac{a_0(a_2 - \tilde{a}_1 c_u) - a_1 \tilde{a}_1}{\tilde{a}_1(a_2 - \tilde{a}_1 c_u)}, v_*, \frac{b_0 - b_1 v_*}{\tilde{b}_1}) \end{aligned}$$

where v_* in the point E_* satisfies the second-degree equation

$$b_3 c_v \tilde{u} v^2 + (b_3 \tilde{u} - c_v \tilde{b}_1 + b_2) v - \tilde{b}_1 = 0$$

Baring in mind that we are working with quantities that represent densities, for the above points to be admissible, all their components must be non-negative, in particular E_* must also have non-null components. We can therefore make the following observations:

- for the existence of E_2:
  i. $b_2 - \tilde{b}_1 c_v > 0$ i.e. $b_2 > c_v \tilde{b}_1$
  ii. $b_0(b_2 - \tilde{b}_1 c_v) - b_1 \tilde{b}_1 \geq 0$ so $\frac{b_0}{b_1} \geq \frac{\tilde{b}_1}{b_2 - c_v \tilde{b}_1}$
- for the existence of E_3:

i. $a_2 - \tilde{a}_1 c_u > 0$ from which follows $a_2 > c_u \tilde{a}_1$

ii. $a_0(a_2 - \tilde{a}_1 c_u) - a_1 \tilde{a}_1 \geq 0$ consequently $\frac{a_0}{a_1} \geq \frac{\tilde{a}_1}{a_2 - c_u \tilde{a}_1}$

- for the existence of E_*:

  i. $a_2 - \tilde{a}_1 c_u > 0$ implying $a_2 > c_u \tilde{a}_1$

  ii. $a_0(a_2 - \tilde{a}_1 c_u) - a_1 \tilde{a}_1 > 0$ that is $\frac{a_0}{a_1} > \frac{\tilde{a}_1}{a_2 - c_u \tilde{a}_1}$

  iii. $b_0 > b_1 v_*$

  iv. v_* positive root: note that the determinant of the second-degree equation to be solved is always positive, so we have always two solutions. We remark, however, that

  – $v_*^{(1)} = \frac{-(b_3\tilde{u} - c_v\tilde{b}_1 + b_2) + \sqrt{(b_3\tilde{u} - c_v\tilde{b}_1 + b_2)^2 + 4b_3 c_v \tilde{u}\tilde{b}_1}}{2b_3 c_v \tilde{u}}$ is always positive, so it will always be acceptable

  – $v_*^{(1)} = \frac{-(b_3\tilde{u} - c_v\tilde{b}_1 + b_2) - \sqrt{(b_3\tilde{u} - c_v\tilde{b}_1 + b_2)^2 + 4b_3 c_v \tilde{u}\tilde{b}_1}}{2b_3 c_v \tilde{u}}$ turns out to be negative when $b_3\tilde{u} - c_v\tilde{b}_1 + b_2 \geq 0$.

  So we will have a single equilibrium point E_* when the following inequality holds: $b_3\tilde{u} - c_v\tilde{b}_1 + b_2 \geq 0$.

As a consequence, we observe that the examined model always has the trivial equilibrium state E_1 without placing conditions on the model parameters (so that it is at least mathematically meaningful): this state can be called healthy, as both the density of toxic $A\beta$ and τP are zero. A classification of the other states is possible. Indeed we speak of a $A\beta$, respectively τ, toxic state in the case where the second component, respectively the fourth, is non-zero; in the opposite case we speak of a $A\beta$, respectively τ, healthy state. If the existence conditions are satisfied, we will have that E_2 is a $A\beta$ healthy and τP toxic state; E_3 is instead $A\beta$ toxic and τP healthy. Regarding the state E_* we note that this can be called a pathological state, as both the second and fourth components are non-zero.
Having identified the stationary points, we can move on to the analysis of their stability. To do this, let us analyze the eigenvalues of the Jacobian matrix of the system 1.5. The Jacobian matrix is

$$\begin{bmatrix} J_{uu} & J_{u\tilde{u}} & 0 & 0 \\ J_{\tilde{u}u} & J_{\tilde{u}\tilde{u}} & 0 & 0 \\ 0 & J_{v\tilde{u}} & J_{vv} & J_{v\tilde{v}} \\ 0 & J_{\tilde{v}\tilde{u}} & J_{\tilde{v}v} & J_{\tilde{v}\tilde{v}} \end{bmatrix}$$

where

$$J_{uu} = -a_1 - \frac{a_2\tilde{u}}{(1+c_u u)^2} \qquad J_{u\tilde{u}} = -\frac{a_2 u}{1+c_u u}$$
$$J_{\tilde{u}u} = \frac{a_2\tilde{u}}{(1+c_u u)^2} \qquad J_{\tilde{u}\tilde{u}} = \frac{a_2 u}{1+c_u u} - \tilde{a}_1$$
$$J_{v\tilde{u}} = -b_3 v\tilde{v} \qquad J_{vv} = -b_1 - b_3\tilde{u}\tilde{v} - \frac{b_2\tilde{v}}{(1+c_v v)^2}$$
$$J_{v\tilde{v}} = -b_3\tilde{u}v - \frac{b_2 v}{1+c_v v} \qquad J_{\tilde{v}\tilde{u}} = b_3 v\tilde{v}$$
$$J_{\tilde{v}v} = b_3\tilde{u}\tilde{v} + \frac{b_2\tilde{v}}{(1+c_v v)^2} \qquad J_{\tilde{v}\tilde{v}} = -\tilde{b}_1 + b_3\tilde{u}v + \frac{b_2 v}{1+c_v v}$$

Since it is a lower triangular block matrix, its eigenvalues will be given by the eigenvalues of the diagonal blocks therefore:

- $(J_{uu} - \lambda)(J_{\tilde{u}\tilde{u}} - \lambda) - J_{\tilde{u}u}J_{u\tilde{u}} = 0$ from which, performing the calculations, we obtain $\lambda^2 - \lambda(J_{uu} + J_{\tilde{u}\tilde{u}}) - J_{\tilde{u}u}J_{u\tilde{u}} + J_{uu}J_{\tilde{u}\tilde{u}} = 0$. Solving we have
$$\lambda_{1,2} = \frac{J_{uu} + J_{\tilde{u}\tilde{u}} \pm \sqrt{(J_{uu} + J_{\tilde{u}\tilde{u}})^2 - 4(J_{uu}J_{\tilde{u}\tilde{u}} - J_{\tilde{u}u}J_{u\tilde{u}})}}{2}$$
- $(J_{vv} - \lambda)(J_{\tilde{v}\tilde{v}} - \lambda) - J_{\tilde{v}v}J_{v\tilde{v}} = 0$ giving
$\lambda^2 - \lambda(J_{vv} + J_{\tilde{v}\tilde{v}}) - J_{\tilde{v}v}J_{v\tilde{v}} + J_{vv}J_{\tilde{v}\tilde{v}} = 0$. Also in this case we obtain
$$\lambda_{3,4} = \frac{J_{vv} + J_{\tilde{v}\tilde{v}} \pm \sqrt{(J_{vv} + J_{\tilde{v}\tilde{v}})^2 - 4(J_{vv}J_{\tilde{v}\tilde{v}} - J_{\tilde{v}v}J_{v\tilde{v}})}}{2}$$

Given an equilibrium point, calculating the Jacobian matrix at the point and consequently its eigenvalues, we will have that if all the eigenvalues have a negative real part, the stationary point is stable, otherwise unstable.

1.3 Clearance inequalities

As mentioned earlier, a crucial aspect in the development of Alzheimer's disease is the failure of the process of "cleaning" and disposing of excess $A\beta$ and τ proteins, referred to in a more specific terminology as the clearance process. Therefore, it is important to observe whether within our model it is possible to identify in some way when this process works properly or fails. Quite naturally, since these are the only degrees of freedom in our model, we come to think that in order to identify the clearance process, we will have to investigate the relationships that must exist between the parameters themselves.
Under standard conditions, that is if the clearance process for both $A\beta$ and τ

proteins functions efficiently and effectively, there is no protein accumulation and no possibility of the misfolding process to start with consequent toxicity of the proteins involved. Thus, for the $A\beta$ healthy - τ healthy state to have medical significance for our model, the following relationships must exist

$$a_0 \leq a_1 \text{ and } b_0 \leq b_1$$

namely the production rate of $A\beta$ (respectively of τ) must be lower than the clearance rate of $A\beta$ (respectively of τ). In the case of failure of the process, so in the event that either the clearance of $A\beta$ (so $0 \leq a_1 < a_0$) or that of τ (in other words $0 \leq b_1 < b_0$) or both fail, we will have that our model will not admit an healthy state that has physical significance. We then consider the following clearance inequalities identified in the paper [30]

$$\frac{a_0}{a_1} < \frac{\tilde{a}_1}{a_2 - c_u\tilde{a}_1} \text{ and } \frac{b_0}{b_1} < \frac{\tilde{b}_1}{b_2 - c_v\tilde{b}_1} \tag{1.8}$$

These allow us to relate the rates of production and clearance of healthy and toxic proteins of $A\beta$ and τ respectively. Assuming these two inequalities hold, we observe that the only stationary point with clinical significance in our system is given by E_1. Let us therefore study its stability by replacing the values of this equilibrium point within the explicit expressions of the eigenvalues of the Jacobian matrix:

- with regard to the eigenvalues $\lambda_{1,2}$ we first calculate the sub-root term

$$\begin{aligned}
\Delta &= (J_{uu} + J_{\tilde{u}\tilde{u}})^2 - 4(J_{uu}J_{\tilde{u}\tilde{u}} - J_{\tilde{u}u}J_{u\tilde{u}}) = \\
&= (a_1 + \tilde{a}_1 - a_2\frac{\frac{a_0}{a_1}}{1 + c_u\frac{a_0}{a_1}})^2 - 4(a_1\tilde{a}_1 - a_1a_2\frac{\frac{a_0}{a_1}}{1 + c_u\frac{a_0}{a_1}}) = \\
&= (a_1 + \tilde{a}_1 - \frac{a_2a_0}{a_1 + c_ua_0})^2 - 4a_1\tilde{a}_1 + 4a_1\frac{a_2a_0}{a_1 + c_ua_0} = \\
&= (a_1 - \tilde{a}_1 + \frac{a_2a_0}{a_1 + c_ua_0})^2
\end{aligned}$$

  so we have that

$$\lambda_1 = \frac{a_2a_0}{a_1 + c_ua_0} - \tilde{a}_1 \text{ and } \lambda_2 = -a_1$$

- with entirely similar calculations for the remaining eigenvalues, we obtain that

$$\lambda_3 = \frac{b_2b_0}{b_1 + c_vb_0} - \tilde{b}_1 \text{ and } \lambda_4 = -b_1$$

Due to the validity of both clearance inequalities, all identified eigenvalues have a negative real part, so the healthy state E_1 is stable. This means that for parameters satisfying these inequalities, as the system is able to eliminate the small amount of toxic proteins present and the excess of healthy

proteins produced, the steady state $A\beta$ healthy - τ healthy will tend to be reached.

At this point, if there are alterations which are against the clearance process of one of the two proteins, at least one of the two inequalities 1.8 will not be satisfied and this will make at least one of the eigenvalues with a null or positive real part and, as a consequence, the equilibrium state E_1 will no longer be stable. In the moment in which at least one of the two inequalities is not satisfied, new stationary points can be admitted. Thus, the considered patient will be susceptible, as defined in [40], to the state of disease at the moment in which at least one of the two inequalities is valid as equality. Indeed, we observe how depending on which of the following inequalities holds

$$\frac{a_0}{a_1} \geq \frac{\tilde{a}_1}{a_2 - c_u \tilde{a}_1} \text{ and/or } \frac{b_0}{b_1} \geq \frac{\tilde{b}_1}{b_2 - c_v \tilde{b}_1}$$

in addition to the examined equilibrium state E_1, the states E_2, E_3 and the pathological state E_* can also come into play with physical and clinical significance.
In order to proceed to a more specific study of these cases, which are experimentally more interesting but more complicated due to the very high number of parameters involved and to the impossibility of deriving the root value explicitly, it is necessary to make use of model simulations. In particular, by fixing the values of certain parameters in accordance with experimental data, it is possible to study their stability, as done in [30] and in [29]. In this study, one can also observe how the development of the disease can follow two alternative routes: primary tauopathy and secondary tauopathy. In the first case, all the equilibrium points have clinical significance and coexist, whereas in the second case, only three equilibrium points coexist (in particular, E_2 cannot be considered). On the first hand, as mentioned in [40], we speak of primary tauopathy as the accumulation of τ protein occurs independently of the $A\beta$ protein and the latter only plays the role of increasing the concentration of toxic τP. On the other hand, for secondary tauopathy we have that the evolution of the density of τ protein depends on the initial accumulation of $A\beta$ protein.
Essentially, all this analysis leads us to assert that the model under consideration is capable of perceiving the key role of the clearance process in the development of the disease.

Chapter 2

Construction and analysis of nonlocal models

2.1 A first nonlocal model

In the above model 1.4 only the interactions of different types of proteins at the same x-point of the domain Ω under consideration were taken in account and then modeled. However, this does not fully reflect reality, as the conversion of healthy to toxic proteins depends not only on the density of the toxic protein at point x, but also on the densities in the spatial neighborhood of this point, as proteins are able to move. As a consequence, it is necessary to introduce new terms to model this type of interaction.
To do this, it is possible to consider what is proposed in [1] in the case of a predator-prey model, by adapting it, namely by considering the healthy protein as prey and the toxic protein as predator. Going into more detail, if the healthy protein at point x can be attacked by toxic proteins present at any point y in the neighborhood of x, it is logical to assume that the spatially closer the latter are to point x, the more they will contribute to the consumption of the healthy protein at this point. Following [31] we will then have to introduce a function $\phi(x-y)$, a description of the competition strength (as defined in [26]) of a quantity at point y to grab resources at point x or even a description of the conversion efficiency. This function ϕ will have to be positive, decreasing as distance increases (as proteins that are too far apart will not be able to consume resources efficiently at point x), even when viewed as a function of distance (since there are no preferential directions for the competitive force) and normalized (i.e. such that $\int_\Omega \phi(x)dx = 1$).
In particular, we will have that

$$J_1(x,t) = \int_\Omega \phi(x-y)\tilde{u}(y,t)dy$$

determines the density of toxic protein that is capable of acting at the point x. Indeed, the integral can be interpreted in the following way: after having weighed the densities of toxic proteins present around x, by means of the competition strength (that is in this case the conversion efficiency and thus the ability to change the nature of healthy protein at point x), we sum them in order to consider the totality of these contributions, obtaining the density of toxic protein acting at point x. Applying this limitation to each spatial point in an independent manner (so the toxic protein at point y attacks healthy protein at point x_1 independently of what it does at point x_2) we will have that the consumption of healthy protein at point x can be given by

$$W_1(x,t) = \frac{a_2 u(x,t)}{1 + c_u u(x,t)} \int_\Omega \phi(x-y)\tilde{u}(y,t)dy \tag{2.1}$$

since $\frac{a_2 u(x,t)}{1+c_u u(x,t)}$ is the density of healthy protein consumed at the point (x,t) by each unit of toxic protein.
Following what was suggested in [6] for the model of competition between two species in population dynamics, we now want to see what reasoning has to be done to introduce the integral term also for $\tilde{u}$. The equation 2.1 describes the competition between misfolded proteins in order to hoard healthy proteins, so to carry out a symmetrical reasoning we need to model the competition between healthy proteins in order to survive. This competition obviously also affects the density of healthy protein that can be attacked by toxic proteins. So the term inside the integral will always keep the same competition kernel but it will weigh the density of healthy protein consumed. In this way we will have that

$$J_2(x,t) = \int_\Omega \phi(x-y) \frac{a_2 u(y,t)}{1 + c_u u(y,t)} dy$$

determines the density of healthy protein consumed by each single unit of toxic protein located at point x (obtained as the sum of the densities consumed in the neighborhood) and thus the production of toxic protein at point x will be given by

$$W_2(x,t) = a_2 \tilde{u}(x,t) \int_\Omega \phi(x-y) \frac{u(y,t)}{1 + c_u u(y,t)} dy$$

An analogous reasoning can be done also with τ protein. Having in mind that for definition of convolution we have $(\phi * \tilde{u})(x,t) = \int_\Omega \phi(x-y)\tilde{u}(y,t)dy$, we get to the model exposed in [29]

$$\begin{cases} \frac{\partial u}{\partial t} = \nabla \cdot (D_1 \nabla u) + a_0 - a_1 u - \frac{a_2 u}{1+c_u u} \phi * \tilde{u} \\ \frac{\partial \tilde{u}}{\partial t} = \nabla \cdot (\tilde{D}_1 \nabla \tilde{u}) - \tilde{a}_1 \tilde{u} + a_2 \tilde{u} \phi * (\frac{u}{1+c_u u}) \\ \frac{\partial v}{\partial t} = \nabla \cdot (D_2 \nabla v) + b_0 - b_1 v - \frac{b_2 v}{1+c_v v} \phi * \tilde{v} - b_3 \tilde{u} v \tilde{v} \\ \frac{\partial \tilde{v}}{\partial t} = \nabla \cdot (\tilde{D}_2 \nabla \tilde{v}) - \tilde{b}_1 \tilde{v} + b_2 \tilde{v} \phi * (\frac{v}{1+c_v v}) + b_3 \tilde{u} v \tilde{v} \end{cases} \tag{2.2}$$

with appropriate initial conditions.
We remark that in this model there is no point mass conservation since the convolution terms subtracted in the case of healthy proteins do not correspond to the ones we summed in the equations referred to toxic proteins. However, as noted in [1], thanks to the symmetry of the kernel we have that

$$\int_\Omega W_1(x,t)dx = \int_\Omega W_2(x,t)dx$$

so we can state that there is conservation of total mass. This fact is also in agreement with the phenomenon to be modeled: since the healthy protein consumed at point x is not exclusively attacked by toxic protein located at the same point, the density of toxic protein formed as a result of the induced misfolding will be distributed among the various spatial positions that contributed to its formation.
At this point the equation 1.3, derived in the paper [40] and taken up in [31], can also be described in more detail. Indeed, the term $\mathcal{A}$ can be expressed by means of a convolution (with a different kernel that, in this case, can be interpreted as the contribution to the damage) expressing how the presence of any damage around the point under consideration contributes to the worsening of the damage at the point. We obtain an equation of the type

$$\frac{\partial q}{\partial t} = (k_1\tilde{u} + k_2\tilde{v} + k_3\tilde{u}\tilde{v} + k_4\psi * q)(1-q) \tag{2.3}$$

Thus, the parameter k_4 takes the meaning of the rate of propagation of the damage, and the convolution term represents the damage as a result of aggregates placed around point x.
For the explicit expression of the kernel used to express the competition strength, numerous papers can be found in the literature in which a number of different forms with pros and cons on their use are exhibited. The first kernel proposed by [6] was the Laplacian

$$\phi(x) = \frac{1}{2\sigma}e^{-\frac{|x|}{\sigma}}$$

As mentioned in [17] the bigger $\frac{1}{\sigma}$, the weaker the nonlocality is, which means that the weights used are large only for tiny neighborhoods of the kernel center. This kernel in particular can be obtained by considering an equation describing the local resources level, as shown in [17]. However, in later papers ([5]) we move on to consider Gaussian kernels of the form

$$\phi(x) = \frac{1}{\sigma\sqrt{\pi}}e^{-\frac{<x,x>}{\sigma^2}}$$

There are several reasons for this. First of all, in [5] and [27], it is observed that the basis of equations involving diffusive phenomena is always the random walks of particles. In order to maintain mathematical consistency, it

makes sense to consider Gaussian kernels, with the aim of essentially introduce an interaction with a stochastic character (future developments could also work on this kernel in order to introduce an even more pronounced stochastic character, which is lacking in the model presented). Moreover, this form of competition is one of the most frequent in epidemiology and ecology, as it not only leads to results in agreement with the experimental data, but also to a mathematical analysis that is easier to carry out ([32], [34]). Following [29], in our case we consider a Gaussian competition kernel (and this choice is also made for the kernel ψ of the equation 2.3 but with a different standard deviation).

Remark 2.1. In our case it is important to note that the choice of a Gaussian kernel may be useful as a first approximation, but its strongly isotropic character is in clear contrast with the biological elements of the model in which there are preferential directions, as already explained by the analysis of the diffusion tensors. Furthermore, in a number of papers, including [32], it has been observed that the Gaussian kernel has limitations because it is exactly the borderline for completely different population dynamics: for one class of competition kernels there is simply a redistribution of the various species involved but uniformly in space, whereas for the second class the species involved form aggregates in specific areas, leaving some spatial zones completely free. Let us give an initial idea of what the discriminating factor is for these antipodal behaviors.
The kernels exposed above can be seen as special cases of the generalized normal distribution $\frac{\beta}{2\alpha\Gamma(1/\beta)}e^{-(|x-\mu|/\alpha)^\beta}$ (we denoted by Γ the Euler's gamma function). In particular with the choice of $\beta = 2$ we obtain the Gaussian distribution while $\beta = 1$ gives the Laplacian distribution. This generalized normal distribution is such that for $\beta < 2$ it presents an increasingly pronounced peak around its mean as β decreases, while for $\beta > 2$ it tends to assume a shape increasingly similar to the uniform distribution.
In the case of n interacting populations in a Lotka-Volterra competition model in [32], it is observed that for positively defined kernels the distribution of the species considered is uniform, otherwise the species will distribute themselves to create aggregates. The Gaussian kernel in this sense turns out to be the limit case between these two behaviors, since for values $\beta > 2$ the positive definite character is lost and thus also the spatially uniform distribution of the species involved. For future developments, one might also consider pursuing this study in the specific case of our model.
Another area of research in the future, concerning again convolution kernels used, could be that of considering a Gaussian kernel that is not only a function of space but also of time and thus achieving a double integration (the probabilistic procedure to determine this type of kernel has already been described in [5]). However, this would make an important change in the

study of the model's temporal dynamics since in this way the integral term would also be strongly linked to temporal aspects and not just spatial ones.

The model 2.2 obtained consists of coupled integro-differential equations. As with the previous model, it comes natural to study the model's temporal dynamics. To do this, the variables involved are studied solely from the temporal point of view and not from the spatial one. In other words, we will have, for example, that $u = u(x,t)$ in this case will be considered as $u = u(t)$ and similarly for the other unknowns. Therefore, when analyzing the integrals in our model, these quantities can be considered as constants in space. To further clarify this, let us take the steps in the case of the integral term included in the first equation of 2.2:

$$\frac{a_2 u(t)}{1 + c_u u(t)} \phi * \tilde{u}(t) = \frac{a_2 u(t)}{1 + c_u u(t)} \int_\Omega \phi(x-y)\tilde{u}(t)dy = \frac{a_2 u(t)}{1 + c_u u(t)} \tilde{u}(t)$$

where, in the last step, the fact that the convolution kernel considered is unitary is exploited. For that reason, the system of ODEs associated with the model 2.2 for the study of temporal dynamics is given by

$$\begin{cases} \frac{du}{dt} = a_0 - a_1 u - \frac{a_2 u}{1+c_u u}\tilde{u} \\ \frac{d\tilde{u}}{dt} = -\tilde{a}_1 \tilde{u} + \frac{a_2 u}{1+c_u u}\tilde{u} \\ \frac{dv}{dt} = b_0 - b_1 v - b_3 \tilde{u} v \tilde{v} - \frac{b_2 v}{1+c_v v}\tilde{v} \\ \frac{d\tilde{v}}{dt} = -\tilde{b}_1 \tilde{v} + b_3 \tilde{u} v \tilde{v} + \frac{b_2 v}{1+c_v v}\tilde{v} \end{cases} \tag{2.4}$$

with non-zero initial conditions. We remark that it is completely analogous to the system already studied in the case of the model 1.4.
A study of the equilibrium points will therefore not be carried out in this case, since the convolution terms, which modify the system exclusively in spatial terms, do not change the calculations previously reported for the temporal dynamics. Thus, the results seen for 1.4 are still valid for this model too.
Instead, it makes sense to pay more attention to the fact that within the model, through the convolution terms, we have also introduced the concept of nonlocality.

2.2 Nonlocality

Historically, the mathematical models developed have mainly consisted of PDEs expressing, in most cases, local information. However, over the years, interest in the study of complex systems has increased, leading to the study of systems with singularities as well as nonlocal interactions. What is meant by nonlocal interactions? Intuitively, it means that what happens in a particular position in space at a specific time is conditioned, in other words it

depends on, events/elements that may happen/are in spatial positions and instants of time different from the one we are considering. Since nonlocality, as mentioned, can be both spatial and temporal in nature, an initial distinction can be made between spatially nonlocal models, such as the one analyzed in the case of AD, and temporally nonlocal models. In the latter case, the nonlocality finds expression mainly in the initial conditions, which are applied in a nonlocal manner that is at different times, rather than at a single time value as in standard problems.
Among the features of nonlocal models there are the property of taking nonlocal interactions explicitly into account and the fact that the models remain valid not only for smooth solutions but also for singular solutions. The negative counterpart is that nonlocal continuous models present more complexities from the point of view of rigorous mathematical analysis. Indeed, the mathematical and numerical theory underlying these nonlocal models are currently under development, as the interest in this type of model is fairly recent. However, at the mathematical level it has been seen that, in general, spatial nonlocality can often be dealt with fractional calculus, while temporal nonlocality can be managed with some of the key ideas from the functional calculus in particular linked to strip-type operators, as explained in [38]. But let us go into more detail for a moment.

The theory behind nonlocal models has been developed at the same time in different fields, due to the fact that the areas of application are very broad. Qiang Du is one of the main representatives who has worked in this field, collecting the main results in the monograph [13] of which we will give a few examples to facilitate understanding.
As mentioned, the historically widespread models consist of ordinary differential equations and are called local models, in the sense that their validity can be verified for solutions in any single state identified by continuous independent variables (in our case space and time). An example is the heat equation $\frac{\partial u}{\partial t}(x,t) = \Delta u(x,t)$ which can be verified by knowing the solution and its derivatives at a point (x,t). These local models provide effective descriptions of the macroscopic world. Equations that do not satisfy the property of local equations are called nonlocal, so they are equations whose validity in a particular point cannot be proven by knowing only the solution at that point, but requires further information on the latter, typically in some different points.

Example 2.1. Suppose working for simplicity in an interval $\Omega \subset \mathbb{R}$. The differential equation

$$\frac{d^2u}{dx^2}(x) = f(x, u(x))$$

with $x \in \Omega$, $f = f(x, u(x))$ known and $u = u(x)$ unknown, is a continuous local model.

Example 2.2. Maintaining the notation of the previous example, we denote by ω_δ a kernel with support consisting of two or more points, expressing nonlocal interactions. For example, if we introduce the operator

$$\mathcal{L}_\delta u(x) = \int_{-\delta}^{\delta} \frac{u(x+s) - 2u(x) + u(x-s)}{s^2} \omega_\delta(s) ds$$

this will have a nonlocal nature and therefore the integral equation given by

$$\mathcal{L}_\delta u(x) = f(x, u(x))$$

with $\delta \in \mathbb{R}_+$ and $x \in \Omega$, will be a nonlocal model.
We remark that in the case where the support of ω_δ consists only in the point of interest, then the equation will take on a local character since the values of the unknown function around the point of interest will no longer be involved.

The nonlocal nature of models immediately leads to increased attention. Thinking about the field of applications, one often works on domains that are limited. In the event that a point is close to the boundary of our domain, the nonlocal interactions to which it is subjected may change with respect to points in the domain further from the boundary. Moreover, mathematically speaking, some additional conditions will be required with respect to a classical boundary problem. [41] for example observes that in the case of Dirichlet boundary conditions, a condition must be given not only on $\partial\Omega$ but also on a δ neighborhood of the domain under consideration.
Proceeding with the analysis, it can be observed how the concept of locality and nonlocality can be related to the chosen description of the system and thus to the variables used to describe the problem. Indeed, in the case of complex systems, reductions in the model are often used in order to facilitate the study of the system (in particular there could be an interest in reducing the degrees of freedom in order to obtain a lower complexity and thus a simpler analysis).

Example 2.3. Consider the system of equations

$$\begin{cases} \frac{dx}{dt} = x + y \\ \frac{dy}{dt} = x - 10y \end{cases}$$

with initial data $y(0) = y_0$. By eliminating the variable y, namely by substituting the formula $y(t) = e^{-10t}[y_0 + \int_0^t x(s)e^{10s}ds]$ obtained by means of the appropriate solution formula into the first equation, we have the following integral nonlocal differential equation (in this case the nonlocality manifests itself over time, with memory effects in the system)

$$\frac{dx}{dt}(t) = x(t) + \int_0^t e^{-10(t-s)}x(s)ds + e^{-10t}y_0$$

Obviously, the opposite process also remains possible: starting from a nonlocal model, it could be derived a local model that is equivalent to it by introducing new unknowns in order to work in a space of greater dimensions than the initial one.

The treatment of nonlocality in time is even more difficult then the spatial one, both from an intuitive and mathematical point of view. As observed by T. Filk in [14], various definitions, all equally valid, can be given for the concept of temporal nonlocality. The one that allows a greater parallelism with what has been said in the case of spatial nonlocality is the one according to which we are dealing with a reciprocal influence between the states of the system for times that are far apart (for more details see the complete work [14], but it is possible to implement this definition if we think of working in the field of relativity and we consider two time-lines obtained by different Minkowski metrics).
Actually, it is also possible to see the concept of temporal nonlocality as the loss of consequentiality of events. Indeed, as it is well known, in the field of classical physics, it is always possible to order events according to a time line, whereas in the field of relativistic physics, if we consider events that are not bound by a cause-effect relationship, their sequentiality depends strongly on the observer.
Temporal nonlocality not only appears within the considered equations but often occurs in the initial conditions, resulting in a nonlocal boundary problem. As mentioned in [28], this allows greater accuracy in modeling and thus better results. Indeed, with a classical local initial condition we only enter information regarding one time instant, whereas in the case of nonlocality we are also able to introduce conditions for further time instants.

Let us now focus our attention for a moment on how nonlocality has come into play in the biological area. In this field there is a need to collect data on different spatial and temporal scales, so, as a consequence, there is the need to increase the "resolution" of the models used in order to provide a multiscale description of the components involved, that could combine macro, meso and micro considerations. As explained in [23], in local models modeling an interaction for spatially neighboring points implicitly implies that the spatial and temporal scales of movement and interaction are of the same order of magnitude. In contrast, in nonlocal models the fact that interactions appear between distant points implies that the spatial scale is larger (but not sufficiently so that different positions can be considered indistinguishable) and the temporal scale smaller than in other processes that are modeled explicitly. Thus, since there is a unification of the spatial and temporal scales at work, nonlocal models represent simplifications of reality in this sense. These characteristics correspond perfectly to the type of data often collected in the biological field: many quantities of interest occur on

such small temporal and spatial scales that it is practically impossible to collect enough data, so the choice is often made to collect data on larger scales. Since, as mentioned, nonlocal models allow the modeling of small-scale processes within larger spatial and temporal scales, these techniques fit exactly the type of data that is often available. These types of phenomena in the biological sphere are often translated into the model as interaction terms in the form of integrals over a spatial or a temporal domain in which the integrand has a kernel, strongly dependent on the model studied, that governs the interactions.
All this general framework can be transferred into our model. Indeed, in the last step of construction, we decided that the conversion of healthy proteins into toxic ones depends on the densities of the various proteins involved in the spatial neighborhood of the point $x \in \Omega$ we are considering. To do this, we have introduced a convolution with a normalized positive kernel allowing each point in the neighborhood to provide the correct contribution. In this way an interaction between spatially distant points of the domain is introduced into the model, and this corresponds exactly to the concept of spatial nonlocality as reported above. Indeed it is not sufficient to know the solution of the system at a single point (x, t) to verify the validity of the equations at the point. Therefore all the convolution terms introduced are manifestations of the spatial nonlocality of our model.

2.3 A second nonlocal model

The model 2.2, described in the section 2.1, can be further improved by assuming a logistic growth rather than an exponential one in the production of healthy proteins of both types, as suggested in [25] and [31]. This logistic curve means that a controlled and limited growth of the healthy populations is involved. Indeed in the context of populations it is unlikely that a population will have unlimited growth over time and therefore a carrying capacity is often introduced as a factor indicating a threshold above which the studied environment is no longer able to support the present population (e.g. it is likely to be assumed that the precursors of the $A\beta$ protein, namely the transmembrane APP proteins, are present in a limited amount and that therefore the population increase cannot be unlimited). Consequently, the expression that is usually assumed to reflect the experimental data obtained in the population is

$$a_0 u(1 - \frac{u}{K})$$

where a_0 represents the production rate and K the carrying capacity. This expression is designed to express the fact that, in the case of limited resources, growth is proportional to the percentage of resources not yet used, i.e. $1 - \frac{u}{K}$. Indeed, it can be assumed that in the case where the population (and thus the protein density in our case) is low, the resources available will

appear to be sufficient and thus the growth will be fast at first. Then, as the population increases the available resources will begin to be a limiting factor for a such rapid population growth. Unwinding the product and unifying the parameters it is possible to express this characteristic in the form that appears in the following model with logistic growths for both healthy proteins

$$\begin{cases} \frac{\partial u}{\partial t} = \nabla \cdot (D_1 \nabla u) + u(a_0 - a_1 u) - \frac{a_2 u}{1+c_u u}\phi * \tilde{u} \\ \frac{\partial \tilde{u}}{\partial t} = \nabla \cdot (\tilde{D}_1 \nabla \tilde{u}) - \tilde{a}_1 \tilde{u} + a_2 \tilde{u}\phi * (\frac{u}{1+c_u u}) \\ \frac{\partial v}{\partial t} = \nabla \cdot (D_2 \nabla v) + v(b_0 - b_1 v) - \frac{b_2 v}{1+c_v v}\phi * \tilde{v} - b_3 \tilde{u} v \tilde{v} \\ \frac{\partial \tilde{v}}{\partial t} = \nabla \cdot (\tilde{D}_2 \nabla \tilde{v}) - \tilde{b}_1 \tilde{v} + b_2 \tilde{v}\phi * (\frac{v}{1+c_v v}) + b_3 \tilde{u} v \tilde{v} \end{cases} \tag{2.5}$$

2.3.1 Analysis of equilibrium points

Having changed the growth considered within our model, let us now establish how the equilibrium points and their stability change in this case.
As in the previous cases, since the equilibrium points and their stability are independent from the spatial dynamics, we can study them by omitting from our model the terms that make an exclusively spatial contribution, namely the diffusive terms. In addition, we can carry out a similar reasoning as before for the convolution terms: noting that these are integrals carried out in the spatial variable, we can exploit the linearity of the integral and the fact that the kernel considered is unitary in order to make simplifications. Thus, the equilibrium points with the relative stability will coincide with those of the following local ODEs system

$$\begin{cases} \frac{du}{dt} = u(a_0 - a_1 u) - \frac{a_2 u}{1+c_u u}\tilde{u} \\ \frac{d\tilde{u}}{dt} = -\tilde{a}_1 \tilde{u} + \frac{a_2 u}{1+c_u u}\tilde{u} \\ \frac{dv}{dt} = v(b_0 - b_1 v) - b_3 \tilde{u} v \tilde{v} - \frac{b_2 v}{1+c_v v}\tilde{v} \\ \frac{d\tilde{v}}{dt} = -\tilde{b}_1 \tilde{v} + b_3 \tilde{u} v \tilde{v} + \frac{b_2 v}{1+c_v v}\tilde{v} \end{cases} \tag{2.6}$$

with non-zero initial condition.
To find all the equilibrium points of our system, we proceed as before: remembering that all our quantities are non-negative, we first look for equilibrium points that have at least one null component, and then for equilibrium points for which all components are strictly greater than zero.
We always fix the convention that the coordinates of the stationary points will be given by $(u, \tilde{u}, v, \tilde{v})$. We begin by looking for axial equilibrium points, i.e. the ones where at least one component is zero.

1. let us assume $u = 0$. Unlike the previous model, in this case $u = 0$ makes the first equation of the system satisfied for every value of the parameters involved, so it makes sense to continue with the calculations.

The system to be solved to find the axial equilibrium points will hence become

$$\begin{cases} u = 0 \\ -\tilde{a}_1\tilde{u} = 0 \\ v(b_0 - b_1 v) - b_3\tilde{u}v\tilde{v} - \frac{b_2 v}{1+c_v v}\tilde{v} = 0 \\ -\tilde{b}_1\tilde{v} + b_3\tilde{u}v\tilde{v} + \frac{b_2 v}{1+c_v v}\tilde{v} = 0 \end{cases}$$

However, having assumed that the rate of clearance of the $A\beta$ toxic protein is $\tilde{a}_1 > 0$ we will have

$$\begin{cases} u = 0 \\ \tilde{u} = 0 \\ v(b_0 - b_1 v) - \frac{b_2 v}{1+c_v v}\tilde{v} = 0 \\ -\tilde{b}_1\tilde{v} + \frac{b_2 v}{1+c_v v}\tilde{v} = 0 \end{cases} \Rightarrow \begin{cases} u = 0 \\ \tilde{u} = 0 \\ v(b_0 - b_1 v) = \tilde{b}_1\tilde{v} \\ -\tilde{b}_1\tilde{v} + \frac{b_2 v}{1+c_v v}\tilde{v} = 0 \end{cases}$$

from which, continuing with the calculations

$$\begin{cases} u = 0 \\ \tilde{u} = 0 \\ \tilde{v} = \frac{v}{\tilde{b}_1}(b_0 - b_1 v) \\ v(b_0 - b_1 v)(1 - \frac{b_2 v}{(1+c_v v)\tilde{b}_1}) = 0 \end{cases}$$

We will obtain then the following solutions:

- $E_0 : \begin{cases} u = 0 \\ \tilde{u} = 0 \\ v = 0 \\ \tilde{v} = 0 \end{cases}$ and $E_1 : \begin{cases} u = 0 \\ \tilde{u} = 0 \\ v = \frac{b_0}{b_1} \\ \tilde{v} = 0 \end{cases}$
- E_2 :

$$\begin{cases} u = 0 \\ \tilde{u} = 0 \\ 1 - \frac{b_2 v}{(1+c_v v)\tilde{b}_1} = 0 \\ \tilde{v} = \frac{v}{\tilde{b}_1}(b_0 - b_1 v) \end{cases} \Rightarrow \begin{cases} u = 0 \\ \tilde{u} = 0 \\ -\tilde{b}_1 - \tilde{b}_1 c_v v + b_2 v = 0 \\ \tilde{v} = \frac{v}{\tilde{b}_1}(b_0 - b_1 v) \end{cases}$$

$$\Rightarrow \begin{cases} u = 0 \\ \tilde{u} = 0 \\ v(b_2 - \tilde{b}_1 c_v) = \tilde{b}_1 \\ \tilde{v} = \frac{v}{\tilde{b}_1}(b_0 - b_1 v) \end{cases} \Rightarrow \begin{cases} u = 0 \\ \tilde{u} = 0 \\ v = \frac{\tilde{b}_1}{b_2 - \tilde{b}_1 c_v} \\ \tilde{v} = \frac{b_0(b_2 - \tilde{b}_1 c_v) - b_1\tilde{b}_1}{(b_2 - \tilde{b}_1 c_v)^2} \end{cases}$$

2. assume $\tilde{u} = 0$. Again, the second equation of the initial system is valid for every value of the model parameters. We will therefore work with the following system:

$$\begin{cases} u(a_0 - a_1 u) = 0 \\ \tilde{u} = 0 \\ v(b_0 - b_1 v) - \frac{b_2 v}{1+c_v v}\tilde{v} = 0 \\ -\tilde{b}_1 \tilde{v} + \frac{b_2 v}{1+c_v v}\tilde{v} = 0 \end{cases}$$

With calculations entirely analogous to the case of $u = 0$ we get the system

$$\begin{cases} u(a_0 - a_1 u) = 0 \\ \tilde{u} = 0 \\ \tilde{v} = \frac{v}{\tilde{b}_1}(b_0 - b_1 v) \\ v(b_0 - b_1 v)(1 - \frac{b_2 v}{(1+c_v v)\tilde{b}_1}) = 0 \end{cases}$$

At this point, we will have to analyze two cases for the equation related to u and three for that related to v. In the case in which $u = 0$, we find a system identical to that obtained by searching for axial stationary points with the first component zero, so we will not explain the calculations again. For that reason we will only perform the calculations for the second case of the equation for u.

$$\begin{cases} u = \frac{a_0}{a_1} \\ \tilde{u} = 0 \\ \tilde{v} = \frac{v}{\tilde{b}_1}(b_0 - b_1 v) \\ v(b_0 - b_1 v)(1 - \frac{b_2 v}{(1+c_v v)\tilde{b}_1}) = 0 \end{cases}$$

We then observe that, having already solved the first of the two pairs of equations, the remaining coupled equations are the same as in the previous case, so the values of v and $\tilde{v}$ that we will obtain are the same as in the initial case. Consequently, the solutions we will have are given by:

- $E_3 : \begin{cases} u = \frac{a_0}{a_1} \\ \tilde{u} = 0 \\ v = 0 \\ \tilde{v} = 0 \end{cases}$ $E_4 : \begin{cases} u = \frac{a_0}{a_1} \\ \tilde{u} = 0 \\ v = \frac{b_0}{b_1} \\ \tilde{v} = 0 \end{cases}$ $E_5 : \begin{cases} u = \frac{a_0}{a_1} \\ \tilde{u} = 0 \\ v = \frac{\tilde{b}_1}{b_2 - \tilde{b}_1 c_y} \\ \tilde{v} = \frac{b_0(b_2 - \tilde{b}_1 c_v) - b_1 \tilde{b}_1}{(b_2 - \tilde{b}_1 c_v)^2} \end{cases}$

3. assume $v = 0$. In contrast to the previous model for $v = 0$, we obtain that the third equation of the initial system is valid for every parameter

value. So it makes sense to continue the analysis of the following system

$$\begin{cases} u(a_0 - a_1 u) - \frac{a_2 u}{1+c_u u}\tilde{u} = 0 \\ -\tilde{a}_1\tilde{u} + \frac{a_2 u}{1+c_u u}\tilde{u} = 0 \\ v = 0 \\ -\tilde{b}_1\tilde{v} = 0 \end{cases}$$

We observe that in this case the calculations are completely symmetrical to those made when posing $u = 0$ by exchanging u for v, $\tilde{u}$ for $\tilde{v}$, a_1 for b_1, a_0 for b_0, $\tilde{a}_1$ for $\tilde{b}_1$, $\tilde{a}_2$ for $\tilde{b}_2$ and c_u for c_v. We will therefore obtain the system

$$\begin{cases} u(a_0 - a_1 u)(1 - \frac{a_2 u}{(1+c_u u)\tilde{a}_1}) = 0 \\ \tilde{u} = \frac{u}{\tilde{a}_1}(a_0 - a_1 u) \\ v = 0 \\ \tilde{v} = 0 \end{cases}$$

which will have solutions

- $E_0 : \begin{cases} u = 0 \\ \tilde{u} = 0 \\ v = 0 \\ \tilde{v} = 0 \end{cases}$ $E_3 : \begin{cases} u = \frac{a_0}{a_1} \\ \tilde{u} = 0 \\ v = 0 \\ \tilde{v} = 0 \end{cases}$ $E_6 : \begin{cases} u = \frac{\tilde{a}_1}{a_2 - c_u\tilde{a}_1} \\ \tilde{u} = \frac{a_0(a_2 - \tilde{a}_1 c_u) - a_1\tilde{a}_1}{(a_2 - \tilde{a}_1 c_u)^2} \\ v = 0 \\ \tilde{v} = 0 \end{cases}$

4. let us assume $\tilde{v} = 0$. The system and the calculations to be performed are completely symmetrical to those shown for $\tilde{u} = 0$. We will find also in this case the three solutions exposed previously for $v = 0$ in addition to those obtained by solving

$$\begin{cases} u(a_0 - a_1 u)(1 - \frac{a_2 u}{(1+c_u u)\tilde{a}_1}) = 0 \\ \tilde{u} = \frac{u}{\tilde{a}_1}(a_0 - a_1 u) \\ v = \frac{b_0}{b_1} \\ \tilde{v} = 0 \end{cases}$$

From which, by analogous reasoning as for $\tilde{u} = 0$, with the appropriate substitutions we get:

- $E_1 : \begin{cases} u = 0 \\ \tilde{u} = 0 \\ v = \frac{b_0}{b_1} \\ \tilde{v} = 0 \end{cases}$ $E_4 : \begin{cases} u = \frac{a_0}{a_1} \\ \tilde{u} = 0 \\ v = \frac{b_0}{b_1} \\ \tilde{v} = 0 \end{cases}$ $E_7 : \begin{cases} u = \frac{\tilde{a}_1}{a_2 - c_u\tilde{a}_1} \\ \tilde{u} = \frac{a_0(a_2 - \tilde{a}_1 c_u) - a_1\tilde{a}_1}{(a_2 - \tilde{a}_1 c_u)^2} \\ v = \frac{b_0}{b_1} \\ \tilde{v} = 0 \end{cases}$

Summarizing, all the axial equilibrium points identified are:

$$E_0 = (0,0,0,0) \qquad E_2 = (0,0,\frac{\tilde{b}_1}{b_2-\tilde{b}_1c_v},\frac{b_0(b_2-\tilde{b}_1c_v)-b_1\tilde{b}_1}{(b_2-\tilde{b}_1c_v)^2})$$

$$E_1 = (0,0,\frac{b_0}{b_1},0) \qquad E_5 = (\frac{a_0}{a_1},0,\frac{\tilde{b}_1}{b_2-\tilde{b}_1c_v},\frac{b_0(b_2-\tilde{b}_1c_v)-b_1\tilde{b}_1}{(b_2-\tilde{b}_1c_v)^2})$$

$$E_3 = (\frac{a_0}{a_1},0,0,0) \qquad E_6 = (\frac{\tilde{a}_1}{a_2-c_u\tilde{a}_1},\frac{a_0(a_2-\tilde{a}_1c_u)-a_1\tilde{a}_1}{(a_2-\tilde{a}_1c_u)^2},0,0)$$

$$E_4 = (\frac{a_0}{a_1},0,\frac{b_0}{b_1},0) \qquad E_7 = (\frac{\tilde{a}_1}{a_2-c_u\tilde{a}_1},\frac{a_0(a_2-\tilde{a}_1c_u)-a_1\tilde{a}_1}{(a_2-\tilde{a}_1c_u)^2},\frac{b_0}{b_1},0)$$

Since each of the quantities involved represents a density in accordance with the aims of the model, in order for these equilibrium points to be meaningful not only mathematically but also physically, it is necessary to ensure that all components are non-negative. Thus we shall have:

- for the existence of E_6 and E_7:
  i. $a_2 - \tilde{a}_1c_u > 0$ i.e. $a_2 > c_u\tilde{a}_1$
  ii. $a_0(a_2-\tilde{a}_1c_u) - a_1\tilde{a}_1 \geq 0$ so $\frac{a_0}{a_1} \geq \frac{\tilde{a}_1}{a_2-c_u\tilde{a}_1}$
- for the existence of E_2 and E_5:
  i. $b_2 - \tilde{b}_1c_v > 0$ from which $b_2 > c_v\tilde{b}_1$
  ii. $b_0(b_2-\tilde{b}_1c_v) - b_1\tilde{b}_1 \geq 0$ therefore $\frac{b_0}{b_1} \geq \frac{\tilde{b}_1}{b_2-c_v\tilde{b}_1}$

The equilibrium point E_0 does not have a distinct physical meaning: it corresponds to the total absence of any protein, which cannot occur in an active brain (as there is naturally production of healthy $A\beta$ and τ proteins) but only in dead cells. As for the other equilibrium states, all of which have at least one null component, they can be classified according to criteria similar to those of the previous case. In particular we have that E_1, E_3, E_4 are healthy states; E_2 and E_5 are $A\beta$ healthy-τ toxic and viceversa E_6 and E_7.
We now want to seek, if it exists, a stationary point that does not have zero components and which will reflect for that reason, following the terminology applied, a pathological state. By imposing that the time derivatives of the system 2.6 are null, we get:

$$\begin{cases} u(a_0-a_1u) - \frac{a_2u}{1+c_uu}\tilde{u} = 0 \\ -\tilde{a}_1\tilde{u} + \frac{a_2u}{1+c_uu}\tilde{u} = 0 \\ v(b_0-b_1v) - b_3\tilde{u}v\tilde{v} - \frac{b_2v}{1+c_vv}\tilde{v} = 0 \\ -\tilde{b}_1\tilde{v} + b_3\tilde{u}v\tilde{v} + \frac{b_2v}{1+c_vv}\tilde{v} = 0 \end{cases} \Rightarrow \begin{cases} u(a_0-a_1u) = \tilde{a}_1\tilde{u} \\ v(b_0-b_1v) = \tilde{b}_1\tilde{v} \\ -\tilde{a}_1\tilde{u} + \frac{a_2u}{1+c_uu}\tilde{u} = 0 \\ -\tilde{b}_1\tilde{v} + b_3\tilde{u}v\tilde{v} + \frac{b_2v}{1+c_vv}\tilde{v} = 0 \end{cases}$$

The system of equations to be solved is therefore given by

$$\begin{cases} \tilde{u} = \dfrac{u(a_0 - a_1 u)}{\tilde{a}_1} & (2.7a) \\ \tilde{v} = \dfrac{v(b_0 - b_1 v)}{\tilde{b}_1} & (2.7b) \\ -u(a_0 - a_1 u) + \dfrac{a_2 u}{1 + c_u u} \dfrac{u(a_0 - a_1 u)}{\tilde{a}_1} = 0 & (2.7c) \\ -v(b_0 - b_1 v) + b_3 \dfrac{u(a_0 - a_1 u) v^2 (b_0 - b_1 v)}{\tilde{a}_1 \tilde{b}_1} + \dfrac{b_2 v^2 (b_0 - b_1 v)}{(1 + c_v v)\tilde{b}_1} = 0 & (2.7d) \end{cases}$$

Analyzing the equation 2.7c which can be rewritten as

$$u(a_0 - a_1 u)(-1 + \frac{a_2 u}{(1 + c_u u)\tilde{a}_1}) = 0$$

it is observed that the solutions given by $u = 0$ and $u = \frac{a_0}{a_1}$ (from which $\tilde{u} = 0$ would follow) are not acceptable as we are looking for a stationary point in which all concentrations are positive. As a consequence the only possible solution in our case will be $u = \frac{\tilde{a}_1}{a_2 - \tilde{a}_1 c_u}$. Then substituting in the expression derived for $\tilde{u}$ we will obtain $\tilde{u} = \frac{a_0 a_2 - a_1 \tilde{a}_1 - a_0 c_u \tilde{a}_1}{(a_2 - \tilde{a}_1 c_u)^2}$.
Turning instead to the analysis of 2.7d and rewriting it as

$$v(b_0 - b_1 v)(-1 + b_3 \frac{u(a_0 - a_1 u)}{\tilde{a}_1} \frac{v}{\tilde{b}_1} + \frac{b_2 v}{1 + c_v v} \frac{1}{\tilde{b}_1}) = 0$$

we have that, for reasons similar to those just stated, the only admissible solution is obtained by solving

$$-1 + b_3 \frac{u(a_0 - a_1 u)}{\tilde{a}_1} \frac{v}{\tilde{b}_1} + \frac{b_2 v}{1 + c_v v} \frac{1}{\tilde{b}_1} = 0$$

But remembering that $\tilde{u} = \frac{u(a_0 - a_1 u)}{\tilde{a}_1}$ we will have

$$-1 + b_3 \tilde{u} \frac{v}{\tilde{b}_1} + \frac{b_2 v}{1 + c_v v} \frac{1}{\tilde{b}_1} = 0 \tag{2.8}$$

Thus, the density of τ protein must satisfy the equation

$$c_v \tilde{u} b_3 v^2 + (b_2 + \tilde{u} b_3 - \tilde{b}_1 c_v) v - \tilde{b}_1 = 0$$

We remark that, as in the determinations of the equilibrium points of the previous models, this expression could also be derived from the last equation of the initial system of ODEs by simply dividing by the variable $\tilde{v}$ since in this case it is assumed to be non-zero. However, by taking this quicker route, we could not have made the following remark.
From the equation 2.8 it is possible to derive a more explicit expression for $\frac{v}{\tilde{b}_1}$.

Indeed substituting in the expression 2.7b we get $\tilde{v} = (b_0 - b_1 v)\frac{1+c_v v}{b_2+b_3\tilde{u}+b_3\tilde{u}c_v v}$. For the admissibility of the just derived stationary point

$$E_* = (\frac{\tilde{a}_1}{a_2 - \tilde{a}_1 c_u}, \frac{a_0 a_2 - a_1\tilde{a}_1 - a_0 c_u \tilde{a}_1}{(a_2 - \tilde{a}_1 c_u)^2}, v_*, (b_0 - b_1 v_*)\frac{1 + c_v v_*}{b_2 + b_3\tilde{u} + b_3\tilde{u}c_v v_*})$$

where v_* satisfies the equation $c_v\tilde{u}b_3 v^2 + (b_2 + \tilde{u}b_3 - \tilde{b}_1 c_v)v - \tilde{b}_1 = 0$, we will have to impose positivity of all components so:

- $u > 0$ whence $a_2 > c_u\tilde{a}_1$
- $\tilde{u} > 0$ therefore $\frac{a_0}{a_1} > \frac{\tilde{a}_1}{a_2 - c_u\tilde{a}_1}$
- $\tilde{v} > 0$ i.e. $b_0 > b_1 v_*$
- $v_* > 0$ positive root of the above equation: we observe that the determinant of the equation is always positive and for an analogous reasoning performed for the first model at least one solution will always exist and will be given by considering the v_* obtained with a second-degree solution formula with a positive sign. Since the equation that must satisfy v_* is analogous to the case analyzed with non-logistic growth, even here we will have that the solution is also unique in the case where $b_3\tilde{u} - c_v\tilde{b}_1 + b_2 \geq 0$.

At this point, having identified the equilibrium points of the system 2.6, we can move on to the study of their stability. To do this, however, it is necessary to determine the Jacobian of the system at a generic point $(u, \tilde{u}, v, \tilde{v})$ and calculate its eigenvalues.
First of all, we observe that the first two equations of the system do not include the variables v and $\tilde{v}$ so there will be a block of zeros in the Jacobian. In addition, the elements obtained by deriving the last two equations with respect to the variable u will also be null. The Jacobian matrix will have the following structure:

$$\begin{bmatrix} J_{uu} & J_{u\tilde{u}} & 0 & 0 \\ J_{\tilde{u}u} & J_{\tilde{u}\tilde{u}} & 0 & 0 \\ 0 & J_{v\tilde{u}} & J_{vv} & J_{v\tilde{v}} \\ 0 & J_{\tilde{v}\tilde{u}} & J_{\tilde{v}v} & J_{\tilde{v}\tilde{v}} \end{bmatrix}$$

where

$$J_{uu} = a_0 - 2a_1u - \frac{a_2\tilde{u}}{(1+c_uu)^2} \qquad J_{u\tilde{u}} = -\frac{a_2u}{1+c_uu}$$
$$J_{\tilde{u}u} = \frac{a_2\tilde{u}}{(1+c_uu)^2} \qquad J_{\tilde{u}\tilde{u}} = -\tilde{a}_1 + \frac{a_2u}{1+c_uu}$$
$$J_{v\tilde{u}} = -b_3v\tilde{v} \qquad J_{vv} = b_0 - 2b_1v - b_3\tilde{u}\tilde{v} - \frac{b_2\tilde{v}}{(1+c_vv)^2}$$
$$J_{v\tilde{v}} = -b_3\tilde{u}v - \frac{b_2v}{1+c_vv} \qquad J_{\tilde{v}\tilde{u}} = b_3v\tilde{v}$$
$$J_{\tilde{v}v} = b_3\tilde{u}\tilde{v} + \frac{b_2\tilde{v}}{(1+c_vv)^2} \qquad J_{\tilde{v}\tilde{v}} = -\tilde{b}_1 + b_3\tilde{u}v + \frac{b_2v}{1+c_vv}$$

We note that the Jacobian is a lower-block triangular matrix, so the determinant is given by the product of the determinants of the diagonal blocks and the eigenvalues are the eigenvalues of the diagonal blocks. In particular the eigenvalues will be given by

- $(J_{uu}-\lambda)(J_{\tilde{u}\tilde{u}}-\lambda) - J_{\tilde{u}u}J_{u\tilde{u}} = 0$ from which we get $\lambda^2 - \lambda(J_{uu}+J_{\tilde{u}\tilde{u}}) - J_{\tilde{u}u}J_{u\tilde{u}} + J_{uu}J_{\tilde{u}\tilde{u}} = 0$. Using the resolutive formula
$$\lambda_{1,2} = \frac{J_{uu}+J_{\tilde{u}\tilde{u}} \pm \sqrt{(J_{uu}+J_{\tilde{u}\tilde{u}})^2 - 4(J_{uu}J_{\tilde{u}\tilde{u}} - J_{\tilde{u}u}J_{u\tilde{u}})}}{2}$$
- $(J_{vv}-\lambda)(J_{\tilde{v}\tilde{v}}-\lambda) - J_{\tilde{v}v}J_{v\tilde{v}} = 0$ by further explicating $\lambda^2 - \lambda(J_{vv}+J_{\tilde{v}\tilde{v}}) - J_{\tilde{v}v}J_{v\tilde{v}} + J_{vv}J_{\tilde{v}\tilde{v}} = 0$ and solving we get to
$$\lambda_{3,4} = \frac{J_{vv}+J_{\tilde{v}\tilde{v}} \pm \sqrt{(J_{vv}+J_{\tilde{v}\tilde{v}})^2 - 4(J_{vv}J_{\tilde{v}\tilde{v}} - J_{\tilde{v}v}J_{v\tilde{v}})}}{2}$$

It can be seen that, depending on the value of the parameters within the model, the number of equilibrium points present changes, as does their stability. As a consequence, in order to continue the study, we will need to fix some of these parameters.

Remark 2.2. Up to this point, we have analyzed two different nonlocal models, one with unlimited growth (2.2) and the other with logistic growth (2.5). In both cases, we have pursued the study of equilibrium points with relative stability. Going to make a brief comparison between the stationary points identified, we observe how the equilibrium points of the second system have more than doubled, going from 4 to 9. Indeed, the introduction of logistic growth in the system increases the number of cases to be studied, in particular it opens up the possibility that the components of stationary points corresponding to healthy proteins may also assume a null value.
We remark that the only equilibrium point remaining unchanged and common to both systems is given by $(\frac{a_0}{a_1}, 0, \frac{b_0}{b_1}, 0)$. If in the second model we

decide to consider the precise definition of a_1 and b_1, i.e. $a_1 = \frac{a_0}{K_1}$ and $b_1 = \frac{b_0}{K_2}$, we note that, in this second case, this common equilibrium point can also be expressed as $(K_1, 0, K_2, 0)$.
Finally, we observe that both 2.2 and 2.5 possess a single pathological equilibrium state, in which the component v is not given explicitly but solves the same second-degree equation, which can always be obtained by dividing the last equation of the ODEs system by $\tilde{v}$. It can therefore be stated that as long as this last equation is not altered, v_* will always be the solution of the same second-degree equation.

2.3.2 Clearance inequalities

As with the 2.2, within the present model it is possible to identify by means of inequalities when the clearance process either works correctly or fails.
By analogous reasoning it will be necessary for a $A\beta$ healthy-τ healthy state to exist, depending on the state we want to consider, that the following relations hold

$$a_0 \leq a_1 \text{ and/or } b_0 \leq b_1$$

These can be rewritten, remembering the definition used in this model of $a_1 = \frac{a_0}{K_1}$ and $b_1 = \frac{b_0}{K_2}$, as

$$K_1 \leq 1 \text{ and/or } K_2 \leq 1$$

In the event that at least one clearance process implicated for the healthy state under consideration fails, i.e. where $0 \leq a_1 < a_0$ and/or $0 \leq b_1 < b_0$, we will have that our model will not admit this state with physical significance. We therefore remark how in this model, having three non-null healthy states and not just one as in previous models, the validity of the inequalities $a_0 \leq a_1$ and $b_0 \leq b_1$ leads to a somewhat more complex analysis of the equilibrium points. In addition to these points, the null equilibrium state E_0 will always be considered as there are particular situations in which this can also be of interest.
Always considering the clearance inequalities given by

$$\frac{a_0}{a_1} < \frac{\tilde{a}_1}{a_2 - c_u\tilde{a}_1} \text{ and } \frac{b_0}{b_1} < \frac{\tilde{b}_1}{b_2 - c_v\tilde{b}_1} \tag{2.9}$$

we move on by studying the stability of the significant equilibrium points. Since both of these inequalities hold, we observe that the equilibrium points with physical significance are E_0, E_1, E_3, E_4. By substituting the appropriate values into the formulas derived above for the eigenvalues of the Jacobian matrix, we obtain the following results.

- equilibrium point E_0 : $\lambda_1 = -\tilde{a}_1$, $\lambda_2 = a_0$, $\lambda_3 = -\tilde{b}_1$ and $\lambda_4 = b_0$. Thus having eigenvalues with positive real part it will result unstable.

- stationary point E_1 : $\lambda_1 = -\tilde{a}_1$, $\lambda_2 = a_0$, $\lambda_3 = -\tilde{b}_1 + \frac{b_2 b_0}{b_1 + c_v b_0}$ and $\lambda_4 = -b_0$. Also this state having only three eigenvalues with negative real part will result unstable.

- steady state $E_3 : \lambda_1 = -\tilde{a}_1 + \frac{a_2 a_0}{a_1 + c_u a_0}$, $\lambda_2 = -a_0$, $\lambda_3 = -\tilde{b}_1$ and $\lambda_4 = b_0$. The point will therefore be unstable.

- equilibrium point E_4 : $\lambda_1 = -a_0$, $\lambda_2 = -\tilde{a}_1 + \frac{a_2 a_0}{a_1 + c_u a_0}$, $\lambda_3 = -b_0$ and finally $\lambda_4 = -\tilde{b}_1 + \frac{b_2 b_0}{b_1 + c_v b_0}$. Since we are assuming that the clearance inequalities hold, we will have that this will be the only stable stationary point in this situation.

At this point, we observe that if there are changes that disrupt the clearance process of one of the two proteins, at least one of the two inequalities will not be fulfilled. This change will keep the equilibrium points E_0, E_1, E_3 unstable while it will make the state E_4 unstable. Simultaneously, we will also have that:

1. If the first clearance inequality fails, the points E_6 and E_7 must also be considered

2. If the second clearance inequality is not satisfied, the points E_2 ed E_5 also become of interest

Furthermore, for appropriate parameter values even the state E_* can acquire physical significance as a pathological state.
Carrying out the stability study in these more complex cases without setting parameter values and without the use of simulations is not convenient. Therefore, please refer to [31] for a more complete study of the stability of equilibrium points obtained by means of the tools outlined above. We can however remark, thanks to the simulations set out in the paper, how in a similar way to the previous model we can reach a distinction between different types of tauopathies (primary and secondary) depending on whether the toxic τ concentration exists independently of the $A\beta$ concentration or not. Anyhow, we will have a greater complexity in the analysis of the various cases of development of the disease by having a greater number of equilibrium points within the model. We can still state that even in this case the model is sensitive to the correct or incorrect functioning of the clearance process within the system we are considering.
Furthermore, as studied in [31], in this case we will also have the possibility of studying how, depending on the connections present between the various areas of the brain, the equilibrium point to which the solution asymptotically tends, changes. In order to make these observations, however, the discrete models associated with the described continuous models and set out in the last chapter, are fundamental.

2.4 A third nonlocal model

Having observed that as the growth trend changes, the equilibrium points of our model also change, what we propose to do in this section is to look at another type of growth and observe what changes this choice leads to.
In particular, Gompertz-type growth can be considered within the model. Its uses are not new in the medical and biological fields, indeed, although it was born for a life expectancy model in the insurance field, it has also found applications for example in the growth of tumors ([8]), weight growth of livestock and particular species such as rats and guinea pigs ([45]).
This type of growth results to have features similar to logistic growth, indeed they both turn out to be special cases of the generalized logistic distribution. Following what was described in [44], this is a family of growths with the characteristic S-shape, the slope of which changes as the parameter ξ that characterizes it varies. The equation that distinguishes it, considering as unknown function for example $u = u(x,t)$, is given by

$$\frac{\partial u}{\partial t} = \frac{a_0}{\xi}\Big[1 - \Big(\frac{u}{K}\Big)^{\xi}\Big]u \tag{2.10}$$

where ξ represents the asymmetry of the growth curve to be considered.
If for example $\xi = 1$ is considered, we obtain a logistic growth equation in which the curve obtained is symmetrical with respect to the curve's inflection point. Choosing instead $\xi = 0$ we obtain the Gompertz model. Obviously, since the parameter ξ is in the denominator, this can only be done by using limits. Recalling that $\lim_{z\to 0} \frac{y^z-1}{z} = ln(y)$ then we will have, in our case that

$$\lim_{\xi\to 0} \frac{1}{\xi}\Big[\Big(\frac{u}{K}\Big)^{\xi} - 1\Big] = ln\Big(\frac{u}{K}\Big)$$

from which we get that the Gompertzian growth equation is given by

$$\frac{\partial u}{\partial t} = -a_0 u\ ln(\frac{u}{K})$$

This same equation, exploiting the properties of logarithms, is often expressed in the literature, posing $c_1 = ln(K)$, as

$$\frac{\partial u}{\partial t} = a_0 u(c_1 - ln(u))$$

We will, however, maintain the previous expression.
Regarding the differences with logistic growth, we have that the Gompertz curve is not symmetrical, so if one thinks that the data can take this form, one must consider this growth. Furthermore, when compared with the logistic growth, the Gompertzian growth has a higher growth at first but approaches the asymptote (which remains the same as the logistic growth)

much more slowly. Thus, the two curves differ in their tails and have different points of inflection.
Introducing this type of growth instead of the logistic one in the model 2.5 we will get

$$\begin{cases} \frac{\partial u}{\partial t} = \nabla \cdot (D_1 \nabla u) - a_0 u \ ln(\frac{u}{K_1}) - \frac{a_2 u}{1+c_u u} \phi * \tilde{u} \\ \frac{\partial \tilde{u}}{\partial t} = \nabla \cdot (\tilde{D}_1 \nabla \tilde{u}) - \tilde{a}_1 \tilde{u} + a_2 \tilde{u} \phi * (\frac{u}{1+c_u u}) \\ \frac{\partial v}{\partial t} = \nabla \cdot (D_2 \nabla v) - b_0 v \ ln(\frac{v}{K_2}) - \frac{b_2 v}{1+c_v v} \phi * \tilde{v} - b_3 \tilde{u} v \tilde{v} \\ \frac{\partial \tilde{v}}{\partial t} = \nabla \cdot (\tilde{D}_2 \nabla \tilde{v}) - \tilde{b}_1 \tilde{v} + b_2 \tilde{v} \phi * (\frac{v}{1+c_v v}) + b_3 \tilde{u} v \tilde{v} \end{cases} \tag{2.11}$$

So having a new model, let's see if and how the equilibrium points change.

2.4.1 Analysis of equilibrium points

Since only the temporal and not the spatial dynamics are of interest for the determination of the equilibrium points, we omit the purely spatial contribution terms, i.e. the diffusive terms, as before. Moreover, since the integral terms are operated in the spatial variable, by reasoning similarly to the previous models, exploiting the unitarity of the convolution kernel we will have a simplified contribution. Therefore, the equilibrium points with their stability will coincide with those of the following local ODEs system

$$\begin{cases} \frac{du}{dt} = -a_0 u \ ln(\frac{u}{K_1}) - \frac{a_2 u}{1+c_u u} \tilde{u} \\ \frac{d\tilde{u}}{dt} = -\tilde{a}_1 \tilde{u} + \frac{a_2 u}{1+c_u u} \tilde{u} \\ \frac{dv}{dt} = -b_0 v \ ln(\frac{v}{K_2}) - b_3 \tilde{u} v \tilde{v} - \frac{b_2 v}{1+c_v v} \tilde{v} \\ \frac{d\tilde{v}}{dt} = -\tilde{b}_1 \tilde{v} + b_3 \tilde{u} v \tilde{v} + \frac{b_2 v}{1+c_v v} \tilde{v} \end{cases} \tag{2.12}$$

with non-zero initial conditions.
Let us determine the equilibrium points by proceeding as in the cases that have been already discussed, namely by identifying first the axial stationary states (with at least one null component).
We immediately observe that it is not possible to consider neither $u = 0$ or $v = 0$ as this would lead to indeterminate forms in the first and third equation of 2.12 respectively. We shall therefore only have to analyze the following two cases.

- $\tilde{u} = 0$: the system 2.12 then becomes

$$\begin{cases} u \ ln(\frac{u}{K_1}) = 0 \\ \tilde{u} = 0 \\ -b_0 v \ ln(\frac{v}{K_2}) - \frac{b_2 v}{1+c_v v} \tilde{v} = 0 \\ -\tilde{b}_1 \tilde{v} + \frac{b_2 v}{1+c_v v} \tilde{v} = 0 \end{cases}$$

However, we note that in the case-by-case analysis of the first equation, it is not possible to consider $u = 0$ as this would lead to indeterminacy. The only acceptable case is therefore that the logarithm is null, i.e.

$$\begin{cases} u = K_1 \\ \tilde{u} = 0 \\ -b_0 v\ ln(\frac{v}{K_2}) - \tilde{b}_1 \tilde{v} = 0 \\ -\tilde{b}_1 \tilde{v} + \frac{b_2 v}{1+c_v v}\tilde{v} = 0 \end{cases} \Rightarrow \begin{cases} u = K_1 \\ \tilde{u} = 0 \\ \tilde{v} = -\frac{b_0}{\tilde{b}_1} v\ ln(\frac{v}{K_2}) \\ b_0 v\ ln(\frac{v}{K_2}) - \frac{b_2 v}{1+c_v v}\frac{b_0}{\tilde{b}_1} v\ ln(\frac{v}{K_2}) = 0 \end{cases}$$

Finishing the calculations of the last equation, we obtain

$$\begin{cases} u = K_1 \\ \tilde{u} = 0 \\ \tilde{v} = -\frac{b_0}{\tilde{b}_1} v\ ln(\frac{v}{K_2}) \\ b_0 v\ ln(\frac{v}{K_2})(\tilde{b}_1(1 + c_v v) - b_2 v) = 0 \end{cases}$$

Here again, we observe that in the last equation $v = 0$ cannot be considered due to the indeterminacy to which it would lead. Therefore we will only have the two stationary points obtained by setting the other two terms equal to zero, i.e.

$$E_1 = (K_1, 0, K_2, 0)$$

$$E_2 = (K_1, 0, \frac{\tilde{b}_1}{b_2 - \tilde{b}_1 c_v}, \frac{b_0}{\tilde{b}_1 c_v - b_2} ln(\frac{\tilde{b}_1}{K_2(b_2 - \tilde{b}_1 c_v)}))$$

- $\tilde{v} = 0$: the calculations necessary in this case are completely symmetrical to the previous case. Indeed we will have to solve the system given by

$$\begin{cases} -a_0 u\ ln(\frac{u}{K_1}) - \frac{a_2 u}{1+c_u u}\tilde{u} = 0 \\ -\tilde{a}_1 \tilde{u} + \frac{a_2 u}{1+c_u u}\tilde{u} = 0 \\ -b_0 v\ ln(\frac{v}{K_2}) = 0 \\ \tilde{v} = 0 \end{cases}$$

Similarly, due to indeterminacy, we can only consider the following case

$$\begin{cases} -a_0 u\ ln(\frac{u}{K_1}) - \frac{a_2 u}{1+c_u u}\tilde{u} = 0 \\ -\tilde{a}_1 \tilde{u} + \frac{a_2 u}{1+c_u u}\tilde{u} = 0 \\ v = K_2 \\ \tilde{v} = 0 \end{cases}$$

Using completely symmetrical calculations from the previous case, we will find the following equilibrium points

$$E_1 = (K_1, 0, K_2, 0)$$

$$E_3 = (\frac{\tilde{a}_1}{a_2 - \tilde{a}_1 c_u}, \frac{a_0}{\tilde{a}_1 c_u - a_2} ln(\frac{\tilde{a}_1}{K_1(a_2 - \tilde{a}_1 c_u)}), K_2, 0)$$

In order for the identified equilibrium points to represent densities, all their components must be non-negative. We observe that in the case of E_1 the non-negativity is already guaranteed. Therefore, in order for the other two equilibrium points to be admissible, we must require

- in the case of E_2:
  i. to be positive the density relative to v we must require that $b_2 - \tilde{b}_1 c_v > 0$ i.e. $b_2 > c_v \tilde{b}_1$
  ii. with regard to the density of $\tilde{v}$ we observe that the factor before the logarithm, because of the request made for the positivity of v, is negative. Therefore we will only have to consider values that give us negative logarithms and thus

$$\frac{\tilde{b}_1}{K_2(b_2 - \tilde{b}_1 c_v)} \leq 1 \Rightarrow \tilde{b}_1 \leq K_2(b_2 - \tilde{b}_1 c_v)$$

- in the case of E_3:
  i. for the positivity of the density relative to u is required $a_2 - \tilde{a}_1 c_u > 0$ so $a_2 > c_u \tilde{a}_1$
  ii. for the density of $\tilde{u}$ we observe that, as a result of the requirement related to the positivity of u, we will have to have a negative logarithm. Therefore we shall only consider

$$\frac{\tilde{a}_1}{K_1(a_2 - \tilde{a}_1 c_u)} \leq 1 \Rightarrow \tilde{a}_1 \leq K_1(a_2 - \tilde{a}_1 c_u)$$

Similarly to the previous models, a classification can be made: the point E_1 will be a healthy state, E_2 will be $A\beta$ healthy-τ toxic and E_3 will be $A\beta$ toxic-τ healthy.
Let us now examine whether this model admits an equilibrium state that has no null components. We shall then proceed to solve the following system

$$\begin{cases} -a_0 u\ ln(\frac{u}{K_1}) - \frac{a_2 u}{1+c_u u}\tilde{u} = 0 \\ -\tilde{a}_1\tilde{u} + \frac{a_2 u}{1+c_u u}\tilde{u} = 0 \\ -b_0 v\ ln(\frac{v}{K_2}) - b_3\tilde{u}v\tilde{v} - \frac{b_2 v}{1+c_v v}\tilde{v} = 0 \\ -\tilde{b}_1\tilde{v} + b_3\tilde{u}v\tilde{v} + \frac{b_2 v}{1+c_v v}\tilde{v} = 0 \end{cases}$$

$$\Rightarrow \begin{cases} \tilde{u} = -a_0 u\ ln(\frac{u}{K_1})\frac{1+c_u u}{a_2 u} \\ a_0 u\ ln(\frac{u}{K_1})(\tilde{a}_1\frac{1+c_u u}{a_2 u} - 1) = 0 \\ -b_0 v\ ln(\frac{v}{K_2}) - b_3\tilde{u}v\tilde{v} - \frac{b_2 v}{1+c_v v}\tilde{v} = 0 \\ -\tilde{b}_1\tilde{v} + b_3\tilde{u}v\tilde{v} + \frac{b_2 v}{1+c_v v}\tilde{v} = 0 \end{cases}$$

Among the cases to be analyzed for the second equation, we note that it is not possible to consider $u = 0$ as this would lead to indeterminacy, nor $u = K_1$ as this would lead to $\tilde{u} = 0$ in contrast to our search for a stationary point without null components. We will therefore only have the following case

$$\begin{cases} \tilde{u} = -\frac{a_0}{a_2 - \tilde{a}_1 c_u}\ ln(\frac{\tilde{a}_1}{K_1(a_2 - \tilde{a}_1 c_u)}) \\ u = \frac{\tilde{a}_1}{a_2 - \tilde{a}_1 c_u} \\ -b_0 v\ ln(\frac{v}{K_2}) - b_3 \tilde{u} v \tilde{v} - \frac{b_2 v}{1 + c_v v}\tilde{v} = 0 \\ -\tilde{b}_1 \tilde{v} + b_3 \tilde{u} v \tilde{v} + \frac{b_2 v}{1 + c_v v}\tilde{v} = 0 \end{cases}$$

Moving on, working on the equations in which the unknowns v and $\tilde{v}$ appear, we can add them up to obtain one equation while the other can be derived by dividing the last equation of the system just written by $\tilde{v}$ (which we are assuming to be non-zero). The solution will then be given by

$$E_* = (\frac{\tilde{a}_1}{a_2 - \tilde{a}_1 c_u}, -\frac{a_0}{a_2 - \tilde{a}_1 c_u}\ ln(\frac{\tilde{a}_1}{K_1(a_2 - \tilde{a}_1 c_u)}), v_*, -\frac{b_0}{b_1} v_*\ ln(\frac{v_*}{K_2}))$$

where v_* is solution of the second-degree equation, equal to that of the models analyzed above, $b_3 c_v \tilde{u} v^2 + (b_3 \tilde{u} - c_v \tilde{b}_1 + b_2)v - \tilde{b}_1 = 0$.
This pathological state of the model in order to exist, i.e. for it to have all non-zero and non-negative components, requires the following conditions:

i. $a_2 - \tilde{a}_1 c_u > 0$ implying $a_2 > c_u \tilde{a}_1$

ii. for the density of $\tilde{u}$ we observe that, since we have required the positivity of u, we must have a negative logarithm. Therefore we shall only consider

$$\frac{\tilde{a}_1}{K_1(a_2 - \tilde{a}_1 c_u)} < 1 \Rightarrow \tilde{a}_1 < K_1(a_2 - \tilde{a}_1 c_u)$$

iii. for the positivity of the component $\tilde{v}$ we will require a negative logarithm, therefore $v_* < K_2$

iv. v_* positive root: note that the determinant of the second-degree equation to be solved is always positive, so we will always have two solutions. However, the one obtained by subtracting the root, as in all previous models since the equation is the same, will turn out to be less than zero in some cases.
We will therefore have a single equilibrium point E_* in the case of $b_3 \tilde{u} - c_v \tilde{b}_1 + b_2 \geq 0$.

At this point, in order to study the stability of the four equilibrium points, which may be present for appropriate parameters, we must calculate the Jacobian of the system at a generic point $(u, \tilde{u}, v, \tilde{v})$ and study its eigenvalues.

Since the first two equations of our model do not involve the variables related to protein τ , the Jacobian matrix will be of the form

$$\begin{bmatrix} J_{uu} & J_{u\tilde{u}} & 0 & 0 \\ J_{\tilde{u}u} & J_{\tilde{u}\tilde{u}} & 0 & 0 \\ 0 & J_{v\tilde{u}} & J_{vv} & J_{v\tilde{v}} \\ 0 & J_{\tilde{v}\tilde{u}} & J_{\tilde{v}v} & J_{\tilde{v}\tilde{v}} \end{bmatrix}$$

with

$$J_{uu} = -a_0\ ln(\frac{u}{K_1}) - a_0 - \frac{a_2\tilde{u}}{(1+c_u u)^2} \qquad J_{u\tilde{u}} = -\frac{a_2 u}{1+c_u u}$$

$$J_{\tilde{u}u} = \frac{a_2\tilde{u}}{(1+c_u u)^2} \qquad J_{\tilde{u}\tilde{u}} = -\tilde{a}_1 + \frac{a_2 u}{1+c_u u}$$

$$J_{vv} = -b_0\ ln(\frac{v}{K_2}) - b_0 - b_3\tilde{u}\tilde{v} - \frac{b_2\tilde{v}}{(1+c_v v)^2} \qquad J_{v\tilde{u}} = -b_3 v\tilde{v}$$

$$J_{v\tilde{v}} = -b_3\tilde{u}v - \frac{b_2 v}{1+c_v v} \qquad J_{\tilde{v}\tilde{u}} = b_3 v\tilde{v}$$

$$J_{\tilde{v}v} = b_3\tilde{u}\tilde{v} + \frac{b_2\tilde{v}}{(1+c_v v)^2} \qquad J_{\tilde{v}\tilde{v}} = -\tilde{b}_1 + b_3\tilde{u}v + \frac{b_2 v}{1+c_v v}$$

As the matrix is a lower triangular block matrix, the eigenvalues will correspond to the eigenvalues of the blocks and will therefore be given by

- $\lambda^2 - \lambda(J_{uu} + J_{\tilde{u}\tilde{u}}) - J_{\tilde{u}u}J_{u\tilde{u}} + J_{uu}J_{\tilde{u}\tilde{u}} = 0$. That is, we shall have

$$\lambda_{1,2} = \frac{J_{uu} + J_{\tilde{u}\tilde{u}} \pm \sqrt{(J_{uu} + J_{\tilde{u}\tilde{u}})^2 - 4(J_{uu}J_{\tilde{u}\tilde{u}} - J_{\tilde{u}u}J_{u\tilde{u}})}}{2}$$

- $\lambda^2 - \lambda(J_{vv} + J_{\tilde{v}\tilde{v}}) - J_{\tilde{v}v}J_{v\tilde{v}} + J_{vv}J_{\tilde{v}\tilde{v}} = 0$ from which we obtain

$$\lambda_{3,4} = \frac{J_{vv} + J_{\tilde{v}\tilde{v}} \pm \sqrt{(J_{vv} + J_{\tilde{v}\tilde{v}})^2 - 4(J_{vv}J_{\tilde{v}\tilde{v}} - J_{\tilde{v}v}J_{v\tilde{v}})}}{2}$$

Given a stationary state, calculating the eigenvalues relative to the Jacobian at the point means that if all eigenvalues have a negative real part, the equilibrium point is stable, otherwise unstable.

Remark 2.3. It is interesting to observe how, by changing the growth type of the model, the equilibrium points have changed again. In this case, as a result of the indeterminacy that prevents taking into account some null components, we again have only four equilibrium points as in the first nonlocal model 2.2. We also have in this case a single healthy state in which only the two carrying capacities for $A\beta$ and τ are involved. Recalling, however, that in the case of logistic growth in the 2.5 model we had indicated $a_1 = \frac{a_0}{K_1}$ and $b_1 = \frac{b_0}{K_2}$, we will have that $\frac{a_0}{a_1} = K_1$ e $\frac{b_0}{b_1} = K_2$. Therefore the

healthy equilibrium point in all analyzed models has always remained the same.
The other common element, in this case also with the first nonlocal model 2.2 is the second-degree equation that must satisfy the component v_* of the point E_*. This is because the equation can be obtained simply by dividing the last equation of the system for v_*, so changing only the type of growth does not affect this last equation.

2.4.2 Clearance inequalities

For this model as well, it is fundamental to determine which mathematical inequalities describe the failure or not of the $A\beta$ and τ protein clearance process. We set out the reasoning in the case of $A\beta$ but it will be analogous in the case of τP . Under standard conditions, protein accumulation does not take place, so for the healthy state of our model to be medically relevant it must be the case that the rate of $A\beta$ production (respectively τ) is less than the rate of $A\beta$ clearance (respectively τ). To express this fact mathematically, it is necessary to use the alternative writing for Gompertzian growth

$$-a_0 u\ ln(\frac{u}{K_1}) = -a_0 u(ln(u) - ln(K_1)) = u(a_0\ ln(K_1) - a_0\ ln(u))$$

Indeed, it allows to identify for the $A\beta$ protein the rate of production equal to $a_0 ln(K_1)$ and clearance equal to a_0.
Thus, for both clearance processes to function properly and therefore for the healthy state to have medical significance, it is necessary that

$$a_0\ ln(K_1) \leq a_0 \text{ and } b_0\ ln(K_2) \leq b_0$$

Using the notation of the previous models, in which a_0, b_0 denoted the production rate of protein $A\beta$ and τ and a_1, b_1 that of the clearance, these inequalities revert to those seen in the previous models, i.e.

$$a_0 \leq a_1 \text{ and } b_0 \leq b_1$$

If at least one of these two inequalities fails, it will not be possible to provide medical meaning to the healthy state of the model.
Let us now consider the clearance inequalities for this model given by

$$\tilde{a}_1 > K_1(a_2 - \tilde{a}_1 c_u) \text{ and } \tilde{b}_1 > K_2(b_2 - \tilde{b}_1 c_v) \tag{2.13}$$

These, by substituting the constants K_1 and K_2 with their respective expressions as a function of a_0, a_1 and b_0, b_1, respectively, allow to relate the rates of production to that of clearance of healthy and toxic proteins $A\beta$ and τ. In the event that both of these inequalities hold, we will have that the

only steady state that can represent densities is given by E_1 . Provided that this is also of interest in the medical field (and therefore that the inequalities outlined above are also fulfilled) it makes sense to study its stability. By calculating the Jacobian matrix at the point and deriving its eigenvalues using the explicit expression already given, we obtain

- for values of $\lambda_{1,2}$ we will have

$$\lambda_{1,2} = \frac{1}{2}(-a_0 - \tilde{a}_1 + \frac{a_2 K_1}{1 + c_u K_1} \pm (a_0 - \tilde{a}_1 + \frac{a_2 K_1}{1 + c_u K_1}))$$

  whence $\lambda_1 = -\tilde{a}_1 + \frac{a_2 K_1}{1+c_u K_1}$ and $\lambda_2 = -a_0$

- with regard to $\lambda_{3,4}$ we will have

$$\lambda_{3,4} = \frac{1}{2}(-b_0 - \tilde{b}_1 + \frac{b_2 K_2}{1 + c_v K_2} \pm (b_0 - \tilde{b}_1 + \frac{b_2 K_2}{1 + c_v K_2}))$$

  from which $\lambda_3 = -\tilde{b}_1 + \frac{b_2 K_2}{1+c_v K_2}$ and $\lambda_4 = -b_0$

Therefore, due to the validity we are assuming of the clearance inequalities 2.13, we have that all identified eigenvalues have negative real part and thus E_1 turns out to be stable.
When at least one of the two inequalities is no longer satisfied, we will have that new equilibrium points in our system can be admitted: if, for example, the first clearance inequality fails, the state E_3 may be admitted, if the second fails E_2 may be considered and if both are violated, we may have E_2, E_3, E_*.
As in previous cases, it is not possible to proceed with the study of these much more complicated cases without making use of simulations, due to the impossibility of explicitly determining the real part of the eigenvectors without fixing certain model parameters. Since we have found no precedents in the use of this Gompertzian growth for models similar to ours, and since we have not developed and analyzed these cases in previous models either, this study will not be carried out. In the future, this could be a very interesting analysis to verify the consistency of this model, which has so far only been developed theoretically.
In spite of this, we note that, as in previous cases, the model is able to individuate the clearance process and gives it a decisive role for the analysis of equilibrium points.

Chapter 3

Construction of discrete models

The presented continuous models do not appear to be optimal for simulations. Indeed, as expressed above, if we wish to carry out a more complete analysis of the stability of equilibrium points, and we wish to verify if the described systems behave in a similar way to the experimental data trends, it is necessary to consider different models. In particular, we need to proceed by means of discretization of the continuous models.
As described in [16], the human brain consists of approximately 100 billions (10^{11}) neurons connected by more than 100 trillions (10^{14}) synapses: in a natural way this organization leads to think of modeling it as a graph. In this context, a very important concept is the so-called connectome, that is a matrix representing all possible connections (in pairs) between the neural elements of the brain. Strictly speaking, the term stands for an ideal state of knowledge of the brain's connection pattern, but in the last 10 years research has begun to refer to this as a matrix of anatomical connections between large-scale brain areas as well as between individual neurons. The study related to the visualization and organization of the neural network on different temporal and spatial scales is called connectomics. This field appears to be very recent, on one hand because a more in-depth study of complex network systems has begun only since the 1980s and, on the other hand, because progresses in the neuroimaging processes on which all modeling techniques are based have been made only since the 1990s.
Over the years, following the multiscale architecture of the human brain, the study of its graph was focused on three different scales of organization

1. microscopic level: the focus is on small brain portions in which each neuron is seen as a node in the graph and each of its connections as an arc.

2. mesoscopic scale: the attention focuses on larger areas in which the

nodes represent anatomical groupings of neurons (identified according to different criteria depending on the available data) and the arcs identify the connecting fibers among them

3. macroscopic level: at this scale, nodes represent distinct cortical regions and arcs bundles of white matter, namely axon bundles. This large scale study is possible thanks to tools as structural magnetic resonance imaging (MRI) and data acquisition with diffusion tensor imaging (DTI) and tractography, which essentially visualize the diffusion of a tracer from the injection site to all brain areas connected to it.

3.1 Modeling the brain connectome

For our purposes, we are interested in reconstructing the connectome at a macroscopic level. Therefore, we are not interested in modeling each individual synapse as an arc of our graph, but rather in finding a global representation of the connections, foregoing the finer details.
As mentioned in [9], three main steps are required to model the connectome from acquired images. First, MRI images are used to proceed to the segmentation of the connectome: this identifies the areas of interest and the most appropriate subdivision of the brain, thus being able to identify the positions in space of the graph nodes. Then, using DTI and tractography, the nerve fibers and axon bundles that connect these areas are identified and thus also the arcs that will be present in our graph are determined. As final step, we construct the connectivity matrix (or in mathematical language the adjacency matrix relative to the graph), that is a matrix that is able to express not only the connections that exist between the various nodes, but also the relative importance of these connections.
Each of these steps can be carried out in different ways, depending on the needs and aims of the study.
For example, for the segmentation phase we can consider the boundaries of the brain areas given naturally by the anatomy of the brain. Since this procedure is standard, there are numerous brain atlases available which allow to distinguish the main cerebral areas: two examples are the atlas of Desikan-Killiany ([11]) and that of Destrieux ([12]). From these, following what is described in [9], it is possible to create a multi-scale segmentation (or parcellation). The result will be five distinct atlases, obtained from each other simply by clustering neighboring regions of the most detailed atlas, to be used accordingly to the aims of the study. To be precise, these atlases will correspond to networks of 1015, 463, 234, 129 and 83 knots.
Instead, with regard to the phase of determining the arcs connecting these nodes, it is necessary to use the images obtained from DTI and tractography. In particular, as explained in [9], the former will be used both to

calculate quantities useful for the determination of the weights to be associated with the arcs and to implement the tractography algorithm, while the latter will be used for the actual determination of the arcs. Different algorithms have been developed, starting from division in voxel of the brain volume, in order to obtain tractography images, and so the identification of all connections. The most frequently used (due to its simplicity) is the deterministic streamline algorithm: m points from each voxel are chosen randomly and from these, following the data from the DTI, the connections are constructed using a fixed step. This propagation can only take place within the white matter, which has been identified according to the segmentation used previously, and ends when the boundary between white and gray matter is encountered, or when the diffusion is in contrast with propagation directions identified in adjacent voxels. Through this algorithm, several different directions are allowed within the same voxel.
Since this technique is very sensitive to noise in DTI images and prone to error propagation, alternative algorithms such as probabilistic tractography and global tractography have also been developed. These differ from the above-mentioned methodology in the choice of the starting points, which in the first case will all be chosen within the same brain region obtained from the initial segmentation, while in the second case no choice will be made as the fibers will be defined by means of a minimization procedure.
Keeping in mind that element (i, j) of the connectivity matrix describes the interaction between the i-th and j-th region of the network, each identified fiber connecting these zones will contribute within the element (i, j).
However, we observe that the process of determining the arcs is carried out for each image, referred to different patients. For that reason it is essential to be able to identify those connections that are common, or at least those that occur most frequently, in order to construct a network that is as general as possible. As a consequence, it could be convenient to use a group representative graph: a model obtained by aggregating information from several subjects that represents the connections, but still maintains the typical characteristics of individuals. As described in details in [4], to obtain such networks it is necessary to make use of thresholds that represent the percentage of individuals that must present that particular fiber, in order to maintain it in the final network. These tolerances may be chosen in different ways and they must take into account the biological properties of the connections that have to be modeled. Generally in our brain, following mechanisms aimed at minimizing the cost-energy ratio, although both short and long-range connections are present, the former are favored. However, as mentioned in [4], longer connections are important individual characteristics that have to be reproduced inside the modeling. Depending on the choice of the threshold, these may or may not be missing. Indeed, if we decide to consider a uniform tolerance τ for all connections, we will obtain a network that underestimates the long-haul connections, as they are

present with much lower frequencies than the short ones. For that reason it is convenient to consider a threshold τ that is a function of distance and thus it is able to maintain the most frequent connections in relation to their length.
Depending on the choice of the type and the value of the threshold, as described in detail in [4], we will obtain different descriptions of the connectome as different arcs will be considered.

Having now obtained a network which describes the connectome, in addition to the use we will make of it, numerous studies can be carried out. For example, in [3] it is shown how it is possible to obtain a good reproduction of the image-based network by just using an algorithm known as partition stability framework, in order to identify brain areas with related connections in terms of a Markov process from a random walk model. As the process evolves, this random walk will progressively explore the entire network, and the segmentation zones (which will become the nodes of our graph) will intuitively be groups of vertexes that "trap" the walk for a particular time scale.
Another field of study is that of generative models ([2]): by means of an algorithm, a synthetic network is produced thanks to the addition at each step of an arc that connects nodes that are not yet connected, until certain criteria are reached. These connections are created according to probabilistic laws that take into account both the Euclidean distance between the nodes (using a parameter that favors or disfavors short-range connections) and other topological characteristics (e.g. the total number of connections, or the number of nodes connected with both nodes considered, ...).
In both of these studies, the interest is in evaluating and comparing these synthesized networks with image-based ones in order to identify strengths and weaknesses of both of them.

Returning to what we are interested in, as set out in [40], we now have at our disposal a network in which the nodes represent certain regions of interest within the domain Ω, while the arcs represent the links, or rather the axon bundles, the white matter tracts. Under this new point of view, the brain connectome can be modeled by means of a graph $\mathcal{G}$ of nodes V and arcs E.
We remark that among the steps indicated in the construction of the connectome it is also necessary to identify the connectivity matrix. We will postpone the discussion about this last detail to the next section, in order to better motivate the choice of weights that we are going to place on the arcs.
To bring our models into this new setting, we must first translate continuous variables into discrete variables. Consequently, we must also define the Laplacian operator on a graph as well as the non local convolution operator

and then proceed to apply these definitions within our system.
With regard to the discretization of the unknown concentrations, having fixed a node j we will denote by $(u_j, \tilde{u}_j)$ the concentrations of healthy and toxic $A\beta$ at this node and similarly by $(v_j, \tilde{v}_j)$ the concentrations of healthy and toxic τP.

3.2 Laplacian operator on a graph

In the following we will denote an undirected graph $\mathcal{G}$ as (V, E), where V indicates the set of vertexes while E denotes the set of arcs. Being an undirected graph, each arc could be represented by a pair of values (a, b) where a and b are the connected nodes. Let us also recall that it is possible to assign weights, that are typically positive real values, to each arc: thus we will obtain a weighted graph. The latter will be denoted by the triplet (V, E, ω) where (V, E) corresponds to the unweighted graph while $\omega : E \to \mathbb{R}$ is the function that associates each arc with its weight. Since we will work with undirected graphs we also observe that we will have $\omega(a, b) = \omega(b, a)$ for each node $a, b \in V$.

Definition 3.1. A given graph (V, E), in which $|V| = n$, can be associated in a natural way with the adjacency matrix $W \in \mathbb{R}^{n \times n}$ given by

$$W_{ij} = \begin{cases} 1 & \text{if } (i, j) \in E \\ 0 & \text{otherwise} \end{cases}$$

Definition 3.2. Given an undirected graph (V, E), the degree of a node a is defined as the number of arcs connected to it namely

$$d(a) = |\{b : (a, b) \in E\}|$$

Completely similar definitions can also be given in the case of a weighted graph.

Definition 3.3. A given weighted graph (V, E, ω), in which $|V| = n$, can be associated with the adjacency matrix $W \in \mathbb{R}^{n \times n}$ given by

$$W_{ij} = \begin{cases} \omega(i, j) & \text{if } (i, j) \in E \\ 0 & \text{otherwise} \end{cases}$$

Furthermore, for each node a it is possible to define

- the combinatorial degree, given by the number of arcs connected to the node itself, so
$$d(a) = |\{b : (a, b) \in E\}|$$

- the weighted degree, given by the sum of the weights of the arcs connected to the node
$$d(a) = \sum_{b:(a,b)\in E} \omega(a,b)$$

Having then defined what is meant by the degree of a node, it is possible to introduce the degree matrix D associated with a graph (both weighted and unweighted) as the $n \times n$ diagonal matrix containing in the i-th diagonal term the degree of the i-th node. In our case when we work with weighted graphs, we will always use the combinatorial degree of the node within the matrix D.

Definition 3.4. Given an undirected, weighted graph (V, E, ω) the non-normalized Laplacian on the graph is the matrix defined as

$$\mathcal{L} = D - W$$

Thus, the action of the Laplacian on any signal modeled on the graph results in

$$(\mathcal{L}u)_j = \sum_{k=1}^{n} \mathcal{L}_{jk} u_k = \sum_{k:(j,k)\in E} W_{jk}(u_j - u_k)$$

Firstly, we note that the notion of derivative on the graph is no longer a limit of an incremental ratio as in the continuous case, but a simple difference. This is an immediate consequence of the fact that the set of nodes constituting the graph is a discrete set.
Moreover we remark that when working with an undirected graph, the adjacency matrix W is symmetrical, so the matrix $\mathcal{L}$ is also symmetrical. As a consequence, since it is a real and symmetrical matrix, $\mathcal{L}$ admits at least one orthonormal basis of eigenvectors that we denote by $\{\chi_l\}_{l=1,\dots,n}$ associated with non-negative eigenvalues $\{\lambda_l\}_{l=1,\dots,n}$, where the eigenvalue $\lambda = 0$ will have multiplicity equal to the number of the connected components of the graph, as observed in [35].
Often, the normalized Laplacian on a graph, defined as $\tilde{\mathcal{L}} = D^{-\frac{1}{2}}\mathcal{L}D^{-\frac{1}{2}}$, is also introduced in the literature, as this allows to identify other eigenvectors and eigenvalues that may be more convenient in certain applications (see [37] for a more detailed analysis of the differences).

All these concepts can be applied in the discretization of our model. As mentioned in the case under analysis, we are in the presence of a graph, whose nodes represent brain areas of interest while the arcs represent axonal bundles. The available graph will be a non-oriented graph: this is because the tractography and diffusion magnetic resonance methods used do not allow the identification of the direction of travel along the axon bundles, but only their spatial orientation, as explained in [16]. With regard to the

definition of the weights associated with the arcs, the last step necessary to complete the construction of the connectome, we find that this varies greatly depending on the interest of the study, the methodologies used for the acquisition of the data and the discretization used (a detailed description is given in [16]). In our case we will use a fairly intuitive reasoning to define the weights: depending on the number of axons constituting the axon bundle linking the two areas of interest and how close these zones are to each other, we will have that some arcs will be more utilized than others. Intuitively, the more axons constitute the bundle, the stronger the communication between the two areas, and the further apart the zones are, the more difficult the communication will be. At this point, we decide to work with a weighted graph, where the weights could be taken according to the criterion of electrical connectivity, namely given by the ratio between the number of fibers connecting two distinct nodes and their average length, as recalled in [39]. Nevertheless, following [40], the weights we will assume are summarized by the adjacency matrix $W \in \mathbb{R}^{n\times n}$, where $n = |V|$, given by

$$W_{ij} = \frac{n_{ij}}{l_{ij}^2}$$

for $i, j = 1, ..., n$, where n_{ij} represents the average number (data obtained by studying various patients) of connecting fibers while l_{ij} is the average distance between nodes i and j. Indeed, the square in the denominator is consistent with the trivial observation that since the Laplacian is a second derivative, it has a squared distance in the denominator.
Having now defined what type of graph we are working with, it is also possible to define the Laplacian associated with it. Indeed, diffusive terms of the form $\nabla\cdot(A\nabla\cdot)$ appear within the continuous models described. All the above-mentioned concepts still hold true, with the use of the adjacency just identified. However, due to the diffusion tensor, we will have to introduce a diffusion coefficient ρ in front of the Laplacian on the graph. Therefore, in our model, the non-normalized Laplacian will be given by

$$\mathcal{L} = \rho(D - W)$$

where ρ represents the diffusion coefficient.

It is now possible to move on to express the model 1.4 on the graph. Recalling that $(u_j, \tilde{u}_j, v_j, \tilde{v}_j)$ are the concentrations of healthy $A\beta$, toxic $A\beta$, healthy τP and toxic τP proteins at node j respectively, we will have for each node $j = 1, ..., n$ the following system of first-order differential equa-

tions:

$$\begin{cases} \frac{du_j}{dt} = -\sum_{k=1}^{n} \mathcal{L}_{jk} u_k + a_0 - a_1 u_j - \frac{a_2 u_j}{1+c_u u_j} \tilde{u}_j \\ \frac{d\tilde{u}_j}{dt} = -\sum_{k=1}^{n} \mathcal{L}_{jk} \tilde{u}_k - \tilde{a}_1 \tilde{u}_j + a_2 \tilde{u}_j \frac{u_j}{1+c_u u_j} \\ \frac{dv_j}{dt} = -\sum_{k=1}^{n} \mathcal{L}_{jk} v_k + b_0 - b_1 v_j - b_3 \tilde{u}_j v_j \tilde{v}_j - \frac{b_2 v_j}{1+c_v v_j} \tilde{v}_j \\ \frac{d\tilde{u}_j}{dt} = -\sum_{k=1}^{n} \mathcal{L}_{jk} \tilde{v}_k - \tilde{b}_1 \tilde{v}_j + b_3 \tilde{u}_j v_j \tilde{v}_j + b_2 \tilde{v}_j \frac{v_j}{1+c_v v_j} \end{cases}$$

obtained by taking the expression of the model 1.4 described in [30]. In the case we want to consider a logistic growth, rather than exponential growth as done in this model, the discrete modeling will not encounter major obstacles: it will be enough to replace the terms $a_0 - a_1 u_j$ and $b_0 - b_1 v_j$ respectively with $u_j(a_0 - a_1 u_j)$ and $v_j(b_0 - b_1 v_j)$.
As far as the discretization of the equation 1.3, following [40], this for each node $j = 1, ..., n$ will take the following form

$$\frac{dq_j}{dt} = (k_1 \tilde{u}_j + k_2 \tilde{v}_j + k_3 \tilde{u}_j \tilde{v}_j + k_4 \sum_{k=1}^{n} W_{ik} q_k)(1 - q_j)$$

with $q_j(0) = 0$.

3.3 Convolution on a graph

The only terms missing for the discretization of the more complex models 2.2, 2.5 and 2.11 are the convolution ones with the normalized kernel

$$\phi(x) = \frac{1}{\sigma\sqrt{\pi}} e^{-\frac{<x,x>}{\sigma^2}}$$

Therefore, the aim now is to formally define a convolution operation on the graph. Recalling that in the case of functions $f, g : \mathbb{R}^m \to \mathbb{R}$ belonging to $L^1(\mathbb{R}^m)$, the convolution is defined as

$$(f * g)(x) = \int_{\mathbb{R}^m} f(y) g(x - y) dy$$

the first intention would be to give a similar definition in the case of a graph. However, it is not immediately trivial to explain the meaning of translation on the vertexes of a graph, since the set of nodes does not constitute a ordered set. We might think to introduce an order, chosen arbitrarily, for the vertexes of the graph (V, E) with $|V| = n$ and we might also define the translation "to the right of k" for a function $f : V \to \mathbb{R}$ as $f(\cdot - k) := f(mod(\cdot - k, n))$. Nevertheless, this definition would depend strongly on the order chosen for the nodes of the graph and so it is unusable from a mathematical point of view, as observed in [35].

Thus, the idea is to exploit the properties of the Fourier transform: in particular we want to define the convolution applying the inverse Fourier transform to the convolution theorem for the Fourier transform, according to which given two functions $f, g \in L^1(\mathbb{R}^m)$ we have that $\widehat{f * g}(\xi) = \hat{f}(\xi)\hat{g}(\xi)$. To do this, it is therefore necessary to define the Fourier transform on a graph.
In the case of a function $f : \mathbb{R}^m \to \mathbb{R}$, $f \in L^2(\mathbb{R}^m)$ the Fourier transform is defined as

$$\hat{f}(\xi) := \int_{\mathbb{R}^m} f(x) e^{-i<x,\xi>} dx$$

for each $\xi \in \mathbb{R}^m$. From a different point of view we can consider the Fourier transform as an expansion of the function f in terms of the eigenfunctions of the m-dimensional Laplace operator ([35]). Indeed, considering the space $L^2(\mathbb{R}^m)$ and defining the scalar product between two functions of the space as $< f, g >_{L^2} := \int_{\mathbb{R}^m} f(x)\bar{g}(x)dx$, we have that for $f \in L^2(\mathbb{R}^m)$ the Fourier transform is nothing but $\hat{f}(\xi) =< e^{-i<\cdot,\xi>}, f >_{L^2}$ where, fixed $\xi \in \mathbb{R}^m$, the function $\mathbb{R}^m \ni x \mapsto e^{-i<x,\xi>}$ is an eigenfunction of the Laplacian since

$$\Delta(e^{-i<x,\xi>}) = -\sum_{j=1}^{m} \frac{\partial^2}{\partial x_j^2} e^{-i<x,\xi>} = -\sum_{j=1}^{m} \xi_j^2 e^{-i<x,\xi>} = -|\xi|^2 e^{-i<x,\xi>}$$

Remark 3.5. Let (V, E) be a graph with $|V| = n$ and let the nodes be identified by indexes (so we identify an order for the nodes of the graph). A function $f : V \to \mathbb{R}$ can be thought of as a vector $f \in \mathbb{R}^n$ in which the i-th component represents the value of the function in the i-th node of the graph considered.

We can now define the Fourier transform, following [36], for any function defined on the vertexes of a graph in the following way.

Definition 3.6. Let $\mathcal{G} = (V, E, \omega)$ be an undirected, weighted graph with $V = \{x_l\}_{l=1,...,n}$. Let $\{\chi_l\}_{l=1,...,n}$ be an orthonormal basis of eigenvectors for the Laplacian matrix $\mathcal{L}$ on the graph, ordered by increasing eigenvalues (so in which, if we denote by λ_l the eigenvalue associated with the eigenvector χ_l, $0 = \lambda_1 \leq \lambda_2 ... \leq \lambda_n$). Let $f : V \to \mathbb{R}$ be a function defined on the nodes of the graph. The Fourier transform of f is defined as the function $\mathcal{F}f : V \to \mathbb{R}$ such that

$$\mathcal{F}f(x_l) = \sum_{x \in V} \chi_l(x) f(x) =< \chi_l, f >$$

for each $l = 1, ..., n$.

Remark 3.7. The above definition can be written in a more compact form as follows, as noted in [46]. Let $\{\chi_l\}_{l=1,...,n}$ be an orthonormal base of

eigenvectors (ordered as defined above) for the matrix $\mathcal{L}$ of the Laplacian on the graph. We define $U \in \mathbb{R}^{n\times n}$ as the matrix in which

$$U_{ij} = \chi_j(x_i)\ \forall i, j = 1, ..., n$$

so U is the matrix whose columns consist of the eigenvectors. Therefore, we will have that U is an orthogonal matrix such that $\mathcal{L} = U\Lambda U^T$ where Λ is a diagonal matrix containing the eigenvalues.
Furthermore, the definition of the Fourier transform on the graph for a function $f : V \to \mathbb{R}$ can be written compactly as $\mathcal{F}f = U^T f$.

Definition 3.8. Suppose the assumptions of definition 3.6 hold. The anti-Fourier transform is defined as the function $\mathcal{F}^{-1}f : V \to \mathbb{R}$ such that

$$\mathcal{F}^{-1}f(x) = \sum_{j=1}^{n} \chi_j(x) f(x_j) = Uf(x)$$

with $x \in V$.

We can finally define the convolution on a graph by inverting the convolution theorem for the Fourier transform. To do this we will use the compact writing also used in [46].

Definition 3.9. Let $\mathcal{G} = (V, E, \omega)$ be a finite graph. Then let $f, g : V \to \mathbb{R}$. The convolution of f with g is defined as the function

$$f * g := \mathcal{F}^{-1}(\mathcal{F}f \odot \mathcal{F}g) = U(U^T f \odot U^T g)$$

where U is the matrix obtained with the previous notation and $\odot$ represents the point-by-point product.

Remark 3.10. The convolution can be made explicit using the given definitions of Fourier transform and anti-transform, taking the form indicated in [36] :

$$(f * g)(x_j) = \sum_{l=1}^{n} \mathcal{F}f(x_l)\mathcal{F}g(x_l)\chi_l(x_j)$$

However, this definition is not useful in our application, since the determination of the U matrix, which is fundamental in order to make the convolution on the graph more explicit, is strongly influenced by the number of nodes used and the choice of weights used for the arcs in our modeling. Since we have not found a way to apply this definition, we have decided to proceed in a much rough manner by discretizing the convolution integral in the following way.

The aim is to define the nonlocal conversion for the discrete model for each of the nodes $j = 1, ..., n$. In order to best explain the reasoning behind

this, let us proceed maintaining a parallelism with the continuous model 2.2 and explaining what was done in [29]. Let us take the following convolution as an example, writing it explicitly

$$(\phi * \tilde{u})(x,t) = \int_\Omega \phi(x-y)\tilde{u}(y,t)dy = \int_\Omega \frac{1}{\sigma\sqrt{\pi}} e^{-\frac{<x-y,x-y>}{\sigma^2}} \tilde{u}(y,t)dy$$

Then, we remark how for each spatial point $x \in \Omega$ we consider a unitary kernel acting on all points $y \in \Omega$ that can be "reached", so with which an interaction will take place, starting from point x.
In the discrete model, we must translate this fact in the following way. We fix a node j in the graph and we identify the set of nodes $V_{j,1}$ that are directly connected to node j by an arc in our graph. Proceeding in a similar manner, we then identify the nodes $V_{j,2}$ directly connected with those belonging to $V_{j,1}$ and so on. In the end, we obtain $V_{j,1}, V_{j,2}, ..., V_{j,m_j}$, so the list of all the nodes connected by a path with node j. We note that the sets identified are not necessarily disjointed, depending on the structure of our graph. For that reason it is necessary to give a more precise order to the elements of these sets. In order to do this, for example in the case of $V_{j,1}$, we decide to order the nodes within it as the distance increases (measured in terms of the Euclidean length of the arc connecting them with node j). Similarly, the nodes of the sets $V_{j,2}, ..., V_{j,m_j}$ will be reordered by increasing distance from node j (measured by the Euclidean length of the segments to be traveled).
It is now necessary to eliminate nodes present in more than one set. Let us suppose, for example, that in the case of node j, the distinct nodes connected to it, in addition to the node itself, are n_j. For each of these nodes, we decide to collect within the set V_j the copy that has the minimum distance (always in terms of the path for arcs in the graph) from node j. We now denote by $k_1, k_2, ..., k_{n_j}$ the nodes of the set V_j in order of increasing distance. We will therefore have $k_1 = j$ at zero distance.
At this point, we can construct the unitary kernel that will act on node j of the graph, which has a structure analogous to the kernel of the continuous model. In this respect, we remark that in the continuous case, for $x, y \in \Omega$ communicating

$$e^{-\frac{<x-y,x-y>}{\sigma^2}} = e^{-\frac{||x-y||^2}{\sigma^2}}$$

where $||\cdot||$ measures the Euclidean distance. In the discrete case, again for nodes capable of communication, as distance we should consider the shorter path by arcs connecting the two nodes of interest.
At this point we define, following this observation, the discrete kernel for the node j as

$$M'_j = (1, e^{-\eta^2(s_{jk_2})^2}, e^{-\eta^2(s_{jk_3})^2}, ..., e^{-\eta^2(s_{jk_{n_j}})^2})$$

where $\eta = \frac{1}{\sigma}$ and s_{jk_i} is the distance of node k_i from node j following the shorter length path by arcs.

In this way the kernel we would use for convolution at node j would not be unitary as in the continuous case so we proceed to its normalization. Accordingly let $M_j = M'_j/|M'_j|$ where

$$|M'_j| = (1 + e^{-\eta^2(s_{jk_2})^2} + e^{-\eta^2(s_{jk_3})^2} + ... + e^{-\eta^2(s_{jk_{n_j}})^2})$$

At this point, we want to be able to express the application of the normalized kernel in the discrete case as a product of vectors. Therefore, let $K_j \in \mathbb{R}^n$ a row vector with $n = |V|$, whose only non-zero elements are given by $M_j(1), M_j(2), ..., M_j(n_j)$ respectively at positions $k_1, k_2, ..., k_{n_j}$.
The convolution at node j in graph $\mathcal{G}$ will then be defined as

$$\phi_j * \tilde{u}_j := \sum_{i=1}^{n} K_j(i)\tilde{u}_i$$

Then, explicating the calculations we have

$$\begin{aligned}\phi_j * \tilde{u}_j := \sum_{i=1}^{n} K_j(i)\tilde{u}_i = K_j(k_1)\tilde{u}_{k_1} + K_j(k_2)\tilde{u}_{k_2} + ... + K_j(k_{n_j})\tilde{u}_{k_{n_j}} = \\ = M_j(1)\tilde{u}_{k_1} + M_j(2)\tilde{u}_{k_2} + ... + M_j(n_j)\tilde{u}_{k_{n_j}} = \\ = \frac{1}{|M'_j|}\tilde{u}_{k_1} + \frac{e^{-\eta^2(s_{jk_2})^2}}{|M'_j|}\tilde{u}_{k_2} + ... + \frac{e^{-\eta^2(s_{jk_{n_j}})^2}}{|M'_j|}\tilde{u}_{k_{n_j}}\end{aligned}$$

Let us observe how the parallelism, always assuming $\eta = \frac{1}{\sigma}$, with the convolution considered in the continuous case

$$(\phi * \tilde{u})(x,t) = \int_\Omega \frac{1}{\sigma\sqrt{\pi}} e^{-\eta^2||x-y||^2}\tilde{u}(y,t)dy$$

is immediately evident. Indeed, in both cases we have:

- a sum over all possible interaction points (y and k_i respectively in the continuous and discrete cases) with the considered point (x and j respectively)
- addends obtained by products of exponentials (with exponents given by the squared distance between the interacting points) normalized according to the overall kernel weight, then multiplied by the value of $\tilde{u}$ calculated at the interaction point considered

Remark 3.11. It is interesting to note that in the continuous case the kernel used was the same for every point x of the considered domain Ω. In the discrete case we observe that, as also suggested by the notation used (so $\phi_j * \tilde{u}_j$ rather then $(\phi * \tilde{u})_j$), distinct kernels are used for distinct nodes. While maintaining the same basic structure, we will work with vectors K_i which may be more or less scattered depending on the number of nodes connected by arc paths to the vertex i.

Remark 3.12. If node j is not connected to other nodes, it follows naturally from the definition of convolution that $\phi_j * \tilde{u}_j = \tilde{u}_j$.

The whole process just described can be repeated for each node of the graph $\mathcal{G}$ and for each convolution that appears in our system, thus concluding the process of discretization of the models.

Thus, taking into account both the definition of the Laplacian and the definition of convolutions, it is possible to construct the nonlocal model on the graph $\mathcal{G}$ corresponding to the model 2.2. Maintaining, as we have always done in the previous notation whereby $(u_j, \tilde{u}_j, v_j, \tilde{v}_j)$ are the concentrations of healthy $A\beta$, toxic $A\beta$, healthy τP and toxic τP proteins at node j respectively, we will have for each node $j = 1, ..., n$ the following system of first-order differential equations

$$\begin{cases} \frac{du_j}{dt} = -\sum_{k=1}^{n} \mathcal{L}_{jk} u_k + a_0 - a_1 u_j - \frac{a_2 u_j}{1+c_u u_j} \phi_j * \tilde{u}_j \\ \frac{d\tilde{u}_j}{dt} = -\sum_{k=1}^{n} \mathcal{L}_{jk} \tilde{u}_k - \tilde{a}_1 \tilde{u}_j + a_2 \tilde{u}_j \phi_j * (\frac{u_j}{1+c_u u_j}) \\ \frac{dv_j}{dt} = -\sum_{k=1}^{n} \mathcal{L}_{jk} v_k + b_0 - b_1 v_j - b_3 \tilde{u}_j v_j \tilde{v}_j - \frac{b_2 v_j}{1+c_v v_j} \phi_j * \tilde{v}_j \\ \frac{d\tilde{u}_j}{dt} = -\sum_{k=1}^{n} \mathcal{L}_{jk} \tilde{v}_k - \tilde{b}_1 \tilde{v}_j + b_3 \tilde{u}_j v_j \tilde{v}_j + b_2 \tilde{v}_j \phi_j * (\frac{v_j}{1+c_v v_j}) \end{cases} \tag{3.1}$$

as reported in [29].
Similarly, combining the observation made above in the case of logistic growth in the discrete model with what is described in [31], we obtain that the discrete model in the case of 2.5 is given by

$$\begin{cases} \frac{du_j}{dt} = -\sum_{k=1}^{n} \mathcal{L}_{jk} u_k + u_j(a_0 - a_1 u_j) - \frac{a_2 u_j}{1+c_u u_j} \phi_j * \tilde{u}_j \\ \frac{d\tilde{u}_j}{dt} = -\sum_{k=1}^{n} \mathcal{L}_{jk} \tilde{u}_k - \tilde{a}_1 \tilde{u}_j + a_2 \tilde{u}_j \phi_j * (\frac{u_j}{1+c_u u_j}) \\ \frac{dv_j}{dt} = -\sum_{k=1}^{n} \mathcal{L}_{jk} v_k + v_j(b_0 - b_1 v_j) - b_3 \tilde{u}_j v_j \tilde{v}_j - \frac{b_2 v_j}{1+c_v v_j} \phi_j * \tilde{v}_j \\ \frac{d\tilde{u}_j}{dt} = -\sum_{k=1}^{n} \mathcal{L}_{jk} \tilde{v}_k - \tilde{b}_1 \tilde{v}_j + b_3 \tilde{u}_j v_j \tilde{v}_j + b_2 \tilde{v}_j \phi_j * (\frac{v_j}{1+c_v v_j}) \end{cases} \tag{3.2}$$

for each node $j = 1, ..., n$.
The last model to be brought onto the graph is 2.11. Gompertzian growth can be brought onto the graph in the same way as logistic growth. So the discrete model in the case of 2.11 is for each node $j = 1, ..., n$

$$\begin{cases} \frac{du_j}{dt} = -\sum_{k=1}^{n} \mathcal{L}_{jk} u_k - a_0 u_j \ ln(\frac{u_j}{K_1}) - \frac{a_2 u_j}{1+c_u u_j} \phi_j * \tilde{u}_j \\ \frac{d\tilde{u}_j}{dt} = -\sum_{k=1}^{n} \mathcal{L}_{jk} \tilde{u}_k - \tilde{a}_1 \tilde{u}_j + a_2 \tilde{u}_j \phi_j * (\frac{u_j}{1+c_u u_j}) \\ \frac{dv_j}{dt} = -\sum_{k=1}^{n} \mathcal{L}_{jk} v_k - b_0 v_j \ ln(\frac{v_j}{K_2}) - b_3 \tilde{u}_j v_j \tilde{v}_j - \frac{b_2 v_j}{1+c_v v_j} \phi_j * \tilde{v}_j \\ \frac{d\tilde{u}_j}{dt} = -\sum_{k=1}^{n} \mathcal{L}_{jk} \tilde{v}_k - \tilde{b}_1 \tilde{v}_j + b_3 \tilde{u}_j v_j \tilde{v}_j + b_2 \tilde{v}_j \phi_j * (\frac{v_j}{1+c_v v_j}) \end{cases} \tag{3.3}$$

To conclude, it is also possible to translate the equation 2.3 on graph $\mathcal{G}$. Let q_j be the neuronal damage of the cells in node j. Then for each node

$j = 1, ..., n$ the discretization of the equation 2.3 will lead to

$$\frac{dq_j}{dt} = (k_1\tilde{u}_j + k_2\tilde{v}_j + k_3\tilde{u}_j\tilde{v}_j + k_4\psi_j * q_j)(1 - q_j)$$

with initial condition $q_j = 0$. Also in this case the convolution will be constructed and then defined in steps similar to the previous ones. Since the kernel ψ, as mentioned above, has a different standard deviation, we will have the parameter μ, instead of the parameter η, defined in a similar manner.

3.4 Simulations results

At this point, having constructed discrete models, it is more easy to carry out simulations to validate them. In particular, in this way we can understand deeply the role and the influence of certain parameters within the model and we can also make comparisons between the results of local and nonlocal models.
The following results and observations will not concern model 3.3 with Gompertz-type growth, since no similar models have been found in the literature and simulations have not yet been carried out.
The first step to achieve sensible results is to set initial conditions in accordance with the medical studies that have been carried out. For each node in our graph, we are going to consider the initial condition $(\frac{a_0}{a_1}, 0, \frac{b_0}{b_1}, 0)$, namely the healthy equilibrium point found in all models. However, these initial conditions are modified at certain nodes in order to allow the development of the disease: it has been seen that the seeding sites for the toxic $A\beta$ protein are the temporobasal and frontomedial regions, while for the toxic τ are the transentorhinal and locus coeruleus regions [40], [15], [22]. Therefore for nodes belonging to seeding site regions, as initial toxic concentration, instead of the null one, is assumed a percentage of the healthy protein concentration present (usually chosen less than 1%). For example, if we consider a node in the temporobasal region and we assume a 1% deviation of the healthy protein concentration, we will have $(\frac{a_0}{a_1}, \frac{a_0}{100a_1}, \frac{b_0}{b_1}, 0)$ as initial condition at the node.
In addition, following experimental data, values will be set for the rates of growth a_0, b_0, clearance $a_1, \tilde{a}_1, b_1, \tilde{b}_1$, protein interaction b_2, b_3 and misfolding c_u, c_v. All these rates will be constant for all nodes, unless otherwise stated.
As a result of this first step, several studies could be carried out highlighting different conditions on the models.
A first interesting remark is set out in [30] in the continuous case and in [29] in the discrete case, where it is observed that, for corresponding times, the mere introduction of the Holling's functional into the model 3.1 causes a reduction of the toxic $A\beta$ and τ concentrations compared to the original

model. Indeed, having fixed the other parameters appropriately, in the local model associated with 3.1 as c_u and c_v increase, a longer time is required for the disease to propagate into the brain connectome. This remark is in accordance with the fact that in the construction of the model the constants c_u and c_v include the necessary misfolding time: the larger this time is, the more the constants will increase and as a consequence the creation of new misfolded proteins will take longer and longer. An entirely similar observation, set out in [31], also applies to model 3.2: an increase in the conversion rates of healthy proteins to toxic configuration leads to an increase in the time required for the disease to propagate throughout the connectome.
In [29], again thanks to simulations results, several interesting phenomena characterizing model 3.1 are observed:

- the distinction between simulations of primary and secondary tauopathy cases can be driven by changing only the parameters b_2 and b_3 (remark also valid in the case of model 3.2)
- the choice of a constant parameter b_3 at all nodes leads to equal spreading patterns and equal invasion time windows for the local and nonlocal models associated for both primary and secondary tauopathy. Things change if we consider a condition of mixed tauopathy, that is assuming parameters b_2 and b_3 that will lead to primary tauopathy in some nodes and different values of them in other nodes to simulate a secondary tauopathy. Indeed, maintaining the same seeding sites described above, it could be observed how in this case the spreading patterns for the nonlocal model and for its associated local counterpart are different. Thus, the introduction of nonlocal interactions leads to changes in the spread of the disease under the more realistic conditions of parameters non-uniformity.

Other interesting results were obtained by means of simulations of model 3.2 in [31]: in this case it is shown that depending on the spatial position of each node, the temporal developments of the concentrations in the node change. If all parameters at each node are kept constant, the concentrations of toxic $A\beta$ and τ can follow different courses. In the case of rates values leading to a primary tauopathy, the developments of toxic $A\beta$ (respectively τ) proteins concentration converges to three distinct values, depending on whether or not the node is connected to other nodes. In the first case, the system solution will tend towards the pathological equilibrium state E_*. Instead, if the node is not connected to other nodes: if it is inside the seeding sites of $A\beta$ or τ it will tend to the equilibrium state E_7 or E_5 respectively; otherwise it will remain in the healthy stationary state E_4 of the system.
Similarly in [31] the study of neuronal damage for both the nonlocal discrete model 3.2 and the associated local model was carried out, with the choice of appropriate parameters. In both cases the damage can follow different

trends, tending to the value of the neuronal damage corresponding to the equilibrium points E_4, E_5, E_7, depending on the type of node connection. In addition, it could be observed that in the case of the nonlocal model, the time required to diffuse the damage to the nodes is longer than in the local model.
This phenomenology is due to the existence of stable manifolds for the semi-stable stationary points E_4, E_5, E_7. This type of equilibrium points is not present in the case of model 3.1.
A similar study can be carried out for parameters leading to secondary tauopathy.
Finally, in [31] it is observed that in model 3.2, when simulating a mixed tauopathy, similarly to what has been described above, the concentrations of all four components are different at each node of the connectome and consequently the time for the nodes to be damaged is also different. Furthermore, as the parameter $\frac{1}{\sigma}$, related to the competition kernel used, decreases, it is remarked how in some nodes (identified according to the value of the their combinatorial degree) there is an higher toxic density accumulation. We can therefore conclude that the spreading pattern in the case of mixed tauopathy is different from the primary and secondary tauopathies.

In the future, it will be interesting to observe how the introduction of Gompertz-type growth in 3.3 could have influenced such simulations in order to see if the true clinical dynamics were modeled in this way.

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