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COUPLED SPATIO-TEMPORAL DYNAMICS AND NONLOCALITY IN ADVANCED MATHEMATICAL MODELS FOR THE ANALYSIS OF COMPLEX NEURODEGENERATIVE DISEASE PATHOLOGIES

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Abstract. One in six of the world's population has to deal with neurodegenerative disorders, and while medical devices exist to detect, prevent, and treat such disorders, some fundamentals of the progression of associated diseases remain ambiguous. In this contribution, we focus on Alzheimer's disease (AD), where amyloid-beta (Aβ) and tau proteins are among the main contributors to the development or propagation of AD. The Aβ proteins clump together to form plaques and disrupt cell functions. Moreover, the abnormal chemical change in the brain helps to build sticky tau tangles that block the neuron's transport system. Astrocytes generally maintain a healthy balance in the brain by clearing the Aβ toxic plaques. Even so, over-activated astrocytes release chemokines and cytokines and also react to pro-inflammatory cytokines, further increasing the production of Aβ. We have provided details of a novel coupled mathematical model that can capture astrocytes' dual behaviour, emphasizing the importance of spatio-temporal coupling and nonlocality. We have demonstrated that the disease propagation depends on memory effects, that is the disease's earlier status, which involves non-Markovian processes. We have explained how to integrate brain connectome data in the network model and to study this effect, as well as the dual role of astrocytes as a coupled phenomenon. Depending on toxic loads in the brain, we have also discussed details of the analysis of the neuronal damage in the brain. We have explained how the memory effect can slow down the propagation of toxic proteins in the brain, decreasing the rate of neuronal damage. Representative numerical examples have been given, and special attention has been paid to nonequilibrium considerations and stochastic modelling frameworks in the study of neurodegenerative diseases.

1 INTRODUCTION

In the forthcoming era of personalized medicine and current global efforts in genome engineering with advances in data analysis [1], increasing attention is being paid to the active matter and its properties at the cell level [13]. This includes cells, their interactions, as well as their intrinsic components such as microtubules, mitochondria, various other organelles, and

nuclei. Some such considerations are also important for neurodegenerative diseases. For example, it is known that abnormal mitochondria in human Alzheimer's disease (AD) brain neurons are being accumulated, which resulted in more refined scrutiny of biogenesis and degradation of mitochondria, as well as the related processes such as mitophagy and neuronal homeostasis [2]. Equally important is further attention to autophagy and nuclear integrity, and in this context it is also known that nucleophagy promotes longevity, given that distortion of nuclear architecture happens during aging, accompanied by age-related pathology such as a disruption of the nuclear lamina, etc. There is also an intrinsic connection between microtubules and AD with other tauopathies due to the regulation of neuronal microtubule dynamics by tau proteins. While some properties of microtubules have been studied (e.g., [14, 15] and references therein), their complex dynamics require their analysis with more vigour due to many time-dependent processes such as disaggregation. The latter plays a critical role in many neuropathologies and neurodegenerative diseases including AD and Parkinson's disease because the disassembly of misfolded protein aggregates is a requirement for the proper functioning of cells in the brain.

The above considerations stimulate the development of advanced coupled spatio-temporal dynamic models for the analysis of neurodegenerative disease pathologies and highlight the importance of accounting for nonlocal and in some cases nonequilibrium, phenomena, as we argue in this contribution.

2 COUPLING NEURONAL AND GLIAL CELLS

In this section, we underline the main types of coupling for modelling and analysis of neurodegenerative diseases. Firstly, we note that neural cells alone are not sufficient, because we have to account for their coupling to another special type of cells, namely glial (non-neuronal) cells (or neuroglia, see [8] and references therein). In this consideration, microglia, which is a type of neuroglia, play an important role. It is located throughout the brain with its volume fraction taking around 10-15% of cells there. Its importance stems from the fact that they are key central nervous system immune cells. In the sense that they destroy pathogens and remove damaged cells, they are similar to macrophages. But they also can be harmful in neurodegenerative diseases, including AD and Parkinson's disease. Hence, it is not surprising that they have been studied extensively [6], albeit in many cases separately from the important coupling considerations mentioned above.

Secondly, it is important to point out that in the coupled neural–glial dynamics, astrocytes also play a critical role when it comes to such neurodegenerative diseases as AD [9]. Often interpreted as the "disease of forgetfulness", AD is associated with the propagation and aggregation of toxic proteins. It was already Alzheimer himself showed the importance of both amyloid beta (Aβ) plaques and tau protein neurofibrillary tangles (NFTs). By now it is well known that in order to construct credible mathematical models in this field, we need to couple the amyloid beta (which forms extracellular aggregates and plaques) and tau proteins (which are intracellular proteins that stabilize axons by cross-linking microtubules that can form largely messy tangles). Apparently, in many cases, it is a necessary, but not sufficient condition because astrocytes and microglial cells constantly clear these plaques and NFTs from the brain. In addition to their functionality related to the transportation of nutrients from the blood to neurons, activated astrocytes produce monocyte chemoattractant protein-1 (MCP-1), which attracts anti-inflammatory macrophages and clears Aβ. The importance of bringing the coupling of astrocytes into the picture comes from two main facts: (a) on the

one hand, the microglia cells are poorly phagocytic for Aβ compared to proinflammatory and anti-inflammatory macrophages, (b) on the other hand, we know that in addition to such distinctive neuropathological features of AD as amyloid beta and tau proteins, neuroinflammation needs to be accounted for. Recently, taking advantage of a coupled mathematical modelling framework, we formulated a network model, accounting for the coupling between neurons and astroglia and integrating all three main neuropathological features with the brain connectome data [9]. We also provided details on the coupled dynamics involving cytokines, astrocytes, and microglia, and applied the developed ideas to the necrosis factor alpha (TNF-α) inhibitor and anti-Aβ drug and analyzed their influence on the brain cells, suggesting conditions under which the drug can prevent cell damage. We have also brought additional features to this coupling, highlighting further the importance of astrocytes [19]. Due to a major challenge of brain network modelling, its multi-scale spatio-temporal nature, covering scales from synapses to the whole brain, it was necessary to develop a particular mathematical framework that would account for the coupled multiphysics and biochemical activities which spread through such a complex system shape brain capacity inside a structure-function relationship. This framework has been part of our development of the next-generation coupled-based mathematical modelling approaches to brain networks and the analysis of data-driven dynamical systems. Not only AD is marked by the presence of amyloid-beta (Aβ) plaques and tau (τ) proteins, but some disease-specific misfolded proteins can interact with healthy proteins to form long chains and aggregates of different sizes that have different transport properties and toxicity. Therefore, we proposed an improved large-scale brain network model to better understand the pathogenesis of AD, especially the role of astrocytes in the presence of misfolded proteins (Aβ and τ). In particular, the model can describe astrocytic clearance, which assists in eliminating toxic Aβ via fragmentation. As a first step, we used the general Smoluchowski theory of nucleation, aggregation, and fragmentation to predict the development and propagation of aggregates of misfolded proteins in the brain. We demonstrated that the developed model leads to different size distributions and propagation along the network and predicted that astrocytic clearance varies with the aggregate size, which is key to slowing down AD progression. Further, we saw that the clearance and fragmentation of toxic proteins span several spatial and temporal scales, highlighting the importance of detailed multi-scale brain modelling and associated couplings mentioned above.

3 COUPLING TO NEURAL DAMAGE AND MEMORY EFFECTS

This level of coupling was developed specifically in the AD context. Known to us due to Alois Alzheimer, who first described the condition in 1906, the AD symptoms are mild at first and become more severe over time. They typically include one of several characteristics such as memory loss, cognitive deficits, problems with recognition, problems with speaking, reading, or writing, and others. According to the Alzheimer's Association, early onset Alzheimer's disease affects around 5.5 million Americans in the U.S., and 44 million worldwide deal with this disease in all ranges of ages, while 10% of the population is suffering over 65 years of age [20]. We recall that the key characteristics of Alzheimer's disease to start with are two abnormal structures called plaques and tangles. They are prime suspects in damaging and killing nerve cells. Hence, it is also important to incorporate into the model the coupling to neural damage. The latter is usually critical in developing treatment strategies. As we mentioned above, plaques are deposits of a protein fragment called Aβ that build up in the spaces between nerve cells,

whereas tangles are twisted fibers of another protein called tau that build up inside cells. To model their dynamics along with other features we mentioned becomes increasingly important also because there is no single test for Alzheimer's disease, and therefore the diagnosis is not always easy. The doctor may carry out the following tests: cognitive and memory tests, to assess the person's ability to think and remember; neurological function tests, to test their balance, senses, and reflexes; a CT scan or MRI scan of the brain; blood or urine tests; genetic testing; and others.

The development of models accounting for the coupling to neural damage needs to account for other levels of coupling already mentioned, in particular, astrocytes notwithstanding because these glial cells can be in contact with thousands of neurons. Along with the features we already mentioned, they are crucial to the nervous system [21] as they regulate synaptic transmission and plasticity and protect neurons against toxic compounds; astrocytes support metabolically to ensure their optimal functioning and without this help, neurons will not communicate; they balance the ion concentrations in the brain; they maintain a healthy balance in the brain by clearing the Aβ plaque; over-activated astrocytes release chemokines and cytokines in the presence of Aβ and also react to pro-inflammatory cytokines, further increasing the production of Aβ. Therefore, as a further development of [3], in [4] the authors have recently constructed a mathematical model that can capture astrocytes' dual behaviour. It was shown that the disease propagation does not depend only on the current time instance; rather, it depends on the disease's earlier status, or to put it simply, the "memory effect". To capture the influence of such memory effect on AD propagation, they proposed a fractional order network mathematical model, which they integrated with brain connectome data in the network model. This allowed them to study the memory effect and the dual role of astrocytes together. The neuronal damage in the brain has been analyzed depending on toxic loads in the brain, so based on the pathology, primary, secondary, and mixed tauopathies parameters were varied in the model. It was revealed that due to the mixed tauopathy, different brain nodes or regions in the brain connectome accumulate different toxic concentrations of toxic Aβ and toxic tau proteins. A new plausible explanation was given on how the memory effect can slow down the propagation of such toxic proteins in the brain, decreasing the rate of neuronal damage.

We note that both developed models, in [3] and [4], are nonlocal, with the first one representing nonlocality by integral convolution terms, and the second one representing nonlocality by fractional time derivatives. Nonlocality can also come from other sources, including boundary and initial conditions and the interested reader can consult [16] and references therein for further details on this.

In both cases, whether we deal with the nonlocal model with integral terms or with fractional time derivatives, as a first step, it is instructive to carry out homogenized systems analyses. For example, before analyzing the full fractional order PDE-based models, we first studied the model's temporal dynamics (e.g., equilibrium points and their stabilities), where spatial dependencies in the corresponding reaction-diffusion models were neglected. This provides additional guidance. In the subsequent steps, we need to move to data-driven models by integrating the data and developing corresponding coupled network models. Our computational scheme for the network model construction can be briefly described as follows:

- first, we import the brain connectome data into the computational environment;
- then, we read the number of nodes, number of edges, mean fiber number and the mean

length between the nodes;

- we compute the Laplacian L for the graph data by using the information on the constructed adjacency matrices;
- finally, we apply an efficient numerical method to solve the resulting coupled network models.

Regarding the data source and associated methodologies for data analysis, we have used the freely available patients connectome data found at and also the data from the Human Connectome Project given by Budapest Reference Connectome v3.0 (). Specifically, we considered brain connectome data consisting of 1,015 vertices and 16,280 edges. The integrated brain connectome data has 49 brain IDs, each containing one or more nodes. Furthermore, each brain region contains one or more brain IDs. All computations have been performed by using our in-house developed code based on C programming language and Matlab. Both explicit and implicit numerical methodologies have been used to solve coupled network models, depending on the network complexity.

Some of the main results of this investigation included the following observations: (a) with an increase in the clearance rate, the brain connectome's toxic loads may decrease or increase, depending on astrocyte carrying capacities, (b) based on the non-Markovian model, the higher memory takes more time to distribute the overall toxic loads in the brain; (c) the analysis of calculated average concentrations for the substances in each brain ID shows that due to the non-uniform parameter set in the tau proteins' equation, the toxic load converges to different concentrations over the brain IDs, (d) the analysis of calculated average concentrations of the substances in each brain region shows similar non-uniform toxic tau protein distributions over the brain regions, but the nonlocal model based on fractional time derivatives slows down the speed of the toxic load distributions in brain regions. As a result, the fractional-derivatives-based model demonstrates less damage compared to the non-fractional integral-terms-based model.

Overall, our fully coupled heterodimer model accounts for the interaction of Aβ and tau protein, astrocytes, and neural damage, incorporating also memory effects in its non-Markovian version. Importantly, the fractional-derivatives-based model includes the astrocytes' equation that allows to account for a dual role of astrocytes before and after the over-activation. The study of memory effects in the disease progression based on the fractional-derivatives-based model shows slowing down the speed of the disease propagation. Further detailed analysis of the node- and region-wise disease propagation in the brain connectome with this model demonstrates less toxic loads compared to the nonlocal model based on integral terms. This model can be used in an experimental set-up for better data fitting due to its multiscale nature and an additional degree of freedom compared to the integer-order nonlocal models.

4 WORKING MEMORY IN NEURODEGENERATIVE DISEASES, STOCHASTIC MODELLING AND NONEQUILIBRIUM CONSIDERATIONS

It is well known that working memory is affected early in many neurodegenerative diseases, including Alzheimer's disease. Although the human brain is the most complicated biological structure on the planet, we also know well by now that conditions for learning do not occur under equilibrium states. This leads us to nonequilibrium considerations once we want to do

our next step in the model development for neurodegenerative diseases. On a bigger scale, life itself is an ultimate nonequilibrium phenomenon, and all models considered in life sciences need to reflect the stochastic nature of the associated dynamics of humans that can be geared toward a better description of nonlocal and nonequilibrium phenomena of such dynamics when it is required [5]. This consideration not only can assist us in a deeper understanding of the link between nonequilibrium phenomena and neurodegenerative diseases, but also provides stairways in biosocial and behavioral psychological approaches via the concept of decision making [22]. Indeed, three stepping stones in these stairways are: 1) knowledge creation and associated decision-making steps are nonequilibrium processes; 2) a critical element for decision-making is working memory, the brain's ability to temporarily store and recall information, 3) working memory is affected early during the onset of neurodegenerative diseases such as Alzheimer's, and can serve as a key to better understanding the course of such diseases and developing treatments.

While there is a wider context where the above nonequilibrium problems are important, our motivation here is routed in the analysis of neurodegenerative diseases. Starting from earlier papers [23, 24], we know that Alzheimer's and other kinds of dementia (e.g., frontotemporal dementia [25]) affect working memory at an early stage, a critical element in decision-making [22]. Specifically, it was observed that working memory is reduced in Alzheimer's patients as it works with semantic memory [23] which helps in understanding and recognizing words for language processing, which is stored in the working memory. Further, we know also from [24] (where working memory was measured by assessing participants' ability to retain numbers) and later works (based on other methodologies) that working memory is reduced in people with mild cognitive impairment compared to those with normal cognitive functioning. In terms of the mathematical modeling framework for working memory, here we follow the premises where the Fokker-Planck equation is derived based on the Langevin equation. In doing so, we can go beyond nonequilibrium models relaxing to equilibrium (e.g., those based on the Langevin equation derived from a Hamiltonian and leading to Maxwell-Boltzmann or other standard models relaxing to equilibrium such as Hohenberg-Halperin). Our interest is in Langevin equations which may not be even based on a Hamiltonian and can generally be far-from-equilibrium models. We can move from this consideration to the Fokker-Planck model which ultimately can even be considered in random (possibly switching) environments (e.g., [26]). As a starting point, we begin with a set of Langevin equations describing the stochastic dynamics of neural networks [27]. The approach is based on the landscape-flux method where one makes use of the fact that the nonequilibrium system is driven by both the non-vanishing steady state irreversible probability flux and the gradient of the potential landscape in the state space (for the equilibrium system, the driving force can be expressed by the gradient of an energy function). Within this approach, various biophysics-based models for working memory can be integrated, with one of the simplest examples found in [27]. As was demonstrated by the authors of this latter paper, the flux can drive the system away from the local attractors, leading to another attractor, and it is due to the existence of non-zero flux, the system never settles to any of the local attractors. They concluded that the non-equilibrium flux facilitates the biological functions of working memory from both the dynamical perspective and the thermodynamic perspective, the situation which is fundamentally different from equilibrium cases.

Nonlocal models that we considered in the previous section are also important at smaller scale levels, including cells under various loading conditions. Indeed, all biological cells are exposed

to a variety of loads that influence cellular processes [13]. Hence, our better understanding of cell mechanics under the application of external stimuli is important for capturing the nuances of physiological and pathological events, and ultimately for the development of modern medical therapies such as tissue engineering and regenerative medicine, as well as in the development of new remedial treatments. As it was shown in [13], such considerations also require nonlocal models. At the same time, at larger scales, such as the whole brain modelling, the current trend focuses on various aspects of multiscale co-simulation protocols, in particular in the context of various neurosurgical procedures such as Deep Brain Stimulation [17, 7].

Stochastic models in this field are not limited to the model we discussed above in this section. Among others, we mention the models developed from the brain information processing perspective, given that the brain is a complex information processing network in which the nervous system receives information from the environment to quickly react to incoming events or learns from experience to sharpen our memory [10]. Since the brain states translate the collective activities of neurons interconnected via synaptic connections, it is also important to study coupled effects of channels and synaptic dynamics under the stochastic influence of healthy brain cells in the context of neurodegenerative disease development. Stochastic models provide a suitable framework for modelling various aspects of neurodegenerative disease especially when combined with advanced tools in data-driven modelling, including the approximate Bayesian computation (ABC) approach [11, 12]. In this spirit, we recently studied the role of astrocytes in amyloid-beta dynamics with modelling of Alzheimer's disease using clinical data and quantified the interplay between amyloid-beta and calcium levels in Alzheimer's disease.

5 KEY MODEL HIGHLIGHTS

The details of the nonlocal model with integral terms can be found in [3]. In what follows, we provide the main details of our spatio-temporal fractional model in a spatial domain $\Omega \subset \mathbb{R}^3$ as [4]:

$$D_t^\alpha u = \nabla \cdot (\mathbf{D}_1 \nabla u) + u(a_0 - a_1 u) - a_2 u\widetilde{u}, \tag{1a}$$

$$D_t^\alpha \widetilde{u} = \nabla \cdot (\widetilde{\mathbf{D}}_1 \nabla \widetilde{u}) - \widetilde{a}_1 \widetilde{u} + a_2 u\widetilde{u} - \mu\widetilde{u}(w - \widetilde{u}), \tag{1b}$$

$$D_t^\alpha v = \nabla \cdot (\mathbf{D}_2 \nabla v) + v(b_0 - b_1 v) - b_2 v\widetilde{v} - b_3 \widetilde{u} v\widetilde{v}, \tag{1c}$$

$$D_t^\alpha \widetilde{v} = \nabla \cdot (\widetilde{\mathbf{D}}_2 \nabla \widetilde{v}) - \widetilde{b}_1 \widetilde{v} + b_2 v\widetilde{v} + b_3 \widetilde{u} v\widetilde{v}, \tag{1d}$$

$$D_t^\alpha w = w(c_0 - w/c_1), \tag{1e}$$

where the first term on the right-hand side in each of the first four equations incorporates the random movement of the concentrations in the domain Ω. We assume that the astrocytes' density remains homogeneous in the whole domain Ω. We consider the same damage equation as

$$D_t^\alpha q = (k_1\widetilde{u} + k_2\widetilde{v} + k_3\widetilde{u}\widetilde{v} + k_4 q)(1 - q), \tag{2}$$

with the non-negative initial condition.

We have extended this model into a network mathematical model on the graph $\mathbf{G}$, whose

dynamics at each node $j(j = 1, 2, 3, \ldots, N)$ are given by

$$D_t^\alpha u_j = -\sum_{k=1}^{N} L_{jk}^u u_j + u_j(a_0 - a_1 u_j) - a_2 u_j \widetilde{u}_j, \tag{3a}$$

$$D_t^\alpha \widetilde{u}_j = -\sum_{k=1}^{N} L_{jk}^{\widetilde{u}} \widetilde{u}_j - \widetilde{a}_1 \widetilde{u}_j + a_2 u_j \widetilde{u}_j - \mu \widetilde{u}_j (w_j - \widetilde{u}_j), \tag{3b}$$

$$D_t^\alpha v_j = -\sum_{k=1}^{N} L_{jk}^v v_j + v_j(b_0 - b_1 v_j) - b_2 v_j \widetilde{v}_j - b_3 \widetilde{u}_j v_j \widetilde{v}_j, \tag{3c}$$

$$D_t^\alpha \widetilde{v}_j = -\sum_{k=1}^{N} L_{jk}^{\widetilde{v}} \widetilde{v}_j - \widetilde{b}_1 \widetilde{v}_j + b_2 v_j \widetilde{v}_j + b_3 \widetilde{u}_j v_j \widetilde{v}_j, \tag{3d}$$

$$D_t^\alpha w_j = w_j(c_0 - w_j/c_1), \tag{3e}$$

and the corresponding damage equation is given by the corresponding fractional differential equation

$$D_t^\alpha q_j = (k_1 \widetilde{u}_j + k_2 \widetilde{v}_j + k_3 \widetilde{u}_j \widetilde{v}_j + k_4 q_j)(1 - q_j), \tag{4}$$

with non-negative initial conditions. Further details and notations can be found in the quoted references.

6 REPRESENTATIVE NUMERICAL RESULTS

In what follows we provide two representative examples obtained with the models discussed above. All parameters that have been used are given in Tables 1, 2, and 3.

In the first figure, we can see the solutions for amyloid-beta concentrations, both healthy and toxic, obtained with the nonlocal model with integral terms. The interest in these quantities has grown dramatically since the introduction of two new Alzheimer's disease drugs. First, in 2021 aducanumab received approval from the U.S. Food and Drug Administration, followed by lecanemab in 2023.

Our second figure here represents a quick visual comparison between the results obtained with the nonlocal model based on integral terms and the nonlocal model based on fractional time derivatives that we discussed in the previous sections. Specifically, we have plotted the brain region-wise average damage propagation.

Table 1: Synthetic parameter values [18].

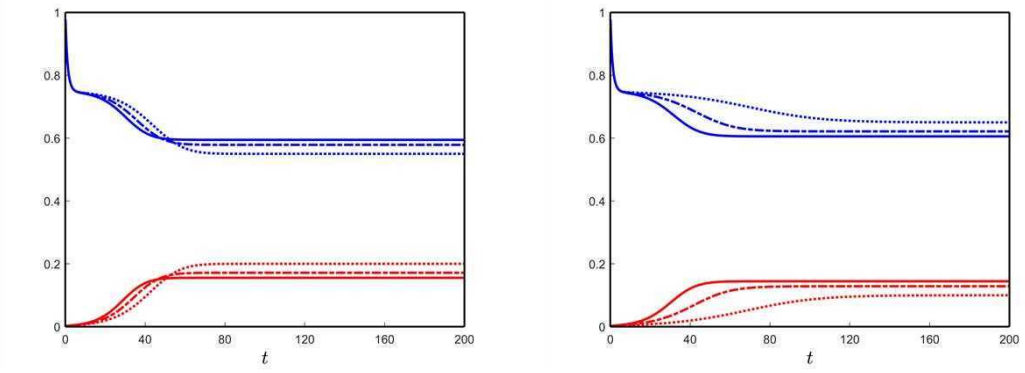
Parameter	Value	Parameter	Value	Parameter	Value	Parameter	Value
a_0	1.035	a_1	1.38	a_2	1.38	$\widetilde{a}_1$	0.828
b_0	0.69	b_1	1.38	b_2	1.035	$\widetilde{b}_1$	0.552
b_3	4.14	c_0	1.0	c_1	0.1	μ	0.1
ρ_1	1.38	ρ_2	0.138	ρ_3	1.38	ρ_4	0.014
k_1	0.0001	k_2	0.01	k_3	0.1	k_4	0.001

Table 2: Modified b_3 parameter values in different brain IDs [18].

Brain ID	Value	Brain ID	Value
Pars opercularis	7.452	Rostral middle frontal gyrus	6.707
Superior frontal gyrus	7.452	Caudal middle frontal gyrus	7.452
Precentral gyrus	5.589	Postcentral gyrus	3.726
Lateral orbitofrontal cortex	6.486	Medial orbitofrontal cortex	6.486
Pars triangularis	5.520e-6	Rostral anterior cingulate	6.210e-6
Posterior cingulate cortex	3.45	Inferior temporal cortex	13.11
Middle temporal gyrus	11.04	Superior temporal sulcus	8.97
Superior temporal gyrus	8.28	Superior parietal lobule	12.42
Cuneus	13.8	Pericalcarine cortex	13.8
Inferior parietal lobule	11.73	Lateral occipital sulcus	15.18
Lingual gyrus	13.8	Fusiform gyrus	7.59
Parahippocampal gyrus	11.04	Temporal pole	1.104e-5

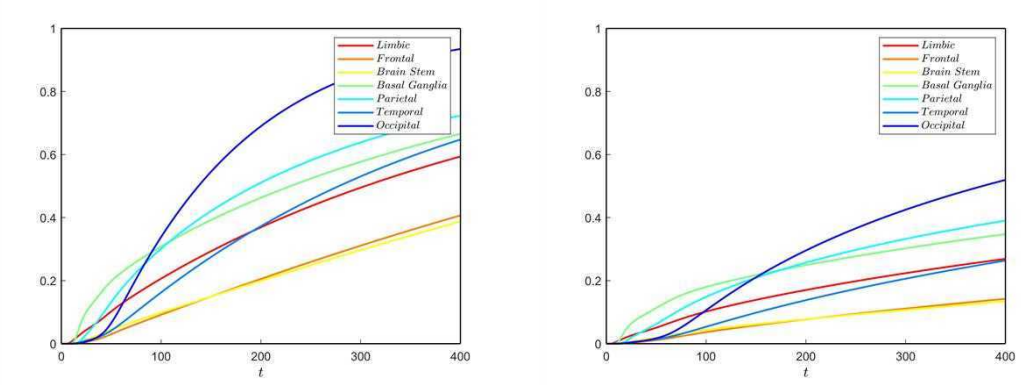
Table 3: Modified b_2 and b_3 parameter values in different brain IDs [18].

Brain ID	Entorhinal cortex	Pallidum	Locus coeruleus	Putamen	Precuneus
b_2	3.125	2.76	1.38	3.795	3.105
b_3	1.104e-5	2.76	1.38	3.795	3.105



(a) (b)

Figure 1: The solutions of amyloid-beta (blue) and toxic amyloid-beta (red) for the non-fractional temporal model of (1) for different values of μ and c_1: (a) $c_1 = 0.1$ and (b) $c_1 = 0.2$. Here, solid curves for $\mu = 0.1$, dashed-dotted curves for $\mu = 0.3$, and dotted curves for $\mu = 0.5$. Other fixed parameter values are mentioned in Table 1.



(a) (b)

Figure 2: (Color online) Brain region-wise average damage propagation: (a) non-fractional model and (b) fractional model with $\alpha = 0.8$. Here, we choose the fixed parameter values $\mu = 0.2$, $c_1 = 0.3$ and Table 1 for all the nodes in the brain connectome except the nodes listed in Tables 2 and 3.

7 CONCLUSIONS

We provided an overview of recently developed nonlocal coupled models to study Alzheimer's disease, where amyloid-beta and tau proteins are among the main contributors to the development or propagation of AD. We emphasized the special dual role of astrocytes and the importance of their coupling modelling in the developed framework. It has been shown that the disease propagation depends on memory effects, requiring a new non-Markovian model. The procedure of the integration of brain connectome data in the network model has been given. Among the results, we pointed out that the memory effect can slow down the propagation of toxic proteins in the brain, decreasing the rate of neuronal damage. The developed nonlocal coupled models can be applied to analyze different pathologies in the brain. We provided representative numerical examples. Additionally, we explained why nonequilibrium considerations and stochastic modelling frameworks in the study of neurodegenerative diseases are becoming increasingly important. In this context, we emphasized that in studying brain network models and associated information dynamics, some particular characteristics such as working memory play a special role. Starting with Langevin equations, we moved to Fokker-Planck type models, where the nonequilibrium landscape-flux method can be applied for the analysis of the system's states. This methodology is traditionally useful in analyzing the systems that can abandon a given attractor, breaks the symmetry of the landscape under certain stimuli or distractor stimuli, erase the previous memory, and encode the new one. Given that this nonequilibrium approach provides a general way to study the dynamics of neural systems and working memory, it can be beneficial to apply it to the analysis of neurodegenerative diseases, including Alzheimer's disease and other types of dementia.

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