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Perspectives

# Alzheimer's disease and the mathematical mind

Travis B. Thompson *, Bradley Z. Vigil, Robert S. Young

*Texas Tech University, Department of Mathematics and Statistics, Lubbock, TX, 79409, United States*

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ABSTRACT

Throughout the 19th and 20th centuries, aided by advances in medical imaging, discoveries in physiology and medicine have added nearly 25 years to the average life expectancy. This resounding success brings with it a need to understand a broad range of age-related health conditions, such as dementia. Today, mathematics, neuroimaging and scientific computing are being combined with fresh insights, from animal models, to study the brain and to better understand the etiology and progression of Alzheimer's disease, the most common cause of age-related dementia in humans. In this manuscript, we offer a brief primer to the reader interested in engaging with the exciting field of mathematical modeling and scientific computing to advance the study of the brain and, in particular, human AD research.

**Statement of Significance**

Modeling Alzheimer's disease is a highly interdisciplinary field and finding an effective starting point can be a considerable challenge. To address this challenge, this manuscript briefly highlights some central components of AD related protein pathology, useful classes of mathematical models for brain and AD research and effective computational resources for the practical prospective practitioner.

## 1. Introduction

'*How do we think?*' is one of the simplest, most profound and scientifically remarkable questions asked by human brains about themselves. Partial responses to this inquiry cut across a range of disciplines, from physics, chemistry and computer science to psychology, neuroscience and medicine. Despite its succinct presentation, the question of how we think is complex and lacks a general and encompassing theory. One difficulty may be in defining the qualifications of what constitutes the act, or experience, of thought.

A simpler, but still quite challenging, related scientific question, of increasing importance, is '*Why does our ability to think decrease as we age?*'. Unlike the more amorphous variations of thinking about thinking, aging is broadly associated with mechanisms such as cellular senescence, DNA damage, genomic instability, the shortening rates of telomeres, an increase in pro-inflammatory secretion and metabolic stress [1,2], all of which have been suggested as participants in the ultimate reduction of cognitive efficacy.

The need to understand age-related pathologies, especially those related to the brain, is rising. The World Health Organization predicts that, by 2050, the world population of those over 60 will double as countries face a continuous acceleration in the median age of their citizenry. Significant investments are therefore being made into research surrounding diseases associated with aging, including cardiovascular diseases, cancers and dementias.

Dementia is an umbrella term which describes a decline in cognitive capacity, memory and behavior. It is projected [3] that more than 50 million people currently live with dementia and that this number will increase by more than 300% by 2050, levying a staggering economic cost on both health care systems and caretakers worldwide. Dementia is mechanistically non-specific and is currently thought to emerge from one or more failures [4,5] in the brain's ability to maintain the appropriate cellular environment for proper neuronal function. Though dementia is more specifically subdivided, such as vascular, frontotemporal and mixed dementia, the most prevalent cause of dementia, accounting for approximately two-thirds of all dementia cases world wide, is Alzheimer's disease (AD).

The pathogenesis of AD, and the pursuant decline into a state of dementia, is not yet fully understood. A number of lifestyle factors have been identified [3] to help reduce the probability of developing AD, but there is currently no cure for the disease. Pharmaceutical studies are numerous [5,6] but have faced various complications and approved endpoints have had less than desirable outcomes on overall disease progression [5,7]. Nevertheless, human AD research has remained resilient by drawing on new perspectives and approaches.

A novel path forward in AD research is *to make the mind mathematical* by combining two areas of scientific progress: advances in neuroimaging; and novel mathematical models of factors contributing

* Corresponding author.
*E-mail address:* travis.thompson@ttu.edu (T.B. Thompson).

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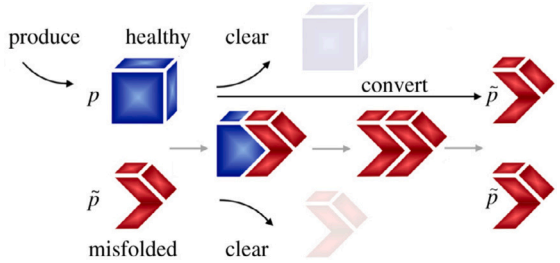


**Fig. 1.** A protein population (blue) is converted to a population in an altered state (red) by an autocatalytic process. The concentration of either population can be reduced by brain clearance mechanisms (transparent blue, red). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

to AD and of AD progression. The latter category expresses the effects of basic mechanisms, mostly discovered through experiments using animal models, as sets of coupled differential equations while the former provides patient specific brain domains on which these equations can be solved. Combined, neuroimaging and mathematical modeling are helping to quantify patient data, make predictions about patient outcomes and explore the potential effects of various mechanisms on human AD progression.

## 2. A brief introduction to AD protein pathology

The discovery of AD is attributed [8] to Alois Alzheimer following a lecture, delivered in the fall of 1906, in which he reported a patient's development of 'a peculiar severe disease process of the cerebral cortex'. His account of the patient's brain autopsy described what we now know today as plaque deposits comprised of the protein amyloid beta (A$\beta$) and neurofibrillary tangles (NFT) made up of the protein tau ($\tau$P). Over 100 years later, the presence of A$\beta$ plaques and $\tau P$ NFT are still considered to be primary pathophysiological markers of AD with atrophy of the brain's hippocampus [9] now recognized alongside them.

To understand contemporary uses of mathematical models in AD research, we briefly highlight a selected number of biological viewpoints that have proven pivotal in this regard.

### 2.1. Perspectives on AD dementia pathogenesis

The precise etiology of AD dementia is currently unknown. As a result, AD research is vibrant and a number [5] of origin theories, both old and new, are present in the literature. For instance, the regional disruption [10] of acetylcholine signaling (the cholinergic hypothesis) was advanced half a century ago. Conversely, the theory of reduced glymphatic system efficacy [11] (lymphatic system hypothesis) and the view of chronic neuronal stress [4] (chronic stress hypothesis) are quite recent.

The most familiar hypotheses for the cause of AD dementia are, unsurprisingly, tied directly to the protein pathology noted by Alois Alzheimer: A$\beta$ plaques and $\tau$P NFT. The amyloid hypothesis [12] posits that dysregulation of APP metabolism, and pursuant A$\beta$ deposition and aggregation, are the primary events that lead to a cascade of pathology and culminates in AD. In a similar vein, the tau propagation hypothesis [13] suggests that aggregates of abnormally phosphorylated tau proteins ($\tau$P) spread through the brain, interrupt signal transmission between, and are toxic to, neurons and may further mediate A$\beta$ toxicity and neuronal death.

### 2.2. The prion-like hypothesis

Self replication of a pathological proteinaceous state is a hallmark [14] of *prion diseases*. Prion diseases were first solidified by Nobel prize winning research, pioneered by Stanley Prusiner, in scrapie, a transmissible spongiform encephalopathy in sheep. In scrapie, healthy $PrP^{C}$ protein (blue, Fig. 1) is converted to misfolded, neurotoxic $PrP^{SC}$ protein (red, Fig. 1) in an autocatalytic fashion.

Many brain disorders are associated with otherwise functional proteins entering into a misfolded state and forming larger fibrillar and aggregated [15,16] structures. AD is such a disease and characterized by A$\beta$ extracellular amyloid plaques and intracellular $\tau P$ NFTs. Soluble monomeric proteins undergo changes and form [17,18] small soluble oligomers. When a critical concentration is reached, a larger, insoluble conformation possess a more desirable free energy state [15] and aggregation towards this energy minimizer is induced.

Misfolded aggregates act [16] in three important ways: first, they continue to recruit lower order structures (elongation); second, they can break apart (fragmentation); and finally, they can enhance the formation of lower-order aggregates at higher rates (secondary nucleation). In these ways, misfolded aggregates are capable of *self replication*. That protein misfolding and aggregation proceeds similarly to prion diseases [19–22] is called the *prion-like hypothesis* of neurodegenerative diseases.

### 2.3. Regional spreading of misfolded proteins

Experimental data suggests that misfolded, seed competent oligomers increase in number among brain regions which are connected via axonal pathways [23–26]. Such spreading has been noted in vitro [24], in animal models [27] and in humans [21,28]. Various experiments have provided evidence consistent with both intracellular [24,26] axonal and extracellular [29–31] spreading; extracellular misfolded protein species may be further impacted by the anisotropic diffusion of brain water molecules as measured by diffusion tensor neuroimaging techniques.

### 2.4. Brain clearance mechanisms

The brain is an active organ, accounting for nearly 20% of the body's daily metabolic energy production. A multitude of proteins are continuously synthesized and degraded to support the brain and its function. It comes as no surprise that a complex, biochemical milieu will give rise to the occasional neurotoxic misfolded protein or oligomer.

The brain has *clearance systems* which act to preserve organ homeostasis. Our current understanding is that protein homeostasis is ensured, in general, by three main modes of clearance: cellular degradation, the blood circulation (perfusion), and the cerebrospinal fluid circulation [11,32,33]. The failure of one or more brain clearance systems is thought to potentially contribute to the etiology of AD, the progression of AD, or both.

## 3. The mathematical mind and AD research

Broadly speaking, there are two classical classes of mathematical approaches for investigating factors relevant to AD at the whole brain level. The first is coupled systems of *partial differential equations* (PDEs) and the second is coupled systems of *ordinary differential equations* (ODEs). Each of these have their advantages and drawbacks. A third class of *network dynamical systems* (NDS) has recently come into use; NDS bridge PDE and ODE models, and strike a balance between the advantages of the two primary classical paradigms.

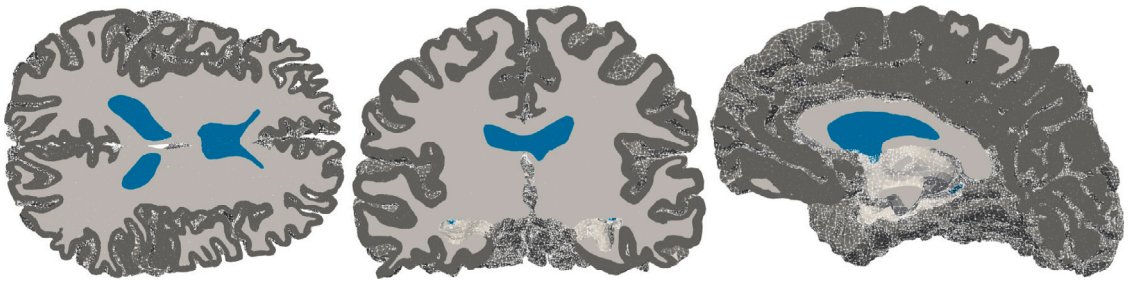

**Fig. 2.** A finite element mesh of the first author's brain; axial (left), coronal (middle) and sagittal (right) sections. The mesh was generated from MRI data using the Surface-Volume Meshing Toolkit (SVM-Tk).

### 3.1. Brain modeling using PDEs

Systems of coupled PDE can express multiphysics quantities of interest in both space and time. The derivation of closed-form solutions to most PDEs is not a feasible approach and discretization methods are used to transform them into corresponding, often large, linear systems that can be solved using computers. The advantage of this approach is two-fold: first, these types of methods can often provide impressive resolution in space and time; second, there are discretization methods, such as the finite element or finite volume methods, that handle complex geometries, such as the brain, quite well.

Models based on PDEs face several challenges. These challenges, broadly speaking, are: the mathematical analyses of PDE models, and their discretizations, are often complicated; the discretized problems, on complex geometries, tend to be computationally expensive to solve; and ascertaining the computational assets, such as brain meshes and white matter diffusion tensors, from patient clinical data can be a difficult task.

#### 3.1.1. The brain as a multi-fluid porous medium

Under normal in vivo conditions, the brain can be modeled as a porous, quasi-static and linearly elastic fluid saturated medium consisting of a solid skeleton of extracellular matrix permeated by one or more fluid networks. The equations describing this paradigm are the MPET, or *multiple network poroelasticity* equations. A simplified form [34] of the MPET equations are

$$-\nabla\cdot\sigma(\mathbf{u})+\sum_{j=1}^{J}\alpha_j\nabla p_j=\mathbf{f}, \tag{1a}$$

$$c_j\dot{p}_j+\nabla\cdot\left(\alpha_j\dot{\mathbf{u}}-\kappa_j\nabla p_j\right)+\sum_{m=1}^{J}\gamma_{m,j}\left(p_j-p_m\right)=g_j. \tag{1b}$$

The model (1a)–(1b) is a system of $J+1$ equations, where $J$ is the total number of fluid networks permeating the poroelastic medium, and is closed by a choice of suitable displacement and pressure boundary conditions.

Momentum balance is expressed by (1a), wherein $\mathbf{u}$ is the displacement of the solid skeleton, $\sigma(\mathbf{u})=2\mu\epsilon(\mathbf{u})+\lambda\mathrm{tr}(\epsilon(\mathbf{u}))$ is the isotropic effective elastic stress tensor, $\epsilon(\mathbf{u})=\frac{1}{2}\left(\nabla\mathbf{u}+\nabla\mathbf{u}^T\right)$ is the strain tensor and $\mu$ and $\lambda$ are the Lamé coefficients of the (brain) poroelastic medium. The Lamé coefficients are related [35] to the Young modulus ($E$) and Poisson ratio ($\nu$) of the (brain) medium by

$$\mu=\frac{E}{1+2\nu},\quad \lambda=\frac{E\nu}{(1-2\nu)(1+\nu)}. \tag{2}$$

The remaining terms in (1a) are the fluid pressures, $p_j$ for $j=1,2,\ldots,J$, in fluid network $j$ and the Biot–Willis coefficients $\alpha_j$, associated to the $j$th network.

There is one mass conservation equation, of the form (1b), for each of the $J$ fluid networks. In (1b), $c_j$ is the storage coefficient and $\kappa_j$ is the hydraulic conductivity for the $j$th network while $\gamma_{m,j}$ is a transfer coefficient determining exchange of pressure between the $m$th and $j$th networks. Additional details regarding the coefficients of (1a)–(1b) can be found in [36]. An extension of (1a)–(1b) includes cross-porosity storage coefficients that manifest [36] under constrained conditions, resulting in additional time derivative terms [37, Eqn. 13] appearing in (1b).

The model (1a)–(1b) has been used, with $J=4$ or $J=6$ fluid networks and biological boundary conditions, in the biomechanics literature to study several factors related to the brain and to AD. It has been used to study hydrocephalus and cerebral edema [38,39] and factors related to AD onset and progression [40–44], such as perfusion and cerebrospinal fluid clearance (Section 2.4), for healthy and cognitively impaired patients.

#### 3.1.2. Numerical methods and neuroimaging meshes

Solving (1a)–(1b) numerically is a challenging task, even in the canonical case of Biot's equations which result from the MPET system (1a)–(1b) when $J=1$. This is especially true in the brain where large disparities in the material coefficients, $1\ll\lambda$, $0<\kappa_j\ll 1$ and $0\leq c_j\ll 1$, can cause numerical instabilities. Numerical concerns aside, the question of how to generate accurate approximations to brain geometries, that a computer can use alongside a numerical method to solve systems like (1a)–(1b), is a practical issue that must also be resolved. There are responses to both of these problems in the literature.

There are several finite element methods for solving (1a)–(1b) that can be implemented using most finite element software solver packages; we highlight only a few recent approaches here. For instance, a mixed finite element method [34] based on introducing a solid pressure into (1a)–(1b) can be used for the case of nearly incompressible materials, $1\ll\lambda$ or equivalently $\nu\approx 1/2$ in (2), with small storage, $0\leq c_j\ll 1$, and transfer, $0\leq\gamma_{m,j}\ll 1$, coefficients. A parameter-robust preconditioner [45] for the solid pressure approach has also been proposed.

In brain modeling, one may also wish to include a Darcy flux in (1a)–(1b), for example, to simulate a drug delivered to the brain or to enhance information regarding perfusion or glymphatic system [11,46] function. It has been shown, at least for $J=1$, that (1a)–(1b) can be augmented with a Darcy flux and robustly solved [47] when $0<\kappa_j\ll 1$, in (1b), without the need for a more restrictive Stokes-Biot [48] numerical stability condition. If (1a)–(1b) is solved as written, and using conforming finite elements as in bioengineering [40–44] research, a-posteriori error estimators and adaptive refinement schemes are now appearing in the literature [49] as well.

There are many more finite element based methods for solving (1a)–(1b), but ascertaining brain meshes from patient data is also a significant barrier for patient-specific modeling in AD research. It is now possible, by combining the open source brain segmentation of FreeSurfer [50,51] and the Python-based Surface Volume Meshing Toolkit [52] (SVM-Tk), to generate brain meshes from neuroimaging data using only a few dozen lines of code. The SVM-Tk supports meshing, re-meshing, smoothing, anatomical regional labeling and diffusion tensor extraction from patient neuroimaging (T1, T2 and DTI) data [52,53].

A comprehensive guide for generating a brain mesh, from MRI patient data, and for getting started with PDE based brain modeling, using FEniCS [54], is available [53]. An example of a full-brain, tetrahedral finite element mesh, generated by the SVM-Tk using a T1 MRI sequence, appears in Fig. 2 with cells tagged for the gray matter (dark gray), white matter (light gray) and the lateral and third ventricles (blue).

### 3.2. Brain modeling using ODEs

Systems of ODEs are especially useful for the modeling of biological phenomena as, often, only a general description of relationships between biological quantities, and not precise conservation laws, may be available. This phenomenon occurs frequently in the context of AD research; laboratory experiments may, for example, exhibit that the production of hyperphosphorylated $\tau P$ is upregulated [55,56] in the presence of $A\beta$ but we otherwise lack a precise notion of the physics of this process across the extracellular space. In this case, an ODE model is arguably the most parsimonious approach given the data at hand.

Brain AD models based on ODEs are more readily formulated, predicated on experimental results, are significantly less computationally expensive to solve, compared to their PDE counterparts, and much can be learned from studying the structure of their equilibria as (biologically meaningful) variations are made to the system's parameters. However, they face a significant drawback: conventional ODE models provide information about the overall state of a system and lack spatial fidelity. Though this perspective can be useful when modeling whole-brain [57] protein aggregate levels, spatio-temporal heterogeneity, of $A\beta$ and $\tau P$, is a well-known characteristic [28,58] of AD progression.

#### 3.2.1. The brain and network dynamical systems

Network dynamical systems are a particular type of compartmental ODE model that can be used to offset the traditional lack of spatial fidelity in ODE systems that otherwise describe evolution in time. NDS are especially useful for modeling many brain diseases, including $A\beta$ and $\tau P$ pathology in AD (Section 3.2.2).

At the simplest level, a NDS begins with a fixed choice of an undirected graph, with no self loops, $G = (V, E)$ having vertex set $V = \{v_1, v_2, \dots, v_N\}$ and edge set $E \subseteq V \times V$. In this case, a symmetric, weighted *adjacency matrix* $\mathbf{A}$ can be defined by $\mathbf{A}_{ij} = w_{ij}$ where $w_{ij} = w_{ji} > 0$ if $(v_i, v_j) \in E$ and $w_{ii} = 0$. A general, autonomous NDS [59] on $G$ takes the form

$$\dot{\mathbf{x}}_i = f_i(\mathbf{x}_i; \boldsymbol{\theta}_i) + \sum_{j=1}^{N} \mathbf{A}_{ij} g_{ij}\left(\mathbf{x}_i, \mathbf{x}_j; \boldsymbol{\theta}_i, \boldsymbol{\theta}_j\right), \tag{3}$$

where $\mathbf{x}_i$ is a vector representing quantities associated to the vertex $v_i \in V$, $f_i(\mathbf{x}_i; \theta_i)$ represents the local dynamics, with parameter vector $\boldsymbol{\theta}_i$, at vertex $v_i$, while $g_{ij}\left(\mathbf{x}_i, \mathbf{x}_j; \boldsymbol{\theta}_i, \boldsymbol{\theta}_j\right)$ describes the interactions between the quantities defined at vertices $v_i$ and $v_j$.

The choice of network, $G$, plays an important role in an NDS model due to its mediation of the dynamics, as in (3), between vertices. Experimental, and histopathological, propagation of $A\beta$ and $\tau P$ pathology is biased (Section 2.3) by the axonal connectivity [24,26,29–31] between gray matter regions of the brain; even extracellular molecules are subject to the anisotropic diffusion of water along axonal fiber bundles. For this reason, a *structural connectome graph* is a good candidate for NDS models of protein pathology in AD.

Structural connectome graphs can be constructed from two ingredients: a patient's diffusion tensor image (DTI) scan, a type of MRI scan that measures the diffusion of water molecules in the brain, and a brain parcellation that labels different gray matter, and subcortical, brain regions. Many connectome graphs are already available [60–62] for download, based on data from the Human Connectome Project, for several different parcellations. Additional connectomes can be constructed using freely available software such as FSL [63,64] and Mrtrix3 [65,66].

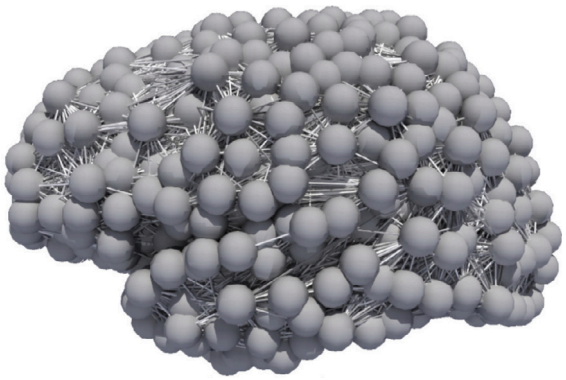

**Fig. 3.** A structural brain connectome composite graph created from 426 patient DTI scans [60–62].

An example of a structural connectome graph, with 1015 vertices and approximately 77,000 edges, appears in Fig. 3. The vertices of the graph correspond to anatomically labeled gray matter and subcortical regions while the edges express the (white matter) axonal fiber connectivity between those regions; edge weights are determined by the patient-averaged strength of the regional connectivity as determined by diffusion tensor analysis.

#### 3.2.2. AD proteopathy models based on NDS

Modeling the progression of AD to dementia is a complex task. A number of overlapping theories (Section 2.1) exist that attempt to define a set of AD-related pathologies that might be causative in producing the downstream attributes concomitant with a clinical diagnosis of dementia; there is not yet a clear consensus in this regard. Toward this end, there has been an ongoing, and international, effort to determine biomarkers [67,68] of AD and their relation to dementia progression.

The National Institute on Aging and Alzheimer's Association (NIA-AA) has released a framework [67] that classifies the AD spectrum in terms of measurable biomarkers; among these are $A\beta$ and $\tau P$ load as determined by positron emission tomography (PET) patient image scans. PET scans are coupled with MRI to provide regional information on $A\beta$ and $\tau P$ load in a patient's brain.

Modeling $A\beta$ and $\tau P$ progression can be done by coupling disease mechanisms, such as regional spreading (Section 2.3), clearance (Section 2.4) and the prion-like hypothesis (Section 2.2), together into an overall model that functions on time scales relevant to observable AD protein pathology dynamics, as detected by $A\beta$ and $\tau P$ PET scans. A reasonable starting point for a model [69], in this vein, is a *diffusion–reaction* system, for a single protein species of interest, that takes the form

$$\dot{p} = \nabla \cdot (\kappa \nabla p) + R(p), \tag{4}$$

where $\kappa = d_\perp \mathbf{I} + (d - d_\perp)\gamma \otimes \gamma$ is the anisotropic diffusion tensor along the brain's axonal (white matter) bundles. In (4), $p$ denotes the concentration of a (single) protein species, $\gamma = \gamma(\mathbf{x}, t)$ is a unit vector oriented along a fiber bundle, at position $\mathbf{x} \in \mathbb{R}^3$, $\mathbf{I}$ is the $3 \times 3$ identity matrix, $d_\perp$ is the radial tissue diffusion constant and $d \gg d_\perp$ is the diffusion constant along the fiber. The term $R(p)$ is the reaction term, which encapsulates the reproduction.

The system (4) can be approximated by a NDS, in the form of (3), by beginning with a structural connectome graph $G = (V, E)$ such as the one shown in Fig. 3. Letting $\mathbf{p}$ be a vector with $N = |V|$ components, we introduce the *graph Laplacian* matrix to approximate the continuous diffusion operator, along axonal fiber bundles, in (4) as $\mathbf{L} = \mathbf{D} - \mathbf{A}$ where $\mathbf{A}$ is an $N \times N$ weighted adjacency matrix, associated to the structural

connectome graph (Section 3.2.1), and $\mathbf{D}$ is the diagonal matrix $D_{ii} = \sum_{j=1}^{N} A_{ij}$. With this ansatz, (4) can be written in component form

$$\dot{\mathbf{p}}_i = -\kappa \sum_{j=1}^{N} \mathbf{L}_{ij}\mathbf{p}_j + R(\mathbf{p}_i), \tag{5}$$

where $\kappa$ is now a characteristic diffusion constant. The model (5) is a special case of (3) where $g_{ij}(\mathbf{p}_i, \mathbf{p}_j; \boldsymbol{\theta}_i, \boldsymbol{\theta}_j) = \kappa\mathbf{p}_j$, $f_i(\mathbf{p}_i; \theta_i) = R(\mathbf{p}_i; \theta_i) - \kappa D_{ii}\mathbf{p}_i$ and $\boldsymbol{\theta}_i$ are any coefficients that may appear in the local reaction term. For simplicity, we drop the explicit emphasis on the functions $f_i$ and $g_{ij}$ in the discussion that follows as the context is similar.

The earliest use of NDS in AD research are network diffusion models [70,71] wherein the reaction term vanishes, i.e. $R(\mathbf{p}_i) = 0$. These studies showed interesting correlations between the eigenmodes of the graph Laplacian, atrophy and hypometabolism in addition to short-time rate of change from a baseline measurement. However, lacking a reaction term, diffusion-only models cannot recapitulate the growth effect observed in longitudinal studies [57,72,73].

A simple model that incorporates both axonal spreading (Section 2.3) and prion-like autocatalytic growth (Section 2.2), which can saturate [57,72], uses a logistic reaction term of the form $R(\mathbf{p}_i) = \alpha\mathbf{p}_i\left(1 - \mathbf{p}_i\right)$ in (5), where $\alpha \in \mathbb{R}$ is a growth rate parameter, and is called the Fisher–Kolmogorov–Petrovsky–Piskunov (FKPP) NDS model for a single prion-like protein species. Despite the stark simplicity of the FKPP NDS model of proteopathy, the model can reproduce [74] observed staging [28,58] patterns of typical $\tau P$ pathology. Due to the model's small number of parameters, it can be used to predict when $A\beta$ or $\tau P$ will reach particular brain regions [75] and to infer patient-specific predictions of both $\tau P$ progression [76–78] and $\tau P$-associated atrophy [73] from patient PET and MRI scans.

The single species (5) NDS model, for either misfolded $A\beta$ or $\tau P$, can be extended in several ways to study other aspects of AD that can be found in the literature. For instance, the model (5) can be extended [79, Eqn. 2.4] to a two-species model to study soluble $A\beta_{42}$, or $A\beta_{40}$, monomers and its aggregated (dimers, trimers, fibrils, etc.) forms or soluble misfolded $\tau P$ monomers and its downstream aggregates.

Extensions of (5) have also been used to study important AD hypotheses noted in animal models, particularly around the primacy of clearance (Section 2.4) mechanisms [11,32,33] and $A\beta$-$\tau P$ interactions [55,80,81] in the etiology and progression of AD. For instance, an NDS $A\beta$-$\tau P$ interaction model [82, Eqn. 3] suggests that regional brain clearance may determine whether the presence of sufficient $A\beta$ is necessary for $\tau P$ pathology to develop. Moreover, $A\beta$ pathology may be rebuffed until brain clearance reaches a critically low, isoform-dependent, level [16] and overall brain clearance can significantly slow [83, Sec. 5.1] the progression of AD while regional brain clearance differences may influence [83, Sec. 5.3] a patient's specific AD subtype, as determined by postmortem histopathology.

## 4. Concluding remarks

The puzzle of AD is a first step on the longer path of understanding the vast breadth of the function of our own minds. There are many, seemingly rudimentary, questions that we still cannot answer. Why is it that the misfolding and aggregation of particular proteins are so associated with cognitive decline? Why do life choices, like exercise, sleep, diet and education play a role in whether or not we develop AD later in life? Why is it that some proteins may go awry in one brain but not another? Why do particular proteins seem to spread preferentially to certain areas of the brain and have different affects? Is protein aggregation the cause or consequence of the path to AD dementia? Can we do anything to detect, stifle, or to halt AD and other terrible neurodegenerative diseases?

Mathematics addresses a critical gap in AD research. Many contemporary discoveries are being made that pertain to AD and most of these discoveries arise from experiments conducted in vitro or using animal models. Mathematics and scientific computing provide a means to test the implications of experiments in a virtual human environment. This manuscript has shown that both PDE and NDS-based ODE models, along with the computational resources supporting their solution, can make predictions and test hypotheses, based on experimental findings and imaging data, that are relevant to human AD pathogenesis and progression.

Today, we have more questions than we have answers about the brain, human cognition, aging and AD. In the future, with a cure in hand, we will look back our on research progress. Quite possibly, we will point to *mathematical models of the mind* as a pivotal step forward in AD research.

## CRediT authorship contribution statement

**Travis B. Thompson:** Conceptualization, Funding acquisition, Project administration, Writing – original draft. **Bradley Z. Vigil:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **Robert S. Young:** Writing – original draft, Writing – review & editing.

## Declaration of competing interest

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

## Data availability

No data was used for the research described in the article.

## Declaration of Generative AI and AI-assisted technologies in the writing process

No form of generative A.I. was used in the writing on this manuscript.

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### *Ethical statement*

No animal or human subjects were used in any of the work performed by authors for the preparation of this manuscript.

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