A Dynamical Systems Approach for Multiscale Synthesis of Alzheimer's Pathogenesis

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Summary

Alzheimer's disease (AD) is a spatially dynamic pathology that implicates a growing volume of multiscale data spanning genetic, cellular, tissue, and organ levels of organisation. This data and bioinformatics analyses provides clear evidence for the interactions within and between these levels. The resulting heterarchy precludes a linear, neuron-centric, approach and necessitates that the numerous interactions are measured in a way that predicts their impact on the emergent dynamics of the disease. This level of complexity confounds intuition, and we propose a new methodology that uses non-linear dynamical systems modelling to augment intuition and that links with a community-wide participatory platform to co-create and test system-level hypotheses and interventions. In addition to enabling integration of multiscale knowledge, key benefits include a more rapid innovation cycle and a rational process for prioritisation of data campaigns. We argue that such an approach is essential to support the discovery of multilevel coordinated polypharmaceutical interventions.

Keywords: Alzheimer's disease, Dementia, Dynamical systems modelling, Systems pathology, Systems biology, Multi-scale data, Data prioritisation, Participatory methodology, Open Innovation Ecosystem, Mathematical modelling

1 Introduction

Alzheimer's disease (AD) is the major cause of dementia and afflicts approximately one per cent of the total population, and five per cent of the population over 60 years [1]. Globally, an estimated 46 million people are living with AD, with numbers expected to more than triple by 2050 [2]. The dominant theory of AD for the last 30 years has been the amyloid hypothesis [3]. When it was first conceptualised, there was perhaps the view that anti-amyloid therapies, if they hit their molecular target, could be a magic bullet for the disease. On June 7, 2021, the US Food and Drug Administration (FDA) approved Aducanumab (Aduhelm) – the first drug therapy for AD, indicating the potential first step along the road to treatment for the disease. However, while Aducanumab certainly hits its molecular target (reducing brain amyloid), many researchers, including some of the FDA assessors themselves, were not convinced of its clinical efficacy [4-6]. More than a year later, results from clinical trials of another anti-amyloid monoclonal antibody, Lecanemab, have demonstrated less cognitive decline when compared to placebo [7] leading to its approval by the FDA as the second drug treatment for AD. However, all can agree that neither drug is close to being a magic bullet for the disease, and that other approaches are also needed. These include perhaps those that simultaneously or sequentially target both amyloid-beta (Aß) and tau proteins [8], because while Lecanemab trials have shown removal of amyloid may slow the rate of progression, it doesn't stop the neurodegenerative process of AD.

So, despite more than 30 years of intensive research, there have been minimal therapeutic advances made beyond symptomatic therapies. With the current lack of therapeutics in the drug pipeline,

finding interventions to treat, and ideally cure AD, has become one of the over-riding health priorities of the 21st century as the disease reaches epidemic proportions in terms of global prevalence and economic cost. There has never been greater urgency to recognise the wider complexity of dynamical systems and processes at play within a healthy brain to understand what sets it along the path of neurodegeneration. This includes the need to understand the connection between individual and collective components and mechanisms that operate across, and feedback positively and negatively between, a wide range of scales of systems. Only with this understanding, can therapeutics be found that will prevent, or at the very least, arrest or slow, the disease's progression.

Although AD has essentially been defined in terms of a tissue-level pathology since it was first described in 1906 [9], both causes and treatments have, to date, been focused on molecular-level phenomena with no single link between these two scales yet established. More recently, technological advancement in the life sciences has enabled measurement across the systems levels from the genetic through to the whole organism, implicating, many would say, an overwhelming level of multi-scale complexity in AD, and ever-increasing numbers of inter-related components.

Mathematical methods have been successfully used in different areas of biomedical research to deal with complexity and support the interpretation of data and the discovery of therapeutic interventions [10-14]. Neuroscience provided one of the earliest exemplars of the successful application of mathematical biology to develop the Hodgkin-Huxley theory of the action potential in neurons [15]. And yet, the AD research community has yet to adopt methods from computational and theoretical physics to extend intuition and yield new insight through using the dynamical systems approach we are introducing in this paper [16]. In fact, we know of no methodology in any scientific field that describes the molecular and community-level dynamics of cells and their interaction with diffusive and convective processes in a dynamic and geometrically complex physical space, that we are now proposing. Certainly, no methodology is currently available to the AD research community that allows for the integration of both the physical and biological processes that are critical to the disease. Perhaps the multi-scale nature of the processes that are implicated in AD, along with the complexity of the brain, even in its healthy state, has up to this point presented a challenge that cannot be fully addressed with the current toolkit available to AD researchers. We propose meeting this challenge head-on by moving towards embracing this complexity and away from the more conventional mindset, where we have expected to understand the tissue-level pathology of AD by looking at each level of the system in isolation. The fact that the field has gone from searching for the elusive magic bullet for AD, to expecting polypharmacy is the most likely way we will develop treatment strategies for the disease, is a tacit acceptance of the need to embrace complexity, in our view of its pathogenesis.

However, we note this current view of polypharmacy in treating AD envisages a linear sequence of events for therapeutic intervention. For example, an amyloid drug would be prescribed 20 years before the onset of any clinical manifestation for individuals at higher risk of developing AD, followed by a microglial drug two to three years later to dampen down chronic neuroinflammation and impair microglial-associated mitophagy. Finally, a drug targeting the spread of tau into the neo-cortex would be prescribed five years later to complete the regime. We believe, just as a neuron-centric linear model of AD is too simplistic, so is this linear approach to drug targets. Instead, we would propose a treatment plan comprised of the minimum optimal number of multi-interventions that simultaneously target specific parts of the AD processes across different system levels, which we consider has a greater chance of success.

We want to highlight the current lack of any rational approach that will aid the discovery and use of such multi-targeted interventions, which can be used to design efficient data campaigns to reach that outcome. Indeed, this is one of the outstanding challenges in the biomedical sciences in general. In this paper we present a methodology that will provide such a rational approach, and which democratises data-enabled innovation by design, to accelerate progress in the AD field. At its core,

the methodology encapsulates, in the form of a set of non-linear dynamical system models, the current consensus on how the components implicated in AD interact. The overall model is not intended to be seen as a complete representation of the pathogenesis of the disease, and its components are by no means exhaustive. Instead, it provides a starting point for expanding the current linear model of AD, by incorporating a system of interacting cell types that together with the temporal, spatial and cellular processes are thought to be critical to the pathogenesis of AD.

We assert that the current state of the field also requires the empowerment provided by an open innovation ecosystem – a global community of researchers bringing together a wide range of specialisms – for example, from the seemingly diverse fields of engineering, physics, neuroscience, cell biology and biotechnology - to collaborate and synthesise their knowledge to build a more complete conceptual model of AD. And through model predictions, identify knowledge gaps and data needs, that can be exploited not only in the field of AD, but in neurodegenerative disease in general.

Our overall objective has been to provide the AD research community with a platform that is not tied to any single hypothesis, but which gives researchers a tool that enables them to test the effects of diverse hypotheses at the molecular, pathway, organelle and organ levels.

2 Our Current Understanding of the Multiscales of Complexity of AD Pathology

AD pathology (**Figure 1**) consists of several tissue-level elements: neural tissue loss, exemplified by increased ventricle size (**Figure 1a**) and deepened and widened sulci, neuritic plaques consisting largely of Aß40+ peptides derived from the cleavage of the APP (amyloid precursor protein) transmembrane protein interleaved with neuronal processes, neurites (**Figure 1b**), intracellular tangles made up of the tau protein found particularly in cortical pyramidal neurons (**Figure 1c**) as well as Aß congophilic angiopathy lining vessel walls (**Figure 1d**).

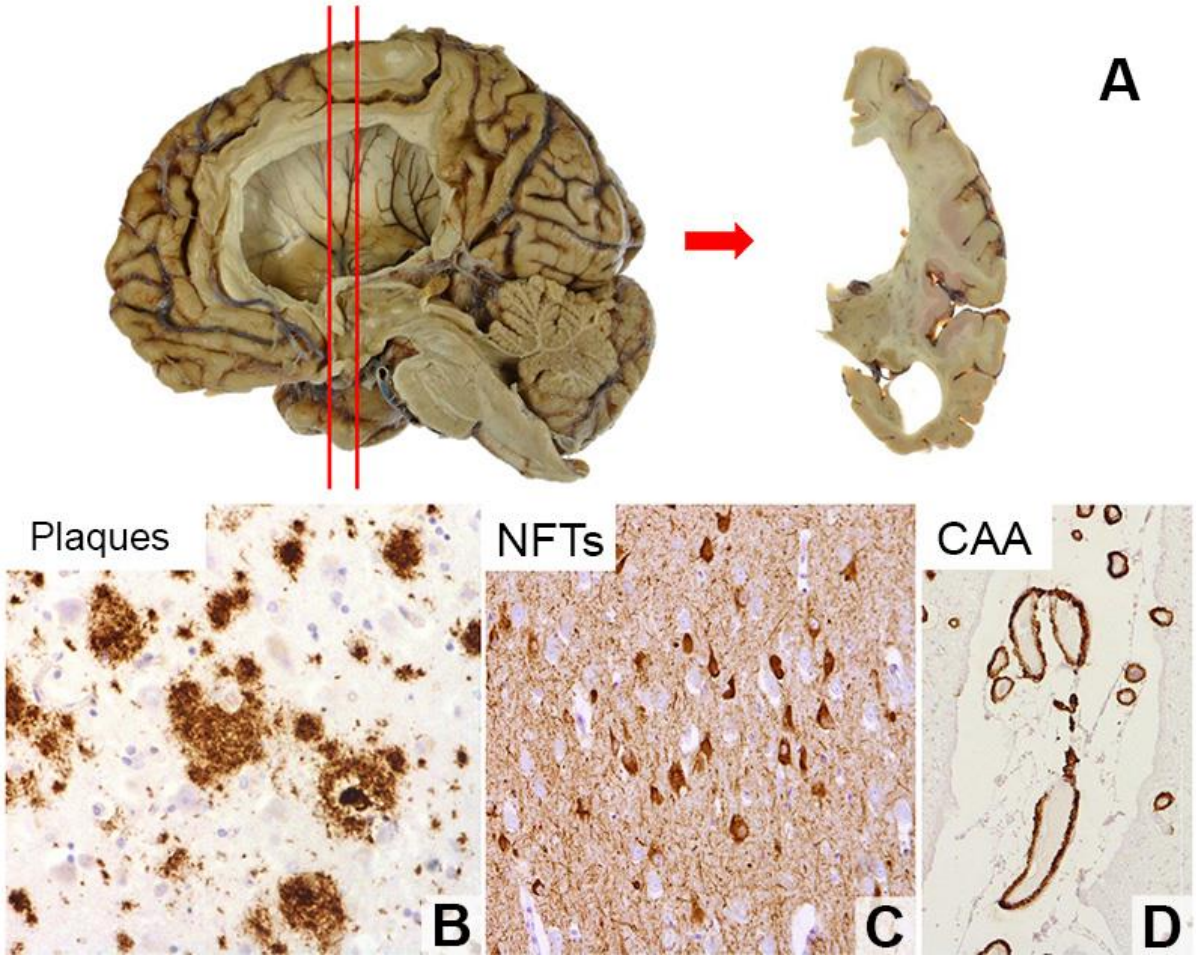

Figure 1: AD pathology showing (a) deepened and widened sulci, (b) neurites and neuritic amyloid plaques, (c) neurofibrillary tangles, and (d) cerebral amyloid angiopathy. (Images courtesy of the Queen Square Brain Bank for Neurological Disorders (QSBB), UCL)

2.1 The Oversimplicity of the Linear Two-dimensional Model of AD

The amyloid hypothesis was largely based on genetic data from rare families with APP and presenilin mutations, which all increase the production, or decrease the solubility of, Aß (amyloid-beta), and from the experimental data using APP and MAPT (microtubule associated protein tau) crossed transgenic mice showing that Aß deposition increased tangle formation. While this linear model almost certainly has some elements of truth to it (refer **Figure 2**) [17], it clearly does not capture the complexity of the disease process in several ways:

- The time frame of the disease is far greater than the model would lead one to expect, with amyloid deposition beginning some 20 years before clinical dementia becomes evident [18]
- The model has no neuroanatomy but AD pathology has a discrete and complicated neuroanatomy with both plaques and tangles having different, but rather predictable, distributions [19]
- The model was built on the genetic findings from Down syndrome and from families with APP and presenilin mutations and from finding MAPT mutations in tangle dementias. These mutations are all rare, and while we had expected genetic risk loci to be directly involved in the same pathways, most of them have been in microglia and involved in lipid metabolism and thus 'outside' of the current model [20].

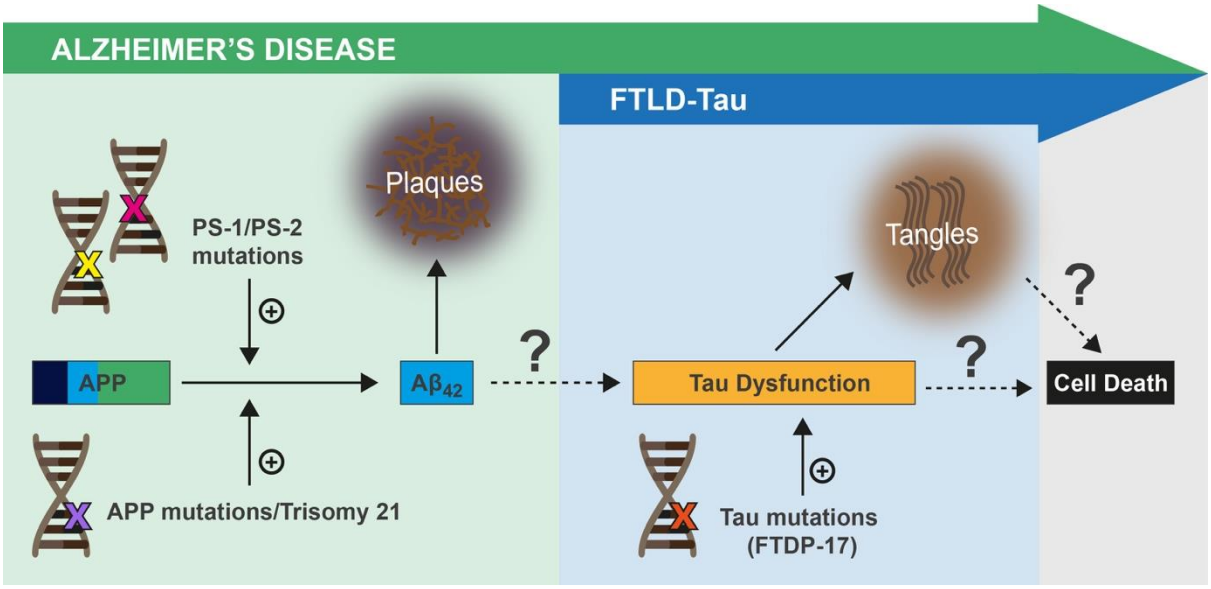

Figure 2: AD/FTLD-Tau pathways to neurodegeneration

This diagram drawn in 1998, postulates the amyloid hypothesis based on the occurrence of AD in Down syndrome, the discovery of APP and presenilin mutations in AD and their effect on APP metabolism, the discovery of MAPT mutations in tangle dementias and the crossing of APP/PSEN1 mice with MAPT mice potentiating tangle pathology. Despite the strength of the genetic data it is worth noting the deficiencies of this linear model: (a) the question marks are still unresolved (b) a biochemical pathway like this might be expected to operate in a rapid time frame (c) only neurons are diagrammed with Aβ being suggested to act on the surface of the neuron causing tau dysfunction within that neuron.

2.2 Expanding the Linear Model into a Non-linear Dynamical Model of AD

The fact that anti-amyloid therapies have either failed to work or, if they have worked, have had only marginal benefit, has also fuelled the realisation that a more complete and inclusive model is needed [21,22], which has the potential to include the spread of pathology, the role of non-neuronal cells, and the time-frame of the various elements of the pathology (see [23]). These complex systems cannot be encapsulated by simple cause and effect arrows. Rather, they require the development of a dynamical model that incorporates non-linear interactions in a complex anatomical environment over time. Such models are clearly beyond pen and paper sketches such as **Figure 2**, but rather require computer simulations which are amenable to hypothesis testing.

The factors which such a model might need to accommodate include, but are not limited to, the following:

1. The original data showing early onset disease is linked to the production of barely soluble Aβ [3]
2. The role of APOE, by far the most important risk factor for disease, in AD pathogenesis [24]
3. The genetic data implicating microglial response to this deposition is important in determining the risk of disease [25]
4. The mechanism by which Aβ accentuates tangle pathology [26]
5. The spread of amyloid pathology, probably by templating [27]
6. The clearance and spread of Aβ along vascular pathways [28]
7. The spread of tau pathology along axons and along neuronal pathways [29]

Going through these points one by one:

1. **The original data showing early onset disease is linked to the production of barely soluble Aβ –** The data showing that the Mendelian genes underlying AD are all likely to do so by making Aβ deposition more inevitable, has been extensively reviewed [3]. Genetic data has strengthened these findings through the identification of variants and mutations in two of the α-secretases, ADAM10 and ADAM17 as risk factors for disease implying that reducing flux through the α-secretase pathway [30-32] increases the likelihood of disease presumably by increasing flux through the β-secretase pathway. From a mechanistic perspective, work on the mechanisms of γ-secretase cleavage and the effects of pathogenic mutations on APP processing have shown that the effects of many of the mutations are to disturb processing leading to the release of longer fragments of the Aβ stub [18].
2. **The role of APOE, by far the most important risk factor for disease, in AD pathogenesis –** APOE4 is easily the most important genetic risk factor for disease with a frequency of 15% in the general population and an associated allelic risk of disease of >3. Despite its clear importance, little has been done to understand its precise mechanism of pathogenesis. APOE4 is associated with more fulminant amyloid pathology and genetic data has indicated that modulating amyloid deposition is its most important contribution to AD pathogenesis [33,34], though the mechanism of this is unclear. APOE expression is largely astrocytic but in the context of amyloid pathology, expression is greatly increased in microglia [35]. The relationship between the cellular expression and the development of pathology remains unclear.
3. **The genetic data implicating microglial response to this is important in determining the risk of disease –** When the data from the first genome wide association studies (GWAS) were analysed it was a surprise to see that the majority of loci were not directly involved in APP processing, but rather in microglial and lipid metabolism [20]. As sample numbers in the GWAS have increased, the number of identified loci also increased, which has remained the case. With exome sequencing came the identification of other genes in these same areas of biology such as TREM2 and ABCA7 [20]. As the number of identified loci increased, our goal was to understand these genes in terms of pathways and processes and in this, there have been three further insights. The first is that many of the microglial risk genes share a myeloid specific promoter element (SPI1 binding sites). The SPI1 gene, PU.1, is itself one of the GWAS hits [36]. Furthermore, much of the variability in AD risk is mapped to microglial enhancer sequences [37]. Thus, a significant proportion of AD risk is driven by a network of co-regulated microglial genes, many of which are directly related to lipid metabolism. The second insight was that many of the AD risk genes appear to be co-ordinately increased in expression in response to amyloid deposition [23] and these responsive microglia largely correspond to the so-called 'Disease Associated Microglia (DAM)' [38]. Overall, these data are consistent with the view that how well you respond to amyloid deposition is important in determining one's risk of dementia. The third relevant piece of data came through the comparison of the genetic analysis of pathologically confirmed AD, with that genetic analysis of amyloid positivity obtained through PET analysis. This showed that amyloid deposition was almost wholly dependent on APOE genotype; dementia, in the context of amyloid deposition, was dependent on the polygenic risk score, which is largely dependent on the microglial loci [39].
4. **The mechanism by which Aβ accentuates tangle pathology –** The original versions of the amyloid hypothesis envisaged a rather direct connection between amyloid and tau, with amyloid outside a neuron and tangles forming inside that neuron possibly instigated by a receptor mediated event, for example [3,17]. However, while several Aβ binding proteins have been identified, none have been implicated convincingly in a pathway between Aβ and tau. Several groups have shown that Aβ deposition drives tangle formation in doubly transgenic mice [40,41]. Most recently, Lee and colleagues [42] showed that an adequate, TREM2 driven, microglial response restrains this potentiation indicating that TREM2 activation of microglia inhibits tangle formation. This places the microglial response between amyloid deposition and tangle formation

and strongly suggests that the microglial response, at least initially, is protective against tangle formation [43].

5. **The spread of amyloid pathology, probably by templating –** The ability of Aβ pathology to spread by templating was first demonstrated in a series of mouse experiments by Jucker and Walker and colleagues [44]. The mice experiments demonstrating spread were carried out in mice overexpressing APP. In these mice, spread was demonstrated both from the periphery to the CNS and also within the CNS reviewed in [44]. In humans, the plausibility of spread in humans has been demonstrated by the observation of amyloid angiopathy in persons after meningeal grafts and, less certainly, by the demonstration of amyloid plaque pathology in individuals dying of iatrogenic CJD [45,46]. These data show that amyloid pathology can spread even from the periphery to the CNS. However, neither the mechanism of spread nor the precise Aβ species that spreads, is clear. Unlike either tau or synuclein spread, which both seem to be largely point-to-point along neuronal pathways [47,48], Aβ spread within the CNS may be largely diffusional in the interstitial fluid or along membranes.
6. **The clearance and spread of Aβ along vascular pathways –** While genetic data has pointed clearly at the potential role of microglial in Aβ metabolism, it is clear too that Aβ can get into the blood stream from the brain and that blood levels reflect (perhaps imperfectly) brain APP metabolism. This, and the occurrence of amyloid along blood vessels in AD as amyloid angiopathy, indicates that there is a relationship between blood vessels and amyloid, but the relationship between perivascular flow and amyloid deposition is disputed [49,50].
7. **The spread of tau pathology along axons and along neuronal pathways –** Braak staging of AD tau pathology [19] suggested there is a stereotypical pattern of the spread of tau pathology, largely along neuronal pathways. This has been elegantly demonstrated in mouse models and reviewed in [51] and some of the underlying mechanisms of this spread have started to be elucidated [52]. The demonstration of the several tangle structures at the molecular level is consistent with the notion that this spread involves templating of structures in tau-expressing neurons [53].

These seven broad features of the disease illustrate the complexity of AD pathogenesis, which occurs in a complex biophysical structure over decades. A simple, linear two-dimensional model cannot capture this adequately. A dynamical model is required that encompasses these disease features and which can incorporate new information in an iterative manner, as well as enabling the generation and testing of different hypotheses.

3 Non-linear Dynamical systems modelling is critical to understanding AD pathogenesis and developing intervention strategies

Our ability to probe processes at a molecular level has created the potential to describe nature at an almost infinite level of detail. The process often followed is to design experiments that identify putative causal interactions with the aim of understanding and then controlling outcomes by designing drug interventions to modify the identified cause-effect relations. In modern biosciences, there is a particular emphasis on building these 'causal maps' using molecular data from cells, although in AD research there is a growing body of information at higher levels of organisation described above. This approach assumes correlation implies causation and that causation implies detection of a correlation. It is the basis of most bioinformatics approaches where the output is some kind of interaction network where nodes are often genes or proteins, and the network links are identified from correlated behaviour between the connected nodes.

3.1 Why dynamical systems modelling is different

For nonlinear systems, correlation does not imply causation, causation does not imply correlation, and even the concept of cause-effect can be difficult to define when multiple interactions, feedbacks and time-delays are involved [54] . The link between a proposed network of non-linear interactions and the dynamics of the system requires not only that the interactions are identified, but that that they are described in terms of quantitative relations between inputs and outputs of each node. Pioneering work on the dynamics of gene networks by Kauffman demonstrates clearly how the behaviour of networks described in these terms defies intuition [55,56]. Significantly, this work also clearly shows that the behaviour of the network as a whole cannot be inferred from the behaviour of the individual nodes or even of sub-networks of nodes [57].

Non-linear dynamical systems approaches are widely applied in the life sciences in general and in health-related research in epidemiology [58]. In relation to specific pathologies, they are perhaps most advanced in the study of cancer. In previous work by us and others, we have outlined how dynamical systems modelling approaches can be used to predict multiple drug interventions in cancer treatments [13,59,60] By comparison, non-linear dynamical systems modelling is far less well developed in the field of AD research [16], although there have been important recent advances.

Progress in developing dynamical systems approaches to AD relate predominantly to predicting the behaviour of the interactions and spread of tau and Aβ pathologies, characterising the network of interactions between different functional regions of the brain, and using the predicted functional connectome together with tau-Aβ interaction models to predict the spatial spread of amyloid and tau pathologies [61]. As can be anticipated, the behaviour at the organ level cannot be predicted solely based on molecular-scale description of tau and Aβ pathologies separately but emerges from the interaction between these pathologies and the factors that control the rate of movement across the brain. This results in counterintuitive relationships between molecular-scale parameters and the rate and patterns of spread across the brain.

These studies demonstrate the potential to link molecular and brain-level processes, although they are still neuro-centric. Based on the discussion in the sections above, there remain important gaps including the incorporation of more cell types and especially microglia, a more complete set of cellular pathways that are known to be implicated in the disease, and brain clearing. These additions will, of course, add additional complexity.

This brings us to one of the outstanding challenges of AD: amongst the almost infinite level of detail that is possible to measure, is it possible to identify the essential detail that is needed to design interventions that control the system-level behaviour? There are some clues to the answer from dynamical systems theory that give us some hope that this question can be answered. For example, widely different systems from earthquakes and economic to ecosystems and cell networks display the same kind of 'critical behaviour' where abrupt changes in the state of the systems can be brought about by small changes in a few or a single control variable [62]. There is some recent evidence that this kind of behaviour also occurs in the brain [63]. Because these behaviours are observed in widely different systems, they are only weakly dependent on the details of the systems, suggesting a path to parsimony. This is an attractive insight and the approach we advocate for in this paper is focussed precisely on determining this pathway to parsimony in AD.

3.2 Principles of a Dynamical Systems Approach

Arising from the previous discussion,, there are four fundamental principles of non-linear systems that cannot be ignored, even though they often are. In the context of AD research these are:

A. **We must embrace ignorance and uncertainty –** A complex non-linear system can, and usually does, behave in a way that cannot be predicted from the behaviour of its parts. Given that we cannot be sure that we have described the system in enough detail to identify treatments and

other intervention strategies, and that the details of the interactions will be highly uncertain, we must account for this in our predictions. Proposed treatments that are robust to this uncertainty are more likely to be successful.

B. **We will never know that our description of the system is complete and must continue to challenge consensus –** We cannot, in principle as well as in practice, know if we have included all the components and interconnections that are needed to identify the interventions that treat the disease. The definition of 'the system' is an ongoing co-creation process carried out by the community of scientists working on different parts of the system. At any one time there will be parallel representations corresponding to the different sets of hypotheses relating to the disease. A continuous refinement of the hypotheses by parallel iterative testing with data and updating is essential.

C. **We cannot design interventions by focusing on part of the network –** When confronted by complexity it is tempting to identify a simpler subsystem and focus on that, usually imagining a unidirectional causal hierarchy from molecule to tissue. Comparing the healthy and diseased (AD) states of the brain in processing a high amyloid load, in **Figure 3** we can see that our current best guess implicates a very complex interplay between different subsystems in the diseased state. The system is best described as a heterarchy because feedbacks jump several levels of organisation. For example, we cannot explain behaviour at the molecular level without accounting for the inflammatory response at the tissue level.

D. **An ecosystem approach that maintains diversity of hypotheses, builds trust and shares results is essential for progress –** Because of the large number of variables in the system, it is prohibitively expensive in time and cost to use controlled random design trials to deliver a systems approach. We now know that in such situations, combinatorial optimisation is a better approach, where different labs or teams undertake their own iterative refinement focusing on a part of the network [64]. Coming together to share these results can help prioritise the data campaign and more quickly identify the best hypotheses.

3.3 Five Steps that Enable a Dynamical Systems Approach to AD

The following offers a set of five steps that are necessary to enable a more efficient and accelerated process towards the identification of treatments for AD and to minimise the numbers of these interventions.

1	**Fully Describe Underlying Assumptions and Clearly Articulate Desired Outcomes**

Everything follows from a list of assumptions (hypotheses) and target outcomes and a library of these is a critical part of the concept of a systems approach. This is critical to removing any bias towards any one single hypothesis and instead providing the ability to generate multiple hypotheses, and through a process of model validation, include or exclude them from the model build.

2	**Identify the System**

This must be an ongoing process because of the above four fundamental principles of the systems approach. Whilst it is tempting to adopt a consensus approach, the combinatorial approach outlined in Principle 3 works best when there is a diversity of hypotheses. Intrinsic uncertainties and ignorance mean we need to simultaneously embrace a range of different hypotheses about the links between cause and effect that constitute the systems map of AD. Each set of hypotheses will have a related level of confidence based on its consistency with available data, and these should be considered when designing interventions based on the full range of hypotheses.

3 Adopt a Multiscale Approach

As is explicitly clear in **Figure 3**, AD is controlled by top-down and bottom-up processes – it is highly non-linear. Therefore, it is incorrect to think of AD as being 'caused' by genetic factors, or by cellular, tissue or environmental factors, but instead by an interplay between all of them. This also has implications for how we treat the disease, since any intervention will have to consider processes across these levels.

4 Adopt a Common Data Infrastructure

A systems approach is contingent on a platform that enables data flow from across the international AD community, irrespective of the level of organisation they are operating at. As part of the top-down and bottom-up approach, any local data infrastructure used must be compatible with a global infrastructure. This infrastructure must adopt FAIR (Findable, Accessible, Interoperable, Reusable) principles [65] to enable access and sharing.

5 Establish an Open Innovation Ecosystem

Treatment of AD is a high-dimensional problem: pathways, genes, cell phenotype, and environmental factors can each vary almost continuously and independently. Controlled random design experiments are a very blunt tool for searching this high dimensional space, where different points represent different outcomes and clues to the treatment of the disease. Synthesising these results using dynamical systems models based on the systems maps in Step 2, provides a rational means to identify the critical pathways involved in the disease and to design the next set of experiments. These non-linear models offer an extension to intuition, which is usually linear and limited to significantly less than 10 interacting parts [66].

The methodology for these steps will be discussed in more detail in Section 4.

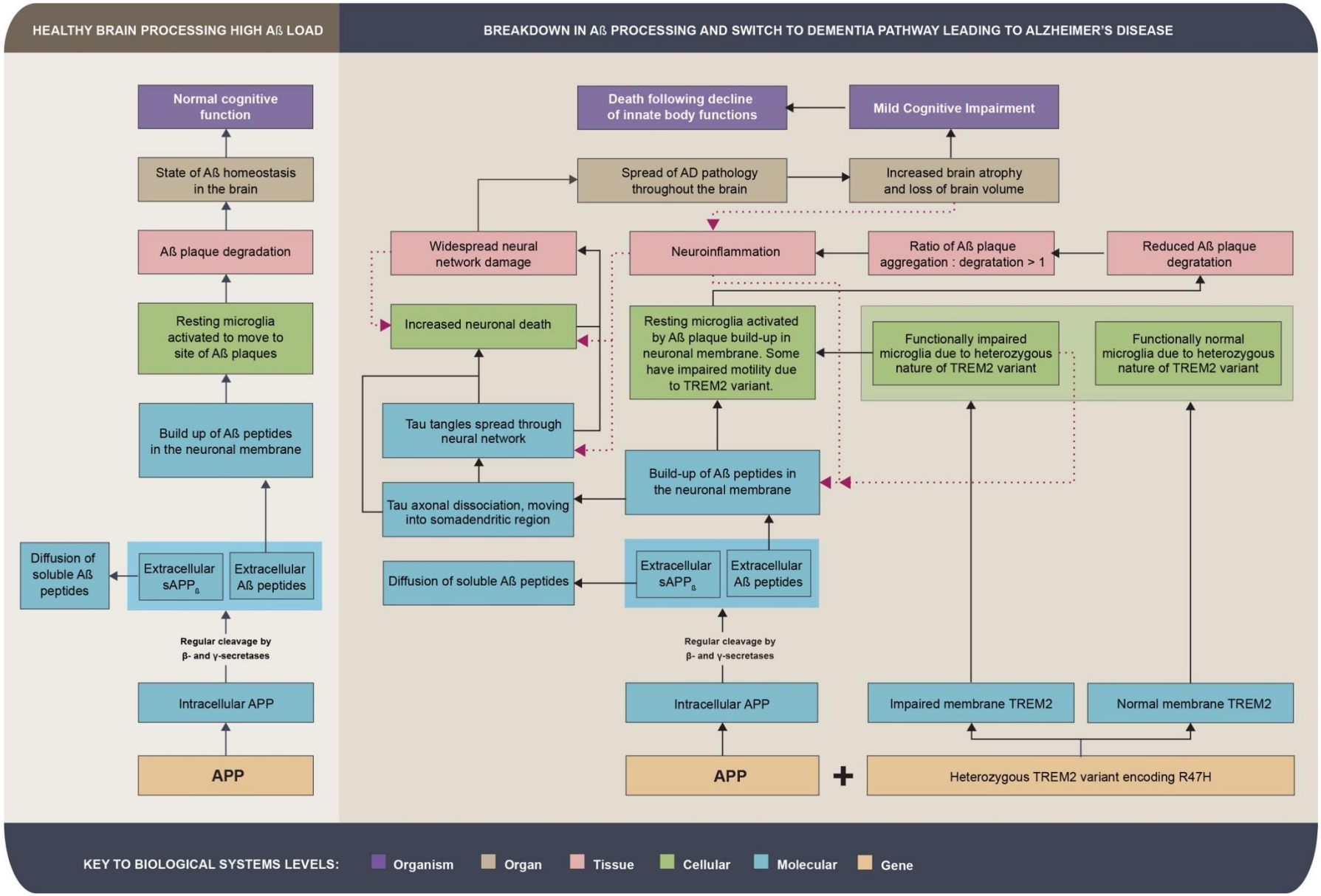

Figure 3: Illustrating the heterarchical nature of AD through a mechanistic example of some of the key stages of the processing of high amyloid build-up by (a) healthy brain (hierarchical), and (b) brain with a TREM2 variant encoding T47H, leading to AD (heterarchical)

4 Introducing a novel AD co-creation platform and open-innovation ecosystem to help integrate multiscale knowledge and data

In accepting the polypharmaceutical approach will be the most likely way forward in treating AD, the central challenge in the field will be to understand the combination, and sequence or simultaneous prescription of interventions that will be required to arrest, slow down, or prevent the disease. While polypharmacy potentially increases the risk of detrimental outcomes for patients, particularly in the more elderly [67,68], our dynamical systems approach opens the door to not only understanding what this requisite combination and sequence of interventions will be, but most importantly, the minimum effective number needed. A systems approach will therefore lead to more effective personalised plans in the treatment of the neuroinflammatory mechanisms in AD [69] studying the disease's progression over time with a dynamical systems approach, will better inform these therapeutic strategies.

In this final section, we present a high-level summary of the methodology we are using, to address this central challenge, starting with the generation of our unique AD co-creation platform. The platform is comprised of a core set of dynamical systems models that are a multi-scale integration of our current understanding of some, but by no means all, of the key physical and biological processes implicated in AD. Through our methodology, we introduce the systems biology concept of 'systems pathology' to the AD research community, which is defined as "the study of disease through the integration of clinical, morphological, quantitative, and molecular parameters using mathematical analytical frameworks" [70]. While we've previously discussed this approach has not been exploited by AD researchers, similar systems approaches have been used effectively to describe mechanisms in other disease modalities including cardiology [71] and cancer [72,73].

With the platform, we provide a tool that we hope will help enable researchers to exploit, rather than be confronted by the challenge of the disease's complexity. We propose these core models will be subjected to both a cumulative and iterative process of development, testing, validation, and refinement by the global research community, working within the context of an OIE (Open Innovation Ecosystem) framework. This critical path of co-creation will continue the progression towards building a more complete model of AD to gain new insights into the mechanisms of the pathogenesis of the disease.

4.1 Addressing the Central Challenge in the AD Field

In the collaborative process of developing a more complete mathematical model of AD, we want to reiterate the importance that needs to be placed on embracing a diversity of assumptions and hypotheses of the mechanisms that could lead to, or contribute to, the pathogenesis of AD. However, to develop a platform that will enable members of the AD OIE to tease out the components that are found to be most critical for inclusion in their co-creation models, we need a starting point.

While there is general consensus around the over-simplicity of the amyloid hypothesis, and indeed some debate as to whether its deterministic chain of events should be used to inform future drug trials of amyloid lowering drugs [74,75], what is clear is that Aβ is only one part of the complex heterarchical cascade of events that mediates the neurodegenerative process of AD [76,77]. Therefore, in an attempt to understand what the potential synergy is between Aβ and tau within human brain tissue, the starting point for our mathematical model of AD extends the amyloid hypothesis – from a neuron-centric linear model into a spatio-temporal model through the inclusion of different cells types and biophysical processes occurring at the brain tissue level. Utilising this systems pathology

approach, we incorporate the non-linear biophysical interactions that we know, or suspect, play out in the complex anatomical environment of both healthy brain tissue and brain tissue affected by AD pathology. We have previously suggested a number of factors that could be included in the model, such as the mechanism by which Aβ accentuates tau pathology and its suspected templated patterning of spread through the neuronal network.

Our core model is based on these factors that come from a diversity of hypotheses, integrating the best available current knowledge about tau, Aβ, and microglia, and the interaction between the three. In fact, we have already demonstrated through a pilot model presented at the Alzheimer's Association International Conference in London, 2017 [78], the feasibility of tissue-level modelling of AD and how systems-level thinking can provide new insights into the processes that regulate the dynamics of the disease. We included several key simulations in the pilot study such as the response of microglial cells to chemotactic signalling from Aβ plaques, and the distribution of tau within a neuron in response to varying strengths in the chemotactic signalling from the plaques. It should again be emphasised that we have focused on a few of the core components of a potential model of AD. This has been done purely to illustrate the potential of our approach, and to provide a starting point for researchers to incorporate, test, include or exclude their own hypotheses moving forward.

4.2 Developing the Integrative Dynamical Model System and Platform

There are two distinct stages to the model and platform development, with the first being made up of the following five steps:

1. Building a model for the three-dimensional biophysical architecture of tissue from regions of the brain that are critical to the different pathological Braak stages [79]
2. Constructing a spatio-temporal model of the key processes of the healthy brain including microglial motility (accounting for example for the TREM2 variant), the role of astroglia in neuronal synaptic health, the brain clearance system, and the tau-Aβ complex
3. Conducting a sensitivity analysis to determine the critical interactions in the system and to establish the role of the physical architecture in the dynamics of the disease
4. Demonstrating the potential of the model to identify novel system-led interventions and to generate testable hypotheses
5. Building a flexible, intuitive graphical user interface (GUI) and interactive output visualisations to enable *in silico* experimentation by non-expert users.

The platform is developed to allow AD researchers the ability to suggest new functionality – additions, modifications, and refinements to the following initial list of key components to the model:

- **Tissue-level architecture** – extra-cellular space, vascular and perivascular structures
- **Cell types** – astrocytes, neurons (different functional types in different brain regions are considered), and microglia ('resting' and 'activated')
- **Cellular and extracellular processes** – tau movement, Aβ aggregation and impact on tau, microglial motility, and chemotaxis
- **Flow dynamics/fluid flow** – associated fluid dynamics and fluid properties including diffusion, convection, viscosity and turbulent/laminar flow

- **Parameterisation** – including density of different cells, rate of astroglial proliferation, initial location of Aβ seeding, strength of chemotactic signals between Aβ plaques, tau and microglia, diffusion and convection coefficients – all parameters are fully controlled by the end-user of the platform through the GUI.

This first stage of the model development provides the basic foundations of a biophysical model simulating brain tissue and enabling the platform user to generate new and testable hypotheses, all controlled through an intuitive GUI. However, it is through the second stage of the modelling approach where the platform user is truly able to start understanding what components of the newly developed three-dimensional model are critical not only to the model itself, but also to help understand what perturbations of the system tip it from a healthy into a pathological state. This will help address the over-riding challenge of the combination of the **where**, **when** and **which**, intervention strategies are most effective in stopping or reversing this tipping point, and the minimum number of interventions required.

4.3 How the Model Addresses the Challenge of Minimising Polypharmaceutical Interventions

The two critical enablers of our modelling approach are its ability to minimise polypharmaceutical intervention through dynamical modelling of disease progression and testing different intervention strategies across the full continuum of different time points from AD's preclinical, prodromal and clinical stages. Our model is used to explore the minimum set of interventions and their timed coordination that returns the modelled diseased state back to the modelled healthy state. These interventions include the representation of existing, putative, or proposed drug therapies. The minimal set presents potential intervention strategies that can be tested on appropriate lab models [80].

In and of themselves, machine-learning (ML) algorithms are useful for teasing out correlations in large and complex datasets, but continue to prove unsuccessful in determining causation [81]. In general, therefore, ML and artificial intelligence (AI) approaches can be used to efficiently search the parameter space of large complex models to find configurations of the system that reproduce the observed healthy state. The volume of the parameter space that corresponds to the healthy state is a measure of the resilience of that state to fluctuations in the parameter values. It is also possible to identify the most sensitive set of parameters and associated processes that change the state of the system when they are simultaneously altered, which identifies the critical control points in the system. The model can be validated by introducing known pathological mutations, such as the example of the heterozygous TREM2 variant encoding R47H that we used in **Figure 3** to show the heterarchical nature of AD, and testing whether the predicted behaviour reproduces that of the pathological state.

The model is also used together with ML approaches to efficiently explore the parameter space to identify regions corresponding to both healthy and diseased states of the system for contrasting tissue architectures. These states are mapped onto the full range of image data corresponding to known clinical manifestations of AD. Comparing the parameter envelope between the healthy and diseased states indicates the system components and interactions implicated in the pathological state of AD. As an example of a pathological mutation, the heterozygous TREM2 variant encoding R47H leads to a reduced inability of microglia to clear Aβ plaques [82]. This is reproduced in the model by changing the chemotactic terms that affect the response of the microglia to cell damage. Using the ML algorithm, the role of the mutation can be identified, and any coincident factors that lead to AD

pathogenesis in the presence of the TREM2 mutation, leading to the generation of new testable hypotheses about the role of TREM2 in AD.

The integrative AD model system involves a number of parameters, some of which are not yet available or cannot be measured. To ensure the parameter values correctly describe each process, the model is constrained to make its outcomes corroborate with available experimental data. For example, constraining the fluid dynamics model to ensure the velocity distribution it simulates is consistent with recent MRI measurements that show interstitial fluid velocity is between 0.25 and 2.0μm/s [83].

4.4 Using the Platform to Generate New or Refined Hypotheses

Our modelling approach starts from the perspective of making best use of the available quantitative and qualitative knowledge, and a 'first-guess' description of the system that employs the minimum level of complexity that we think is sufficient to capture the detail needed. For definiteness, consider a system described by an interaction network of large numbers of interacting nodes, for example, microglia and Aβ plaques. It is important to note, that there may not be much available qualitative or quantitative data relating to some of the interactions, so different versions ('parameterisations') of the model are built that span the inherent uncertainty. From this starting point, the iterative process begins using the different models to infer the sensitivity of the behaviour of the system to our uncertainties, and to specific details of the network. For those parts where sensitivity is low, the uncertainties don't matter, and detail can be removed. High sensitivity identifies where more detail and better data is needed to ensure the model captures the essential features of the system. Should the model not capture the observed behaviour, even taking into account the uncertainties, then the model is wrong, and additional nodes and interactions need to be included. This process continues until modelled and observed behaviour converge. This iterative process is automated using both AI and ML technologies.

4.5 Establishing an Open Innovation Ecosystem

In our opinion there are four equally important critical enablers to the success of our integrative model system and platform – **science**, **data**, **tools and technology**, and **people**. We would even argue that people are the most critical enablers. We have already shown that a good understanding of the current science of AD has enabled us to start developing our system of models. Globally, AD researchers have access to an overwhelming quantity of data of both qualitative and quantitative data, and we have the tools and technology to interpret and make best use of it. The key to the ultimate success of building a more complete model of AD is to pull these elements together into a formal framework that is openly available to everyone involved in AD research, and which fosters collaboration and leverages shared innovation for the mutual benefit of the research community, and ultimately to people living with AD. Our proposed framework is an Open Innovation Ecosystem (OIE), which we define as:

> *A dynamic and collaborative global community of universities, research institutes, industry partners, and multi-disciplinary researchers interconnected, organised and focused around the development of a self-sustaining AD platform that enables the co-creation of value to the global AD research community as a whole.*

Overall, we encourage a culture of inter-disciplinary diversity within the OIE including researchers from often seemingly disparate backgrounds (for example, engineers, computational modellers, and mathematicians). Each will bring a unique offering of skills that might otherwise be unavailable to life scientists. The OIE community will drive innovation and the ultimate success of the platform's

uptake within the wider AD research community. An AD OIE will also create an environment for the development of best practices that will ensure equality in both access and sharing of data between its members.

We acknowledge the challenge in bringing data from such different sources across wide ranges of spatio-temporal scales, and both sharing and analysing it within the framework of an OIE. Another group – The Accelerating Medicines Partnership Parkinson's Disease (PD) program has met this challenge through the development of a platform that integrates the storage and analysis of data: whole-genome sequencing, RNA and clinical [84].

And finally, through a big picture overview in **Figure 4,** we summarise our dynamical systems approach that begins the process of building a more complete model of AD within a collaborative OIE, to help unify the characterisation and treatment of AD.

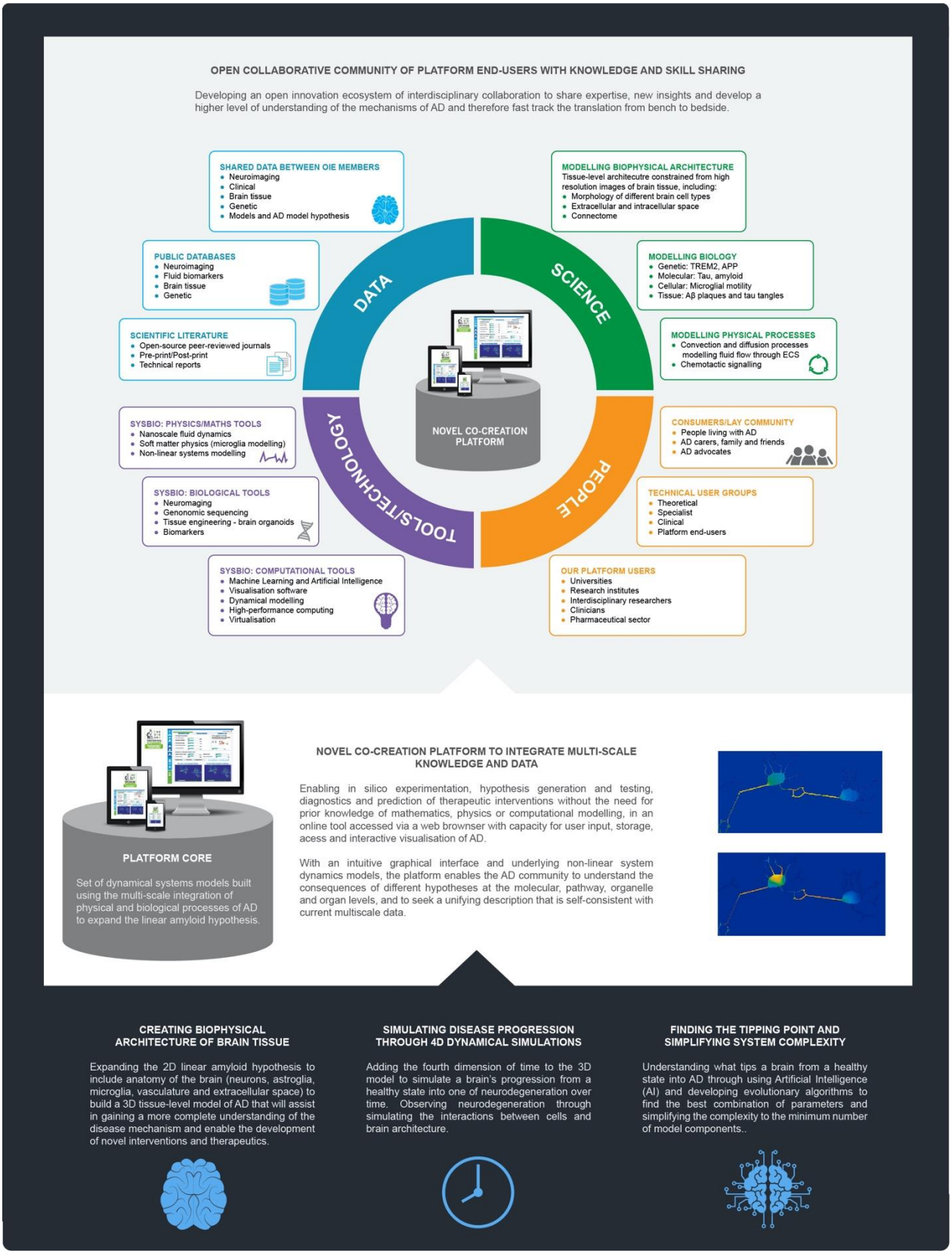

Figure 4: The big picture overview illustrating the key stages of building a more complete 4D tissue-level model of AD – from the core set of dynamical systems models that underpin the co-creation platform and which is overall enabled through an open innovation ecosystem.

5 Conclusions and Next Steps

We have reviewed the multi-scale nature of AD and shown that the current best knowledge implicates a heterarchical network of interactions between the known components of the disease. Given the overwhelming likelihood that these interactions will be strong and non-linear, this network forms an irreducible system. This means the components cannot be studied in isolation without introducing inestimable errors. Furthermore, the progressive nature of AD means that identification of the interactions is not sufficient to identify interventions, and each interaction must be characterised in ways that allow us to predict how that interaction contributes to the dynamics of the disease. We have also outlined why multiscale complexity means that the most effective interventions are likely to be coordinated across multiple targets, why the normal notion of cause-effect may not be relevant, and why intuition on its own is unlikely to be a guide in identifying treatments.

If we accept the multiplicity and irreducibility of the networks implicated in AD, and that AD must be understood as a progressive disease, then the way that the science is currently being carried out is suboptimal. We propose a different way for the AD community to work together that comprises an iterative interplay between (i) an open-innovation ecosystem that supports sharing of knowledge across scales and develops hypotheses to integrate that knowledge; (ii) a co-creation platform that translates these hypotheses into dynamical systems models and tests the hypotheses by comparing the predicted spatio-temporal behaviour against the available data. The open innovation ecosystem and the co-creation platform are part of an iterative process of refining hypotheses, and identification of critical interactions including prioritising new data collection. The outcome is an encapsulation of the current best knowledge of the whole AD system and how it fits together, as a means of prioritising data campaigns, generation of novel and non-intuitive hypotheses, and the ability to predict multiple coordinated interventions that impact on the disease.

We have outlined our own dynamical systems modelling approach and highlighted recent progress in whole-brain modelling of AD that provides evidence that a co-creation platform can be built. The appetite to create an associated open innovation ecosystem is unclear and is unlikely to emerge without facilitation.

To progress, we propose a carefully designed workshop that brings together AD researchers with expertise spanning the range of scales implicated in the disease, experts on dynamical systems theory, and representatives from the relevant societies and industry. There should be five objectives: (i) to reach a common understanding of the opportunities and challenges of integrating knowledge across scales; (ii) to design the required open innovation ecosystem; (iii) agree on the key features of the co-creation platform; (iv) formalise a collaboration; and (v) coordinate a collective action to raise the necessary resource.

The outcome of this workshop will be an understanding of the willingness of the community to work collectively to understand AD as a multiscale dynamical system. There will be a better understanding of what dynamical systems theory can offer lab-based and clinical researchers, a depiction of the current complexity of the disease, the data that is available to be shared, and the tractability of computational modelling. This on its own will be a worthwhile outcome, but with the support of industry and the Alzheimer's societies, there will be potential to create a new alliance of the willing. An alliance with the capacity and capability to build a new synthesis of the key elements of AD pathology, and to explore new interventions that are currently conceptually inaccessible.

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