Computational models of Alzheimer's disease

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- **Dr. Vassilis Cutsuridis**, School of Computer Science, University of Lincoln, Lincolnshire, U.K.
- **Dr. Ahmed A Moustafa**, Western Sydney Univ, Sydney, NSW, Ausralia

Contents

What is Alzheimer’s disease

Alzheimer's disease (AD) is the most common neurodegenerative aging disorder affecting millions of individual worldwide. AD is associated with memory decline as well as impairment in language and executive function. These symptoms become more severe with disease progression. It is estimated that 25–35% of the population over the age of 85 years old have Alzheimer disease. The number of patients with AD is expected to rise in the near future as people are now living longer.

The formation of beta-amyloid plaques and neurofibrillary tangles in the brains of the patients were found to be related to dementia symptoms (Wilcock & Esiri, 1982). It is not known which factors lead the formation of plaques and tangles in some individuals and how exactly they relate to different symptoms in AD. In addition, several neuropsychological and fMRI reports show hippocampal dysfunction in Alzheimer’s disease patients (Apostolova et al., 2006; de Leon et al., 1989; Jack et al., 2000; Allen et al., 2007; Schuff et al., 2008). Current studies attempt to develop deep brain stimulation therapy for AD targeting different hippocampal regions, including the hippocampus, fornix, and entorhinal cortex (Hescham et al., 2013; Suthana et al., 2012).

It has been found that variations in apolipoprotein E (APOE) genotype are associated with increased risk of developing AD (Jack et al., 1998). There are three different genetic alleles that encode the APOE gene: ε2, ε3, and ε4. Approximately 15% of the population carry the APOE ε4 allele, while the rest carry the APOE ε2 or APOE ε3 allele. Importantly, APOE ε4 has been linked to AD pathology more than the other alleles. Carriers of the APOE ε4 genotype have been shown to have larger temporal lobe atrophy and poorer memory functions than non-carriers (Dhikav & Anand, 2011). Similarly, it was found that APOE ε4 allele is associated with a small hippocampal volume in healthy older subjects. Further, studies have also reported reduced acetylcholine levels in the hippocampus in AD patients (Kihara & Shimohama, 2004).

There are many medications approved for AD, including donepezil, galantamine, rivastigmine, and memantine. Some of these pharmacological agents (donepezil, galantamine, rivastigmine) are cholinesterase inhibitors and thus increase acetylcholine (ACh) levels in the brain, while memantine is an NMDA antagonist. However, memantine was shown to increase ACh levels in the hippocampus, although it did not improve memory performance in rats (Ihalainen et al., 2011). This is in contrast to studies showing that ACh inhibitors increase ACh levels and also improve memory function in animal models and patients with AD (Bitner et al., 2009; Chalmers et al., 2009). Howard and colleagues (Howard et al., 2012) have found that donepezil or memantine are effective for enhancing memory in moderate-to-severe AD patients, although adding both together does not lead to more improvement. One major problem with currently approved AD drugs (ACh inhibitors and NMDA antagonists) is that they are symptomatic and work for a short period of time.

Competing hypotheses

Several competing hypotheses have been put forward to explain the causes and symptoms of the disease:

- Cholinergic hypothesis: The cholinergic hypothesis proposes that the memory deterioration observed in AD patients is caused by reduced synthesis of acetylcholine (ACh), choline uptake, and ACh release (Francis et al., 1999).
- Amyloid hypothesis: The amyloid hypothesis (Hardy & Selkoe, 2002) proposes that extracellular beta-amyloid (Aβ) plaques are the fundamental cause of the disease. Aβ is a fragment of a transmembrane protein that penetrates through the neuron's membrane, the amyloid precursor protein (APP). In AD, APP is divided into smaller fragments by proteolytic enzymes. One of these fragments (39-43 amino acids in length) form dense formations (Aβ plaques) in the extracellular space of neurons.
- Tau hypothesis: The tau hypothesis (Boutajangout & Wisniewski, 2014) proposes that hyperphosphorylated tau proteins form neurofibrillary tangles inside the nerve cell bodies, causing microtubules to disintegrate, collapsing the neuron's transport system. As Aβ plaques and neurofibrillary tangles accumulate in the brain, synaptic and neuronal losses occur on a large scale affecting the entire cerebral cortex, the hippocampus and neighboring brain regions.
- Glucose synthase kinase 3 (GSK3) hypothesis: According to GSK3 hypothesis over-activity of GSK3, a proline-directed serine/threonine kinase, accounts for memory impairment, tau hyper-phosphorylation, increased Aβ production, reduction of ACh synthesis, cell apoptosis, and local plaque-associated microglial-mediated inflammatory responses, all of which are principal characteristics of AD (Hooper et al., 2008).
- Other hypotheses: Oxidative stress (Christen, 2000), reduced hippocampal volume (Dhikav and Anand, 2011), cerebrovascular disease and inflammation (Spangenberg and Green, 2016) may be significant in the formation of the pathology.

Each of these cascades produce secondary effects to the nerve cells which may result in cell death (Kosik et al., 1991), synapse loss (Hamos et al., 1989; Terry et al., 2000; Knobloch & Mansuy, 2008), alterations of ionic and synaptic channels (Kuchibhotla et al., 2009; Snyder et al., 2005; Sato et al., 2008; Texido et al., 2011), impairments in synaptic transmission and plasticity (Hsia et al., 1999; Chapman et al., 1999; Walsh et al., 2002), destabilization of neural network activity (Palop et al., 2007; Palop & Mucke, 2010), inhibitory interneuron dysfunction (Ramos et al., 2006; Verret et al., 2012; Palop and Mucke, 2016) and aberrant network synchronization (Busche et al., 2008; Palop and Mucke, 2010), alterations in microglia response (Brown & Neher, 2010; Mandrekar-Colucci & Landreth, 2010; Cameron & Landreth, 2010), or CREB down-regulation throughout the cerebral cortex and hippocampus (Barco & Marie, 2011).

It is experimentally very difficult to understand how the interactions of all these mechanisms lead to the pathogenesis of the disease. This is mainly because experimental studies are usually carried out to isolate the

effects of a single mechanism and not to investigate the interactions of many mechanisms. This leads to a set of results that are conflicting or very difficult to interpret.

Mathematical and computational models are invaluable tools in resolving such conflicts, because they can tie together in a single framework advances from various levels of detail. In the next section we will describe a number of computational modelling attempts ranging from the biochemical level to the systems-level in order to understand the pathogenesis and symptoms of AD.

Computational models

There have been a few attempts to design computational models of AD. Some of these models focus on hippocampus function and failed to simulate the exact effects of amyloid plaques and neurofibrillary tangles due to their sheer interaction complexity. See Duch (2007) for a review of some AD models. Below, we discuss biochemical, single cell, biophysical spiking, and systems-level and abstract models of AD.

Biochemical models

Models of amyloid cascade hypothesis

Early mathematical and computational biochemical modelling of AD focused on the Aβ hypothesis. Deposition of Aβ as insoluble fibrillar aggregates is known to be one of the defining pathological features of Alzheimer's disease. The pathway, kinetics and factors of Aβ fibrillogenesis have been the subject of intense experimental (Murphy & Pallitto, 2000; McLaurin et al. (2000)) and theoretical (Tomski & Murphy, 1992; Jarrett et al., 1993; Lomakin et al., 1996; Naiki & Nakakuki, 1996; Harper & Lansbury, 1997; Lomakin et al., 1997; Walsh et al., 1997; Inouye & Kirschner, 2000; Kim et al., 2004) investigation. Tomski and Murphy (1992) were the first to derive a computational model of the kinetics of fibril elongation. Jarrett and colleagues (1993) proposed a three phase (a lag phase, a rapid growth phase, and a plateau phase) kinetic model for Aβ self-association. Naiki and Nakakuki (1996) proposed that elongation of fibrils is due to reversible addition of monomer to preexisting fibrils. Lomakin et al. (1996, 1997) computationally investigated how monomers were rapidly and reversibly formed micelles from which nuclei slowly but irreversibly emerged and how fibrils elongated by addition of monomer to nuclei or other fibrils. Their model accounted for the presence of both monomer and fibrillar forms, and predicted both the mass concentration of fibrils and fibril length as a function of time. The experiments upon which these models were based were conducted at nonphysiological conditions (pH~1). Also, none of these kinetic models distinguish between filaments and fibrils, or accounted for conversion between these two states (Harper et al., 1999).

Significant improvement over previous mathematical models was the Pallitto and Murphy (2001) model of the kinetics of Aβ aggregation. Their model featured 1) experimental data collected at physiological pH, 2) initiation and growth mechanisms, 3) monomer addition and fibril-fibril association as growth mechanisms, 4) both filaments and fibrils, and 5) mass fractions and filament/fibril lengths. Key feature of their model was that unfolded Aβ, upon dilution into a folding buffer, rapidly and irreversibly partitioned between two pathways: (1) one pathway producing monomers and dimers of stable (but undefined) structure, and (2) another pathway generating an unstable intermediate, likely b-sheet-containing oligomers (Barrow et al., 1992) that aggregated further. Conversion of the unstable intermediate to larger aggregates proceeded via four steps (Fig. 1): initiation via cooperative association of intermediate, elongation by addition of monomer to filament, lateral aggregation of filament to fibril, and elongation by end-to-end association of shorter fibrils or filaments. These four steps were consistent with the group's and others' experimental evidence (Harper et al., 1999). Both the initial size of aggregates and the rate of growth were shown to be highly concentration-dependent. At lower concentrations, elongation is relatively more important and a few long filaments are produced, whereas at higher concentrations, initiation and lateral aggregation become more dominant

features.

Kim and colleagues (2004) further examined how Aβ oligomers, the intermediates in the fibrillogenic pathway, could be controlled, by investigating the effect of urea on secondary structure, size distribution, aggregation kinetics, and aggregate morphology. Increased urea concentration led to β-sheet content and the fraction of aggregated peptide decrease, reduced average size of aggregates, and changes in the morphology of aggregates. The model results were consistent with the hypothesis that the globular aggregates were intermediates in the amyloidogenesis pathway rather than alternatively aggregated species.

Other modelling attempts have focused on plaque formation (Cruz et al., 1997; Urbanc et al., 1999), the kinetics of APP processing (Schmidt et al., 2011; Ortega et al., 2013) and the interactions of intracellular Ca^{2+} and Aβ (De Caluwe & Dupont, 2013) in the Alzheimer's brain. Consecutive cleavage of amyloid precursor protein (APP) by α-, β- and γ-secretases produce Aβ plaques in the brain. It is hypothesized that secretase inhibitors can reduce the production of Aβ in the brain and thus may slow the progression of Alzheimer disease. Paradoxically, it has been shown that low to moderate inhibitor concentrations cause a rise in Aβ production in different cell lines, in different animal models, and also in humans. Ortega et al. (2013) developed a minimal mechanistic understanding of Aβ dynamics in cell lines that exhibit the rise as well as in cell lines that do not. The model showed that the cross-talk between the amyloidogenic and the non amyloidogenic pathways accounts for the increase in Aβ production in response to inhibitor, i.e. an increase in C99 will inhibit the non-amyloidogenic pathway, redirecting APP to be cleaved by β-secretase, leading to an additional increase in C99 that overcomes the loss in γ-secretase activity. De Caluwe and Dupont (2013) developed a minimal model that qualitatively described the interactions between intracellular Ca^{2+} and Aβ. The model accounted for known characteristics of the disease, such as its irreversibility, the threshold-like transition to a severe pathology after the rather slow accumulation of symptoms, the so-called 'prion-like' autocatalytic behaviour, and the inherent random character of the apparition of the disease that is well-known for the sporadic form of AD.

Models of other cascade hypotheses and their interactions

Recently, as our knowledge of the AD pathology grew, there have been more complex models of AD development. A comprehensive model of AD development based on the amyloid hypothesis was advanced by Anastasio (2011). The model's Aβ regulation pathways were specified with sets of interrelated equations and rules written in the Maude environment. The resulting Maude specifications were then converted to Petri net models, which are then executed and analyzed using innate to Maude Petri net tools. The molecules and conditions represented in the model are assigned arbitrary integer values and the equations and rules specify how changes in the levels of some model elements change the levels of other elements. The model demonstrated how Aβ regulation can be disrupted through the interaction of pathological processes such as cerebrovascular disease (CVD), inflammation and oxidative stress (OS). Particularly it showed how incipient CVD can trigger AD. It also showed how treatments directed at multiple targets can be more effective than single target therapies.

Anastasio (2013) extended its previous model to account for the many factors including estrogen that participate in the regulation of Aβ, and to explore ways in which estrogen therapy might be used more effectively in AD treatment, perhaps by administering estrogen in conjunction with other agents. The main finding of this model was that, under conditions of very low estrogen and incipient CVD, the level of Aβ could be reduced, possibly to normative levels, with a combination of a non-steriodal anti-inflammatory drug (NSAID) that promotes peroxisome proliferator-activated receptor (PPAR) expression, a compound that blocks hypoxia inducible factor (HIF), and estrogen itself. The model suggested that estrogen would provide the main benefit, reducing Aβ directly (e.g., by enhancing neprilysin (NEP) expression) and indirectly by reducing inflammation and OS (e.g., by enhancing superoxide dismutase (SOD) expression), thereby

disrupting pathological processes that contribute to Aβ accumulation. With estrogen itself providing the main benefit, an NSAID and a HIF-blocker can each provide a small additional benefit, and these two benefits are additive in combination.

Using a similar modelling approach Anastasio (2014) attempted to understand the dysregulation of synaptic plasticity by Aβ. In the normal synapse where Aβ is absent the model suggests that PKA is responsible for keeping striatal-enriched protein tyrosine phosphatase (STEP) (and other key LTD drivers) inactive when Ca^{2+} is high enough to elicit LTP. In the diseased synapse where Aβ is present, the model suggests that the action of PKA is instrumental in preventing LTD from occurring at all non-zero levels of presynaptic activity including that which would evoke LTP in the normal synapse. In the model PKA is the mediator that keeps the diseased synapse at least at baseline at high levels of presynaptic activity. The model provides an initial framework for understanding how various drugs and drug combinations might operate in the diseased synapse. The model suggests that normalization of nicotinic acetylcholine receptors (nAChR) function may be the most effective way to counteract the adverse effects of Aβ on synaptic plasticity, lending some modelling support to the suggestion that disordered nAChR function is the main route by which Aβ dysregulates synaptic plasticity (Wang et al., 2000; Snyder et al., 2005; Shankar et al., 2008).

In line with the Anastasio (2014) study, Craft and colleagues (2002) used a mathematical model to assess the effect of AD treatment on Aβ levels in various compartments of the body. Using an infinite set of nonlinear differential equations they studied the dynamics of Aβ levels in the brain, CSF and plasma, both before and after treatment. Their mathematical analysis revealed two possible regimes, depending on the value of a polymerization ratio, r, in the brain, which was the product of the effective production rate and elongation rate divided by the product of the effective loss rate and the fragmentation rate. When the polymerization ratio was less than 1, steady-state Aβ levels were achieved throughout the body. When the polymerization ratio was greater than 1, then the Aβ accumulation grew indefinitely, whereas the Aβ levels in the CSF and plasma remained in a steady state.

Other modelling attempts investigated the relationship between GSK3b, p53, Aβ and tau (Proctor & Gray, 2010). The Proctor and Gray (2010) model was a multi-modular one that included regulatory components for DNA damage, p53 regulation, GSK3 activity, Aβ turnover, tau dynamics and the aggregation of Aβ and tau. The model showed that a sudden increase in DNA damage leads to oscillations of p53 and Mdm2. Disruption of the Mdm2/p53 complex, allows the formation of GSK3b/p53 complexes which results in increased transcriptional activity of p53 and increased kinase activity of GSK3b. This led to an increase in Aβ production, an increase in Mdm2 mRNA and an increase in tau phosphorylation. Under normal conditions, the model predicted that Aβ is cleared from cells and so it does not accumulate, and tau is dephosphorylated to maintain the correct balance of phosphorylated and un-phosphorylated tau. However, after a stress event, the DNA damage response leads to increased activity of p53 and GSK3b which results in increased production of Aβ and increased phosphorylation of tau. If the parameter for DNA repair was set so that most DNA damage is repaired in 24 hours, then Aβ is cleared and tau is de-phosphorylated, so that aggregates do not accumulate. In the aging brain Proctor and Gray hypothesized that DNA damage may persist for longer periods of time either due to a decline in repair mechanisms or an increase in reactive oxygen species (ROS) production. Then aggregates are much more likely to accumulate which in turn lead to increased ROS production and further DNA damage which leads to further activation of p53 and GSK3b and even more aggregation. Their model also predicted that the formation of plaques and tangles are independent events, but that they share a common cause, namely GSK3b overactivity.

Proctor and colleagues (2013) extended their model to investigate the effects of passive and active immunization against Aβ and this intervention effects on soluble Aβ, plaques, phosphorylated tau and tangles. Aβ clearance proceeded into steps where administration of antibodies were modelled by adding a species named "anti Aβ" to represent the addition of antibodies (i.e. passive immunization) and another

species named "Glia" to represent microglia. The addition of antibodies and microglia were done at predetermined time points during the simulation. The aggregation process started with the formation of Aβ dimmers from two monomers, but this reaction was reversible. Under normal conditions, model Aβ levels started at very low values and Aβ was continually produced and degraded. The model predicted that immunization leads to clearance of plaques, but has small effect on soluble Aβ, tau and tangles. The model suggested that immunotherapy against Aβ is more effective when it is applied to in the early stages of the disease.

Kyrtsos and Baras network interaction model of Aβ, neuro-inflammation, mitochondrial dysfunction, and lipid metabolism dysregulation to study the varying effects of variations in the ApoE allele present, as well as the effects of short term and periodic inflammation at low to moderate levels. Red nodes represent molecules involved in the inflammatory process; green nodes represent proteins; orange nodes represent an interaction with ApoE; blue nodes represent molecules involved in energy metabolism; light blue nodes represent protein–lipid complexes; and purple nodes represent lipid metabolism. Conservation of mass allows molecules to interact in more than one set of interactions. The associated equations are indicated by the red numbers near the nodes (adapted with permission from Kyrtsos & Baras, 2013).]]Kyrtsos and Baras (2013) advanced a network interaction model of Aβ, neuro-inflammation, mitochondrial dysfunction, and lipid metabolism dysregulation to study the varying effects of variations in the ApoE allele present, as well as the effects of short term and periodic inflammation at low to moderate levels. Their model was a two level (cellular and molecular) hierarchy model, where at the cellular level four main cell types (neurons, astrocytes, microglia, and brain endothelial cells) were allowed to interact with each other and at the molecular level, each of these cell types had their own metabolic network that generated molecules related to their specific cellular function (Fig 2). The cellular products were then allowed to interact with the molecular products of other cellular networks. The chemical species of each cell type was modeled by the average distribution and adjusted based on the number of cells of that type present. Simulations demonstrated that having even one ApoE4 allele eventually lead to a significant local increase in Aβ that leads to the collapse of ATP levels, subsequent elevation of glutamate and loss of all neurons in a local region over the course of an equivalent 1-1.5 years. Simulations on the effect of short-term inflammation showed that the level of neuronal cholesterol increased nearly immediately in response to the inflammatory response, regardless of the ApoE genotype, before returning to baseline levels. The elevated cholesterol levels suppressed cleavage of APP into Aβ during this period, which subsequently eliminated the variability of neuronal ATP levels. Suppression of ATP variability allowed the ATP levels to decrease slowly, which eventually led to a slow increase in Aβ and the eventual neuronal cell death. ApoE4 homozygotes appeared to benefit from this short inflammatory pulse by delaying the neuronal cell loss, while ApoE2 and 3 homozygotes appeared to be harmed in the long-term by the inflammatory pulse. Periodic and chronic inflammation via different pathways had similar effects as short-term inflammation. The model showed that inflammation may play a role in the AD process, but that the duration of the inflammation, as well as the strength of the inflammation, are important in determining whether the pro-inflammatory state will contribute, lessen or not even affect Aβ generation and AD progression.

Single cell models

Experimental studies have reported that Aβ exposure of cells leads to disruptions of intrinsic electrical properties in dendrites of cells in the hippocampus (Chen, 2005). In particular, one experimental study reported that application of Aβ blocks A-type K^+ channels in pyramidal cell dendrites, causes an increase in dendritic membrane excitability and Ca^{2+} influx due to an enhanced back-propagating action potentials (bAPs) (Chen, 2005). This dendritic hyper-excitability eventually leads to cell excitotoxicity and other degenerative changes (Good & Murphy, 1996). A similar Aβ block of IA has been observed in dissociated (Xu et al., 1998) and cultured (Zhang & Yang, 2006) hippocampal CA1 neurons and in cholinergic basal forebrain

neurons (Jhamandas et al., 2001) and neocortical neurons (Ye et al., 2003). Morse and colleagues (2010) were the first to computationally investigate in a detailed biophysical model of a CA1 pyramidal cell these experimental findings in the fine oblique branches of its apical dendritic tree. The effect of Aβ was modelled as a reduction of the maximal conductance of the transient A-type K^+. The simulation results supported the experimental results (Chen, 2005) that a selective effect of Aβ on K^+ current increases the extent of invasion of bAPs from the cell body into the apical dendritic trunk of CA1 pyramidal neurons, as it has been seen with pharmacological blockade of the A-type K^+ current (Hoffman et al., 1997). The simulation results showed for the first time that the effect of a disruption of normal dendritic electrical activity by IA blockade appears to have a much larger difference between the depolarizations in the Aβ and normal cases in the distal oblique branches compared to the dendritic trunk.

In subsequent studies, some researchers (Culmone & Migliore, 2012; Wilson et al., 2013) investigated how further modifications of synaptic and membrane properties caused by Aβ accumulation can affect the main firing properties of a CA1 pyramidal neuron under current and voltage clamp conditions. Both studies made recommendations which mechanisms could be targeted by drugs to restore the original firing conditions.

Experimental evidence has also demonstrated that an acute enhancement of endogenous Aβ leads to an increase in the initial release probability (p_0) at the CA3-CA1 synapses of the hippocampus, without altering postsynaptic function or intrinsic neuronal excitability (Abramov et al., 2009). This increase in p_0 has also been associated with an Aβ-induced increase in vesicle depletion (Parodi et al., 2010). Romani and colleagues (2013) using a realistic model of hippocampal CA1 pyramidal neuron investigated how this enhancement in p_0 influences synaptic short-term plasticity of the synapse and the firing probability of the CA1 output neuron. They demonstrated that this synaptic modification can significantly alter synaptic integration properties in a wide range of physiologically relevant input frequencies especially in the theta and gamma ranges.

Biophysical spiking models

EEG studies in AD patients have shown that beta band power (13–30 Hz) decreased in the early stages of the disease with a parallel increase in theta band power (4–7 Hz). This abnormal change progresses with the later stages of the disease but with decreased power spectra in other fast frequency bands plus an increase in delta band power (1–3 Hz). The mechanisms underlying such changes in brain oscillations are still unclear. Zoo and colleagues (2011) used a biophysical hippocampal CA1-medial septum network model to investigate how changes in four ionic channels (L-type Ca^{2+} channel, delayed rectifying K^+ channel, A-type fast-inactivating K^+ channel and large-conductance Ca^{2+}-activated K^+ channel) known to be affected by Aβ exposure lead to the reported theta band power changes and the subsequent toxicity of the hippocampal pyramidal neurons. Simulation results demonstrated that only the Aβ inhibited A-type fast-inactivating K^+ channels induce increases in hippocampo-septal theta band power due to enhanced synchrony between pyramidal neurons, while other channels do not affect the theta rhythm.

Abuhassan and colleagues (2012) investigated the causes of abnormal cortical oscillations in AD using two heterogeneous neuronal network models. They examined the effects of neuronal and synaptic loss and deregulation of negative feedback to the membrane potential of cortical neurons mainly from Aβ-induced dysfunctional K^+ channels on the oscillatory activity of cortical networks. Simulation results show that, despite the heterogeneity of the network models, the beta band power is more significantly affected by excitatory neural and synaptic loss in comparison to other bands.

Other modelling studies focused on the mechanisms causing cell death and synapse dysfunction in AD. As cells die and synapses lose their drive, the remaining cells in the network suffer an initial decrease in activity. Neuronal homeostatic synaptic scaling then provides a feedback mechanism to restore activity. This homeostatic mechanism is believed to sense levels of activity-dependent cytosolic calcium within the cell and

to adjust neuronal firing activity by increasing the density of AMPA synapses at remaining synapses to achieve balance. The scaling mechanism increases the firing rates of remaining cells in the network to compensate for decreases in network activity. However, this effect can itself become a pathology, as it produces increased imbalance between excitatory and inhibitory circuits, leading to greater susceptibility to further cell loss via calcium-mediated excitotoxicity. Rowan and colleagues (2014) advanced a mechanistic explanation of how directed brain stimulation might be expected to slow AD progression based on computational simulations in a 470-neuron biomimetic model of a neocortical column. The simulations demonstrated that therapeutic low-intensity low-frequency electro-stimulation could act on homeostatic synaptic scaling mechanisms to reduce the pathological effect of excessive compensatory scaling in AD disease. The increase in activity within the remaining cells in the column results in lower scaling-driven AMPAR up regulation, reduced imbalances in excitatory and inhibitory circuits, and lower susceptibility to ongoing damage.

Menschik and Finkel (1998) advanced a model of hippocampal CA3 network dynamics inspired by the Buzsaki "two-stage" memory model (Buszaki, 1989; Buzsaki & Chrobak, 1995) and the suggested role for interneurons, basket and chandelier cells, and the Lisman and colleagues model on embedded gamma cycles within the theta rhythm (Lisman & Idiart, 1995; Lisman, 2005) in order to study the modulation and control of storage and recall dynamics in AD by subcortical cholinergic and GABAergic input to the hippocampus. They showed that synchronization in the gamma frequency range can implement an attractor based auto-associative memory, where each new input pattern that arrives at the beginning of each theta cycle comprised of 5-10 embedded gamma cycles drives the network activity to converge over several gamma cycles to a stable attractor that represents the stored memory. Their results supported the hypothesis that spiking and bursting in CA3 pyramidal cells mediate separate behavioral functions and that cholinergic input regulates the transition between behavioral states associated with the online processing and recall of information. Cholinergic deprivation led to the slowing of gamma frequency, which reduced the number of "gamma cycles" within the theta rhythm available to reach the desired attractor state (i.e. memory loss and cognitive slowing seen in AD).

Inspired by the Cutsuridis and colleagues (2010) modeling study, Bianchi et al. (2014) investigated the conditions under which the properties of hippocampal CA1 pyramidal neurons altered by increasing CREB activity can contribute to memory storage and recall improvements. The effects of CREB were modelled as decreases in the peak conductances of mAHP and sAHP currents by 52% and by 64% respectively and an increase in the peak AMPA conductance by 266%. With a set of patterns already stored in the network, they found that the pattern recall quality under AD-like conditions (i.e. when the number of synapses involved in storage is reduced and/or the peak AMPA conductance is reduced) is significantly better when boosting CREB function. They inferred that the use of CREB-based therapies could provide a new approach to treat AD.

Systems level models

One early connectionist model focused on understanding difficulty in naming objects in AD patients, especially of low-quality object stimuli as well as less frequent objects (Tippett & Farah, 1994). This feedforward model was trained using Hebbian learning, and showed how semantic memory deficit can explain naming difficulty in AD patients. The model consisted of five layers: name input, visual input (and two hidden layers for each), and semantic representation layer. The model specifically showed that lesioning a random subset of semantic neurons (presumably mimicking neural dysfunction in AD) leads to impairment processing inputs and eventually impairments in naming objects (for discussion on this model, see Harley, 1998).

Unlike prior models that focus on simulating AD as involving damage to neurons, one class of models showed that synaptic abnormalities are related to memory decline in AD (Horn et al., 1993; Ruppin & Reggia, 1995).

Horn and colleagues provided a model based on the Hopfield network in which memories correspond to different attractor states. The model showed how deleting random weights (synaptic deletion) impact attractor dynamics. They also showed that a compensation mechanism (increasing the value of remaining weight) can bring the network back to normal conditions. Another model used the synaptic deletion hypothesis to simulate impairment in retrieval of recent, but not remote, memories in AD patients (Ruppin & Reggia, 1995).

Using the runaway synaptic modification hypothesis (which is exponential growth in synaptic weight values), Hasselmo provided a two-layer feedforward network to simulate memory impairment in AD. Hasselmo used this model to explain the effects of hippocampal dysfunction in cortical information processing in AD (Hasselmo, 1994; Hasselmo, 1997). Hasselemo showed that impaired memory encoding of new information in the hippocampus (i.e., impaired pattern separation and confusing new and old memory representations) can explain memory decline in AD. He also argued impaired pattern separation can perhaps explain memory retrieval impairment in AD patients.

One more recent model by Bhattacharya and colleagues studies the relationship between active synapses and alpha frequency in healthy populations, individuals with mild cognitive impairment, and AD patients (Bhattacharya et al., 2011) to replicate experimental data of dysfunctional EEG in AD patients. Each brain region simulated in this model is composed of different layers of neurons (3 for the thalamus module, and 4 for the cortex module). One limitation of the model, as mentioned by the authors, was not simulating the relationship between ACh and alpha band frequencies. Future modeling work should also link changes in alpha band power to dementia symptoms in AD patients.

A different class of models by Meeter and colleagues were used to explain anterograde amnesia in semantic dementia. Using a two-layer network model that corresponds to cortex and hippocampus (known as TraceLink model), Meeter and Murre (2005) showed that a simulated lesion to the hippocampus (disabling hippocampal neurons) can lead to anterograde amnesia. As in Hasselmo models, Meeter and colleagues argued that the formation and maintenance of declarative memories takes place in the cortex, and thus damaging the hippocampus leads to anterograde amnesia (ie., recall and formation of recent, but not, remote memories). Although this model was applied to semantic dementia patients, similar methods and results can be predicted for AD patients.

Gluck, Myers, Nicolle, and Johnson (2006) provided a computational analysis (though not a simulation model) of how Alzheimer's disease might affect hippocampal functioning and behavioral performance, especially in learning and transfer generalization of learned information to new contexts. Specifically, Gluck and colleagues argue that cognitive decline in AD was related to inability to generalize prior learning to novel contexts. Buildong on the Gluck, Myers, Nicolle, and Johnson (2006) modeling framework, Moustafa and colleagues provided a two-layer neural network of the basal ganglia and hippocampal region interaction that simulate learning and generalization. The model was trained using both Hebbian learning and temporal difference algorithms. The model showed that damage to the hippocampus (that is, removal of the simulated hippocampal region from the model) leads to impaired of generalization of learning performance (Moustafa et al., 2010), as reported in behavioral studies (Bodi et al., 2009).

McAuley et al. (2009) designed an abstract computational model to explain the relationship between cortisol and hippocampus function in aging populations and AD patients. The model showed that increase in cortisol levels inhibits hippocampal function and leads to memory decline, which has been reported in Alzheimer's disease patients. The model assumed that by age 90, increase in cortisol leads to a decrease in hippocampal activity of 30%. One limitation of this model was focusing only on cortisol receptors in the hippocampus, and not in other brain regions.

One abstract model focued on language production impairment in AD patients (Conley et al., 2001). Unlike

prior models, Conley and colleagues argued that denser memory representations in AD patients than in older populations reach saturation levels, and lead to impairment in language production. The model was based on the authors' prior model known as the Hyperspace Analogue of Language, which has semantic representation of millions of words as well as semantic relationship among these words. Based on inputs from interviews conducted with AD patients and controls, the input the model was 19,000 words (in each group), and the output was the measure of density of representation (distance between a word and its neighbors in the Hyperspace Analogue of Language). Conley and colleagues found that AD patients have denser representations. However, it is not known how these representations relate to AD symptoms.

Conclusions

Although there have been several attempts to model AD, there are many limitations. Most existing models have not attempted to explain the relationship between neural changes (formation of plaques and tangles, reduction in ACh levels) to behavioral symptoms (memory decline, semantic memory deficits, executive dysfunction) in AD. This is in contrast to other brain disorders, such as Parkinson's disease, where there have been some successful attempts to simulate neural-behavioral relationship. Further, unlike models of Parkinson's disease, existing models of AD did not simulate the effects of medications (donepezil, galantamine, rivastigmine, and memantine) on neural and behavioral processes. Future models should explain how increasing ACh levels and NMDA antagonists does relate to memory improvement. Further, although most (if not all) of the neural and behavioral studies differentiate between mild-to-moderate vs. severe AD patients, and also whether patients are APOE ε4 carriers or not, computational modelling studies did not address these subgroups of AD patients.

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