



ELSEVIER  
 DRUG DISCOVERY  
 TODAY  
 DISEASE  
 MODELS

Editors-in-Chief

Jan Tornell – AstraZeneca, Sweden

Andrew McCulloch – University of California, San Diego, USA

# Multiscale models of pharmacological, immunological and neurostimulation treatments in Alzheimer's disease

Vassilis Cutsuridis<sup>1,\*</sup>, Ahmed A. Moustafa<sup>2,\*</sup>

<sup>1</sup>Institute of Molecular Biology & Biotechnology, Foundation for Research and Technology – Hellas, Heraklion, Crete, Greece

<sup>2</sup>Marcus Institute for Brain, Behaviour, and Development, School of Social Sciences and Psychology, Western Sydney University, Sydney, Australia

The current study reviews computational models that embody a hypothesis and/or a theory of mechanisms of how AD impacts the brain and cognition as well as provide a critical analysis of strengths and weaknesses of these models. Existing models assume AD symptoms stem from abnormalities to cell structure, synaptic connections, neuro-chemicals, as well as other neural circuits and systems. We also discuss how mathematical formulation of the known biology of AD can help us understand AD symptoms and how pharmacological medications and neurostimulation therapies may work. Finally, we discuss general research directions that may improve future treatments of the disease.

## What is AD

Alzheimer's disease (AD) is the most common neurodegenerative aging disorder affecting millions of individuals 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 AD. The number of patients with AD is

## Section editors:

Samuel Neymotin, Dept. Physiology & Pharmacology SUNY Downstate Medical Center, Brooklyn, NY, USA.  
 William Lytton, Dept. Physiology & Pharmacology SUNY Downstate Medical Center, Brooklyn, NY, USA; Dept. Neurology Kings County Hospital Center, Brooklyn, NY, USA.

expected to rise in the near future as people are now living longer.

The formation of the beta-amyloid plaques and neurofibrillary tangles in the brains of the patients were found to be related to dementia symptoms [1]. 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 AD patients [2–6]. Current studies attempt to develop deep brain stimulation therapy for AD targeting different hippocampal regions, including the hippocampus, fornix, and entorhinal cortex [7,8].

It has been found that variations in apolipoprotein E (APOE) genotype are associated with increased risk of developing AD [9]. There are three different genetic alleles that encode the APOE gene:  $\epsilon 2$ ,  $\epsilon 3$ , and  $\epsilon 4$ . Approximately, 15% of the population carry the APOE  $\epsilon 4$  allele, while the rest carry the APOE  $\epsilon 2$  or APOE  $\epsilon 3$  allele. Importantly, APOE  $\epsilon 4$  has been

\*Corresponding authors: V. Cutsuridis (vcutsuridis@gmail.com), A.A. Moustafa (a.moustafa@westernsydney.edu.au)

linked to AD pathology more than the other alleles. Along the same lines, carriers of the APOE  $\epsilon$ 4 genotype have been shown to have larger temporal lobe atrophy (a brain area implicated in AD) and poorer memory functions than non-carriers [10]. Similarly, it was found that APOE  $\epsilon$ 4 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 [11].

### AD etiologies

The etiology of AD is very complex and several hypotheses have been put forward to explain the pathogenesis of the disease. Below, we describe some of the most prominent hypotheses and present experimental supporting evidence for each one.

#### Amyloid hypothesis

The amyloid hypothesis proposes that extracellular beta-amyloid ( $A\beta$ ) plaques are the fundamental cause of the disease [12].  $A\beta$  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 including  $\beta$ -APP cleaving enzyme (BACE) [13–15] and  $\gamma$ -secretase [16,17]. One of these fragments (39–43 amino acids in length) form dense formations ( $A\beta$  plaques) in the extracellular space of neurons. Amyloid hypothesis is further supported by the discovery that AD could also be caused by autosomal dominant mutations in presenilin 1 (PSEN1) [18] and PSEN2 [19,20], which are both homologous proteins that can form the catalytic active site of  $\gamma$ -secretase. As mentioned previously, the APOE gene represents the major genetic risk factor for AD [21,22] with the possession of the APOE4 allele speeding considerably the age of disease.

#### Cholinergic hypothesis

The cholinergic hypothesis proposes that memory deterioration observed in AD patients is caused by a reduced synthesis of acetylcholine (ACh), choline uptake, and ACh release [23]. The correlation of deficits in brain cholinergic system and AD symptom severity is supported by various cell culture and animal model studies that show a central role of ACh regulating amyloidogenic processing of APP and hyperphosphorylation of tau.

#### Tau hypothesis

The tau hypothesis [24] proposes that hyperphosphorylated tau proteins form neurofibrillary tangles inside the nerve cell bodies, causing microtubules to disintegrate, collapsing the neuron's transport system. As  $A\beta$  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 this hypothesis, over-activity of GSK3, a proline-directed serine/threonine kinase, accounts for memory impairment, tau hyper-phosphorylation, increased  $A\beta$  production, reduction of ACh synthesis, cell apoptosis, and local plaque-associated microglial-mediated inflammatory responses, all of which are principal characteristics of AD [25].

#### Oxidative stress hypothesis

According to this hypothesis, increased oxidative stress leads to AD [26]. Increased oxidative stress in the brains of AD patients is correlated with increased levels of free radicals and metals (iron, copper, zinc, and aluminum), increased inflammatory response from activated microglia and astroglia, and increased levels of advanced glycation endproducts (AGE). The imbalance between the generation of free radicals and age-related accumulation of reactive oxygen species (ROS) results in a damage to major components of cells: nucleus, mitochondrial DNA, membranes, and cytoplasmic proteins.  $A\beta$  has been found to be sensitive to the action of free radicals, contributing to aggregation and itself producing peptides in free radical form [26]. APOE is subject to free radical attacks, and APOE peroxidation has been correlated with AD [26].

Each of these cascades produces *secondary effects* to the nerve cells which may result in cell death [27], synaptic loss [28], alterations of ionic and synaptic channels [29], impairments in synaptic transmission and plasticity [30], destabilization of neural network activity [31,32], aberrant network synchronization [32], alterations in microglia response [33], or CREB down-regulation [34] throughout the cerebral cortex and hippocampus.

### AD therapies

There are many pharmacological 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 levels in the brain, while memantine is an NMDA antagonist. Memantine was shown to increase acetylcholine (ACh) levels in the hippocampus, but it does not improve memory performance in rats [35]. 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. Howard and colleagues [36] 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 any additional 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.

Alternative forms of treatment to pharmacoresistant AD patients are electrical stimulation techniques including

transcranial electrical nerve stimulation, radioelectrical asymmetrical brain stimulation, vagal nerve stimulation and deep brain stimulation. Transcranial electrical nerve stimulation of hippocampal structures has been associated with memory improvement in patients with AD [37]. Vagal nerve stimulation improve cognitive outcome in AD patients [38]. Radioelectrical asymmetrical brain stimulation using radiofrequency bursts have shown improvements in MMSE (Mini Mental State Examination) scores in AD [39]. Clinical DBS stimulation studies in the fornix, entorhinal cortex, hippocampus and nucleus basalis of Meynert have shown that DBS has the potential to enhance memory function in human patients and animal models [7,8,40–42]. Suthana and colleagues [8] have shown that stimulation of the entorhinal region enhanced spatial memory when applied during learning. Toda and colleagues [42] have shown that electrical stimulation can enhance neurogenesis in the hippocampus. Despite these electrostimulation memory enhancement and restoration, the nature of the stimulation-induced modification of the neural circuits that result in memory improvement in AD patients is still not completely understood.

### Computational multiscale models of AD drug discovery and treatment

As we described above it is experimentally very difficult to understand how the interactions of the various molecular pathways and mechanisms lead to the pathogenesis of AD and its symptoms. Equally difficult are the various potential routes of cure by drug and electrostimulation therapies. This is mainly because experimental studies are usually carried out to isolate the effects of a single mechanism and do not investigate the interactions of many mechanisms. This leads to a set of results that are conflicting, very difficult to interpret, or not integrated in a unified framework.

Mathematical and computational models are invaluable tools in resolving such conflicts, because they provide coherent conceptual frameworks for integrating many different spatial and temporal scales and resolutions that allow for observing and experimenting with the neural system as a whole. Computational modellers then have precise control of experimental conditions needed for the replicability of experimental results. Because the process takes place in a computer, the investigator can perform multiple virtual experiments by preparing and manipulating the system in precisely repeatable ways and observe every aspect of the system without interference.

In the next section we will describe computational multiscale modelling attempts ranging from molecular and biochemical level to neural circuits and systems level of AD pathogenesis and pharmacological, immunological and neurostimulation treatments.

### Multiscale models of pharmacological and immunological therapies

#### Molecular and biochemical models

Early mathematical and computational biochemical modelling of AD focused on the amyloid  $\beta$  ( $A\beta$ ) fibrillogenesis, a key defining pathological feature of AD. As mentioned before,  $A\beta$  is a fragment of a transmembrane protein that penetrates through the neuron's membrane, the amyloid precursor protein (APP). In AD, APP is cleaved into smaller fragments by proteolytic enzymes including  $\alpha$ -,  $\beta$ - and  $\gamma$ -secretases and produce  $A\beta$  plaques in the brain. It was hypothesized that secretase inhibitors can reduce the production of  $A\beta$  in the brain and thus may slow the progression of AD. Paradoxically, it has been shown that low to moderate inhibitor concentrations cause a rise in  $A\beta$  production in different cell lines, in different animal models, and also in humans. Ortega and colleagues [43] developed a minimal mechanistic understanding of  $A\beta$  dynamics in cell lines that either exhibit the rise or not. They showed that the cross-talk between the amyloidogenic and the non amyloidogenic pathways accounts for the increase in  $A\beta$  production in response to inhibitor (C99) redirecting this way APP to be cleaved by  $\beta$ -secretase, leading to an additional increase in C99 that overcomes the loss in  $\gamma$ -secretase activity. The model had a widespread impact on the development of drugs targeting  $A\beta$  production in AD. It could be used to form decisions about *in vitro* cell lines and *in vivo* models used in drug discovery studies. It could also be used to investigate the implications of alternative therapies, such as  $\beta$ -secretase inhibition or  $\alpha$ -secretase promotion, as well as combination therapies.

Others investigated more complex factors and processes that may disrupt  $A\beta$  regulation. Anastasio [44] computationally demonstrated how incipient cerebrovascular disease (CVD), inflammation and oxidative stress (OS) can be such pathological processes. Particularly he suggested treatments directed at multiple targets can be more effective than single target therapies. In another study, ways by which estrogen therapy might be used more effectively in AD treatment, perhaps by administering estrogen in conjunction with other agents were explored [45]. Under conditions of very low estrogen and incipient CVD, the level of  $A\beta$  could be reduced, possibly to normative levels, with a combination of a non-steroidal 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  $A\beta$  directly (e.g., by enhancing neprilysin (NEP) expression) and indirectly by reducing inflammation and OS (e.g., by enhancing superoxide dismutase expression), thereby disrupting pathological processes that contribute to  $A\beta$  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.

Another defining characteristic of AD is the dysregulation of synaptic plasticity by A $\beta$ . In the normal synapse where A $\beta$  is absent, PKA is responsible for keeping striatal-enriched protein tyrosine phosphatase (STEP) (and other key LTD drivers) inactive when Ca<sup>2+</sup> is high enough to elicit LTP. On the other hand, in the diseased synapse where A $\beta$  is present, 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. PKA is thus the mediator that keeps the diseased synapse at least at baseline at high levels of presynaptic activity. Anastasio [46] provided an initial modeling framework for understanding how various drugs and drug combinations might operate in the diseased synapse. It suggested that normalization of nicotinic acetylcholine receptors (nAChR) function may be the most effective way to counteract the adverse effects of A $\beta$  on synaptic plasticity, lending some modelling support to the suggestion that disordered nAChR function is the main route by which A $\beta$  dysregulates synaptic plasticity [47].

Immunotherapy against A $\beta$  has recently been shown to be more effective when it is applied to in the early stages of the disease. The effects of passive and active immunization on soluble A $\beta$ , plaques, phosphorylated tau and tangles showed that A $\beta$  clearance proceeds into steps with the administration of antibodies and microglia. Proctor and colleagues [48] modelled the effects of immunotherapy by adding a species named 'anti A $\beta$ ' 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 A $\beta$  dimers from two monomers, but this reaction was reversible. Under normal conditions, model A $\beta$  levels started at very low values and A $\beta$  was continually produced and degraded. The model predicted that immunization leads to clearance of plaques, but has small effect on soluble A $\beta$ , tau and tangles.

Treatment combinations of 10 FDA approved drugs (auranofin, bortezomib, dasatinib, glimepiride, ibuprofen, naloxone, nicotine, rosiglitazone, ruxolitinib, and thalidomide) were investigated in reducing microglial inflammation in AD [49]. Out of the 1024 possible drug combinations, simulations identified only 7 combinations of the auranofin, glimepiride, ibuprofen, rosiglitazone, nicotine and naloxone drugs were able to reduce microglial inflammation in AD. Analysis showed that out of the 7 most efficacious combinations, the 'glimepiride/ibuprofen' and the 'glimepiride/ibuprofen/nicotine' administrations stand out as superior both in strength and reliability to completely reverse the neurotoxic effects of AD inflammation.

### Neural circuits and systems models

Essential steps in drug discovery and therapy of neurodegenerative disorders such as AD are the development of computational models that bridge the gap between behavior, cellular physiology and molecular biology in the study of human memory. The effects of scopolamine, a drug that blocks the cellular effects of acetylcholine, were investigated in the encoding and retrieval of memories in a cortico-hippocampal model (EC-Dentate gyrus-CA3-CA1) [50]. 'Memory' was represented as a pattern of neural activation in each module, with information flowing from EC to DG to CA3 to CA1. Simulations showed that scopolamine blockade of ACh impaired the encoding of new input patterns, but had no effect in the free recall of input patterns learned before the blockade. This was due to scopolamine blocking the strengthening of recurrent connections in region CA3 to form attractor states for new items (encoding impaired), while allowing recurrent excitation to drive the network into previously stored attractor states (retrieval spared). Despite its successes, the model's network dynamics were based on abstract formulations of cells and their interactions. Furthermore, it failed to consider the cellular consequences of ACh in the intrinsic cell firing.

The differential effect of memantine, an NMDA inhibitor, in early and late AD pathology was examined by a biophysically realistic model of cortical circuitry simulating working memory as a measure for cognitive function [51]. The pathology of AD was implemented as synaptic and neuronal loss and a decrease in cholinergic tone [51]. The model was subsequently calibrated using preclinical data on receptor pharmacology of catecholamine and cholinergic neurotransmitters [51]. Simulations showed that inhibition of the NMDA receptor NR2C/NR2D subunits located on inhibitory interneurons compensated for the greater excitatory decline observed with AD pathology [51]. Like any other model, the Roberts' model was also bounded by limitations including the relatively low number of neurons used and the rather simple morphological representation of excitatory and inhibitory cells in the network.

Pharmacological manipulations of experience-dependent activation of specific transcription factors (e.g., cAMP Response Element Binding protein (CREB)) and their resulting gene alterations have suggested improvements of memory impairments due to AD [52,53]. Experimental work in rodent hippocampus has shown that CREB activity increases in regions CA1 or dentate gyrus memory formation, storage and recall, enhancements and restorations [54,55]. Inspired by the modeling work of Cutsuridis and colleagues [56], Bianchi *et al.* [57] investigated the conditions in the CA1 microcircuit under which the properties of 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.

#### *Models of neurostimulation therapy*

As AD progresses, cells die and synapses lose their drive, causing the remaining cells in the network to suffer an initial decrease in activity due to homeostatic synaptic scaling. 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 [58] 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.

#### **Conclusions and future work**

We have provided here the first extensive review of computational multiscale attempts of AD pathogenesis and treatment ranging from molecular and biochemical to neural circuits and systems level. The models embodied a hypothesis and/or a theory of mechanisms of AD. Each model's main computational elements are highlighted and a critical analysis of each model's strengths and weaknesses is also provided. Existing models assume that AD symptoms stem from abnormalities to molecular pathways, cell structure, synaptic connection, neurochemicals, as well as other neural systems.

We suggest below general research directions that were omitted from the current models in order to improve future treatments of the disease. Future models should include sufficient details on the structural and functional subunits of the neurons, so they are able to simulate molecular effects

of pharmacological treatments (e.g., effects of drugs on receptors and dendrites).

Furthermore, future models should 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. They should focus on simulating memory decline as well as simulate other AD neural and behavioral abnormalities such as executive dysfunction or apraxia.

Moreover, future models should simulate the effects of medications (donepezil, galantamine, rivastigmine, and memantine) on neural and behavioral processes. They should explain how increasing Ach levels and NMDA antagonists does relate to memory improvement as well as how they affect other symptoms of AD. 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  $\epsilon$ 4 carriers or not, computational modeling studies should address these subgroups of AD patients.

Finally, as many experimental studies explore the benefits of deep brain stimulation therapy for AD [7,8], it is expected that computational models will be needed to explore how it works and best ways to find best deep brain stimulation parameter values for frequency, pulse width, and voltage (as well as locations within the hippocampal region) to treat AD. Such work can greatly benefit from existing models of deep brain stimulation applied to Parkinson's disease [59,60], to explore how it may reduce AD symptoms.

#### **Conflict of interest**

The authors declare that they have no competing financial interests.

#### **References**

- [1] Wilcock GK, Esiri MM. Plaques, tangles and dementia. A quantitative study. *J Neurol Sci* 1982;56(2-3):343-56.
- [2] Apostolova LG, Lu PH, Rogers S, Dutton RA, Hayashi KM, Toga AW, et al. 3D mapping of mini-mental state examination performance in clinical and preclinical Alzheimer disease? *Alzheimer Dis Assoc Disord* 2006;20(4):224-31.
- [3] de Leon MJ, George AE, Stylopoulos LA, Smith G, Miller DC. Early marker for Alzheimer's disease: the atrophic hippocampus? *Lancet* 1989;2(8664):672-3.
- [4] Jack Jr CR, Petersen RC, Xu Y, O'Brien PC, Smith GE, Ivnik RJ, et al. Rates of hippocampal atrophy correlate with change in clinical status in aging and AD. *Neurology* 2000;55(4):484-9.
- [5] Allen G, Barnard H, McColl R, Hester AL, Fields JA, Weiner MF, et al. Reduced hippocampal functional connectivity in Alzheimer disease. *Arch Neurol* 2007;64(10):1482-7.
- [6] Schuff N, Neylan TC, Fox-Bosetti S, Lenoci M, Samuelson KW, Studholme C, et al. Abnormal N-acetylaspartate in hippocampus and anterior cingulate in posttraumatic stress disorder. *Psychiatry Res* 2008;162(2):147-57.
- [7] Heschem S, Lim LW, Jahanshahi A, Blokland A, Temel Y. Deep brain stimulation in dementia-related disorders. *Neurosci Biobehav Rev* 2013;37(10 Pt 2):2666-75.

- [8] Suthana N, Haneef Z, Stern J, Mukamel R, Behnke E, Knowlton B, et al. Memory enhancement and deep-brain stimulation of the entorhinal area. *N Engl J Med* 2012;366(6):502–10.
- [9] Jack Jr CR, Petersen RC, Xu YC, O'Brien PC, Waring SC, Tangalos EG, et al. Hippocampal atrophy and apolipoprotein E genotype are independently associated with Alzheimer's disease. *Ann Neurol* 1998;43(3):303–10.
- [10] Dhikav V, Anand K. Potential predictors of hippocampal atrophy in Alzheimer's disease? *Drugs Aging* 2011;28(1):1–11.
- [11] Kihara T, Shimohama S. Alzheimer's disease and acetylcholine receptors? *Acta Neurobiol Exp (Wars)* 2004;64(1):99–105.
- [12] Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science* 2002;297:353–6.
- [13] Sinha S, Anderson JP, Barbour R, Basi GS, Caccavello R, Davis D, et al. Purification and cloning of amyloid precursor protein  $\beta$ -secretase from human brain. *Nature* 1999;402:537–40.
- [14] Vassar R, Bennett BD, Babu-Khan S, Kahn S, Mendiaz EA, Denis P, et al.  $\beta$ -secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE. *Science* 1999;286:735–41.
- [15] Yan R, Bienkowski MJ, Shuck ME, Miao H, Tory MC, Pauley AM, et al. Membrane-anchored aspartyl protease with Alzheimer's disease  $\beta$ -secretase activity. *Nature* 1999;402:533–7.
- [16] De Strooper B, Saftig P, Craessaerts K, Vanderstichele H, Guhde G, Annaert W, et al. Deficiency of presenilin-1 inhibits the normal cleavage of amyloid precursor protein. *Nature* 1998;391:387–90.
- [17] Wolfe MS, Xia W, Ostaszewski BL, Diehl TS, Kimberly WT, Selkoe DJ. Two transmembrane aspartates in presenilin-1 required for presenilin endoproteolysis and  $\gamma$ -secretase activity. *Nature* 1999;398:513–7.
- [18] Sherrington R, Rogaev EI, Liang Y, Rogaeva EA, Levesque G, Ikeda M, et al. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. *Nature* 1995;375:754–60.
- [19] Levy-Lahad E, Wasco W, Poorkaj P, Romano DM, Oshima J, Pettingell WH, et al. Candidate gene for the chromosome 1 familial Alzheimer's disease locus. *Science* 1995;269:973–7.
- [20] Rogaev EI, Sherrington R, Rogaeva EA, Levesque G, Ikeda M, Liang Y, et al. Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene. *Nature* 1995;376:775–8.
- [21] Corder EH, Saunders AM, Risch NJ, Strittmatter WJ, Schmechel DE, Gaskell Jr PC, et al. Gene dosage of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993;261:921–3.
- [22] Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, et al. Apolipoprotein E: high avidity binding to  $\beta$ -amyloid and increased frequency of type 4 allele in late onset familial Alzheimer disease. *Proc Natl Acad Sci USA* 1993;90:1977–81.
- [23] Francis PT, Palmer AM, Snape M, Wilcock GK. The cholinergic hypothesis of Alzheimer's disease: a review of progress. *J Neurol Neurosurg Psychiatry* 1999;66:137–47.
- [24] Boutajangout A, Wisniewski T. Tau-based therapeutic approaches for Alzheimer's disease – a mini-review. *Gerontology* 2014;60(5):381–5.
- [25] Hooper C, Killick R, Lovestone S. The GSK3 hypothesis of Alzheimer's disease. *J Neurochem* 2008;104:1433–9.
- [26] Christen Y. Oxidative stress and Alzheimer's disease. *Am J Clin Nutr* 2000;71(Suppl):621S–9S.
- [27] Kosik KS. Alzheimer's plaques and tangles: advances in both fronts. *TINS* 1991;14:218–9.
- [28] Terry RD. Cell death or synaptic loss in Alzheimer disease. *J Neuropathol Exp Neurol* 2000;59:1118–9.
- [29] Texidó L, Martín-Satué M, Alberdi E, Solsona C, Matute C. Amyloid  $\beta$  peptide oligomers directly activate NMDA receptors. *Cell Calcium* 2011;49:184–90.
- [30] Chapman PF, White GL, Jones MW, Cooper-Blacketer D, Marshall VJ, Irizarry M, et al. Impaired synaptic plasticity and learning in aged amyloid precursor protein transgenic mice. *Nat Neurosci* 1999;2:271–6.
- [31] Palop JJ, Chin J, Robertson ED, Wang J, Thwin MT, Bien-Ly N, et al. Aberrant excitatory neuronal activity and compensatory remodeling of inhibitory hippocampal circuits in mouse models of Alzheimer's disease. *Neuron* 2007;55:697–711.
- [32] Palop JJ, Mucke L. Amyloid- $\beta$  induced neuronal dysfunction in Alzheimer's disease: from synapses toward neural networks. *Nat Neurosci* 2010;13(7):812–8.
- [33] Brown GC, Neher JJ. Inflammatory neurodegeneration and mechanisms of microglial killing of neurons. *Mol Neurobiol* 2010;41:242–7.
- [34] Barco A, Marie H. Genetic approaches to investigate the role of CREB in neuronal plasticity and memory. *Mol Neurobiol* 2011;44:330–49.
- [35] Ihalainen J, Sarajarvi T, Rasmusson D, Kemppainen S, Keski-Rahkonen P, Lehtonen M, et al. Effects of memantine and donepezil on cortical and hippocampal acetylcholine levels and object recognition memory in rats? *Neuropharmacology* 2011;61(5–6):891–9.
- [36] Howard R, McShane R, Lindesay J, Ritchie C, Baldwin A, Barber R, et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. *N Engl J Med* 2012;366(10):893–903.
- [37] Guo Y, Shi X, Uchiyama H, Hasegawa A, Nakagawa Y, Tanaka M, et al. A study on the rehabilitation of cognitive function and short-term memory in patients with Alzheimer's disease using transcutaneous electrical nerve stimulation. *Front Med Biol Eng* 2002;11:237–47.
- [38] Sjögren MJ, Hellström PT, Jonsson MA, Runnerstam M, Silander HC, Ben-Menachem E. Cognition-enhancing effect of vagus nerve stimulation in patients with Alzheimer's disease: a pilot study. *J Clin Psychiatry* 2002;63:972–80.
- [39] Mannu P, Rinaldi S, Fontani V, Castagna A. Radio electric asymmetric brain stimulation in the treatment of behavioral and psychiatric symptoms in Alzheimer disease. *Clin Interv Aging* 2011;6:207–11.
- [40] Lacruz ME, Valentín A, Seoane JJ, Morris RG, Selway RP, Alarcón G. Single pulse electrical stimulation of the hippocampus is sufficient to impair human episodic memory. *Neuroscience* 2010;170(2):623–32. <http://dx.doi.org/10.1016/j.neuroscience.2010.06.042>.
- [41] Laxton AW, Lozano AM. Deep brain stimulation for the treatment of Alzheimer's disease and dementias. *World Neurosurg* 2013;80(3/4):S28.E1–8.
- [42] Toda H, Hamani C, Fawcett AP, Hutchison WD, Lozano AM. The regulation of adult rodent hippocampal neurogenesis by deep brain stimulation. *J Neurosurg* 2008;108(1):132–8. <http://dx.doi.org/10.3171/JNS/2008/108/01/0132>.
- [43] Ortega F, Stott J, Visser S, Bendtsen C. Interplay between  $\alpha$ ,  $\beta$ , and  $\gamma$ -secretases determines biphasic amyloid- $\beta$  level in the presence of  $\gamma$ -secretases inhibitor. *J Biol Chem* 2013;288:785–92.
- [44] Anastasio TJ. Data driven modelling of Alzheimer's disease pathogenesis. *J Theor Biol* 2011;290:60–72.
- [45] Anastasio TJ. Exploring the contribution of estrogen to amyloid-beta regulation: a novel multifactorial computational modelling approach. *Front Pharmacol* 2013;4:16.
- [46] Anastasio TJ. Computational identification of potential multi-target treatments for ameliorating the adverse effects of amyloid- $\beta$  on synaptic plasticity. *Front Pharmacol* 2014;5:85.
- [47] Snyder EM, Nong Y, Almeida CG, Paul S, Moran T, Choi EY, et al. Regulation of NMDA receptor trafficking by amyloid-beta. *Nat Neurosci* 2005;8:1051–8.
- [48] Proctor CJ, Boche D, Gray DA, Nicoll JAR. Investigating interventions in Alzheimer's disease with computer simulation models. *PLoS ONE* 2013;8(9):e73631. <http://dx.doi.org/10.1371/journal.pone.0073631>.
- [49] Anastasio TJ. Computational identification of potential multi-drug combinations for reduction of microglial inflammation in Alzheimer's disease. *Front Pharmacol* 2015;6:116.
- [50] Hasselmo ME, Wyble BP. Free recall and recognition in a network model of the hippocampus: simulating effects of scopolamine on human memory function. *Behav Brain Res* 1997;89(1–2):1–34.
- [51] Roberts PD, Spiros A, Geerts H. Simulations of symptomatic treatments for Alzheimer's disease: computational analysis of pathology and mechanisms of drug action. *Alzheimer's Res Ther* 2012;4:50.
- [52] Tully T, Bourchouladze R, Scott R, Tallman J. Targeting the CREB pathway for memory enhancers. *Nat Rev Drug Discov* 2003;2:267–77.
- [53] Bitner R. Cyclic AMP response element-binding protein (CREB) phosphorylation: a mechanistic marker in the development of memory enhancing Alzheimer's disease therapeutics. *Biochem Pharmacol* 2012;83:705–14.

- [54] Restivo L, Tafi E, Ammassari-Teule M, Marie H. Viral-mediated expression of a constitutively active form of CREB in hippocampal neurons increases memory. *Hippocampus* 2008;19:228–34.
- [55] Sekeres MJ, Neve RL, Frankland PW, Josselyn SA. Dorsal hippocampal CREB is both necessary and sufficient for spatial memory. *Learn Mem* 2010;17:280–3.
- [56] Cutsuridis V, Graham BP, Cobb S. Encoding and retrieval in the hippocampal CA1 microcircuit model. *Hippocampus* 2010;20(3):423–46.
- [57] Bianchi D, De Michele P, Marchetti C, Tirozzi B, Cuomo S, Marie H, et al. Effects of increasing CREB-dependent transcription on the storage and recall processes in a hippocampal CA1 microcircuit. *Hippocampus* 2014;24(2):165–77.
- [58] Rowan MS, Neymotin S, Lytton WW. Electrostimulation to reduce synaptic scaling driven progression of Alzheimer's disease. *Front Comput Neurosci* 2014;8:39.
- [59] Frank MJ, Samanta J, Moustafa AA, Sherman SJ. Hold your horses: impulsivity, deep brain stimulation, and medication in parkinsonism. *Science (New York NY)* 2007;318(5854):1309–12.
- [60] McIntyre CC, Foutz TJ. Computational modeling of deep brain stimulation. *Handb Clin Neurol* 2013;116:55–61. <http://dx.doi.org/10.1016/B978-0-444-53497-2.00005-X>.