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Computational Models of Pharmacological and Immunological Treatment in Alzheimer's Disease

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What is Alzheimer's Disease?

Alzheimer's disease (AD) is a neurological disorder, mostly associated with cognitive decline in older age, although it can also happen in younger age (under 55 years old). The prevalence of AD increases as we get older, with at least a quarter of the population over 85 being diagnosed with the disease. The exact causes of AD and how it progresses over age are not known, but research has identified many factors, including behavioral, metabolic, genetic, and immunological ones. Beside memory decline, patients with AD also show language deficits, including difficulty remembering meaning of words and naming objects (Tippett & Farah, 1994) and word finding and comprehension (Ferris & Farlow, 2013). Patients with AD also exhibit impairment in executive processes in comparison to age-matched healthy controls (Baudic, Barba, Thibaudet, Smagghe, Remy, & Traykov, 2006; Perry & Hodges, 1999), such as driving. So in short, AD is characterized by a complex cluster of symptoms spanning memory, attentional, linguistic, and executive processes.

Like behavioral deficits, AD is associated with multiple neural abnormalities. One

active research area is to understand which neural abnormalities underlie the different behavioral deficits in AD. Several studies report changes to hippocampal structure and function in patients with AD (Allen et al., 2007; Apostolova et al., 2006; de Leon, George, Stylopoulos, Smith, & Miller, 1989; Jack et al., 2000; Schuff et al., 2009; Wang et al., 2006). A smaller size of the hippocampus in AD patients has been found to be related to genetic risk factor: $\epsilon 4$ allele form of the *APOE* gene (Dhikav & Anand, 2011; Jack et al., 1998). It is important to note that only a small percentage of individuals who carry the $\epsilon 4$ allele form of the *APOE* gene develop AD, and there are patients with AD who do not carry *APOE* $\epsilon 4$ (Corder, 1993). However, a large percentage of AD patients carry *APOE* $\epsilon 4$ (for a review, see Tang, 1998).

Further, many studies have linked reduction of acetylcholine (ACh) to AD symptoms, including memory decline (Kihara & Shimohama, 2004; McGleenon, Dynan, & Passmore, 1999). Although the hippocampus and cortex are main targets for ACh projections, few studies link AD symptoms to reduction of cortical ACh (Coyle, Price, & DeLong, 1983; Nordberg & Winblad, 1986; Whitehouse, 1986, 1988; Wilcock & Esiri,

1982). The role played by hippocampal ACh in AD symptoms is inconclusive. Another neural characteristic of AD is the formation of the beta-amyloid plaques (protein that penetrates through the neuron's membrane) and neurofibrillary tangles (causing the formation of hyperphosphorylated tau proteins) in the hippocampus and cerebral cortex (Wilcock et al., 2009). It is however not known how exactly they relate to different symptoms in AD. Besides ACh, abnormalities to glutamate (including excitotoxicity) were also reported in AD, although it is not clear how they relate to AD symptoms (Butterfield & Pocernich, 2003; Danysz & Parsons, 2009).

AD Stages

AD is a progressive disorder, as severity of symptoms increase over time. The severity of AD symptoms is measured using various clinical assessments including the Global Deterioration Scale (GDS) (Reisberg, Ferris, de Leon, & Crook, 1982; Reisberg, Ferris, Kluger, Franssen, Wegiel, & de Leon, 2008) and Clinical Dementia Rating (CDR) (Morris, 1993). These assessments classify mild, moderate, and severe stages of AD, as well as prodromal stages of the disease, known as mild cognitive impairment (MCI). One main open research questions is how the various behavioral impairments in AD (memory decline, language deficits, and executive dysfunction, among others) manifests across the different AD stages. For example, one study found that memory decline and executive dysfunction occur in the early stages of the disease, and precede the occurrence of language deficits and praxis (inability to perform some actions) (Baudic, 2006). Further, although there are a few studies that have investigated neural damage across different stages of AD, one study suggested that the formation of beta amyloid precedes neurofibrillary tangles (Oddo, Caccamo, Kitazawa, Tseng, & LaFerla, 2003).

AD Treatment and Mechanism of Action

Most of the clinically approved medications for AD are cholinesterase inhibitors, including galantamine, rivastigmine, and donepezil. These pharmacological agents, however, have different effects on AD symptoms, suggesting that their mechanisms of action include other effects on the brain, in addition to increasing ACh levels.

There are conflicting results on the effects of ACh inhibitors and nicotine ACh agonists on tau phosphorylation. For example, Bitner and colleagues (2009) have shown that nicotine ACh agonists decrease tau phosphorylation in the brain. Interestingly, a study has shown that cholinesterase inhibitors further increase tau phosphorylation in AD (Chalmers et al., 2009), and thus cause side effects.

To our knowledge, memantine is the only approved NMDA antagonist for AD. It is known how NMDA dysfunction relates to AD symptoms, and how. Another potential function of memantine is it increases ACh levels in the hippocampus (Ihalainen et al., 2011). Dominguez, Chin, Chen, and Wu (2011) argue that NMDA antagonists (e.g., memantine) might down-regulate tau phosphorylation.

Previously discussed treatments are symptomatic. There has been an interest in developing disease-modifying drugs (see the discussion in Galimberti & Scarpini, 2011). Beside pharmacological treatments, there have been studies investigating immunological treatments in AD, including vaccinations. For example, bapineuzumab has been administered either subcutaneously (s.c.) or intravenously (i.v.) to AD patients as a potential immunological agent to treat AD (Menendez-Gonzalez, Perez-Pinera, Martinez-Rivera, Muniz, & Vega, 2011; Oddo, Billings, Kesslak, Cribbs, & LaFerla, 2004). According to Kerchner and Boxer (2010), subcutaneous bapineuzumab is still being used in clinical trials by Pfizer, and is likely to become the first vaccine to pass phase III of clinical trials for the treatment of AD. Up until recently, beside bapineuzumab, some other vaccines,

including solanezumab and Gammagard were also in phase III clinical trials, as potential treatments for AD. However, many of the existing immunological treatments target beta amyloid formation. Many beta-amyloid vaccines have been discontinued because they caused major side effects in clinical trials (e.g., meningoencephalitis, see, for example, Menendez-Gonzalez et al., 2011; Shah & Federoff, 2011). However, as of today, there are still ongoing clinical trials (phase III) on relatively newer vaccines (bapineuzumab and solanezumab), but results are not known yet. Importantly, most of the vaccines are designed to target beta-amyloid plaques. Some have been shown to be effective in reducing beta-amyloid plaques in a mouse model of AD (Wiessner et al., 2011). It was also found that beta-amyloid vaccines reduce tau phosphorylation (Oddo et al., 2003, 2004; Wilcock et al., 2009).

Computational Models of AD Therapy and Drug Discovery

Current experimental approaches to AD drug development and testing include *in vitro* and *in vivo* preparations, transgenic and other animal models, as well as human tissue preparations. All of these experimental models, although successful in their own regards, have limitations. One such limitation is their removal from the reality of the whole, integrated physiological system, thus making it impossible to study the full spectrum of behavioral, neurobiological, and clinical aspects of the disease.

Attractive alternatives to the animal and human experimental modeling approaches are the “multi-scale,” “multi-level” computational modeling approaches to AD drug discovery and therapy. Computational models provide coherent conceptual frameworks for integrating many different formalisms, spatial and temporal scales, and resolutions that allow for observing and experimenting with the neural system as a whole (as in *in vivo*

preparations) as well as enabling the precise control of experimental conditions needed for the replicability of experimental results (as in *in vitro* preparations). 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.

Below we describe computational models ranging from the molecular and biochemical level to neural network level of AD treatment and drug discovery.

Molecular and Biochemical Models

Early mathematical and computational biochemical modeling of AD focused on the amyloid β ($A\beta$) fibrillogenesis, a key defining pathological feature of AD. The pathway, kinetics, and factors of $A\beta$ fibrillogenesis have been the subject of intense experimental (Murphy & Pallitto, 2000) and theoretical (Harper, Wong, Lieber, & Lansbury, 1999; Inouye & Kirschner, 2000; Jarrett, Berger, & Lansbury, 1993; Kim, Muresan, Lee, & Murphy, 2004; Naiki & Nakakuki, 1996; Tomski & Murphy, 1992; Walsh, Lomakin, Benedek, Condron, & Teplow, 1997; Lomakin, Chung, Benedek, Kirschner, & Teplow, 1996; Lomakin, Teplow, Kirschner, & Benedek, 1997) investigation. Other modeling attempts have focused on understanding the neural mechanism of plaque formation (Urbanc et al., 1999), the kinetics of amyloid precursor protein (APP) processing (Ortega, Stott, Visser, & Bendtsen, 2013; Schmidt et al., 2011), and the interactions of intracellular Ca^{2+} and $A\beta$ (de Caluwe and Dupont, 2013) in the AD brain. However, none of these models attempted to link AD pathogenesis to drug therapy.

As the knowledge of the AD pathology has become more complex, biochemical and molecular models of AD development have been developed. A comprehensive model of AD development based on the amyloid hypothesis was advanced by Anastasio (2011). Most $A\beta$ regulation pathways were modeled by nonlinearly coupled equations

and rules written in the Maude environment, which were then executed and analyzed using innate to Maude Petri net tools. Petri nets are directed bipartite graphs consisting of *places* (i.e., conditions, signified by circles), *transitions* (i.e., events that may occur, signified by bars), and *arcs* (signified by arrows). Arcs run from a place to a transition or vice versa, never between places or between transitions. The places from which an arc runs to a transition are called the *input places* of the transition; the places to which arcs run from a transition are called the *output places* of the transition. 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 A β regulation can be disrupted through the interaction of pathological processes such as cerebrovascular disease, inflammation, and oxidative stress. Particularly it showed how incipient cerebrovascular disease can trigger AD. It also showed how treatments directed at multiple targets can be more effective than single target therapies.

Anastasio (2013) extended the previous model to account for the many factors including estrogen that participate in the regulation of A β , 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. Under simulated conditions of very low estrogen and incipient cerebrovascular disease and a combination of a nonsteroidal anti-inflammatory drug (NSAID) that promotes peroxisome proliferator-activated receptor expression, a compound that blocks hypoxia inducible factor and estrogen itself, the level of A β was reduced to normative levels. The model inferred that while estrogen provides the main benefit, that is, reducing A β directly (e.g., by enhancing neprilysin expression) and indirectly by reducing inflammation and oxidative stress (e.g., by enhancing superoxide dismutase expression), thereby disrupting pathological processes that contribute to A β accumulation,

an NSAID and a hypoxia inducible factor blocker can each provide a small additional benefit, and these two benefits are additive in combination.

Using a similar modeling approach, Anastasio (2014) attempted to investigate another defining feature of AD, the dysregulation of synaptic plasticity by A β . In the simulated normal synapse where A β is absent, protein kinase-A is responsible for keeping striatal-enriched protein tyrosine phosphatase (and other key LTD drivers) inactive when Ca²⁺ is high enough to elicit LTP. In the simulated diseased synapse where A β is present, the action of protein kinase-A is instrumental in preventing LTD from occurring at all nonzero levels of presynaptic activity including that which would evoke LTP in the normal synapse. The model provides an initial framework for understanding how various drugs and drug combinations might operate in the diseased synapse. The model suggests that the normalization of nicotinic acetylcholine receptor (nAChR) function may be the most effective way to counteract the adverse effects of A β on synaptic plasticity, lending some modeling support to the suggestion that disordered nAChR function is the main route by which A β dysregulates synaptic plasticity (Wang et al., 2006).

Recently, Anastasio (2015) computationally investigated which combinations of 10 Food and Drug Administration (FDA)-approved drugs (auranofin, bortezomib, dasatinib, glimepiride, ibuprofen, naloxone, nicotine, rosiglitazone, ruxolitinib, and thalidomide) are potentially more effective than single drugs in reducing microglial inflammation in AD. Out of the 1,024 possible drug combinations, simulations identified that only seven combinations of the auranofin, glimepiride, ibuprofen, rosiglitazone, nicotine, and naloxone drugs were able to reduce microglial inflammation in AD. Further analysis showed that out of the seven most efficacious combinations, the “glimepiride/ibuprofen” and the “glimepiride/ibuprofen/nicotine” administrations stood out as superior both in strength and reliability to completely reverse the neurotoxic effects of AD inflammation.

In line with the Anastasio (2014) study, Craft, Wein, and Selkoe (2002) used a mathematical model to assess the effect of AD treatment on A β levels in various compartments of the body: the brain, cerebrospinal fluid, and plasma. 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 A β levels were achieved throughout the body. When the polymerization ratio was greater than 1, then the A β accumulation grew indefinitely, whereas the A β levels in the cerebrospinal fluid and plasma remained in a steady state.

Proctor, Boche, Gray, & Nicoll, 2013) introduced a multi-modular model that included regulatory components for DNA damage, p53 regulation, GSK3 activity, A β turnover, tau dynamics, and the aggregation of A β and tau to investigate the effects of passive and active immunization against A β and this intervention's effects on soluble A β , plaques, phosphorylated tau, and tangles. A β clearance proceeded into steps where the administration of antibodies were modeled by adding a species named "anti A β " to represent the addition of antibodies (i.e., passive immunization) and another species named "Glia" to represent microglia. The additions of antibodies and microglia were done at pre-determined time points during the simulation. The aggregation process started with the formation of A β dimers from two monomers, but this reaction was reversible. Under normal conditions, the simulated A β levels started at very low values and A β was continually produced and degraded. The model predicted that immunization would lead to a clearance of plaques, but would have little effect on soluble A β , tau, and tangles. The model suggested that immunotherapy against A β is more effective when it is applied in the early stages of the disease.

Li, Zhu, and Chen (2009) developed a computational framework to build disease-specific drug-protein connectivity maps by

integrating gene/protein and drug connectivity information based on protein interaction networks and PubMed abstract mining techniques. The resulted connectivity maps and further statistical analysis uncovered hidden relationships between drugs such as diltiazem and quinidine, and AD, and led to recommendations for further investigations between these drugs and AD treatment.

Neural Network Models

Hasselmo and Wyble (1997) introduced a neural network model of the cortico-hippocampal formation interactions to investigate the effects of scopolamine, a drug that blocks the cellular effects of acetylcholine, in the encoding and retrieval of memories in a paired associate task. Their model consists of four modules, the entorhinal cortex (EC), the dentate gyrus (DG), region CA3, and region CA1. A "memory" is represented as a pattern of neural activation in each module, with information flowing from EC to DG to CA3 to CA1. In the model, CA3 neurons representing items (individual words) had weaker recurrent connections than neurons representing contextual information. Computer simulations showed that a scopolamine blockade of ACh impaired the encoding of new input patterns (as measured by delayed free recall), but did not have any effect on the delayed free recall of input patterns learned before the blockade. This meant that the impairment was selective to free recall, but not to recognition of items already encoded. 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). The Hasselmo and Wyble (1997) model was the first attempt at the neural network level to simulate the effects of drug administration in a human memory experiment by quantitatively investigating its physiological effects at the cellular level. This modeling work is an essential step in the drug discovery and therapy of neurodegenerative

disorders such as AD, because it allows the bridging of the gap between behavior and cellular physiology and molecular biology to constrain models of human memory function.

Meschnik & Finkel (1998) proposed a model of hippocampal CA3 network dynamics in order to study the modulation and control of storage and recall dynamics in AD by subcortical cholinergic and GABAergic input to the hippocampus. This model is inspired by the Buzsáki “two-stage” memory model (Buzsáki, 1989; Buzsáki & 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, 2005; Lisman & Idiart, 1995). 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 comprising 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).

Roberts, Spiros, & Geerts (2012) introduced a biophysically realistic computational model of cortical circuitry to simulate working memory as a measure for cognitive function. The model was initially calibrated using preclinical data on receptor pharmacology of catecholamine and cholinergic neurotransmitters. The pathology of AD was subsequently implemented as synaptic and neuronal loss and a decrease in cholinergic tone. The model demonstrated the differential effect of memantine, an NMDA inhibitor, in early and late AD pathology, and showed

that inhibition of the NMDA receptor NR2C/NR2D subunits located on inhibitory interneurons compensates for the greater excitatory decline observed with pathology.

Bianchi and colleagues (2014), using a well-established model of memory encoding and retrieval in the hippocampus (Cutsuridis, Graham, & Cobb, 2010), investigated the conditions under which the properties of hippocampal CA1 pyramidal neurons altered by increasing cAMP Response Element-Binding (CREB) activity can contribute to memory storage and recall improvements. The effects of CREB were modeled as decreases in the peak conductances of medium after-hyperpolarizing potential (mAHP) and slow after-hyperpolarizing potential (AHP) 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.

Future Directions and Conclusions

There are some limitations and potential extensions with the current models of treatment in AD. Most of these models did not explain how various treatments target key neural biomarkers of AD, such as reduced hippocampal size, plaques, tangles, and reduction in ACh levels. These models also did not show how treatments impact the various behavioral deficits in AD, such as cognitive decline and executive dysfunction. Specifically, future models should provide a theory of how increasing ACh levels using cholinesterase inhibitors and NMDA antagonists impact neural and behavioral processes in AD. Further, although there have been models simulating ACh dysfunction in AD (Hasselmo

& Wyble, 1997), to our knowledge, no model has focused on simulating the different roles of ACh in hippocampus and cortex, and how cholinesterase inhibitors impact both. It is also possible to extend the models by Anastasio (summarized above) to further simulate links between beta amyloids and ACh, as reported in experimental studies (Pedersen, Kloczewiak, & Blusztajn, 1996). Such models can help bridge the gap between the use of cholinesterase inhibitors

and clearance of beta-amyloid proteins, as reported in experimental studies (Castro & Martinez, 2006) as well as targeting tau phosphorylation (Eskander, Nagykerly, Leung, Khelghati, & Geula, 2005). The same can also be done as models should also investigate how memantine (NMDA antagonists) can reduce toxicity of beta amyloids as reported in experimental studies (Li et al., 2013; Song, Rauw, Baker, & Kar, 2008).

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