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FUTURE PERSPECTIVES ON ALZHEIMER'S DISEASE COMPUTATIONAL MODELING – A REVIEW

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Abstract
Alzheimer's disease (AD), which is one of the most common age – associated neurodegenerative disorders, has been proven to be of a multifactorial and polygenic disease. No single gene mutations alone or environmental factors can be associated to AD development, except for the close and complex interactions in human genome and metabolome. This is the reason why AD exhibits many phenotypic features correlated to common and specific neuropsychiatric symptoms. Such complex diseases can only be understood by correlating a large amount of data and knowledge which can be possible only in a high performance algorithmic system available nowadays through computational modeling. There are many computational models to correlate different features of AD and to highlight new features of AD. Based on a rigorous scientific articles database analysis, this review aims to bring together some of the most representative computational AD modeling studies and to propose new ways of using computational algorithms in AD research.

Abbreviations: AD - Alzheimer's disease, ADMET - Absorption, Digestion, Metabolism, Excretion and Toxicity, APOE – apolipoprotein E, CN - Computational Neuroscience, CoMFA - comparative molecular field analysis, CoMSIA - comparative molecular similarity indices analysis, ECSIT - evolutionarily conserved signaling intermediate in Toll pathway, QSAR - quantitative structure-activity relationship, PDCD4 - Programmed cell death protein 4, P2X7 – purinoreceptor 7, P2Y2 – purinoreceptor 2.

Key words*:* memory loss, neuronal loss, brain waves, computational modeling, microarray, MRI, brain neuronal network, drug targets, APOE.

Introduction

Human brain is the most surprising natural computing machine that humanity could ever see and get the occasion to study. Due to its immense capacity of understanding, analyzing, compiling and reordering huge amounts of information brought not only by outside environmental conditions, sensations, language, gestures but also due to its fabulous way of controlling a natural perfect clockwork system, a true living and moving actual algorithmic body, it is believed that the brain is the most complex organ. However, sometimes this perfectly balanced machine gets to be affected by internal or external factors that perturb its normal activity. Many of the brain's pathologies are exhibited as a result of a complex interaction of factors.

AD is one of the most common but highly destructive neuropsychiatric syndromes of whom cause is yet to be discovered. The most visible feature of AD is cognitive defect acquiring, marked by memory loss. In many years of research and etiology desperate search, it has been proven that this may be just an externally manifested effect of the true disease's cause. Along time findings show that memory loss is due to key brain regions active neuron loss and synapse number decrease (Wenk et al., 2003). This gradual loss leads to mass atrophy of the impaired regions to almost entire inactivation (Braak et al., 2007). Neurons disable and synapse discrepancy is further caused by a lower level of organization problem. Amyloid plaques and neurofibrillary tangles are highly present in AD patients' brain tissue (Maurer et al., 1997). These are due to molecular mechanisms disturbance. Protein missfolding, enzymatic activity disturbance, or even genetic expression mistakes or genetic mutations can be keys of the true AD cause (Priller et al., 2006 ; Hernandez et al., 2007). While its biochemical mechanisms are well documented, the exact cause of AD is still not known. Just a small percent (1-5%) of the AD cases are surely confirmed of a molecular genetic cause (AS, 2014). Due to this aspect, AD was categorized in early-onset AD (hereditary gene mutations specific to AD mechanisms) and late-onset AD (idiopathic, multifactorial and occurring commonly after 70 years old) (AS, 2014). The best available interventions in AD patients support remain merely symptomatic. This is the reason why detection and diagnosis in clinical research, and techniques using brain imaging, biochemical and genetic markers must be considered as tools for early detection of AD and further research for a suitable way of preventing AD.

Computational approaches in Neurosciences

One of the boldest approaches in Neurosciences is computational modeling. At the same time, because the brain acts like as of an unmeasured power computer, the only most accurate mean to study and understand how human brain works, is by using high performance computer simulations. Nowadays, this forms a distinct branch in Neurosciences called Theoretical Neuroscience or CN. CN studies brain functions as an interdisciplinary complex connecting cognitive science and psychology with engineering, computer science, mathematics, and physics (Churchland et al., 1993). CN almost always refers to essential features of biological systems studied in multiple spatial-temporal contexts (membrane currents, proteins, and chemical coupling to electrochemical oscillations, columnar and topographic architecture, and learning and memory) being used to study hypothesis that can be tested experimentally.

Computational approaches in Neurosciences can be organized in several lines of interest. Often, new models in experimental biology are tested and analyzed by both experimentalists and IT engineers. Topics such as neuron modeling, sensory modeling, synapse and memory formation, cognition, learning, and consciousness are considered main guidelines in CN.

As it has been stated before, the human brain works as a whole in order to guide whole's body movement, responses and actions towards environmental and inside factors. This makes it a complex analysis and coordinating system that computes and calculates each and every literal move of the body. It has been shown that neurons can perform computations through their complex biophysical characteristics (Forrest, 2014). Neurons are themselves complex computational machines. Theories of dendritic, somatic, and axonal functions have matured well beyond the traditional scheme of "input–integration–output". Single neurons and their arbors are considered sophisticated time filters, coincidence detectors, internally distributed devices of local memory storage, and dynamic metabolic assemblies with high internal spatial specificity (Ascoli 2002; Senft and Ascoli 1999). Though a very accurate computed system in predicting timing and qualitative features of neuron's action potential, it has never been engineered a model that can compute and simulate adaptation or shunting. Therefore, nowadays CN terms neuron science as an important topic that includes voltage-sensitive currents and their dynamics, modulations, and sensitivity studies (Wu et al., 1995). Geometric properties of neurons and computational functions of dendrite

are also a subject of intense study (Koch et al., 1999). Many questions about developmental tendencies of neuronal axons and dendrites, neuronal migrations, chemical signaling, growth factor and hormones releasing and modulation have also been answered through theoretical investigations often involving computational modeling and computer simulations (Chkolovskii et al., 2004). Since the early models in sensory percepts represented by Barlow models and minimal wiring hypothesis pursue, many computational models that study sensation perception are guided in one way or another through computational modeling also pursuing minimal wiring hypothesis (Durgin et al., 2005). Furthermore the establishment of neuroanatomical databases and the development of computer graphics have resulted in a plethora of high-level research projects focusing on computational modeling (Ascoli 2002; Ascoli 1999). These studies range from the description of dendritic morphology and the characterization of its relationship with electrophysiology to the analysis of the structural determinants of higher brain functions via the detailed mechanism of neuronal assemblage into functional networks. Another highly questioned brain process is memory formation. Early modeling based on Hebbian learning postulates and Hopfield net model of associative memory. These models addressed to hippocampal memory (medium and long-termed). Prefrontal cortex related memory was modeled through theories such as network oscillations and persistent activity (Durstewitz et al., 2000). The latest models comprise synapse models with multiple timescale function (Fusi et al., 2005) and Monte Carlo method to detail acetylcholine receptor based synapses (Coggan et al., 2005). An even more challenging modeling research is made on the behavior of neuron networks because no artificial model has ever managed to simulate the recurrent, sparse and specific traits of biological networks. Ising model refers to such simulation in which small artificial neuronal networks interactions are closely followed (Schneidman et al., 2006).

Computational modeling of higher cognitive functions has recently showed that even cognition and learning can be modeled. Through single-unit recording in primates, studies proved that frontal and parietal lobes function as integrators of information from the main sensoria.

One of the ultimate goals in Neuroscience is explaining the everyday experience of conscious life. Crick and Koch formulated a consistent framework for neural correlates of consciousness, but the hypothesis remains speculative (Crick et al., 2003). The newest branch of CN, Computational clinical neuroscience brings

neuroscience, neurology, psychiatry, and computational modeling together to define and investigate neurological and psychiatric diseases, and to train scientists and clinicians that wish to apply these models to diagnosis and treatment (Adaszewski et al., 2013; Friston et al., 2014).

Computational models in AD research

In the past decades, many studies have been conducted in computational modeling, from non-invasive imaging of the human brain to uncovering the molecular mechanisms of some complex processes and disease states. Initial studies relied on classical brainwaves modeling and neuronal oscillator markers monitoring (Başar-Eroglu et al., 1992; Schurmann et al., 2000). Years later a part of these were proposed as markers in cognitive disorders diagnosis (Başar et al., 2008). Many of the computational modeling studies were unfortunately conducted mostly on schizophrenia and lesser in other neuro-affective disorders.

In Alzheimer's disease, computational approaches referred to many branches of neuroscience and brain research. The elder studies used classical and non-invasive approaches such as brain waves measurement, computational age/dementia development marker screening, and brain volume calculation algorithms and so on. The new progress in computational science today permits approaches like microarray algorithms, molecular modeling, inhibitor computational simulations, and brain activity matrix pre-evaluations. All of these genuinely aim to find a way to cure human kind's intelligence and personality plague or, at least, to previsualize AD development in individuals.

One of the many studies in AD computational modeling refers to changes in representations in subjects correlated to AD and age (Conley et al., 2001). In this way, the group used a matrix system based on HAL (hyperspace analogue to language) in order to compute and correlate semantic density (using several criteria such as amount of text, topic breadth, and number of unique words) with memory decline rate and age of subjects. This can be considered a rudimentary computational study based on cognitive algorithms (in this case, speech, semantics) that can easily calculate a dependency function between correlative criteria in a high dimensional model of memory. Thus, it has been shown that older adults tend to have denser language representations than youngers. More than that, attributing this model in Alzheimer study, it seems that age correlates with Alzheimer status in the way that adults with Alzheimer's have still denser

representations than normal older adults. These results came to support the hypothesis that greater density, normally associated in the model with good semantic depth, may reach "saturation points" and affect retrieval in older adults and especially adults with Alzheimer's.

Another computational approach was designed by De Haan et al. (2012) in order to study activity dependent degeneration and hub vulnerability. It seems that highly connected 'hub' regions are particularly vulnerable to Alzheimer pathology in the way that they show marked beta-amyloid depositions possibly caused by excessive local neuronal activity. In this way, using a computational model and testing hub regions that possess the highest level of activity or vulnerability in Alzheimer's disease, it has been shown that the modeled neural masses described average activity. The computational modeling of neural masses was based on human DTI-based cortical topology and registration of spike densities and spectral power. In this way, the higher activity of hub regions was confirmed. Also, simulations of activity dependent degeneration were conducted and compared to random degeneration. Conclusively, this model of computational study showed that excessive neuronal activity may lead to degeneration this being a possible existence and explanation for hub vulnerability in Alzheimer's disease.

Later on, computational modeling studies even got further by combining computational neuroscience and body sensor networking (Bergmann et al., 2012). They emphasized the importance of early intervention to the efficacy of treatments by the imperious need for ways of detection and diagnosis in clinical research. Based on the hypothesis the techniques using imaging, biomarkers and genetic information as tools for detection, it has been proved that multifaceted non-invasive screening tools that incorporate computational algorithms, but not relying on imaging, can be in fact a more useful tool than the others. It has been stated that a computation method originally developed to explain mental processes can be adapted to assist in the early detection of Alzheimer's disease by taking advantages of the observable changes in behavior and speech. In this way, a body sensor network system can be used to collect temporal information and computed to an algorithm also simulating natural randomness. Thus, it has been shown that body sensor networking can be used as a computational model for diagnostic purposes or treatment screening in Alzheimer's disease.

On the opposite site of domain methods stand the imaging correlated computational models. A correlation between gray matter volume and depression has been made in the context of putting together common imaging techniques and

highly specialized computational algorithmics (Son et al., 2014). In order to determine whether if depression is an aggravating factor in Alzheimer's disease, depressive symptoms and grey matter volume were compared in a computational system of algorithms based on Consortium to Establish a Registry for Alzheimer's disease (CERAD), Geriatric Depression Scale (GDS), magnetic resonance imaging and voxel-based morphometry (VBM). In this way, it have been shown that decreased gray matter volume in the right hippocampal gyrus correlated to depressive symptoms may be associated with the volume changes of frontal and temporal lobe in patients with Alzheimer's disease.

The correlation between depressive symptoms effects on Alzheimer's disease brain was also demonstrated by the study of regional cerebral brain flow in depressive state of patients (Terada et al., 2014). Thus, regional cerebral blood flow was tracked by single photon emission computed tomography with correction for gamma ray attenuation (Chang method). Depressive status was measures by Neuropsychiatric Inventory, Addenbrooke's Cognitive Examination, Mini Mental State Examination, Frontal Assessment Battery and according to the criteria formulated by the NINCDS-ADRDA. Spatial reprocessing and statistical analysis of images was performed on a voxel-by-voxel basis using Statistical Parametric Mapping 8 on MATLAB. In this way, it has been shown that a group of classical evaluation techniques can be associated with high precision computational modeling in order to correlate visual behavioral effects of Alzheimer's with cerebral fine changes. Thus, the study showed that clusters of voxels in the left middle frontal gyrus were similar to the areas in the simple correlation analysis and the dorsolateral prefrontal area is significantly involved in the pathogenesis of depressive symptoms in AD.

Computational modeling is not limited only in imaging or behavioral areas, but also in more complex and profound levels of organization. In this way, many genetic studies often include computational strategies due to the complex and yet not fully known gene expression mechanisms. A relevant study mentions that microarray analysis may be a useful tool in gene expression evaluation (Panigrahi et al., 2013). In order to determine the regulatory patterns in associated pathways of Alzheimer's disease, it has been used several computational algorithms such as microarray matrix analysis, genetic variation tendencies computing with gene interaction and phenotype determinism. This complex data analysis revealed a common sharing of important biological processes and putative candidate genes

among Alzheimer's and aging. Thus, ten major classes of transcriptional factors were associated with Alzheimer's and other diseases.

Another relevant genetic computational study compares grey matter density in Alzheimer's disease (Zieselman et al., 2014). It have been stated that a bioinformatics approach to the genetic analysis of grey matter density in the context of endophenotyping of late onset Alzheimer's disease. In this way, a machine learning analysis of gene-gene interactions and a large-scale functional genomics data were compiled in order to demonstrate that two single nucleotide polymorphisms interact synergically. Unfortunately, this model could not be replicated in independent datasets, but the genes of which SNPs were connected have high-confidence biological relationships confirmed in sensory processes implication. In this way, it has been proven that missing heritability percents are due to gene-gene or gene-environment interaction models.

Even drug testing and molecular metabolism simulations have been studied using computational modeling. A review study in 2010 (Gupta et al., 2010) shows that there were many computational studies conducted on acetilcholinesterase and beta-secretase 1 interaction hypothesis. More than that, further computational studies were based on finding a strategy to identify dual inhibitors. In this way, multi-targeted directed drugs have been found effective in many central nervous system diseases by drugs and leading inhibitor molecules compiling in ADMET analysis. Three-dimensional QSAR models for 43-hydroxyethylamine derivatives and beta-secretase inhibitors were developed by CoMFA and CoMSIA techniques. Thus, information gathered from the 3D-QSAR contribution maps, and the developed models revealed some of the effects of the substitutional patterns related to the biological activity of anti-Alzheimer compounds.

Computational modeling also revealed important features of Alzheimer's disease mecanistics. In this way, a case study (Charzyńska et al., 2014) describes an interesting computational model for sphingolipid metabolism as a point of origin for further analysis in Alzheimer's disease mechanisms. Based on the fact that sphingolipids are surprisingly involved in apoptosis and cell signaling, the group developed a modeled pattern using computational science in order to describe that sphigolipid metabolism models must not be concentrated only on synthesis form ceramide and biochemical transformations in particular subspecies, but also to other biochemical features such as organelle compartimentization. In this way, the authors claim that a similar computational model can be used for the study of molecular processes underlying Alzheimer's disease.

Apolipoprotein E4 inhibitors were also studied using computational design (Huang et al., 2014). As APOE4 is a confirmed major genetic risk factor for Alzheimer's disease, finding an inhibitor for it can be a step forward in therapy and pharmacology. In this way, using virtual screening of traditional Chinese medicine database and investigating potential compounds for the inhibition of ApoE4, major candidates have been selected: solapalmitine, isodesacetyluvaricin and budmunchiamine L5. Computational dynamics analysis and molecular dynamics in simulated conditions were used to observe protein-ligand complexes interactions and variations. Conclusively, it seems that budmunchiamine L5 can be easily absorbed, can penetrate blood brain barrier, and be lesser toxic according to ADMET prediction.

Ethical considerations

Computational methods and simulations when conducted effectively and ethically could have a substantial impact on medical progression and could lead to a better understanding of Alzheimer's disease underlying pathophysiological mechanisms.

There is no meaning in using sophisticated computer models in medical research if they are not reliable, safe and if they cannot provide a genuine improvement to the humanity. According to the Code of Professional Ethics for Simulations, for every computer model or simulation a full disclosure of system design and assumptions and known limitations should be provided, the researchers should be explicit and unequivocal about the conditions of applicability of specific models and associated simulation results, and furthermore they should assure thorough and unbiased interpretations and evaluations of the results of modelling and simulation studies (Oren, 2016).

Computer models can be easily repeated, usually with low time and money cost. Moreover computer models and simulations can significantly decrease the use of animals in medical research, and they could also prove beneficial because they allow for valuable resources to be better prioritized on successful plans rather than on works in progress, securing that a plan is in proper working order and therefore decreasing to the least the possible detrimental side effects or shortcomings, being safe for use by humans before it is officially set into action.

Tongen and Adam proposed a verification procedure for computational models and simulations that would be used for human clinical tests (Tongen & Adam, 2016). According to this procedure a proper verification of the mathematical model, proper understanding of the model to human pyshiology relationship,

proper verification of margins of error, and proper verification of the rists and benefits of the technology should be ensured in order to eliminate the possible risk on human beings. As medicines and medical tools must be assessed for safety before use on human subjects, computational models used in medical decision-making should be evaluated as methodically, while gone unchecked, could have detrimental effects (Tongen & Adam, 2016).

Future perspectives

Many of the already conducted studies give interestingly perspectives in Alzheimer's disease research. In this way, future perspectives can aim to any of the existent in queue studies' conclusions targeting pathways description or simulation, drug testing simulations, and even revolutionary to bearer diagnostic or monitoring techniques. Considering that computational models reflect human neural mechanism, some therapeutics suggestions can arise: slowing of stopping the degeneration of synaptic connections and thus the development of the disease in its early stages of further understanding of neuronal networking of brain in terms of describing psychiatric symptomatology or psychopharmacology (Duch, 1997; Duch, 2000; Duch, 2007).

As AD reveals itself as an extremely complex disease, it seems that a complex system of algorithms is needed in order to correlate all the pathophysiological features and physiological contexts with the known molecular background and to find new information regarding the complicated brain network function and connection to normal and pathological pathways. For example, only by using a complex computational genetic tool (Panigrahi et al., 2013) it was possible to reveal the association between aging and AD and also the differences between the normal aging process and the neurodegenerative states which lead to dementia. Obviously, all of these findings were possible only by correlating huge amounts of data obtained from complex RNA microarray analysis which is actually a very delicate genetic tool, but which can provide innovative responses to unsolved chapters in brain physiology and pathology.

More than that, tens of AD risk factors were revealed also through computational analysis of information obtained through genetic studies. For example, many of the interactions between AD causative/susceptibility genes were revealed (Soler-Lopez et al., 2011) in a study which provided the most complete interactome of AD by analyzing the global properties, its functional modularity. In this way, it has been shown that a putative role in the case of PDCD4 as a neuronal death

regulator or ECSIT which is the key molecule linking oxidative stress, inflammation, and mitochondrial dysfunction to AD pathology.

In the same way, by complex computational modeling and in vivo observation, it was possible to asses and investigate many receptors thought to be involved in AD pathology. P2X7 and P2Y2 receptors were shown to be linked to APP processing through secretase activity (Miras-Portugal et al., 2015) in a rather far-reaching study reviewing immunochemistry, genetic and computational tools.

Also, new targets in treatment and new active molecules were found or designed through computational modeling. An interesting computational study reveals a new binding site on the acetylcholine esterase molecule on which inhibitors may form stable complexes which can be further exploited in the drug design of new inhibitors of the acetylcholine esterase based on C60 fullerene derivatives (Goncalves et al., 2015).

Therefore, it seems that the most optimistic approach due to the complex features of AD is the computational modeling. In this way, computational modeling together with animal modeling can provide answers to the AD complicated implications and links at a molecular level which are extremely delicate to handle even through the revolutionary molecular biology techniques. In the biotechnological context, these answers can easily be converted to revolutionary lines in drug biotechnology, computational engineering or laboratory animal model engineering. Moreover, it seems that computational modeling is rather the best tool to predict and evaluate in a simulative manner the capacity of a certain potentially therapeutic molecules to interact with the human complex molecular systems such as the active sites of the proteins involved in the APP metabolism, or the beta amyloid receptors (Barman et al., 2014, Devarajan et al., 2014).

Conclusions

1. Alzheimer's disease is a multifactorial disease that affects central nervous system and cause neuronal loss exhibited in memory loss of unknown etiology. Furthermore, many behavioral, physiological, biochemical and even genetic features have been described through revolutionary computational modeling, all of these in the effort of finding causes or interactions that can lead to the so complex pathology of Alzheimer's disease.

2. Many studies describe various computing analysis techniques meant to shed some light on the pathological pathways of Alzheimer's, but until now, it remains unclear although clear progress have been made.
3. Computational science can offer great opportunities in further research in order to understand neuronal networking of brain, information that can correlate behavior to biochemical pathways and genetics.
4. Computational modeling can provide answers to essential matters which molecular biology alone could not solve.
5. Computational modeling could be a real breakthrgouh in the realm of neuroscience and medical research, but only when and if it is done with full respect to the basic principles of Ethics on Medical Research, and under the Code of Professionall Ethics for Simulations

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