REVIEW

What can computational modeling offer for studying the Ca^{2+} dysregulation in Alzheimer's disease: current research and future directions

Jingyi Liang, Don Kulasiri*
Centre for Advanced Computational Solutions (C-fACS), Lincoln University, Christchurch, New Zealand

Abstract
Ca^{2+} dysregulation is an early event observed in Alzheimer's disease (AD) patients preceding the presence of its clinical symptoms. Dysregulation of neuronal Ca^{2+} will cause synaptic loss and neuronal death, eventually leading to memory impairments and cognitive decline. Treatments targeting Ca^{2+} signaling pathways are potential therapeutic strategies against AD. The complicated interactions make it challenging and expensive to study the underlying mechanisms as to how Ca^{2+} signaling contributes to the pathogenesis of AD. Computational modeling offers new opportunities to study the signaling pathway and test proposed mechanisms. In this mini-review, we present some computational approaches that have been used to study Ca^{2+} dysregulation of AD by simulating Ca^{2+} signaling at various levels. We also pointed out the future directions that computational modeling can be done in studying the Ca^{2+} dysregulation in AD.

***Correspondence to:**
Don Kulasiri, Ph.D., don.kulasiri@lincoln.ac.nz.

orcid:
0000-0001-8744-1578 (Don Kulasiri)

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Alzheimer's disease (AD) is a neurodegenerative disease that accounts for more than 60% of dementia cases worldwide (Alzheimer's Association, 2017). The exact underlying mechanisms of the disease pathogenesis are not yet understood and effective treatments that stop or even reverse AD are badly needed. Among hypotheses proposed to explain the pathogenesis of AD, amyloid cascade hypothesis is a dominant one, and an extensive amount of research is conducted on the investigation into the infamous extracellular amyloid-β (Aβ). Aβ is the main component of the amyloid plaques, a hallmark of AD, and is believed to be the major cause that leads to the neurodegeneration of AD (Hardy and Selkoe, 2002; Karran et al., 2011). Most clinical trials target relatively late phase of the disease by reducing the Aβ accumulation in the brain. However, the continued failures of clinical trials of anti-amyloid suggest that the need for new approaches for the prevention of disease progression is urgent. Accumulating experimental evidence suggests that the aggregation of Aβ induces the intracellular Ca^{2+} dysregulation, which is an early event prior to the presence of clinical symptoms of AD and is believed to be crucial to its pathogenesis (Bezprozvanny and Mattson, 2008; Berridge, 2010). Numerous research has been conducted to study the mechanisms through which Aβ causes the Ca^{2+} dysregulation leading to neurodegeneration in AD, to offer new therapeutic strategies. Therefore, treatments of Ca^{2+} dysregulation provide an alternative direction in addition to the anti-amyloid approach. Attenuation of the dysfunctions of intracellular organelles, endoplasmic reticulum (ER) and mitochondria, and modulation or stabilisation activities of Ca^{2+} channels in plasma membrane or ER are potential therapeutic strategies for early stage of AD (Popugaeva and Bezprozvanny, 2013; Popugaeva et al., 2017).

Under experimental conditions, the disturbances in AD are mostly studied in transgenic animal models of AD or by injecting certain compunds, such as Aβ, into healthy animals or cells. The research generally focuses on the individual disturbances and effects. Aβ is reported to interact with multiple key proteins in various pathways (Berridge, 2010), therefore, it is difficult to isolate the individual effects or study the complex interactions across different pathways because of the limitations of currently available technology. Besides, due to the selection of experiment materials or/and methods by different research groups, controversial results and conflicting interpretations exist.

Computational biology offers great opportunities to study this kind of problem. Basing on conceptual models which integrate different components and pathways, disturbances or alterations in AD can be investigated both individually or comprehensively. Through thoughtfully-designed computational experiments, insights can be obtained by proper interpretation of the simulation results.

Computational modeling approach is a powerful tool

that provides great opportunities to investigate and predict Ca^{2+} signaling through the simulation of the interaction of multiple Ca^{2+}-dependent pathways. Cytosolic Ca^{2+} oscillations and waves in a variety of cell types have been extensively modelled. Details of modeling on cytoplasmic Ca^{2+} signaling are well reviewed by Schuster et al. (2002) and Blackwell (2013). During the past two-three decades, computational modeling of intracellular signaling has become an increasingly valuable approach in neuroscience to study the temporal and spatial complexities of nerve system. Computational models with Ca^{2+}-dependent mechanisms are constructed at different biological scales, ranging from single ion channels to neurons and neural networks. The levels of detail for these models are diverse and depend on the research questions to be answered. They contain mechanisms such as influx of Ca^{2+} through membrane channels, extrusion by membrane Ca^{2+} pumps, intracellular diffusion of Ca^{2+}, interaction of Ca^{2+} with other molecules and Ca^{2+} handling by intracellular organelles.

The developments in computational neuroscience, especially on Ca^{2+} signaling, provide a useful framework and foundation for modeling studies of AD and other neurodegenerative diseases. There are a few computational models that partially capture the Ca^{2+} dysregulation related to AD. For example, Good and Murphy developed a mathematical model of Aβ-mediated blockages of fast-inactivating K^+ channels in neuronal plasma membranes, based on their experimental result: Aβ induced a voltage-dependent decrease in membrane conductance (Good and Murphy, 1996). They proposed an Aβ concentration-dependent effect in the membrane current and simulated this effect by fitting experimental data to a simple inhibition function. Their simulation results are consistent with the experimental observations and suggest that the blockage by Aβ of the fast-inactivating K^+ current is one of the most feasible mechanisms that cause the intracellular Ca^{2+} overload and consequently leads to neurotoxicity. In a study carried by Morse et al., a realistic multi-compartment model was developed to investigate the Aβ-mediated block of A-type K^+ currents and its hyperexcitability effects in proximal dendrites in AD (Morse et al., 2010). The simulation results predicted that the oblique branch is the most vulnerable target of Aβ to disrupt the A-type K^+ currents and signal integration. They also suggested that the above alterations may account for the decline of cognitive function in the early phase of AD.

In spite of an extensive amount of research that carried on studying the dysregulation of Ca^{2+} signaling pathways in AD both *in vitro* and *in vivo*, the computational modeling on this field is still in its infancy. Tiveci et al. developed a computational model that integrated a hemodynamic model with Ca^{2+} signaling pathway to study the brain energy metabolism (Tiveci et al., 2005). They used this model to investigate the effects of Ca^{2+} dynamics on the blood oxygenation level-dependent signal under healthy and AD conditions. The simulation results revealed that the alteration in cerebral blood flow reported in AD leads to a negative effect on the blood oxygenation level-dependent signal and an increase in the intracellular Ca^{2+} concentration. In another study carried by Toivari et al., they developed a stochastic model of Ca^{2+} signaling in astrocyte, the predominant glial cells in the central nervous system (Toivari et al., 2011). The simulation results confirmed the effects of Aβ and neuron transmitters on inducing Ca^{2+} transients in astrocyte, which was consistent with their experimental observations.

Due to the challenges in quantitative studies of Aβ-mediated alteration in Ca^{2+} signaling, Aβ under the experimental conditions usually are given at a much higher concentration compared to the concentration in human brains with AD. This creates difficulties in studying the concentration dependence of Aβ disturbances. Therefore, a compromise solution in computational modeling study is to mimic the disturbances of Aβ by perturbing the related key parameters (Liang et al., 2017). Liang et al. (2017) developed a computational model according to the characteristic of a typical neuron to represent the healthy condition. The key parameters which reflect the Aβ-induced alterations are selected based on the experimental observations. When simulating the AD condition, the perturbations in these parameters are imposed to represent the degree of Aβ disturbances at different stages of AD. Another option is to develop highly conceptual models to study Aβ-mediated alterations in Ca^{2+} signaling. De Caluwé and Dupont proposed a simple mathematical model which models the interplay between Aβ-mediated neuronal Ca^{2+} level and the production of amyloids (De Caluwé and Dupont, 2013). This minimal qualitative model contained a positive feed-forward loop between intracellular Ca^{2+} and Aβ, and excluded the detailed molecular mechanisms. Simulation results showed an Aβ-dependent bistable switch between the healthy and pathological states. The model suggested that AD onset can be induced by a large enough perturbation in amyloid metabolism or upregulation of Ca^{2+} homeostasis, bringing insights into therapeutic research on the inhibition of disease onset and deceleration of its progression.

There are numerous simulation tools available for scientists with different backgrounds and for different research purposes (reviewed in Brette et al., 2007; Blackwell, 2013). There are two types tools: general purpose tools and biological simulation tools. The former generally have command-line interfaces or use scripting languages for modeling, therefore, requires users to have certain programming capability. At the same time, they offer users high degree of freedom in model analysis. Most popular tools belong to the former category are MATLAB, Mathematica, Python and R. The latter are tools that have built-in capabilities for simulation biological processes and mostly have friendly graphical user interfaces. They are suitable for sceintists who do not have programming backgrounds. This category includes the tools for general biological simulation (such as CellDesigner, MCell and COPASI) and specific software packages particularly for neuronal simulation (such as NEURON and GENESIS).

In conclusion, computational modeling has been applied to study the general Ca^{2+} dynamics. Current computational models provide a good foundation to help scientists to study the underlying mechanisms of Ca^{2+} dysregulation in AD. Most current models are relatively simple, but they still can provide useful insights on Ca^{2+} dysregulation in AD. However, comprehensive disease-specific models of Ca^{2+} dysregulation are yet to be developed in order to study how different factors lead to intracellular Ca^{2+} dysregulation. Besides, future models should include downstream factors to explain how Ca^{2+} dysregulation contribute to other neuronal alterations in AD. Moreover, models for therapeutic purposes should be able to directly test the medication effects, to provide potentials in drug discovery for AD.

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