CA1 and CA3 pyramidal cell morphologies under Alzheimer's disease amyloid beta interaction

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Abstract. Alzheimer's disease (AD) is a fatal neurodegenerative disorder which imposes a growing burden on society and health systems worldwide. Besides the existence of few computational models for AD in comparison to other neuropathologies, neural morphologic variability and its dendritic tree complexity are usually disregarded. The hippocampus is one of the first regions to present signals of atrophy and neuronal loss and it acts as structural predictor of AD progression. Here it is simulated how the morphologically realistic models from CA1 and CA3 hippocampal neurons decreases the firing probability given an implementation of AD's Amyloid-β (Aβ) interaction. Focusing on the synaptic integration by the morphologic features, here the same stimulation protocol is used to evaluate single spike behavior. The experiment shows that under same spiking conditions the probability of CA1 to fire is, in average, lower than CA3 when the parameter of Aβ in the total neuron membrane is variated. The observation suggests that there is a morphological firing facilitation for CA3 neurons, thus dendritic computation details should be considered for futures AD models due to its importance for synaptic summation.

Keywords: Alzheimer's disease, realistic morphology, NEURON, CA1, CA3.

1 Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by memory impairment affecting mainly elderly people. It is currently irreversible [1]. The understanding of underlying mechanisms through computational modeling is an important ally to drug-targeting. There is a broad range of therapeutics strategies, from cognitive enhancement training [14] to the cholinergic system modulation [7], however, acting as palliative care for mild and advanced late onset AD [1]. For this reason, early-stage identification and computational modeling of AD is useful for disease-altering research [8]. A key region for understanding AD progression is the hippocampus which its shrinking leads to memory and spatial coordination loss [8]. Computational models for AD objectively measuring hippocampal alterations focuses mainly on the synaptic dysfunction [4] and proteins aggregation dynamics [5], over such partial AD neuropathology drug targets has been proposed. From this point of view, it is invaluable to observe how morphological variability between hippocampal regions reacts to AD. Here, it is showed *in silico* how realistic reconstruction of CA1 and CA3 neurons have its spiking probability modified as a result of the AD effects mediated by Amyloid-β (Aβ) protein.

Computational neuroscience allows simulating brain dynamic components in several scales opening a whole new branch of experiments. There are multiple directions in which computational models would propose a way to change the AD disease status at least in cellular and molecular level. The number of assumptions [5] required to cover AD experimental findings [6] are a limitation for simulation neuroscience since there is no consensus among community regarding the cause that triggers AD [3]. This scenario is worsened by the lack of connections between methodological approaches which have its own temporal and spatial resolution to observe neuropathologies [9]. A neuro-centric strategy is to adjust the firing properties of AD-affected neurons to behave as healthy ones. A promising research is presented by H. F. Iaccarino [12] where they show that modulating AD neuronal oscillations with optogenetics enables one to replicate healthy spiking patterns, resulting in an increase of Aβ endocytosis by microglia recruiting. Another work, focusing on the single neuron scale *in silico* was conducted by V. Culmotni et al. [4]. They are able to show how ion channel conductances changes in a morphologically realistic CA1's pyramidal cell would mitigate simulated Aβ deposition effects in the spiking probability. However, there are no considerations regarding how morphological variations from other hippocampus regions would affect the spike probability influences. Here let's observe the role of morphologic strains of CA1 and CA3 neurons when the Aβ is included through conductance reduction in the synaptic transmission in a compartment based model.

2 Data and Methods

The simulations were carried out in Python (v 2.7) and NEURON (v 7.2) [11], morphologic realistic reconstruction obtained in Neuromorpho.org from rat's hippocampus CA1 (n=41) and CA3 (n=43) were filtered using metadata with complete basal and apical dendritic tree, incomplete axon and soma. In order to evaluate the spike probability, which is defined as the chance of a given synaptic input to provoke a spike, we adapt the stimulation protocol [4]. Here, let's use two sets of 25 AMPA-induced synapses distributed between the proximal and distal regions in apical dendrites, in which apical receives synapses with 10 ms of time decay whereas proximal receives 5ms. Synaptic distribution rule depends on the neuron size, here is considered proximal-apical region until 3/4 of distance from soma to the distant apical segment, whereas distal region is set after 3/4 [15]. Peak synaptic conductances are set to 0.87 nS to the proximal and distal synapses are three times weaker. AD effects in neurons are stimulated through membrane conductances reductions randomly imputed for a given percentage of neuron surface area [4]. When a synapse is set in a segment affected by AD it reduces the peak synaptic conductance in 50% [20]. The start time activation for synaptic stimulation is given by a Gaussian distribution (μ=50 ms, σ^2=5 ms) to account for γ-cycle positive sweep[4]. Moreover, distal synapses are activated with a delay of 5ms to simulate synaptic arriving delay between Perforant Path and

Schaeffer Collaterals [16]. Despite this delay being biologically plausible for CA1 which anatomically receives inputs from CA3, we keep the same stimulation protocol in order to compare synaptic summation among these hippocampal different neuron morphologies. Using L-measures software [22] is possible to evaluate topological and compartment level measures for CA1 and CA3 morphologies as depicted in the Figures 1 and 2. The complete dataset of neuron reconstructions and its morphometrics extracted features are available at GitHub repository for pattern recognition further studies.

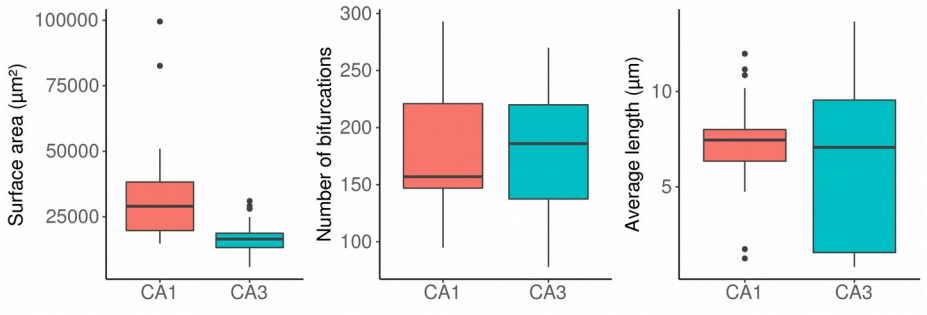

Fig. 1. From left to right boxplots, respectively, the neuron surface area, the number of dendrite bifurcations, and the average reconstruction compartmental length.

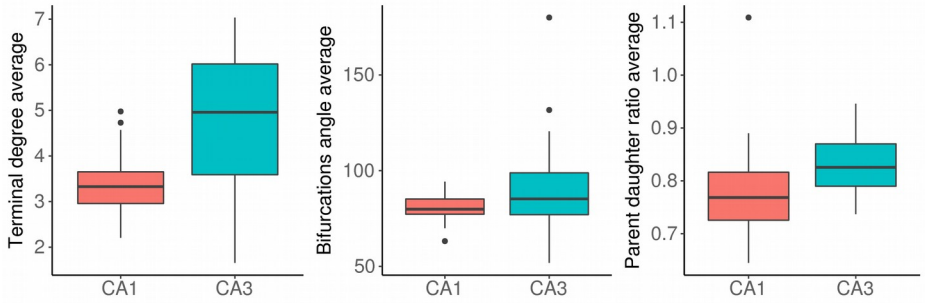

Fig. 2. From left to right boxplots, respectively, the terminal degree average, the bifurcation angle averages, and the parent-daughter ratio average.

Membrane resistance properties for batch simulation were fixed differently for CA1 and CA3 based on the description given [17] and [10], respectively. Each percentage of affected membrane is repeated 10 times and averaged. Classes of ion channels densities varying linearly with the distance from the soma as described in [17] for CA1 were implemented equivalently for CA1 and CA3. The ion-channels used are Ih, K_A, K_{DR} and Na, the conductances reductions to resemble AD are respectively, K_A (-60%), K_{DR} (-40%) and Na (-50%) as done in [4].

3 Results

Computational neuroscience applied to neuropathologies provides drug targets to be tested in order to simulate healthy neuron behavior [5]. The fine-tuning for drugs obtained in silico environment should account for as much variability as possible in order to avoid non-desired interactions. Particularly in AD, a model previously proposed [4] suggest a drug target observing a single pyramidal CA1 neuron morphology disregarding between-region variability. Here, the effect of Aβ in a computational model of AD is studied using various single cells morphologies from hippocampus CA1 and CA3 due to this region being a predictor of AD progression [20]. Other approaches to AD by means of computational modeling explores different levels than single cells (network and molecular) looking forward to possible interventions able to reduce AD effects. It is noticeable that modeling AD tentatives have been quite a few compared to other neuropathologies [5]. Here is shown how realistic morphologies are impaired differently through ion channels and synaptic transmission modifications.

Consider CA's neurons as isolated units is useful to understand its computational roles, for example, how different morphologies benefits firing probability [18]. Other elements, such as plasticity and wiring connectivity patterns may give rise to firing differences between hippocampal regions studied. That is, morphology is one of the many determinants of spiking behavior. An example of that is given by Mizuseki et al [18] which show that dominance of spike probability between CA1 and CA3 depends on the brain state activity (e.g. theta oscillations periods and rapid eyes movement) and the firing pattern (e.g. burst firing and single spike) which is defined by the inter-spike interval statistics. They show that CA3 pyramidal cells had a higher probability of long bursts, conversely, the brain states studied by Mizuseki et al. the CA1 presents an overall higher firing rate. Here, under a synaptic stimulation protocol, the morphology-based comparison suggests that CA3 neurons have a higher average probability in single spike firing in comparison to CA1. The same dominance is found given when using the implementation of membrane proportion affected by the Aβ [4].

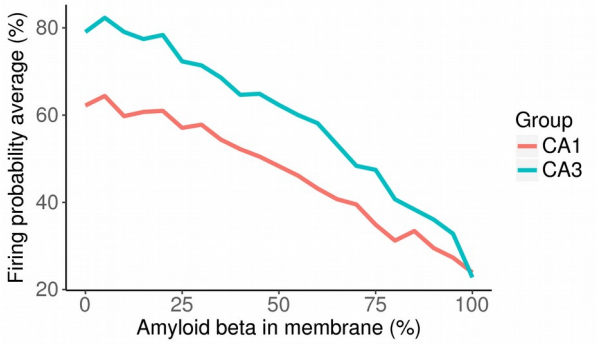

Fig. 3. Firing probability average for CA1 and CA3 regions given the Aβ in the membrane.

It is noticeable by the figure 3, despite CA1 has a basal firing probability lower than CA3 under same input, the CA3 has faster decreasing when Aβ membrane affected increases. Currently, there are no studies defining the minimum firing activity in terms of population spike probability to sustain an expected behavior for a given task in CA1 and CA3. That is, which is the maximum damage a region can tolerate prior to its multiple related functions became impaired and how to measure this damage? Supporting evidence suggest that CA1 has greater loss of neuronal density in comparison to CA3 than any other hippocampal area in humans [19]. Research is required in order to define the weakest feature and its rate of impairment in a scale that allows the computational modeling, e.g. morphologic features, wiring connectivity patterns, neural density, glial interactions, excitatory-inhibitory imbalance.

Here, besides simple neuron model represents fairly well the neuronal behavior the realistic morphology is used since they are crucial to incorporate dendritic computation characteristics inheriting neurons synaptic summation profile. Also, this choice is due to the further plans to implement age-related dendritic defects which would play an important role in AD pathology. Alternatively, ball-and-stick neurons would have an increased performance gain in network simulation, however, to model the same AD analogy presented here for networks, membrane modifications in area dependent mechanisms should be parametrized. There are efforts in computationally model a range of AD features networks. For instance, Rotgerink [21] implements a network model of synaptic loss focusing in mapping AD synaptic parameters using data obtained from microelectrode arrays (MEA) under injected Aβ. Another example of AD model in the network is given by Sergio et al. [23] in which is observed retrieval properties (memory analogy paradigm) in a Venn's network by means of simulated synaptic loss in a conceptual model of AD. Despite computational neuroscience advances being increasingly scaling-up models based on neuronal measures there is yet a significant lack of information to link it with AD staging. This is due to the fact the most of the modeling parameters are obtained from rat models which are induced to produce Aβ differing from humans AD sporadic form.

4 Conclusion

Here, one of the main hypothesis of AD, the Aβ protein accumulation, is simulated in order to show the role of morphologic features in synaptic integration. There are differences in the way in which different cellular types responds to Amyloid-β (Aβ) suggesting, through this computational study, that the morphologic variability must be taken into account in drug targeting discovery. Yet, there are much more to cover to reach biological plausibility. For instance, there is a substantial loss of dendritic tree complexity in normal aging and such dynamic mechanisms of branching should be analyzed in the computational context to evaluate synaptic integration. However, this

is constrained by data resources which more difficult to sample than neuron morphology reconstructions. Differently, new resources are available such as electrophysiological measures from other AD hallmarks. For instance, the tau protein which has been demonstrated to reduce synapses transmission by preventing healthy vesicle release. AD and computation neuroscience would benefit how neurological disorders are modeled in order to understand the disease or even to find a way to give AD patients a way to live better. Maybe a future in which we cure AD is bounded to the way in which data is produced and shared.

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