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Computational study of the progression of Alzheimer's disease and changes in hippocampal theta rhythm activities due to beta-amyloid altered calcium dependent ionic channels

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Abstract: Although, Amyloid beta (β-amyloid) and neurofibrillary tangles are the assay mark of Alzheimer's disease (AD), cognitive decline is best concerned with synaptic loss, rather than tangles or plaques. The pyramidal neurons in Hippocampus are highly affected by AD. Therefore, pyramidal neurons are prime focus in our study. Pyramidal neurons have extensively developed calcium signalling, a phenomenon that controls the neuronal rhythms desirable for memory processing and cognition, for regulating wide range of functions like controlling rhythmic activities, information processing and memory binding. The focus of our work is to inspect the impact of β-amyloid on calcium signalling and progression of AD through computational study.

Keywords: Alzheimer's disease; calcium signalling; pyramidal neurons; hippocampus.

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1 Introduction

A human brain is a complex structure which comprises of different partitions. Among all those partitions, hippocampus (in the medial lobe) is the foremost region which gets affected by AD. AD is a neurological degradation coupled with memory slippage and cognitive decrease. Many factors are contributing to memory deficit and cognitive decline such as pathological changes (Ludovico et al., 2009), traumatic brain injuries (Maia and Kutz, 2014) and many more, but the root cause is still a big uncertainty.

In the initial stages of AD, the pyramidal neurons in the hippocampus (where Information is processed) are highly affected (Hojjat et al., 2005; Li et al., 2011). Any kind of damage to hippocampus may cause intense amnesia like memory blackout, stupor, agnosia, hallucination and many more. In memory and information processing, Hippocampal septal theta oscillations of 4 – 7 Hz frequency range constitute to play major role and hence deformity in theta rhythm activities is connected with memory decline and pathological transformation of the brain (Robert, 2005; Luis, 2006). Therefore, theta band power changes are used in the form of ionic equations to examine the dynamical deformity in hippocampus.

AD is categorised by senile plaques β-amyloid and neurofibrillary tangles, the two deleterious pathological structures and neurotoxins which causes neuronal dysfunction and cell death (Hardy and Higgins, 1992). β-amyloid may alter the behaviour of certain ionic current channels in pyramidal neurons like calcium (I_{Ca}) (Webster et al., 2006), delayed rectifiers K^+ channels (I_K), fast- inactivating A-type transient K^+ channels (I_A)

(Good et al., 1996) and calcium activated large conductance K^+ channels (ICT) (Ye et al., 2010; Chi and Qi, 2006). β-amyloid is also responsible for alterations in neuro modulators (Tran et al., 2002; Palop et al., 2007) used for memory recalls and encoding (Hasselmo et al., 1996). Since β-amyloid introduces tan protein in the succession of AD (Takahashi et al., 2010), hence this work emphasises on the studies of consequences of β-amyloid on hippocampus and progression of AD.

Comprehensive computational task has been carried out to explore the AD – induced in hippocampus and how it effects memory encoding and binding, difficulty in regaining memory and pathological changes in synapses. By assessing changes in theta band power, we have deduced the consequence of the effect of β-amyloid on hippocampus and its network dynamics.

2 Methodology used

2.1 Conductance-based network model

We have constructed a mathematical model of the architecture presented in Hajos et al. (2004), based on the Hodgkin-Huxley formalisms. The network includes three neurons from CA1 hippocampus, i.e., pyramidal, OLM and Basket neurons and MSGABA from medial-septum region. These neurons are said to contribute in theta rhythm activities (Csicsvari et al., 1999; Ylinen et al., 1995; Klausberger et al., 2003). In this network, the theta oscillations are produced from inherent theta oscillations of MSGABA neurons (Stewart and Fox, 1990; Cobb et al., 1995; Wang, 2002; Freund and Antal, 1988; Toth et al., 1997).

The pyramidal neuron, as its name specifies that it is a two-partition model, one is the soma and other is the dendrite. Similar to the concept intended in Wang (1998), the Soma partition has action potential conducting currents I_{Na} and I_K and dendritic section has calcium determined potassium current I_{AHP}. Both the partitions of pyramidal neuron have some common ionic currents, i.e., leakage current I_L and calcium current (L-Type) I_{Ca}. According to Warner et al. (1994) the pyramidal neuron in CA1 region also consists of some other ionic currents. The membrane potential dynamical equations are:

$$\dot{V}_s = -I_L - I_{Na} - I_K - I_{Ca} - I_A - I_{CT} - \frac{g_c}{p}(V_s - V_d) - I_{syn,s} + I \tag{1}$$

$$\dot{V}_d = -I_L - I_{C\alpha} - I_{AHP} - I_{C\alpha} - I_A - I_{CT} - \frac{g_c}{1-p}(V_d - V_s) - I_{syn,d} \tag{2}$$

To mimic the heterogeneities within the brain, the induced DC current injected into each neuron is not selected to be uniform. Instead, the induced current (I) follows a Gaussian distribution with mean and standard deviation. The other three neurons are single partition models, formulated in the same way as given in Wang, (2002), Freund and Buzaski (1996). The OLM neuron model (3) has I_K, I_{Na}, I_{Ca}, I_L, I_h (hyperpolarisation activated current) and I_{AHP} (After Hyperpolarisation current). The Basket neuron model (4) constitutes of I_L, I_K and I_{Na}. The MSGABA neuron equation (5) consists of I_L, I_K, I_{Na} and I_{KS}.

$$V_{OLM} = -I_L - I_{Na} - I_K - I_{Ca} - I_h - I_{AHP} - I_{syn} + 1 \tag{3}$$

$$V_{Basket} = -I_L - I_{Na} - I_K - I_{syn} + 1 \tag{4}$$

$$V_{MSGABA} = -I_L - I_{Na} - I_K - I_{KS} - I_{syn} + 1 \tag{5}$$

For other three neurons, i.e., basket, OLM and MSGABA, the mean is taken as 1.4μA/cm^2; 0μA/cm^2; 2.2μA/cm^2, respectively, and standard deviation is taken as 0.1 μA/cm^2. Although, the inclusion of heterogeneity in the network leads to complex analysis, yet it is an important factor, taken into consideration, if we want to emulate the functionality in the brain. The connection topology of Pyramidal Neuron incorporates AMPA-type receptor between pyramidal and basket neuron. Pyramidal neuron also innervates OLM neuron via AMPA and NMDA type receptors. MSGABA neuron actifies OLM and Basket neurons via GABA type receptor. OLM activise Pyramidal, MSGABA and Basket neurons via GABA-type receptor. Basket neuron supplies to Pyramidal neuron via AMPA-type receptor. The interconnection between neurons is based on detailed in Freund and Antal (1988) and Warman et al. (1994). Noise is introduced in the network by allowing a normal distribution with μ = 0 (mean) and σ = 1.1 μA/cm^2 (standard deviation). Noise in the membrane potential is generated randomly in each trail.

2.2 Reduction in multi-compartment neuron model for efficient analysis

The complexity of multi-compartment model of pyramidal neuron makes it difficult analyse the entire network. As the number of neurons in a network increase the complexity. Because pyramidal neuron has separate equation for both soma and dendrite, it is a necessity that the separate equations of multiple-section model of pyramidal neuron should be merged and reduced to a combined model, keeping the network dynamics unaffected. Subject to this issue, the multi-compartment pyramidal neuron model is combined to single-compartment model by sustaining few ionic currents (Kaushik et al., 2020). In our work, we have incorporated those currents which have been seen to be affected by Amyloid-beta. Resulting in a reduced pyramidal neuron model, our model equation constitutes of I_L, I_K, I_{Na}, I_{AHP}, I_{Ca}, I_{CT}, I_A. The dynamical variables of the multi-compartment pyramidal model have also been reduced depending upon the same approximation. The final reduced equation for pyramidal neuron is:

$$\dot{V}_{pyr} = I - I_{Na} - I_K - I_L - I_{Ca} - I_A - I_{AHP} - I_{CT} \tag{6}$$

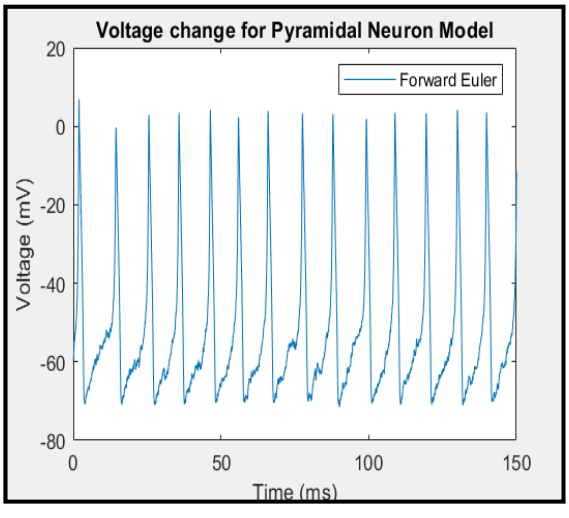
The objective of model reduction is to use minimal dynamical variables as with two compartments, recurring ionic channels has their associated dynamical variables and it make complex simulation of the network. This reduced equation (6) for pyramidal neuron will be used to carry out the simulation proposed in our model.

3 Result

The network model constructed generates theta rhythm oscillations as seen in CA1 and medial septum. In this work, calcium dependent currents and calcium concentration are examined. The maximum conductance of g_{Ca}, g_{AHP} and Ca concentration is used to simulate β-amyloid blocked I_{Ca} and I_{AHP} in the dendrite.

In every iteration, the g_{Ca}, g_{AHP} and Ca conc. has been decreased with a fixed percentage (10% decrease). The obtained results of theta band power with discrete values of g_{Ca}, g_{AHP} and Ca conc. is illustrated in Fig 2. Interestingly, it is observed that initial decrease in above mentioned conductance and concentration does not show any remarkable change in spike generation. This means that during initial stages of AD, it does not show any sure shot signal. At the later stages when the disease progresses, it starts to show some remarkable changes. In our model, it is demonstrated after 30% decrease in the value of conductance(s) and concentration, it starts to show irregularity in the pattern (action potential). Later on, during the later stages, the action potential starts to disappear. This shows that when the disease is in later stages, the memory gets declining and the person starts forgetting its memories. To demonstrate the effect of β-amyloid over calcium dependent currents and calcium concentration, 15 independent trials are performed on proposed model and on original model and error term is calculated to justify the result. Out of total trials, 13 trails have shown efficient results whereas 2 trails have distorted results. This means that the proposed model works with 87% accuracy. The simulation results are as follows: Under normal conditions, when a person is not affected by the disease then the pattern of action potential generation is regular. Figure 1 demonstrates normal membrane potential for pyramidal neuron.

Figure 1 Membrane potential for pyramidal neuron under normal conditions for a healthy neuron (see online version for colours)



In the early onset of AD, our network model does not show any remarkable signal. Table 1 shows the progression of AD due to decrease in calcium dependent conductance and calcium concentration.

Table 1 Progression of AD due to decrease in calcium dependent conductance and calcium concentration

Stages	*Percentage decrease*	*Ca conc.*	*Ca Conductance*	*AHP conductance*
Stage 1	10% ↓	0.00045	0.009	0.0297
	20% ↓	0.00040	0.008	0.0264
	30% ↓	0.00035	0.007	0.0231
Stage 2	40% ↓	0.00030	0.006	0.0198
	50% ↓	0.00025	0.005	0.0165
	60% ↓	0.00020	0.004	0.0132
Stage 3	70% ↓	0.00015	0.003	0.0099
	80% ↓	0.00010	0.002	0.0066
	90% ↓	0.00005	0.001	0.0033

In our model, every percentage decrease in conductance and concentration values shows the progression of AD in the form of stages. Stage 1 gives the idea of early onset of AD. Stage 2 talks about the MCI, i.e., mild cognitive impairment. Stage 3 defines the later stages of AD.

Simulation results shown in Figure 2 demonstrates the early stage of AD where it does not show any critical difference in the action potential pattern. This conveys that 10% decrease means initial stage of the disease. In the early stage, it doesn't show any sure sign. When the disease progresses, the spike generation in pyramidal neuron becomes irregular. Figure 3 shows significant changes in theta band power in pyramidal neuron and irregularity in spike generation in Pyramidal neurons. This indicates a mild cognitive impairment stage with 40% decrease in conductance and concentration values. Figure 4 gives a clear view of cognitive impairment in pyramidal neuron where information processing and memory building takes place. Simulation results shown in Figure 5 indicates 90% decrease in conductance and concentration values which shows later stages of AD when memories get faded away and learning process is also slowed down.

Figure 2 10% decrease in conductance and concentration (see online version for colours)

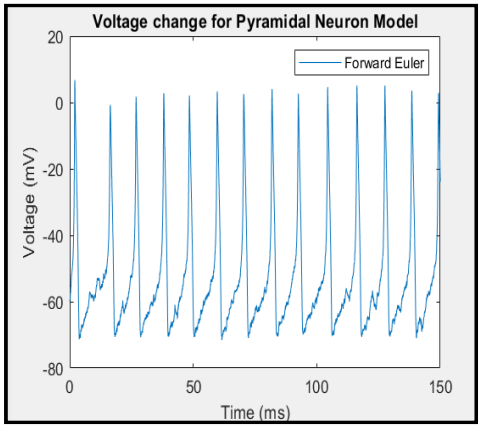


Figure 3 40% decrease in conductance and concentration (see online version for colours)

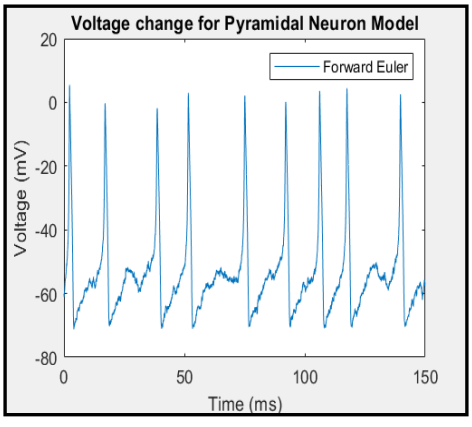


Figure 4 60% decrease in conductance and concentration (see online version for colours)

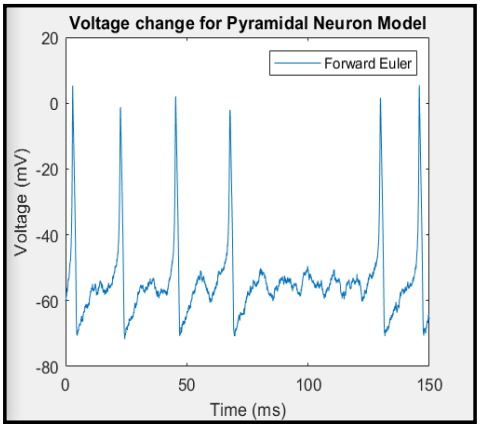
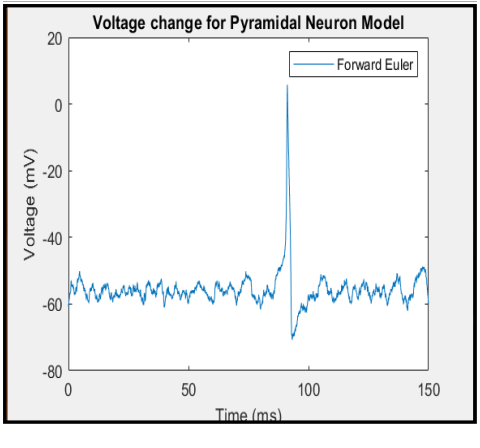


Figure 5 90% decrease in conductance and concentration (see online version for colours)



Our model approximates the idea used in Zou et al. (2012). Therefore, to validate our findings, results from 15 trial are obtained and error term is calculated between results obtained from original and proposed model. Comparative result is shown in Table 2.

Table 2 Comparative results using error-term analysis for validation of our findings

Trials ↓	*Error term analysis*			
	MSGABA	*OLM*	*Basket*	*Pyramid*
Trial 1	0.024959	–3.06023	–0.12916	–0.00305
Trial 2	–0.46293	–2.38465	–0.05685	0.197242
Trial 3	–1.34524	–2.98571	–0.12145	–0.08303
Trial 4	–0.60357	–3.03267	–0.31023	–0.4128
Trial 5	0.436881	–2.78913	0.029652	–0.06657
Trial 6	–0.00657	–2.8017	0.157883	–0.26919
Trial 7	–0.64106	–2.55771	–0.33618	0.030669
Trial 8	0.714314	–2.95152	0.15943	–0.20894
Trial 9	0.462607	–3.28387	–0.36789	–0.19341
Trial 10	0.626328	–2.63689	0.367339	–0.10616
Trial 11	0.234903	–2.46612	0.260858	–0.1725
Trial 12	0.746387	–2.60077	0.753132	–0.39623
Trial 13	–1.14637	–2.21716	0.604196	0.270481
Trial 14	0.384825	–2.38516	–0.03308	–0.10383
Trial 15	0.001679	–2.40359	–0.80327	–0.16719

4 Discussion

In our work, with regards to the technique underlying generation of theta rhythm activity in hippocampus, there are several hypotheses existing. One theory hypothesised that unusual β-amyloid aggravation develops an up regulation in neuronal calcium signalling, causing an inceptive wane in memory and in the later stage, it progresses and causes apoptosis (Khachaturian, 1989; LaFerla, 2002; Stutzman, 2007; Thibault et al., 2007). However, some other studies show that down regulating of calcium buffer calbindin D-28k is also associated with AD. It is known that, during ordinary aging, gradual transformations in some calcium signals may increase neuronal excitability which leads to cell death. A decline in this calcium buffer may also exaggerate the beginning of AD. Our model supports both the hypotheses, i.e., the up regulation of calcium signalling and down regulation of calcium buffer leads to neuronal dysfunction and hence it leads to cell death. The experimental results in our model show that the changes in calcium dependent channels and decrease in calcium concentration results in slow degradation of spike generation and later on leads to learning and memory deficit. However, what leads to the memory and learning deficit during the initial stage of AD is still an uncertainty.

5 Conclusions

To conclude, we have presented that β-amyloid accumulation over synaptic interconnections may cause behavioural changes in hippocampus network. However, we focused only on the dynamical changes in the system, originated due to pathological changes in pyramidal neuron. In this paper, we have analysed several ion – channels in hippocampal CA1 pyramidal neurons and identified that deposition of β-amyloid over synapses blocked calcium dependent channels and hence mitigate calcium concentration, through mathematical and systematic investigation. However, it should be considered that β-amyloid induced into hippocampus may be more complex. Some other researches find that I_h (slowly deactivated hyperpolarisation activated current) in pyramidal and OLM neurons may also promote to theta rhythm activity (Rotstein et al., 2005). Orban et al. (2006) has shown that I_h itself acts as a standalone pace maker of theta activity in hippocampus. Investigation on these aspects will be the subject of future research.

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