Influence of Aging and Aging-Related Neurodegenerative Disease: From Single Neuron Model to Simple Neural Network

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Abstract

During normal aging, quite a lot of age-related changes happen like short-term memory, shakiness and muscle weakness occurring in human beings, and further affect the brain function, such as the altered calcium influx through the calcium ion channels, neural plasticity deficits, and other neurodegenerative processes. Some of them will even develop to a fatal neurodegenerative disorder like Alzheimer's disease (AD) or Parkinson's disease. By modeling the effects of these changes on both the single neuron level and neural network, we can understand how the neural properties are linked to the function loss and death of neurons in different scales. In this project, we employ the powerful biological neuron models, especially the Morris–Lecar model with different physiology parameters along aging. By simulating both single neuron model and simple synaptic motif model and comparing the different neurodynamics between the young and old individuals, as well as the healthy people and patients with neurodegenerative diseases especially AD, we show the results that aging process does hinder neural spiking activity, slow down and reduce the action potential propagation, weaken the sensitivity to stimulus, and so forth.

1. Introduction

Aging is the process of getting older, representing the accumulation of changes in human bodies over time. The concept of aging we are discussing about in the project is biological aging which refers to the physical state of an organism as it gets old. Moreover, we are more focused on neural aging.

Several age-related neurological changes have been identified during aging: altered calcium influx[1], [6], neural plasticity deficients[4], myelination loss (shown in Fig. 1) and changes in

neurotransmitters[8]. Those changes cause short-term memory, memory loss, shakiness, muscle weakness retardation and so on in the end [17]. Among those aging-related deficients, the cognitive deficients attract more attention which appears especially more on the disease of dementia. Dementia pathologically includes memory deficits, slower responses and other symptoms.

Apart from cognitive deficiencies, age-related changes in cell excitability are reported in the previous study[5], especially that cell excitability is reduced in the hippocampus and cerebellum of aged animals. One conspicuous characteristic of aging hippocampal neurons is an increase in the magnitude of the Ca^{2+}-dependent, K^{+}-mediated afterhyperpolarization. The changes will affect the resting membrane potential, especially through the Ca^{2+} and K^{+} Nernst reversal potential.

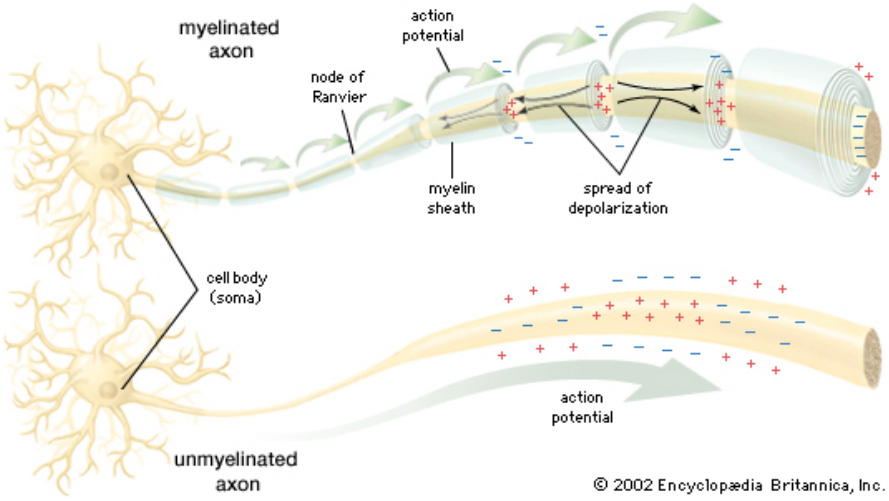

Fig. 1: Myelinated axon and unmyelinated axon.

Alzheimer's Disease (AD) is a progressive, degenerative brain disease that slowly erodes memory and thinking skills, and eventually even the ability to carry out simple tasks. It is the most common cause of dementia. Some symptoms of AD are shown as the following[9]:

1. Age-related myelin breakdown has been reported be involved in AD[12], [13].
2. Ionic conductance dysfunction (such as K^{+}) in humans caused by beta-amyloid toxicity could contribute to the learning disability and memory loss in AD[14].
3. Elevated cytosolic calcium concentration is shown to stimulate Aβ aggregation and amyloidogenesis in AD[18], [19].
4. Neurotransmitter (such as acetylcholine) essential for processing memory and learning, is decreased in both concentration and function in patients with AD[10].

2. Methods

We involved 3 models in the project: single neuron model, simple synaptic model and 4 neuron motif. For the single neuron model, we use Morris-Lecar (ML) model and have two main hypotheses:

1. Aging neuron is difficult to get excited.
2. Aging neuron has deficient neural spiking ability compared with the neuron in young group under the same external current.

In ML model, there is an important assumption that there are two persistent (non-inactivating) voltage-gated currents with oppositely biased reversal potentials. The depolarizing current is carried by Na^+ or Ca^{2+} ions or both, depending on the system to be modeled, and the hyperpolarizing current is carried by K^+. In the model we are using here shown in Fig. 2, Ca^{2+} is the only ion taking charge of the depolarization process. And the leakage conductance takes charge of the entire process[3], [7].

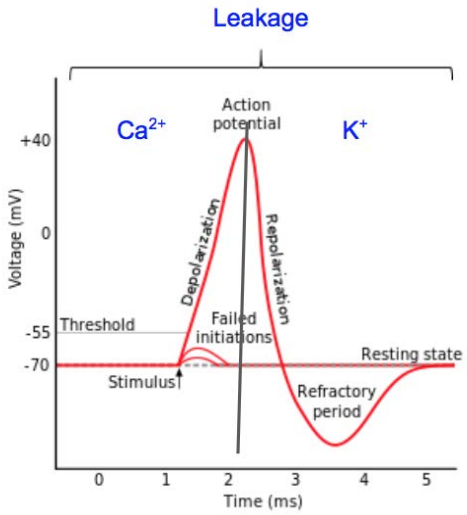

Fig. 2: The process of the action potential in ML model.

Also, the governing equations for ML model are shown below:

$$C_m \frac{dV}{dt} = -I_{Ca} - I_K - I_L + I_{ext}$$
$$I_{Ca} = g_{Ca} m_\infty(V) * (V - E_{Ca})$$
$$I_K = g_k \omega(V,t) * (V - E_K)$$
$$I_K = g_L * (V - E_L)$$
$$\frac{d\omega}{dt} = \frac{\omega_\infty(V) - \omega}{\tau_\omega(V)}$$
$$m_\infty(V) = 0.5(1 + tanh[(V - V_1)/V_2])$$
$$\omega_\infty(V) = 0.5(1 + tanh[(V - V_3)/V_4])$$
$$\tau_\omega(V) = \Phi/cosh[(V - V_3)/2V_4]$$

The parameters and constants include I_{ext} as the external current, C_m as the membrane capacitance, g_K, g_{Ca}, g_L as the leak, Ca^{2+}, K^+ conductances through the corresponding ion channels, V as the membrane potential, m, τ, ω as the kinetics of gating variables (voltage dependence).

Simulated with ML model, we mainly choose the following parameters to test the effects:

a. Effect of leak current[11], e.g. loss of myelination.
b. Effect of the K^+ ion conductance and Nernst reversal potential.
c. Effect of the Ca^{2+} ion conductance and Nernst reversal potential.
d. Modified synaptic currents.
    i. Synaptic conductance of excitatory neurotransmitter, i.e. glutamate, g_{Glu}
e. The aging model we are using here has the following properties[4-7].
    i. g_K, g_{Ca}, g_L increase by 5% setting
    ii. E_K, E_{Ca}, E_L decrease by 5% setting

For the simple synaptic model, we use the excitatory synapse to do the simulation. We also have the hypothesis that spiking ability of the postsynaptic neuron in the aging group decreases. The schematic model is shown in Fig. 3. Two types are employed here, one without feedback and one with positive feedback. Only two neurons are employed in this model. For the young group, neuron A and B are both young neurons. For the aging group, neuron A and B are both aging neuron. For aging group, both aging neurons utilize the same parameters as the single neuron model, and g_{Glu} changes with the group.

Fig. 3: The schematic model of excitatory synapse with no-feedback or positive feedback loop.

For the 4 neuron motif, we have the hypothesis that the aging group has weak capacity to retain signal, less spiking pattern and so forth. The schematic model is shown in Fig. 4. Four neurons are employed in this model. The external current is injected into neuron A, and the output of neuron D is recorded correspondingly. The excitatory path from neuron A to neuron D in order is fixed. Each neuron is excited by the one before itself. Apart from this path, each neuron can also be excited by a random neuron except itself. For example, neuron B could probably get the input from neuron A, and it can also get the other input from neuron A, C or D randomly. This model is aimed to mimic the general behavior of a simple neural network. For the aging group, 4 neurons are all the same aging neuron as the single neuron model, and $g_{Glu}$and $g_L$are different for young and aging groups.

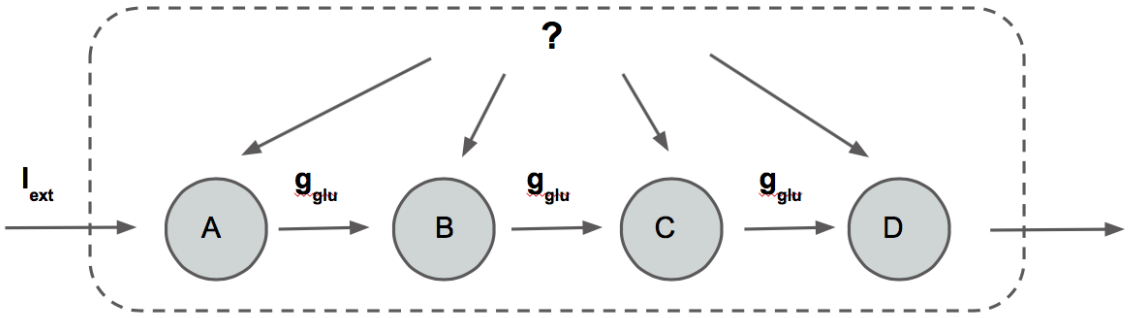

Fig. 4: The schematic model of the 4 neuron motif.

3. Results and Discussion

3.1. Single Neuron Model

First, we use single neuron Morris–Lecar (ML) model to do the simulation and comparison between aging group and young group. The result in Fig. 5 shows that aging group is much more difficult to get excited than young group, but aging group has higher spiking frequency than normal group under very high external current, i.e. aging group is more sensitive with higher external current. In order to understand the underlying function of different ions and membrane leak property in ML model, we start to look at the effect of each individual parameter on the both neural excitability and firing capability, including different currents and different conductances.

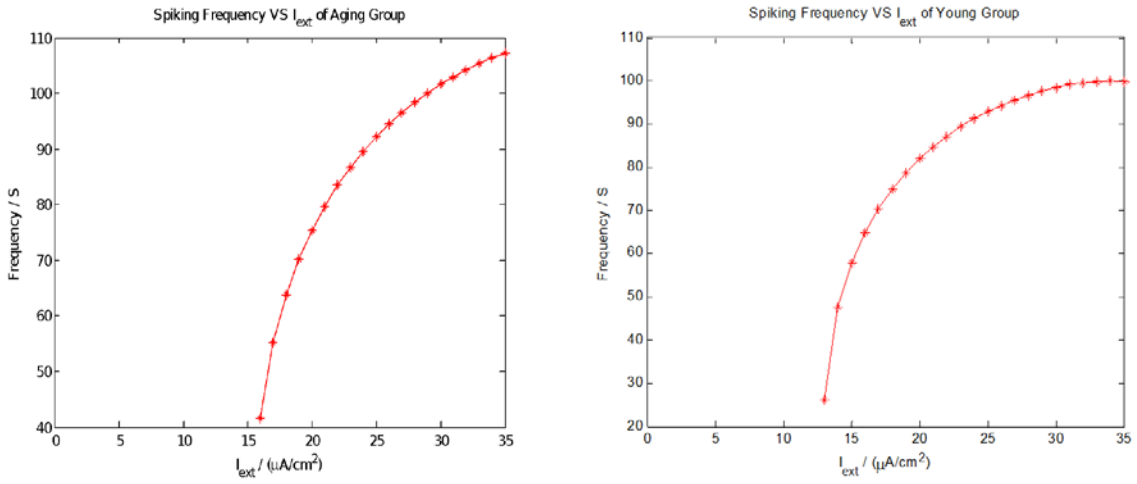

Fig. 5: The results of the relation between spiking frequency and external current in both young and aging group.

Based on the study that age-related myelin breakdown is involved in AD[12], [13], we start to test both the excitability and firing capability due to myelin loss. For leak current, it takes care of other channel types like Cl^- ion as well as less myelination. The Fig. 6 shows leak current negatively affects the neural excitability but the aging group would have similar spiking frequency as the young group with very large external current, which is non-physiological. In aging group the amount of myelination of the neuron among the objectives decreases, and this causes the aging neuron to have larger E_L. Larger E_L means the neuron is more hyperpolarized, i.e. the neuron has more negative potential, which makes it become farther from the spiking threshold. Thus, it needs larger external current to get excited. As the increase of I_{ext}, it is large enough to ignore the effect of the leaking conductance, which results neurons with different leaking conductance spike at the similar frequency.

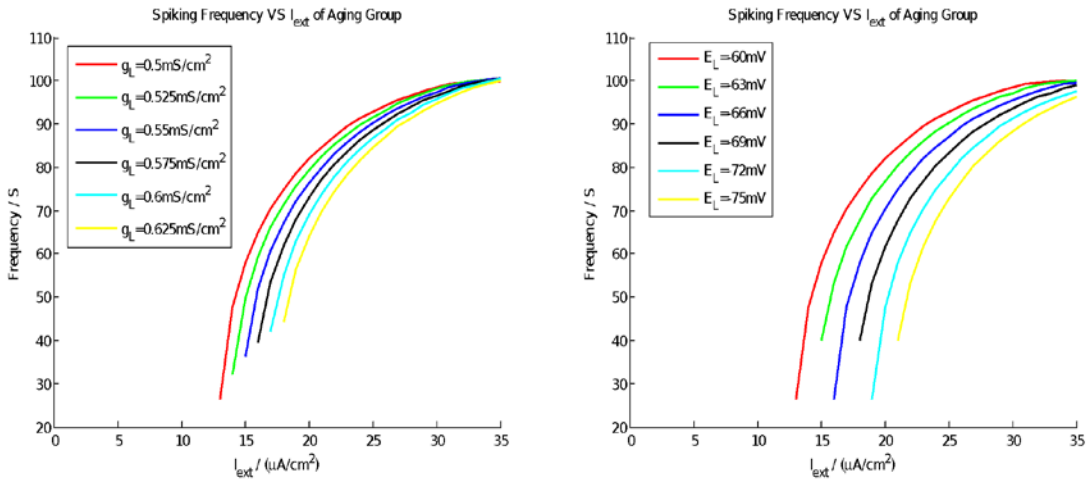

Fig. 6: The results of the relation between spiking frequency and external current in the aging group with different leak current and conductance only.

From some previous studies[18], [19], the Ca^{2+} ion influx and the intracellular concentration of Ca^{2+} ions in the aging group with AD increases.

According to the Nernst equation shown below

$$V_s = \frac{KT}{q} \frac{\ln[S]_o}{[S]_i},$$

these changes lead to a reduction of calcium Nernst potential, i.e. making neuron become more hyperpolarized.

The Fig. 7 shows the negative effect of Ca^{2+} dysregulation on excitability. Based on the assumptions of ML model, calcium ion is in charge of the depolarization process. With the increase of conductance, the amplitude of the action potential reaches higher value (easier to excite and less depolarized), which causes neuron to take longer to recover back to the rest state, i.e. slower firing.

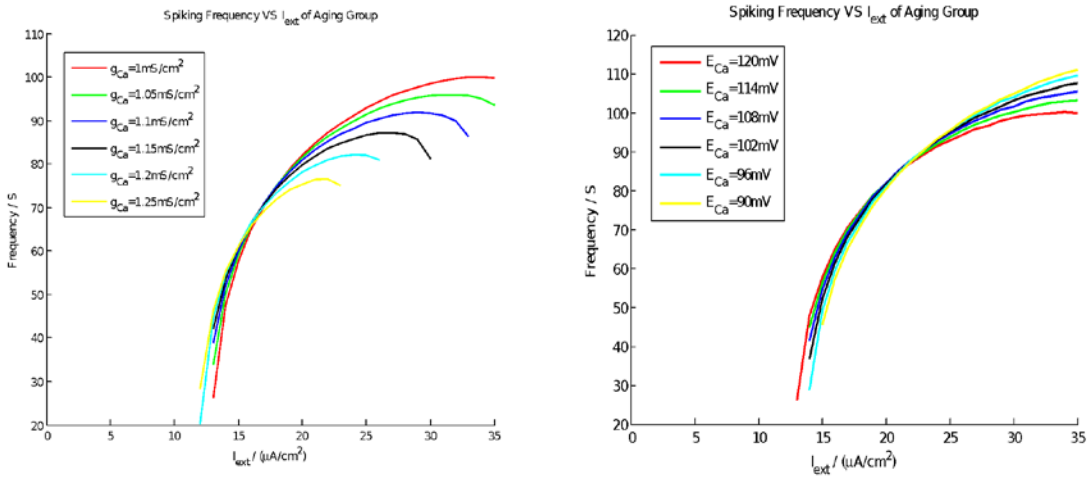

Fig. 7: The results of the relation between spiking frequency and external current in the aging group with different calcium ion current and conductance only.

Moreover, there are studies showing that K^+ conductance dysfunction in humans caused by beta-amyloid toxicity could contribute to the learning disability and memory loss in AD[14]. And in aging group, K^+ conductance increases and then it suppresses the neural excitability[20], [21].

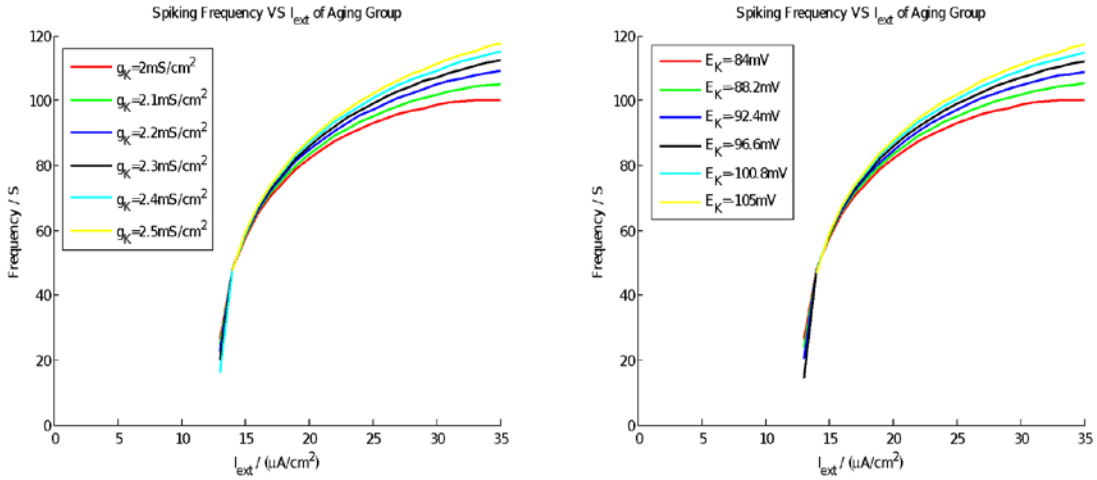

Fig. 8: The results of the relation between spiking frequency and external current in the aging group with different potassium ion current and conductance only.

The effect of K^+ dysfunction on neural excitability is shown in Fig. 8. Based on the assumptions of ML model, potassium ion is in charge of the repolarization process. Under the same amplitude of the action potential, neuron with a larger potassium conductance (more hyperpolarized from Goldman–Hodgkin–Katz voltage equation) takes less time to recover back to the rest state through repolarization to reach faster firing. More negative K^+ reversal potential results in more depolarization and making neurons become more hyperpolarized, i.e. inhibiting action potentials.

After the neuron spikes, it may be faster for the neuron to repolarize due to higher K^+ gradient and fire faster, because the K^+ ion channel contributes to the repolarization process during action potential.

3.2. Single Synaptic Model

For simple synaptic model, we start with single excitatory synaptic model. In the no-feedback loop shown in Fig. 9, both presynaptic neuron A and postsynaptic neuron B are affected by increasing leak conductance, which leads to a decreasing spiking frequency as Fig. 10 shows.

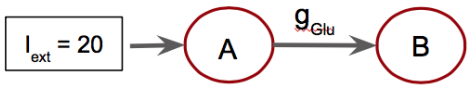

Fig. 9: The schematic model of excitatory synapse with no-feedback.

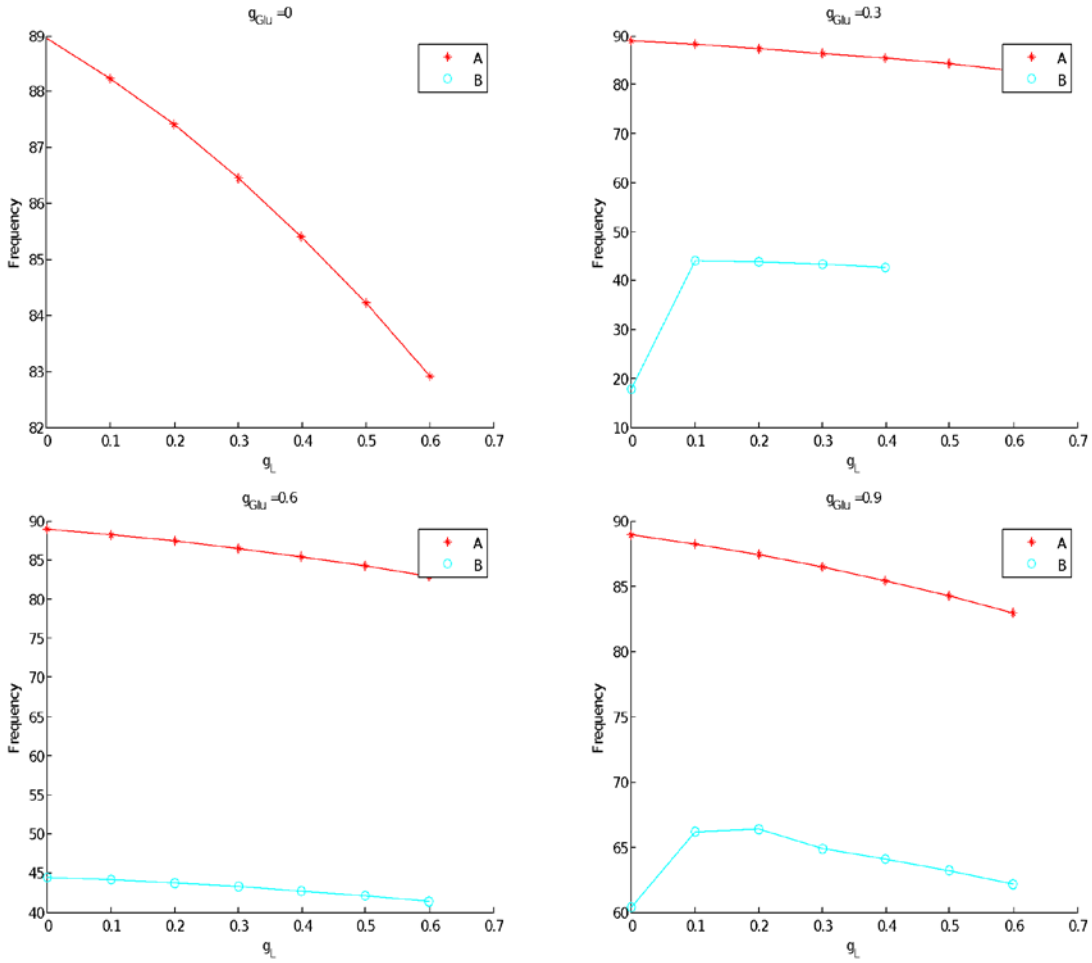

Fig. 10: The effects of the leak conductance on the spiking frequency in the no-feedback synaptic model.

In the same no-feedback loop, with higher g_{Glu} postsynaptic neuron has a higher spiking frequency as Fig. 11 shows, which indicates a better neural excitability.

The changes of both the neural excitability and firing frequency are quite straightforward in the simple excitatory synaptic model.

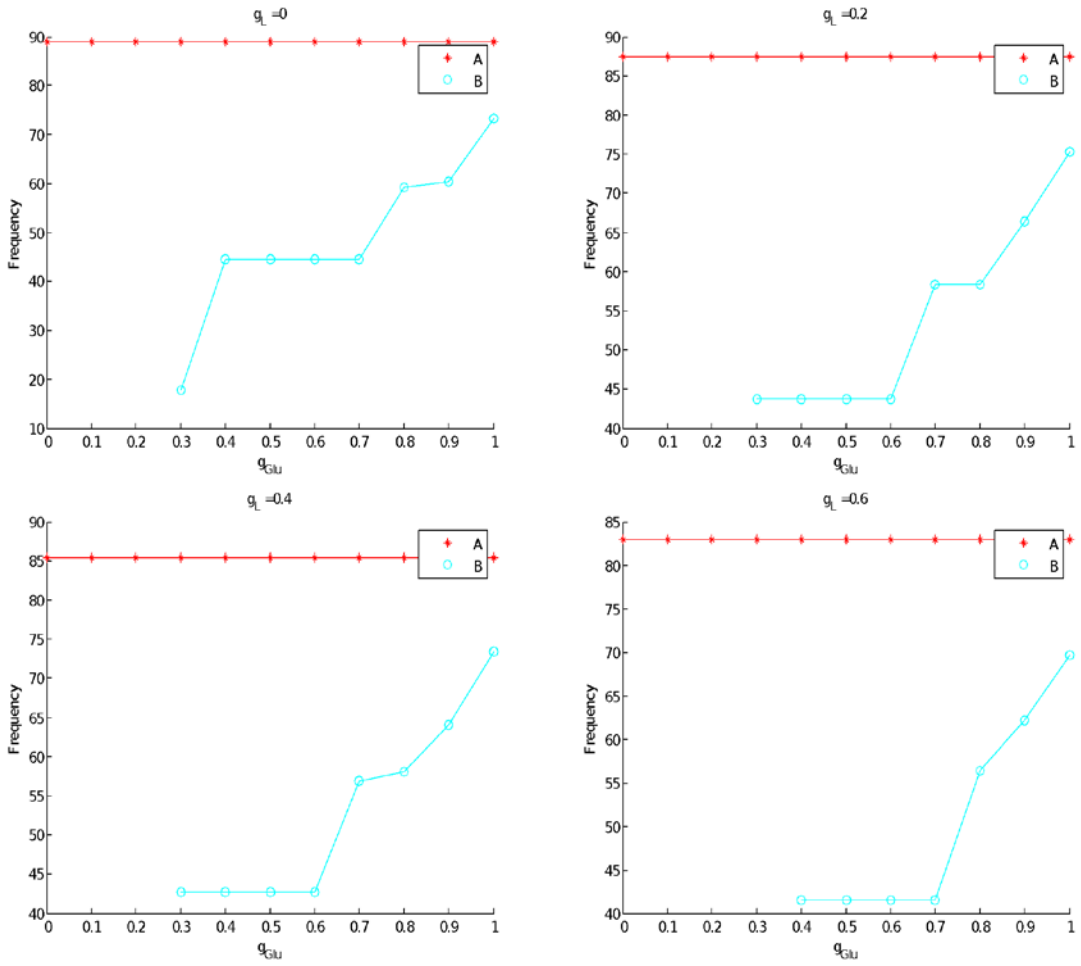

Fig. 11: The effects of the synaptic conductance of glutamate on the spiking frequency in the no-feedback synaptic model.

The excitatory synaptic model with positive feedback is shown in Fig. 12.

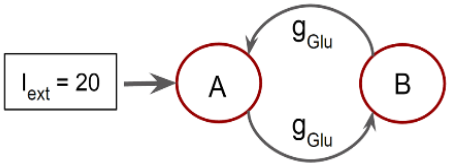

Fig. 12: The schematic model of excitatory synapse with positive feedback.

When the glutamate conductance is fixed, we have the following results in Fig. 13.

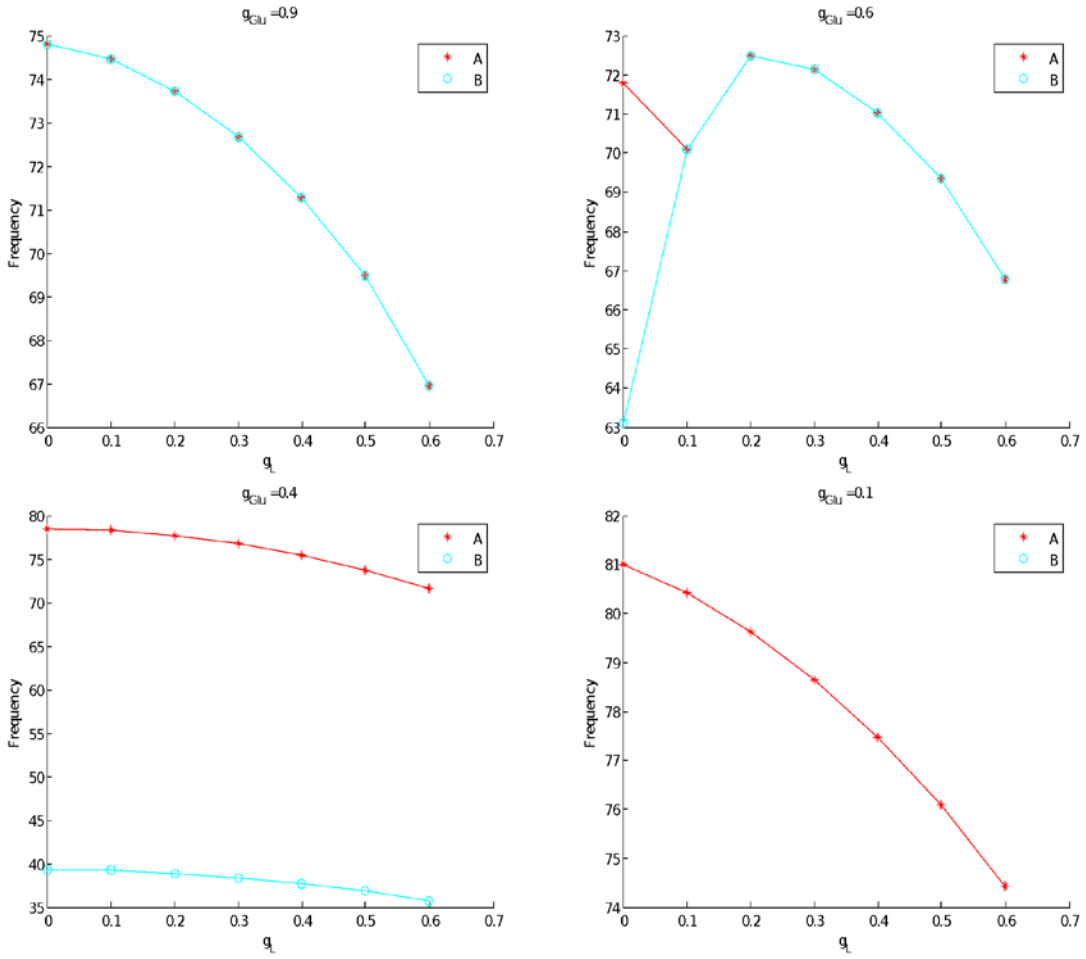

Fig. 13: The spiking frequency along the change of leak conductance under certain glutamate conductance (The red line indicates neuron A and light blue indicates neuron B).

As we can see in the Fig. 13, in the positive feedback loop, the presynaptic neuron A is affected by the g_{Glu} from the postsynaptic neuron B, the injected current, and its own leak current. As the leak current increases, the spiking frequency decreases. For the postsynaptic neuron B, its spiking behavior is largely decided by the glutamate conductance. As g_{Glu} decreases, neuron B finally lost the synchronization with neuron A. When the glutamate conductance stays very high, A and B will both spike at the same frequency. When it decreases to some level, there will be

another form of synchronization, where B spikes once while A spikes twice. Finally, when glutamate conductance is very low, the synchronization disappears.

When the leak conductance is fixed, we have the following results in Fig. 14.

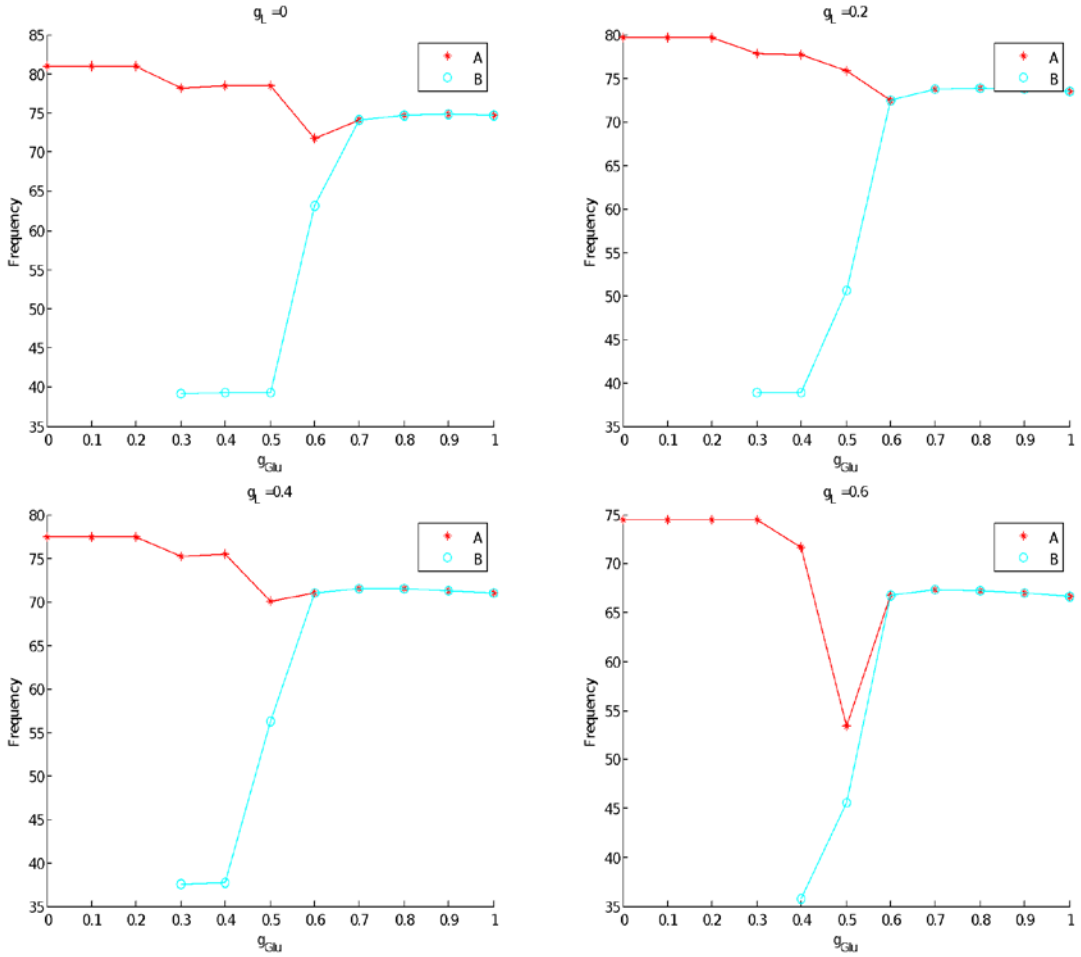

Fig. 14: The spiking frequency along the change of glutamate conductance under certain leak conductance (The red line indicates neuron A and light blue indicates neuron B).

In the Fig. 14, as the leak conductance increases, the spiking frequency decreases when neuron A and neuron B are synchronized. Also, when the leak conductance is really high, A is largely influenced by the spiking behavior of neuron B.

The 4 neuron motif model with random inputs on different neurons is shown in Fig. 4. For the 4-neuron motif, excite the neuron A 50 times and monitor the spiking behavior of A, B, C, and D under the random connection.
For the young group, the spike raster plot is shown in Fig. 15.

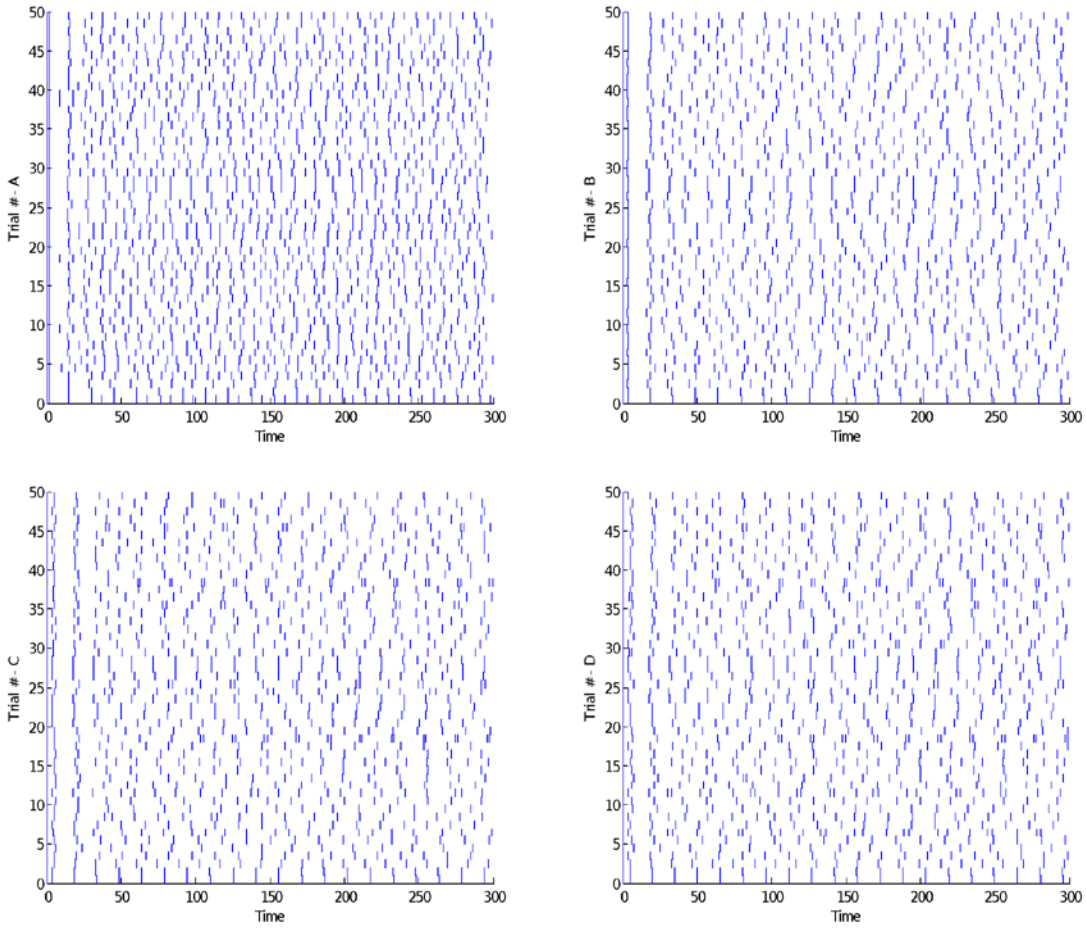

Fig. 15: The spike raster plot of fifty random trials on 4 neuron motif in young group.

For the aging group, the spike raster plot is shown in Fig. 15.

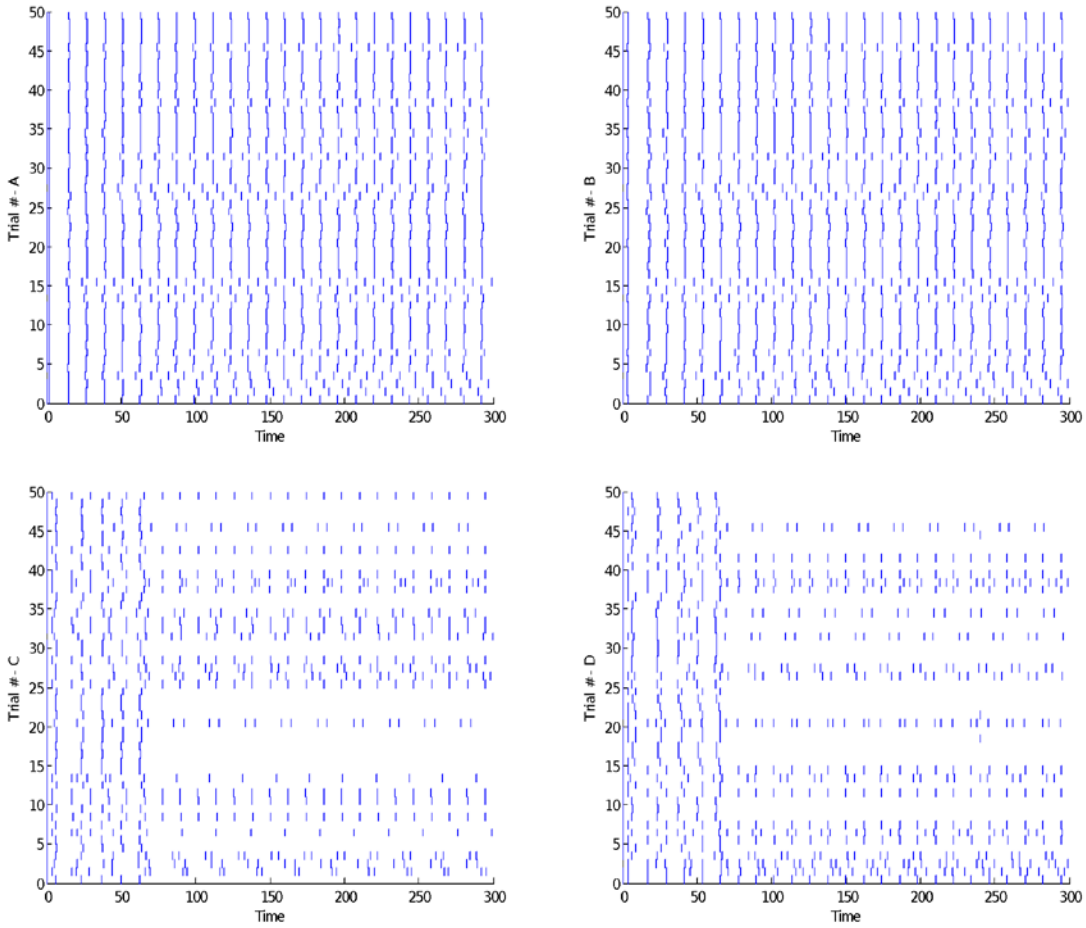

Fig. 16: The spike raster plot of fifty random trials on 4-neuron motif in aging group.

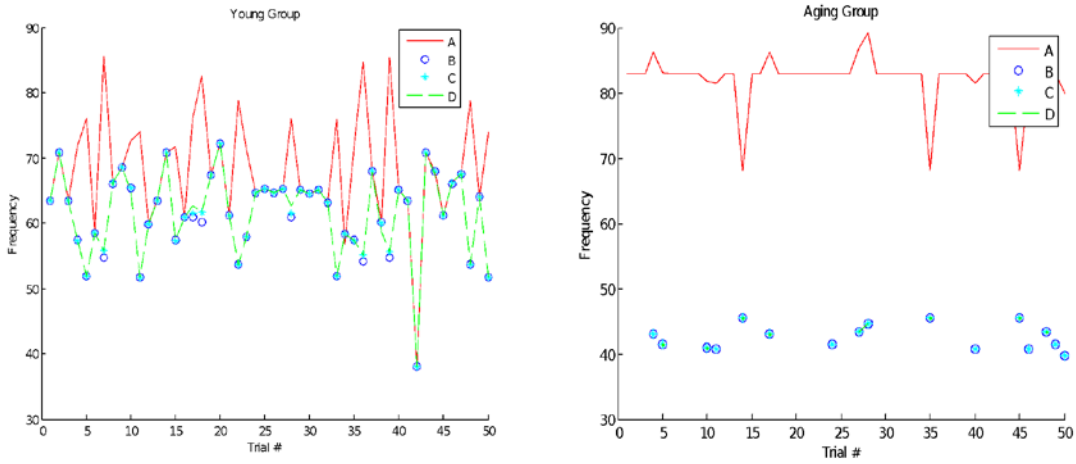

Fig. 17: Spiking frequency against trials in both young and aging group.

As shown in the above Fig.15, Fig.16 and Fig. 17, neuron C and D in aging group cannot spike in some trials, which indicates information loss. In addition, the spiking pattern of neuron A and B are also less than in the young group.

In conclusion, the main differences between young and aging group is shown as the Table 1 below:

Young Group	Aging Group
Signal retaining	Signal lost
Diversity of spiking pattern	Lost of spiking pattern
More synchronization pattern	Less synchronization pattern

Table 1: The differences between young and aging group based on the 4 neuron motif model.

Based on all of these, the aging group is featured in,

1. Weak neural network communication and plasticity (memory process[15]).
2. Disrupted neural synchronization (autism development[16]).

4. Conclusion

By using single neuron ML model and simple excitatory synaptic model as well as the 4 neuron motif model, we compare the effects of different parameters, including calcium ion, potassium ion, leak current and some others on the excitability and spiking capability in both young and old individuals. And the results clearly show that aging does suppress the neural spiking capability, disrupt the signal retaining ability of the neuron network, and weaken the sensitivity to external stimulus. In the future, applying some other single neuron models like Hodgkin–Huxley model and doing the corresponding comparison would be helpful to have a better understanding on the differences between young and aging neuron. In addition, quantifying more parameters involved in aging process and then applying to our model, as well as expanding the 4 neuron motif to a bigger scale like 50 neurons could show more sophisticated behavior and features of the network and provide more insight on the protection against aging and aging-related neurodegenerative disease.

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6. Reference

1. Campbell, Lee W., et al. "Aging changes in voltage-gated calcium currents in hippocampal CA1 neurons." *The Journal of neuroscience* 16.19 (1996): 6286-6295.
2. Handbook of Theories of Aging, Second Edition
3. http://neuronaldynamics.epfl.ch/online/Ch2.S2.html. Gerstner, Wulfram, et al. *Neuronal Dynamics: From Single Neurons to Networks and Models of Cognition*. Cambridge University Press, 2014.
4. Burke, Sara N., and Carol A. Barnes. "Neural plasticity in the ageing brain."*Nature Reviews Neuroscience* 7.1 (2006): 30-40.
5. De Luca, Annamaria, Mercede Mambrini, and Diana Conte Camerino. "Changes in membrane ionic conductances and excitability characteristics of rat skeletal muscle during aging." *Pflügers Archiv* 415.5 (1990): 642-644.
6. Landfield, Philip W. "'Increased calcium-current'hypothesis of brain aging."*Neurobiology of aging* 8.4 (1987): 346-347.
7. Montejo, N., et al. "Noise correlation length effects on a Morris-Lecar neural network." Physical Review E 72.1 (2005): 011902.
8. Hof, Patrick R., et al. "Age-related changes in GluR2 and NMDAR1 glutamate receptor subunit protein immunoreactivity in corticocortically projecting neurons in macaque and patas monkeys." *Brain research* 928.1 (2002): 175-186.
9. Alzheimer Diesase http://www.nejm.org/doi/full/10.1056/NEJMra0909142
10. Francis, Paul T. "The interplay of neurotransmitters in Alzheimer's disease." *CNS spectrums* 10.11 Suppl 18 (2005): 6-9.
11. Fernandez, Fernando R., and John A. White. "Reduction of spike afterdepolarization by increased leak conductance alters interspike interval variability." The Journal of Neuroscience 29.4 (2009): 973-986.
12. Bartzokis, George. "Age-related myelin breakdown: a developmental model of cognitive decline and Alzheimer's disease." *Neurobiology of aging* 25.1 (2004): 5-18.
13. http://www.britannica.com/EBchecked/topic/417103/node-of-Ranvier
14. Alkon, Daniel L. "Ionic conductance determinants of synaptic memory nets and their implications for Alzheimer's disease." *Journal of neuroscience research*58.1 (1999): 24-32.
15. Fell, Juergen, and Nikolai Axmacher. "The role of phase synchronization in memory processes." *Nature Reviews Neuroscience* 12.2 (2011): 105-118.
16. Dinstein, Ilan, et al. "Disrupted neural synchronization in toddlers with autism."*Neuron* 70.6 (2011): 1218-1225.
17. Bhat, Rekha, et al. "Astrocyte senescence as a component of Alzheimer's disease." *PloS one* 7.9 (2012): e45069.
18. Chua, Sook W., Michael Kassiou, and Lars M. Ittner. "The translocator protein as a drug target in Alzheimer's disease." *Expert review of neurotherapeutics* 14.4 (2014): 439-448.
19. Isaacs AM, Senn DB, Yuan M, Shine JP, Yankner BA. Acceleration of Amyloid β-

Peptide Aggregation by Physiological Concentrations of Calcium. *The Journal of biological chemistry* 2006;281(38):27916-27923.

20. Papatheodoropoulos, Costas, and George Kostopoulos. "Age-related Changes in Excitability and Recurrent Inhibition in the Rat CA1 Hippocampal Region." European Journal of Neuroscience 8.3 (1996): 510-520.
21. Barnes CA, McNaughton BL. Physiological compensation for loss of afferent synapses in rat hippocampal granule cells during senescence. J Physiol. 1980;309:473.