A model of CA1 neurons with astrocytic input: a study of epileptiform bursting

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MOTIVATION

Temporal Lobe Epilepsy is a chronic neurological disorder that affects people worldwide. It is characterized by recurrent seizures which occur when a large population of neurons in the temporal lobe synchronize. The CA1 (Cornu Ammonis 1) pyramidal cell in the hippocampus is particularly susceptible to an electrical bursting behaviour that is common in these seizures, and thus is the focus of much research. However, recently it has been suggested that the synchronized bursting in CA1 cells is not caused by pathology of the neurons themselves, but by the astrocytes (Tian, 2005) - a type of glial cell known for its auxiliary role in structural, metabolic and functional support.

An understanding of the origin of this epileptiform bursting activity will be facilitated by the existence of a simple yet biologically realistic model that corresponds with current empirical data. Our goal is to create such a model.

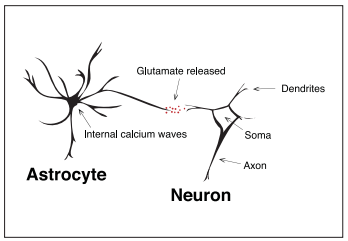

Figure 1: An astrocyte communicating with a neuron. Once activated, an astrocyte produces internal Ca^{2+} waves which results in the release of a neurotransmitter called glutamate. Glutamate is known to activate CA1 neuronal NMDA receptors, which may result in epileptiform bursting.

THE MODEL

To reproduce the bursting behaviour of the CA1 neuron, we created a 2-compartment model (Fig. 2) similar to the CA3 neuron model of Pinsky and Rinzel (1994). This is established by clumping the soma and proximal dendrites into one compartment, and the distal dendrites into the other.

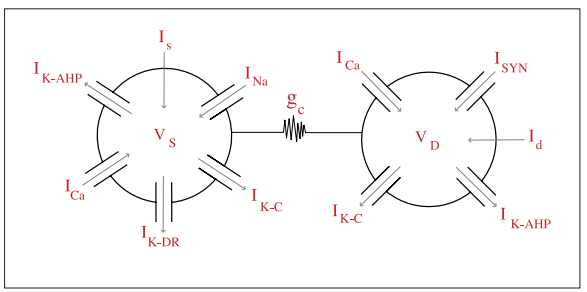

Figure 2: The schematic representation of our 2-compartment CA1 neuron model. The applied currents (I_S, I_d), inward and outward ionic currents, synaptic currents (I_{SYN}) and the coupling conductance (g_c) are shown.

We used a Hodgkin-Huxley model, treating the neuron as an electric circuit. Then the change in voltage can be represented in terms of the membrane capacitance, the ionic currents, synaptic currents, applied currents, and the coupling between the two compartments.

$$\frac{dV_s}{dt} = \frac{1}{C_m}\left\{-I_{leak,s} - I_{ionic,s} + \frac{g_c}{p}(V_d - V_s) + \frac{I_s}{p}\right\}$$
$$\frac{dV_d}{dt} = \frac{1}{C_m}\left\{-I_{leak,d} - I_{ionic,d} - \frac{Isyn}{(1-p)} + \frac{g_c}{(1-p)}(V_s - V_d) + \frac{I_d}{(1-p)}\right\}$$

where *s* and *d* distinguish between the somatic and dendritic compartments respectively, and I_{ionic} represents the ionic currents through the appropriate channels.

These ionic currents are given by

$$I_i(t) = \bar{g}_i y^p z^q (V - E_i)$$

where I_i is the curent through the ion channel i, $\bar{g}_i$ is the maximal conductance of i, y and z are the gating variables, V is V_d or V_S depending on where i is located, and E_i is the equilibrium potential for the ion i.

How do CA1 neurons communicate with each other?

When excited, the presynaptic neuron releases neurotransmitters into the synaptic cleft to signal its postsynaptic neighbour. According to Pinsky and Rinzel (1994), these neurotransmitters primarily activate the AMPA receptors on the postsynaptic neuronal membrane. We represent this dynamic by

$$I_{AMPA} = g_{AMPA} X_{AMPA} (V_d - V_{syn})$$

where

$$\frac{dX_{AMPA}}{dt} = H(V_s - V_{AMPA}) - \frac{X_{AMPA}}{\tau_{AMPA}}$$

and H(x)=1 if x≥0, and 0 otherwise. τ_{AMPA} is the time constant with which the AMPA-activated channels close.

How do astrocytes communicate with the CA1 neuron?

An activated astrocyte produces internal Ca^{2+} waves, and as a result glutamate is released into the extracellular space (Fig. 1). The glutamate activates NMDA receptors on the neuron's dendrites, creating a slow inward current (SIC) into the cell (Fig. 4).

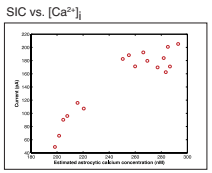

Figure 4: A rise in the internal astrocytic Ca^{2+} level results in an increase in neighbouring neuronal inward current. Figure taken from Parpura,V. & Haydon,P.G., 2000.

We can represent this dynamic with:

$$I_{NMDA} = g_{NMDA} X_{NMDA} (V_d - V_{syn}) / (1 + 0.28 e^{-0.062(V_d - V_{syn})})$$

where

$$\frac{dX_{NMDA}}{dt} = f([Ca^{2+}](t)) - \frac{X_{NMDA}}{\tau_{NMDA}}$$

$f([Ca^{2+}](t))$ is a function of the Ca^{2+} concentration that we determined by fitting it with Parpura and Haydon's data (Parpura, 2000) (Fig. 4). τ_{NMDA} is the time constant with which the NMDA-activated channels close.

Then our total synaptic current is:

$$I_{syn} = I_{AMPA} + I_{NMDA}$$

RESULTS

The qualitative accuracy of our model is best decribed by the following simulations:

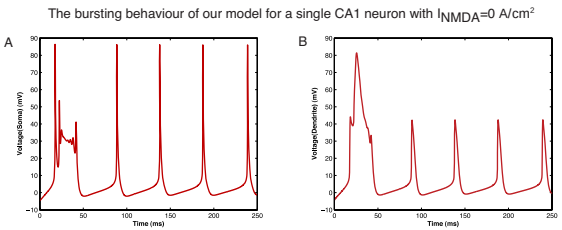

Figure 5: An applied current to the dendrite compartment of I_d=1.75 A/cm² results in a full burst followed by repetitive action potentials in the soma compartment (A) and in the dendrite compartment (B). This behaviour accurately models the characteristic bursting behaviour of hippocampal CA1 neurons (Traub, 1979).

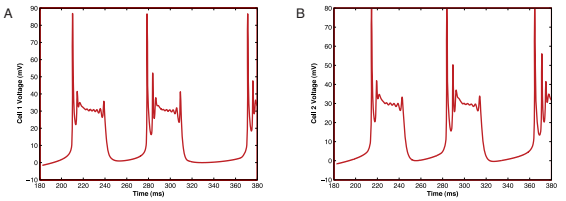

Figure 6: We reduced the K^+ conductance in two slightly different cell models (A: $V_{S,cell1}$, B:$V_{S,cell2}$) to simulate the application of a K^+ channel blocker (4-AP). This caused repetitive and synchronized epileptiform bursting behaviour, coinciding with Tian's experimental results (Tian, 2005). Both I_{NMDA} and I_{AMPA} are present, and Ca^{2+}(t)=87*exp(0.0094*250*exp(-0.075t)) nM.

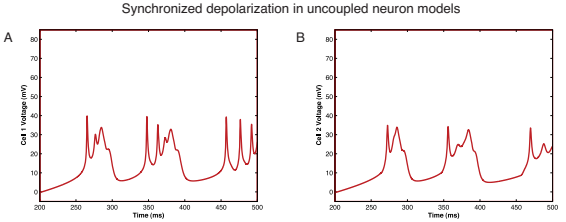

Figure 7: The connection between two modelled neurons has been cut by setting the AMPA conductance to zero and by reducing the Na^+ and Ca^{2+} conductances. However, the neuron models have paroxysmal depolarization shifts (PDSs) that maintain their synchrony. This replicates the experimental findings of Tian et al. (2005), which suggests astrocytes are responsible for the synchronous bursts, not neurons, since I_{NMDA} is present but not I_{AMPA}. (A: $V_{S,cell1}$, B:$V_{S,cell2}$). Again, Ca^{2+}(t)=87*exp(0.0094*250*exp(-0.075t)) nM.

CONCLUSION AND COMMENTS

We have created a 2-compartment model to represent coupled CA1 neurons with their Ca^{2+}-dependent astrocytic input. This enables us to explore the possibility that astrocytic pathology may be the root of hippocampal seizures, a hypothesis made by researchers such as Tian et al. (2005). Qualitative effects of the astrocyte-neuron dynamics were shown to coincide with recent empirical data (Tian, 2005), while biologically realistic parameters were maintained. Because of the simplicity of the model, potential future projects are plentiful. For example, the model can be expanded to a large network, and neuron dynamics with various amounts of astrocytic involvement can be examined.

LITERATURE CITED

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FOR FURTHER INFORMATION

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