A minimal biophysical model of phase precession

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Abstract

Place cells are excitable pyramidal neurons in the hippocampus. These neurons fire preferentially to a rat's location in the environment, which is referred to as the place field. Place cells also fire preferentially to a particular phase of the theta rhythm, which is an electroencephalograph recording of the hippocampus observed in rats during exploratory movement. As the rat moves through a place field, the particular phase of the theta rhythm at which the place cell fires has been observed to systematically precess, i.e. firing occurs at progressively earlier phases of the theta rhythm. The underlying neural mechanism of phase precession might be the basis of a temporal code utilized for further information processing in the hippocampus. We construct a network model of connected neurons in order to generate phase precession. Each neuron is modeled by considering a conductance based cell model.

1 Introduction

Our objective of this paper is to model the phase precession phenomenon. We explore a minimal biophysical model adaptation of the Hodgkin and Huxley model to capture the firing patterns of place cells and local interneurons [1]. Once we model the spiking behavior of the place cells and interneurons, we will connect them in a network. Our aim is to generate phase precession using this network.

O'Keefe and Nadel observed that place cells in the hippocampus of rats fire preferentially to their location in the environment [10, 9, 12]. This preferred location of firing is referred to as a place field. Place fields have been observed while a rat has freedom of movement in a confined space regardless of size and shape [6]. This phenomenon can be witnessed by looking at recordings of these neurons and observing increased firing frequency at specific locations within the environment. This evidence supports the idea of place cells being neural substrates of a cognitive map, i.e. a neuronal representation of

the environment [10, 9].

CA3 is an area of the hippocampus containing interneurons and pyramidal neurons or place cells, both terms used interchangeably. Interneurons inhibit place cell firing via a neurotransmitter GABA. Place cells excite interneurons via a neurontransmitter glutamate. These neurons vary in morphology allowing division of the CA3 area into three regions based on these morphologies [7]. In our paper we focus on place cells and interneurons in the CA3b region [7].

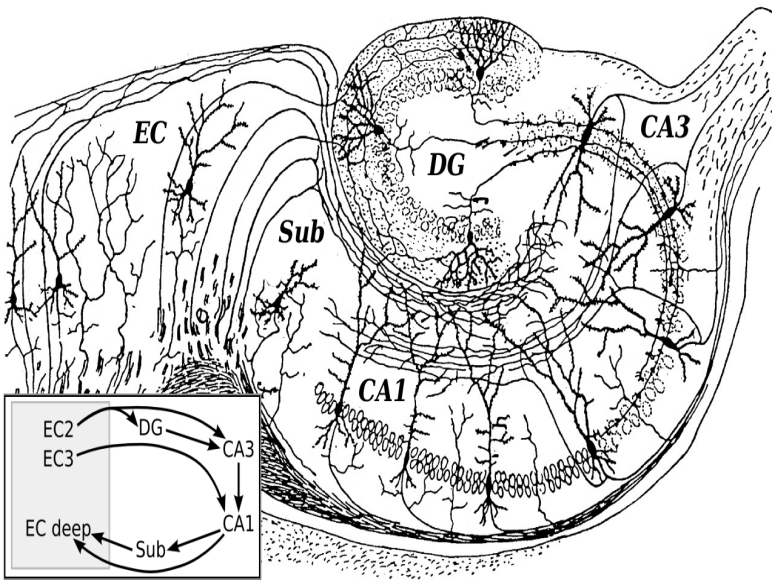

Figure 1: The hippocampus with various regions labeled including the CA3 region which receives input from the dentate gyrus (DG) and the enthorial cortex (EC).

Theta oscillations are electroencephalograph recordings of the hippocampus typically between 4-12 Hertz [10, 11]. These oscillations are the result of multiple complex interactions of regions in the hippocampus, entorhinal cortex and medial septum [5]. Comparitively speaking, theta osciallations in rats are more correlated with motor movement or exploratory activity and during the REM sleep cycle [13]. The precise utlity or function of the theta rhythm is unknown but one school of thought believes it to be associated with spatial information processing, i.e. a mechanism for the rat to keep track of its location in the environment [10, 9]. Place cells have been observed to fire preferentially to particular phases of the the theta rhythm. As a rat runs through the place field, the phase at which place cells fire occurs at progressively earlier phases, i.e. phase precession [4, 10, 3].

Our method is to first construct a simplified version of a conductance based neuron model that captures the firing patterns of place cells and interneurons. After analyzing the behavior of uncoupled neurons, we will couple the cells into a network and explore changes in synaptic and network connectivity in order to study the generation of phase precession.

2 Model Description

In the following section we describe how neuronal place cell and interneuron cell dynamics may be captured by considering the electrical properties of the cell membrane.

Neurons including place cells generate and propagate electrical signals by a sudden increase in the membrane voltage, i.e. an action potential [8]. Charged particles called Ions move in and out of the neuron resulting in a change of membrane voltage potential. The charged particles flow through the cell membrane via voltage-gated ion channels, which are embedded proteing in the cell membrane. The charged particles we consider are sodium ions Na^+ and potassium ions K^+ both with positive charge.

There are two mechanisms by which these ions move through their memebrane channels. They diffuse through the membrane to move down their concentration gradient or by an electric potential gradient [8]. Ions diffuse down their concentration gradient means they move from an area of high concentration to an area of low concentration, however, this movement results in an electic potential that works against diffusion. The Nernst Equilibrium of the ion is reached when these these two opposite forces equal each other and there is no cross-membrane potential [8]. We refer to E_{Na} and E_K as the Nernst Equilibrium potentials of sodium and potassium, respectively.

Let the total sodium current be:

$$\left\{ \begin{array}{rcl} I_{Na} & = & g_{Na}(V - E_{Na}), \end{array} \right. \tag{1}$$

where g_{Na} is sodium conductance and (V-E_{Na}) is the difference between the cell membrane potential and the Nernst Equilibrium of sodium. Observe that total current of sodium is zero if the cell membrane potential equals the Na^+ Nernst Equilibrium.

Similarly, let total potassium current be:

$$\left\{ \begin{array}{rcl} I_K & = & g_K(V - E_K), \end{array} \right. \tag{2}$$

As mentioned previously, we are considering voltage-gated ionic channels. This means ionic channels open or close due to changes in the membrane potential,i.e. they may

activate or inactivate. If we let m be the proportion of sodium channels in the active state, then I_{Na} becomes:

$$\left\{ \begin{array}{rcl} I_{Na} & = & g_{Na} m (V - E_{Na}), \end{array} \right. \tag{3}$$

Similarly, if n is the proportion of potassium channels in the active state, then I_n becomes:

$$\left\{ \begin{array}{rcl} I_K & = & g_K n (V - E_K), \end{array} \right. \tag{4}$$

By Kirchhoff's law, we consider the total current, I, flowing through a patch of membrane to be:

$$\left\{ \begin{array}{rcl} I & = & C\dot{V} + I_{Na} + I_K + I_L, \end{array} \right. \tag{5}$$

where $C\dot{V}$ is the capacitve current and I_{Na}, I_K are sodium and potassium currents respectively [8]. I_L is current leaking from the cell and I is considered to be current from an alternative source, e.g. injected current.

The neuronal dynamics of each pyramidal place cell can be modeled by considering the rate of change of membrane potential, activation kinetics of a Na^+, and the activation kintetics of a K^+. Let the rate change of the membrane potential be described by:

$$\left\{ \begin{array}{rcl} C\dot{V} & = & I - g_L(V - E_L) - g_{Na} m_\infty(V)(V - E_{Na}) - g_K n (V - E_K), \\ \\ \dot{n} & = & \dfrac{n_\infty - n}{\tau(V)}, \end{array} \right. \tag{6}$$

with,

$$\left\{ \begin{array}{rcl} m_\infty(V) & = & \dfrac{1}{1 + exp\frac{V_{half} - V}{k_m}}, \\ \\ n_\infty(V) & = & \dfrac{1}{1 + exp\frac{V_{half} - V}{k_n}}, \end{array} \right. \tag{7}$$

m_∞(V) and n_∞(V) were derived using voltage-clamp experimentation [8]. They are functions of voltage which give the asymptotic vaule of the proportion of open gates for a particular voltage membrane potential, see Figure(2). Since the range of these functions is between 0 and 1, the probability of the sodium gate being open is m_∞(V). Similarly the potassium gate has probability n of being in the open state. $\dot{n}$ describes the rate at which the potassium gates open. The sodium gate activates instantaneously, i.e. m instantly reaches its asymptotic value for a given membrane potential, and therefore $\dot{m}$=0. τ(V) is the time constant which controls how fast the potassium gate opens, i.e. a higher τ(V) value results in slower potassium gate activation.

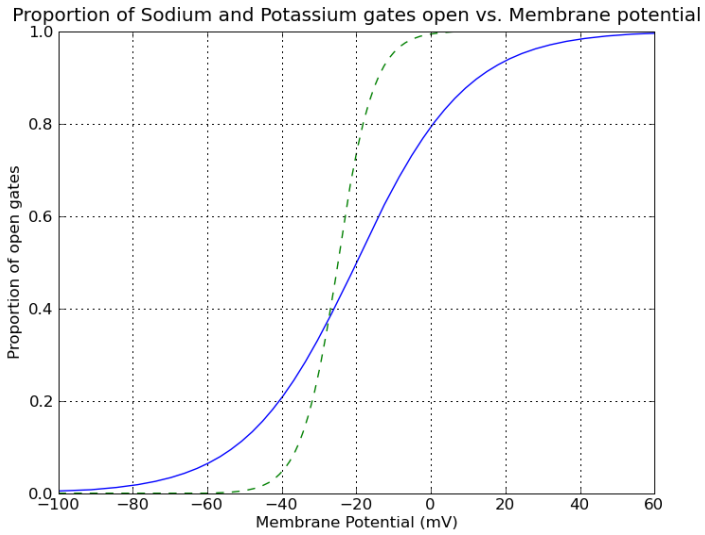

Figure 2: Steady State curves for sodium, $m_\infty(V)$ (solid line), and potassium, $n_\infty(V)$ (dotted line), activation gates. Both gates are sensitive and thus open as the membrane potential increases.

3 Analyzing a Place cell

In order to capture firing patterns outside of the network, we analyze an uncoupled place cell in this section. We can investigate the dynamics of our place cell via phase plane analysis. This gives us insight to the changes in the qualitative behavior based on changes in parameter values. Refer to the Table below for parameter values used in the following numerical simulations [8].

Parameters	Value	Biological meaning
C_m	$1\frac{uF}{cm^2}$	membrane capacitance
g_{Na}	$20\frac{mS}{cm^2}$	sodium conductance
g_k	$10\frac{mS}{cm^2}$	potassium conductance
g_L	$8\ \frac{mS}{cm^2}$	leak conductance
E_{Na}	60 mV	Reverse potential for sodium current
E_k	-90 mV	Reverse potential for potassium current
E_L	-78 mV	Reverse potential for leak current

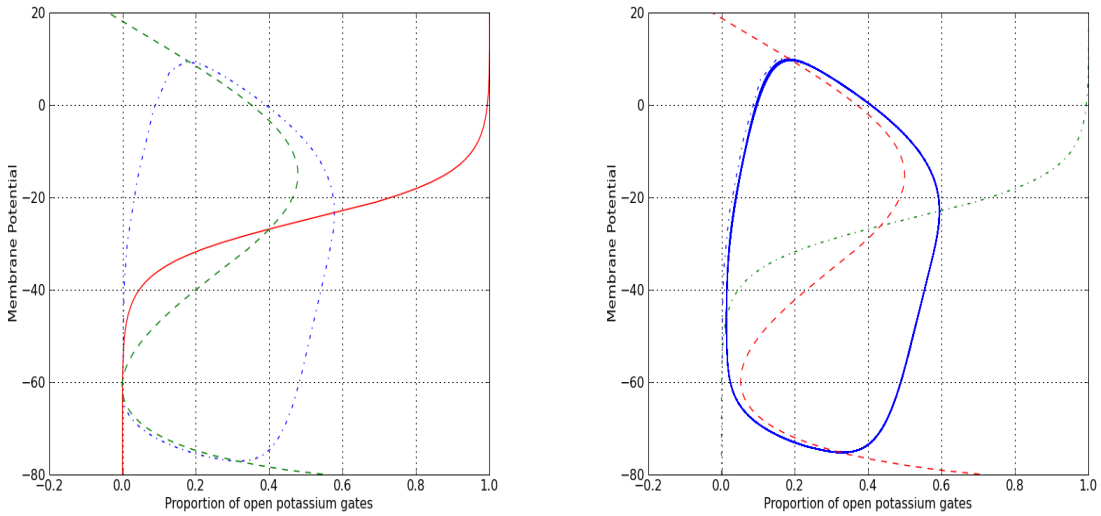

Figure 3: **Left:** Increasing the external current, I, results in a saddle-node bifurcation. This coalescence of two equilibrium points occurs on a homoclinic orbit, shown as a dash-dotted curve. **Right:** Saddle-node bifurcation on an invariant circle. The limit cycle results from injected current exceeding I $>$ 5.

3.1 Membrane potential dynamics and class 1 excitability

Class 1 excitability is a classification of neurons based on their response to injected current. These neurons are sensitive to the externally applied current, they exhibit low spiking frequency, and increase in their spiking frequency in response to increased injected current, see Figure (4) . If v_{half} = -25 in the function n_∞(V), i.e. half of the potassium gates open at -25mV, then a place cell will exhibit class 1 excitability. If no current is injected into the system, i.e. I=0, then there are three equilibrium points represented by the intersection of the V and n nullclines. As shown in Figure(3), increasing the injected current two equilibria coalece and the system bifurcates into a stable limit cycle via saddle-node on an invariant circle bifurcation. This results in sustained oscillations for the membrane potential.

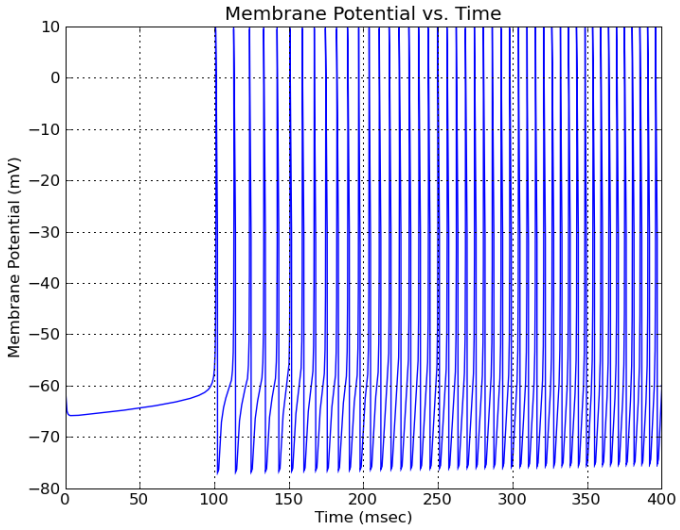

Figure 4: Injected ramp current on Class 1 excitable neuron. Notice the spiking delay and increased spiking frequency due to increased current.

3.2 Membrane dynamics and class 2 excitability

Class 2 excitability is a classification of neurons which remain relatively insensitive to increased external current. If we assume v_{half} = -45mV, then the system will display class 2 excitability. As shown in Figure(5), the V and n nullclines intersect at one location marking an equilibrium point. If we apply no current to the place cell, the membrane potential will approach the resting state around -78 mV, i.e the only stable point is the expected resting potential of the place cell. Applying current, I $>$ 5, the membrane potential undergoes sustained oscillations indicative of a stable limit cycle, see Figure (6). As current is applied, the v-nullcline is moving up on the phase space such that the equilibrium point loses stability via Hopf bifurcation. Also, the membrane potential exhibits damped subthreshold oscillations, see Figure(7). This is chatacteristic of a resonating neuron. In dynamical systems terms, this means the resting potential lies near Hopf bifurcation. These neurons prefer external input an a narrow frequency band [8]. Unlike integrating neurons, resonators don't have a clearly defined threshold from resting to spiking. Merely applying high frequency current may not result in an action potential.

If the threshold for potassium gate activation is increased to v_{half} to -25mV in the function n_∞(V) and adjusting τ(V) = 0.16, there exists three equilibrium points with no applied external current as described previously, see Figure (8). Increasing the external current results in the appearance of a limit cycle from a saddle homoclinic orbit bifurcation, see Figure (9). The homoclinic orbit connects to a saddle instead of a saddle-node as discussed previously. Applying ramp current results in a delay to spking, characteritic

of an integrator, see Figure(10). These neurons prefer high frequency external input. A neuron may be an integrator or resonator, i.e. it may have a resting state near either a saddle homolcinic or Hopf bifurcation respectively, and exhibit class 2 excitability.

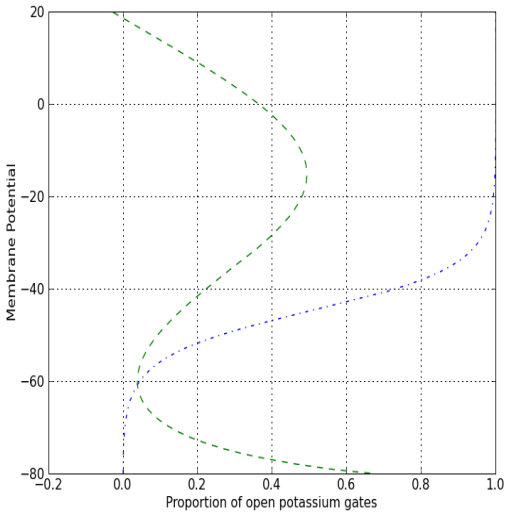

Figure 5: Increasing the injected current, I $>$ 4, results in a saddle homoclinic orbit bifurcation.

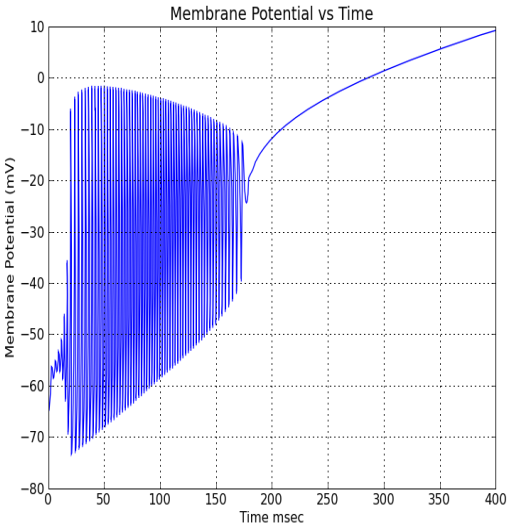

Figure 7: Injected ramp current, i.e. increasing current over time, elicits a supercritical hopf bifurcation from resting potential to periodic spiking.

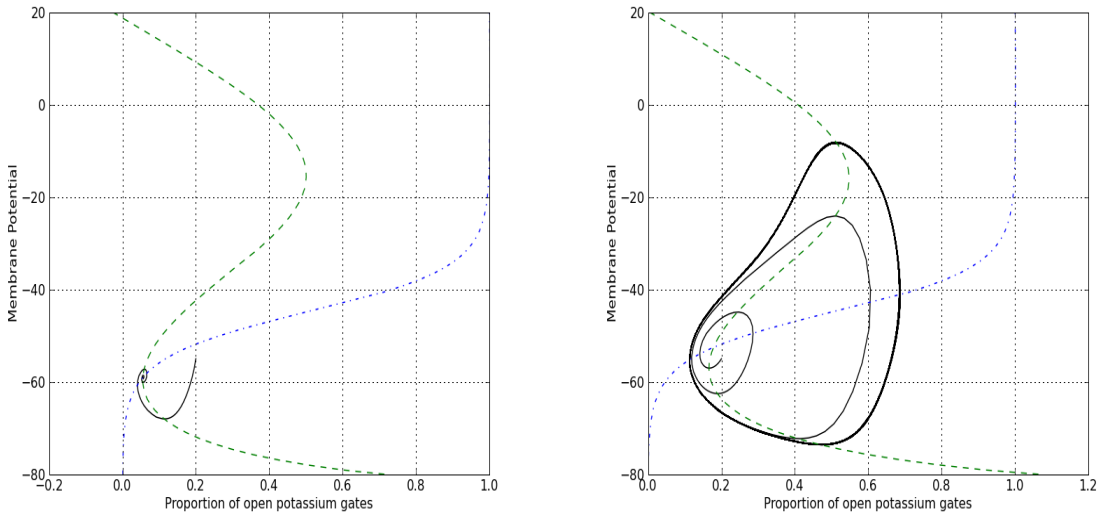

Figure 6: **Left:** Appling ramp current to the membrane potential results in a delay to spiking. Further increase in the injected current gives increased spiking frequency. **Right:** Increasing the injected current, I > 4, results in a saddle homoclinic orbit bifurcation.

3.2.1 Saddle homoclinic orbit bifurcation

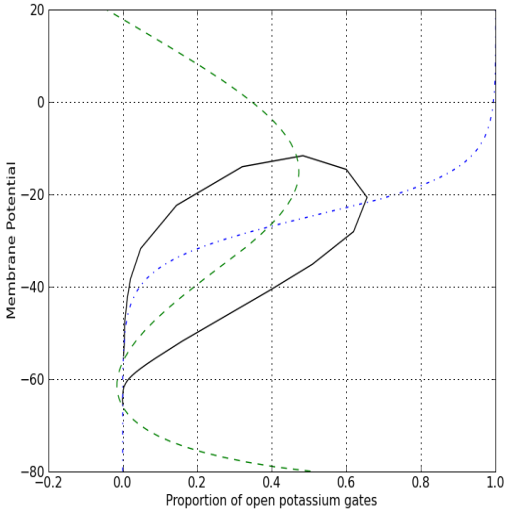

Figure 8: Adjusting the model parameters such that the potassium gates open at a faster rate, i.e. $\tau = 0.16$, and injecting no current results in three equilibrium points represented by the intersecting null-clines. The solid solution curve settles to the stable equilibrium point representing the resting membrane potential.

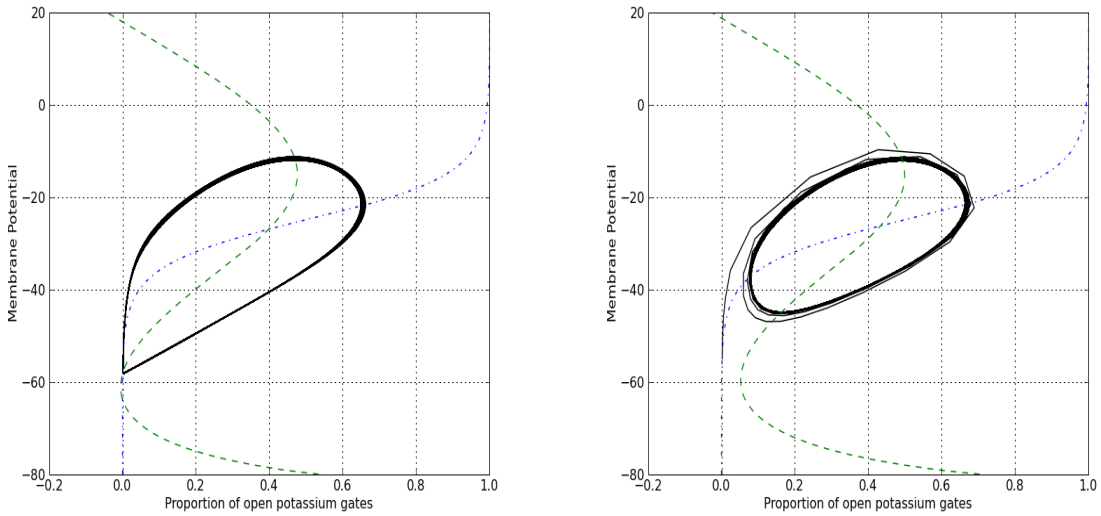

Figure 9: **Left:** The solid curve represents a homoclinc orbit at the saddle point. **Right:** Increasing the externally applied current, I $>$ 4, results in a saddle homoclinic orbit bifurcation.

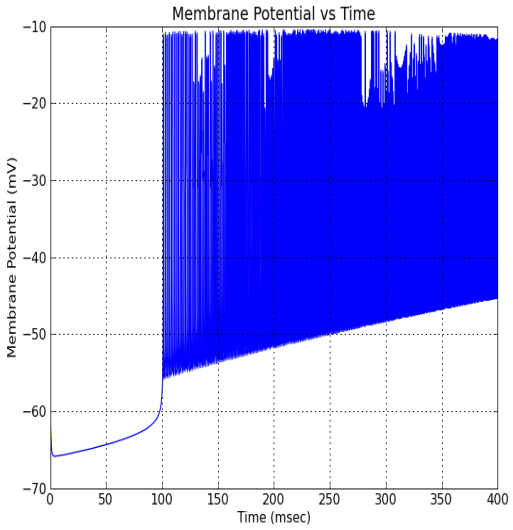

Figure 10: Appling ramp current to the membrane potential results in a delay to spiking. Further increase in the injected current gives increased spiking frequency.

Hodgkin neuron excitability classifications are determined by the spiking pattern of the membrane potential when applying external ramp current. In terms of dynamical systems, class 1 excitability is observed in neurons near saddle-node bifurcations on invariant circles. Class 2 excitability is observed in neurons near both Hopf and saddle homoclinic orbit bifurcations. Therefore, a class 2 neuron may either be a resonator or an integrator characterized by the resting state lying near either a Hopf or saddle homoclinic orbit bifurcation respectively. In the following section, a network of resonating neurons exhibiting class 2 excitability is contructed.

4 Coupling a place cell and an interneuron

We will use a network of neurons proposed by Bose and Reece, see Figure (4.1) [2]. They propose a one place cell P, two interneurons I_1 and I_2, a theta modulator T and a dentate gyrus cell D. The place cell receives slow inhibition from interneuron 2, I_2, which in turn receives fast inhibition from the theta modulator, T. Interneuron 2 also recevies slow inhibtion from interneuron 1, I_1. I_1 receives fast excitation from the place cell and fast inhibition from the theta modulator. The dentate gyrus cell, D, excites the place cell once the rat has entered a place field.

4.1 Synaptic connections

GABA is a neurotransmitter that is released from the presynaptic cell and binds to the postsynaptic cell inhibiting an action potential. We model inhibitiory connections as outward flowing currents. Glutamate is a neurotransmitter which elicits an action potential. It is defined as an inward flowing current. Both excitatory and inhibitory synaptic connections are defined by:

$$\left\{ \begin{array}{rcl} I_{xy} & = & g_{xy} w_{xy} (V_x - V_{xy}), \end{array} \right. \tag{8}$$

where x is the presynaptic cell and y is the postsynaptic cell. We vary V_{xy} to achieve fast and slow inhibtion or excitation.

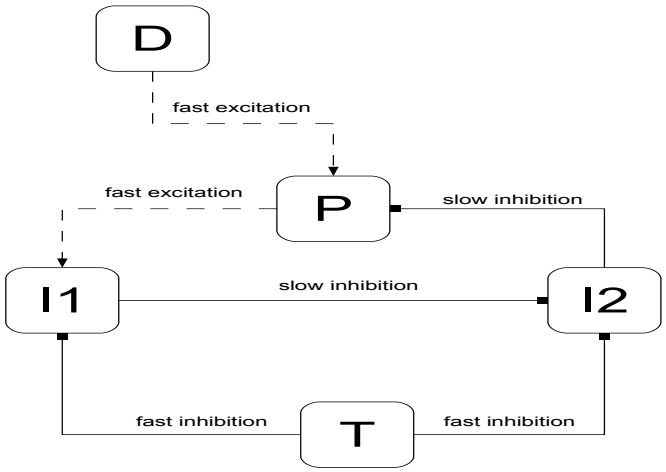

Figure 11: Network diagram showing connectivity among neurons in the hippocampus.

5 Results

The network exhibits two behaviors, the rat outside of the place field and the rat inside the place field. When the rat is outside the place field we expect synchronization of the place cell and the theta modulator. The theta modulator inhibits I_2 which in turn inhibits the place cell, therefore the place cell is synchronized with theta. Once the rat enters the place field, the place cell gets a one-time dose of excitation from D, the dentate gyrus. This causes the place cell to elicit an action potential from I_1, which inhibits I_2 thus the place cell is freed from the theta modulator. As a result the place cell will fire at progressively earlier phases of the theta modulator. Eventually the theta modulator will gain control of I_1 and I_2 and return the place cell to theta phase synchronization.

As shown in Figure (5), give a breif 1 millisecond excitation to P from D. The place cell then systematically precesses for the next 5 cycles of theta, T. After 1 second, T is able to recaputre and inhibit I_1 and I_2 which in turn inhibits P to bring both P and T back to synchroniztion. However the model doesn't exactly exhibit the behavior we expect. First the place cell doesn't always stay synchronized with theta before we give the brief dose of excitation. Second the place cell goes in and out of phase with theta after phase precession. In order to solve these problems, we need to explore synaptic strengths between all the neurons. It is important to have both interneurons synchronized with theta since they keep the place cell phase-locked with theta.

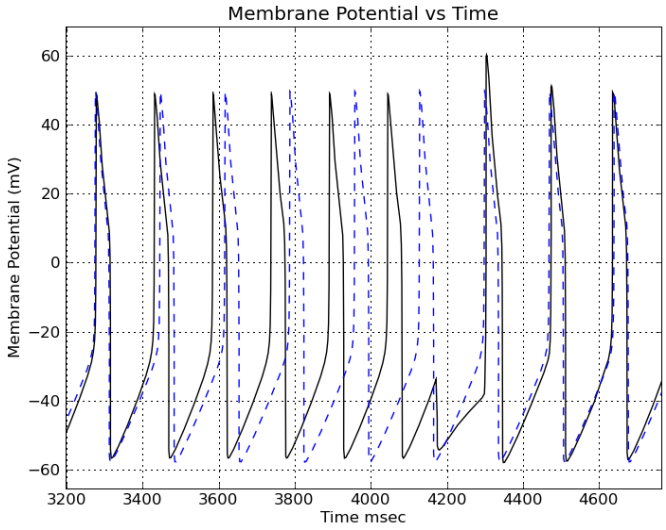

Figure 12: Theta modulator is represented as the dotted line and the place cell represented as the solid line. Beginning at 3.5 seconds, place cell phase precesses until synchronization around 4.3 seconds.

6 Discussion

In order to generate phase precession from a network of neurons in the hippocampus, we began by constructing a place cell. This was done by using a simplified version of a Hodgkin Huxley type model of an excitable neuron. We derived the model based on Ohm's law and expressing the change of membrane potential as summing the inward flowing current, sodium, and the outward flowing currents including potassium and the leaky current.

We assumed the voltage-gated sodium current opens instantaneously and the potassium gate opens at a slower rate governed by $\dot{n}$. The potassium and sodium gate channels open as the membrane potential increses, therefore the proportion of open gates is a function of the membrane potential. The asymptotic vaules of the proportion of open gates are governed by a sigmoid fucntion ranging from 0 to 1. As stated previously we assume the sodium gate instantaneously reaches this aymptotic vaule of proportion of gates open but the potassium gate exponentially grows or decays toward its aymptotic vaule goverened by the time constant $\tau(\mathrm{V})$. Varying the rate at which the potassium gate opens gives us qualitvative differnces in our membrane potential solution curve, i.e. the spiking behavior of our neuron.

Assuming half the potassium gates are open at a relatively high membrane potenital we get class 1 spiking behavior. This behavior includes delay in spiking. Adding current

to this class 1 neuron results in a bifurcation from the resting state membrane potential to periodic solutions or spiking as a result of a birth of a limit cycle from saddle-node bifurcation on an invariant circle. This neuron has a clearly defined threshold to spiking and prefers high frequency external current. These neurons are called integrators, since integrating enough external current results in aciton potentials.

Assuming half the potassium gates open at a lower membrane potential, we get class 2 spiking behavior. The spiking frequecny is relatively insensitive to applied external current compared to class 1 spiking. Injecting current into the class 2 neuron results in periodic solutions of the membrane potentital via Hopf or saddle homoclinic orbit bifurcation. Decreaing the time constant τ(V), which is effectively increasing the rate of openning potassium gates, still gives us class 2 spiking behavior. However, the bifurcation from the resting membrane potential to periodic spiking is a result of saddle homoclinc orbit bifurcation. Therefore, a class 2 excitable neuron can either be a resonator or an integrator.

A network was constructed coupling resonating neurons exhibiting class 2 spiking behavior. The place cell excites one interneuron via glutamic excitation and is inhibited by another interneuron via GABA inhibition. Both interneurons receive fast inhibtion from the theta modulator. Interneuron 2 also receives inhibition from interneuron 1.

The network has two behaviors. The first behavior has the place cell and the interneuron synchronized with the theta rhythm. This occurs because the theta rhythm causes I_2 to spike after releasing it from inhibition which in turn causes the place cell to fire after it is released from inhibition from I_2. This synchronized behavior is behavior of the rat outside the place field where the place cell does not phase precess.

The second network behavior is desychronization. Once the rat enters a place field, the place cell is given a 1 millisecond pulse of excitation from the dentate gyrus, D. What this means, in terms of the network behavior, is that now the place cell fires before it receives inhibition from I_2. P can now fire at its own intrinsic frequency which is now greater than T, thus phase precession. I_1 fires as a result of the excitation from the place cell which inhibits I_2 from inhibiting the place cell. As long as the place cell excites I_1 we get desynchronization with respect to the theta rhythm. At a later time the theta rhythm is able to regain control of the interneurons which in turn gains control of the place cell resulting in synchronization. This marks the end of the place field. This is the basic scheme of how our model should work but as discussed previously we need to explore different synaptic strengths to capture this behavior.

Once we work out the bugs in our simulation we would like to address the dependency of phase precession on the network architecture. If it doesn't depend on network architecture, then given an all-to-all connectivity does phase precession depend on the synaptic weights. In future work we will explore different networks including all-to-all in order to address this issue.

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