A Single Pyramidal-Cell and Network Computational Model of the Hippocampal CA3 Region

Sami Utku Celikok1, Eva M. Navarro-López2, Neslihan Serap Şengör3
1 Biomedical Engineering Department, Boğaziçi University, Istanbul, 34342, Turkey.
2 School of Computer Science, The University of Manchester, Manchester, M13 9PL, UK
3 Electronics and Communication Department, Istanbul Technical University, Istanbul, 34469, Turkey
E-mail: utku.celikok@boun.edu.tr

The hippocampal formation consists of the dentate gyrus, the Cornu Ammonis (CA) subregions (also called hippocampus proper or Ammon's horn), the subiculum, and the entorhinal cortex. There are four histological subdivisions in the CA, namely: CA1, CA2, CA3 and CA4. Subarea CA3 has drawn attention for its major role in encoding spatial representations and episodic memories [1, 2]. Due to the presence of rich recurrent feedback connections, CA3 has been considered to play a key role in long-term memory formation. Moreover, CA3 has long been proposed as an auto-associative network capable of pattern completion and path integration for the retrieval and storage of episodic/declarative memory traces [3, 4]. It was hypothesised that a memory can be recalled using only a part of the memory as a cue [5]. CA3 may therefore be characterised as a pattern-completion network which auto-associatively matches new information coming from the entorhinal cortex with familiar experiences.

A broad range of experimental studies have supported the idea that hippocampal oscillations must be taken into consideration while investigating the region as a memory network [6]. Rhythmic oscillations in the hippocampal network have been shown to be related with memory functions in a behaviour-dependent context [7]. Empirically-validated studies on freely moving rats have identified two major oscillatory patterns of hippocampal activity: theta-(4–8 Hz) and gamma-band (30–100 Hz) frequency rhythms [8, 9]. Oscillations in these frequency ranges may occur separately or simultaneously and can interact with each other during memory functions [10]. Multiple memory items are maintained in the synchronised activity of neural assemblies. During memory load, items are maintained by synchronised activity in the gamma frequency-band range, and the overall refresh cycle of total memories held in mind is repeated at the theta frequency-band oscillations [11]. Additionally, the phase of theta oscillation modulates the amplitude of gamma oscillations [12]. All these facts might be considered as evidences for the interdependence of the two rhythms in memory encoding and retrieval [13].

In rodents and humans, gamma rhythms embedded into theta oscillations become prominent during memory functions, locomotion activities, object exploration, and spatial navigation, as well as during rapid-eye-movement sleep [1]. Theta-band activity is most pronounced in the CA1 region. However, recent studies have provided evidence that theta-band activity can be generated intrinsically in both CA1 and CA3 regions of the hippocampus [14, 15]. On the other hand, gamma rhythms are shown to be generated locally through synchronised activity in the CA3 pyramidal population. Unlike theta-band rhythms, gamma oscillations occur as a burst of spikes embedded into the theta cycle [16].

The understanding of the mechanisms underlying various frequency-band rhythms of network activity and their functions in memory acquisition is today a major problem in hippocampal neurobiology. The consideration of the spiking patterns of the neurons during oscillatory regimes is key to uncover the significance of hippocampal network oscillations in different processes. When the broad electrophysiological repertoire of CA3 pyramidal cells is considered, the computational description of the network requires a neural model. This model has to be simple enough to support a large hippocampal network, but still rich enough to capture complex pyramidal-cell dynamics. This is precisely what we propose here: a single-cell computational model for a CA3 pyramidal neuron that is used as the basic element to form a CA3 network model which will be able to reproduce key hippocampal oscillatory patterns. The spiking patterns of the offered single-cell model match with experimental pyramidal-cell responses and capture some essential features of well-known hippocampal spiking behaviour, such as: spike broadening at the end of a burst, rebound burst firing in response to a hyperpolarising input, low-frequency bursts, and high-frequency tonic spiking. Moreover, the model for the CA3 population is also able to generate theta and gamma-band oscillations, known to be present in the CA3 region. These theta and gamma rhythmic oscillations are generated regardless of the type of the input current, Poisson-like or direct current (DC).
Methods
Each individual neuron is modelled as a spiking point-like neuron of the threshold-firing type. We employ the model proposed by Izhikevich for spike generation [17]. However, we extend the standard Izhikevich's model by adding the conductance-based contribution of Ca²⁺ currents. Apart from this expansion, we also modify the computation of the recovery current and the reset conditions of the model parameters for the spike generation, in order to match the model's behaviour with experimental results. Since the proposed model is a simple model, we first determine the fundamental firing features of CA3 pyramidal cells to be considered for the single-cell model. This section gives a brief description of the CA3 pyramidal-cell physiology that is considered in the construction of our model.

Pyramidal neurons have multiple types of voltage-dependent potassium (K⁺), calcium (Ca²⁺), and sodium (Na⁺) channels, whose activation shapes the spike width; in addition, the subthreshold voltages modulate the firing frequency. In previous years, it has been shown that Na⁺ and T-type Ca²⁺ currents contribute to the bursting in CA3 pyramidal neurons [1]. Calcium-conductance dynamics are particularly critical for the generation of bursting envelopes. The expansion of the computational model by introducing the conductance-based current implementation along with an activation function whose value depends on the membrane potential has allowed us to reproduce the Ca²⁺ ion channel contribution and the membrane potential dependent on the ion channel efficiency. We also consider incomplete repolarisation in order to support fast-spike depolarisations during the bursting envelope in response to hyperpolarising inputs. A hyperpolarising current causes a burst of spikes as a drop in the membrane potential that recovers T-type Ca²⁺ channels from inactivation. The Ca²⁺ channels then open and cause a rebound excitation. Another interesting feature of CA3 firing is that as the depolarisation increases with the injected current, the neuron switches from regular bursting to irregular bursts to repetitive single-action potentials [18]. Further depolarisation increases the accessibility of Ca²⁺ currents and keeps the membrane potential high enough for repetitive single spikes. The ultimate goal is to interconnect the single-cell model to form a network. The network model successfully reproduces the hippocampal theta and gamma rhythms of the CA3 region. The CA3 population consists of 500 neurons which are connected to each other in a one-to-one fashion. For the simulations (10 seconds), we apply input currents in the form of Poisson-like or DC inputs.

Results
The firing behaviours of the single-cell model and the spectrogram results of the population model are given in Figure 1. In the model, the initial spike generation occurs after a long delay [19]. Apart from the spike latency, as the spike threshold is exceeded, the incomplete repolarisation causes a bursting envelope and an increased Ca²⁺-channel efficiency results in increased spikes within the bursting state. More, a brief hyperpolarising injection to the cell causes a burst of spikes after the hyperpolarisation is removed. Finally, a transition occurs in the spiking behaviour of the neuron model from low-frequency bursts to tonic spike trains as the injected current increases.

The population model is able to generate theta-band synchronised activity in response to a depolarising DC input (DC=350pA). The same oscillatory pattern is also observed while neurons are stimulated by a Poisson-like input. During the generation of gamma-band oscillations, the applied current increases to a level where the single-cell model is not able to fire in the gamma-band range; recurrent collaterals in the network make the population activity increase up to gamma frequency-band (DC=600pA). Additionally, the gamma-band activity is shown to be embedded in a theta cycle.

Conclusions
We have proposed an electrophysiologically-realistic and simple model that reproduces key features of the hippocampal CA3 region. The advantage of our model over existing ones is that, despite of its simplicity, it captures a wide variety of pyramidal-cell electrical dynamics at single-cell and network level. However, the results obtained should be tempered by an awareness of its limitations. A more practical use of the model can be achieved by its implementation in large-scale models for the characterisation of the brain rhythms observed in specific memory functions [20].

References