Extracellular synaptic and action potential signatures in the hippocampal formation: a modelling study

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Introduction

Simulating extracellular recordings of neuronal populations is a challenging task for understanding the nature of extracellular field potentials (LFPs), investigating specific brain structures and mapping cognitive functions. In general, it is assumed that extracellular recording devices (micro and/or macro-electrodes) record a mixture of low frequency patterns, mainly attributed to the synaptic currents and high-frequency components reflecting action potentials (APs) activity. Simulating such signals often require a high computational burden due to the multicompartmental neuron models used [1]. Therefore, different LFP proxies coexist in the litterature, most of them only reproducing some of the features of experimental signals [2]. This may be an issue in producing and validating computational models of phenomenons where the fast and slow components of neural activity are equally important, such as hippocampal oscillations [3]. In this work, we propose an original approach for simulating large scale neural networks efficiently while computing a realistic approximation of the LFP signal including both synaptic and action potentials extracellular signatures. We apply this method on a hippocampal network [4] and compare the simulated signal with intracranial measurements made on human patients.

Methods

Computational model. The first step of our method consists in simulating an anatomical and functional realistic hippocampal network, using the macroscopic hippocampal anatomy. The modelled hippocampal formation includes four of its areas (CA1, CA3, dentate gyrus and the entorhinal cortex) and contains more than 32.000 neurons placed in an anatomically realistic manner to be able to simulate various fast and slow oscillations rhythms. The neurons inside each of the 4 regions were simulated with minimal LFP producing morphologies (2 compartments, approximated thus by a dipole). Each neuron' dynamics was modelled using Hodgkin-Huxley type equations (a specific Calcium-Activated-Nonspecific / CAN channel was added for simulating a richer dynamics). The connections within and between the modelled regions were set according to the available neurobiological literature or tuned in order to obtain realistic outputs (various fast and slow oscillatory rhythms, such as theta-nested gamma oscillations and sharp-wave ripple complexes). For details of this model, see [4].

The input of the model was modelled as a random (Poisson) process with variable intensity (firing rate). This intensity / firing rate was extracted from the enveloppes of real depth EEG recordings from cerebral areas projecting onto the Entorhinal cortex of human epileptic patients (recorded during presurgical evaluation in the Neurology Service of the Nancy University Hospital - CHU Nancy).

The output of the model was the LFP generated by the network on an sEEG electrode, to be compared with real depth intrahippocampal sEEG signals (see Figure 1 for the localization of the electrodes). It is described in more details in the next section.

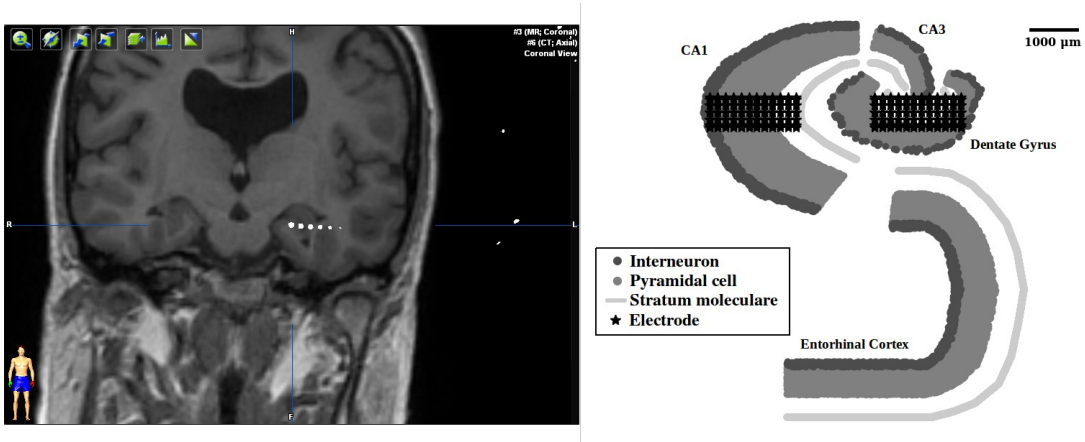

Figure 1 : Left - Coregistered CT-MRI image of the implantation of an SEEG electrode in the patient's hippocampus (coronal view). Right - Topology of the modeled hippocampal network.

LFP model. Realistic simulations of LFP imply compartmental neuron models with detailed morphologies. For a large population, these simulations are time consuming and need powerful computers. We propose to use a simpler approach. First, we modelled the extracellular potentials as a sum of synaptic and action potential related currents, assumed to be the main contributors [5]. Next, the contribution of synaptic currents was obtained by considering each pyramidal neuron as a fixed current dipole (between soma and dendrites). The generated electrical potentials (LFP) were computed at specific points in space, corresponding to the extracellular electrode positions, assuming that the propagation medium is homogeneous isotropic. We focused on the pyramidal neurons contributions, significantly higher than those of interneurons [2].

Concerning the extracellular waveforms of the action potentials, a realistic simulation might take into account several factors, such as the presence and density of specific ion channels for every compartment, the neuron morphology and the electrode position in relation to it [6]. Indeed, for compartmental models, the potential recorded by an extracellular electrode is a weighted sum of the membrane currents of all compartments, the weights depending on the medium conductivity and the distances between each compartment and the electrode (thus on the neuron geometry). For our population, we used the simplified model proposed previously [7] which consists of a lumped soma attached to an axon subdivided into fixed-length compartments. With this type of morphology, one can obtain the extracellular action potentials (EAP) using a fast morphological filtering approach [7]. The coefficients of the filter depend on the neuron morphology. Here, the axon diameter is set to 2 um for both types excitatory and inhibitory neurons and its length is 1000 um for the former and 400 um for latter. The axons of both populations for each hippocampus regions were oriented in a realistic manner. Having obtained the EAPs for every neuron, we next generated the total population contribution for each electrode by convolving the EAPs of each neuron with the raster plot given by the computational model described in the previous section and summing up.

The final simulated LFP, recorded by a finite electrode size, was obtained by a weighted average of synaptic and EAP contributions over the surface of the sEEG electrodes, sampled using a regular grid of 288 points.

Results and conclusions

To evaluate the how realistic our model is, we compared the frequency properties of our simulated signal and one recorded at the CHRU Nancy in an awake patient's hippocampus, presenting theta and gamma waves (see Figure 2 below). More precisely, we computed the norm of the difference between the real and simulated signal spectra on different frequency bands. By choosing a pair of weights balancing the contributions of the action potentials and the synaptic currents (called w_{AP} and w_{syn} respectively), it is possible to adapt our model so that it specifically reproduces either theta or gamma oscillations.

It should be noted that though action potentials and synaptic currents play a similar role in

determining the LFP in the gamma band, it is not true for lower frequencies, where the action potentials contribution is less significant.

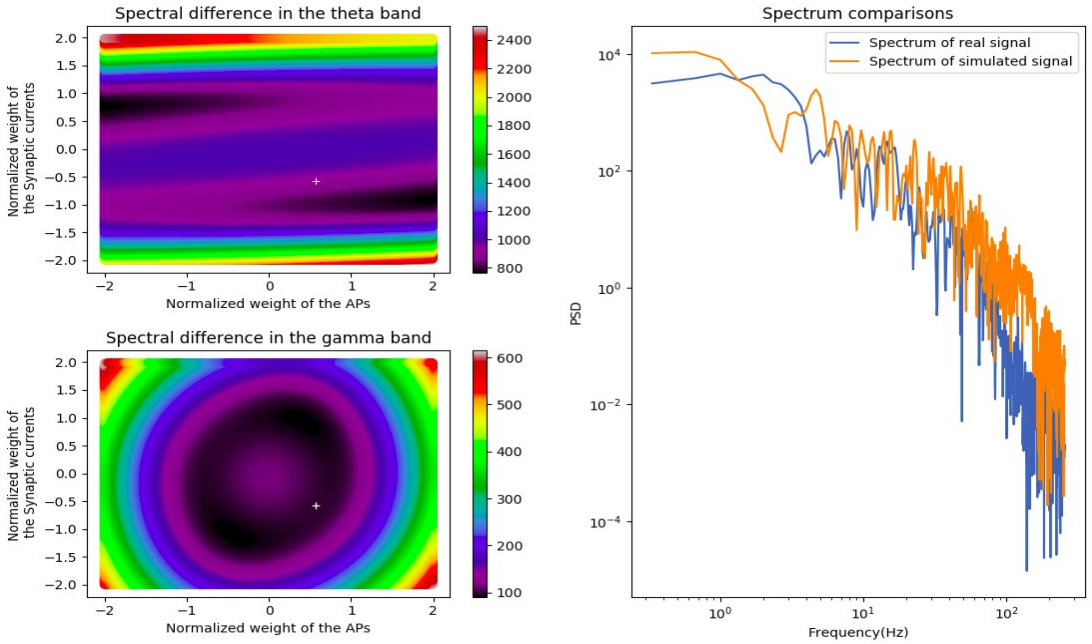

Figure 2 : Left - Observed difference in the frequency domain between the real and simulated signals, with varying contributions of the action potentials and synaptic currents, in the theta band (top) and gamma band (bottom). Right - Power spectrum of the real and simulated signals after optimal weighting of the AP and synaptic contributions to the LFP (w_{AP}=-$w_{syn,}$ white dot on the left images)

Overall, this work shows the importance of considering both action potentials and synaptic currents contributions to the LFPs, even in rather low frequency bands (such as gamma), while presenting a computationally efficient way of calculating them.

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