A large-scale network computational model of bilaterally coupled neuron-glia masses

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INTRODUCTION

Large-scale biophysically plausible computational models of brain activities are useful for understanding the mechanisms underlying the genesis of brain dynamics in healthy and pathological conditions [1]. However, many challenges are yet to be overcome and a mechanistic explanation comprising all the different phenomena observed in the brain is yet to be proposed. Indeed, for instance, for most computational models proposed in the literature, the large-scale models only account for the neuronal processes neglecting metabolic processes such as the astrocytic ones, and this may hinder the resulting data interpretation and meaning.

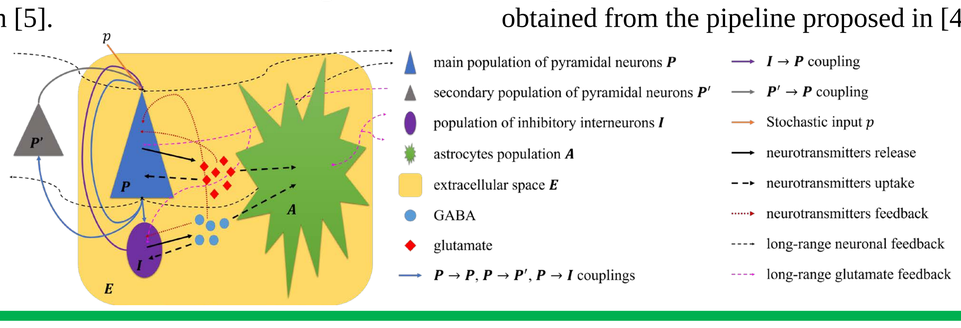
In this study we propose a step forward by introducing a large-scale (whole-brain) network model of bilaterally coupled neuron-glia masses, constrained by two different structural connectomes. This model notably embodies both metabolic and electrical activity at the mesoscopic brain scale. We propose as an illustration, a simulation scheme showing neurons firing blockage as a result of GABA excess at the *brain* scale and the impact of astrocytic network feedback on pyramidal cells and inhibitory interneurons.

METHOD

NETWORK MODEL *(an extension of the neuron-glia mass model introduced in [2,3])*

The **neuronal network** was based on a realistic human structural connectivity as obtained from the pipeline proposed in [4]. Artificial homotopic connections were added to it following the results presented in [5].

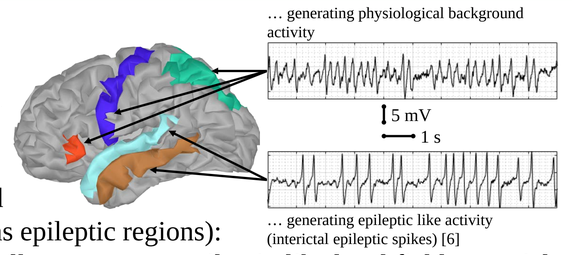
The **astrocytic network** was such that astrocytes pools only communicated to their nearest neighbors (as a first approximation, calculations were done using the information of the tract length matrix obtained from the pipeline proposed in [4]).



THEORETICAL EXPERIMENT

The main parametrizations were the following:

- Network composed of 998 regions of interest grouped in 66 larger regions (based on the Desikan-Killiany atlas [4])
- For two regions of the left hemisphere, the middle and superior temporal gyri (considered in this simulation as epileptic regions): neuron-glia masses (NGM) parametrized to preferentially generate an epileptic-like local field potential (LFP) activity [6] (the *Noise Induced Spiking* dynamical behavior [2]).
- For all other regions, NGM parametrized to undergo a noise-driven oscillatory mode (the *Noise Induced Spiking and Subthreshold Oscillations* dynamical behavior [2]).
- All the parameters of the astrocytes compartment were the same for all NGM.
- The diffusion coefficient for the impact of extracellular glutamate on the GABA flux was higher than on the glutamate flux.

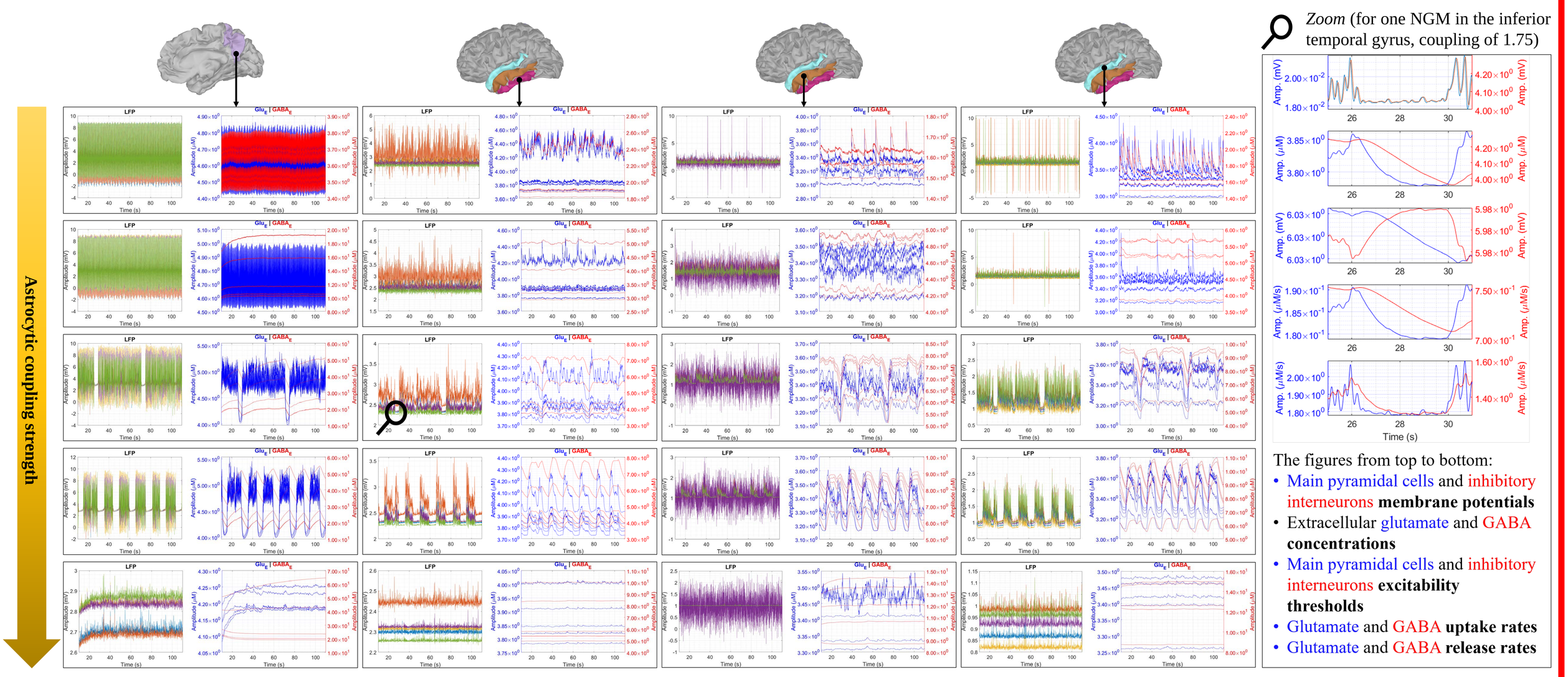


RESULTS

In the following figures, we report the simulated LFP in millivolt and extracellular glutamate/GABA (Glu_E/$GABA_E$) in micromole for:

- the time interval 10 to 110 seconds;
- five different NGM in each of the following four regions: the two epileptic regions, the right precuneus (far from the epileptic regions) and the inferior temporal gyrus (close to the epileptic regions);
- and five astrocytic coupling strength levels: 0, 1, 1.75, 2 and 3.

Summary of the simulated mechanism [see 🔍 *Zoom*]: When the extracellular glutamate concentration increases (graph 2), more inhibitory interneurons get activated (graphs 1 and 3) and more GABA get released (graph 5). Meanwhile, as the extracellular GABA concentration increases (graph 2), less pyramidal neurons get activated (graphs 1 and 3) and less glutamate are released up to a time when the pyramidal cells momentarily stop firing (*total* inhibition). At this moment, the inhibitory interneurons stop firing and the glutamate and GABA are slowly recycled allowing the pyramidal cells to recover their excitability. Finally, this cycle begins anew due to network interactions. This is a competition between glutamate release/uptake and GABA release/uptake at the (whole-brain) network level.



- For low astrocytic coupling: the epileptic regions displayed an alternance between isolated high amplitudes spikes and a quiescent phase (the duration of the quiescent phase increased as the astrocytic coupling increased) while the other regions displayed an oscillatory activity but a with slightly decreased peak-to-peak amplitude.
- For moderate astrocytic coupling: the duration of the quiescent phase and its frequency increased (due to increased astrocytic network feedback). In addition, a subset of regions oscillated with a very low amplitude (due to the overall decreased neuronal network feedback) while for the epileptic regions, the spikes were suppressed.
- For high astrocytic coupling: due to the excess of extracellular GABA, all the regions shared the same quiescent period (which spanned the whole simulated duration).

DISCUSSION and CONCLUSION

- The phenomenon illustrated in the present study was the periodic inhibition of neurons due to globally increased astrocytic coupling, and a resulting competition between GABA release by interneurons and glutamate release by the pyramidal cells and overall neurotransmitters uptake. The period at which the inhibition occurred was tunable and measured at the scale of tens of seconds (for the presented simulations). Interestingly, for low astrocytic coupling, the amplitude of the low-frequency fluctuations of the neuronal activity was correlated and coherent with the metabolic activity.
- Of practical importance was the size and spatial structure of the two anatomical connectomes. For instance, homotopic connections which are typically underestimated by diffusion pipelines play a major role in shaping functional connectivity [5]. For this study, we did not optimize the neuronal coupling but we plan to carefully study its influence. In addition, a preliminary analysis of functional coherence revealed the astrocytic preferential network over the neuronal network and strong astrocytic coupling promoted functional segregation. We plan to further study the mutual interactions between the neuronal and astrocytic networks.
- This model offers the unique opportunity to investigate the brain metabolism at the mesoscopic scale besides the electrical activity, although only the glutamate and GABA are accounted, and it allows to introduce slow dynamic processes at the scale of minutes on top of the neuronal processes at the scale of milliseconds and seconds. In addition, the presence of two different anatomical connectomes, neuronal which shapes long-range synchrony and astrocytic which imposes short-range synchrony, show interesting and promising dynamical behaviors which we plan to further investigate.

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