**Soutenance de stage**

**Introduction**

As part of my engineer formation at Polytech-Sorbonne, I was brought to fulfill an end-of-studies engineering internship which happened to the team of Computational Neurosciences (Destexhe, Carlu and Damien) UNIC-CNRS.

Computational neuroscience is such a timely topic because, with the amount of data being recorded continually increasing, along with its complexity, we really need theory and analysis tools to handle it al. The field tends to go towards using data to fit neural networks, which then serve as a computational tool to extract meaning where it is necessary to link micro and mesoscopic levels and that is exactly what models under study aim to do.

**Fundamentals:**

A neuron will generate a spike at a frequency called the firing rate, when the threshold, the value of the membrane potential required to activate voltage-dependent positive ion channels is reached. The spike propagates along the axon and eventually arrives at the synapses, contact points between two neurons (syn and dendrites). Thanks to neurotransmitter releases which determine either rs or fs, the membrane voltage changes and the spike is sent towards the other neuron with the transmission delay.

In the cortex, the neurons will form groups and will connect with each other group in a perpendicular cylindric-like shape referred as the cortical column. The cortex displays asynchronous irregular (AI) states during wakefulness that could be described as de-synchronized states without specific patterns and synchronized brain states consisting of the alternation between periods of tonic firing (UP states) and periods of quiescence (DOWN states) which are taking place during slow-wave-sleep.

**Project outline**

First and foremost, at the low mesoscopic level, I simulated a simple column composed of two populations, in order to determine how this column system behaves and what are the critical parameters involved. Subsequently, I considered the corresponding mean-field model and see if it displayed the same dynamics.

Eventually, inspired by the Virtual Brain approach, I scaled up the approach where two columns interact, connecting therefore four populations (two FS and two RS neural groups) which helped ascertaining the bifurcation states map for a better understanding of the interactions of time-varying parameters with the dynamics of larger neural populations.

**AdEx**

Adaptive exponential integrate-and-fire model is simply a two-dimensional improved integrate-and fire model (where the neuron is described by a passive membrane with a threshold, a close analogy to the electrical circuit R-C) with the addition of the adaptation variable w and the spike generation being exponential. This is by far, one of the most realistic model of neurons intrinsic properties such as the higher excitability of FS cells which has potentially important consequences at the large-scale level. For this model, each neuron connects with its surrounding neurons (one by one), the 2 sde integrated for each neuron within the model, e.g., 40 000 equations have to be integrated for a two-column model with 10 000 neurons for each column (2\*2\*10 000). Time consuming

**MF**

The dynamic mean field model was developed according to the following two steps:

* In the first step, a microscopic mean field model is derived from the high dimensional stochastic model (AdeX) by taking the expectation (noise average)
* In the second step, a macroscopic mean field model is derived from the microscopic model by taking the average over the population => only 2 ODES or 1 for each population under consideration

writing down ordinary differential equations for the statistical moments of the probability distribution function

We consider a Markov dynamic, the probability of spiking during T, generate a fixed set of connections through a Bernoulli process (exemple simple de chaine de Markov). We can benefit from the Fokker-plank approach to compute different transfer functions for our neurons thanks to the transition operator W(\nu|\nu'), using the conditional probability density P\_\alpha(\nu). This fundamental condition requires one \gls{neuron} to spike only once during the period of time T. This formalism yields a population scale description of the continuous master equation.

**Code adex brian :**

* After creating neurongroup and connecting corresponding synapses, for generating spike according to a Poisson point process (By definition, a Poisson point process has the property that the number of points in a bounded region of the process's underlying space is a Poisson-distributed random variable => independence implies the Poisson distribution of point counts, but not the converse), PoissonGroup can be used (is connected with Synapsesgp to a Neurongp). Indeed, this is only a source of input to a neuron (i.e., the individually generated spikes are not important, just overall impact on the target cell is). In the code, we create two groups of 8000 independent spikes and both groups fire at 0.8 Hz.
* Recording spike of Neurongp and the fr of the population (PopulationRateMonitor) => only the time of the spike and the index of the neuron that spiked
* The bin\\_array function, takes the time\\_array of size 10^5 and reshape the 1D array passed, the first argument, as a 2D array with N0=50 columns and N1=1999 rows. The final binned array will be the means of each column with the last 50 elements removed. That is how we obtain the population firing rate, the mean of all the neurons' firing rates within the Neurongp

**Architecture of MF in code:**

* From cell and synapses library, we take the configuration of synapses connectivity and parameters for RS/FS cells that we want as a template for the model
* With these parameters, the construct files we build the (for cells the membrane equation and synapses ones with brian2) and for the synapses the connections when you specify the indexes (receiving and sending)
* Afterwards, the semi-analytical (phenological) TF will be computed based on subthreshold moments (display eq zerlaut) and used as the final template
* The function load\_config will load the two TF (for two pop) to use it as a parameter for the MF\_functtion computing the master equation which will be the on integrated

**Numerical Integration: Only evaluate the trend at a given point**

1. Load TF template computed by AdEx sim and subthreshold moments
2. Collect the inhibitory and excitatory contributions (including the Poisson drive): using an array to pass all the input arguments which are weighted averages and the delay added as an index of arguments for localization over the time through the delay line
3. Thanks to a pointer on this array passed through the template we got for TF, we can map every argument and compute their partial derivatives of transfer function
4. Inject these in the formula of the temporal ones to integrate them and evaluate the TF
5. Output mean-firing rate and adaptation (e1 et e2 only) for each pop as well as their correlation terms => second order RK4

**Results interconnected MF:**

1. **Simulation et structure**

In order to simplify the problem, given neuron receives “local” connections from its own network (excitatory and inhibitory with fixed parameters) and external excitatory connections only, from the other MF, with varying delay delay (from 1ms, close columns, to 5ms, the most distant column) and qe.

small value of the adaptation b, which corresponds to the state of an attentive, fully awake brain.

**Results**

By gradually changing the delay and qe, we map out the state space of the system, depicted in the bifurcation diagrams (fig).

The two excitatory populations and inhibitory ones almost have the same dynamics except for a few areas which will be discussed further:

1. Slow excitation-adaptation limit cycles: Synchronous regular waves, almost remain at the same frequency and amplitude but their minimum reach 0 or almost 0 Hz in the Figures (time traces). they seem to appear for rather low excitatory synaptic weight and need a higher delay to emerge at higher values QE
2. Metastable: Synchronous irregular waves are bursting afterwards as shown in Figures. The phase delay peaks correspond to the unstable equilibrium point that threads the cortex's limit cycles (we will see afterwards).
3. Fast excitation-inhibition limit cycle: LC\_{EI} with an alternating activity between the two populations. In this case, the two limit cycles will keep periodically oscillating with long-term behavior (cf. time traces). As the value of synaptic weight increases, the system dynamics vary a two limit cycles cohabitation (phase planes).
4. Chaotic-like states or Period doubling cascade: At 4 ms of delay, the dynamics of the simulations exhibit period-doubling cascade. When the excitatory synaptic value increases to the range maximum value, the period increases by Two to the power of n, with n the number of previous limit cycles. In the phase planes, it represents 16 limit cycles. As a result, the occurrence of complex periodic behaviors and chaotic dynamics are pinpointed in the time traces at 1.92 nS and 1.85 nS.
5. Pop E1 => We observe in the phase space a chaotic spiral. Indeed, our spiral follows a period-doubling cascade here, due to two unstable limit cycles which start and finish at the same attractor inside each other cycles. Possibly chaotic dynamics as witnessed in Figure.
6. Pop E2 => In Figure we detect so-called canard cycles consisting of a fast orbit, turning around the Möbius strip. there are mixed mode oscillations corresponding to switches between small amplitude oscillations and relaxation oscillations owing to slow passage through a delayed Hopf bifurcation. This transition, also called canard explosion, but they are hard to observe in an experiment or simulation because of sensitivity to the control of parameters and also because of sensitivity to noise.
7. Auto resonance: neurons fire for delayed connections at 2 ms, strengthen outward connections while weakening inputs for the population E2. Neurons given lower external inputs, like in the population E1, do the opposite, strengthening inputs and weakening outputs.
8. AI States: For both populations, we can easily notice, the constant range of spiking over the time with asynchronous patterns. We have determined them thanks to the standard deviation for each population, if it equals 0, we are in asynchronous irregular state.

Inhibitory populations follow approximately the same states and their position according to the delays and Qe. However, we perceive that $LC\_{EA}$ are absent from the simulations, which could be explained by the fact that adaptation does not produce such slow limit cycle while being coupled with inhibition.

Moreover, we are catching the sight of a strange phenomenon at the highest excitatory synaptic weight value for the population I2, there is a drop of the mean firing rate from the gamma frequencies range to the beta one.

**Results outcomes:**

* **Mean field models seem to simulate asynchronous irregular states very well**, which is not surprising since MF were invented to specifically model these states (states considered to be the most representative of the cortical main activity).
* Here, chaotic-like phenomena (around 3 and 4 ms of delay), probably displaying the the MF limit**. Then, appears to be a relationship between the delay and the stabilization of the system, the higher the delay is the more rapidly there is transition from chaos to LCEI for lower Qe values.**
* The new relation between delay and Qe synaptic has been discovered: **The dominant inhibition state transition, determined by g ratios, seems delay dependent when delay ≥ 5 ms.** The higher mean input => dominant inhibition. **Hence, a long delay could hypothetically switch the dominant population thus the transition between states**
* At 2 ms an interesting phenomenon is observed for fairly low to high Qe values called the θ-auto-resonance takes place in learning process. Sequences of place cells activation are replay events that can occur in either the forward (being more prevalent during sleep) or reverse (the network is reactivated by oscillating input) direction within the hippocampus, an elaboration of the edges of the cerebral cortex, which encode spatial and contextual information. **Eventually, we could hypothetically state that the population could correspond to two cortical column parts in different learning processes.**

**Limits**

* For a small adaptation value, we could suspect that the oscillatory states are where the steady-state approximations that are used to construct the mean-field model break down due to the fast temporal dynamics in this state.
* No model is able to describe the dynamics of second-order statistics at the network level. In this case, the discrepancies observed are likely due to residual correlations caused by finite size effects and the phenomenological (semi-analytical) transfer function (moments statistics).
* Moreover, the use of so called "tricks" in the MF model in order to produce AdEx results are commonly used for forcing the system to be asymmetrical or correcting abnormal values obtained by the integration methods. These values or the symmetry we have exceeded the validity scope of the MF models, whose boundaries are still unknown, which suggests that models such as the connectome of the Virtual brain may induce errors in simulations of the cerebral cortex’s states (with serious consequences if used for diagnostic purposes as it is intended to).

**Improv**

* Interconn Adex: compare and check results
* Due to small adaptation limit, we have fr fluctuation increased for small tau\_w. it would be interesting deriving a second order mean field also in the variable of adaptation w.
* For now, on, no real comparison between the two models under focus has been made on a macroscopic scale (e.g., SpiNNaker is large-scale neuromorphic machines composed of millions of connected cortical columns modeled by AdEx). However, the simulations cannot access the vastly different timescales. Moreover, the implementation of the MF version is still in process but would be an important tool to check the MF validity scope on the brain scale.
* We witnessed a phenomenon close to learning => is the simulation conscious (phenomenological consciousness)? applying protecting rules. Manipulating society and integrating in an environment