Modelling the dynamics of optogenetic stimulation at the whole-brain level

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Abstract

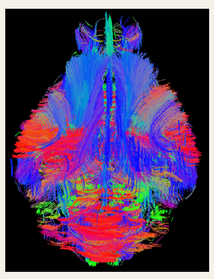
Brain stimulation is used to cure different pathological conditions, such as Parkinson's disease, epilepsy, essential tremor and psychiatric diseases. However, there is scant knowledge regarding the way of stimulating the brain to cause a predictable and beneficial effect. In fact, the choice of where and how to stimulate remain empirical [1,2]. In order to approach these questions in a theoretical framework, it is important to understand how stimulation propagates and influences the dynamics at the whole-brain level. For a clear understanding of the functional consequences of brain stimulation, an optogenetic approach is preferred since it allows the activation/inactivation of specific cell-types in brain regions of interest, therefore not confounding the functional circuitry. Then, one can keep track of the functional activity of a mouse brain *in vivo* during the stimulation by using Optogenetic fMRI techniques [3].

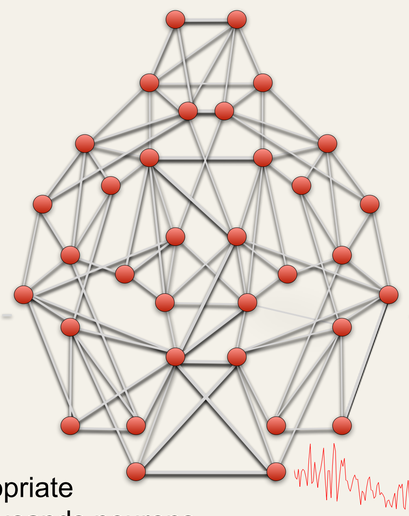
In this work we set up a theoretical framework in order to study *in silico* the effects of an optogenetic stimulation at the brain network level. The local node dynamics is described by a "Next Generation Neural Mass Model" derived analytically as the infinite number of all-to-all coupled QIF neurons [4,5]. Differently from standard NMMs [6], the chosen model is able to keep track of the internal amount of synchronization of the constituent neurons. This is a desired property since the stimulation of a brain region can alter the *local* synchronization pattern and this in turn can modulate the *global* rhythms [7]. The network dynamics is then analyzed using *The Virtual Brain* open access platform [8,9]. The local modes are coupled over a mouse connectome extracted from the tractography experiments of the *Allen Institute*, and the resulting system of equations is solved numerically. Tuning the global coupling parameter G we are able to qualitatively reproduce the typical switching of functional activity patterns in time, which is also observed in experimental data [10]. From the internal state of synchronization in each node we define several global synchronization measures and we investigate their behavior for different values of G. Our results show that the switching functional behavior appears for values of the global coupling which are close to criticality, i.e. at the onset of each phase transition of the system.

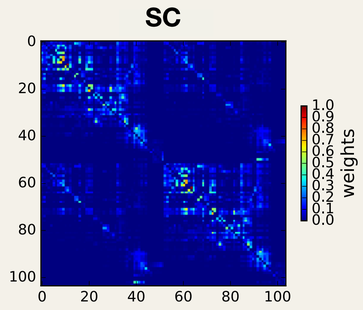
Methods

The Virtual Mouse Brain [8,9]

Structural Connectivity
(e.g., from Allen Institute tracer experiments)

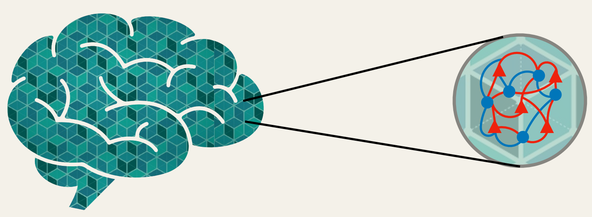






In TVB one assigns to each node a **Neural Mass Model**

- Expected to provide appropriate level of description for thousands neurons
- Justified by coarse resolution of whole-brain imaging
- Inside the node many things can happen *e.g., changing patterns of synchronization, ERS* [11]



The numerical solution of the model equations coupled through the structural connectivity results in a simulated brain signal for each node.

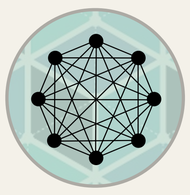
Next Generation Neural Mass Models [4,5]

We use a 2D model which carries infos about the state of synchronization *inside* the node

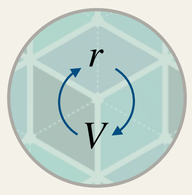
- Local synchronization can modulate global rhythms [7]
- Link to spiking neural networks

N all-to-all connected QIF

$$\dot{V}_i = V_i^2 + \eta_i + Js(t) + I(t)$$



$N \to \infty$



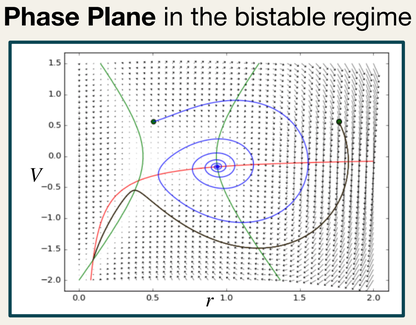
Mean firing rate

$$\dot{r} = \Delta + 2rV$$

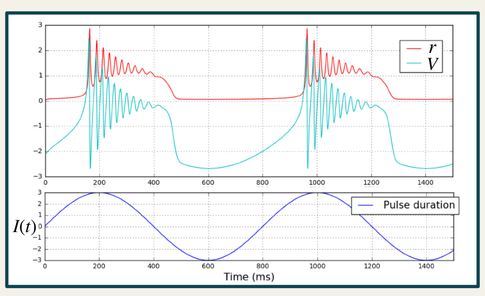
Mean membrane potential

$$\dot{V} = V^2 - \pi^2 r^2 + Jr + \eta + \gamma I$$

Phase Plane in the bistable regime



Event Related Synchronization



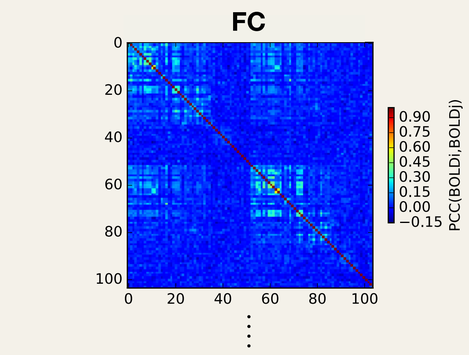
The state variables are linked to the **Kuramoto parameter** through a conformal transform

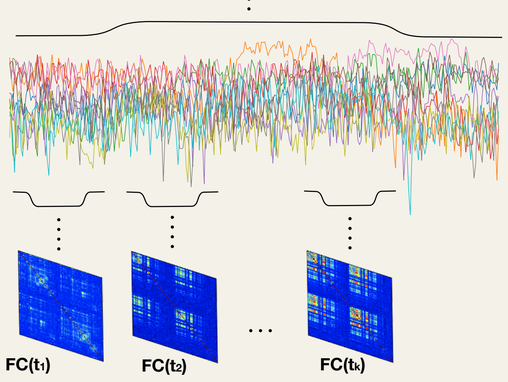
$$W = \pi r + iV \qquad Z = \frac{1 - W^\star}{1 + W^\star} = K(t)e^{i\theta(t)} \qquad K(t) = \text{"Internal synchronization level"}$$

Results

Coupled Dynamics [10]

The Pearson Correlation between each simulated time series defines the virtual **Functional Connectivity**.



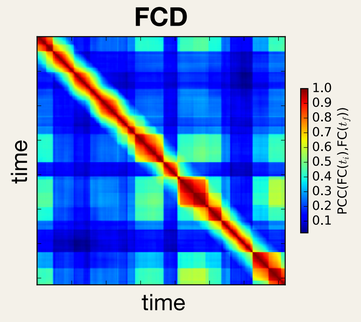


The results depend on parameters choice

- G → Global coupling i.e., how much the structure shapes the dynamics
- N → Noise of the time series

For an appropriate set of parameters the model used shows functional patterns of activity switching in time, in accordance with experimental findings.

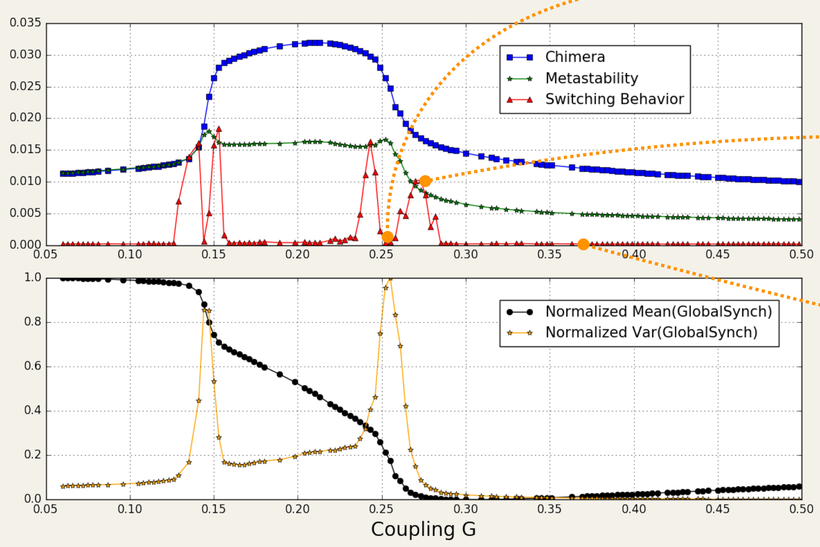
Functional Connectivity Dynamics, defined as the Pearson Correlation of FC matrices taken at different time windows, measures the variety of dynamical regimes explored by the system in time.

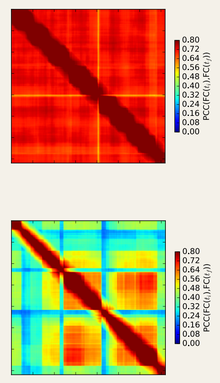


Synchronization Features [12]

Knowing the amount of synchronization $K_n(t)$ in each region n one can define global measures

- Mean and Variance of the **Global Synchronization** $\textbf{mean}_n(K)$
- **Metastability** $\textbf{mean}_n(\textbf{var}_t(K))$
  i.e., "how distant is the network from a stable state"
- **Chimera** $\textbf{mean}_t(\textbf{var}_n(K))$
  i.e., "tendency of the network to spontaneously partition into synchronized vs desynchronized subsystems"





Discussion and Perspectives

- We set up a framework for the analysis of stimulus propagation and mechanisms of communication among regions in terms of network synchronization features
- We coupled on an experimentally-extracted mouse connectome a neural mass model with the special property of carrying the information about the level of internal synchronization of its constituent neurons.
- The system shows a non-trivial FCD matrix for critical values of the global coupling G
- We observe a relation among the "raw" signals and the "extracted" BOLD signal used to build the FCD matrix
- The model will be extended in order to include for each region excitatory and Inhibitory populations
- This work is the first step in a wider project which sees the collaboration with partner institutions (**Jin Hyung Lee Lab, Stanford, USA** and **Itamar Kahn Lab, Israel Institute of Technology**) where *in vivo* optogenetic fMRI and chemogenetics datasets will be collect. Our framework will be used in this context to make predictions and provide evidences that whole-brain dynamics can be directly controlled to desired functional regimes.

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