# Data-Driven Kuramoto Model Simulation of Microscale Neuronal Interactions from Calcium Imaging Data

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This manuscript was compiled on May 6, 2020

**The topological structure of the wiring of the mammalian brain cortex plays an important role in shaping the functional dynamics of neural activity. This structure is believed to exist on a transition state between several regimes and constantly switching depending on age, task or disease. One of the ways of quantifying this variation is measuring the synchrony of populations of neurons. Here, in this project, I used Kuramoto model to mimic the calcium imaging data obtained from the epileptic mice. Assuming that each neuron in the movie is a Kuramoto oscillator with some internal frequency $\omega_i$ and an initial state $\theta_i(t)$ as the calcium dynamics inside of a cell, I initialized the Kuramoto model according to the data obtained from three epochs leading to the seizure and looked at the global synchrony, phase coherence $r(t)$ and the fraction of synchronized node pairs $r_{link}(t)$, as a function of coupling strength, network topologies and varying distributions of the type of the oscillators. Some preliminary results showed that there is a transition state between baseline and preictal periods of the coupled oscillators measured by $r_{link}$. Moreover, a critical regime is observed for the values of coupling strength $\lambda$ near $0.2$. Although varying the distributions of the oscillators in the networks seemed to not change any results in the complete networks, configuration networks with normal and gamma distributions seemed to move towards dyssynchrony right after initialization.**

Kuramoto Model | Calcium imaging | Synchronization | Data-Driven

Mammallian brain cortex is a highly complex structure that processes a huge amount of data in a matter of couple milliseconds. The underlying topology of the wiring structure of the ball of these fundamental units, neurons, is still far from being understood. Recent techniques such as two-photon microscopy enable this research to take a different route in the sense that we can eavesdrop on groups of neurons and record their simultaneous calcium activity.(1)

The rhythmic activity of these small building blocks somehow is leading to a complex structure to emerge. In this regard models of neuronal oscillation has been used to simulate the activity of both microscale and macroscale activities of the nervous system(2).

Kuramoto model in this sense is a highly beneficial model in which each oscillator $i$ has an internal clock ($\omega_i$) that tries to get synchronized with it's neighbors on a connected network (3). The fundamental equation is given by

$$\frac{d\theta_i}{dt} = \omega_i + \lambda \sum_{j \in N_i} W_{i,j} \sin(\theta_j - \theta_i)$$

where $\theta_i$ is the state of the oscillator, $\lambda$ is the coupling strength, $W_{i,j}$ is the weighted or unweighted adjacency matrix and $N_i$ is the neighbors of the node $i$.

Embracing the data-driven network science as a main mathematical framework to understand the brain network topology changes during a process leading to a an epilepsy seizure, I initialized networks according to a synchrony measure of the calcium dynamics of the cells and ran the Kuramoto model to simulate interactions through synchrony on the basis of several parameter changes such as network topology, coupling strength and internal oscillatory frequency distribution. Playing around with these variables and calculating the global synchrony yielded some state changes in the Kuramoto model that the actual system might possibly be undergoing.

The current data we have, the epileptic mice, consists of 20 animals each having 3 epochs, *baseline*, *early*, *pre*, indicating the process leading to seizure. In the population of 20, some mice are healthy and some of them are induced an epileptic seizure when they are heated up. During *baseline*, we examine the default activity of the brain region we are eavesdropping.

## Significance Statement

Two-Photon Microscopy is an imaging technique that allows living tissues to be eavesdropped on cellular level in real time. One of the most frequent usage of this novel technique is in the domain of neuroscience. Indeed, this method can be used to record the simultaneous activity of hundreds of neurons in the mammalian cortex to investigate the microscale network properties of the nervous system by using different, chemical or genetically encoded, calcium indicators that emits fuorescence when they are hit by photons. However, this type of research entails some predetermined assumptions and parameter choices which may drastically change the conclusions that can be drawn and creates huge variability on the repeated trials. This work can be a roadmap for simulation of this type of a system using one of the neuronal oscillatory models, Kuramoto model, to examine the epileptic state of a population of oscillators driven by the data extracted from the epileptic mice. Playing with the different variables along the way yields to find out the parameters in these models that are more robust/sensitive to the perturbations and noise in the systems. What could be done further for this project is possibly marking the oscillators as excitatory/inhibitory and giving the appropriate properties and running this type of simulation (4). It is not the most comprehensive study in the sense that the effect of all network topologies is taken into consideration nor the distributions of the angular velocities.

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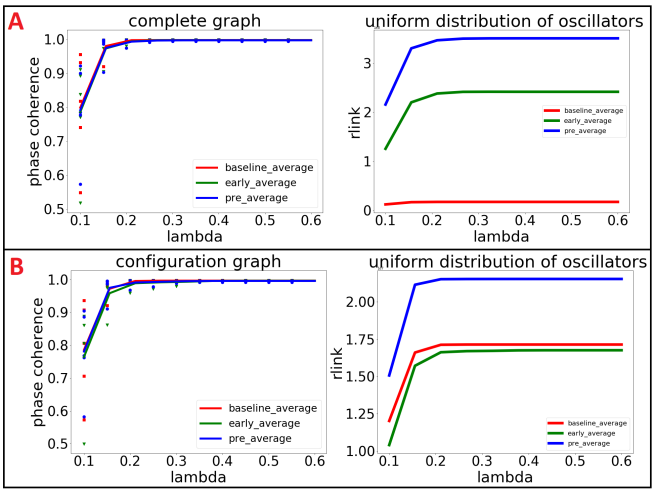


**Fig. 1.** A. The change in phase coherence and $r_{link}$ shown as a function of coupling strength in a complete graph where dots represent the individual simulations with uniform distribution of internal frequencies of oscillators. B. Same model as A but the networks are initialized according to configuration graph where the degree distributions are proportional to edgewise synchrony of the cells in the data.

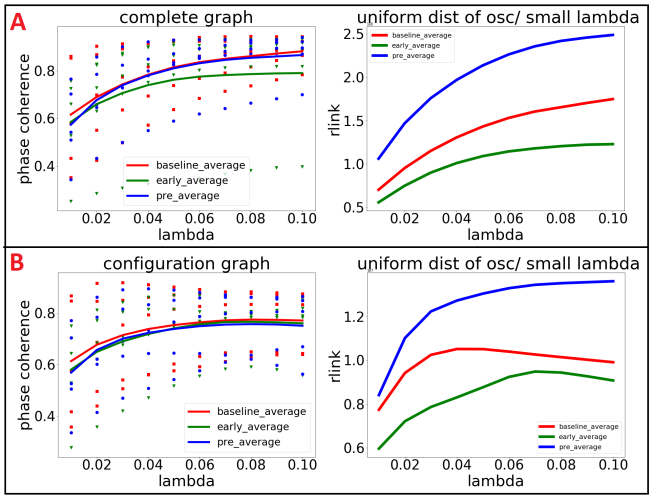


**Fig. 2.** A. The change in phase coherence and $r_{link}$ shown as a function of coupling strength $\lambda$ when $0.01 < \lambda < 0.1$, oscillators are uniformly distributed and network is initialized as a complete graph. Values of $r(t)$ and $r_{link}(t)$ are averaged across time $T = 1000$ and across the $N = 5$ subjects. B. All the parameters are kept the same except the network of oscillators are initialized according to the configuration model where the degree sequence for the nodes are proportional to the edgewise synchrony of the corresponding cleaned calcium traces obtained from the data.

On *early*, mice gets started to heated up and during *pre* they experience an epilepsy seizure, if they do. We have all the cleaned and deconvolved traces for the temporal data of $3 \times 8000$ time frames indicating the calcium dynamics of a manually segmented region of interest(ROI), or a neuron, in the brain region. Reading all the data together, I randomly selected $N = 5$ animals(due to computational complexity), each having 3 epochs and created total of 15 networks with the respective number of Kuramoto oscillators in each epoch and for every animal.

The main goal of this project is simulating an epileptic seizure like behavior in a population of coupled oscillators and examining the global synchrony of these systems to understand the phase changes that the system might actually be going through. In order to do that, one of the natural assumptions to make is taking the amount of calcium inside a cell(that is a number between $(0, 1)$ and it's not a literal amount of calcium in the cell but can be thought of, after all the preprocessing of the fluorescence, as the relative amount of calcium in the cell?) as the state $\theta(t)$ of the cell in the Kuramoto model and calculating the intrinsic properties of the model and environment from the actual data. Having this goal in mind, one can manipulate the variables of the model that is richer in the actual *Python* package (5) *KMCalcium*[*] and seek for a better understanding of the mechanisms driving the neuronal interactions and the global state changes of similar systems.

## Methods

First of all, in order to simulate a Kuramoto model, we need to come up with a way of creating a network. In the homework assignment, we examined different network topologies to overcome this task. Here, I picked two different network topologies to carry on the model. First one is a complete graph network where no parameter selection is needed except the number of nodes that we already know for each calcium movie we want to simulate. Second types of networks are created according to the configuration model where the degree distribution is taken as the total edgewise synchrony of each node extracted from the data.

In all the models, initial state of each oscillator is defined as the average calcium level over 8000 time frames.

All the simulations are ran $T = 1000$ times and explorative longer runs $T = 8000$ didn't change the nature of the results because all phase coherences reached 1 mostly around $T = 1000$ and the value of $r_{link}$ kept linearly increasing for $T > 1000$. One of the things that should be done is probably adding a transient time $\tau = 400$ at the beginning of the simulation and using the last 1000 iteration.

As a global measure of the system, the synchronization of the population of $N$ coupled oscillators can be obtained by

$$r(t) = |z(t)| = \frac{1}{N} \left| \sum_{j=1}^{N} e^{i\theta_j(t)} \right|$$

and is called **phase coherence**.

In addition to phase coherence, the **edgewise synchrony** provides information about the state of the network(6). Edgewise synchrony between the nodes $i$ and $j$ is given by

$$C_{i,j} = \frac{1}{\delta t} \left| \sum_{\tau}^{\tau+\delta t} e^{i[\theta_i(t) - \theta_j(t)]} \right|$$

forming the coupling matrix $C$.

This matrix $C$ has another important meaning when averaged over all edges, another global measure of synchrony, $r_{link}$, defined by

$$r_{link} = \frac{1}{N(N-1)} \sum_{i,j} C_{i,j}$$

where $N$ is the total number of nodes of the network. The phase coherence $r$ and the fraction of synchronized node pairs $r_{link}$ together describe the global dynamics of the system.

[*] Constructed and edited by Bengier Ülgen Kılıç, https://github.com/ulgenklc/KMCalcium

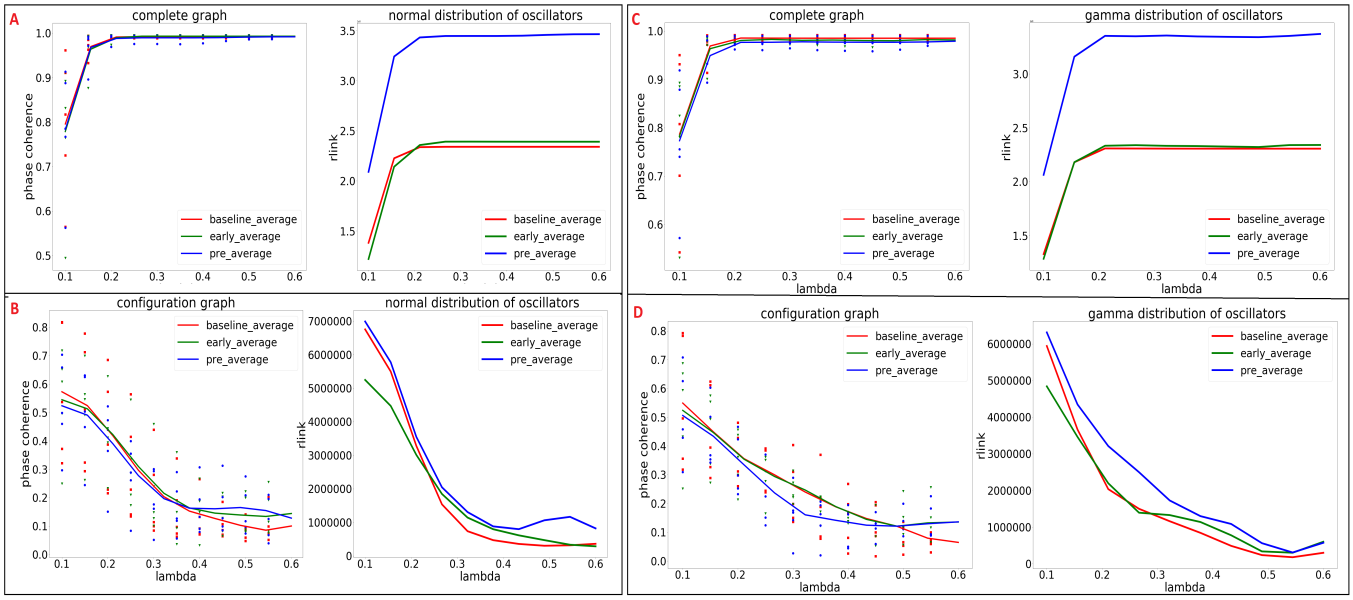


**Fig. 3.** A. Change in $r(t)$ and $r_{link}(t)$ for complete graph where the coupling strength $\lambda \in [0.1, 0.6]$ and oscillators are initialized according to the Gaussian distribution with $\mu = 1$ and $\sigma = 0.05$. B. Same model as in A but for the networks are initialized as configuration graphs where the degree distribution is obtained by the edgewise synchrony of calcium levels between ROIs in the calcium movies. C. Same model in A but the oscillators are initialized according to gamma distribution with $k = 1$ and $\theta = 0.05$. D. Same model in C but for configuration model in which the degree distributions are measured as extracted cleaned calcium traces from the data

## Results

Assessing the standard global synchrony measure, phase coherence, on the microscale simulation of individual Kuramoto models for each epoch did not reveal any significant results as a functions of varying synchronization thresholds i.e. all the networks seemed that they 'synchronize' randomly, however, some simulations corresponding to *early* stage displayed a plateau when the phase synchrony is between 0.9 and 1.0 which can be interpreted as two communities of oscillators trying to synchronize up 4.

Since comparing separate animals in different epochs for 1000 time steps gets messy and expensive I carried on the rest of the analysis by averaging the results over subjects as well as over iterations and varied a single variable $\lambda$– the coupling strength of the oscillators. Initializing a uniform distribution of the oscillators on all the networks, first, I compared the effect of the network topology on the phase coherence $r(t)$ and fraction of synchronized edge pairs $r_{link}(t)$ for varying $\lambda$. 1. Even though both $r(t)$ and $r_{link}(t)$ didn't show any significant differences with respect to distinct network topologies, $r_{link}$ was consistently higher during the *preictal* stage simulation than the other two stages for both network topologies demonstrating a higher synchrony during the seizure which may also be an affect of the heat. For values of $\lambda > 0.3$, systems didn't seem to vary too much i.e. no significant phase transition is observed.

To answer how much of the above results is driven by the scale we are at, I repeated both simulations for smaller $\lambda$ values for $0.01 < \lambda < 0.1$ and verified the significance measured by the $r_{link}$ on average in the *preictal* stage 2.

Furthermore, I examined the influence of one of the other primary variables in the simulations $\omega_i$–the distributions of the internal angular velocities across the individual networks and initialized a normal distribution of the oscillators with $\mu = 1$ and $\sigma = 0.05$. Even though the results for the complete network for both global synchrony measures $r$ and $r_{link}$ have shown nothing interesting in particular, the configuration models seemed to shift towards dyssynchrony once the simulations has started in every epochs, possibly because of the weaker wiring of the network compared to complete topology.3

To investigate this variance between network topologies in the fraction of synchronized edge pairs, I initialized another groups of simulations for the gamma distribution with $1 \pm \Gamma$ where $\Gamma$ is the gamma distribution with shape parameter $k = 1$ and scale parameter $\theta = 0.05$. The movement of the system towards dyssynchrony measured by both of our global synchrony measures was parallel to the previous findings 3.

Individual differences scattered on the phase coherences in all the plots didn't seem to change average i.e. no pathologies are observed.

## Discussion

I started with 5 animals whose particular brain region are observed under two-photon microscopy during a process leading to an epilepsy seizure. Each time series is divided into 3 epochs: *baseline*, *early* and *pre* total of 15 movies with some number of ROIs changing calcium dynamics.

This data-driven model entails two things that is related to the data. First, for the complete networks, we extract the number of ROIs from the 5 test animals for each epoch I randomly selected. Secondly, configuration networks are initialized according to the same size of the populations as complete networks and in addition to that they are provided with a degree sequence proportional to the edgewise synchrony of the calcium dynamics in the movies i.e. every node has a degree proportional to it's total edgewise synchrony. Edgewise synchrony is only given by the state $\theta_i$ of the oscillator $i$ and it's neigbors' $j \in N_i$ state $\theta_j$ which we take as the calcium

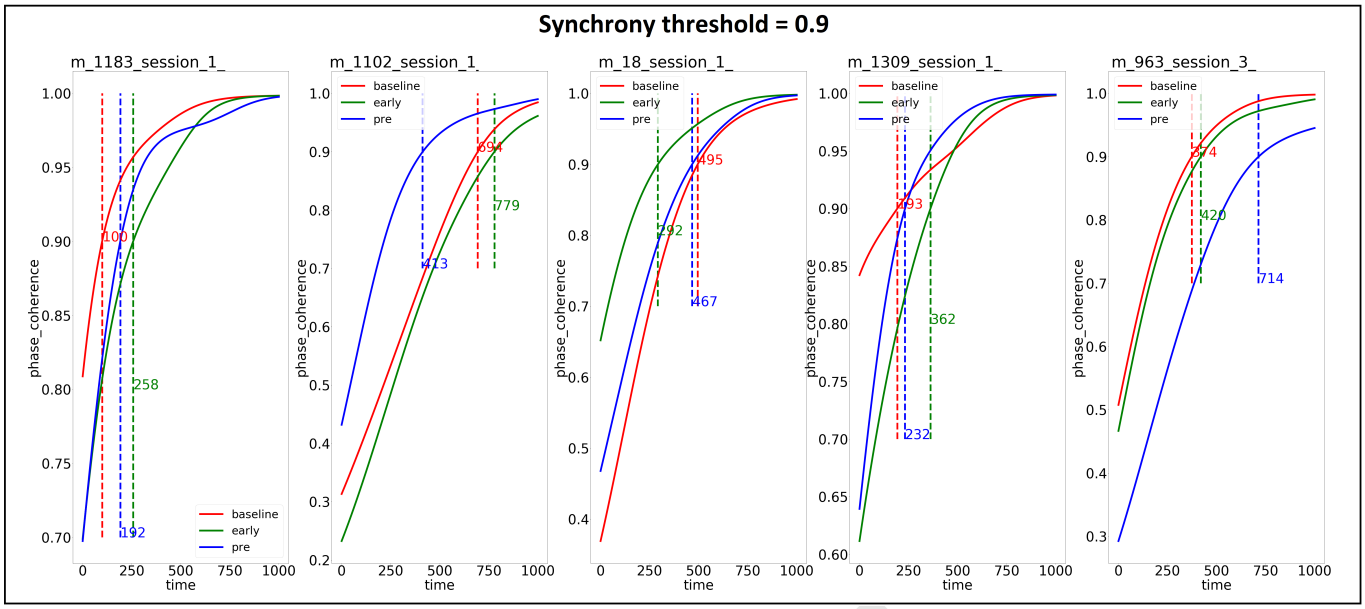


**Fig. 4.** Synchrony of individual network simulations by subjects and epochs. Vertical dashed lines indicate the time step where the phase coherence passes the given threshold $= 0.9$. A plateau can be observed for m-1183-session-1 *pre* stage indicating two communities trying to synchronize up at the end of the simulation.

trace inside of the cell.

Running the simulations for $T = 1000$ iterations according to the Kuramoto models initialized with respect to different variables and assessing the global synchrony, $r(t)$ and $r_{link}(t)$ as a function of coupling strength $\lambda$ yielded some differences between the three epochs as well as some state changes.

When the oscillators are uniformly distributed across the networks, networks seemed to have a phase change near $\lambda = 0.15$ both for complete and the configuration graphs which was kind of expected because as the $\lambda$ gets greater, systems will have a higher point of phase coherence on average due to the coupling strength. Moreover, a higher level of $r_{link}$ is observed for *preictal* networks for both complete and the configuration graphs telling that these initializations are leading to a higher global synchrony in the systems1 which can be a result of higher integration and lower segregation during seizure.

Repeating these simulations for smaller values of $\lambda \in [0.01, 0.1]$ verified our findings that the critical values of $\lambda$ are between $[0.05, 0.2]$ and an increased global synchrony in the *preictal* networks both for the complete graph and the configuration graph measured by $r_{link}$ when the oscillators are distributed uniformly2.

When the oscillators are distributed non-uniformly, however, configuration networks seemed to disperse meaning that they lose their synchrony even when the tests are ran more than $T = 1000$ iterations. The reason behind that is possibly the networks are not being strongly coupled enough at the beginning in the configuration networks so that even a group of strongly coupled oscillators in the Gaussian and the Gamma distributions would not be enough to synchronize up the systems as the time goes by 3. Moreover, a similar increase in the fraction of synchronized node pairs for *preictal* networks.

Overall, this type of study seemed promising in the sense that it is prone to the further meticulous analysis mentioned throughout this text.

**Addtional.** Randomly selected animals are: m-1183-session-1, m-1102-session-1, m-18-session-1, m-1309-session-1, m-963-session-3.


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