# Dynamics in brain networks: application to epilepsy

**Marinho Lopes**
Luke Tait, Alex Shaw, Dominik Krzemiński
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# Epilepsy

- What is epilepsy?
  - *Epilepsy is a brain disorder characterized by recurrent and unpredictable seizures.*

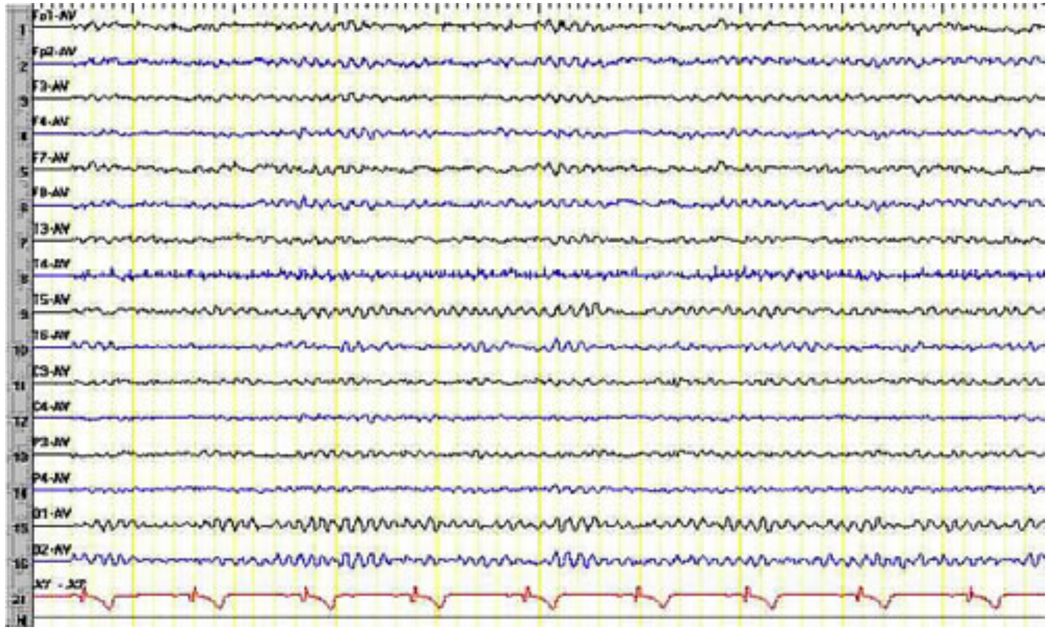
- What is a seizure?
  - *A seizure is a "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain."*

Fisher, Robert S., et al. "Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE)." *Epilepsia* 46.4 (2005): 470-472.

# Epilepsy – the role of EEG

- The electroencephalogram (EEG) plays a central role in the diagnosis of epilepsy.

EEG of a healthy individual at rest (eyes closed):



https://projects.exeter.ac.uk/time/methods.php?cat=eeg

# Epilepsy – the role of EEG

- The electroencephalogram (EEG) plays a central role in the diagnosis of epilepsy.

EEG of an (absence) epileptic seizure:

https://projects.exeter.ac.uk/time/methods.php?cat=eeg

# Some key questions about epilepsy

- What makes a brain susceptible to generate seizures?
- What mechanisms underlie the transition from “normal” brain activity to seizures?
- Network neuroscience has shown that people with epilepsy have abnormal brain networks.
  - *To move from correlation to causality we need to understand why such abnormalities “imply” epilepsy.*

Richardson, Mark P. "Large scale brain models of epilepsy: dynamics meets connectomics." *Journal of Neurology, Neurosurgery & Psychiatry* 83.12 (2012): 1238-1248.

# Modelling epilepsy

- Mathematical modelling of brain activity may help us answer these questions.

- What models shall we use?
  - *Microscale or macroscale models?*
  - *Biophysical or phenomenological models?*

- It depends on the question and on the current knowledge.

# Possible models - microscale

| Models | biophysically meaningful | tonic spiking | phasic spiking | tonic bursting | phasic bursting | mixed mode | spike frequency adaptation | class 1 excitable | class 2 excitable | spike latency | subthreshold oscillations | resonator | integrator | rebound spike | rebound burst | threshold variability | bistability | DAP | accommodation | inhibition-induced spiking | inhibition-induced bursting | chaos | # of FLOPS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| integrate-and-fire | - | + | - | - | - | - | - | + | - | - | - | - | + | - | - | - | - | - | - | - | - | - | 5 |
| integrate-and-fire with adapt. | - | + | - | - | - | - | + | + | - | - | - | - | + | - | - | - | - | + | - | - | - | - | 10 |
| integrate-and-fire-or-burst | - | + | + | | + | - | + | + | - | - | - | - | + | + | + | - | + | + | - | - | - | | 13 |
| resonate-and-fire | - | + | + | - | - | - | - | + | + | - | + | + | + | + | - | - | + | + | + | - | - | + | 10 |
| quadratic integrate-and-fire | - | + | - | - | - | - | - | + | - | + | - | - | + | - | - | + | + | - | - | - | - | - | 7 |
| Izhikevich (2003) | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 13 |
| FitzHugh-Nagumo | - | + | + | - | | - | - | + | - | + | + | + | - | + | - | + | + | - | + | + | - | - | 72 |
| Hindmarsh-Rose | - | + | + | + | | | + | + | + | + | + | + | + | + | + | + | + | + | + | + | | + | 120 |
| Morris-Lecar | + | + | + | - | | - | - | + | + | + | + | + | + | + | | + | + | - | + | + | - | - | 600 |
| Wilson | - | + | + | + | | | + | + | + | + | + | + | + | + | + | + | | + | + | | | | 180 |
| Hodgkin-Huxley | + | + | + | + | | | + | + | + | + | + | + | + | + | + | + | + | + | + | + | | + | 1200 |

I&F:

$$v' = I + a - bv,\ \text{if } v \geq v_{\text{thresh}},\ \text{then } v \leftarrow c$$

Morris-Lecar:

$$C\dot{V} = I - g_L(V - V_L) - g_{\text{Ca}} m_\infty(V) \times (V - V_{\text{Ca}}) - g_K n(V - V_K)$$

$$\dot{n} = \lambda(V)(n_\infty(V) - n)$$

$$m_\infty(V) = \frac{1}{2}\left\{1 + \tanh\left[\frac{(V - V_1)}{V_2}\right]\right\}$$

$$n_\infty(V) = \frac{1}{2}\left\{1 + \tanh\left[\frac{(V - V_3)}{V_4}\right]\right\}$$

$$\lambda(V) = \bar{\lambda}\cosh\left[\frac{(V - V_3)}{(2V_4)}\right]$$

Izhikevich, Eugene M. "Which model to use for cortical spiking neurons?." *IEEE transactions on neural networks* 15.5 (2004): 1063-1070.

# Possible models - macroscale

- Neuronal network models (meso/macroscale)
  - *e.g. Izhikevich and Edelman (2008) – 1 million neurons, ~half billion synapses*
- Neural mass models (and networks of neural mass models)
  - *e.g. Wilson-Cowan model; Jansen-Rit model; Wendling model; …*

- More on this: Breakspear, Michael. "Dynamic models of large-scale brain activity." *Nature neuroscience* 20.3 (2017): 340.

Izhikevich, Eugene M., and Gerald M. Edelman. "Large-scale model of mammalian thalamocortical systems." Proceedings of the national academy of sciences 105.9 (2008): 3593-3598.

# A phenomenological model of seizure transitions

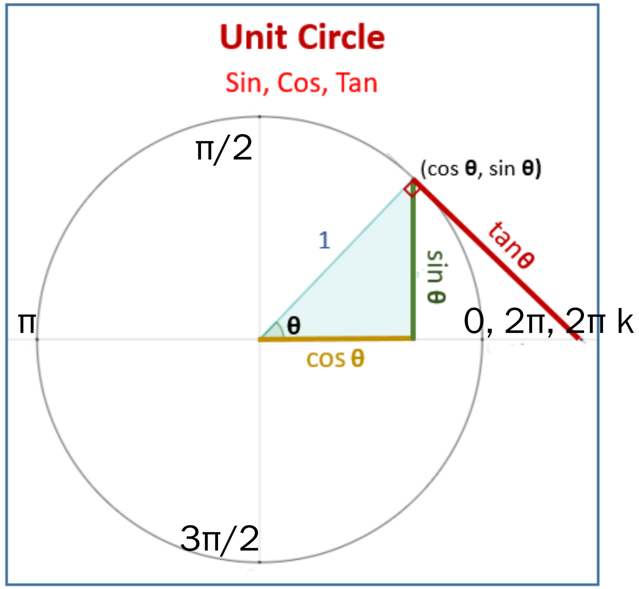
- Models in epilepsy:
  - *Wendling model [1], Benjamin model [2], epileptor [3], …*

- We will consider the "theta model" [4], a phase oscillator model:

$$\frac{d\theta}{dt} = 1 - \cos\theta + (1 + \cos\theta) I(t)$$

[1] Wendling, F., et al. "Epileptic fast activity can be explained by a model of impaired GABAergic dendritic inhibition." *European Journal of Neuroscience* 15.9 (2002): 1499-1508.
[2] Benjamin, Oscar, et al. "A phenomenological model of seizure initiation suggests network structure may explain seizure frequency in idiopathic generalised epilepsy." The Journal of Mathematical Neuroscience 2.1 (2012): 1.
[3] Jirsa, Viktor K., et al. "On the nature of seizure dynamics." Brain 137.8 (2014): 2210-2230.
[4] Lopes, Marinho A., et al. "An optimal strategy for epilepsy surgery: Disruption of the rich-club?." PLoS computational biology 13.8 (2017); http://www.scholarpedia.org/article/Ermentrout-Kopell_canonical_model ; https://en.wikipedia.org/wiki/Theta_model

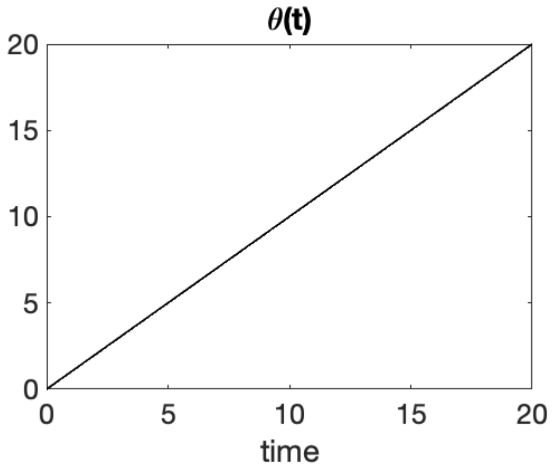
# What does it mean?

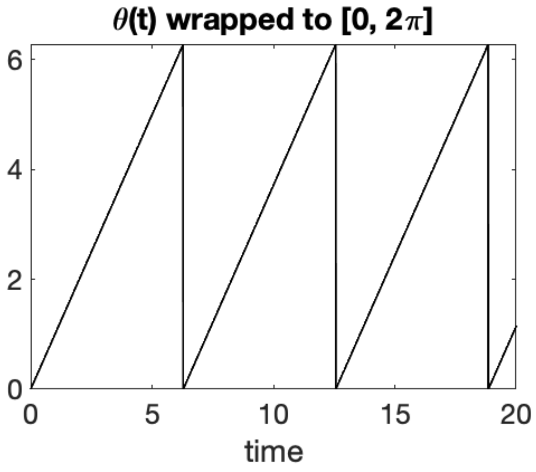


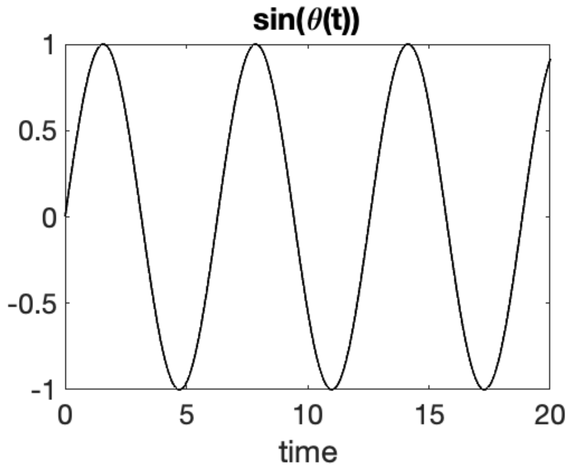

- Theta model:

$$\frac{d\theta}{dt} = 1 - \cos\theta + (1 + \cos\theta)I(t)$$

  - Theta, $\theta$, is the phase of an oscillator, i.e. an angle in the unit circle
  - $I(t)$ is a (time-dependent) current/perturbation



# Why use the theta model?

- The model describes two states: a stable state (normal) and oscillations (seizures)
- It is a minimal/ canonical model.
- It is NOT sufficiently complex to describe different normal states, or pre-ictal states, seizure evolution, etc.
- However, it may be sufficient to understand why some brain networks are prone to generate seizures.

# Let’s play with the model!

- To start understanding a model, it is convenient to find its steady states.

- How do we find the steady states of the theta model?

$$\frac{d\theta}{dt} = \dot{\theta} = 1 - \cos\theta + (1 + \cos\theta)I$$

- We solve: $\dot{\theta} = 0$

# Theta model: steady states

- For simplicity, let's assume $I(t) = I$

$$\dot{\theta} = 1 - \cos\theta + (1 + \cos\theta)I$$

$$\dot{\theta} = 0$$

$$1 - \cos\theta + (1 + \cos\theta)I = 0$$

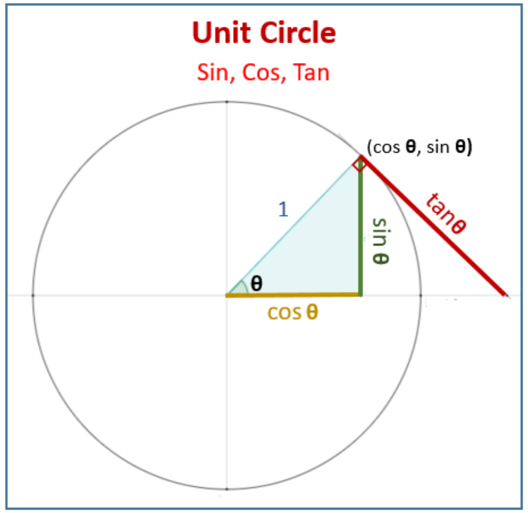
$$\cos\theta(-1 + I) = -1 - I$$

$$\cos\theta = \frac{1 + I}{1 - I}$$

$$\theta = \cos^{-1}\left(\frac{1 + I}{1 - I}\right)$$

What are the consequences of this result?

# Theta model: steady states

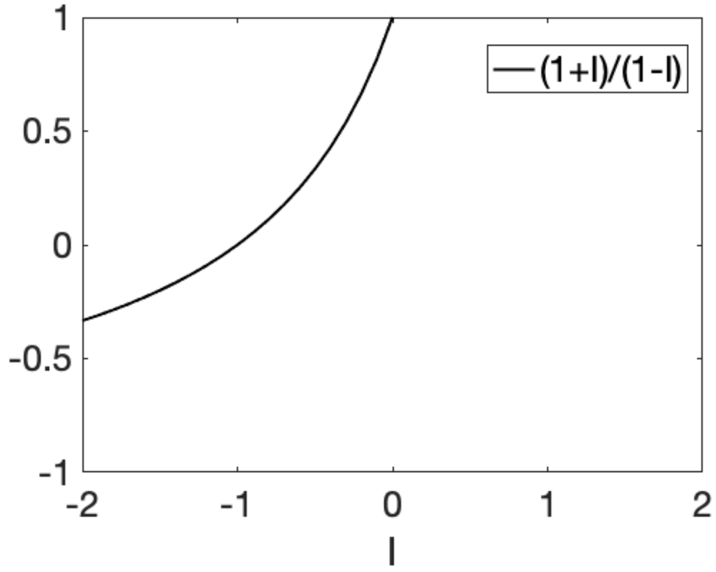



- To understand $\cos\theta = \dfrac{1+I}{1-I}$ consider the unit circle:

$$-1 \le \cos\theta \le 1$$

$$\Downarrow$$

$$-1 \le \frac{1+I}{1-I} \le 1$$




Depending on $I$, we find:

- One solution at $I = 0$, which is $\cos\theta = 1$, i.e. $\theta = 0$
- Two solutions at $I < 0$, because there are two angles for which $-1 < \cos\theta < 1$
- No solution at $I > 0$. What does it mean?

# Let’s look at the dynamics

- To simulate the theta model we can use Euler’s method:

$$\frac{d\theta}{dt} \approx \frac{\theta(t + \Delta t) - \theta(t)}{\Delta t}$$

$$\theta(t + \Delta t) = \theta(t) + \Delta t \frac{d\theta}{dt}$$

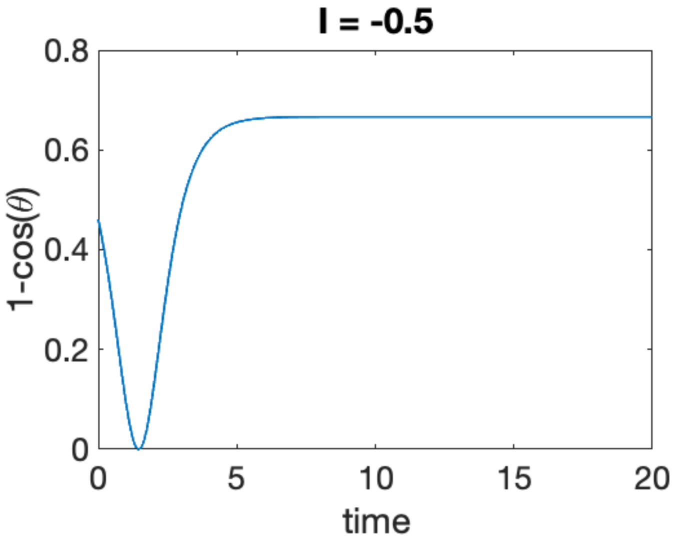
$$\frac{d\theta}{dt} = 1 - \cos\theta + (1 + \cos\theta)I$$

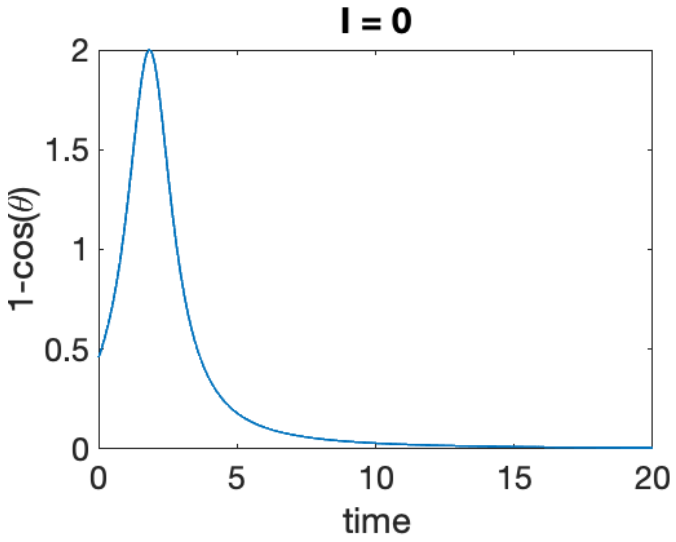
$$\theta(t + \Delta t) = \theta(t) + \Delta t[1 - \cos\theta + (1 + \cos\theta)I]$$

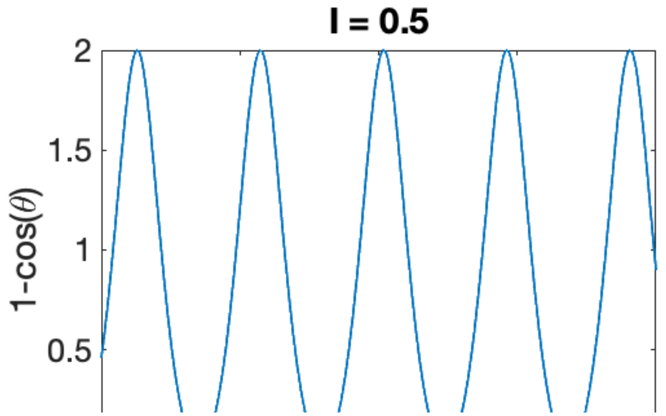
This will be one of your tasks in the practical session

# Dynamics of one theta oscillator

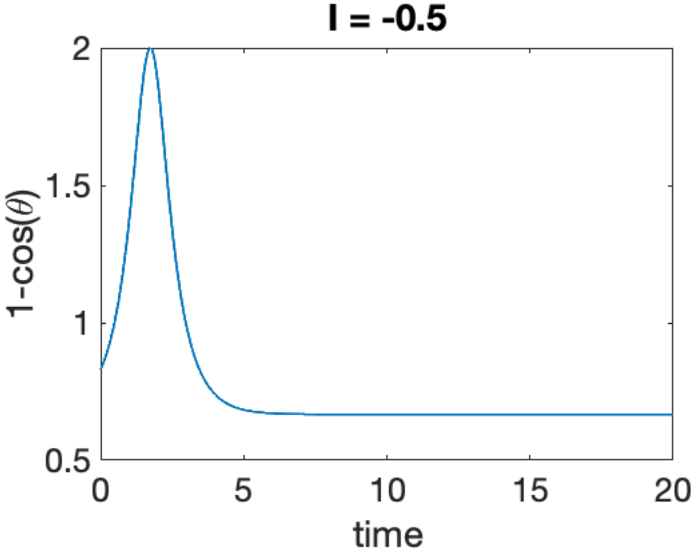
- What happens when $I < 0$, $I = 0$ and $I > 0$?



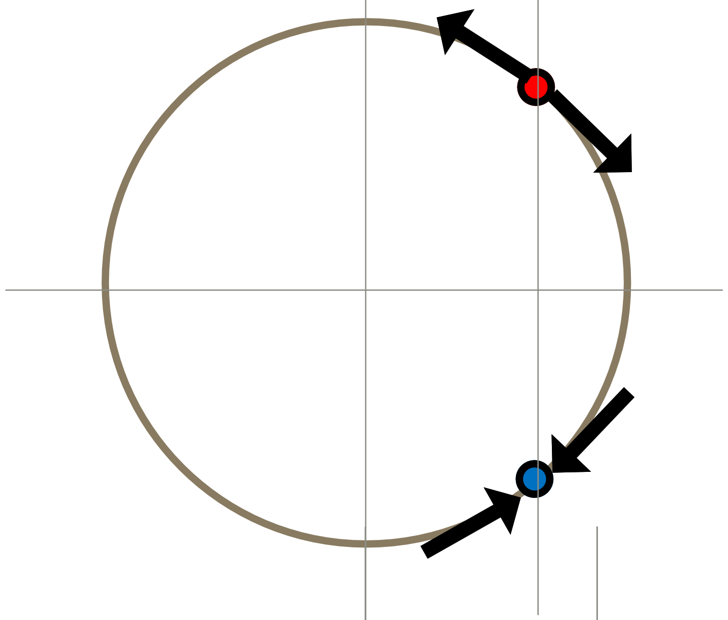



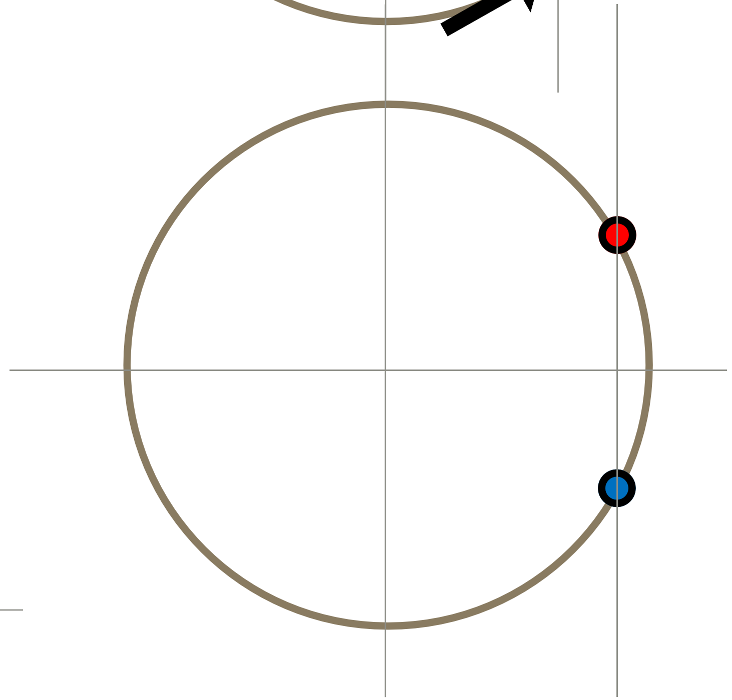

- At $I < 0$, there is a dependence on the initial condition:



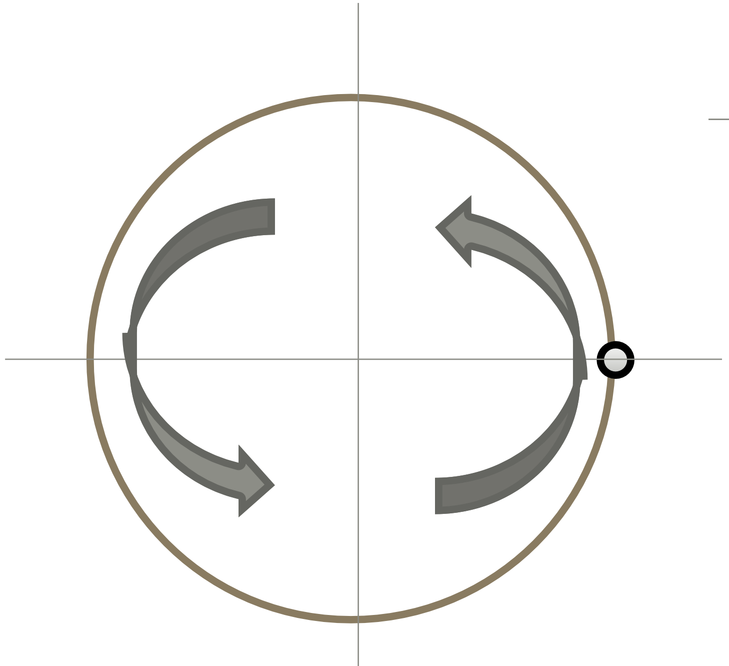

You will explore this in the practical session

# Theta model: steady states





- At $I < 0$, there are two steady states (stable and unstable):
- As $I$ tends to zero, the two points get closer.
- At $I = 0$, the two points merge
  - *Saddle point*
- At $I > 0$, oscillations emerge



# The theta model undergoes a bifurcation

- At $I = 0$ there is a bifurcation
- A bifurcation corresponds to a qualitative change in the dynamics
  - *In the theta model, oscillations emerge.*

- There are many types of bifurcations (saddle-node, Hopf, pitchfork, period-doubling, …)
- Different bifurcations relate to different kinds of changes, with different properties:

| Bifurcation of equilibrium | Behaviour | Frequency | Amplitude |
|---|---|---|---|
| **Saddle-node** | Bistable | Fixed | Fixed |
| **SNIC** | Monostable | Zero ($\sqrt{\lambda}$) | Fixed |
| **Supercritical Hopf** | Monostable | Fixed | Zero ($\sqrt{\lambda}$) |
| **Subcritical Hopf** | Bistable | Fixed | Arbitrary |

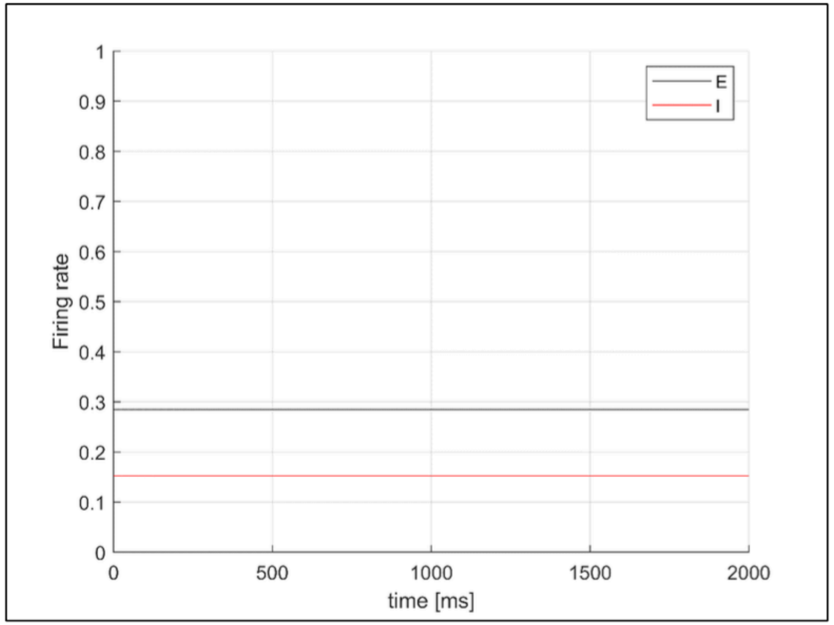
Jirsa, Viktor K., et al. "On the nature of seizure dynamics." Brain 137.8 (2014): 2210-2230.

# You have already met a Hopf bifurcation

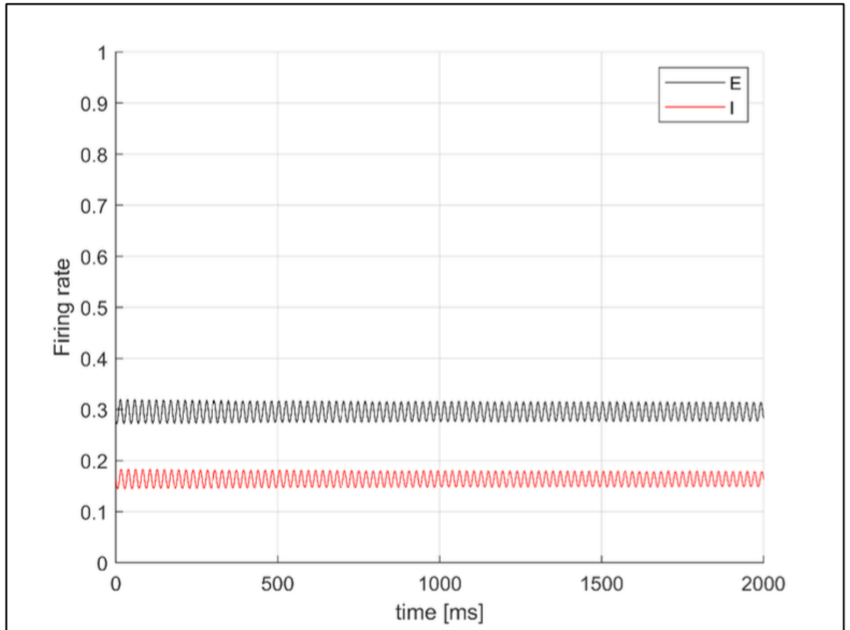
- If you did the previous practical session, you may remember:

6. In the script `SimulateWilsonCowan.m`, increase the value of `P` (input to the system) on line 8 for values between 0 and 2 and run the script again. What happens as this input to the excitatory population increases?

`P=0.39`




`P=0.40`



# Back to our phase oscillator

- To summarize, the theta model allows us to simulate
  - *a steady state* ⟹ *a 'normal state'*
  - *an oscillatory state* ⟹ *a 'seizure state'*

- To make the model more useful, it is convenient to add a mechanism of seizure transitions.
- One way is to make the current $I$ noisy:

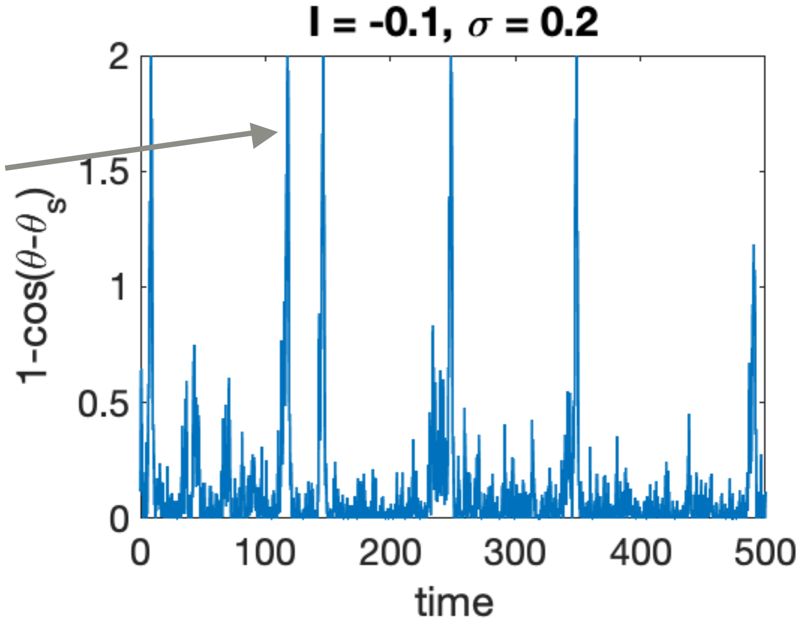
$$I(t) = I_0 + \xi(t)$$

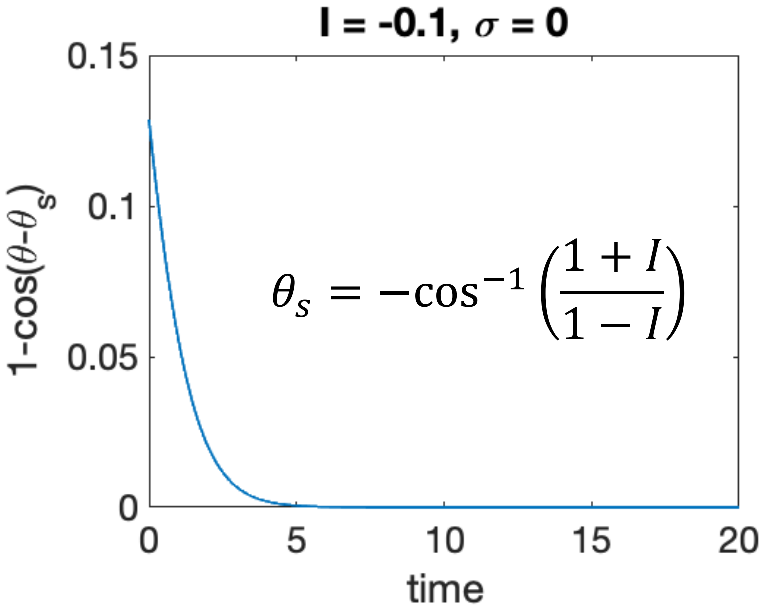
# A noisy phase oscillator

- What are the consequences of a noisy current? $$\frac{d\theta}{dt} = 1 - \cos\theta + (1 + \cos\theta)[I_0 + \xi(t)]$$

In the steady state:

interictal spikes




$$\theta_s = -\cos^{-1}\left(\frac{1+I}{1-I}\right)$$

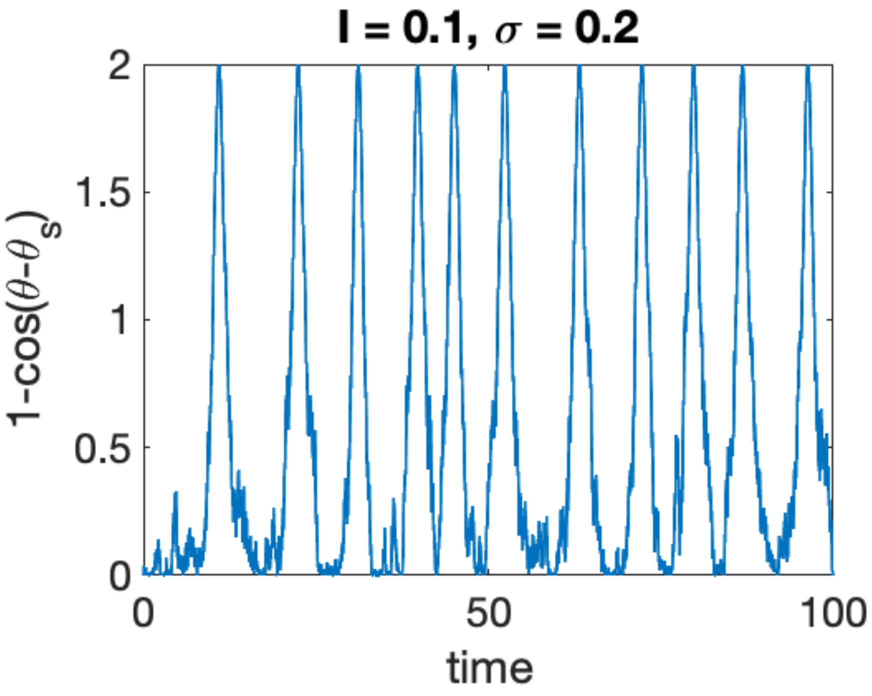
What's the origin of these spikes?

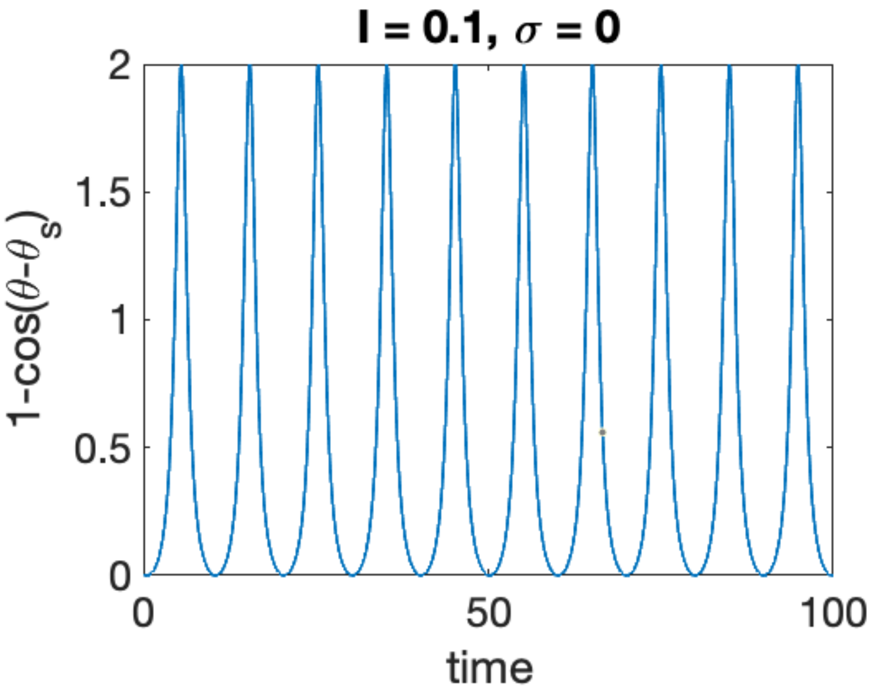
What happens if we set $I_0$ closer to zero?

You will explore this in more detail in the practical session

# A noisy phase oscillator

- The consequences on the oscillations:



# What can we do with our oscillator model?

- We can use it to represent the brain activity at one brain region
- Since we are interested in **brain networks**, we need to consider multiple brain regions and consequently multiple oscillators.

- If we consider two regions (A and B), we have two ODEs:

$$\dot{\theta}_A = 1 - \cos\theta_A + (1 + \cos\theta_A)I_A(t)$$

$$\dot{\theta}_B = 1 - \cos\theta_B + (1 + \cos\theta_B)I_B(t)$$

- What do we need so that the two oscillators interact with each other?

$$I_A(t) = f(\theta_B(t), \dots)$$

$$I_B(t) = f(\theta_A(t), \dots)$$

# Two interacting oscillators

- How shall we make the two oscillators to interact?
- A simple way is to assume one can 'excite' the other with its output:

$$I_A(t) = I_0 + \xi(t) + 1 - \cos(\theta_B - \theta_s)$$
$$I_B(t) = I_0 + \xi(t) + 1 - \cos(\theta_A - \theta_s)$$

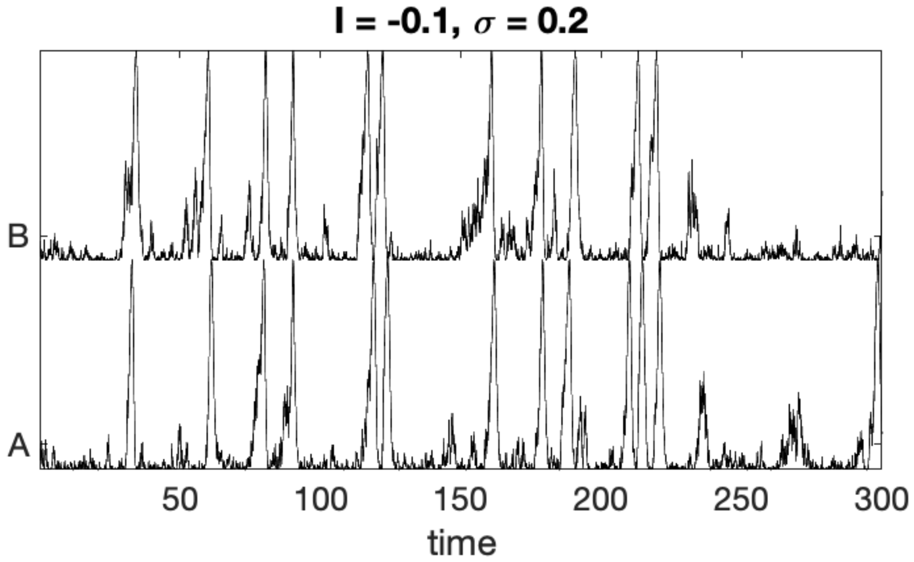
- Therefore, we get the two following SDEs:

$$\dot{\theta}_A = 1 - \cos\theta_A + (1 + \cos\theta_A)[I_0 + \xi(t) + 1 - \cos(\theta_B - \theta_s)]$$

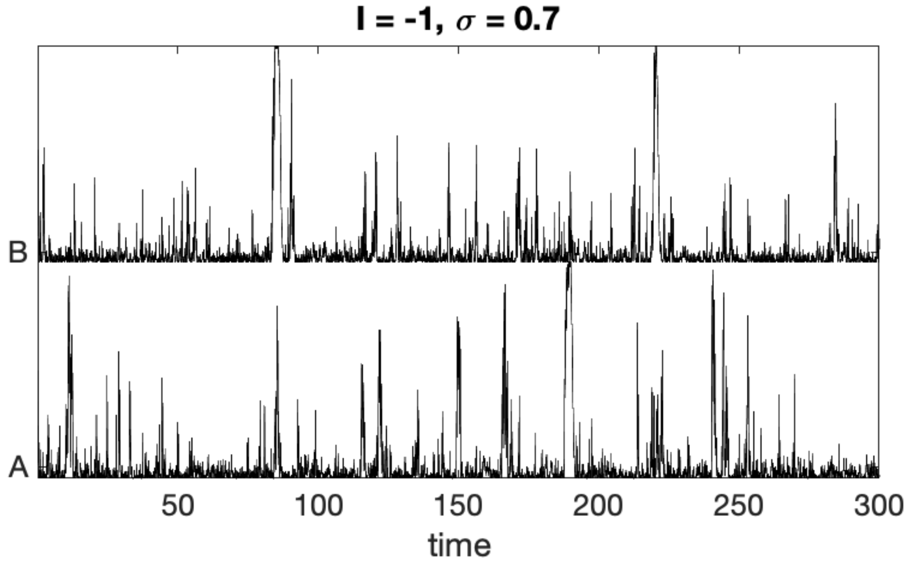
$$\dot{\theta}_B = 1 - \cos\theta_B + (1 + \cos\theta_B)[I_0 + \xi(t) + 1 - \cos(\theta_A - \theta_s)]$$

# Two interacting oscillators

- Their dynamics can be correlated:




- … or not:




What defines whether they are correlated?

# A network of oscillators

- The brain has more than two regions…
- N interacting regions can be represented by N theta oscillators:

$$\dot{\theta}_1 = 1 - \cos\theta_1 + (1 + \cos\theta_1) I_1(t), \text{where } I_1(t) = f(\theta_2, \theta_3, \dots, \theta_N)$$

$$\dot{\theta}_2 = 1 - \cos\theta_2 + (1 + \cos\theta_2) I_2(t), \text{where } I_2(t) = f(\theta_1, \theta_3, \dots, \theta_N)$$

$$\dots$$

$$\dot{\theta}_N = 1 - \cos\theta_N + (1 + \cos\theta_N) I_N(t), \text{where } I_N(t) = f(\theta_1, \theta_2, \dots, \theta_{N-1})$$

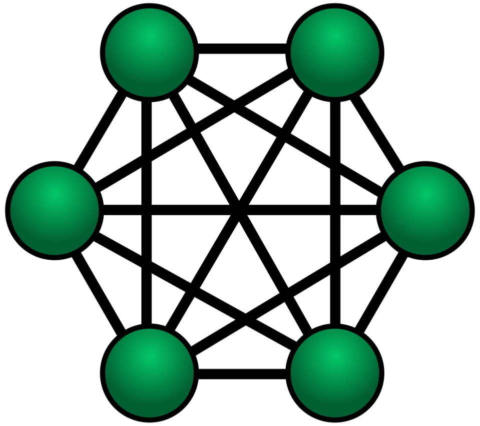
# A network of oscillators

- If all oscillators interact with all other oscillators, then:

$$\dot{\theta}_i = 1 - \cos\theta_i + (1 + \cos\theta_i) I_i(t)$$

$$I_i(t) = I_0 + \xi(t) + \sum_{j \neq i} 1 - \cos(\theta_j - \theta_s)$$

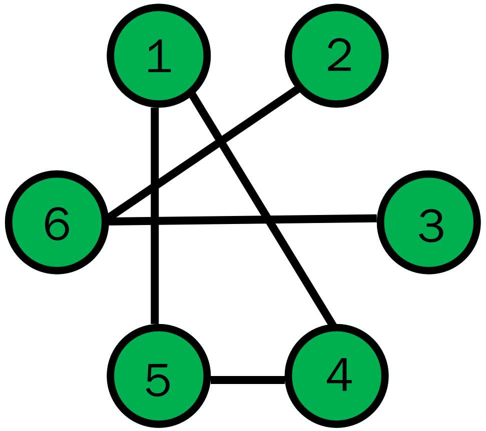
- This is a special case when the underlying network is fully connected:



A network is a set of nodes connected by links

Network = graph
Node=vertex
Connection/link = edge

# A network of oscillators




- What if nodes (i.e. oscillators) are connected at random?

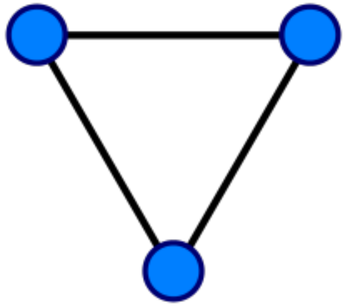
$$I_i(t) = I_0 + \xi(t) + \sum_{j \neq i} \boxed{a_{ji}} \left(1 - \cos\left(\theta_j - \theta_s\right)\right)$$

$$\boldsymbol{A} = \begin{pmatrix} 0 & 0 & 0 & 1 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 1 \\ 1 & 0 & 0 & 0 & 1 & 0 \\ 1 & 0 & 0 & 1 & 0 & 0 \\ 0 & 1 & 1 & 0 & 0 & 0 \end{pmatrix}$$

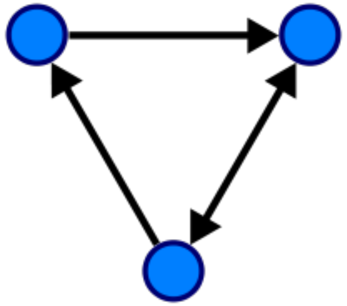
- The matrix $\boldsymbol{A} = (a_{ji})$ allow us to define whether node $j$ is connected to $i$:
  - If $j$ is connected to $i$, then $a_{ji} = 1$
  - Otherwise, $a_{ji} = 0$
- $\boldsymbol{A} = (a_{ji})$ is called the adjacency matrix of the network
  - It is a square matrix $N \times N$, where each element refers to a possible connection
  - Diagonal elements, $a_{ii}$, correspond to self-connections, which we do not consider

# Side note: Types of networks

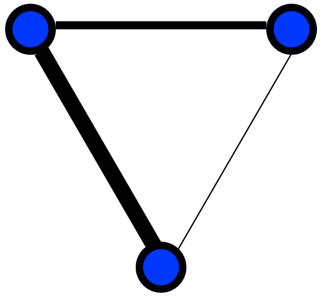
- A network may be
  - Undirected
    - $a_{ji} = a_{ij}$



  - Directed
    - $a_{ji} \neq a_{ij}$



  - Weighted
    - $a_{ji}$ can be a real number (i.e. the matrix is not binary)



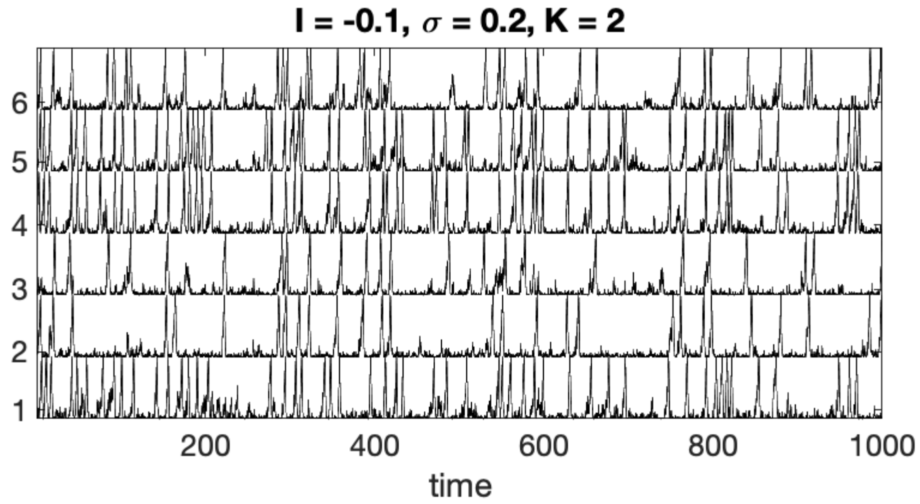
- Whether the brain is better represented by an undirected or directed, binary or weighted network is an open question.
- Different methods can give you different types of networks from the same data.

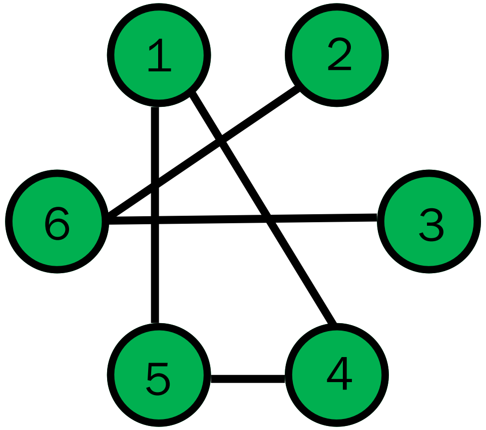
# Back to a network of oscillators

- Since different networks may have different characteristics, it is convenient to add an additional parameter:

$$I_i(t) = I_0 + \xi(t) + \boxed{\frac{K}{N}}\sum_{j \neq i} a_{ji}\left(1 - \cos\left(\theta_j - \theta_s\right)\right)$$

- What kind of dynamics can we observe in a random network?




You will explore this in more detail in the practical session (with some small differences)

# What is this useful for?

- Such framework allows us to test a number of hypothesis:
- The structure of a brain network may define its propensity to generate seizures
- Diagnosis of epilepsy:
  - brain networks from healthy people may spike more than brain networks from people with epilepsy in model simulations
- Diagnosis of epilepsy type, generalised vs focal:
  - brain networks from people with generalised epilepsy may have more widespread seizure-like activity in model simulations
- Epilepsy treatments, such as brain surgery:
  - Node removal may represent resective surgery, and simulations of different removals allows us test different possible surgeries

# Applications of the framework in the literature

- Diagnosis of epilepsy:

Lopes, M.A., et al., (2020). https://www.medrxiv.org/content/10.1101/2020.05.18.20102681v1

- Diagnosis of epilepsy type:

Lopes, M. A., et al. (2019). Sci Rep, 9(1), 1-10. https://www.nature.com/articles/s41598-019-46633-7

- Epilepsy surgery:

Lopes, M.A., et al. (2017). PLoS CB, 13(8). https://doi.org/10.1371/journal.pcbi.1005637
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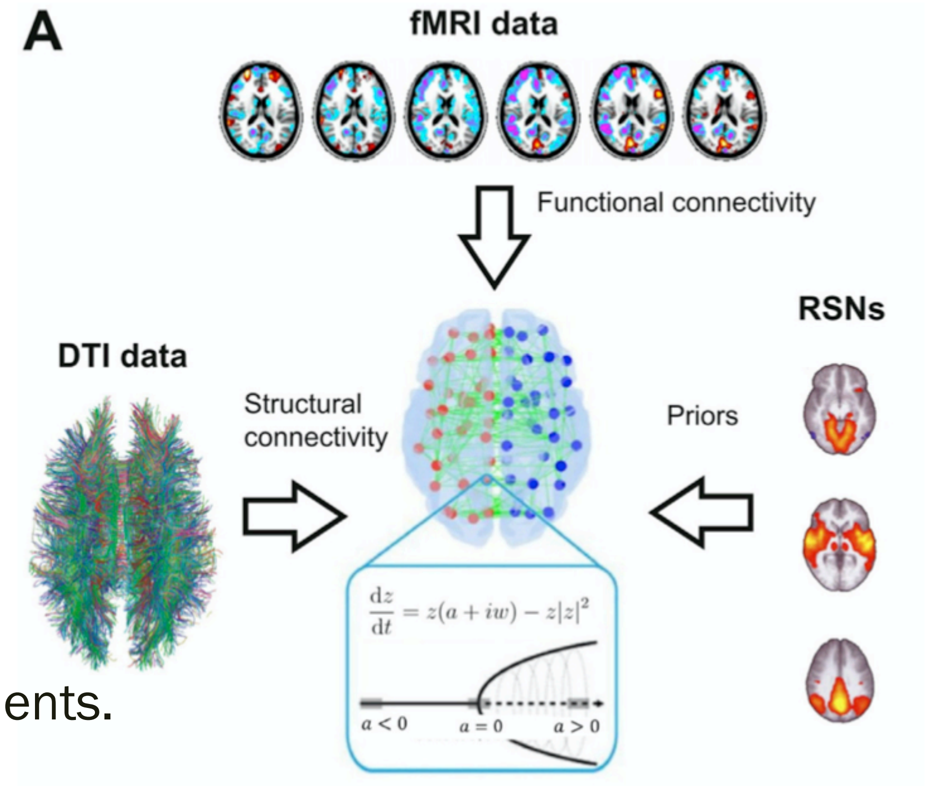
Junges, L., et al. (2019). Sci Rep, 9(1), 1-12. https://www.nature.com/articles/s41598-019-43871-7
Laiou, P., et al. (2019). Front Neurol, 10, 1045. https://www.frontiersin.org/articles/10.3389/fneur.2019.01045/full
Lopes, M. A., et al. (2020). Clin Neurophysiol, 131(1), 225-234. https://doi.org/10.1016/j.clinph.2019.10.027
Lopes, M. A., et al. (2019). Front Comput Neurosci, 13, 25. https://doi.org/10.3389/fncom.2019.00025
Lopes, M. A., et al. (2020). Front Neurol, 11, 74. https://www.frontiersin.org/articles/10.3389/fneur.2020.00074/full

- Animal models of epilepsy:

Słowiński, P., et al. (2019). eNeuro, 6(4). https://www.eneuro.org/content/6/4/ENEURO.0059-19.2019

# Is this only useful for epilepsy?

- No!
- It may help understand the differences and transitions between wakefulness and sleep states:
  - *Ipiña, I.P., et al. (2020). NeuroImage, 116833.*
- It may help understand how functional networks emerge from structural networks; their relation; etc.
- To study how neuronal dynamics can be robust to changes in white matter connectivity (in aging, development and diseases)
  - Abeysuriya, R.G., et al. (2018). *PLoS CB*, *14*(2), e1006007.
- To understand other neurological diseases and treatments.



# Practical session: **Modelling the emergence of seizures in networks**

- The practical session is divided in three parts:
  - Simulate a deterministic phase oscillator (15 min + 5 min for solutions)
  - Simulate a stochastic phase oscillator (10 min + 5 min for solutions)
  - Simulate a network of interacting phase oscillators (15 min + 5 min for solutions)
- Download and extract the git repository www.github.com/lukewtait/intro_to_modelling/
- In this folder, open the subfolder practical2 and open the document Worksheet2.pdf.
- This directory also contains some Matlab codes that you will need to use, so make sure when you open Matlab you change to this directory.
- There are solutions in the subdirectory practical2/solutions. Try to solve the problems yourself or ask a tutor first, but if you get stuck you can use these solutions to help you.
- You will be assigned to a breakout room, where you can ask questions to other people in the room
- There will be one tutor per breakout room. Solutions will be discussed in the main room.