Real time network modulation for intractable epilepsy

Behnaam Aazhang

Electrical and Computer Engineering
Rice University

and

Center for Wireless Communications
University of Oulu
Finland

Real time network modulation for intractable epilepsy

Behnaam Aazhang

Electrical and Computer Engineering
Rice University

and

Center for Wireless Communications
University of Oulu
Finland

Real time network modulation for intractable epilepsy

Behnaam Aazhang

Electrical and Computer Engineering
Rice University

and

Center for Wireless Communications
University of Oulu
Finland

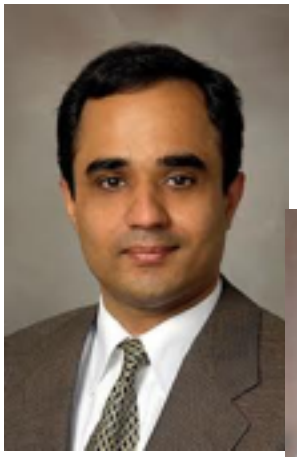
acknowledgement

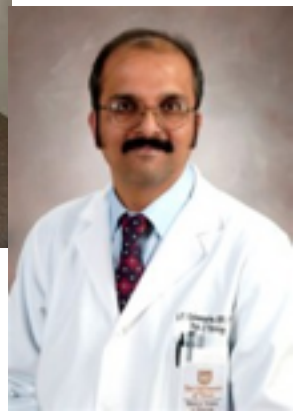
acknowledgement

- Rakesh Malladi

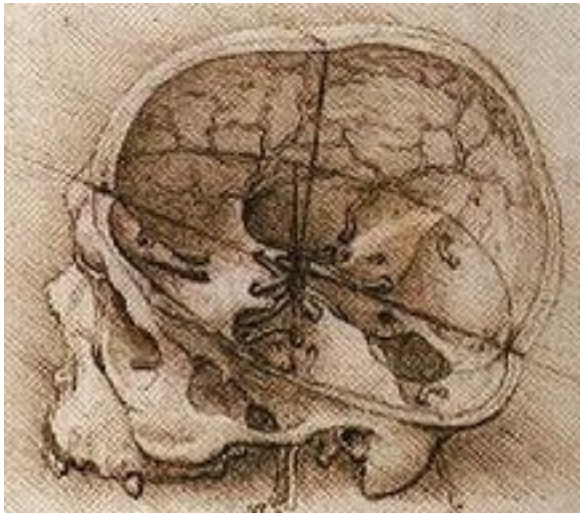
acknowledgement

- Rakesh Malladi
- Nitin Tandon, MD at UTHSC
- Giridhar Kalamangalam, MD at UTHSC



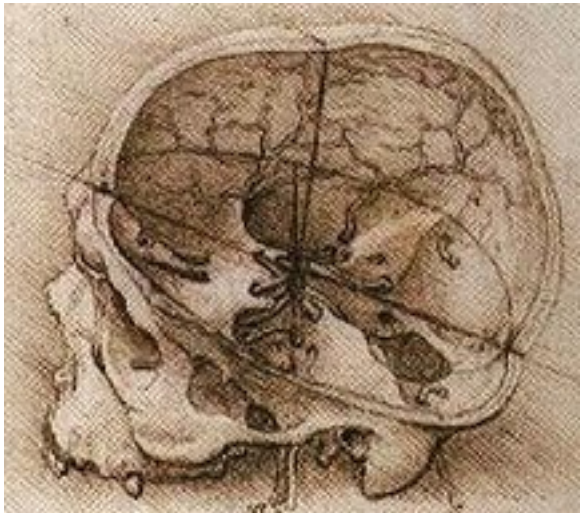


a scientific curiosity



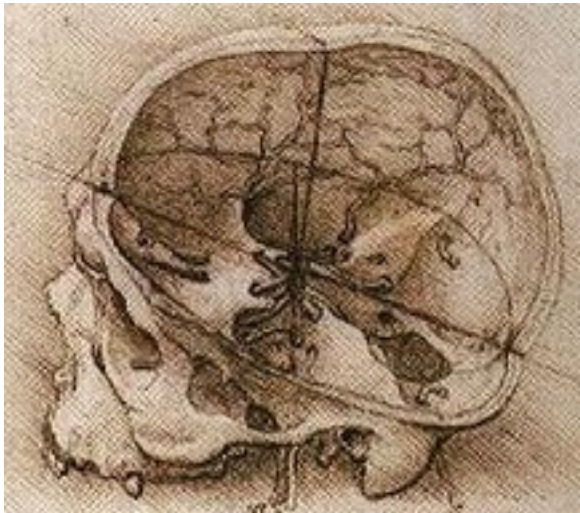
a scientific curiosity

- How does human brain work?
    - Ancient Egypt and Greece
    - Roman empire
        - the seat of intelligence



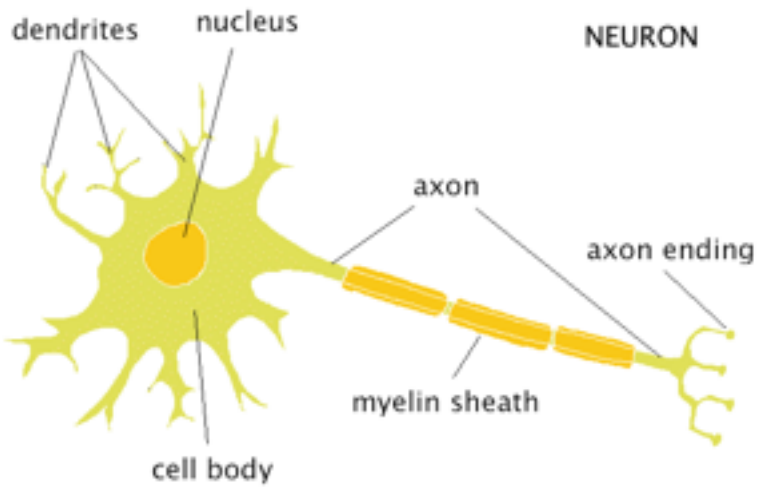
a scientific curiosity

- How does human brain work?
  - Ancient Egypt and Greece
  - Roman empire
    - the seat of intelligence
  - 19th century
  - 90s the “decade of the brain”
  - 2013 “the brain initiative”



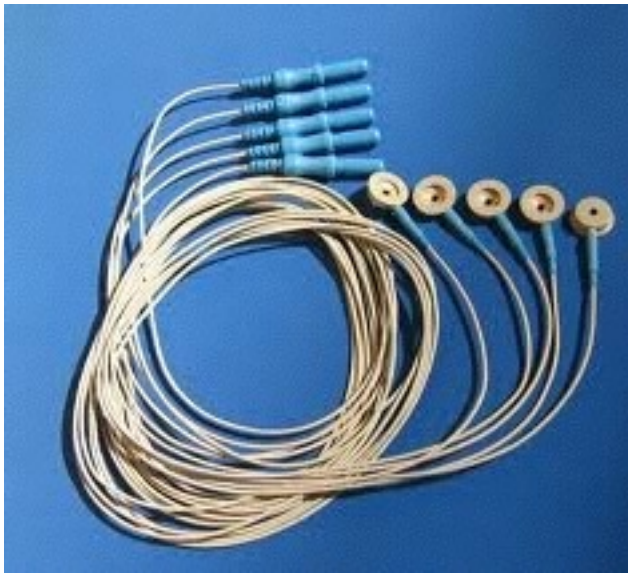
understanding

- quantum leap
    - neuron doctrine



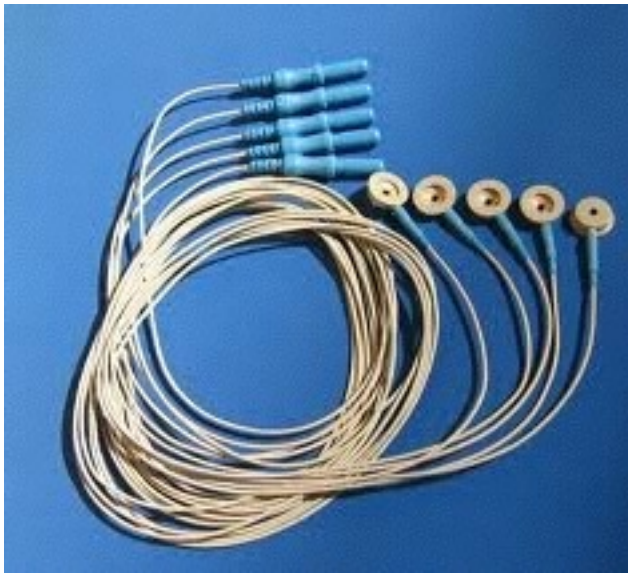
understanding

- quantum leap
    - neuron doctrine
    - electrical circuit
    - electrical excitability



understanding

- quantum leap
  - neuron doctrine
  - electrical circuit
  - electrical excitability
    - enabler
      - tools
        - microscope
        - electrodes



grand challenges

- ...
- relation
  - neuronal circuit connectivity and behavior

grand challenges

- ...
- relation
  - neuronal circuit connectivity and behavior
    - transition of neuronal circuits
      - disease state to healthy state
      - learning
- ...

our research focus

- network modulation as a reparative therapy
    - epilepsy, parkinson, alzheimers
- circuits connectivity—behavior
    - common theme
        - tools
        - influence on network

this talk

- network modulation as a reparative therapy
    - epilepsy, parkinson, alzheimers
- circuits connectivity—behavior
    - common theme
        - tools
        - influence on network

neurological disorders

- human nervous system
    - a gigantic network with nano scale structures
    - 200 billion neurons and trillions of connections

neurological disorders

- human nervous system
  - a gigantic network with nano scale structures
  - 200 billion neurons and trillions of connections
- over 200 identified neurological disorders
- “cost” of neurological diseases
  - $600 billion annually

epilepsy

- unprovoked and recurring seizures
- seizure
  - no standard definition

epilepsy

- unprovoked and recurring seizures
- seizure
  - no standard definition
  - abnormally synchronized hyper-excited neuronal activities
  - variations
    - sub-clinical seizure burst——full blown seizure
    - single focal seizure——multifocal seizure

epilepsy

- effects 3 million patients in the USA
    - medication
    - resection
    - stimulation (modulation)
        - neurons respond to electric signals !

epilepsy

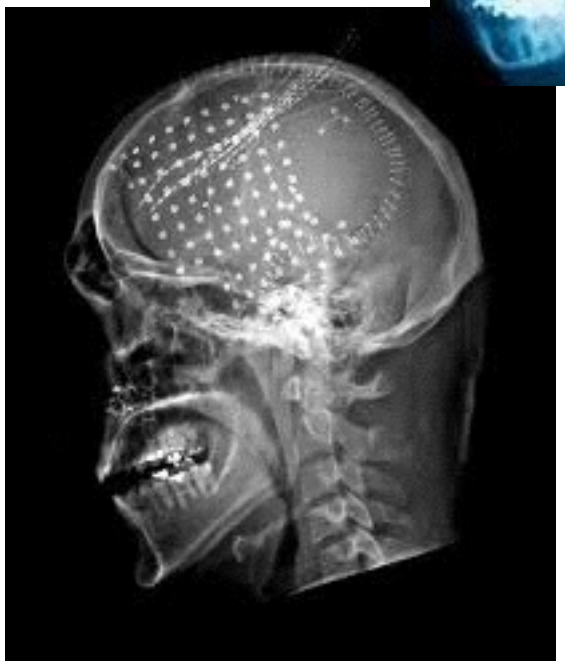
- effects 3 million patients in the USA
    - medication
    - resection
    - stimulation (modulation)
        - neurons respond to electric signals !

recording-stimulation

- deep brain

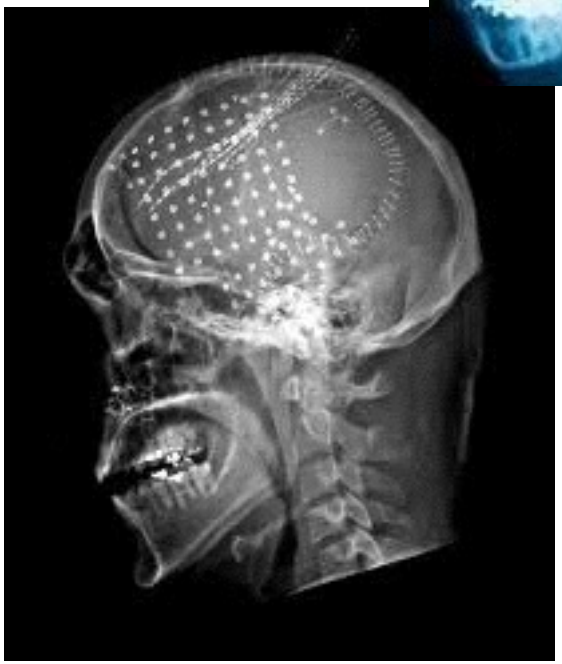
recording-stimulation

- deep brain
- subdural



recording-stimulation

- deep brain
- subdural
- trans-cranial



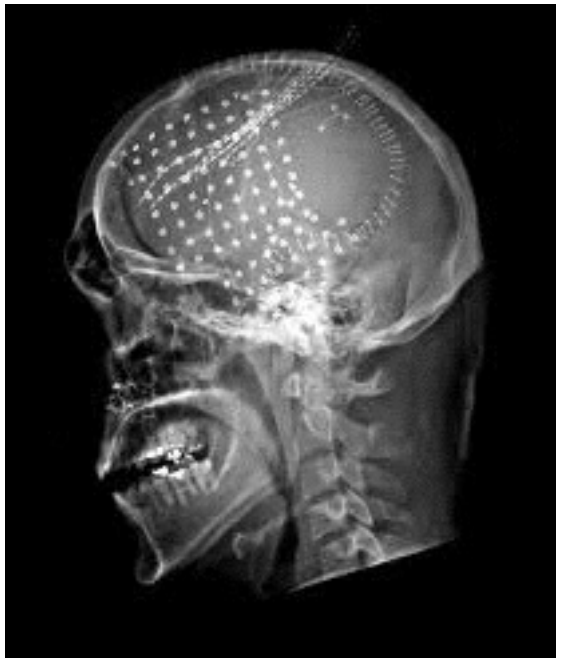
recording-stimulation

- deep brain
- subdural
- trans-cranial

tradeoff: invasive versus effective

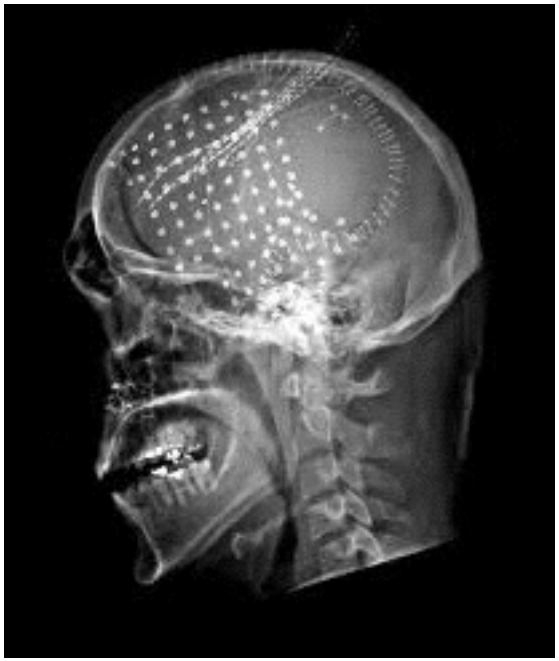
our methodology

- deep brain
- subdural
- trans-cranial



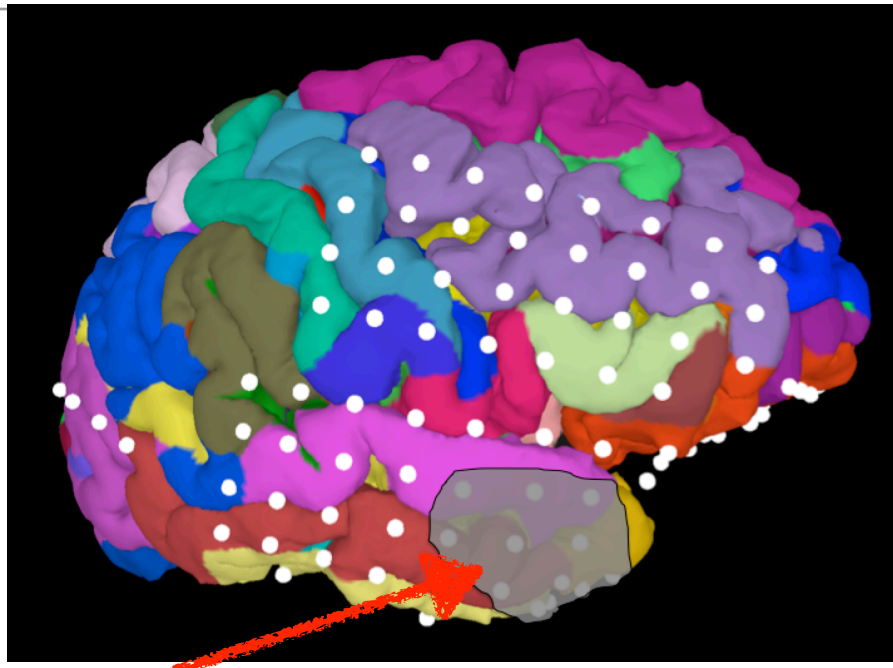
today's application

- subdural recording
  - identify epileptic zone



today's application

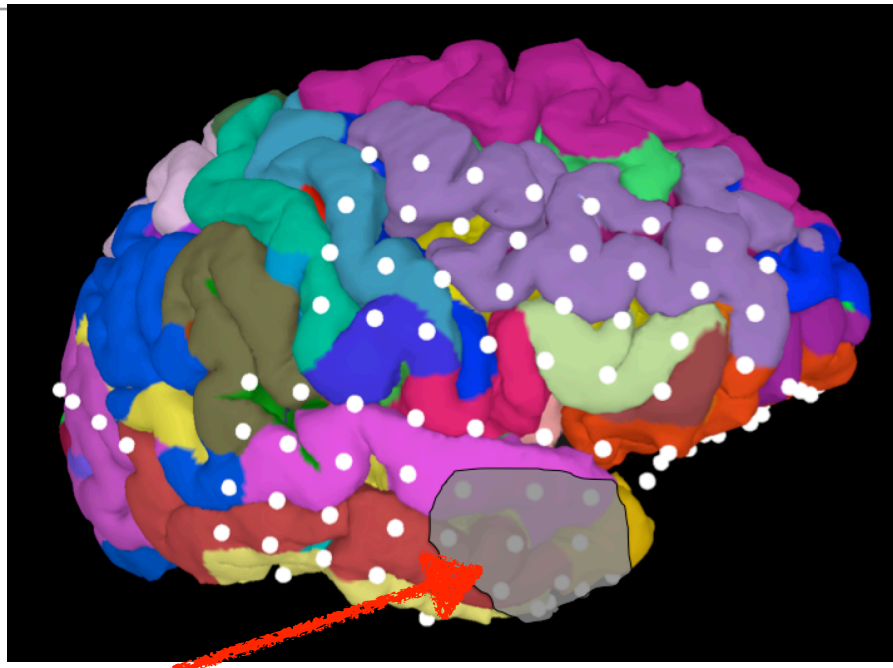
- subdural recording
  - identify epileptic zone
  - resection!



epileptic zone

potential application

- subdural stimulation



epileptic zone

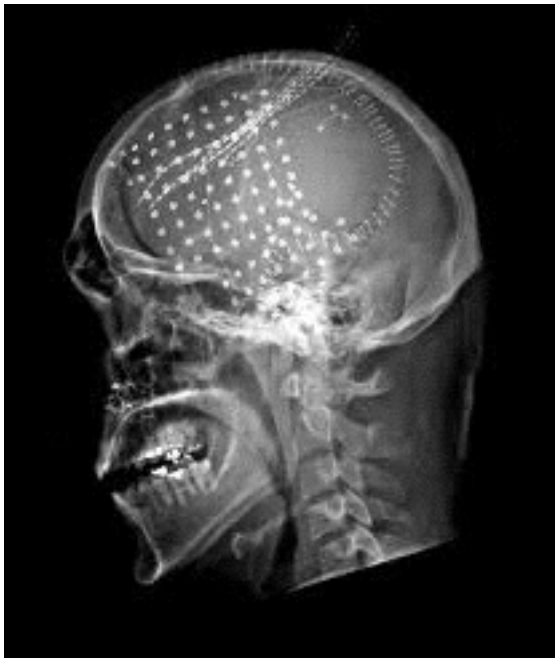
challenges in stimulation

- prevent the network “from going to” hyperexcitable state
- identify seizure zone
- identify temporal markers
    - low frequency stimulation

seizure markers!

subdural recording and stimulation

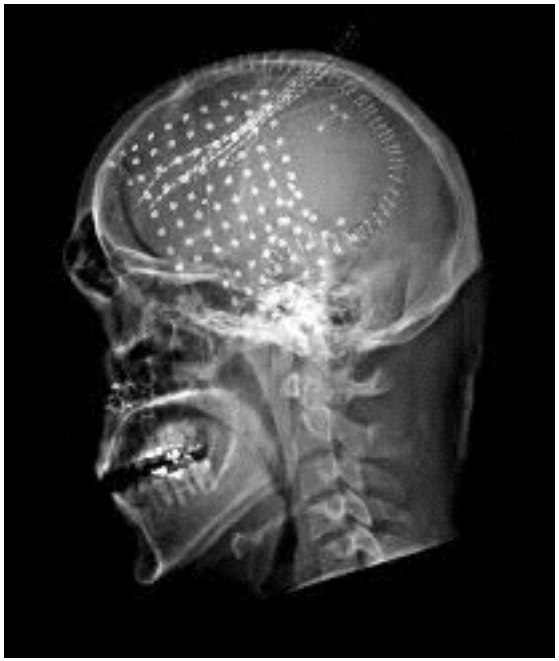
- wish list
  - real time
  - closed loop



let’s do this!

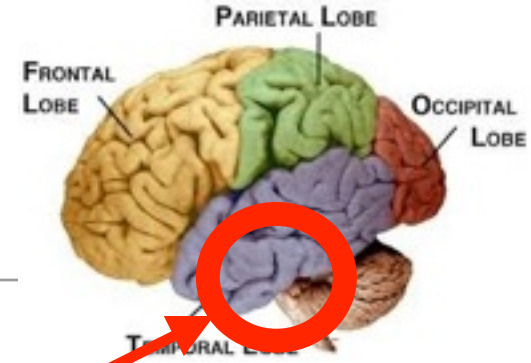
subdural recording and modulation

- electro-cortico-graphy (ECoG)
  - subdural
  - 154 channels (electrodes)

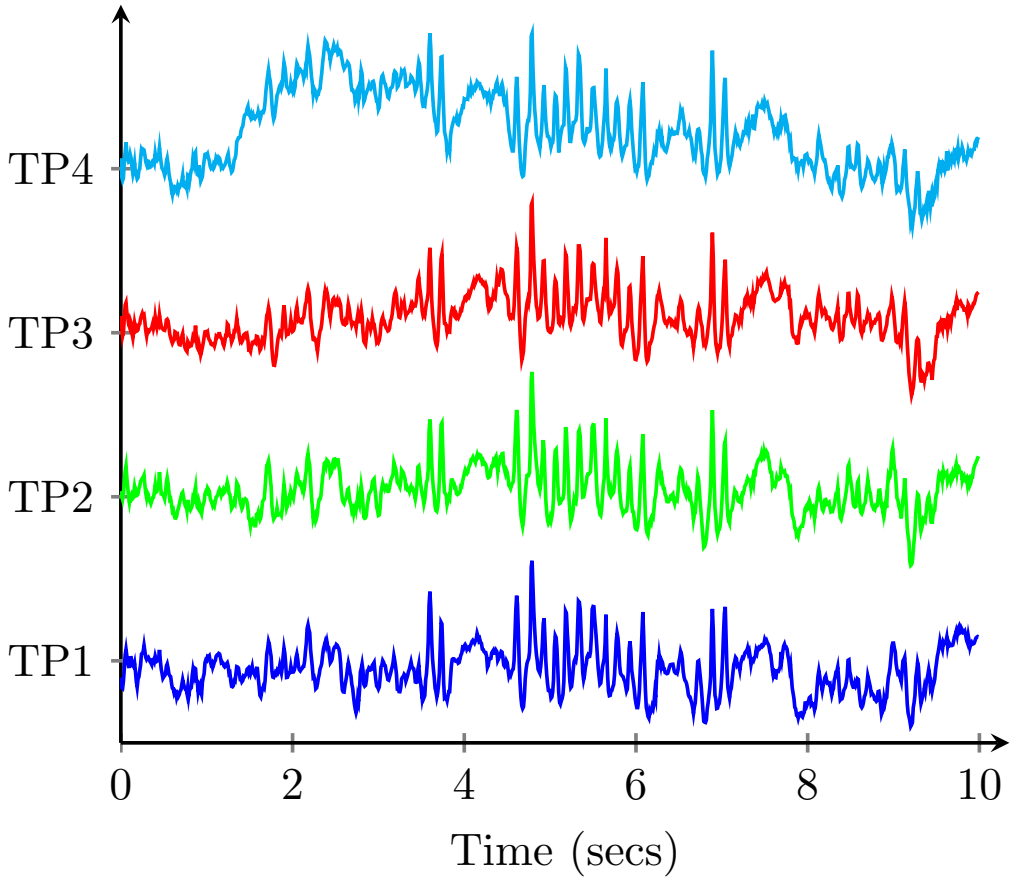


recording

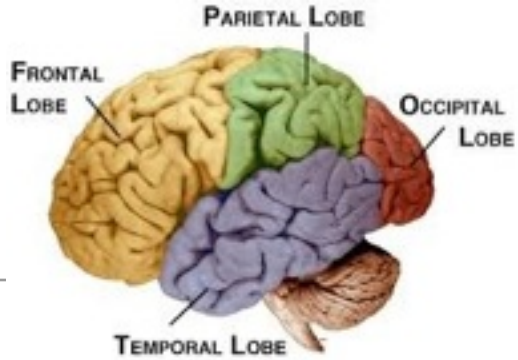
- electro-cortico-graphy (ECoG)
  - subdural
  - 154 channels (electrodes)
- recording



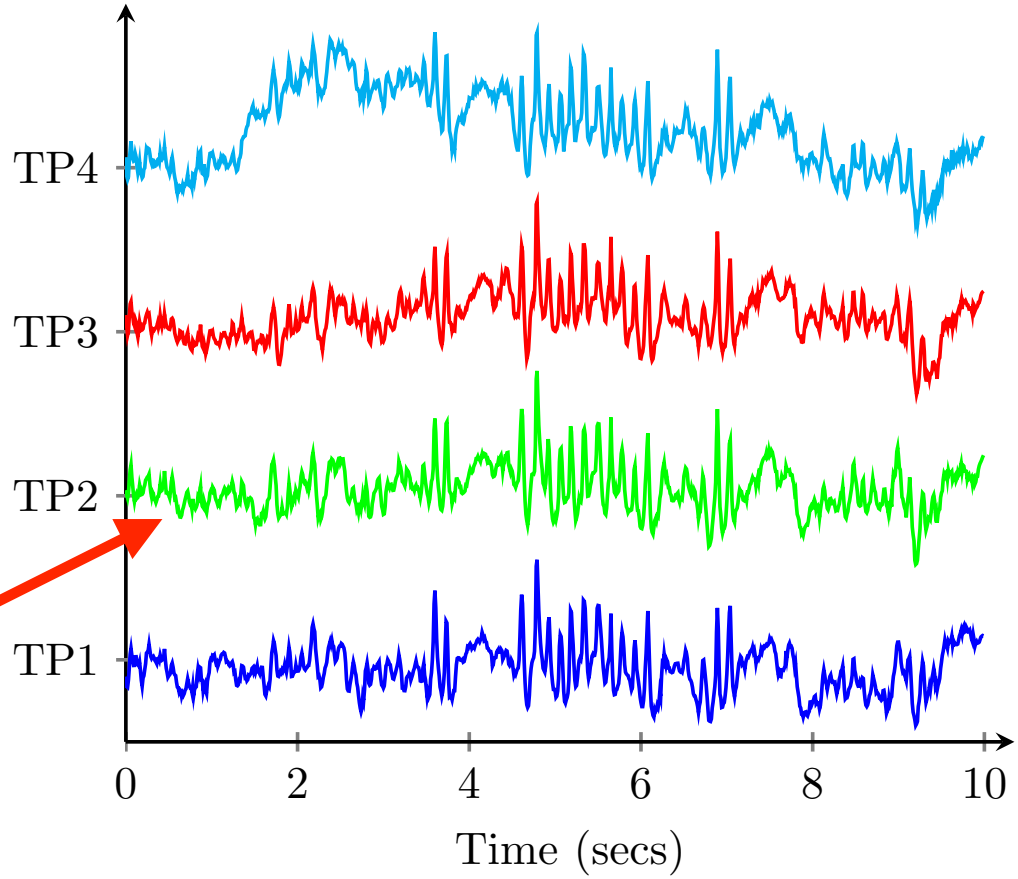
temporpolar



recording

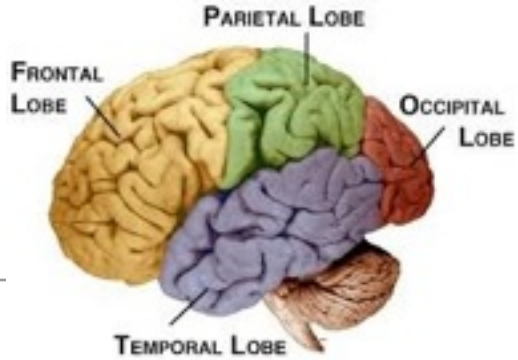


- electro-cortico-graphy (ECoG)
  - subdural
  - 154 channels (electrodes)
  - recording

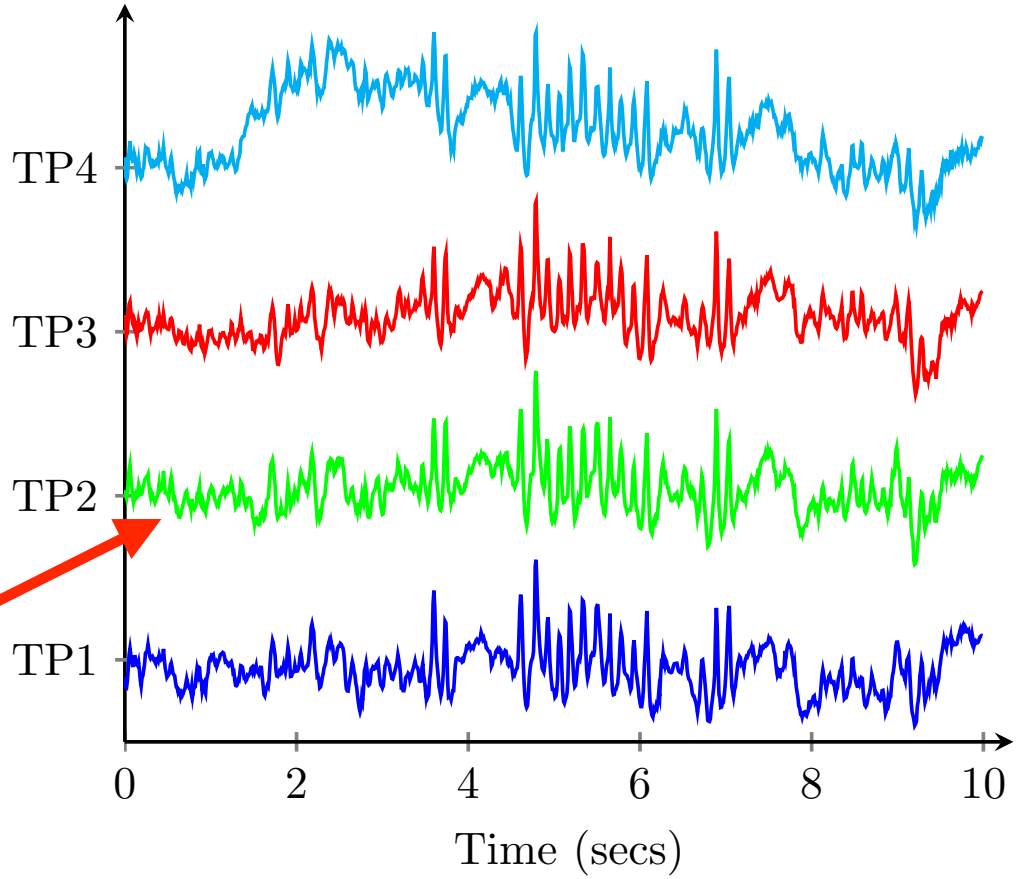


these are not spikes

recording



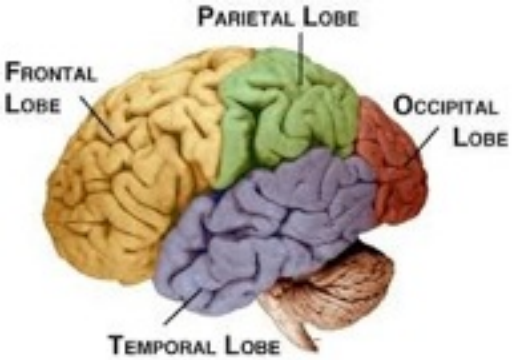
- electro-cortico-graphy (ECoG)
  - subdural
  - 154 channels (electrodes)
  - recording



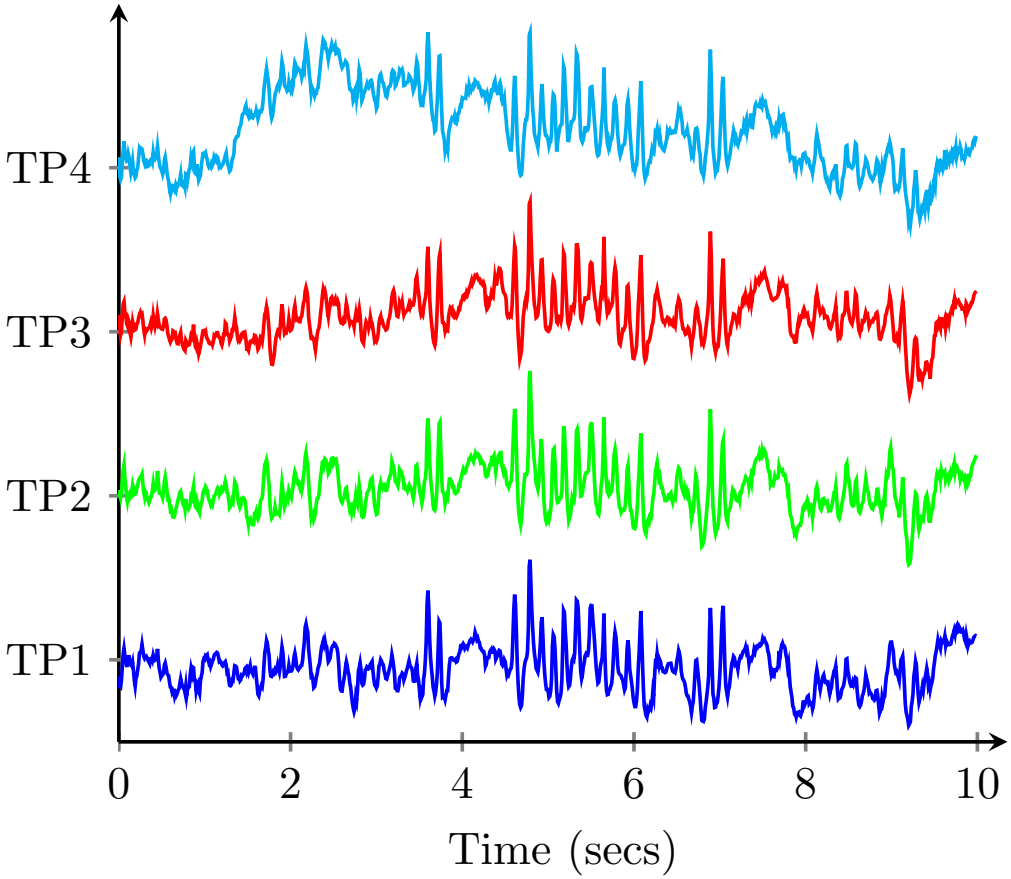
these are not spikes

local field potentials

recording

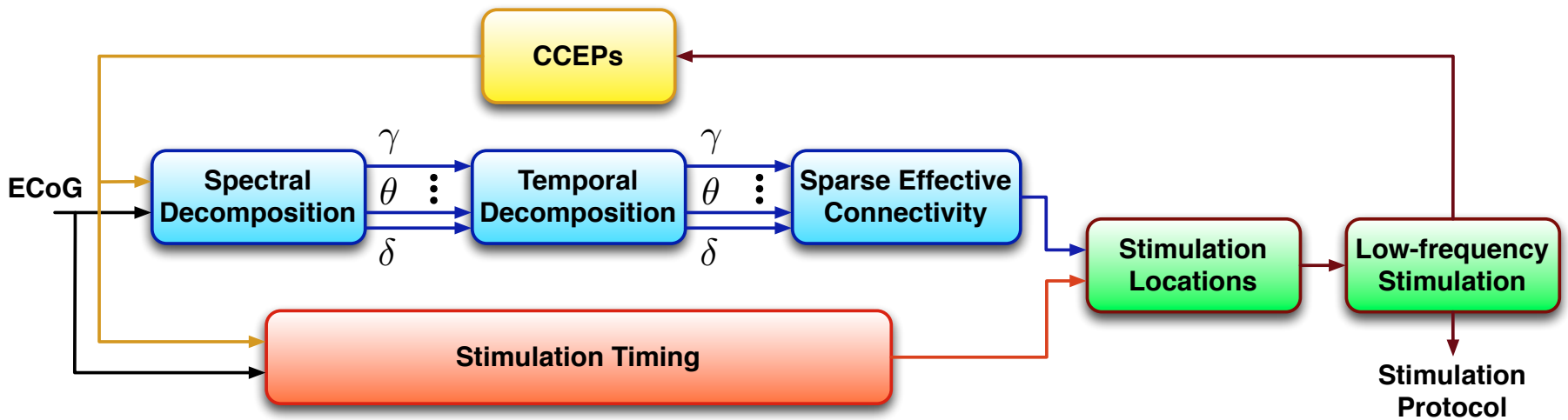


- electro-cortico-graphy (ECoG)
  - subdural
  - 154 channels (electrodes)
- recording
- stimulation?



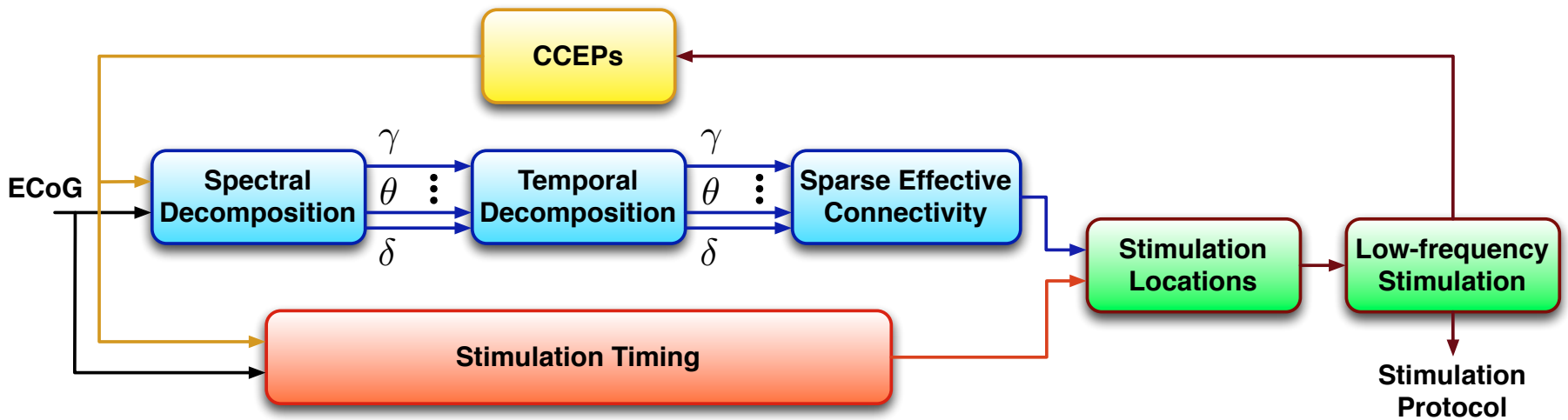
stimulation (modulation)

- protocol
  - depress the influence of one population of neurons on another
  - temporally precise low frequency stimulation of selected electrodes



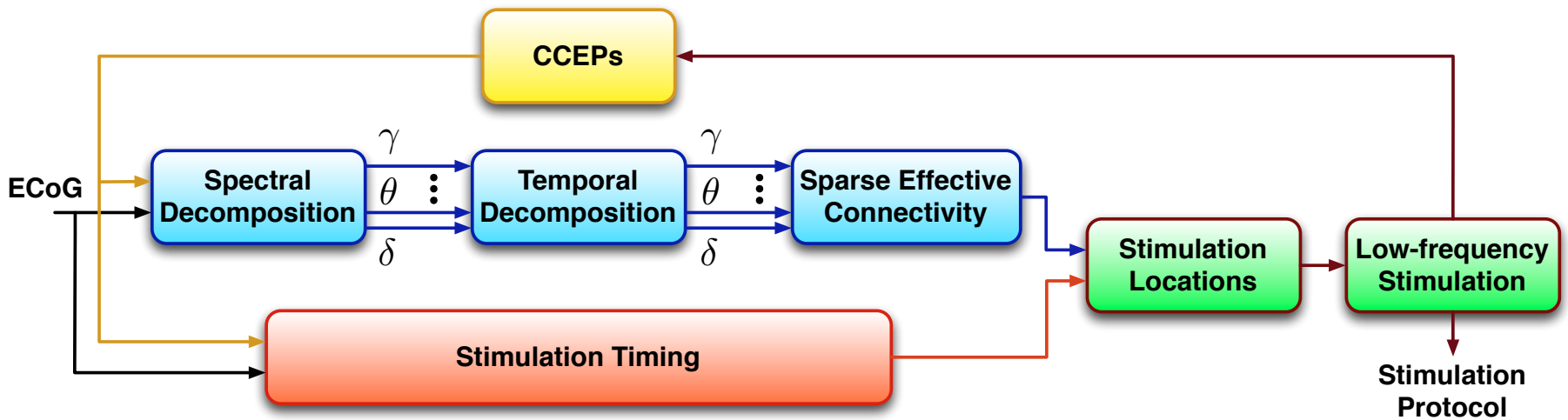
research agenda

- temporally precise low frequency stimulation of selected electrodes



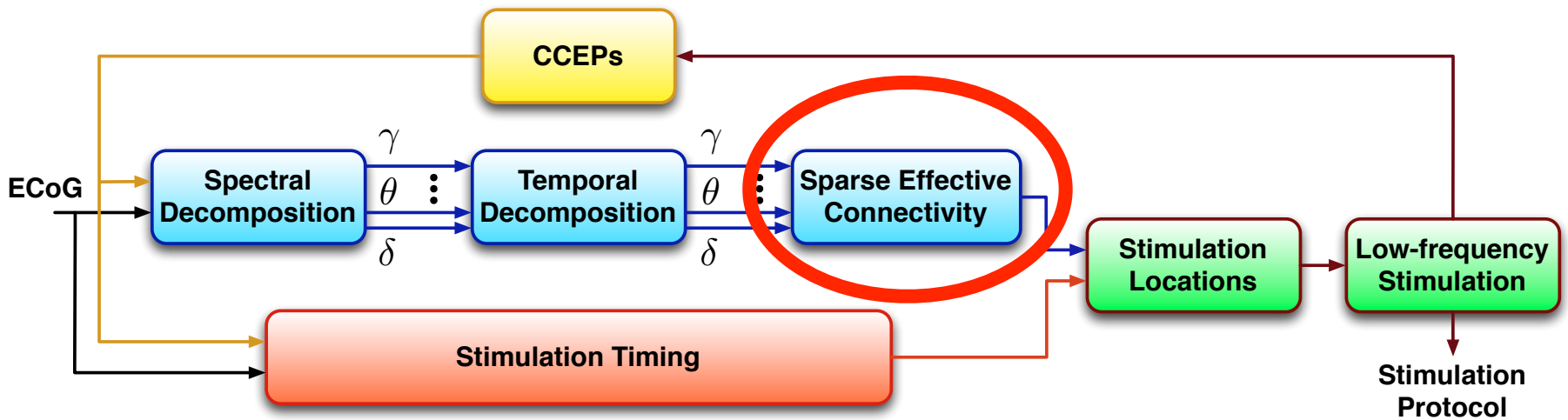
research agenda

- temporally precise low frequency stimulation of selected electrodes
- develop a model and protocols—real-time, closed loop,
- build the system
- clinical trial

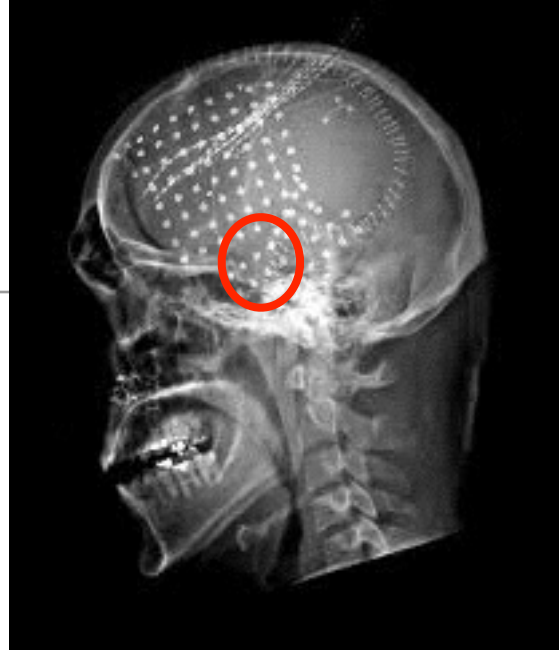


today's talk

- develop
  - sparse effective connectivity



modeling



- time series of length N
- d channels

$$\mathbf{X}_1^N = (\mathbf{x}_1, \mathbf{x}_2, \cdots, \mathbf{x}_N)$$

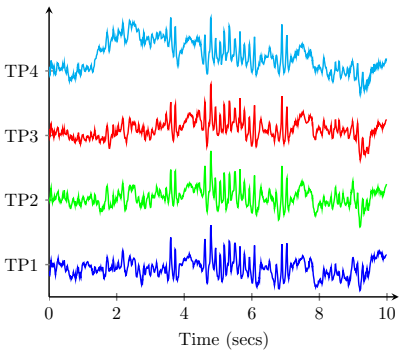
$$\mathbf{x}_n = [x_n(1), x_n(2), \cdots, x_n(d)]^T \in \Re^d \ \forall n$$

modeling

- time series of length N
- d channels

these are not spikes

local field potentials



$$\mathbf{X}_1^N = (\mathbf{x}_1, \mathbf{x}_2, \cdots, \mathbf{x}_N)$$

$$\mathbf{x}_n = [x_n(1), x_n(2), \cdots, x_n(d)]^T \in \Re^d \ \forall n$$

modeling

- time series of length N——hours and hours of observations
- d channels——154

$$\mathbf{X}_1^N = (\mathbf{x}_1, \mathbf{x}_2, \cdots, \mathbf{x}_N)$$

$$\mathbf{x}_n = [x_n(1), x_n(2), \cdots, x_n(d)]^T \in \Re^d \ \forall n$$

modeling

- time series of length N——hours and hours of observations
- d channels——154

exploit natural sparsity

modeling

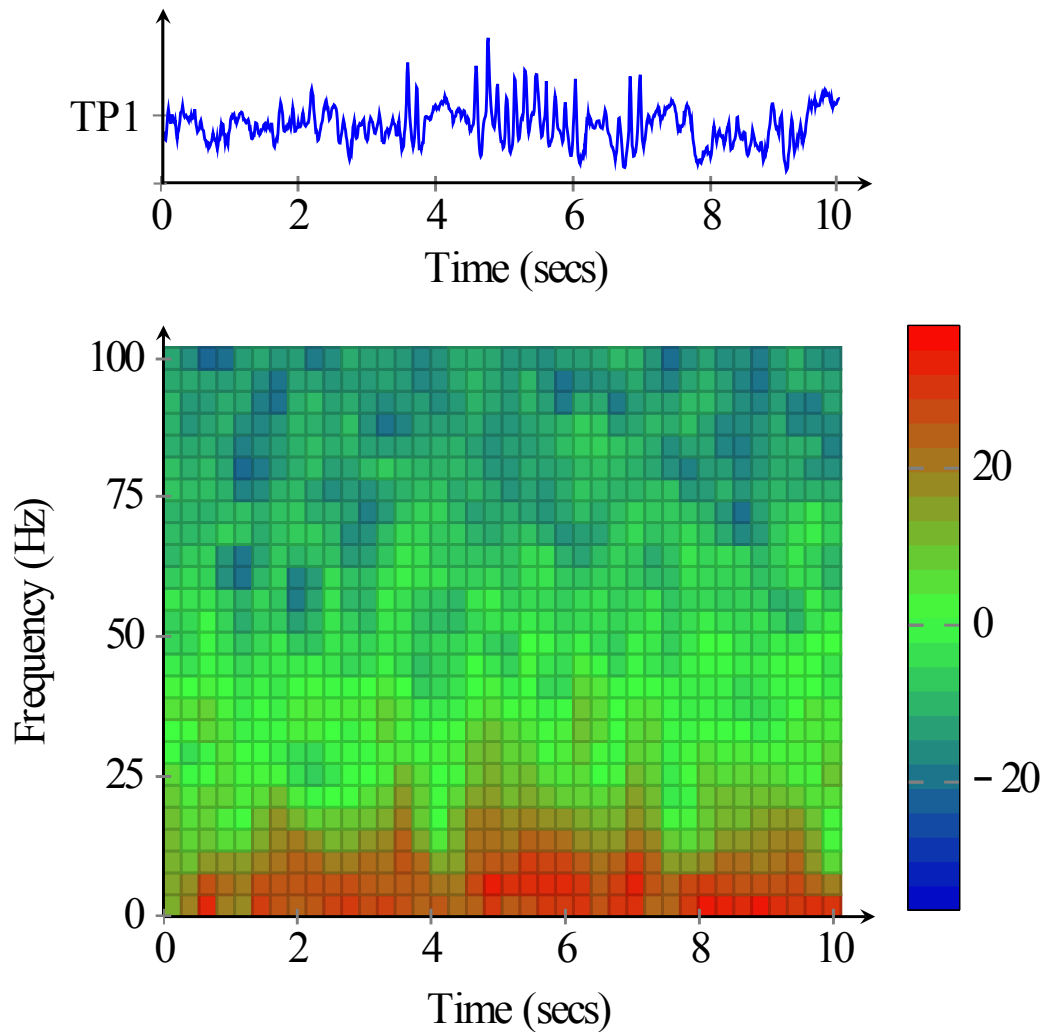
- time series of length N——hours and hours of observations
- d channels——154

exploit natural sparsity

spectral? temporal? spatial?

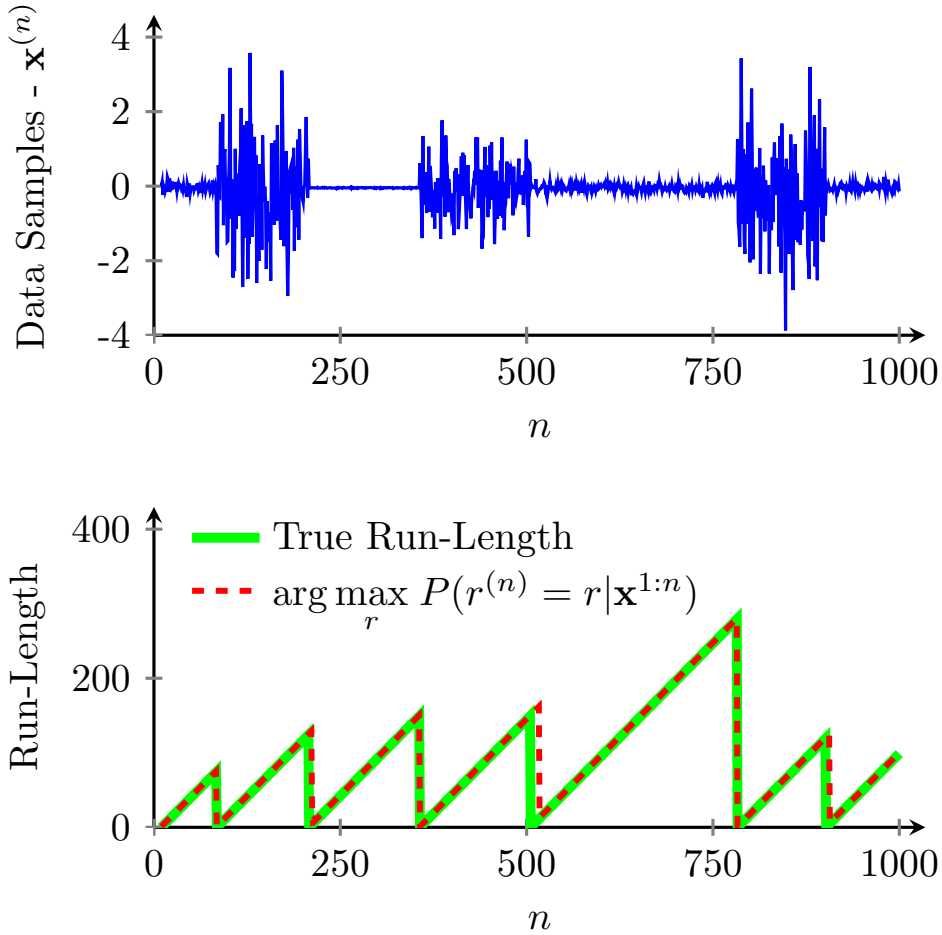
spectral decomposition

- time-frequency analysis
  - 0.1-4 Hz δ band
  - 4-8 Hz θ band
  - 8-14 α band
  - 14-30 β band
  - > 30 γ band



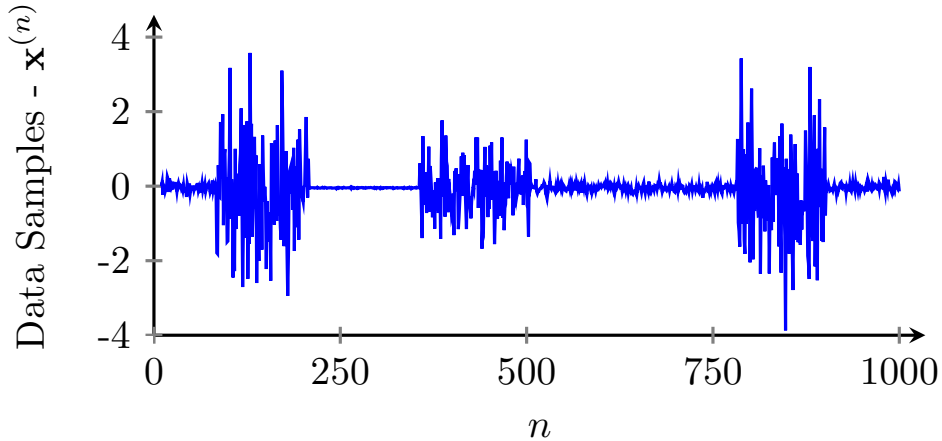
temporal segmentation

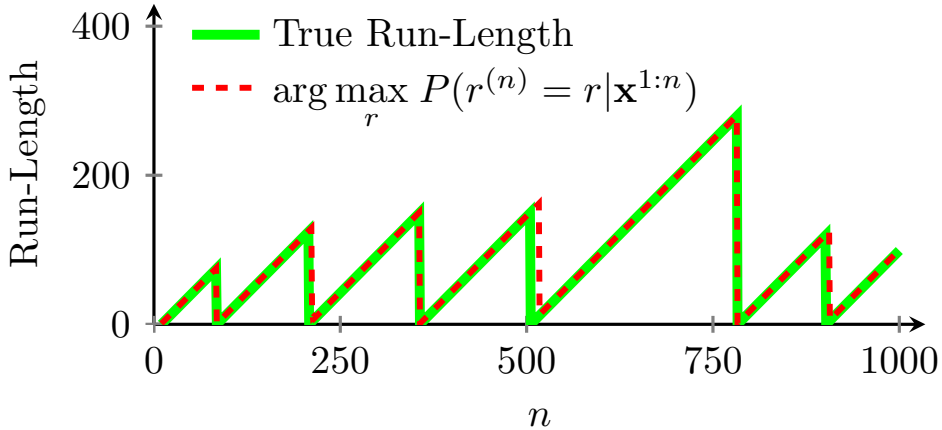
- Bayesian change detection
  - run length



temporal segmentation

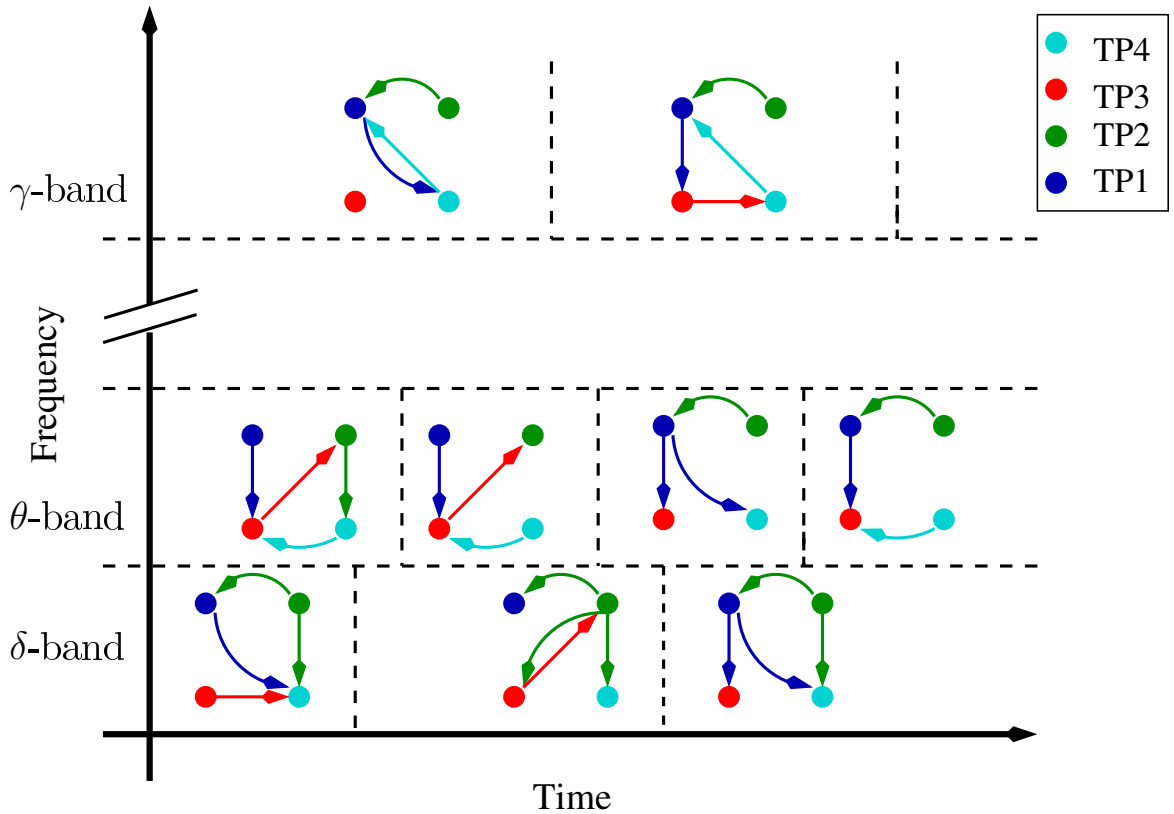
- Bayesian change detection
  - run length
- seizure markers
  - inter-ictal spikes
  - high frequency oscillations





spatial connectivity

- graphical model
  - connectivity
  - causality



Granger causality

- one time series forecasting another
    - economics
    - transportation
    - …

Granger causality

- one time series forecasting another
  - economics
  - transportation
  - …
    - Norbert Wiener (1956)
    - Clive Granger (1969)
    - Hans Marko (1973)
    - James Massey (1990)

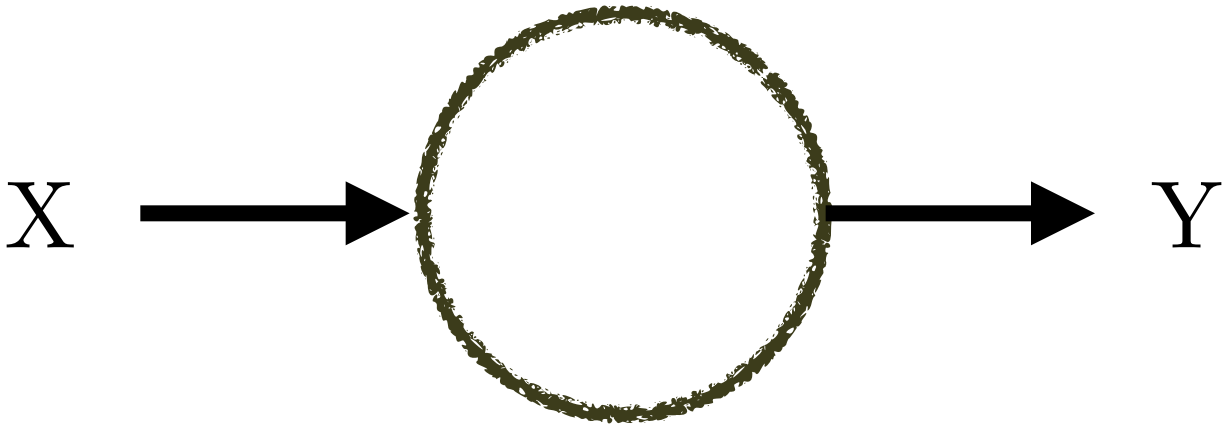
a little background

a little background

- mutual information

$$I(X;Y) = \int f_{XY} \log \frac{f_{XY}}{f_X f_Y}$$

- average information about **X** provided by **Y**



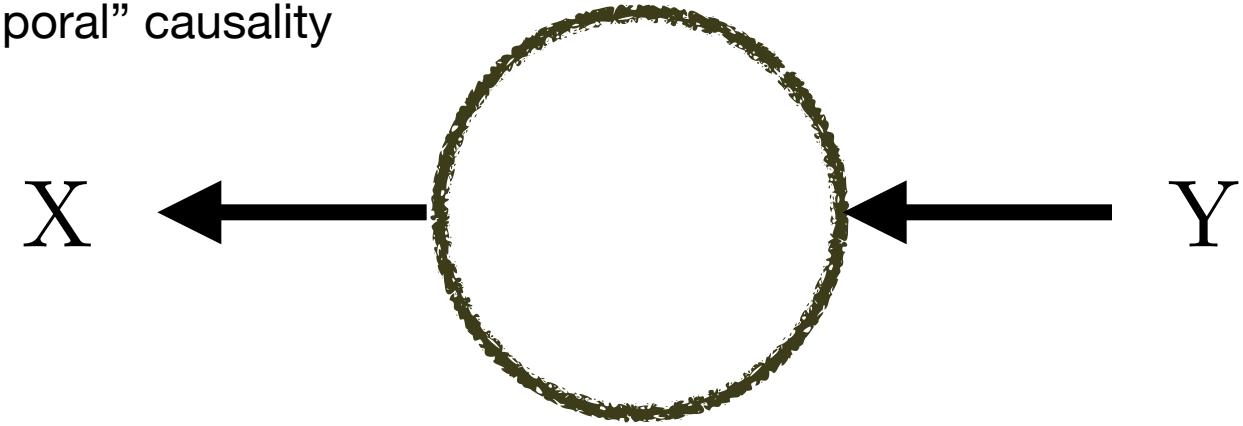
a little background

- mutual information

$$I(X;Y) = \int f_{XY} \log \frac{f_{XY}}{f_X f_Y}$$

- not directional

- no “temporal” causality



a little background

- directed information and causality

$$I(X_1^N \rightarrow Y_1^N) = \sum_{n=1}^{N} I(X_1^n; Y_n | Y_1^{n-1})$$

- directional

$$X_1^N \equiv (X_1, X_2, \ldots, X_N) \longrightarrow Y_1^N \equiv (Y_1, Y_2, \ldots, Y_N)$$

a little background

- mutual information of time series

$$I(X_1^N; Y_1^N) = \sum_{n=1}^{N} I(X_1^N; Y_n | Y_1^{n-1})$$

- causality?

$$X_1^N \equiv (X_1, X_2, \ldots, X_N) \longrightarrow Y_1^N \equiv (Y_1, Y_2, \ldots, Y_N)$$

a little background

$$I(X_1^N \rightarrow Y_1^N) = \sum_{n=1}^{N} I(X_1^n; Y_n | Y_1^{n-1})$$

- mutual information of time series

$$I(X_1^N; Y_1^N) = \sum_{n=1}^{N} I(X_1^N, Y_n | Y_1^{n-1})$$

- causality?

$$X_1^N \equiv (X_1, X_2, \ldots, X_N) \longrightarrow Y_1^N \equiv (Y_1, Y_2, \ldots, Y_N)$$

insight

- time series
    - Does knowing time series *X* help with prediction of time series *Y*?

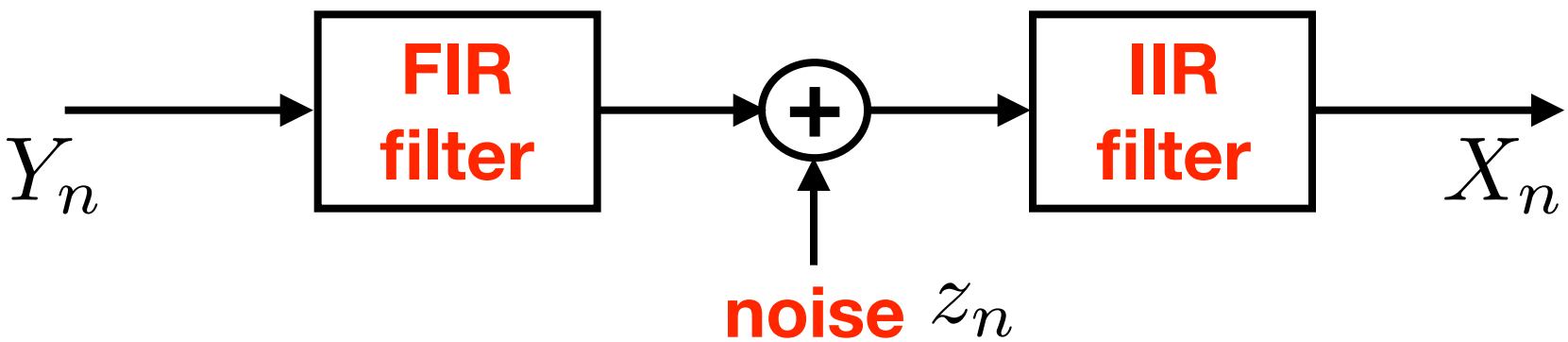
insight

- time series
  - Does knowing time series *X* help with prediction of time series *Y*?
  - Does knowing time series *Y* help with prediction of time series *X*? if directionality is not clear.

insight

- time series (specific underlying assumption!!)
  - causality

$$X_n = \sum_{p=1}^{P} U_p X_{n-p} + \sum_{q=0}^{Q} V_q Y_{n-q} + z_n$$



insight

- time series (specific underlying assumption!!)
  - causality

$$X_n = \sum_{p=1}^{P} U_p X_{n-p} + \sum_{q=0}^{Q} V_q Y_{n-q} + z_n$$

  - what is

$$I(X_1^N \rightarrow Y_1^N) = \sum_{n=1}^{N} I(X_1^n; Y_n | Y_1^{n-1})$$

2 examples

example 1

$$X_n = Y_{n-1} + z_n$$

- with i.i.d.

$$Y_n \sim \text{Gaussian}(0, \sigma_Y^2)$$

$$z_n \sim \text{Gaussian}(0, \sigma_z^2)$$

example 1

independent

$$X_n = Y_{n-1} + z_n$$

- with i.i.d.

$$Y_n \sim \text{Gaussian}(0, \sigma_Y^2)$$

$$z_n \sim \text{Gaussian}(0, \sigma_z^2)$$

$$Y_n \sim \text{Gaussian}(0, \sigma_Y^2)$$
$$z_n \sim \text{Gaussian}(0, \sigma_z^2)$$

example 1

$$X_n = Y_{n-1} + z_n$$

- then

$$I(Y \to X) = \frac{1}{2}\log(1 + \frac{\sigma_Y^2}{\sigma_z^2})$$

$$I(X \to Y) = 0$$

example 2

$$X_n = Y_n + z_n$$

- with i.i.d.

$$Y_n \sim \text{Gaussian}(0, \sigma_Y^2)$$

$$z_n \sim \text{Gaussian}(0, \sigma_z^2)$$

example 2

independent

$$X_n = Y_n + z_n$$

- with i.i.d.

$$Y_n \sim \text{Gaussian}(0, \sigma_Y^2)$$

$$z_n \sim \text{Gaussian}(0, \sigma_z^2)$$

$$Y_n \sim \text{Gaussian}(0, \sigma_Y^2)$$
$$z_n \sim \text{Gaussian}(0, \sigma_z^2)$$

example 2

$$X_n = Y_n + z_n$$

- then

$$I(Y \to X) = I(X \to Y) = I(X; Y) = \frac{1}{2}\log(1 + \frac{\sigma_Y^2}{\sigma_z^2})$$

insight

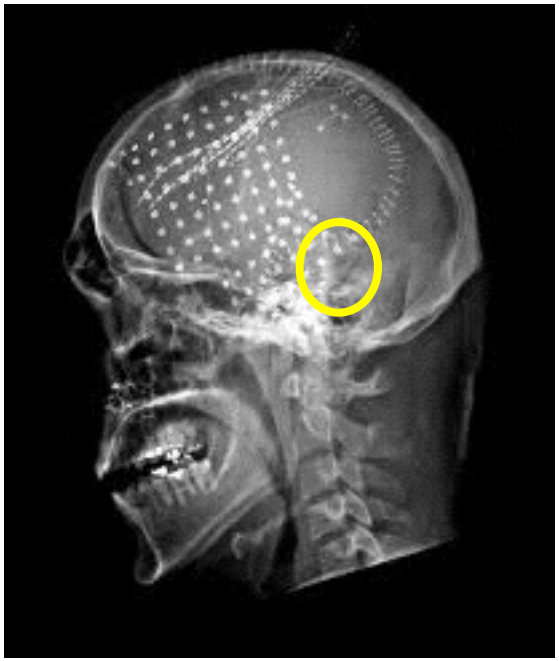
- time series
  - Gaussian
  - moving average autoregressive
  - Granger causality = directed information

$$X_n = \sum_{p=1}^{P} U_p X_{n-p} + \sum_{q=0}^{Q} V_q Y_{n-q} + z_n$$

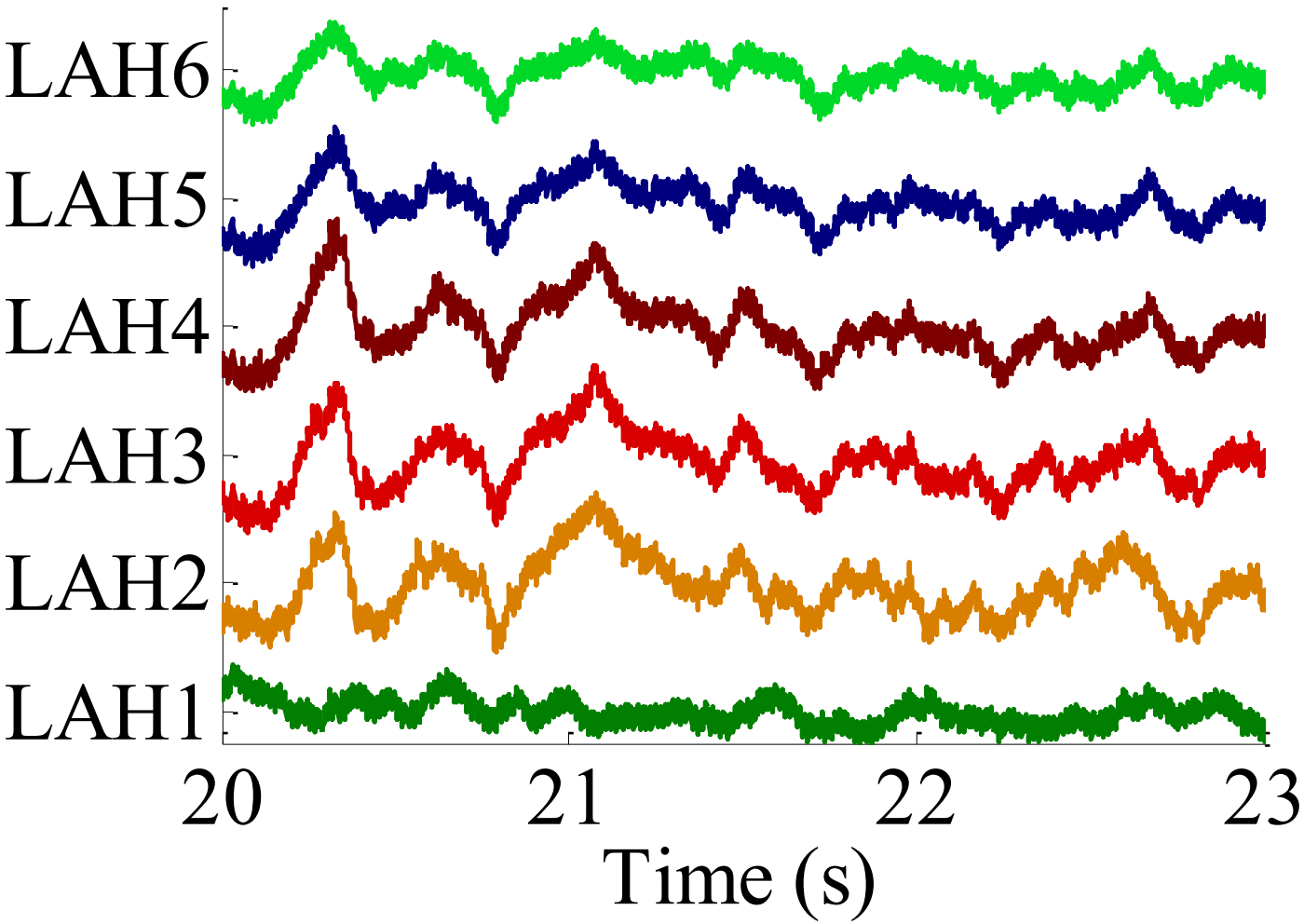
$$I(X_1^N \rightarrow Y_1^N) = \sum_{n=1}^{N} I(X_1^n; Y_n | Y_1^{n-1})$$

back to real data!

- subdural recording from epileptic patients
  - left hippocampus region
  - 151 channels
  - sampling rate 1khz
  - focus
    - 6 channels
    - 100 seconds

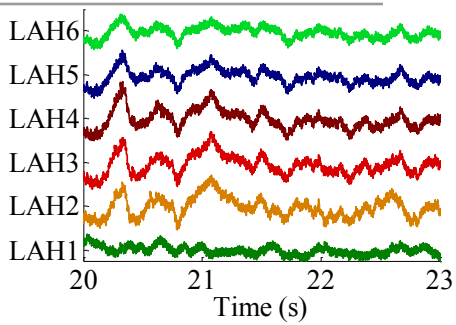


real data



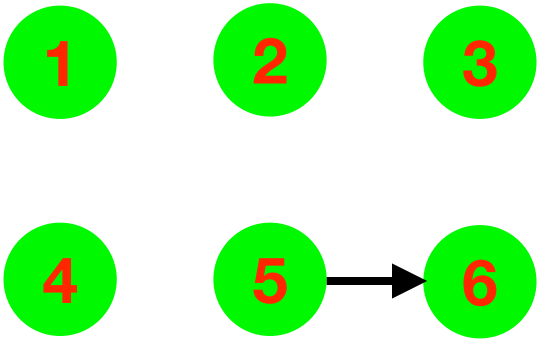
real data

- Gaussian?
- linear moving average autoregressive model?



real data

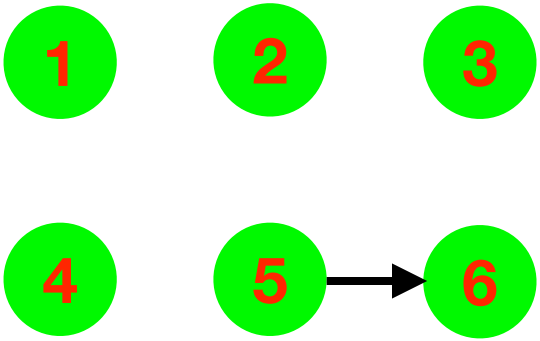
- model order in the range $P, Q \in [75, 125]$
- electrodes labeled LAH1-LAH6



$$X_n^{(6)} = \sum_{p=1}^{P} U_p X_{n-p}^{(6)} + \sum_{q=0}^{Q} V_q X_{n-q}^{(5)} + z_n$$

real data

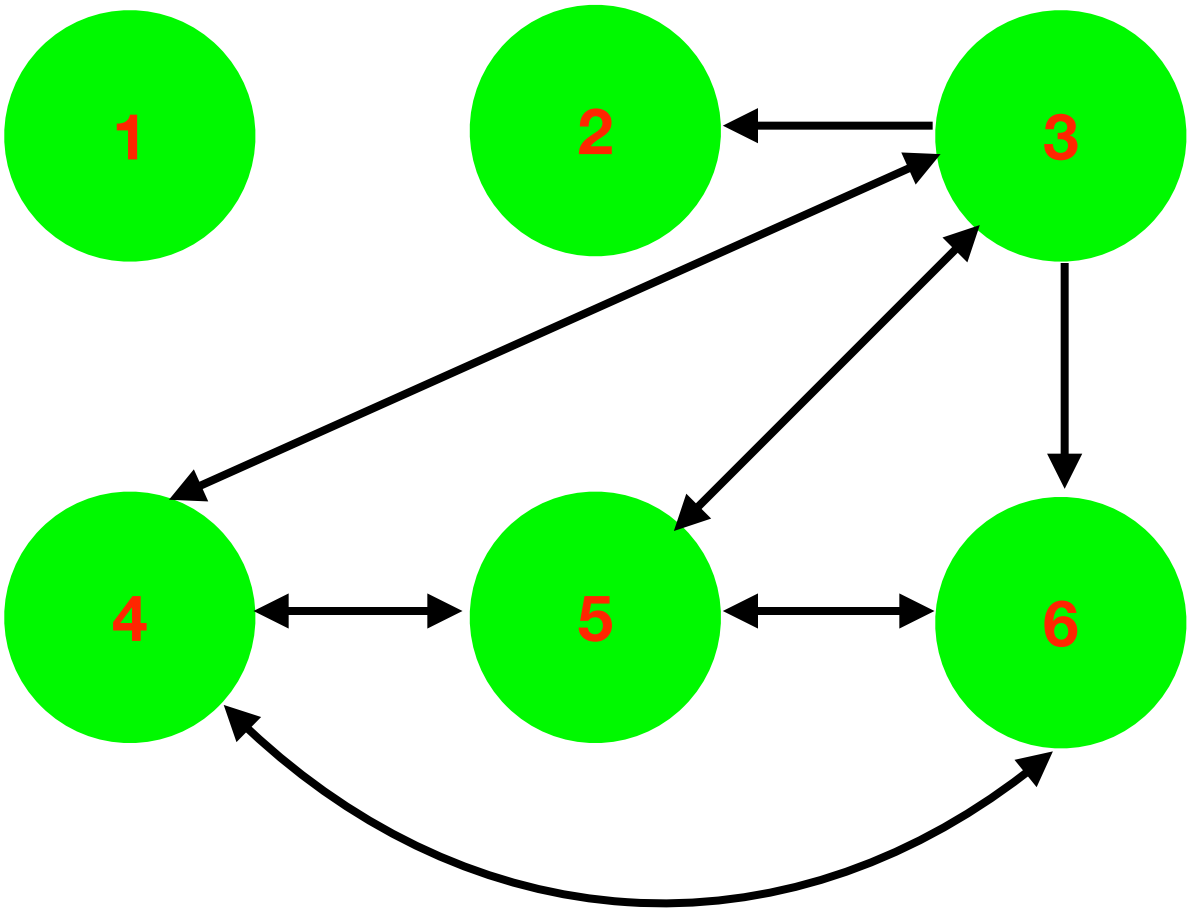
- directed information



$$\{I(X^{(i)} \to X^{(j)})\}_{6\times 6} = \begin{pmatrix} - & 0.11 & 0.05 & 0.05 & 0.06 & 0.08 \\ 0.08 & - & 0.07 & 0.09 & 0.09 & 0.10 \\ 0.07 & 0.31 & - & 0.86 & 0.48 & 0.32 \\ 0.05 & 0.20 & 0.84 & - & 0.85 & 0.47 \\ 0.05 & 0.16 & 0.43 & 0.82 & - & 0.91 \\ 0.06 & 0.14 & 0.25 & 0.41 & 0.89 & - \end{pmatrix}$$

strong connections

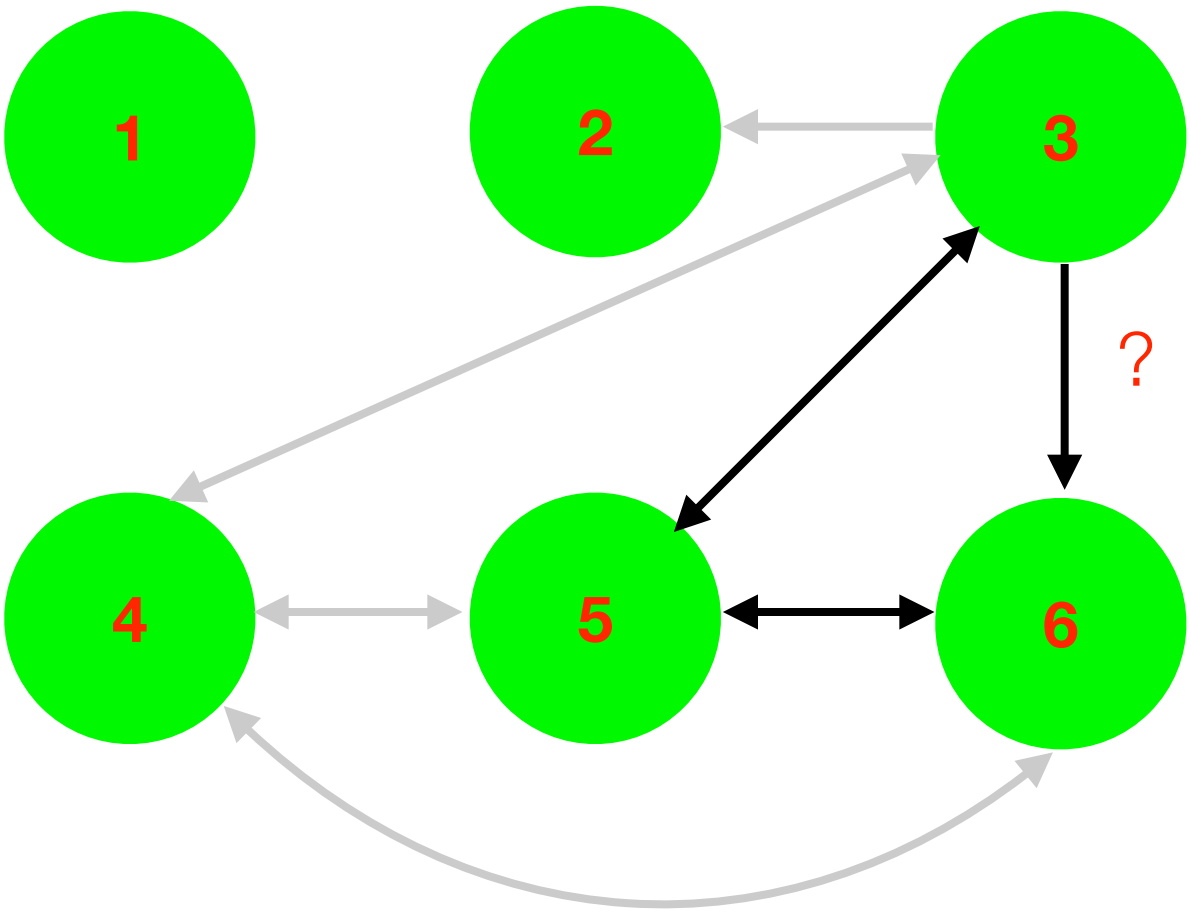
- directed information



strong connections

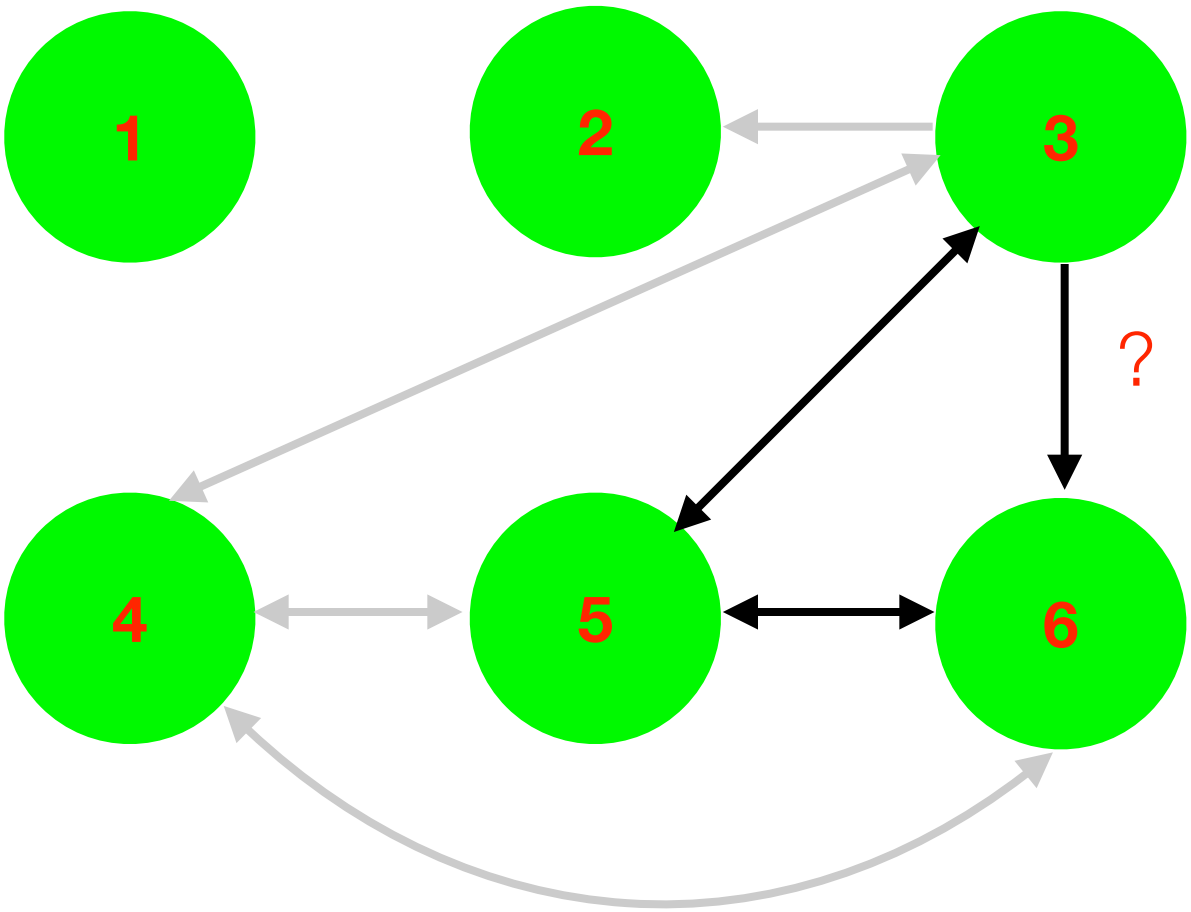
- directed information?

$$I(X^{(3)} \to X^{(6)}) = 0.32$$



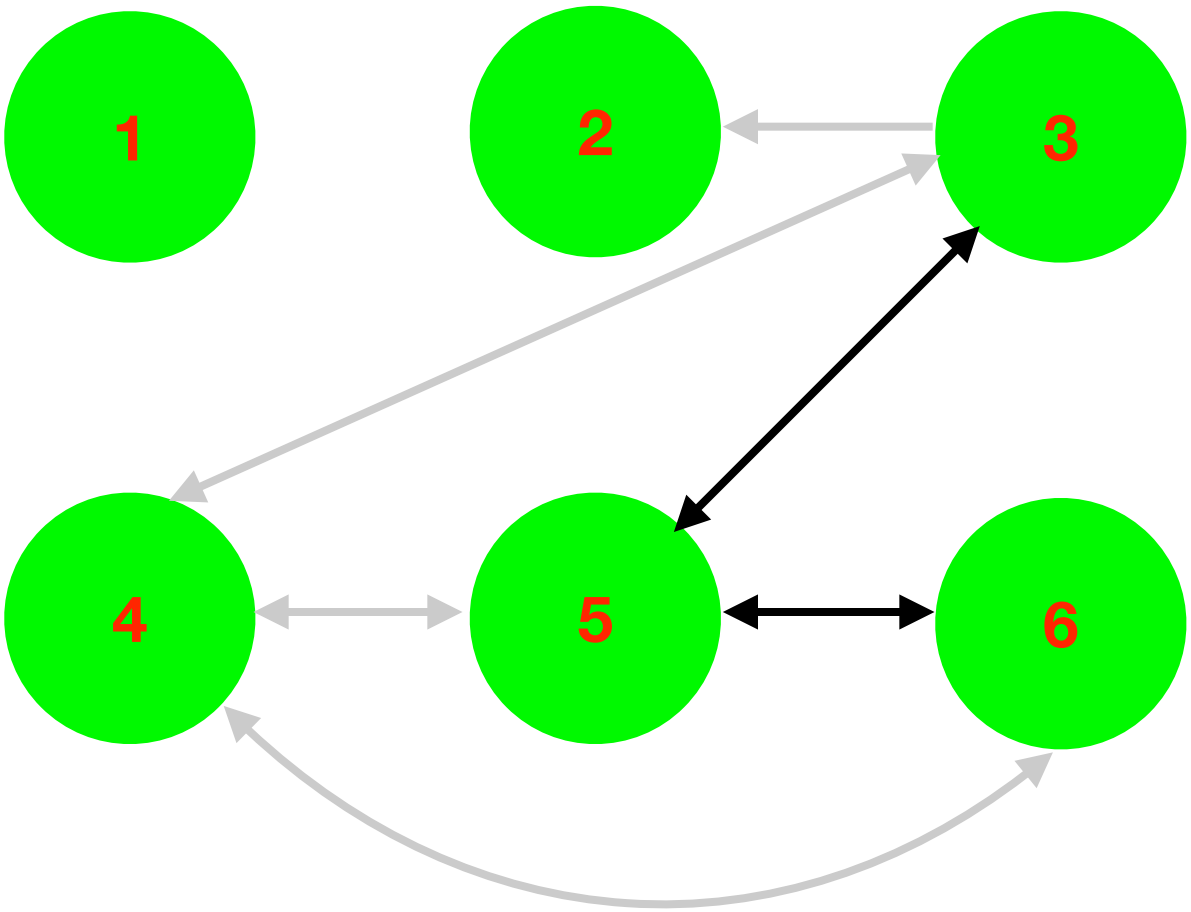
strong connections

- conditional directed information $I(X^{(3)} \to X^{(6)} | X^{(5)}) = 0.0$



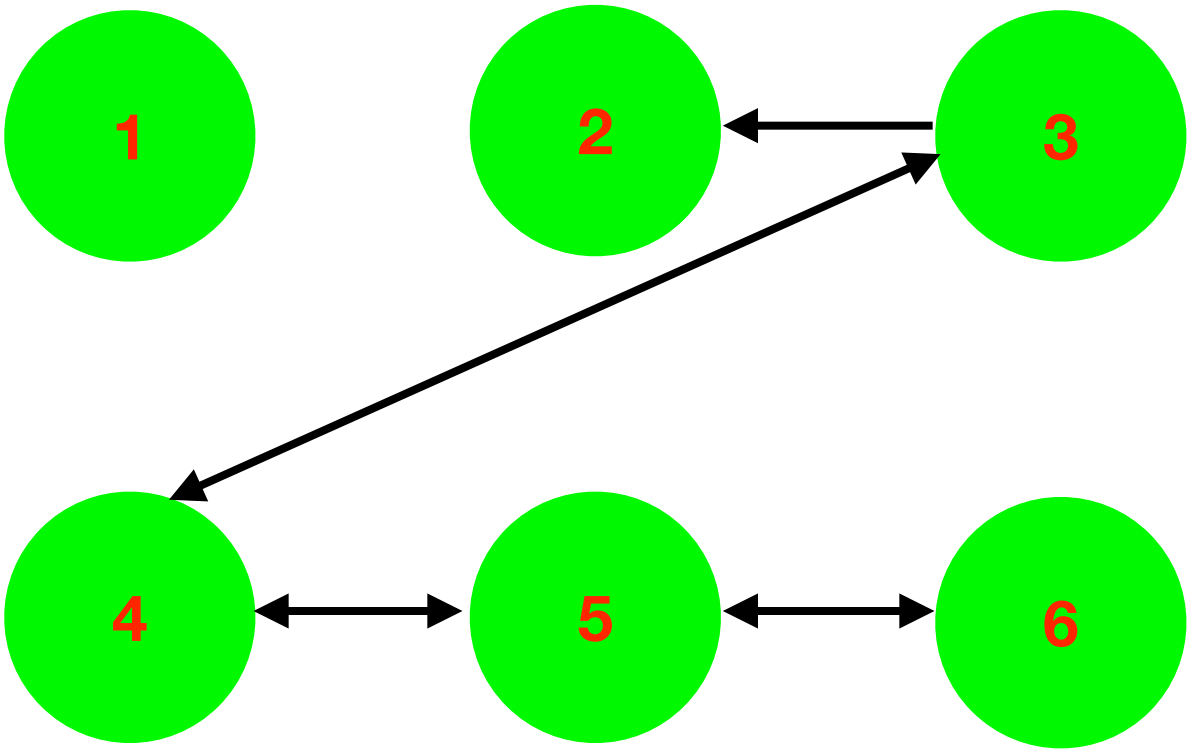
strong connections

- conditional directed information $I(X^{(3)} \to X^{(6)} | X^{(5)}) = 0.0$



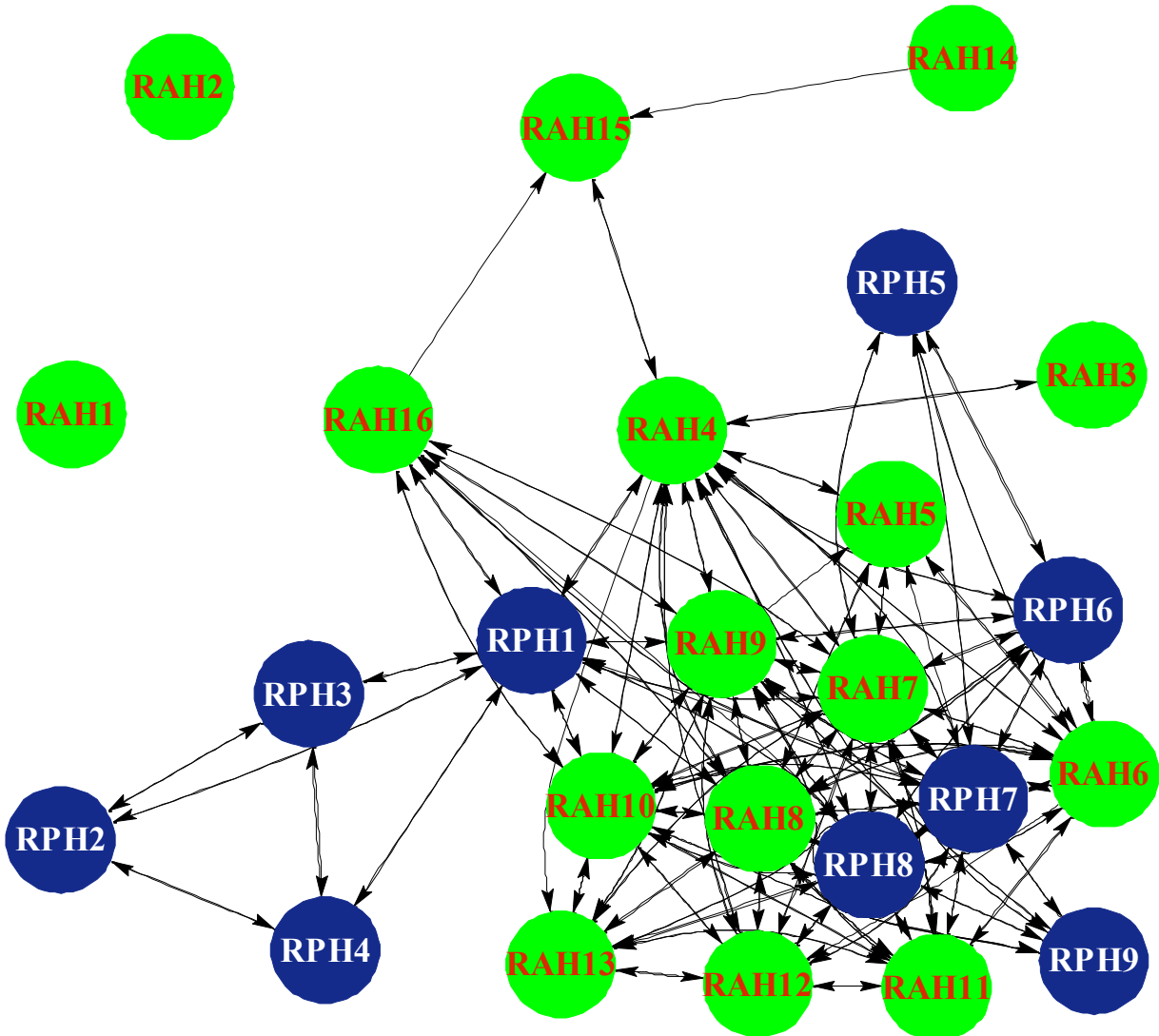
strong connections

- eliminating indirect influence



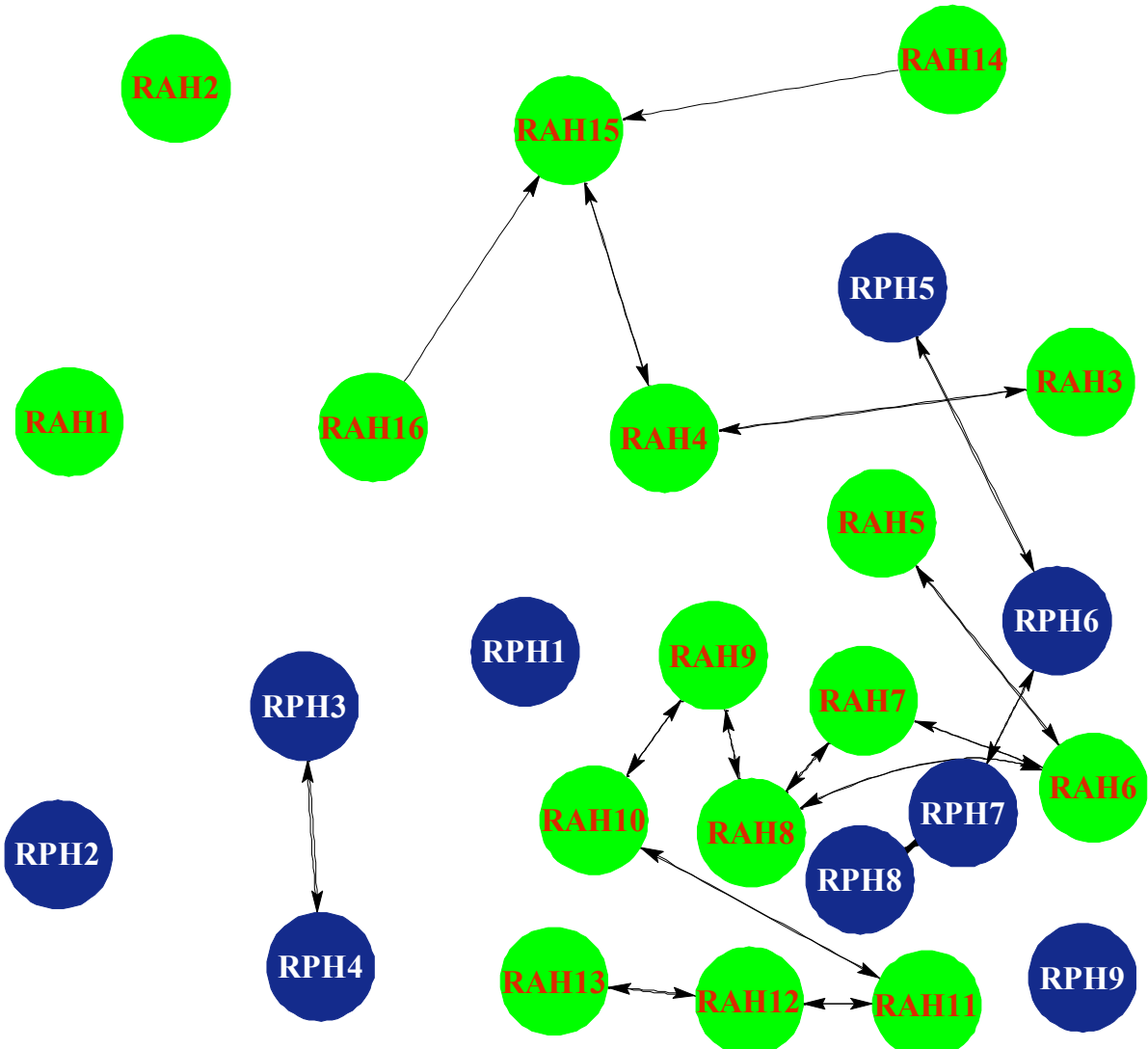
a broader view—all the electrodes

- not sparse



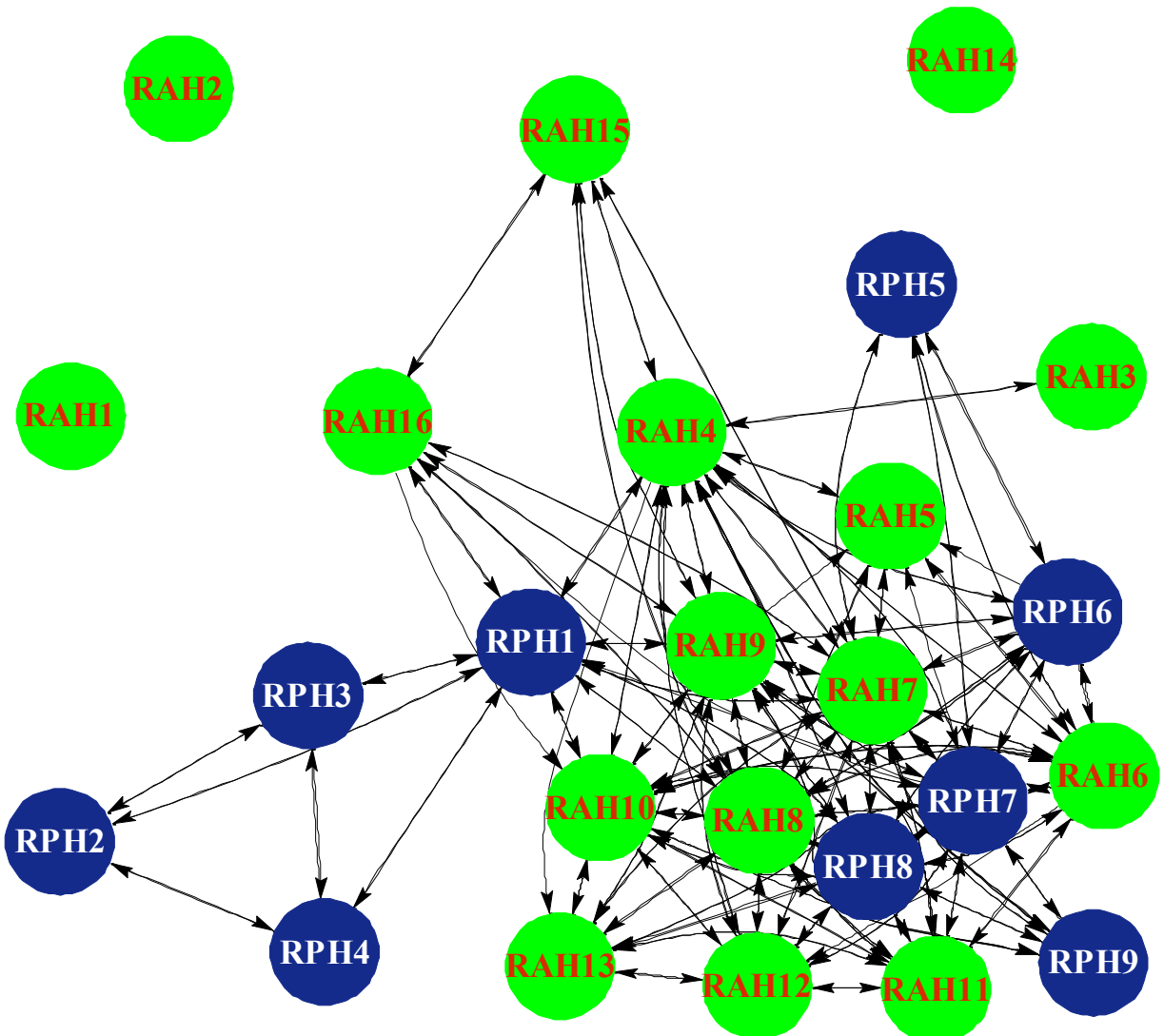
a broader view

- eliminating indirect influences



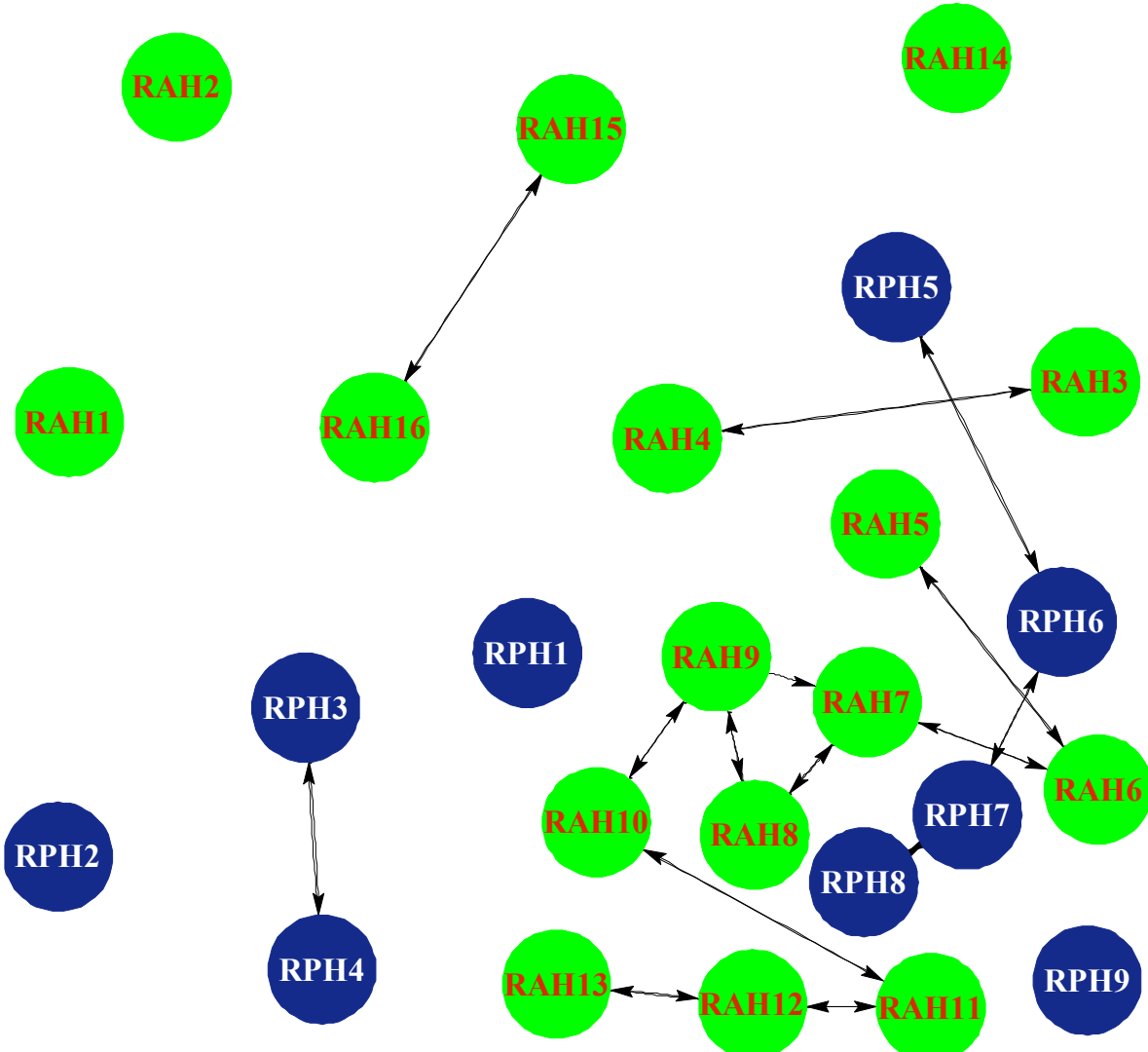
a broader view

- not sparse
- temporal variations



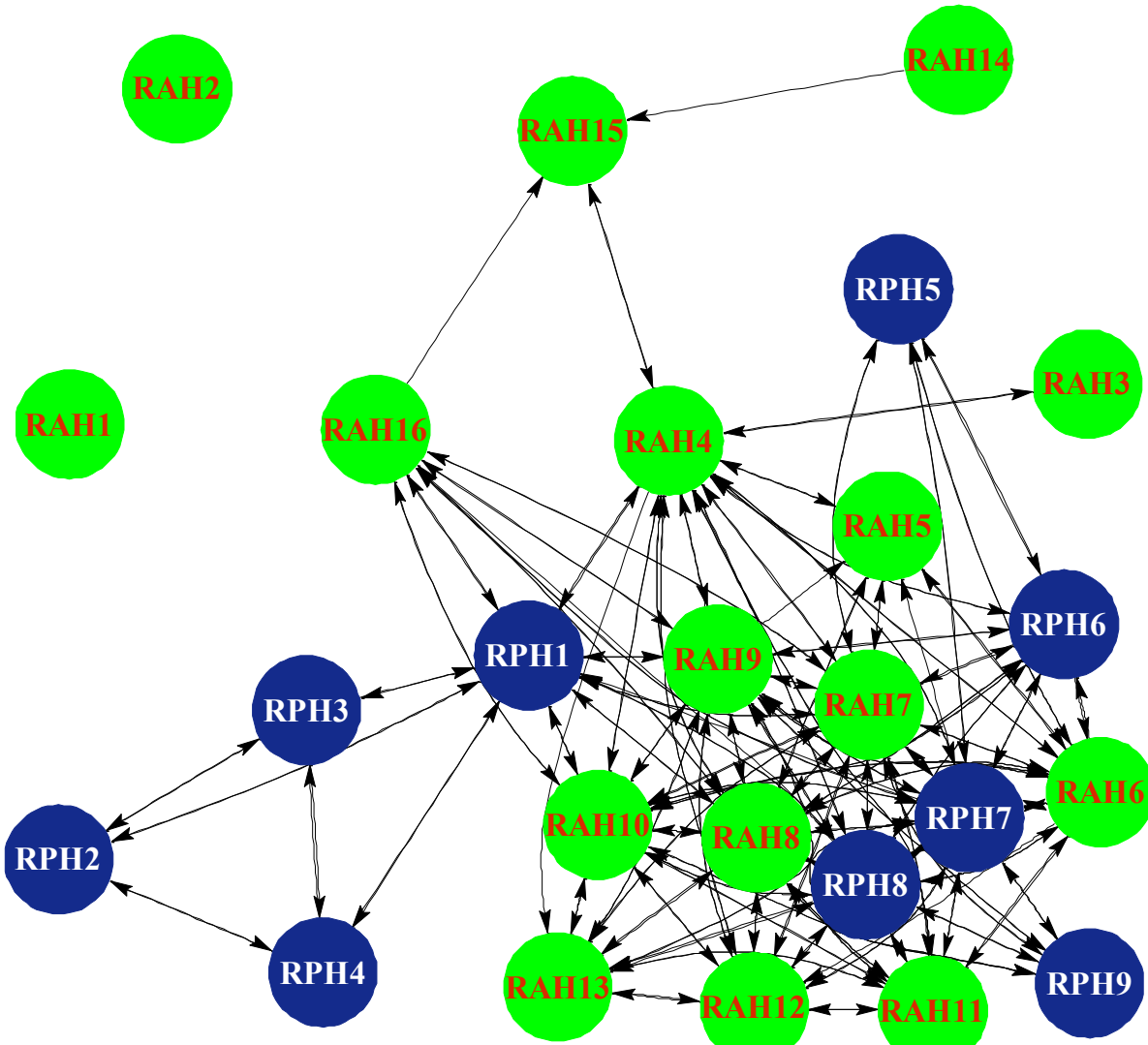
a broader view

- eliminating indirect influences



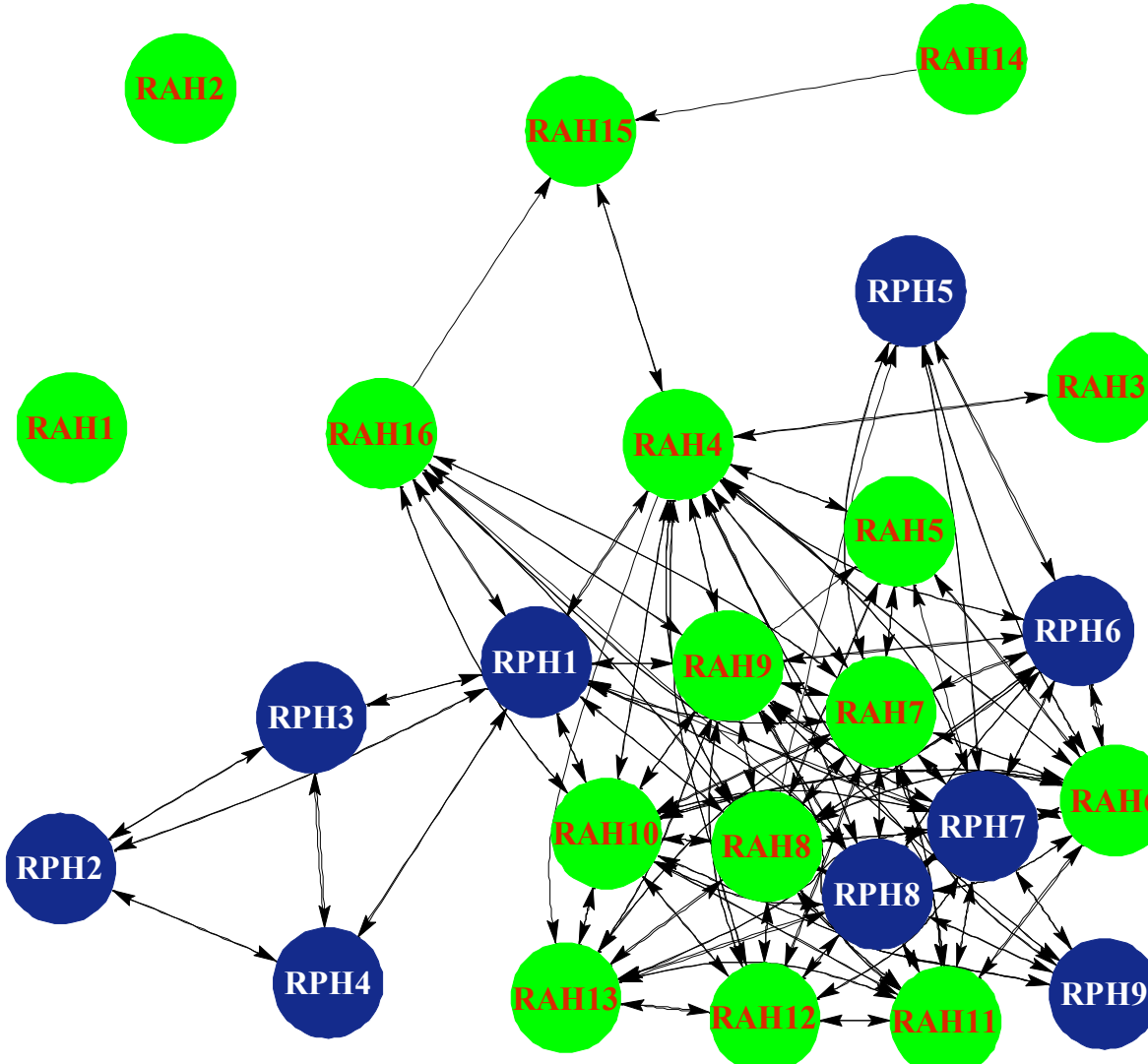
a broader view

- not sparse
- spectral variations?



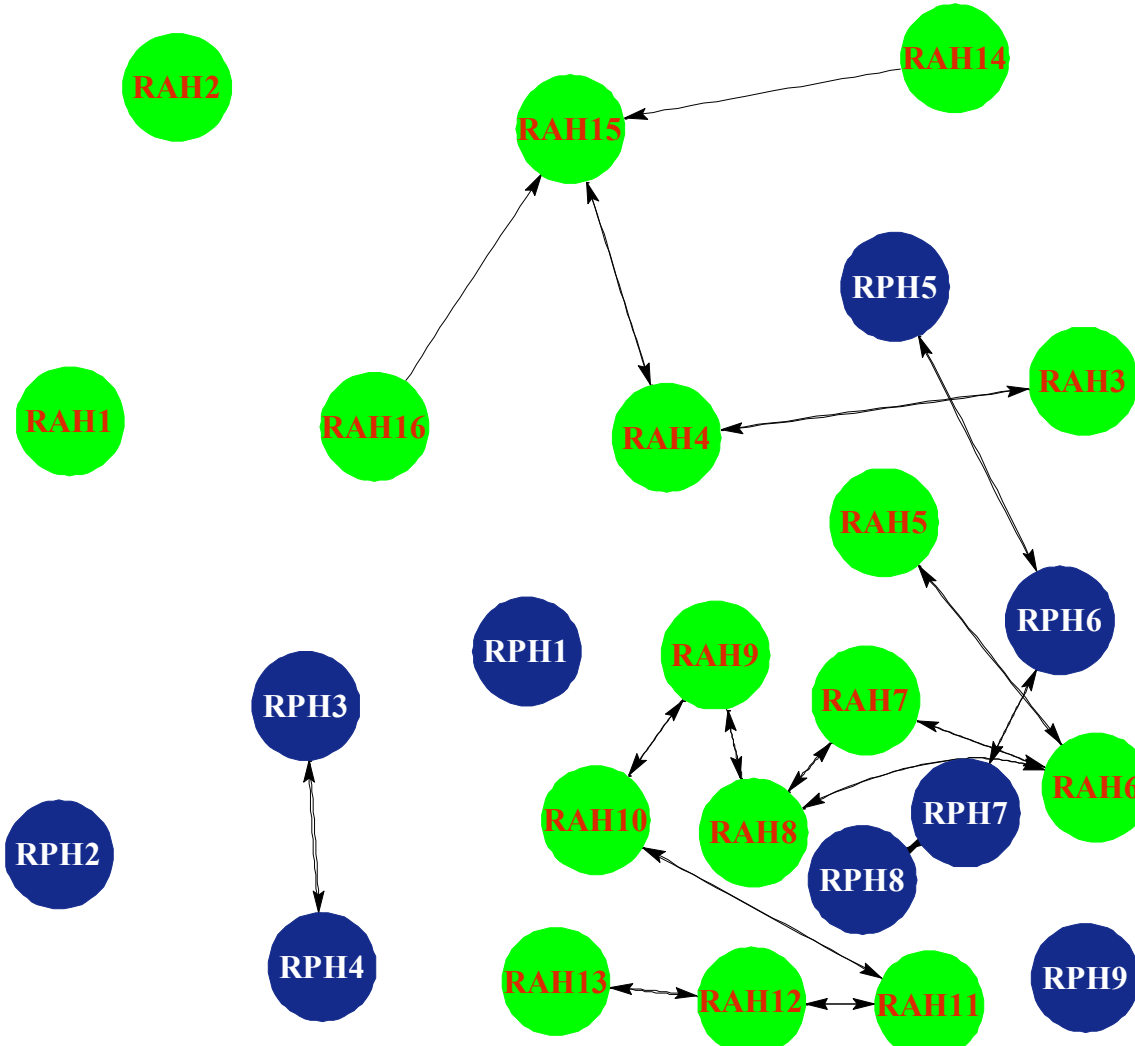
a broader view

- not sparse
- spectral variations
  - 4-8 Hz θ band



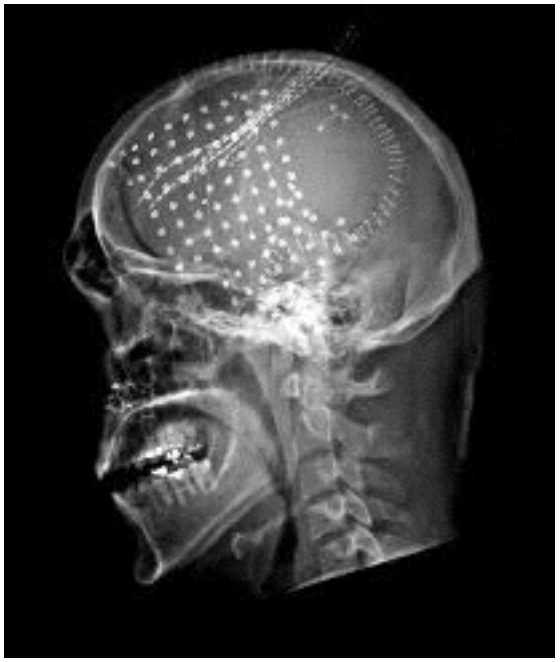
a broader view

- eliminating indirect influences



final thoughts

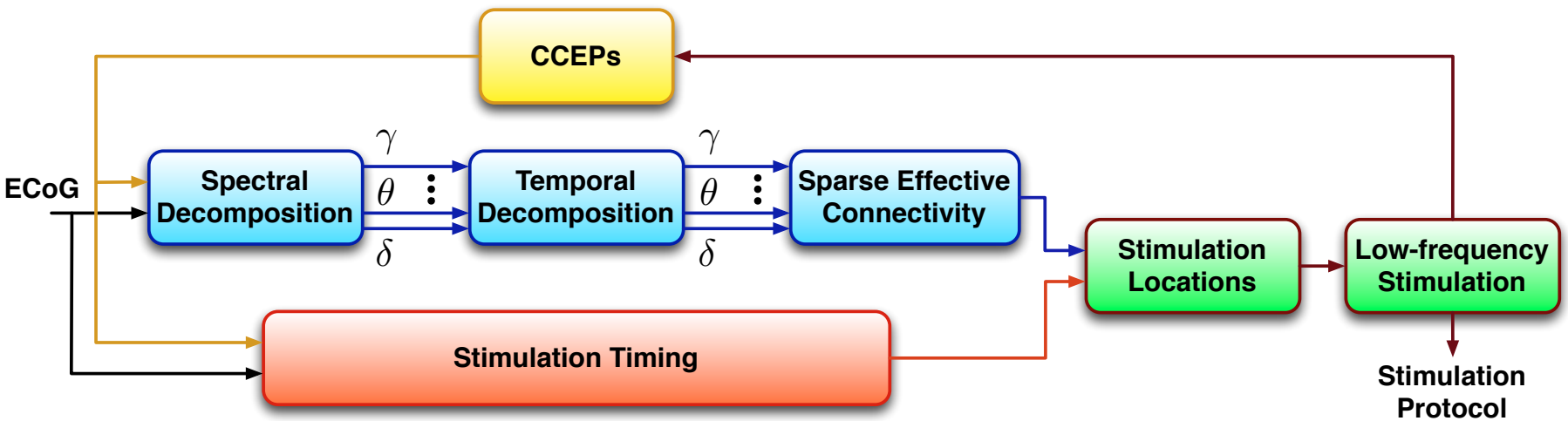
- closed loop stimulation
  - markers
    - spectral
    - temporal
    - spatial



final thoughts

- closed loop stimulation
  - markers
  - real time

low frequency stimulation to depress the excitable state



final thoughts

- develop protocols
    - temporal markers
    - directed connectivity
- build the system
- clinical trial !!!!!