Computational Approaches to Signal Processing for Sleep

An Introduction to Network Analysis & EEG Interpretation

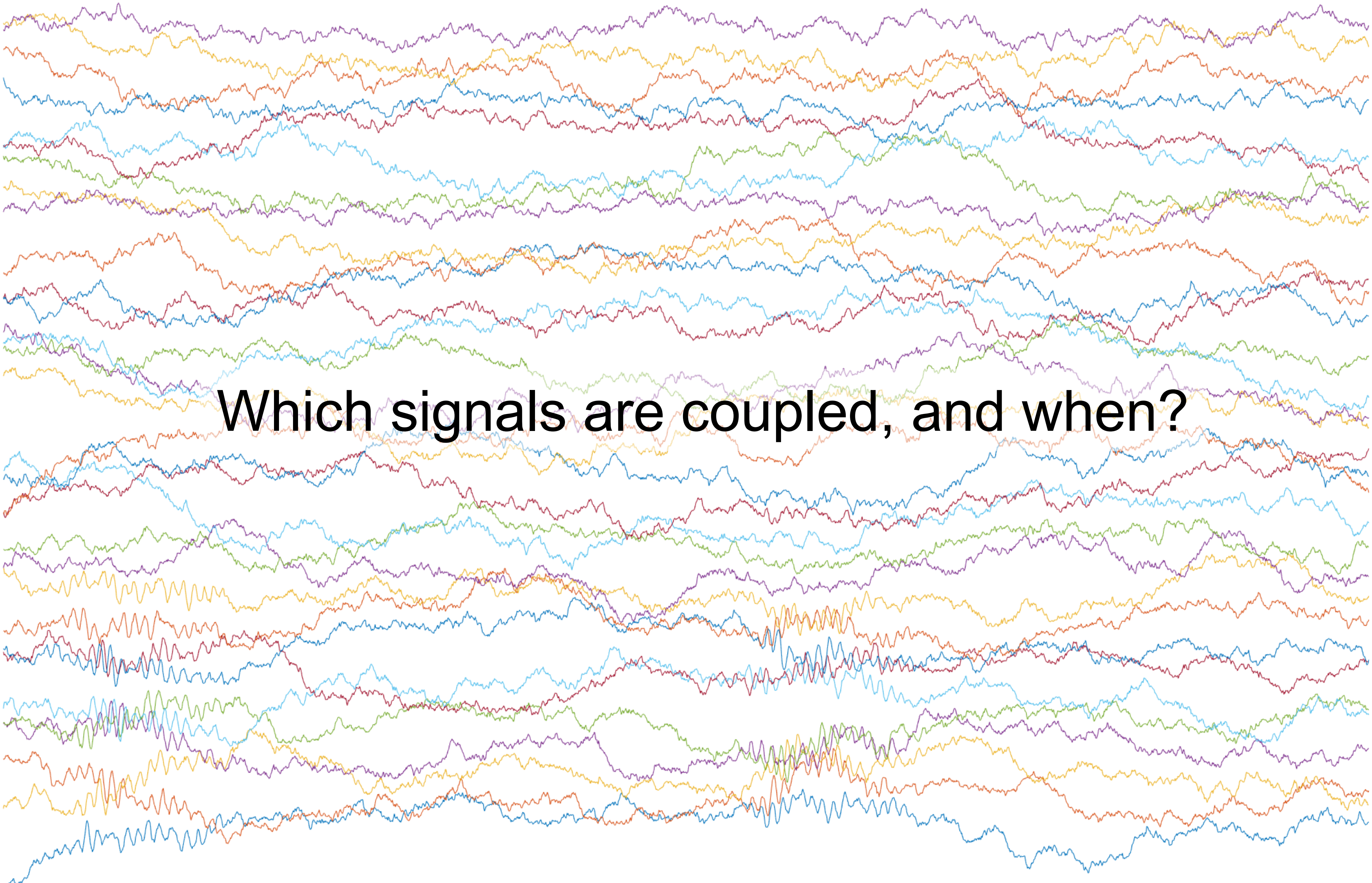
June 2021

Mark Kramer, Mathematics & Statistics, Boston University

Outline

- Functional connectivity (epilepsy)
- Data analysis pipeline: data → network
- Example application: sleep spindles

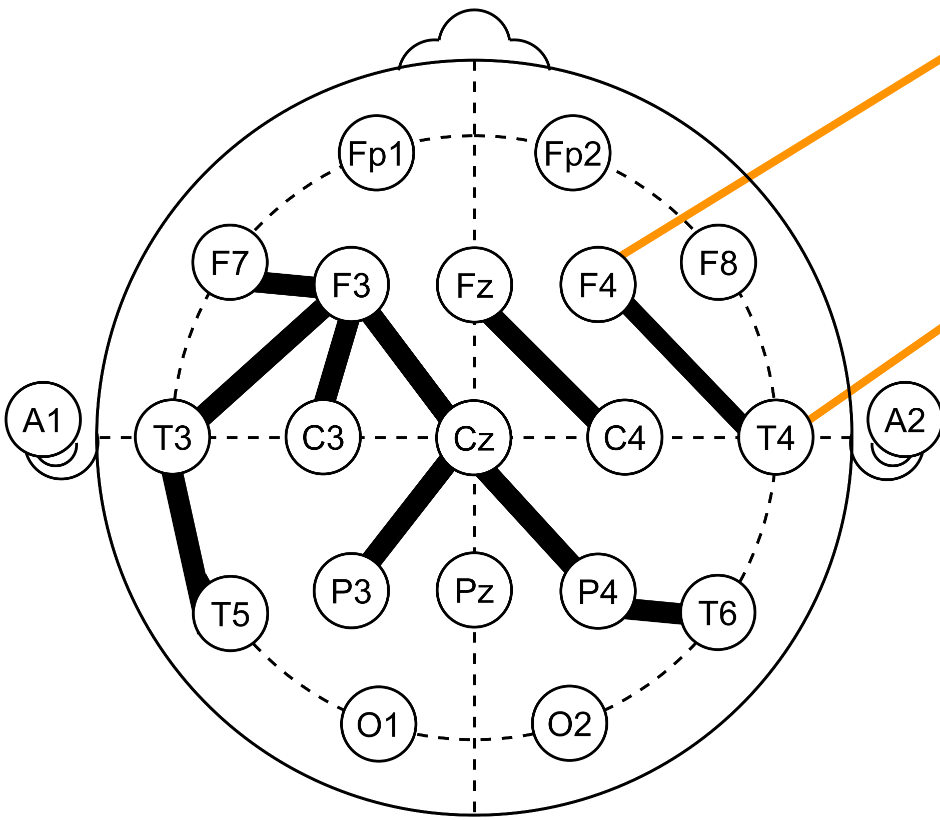
Motivating question

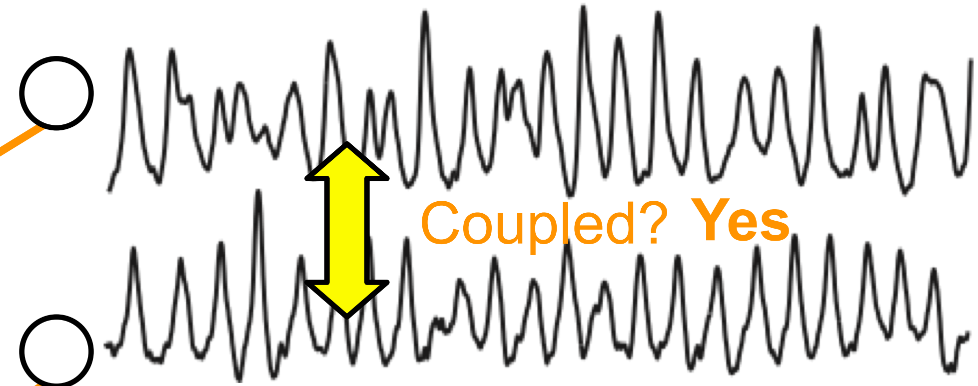


Which signals are coupled, and when?

Functional Connectivity

Multiple electrodes





Long history

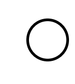
[Brazier, 1972 & 1973; Gotman, 1981 & 1983; ...]

Many coupling measures

[Pereda et al, 2005; Greenblatt et al, 2012]

Repeat for all electrode pairs:

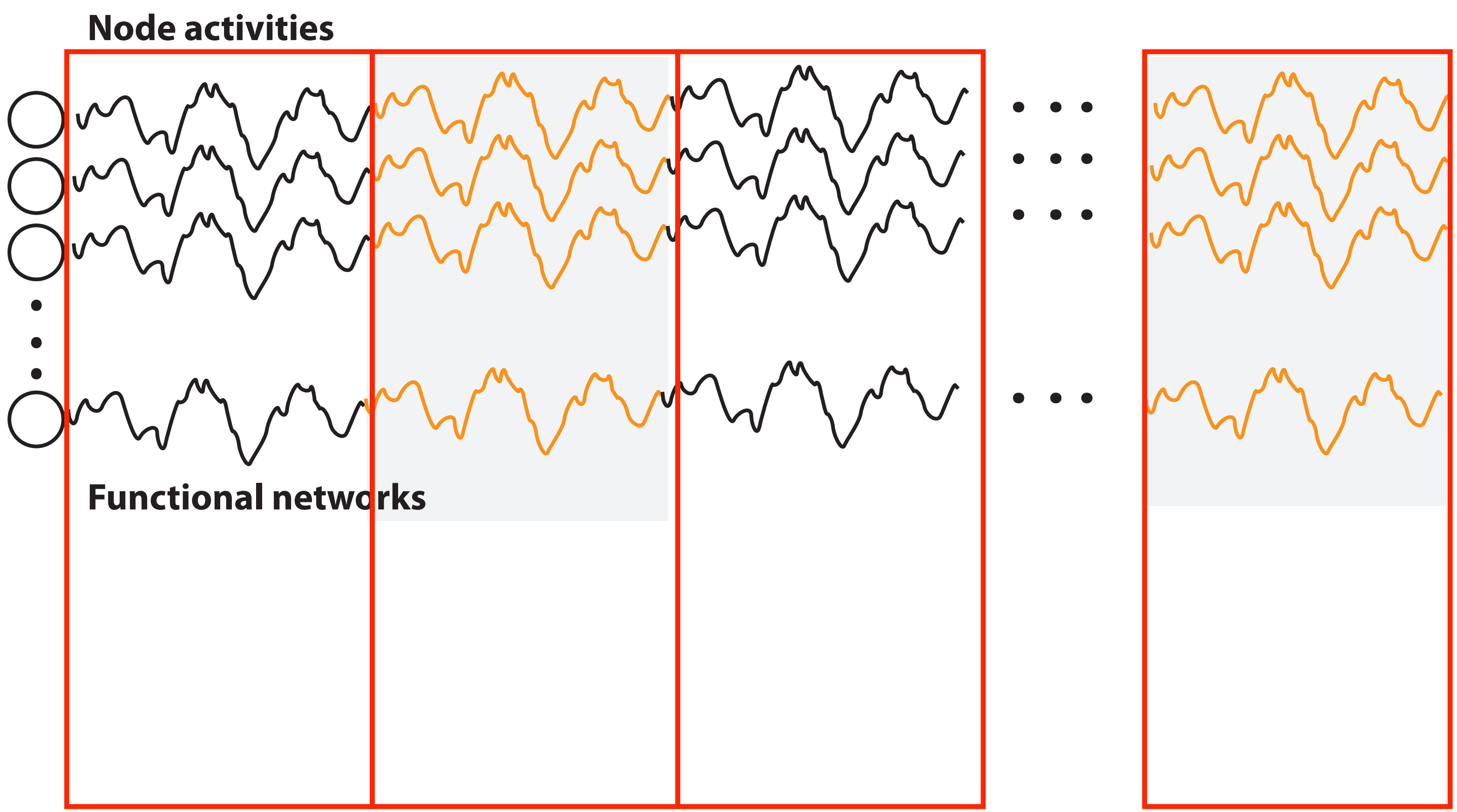
Functional network:



node
edge

Functional Connectivity

Networks evolving in time



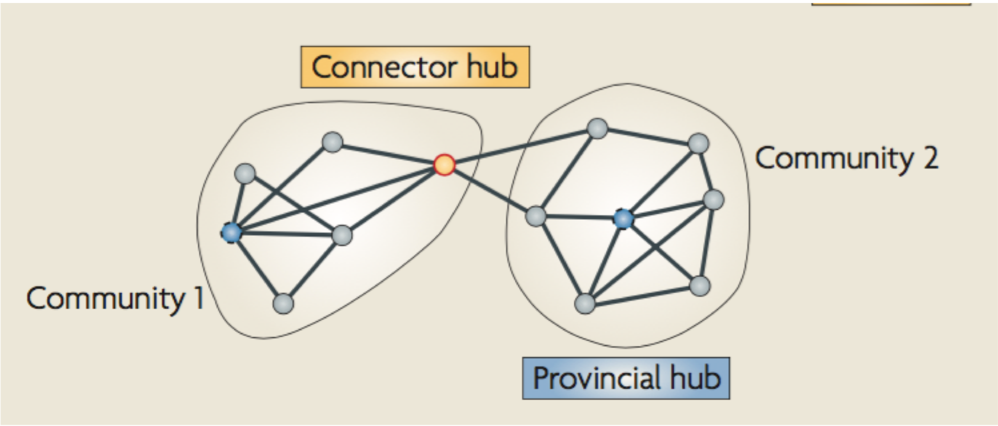
Q: How do functional networks evolve (during seizure)?

[Kramer and Cash, 2012]

One example …

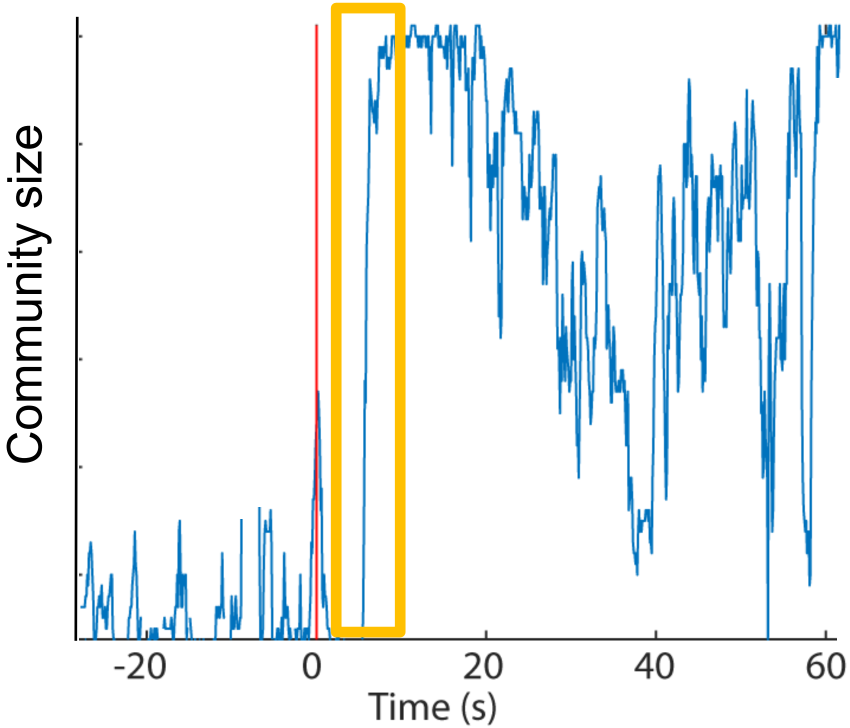
Example

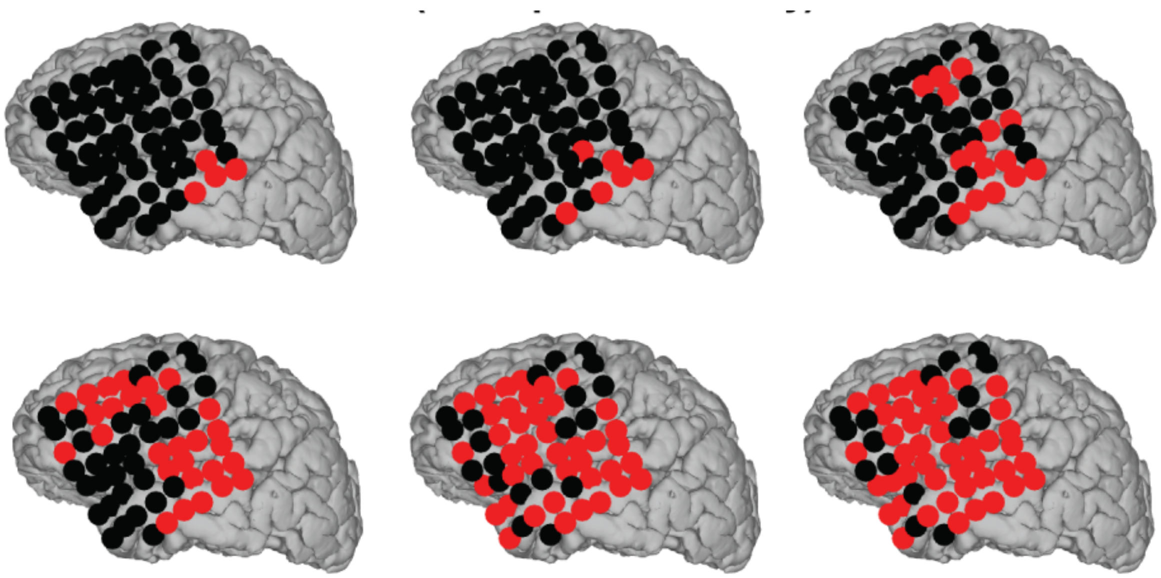
... sudden emergence of a large community at seizure onset.



[Bassett and Sporns 2017]

Large community suddenly forms

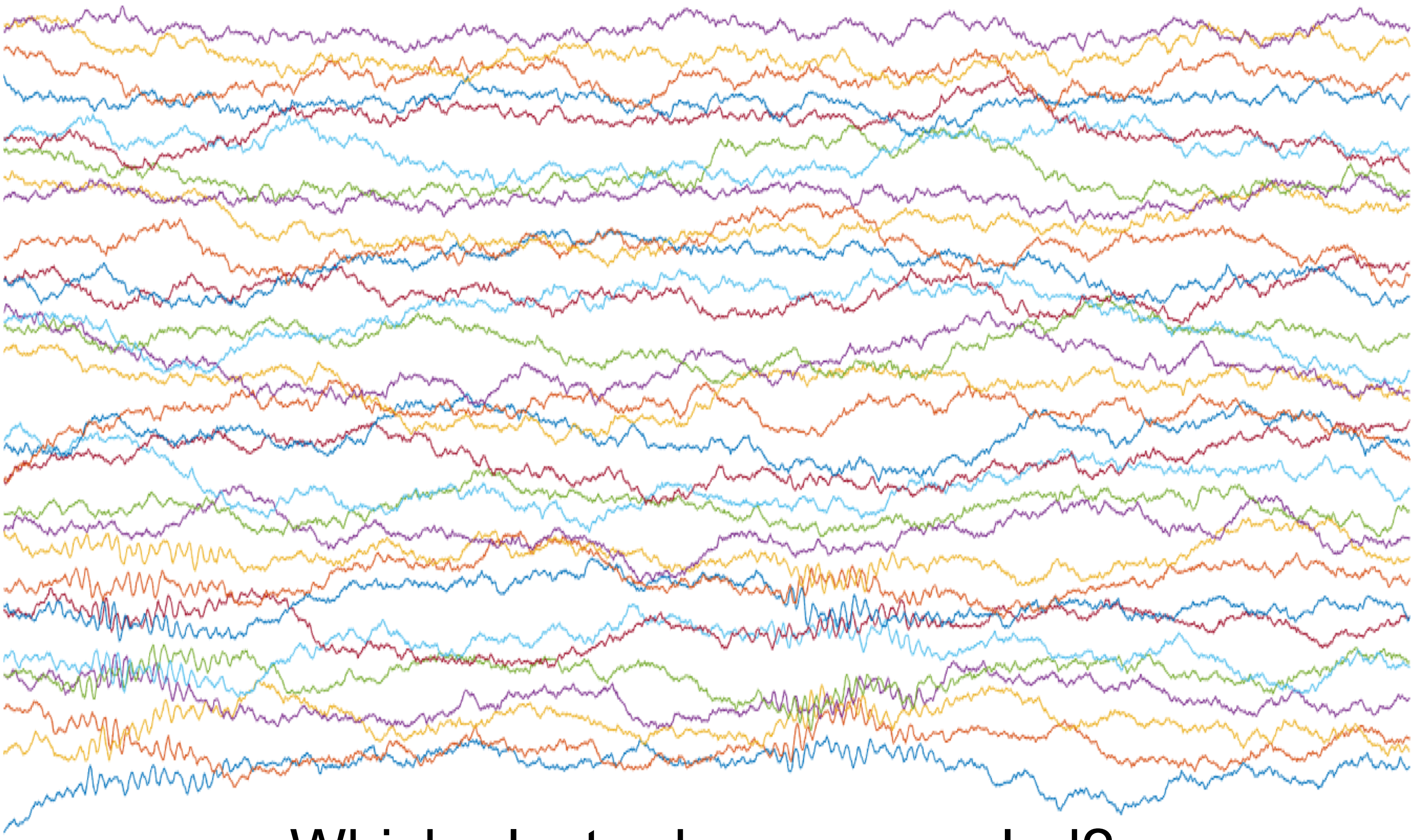




red = member of community

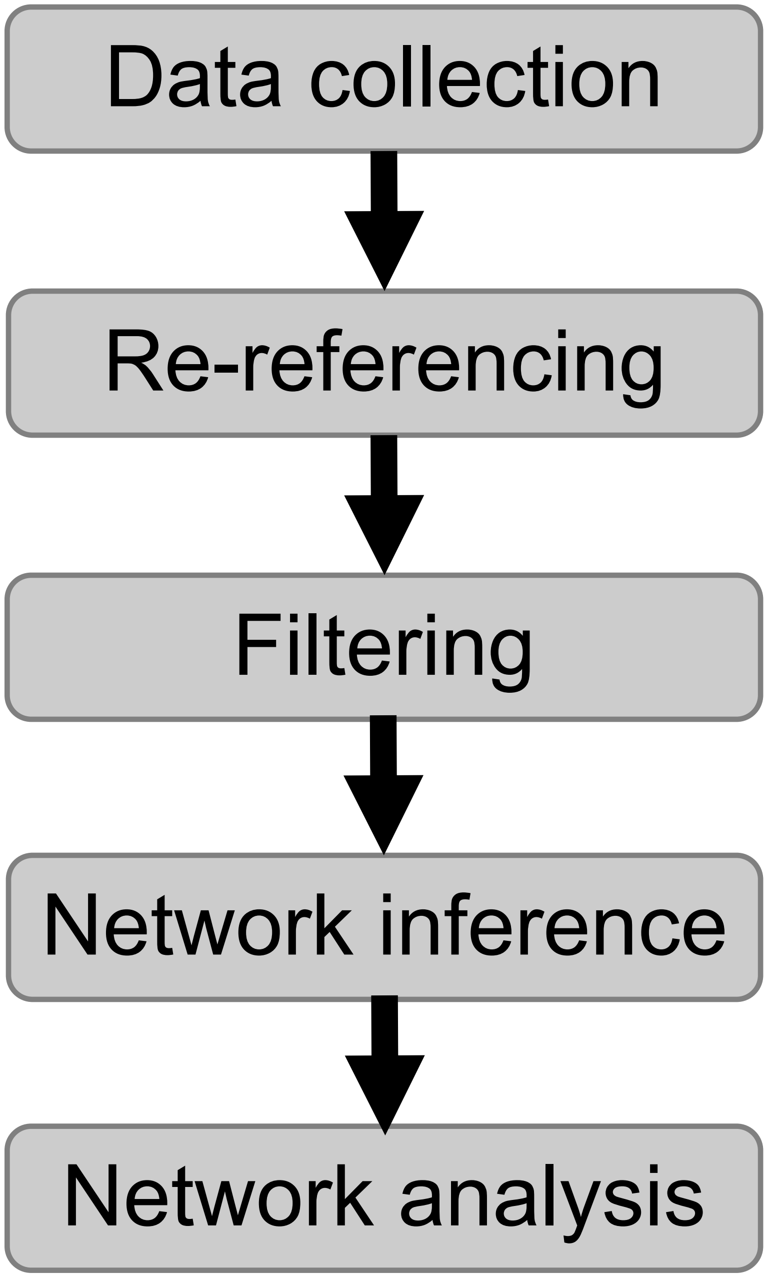
How seizure spreads on cortex? [Martinet, Kramer et al., Nat Comm, 2020]

Challenge



Which electrodes are coupled?

Pipeline

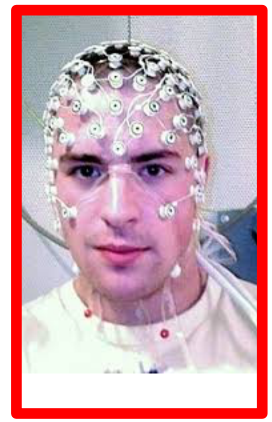


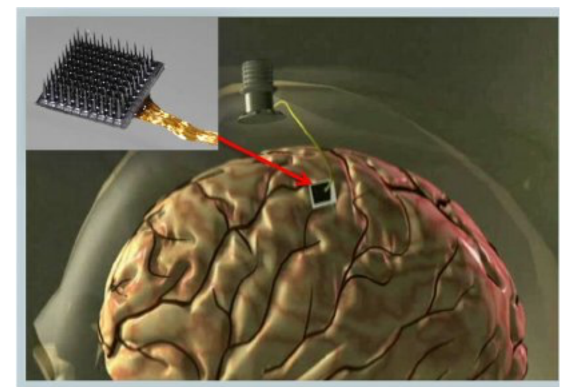
Each step, a new challenge

Pipeline

- **Data collection**
- Re-referencing
- Filtering
- Network inference
- Network analysis

- Brain coverage vs spatial sampling.

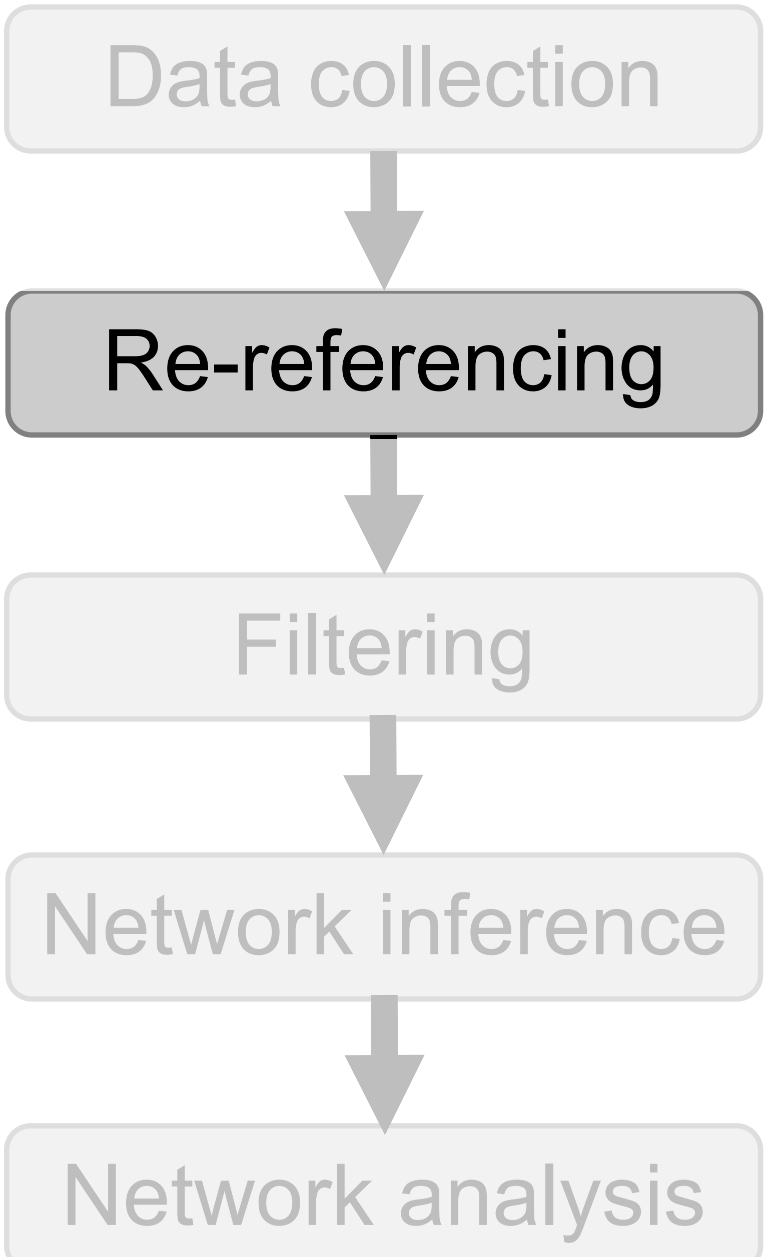




[Nurmikko et al, 2010]

- EEG: high or low density
  … nodes in the network
- Sampling rate
  … rhythms observable

Pipeline

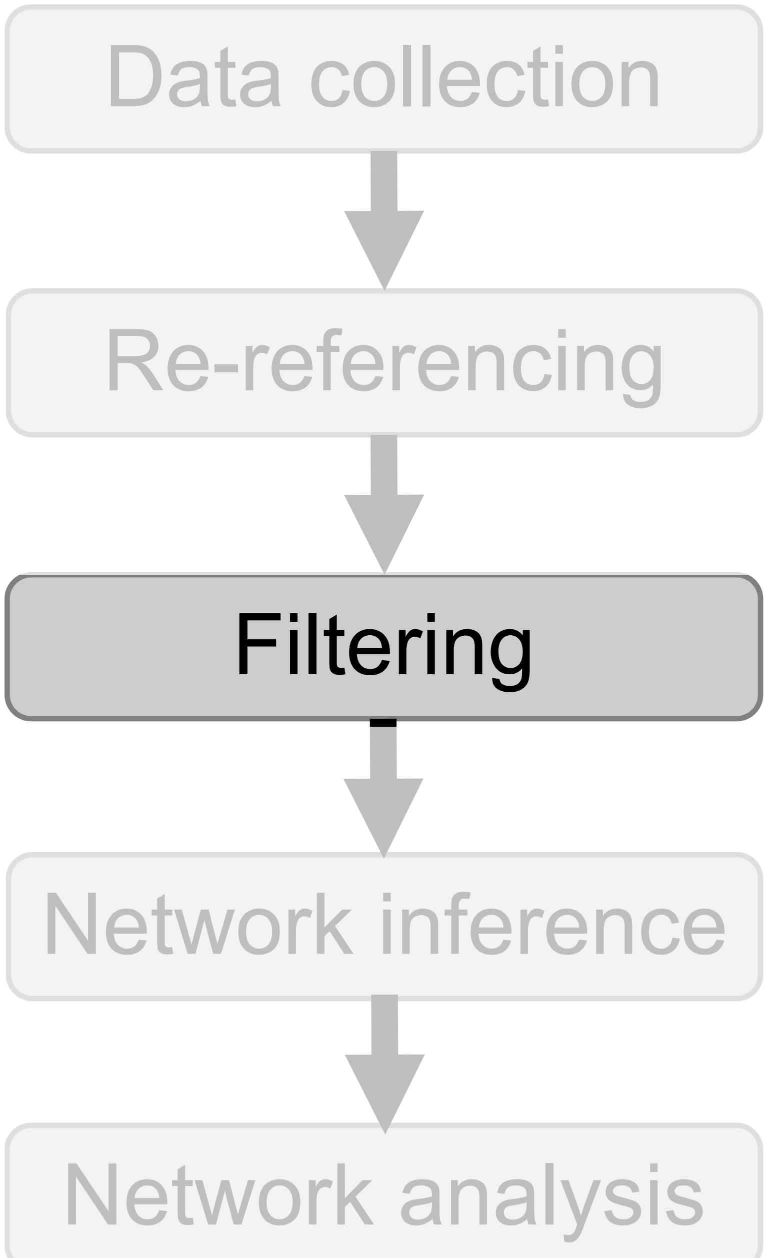


- Physical
- Bipolar
  … reduces number of nodes.
- Common average
  … introduces shared signal?
- Laplacian
- Reference electrode standardization technique (REST)

[Chella et al, J Neural Eng, 2016]

[Nunez & Srinivasan, 2005]

Pipeline



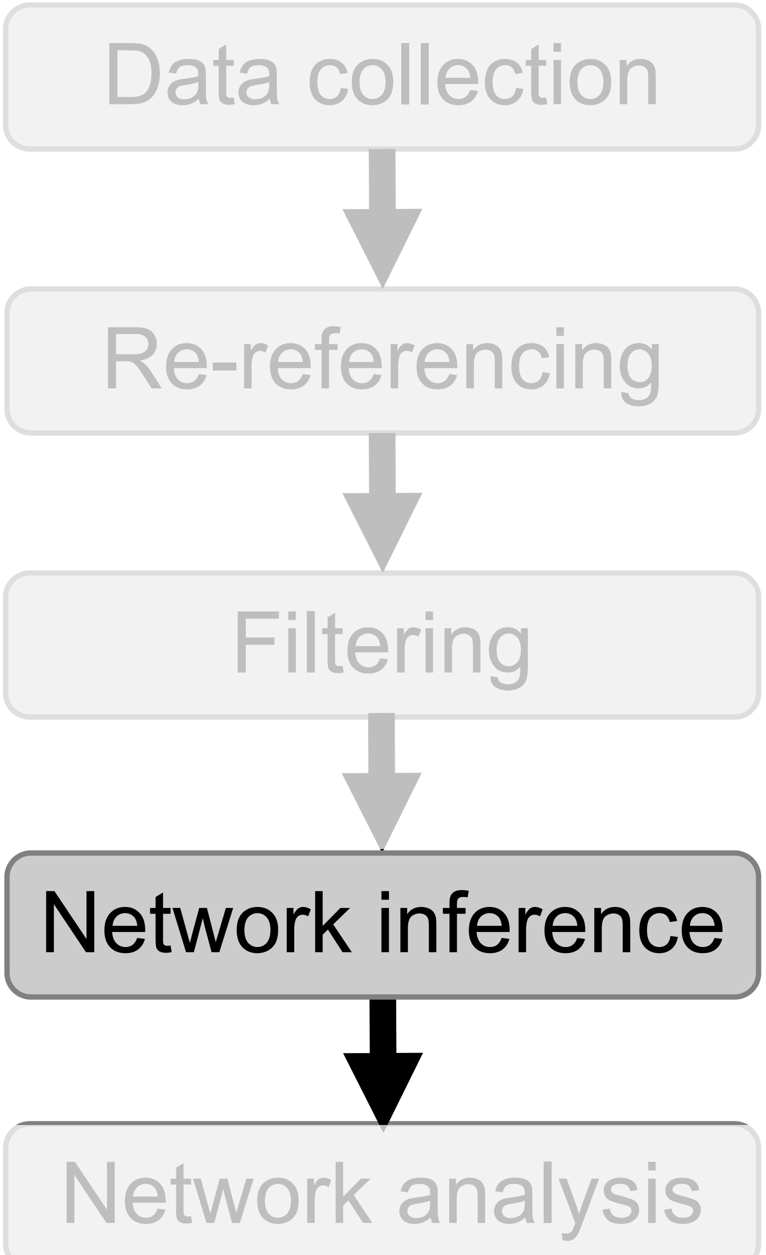
- Which frequency band?

  … to keep: delta, HFO

  … to remove: sweat artifact, 60 Hz

- Filter parameters
  - Type:
    - FIR, IIR, …
    - High-pass, low-pass, …

Pipeline

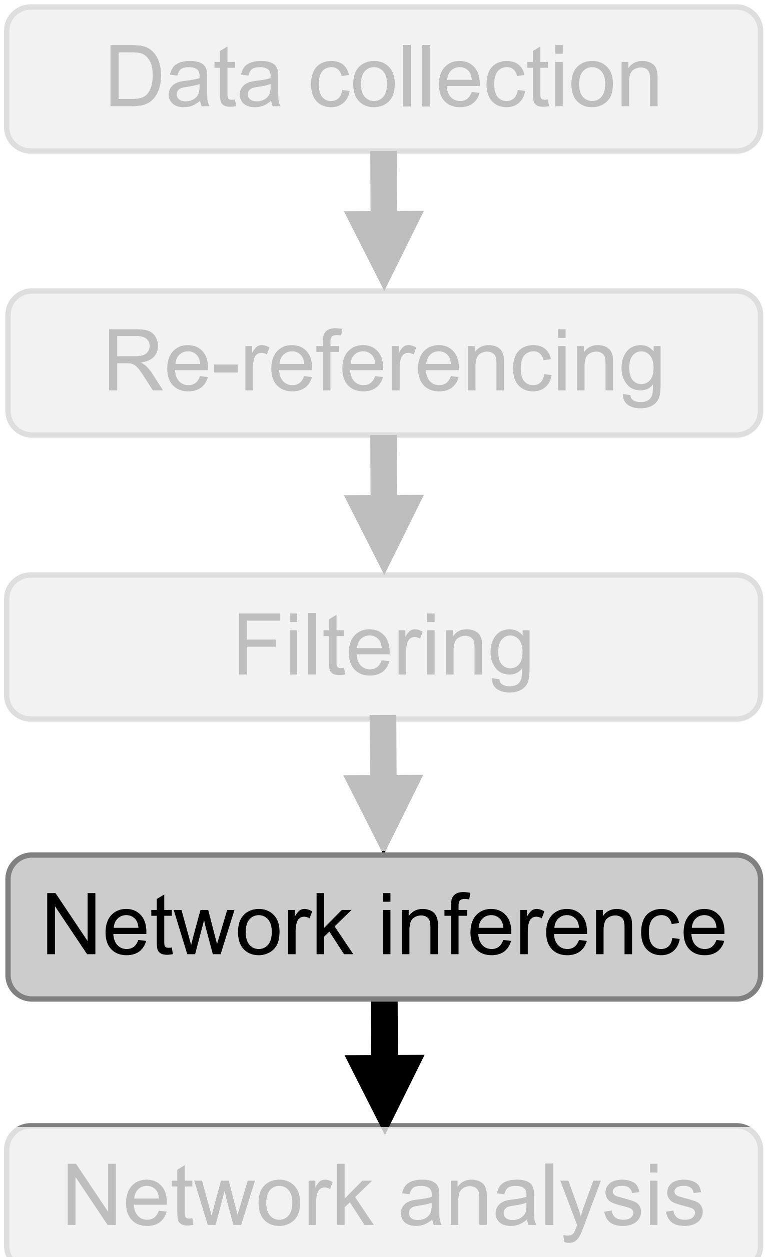


Coupling measure

- Linear (correlation)
  … simple, fast, well understood
- Nonlinear (information)
  … powerful, more complex
- Model based (Granger)
  … address confounds, slow

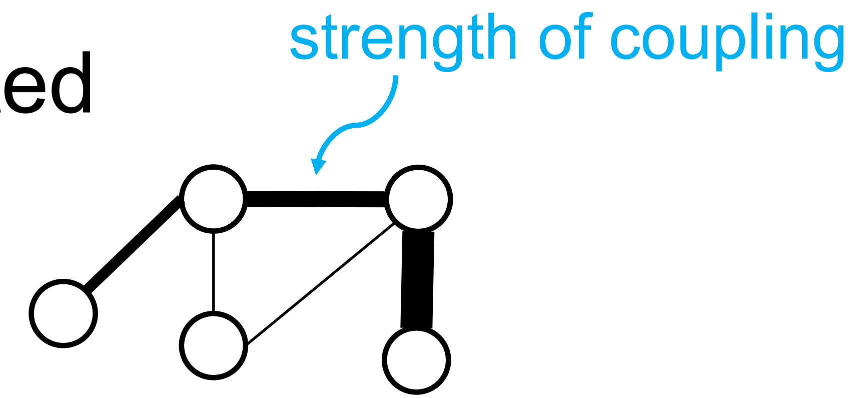
[Spencer et al 2018; Greenblatt et al 2012; Pereda et al 2005; Nunez et al, 1997]

Pipeline

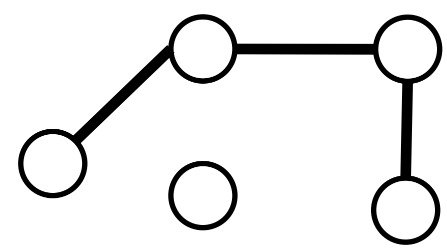


Apply the coupling measure, then create the network:

Weighted



Binary



Threshold:

- Coupling measure
- p-value

Pipeline

Data collection

↓

Re-referencing

↓

Filtering

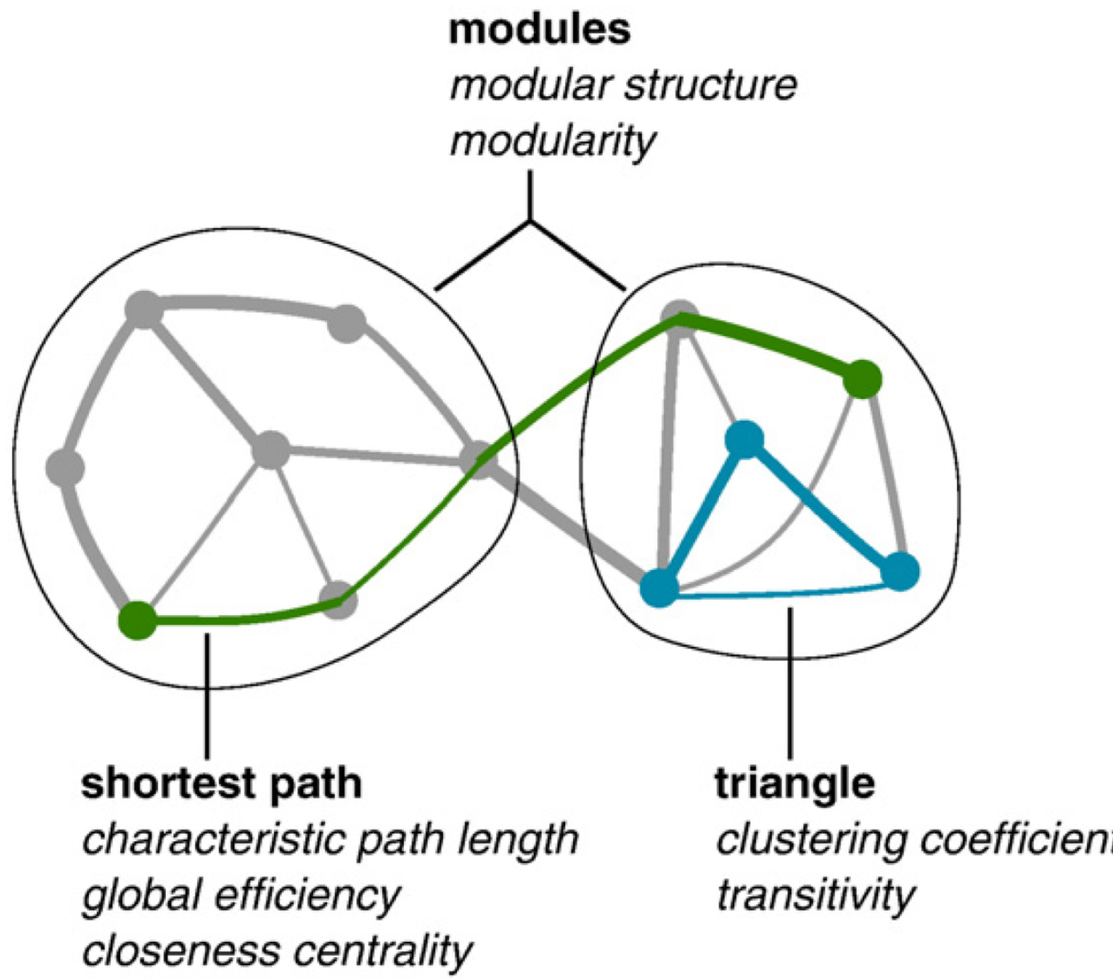
↓

Network inference

↓

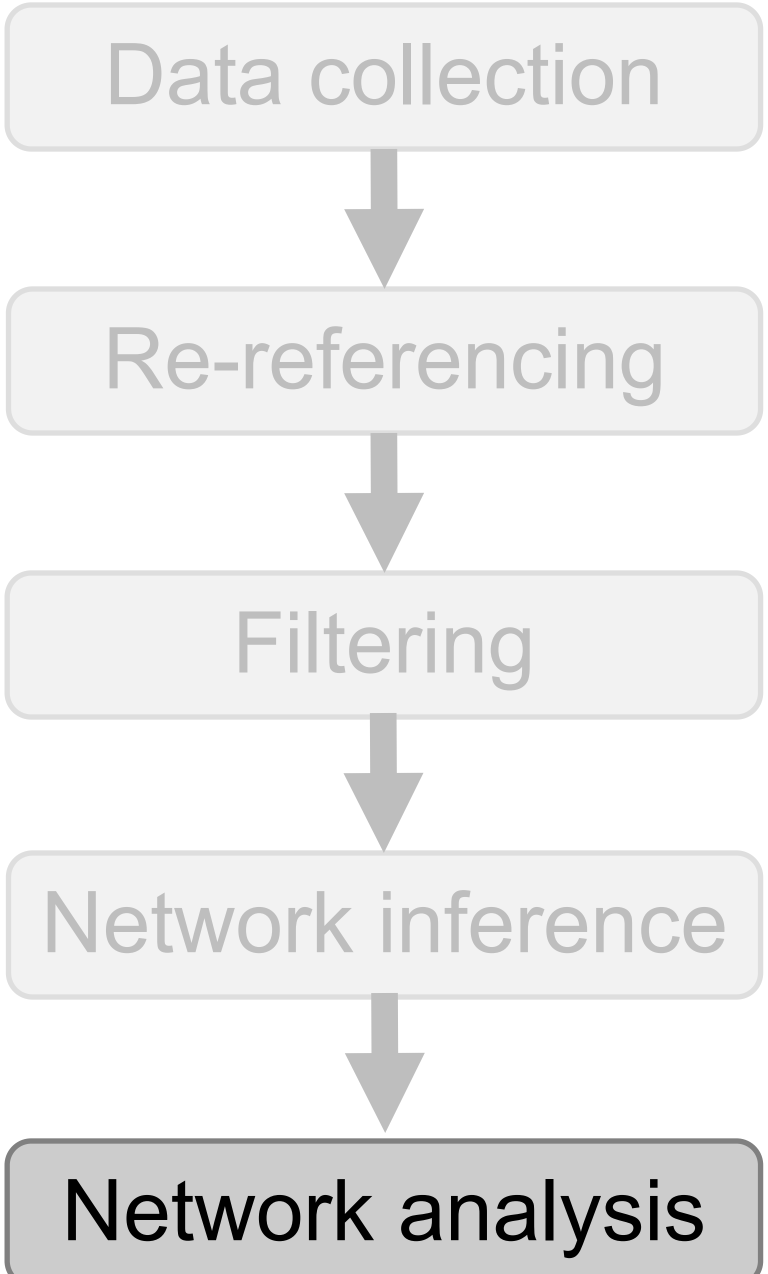
Network analysis

- Static network measures

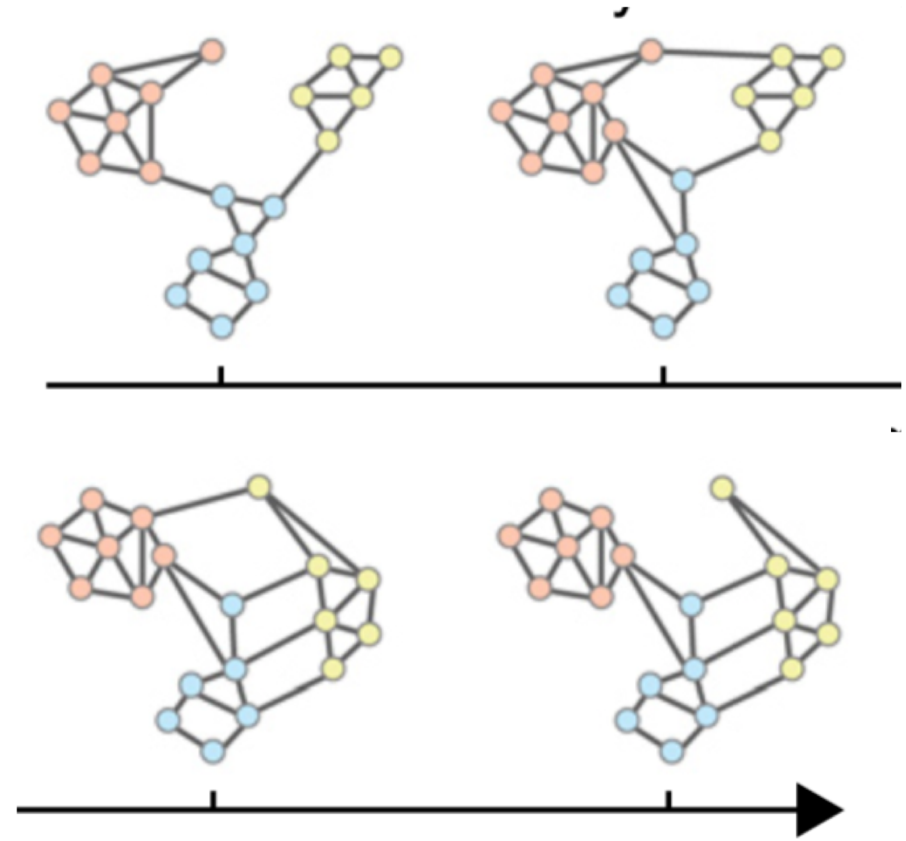


[Rubinov & Sporns, 2010]

Pipeline

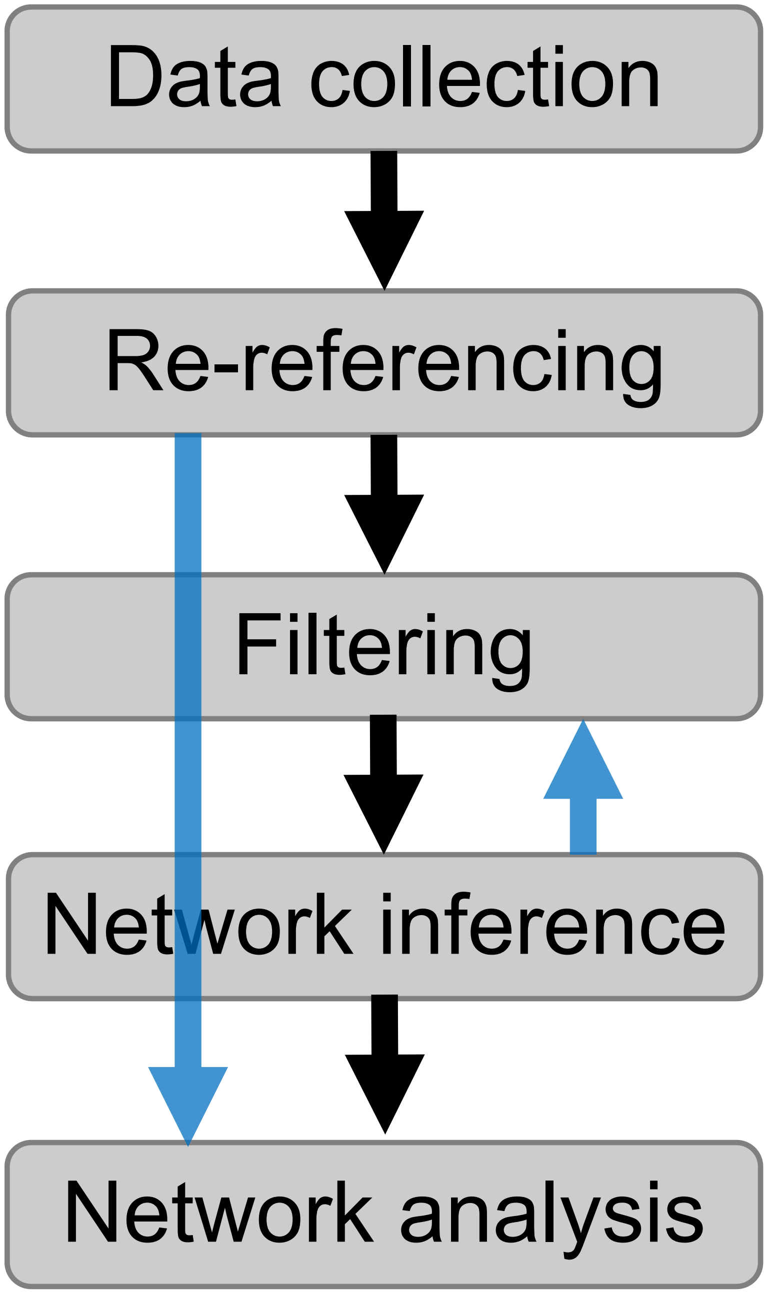


- Dynamic network measures



[Bassett & Sporns, 2017]

Pipeline



are interconnected …

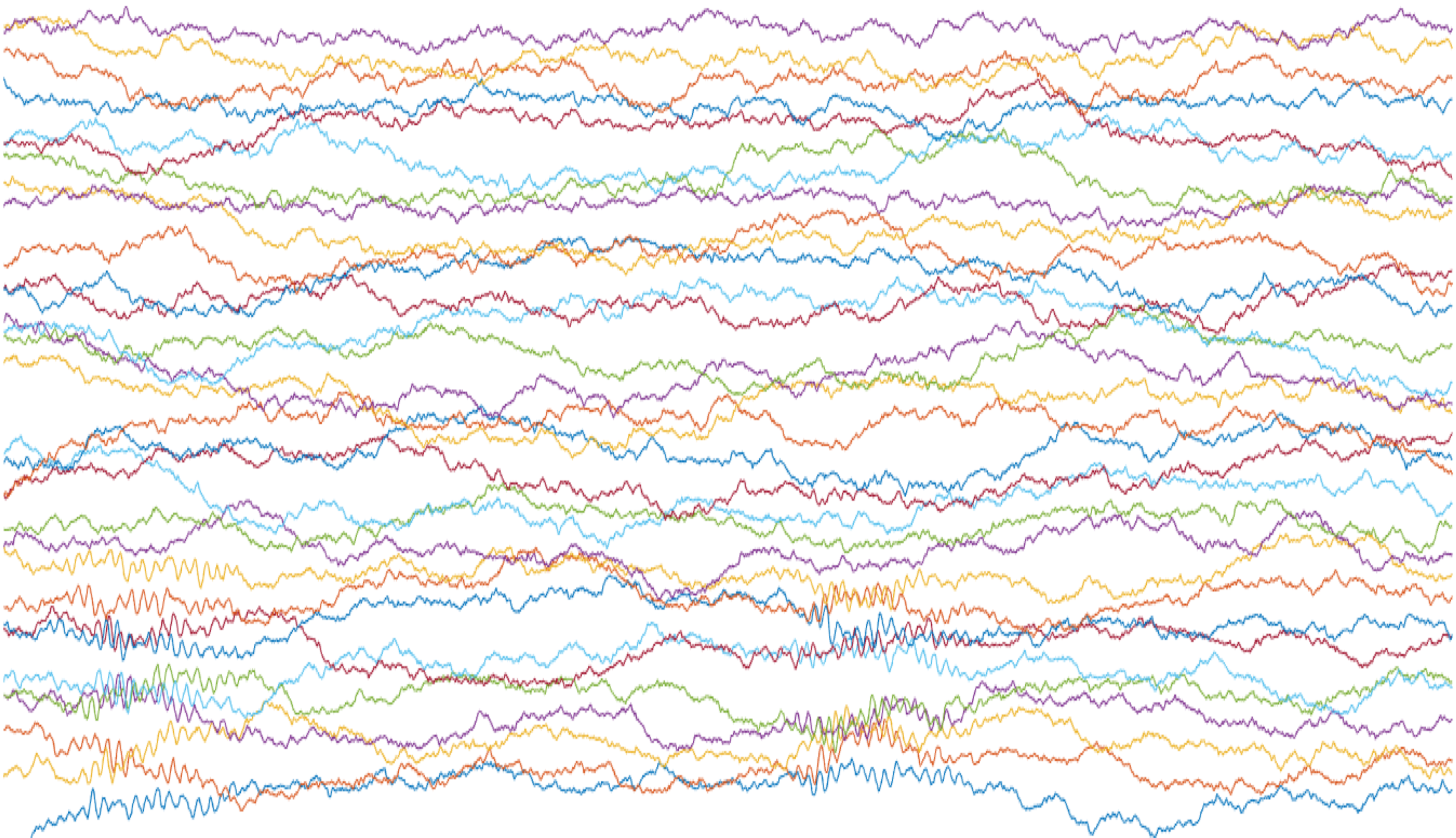
Reference choice impacts network result.

… common average reference.

Network inference method may impact filtering choice

… coherence in a specific band.

Implement the pipeline in an example ...



Example

https://github.com/Mark-Kramer/Sleep-Networks-2021/

Sleep-Networks-2021

An Introduction to Network Analysis & EEG Interpretation

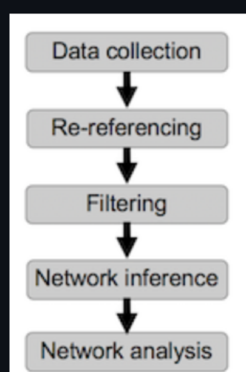
This respository includes an example data set

`Example_sleep_data.mat`

and an example script to analyze these data

`Example_sleep_data_analysis.m`

Open the script and run it to implement specific choices for this data analysis pipeline:



The pipeline begins with a multielectrode recording and ends with a functional network. The pipeline is described in more detail in this presentation at the Virtual Seminar Series: Computational Approaches to Signal Processing for Sleep.

The analysis pipeline illustrates one example approach. There are many others.

Example

https://github.com/Mark-Kramer/Sleep-Networks-2021/

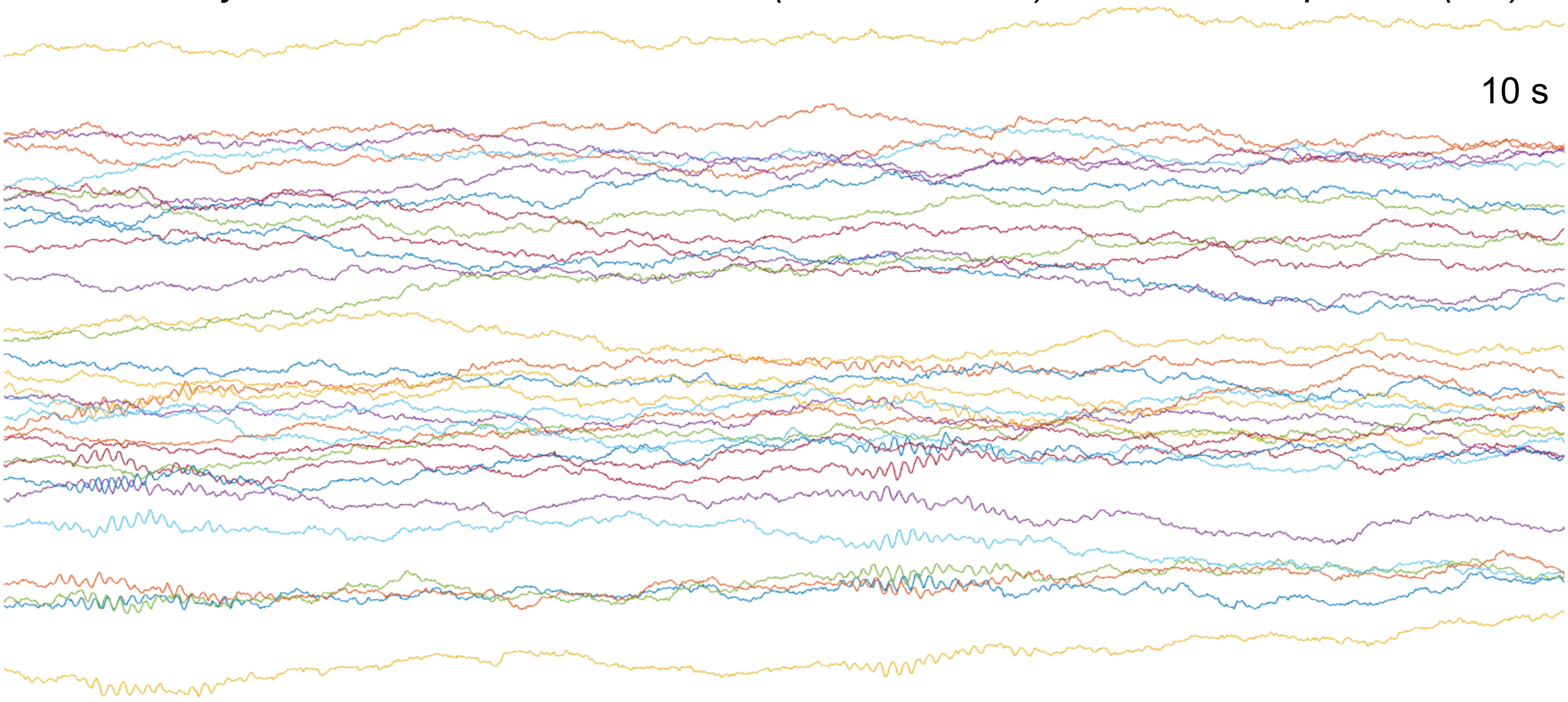
```matlab
%% Step 1a. Data collection -------------------------------------------------

load('Example_sleep_data.mat')         % Load the data
                                       %    d = the data [ time, electrodes ]
                                       %    t = the time axis, in units of seconds.
                                       %    detections = spindle detections [time, electrodes]
figure(); eeg_plot(t,d,'')             % It's always a good idea to look at the raw data.
title('EEG data'); xlabel('Time [s]')

%% Step 1b. Spectrogram ------------------------------------------------------
%
%
simple_spectrogram(d(:,1),t);          % Make spectrogram for 1st electrode.

%% Step 2. Re-referencing ----------------------------------------------------
%
% N/A
```

see code

Example

https://github.com/Mark-Kramer/Sleep-Networks-2021/

Motivated by work with Dr. Catherine Chu (Harvard/MGH) & Elizabeth Spencer (BU)



EEG, 32 channels, 256 Hz

Observations (rhythms)?

Coupling?

Example

https://github.com/Mark-Kramer/Sleep-Networks-2021/

```
%% Step 1a. Data collection ------------------------------------------------

load('Example_sleep_data.mat')       % Load the data
                                     %    d = the data [ time, electrodes ]
                                     %    t = the time axis, in units of seconds.
                                     %    detections = spindle detections [time, electrodes]
figure(); eeg_plot(t,d,'')           % It's always a good idea to look at the raw data.
title('EEG data'); xlabel('Time [s]')

%% Step 1b. Spectrogram ----------------------------------------------------
%
%
simple_spectrogram(d(:,1),t);        % Make spectrogram for 1st electrode.
```

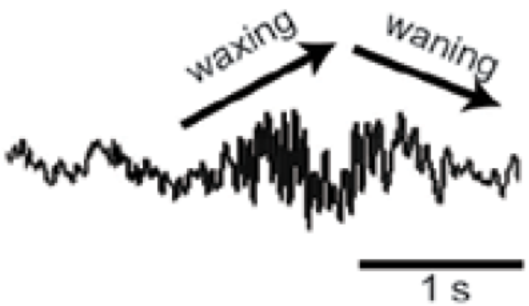
see code

Example

Rhythms?

- transient 0.5 – 2 s
- 9-16 Hz

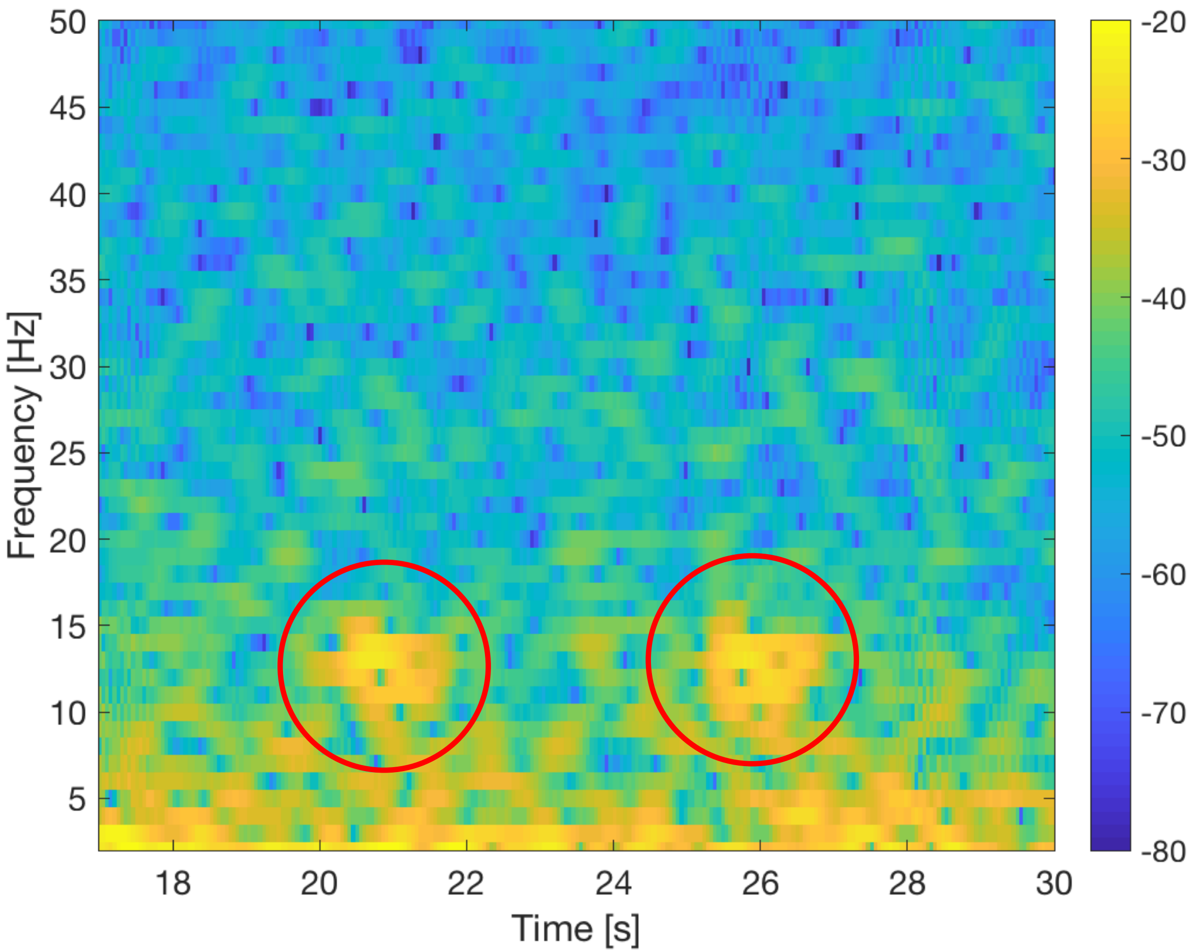
<u>spindles</u>



[Lüthi, Neuroscientist, 2014]

Network inference

... for rhythmic data?

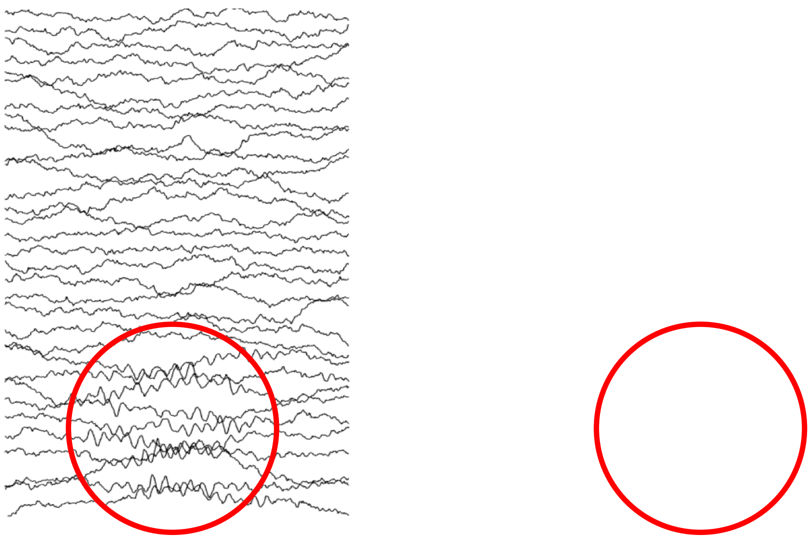


<u>coherence</u> makes sense ...

[Wamsley et al., Biological Psychiatry, 2012;
Ngo et al., eLife, 2020]

Example

Coherence Treat each spindle epoch as a trial:



spindle epoch spindle epoch

Ask: between two electrodes, is there a constant phase relationship at 9-16 Hz across trials (i.e., when spindles occur)?

Guess?

Example

https://github.com/Mark-Kramer/Sleep-Networks-2021/

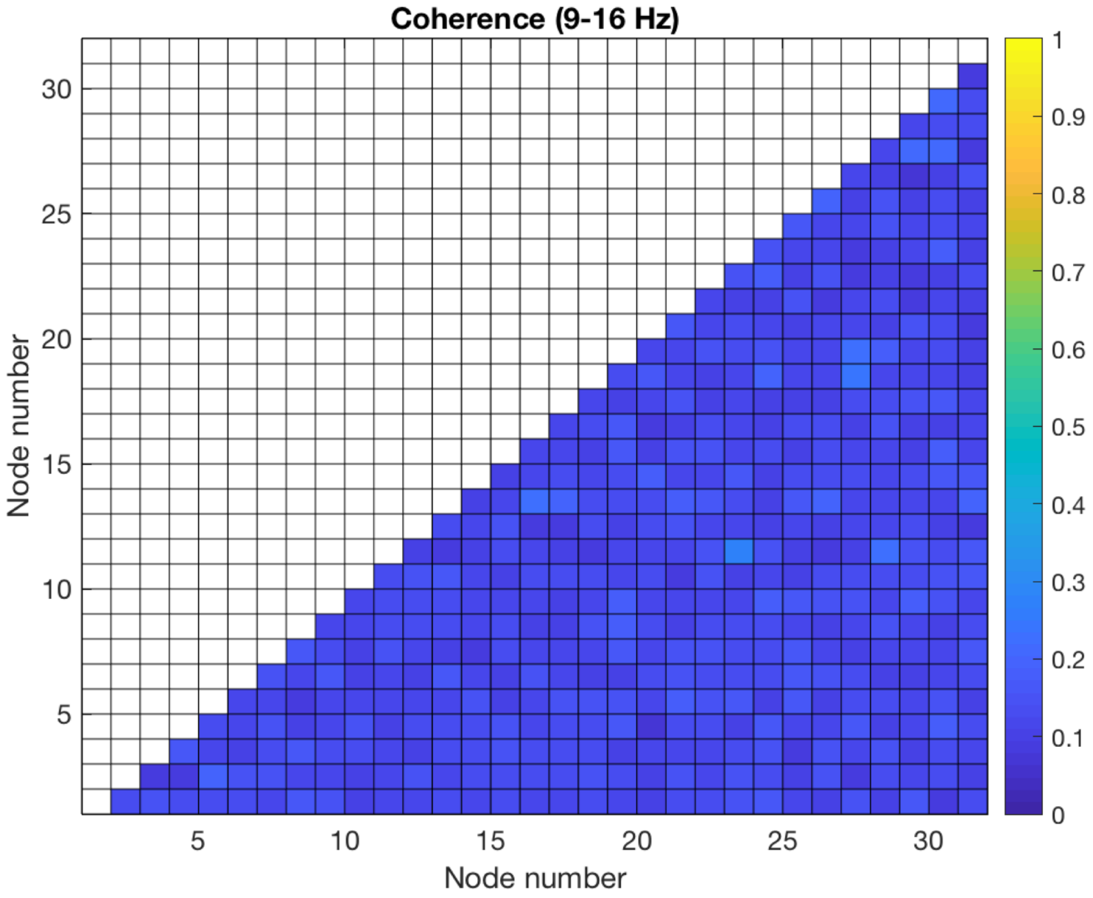
```
%% Step 2. Re-referencing -----------------------------------------------------
%
% N/A

%% Step 3. Filtering ----------------------------------------------------------
%
% N/A

%% Step 4. Network inference --------------------------------------------------
%
%                                    % Infer the functional connectivity,
[C] = infer_network_coherence(t,d,detections);
figure(); pcolor(C); caxis([0,1])   % ... and visualize it.
xlabel('Node number'); ylabel('Node number'); title('Coherence (9-16 Hz)')
```

see code

Example

Coherence

Adjacency matrix



1 = strong coherence
0 = weak coherence

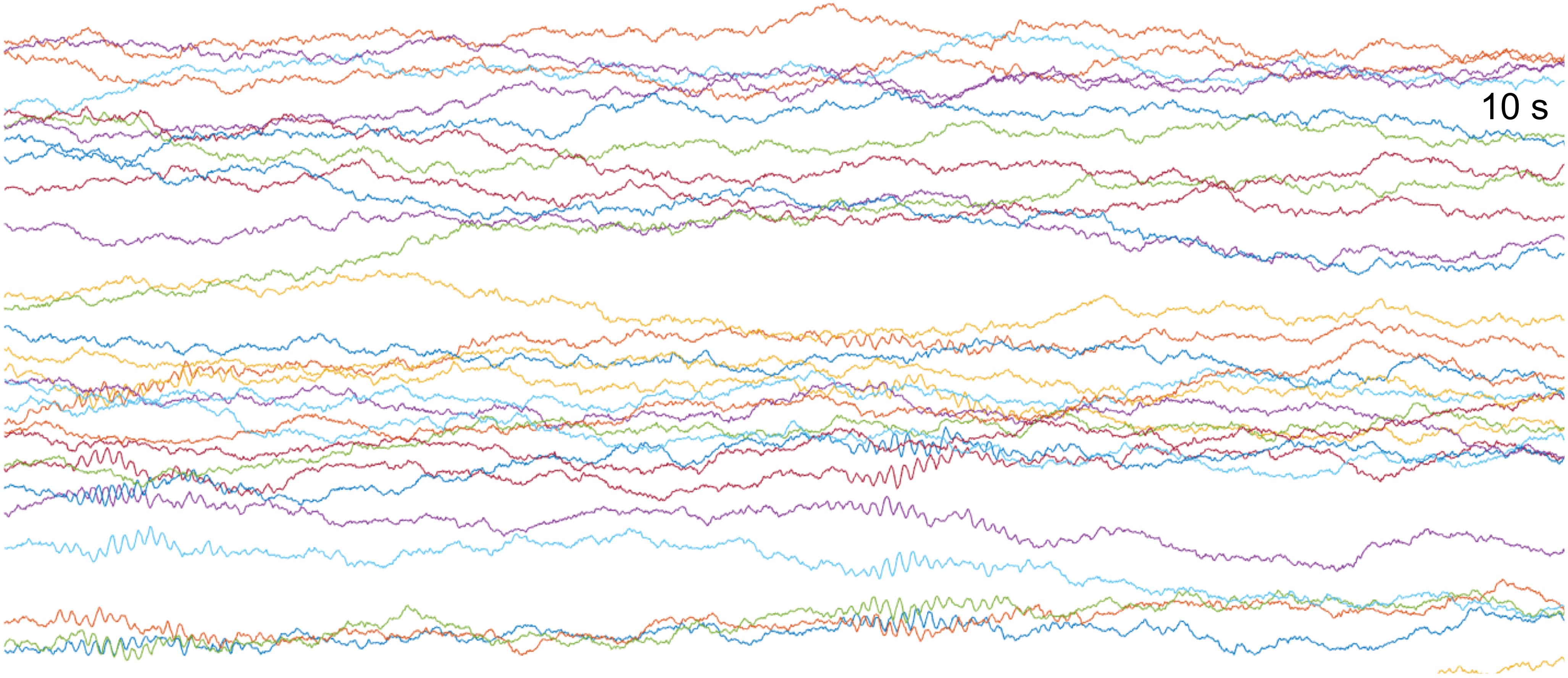
Conclusion:

No evidence of coherence?

Example

Coherence Result: no coherence

Remember visual inspection



Does this result make sense?

Example

Coherence Result: no coherence

Confusing ...

Why?

1) Our spindle detector is bad?

Let's look ...

Example

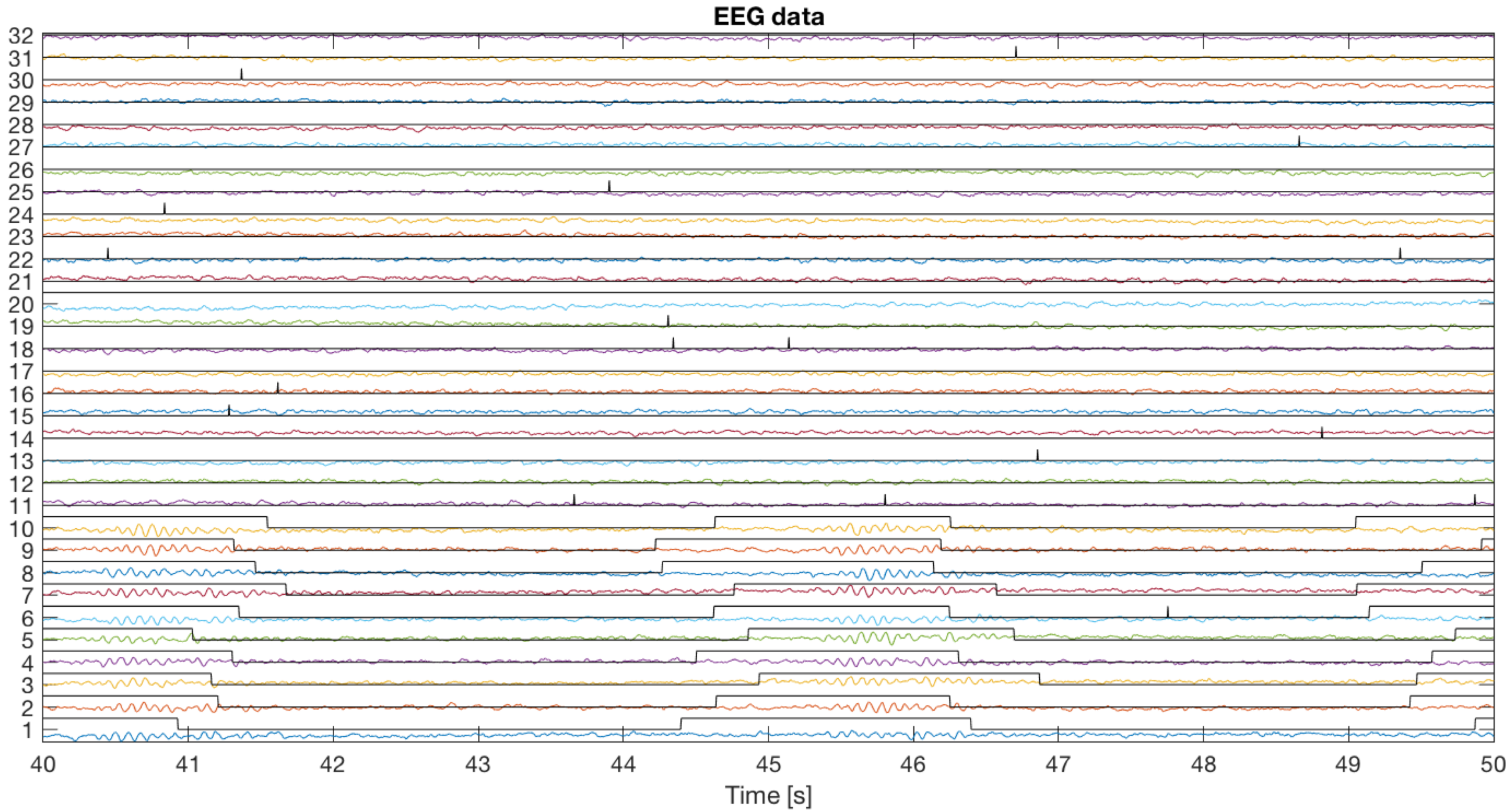
https://github.com/Mark-Kramer/Sleep-Networks-2021/

```
%% TRY AGAIN ...

%% Step 3. Filter & visualize spindle detections ---------------------------
%
%
Wn = [2,50];                         % Choose filter range from [1,50] Hz,
d_filtered = simple_filter(t,d,Wn); % ... apply the filter,
figure(); eeg_plot(t,d_filtered,''); hold on; eeg_plot(t,detections,'k'); hold off
title('EEG data'); xlabel('Time [s]')
```

see code

Example

https://github.com/Mark-Kramer/Sleep-Networks-2021/



What do you think of the detector?

Example

Coherence Result: no coherence <u>Why</u>?

~~1) Our spindle detector is bad?~~ No

Visual inspection suggests spindle detector <u>ok</u>.

[Wamsley et al, Biol Psych, 2012; Warby et al., Nature Methods, 2014; Kramer et al., J Neurosci, 2021]

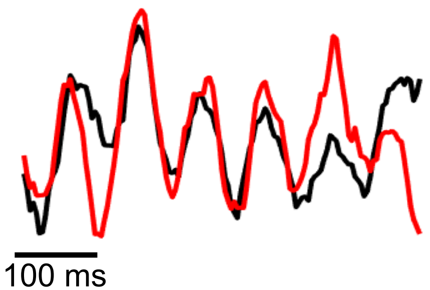
What else?

Example

Coherence Result: no coherence <u>Why</u>?

Consider spindle epochs at 2 electrodes:

trial$_1$



spindles: in phase phase shifted phase shifted out of phase

<u>Conclusion</u>: between these 2 electrodes, no evidence of a constant phase relationship across spindle epochs (trials).

Coherence ≈ 0

Example

initial plan

Network inference

... for rhythmic data?

coherence makes sense.

spindles are not coherent.

Phase relationship between spindles?

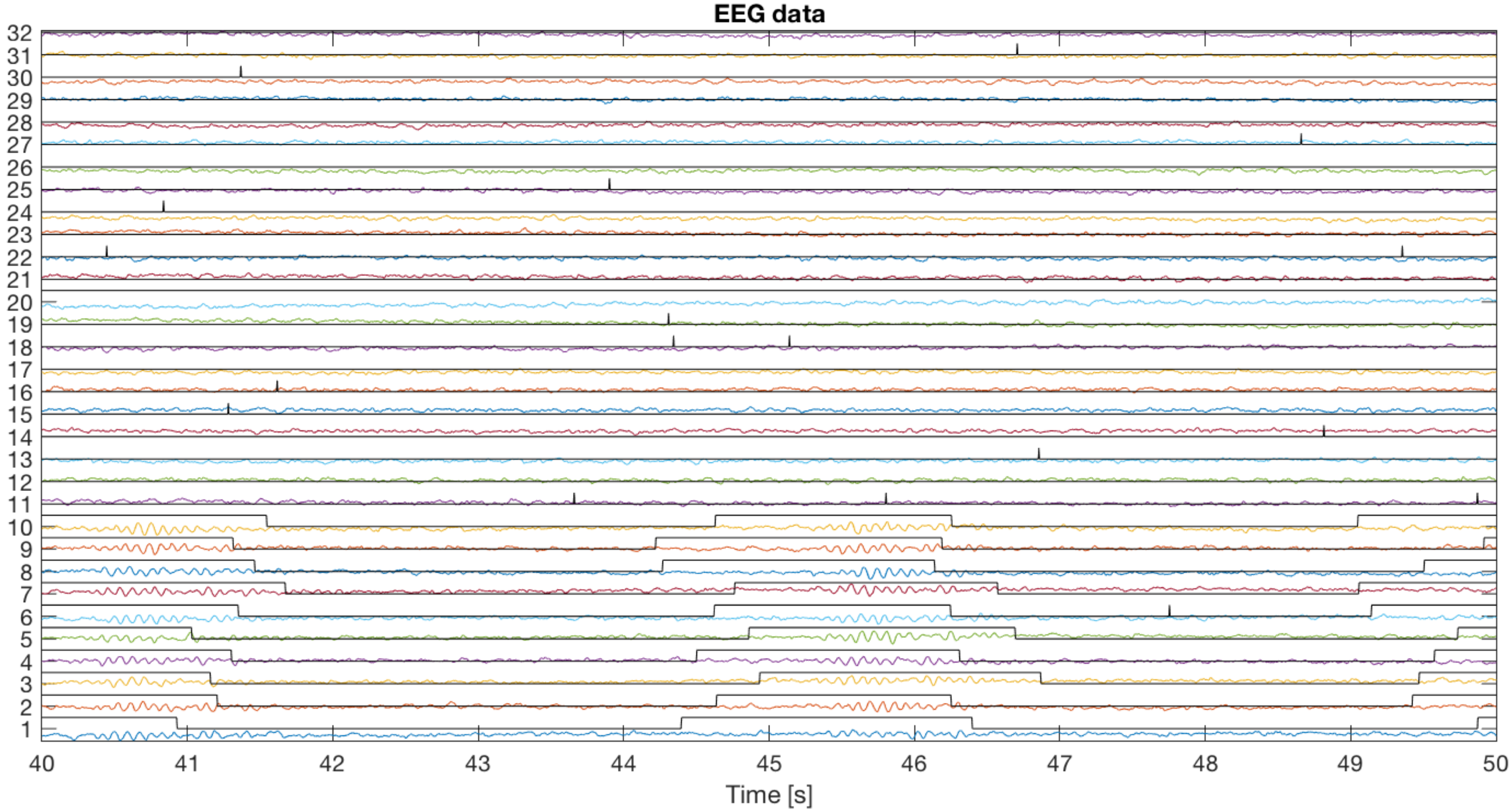
... fine temporal structure

Interesting, but maybe there's more?

Consider ...

Example

Look at the data (again)

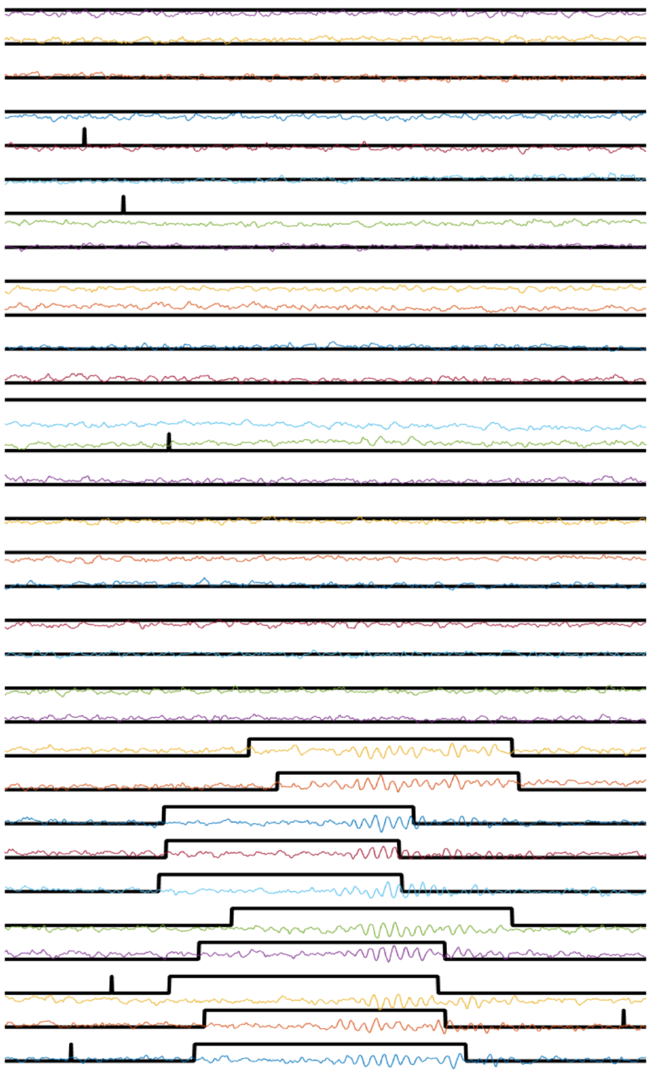


What stands out: detections overlap across electrodes

Instead of coupling in voltages, coupling of detections?

Example

Network inference



... do spindles occur at the same time?

Compute <u>coincidence</u>

When detections overlap, product = 1

detection signal

...0000011111111111111100000...

...001111111111111100000000...

...000001111111111100000000... **sum**

= big number,
when many detections overlap

Example

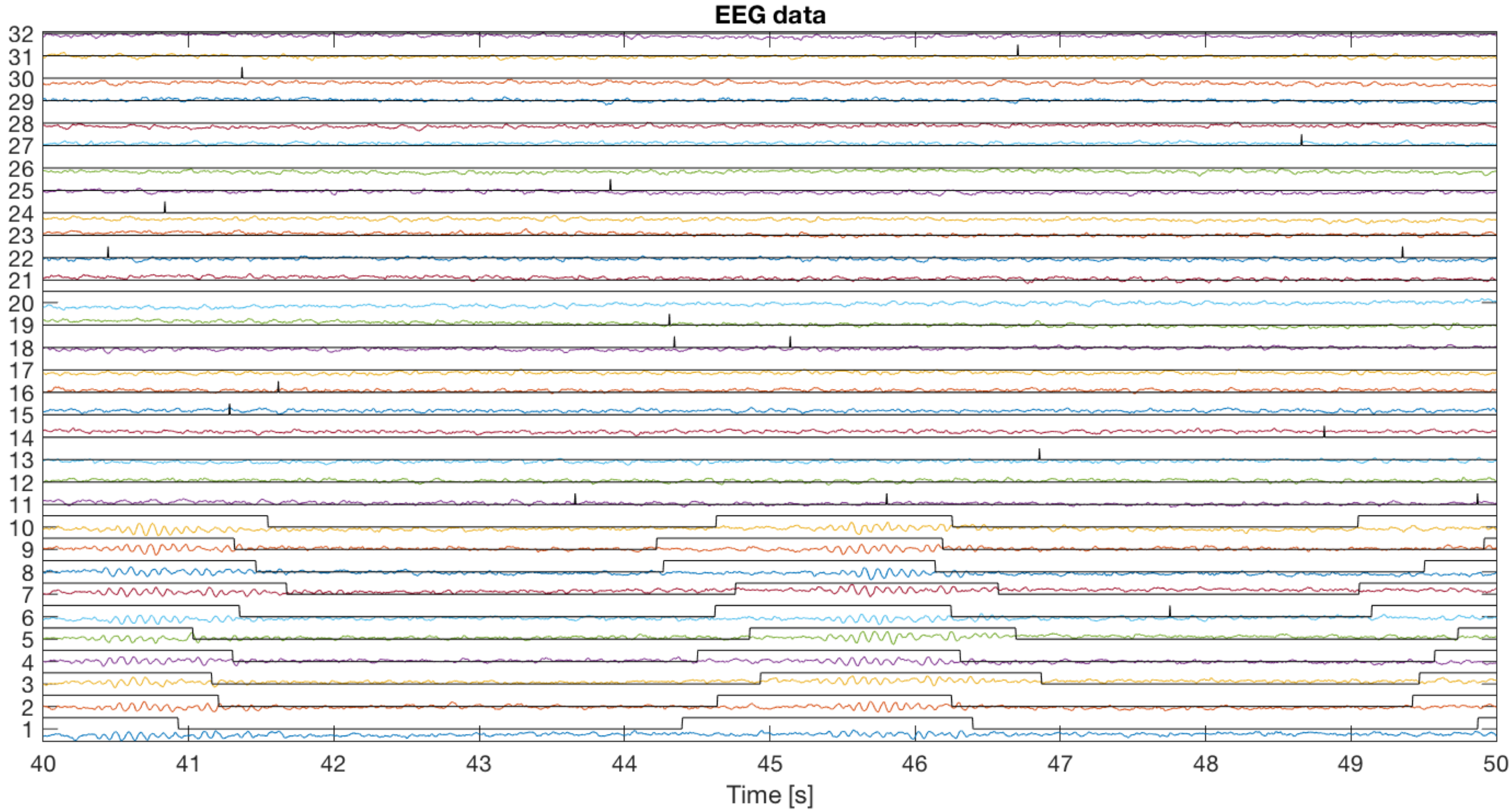
https://github.com/Mark-Kramer/Sleep-Networks-2021/

```
%% Step 4. Network inference ---------------------------------------------------------
%
%                                           % Infer the functional connectivity,
[C] = infer_network_coincidence(t,d,detections);
figure(); pcolor(C); colorbar;              % ... and visualize it.
xlabel('Node number'); ylabel('Node number'); title('Coincidence')
```

see code

Example

Which electrodes do you expect to be coincident?



Example

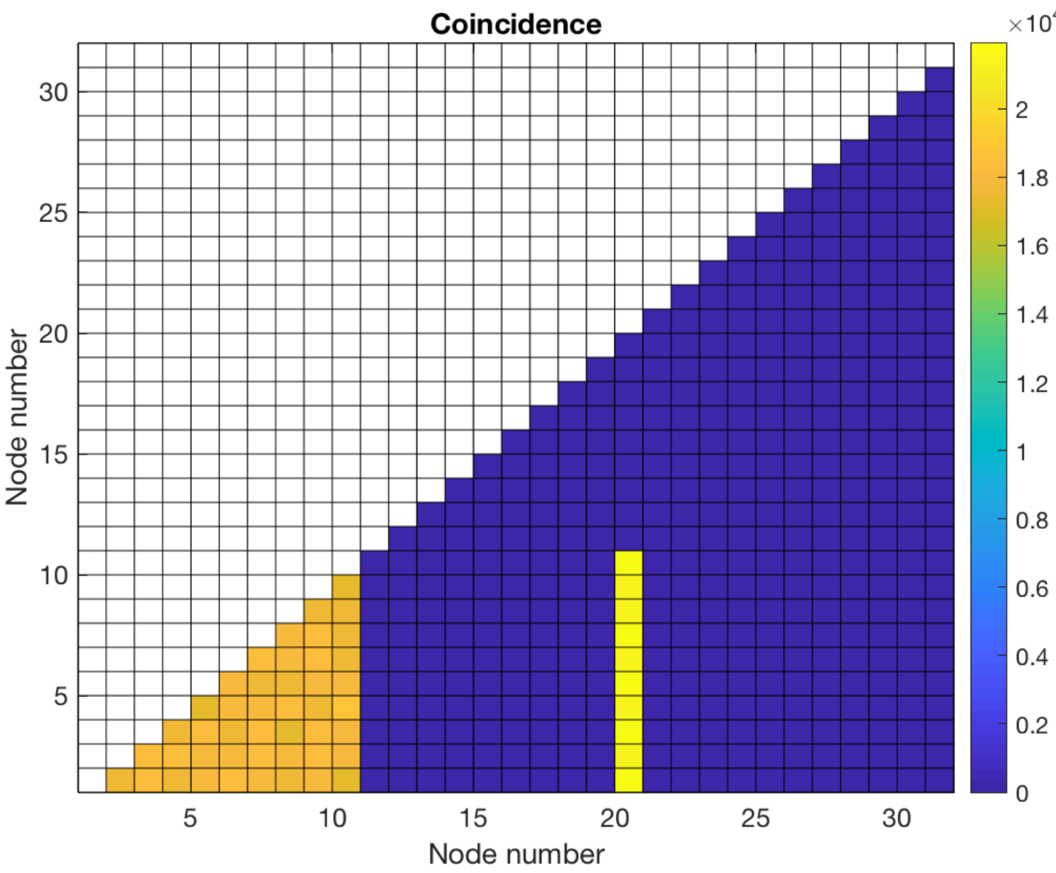
Compute <u>coincidence</u>

Conclusion:

Evidence of coincidence

1-10 coincident

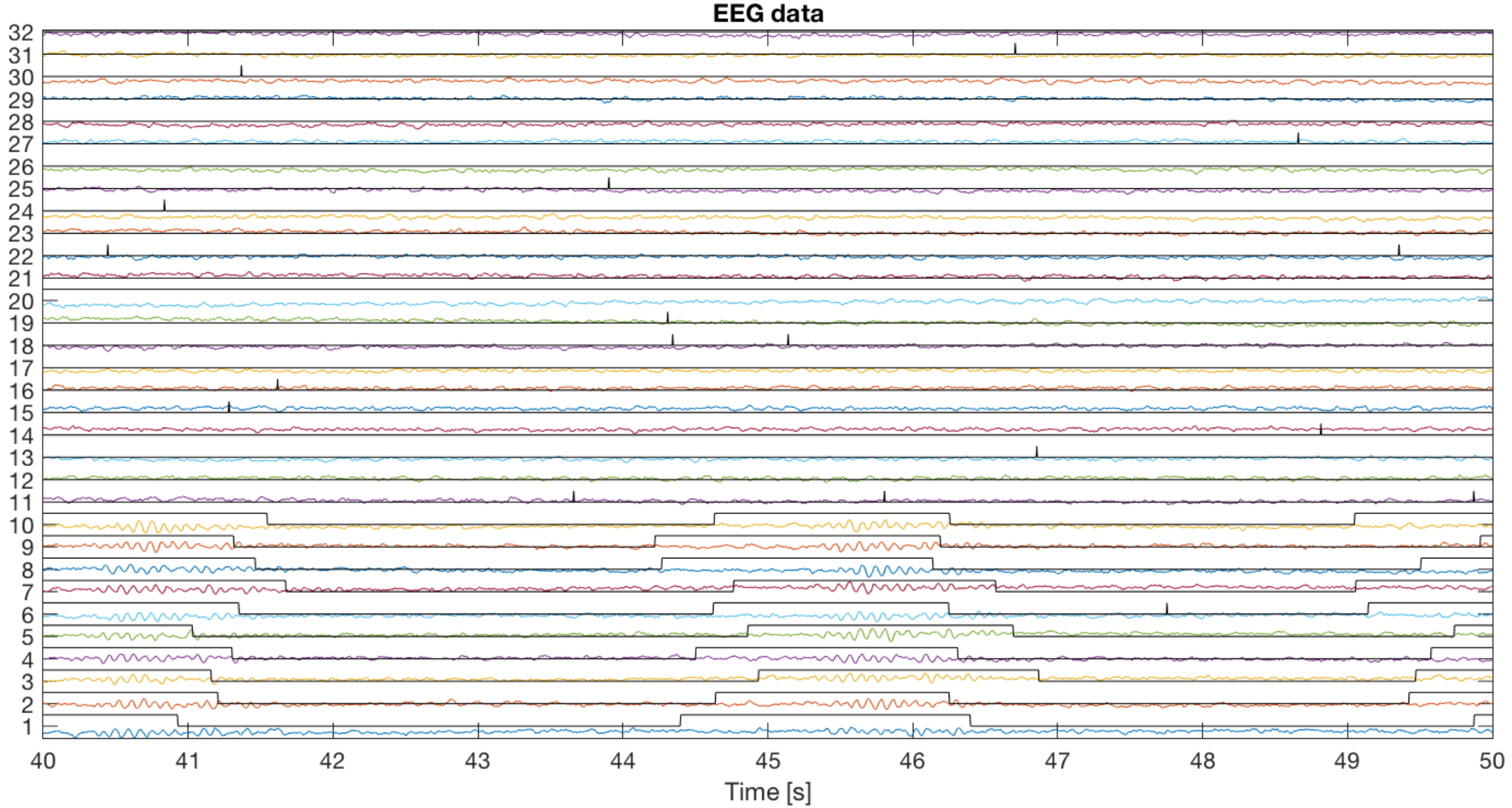
20? coincident



That's interesting .... there's a problem?

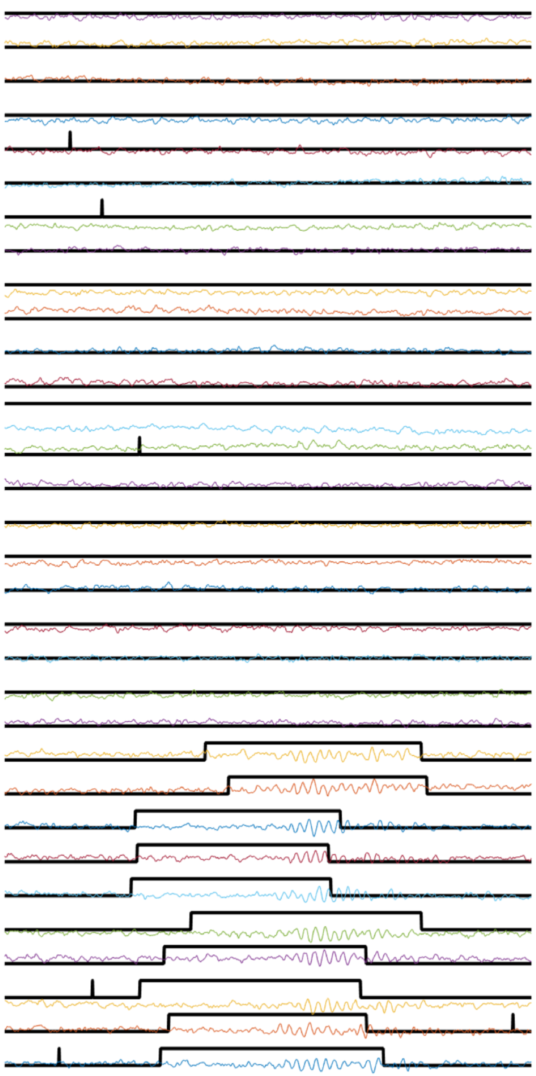
Example

It’s here, but very subtle ...

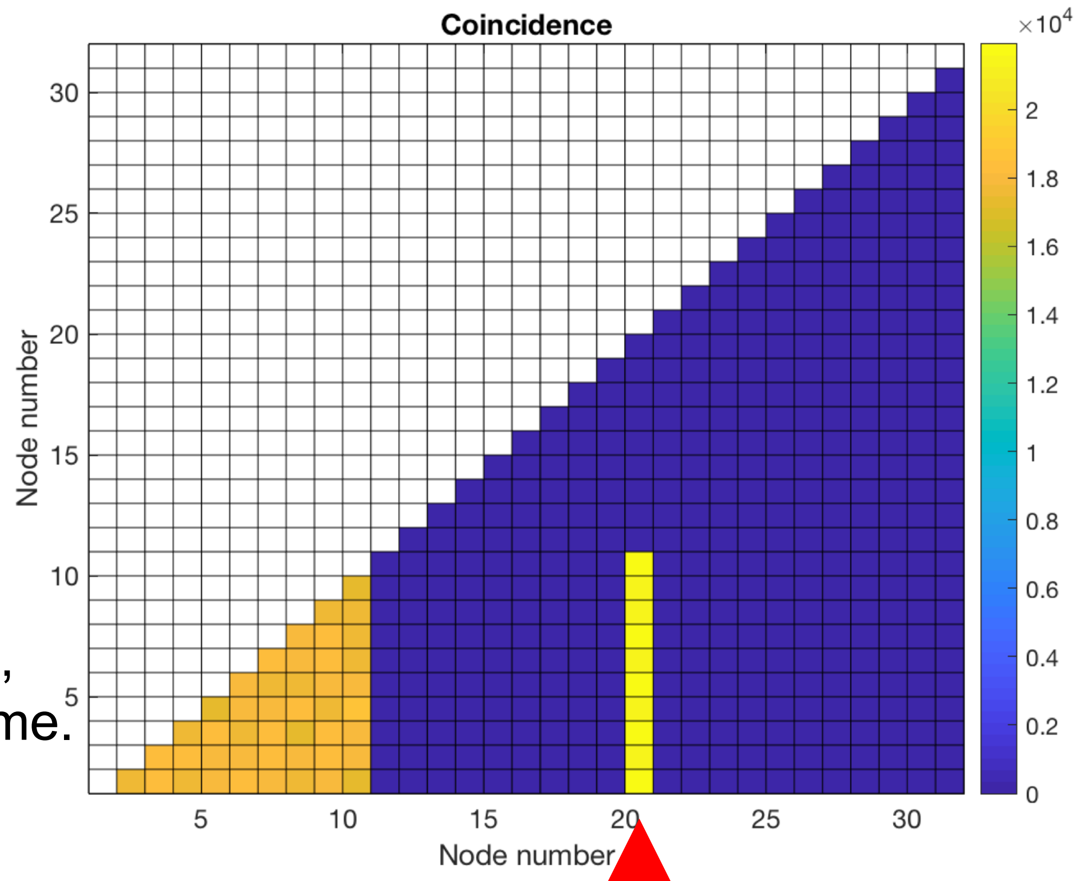


Example

Problem coincidence



Detector says:
at electrode 20,
spindle at all time.



High detection rate = high coincidence

Example: sleep spindles

Solution <u>scaled</u> coincidence

...00000111111111111100000... sum = s_1

...00111111111111100000000... sum = s_2

...00000111111111100000000... sum = s_{12}

scaled coincidence = s_{12} / (s_1 s_2)

scale by detection rate at each electrode

Rate impacts coupling measures [Cohen & Kohn, Nat Neuro, 2011; Lepage et al., Neural Comp, 2011]

Example

https://github.com/Mark-Kramer/Sleep-Networks-2021/

```
%% TRY AGAIN ...

%% Step 4. Network inference -------------------------------------------------
%
%                                     % Infer the functional connectivity,
[C] = infer_network_coincidence_scaled(t,d,detections);
figure(); pcolor(C); colorbar;        % ... and visualize it.
xlabel('Node number'); ylabel('Node number'); title('Coincidence scaled')
```

see code

Example

Compute <u>scaled</u> coincidence

Conclusion:

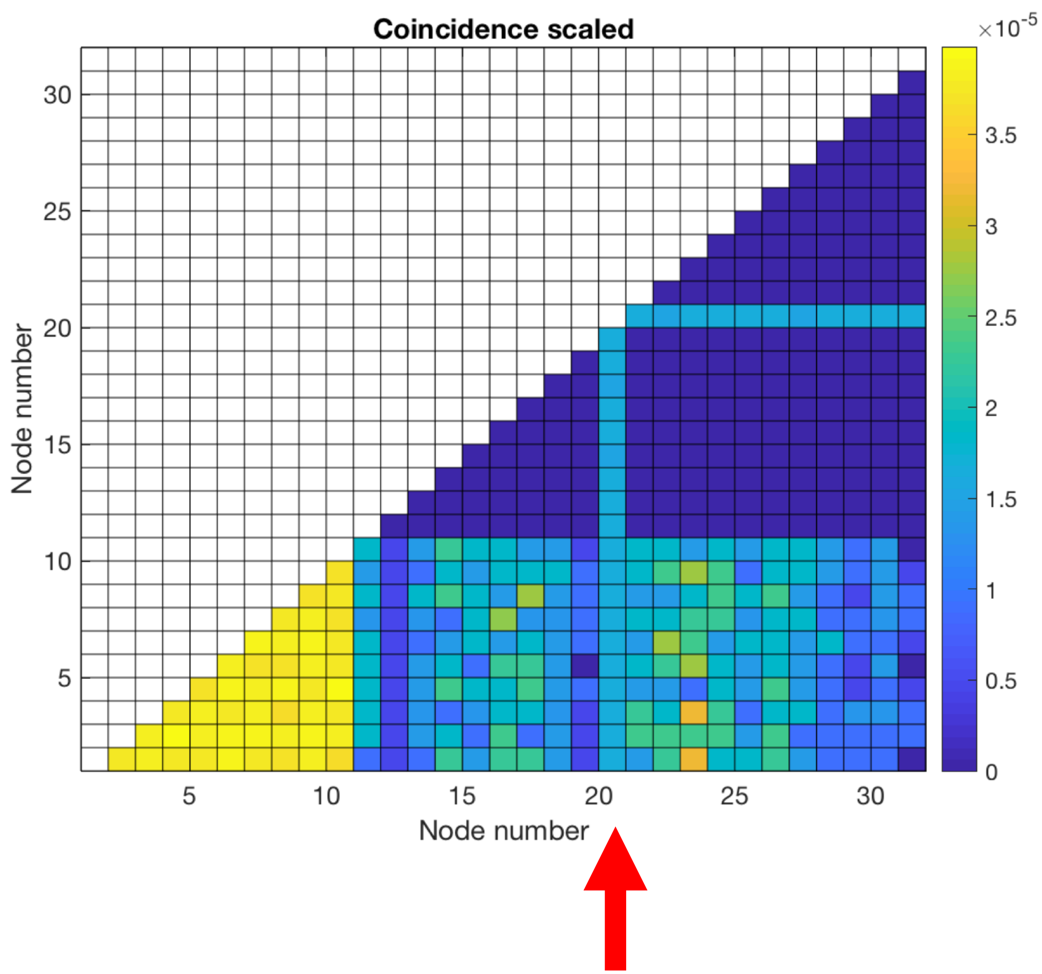
Evidence of coincidence

1-10 coincident

~~20? coincident~~

Network inference

Problem solved?



Conclusions

https://github.com/Mark-Kramer/Sleep-Networks-2021/

Data collection	Load .mat file
↓ Re-referencing	N/A
↓ Filtering	N/A (except for visualization)
↓ Network inference	~~Coherence~~ Coincidence of spindle detections
↓ Network analysis	? Brain Connectivity Toolbox

Conclusions

Characterizing functional connectivity in the brain is:

... filled with pitfalls.

... requires careful decisions & interpretation.

... can be useful.

Thank you

Dr. Prerau, organizer, Computational Approaches to Signal Processing for Sleep

Elizabeth Spencer, Uri Eden, Boston University, USA
Catherine Chu, Mass General Hospital / Harvard University, USA

https://github.com/Mark-Kramer/Sleep-Networks-2021/

NSF DMS #1451384
NIH R01NS115868
NIH R01EB026938