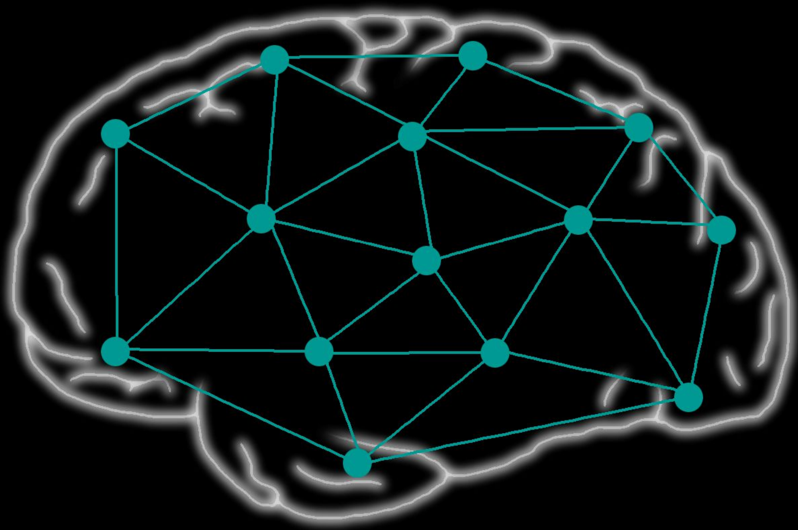
Deriving Functional Brain Networks from Data: A Critical Assessment

Klaus Lehnertz



Interdisciplinary Center
for Complex Systems

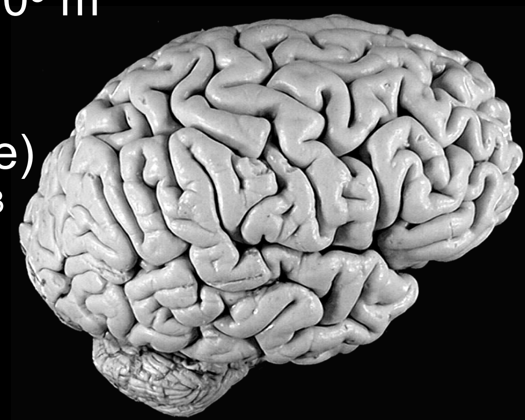
Dept. of Epileptology
Neurophysics Group

University of Bonn, Germany

Helmholtz-Institute
for Radiation- and
Nuclear Physics

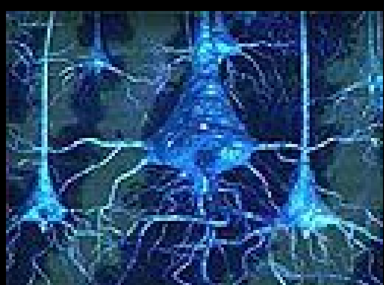
Complex (or Complicated?) Network Brain

\# neurons: ~ 10^{10}
\# synapses/neuron: ~ 10^3 - 10^4
length of all connections: ~ 10^7 - 10^9 m
(~2.5 x distance earth-moon)
connectivity factor: ~ 10^{-6} (adult)
connectivity factor: ~ 10^{-4} (juvenile)
ion channels / neuron: ~ 10^2 - 10^3
neurotransmitter &
other active substances: ~ 50
\# glia cells: ~3-fold # neurons



control; movement;
perception; attention;
learning; memory;
knowledge; emotions;
motivation; language;
thinking; planning;
personality; self-identity;
consciousness; …;
dysfunctions

structure ⟷ function



fluctuations
(endogenous/exogenous)

order ⟷ disorder

Brain Networks - Relevance

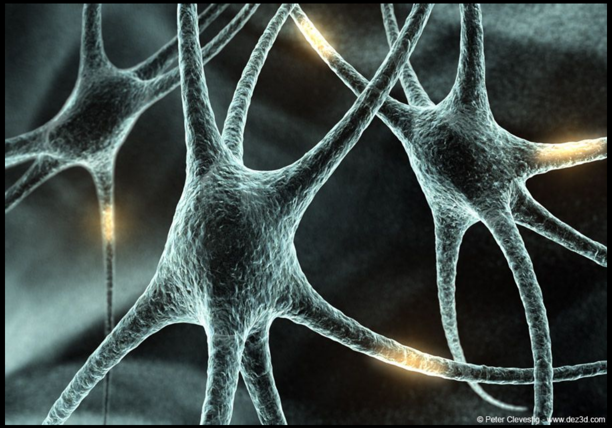
properties of functional/structural brain networks are sensitive to:

behavioral variability
cognitive ability
genetic information
shared genetic factors
gender
age
drugs
…

Alzheimer's disease
schizophrenia
acute depression
multiple sclerosis
attention deficit hyperact. dis.
spinal cord injury
epilepsy
…

Inferring Networks of the Brain - Structure

small-scale:

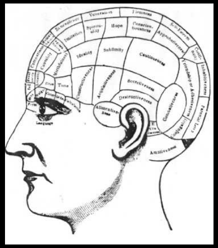


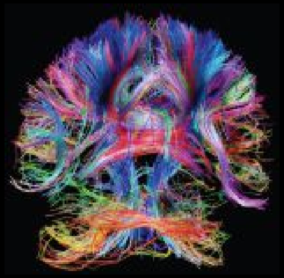
nodes → neurons (glia cells?)
links → synapses

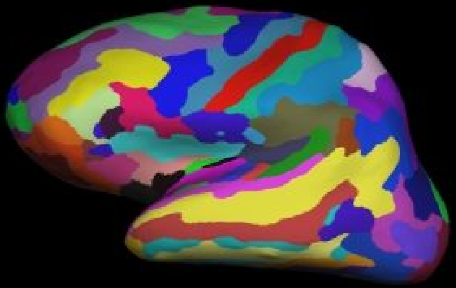
desirable, but hard (impossible?) to access

medium-scale: ???

large-scale:





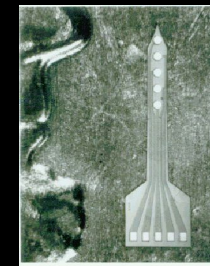


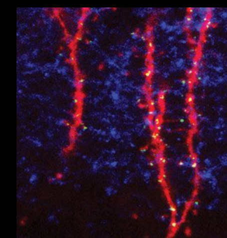
nodes → brain regions
links → fiber bundles

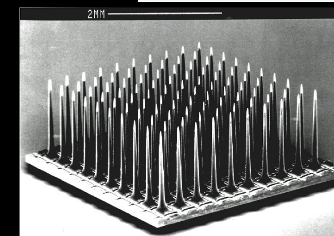
high-res. MRI, DTI, parcellation schemes, …

Inferring Networks of the Brain - Function

small-scale:

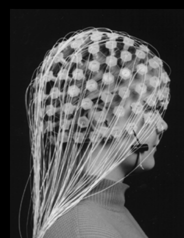


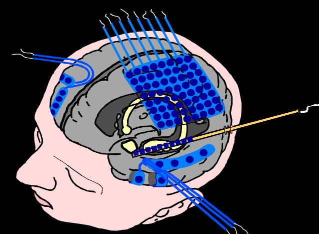




nodes → single neuron (glia) dynamics
links → synaptic (other) interactions

emerging technology





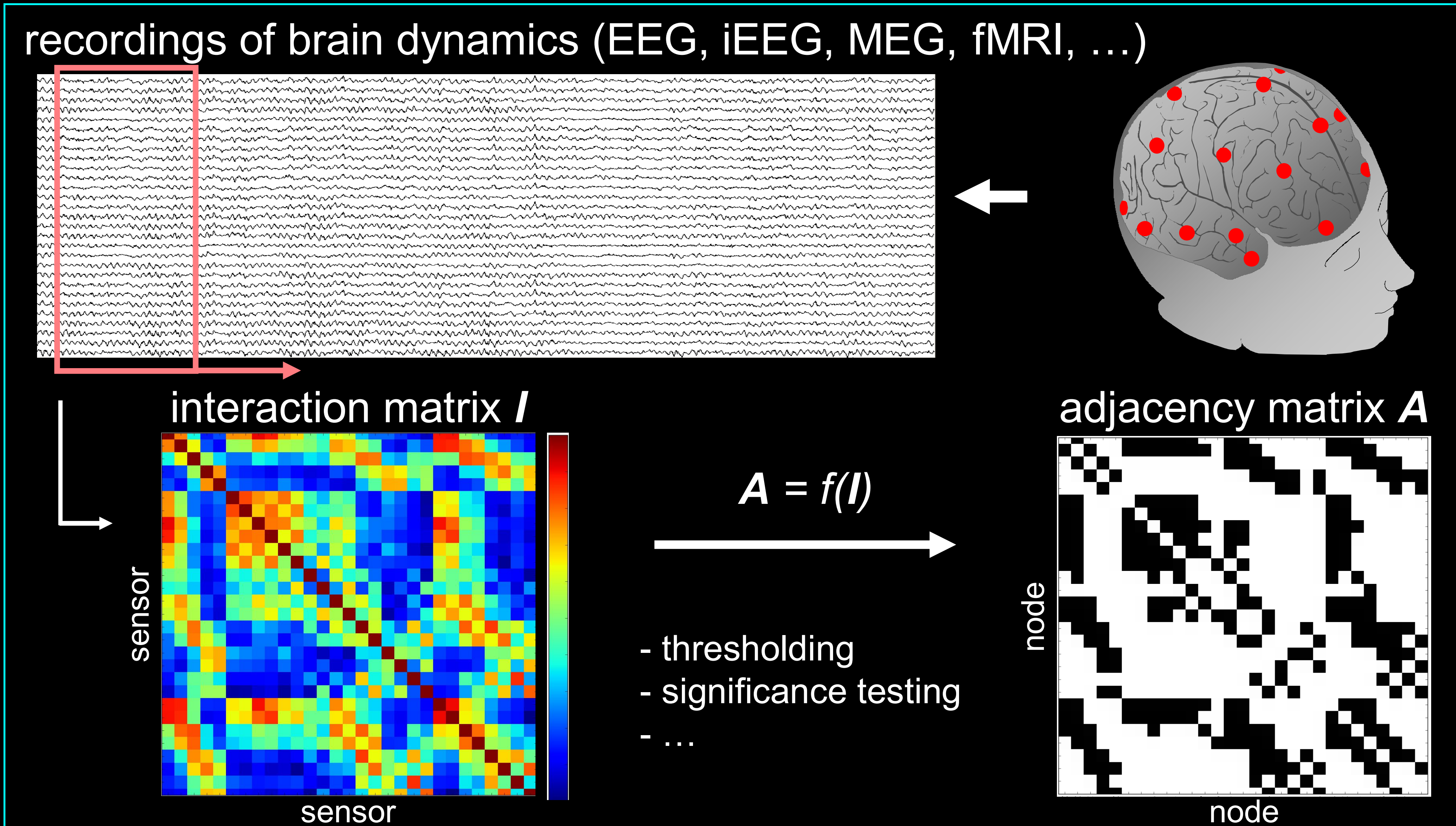
large-scale:

nodes → sensors (dynamics of *networks of neuron networks*)
links → interactions (weighted and/or directed),
time series analysis

EEG, iEEG, MEG, fMRI, …

medium-scale: ???

Inferring Functional (Interaction) Brain Networks



From Multichannel Data to Networks

Network:

set of nodes connected by links
binary, weighted, directed, weighted and directed
various approaches for characterization

Ansatz for node and link identification:

nodes ↔ sensors ↔ subsystems
links ↔ interactions between subsystems

Caveat:

network inference is an inverse problem … no unique solution !

Challenges

- node identification (nodes ↔ sensors ↔ subsystems)
spatial sampling, discretization

- link identification (link ↔ interactions)
temporal sampling
indirect vs. direct interactions, common sources
reliability of estimators for interactions

- interpretation of findings
comparison of empirical networks
appropriate null models / surrogate networks

Node Identification

spatially extended dynamical system (brain, climate, etc)

decomposition into (independent) subsystems ……. justified?

placement of sensors

- optimal sampling of dynamics of subsystems
- spatial organization of subsystems usually not known
- educated guess
- mostly rectangular arrangement of sensors ….. other?
- distance between sensors ?
  Nyquist-Shannon sampling theorem,
  but requires knowledge about (sub-)system(s) dynamics
- accuracy / reproducibility of sensor placement

Node Identification

CHAOS **20**, 013134 (2010)

From brain to earth and climate systems: Small-world interaction networks or not?

Stephan Bialonski,[a)] Marie-Therese Horstmann, and Klaus Lehnertz[b)]
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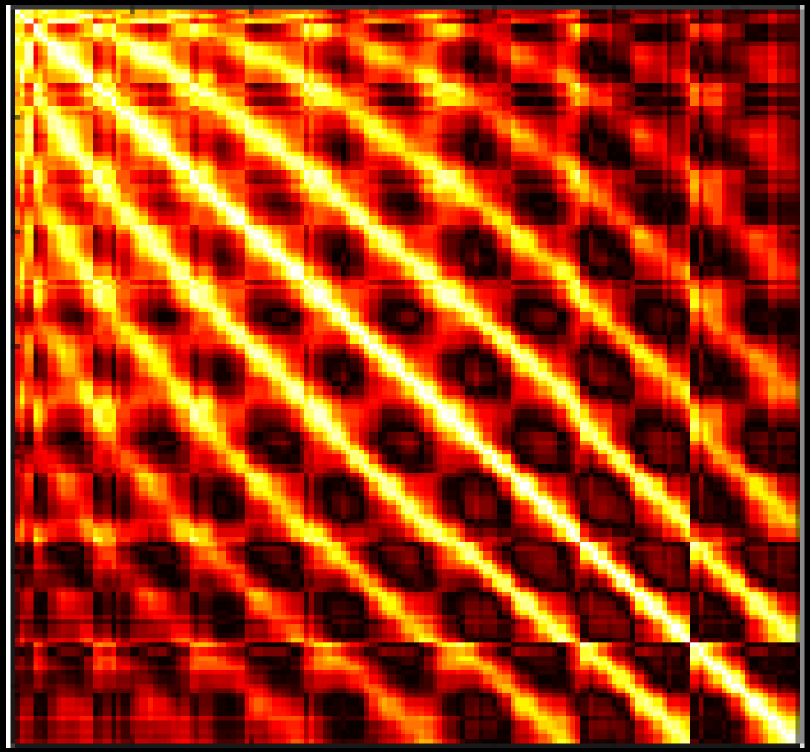
We consider recent reports on small-world topologies of interaction networks derived from the dynamics of spatially extended systems that are investigated in diverse scientific fields such as neurosciences, geophysics, or meteorology. With numerical simulations that mimic typical experimental situations, we have identified an important constraint when characterizing such networks: indications of a small-world topology can be expected solely due to the spatial sampling of the system along with the commonly used time series analysis based approaches to network characterization. © *2010 American Institute of Physics*. [doi:10.1063/1.3360561]

Node Identification

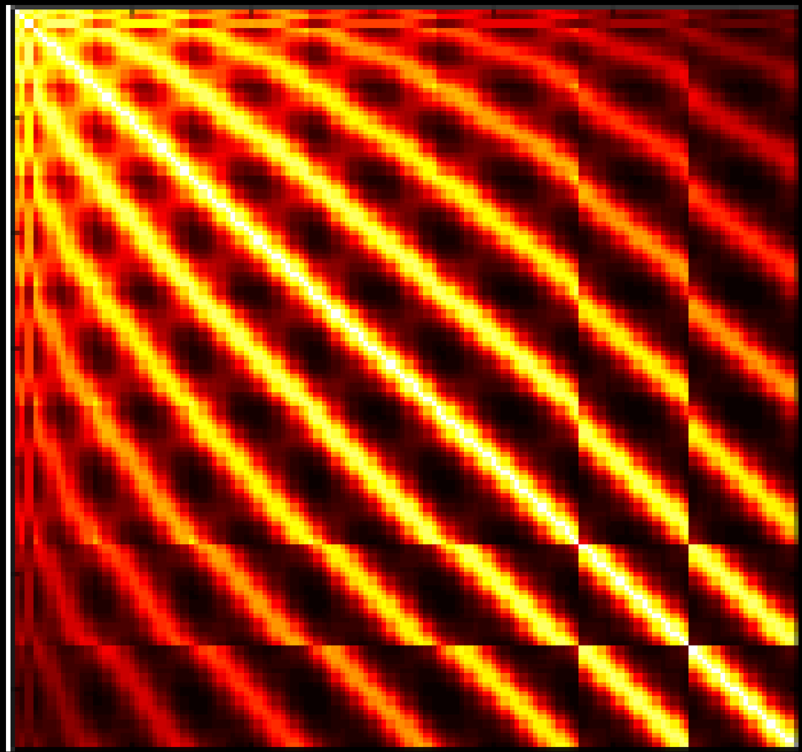
brain activity (MEG)

spatial model

$$F(d_{ij})=(1+\exp(u(d_{ij}-v)))^{-1}$$



$C = 0.58$; $L = 3.13$



$C = 0.57$; $L = 3.14$

S. Bialonski, MT Horstmann & KL
***Chaos** 20, 013134, 2010*

Node Identification

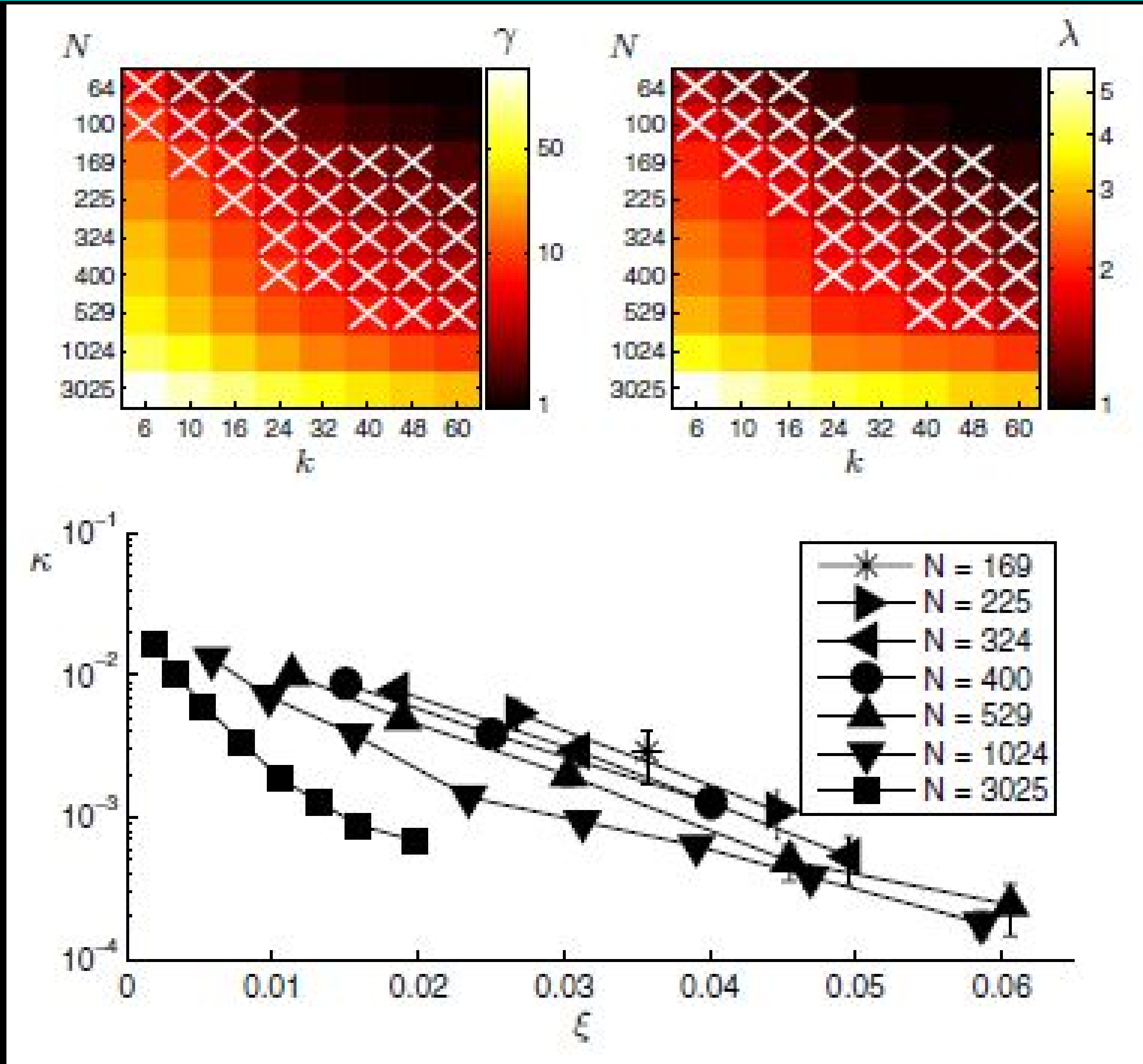


FIG. 2. (Color online) Top: mean values of the normalized clustering coefficient γ (left) and the normalized average shortest path length λ (right) for two-dimensional square lattices with different numbers of nodes N and mean degrees k (maximum standard deviations: $\sigma_\gamma=0.02$ and $\sigma_\lambda=0.02$). White crosses mark (N,k) configurations for which lattices will be classified as SWN if $\gamma>2$ and $\lambda<2$ is chosen as a practical criterion. Bottom: minimum fraction of randomly replaced links κ for which the resulting network would be classified as SWN ($\lambda<2$) in dependence on the density of links ξ. Error bars denote standard deviations derived from 100 independent replacement runs, and lines are for eye guidance only. Note that error bars are smaller than symbol size in the majority of cases.

rectangular arrangement
of sensors
+
link identification error
in the per mille – percent

→ small world network

S. Bialonski, MT Horstmann & KL
***Chaos** 20, 013134, 2010*

Node Identification

nodes ↔ sensors ↔ subsystems

- ansatz appears justified in many cases

- caveat: “wrong” spatial sampling can lead to mis-characterization of network properties

- are there better approaches ?
  - refine sampling strategies ?
  - determine the actual structural organization?
  - coarse graining?

Link Identification

link $\leftrightarrow$ interactions

- “good” observables, time scales

- temporal sampling (Nyquist-Shannon sampling theorem)

- measuring interactions

- confounding variables

Link Identification: Temporal Sampling

Unraveling Spurious Properties of Interaction Networks with Tailored Random Networks

Stephan Bialonski[1,2,3*], Martin Wendler[4], Klaus Lehnertz[1,2,3]

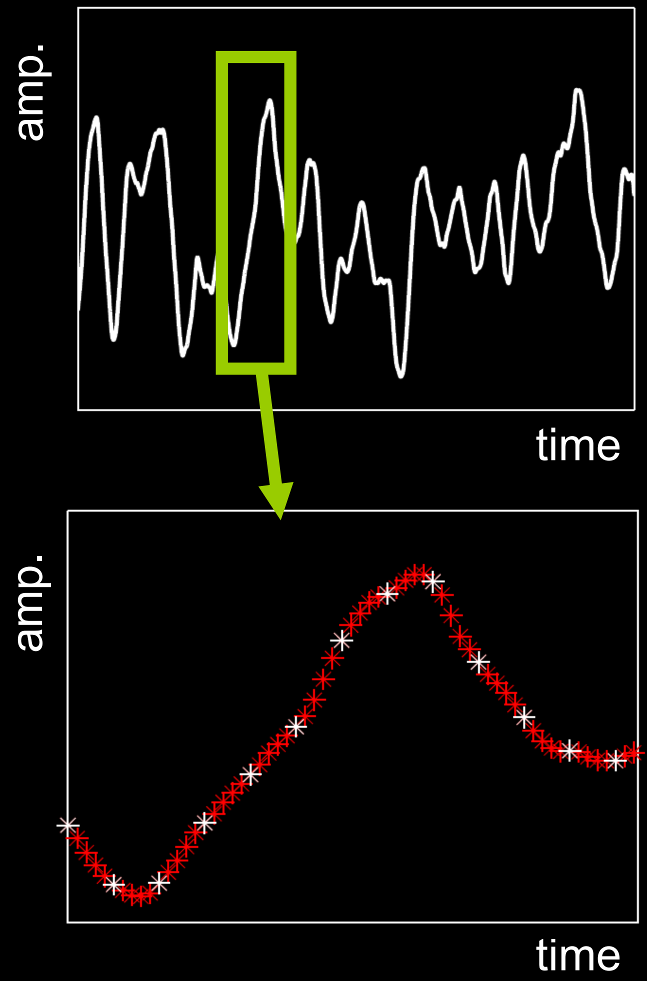
1 Department of Epileptology, University of Bonn, Bonn, Germany, **2** Helmholtz Institute for Radiation and Nuclear Physics, University of Bonn, Bonn, Germany, **3** Interdisciplinary Center for Complex Systems, University of Bonn, Bonn, Germany, **4** Fakultät für Mathematik, Ruhr-Universität Bochum, Bochum, Germany

Abstract

We investigate interaction networks that we derive from multivariate time series with methods frequently employed in diverse scientific fields such as biology, quantitative finance, physics, earth and climate sciences, and the neurosciences. Mimicking experimental situations, we generate time series with finite length and varying frequency content but from independent stochastic processes. Using the correlation coefficient and the maximum cross-correlation, we estimate interdependencies between these time series. With clustering coefficient and average shortest path length, we observe unweighted interaction networks, derived via thresholding the values of interdependence, to possess non-trivial topologies as compared to Erdös-Rényi networks, which would indicate small-world characteristics. These topologies reflect the mostly unavoidable finiteness of the data, which limits the reliability of typically used estimators of signal interdependence. We propose random networks that are tailored to the way interaction networks are derived from empirical data. Through an exemplary investigation of multichannel electroencephalographic recordings of epileptic seizures – known for their complex spatial and temporal dynamics – we show that such random networks help to distinguish network properties of interdependence structures related to seizure dynamics from those spuriously induced by the applied methods of analysis.

Citation: Bialonski S, Wendler M, Lehnertz K (2011) Unraveling Spurious Properties of Interaction Networks with Tailored Random Networks. PLoS ONE 6(8): e22826. doi:10.1371/journal.pone.0022826

Link Identification: Temporal Sampling



– time scales of the system

– choices to make:
- observation time
- (temporal) sampling frequency

→ determines length of time series

temporal oversampling:

→ temporal correlations

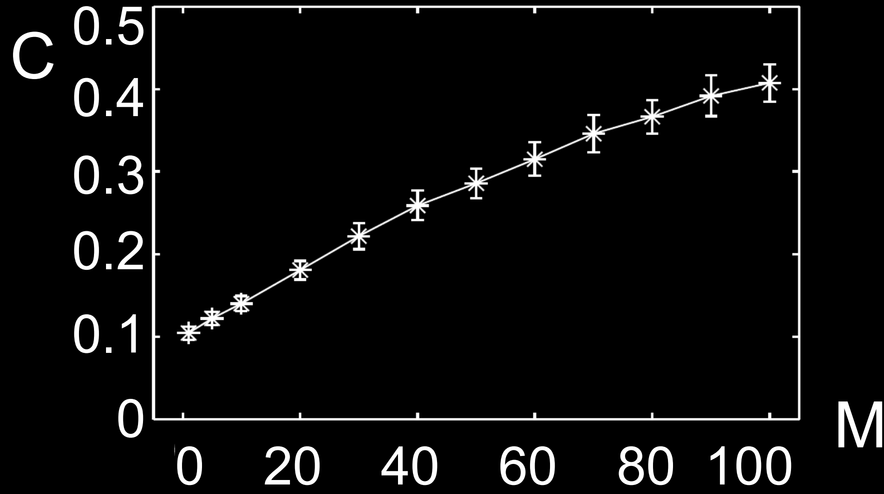
Link Identification: Temporal Sampling

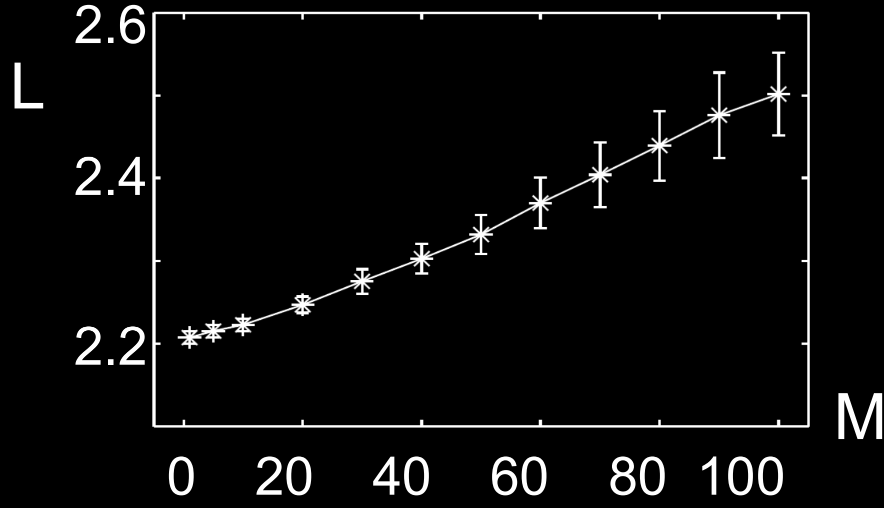
– N = 100 time series
(T = 500 sampling points)

– for each time series:
  – values independently drawn
  from some probability distribution
  – temporal correlations induced
  by moving average of size M

– signal interdependence:
abs. value of correlation coefficient

– binary networks via thresholding
(link density = 0.1)





Link Identification: Temporal Sampling

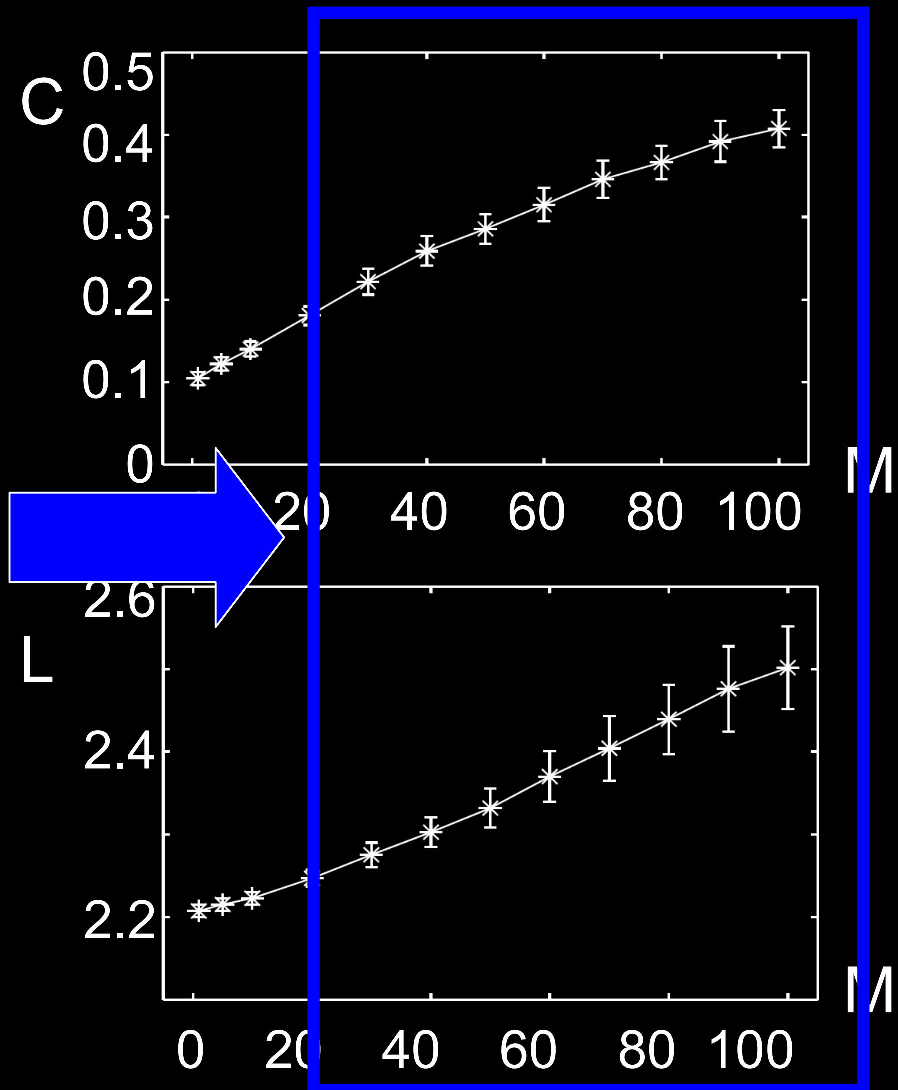
– N = 100 time series
(T = 500 sampling points)

– for each time series:
– values independently drawn
fror
– tem
by r

– sign
abs. value of correlation coefficient

– binary networks via thresholding
(link density = 0.1)

small-world networks
($C/C_r > 2$, $L/L_r < 2$)



S. Bialonski, M Wendler & KL
***Plos One** 6, e22826, 2011*

Link Identification: Temporal Sampling

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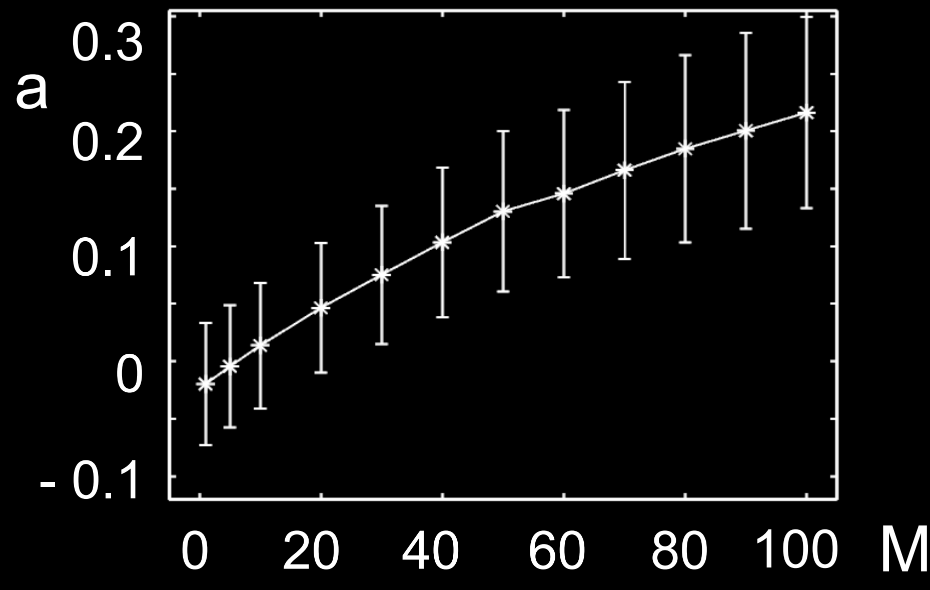


– signal interdependence
  abs. value of correlation coefficient

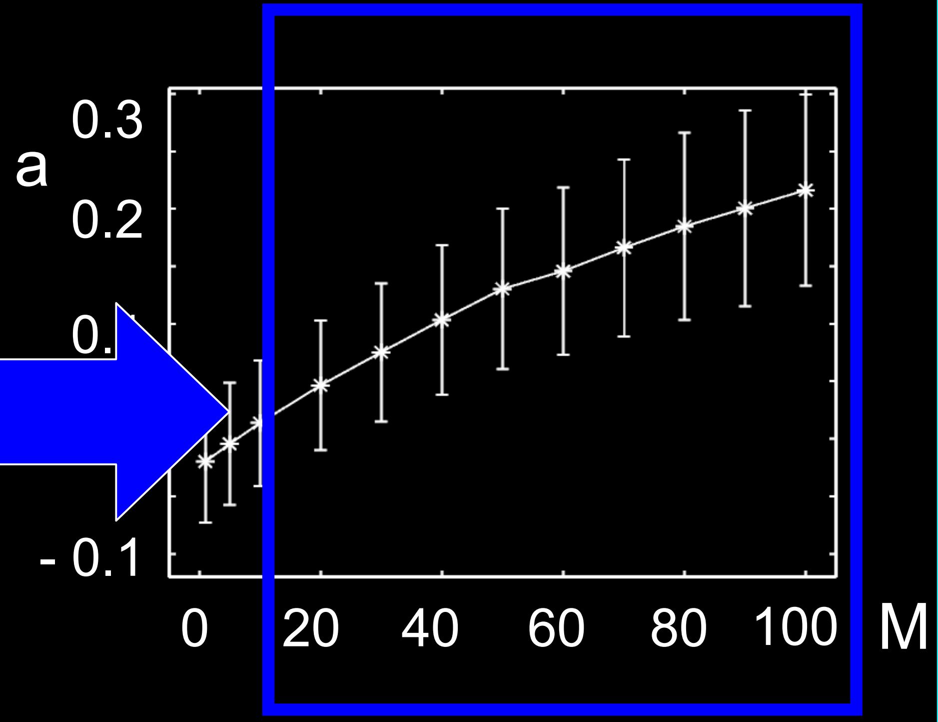
– binary networks via thresholding
  (link density = 0.1)

Link Identification: Temporal Sampling

– N = 100 time series
(T = 500 sampling points)

– for each time series:
– value
from
– temp
by mo

assortative networks
(a>0)



– signal interdependence
abs. value of correlation coefficient

– binary networks via thresholding
(link density = 0.1)

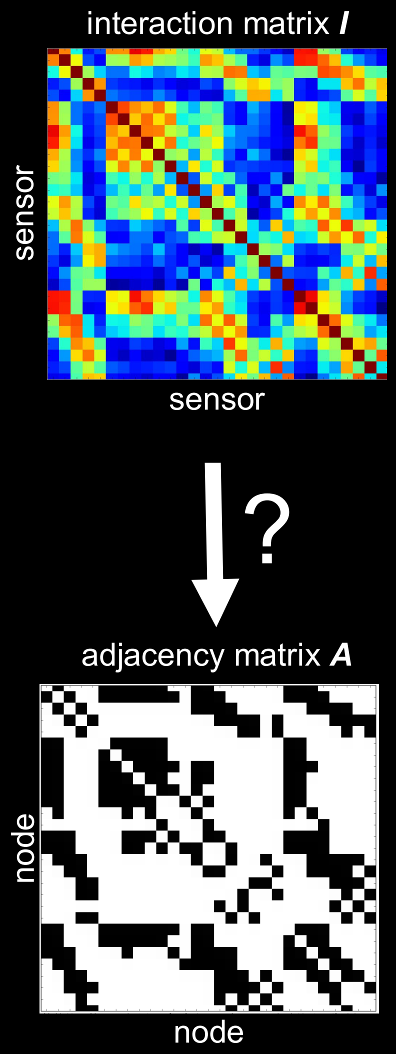
Link Identification: Measuring Interactions

binary networks

- *thresholding*
  - criteria for threshold selection
  - uniqueness of threshold
  - “reliability” of links

- *significance testing*
  - choice of significance level
  - multiple testing problem
  - “reliability” of links

which to choose? …. other methods ?

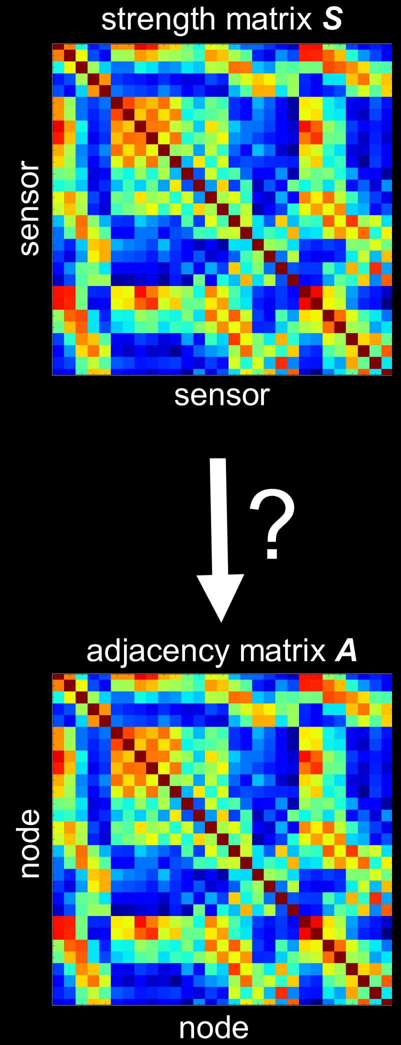


Link Identification: Measuring Interactions

weighted networks

- est. strength of interaction (*s*)
  - ~ coupling strength (*k*);
  - ~ structural properties (σ)
  - ~ *other?*
- *s = F(k, σ,…)*
- how does *F* look like?
- given *F*, resolve "weak" ("strong") couplings

- which nontrivial properties of data are captured by network measures?



Link Identification: Measuring Interactions

link ↔ interactions

assumption: (sub-)systems interact!

probing (active) vs. observing (passive)

probing (*actio est reactio*)
repeated measurements,
limited number of data points,
nonstationarity, “true” dynamics?

observing (if probing is not possible)
large amount of data, nonstationarity

Link Identification: Measuring Interactions

(linear/nonlinear) time series analysis techniques
- statistical approaches
- approaches in time/frequency domain
- information theoretical approaches
- state-space-based approaches
- Fokker-Planck-formalism
- …

requirements
- different aspects of dynamics / synchronization phenomena
- robustness against noise/measurement errors
- strength and/or direction of interaction (other properties?)
- computing time (field data analyses)
- interpretability (causality? direct vs. indirect; common sources)

Link Identification: Measuring Interactions

- mostly bivariate analysis techniques

- applied to all pairwise interactions ..… justified ?

- impact of indirect interactions (other confounders ?)
    → partial measures ….. only recently
        ….. reliable ? …..widely applicable ?

- *true* multivariate approaches
    MVAR, random matrix theory ..… rare ….. reliable ?
    …..other ?
    wide applicability not yet shown

Link Identification: Confounding Variables

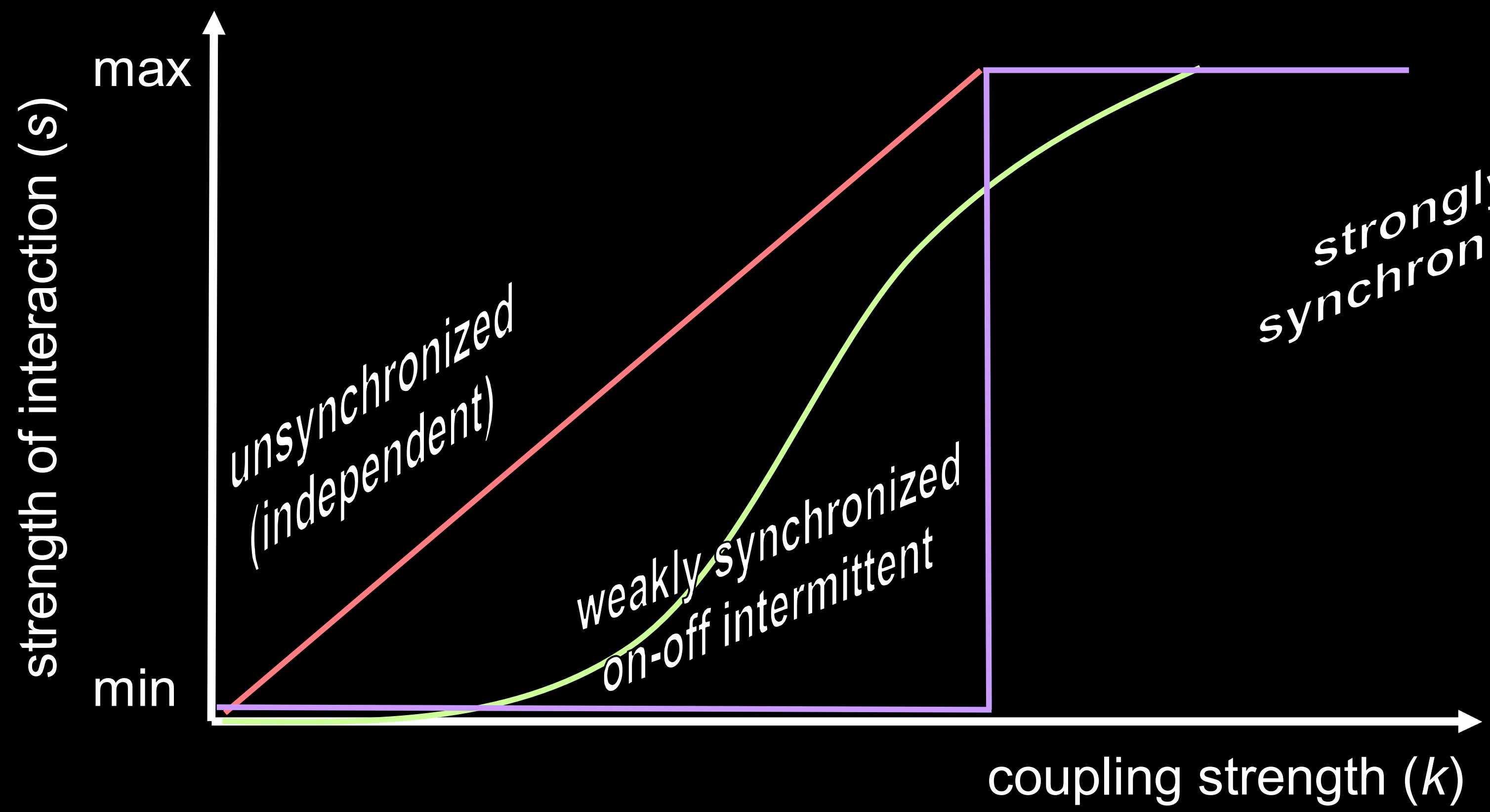
- node dynamics
  different natural frequencies, noise distributions, dimensionalities,..
  more active vs. more passive system
- finiteness of data (*N* and *T*)
- univariate properties of dynamics (e.g. power spectral contents)
- time scales (node dynamics, coupling, due to sampling)
- bias due to time series analysis techniques

- incomplete measurements
  direct/indirect interactions, differentiability?
  common sources

- other ?

Strength of Interactions and Couplings

active experiment: coupling function known, coupling strength *k* adjustable



… and with unknown systems?

Confounding Variables: Common Sources

mean phase coherence

$$R = \left| \frac{1}{N} \sum_{j=1}^{N} \exp\left(i(\Phi_a(j) - \Phi_b(j))\right) \right|.$$

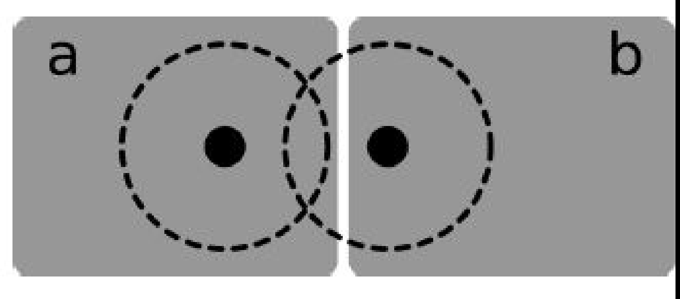
phase lag index

$$P = \left| \frac{1}{N} \sum_{j=1}^{N} \mathrm{sgn}[\sin(\Phi_a(j) - \Phi_b(j))] \right|.$$

weighted phase lag index

$$P_{\mathrm{w}} = \frac{\left| \sum_{j=1}^{N} \sin\left(\Phi_a(j) - \Phi_b(j)\right) \right|}{\sum_{j=1}^{N} |\sin(\Phi_a(j) - \Phi_b(j))|}.$$

Modeling impact of common sources



superposition with $\alpha \in [0,1)$

$$\tilde{s}_a(j) = (1-\alpha)s_a(j) + \alpha s_b(j),\ \tilde{s}_b(j) = s_b(j), \text{ or}$$
$$\tilde{s}_b(j) = (1-\alpha)s_b(j) + \alpha s_a(j),\ \tilde{s}_a(j) = s_a(j),$$

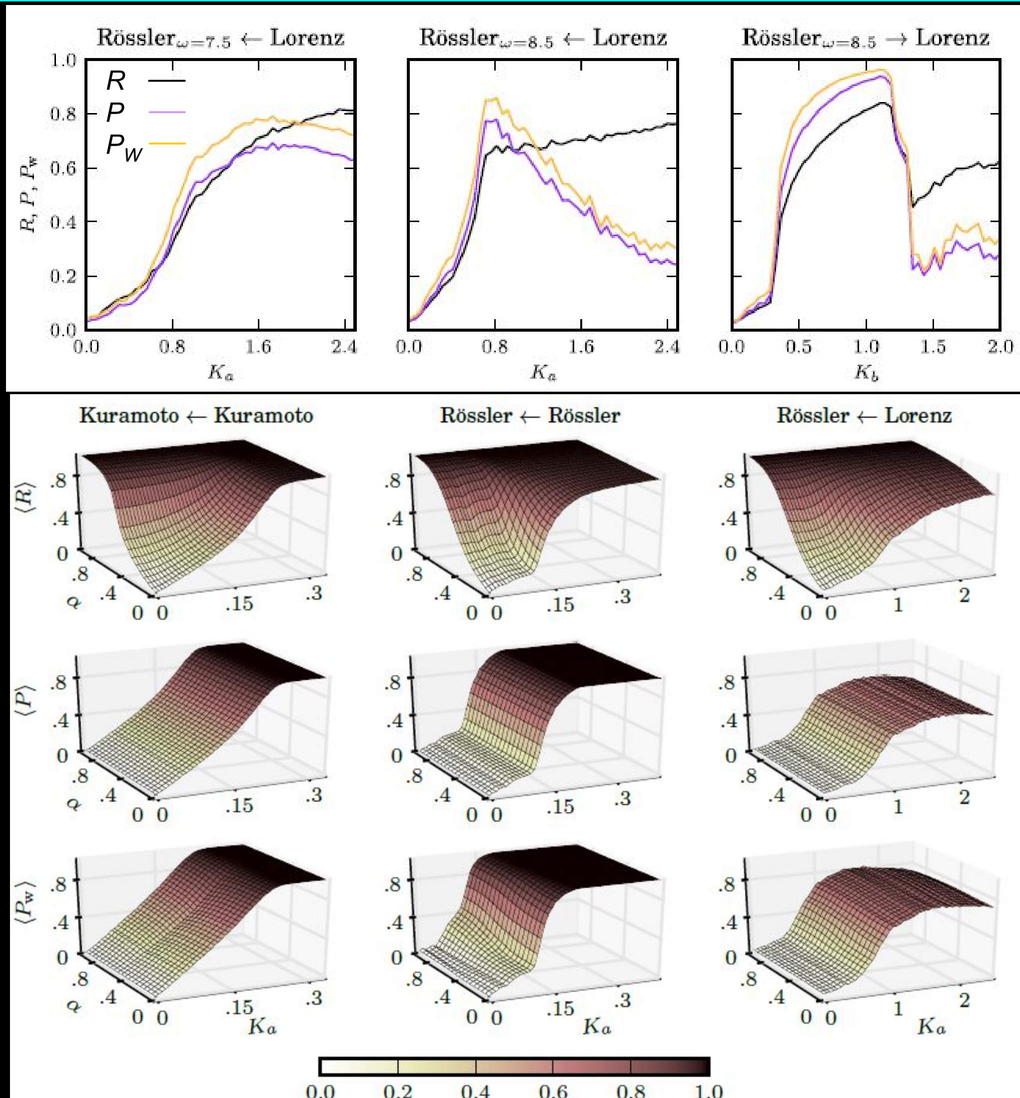
mixing with $\alpha \in [0,0.5)$

$$\tilde{s}_a(j) = (1-\alpha)s_a(j) + \alpha s_b(j),$$
$$\tilde{s}_b(j) = (1-\alpha)s_b(j) + \alpha s_a(j),$$

*F. Mormann et al., **Physica D** 144, 358, 2000*
*C. J. Stam et al. **Hum Brain Mapp** 28, 1178, 2007*
*M. Vinck et al. **NeuroImage** 55, 1548, 2011*

*S. Porz, M. Kiel & KL **Chaos** 24, 033112, 2014*

Confounding Variables: Common Sources



coupled oscillator models

R

- strongly affected by CS
- more robust to noise (meas. + dyn.)

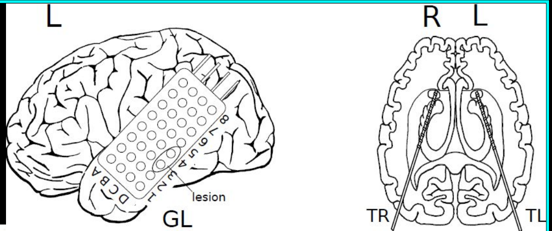
P and P_W

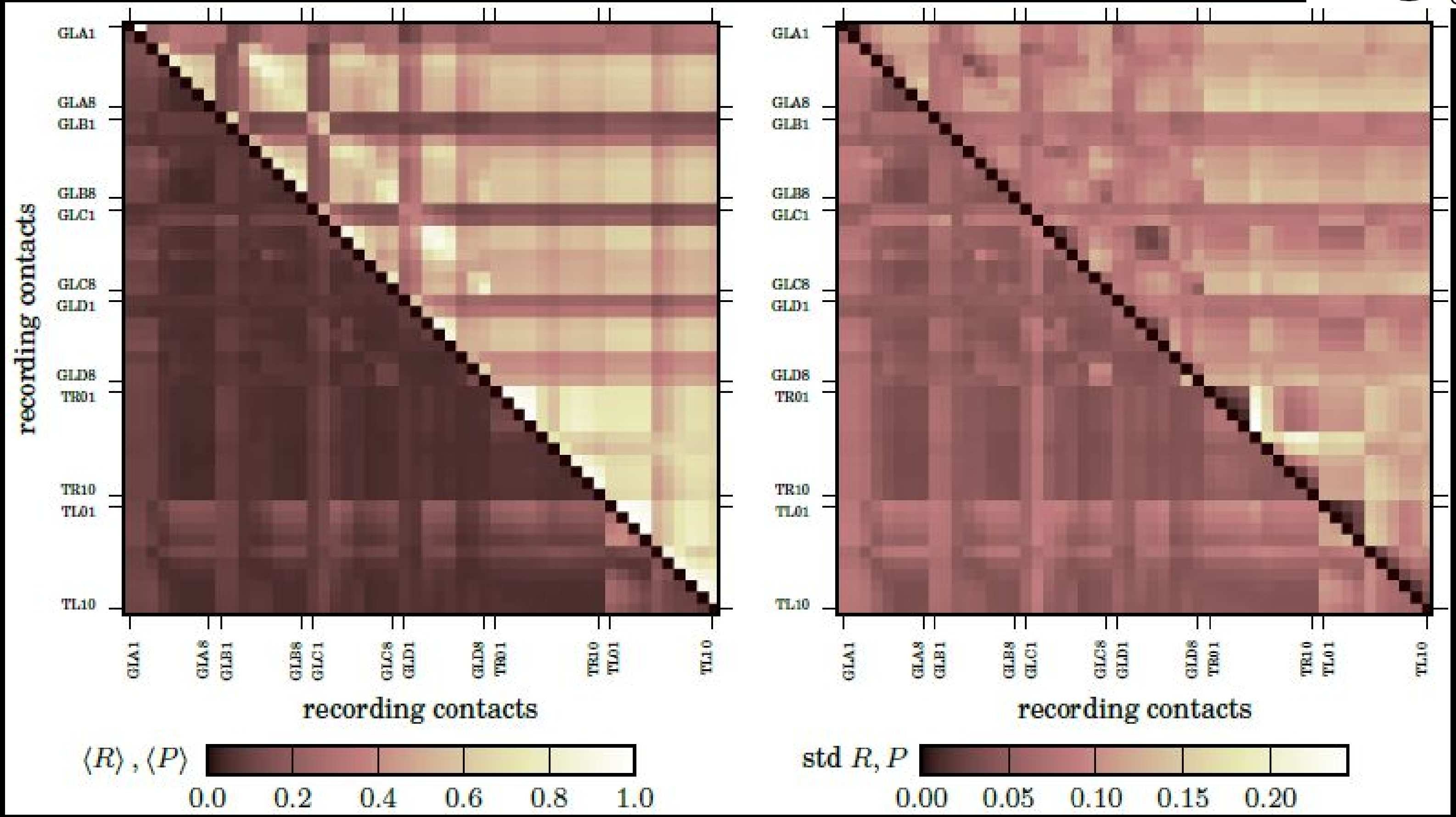
- less influenced by CS
- less robust to noise (compared to R)
- dependent on oscillator type and direction of coupling !
- no advantage of P_W over P

S. Porz, M. Kiel & KL ***Chaos*** *24, 033112, 2014*

Confounding Variables: Common Sources

- 20 h iEEG recording, seizure-free interval
- moving-window analysis (20,48 s; 4096 data points)





Ref-Electr.:
GLA1+GLA2

SOZ:
GLA6

Lesion:
GLD3+GLD4

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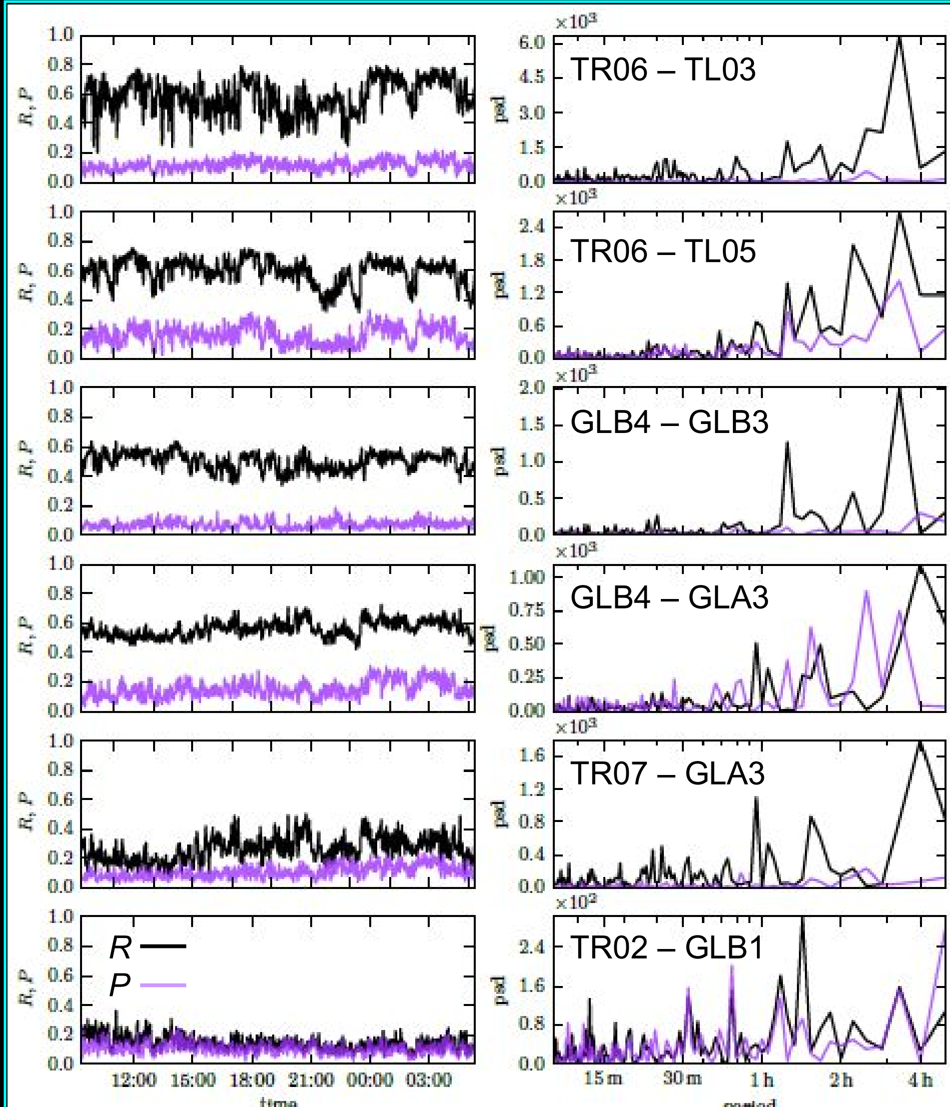
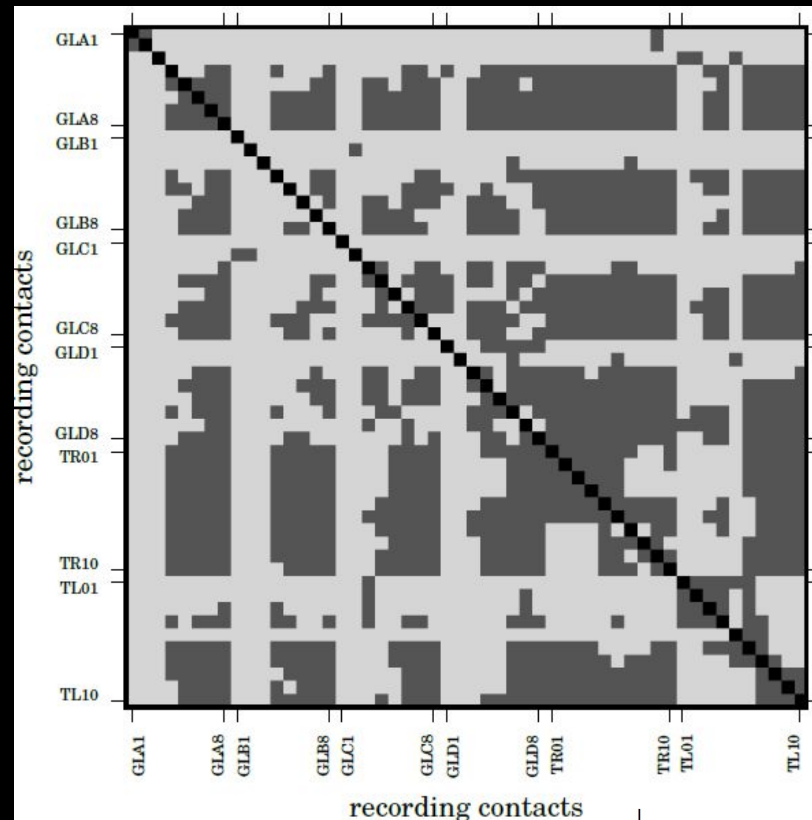
Confounding Variables: Common Sources

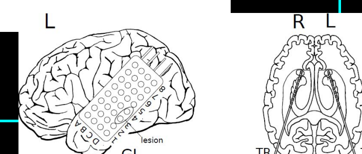


equivalence (light gray)
non-equivalence (dark gray)
of power spectra



$R - P$

$R - P_W$



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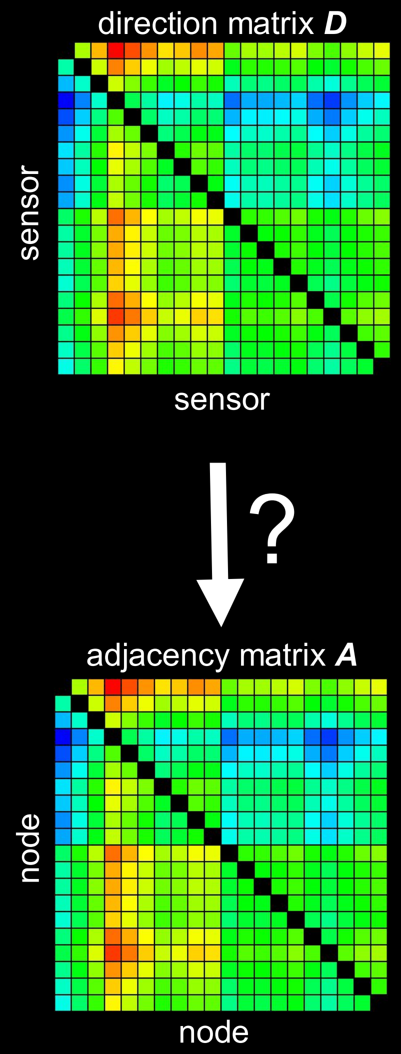
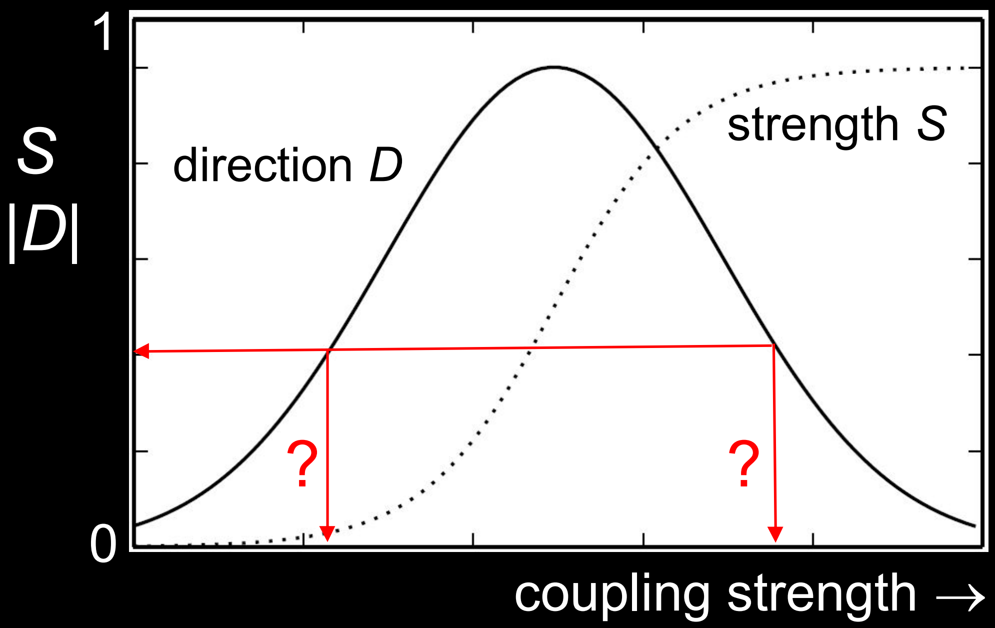
Link Identification: Measuring Interactions

directed networks

- est. direction of interaction (*d*)
  - ~ coupling direction (Δ)
  - ~ structural properties (σ)
  - ~ coupling strength (*k*)
  - ~ node dynamics
  - ~ *other?*
- *d = F*(Δ, σ, *k*, …)
- *F* ?
- resolve "correct" directionality / causality
- distinguish directionality *@k=0* and *@k=max*
- which nontrivial properties of data are captured by network measures?



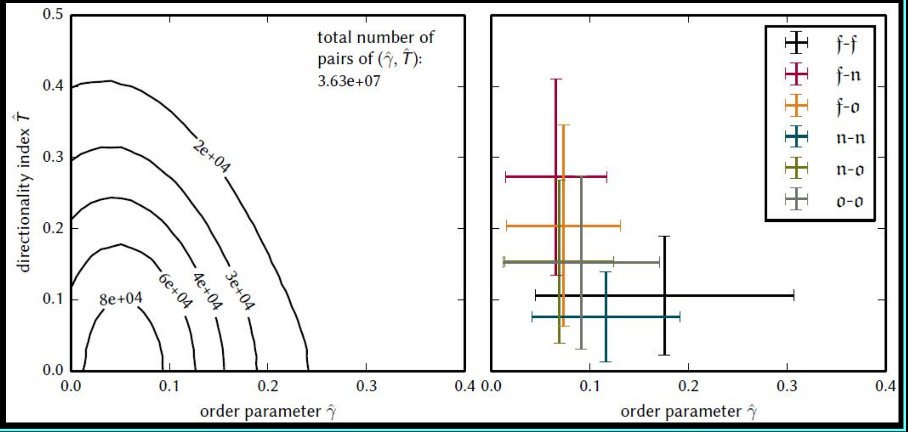
Measuring Directional Interactions



influencing factors:

- number of data points
- noise
- system properties
- uncoupled vs. fully coupled

evaluate both
strength ***and*** direction

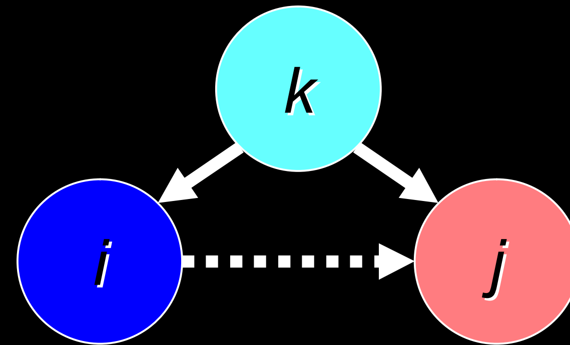


H. Osterhage et al., **Phys Rev E** 77, 011914, 2008;
KL & H. Dickten, **Phil Trans Roy Soc** A 373, 20140094, 2015

Confounding Variables: Indirect Interactions

direct interaction

indirect interaction



(Pearson) correlation coefficient

$$r_{ij} = \frac{\mathrm{cov}(i,j)}{\sqrt{\mathrm{var}(i)\mathrm{var}(j)}}$$

partial correlation coefficient

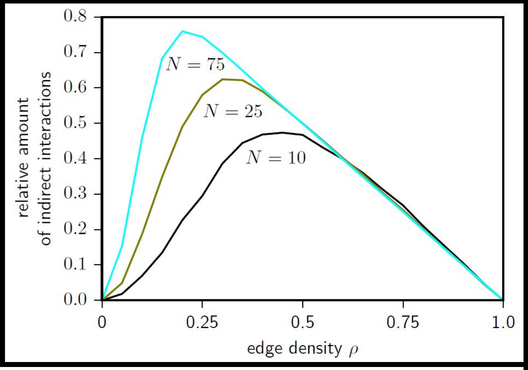
$$r_{ijk} = \frac{r_{ij} - r_{jk} r_{ik}}{\sqrt{(1-r_{ik}^2)(1-r_{jk}^2)}}$$

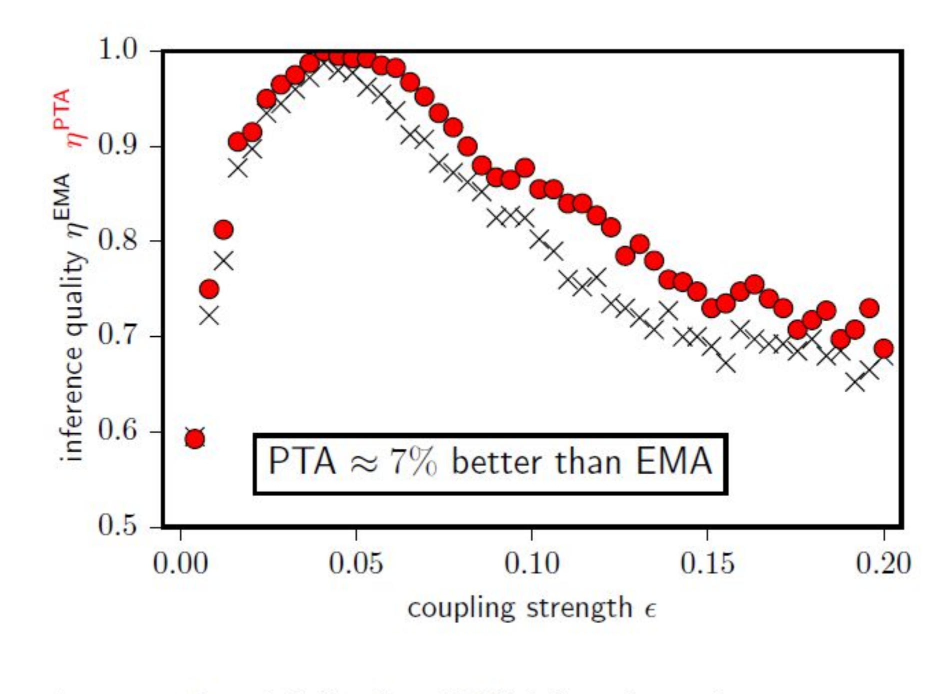
similar approaches for other measures:

(renormalized) partial directed coherence,
partial (symbolic) transfer entropy,
partial phase dynamics, ….

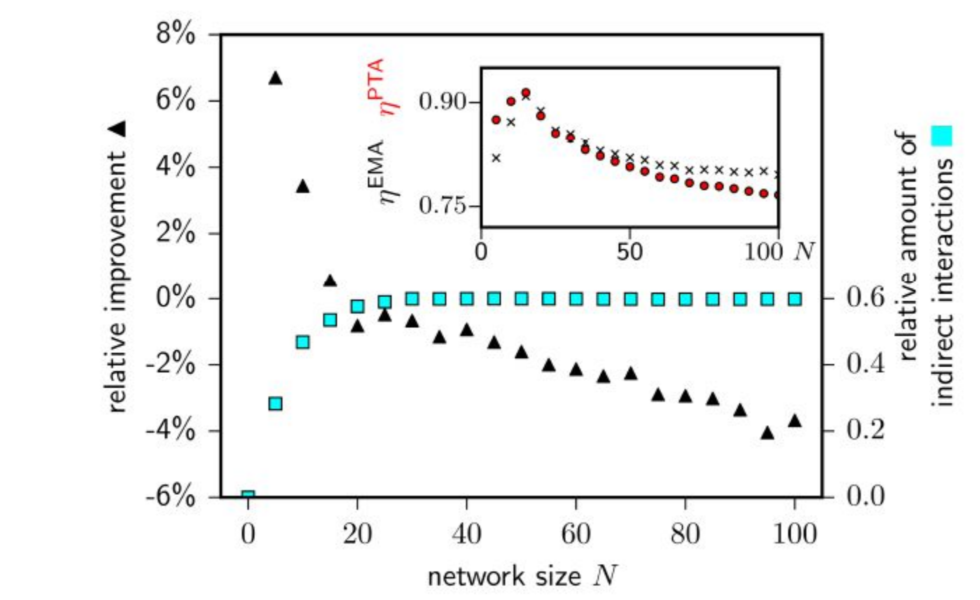
Confounding Variables: Indirect Interactions

- network of diffusively coupled Rössler oscillators
- adjustable: network size, coupling strength and topology, edge density, amount of indirect interactions





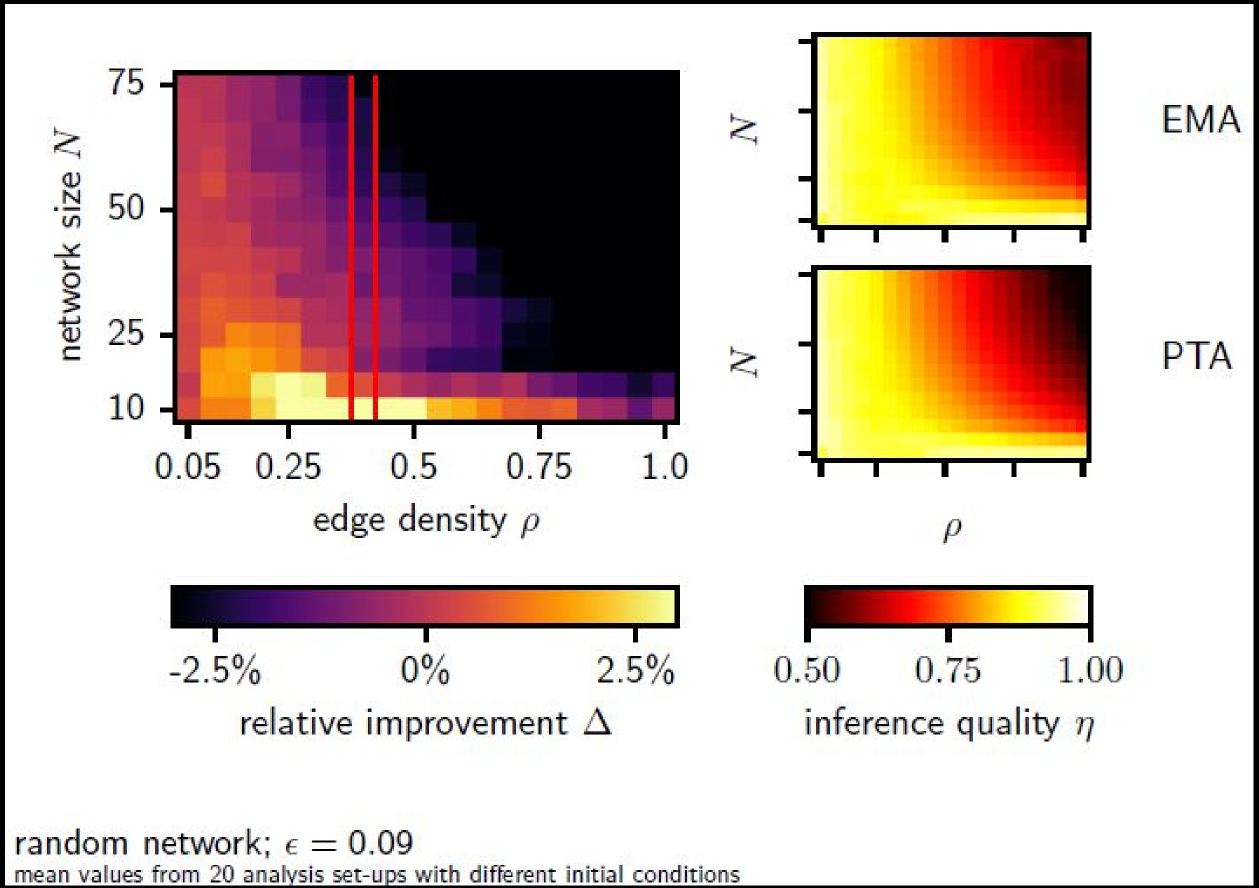
random network; ρ=0.4, $N = 5 \rightarrow$ 28.5% indirect interactions
mean values from 20 analysis set-ups with different initial conditions



$$▲ = \frac{\eta^{\text{EMA}} - \eta^{\text{PTA}}}{\eta^{\text{EMA}}}$$

random network; ρ=0.4, $\epsilon = 0.09$
mean values from 20 analysis set-ups with different initial conditions

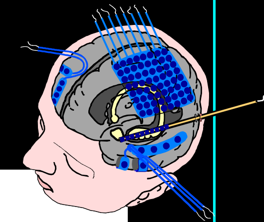
Confounding Variables: Indirect Interactions



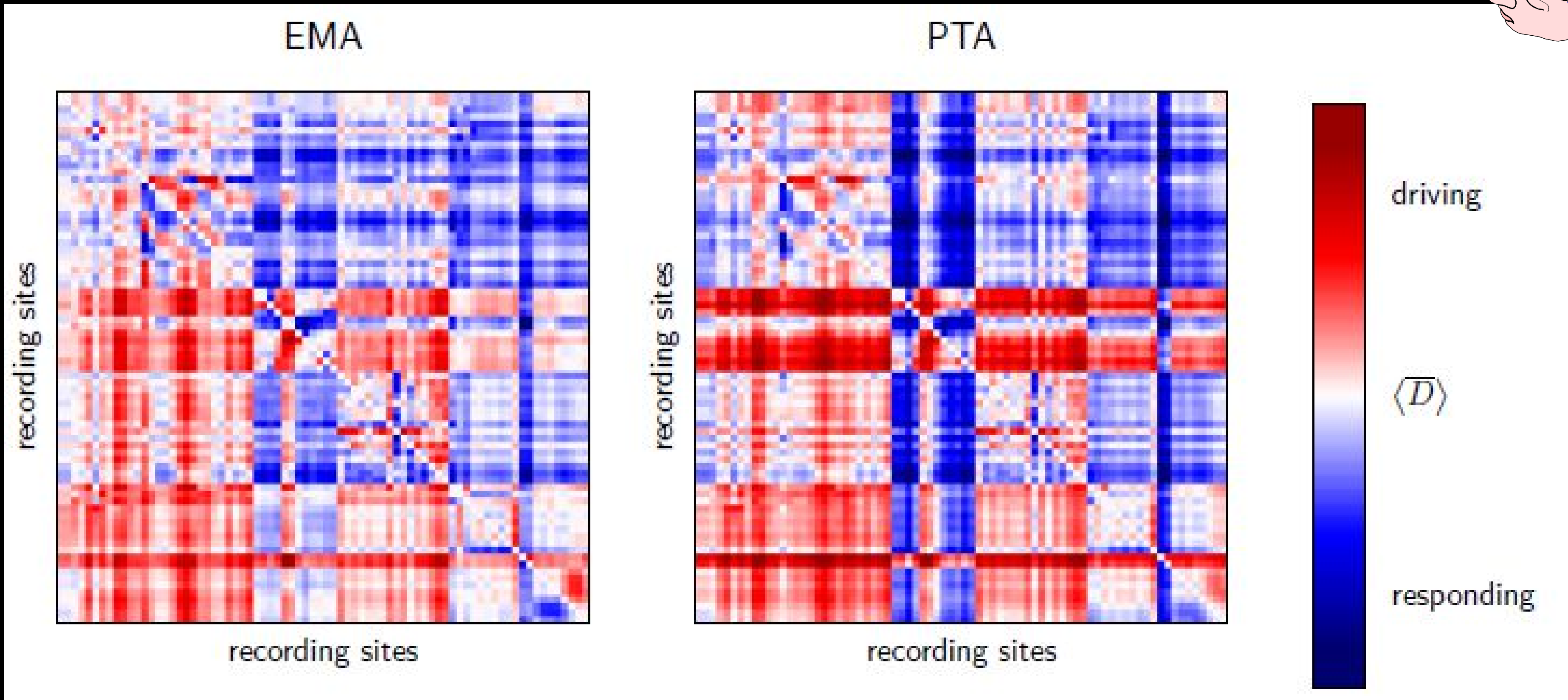
similar findings for:
- small-world networks
- scale-free networks

partialized approach (slightly) more efficient
for small networks or for large but sparse networks

Confounding Variables: Indirect Interactions



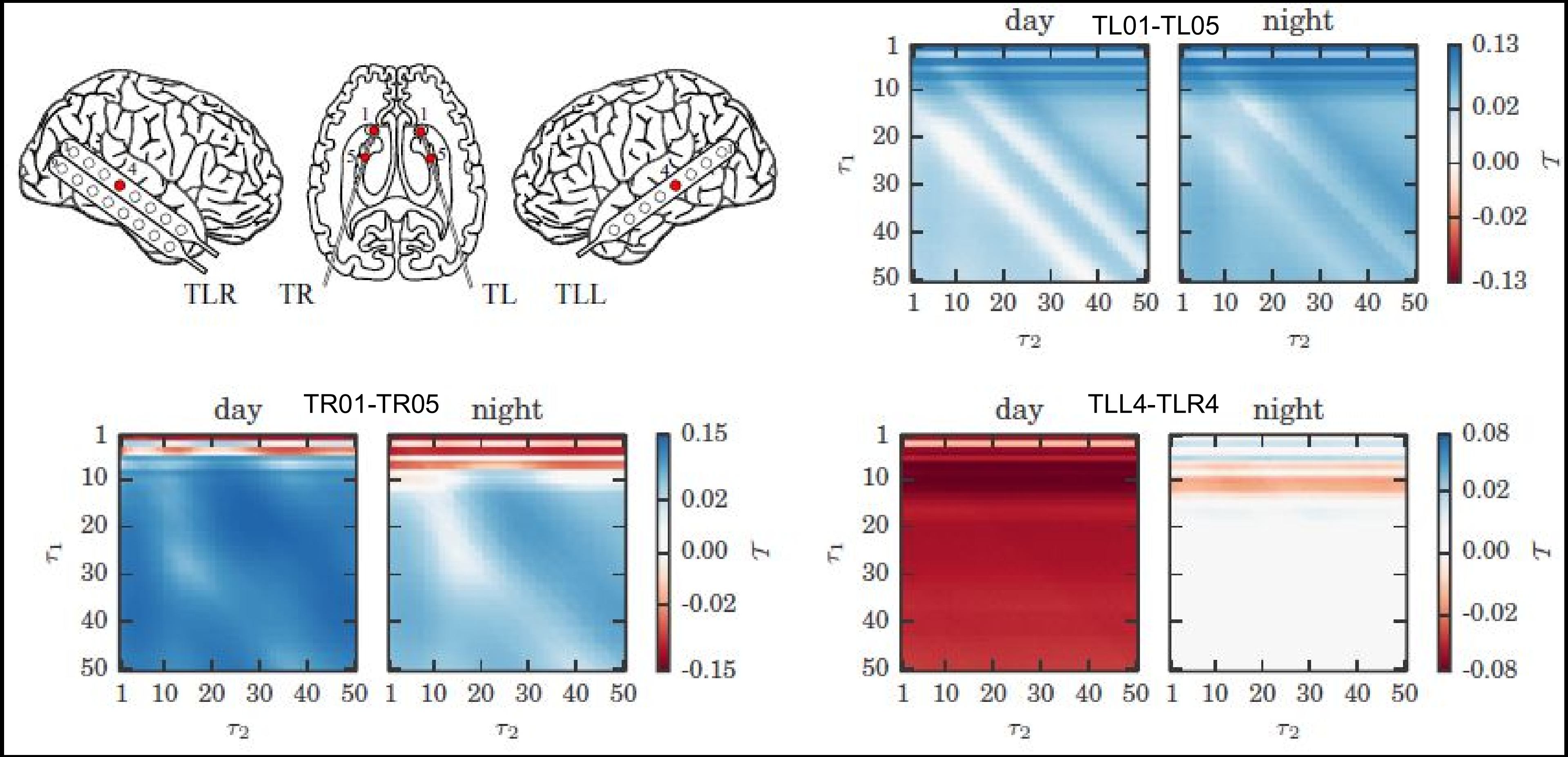
intracranial EEG recording (76 hrs) from an epilepsy patient
76 recording sites, moving-window phase-based directionality estimation



consistent estimation of directionality: 95 % match

$$\overline{\mathcal{D}}_{k,l} = \frac{\mathcal{D}_{k\to l} - \mathcal{D}_{l\to k}}{\mathcal{D}_{k\to l} + \mathcal{D}_{l\to k}}$$

Delayed Directed Interactions



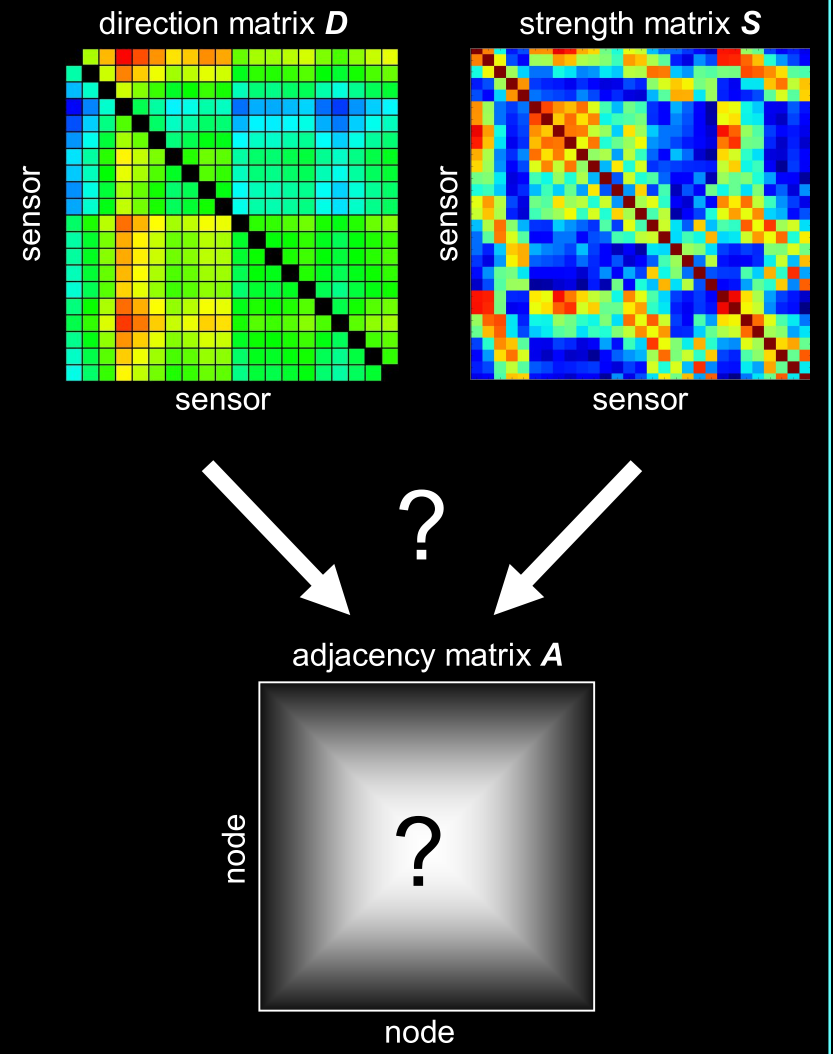
- 36 h iEEG recording, patient with right MTLE
- averaged delayed symbolic transfer entropy
- driving post. MTL -> ant. MTL
- delay times: ~ 50 - 60 ms

*H Dickten & KL, **Phys Rev E** 90, 062796,2014*

Link Identification: Measuring Interactions

weighted and directed networks

- as before
- measures that can do both?
- if not, how to combine?



Interpretation of findings

comparison of empirical networks

- how similar are empirical networks?
  group statistics, detection of changes,
  temporal networks, …

- which “distance” measures to choose

- what can trivially be expected?
  … how to differentiate?

- is the network approach really necessary ??

Interpretation of findings

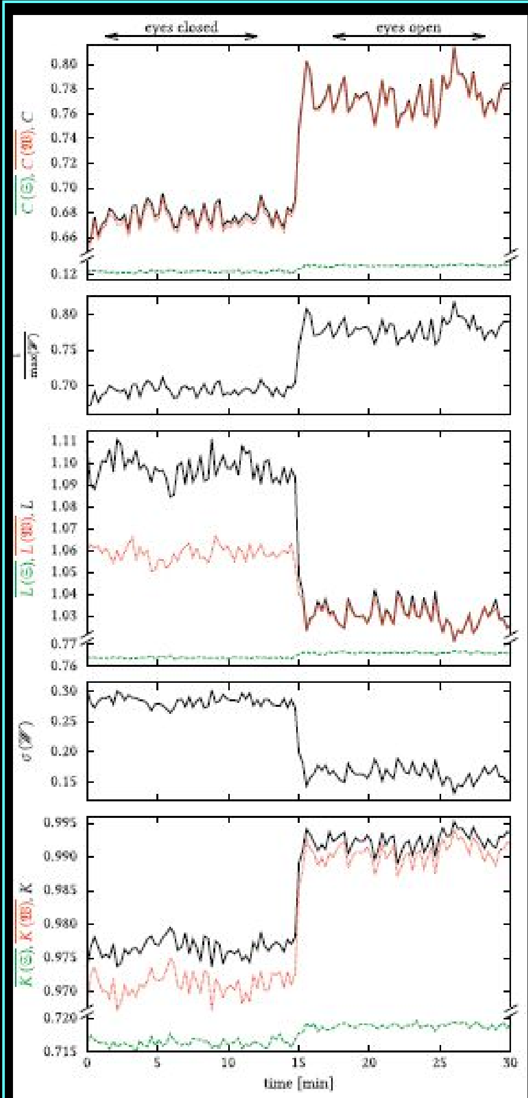
null models and surrogates

analytical results for random graphs or lattices
(with prescribed properties, e.g. degree distr.)

surrogate networks from Monte Carlo simulations
preservation of arbitrary properties, define constraints,
null hypothesis testing

time series surrogates
phase-randomization, IAAFT, …

Interpretation of findings



weighted functional networks:

- trivial properties of link weights or nodes strengths influence *C* and *L*

- surrogate networks preserve link weight and/or node strength

- surrogate normalization
  improve differentiability
  improve interpretability

$$C := \binom{n}{3}^{-1} \sum_{i=1}^{n} \sum_{j=1}^{i-1} \sum_{k=1}^{j-1} \frac{\sqrt[3]{W_{ij} W_{jk} W_{ki}}}{\max(W)}$$

$$L := \binom{n}{2}^{-1} \sum_{i=1}^{n} \sum_{j=1}^{i-1} \min_{l} \min_{P \in \mathcal{P}_{ij}^{l}} \sum_{k=1}^{l-1} W_{P_k P_{k+1}}^{-1},$$

*G. Ansmann & KL, **Phys. Rev. E** 84, 026103, 2011;*
***J Neurosci Methods** 208, 165, 2012*

Interpretation of findings

if networks do not differ, what does this mean?

- methodology
- statistical issues
- …

if networks differ, what does this mean?

- relation to system dynamics
- other possible explanations
- …

What's next?

- ignore
- be careful (particularly when using toolboxes)
- interpret only changes
- test inference sensitivity using numerical simulations
- model both system dynamics and observation process

- improve methodologies!