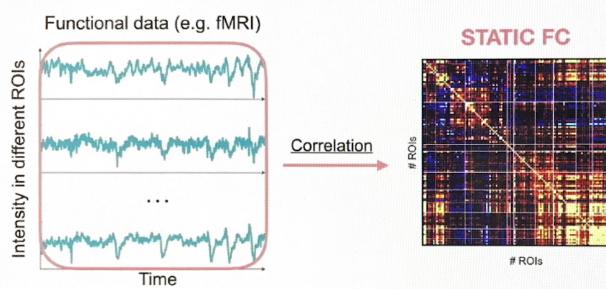


Time - Varying Connectivity in rs-fMRI

Functional Connectivity (FC) - statistical dependence b/w functional signals from diff. brain locat's



Static FC

→ AVERAGED
(only 1 measure for
entire Time length)

↓
MEMORYLESS

(invariant to reordering
time points)

⇒ Time -Varying (TV) FC

- Sliding windows
- CAPs
- etc.

⇒ Dynamic FC (dFC)

- AR Models
- iCAPs
- spectral
- etc.

Methodological Framework

▪ Time-varying FC approaches

1.1 ▪ Sliding-window FC analysis

- Overcoming parcellation limits
- Overcoming window limits

→ commonly used

1.2 ▪ Beyond the window: Frame-wise analysis

- LEiDA
- Coactivation patterns (CAPs)

▪ Dynamic FC approaches

2.1 ▪ Revisiting frame-wise analysis: innovation-driven coactivation patterns (iCAPs)

2.2 ▪ Temporal modeling: autoregressive models

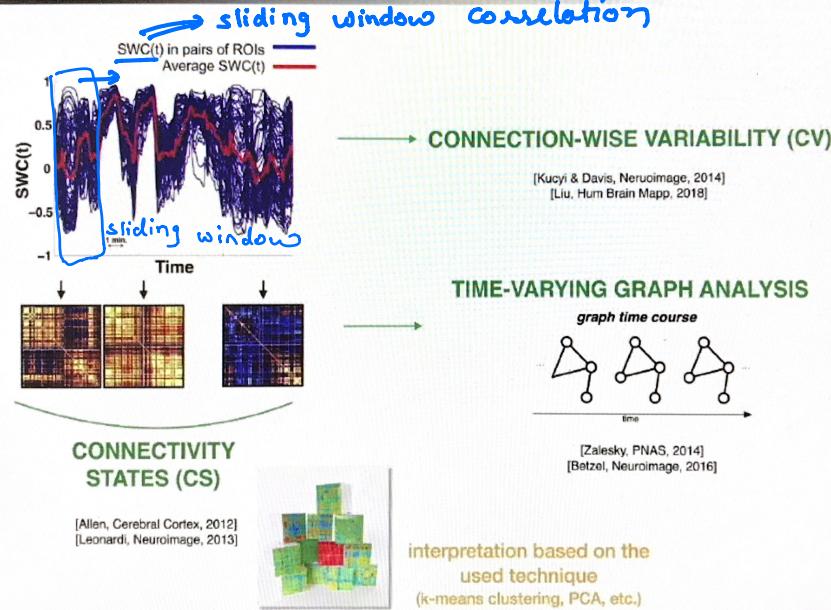
- Dynamic mode decomposition

▪ Structure - Function coupling

3.1 ▪ Graph Signal Processing

3.2 ▪ Whole-brain computational models

1.1 Time-varying Functional Connectivity



Overcoming TV FC limitations

- choice window parameters
 - window length (W)
- trade off**
- SENSITIVITY**

W short enough not to miss REAL FC fluctuations

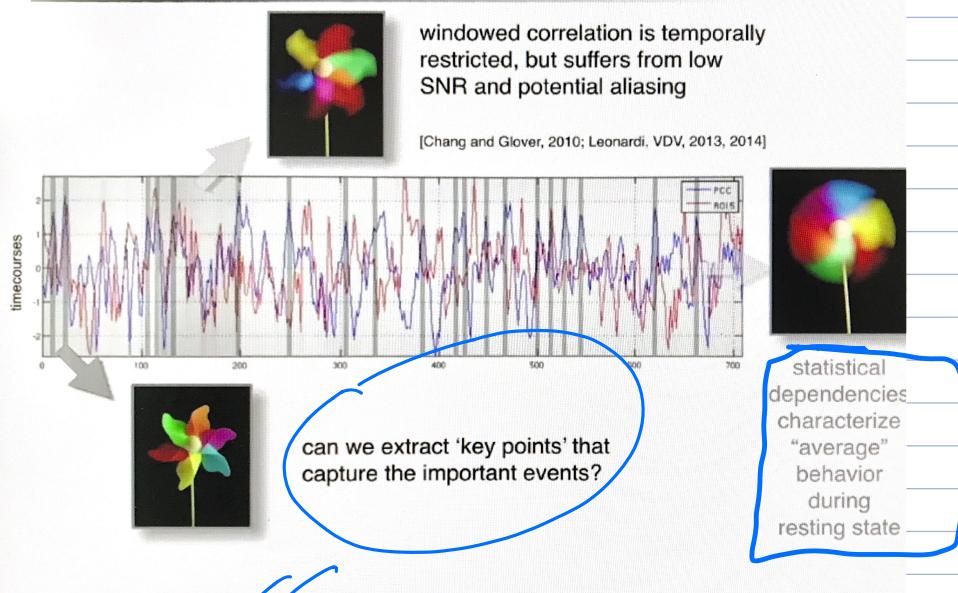
SPECIFICITY

W long enough to detect ONLY REAL fluctuations

$W > 1 / f_{\min}$

[Leonardi & Van De Ville, 2015]
- window shape
 - RECTANGULAR
 - TAPERED
 - choice of parcellation (functional, anatomical, multimodal, ICA)

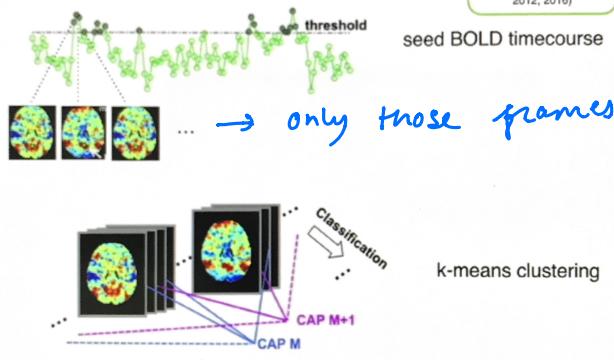
From sliding window to single frames



Frame-wise analysis

- Coactivation Patterns (CAPs) [Liu and Dux, 2013]

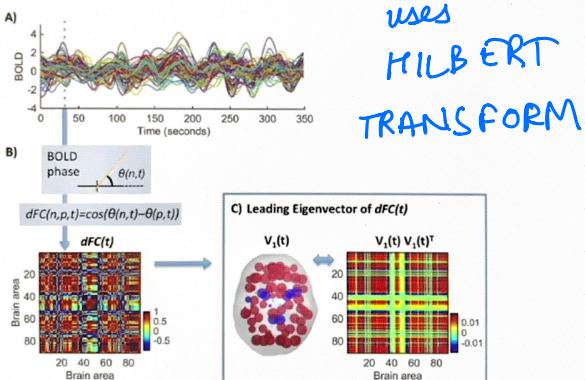
Inspired by Point Process Analysis (PPA)
(Tagliazucchi et al., 2011, 2012, 2016)



which are above threshold

Frame-wise analysis

- Leading Eigenvector Dynamics Analysis (LEiDA)



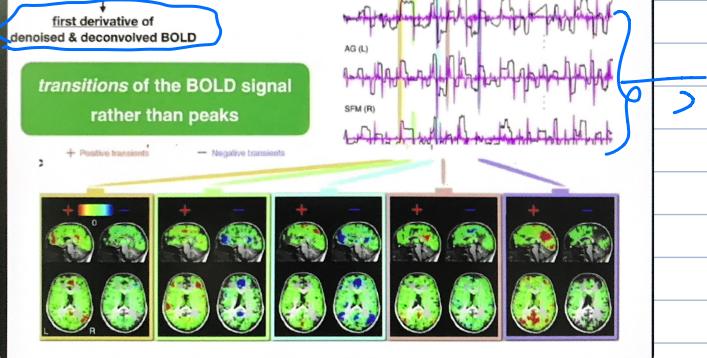
[Cabral, Scientific Reports, 2017]

2.1

Revisiting frame-wise analysis

- Innovation-driven CAPs (iCAPs) [Karanoglu & Van De Ville, 2015]

Innovation signals entering the clustering

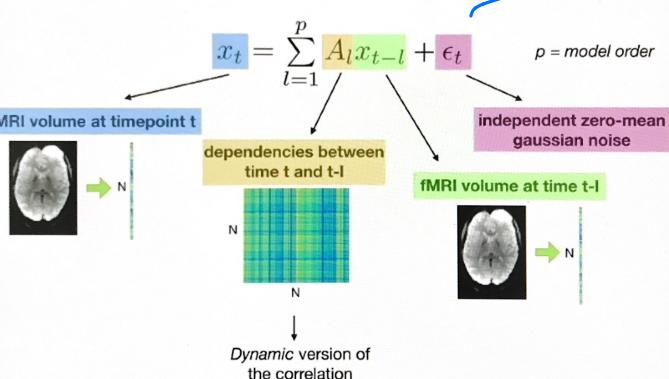


looks Relatable! :)

2.2

Temporal Modeling for dFC

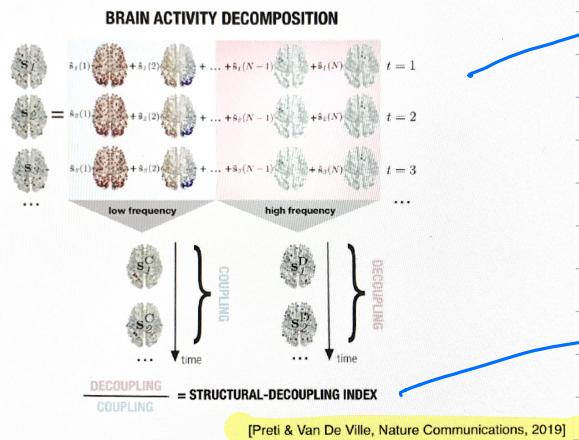
Autoregressive models



learned it in
Time series Analysis's
course

GSP to explore coupling function - structure

3:1



Same Approach used by that LSD
harmonics paper (look Oral
Awareness... notes)

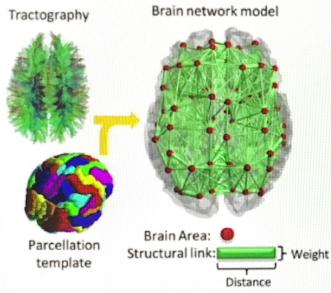
→ It has Behavioral significance

→ TODO

3.2

Dynamic Function on static structural backbone

- *Whole-brain computational models*



Simulated data should satisfy:

- **Spatial validation**
FC spatial patterns should be reproduced
 - **Spectral validation**
The whole frequency spectrum of RS rhythms should be addressed
 - **Temporal validation**
FC temporal evolution should be replicated

[Honey, PNAS, 2009]

[Cabral, Neuroimage, 2017]

[Deco, J. Neurosci., 2011]

Null models of fMRI time series

→ Basically, we are trying to make a null model of data

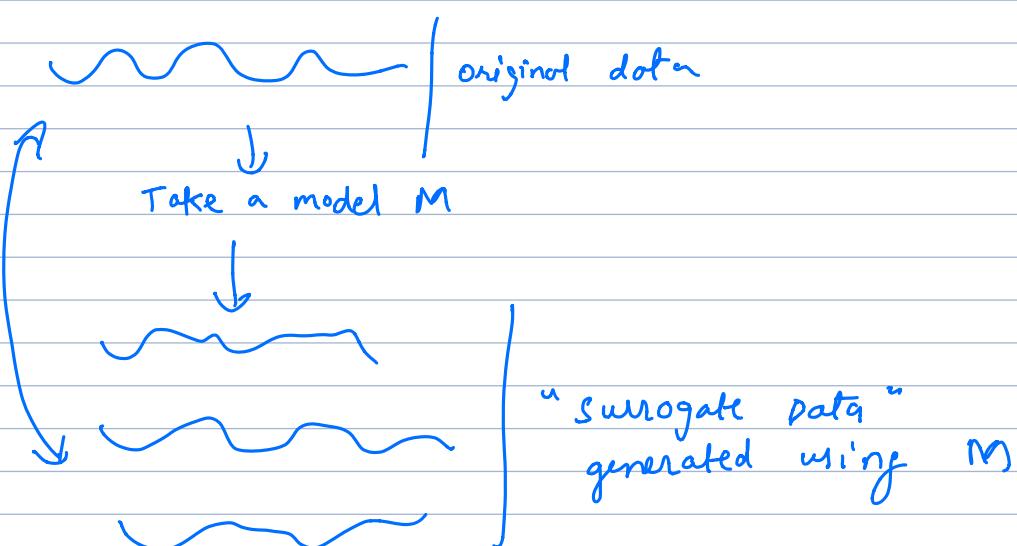
Compare a measure m^n in original vs surrogate

if $m_0 \neq m_S$

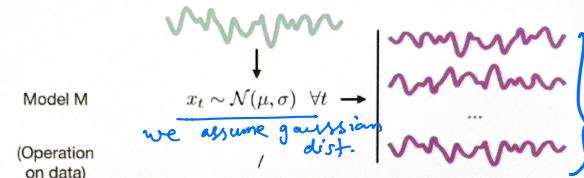
11

Model M is insufficient

if $m_o = m_s \Rightarrow$ No evidence that m is insufficient



Example 1: univariate Gaussian null



Data properties preserved

μ, σ

Example of test

- Compare counts of threshold crossing
- Compare kurtosis
- Etc. (but nothing involving μ or σ)



If $m_o \neq m_s$

→ Data cannot be fully explained by a Gaussian
 μ, σ are not sufficient to fully characterise the data

Conclusion

if $m_o = m_s$

→ No evidence that data cannot be explained by a gaussian dist.

generated using gaussian dist.

Example 2: shuffling

→ Nice example

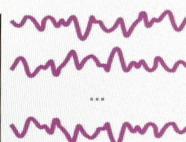


Model M

(Operation on data)

$x_t \sim D + t$

Shuffling all time points →



Q1. Which null-model M is associated to this operation?

- A. The same as in example 1 (data is univariate Gaussian), using another procedure
- B. Data is i.i.d., with a distribution matched to the original one
- C. Data follows a first-order autoregressive model

Example 2: shuffling

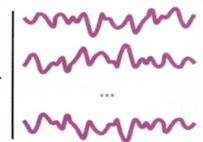


Model M

(Operation on data)

$x_t \sim D \quad \forall t$

Shuffling all time points →



Data properties preserved

All statistics computed from D : μ, σ , kurtosis, etc.

Example of test

- Compare counts of threshold crossing
- Compare autocorrelation
- Etc. (but nothing involving D)

Conclusion

If $m_o \neq m_s$

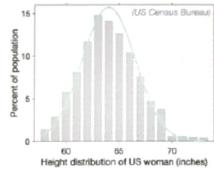
→ Data contains some form of autocorrelation
 If $m_o = m_s$
 → No evidence that temporal ordering is important



Results require careful interpretation

- Null-hypothesis testing ≠ 'relevance' testing
- Stationarity is usually assumed in null-models
 → Non-stationarity is a (non-specific) interpretation for model rejection
- Rejecting the null-model → Model is useless

Consider the following example



Model M:
 Height distribution is Gaussian
 $(\mu = 64 \text{ in}; \sigma = 2.7 \text{ in})$
 Test statistic:
 $m = \#\text{individuals} > 75 \text{ in} (\sim 190 \text{ cm})$

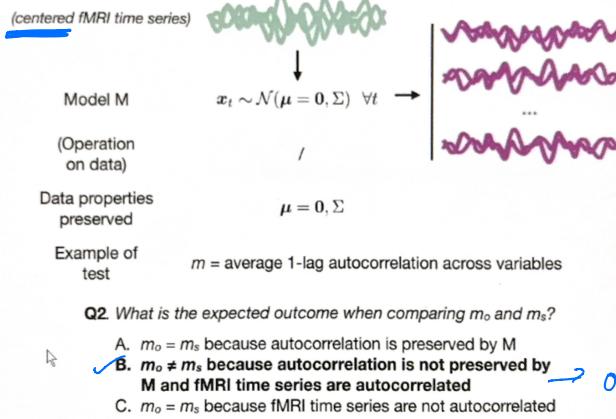
→ $m_o \neq m_s$

→ Still, the model is useful for us

Null - models for fMRI time seri

(Null models can be used to account for sampling variability)

fMRI null-model 1: multivariate Gaussian

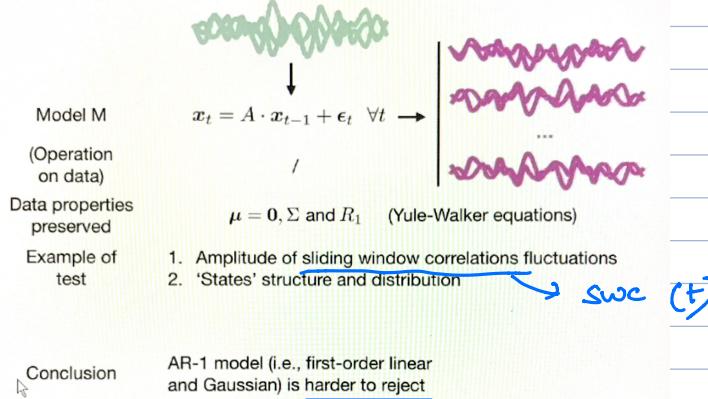


$\rightarrow m_o \neq m_s$

\Rightarrow Data cannot be fully explained by multivariate gaussian

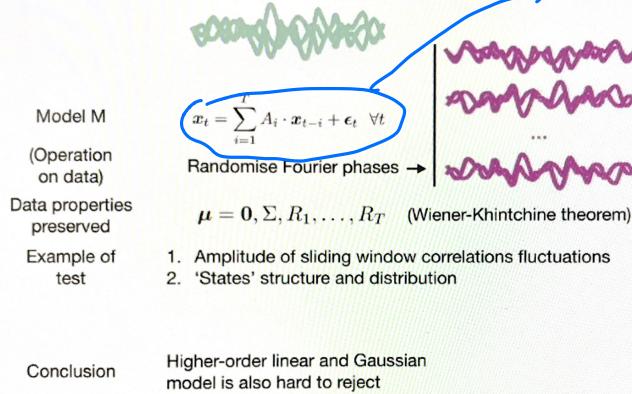
obviously!

fMRI null-model 2: First-order autoregressive (AR-1)



Liégeois et al., 2017

fMRI null-model 3: Phase Randomisation (PR)



we get this model as an outcome of the operatn of randomizing Fourier phases

Three null-models of (centered) fMRI time series

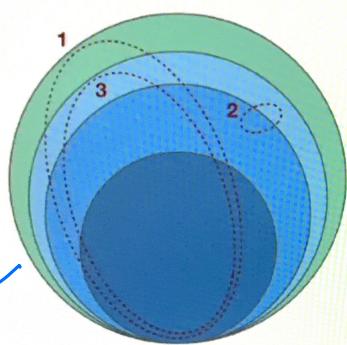
Model	Multivariate Gaussian	First-order AR (Linear & Gaussian)	Higher-order AR (Linear & Gaussian)
(Operation on data)	/	/	PR: Phase Randomisation
Data properties preserved	Σ	Σ, R_1, \dots, R_T	Σ, R_1, \dots, R_T
Result on fMRI	Easily rejected	Harder to reject	Harder to reject

\Rightarrow Summary \rightarrow



Q: Do my results need to be different on original vs. surrogate data in order to be relevant/interesting/meaningful?

A: No



- Statistical information contained in fMRI time series
- Statistical information captured by a multivariate Gaussian model
- Statistical information captured by an AR-1 model
- Statistical information captured by an AR-T model (PR null)

Case 1: results are the same on original and AR-1 surrogate data
→ Method exploits info *within* the one preserved by the AR-1 null

Case 2: results are different on original and PR surrogate data

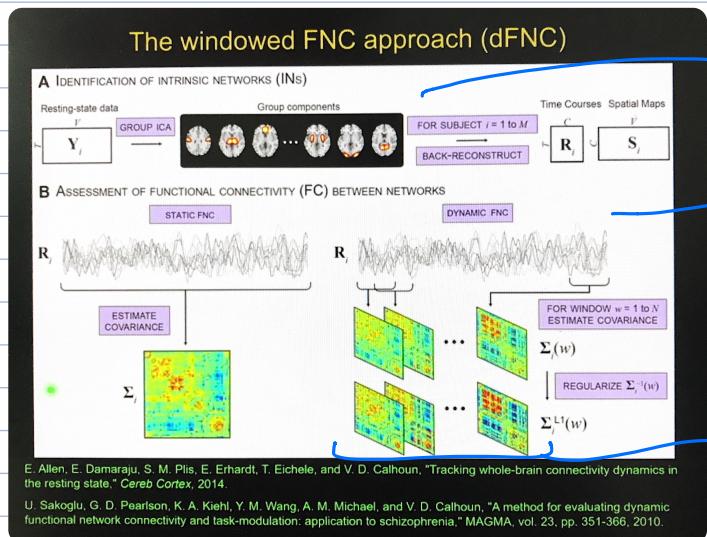
Q3. Which curve could represent information used in this case?

- A. Curve 1
- B. Curve 2
- C. Curve 3

→ some info goes beyond the scope of PR null

We can see that AR-1 & PR null seem to be "fair" models of fMRI time series

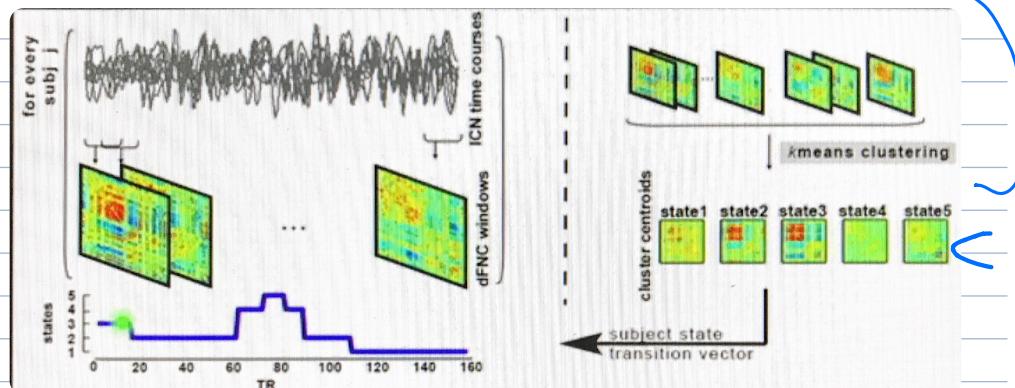
Time-varying connectivity : Data-driven approaches & clinical application



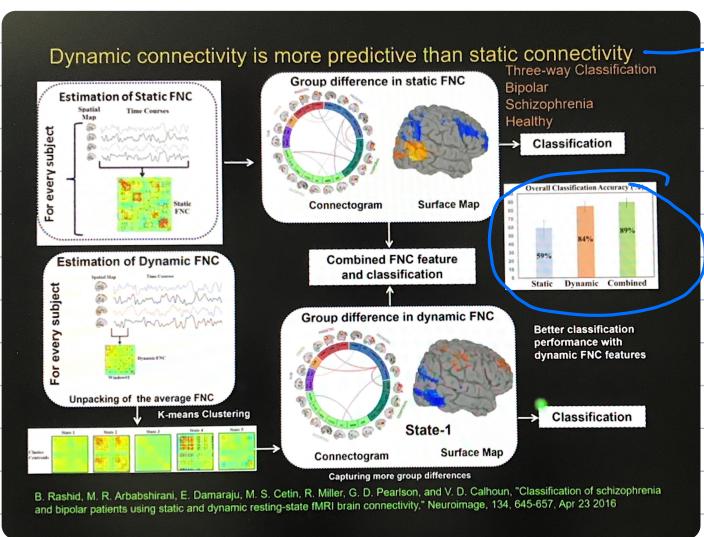
ICA!

Same thing learned previously

k-means clustering ⇒ we will get different brain states



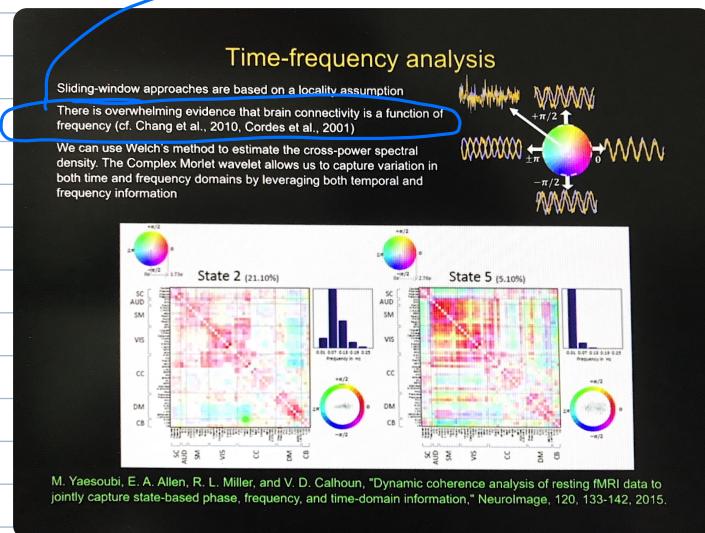
- The evidence of states are also in EEG data.
- Using states we can predict many things (eg: sleep, rest, wakefulness, problem solving)



→ combined has best accuracy

Such work is useful in studying disorders, drugs etc.

- Approaches other than dFNC



b) Windowless approach - Machine learning etc.

c) Filter bank connectivity → capturing all window sizes in dFNC
(window is like a filter, so we make a bank of such filters)

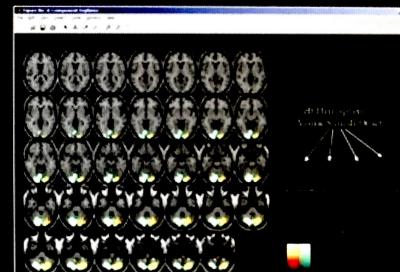
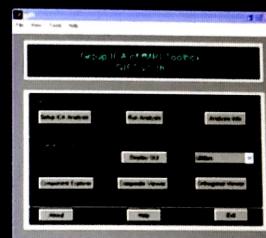
d) Brain trajectory dynamics

e) Using Temporal derivatives

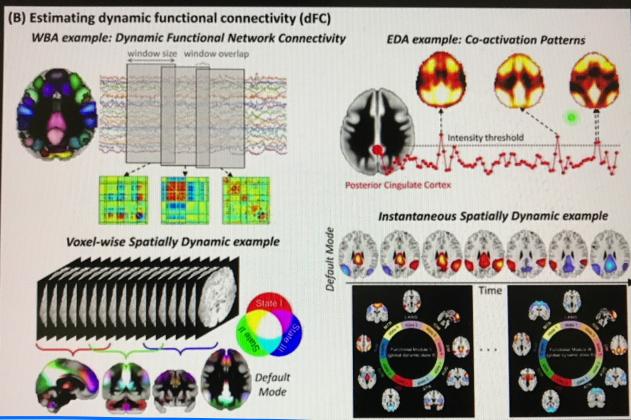
f) etc.

Software

- <http://trendscenter.org/software>
- freeware, written in MATLAB (also offering compiled versions), python, etc: over 11,000 unique downloads
- GIFT (Group ICA of fMRI Toolbox)
 - Single subject/Group ICA
 - MANCOVA testing framework
 - Source based morphometry
 - ICASSO (clustering/stability)
 - Dynamic FNC/Coherence
- FIT (Fusion ICA Toolbox)
 - Parallel ICA, jICA
 - mCCA+jICA & much more!
- Simulation Toolbox (SimTB)
 - Flexible generation of fMRI-like data
- COINS (data management/capture/sharing)
 - <http://coins.trendscenter.org>
- COINSTAC (decentralized analysis, privacy)
 - <https://github.com/MRN-Code/coinstac>
- CORTEX (deep learning)
 - <https://github.com/rdevon/cortex>



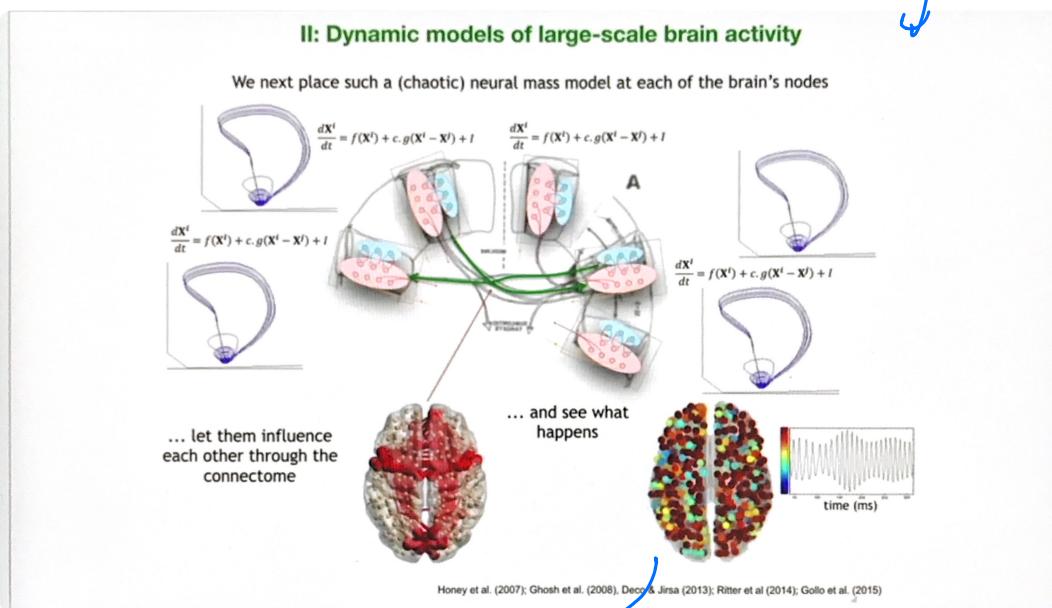
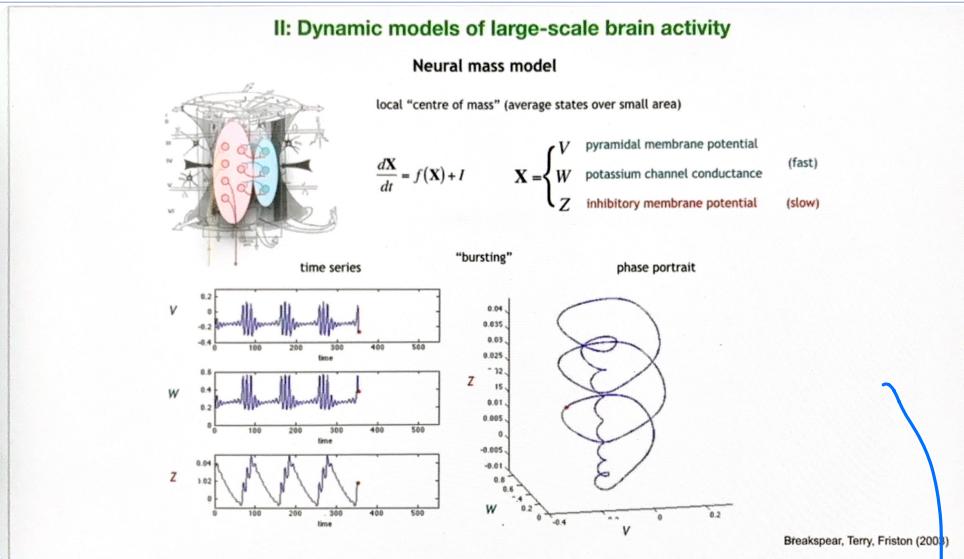
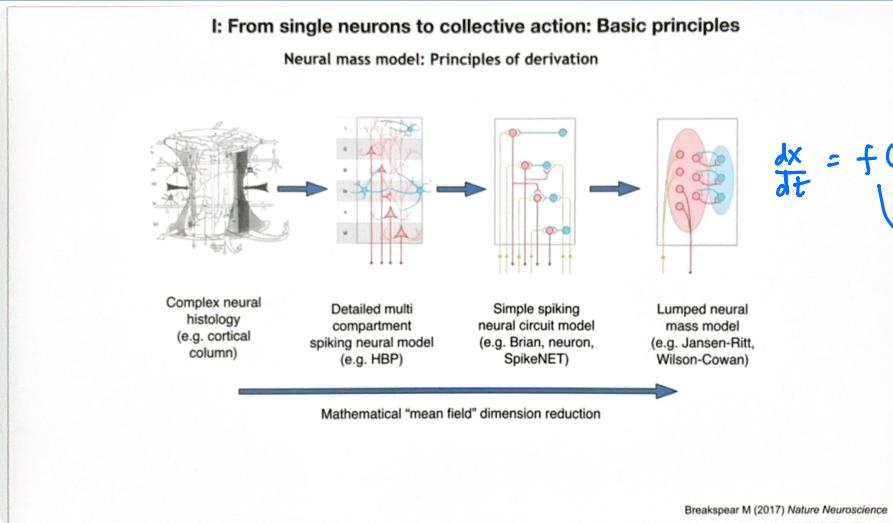
For more details on dynamic connectivity



A. Iraji, A. Faghiri, N. Lewis, Z. Fu, S. Rachkonda, and V. D. Calhoun, "Tools of the trade: Estimating time-varying connectivity patterns from fMRI data," *PsyArXiv*, 2020, <https://doi.org/10.31234/osf.io/mvqj4>

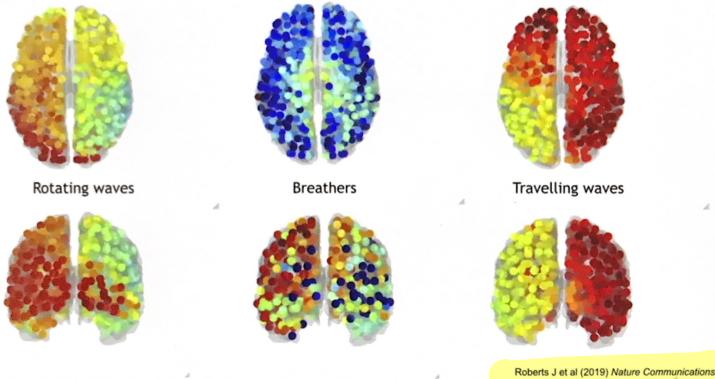
Review paper.
Read this to learn more

Neuronal models of dynamic functional connectivity : Linking scales & data modalities.



III: Metastable brain waves

Strong coupling through the connectome leads to a variety of spatiotemporal patterns

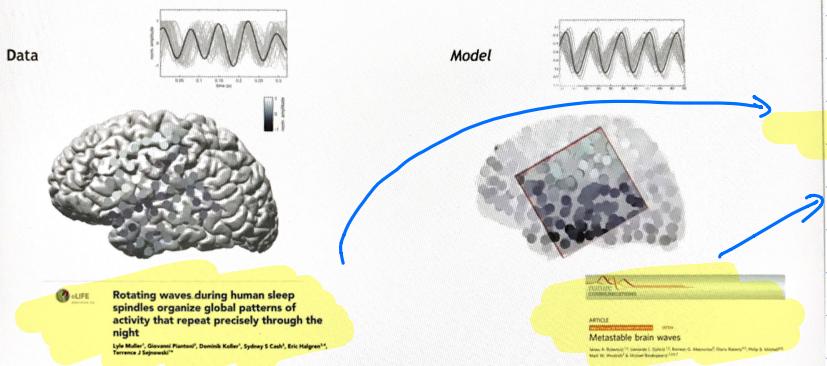


wow

what about -psychedelics?
Binaural Beats?

III: Metastable brain waves

Interestingly, these predictions bear close relationship with waves in recently acquired human spindles waves during sleep



IV) Open-source simulation engines

The Virtual Brain
Brain dynamics toolbox

V) Modelling Brain & Body

Take models of brain, heart ---- & then couple them together



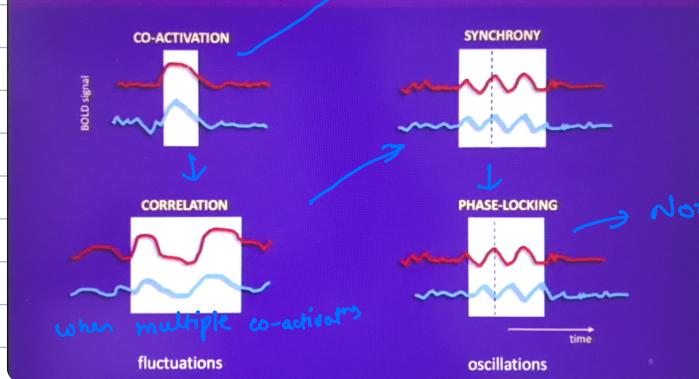
Wandering around functionally relevant Network States

Dynamic Systems Theory

→ e.g. flock of birds display their own system, which isn't understood by looking at a single bird

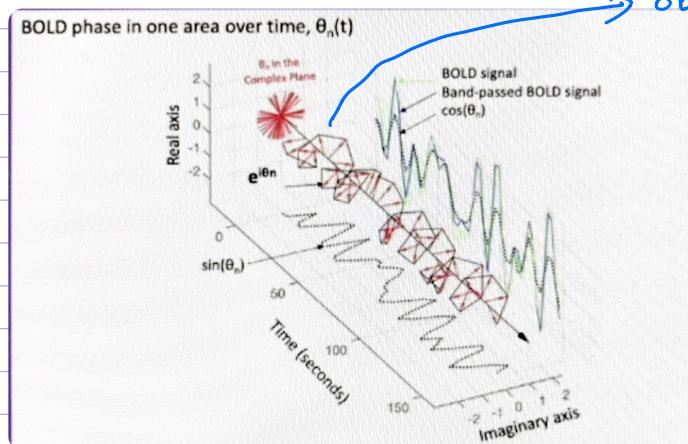
→ It displays Butterfly Effect!

Introduction
Synchrony and Phase-locking



In dynamical systems [full synchrony is only 1 possible oscillatory mode/state]
[there can be as phase locked oscillatory modes]

Hypothesis: brain functional networks are phase-lock modes in BOLD



Q) How to characterize BOLD phase relationship at whole brain level?

⇒ LE IDA (mentioned earlier in this document)

project of BOLD phase into the leading phase eigenvector

→ Read "Cobral_2017" she first developed it, she is also the speaker of this video.

(Skipped many slides, explanation was amazing but too many details)

Timescales of Variation in Human Functional Brain Networks →

(Not much was there in this lecture)

Conclusions and Recommendations for Studying Dynamics in FC

- Define terminology/construct clearly
- Address other potential sources of variation
 - Sampling variability → null model
 - Motion & respiration → denoising
 - Arousal → measurement or interpretation
- Collect substantial amounts of data per subject

Time-varying connectivity in resting-state fMRI: methods, interpretations and clinical use.

Vince Calhoun Co Organizer

Georgia State/Georgia Tech/Emory

TReNDS

Atlanta, GA

United States

Raphael Liegeois Organizer

École Polytechnique Fédérale de Lausanne

Geneva, Geneva

Switzerland

Recent converging evidence suggests that a static representation of FC, e.g. based on the correlation between entire fMRI time series, misses important information encoded in fMRI data. Hence, various methods have been developed in recent years to exploit the information encoded beyond such static measures. The researcher interested in exploring time-varying FC properties has to select among the multitude of proposed methods, each one having different properties and underlying assumptions. The goal of this course is to provide guidance in the choice of an adequate time-varying FC method to address a specific neuroscientific question. In the first part of the course we will recall the definitions of the most important mathematical notions required to characterize temporal fluctuations of functional connectivity. Then, we will provide an overview of the main approaches used to explore functional connectivity beyond the classical static paradigm (e.g. brain states, co-activation patterns, autoregressive models), including concrete examples of how these methods have been used in clinical applications. The second part of the course will be devoted to the interpretation of FC fluctuations. We will detail their links to micro-scale (i.e. neuronal) dynamics as well as their behavioral counterparts. We will conclude by summarizing the main remaining controversies of the field. In order to maximize learning outcomes for participants, we will discuss multiple-choice questions at the end of each talk, and take questions from the audience using the OHBM interactive tool.

We finally note that last year's course room was overfull, with many attendees standing or sitting on the ground and others not being able to enter the room (this was to a lesser extent also the case in OHBM-Singapore). We believe this further reflects the interest of our community in the proposed course.

Objective

1. Definition of various terms important to the study of time-varying connectivity including 'stationary', 'dynamic', 'static', 'time-varying'

2. Step-by-step explanation of popular methods used to explore the time-varying nature of FC (including demos using popular toolboxes) and application to real datasets
3. Interpretation of the temporal fluctuations of FC in terms of (i) links to micro-scale (neuronal) dynamics and (ii) behavioral counterparts.

Target Audience

The target audience for this course are researchers interested in (the time-varying properties of) functional connectivity. While we will mainly discuss FC evaluated from fMRI data with some emphasis on multimodal studies as well. The proposed theoretical background and interpretations can be applied to any modality involving time series (e.g. MEG, EEG).

Presentations

Going beyond the static functional connectome: a theoretical and methodological framework

In this introductory talk, we first review the main theoretical notions necessary to characterize the vast repertoire of methods extending static models of the functional connectome (FC). We make the distinction between “time-varying” approaches that exploit temporal fluctuations of functional interactions, and “dynamic” frameworks that use time series models. The most common time-varying method consists in computing pairwise correlations between fMRI time courses of different brain regions using a sliding-window framework. We introduce its use, and discuss the improvements that have been proposed, concerning in particular: (1) the choice of the most suitable window characteristics; (2) alternative metrics to assess FC inside the window; (3) how to extract interpretable information from the FC patterns, i.e. by determining FC states. Then, the simplest dynamic model of the functional connectome relies on autoregressive models of neuroimaging time series. We will review its use, applications, and compare the properties of dynamic and time-varying approaches. Finally, we introduce some promising alternatives to these classical approaches, including framewise-based analyses and nonlinear time series models.

Presenter

Maria Giulia Preti, École Polytechnique Fédérale de Lausanne Geneva, Geneva
Switzerland

How null-models can (or not) be used to detect time-varying functional connectivity

Null-models are widely used as a means to generate surrogate data and explore data properties. Various null-models have been proposed to refine the characterization of neuroimaging time series, but the interpretation of null-model testing should be cautious. In this talk, I will first introduce the basic theoretical foundations of null-model testing. In particular I will show that in most cases, more than one statistical property is attached to a given null-model. Therefore, the outcome of the corresponding tests might in general have multiple interpretations. I

will then present the most popular null-models of neuroimaging data and detail which statistical properties they are testing for. I will conclude by emphasizing that instead of testing for the presence or absence of "time-varying" of "dynamic" functional connectivity, null-models should rather be used to characterize the nature of the temporal fluctuations of neuroimaging metrics.

Presenter

Raphael Liegeois, École Polytechnique Fédérale de Lausanne Geneva, Geneva Switzerland

Time-varying connectivity: Data-driven approaches and clinical applications

The study of complex mental illness can greatly benefit from flexible analytic approaches. In particular, the advent of data-driven approaches to identify time-varying connectivity and activity has revealed a number of interesting clinically-relevant variation in the data which, when ignored, can provide misleading information. In this lecture I will provide a comparative introduction of a range of data-driven approaches to estimating time-varying connectivity. I will also present detailed examples where studies of mental illness have been advanced by approaches designed to capture and estimate time-varying information in resting fMRI data. As part of this, I will review several exemplar data sets analyzed in different ways to demonstrate the complementarity as well as trade-offs of various modeling approaches to answer questions about complex mental illness. Finally, I will review and provide examples of strategies for validating TVC including simulations, multimodal imaging, and comparative prediction within clinical populations, among others. As part of the interactive aspect I will provide a hands-on guide to the dynamic functional network connectivity toolbox within the GIFT software, including an online didactic analytic decision tree to introduce the various concepts and decisions that need to be made when using such tools.

Presenter

Vince Calhoun, Georgia State/Georgia Tech/Emory
TReNDS
Atlanta, GA
United States

Neuronal models of dynamic functional connectivity: Linking scales and data modalities.

Dynamic functional connectivity arises from complex patterns of activity in large-scale neuronal systems. In this talk, I will introduce the basic approach to understanding and modelling neuronal dynamics across different spatial and temporal scales. I will explain how large-scale brain dynamics in circuits and networks can arise from the collective activity amongst individual neurons, and how slow dynamics (on the time-scale of the BOLD signal)

emerge from fluctuations in fast spiking neurons. Candidate dynamic mechanisms of dynamic functional connectivity include metastability, criticality and multistability which reflect different types of instabilities in a complex system. I will end with a hands-on guide to the main toolboxes that researchers can use to model these dynamics.

Presenter

Michael Breakspear, University of Newcastle Newcastle, New South Wales Australia

Wandering around functionally relevant Network States

Functionally-relevant network patterns form transiently in brain activity during rest, where a given subset of brain areas exhibits temporally synchronized BOLD signals. To adequately assess the biophysical mechanisms driving resting-state activity, a detailed characterization of the dynamical features of functional networks is needed from the experimental side to inform theoretical models. Borrowing tools from Dynamical Systems' Theory, such as Markovian chains, dwelling times, recurrence times and switching probabilities, one can characterize resting-state brain dynamics in the form of trajectories within a low-dimensional state space, providing insights into the universal principles governing brain activity in the spontaneous state. In this framework, functional brain subsystems emerge as recurrent ghost-attractors whose properties appear consistent across healthy subjects but appear disrupted in neuropsychiatric disorders, reinforcing the importance of addressing dynamical features of functional brain networks to gain insight into brain function.

Presenter

Joana Cabral, University of Oxford Oxford, Oxford United Kingdom

Timescales of variation in human functional brain networks

Functional connectivity may be used for a variety of applications, from identification of brain disorder biomarkers to measuring task states and spontaneous cognition. These applications depend on functional networks exhibiting variation at very different timescales. In this presentation, we will review evidence that fMRI functional networks are largely stable, driven by group commonalities and individual features. Variation at faster time-scales (due to day-to-day or task-state differences) is also evident, but substantially smaller in magnitude. Once artifacts are accounted for, we find that variation in functional connectivity during resting-state is primarily driven by differences in arousal. We will close by discussing implications of these findings for applications of functional connectivity.

Presenter

Caterina Gratton, Northwestern Evanston, IL United States
