SPECTRAL GRAPH MODEL OF BRAIN OSCILLATIONS:

A) Fitting to empirical fMRI and MEG
B) Dynamics and stability of model
C) Applications in neurological disease

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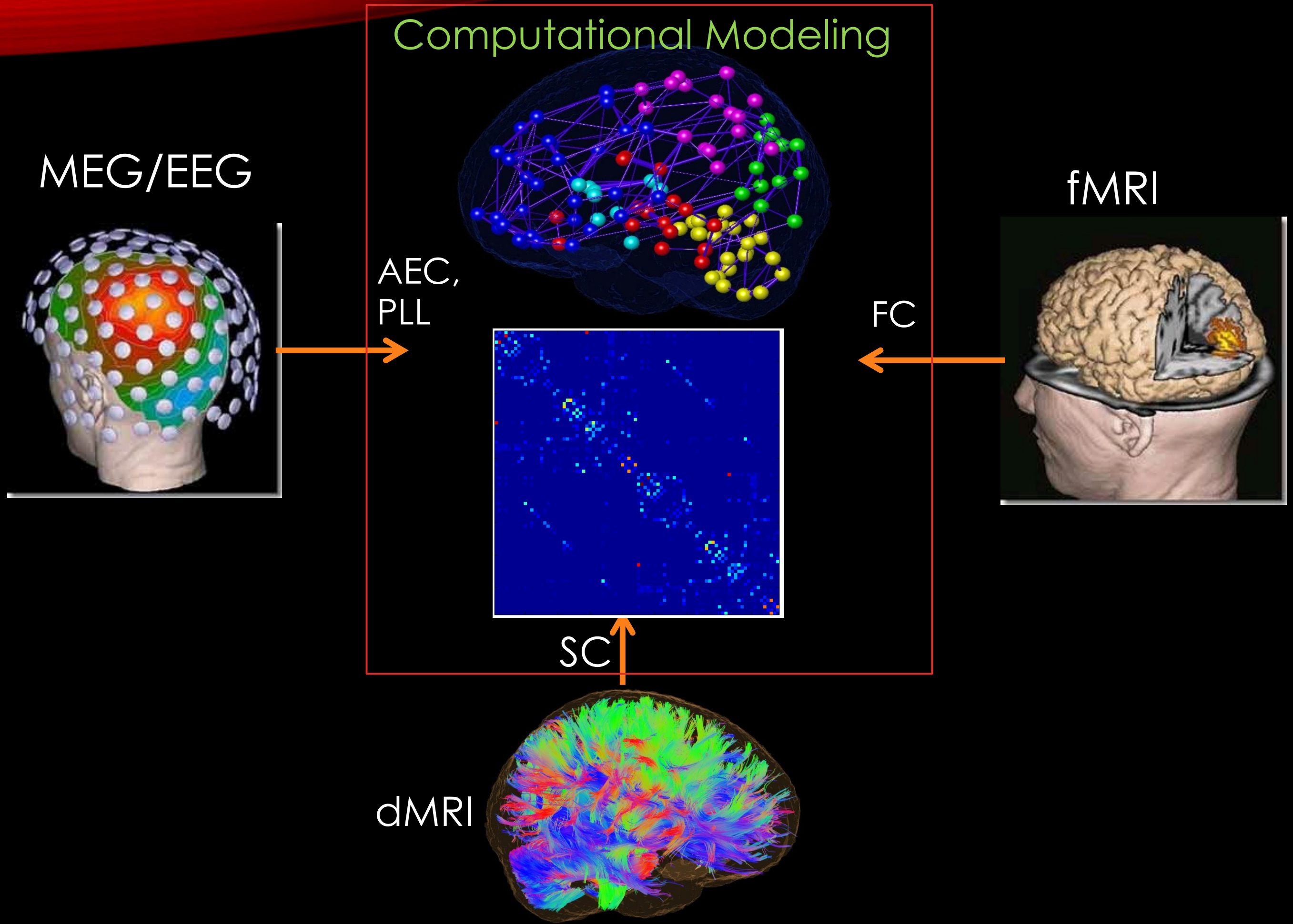
Declaration of Financial Interests or Relationships

Speaker Name: Ashish Raj

I have no financial interests or relationships to disclose with regard to the subject matter of this presentation.

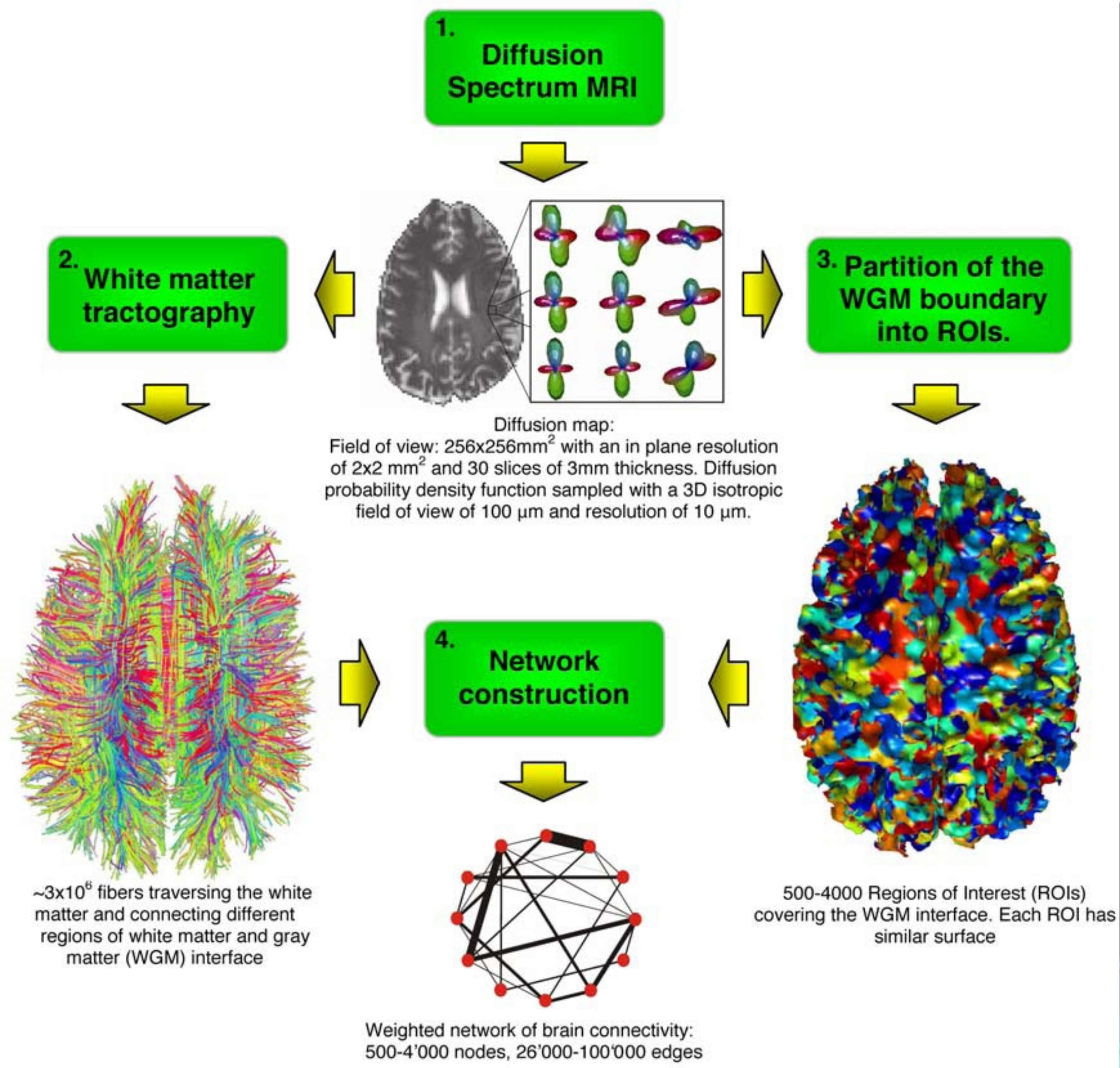
MULTIMODAL INTEGRATION VIA NETWORKS



THE STRUCTURE-FUNCTION QUESTION

- FC = Statistical corr of signals from 2 regions
- Anatomic = structural connectivity (SC)
- The exact relationship between FC and anatomic connectivity is an unresolved, major question
- SC ➔ FC, but NOT vice versa
- Can math models predict FC, given SC?

<u>Key ideas in this lecture</u>:
1) Connectivity graph is an excellent medium for cross-modality integration
2) Need math/graph models rather than statistical associations
2) Simple, linear network models can capture SC-FC better than non-linear generative models



Mapping Human Whole-Brain Structural Networks with Diffusion MRI
Patric Hagmann, Maciej Kurant, Xavier Gigandet, Patrick Thiran, Van J. Wedeen, Reto Meuli, Jean-Philippe Thiran, PLoS ONE 2(7)

A LINEAR NETWORK DIFFUSION MODEL OF ACTIVITY SPREAD

- Between any two regions R1 and R2, the signal is x1(t) and x2(t)

$$\frac{\mathrm{d}x_1(t)}{\mathrm{d}t} = \beta\left(\frac{1}{V_1}c_{1,2}\frac{1}{\delta_2}V_2x_2(t) - x_1(t)\right)$$

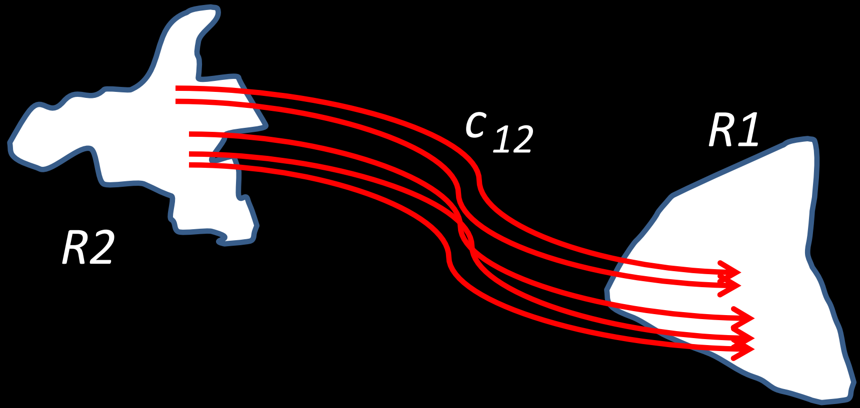
- On whole brain

$$\frac{\mathrm{d}\mathbf{x}(t)}{\mathrm{d}t} = -\beta\mathcal{L}\mathbf{x}(t),$$

$$\mathcal{L} = I - \Delta^{-1/2}\mathbf{C}\Delta^{-1/2}.$$

$$\mathbf{x}(t) = \exp(-\beta\mathcal{L}t)\mathbf{x}_0,$$

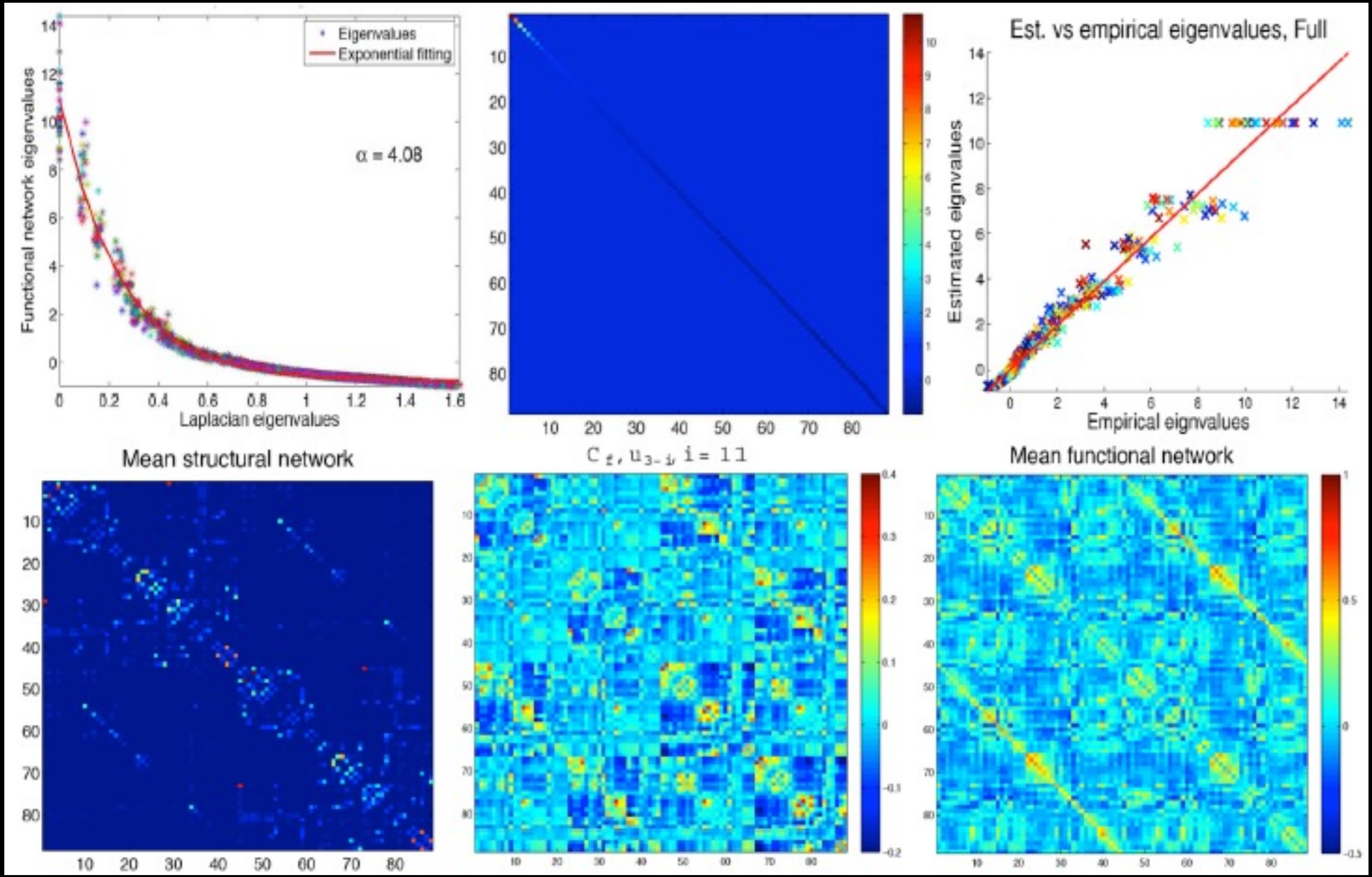
$$\mathcal{C}_f(t_{crit}) = \exp(-\beta\mathcal{L}t_{crit}).$$



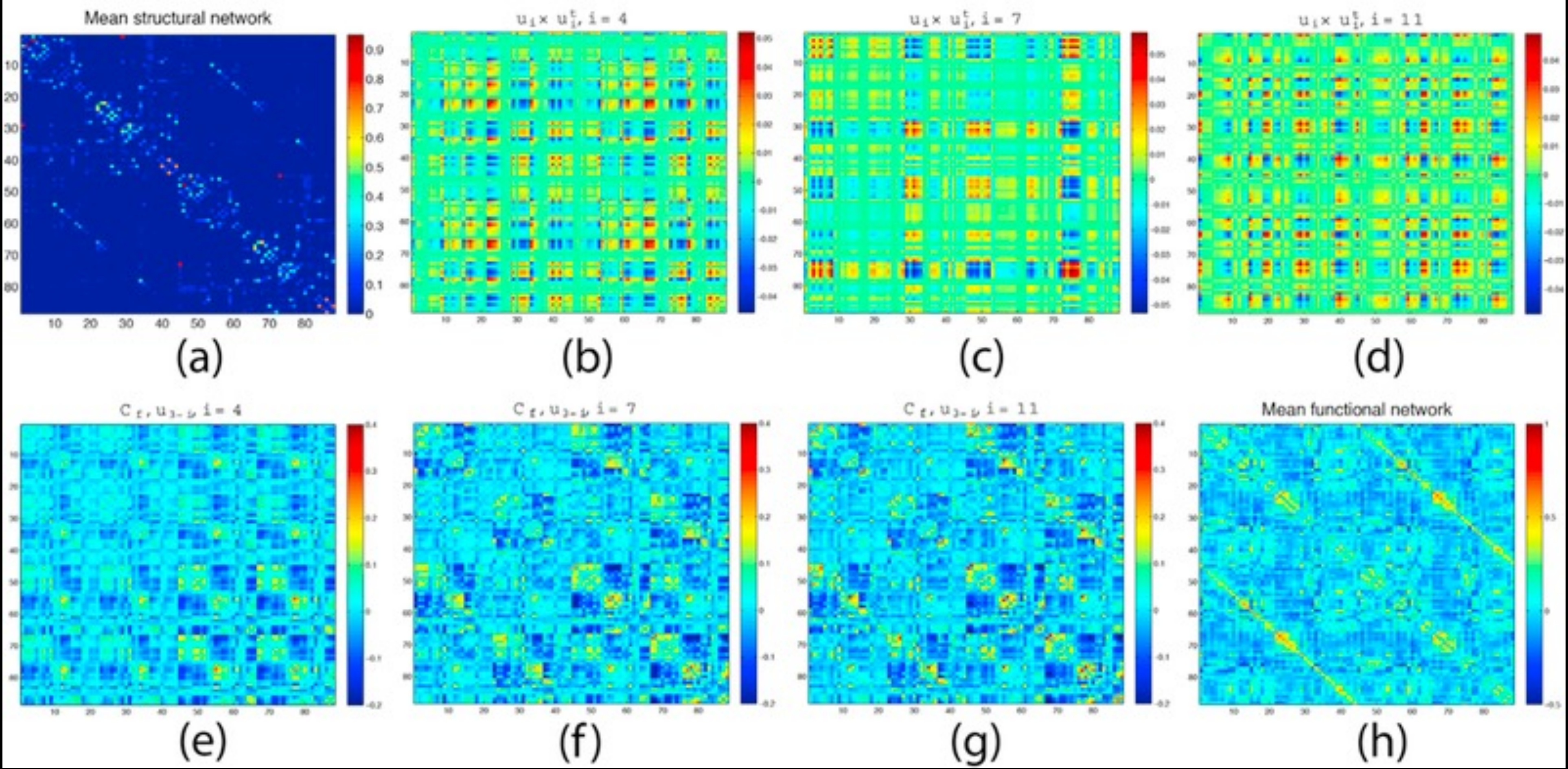
Abdelnour, Voss, Raj. Network diffusion accurately models the relationship between structural and functional brain connectivity networks. NeuroImage 2014

SPECTRAL" GRAPH THEORY OF SC-FC

- SC and FC are related by graph spectra (eigens)

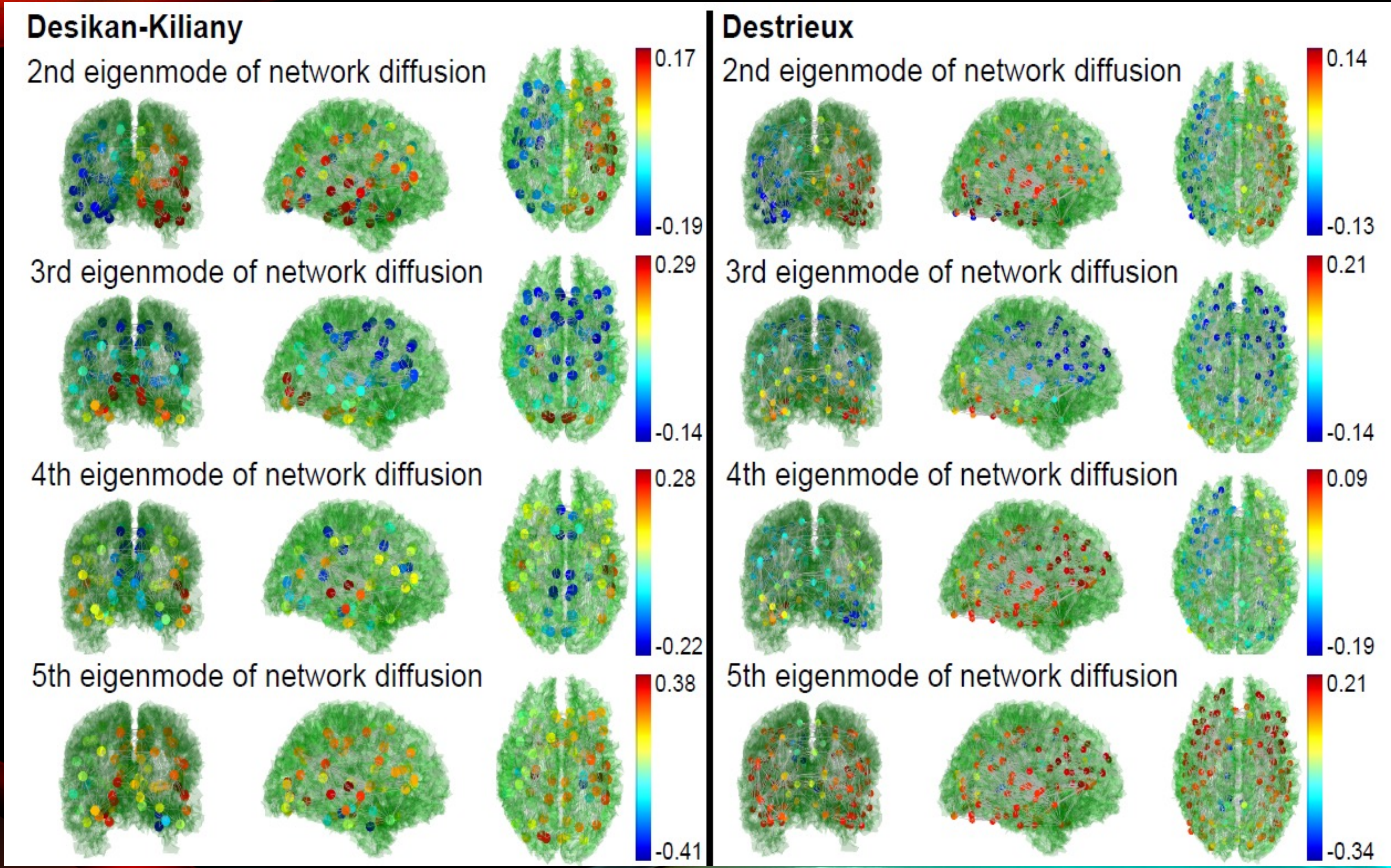


Abdelnour, Voss, Raj. NeuroImage 2014



Mean structural network
(a)
(b)
(c)
(d)
(e)
(f)
(g)
Mean functional network
(h)

Network Eigenmodes of the Structural Connectome



Wang, Owen, Mukherjee, Raj, PLoS Comput Biol (2017)

INVITED PAPER

A Graph Signal Processing Perspective on Functional Brain Imaging

By Weiyu Huang, Thomas A. W. Bolton, *Student Member IEEE* John D. Medaglia, Danielle S. Bassett, Alejandro Ribeiro, and Dimitri Van De Ville, *Senior Member IEEE*

nature COMMUNICATIONS

Article | OPEN | Published: 21 January 2016

Human brain networks function in connectome-specific harmonic waves

Selen Atasoy, Isaac Donnelly & Joel Pearson

Nature Communications 7, Article number: 10340 (2016) | Download Citation

ELSEVIER

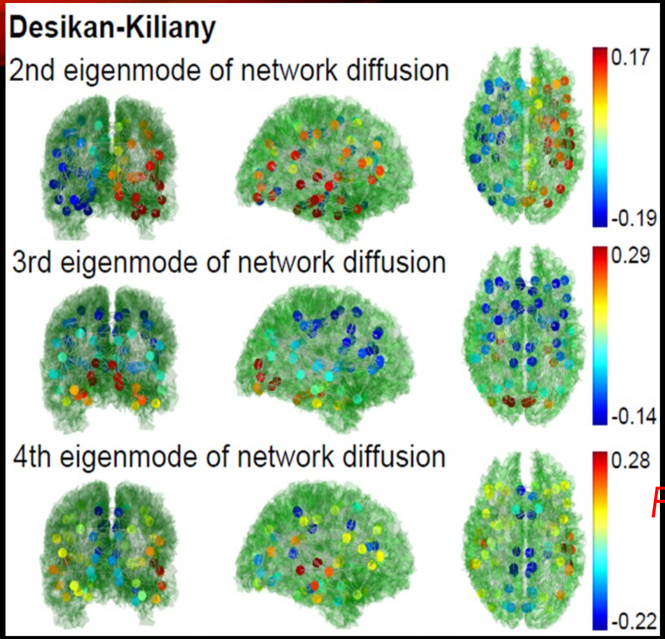
NeuroImage

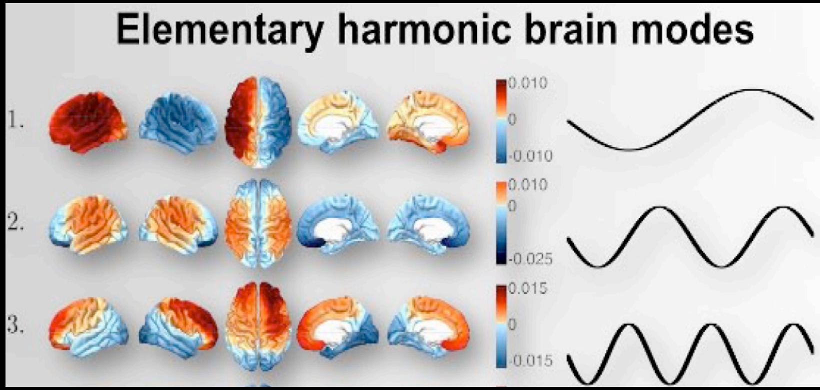
Volume 172, 15 May 2018, Pages 728-739

Functional brain connectivity is predictable from anatomic network's Laplacian eigen-structure

Farras Abdelnour [a], Michael Dayan [a], Orrin Devinsky [b], Thomas Thesen [b, c], Ashish Raj [a]

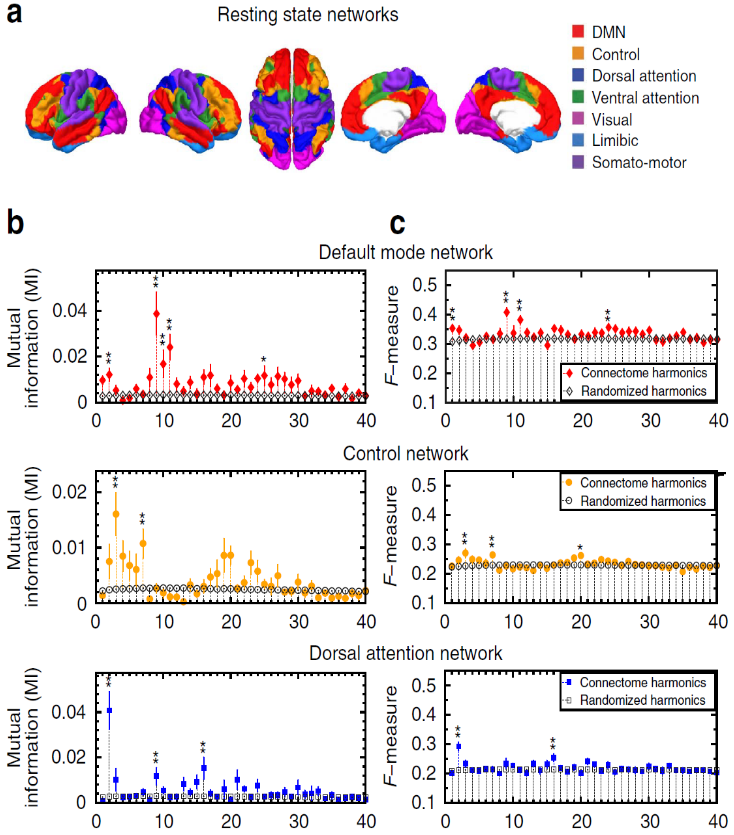
Structural Eigenmodes and Resting State fMRI Networks

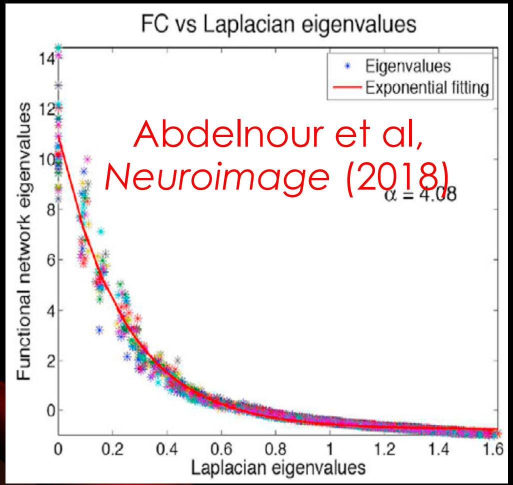




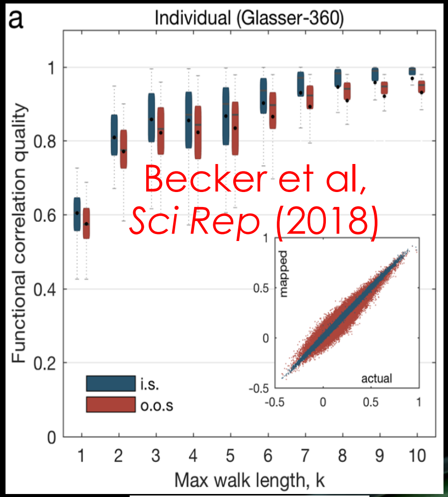
Wang et al., *PLoS Comput Biol* (2017)

Atasoy et al., *Neuroscientist*





Abdelnour et al, *Neuroimage* (2018)

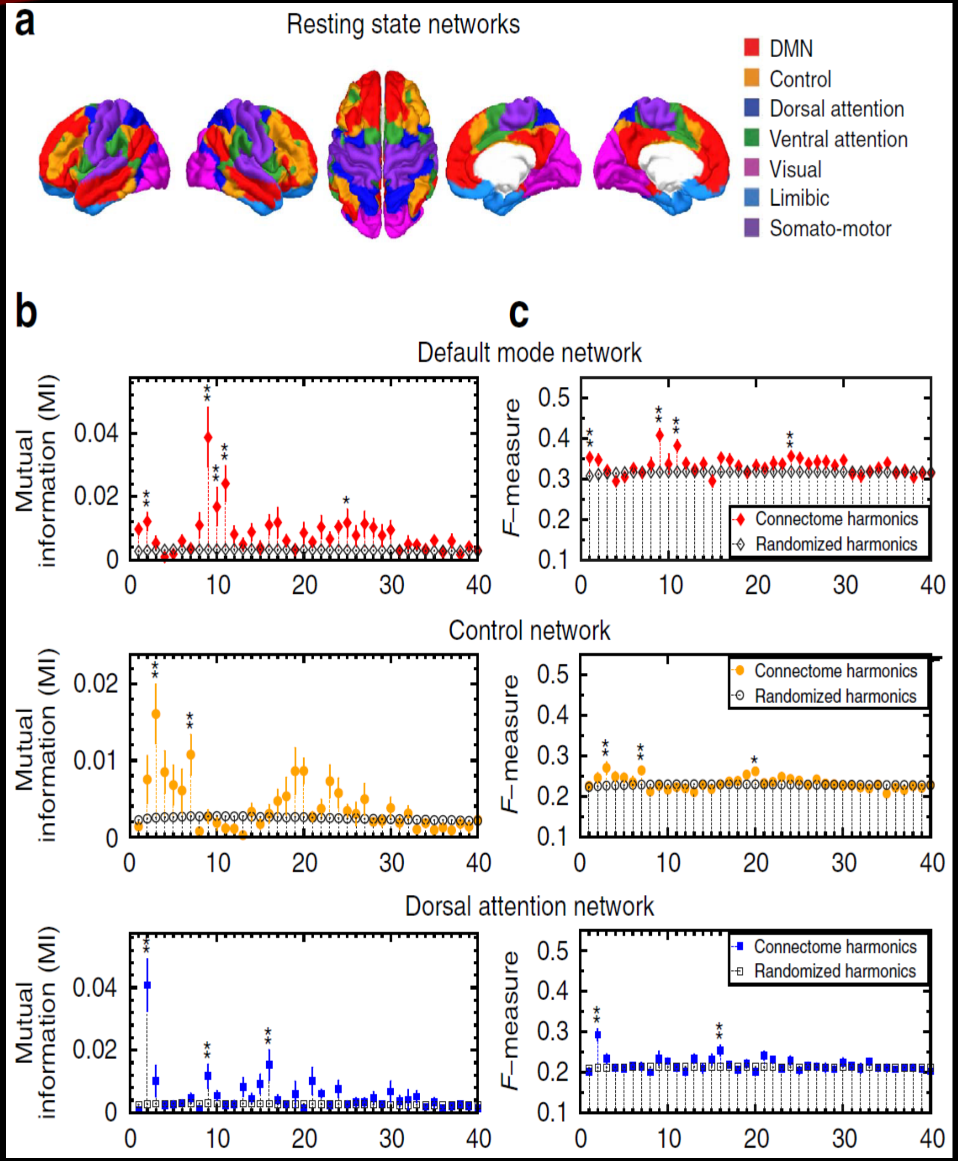


Becker et al, *Sci Rep* (2018)

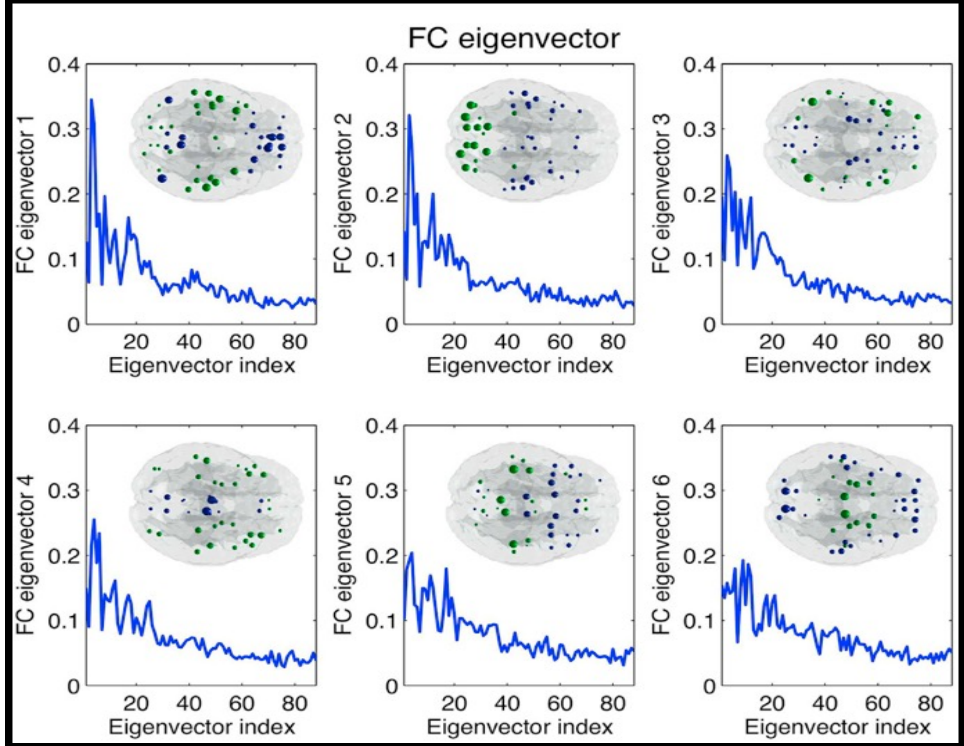
$$\frac{d\mathbf{x}(t)}{dt} = -\beta\mathscr{L}(\mathbf{x}(t) - \mathbf{x}^*), \quad \mathbf{C}_f^{eig} = ae^{-\beta\mathscr{L}t} + \mathbf{K}$$

$$\hat{F} = R^* \left(\sum_{i=0}^{k} a_i^* S^i \right) (R^*)^{\mathrm{T}}$$

GRAPH EIGENMODES CAN SPARSELY REPRESENT FC



Atasoy, 2016



Abdelnour, …, Raj. *Neuroimage* (2014, 2018)

SPECTRAL GRAPH THEORIES OF FMRI AND FC

- Christopher J Honey, Rolf Kötter, Michael Breakspear, and Olaf Sporns. Network structure of cerebral cortex shapes functional connectivity on multiple time scales. Proceedings of the National Academy of Sciences, 104(24):10240–10245, 2007
- Farras Abdelnour, Henning U. Voss, and Ashish Raj. Network diffusion accurately models the relationship between structural and functional brain connectivity networks. NeuroImage, 90:335–347, 2014
- Selen Atasoy, Isaac Donnelly, and Joel Pearson. Human brain networks function in connectome-specific harmonic waves. Nature Communications, 7:10340, 2016
- Farras Abdelnour, Michael Dayan, Orrin Devinsky, Thomas Thesen, and Ashish Raj. Functional brain connectivity is predictable from anatomic network's Laplacian eigen-structure. NeuroImage, 172:728–739, 2018

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INTRODUCING A "COMPLEX" LAPLACIAN

- Novel concept in brain graph theory

$$\frac{\mathrm{d}x_1(t)}{\mathrm{d}t} = \beta\left(\frac{1}{V_1}c_{1,2}\frac{1}{\delta_2}V_2x_2(t) - x_1(t)\right)$$

$t \to t - \tau_{1,2}$

- Delays become phases in Fourier space: $\mathcal{F}(x(t-\tau_{1,2})) = X(\omega)e^{-i\,\tau_{1,2}\omega}$
- Hence define a complex connectivity matrix $C^*(\omega) = \{c_{jk}e^{-i\,\tau_{jk}\omega}\}$

  where delays come from global speed constant: $\tau_{jk} = \frac{\mathrm{d_{jk}}}{v}$

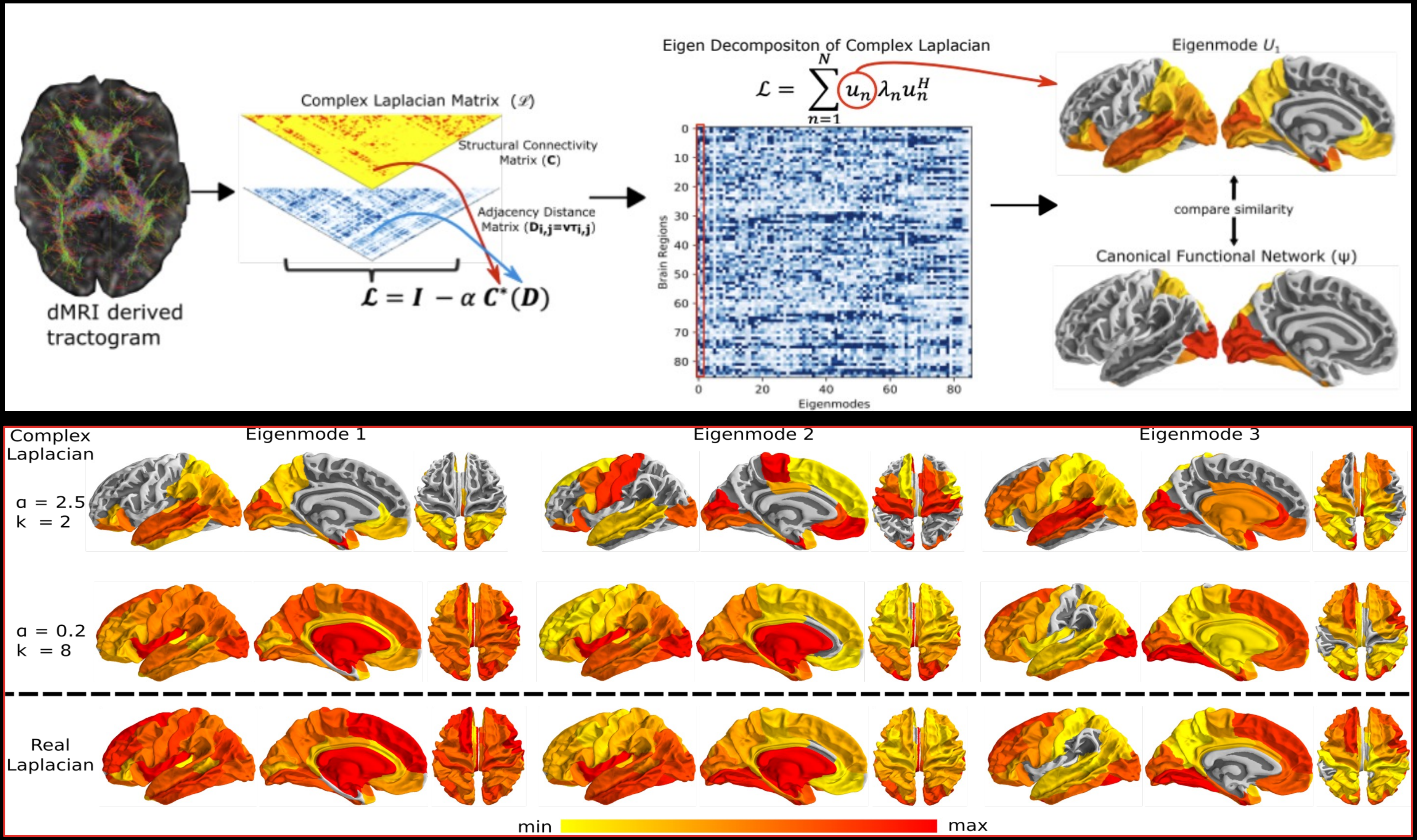
  and the complex Laplacian

  $$\mathcal{L}(\omega|v,\alpha) = I - \alpha C^*(\omega|v)$$

- Define a "wavenumber" $k = \omega/v$, then we define $\mathcal{L}(k,\alpha)$

Xie, Cai, Damasceno, Nagarajan, Raj. Emergence of canonical functional networks from the structural connectome, NeuroImage, 2021

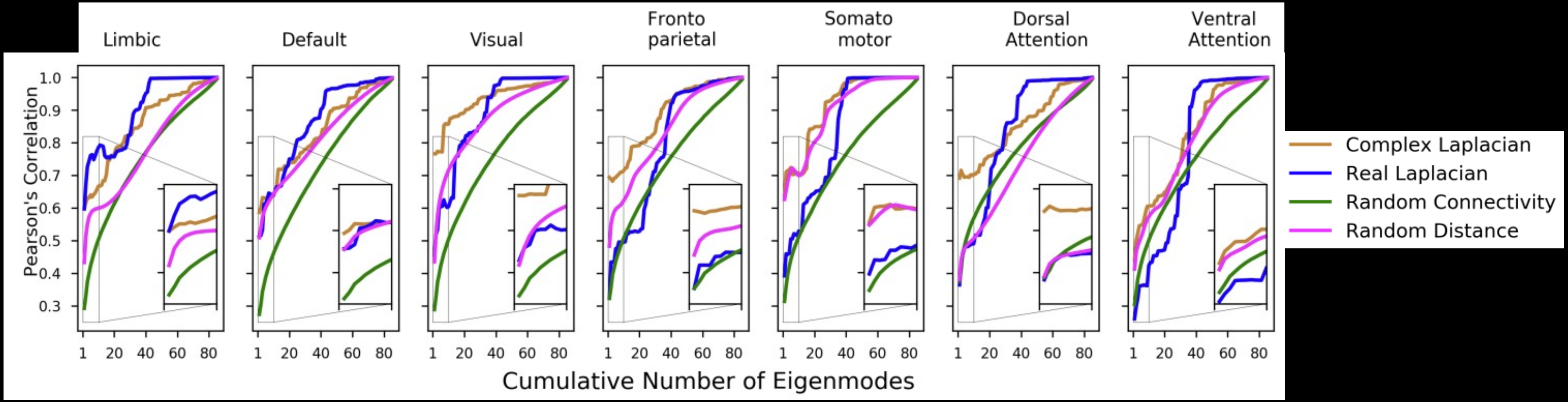
WHAT DO THESE EIGENMODES LOOK LIKE?



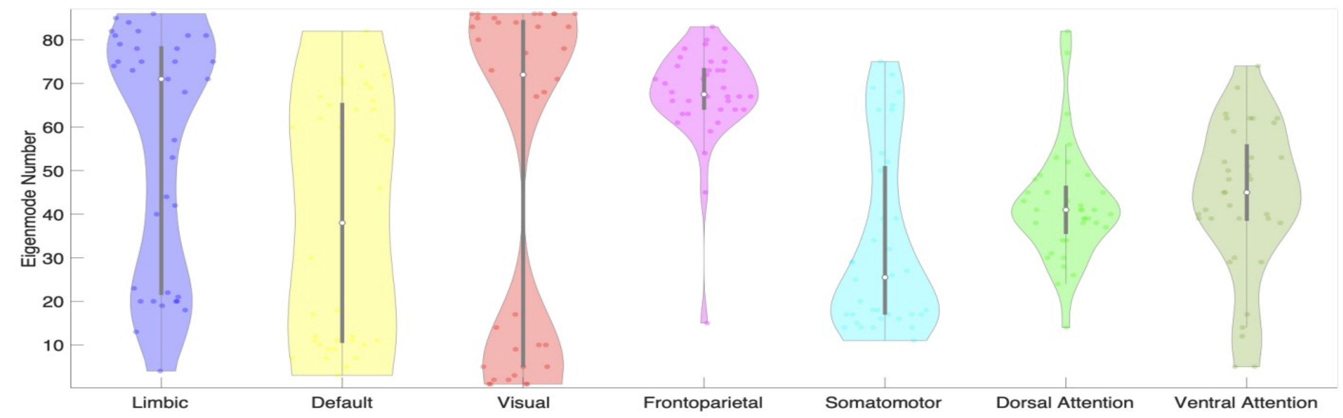
Xihe Xie, Chang Cai, Pablo F. Damasceno, Srikantan S. Nagarajan, Ashish Raj, Emergence of canonical functional networks from the structural connectome, NeuroImage, 2021

COMPLEX LAPLACIAN EIGENMODES FIT CANONICAL FCN'S

- A few e-modes are sufficient to predict any FCN
- Complex e-modes are better than real ones; and both are better than random conns



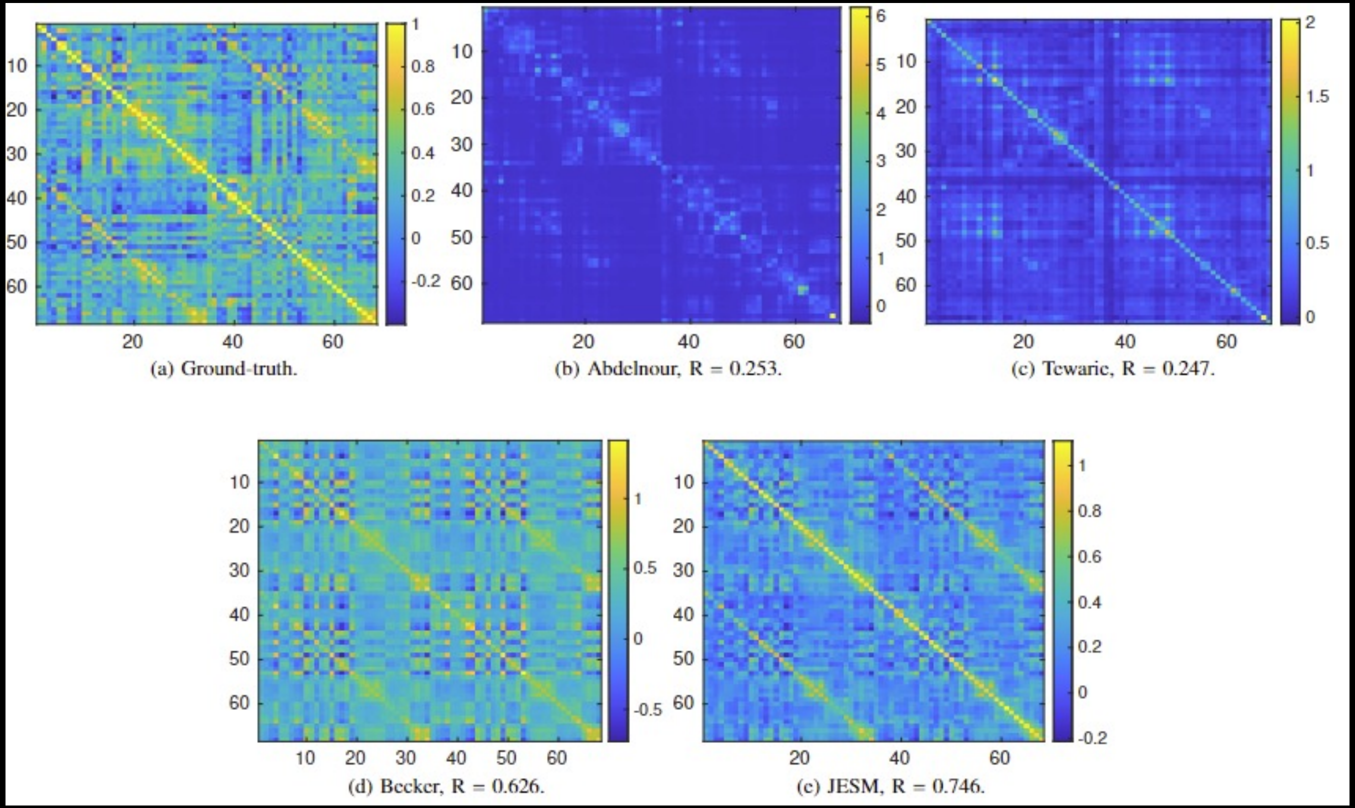
- Complex e-modes respond to specific FCNs

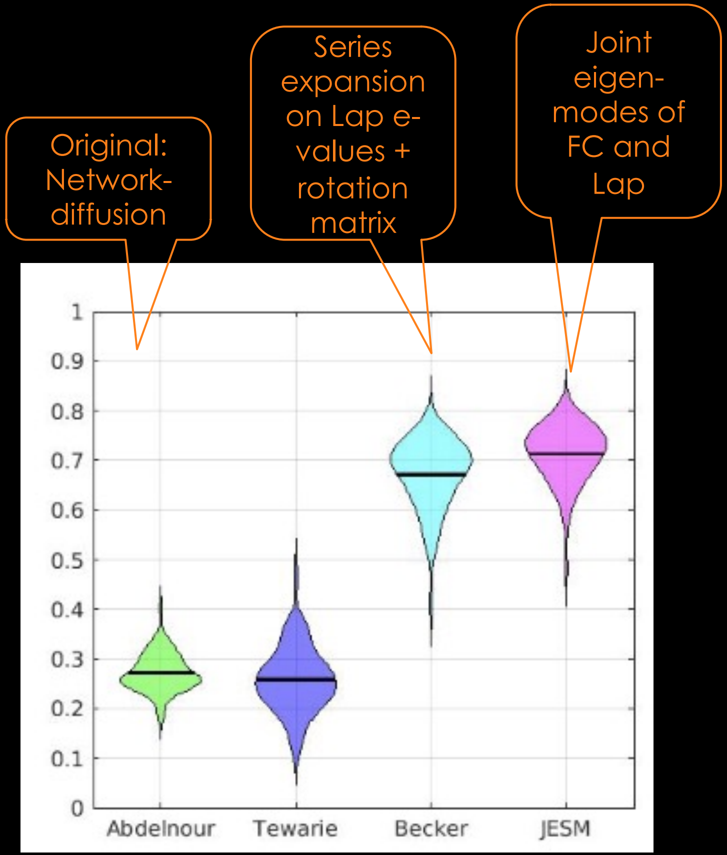


X Xie, C Cai, P Damasceno, S Nagarajan, A Raj, Emergence of canonical functional networks from the structural connectome, NeuroImage, 2021

STRUCTURE-FUNCTION MAPPING

- Highlighting the eigen-mapping technique:
  - Reasonable performance with very simply approach
  - Exploits the relationship between the eigenvalues and eigenvectors of the FC and SC (esp latter's Laplacian)
  - FC eigenvectors == Laplacian eigenvectors
  - FC eigenvalues = func(Lap eigenvalues)
- Example results





Ghosh, Raj, Nagarajan. submitted

SUGGESTED READING

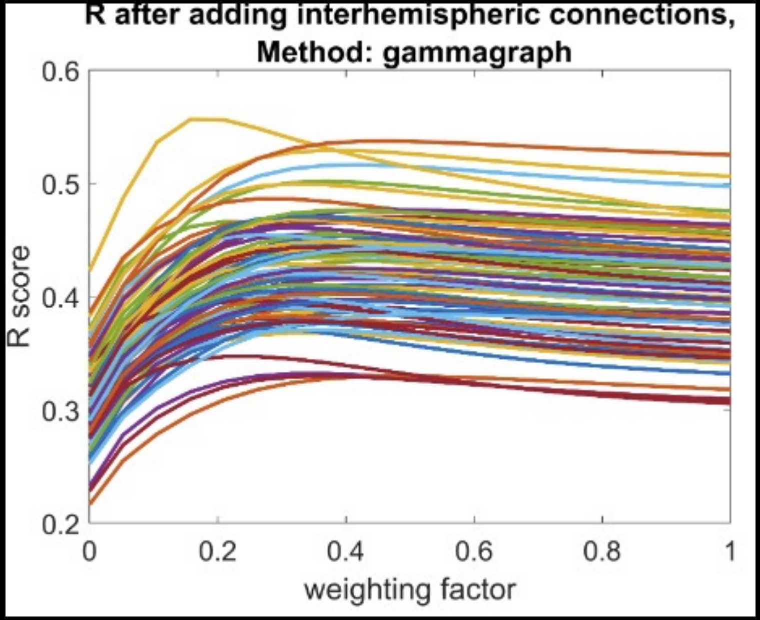
- Christopher Honey, Rolf Kötter, Michael Breakspear, Olaf Sporns. Network structure of cerebral cortex shapes functional connectivity on multiple time scales. Proceedings of the National Academy of Sciences, 104(24):10240–10245, 2007
- G Deco, V Jirsa, A McIntosh, O Sporns, R Kotter. Key role of coupling, delay, and noise in resting brain fluctuations. Proceedings of the National Academy of Sciences, 106(25):10302–10307, 2009
- Farras Abdelnour, Henning Voss, Ashish Raj. Network diffusion accurately models the relationship between structural and functional brain connectivity networks. NeuroImage, 90:335–347, 2014
- Selen Atasoy, Isaac Donnelly, Joel Pearson. Human brain networks function in connectome-specific harmonic waves. Nature Communications, 7:10340, 2016
- Farras Abdelnour, Michael Dayan, Orrin Devinsky, Thomas Thesen, Ashish Raj. Functional brain connectivity is predictable from anatomic network's Laplacian eigen-structure. NeuroImage, 172:728–739, 2018.
- Cassiano Becker, Sérgio Pequito, George Pappas, Michael Miller, Scott Grafton, Danielle Bassett, Victor Preciado. Spectral mapping of brain functional connectivity from diffusion imaging. Nature Scientific Reports, 8(1411), 2018
- Prejaas Tewarie, B Prasse, J Meier, F Santos, L Douw, M Schoonheim, C Stam, P Van Mieghem, A Hillebrand. Mapping functional brain networks from the structural connectome: Relating the series expansion and eigenmode approaches. Neuroimage, 216:116805, 2020
- Raphael Liégeois, Augusto Santos, Vincenzo Matta, Dimitri Van De Ville, Ali Sayed. Revisiting correlation-based functional connectivity and its relationship with structural connectivity. Network Neuroscience, 4(4):1235–1251, 12 2020
- Laura Suárez, Ross Markello, Richard Betzel, Bratislav Misic. Linking structure and function in macroscale brain networks. Trends in Cognitive Sciences, 24(4):302–315, 2020
- Xie, Cai, Damasceno, Nagarajan, Raj. Emergence of canonical functional networks from the structural connectome, NeuroImage, 2021

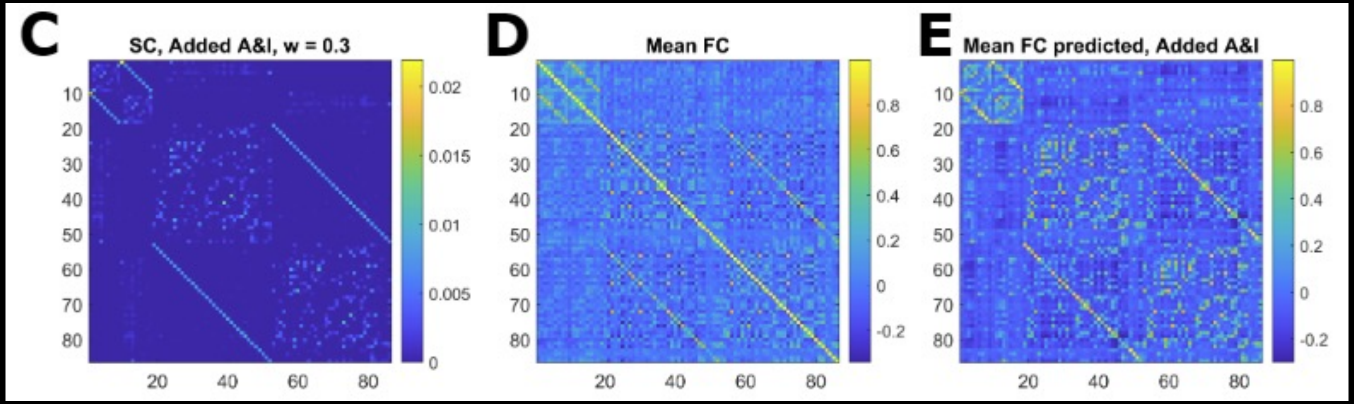
IMPROVING SC-FC CORRESPONDENCE USING GRAPH SPECTRA

- Further improvements can come from better mapping between FC and SC e-values
- E.g. replace exponential decay with Gamma function
- Adding latent and hard-to-measure inter-hemispheric connections between homologous regions greatly improves performance

  Cummings J, Sipes B, Mathalon D, Raj A. Predicting Functional Connectivity from Observed and Latent Structural Connectivity via Eigenvalue Mapping. Frontiers in Neuroscience, 2022.

- Future extensions could explore other data-driven mappings





CAN MODELS FIT SPECTRAL FEATURES (0 – 0.25 HZ) OF FMRI?

Need new analysis methods!

Presenting a simple rate model for fMRI

- Signal equation

$$\frac{dx_l(t)}{dt} = -1/\tau f(t) * (x_l(t) - \alpha \sum_{l \neq m}^{m} c_{l,m} x_m) + p_l(t)$$

- Laplacian Matrix

$$\mathcal{L}(\alpha) = \boldsymbol{I} - \alpha \boldsymbol{C}$$

- Graph equation

$$\frac{d\mathbf{x}(t)}{dt} = -\frac{1}{\tau} f(t) \star \mathcal{L}(\alpha)\mathbf{x}(t) + \mathbf{p}(t).$$

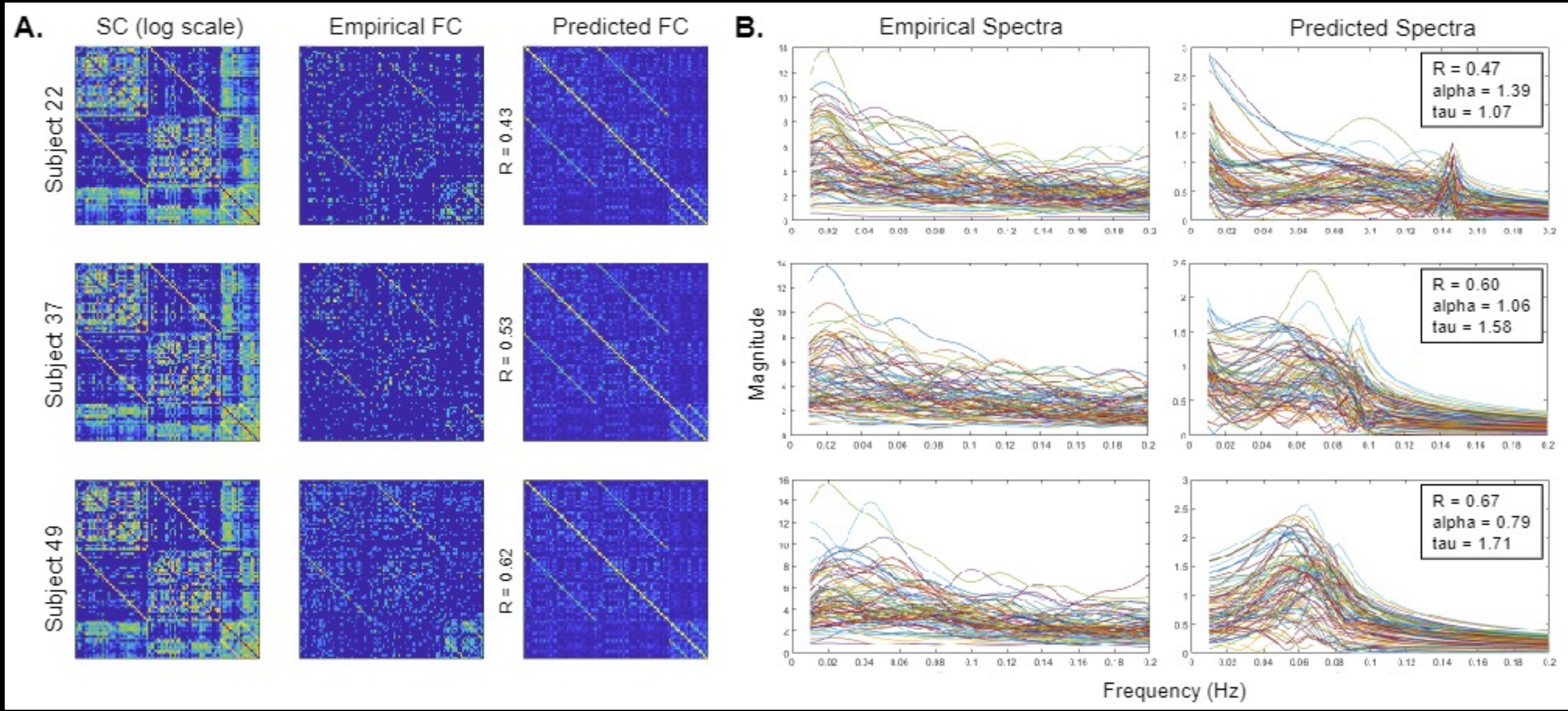
$$\boldsymbol{X}(\omega) = \sum_{k=1}^{N} \frac{\mathbf{u}_k \mathbf{u}_k^H}{j\omega + \tau^{-1}\lambda_k(\alpha) F(\omega)} \mathbf{P}(\omega),$$

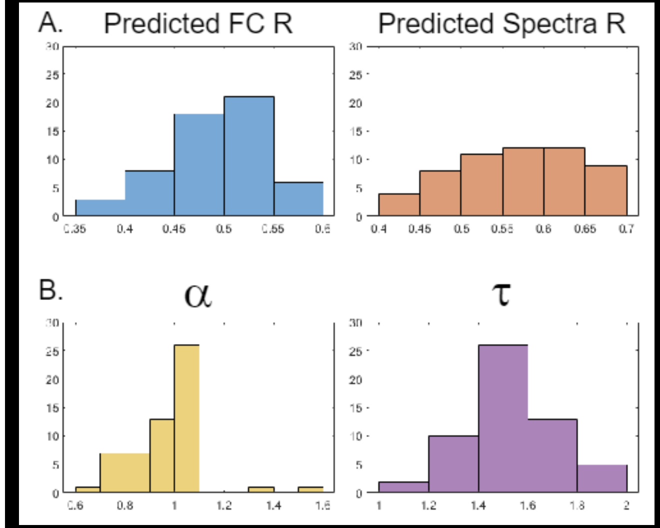
Frequency-response of fMRI can be explicitly written as sum over eigenmodes of Lap!

Eigenmodes predict spatial patterns

Each pattern has a spectral response that is a function of e-values

RESULTS – SGM FOR FMRI





- SGM predicts both FC matrix and regional power spectra of fMRI
- Fitted model parameters may be interpreted as "computational biomakrkers" of brain state or disease?
- Perhaps the first model that predicts and exploits higher-frequencies of fMRI?

IS THIS SAME AS SPECTRAL DCM?

Spectral DCM also seeks frequency-dependent generative model of fMRI

- DCM Signal equation

$$\frac{dx(t)}{dt} = Ax(t) + Bu(t) + v(t)$$

- In Fourier domain, written as transfer function involving the cross-spectral density of x and v:

$$PSD_X(\omega) = TF(\omega)\ PSD_v(\omega)$$

- Usually, *v* is assumed an autocorrelative signal
- Both SGM and spectral DCM use spectral features of signal
- BUT: this is where similarities end
  - Spectral DCM: estimate $A = \{a_{ij}\}$
  - SGM: use a known matrix $\mathcal{L}$, fit for global parameters that determine shape of spectral response
  - Hence SGM seeks a structure-function model, DCM seeks effective connectivity

MEG AND EEG: A SPECTRAL GRAPH MODEL OF HIGHER BRAIN OSCILLATIONS

HUMAN BRAIN MAPPING
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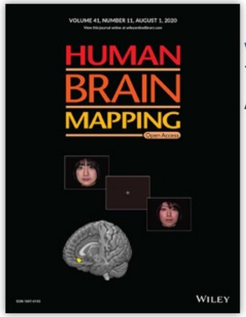
RESEARCH ARTICLE | Open Access

Spectral graph theory of brain oscillations

Ashish Raj, Chang Cai, Xihe Xie, Eva Palacios, Julia Owen ... See all authors

First published: 23 March 2020 | https://doi.org/10.1002/hbm.24991



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Pages 2980-2998

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Spectral graph theory model (SGM)

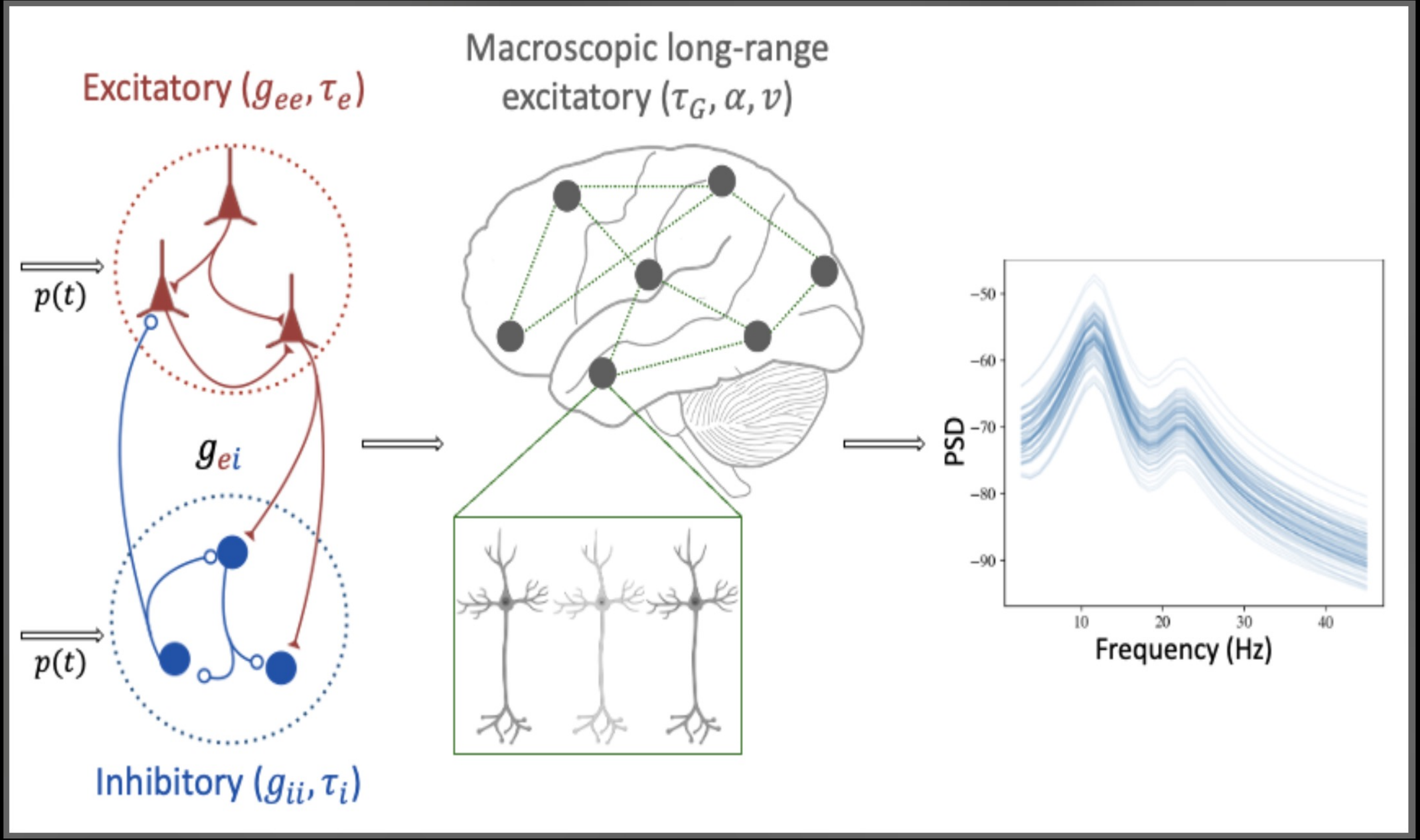
Local neural assemblies g_{ee}, g_{ii}, g_{ei}, τ_e, τ_i + White noise

↓

Macroscopic long-range connections τ_e, α, τ_G, v + Str connectivity matrix

↓

Frequency spectra -- Magnetoencephalography



MODELING HIGHER FREQUENCIES – EEG/MEG

- Need to introduce conduction speed, cortical processing delays
- The model is no longer network diffusion, strictly
- Closed form solution of steady state frequency behaviour

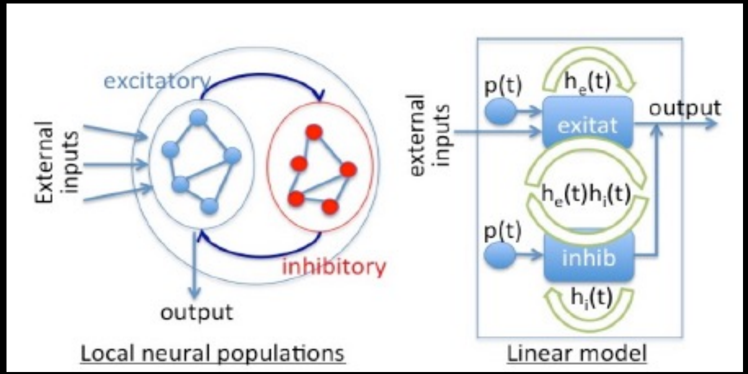
$$\frac{dx_{e/i}(t)}{dt} = -\frac{1}{\tau_{e/i}} f_{e/i}(t) * x_{e/i}(t) + \frac{1}{\tau_{e/i}} f_{e/i}(t) * \sum_{j,k} c_{jk} x_{e/i}(t - \tau^v_{jk}) + p_{e/i}(t)$$

Gamma-shaped neural response function

Complex Connectome

$$C^*(\omega|\boldsymbol{v}) = \{c_{jk} \exp(-i\, \tau^v_{jk}\, \omega)\}$$

$$\mathcal{L}(\omega|v, \alpha) = I - \alpha C^*(\omega|v)$$



eigenmodes

$$\boldsymbol{X}(\omega) = \sum_i \frac{\boldsymbol{u}_i(\omega)\boldsymbol{u}_i^H(\omega)}{j\omega + \frac{1}{\tau_G}\lambda_i(\omega)F_e(\omega)} H_{local}(\omega)\boldsymbol{P}(\omega)$$

eigenvalues

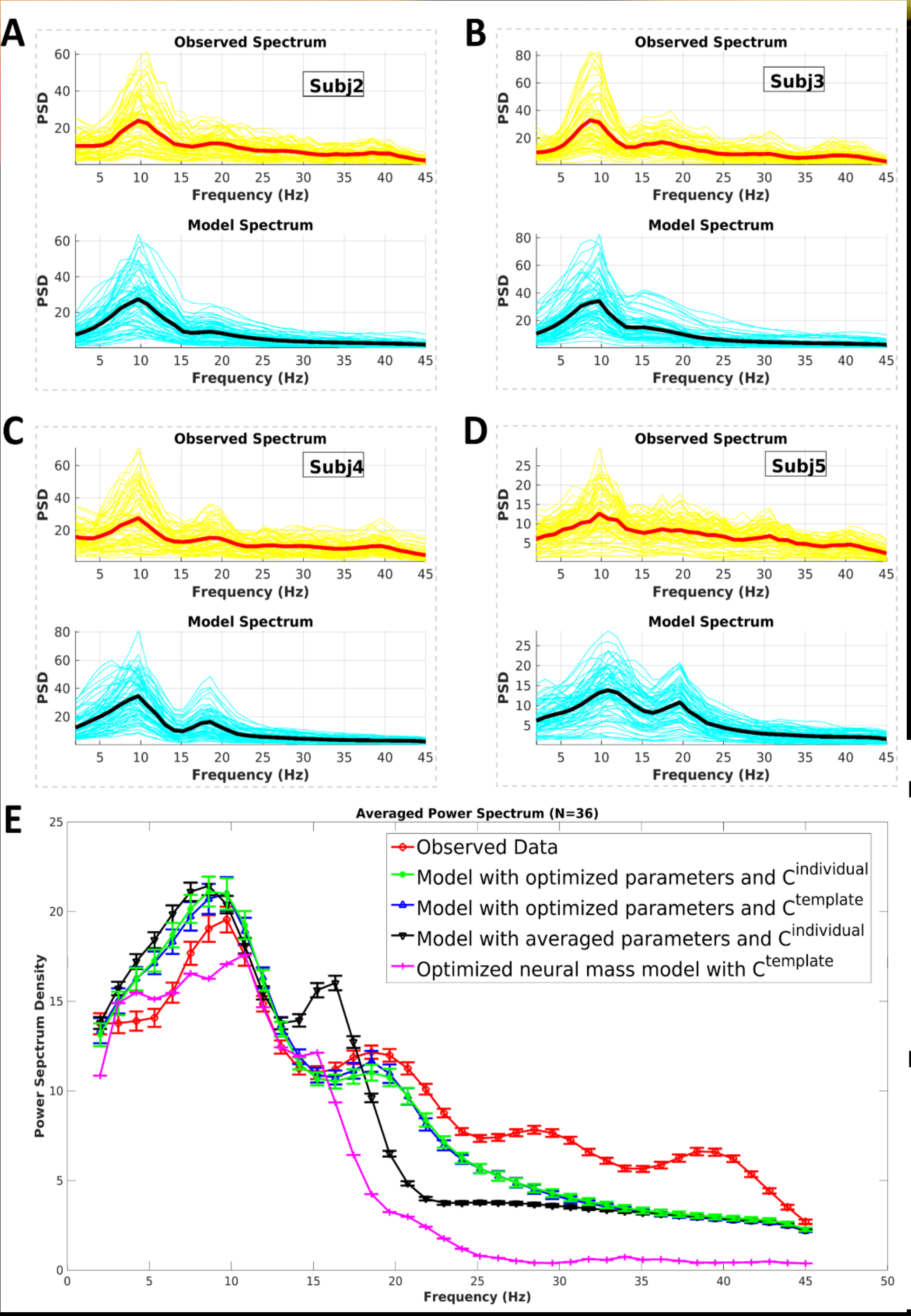
Raj et al. Spectral graph theory of brain oscillations. Human Brain Mapping 2020

Verma *et al. SGM Revisited, Neuroimage 2022*

RESULTS

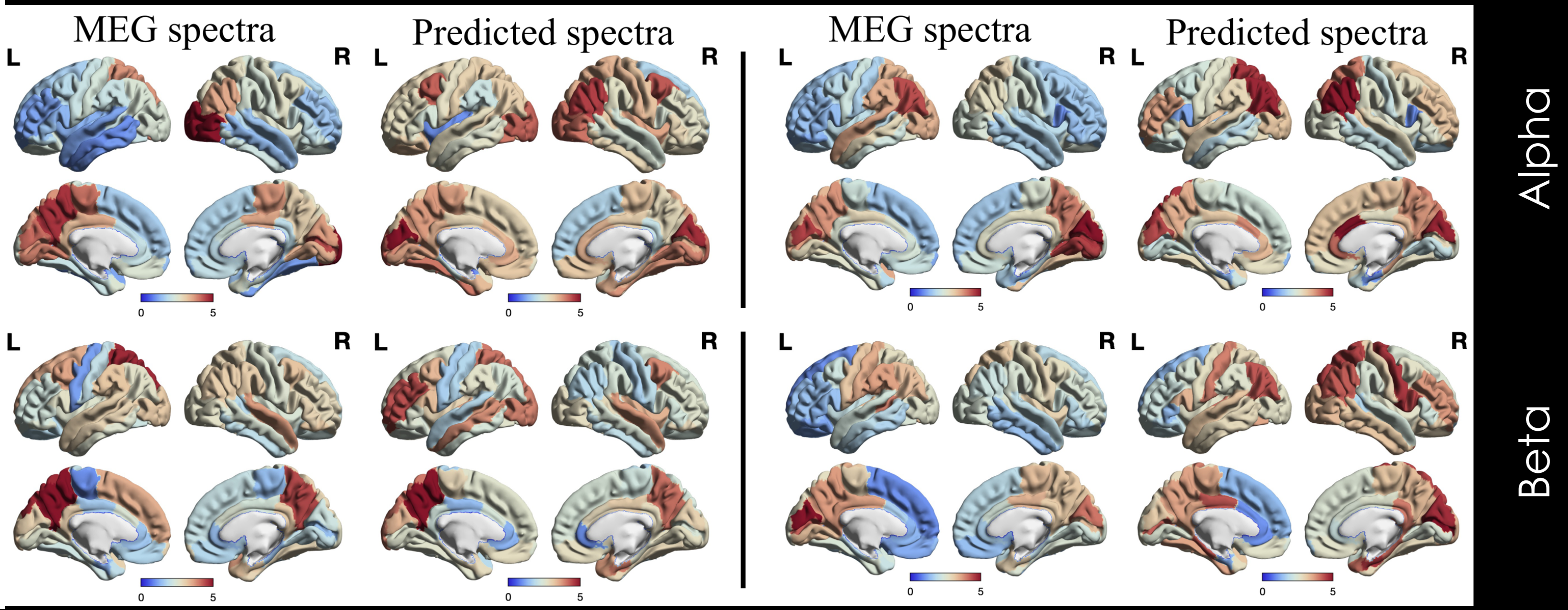
Raj, Ashish, et al. *Human brain mapping* (2020)

- SGM correctly fits empirical MEG power spectra
- Does better than NMM
- Sensitive to model parameters (need to be optimized)
- Simultaneously predicts spatial patterns!



Verma *et al.*, 2022, *Neuroimage*

Band-specific spatial distribution



SGM VS NEURAL MASS MODEL

Neural Mass Model

Spectral Graph Model

- Node-level local NMMs coupled via connectome
- Solved by differential equations
- Can simulate neural activity on the whole brain network
- Proven in M/EEG and fMRI

Neural Mass Model:

- Large # of coupled non-linear 2^{nd} order Diff Eqns
- Numerical integration used to simulate over long model times
- Activity and FC patterns indirectly observed from simulations
- Parameter inference is very tough
  - Requires step-wise, manual or heuristic optimization

Spectral Graph Model:

- Linear vector-valued 1st order Diff Eqn
- Has closed-form solution in Fourier domain!
- Activity and FC directly given by solution
- Going to linear does not cause loss of performance!
  - Frequently better than coupled NMMs
- Parameter inference is simple and fast, no hand-selection needed

SGM: STABILITY AND DYNAMICS

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Spectral graph theory model (SGM)

Local neural assemblies - $g_{ee}, g_{ii}, g_{ei}, \tau_e, \tau_i$

White noise

Macroscopic long-range connections - $\tau_e, \alpha, \tau_G, v$

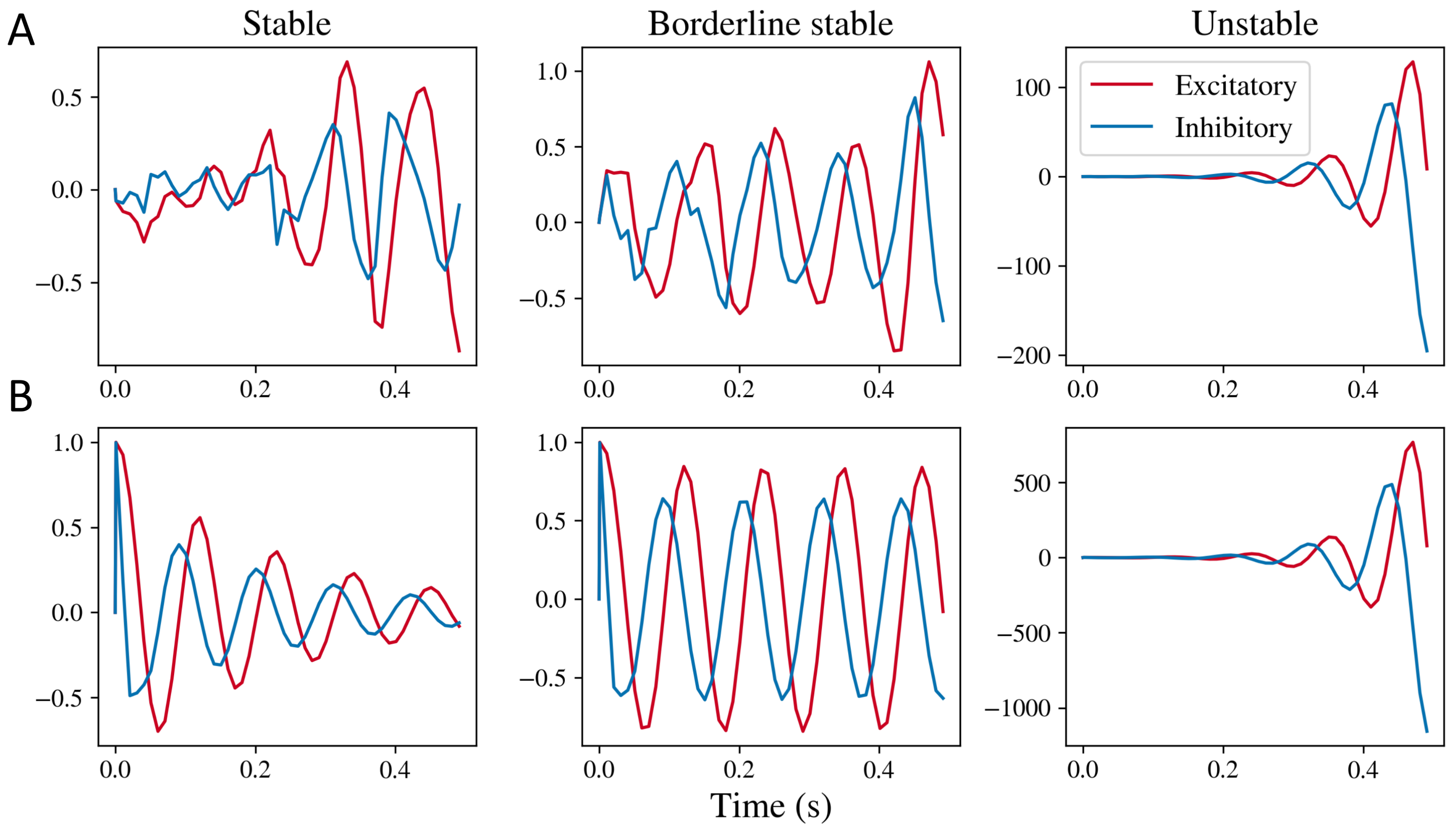
Structural connectivity matrix (Diffusion MRI)

Frequency spectra -- Magnetoencephalography

Local neural assemblies - simulations

With noise

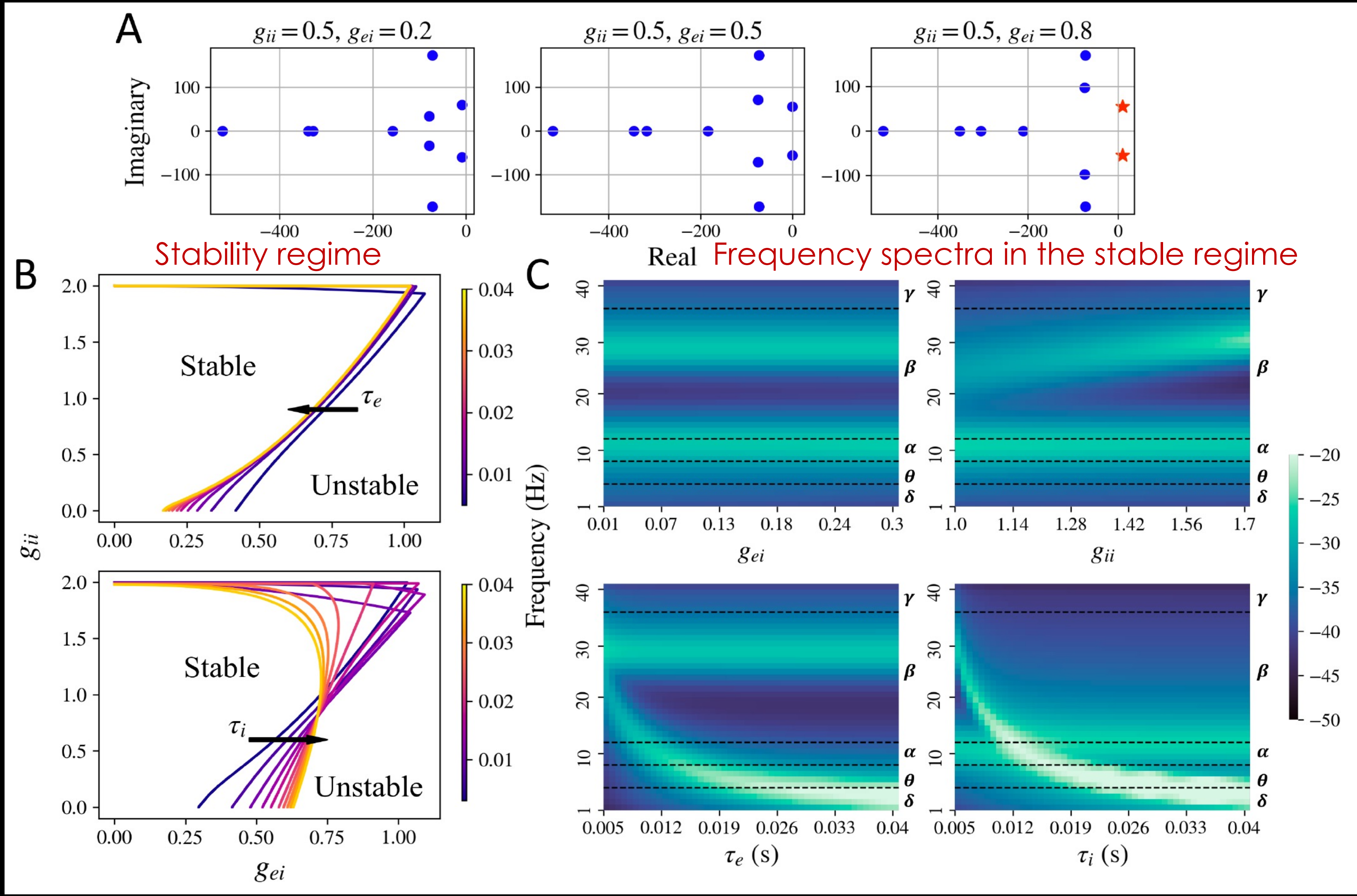
Without noise



- In a linear system, stability is a function strictly of model parameters, not of input noise
- Recall in nonlinear coupled NMMs, meta-/multi-stability is governed by noise

Verma *et al.*, 2022, Network Neuroscience

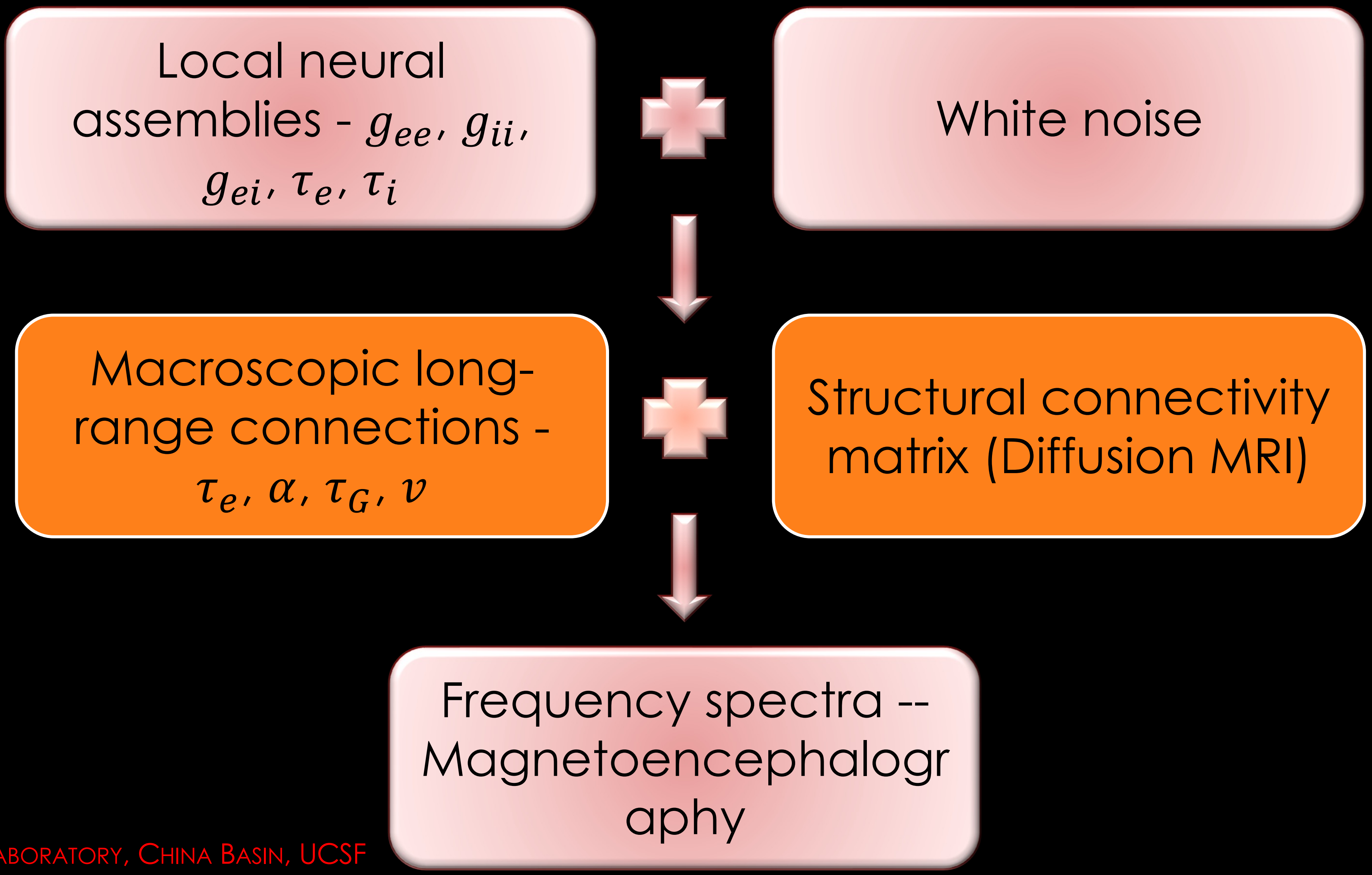
Stability of local SGM



Raj Laboratory, China Basin, UCSF

Verma *et al.*, 2022, Network Neuroscience

Spectral graph theory model (SGM)

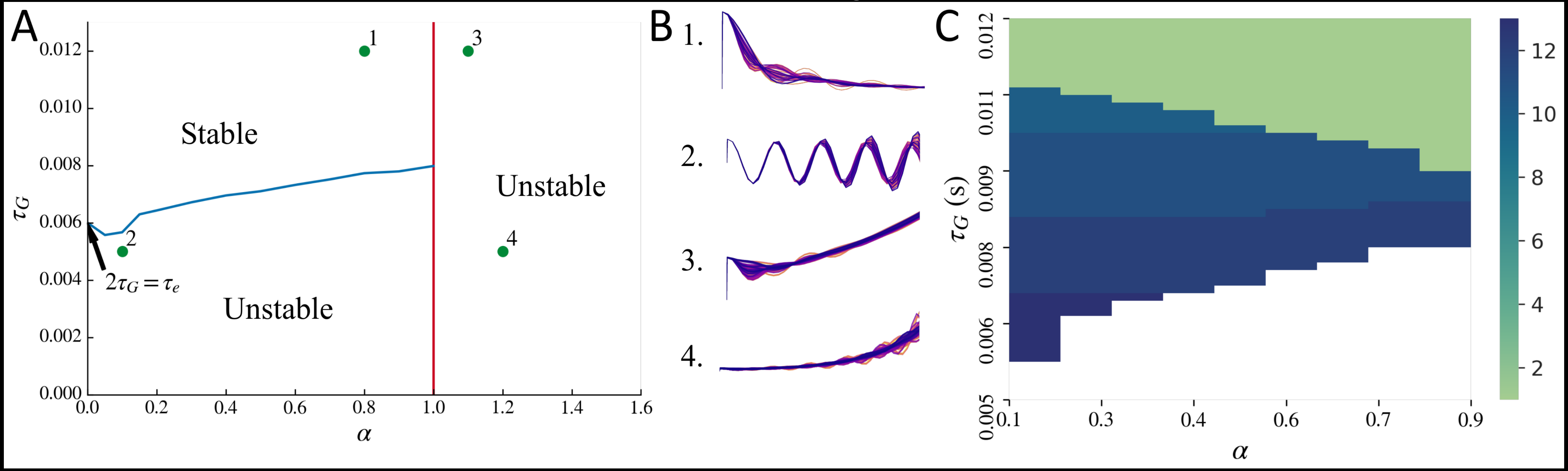


Stability of macroscopic SGM

Stability regimes

Simulations in different regimes

Peak frequency of macro signal



Verma *et al.*, 2022, Network Neuroscience

Dynamics in MEG ➔ dynamics in model parameters

Stability and dynamics of a spectral graph model of brain oscillations

Poster No:

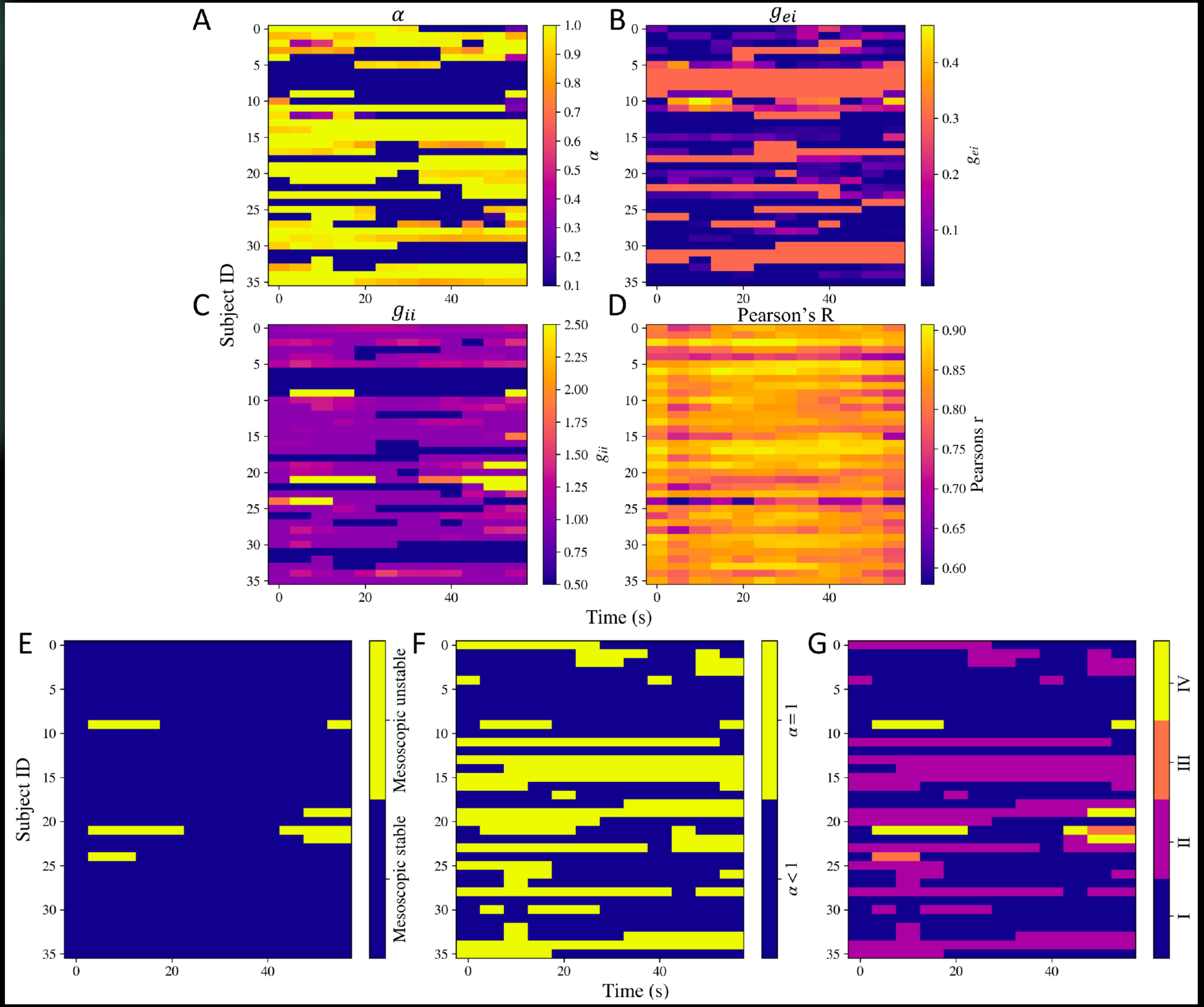
1732

Submission Type:

Abstract Submission

Authors:

Parul Verma[1], Srikantan Nagarajan[1], Ashish Raj[1]



Verma *et al.*, 2022, Network Neuroscience

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SGM: APPLICATIONS IN NEUROLOGICAL DISEASE (ALZHEIMER'S)

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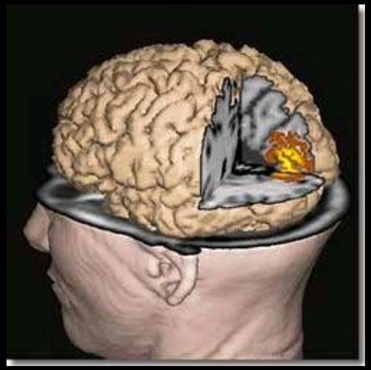
FROM MEG AND FMRI TO BIOLOGICAL PARAMETERS TO DISEASE BIOMARKERS



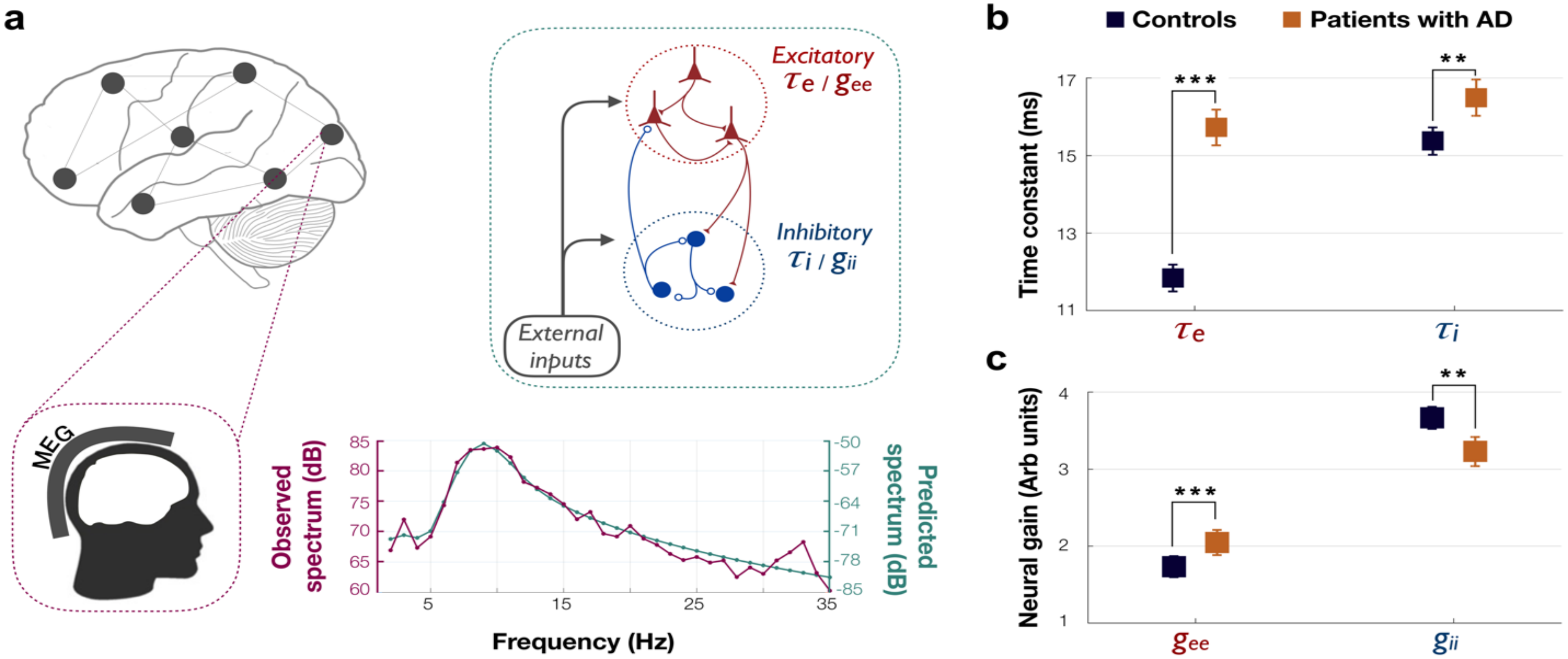
Fitted model parameters (with biophysical meaning)

- Wish to infer model parameters that give rise to given MEG, EEG and fMRI
- SGM gives a small set of only 6 biophysically interpretable global model parameters
- Local model inferred by fitting regional frequency spectra
- Global parameters by fitting regional spectra AND spatial distributions of different frequency bands
- Application: inferred parameters can serve as biomarkers of disease
  - e.g. Schizophrenia, autism, epilepsy, Alzheimer,…

Extension: time-varying (dynamic) models to capture brain states

LOCAL NEURAL ASSEMBLIES – APPLICATION TO AD

- AD shows a strong down-shift in alpha band power and frequency
  - Strong up-shift in delta-theta power
- First we explore local-only models
- i.e. local (mesoscopic) parameters as biomarkers



Raj Laboratory, China Basin, UCSF

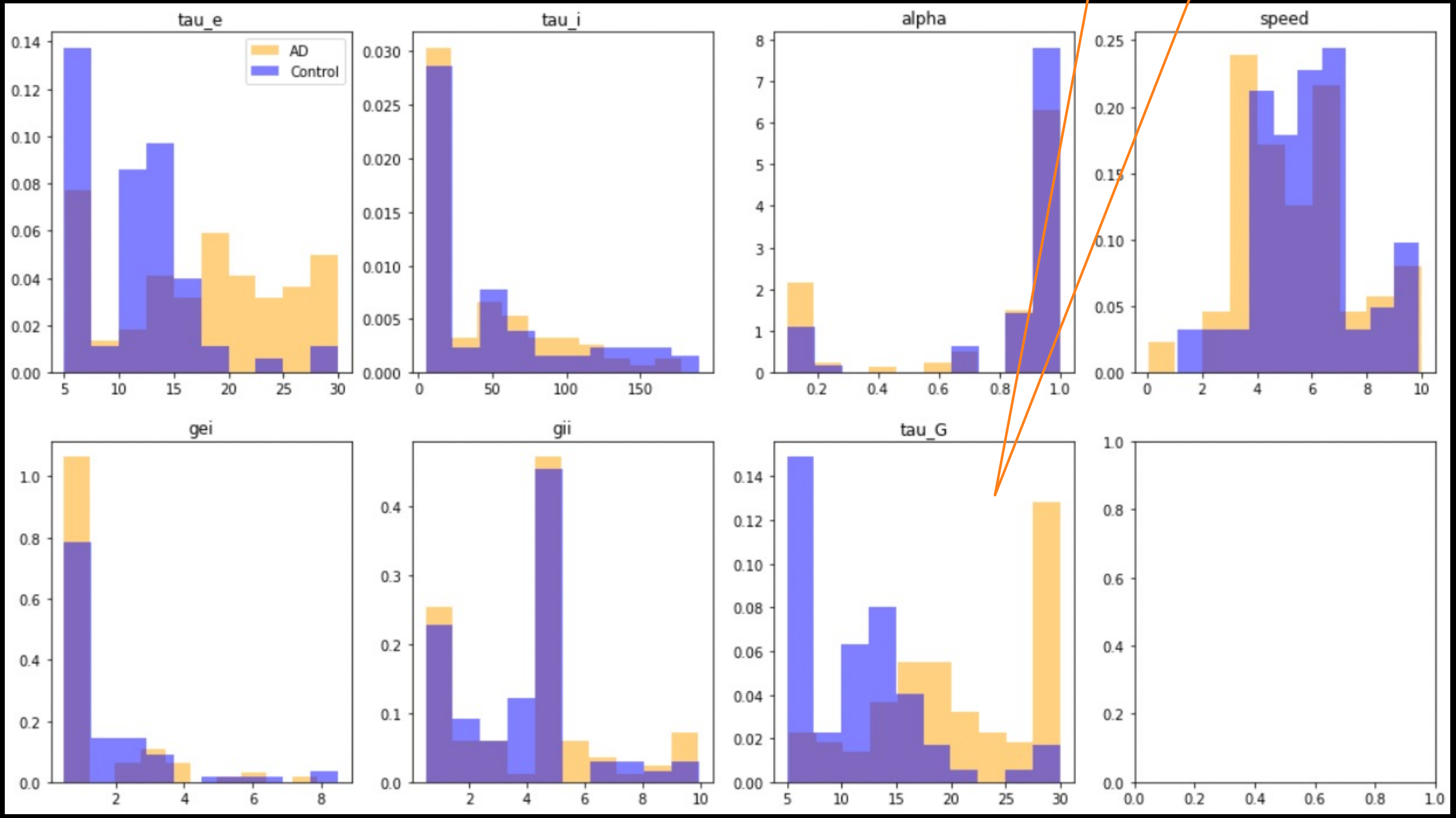
Ranasinghe *et al.*, 2022, eLife, *in print*

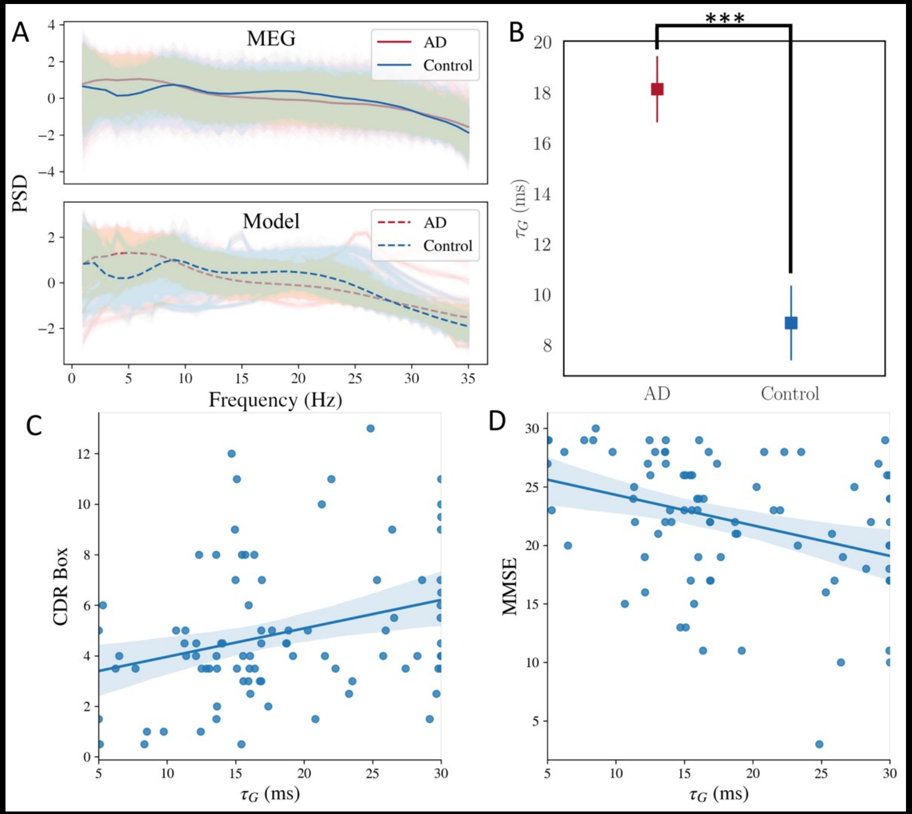
MACROSCOPIC SGM – APPLICATION TO AD

- Fitting macroscopic SGM only (keep all local parameters uniform)
- SGM needs only 6 biophysical global parameters

Example: global fitting to MEG in Alzheimer's disease

Single-most important change





Verma *et al.*, 2022, *submitted*

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- Chang Cai

Collaborators

- Fei Jiang
- Kamalini Ranasinghe

WE ARE HIRING!

Please contact for inquiries and job opportunities

- Ashish.raj@ucsf.edu
- https://radiology.ucsf.edu/research/labs/brain-networks-lab
- Lots of code on GitHub: https://github.com/Raj-Lab-UCSF