Assessing uncertainty in dynamic functional connectivity estimation

Jaroslaw Harezlak, Ph.D.
Indiana University RM Fairbanks School of Public Health

BIRS, Banff, AB, Canada
02/02/2016

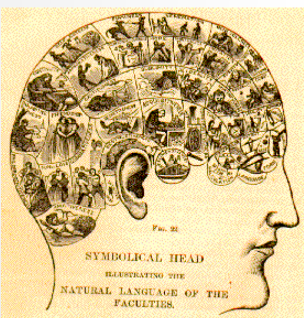
Background

Localizationism

Functions are localized
in anatomic cortical regions

Damage to a region results
in loss of function

Key 19th Century proponents:
Gall, Spurzheim



Functional Segregation

Functions are carried out by
specific areas/cells in the
cortex that can be anatomically
separated

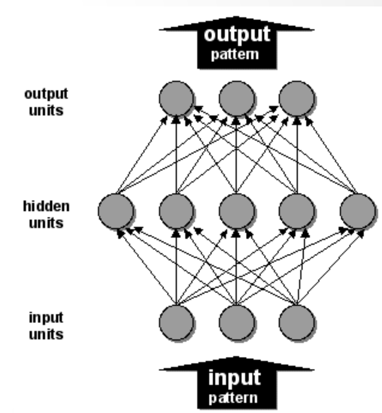
Globalism

The brain works as a whole,
extent of brain damage is
more important than its
location

Key 19th Century proponents:
Flourens, Goltz

Connectionism

Networks link different
specialised areas/cells



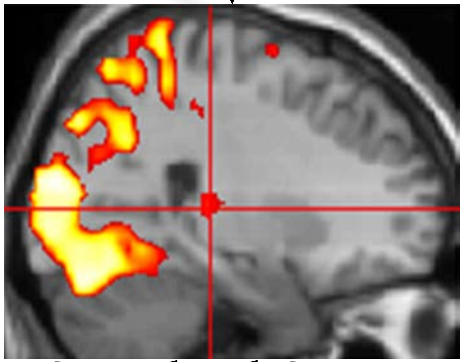
Functional Specialisation
Different areas of the brain are
specialised for different functions

Functional Integration
Networks of interactions among
specialised areas

Systems analysis in functional neuroimaging

Functional Segregation
Specialized areas exist in the cortex

- Analyses of regionally specific effects
- Identifies regions specialized for a particular task.
- Univariate analysis



Standard SPM

Functional Integration
Networks of interactions among specialized areas

- Analysis of how different regions in a neuronal system interact (coupling).
- Determines how an experimental manipulation affects coupling between regions.
- Univariate & Multivariate analysis

Functional connectivity

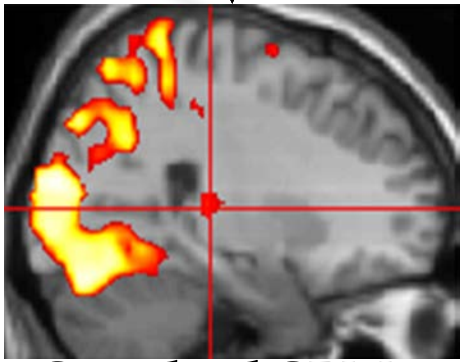
Effective connectivity

Adapted from D. Gitelman, 2011

Systems analysis in functional neuroimaging

Functional Segregation
Specialised areas exist in the cortex

- Analyses of regionally specific effects
- Identifies regions specialized for a particular task.
- Univariate analysis



Standard SPM

Functional Integration
Networks of interactions among specialised areas

- Analysis of how different regions in a neuronal system interact (coupling).
- Determines how an experimental manipulation affects coupling between regions.
- Univariate & Multivariate analysis

Functional connectivity

Effective connectivity

Adapted from D. Gitelman, 2011

Basic terminology

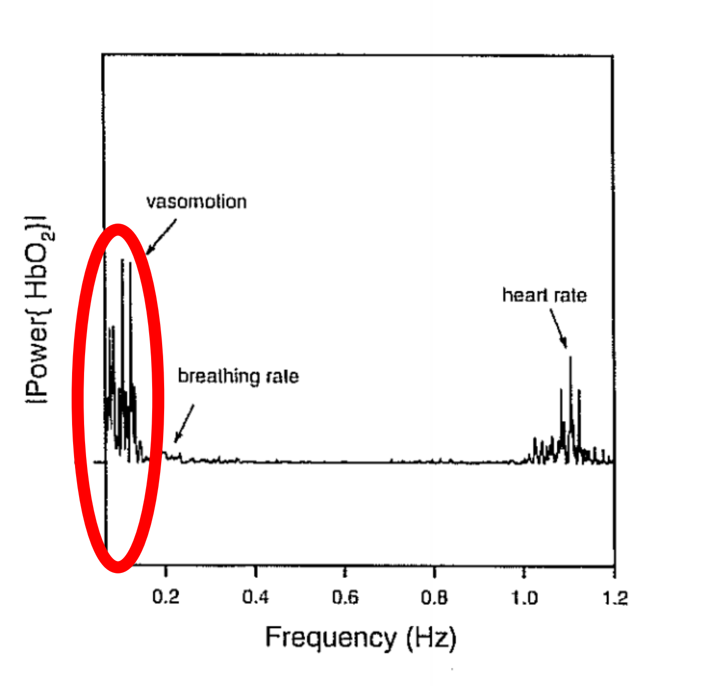
- Functional connectivity (FC) evaluates functional magnetic resonance imaging (fMRI) data for statistical associations or dependency among two or more anatomically distinct time-series.
- Correlation is the most popular measure of FC.
- One of the most popular methods to assess dynamically changing FC is the sliding window technique.
- “Rest” is a task state in itself, with potential performance differences, rather than differences in the underlying, stable brain organisation (Buckner et al., 2008, 2013)

Spontaneous BOLD activity

- brain is always active, even in the absence of explicit input or output
  - task-related changes in neuronal metabolism are only about 5% of brain's total energy consumption

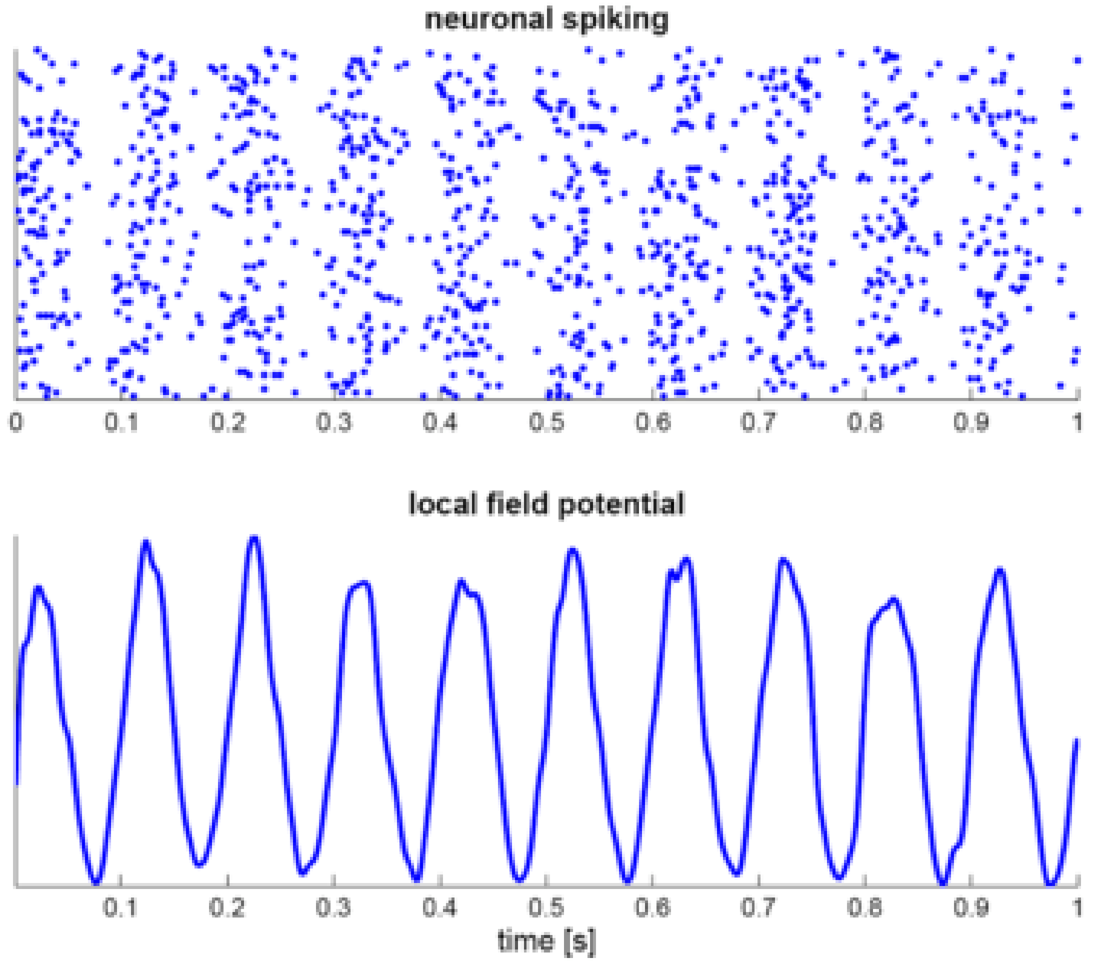
- what is the "noise" in standard activation studies?
  - faster frequencies related to respiratory and cardiac activities
  - spontaneous, neuronal oscillations between 0.01 – 0.10 Hz

< 0.10 Hz



Changes in reflected and scattered light signal (indicating neuronal activity) at a pervasive low-frequency (0.1-Hz) oscillation correlate with vasomotion signals (Mayhew et al., 1996)

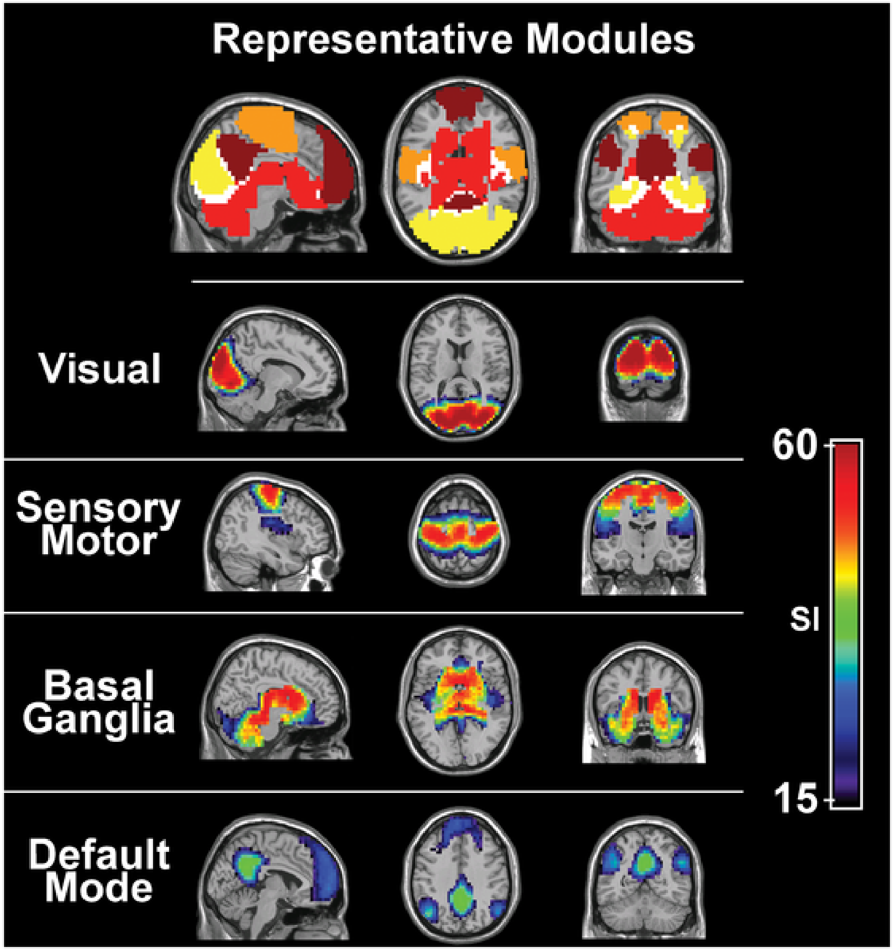
Brain is never static!



Connected neural populations tend to synchronize and oscillate together.

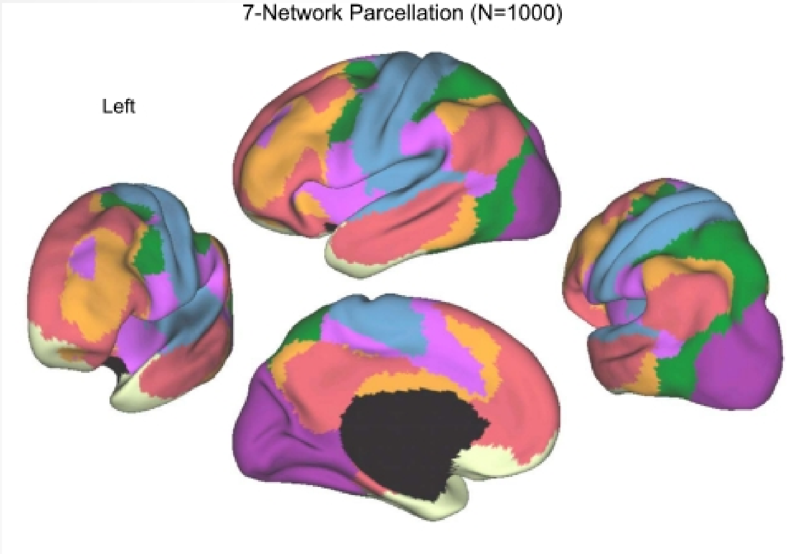
Resting-state networks (RSNs)

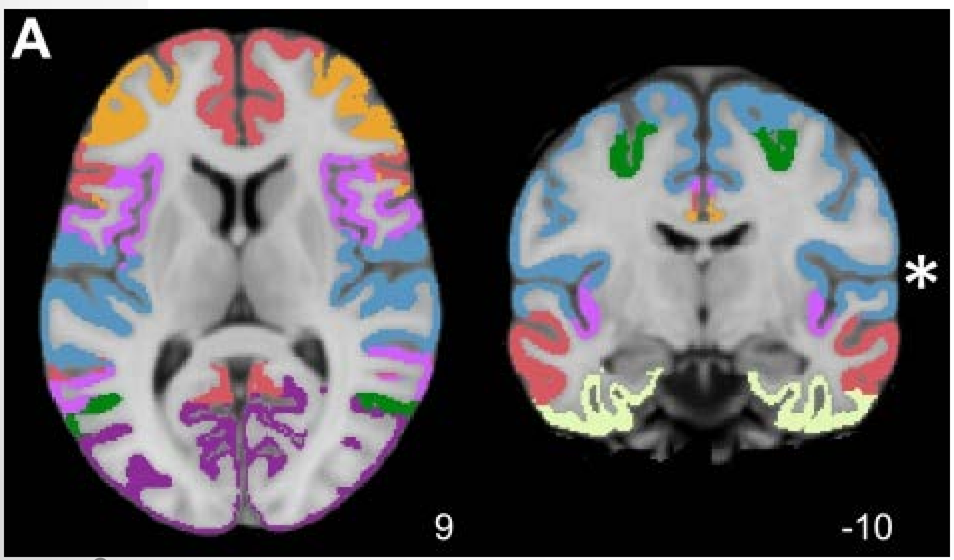
- Multiple resting-state networks (RSNs) have been found
  - All show activity during rest and during tasks
  - One of the RSNs, the default mode network (DMN), shows a decrease in activity during cognitive tasks



Moussa et al (2012)

Example -Yeo 7



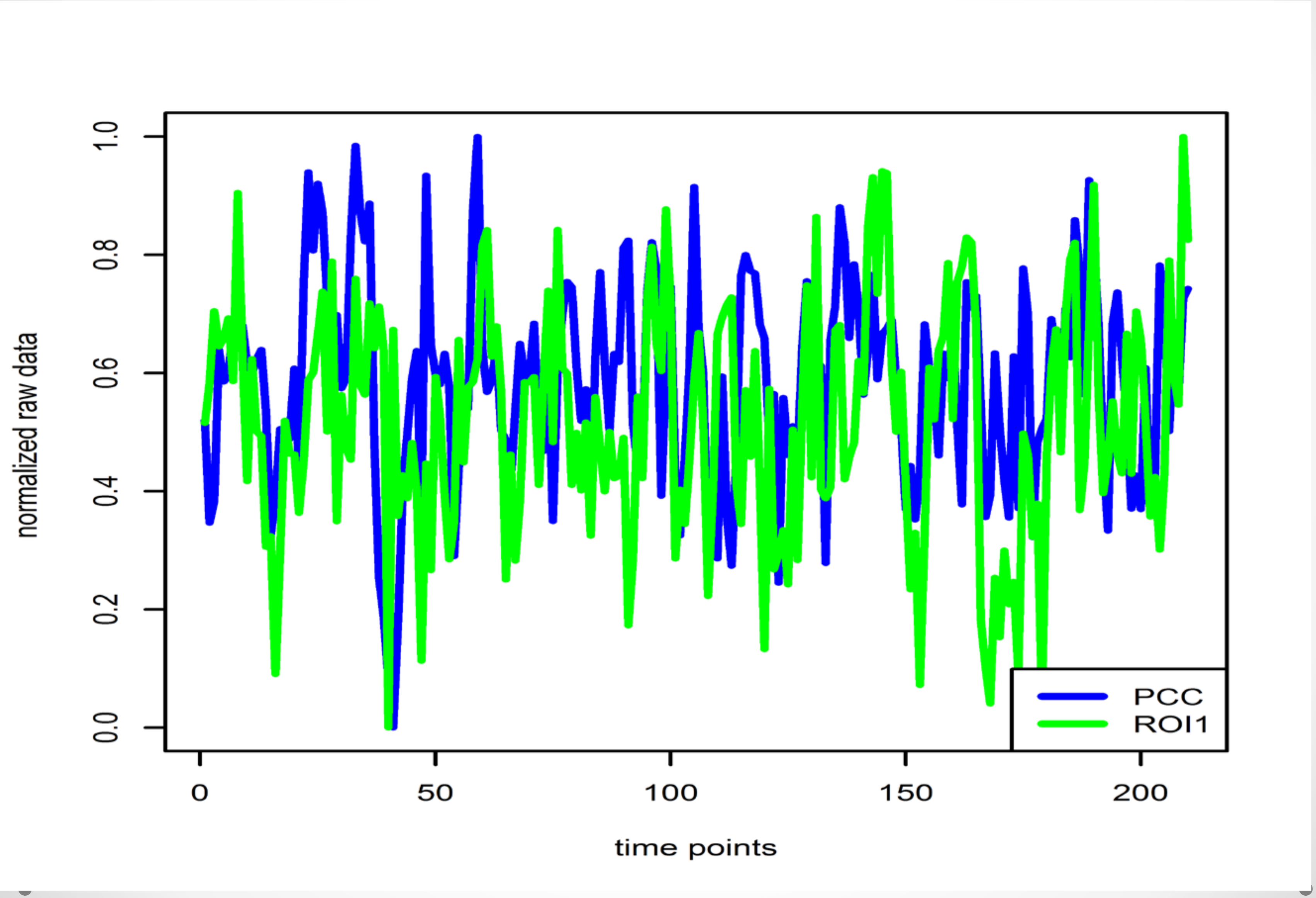


- Purple (Visual)
- Blue (Somatomotor)
- Green (Dorsal Attention)
- Violet (Ventral Attention)
- Cream (Limbic)
- Orange (Frontoparietal)
- Red (Default)

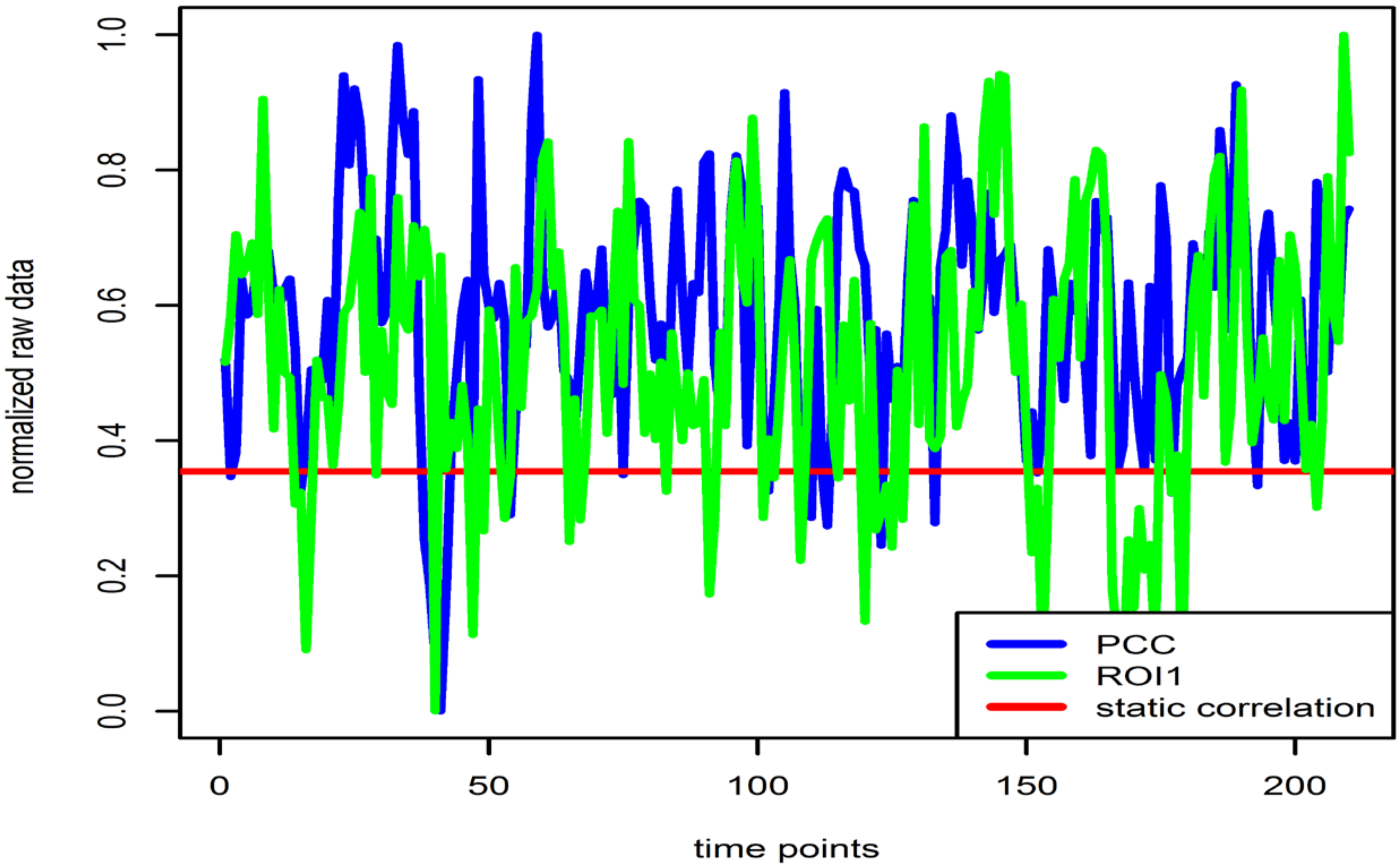
Our goals

- Assessment of uncertainty in the dynamic functional connectivity
- Hypothesis testing for differences in the dynamic functional connectivity arising in the task-based experiments

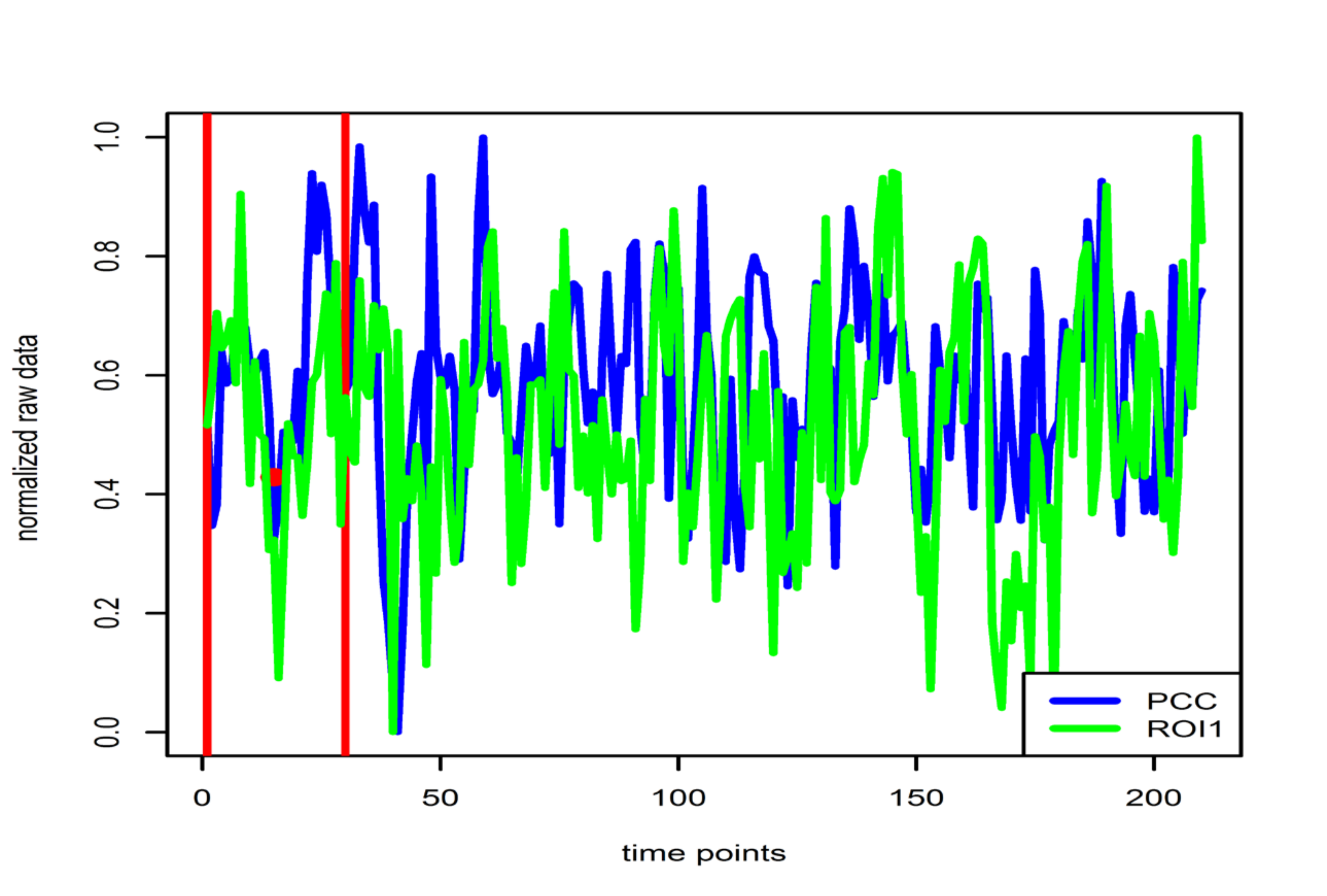
Problem introduction



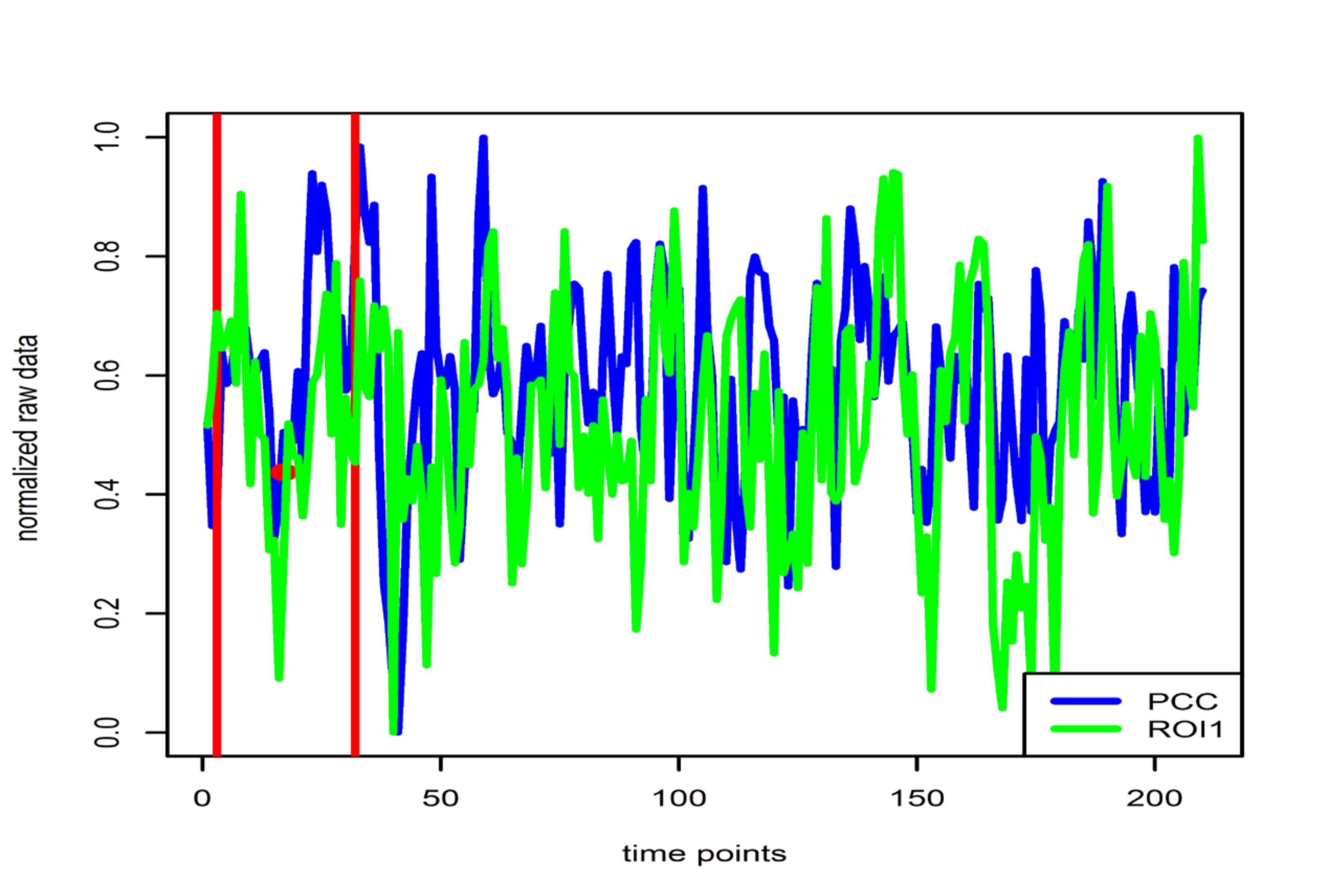
Static correlation



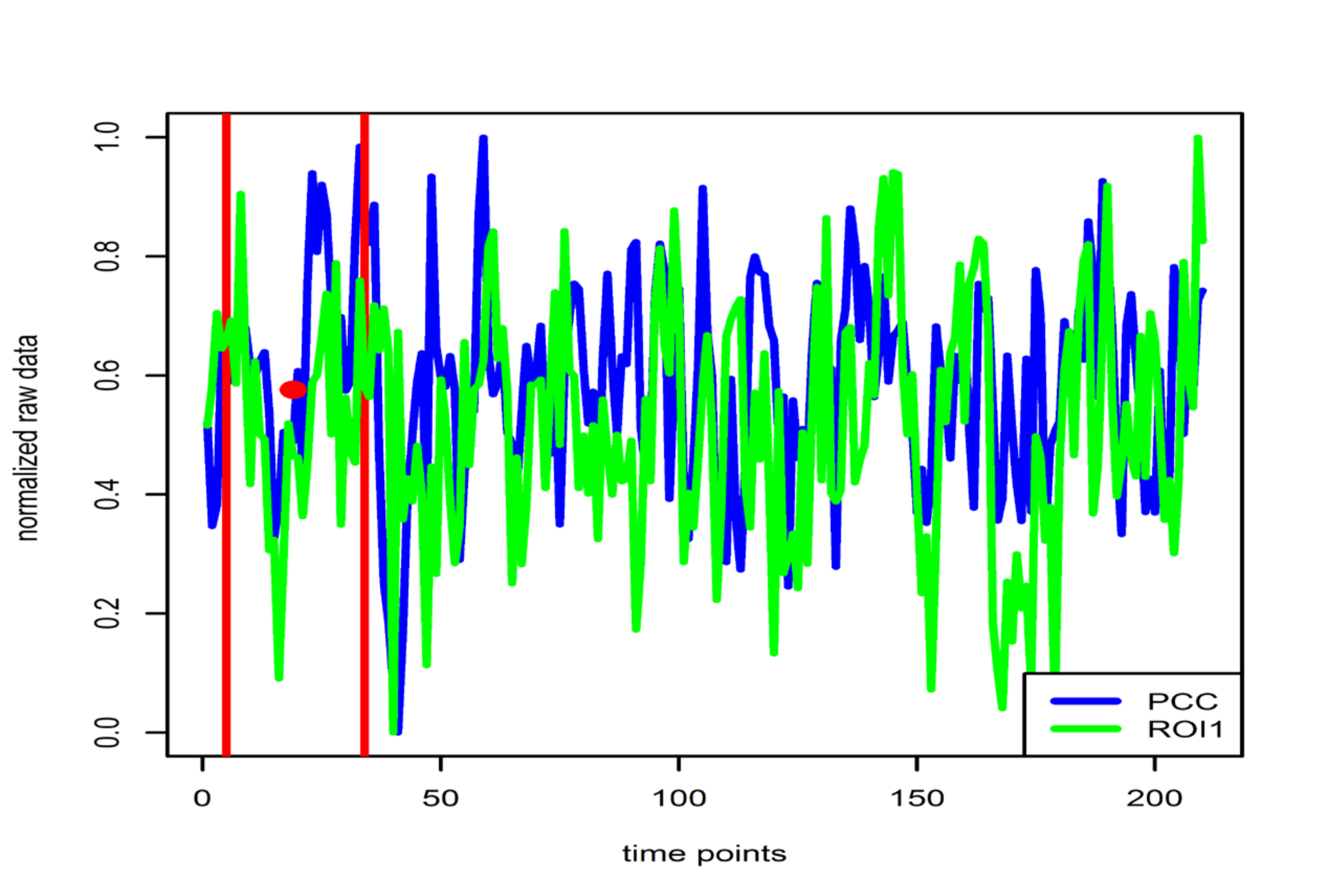
The sliding window technique



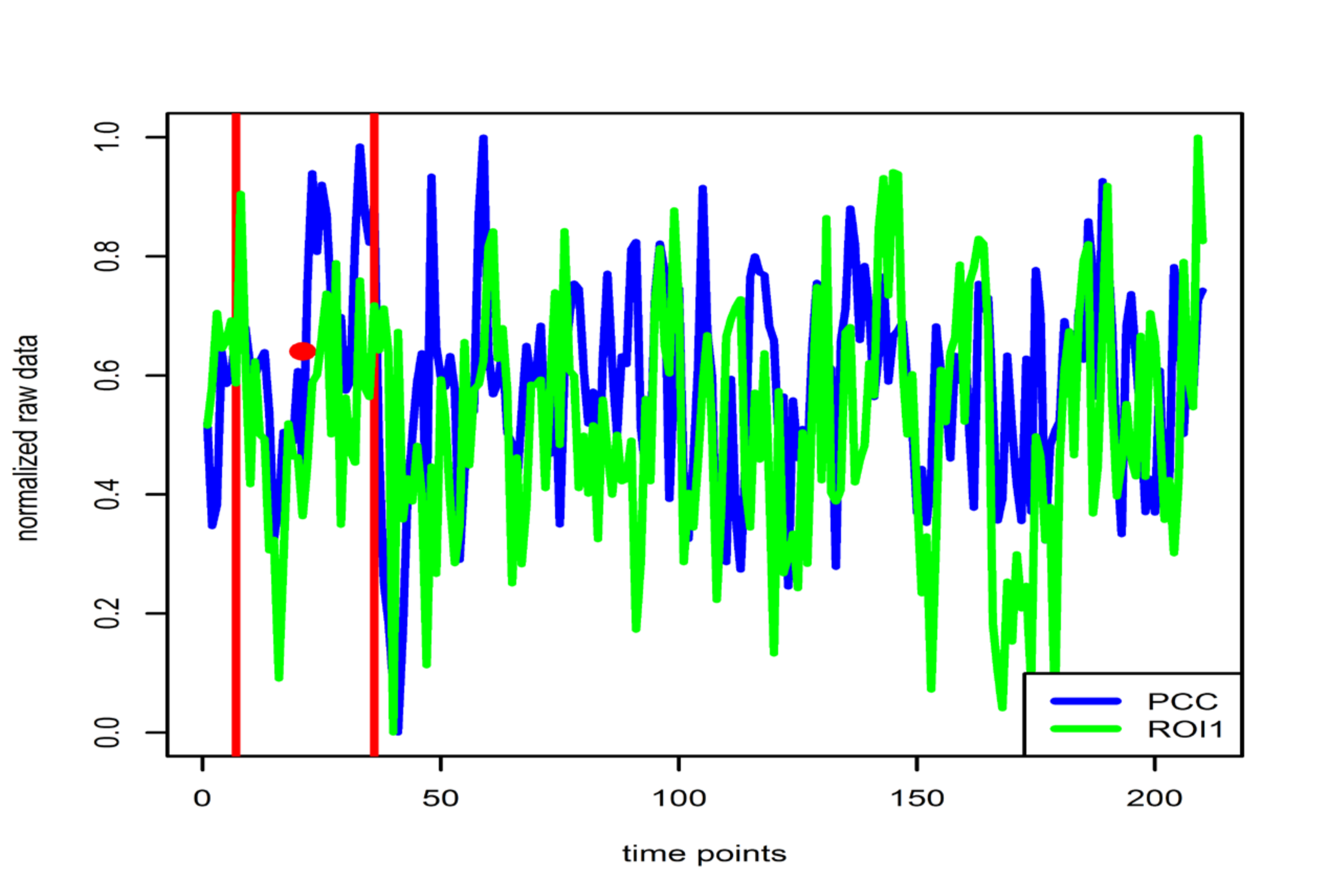
The sliding window technique



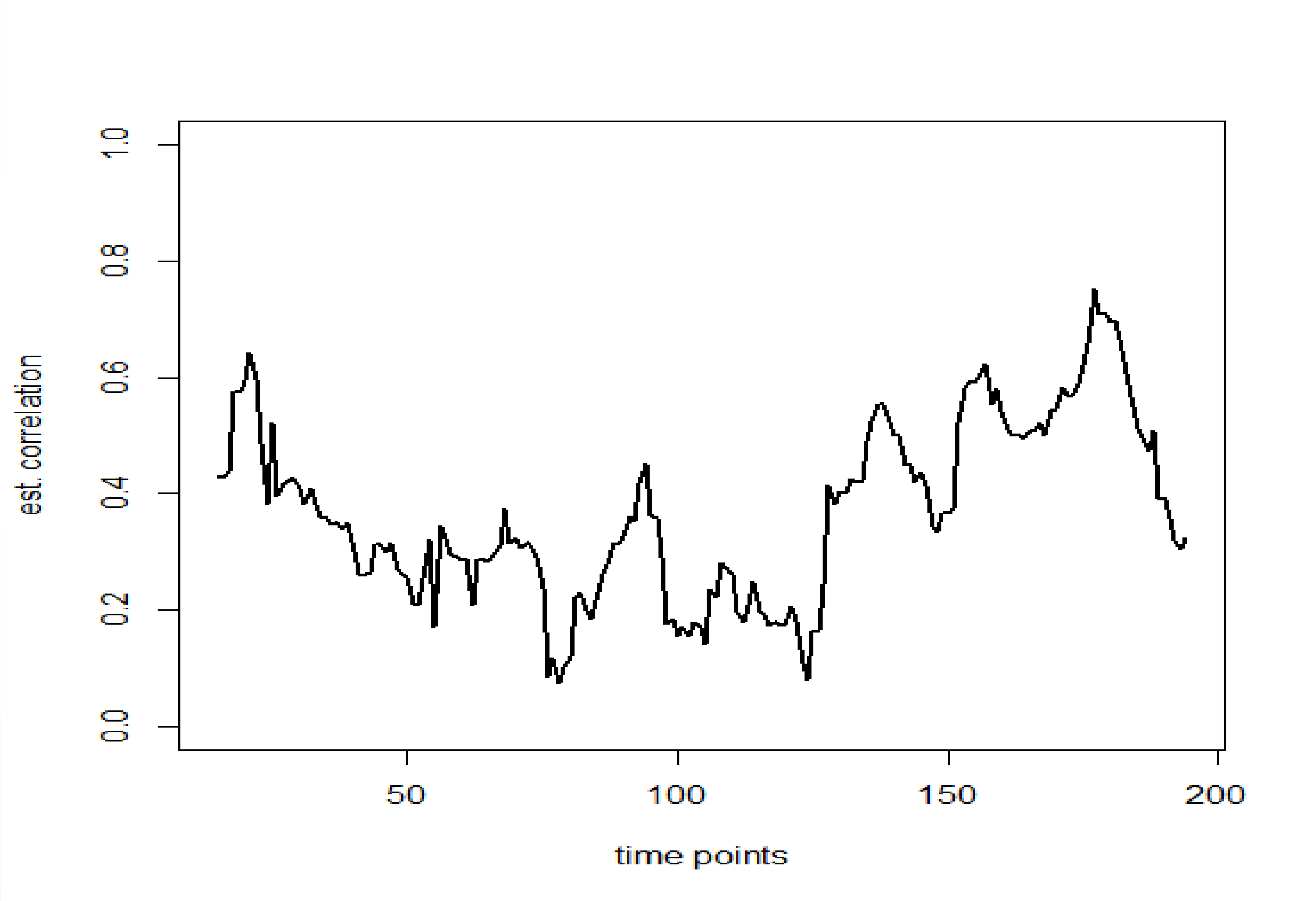
The sliding window technique



The sliding window technique



Sliding window-based correlation estimate



Pros and cons of the sliding window method

Pros:

- Intuitive
- Simple to implement
- Model-free (nonparametric)
- Distribution-free

Cons:

- Arbitrary window lengths
- Inability to deal with abrupt changes
- Equal weight given to all observations within a window
- Inherent variation present in the estimate

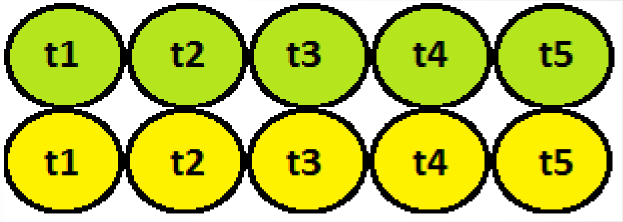
Our proposal for the FC uncertainty estimation

- Estimate is nonparametric and distribution-free
- Asymptotic methods rely on relatively large sample sizes
- Bootstrap to the rescue
- However, we need a sophisticated bootstrap approach

Multivariate Linear Process Bootstrap(MLPB)

- Common bootstrap methods are not applicable to the time series data.

- MLPB allows us to resample multivariate time series data.



Intuition behind MLPB

Assume that $Y \sim N(0, \Sigma)$

$$W = \Sigma^{-1/2} * Y \sim N(0, I_n)$$

Resample $W \implies W^*$.

Generate a bootstrap sample:

$$Y^* = \Sigma^{1/2} * W^*$$

MLPB algorithm

1. Let X be the $(d \times n)$ data matrix consisting of $\mathbb{R}^d$ valued time series data $\underline{X}_1, \cdots, \underline{X}_n$ of sample size n. Compute the centered observations $\underline{Y}_t = \underline{X}_t - \overline{\underline{X}}$ where $\overline{\underline{X}} = \frac{1}{n}\sum_{t=1}^{n} \underline{X}_t$, let Y be the corresponding $(d \times n)$ matrix of centered observations and define $\underline{Y} = vec(Y)$ to be dn − dimensional vectorized version of Y.

2. Compute $\underline{W} = \left(\hat{\Gamma}^{\epsilon}_{\kappa,l}\right)^{-\frac{1}{2}} \underline{Y}$, where $\left(\hat{\Gamma}^{\epsilon}_{\kappa,l}\right)^{\frac{1}{2}}$ denotes the lower left triangular matrix L of Cholesky decomposition $\hat{\Gamma}^{\epsilon}_{\kappa,l} = LL^T$

3. Let $\underline{Z}$ be the standardized version of $\underline{W}$, that is, $Z_i = \frac{W_i - \overline{W}}{\hat{\sigma}_W}, i = 1, \cdots, dn$, where $\overline{W} = \frac{1}{dn}\sum_{t=1}^{dn} W_t$ and $\hat{\sigma}^2_W = \frac{1}{dn}\sum_{t=1}^{dn}(W_t - \overline{W})^2$.

4. Generate $\underline{Z}^* = (Z^*_1, \cdots, Z^*_{dn})^T$ by performing i.i.d. resampling from $\{Z_1, \cdots Z_{dn}\}$.

5. Compute $\underline{Y}^* = \left(\hat{\Gamma}^{\epsilon}_{\kappa,l}\right)^{\frac{1}{2}} \underline{Z}^*$ and let Y^* be the matrix that is obtained by placing this vector column-wise into an $(d \times n)$ matrix with columns $\underline{Y}^*_1, \cdots, \underline{Y}^*_n$. Define X^* to be $(d \times n)$ matrix consisting of columns $\underline{X}^*_t = \underline{Y}^*_t + \overline{\underline{X}}$

Key idea behind MLPB

- Obtain an estimator $\hat{\Gamma}^{\epsilon}_{\kappa,l}$ of Γ_{dn} , which is consistent and positive definite for all finite sample sizes (needed for Cholesky decomposition).

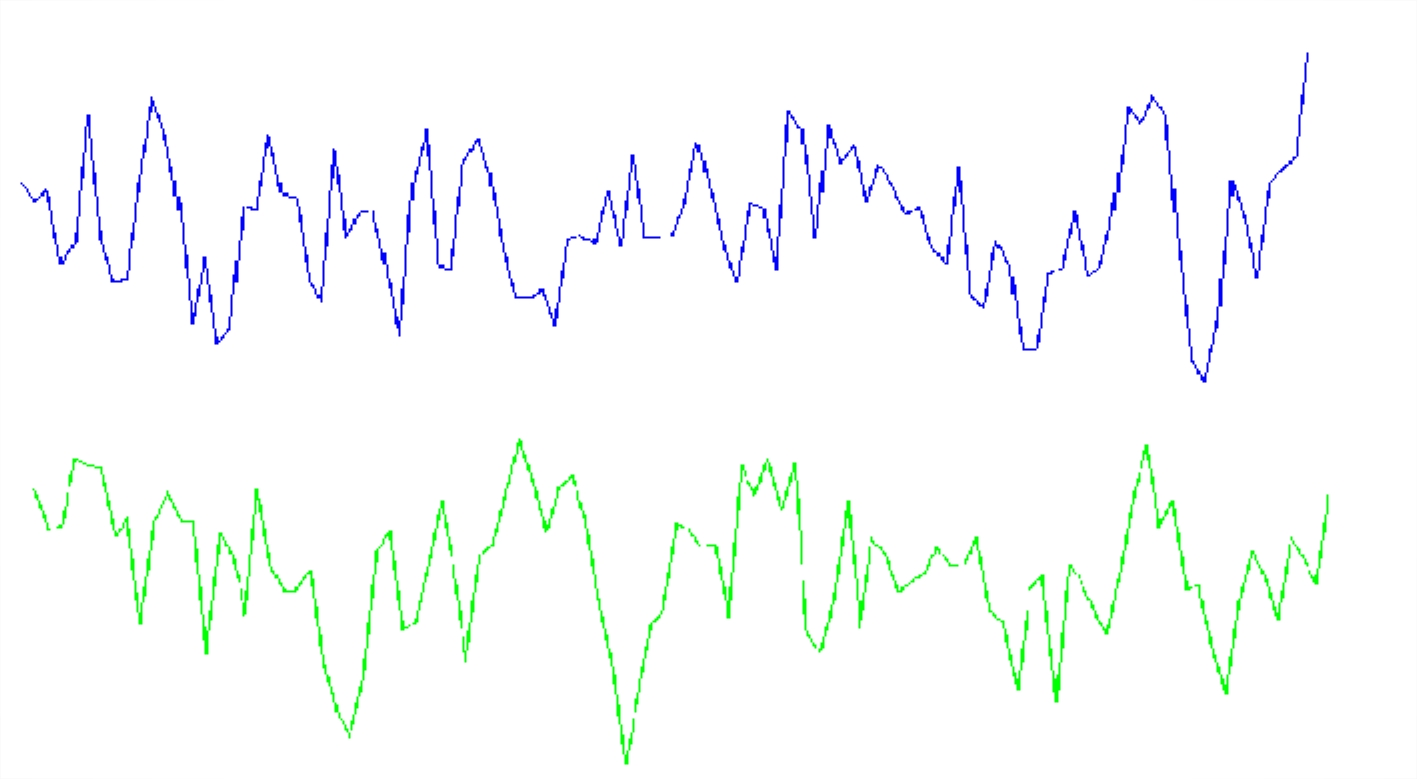
- One possibility: tapered kernel functions, spectral factorization and adjusting the eigenvalues of correlation matrix

$$\hat{V} = diag\left(\hat{\Gamma}_{dn}\right) - \text{sample variances}$$

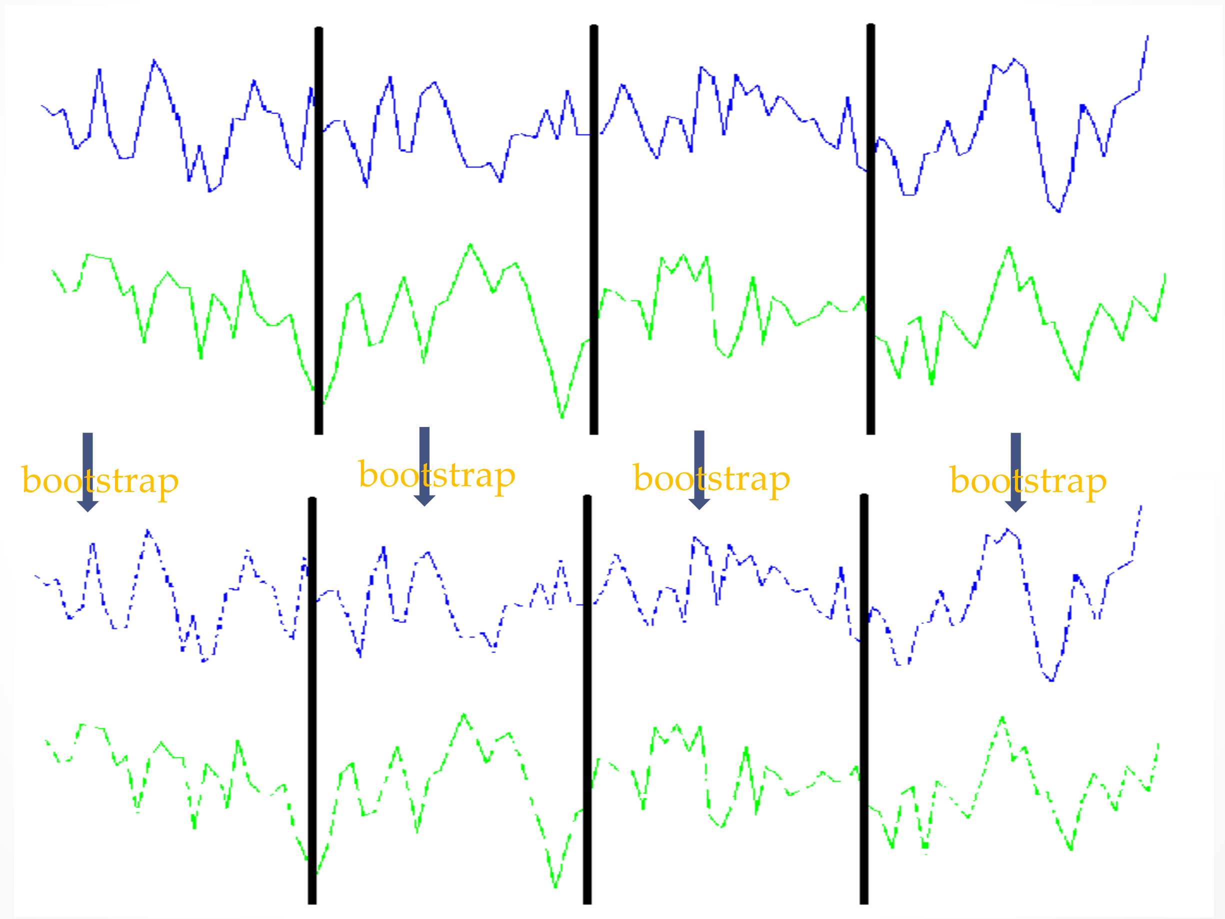
$$\hat{\Gamma}^{\epsilon}_{\kappa,l} = \hat{V}^{1/2} \hat{R}^{\epsilon}_{\kappa,l}\, \hat{V}^{1/2} \underset{spectral\ factorization}{\Longleftrightarrow} \hat{V}^{1/2} S D^{\epsilon} S^{T}\, \hat{V}^{1/2}$$

- where $D^{\epsilon} = diag(r^{\epsilon}_{1}, \cdots, r^{\epsilon}_{dn})$ and $r^{\epsilon}_{i} = \max(r_i, \epsilon n^{-\beta})$
- $\beta > \frac{1}{2}$ and $\epsilon > 0$

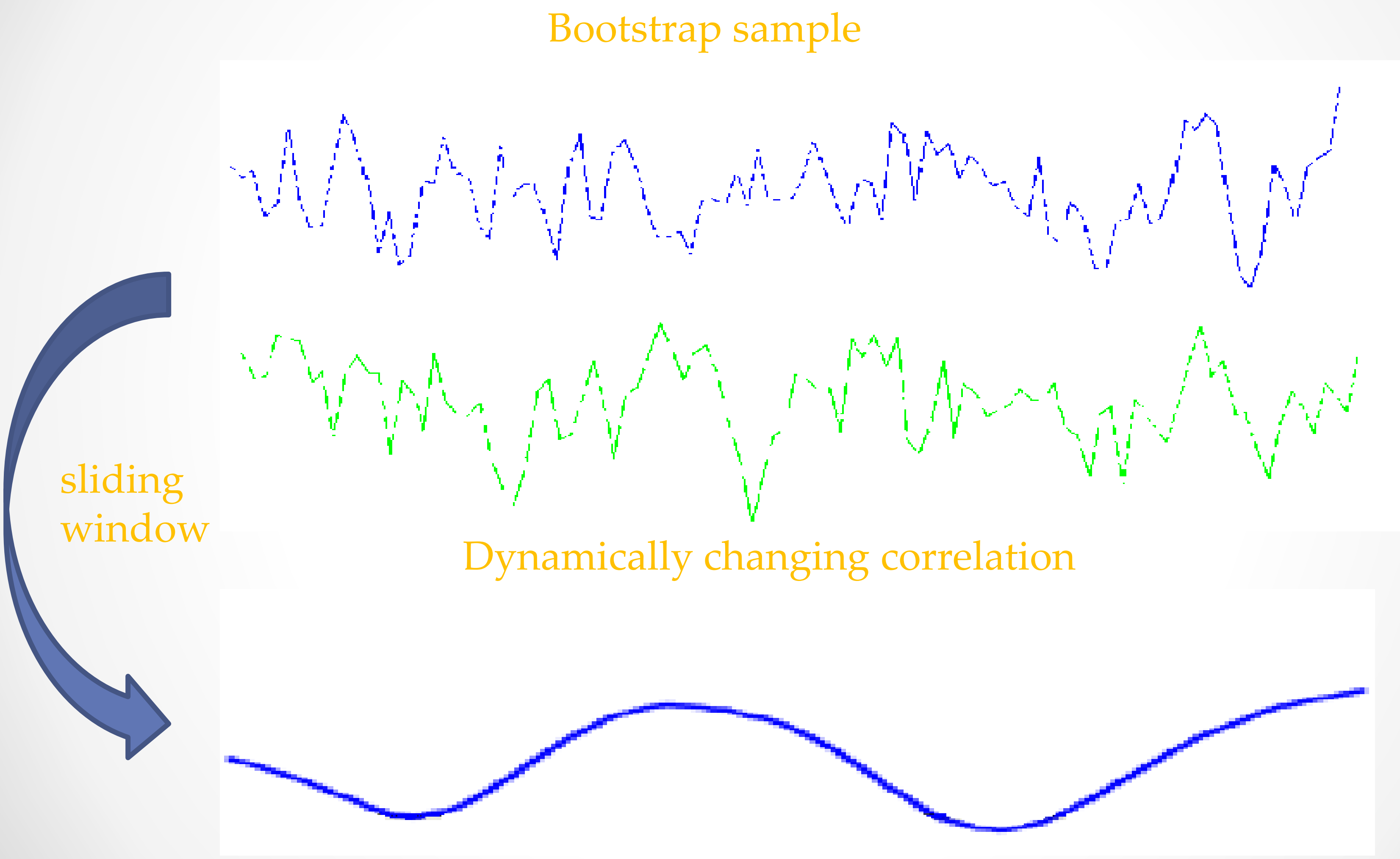
DCBootCB algorithm



DCBootCB Bands algorithm



DCBootCB Bands algorithm



DCBootCB Bands algorithm

Notation:

$\boldsymbol{X}$ is an $(2 \times \mathrm{n})$ data matrix consisting of vectors $\overline{X_1}, \overline{X_2}$ of size **n** representing the fMRI time series from 2 ROIs and $\mathbf{w}$ is an integer block length.

Algorithm:

1. Partition matrix $\boldsymbol{X}$ into ($2 \times \frac{n}{w}$) adjacent blocks.
2. Within each adjacent block of data, apply MLPB to obtain one 2 x $\mathbf{w}$ bootstrap sample. Combine 2-dimensional adjacent blocks of bootstrap samples into a one $(2 \times \mathrm{n})$ data matrix $\boldsymbol{X^*}$.
3. Let $\boldsymbol{X_{i,w}}$ be a 2 x $\mathbf{w}$ bootstrap block of $\mathbf{w}$ consecutive observations starting at time index i from matrix $\boldsymbol{X^*}$.
4. For each $\boldsymbol{X_{i,w}}$ estimate correlations at time index i.
5. Repeat steps 2 to 4 **B** times.
6. Use a Gaussian kernel smoothing technique to obtain estimated correlation trajectories.

The whole set of bootstrap samples enables the calculation of the correlation coefficient and its confidence interval using quantiles of their empirical distribution.

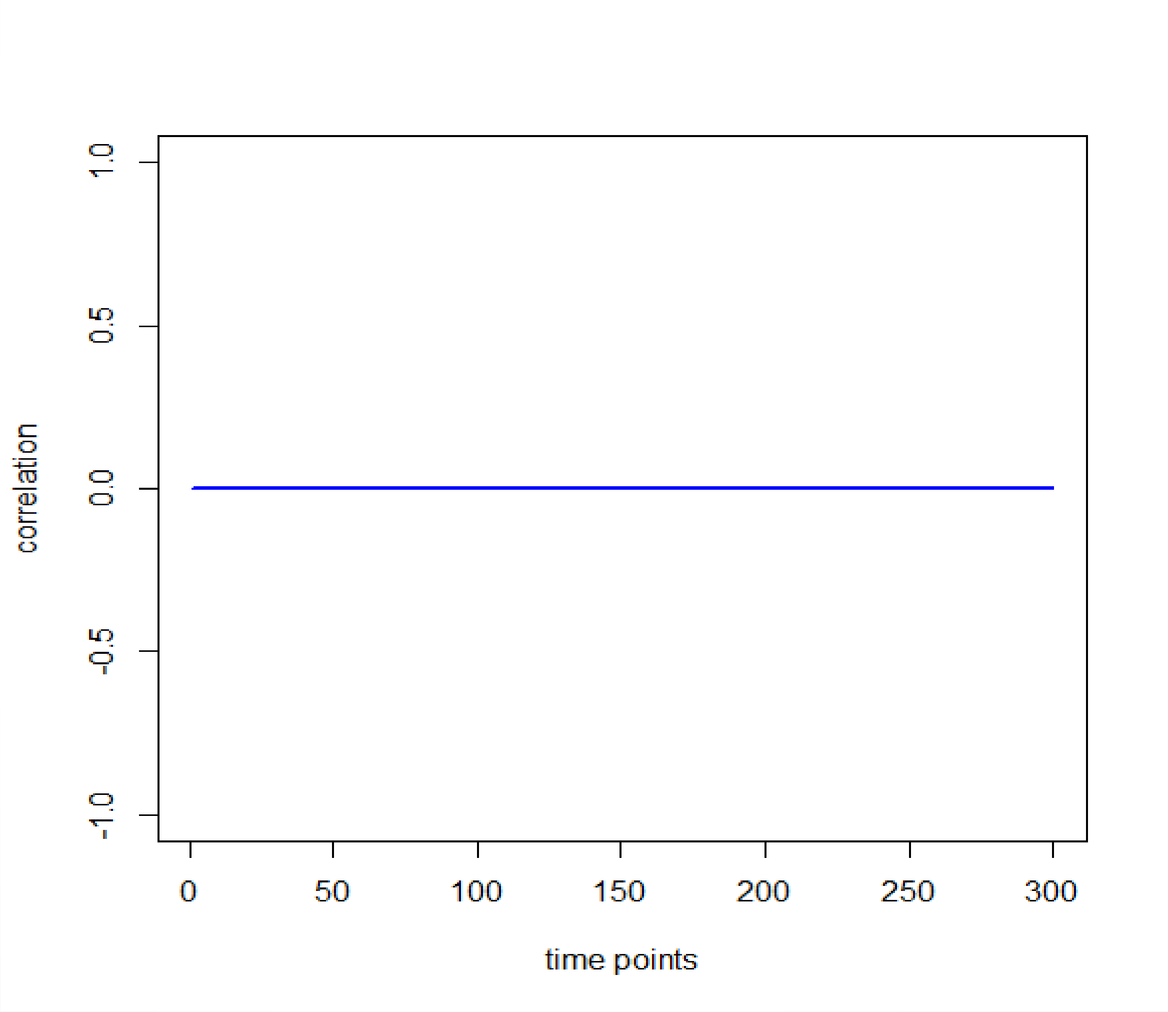
Simulation study

Two time series X_1, X_2 were generated from bivariate normal distribution with mean zero, constant variance and correlation changing according to the following scenarios:

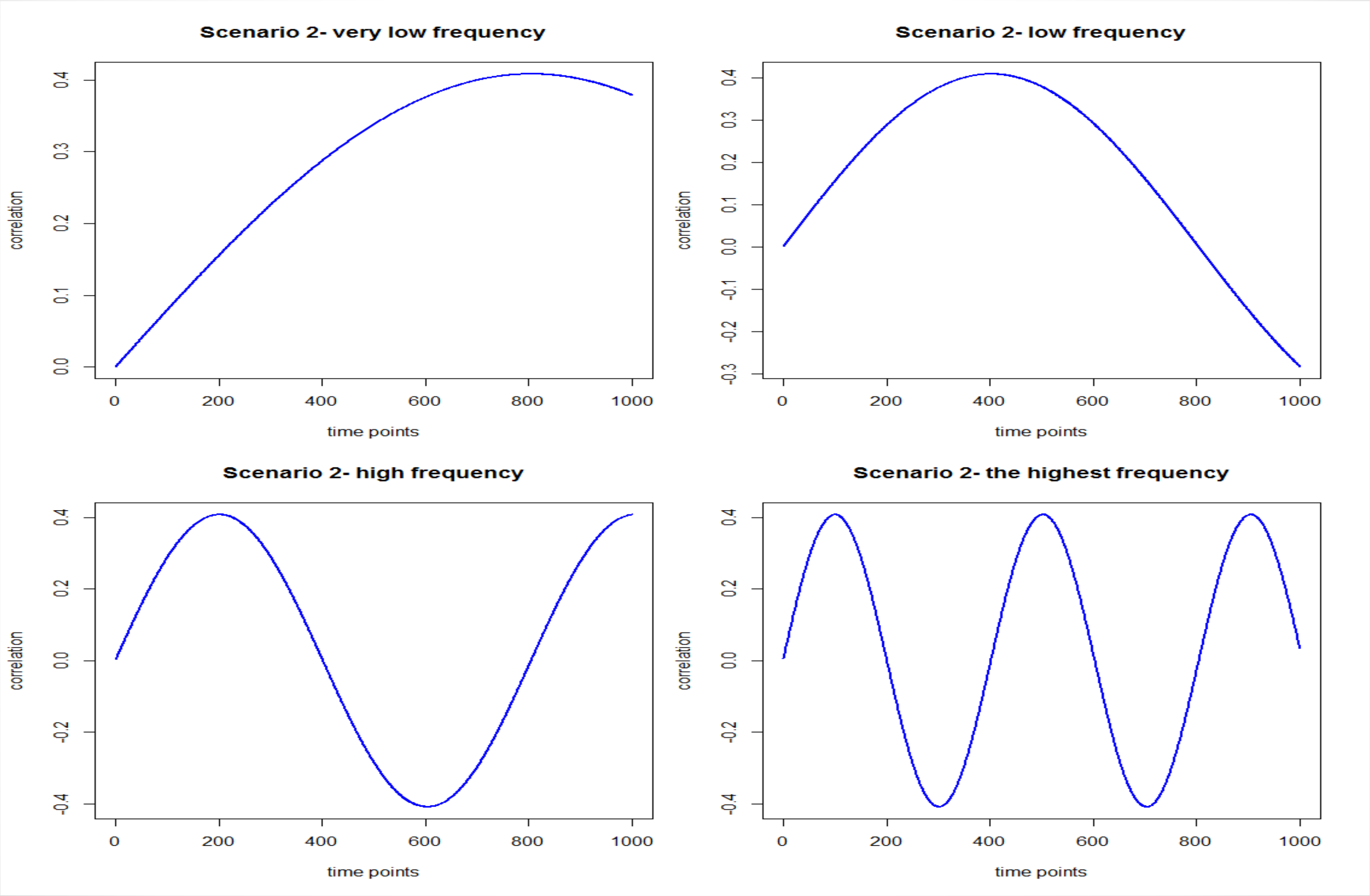
1. Constant correlation **ρ**=0 at all time points ***t***.
2. Correlation changes in the piecewise linear fashion with **ρ**= 0, 0.6 and 0.2.
3. Correlation changes in 0.1 steps from **ρ**=0 to 0.5 and back to 0.
4. Correlation changes according to sine function with four different frequencies.
5. Correlation changes according to a Gaussian kernel with four different variances..

- For scenario 1, ***t*** = 150, 300, 600. For scenarios 2 and 3, a piecewise constant intervals are ***t*** = 50, 100, 200. For scenarios 4 and 5, ***t*** = 1000.

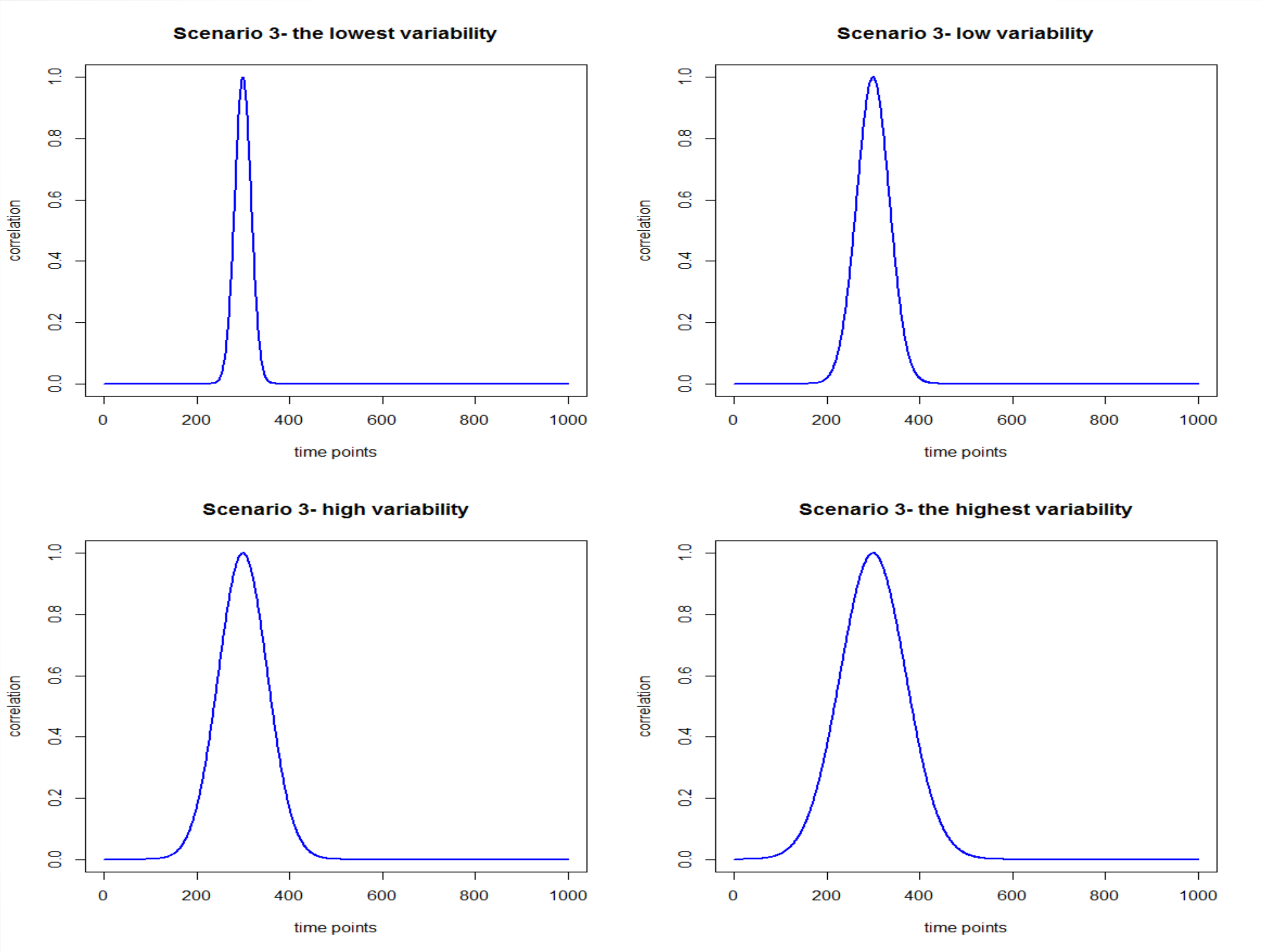
Scenario 1 – zero correlation



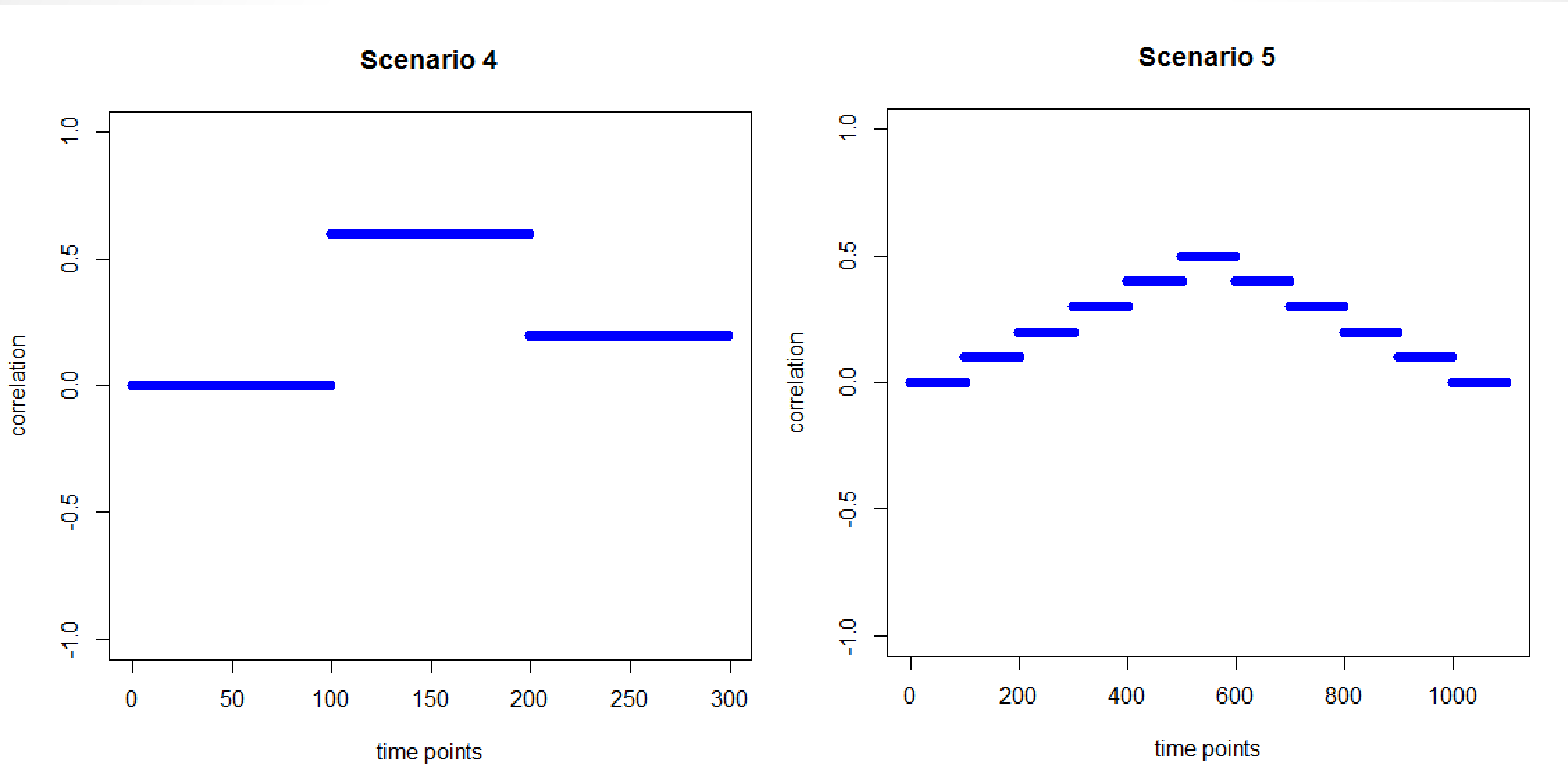
Scenario 2


Scenario 2- very low frequency
Scenario 2- low frequency
Scenario 2- high frequency
Scenario 2- the highest frequency
correlation
time points
0.0
0.1
0.2
0.3
0.4
-0.1
-0.2
-0.3
-0.4
0
200
400
600
800
1000

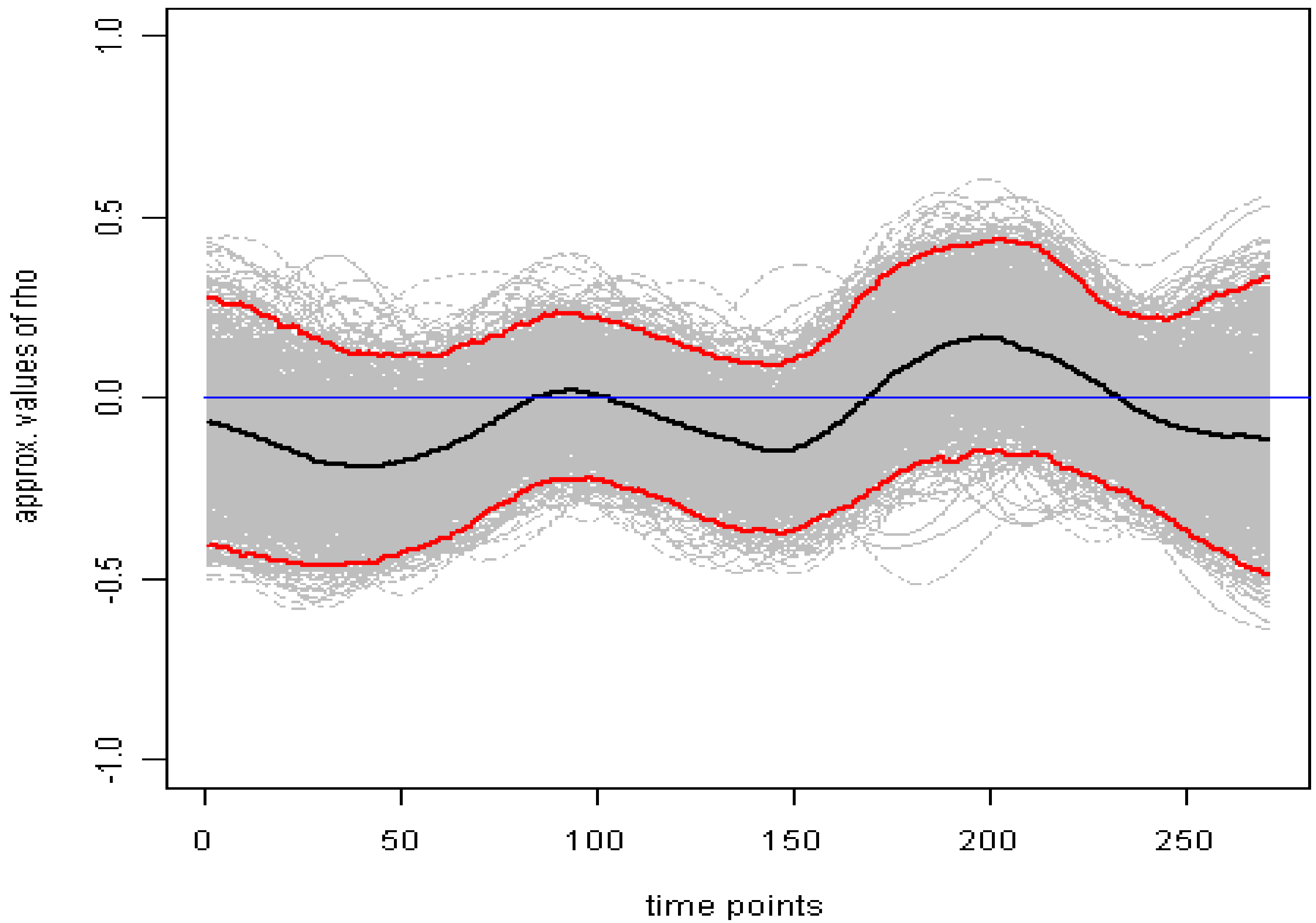
Scenario 3


Scenario 3- the lowest variability
Scenario 3- low variability
Scenario 3- high variability
Scenario 3- the highest variability
correlation
0.0
0.2
0.4
0.6
0.8
1.0
0
200
400
600
800
1000
time points

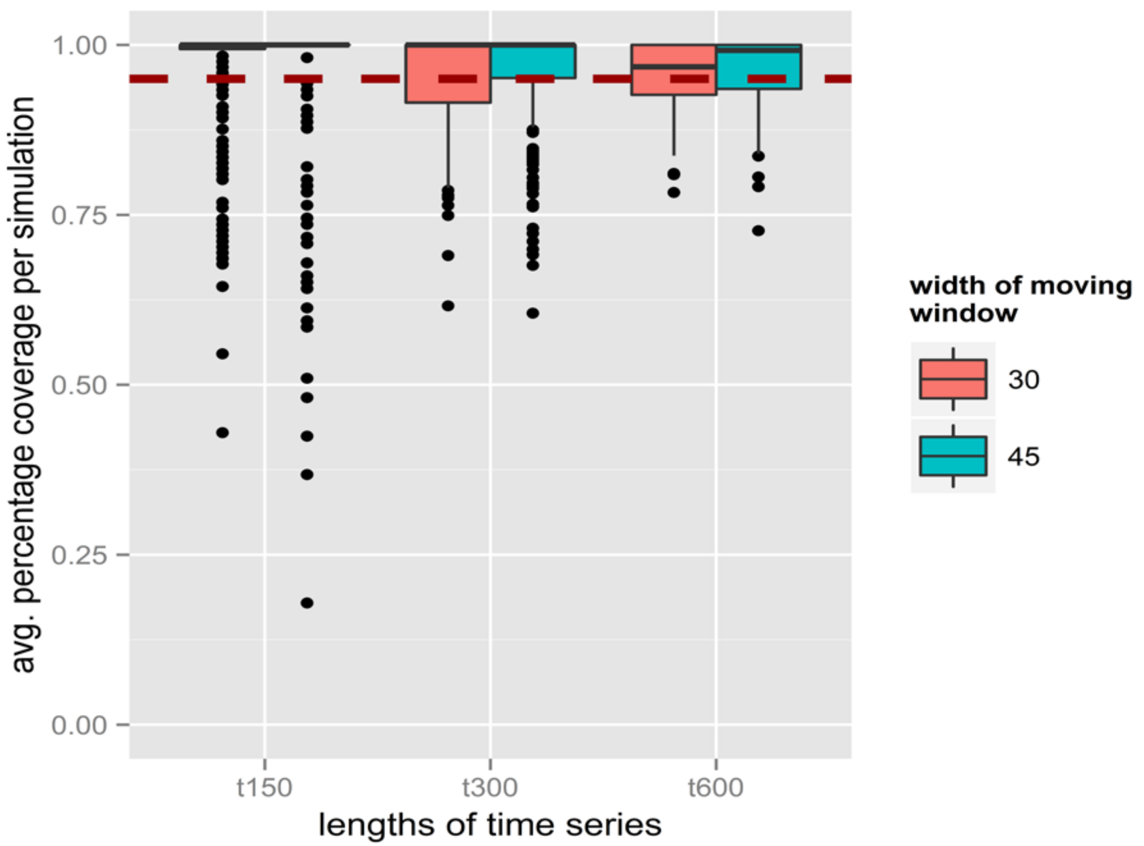
Scenarios 4 and 5



Scenario 1 (zero correlation) a single simulation run

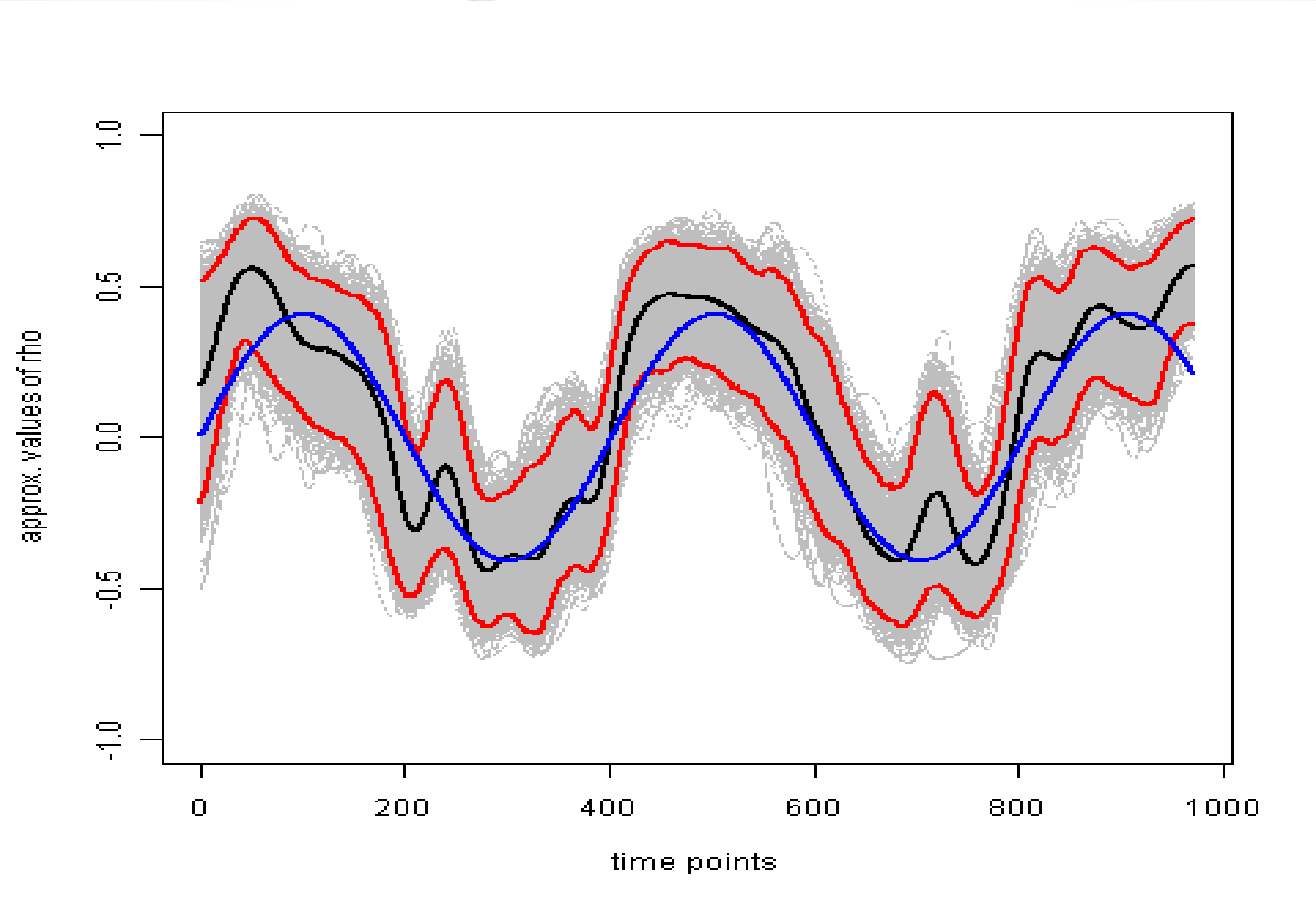


Coverage of a true constant correlation coefficient by the 95% confidence interval

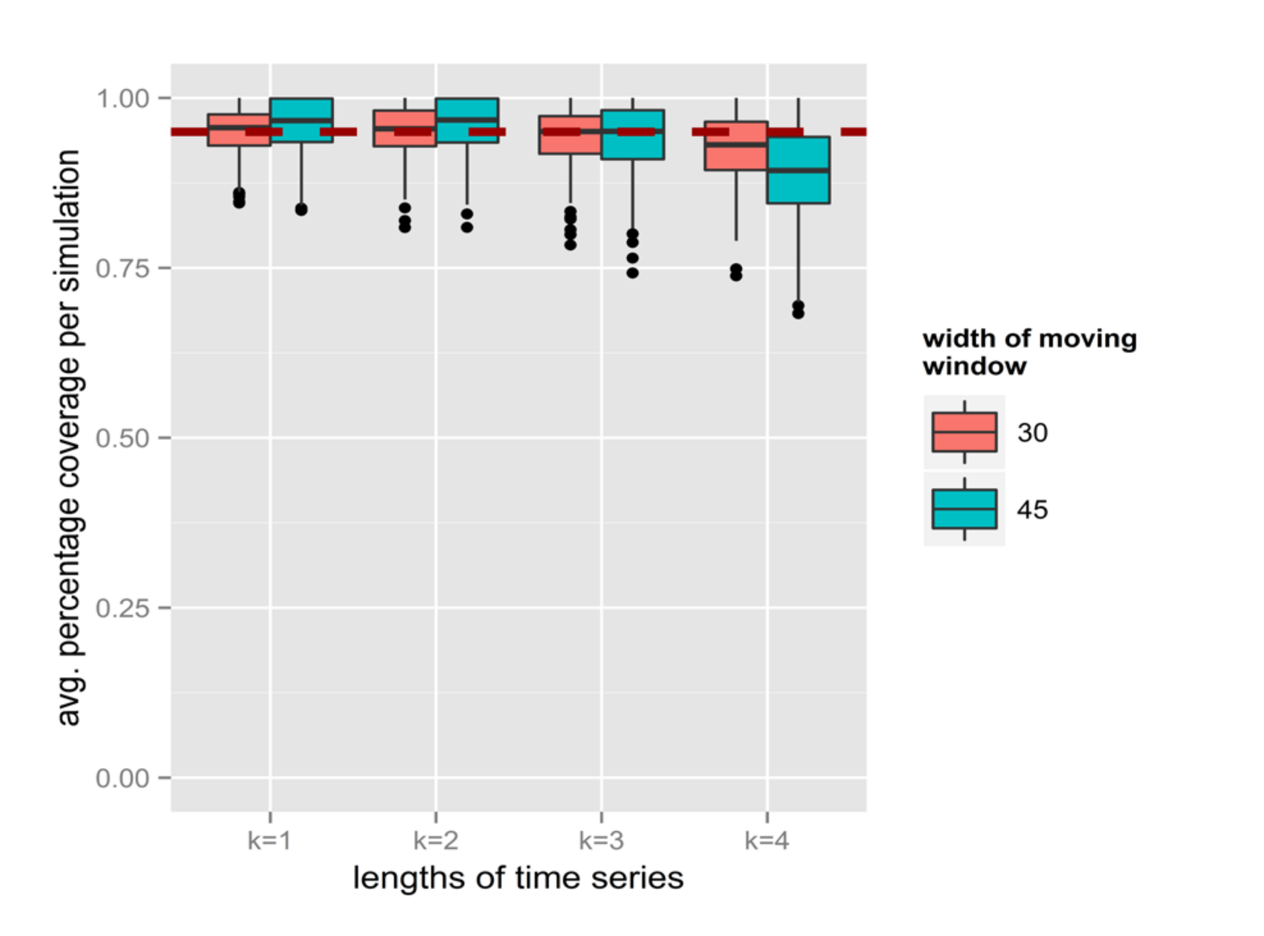


Scenario 2 (sine function)

a single simulation run



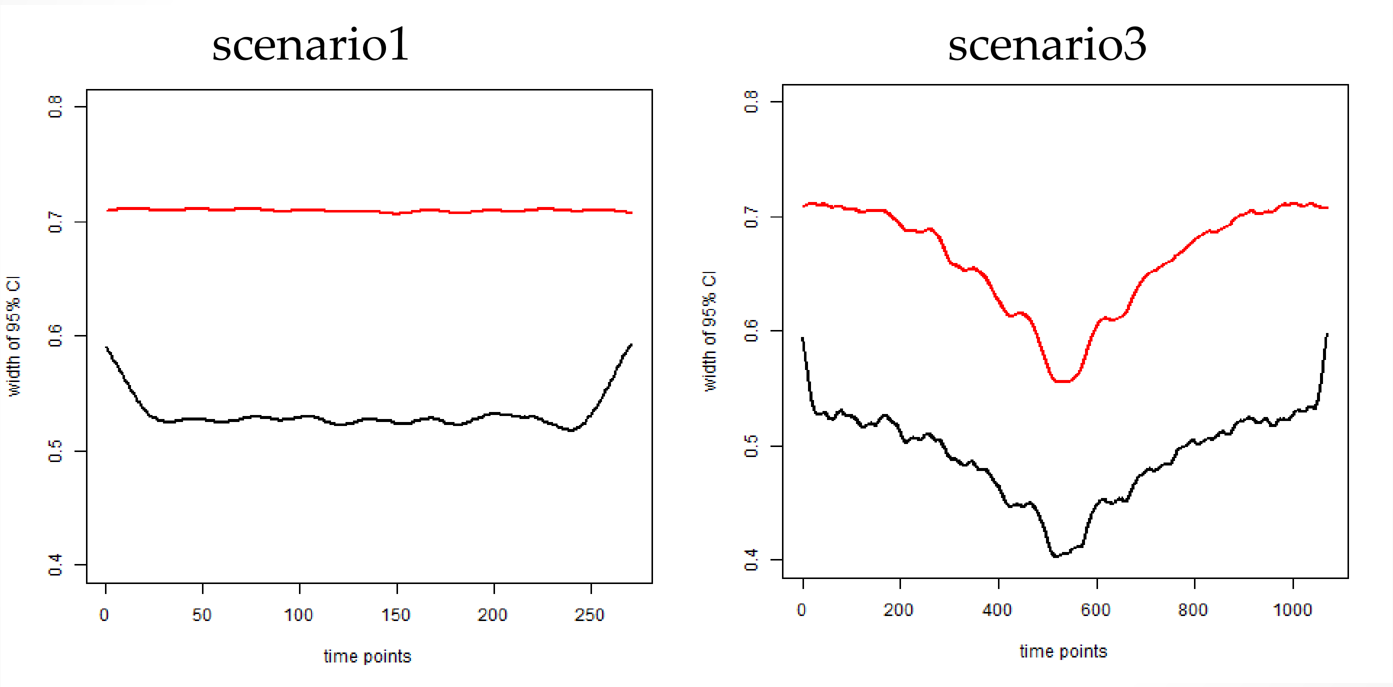
Coverage of a true correlation coefficient (sine function) by the 95% confidence interval



Comparison of coverage of a true correlation coefficient (sine function) by the 95% confidence interval

ρ function	k	window size	Coverage in percent our method aveg. (Q1, Q2, Q3)	Coverage in percent Fisher aveg. (Q1, Q2, Q3)
sine	k=1	30	95.14 (92.99, 95.62, 97.58)	99.42 (99.28, 100, 100)
		45	96.02 (93.51, 96.65, 99.90)	99.03 (98.43, 100, 100)
	k=2	30	95.11 (92.89, 95.46, 98.14)	99.39 (99.59, 100, 100)
		45	95.91 (93.43, 96.75, 99.90)	98.92 (98.43, 100, 100)
	k=3	30	94.23 (91.78, 95.05, 97.32)	99.25(98.76, 100, 100)
		45	94.08 (90.99, 95.08, 98.19)	98.11 (96.47, 100, 100)
	k=4	30	92.55 (89.41, 93.09, 96.49)	98.76 (97.94, 100, 100)
		45	88.86 (84.50, 89.32, 94.24)	95.72 (93.32, 96.54, 99.63)

Average width of confidence interval for simulation scenario1 and scenario3



Red curve average width of confidence bands using Fisher approximation
Black curve average width of confidence bands using DCBootCB.

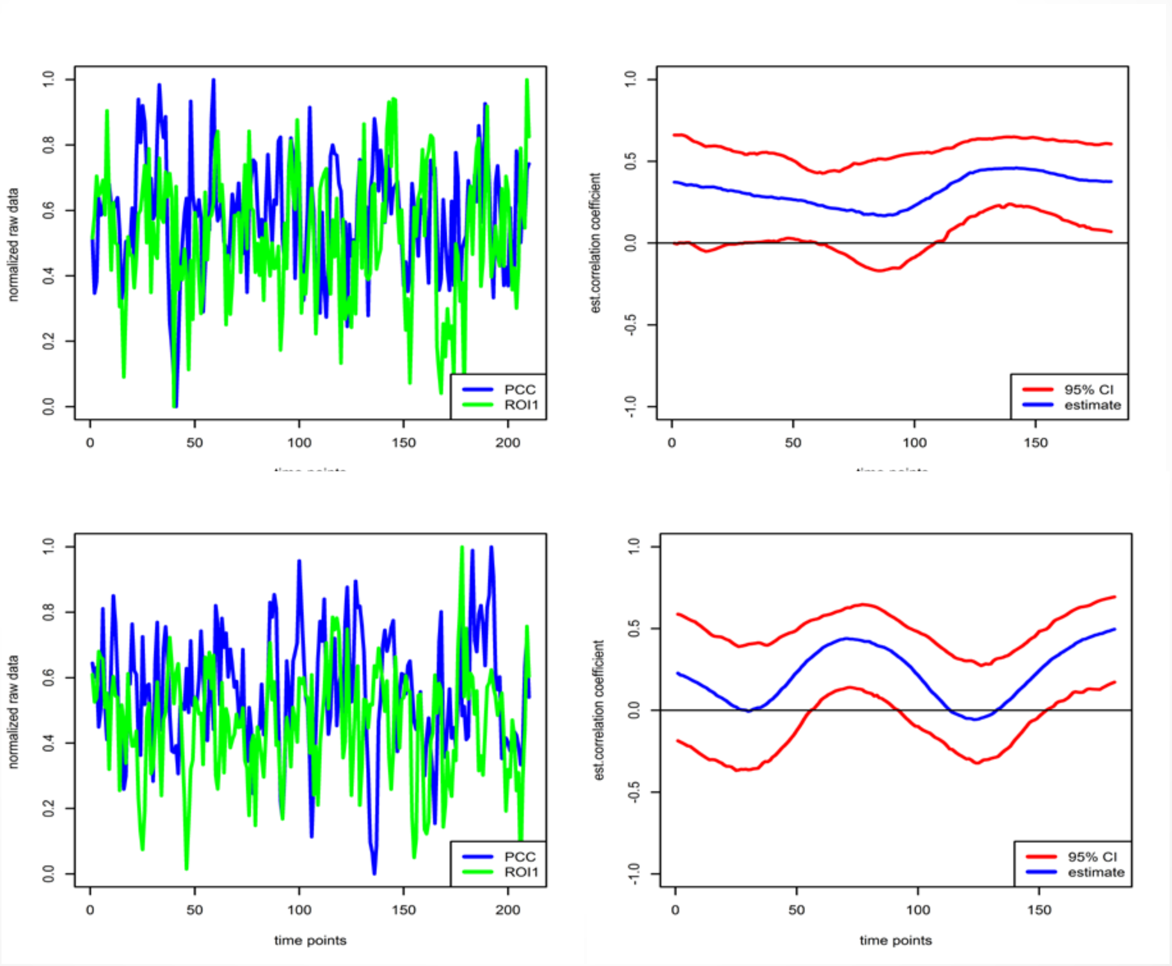
Resting state functional connectivity data

- Kirby 21 dataset (Landman et al., 2011)
- 20 healthy adults
- Two resting state fMRI scans lasting 7 minutes (210 observations)
- Six regions of interest analyzed (Chang & Glover, 2010):
    a. posterior cingulate cortex (PCC)
    b. right interior parietal cortex,
    c. frontal operculum,
    d. temporal cortex,
    e. orbitofrontal cortex
    f. anterior cingulate cortex

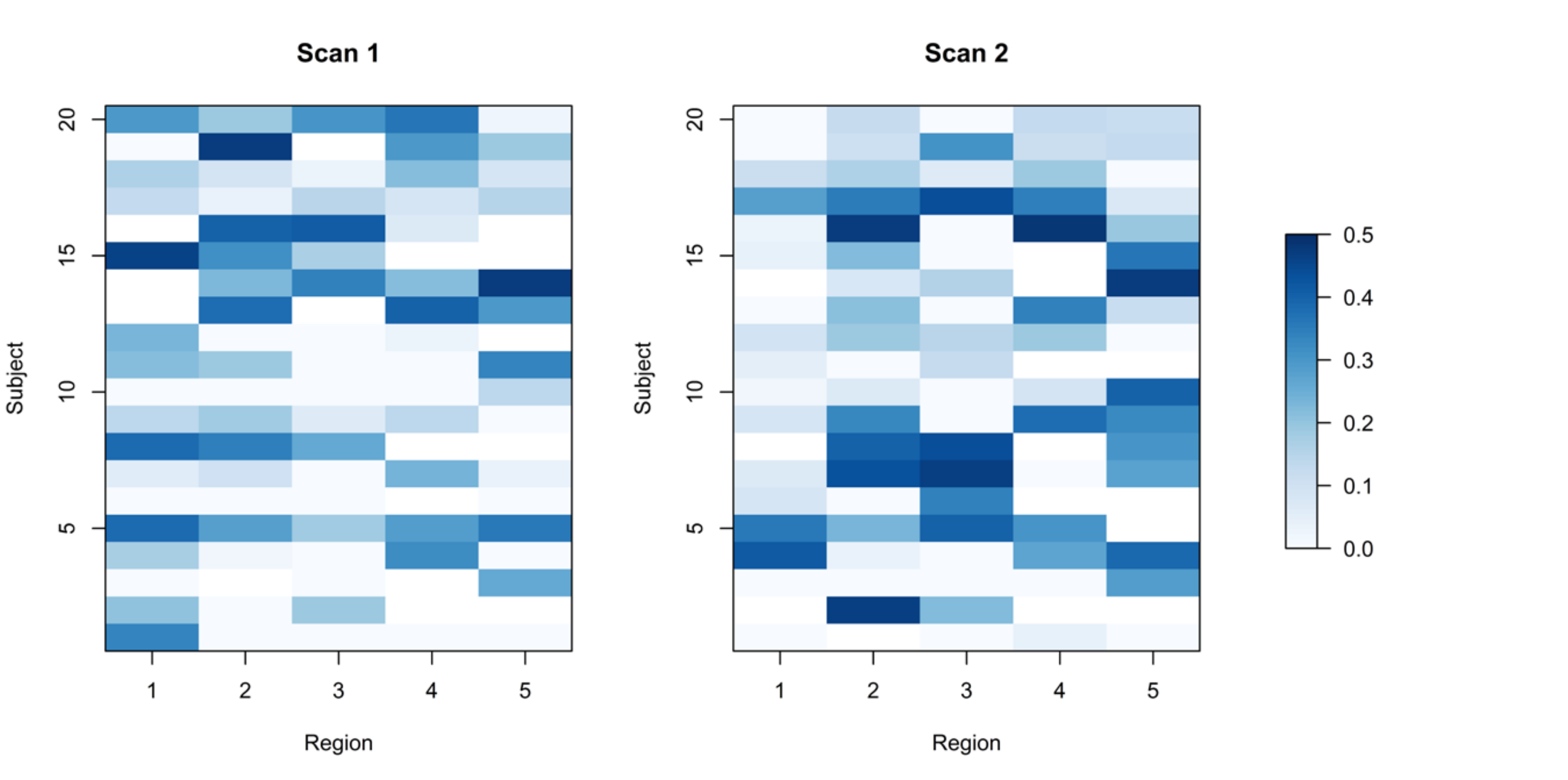
Raw data and estimated dynamic connectivity with confidence bands

Subject 1

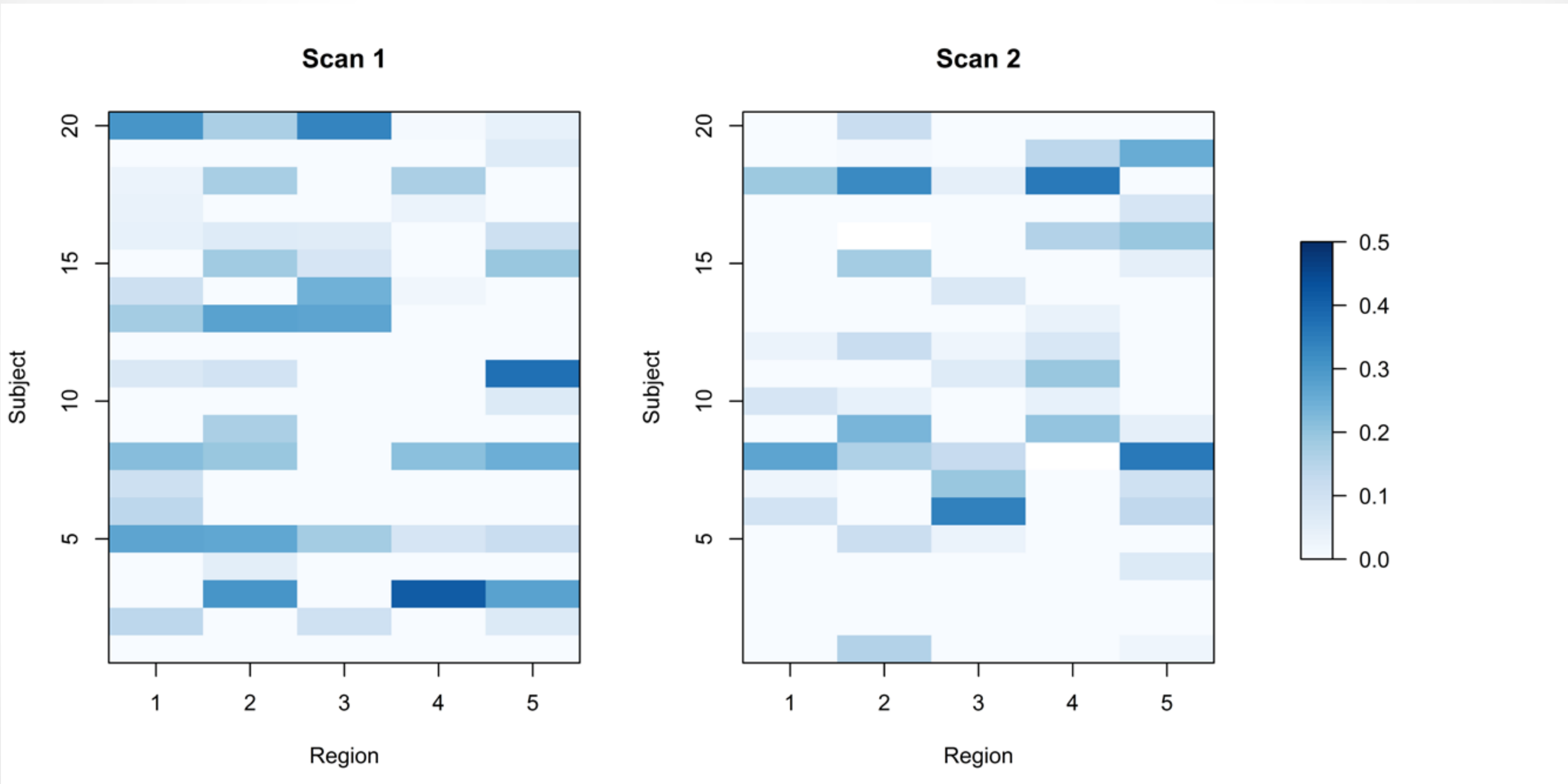
Subject 2



Non-(zero coverage)



Non-(static correlation coverage)



Task-based connectivity

- Dynamically changing correlation functions exhibit complex correlation structure
- Different sources of variability

Our goal

- Develop a testing procedure for the equality of two possibly correlated functional processes

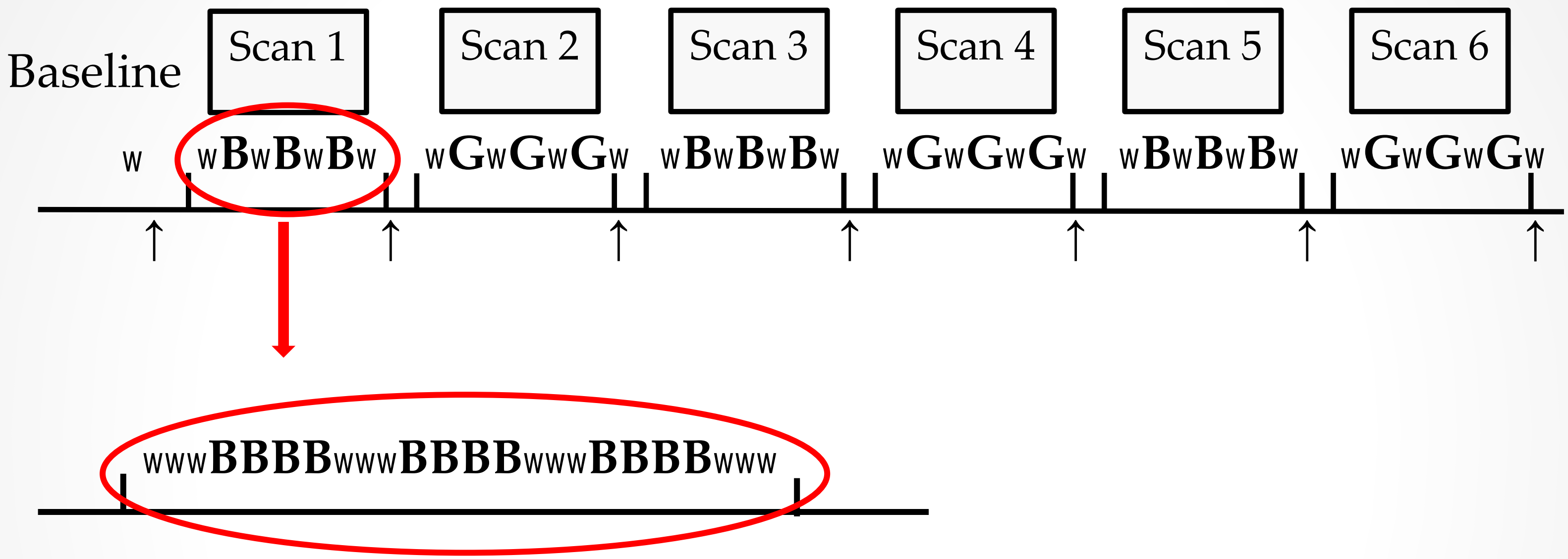
Motivating example
GPTF Experiment

- Cue reactivity in frontal and limbic regions in college-age male drinkers (n=29) to the taste of:
  - Beer (Flavor **B**) or
  - Gatorade© (an appetitive flavor control; Flavor **G**).

- Flavors delivered in 1-sec sprays (trials) on subjects' tongues, totaling 26 and 30 ml, respectively, interspersed with neutral water (**w**; a flavorless sensory baseline).

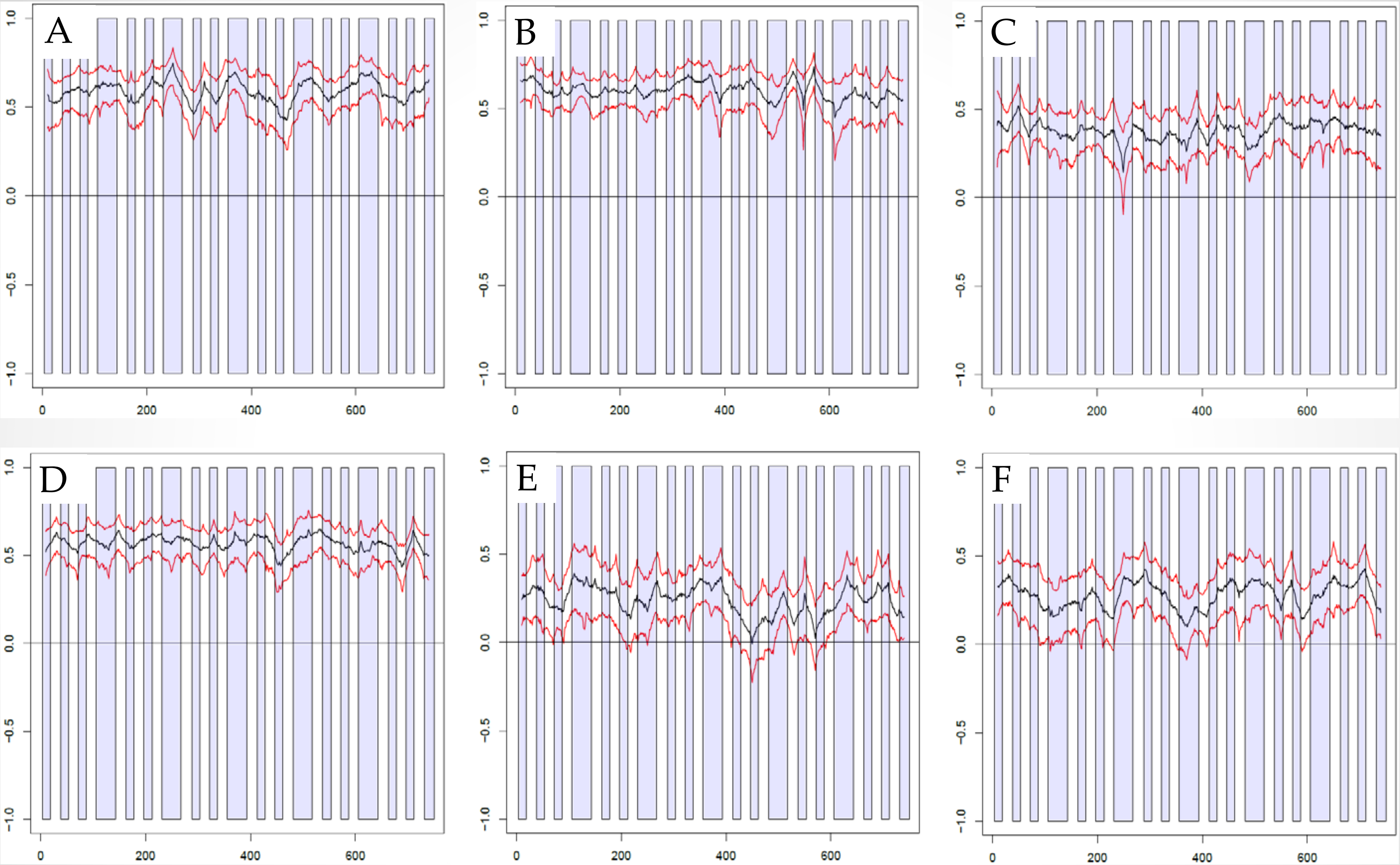
- Subjects participated in one imaging session, during which they were exposed to different tastes.

Experimental design

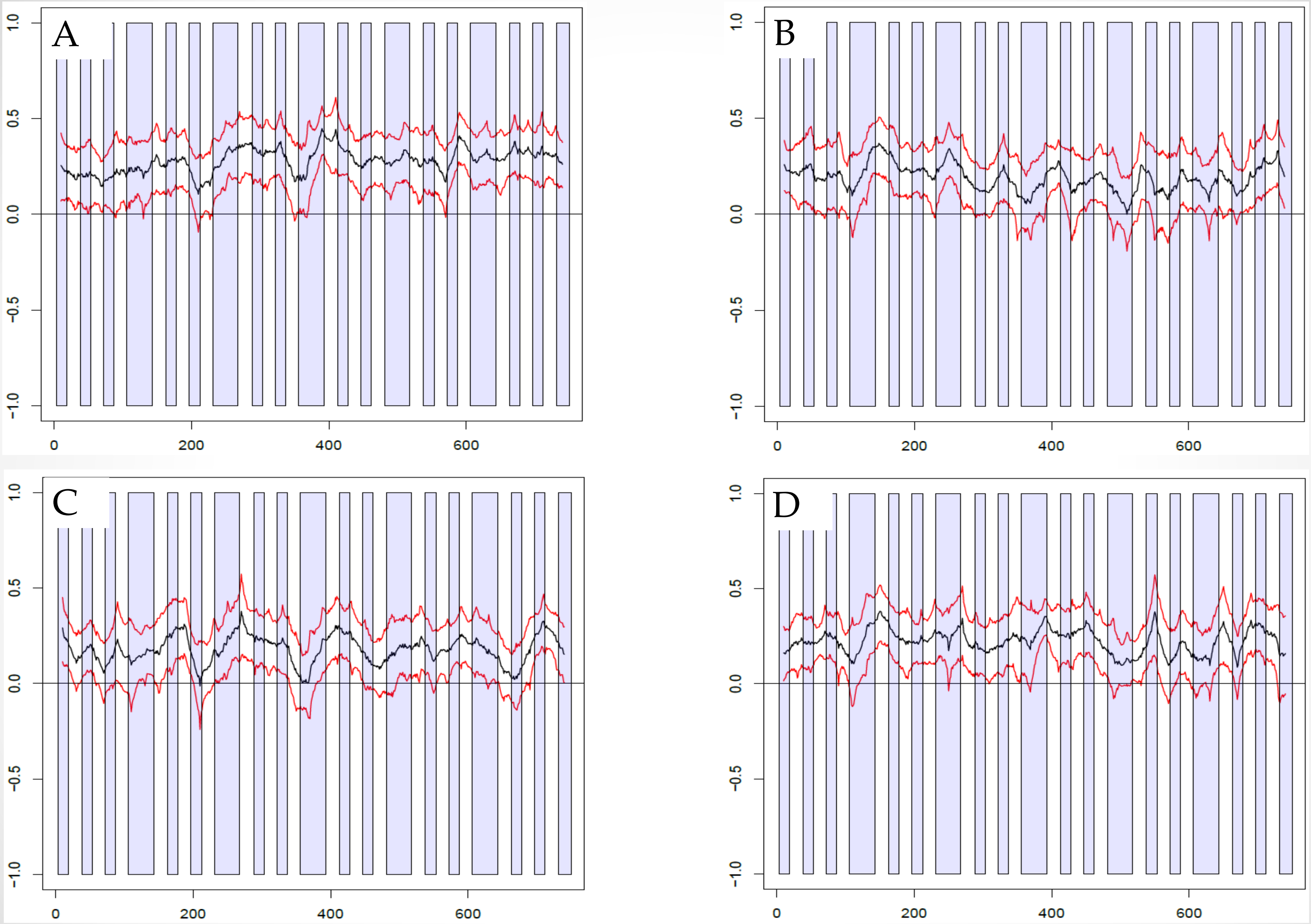


- Signal acquired every TR=2.25 s
- 11s – interstimulus period

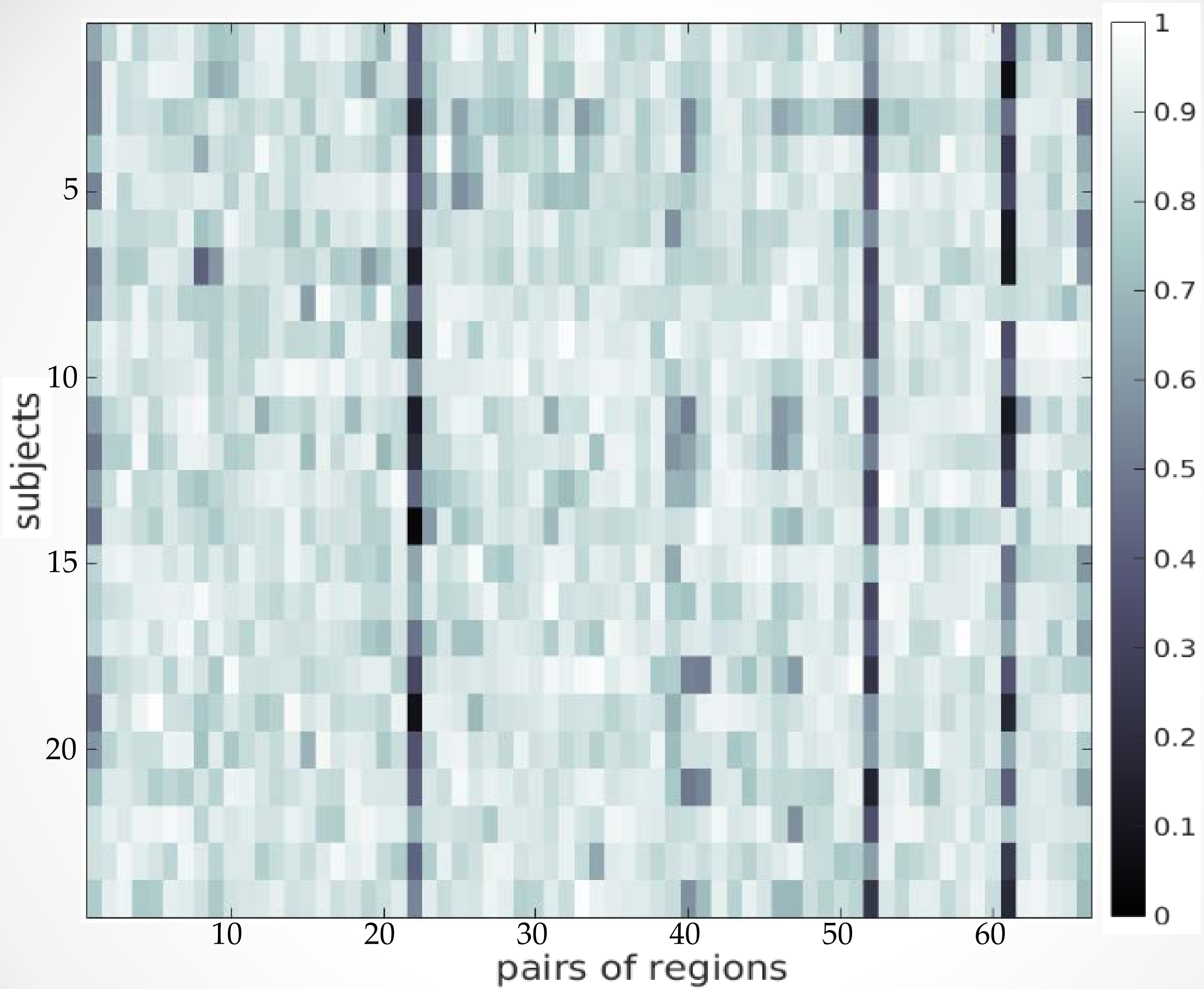
Ref. Brandon Oberlin



Group-averaged dynamic FC estimates across 6 scans (750 time points) for the homologous regions of: A: SMC; B: Amygdala; C: Insula; D: VST; E: OFC; F: STG. Black line is the dynamic FC estimate, red lines indicate confidence intervals, white vertical bands indicate flavor stimulation and shaded bands water stimulation.



Group-averaged dynamic FC estimates across 6 scans (750 time points) for the:
ipsilateral (A: OFC_L vs. VST_L; B: OFC_R vs. VST_R) and contralateral (C: OFC_L vs. VST_R; D: OFC_R vs. VST_L) regions.



Percentage of time points where the dynamic correlation is zero with 95% confidence on a subject-by-subject basis (rows). Dark-shaded cells represent lower percentage of time with zero connectivity. Columns 22, 52 and 61 correspond to the connectivity between homologous areas: amygdala, VST and SMC, respectively.

Conclusions

- Provided model-free estimation of confidence intervals for the dynamically changing correlation coefficient estimate.
- Simulation studies show that the theoretical results are supported by the empirical evidence.
- An application to the resting-state Kirby 21 data demonstrates that the assumption of static correlation amongst the considered ROIs is not fully appropriate.
- Task-based connectivity testing in early development.

Acknowledgements

- Maria Kudela, PhD student
- Martin Lindquist

- Mario Dzemidzic
- David Kareken
- Brandon Oberlin
- Joaquin Goni

Thank you