Nonstationary time series models for dynamic correlation analysis

20 November 2014

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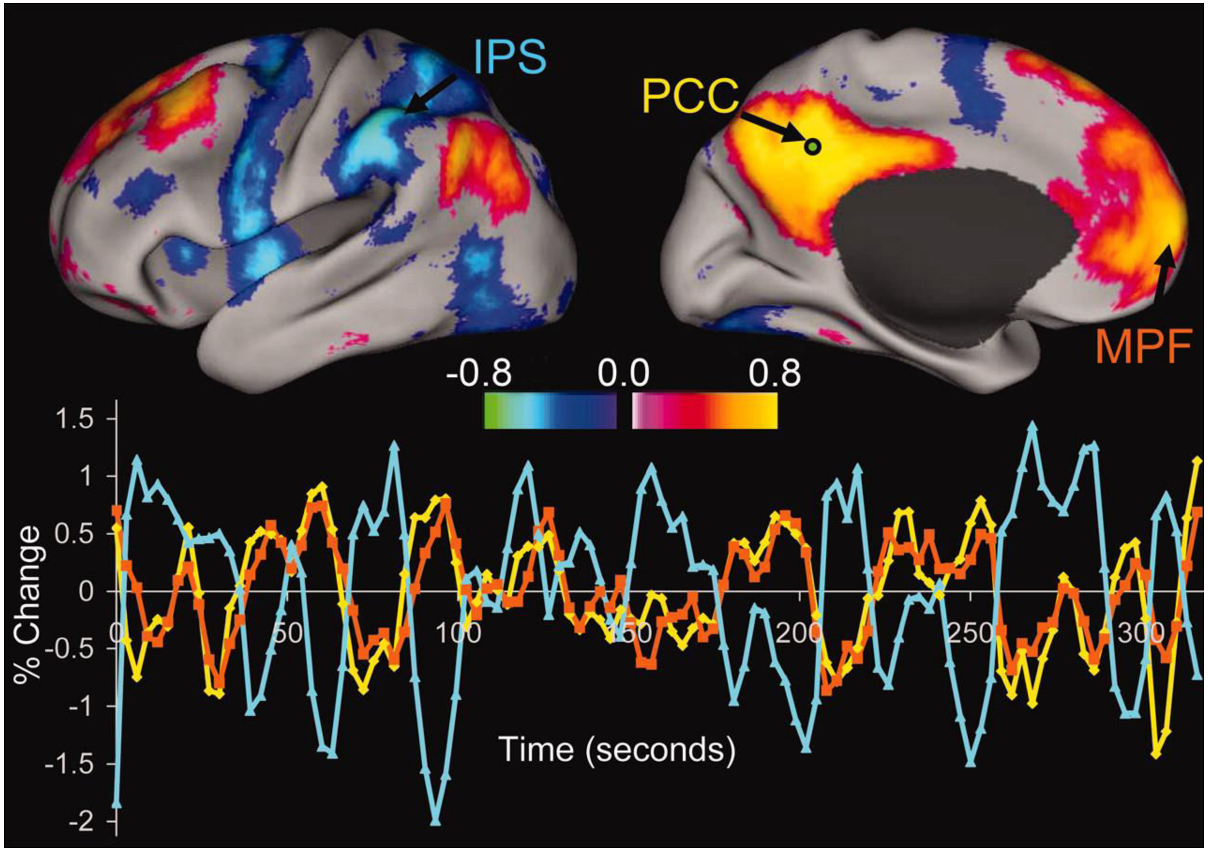
Functional Connectivity



The human brain is intrinsically organized into dynamic, anticorrelated functional networks

Michael D. Fox*,†, Abraham Z. Snyder*,‡, Justin L. Vincent*, Maurizio Corbetta‡, David C. Van Essen§, and Marcus E. Raichle*,‡,§,¶

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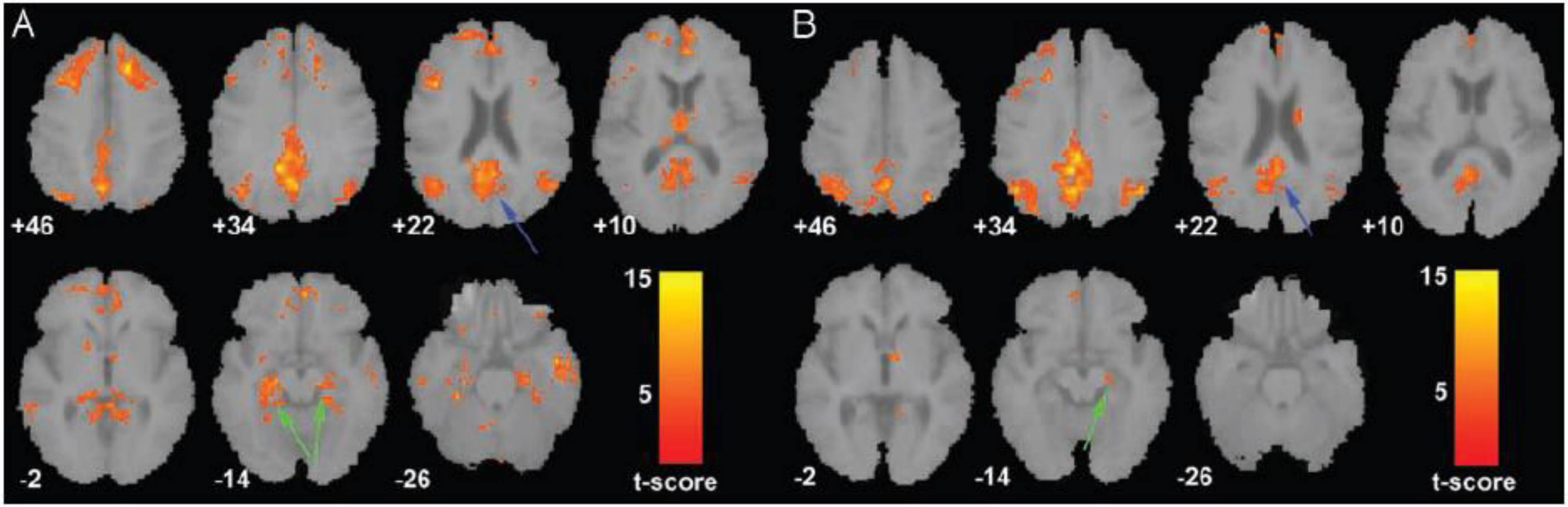
Functional Connectivity



Default-mode network activity distinguishes Alzheimer's disease from healthy aging: Evidence from functional MRI

Michael D. Greicius[†‡§], Gaurav Srivastava[‡¶], Allan L. Reiss[‡‖††], and Vinod Menon[‡‖††]

Clinical Utility of RS-FC

Disease/condition	References	Findings
Alzheimer's	(Li et al., 2002; Greicius et al., 2004; Wang et al., 2006a,b, 2007; Allen et al., 2007; Supekar et al., 2008)	Decreased correlations within the DMN including hippocampi, decreased anticorrelations with the DMN, and reduced local connectivity as reflected in clustering coefficients
PIB positive	(Hedden et al., 2009; Sheline et al., 2010)	Decreased correlations within the DMN
Mild cognitive impairment	(Li et al., 2002; Sorg et al., 2007)	Decreased correlations within the DMN and decreased anticorrelations with the DMN.
Fronto-temporal dementia	(Seeley et al., 2007a, 2008)	Decreased correlations within the salience network
Healthy aging	(Andrews-Hanna et al., 2007; Damoiseaux et al., 2008)	Decreased correlations within the DMN
Multiple sclerosis	(Lowe et al., 2002; De Luca et al., 2005)	Decreased correlations within the somatomotor network
ALS	(Mohammadi et al., 2009)	Decreased connectivity within the DMN and within the somatomotor network (esp. premotor cortex)
Depression	(Anand et al., 2005a,b, 2009; Greicius et al., 2007; Bluhm et al., 2009a)	Variable: Decreased corticolimbic connectivity (esp. with dorsal anterior cingulate), increased connectivity within the DMN (esp. subgenual prefrontal cortex), decreased connectivity between DMN and caudate
Bipolar	(Anand et al., 2009)	Decreased corticolimbic connectivity
PTSD	(Bluhm et al., 2009c)	Decreased connectivity within the DMN

Fox and Greicius, 2010

Clinical Utility of RS-FC

Disease/condition	References	Findings
Schizophrenia	(Liang et al., 2006; Liu et al., 2006, 2008; Bluhm et al., 2007, 2009b; Salvador et al., 2007; Zhou et al., 2007; Jafri et al., 2008; Whitfield-Gabrieli et al., 2009)	Variable: Decreased or increased correlations within the DMN. Decreased, increased or unchanged correlations and anticorrelations between the DMN and other systems.
Schizophrenia 1° relatives	(Whitfield-Gabrieli et al., 2009)	Increased connectivity within the DMN
ADHD	(Zhu et al., 2005, 2008; Cao et al., 2006; Tian et al., 2006; Zang et al., 2007; Castellanos et al., 2008; Wang et al., 2009)	Variable: reduced connectivity within the DMN, reduced anticorrelations with the DMN, increased connectivity in the salience network
Autism	(Cherkassky et al., 2006; Kennedy and Courchesne, 2008; Monk et al., 2009; Weng et al., 2010)	Decreased connectivity within the DMN (although hippocampus is variable and connectivity may be increased in younger patients)
Tourette syndrome	(Church et al., 2009)	Delayed maturation of task-control and cingulo-opercular networks
Epilepsy	(Waites et al., 2006; Lui et al., 2008; Bettus et al., 2009; Zhang et al., 2009b,c)	Variable: decreased connectivity in multiple networks including the medial temporal lobe, decreased connectivity within the DMN (esp. in patients with generalized seizures)
Blindness	(Liu et al., 2007; Yu et al., 2008)	Decreased connectivity within the visual cortices and between visual cortices and other sensory and multimodal regions

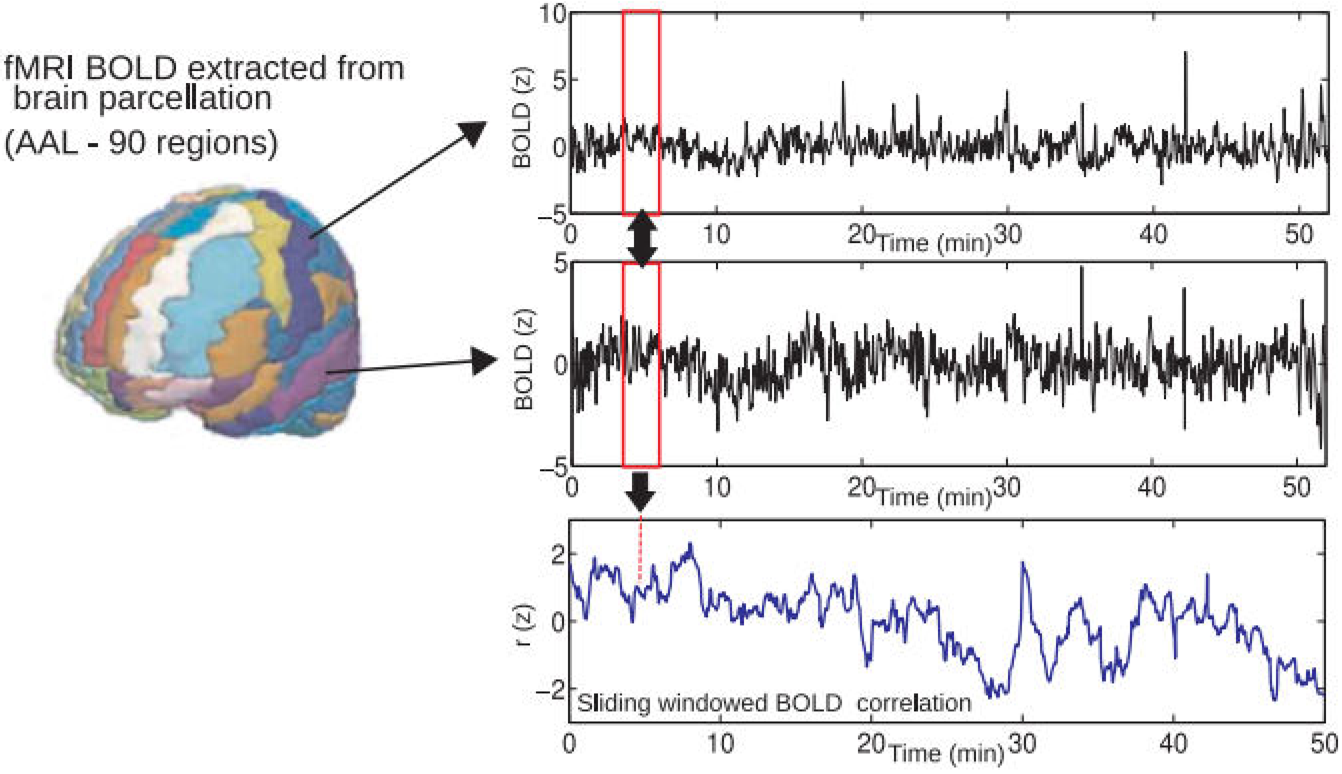
Fox and Greicius, 2010

Clinical Utility of RS-FC

Disease/condition	References	Findings
Chronic pain	(Greicius et al., 2008a; Cauda et al., 2009a,c,d)	Variable: Increased/decreased connectivity within the salience network, decreased connectivity in attention networks
Neglect	(He et al., 2007)	Decreased connectivity within the dorsal and ventral attention networks
Coma/vegetative state	(Boly et al., 2009; Cauda et al., 2009b; Vanhaudenhuyse et al., 2010)	Progressively decreased DMN connectivity with progressive states of impaired consciousness
Generalized anxiety disorder	(Etkin et al., 2009)	increased connectivity between amygdala and frontoparietal control network and decreased connectivity between amygdala and salience network

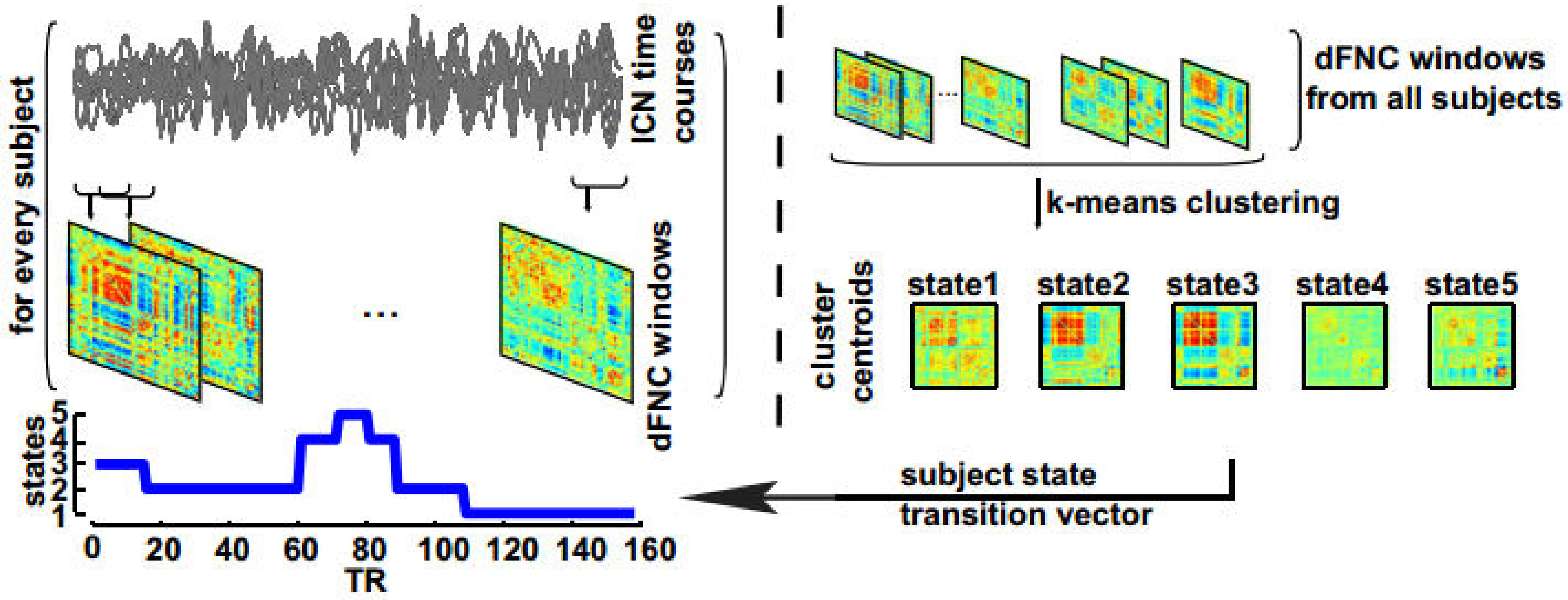
Fox and Greicius, 2010

Time-Varying Connectivity



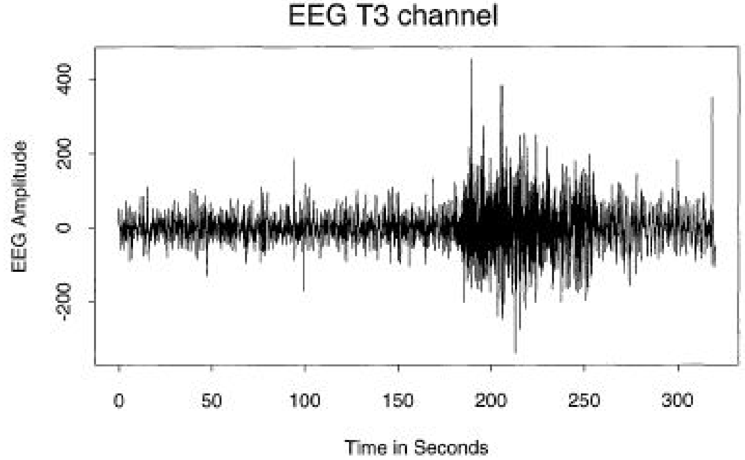
Tagliazucchi et al, 2012

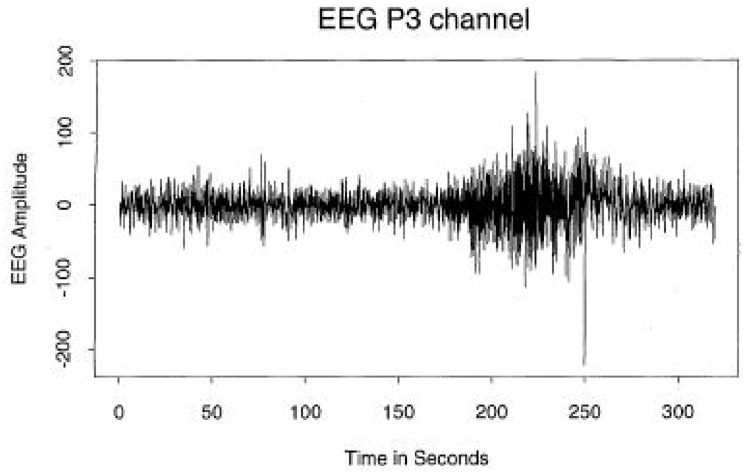
Time-Varying Connectivity



Damaraju et al, 2014

Time-Varying Connectivity





Ombao et al, 2001

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Other Examples

Dynamic functional connectivity analysis reveals transient states of dysconnectivity in schizophrenia

E. Damaraju[a,*], E.A. Allen[a,b], A. Belger[c], J.M. Ford[d,e], S. McEwen[f], D.H. Mathalon[d,e], B.A. Mueller[g], G.D. Pearlson[h], S.G. Potkin[i], A. Preda[i], J.A. Turner[j], J.G. Vaidya[k], T.G. van Erp[i], V.D. Calhoun[a,l]

Dynamic connectivity states estimated from resting fMRI Identify differences among Schizophrenia, bipolar disorder, and healthy control subjects

Barnaly Rashid[1,2], Eswar Damaraju[1,2], Godfrey D. Pearlson[3,4,5] and  Vince D. Calhoun[1,2,3,4*]

Dynamic connectivity regression: Determining state-related changes in brain connectivity

Ivor Cribben [a], Ragnheidur Haraldsdottir [a], Lauren Y. Atlas [b], Tor D. Wager [c], Martin A. Lindquist [a,*]

The Chronnectome: Time-Varying Connectivity Networks as the Next Frontier in fMRI Data Discovery

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http://dx.doi.org/10.1016/j.neuron.2014.10.015

Outline

1) Weakly Stationary Time Series
2) Nonstationary Time Series
3) Dynamic Correlation Analysis
4) Summary and Discussion

WEAKLY STATIONARY TIME SERIES

Definition

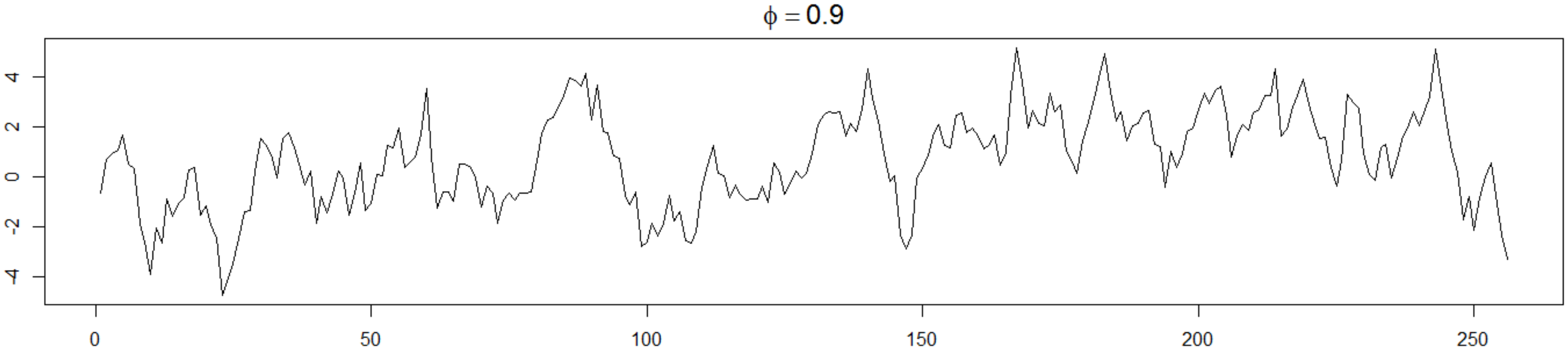
X_t is said to be weakly stationary if its first two moments are invariant with respect to time.

AR(1)

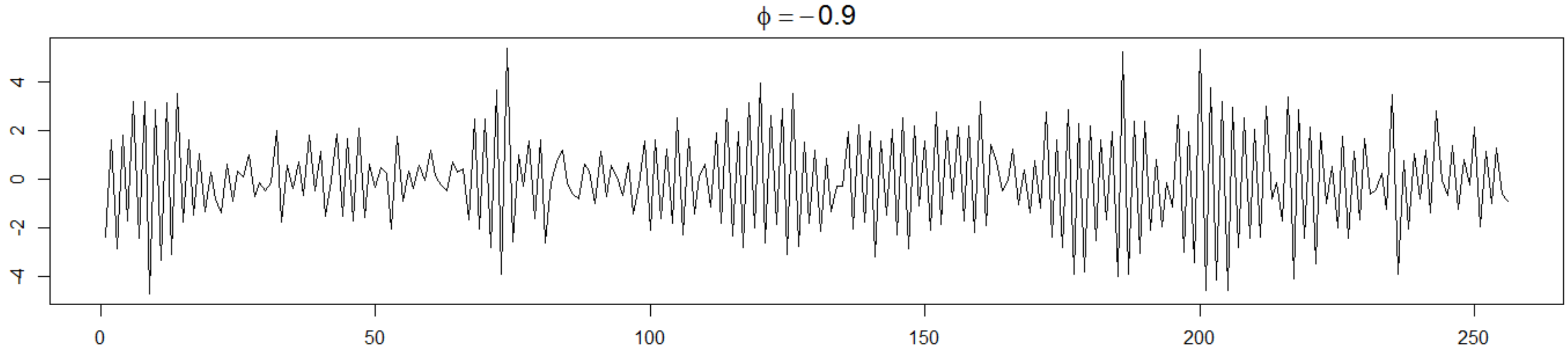
$$X_t = \phi X_{t-1} + Z_t$$

Z_t is white noise $(0, \sigma^2)$

AR(1)



$\phi = 0.9$
4
2
0
-2
-4
0
50
100
150
200
250



$\phi = -0.9$
4
2
0
-2
-4
0
50
100
150
200
250

VAR(1)

$$\begin{pmatrix} X_t \\ Y_t \end{pmatrix} = \begin{pmatrix} \phi_{11} & \phi_{12} \\ \phi_{21} & \phi_{22} \end{pmatrix} \begin{pmatrix} X_{t-1} \\ Y_{t-1} \end{pmatrix} + \begin{pmatrix} Z_{1,t} \\ Z_{2,t} \end{pmatrix}$$

$$Var(\mathbf{Z}_t) = \Sigma = \begin{pmatrix} \sigma_{11}^2 \sigma_{12} \\ \sigma_{21} \sigma_{22}^2 \end{pmatrix}$$

VAR(1)

$$\begin{pmatrix} X_t \\ Y_t \end{pmatrix} = \begin{pmatrix} \phi_{11} & \phi_{12} \\ \phi_{21} & \phi_{22} \end{pmatrix} \begin{pmatrix} X_{t-1} \\ Y_{t-1} \end{pmatrix} + \begin{pmatrix} Z_{1,t} \\ Z_{2,t} \end{pmatrix}$$

$$Var(\mathbf{Z}_t) = \Sigma = \begin{pmatrix} \sigma_{11}^2 & \sigma_{12} \\ \sigma_{21} & \sigma_{22}^2 \end{pmatrix}$$

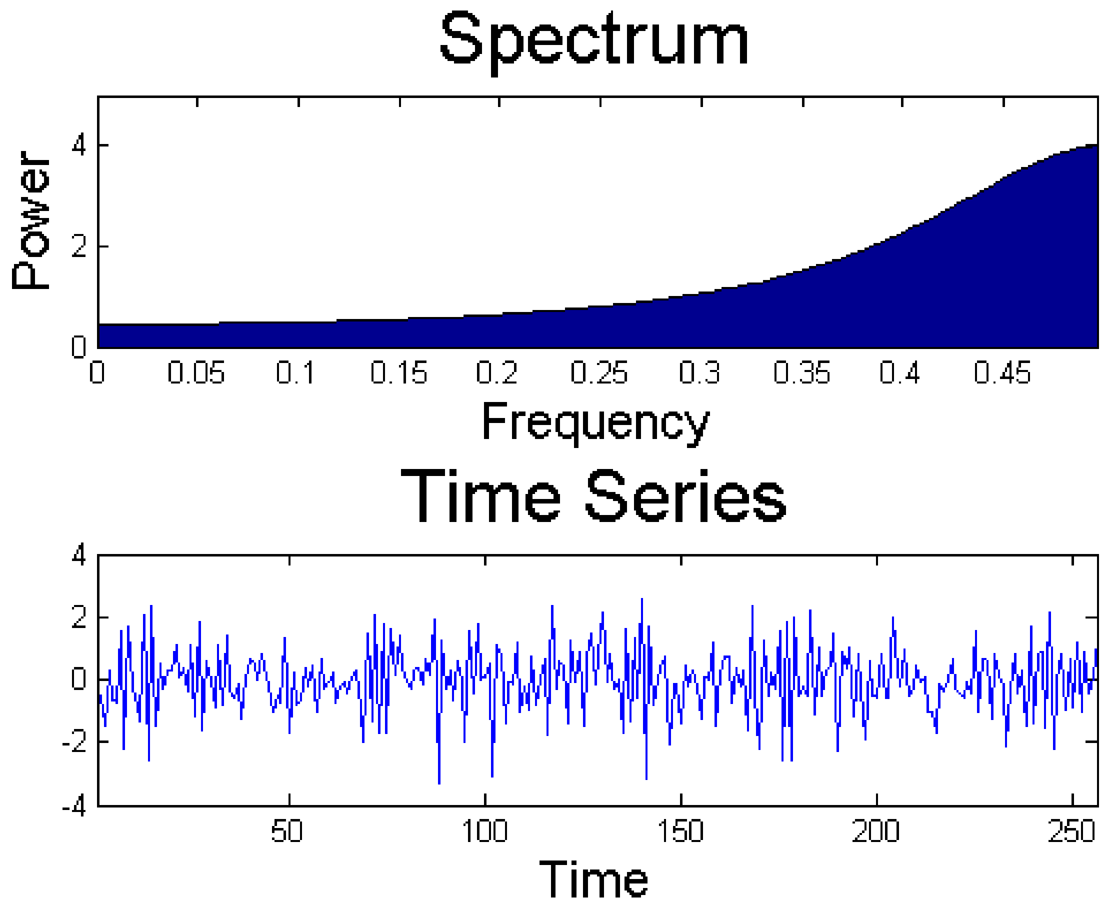
Estimation

- Usually (conditional) least squares, maximum likelihood, or Yule-Walker estimation (Brockwell and Davis, 2002).
- stats and vars packages in R has the tools for estimation
- Can be modified for multi-subject analyses (Fiecas et al, 2011; Gorrostieta et al, 2012, 2013)

The Cramer Representation

$$\mathbf{X}_t = \int_{-0.5}^{0.5} \mathbf{A}(\omega) \exp(-i2\pi\omega t) d\mathbf{Z}(\omega)$$

Examples – Univariate Time Series



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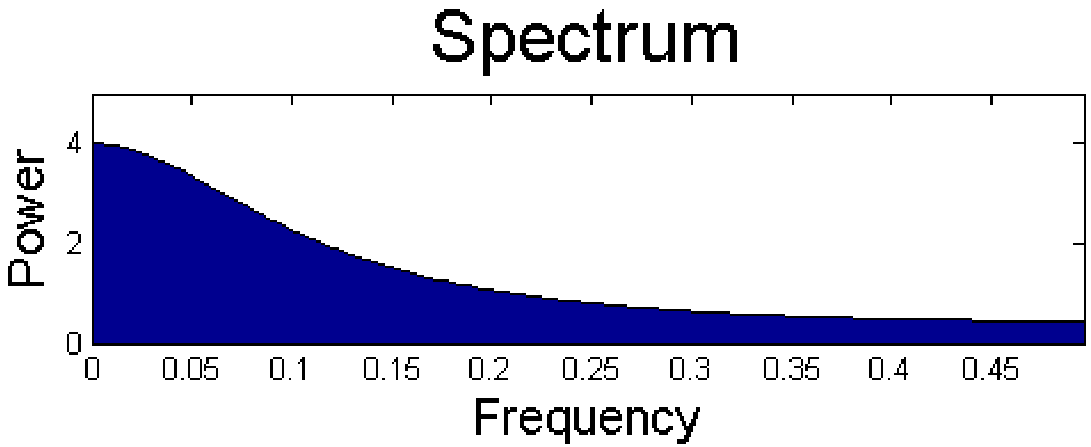
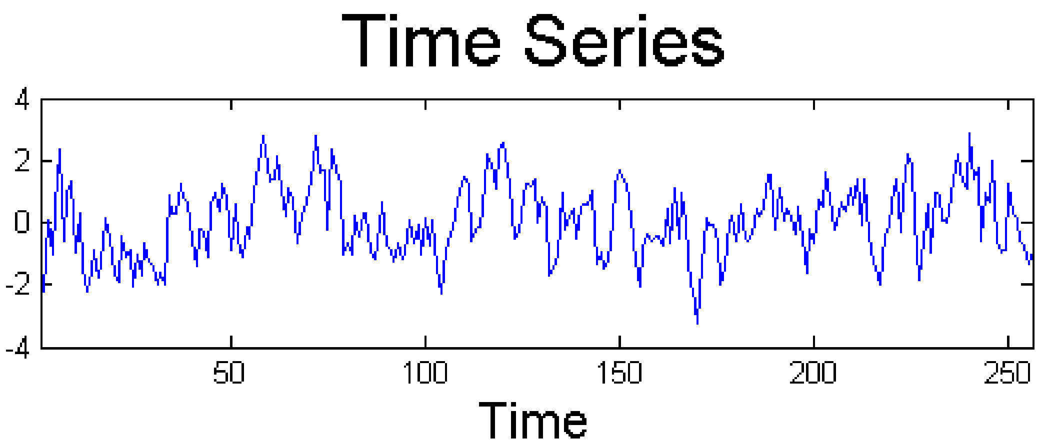
Examples – Univariate Time Series





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Estimation

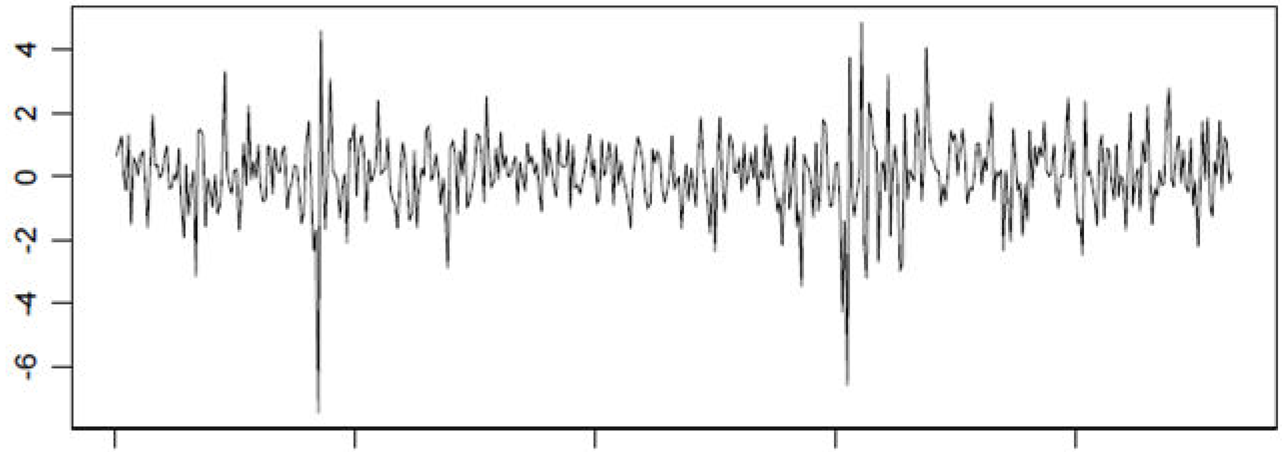
- Usually estimated nonparametrically (Brillinger, 2001; Shumway and Stoffer, 2004)
- For univariate time series, the stats package in R has the tools for estimation
- For multivariate time series, see the astsa package in R

For Functional Connectivity…

Many metrics for quantifying functional connectivity assume that the data are weakly stationary. (See Zhou et al, 2009; Fiecas et al, 2013)

NONSTATIONARY TIME SERIES

Motivation

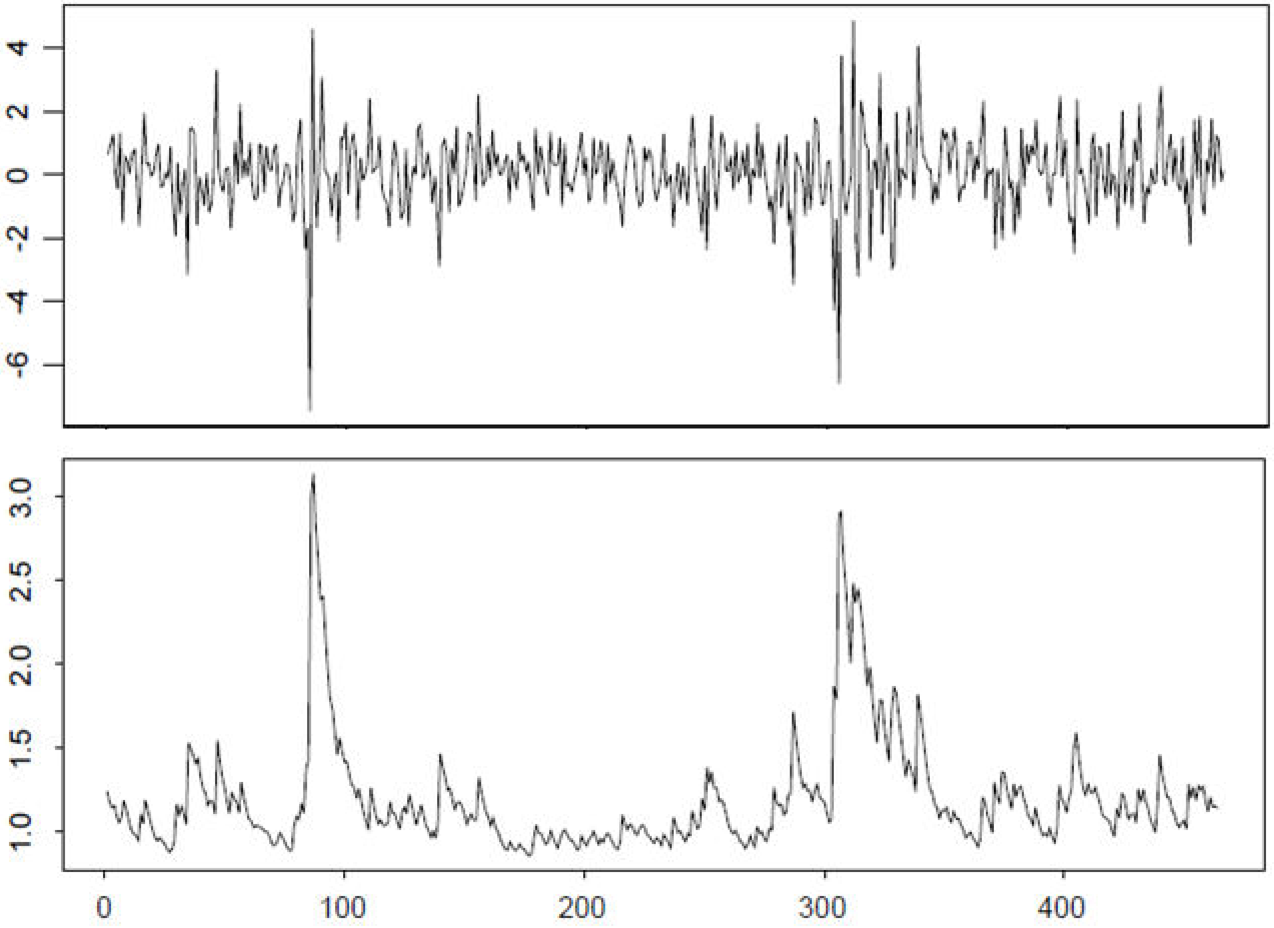


Brockwell and Davis, 2002

Motivation

What if the second moment of the data is changing over time?

Volatility



Brockwell and Davis, 2002

The ARCH Model

The ARCH(p) (Autoregressive Conditional Heteroskedasticity) model:

$$X_t = \sigma_t Z_t,$$

where Z_t iid (0,1), and

$$\sigma_t^2 = \alpha_0 + \alpha_1 X_{t-1}^2 + \cdots + \alpha_p X_{t-p}^2$$

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The GARCH Model

The GARCH(p,q) model:

$$X_t = \sigma_t Z_t,$$

where Z_t iid (0,1), and

$$\sigma_t^2 = \alpha_0 + \sum_{j=1}^{p} \alpha_j X_{t-j}^2 + \sum_{k=1}^{q} \beta_k \sigma_{t-k}^2$$

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Estimation

- Usually done through maximum likelihood (Brockwell and Davis, 2002)
- See the rugarch package in R

TV-AR(1)

$$X_t = \phi_t X_{t-1} + Z_t$$

Z_t is white noise $(0, \sigma^2)$

Estimation

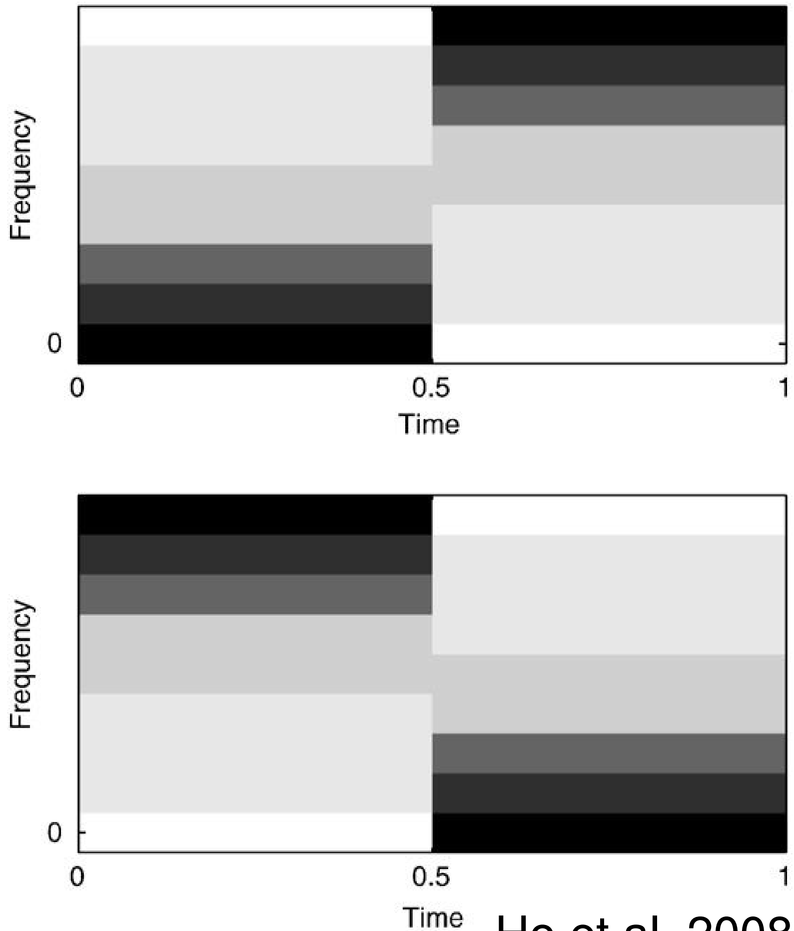
- Many ways to estimate the time-varying parameter (e.g., splines, wavelets)
- No readily available package

The Cramer Representation

Recall for weakly stationary time series:

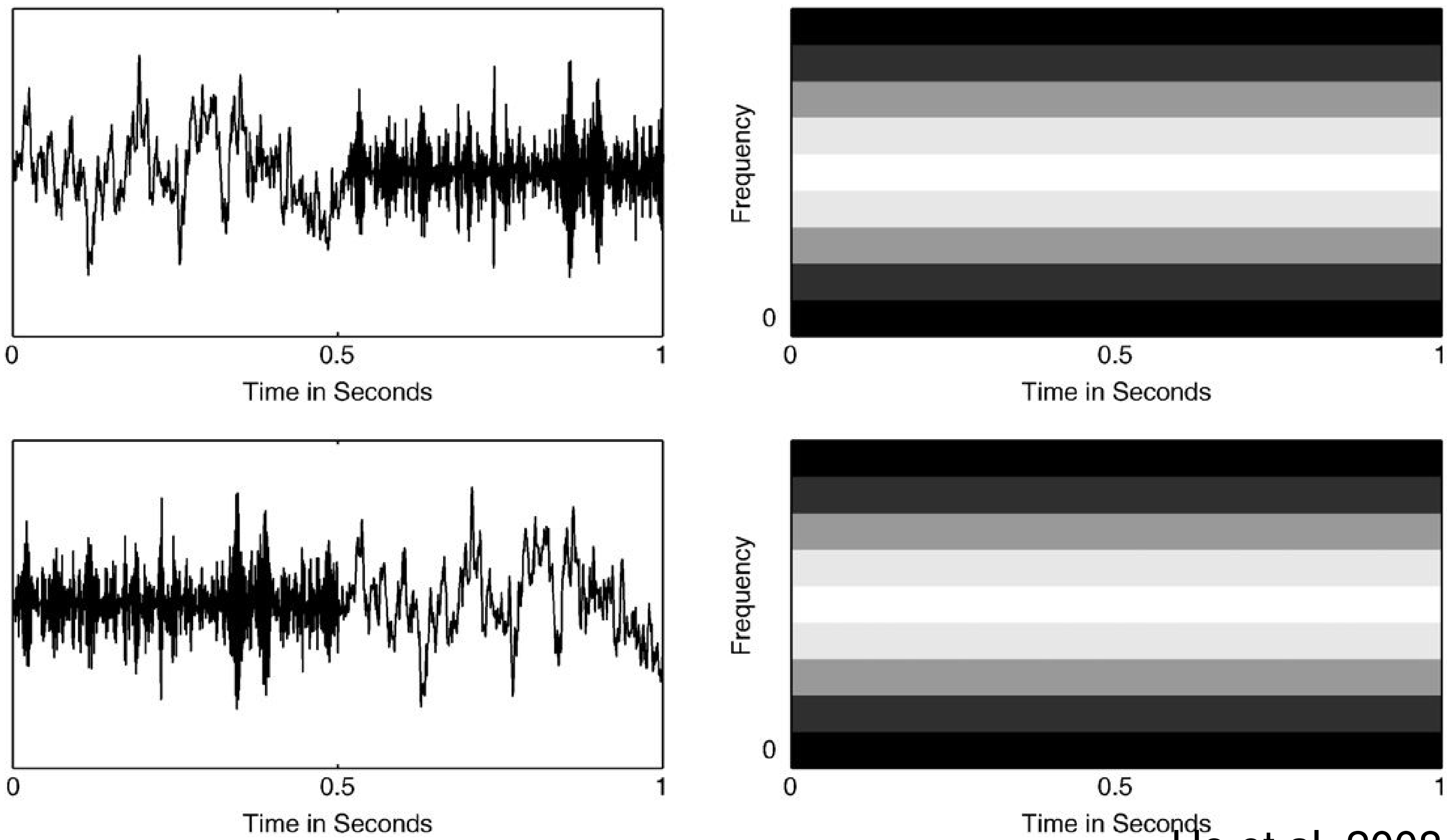
$$\mathbf{X}_t = \int_{-0.5}^{0.5} \mathbf{A}(\omega) \exp(-i2\pi\omega t) d\mathbf{Z}(\omega)$$

Time-Frequency Plots



Ho et al, 2008

Time-Frequency Plots



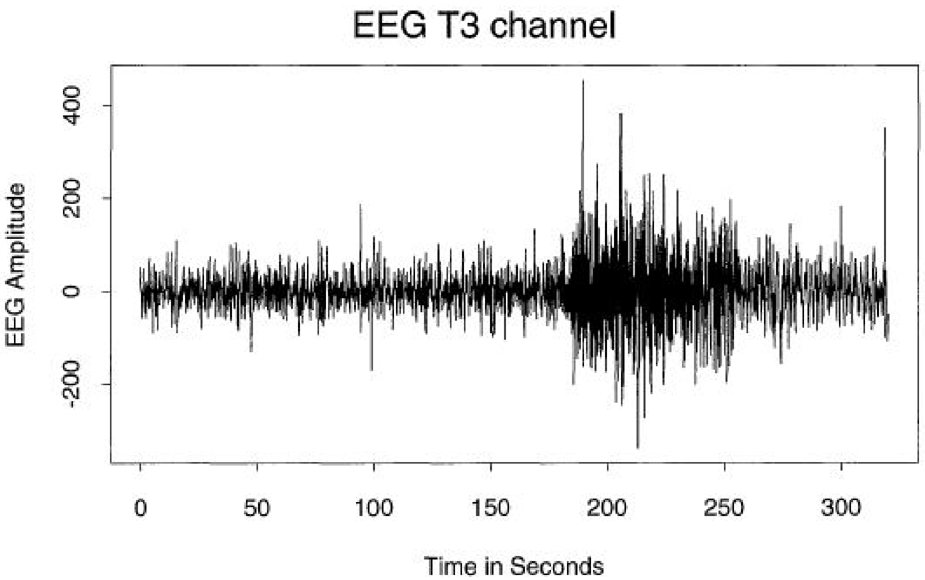
Ho et al, 2008

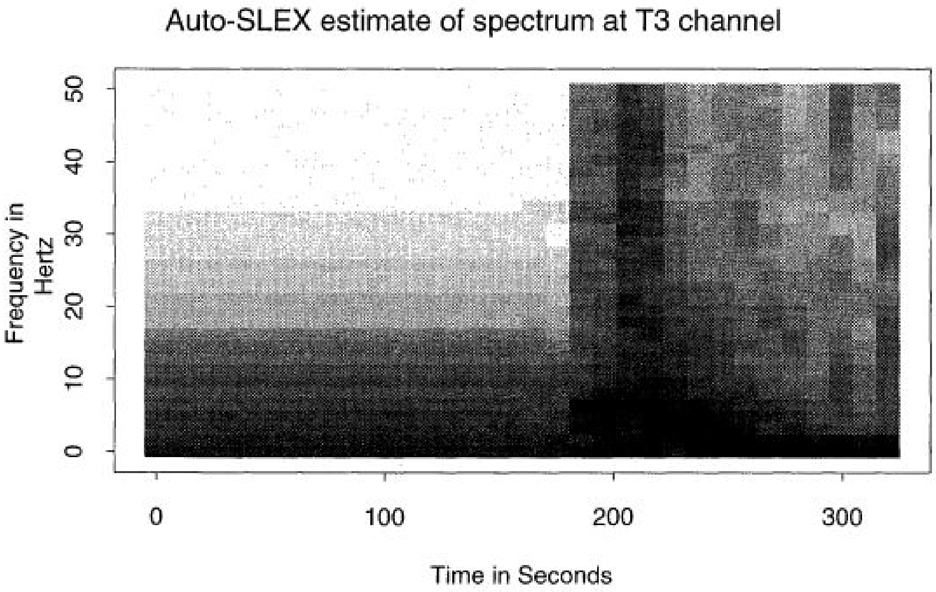
The Dahlhaus Model

Locally stationary time series (Dahlhaus, 1997,2000; Guo et al, 2003):

$$\mathbf{X}_t = \int_{-0.5}^{0.5} \mathbf{A}(t/T, \omega) \exp(-i2\pi\omega t) d\mathbf{Z}(\omega)$$

The Dahlhaus Model



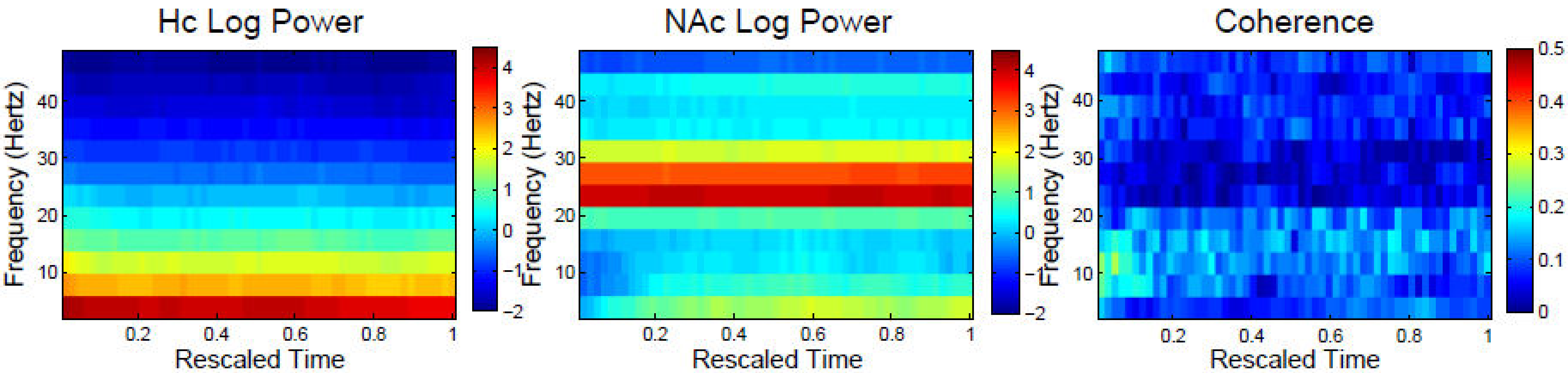


Ombao et al, 2001

Estimation

- Usually done nonparametrically (Dahlhaus 2000; Ombao et al 2001, 2005; Fiecas and Ombao, 2014)
- You can "easily" modify the astsa package in R to obtain naïve estimates.
- See me for matlab code

Nonstationarity Over Time and Over the Experiment



Fiecas and Ombao, 2014

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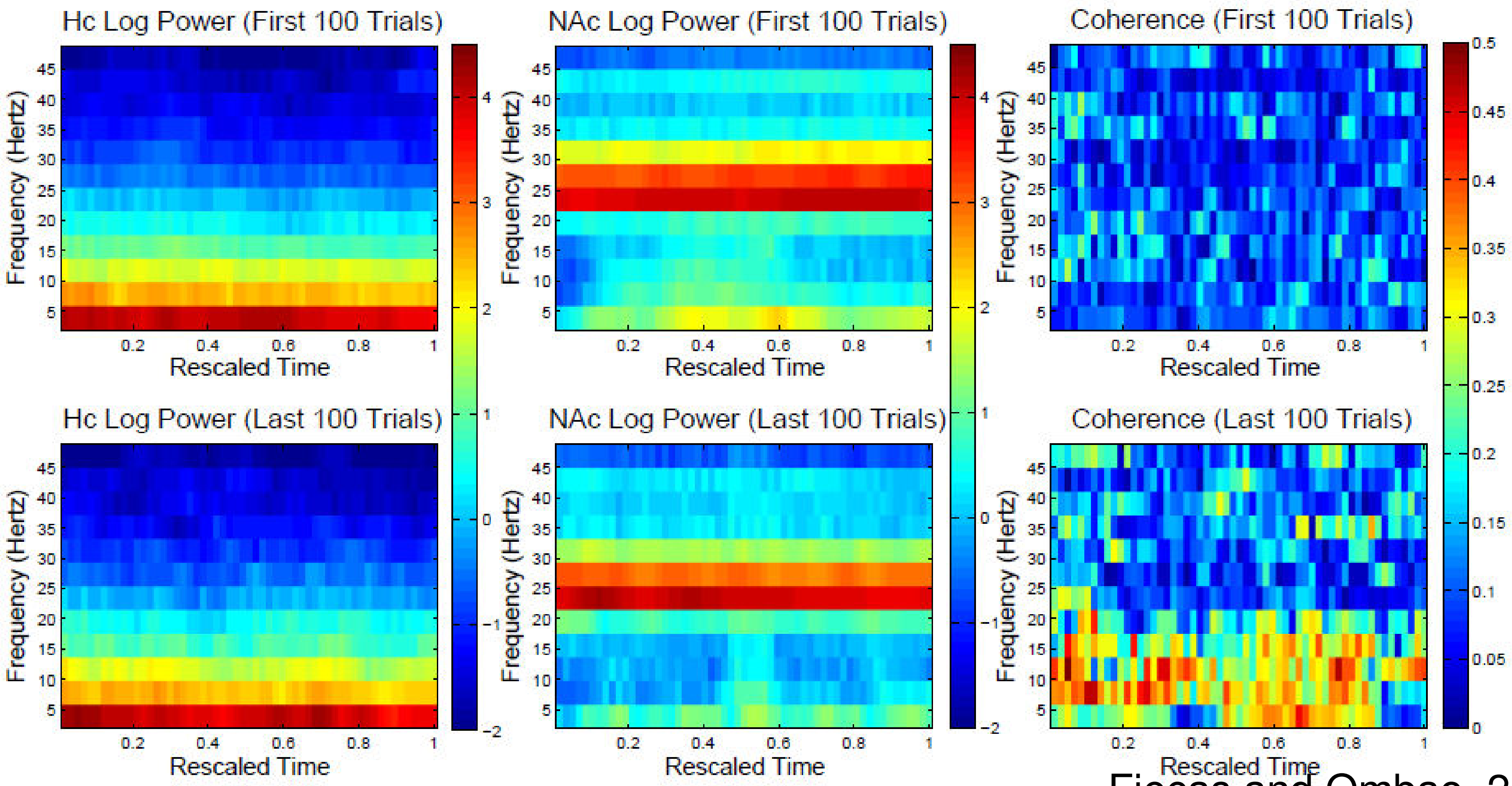
Nonstationarity Over Time and Over the Experiment



Fiecas and Ombao, 2014

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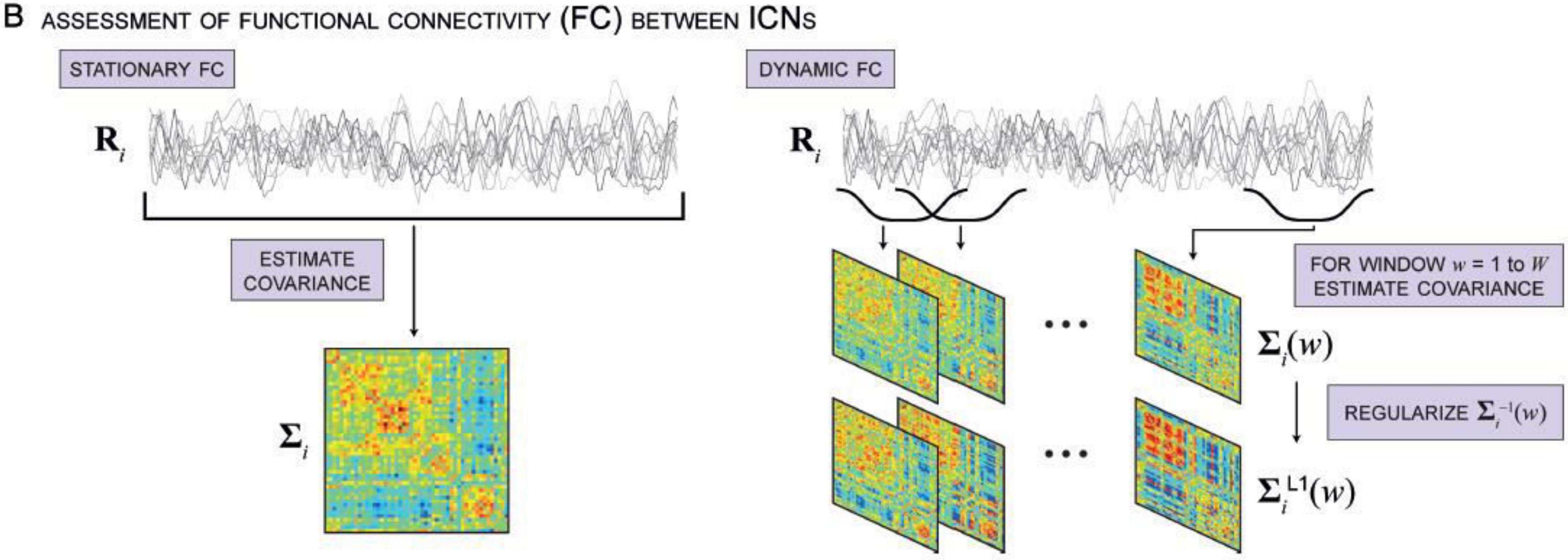
DYNAMIC CORRELATION ANALYSIS

Sliding Window Approach



Allen et al, 2013

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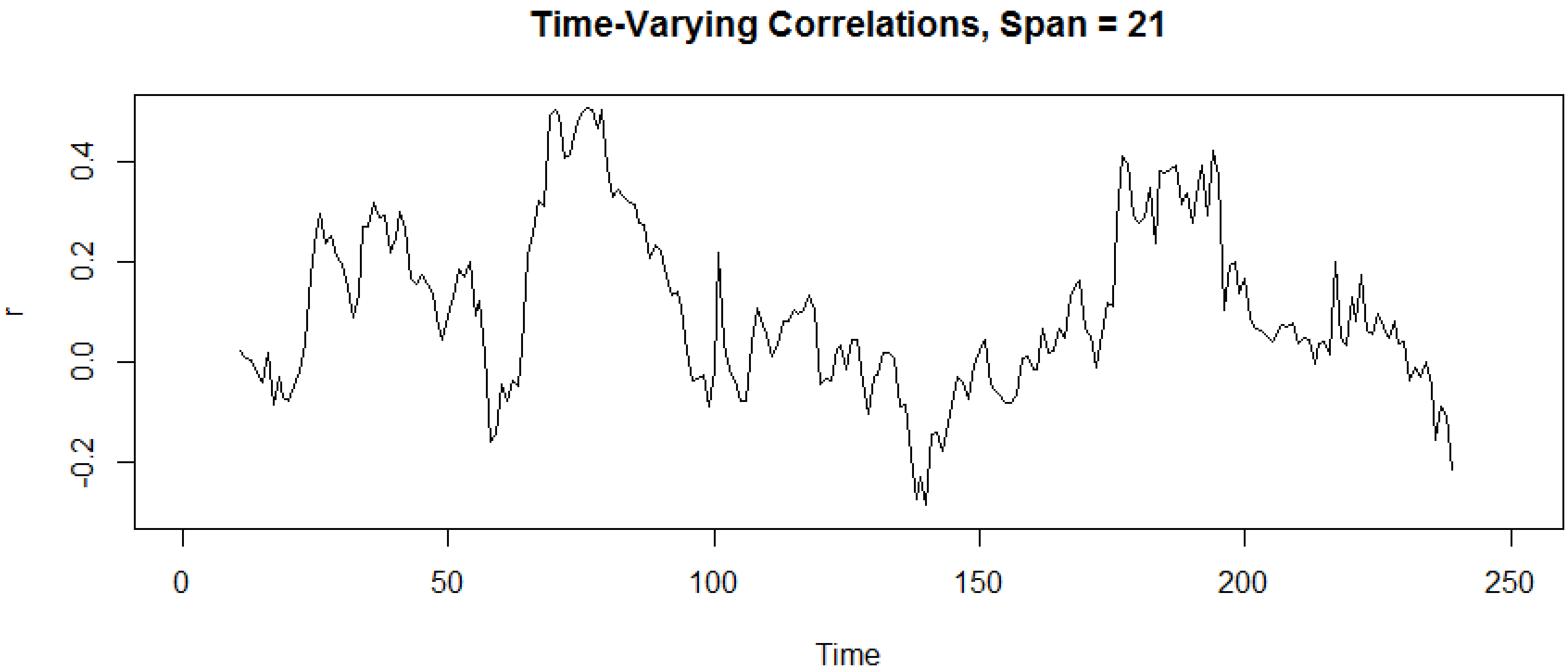
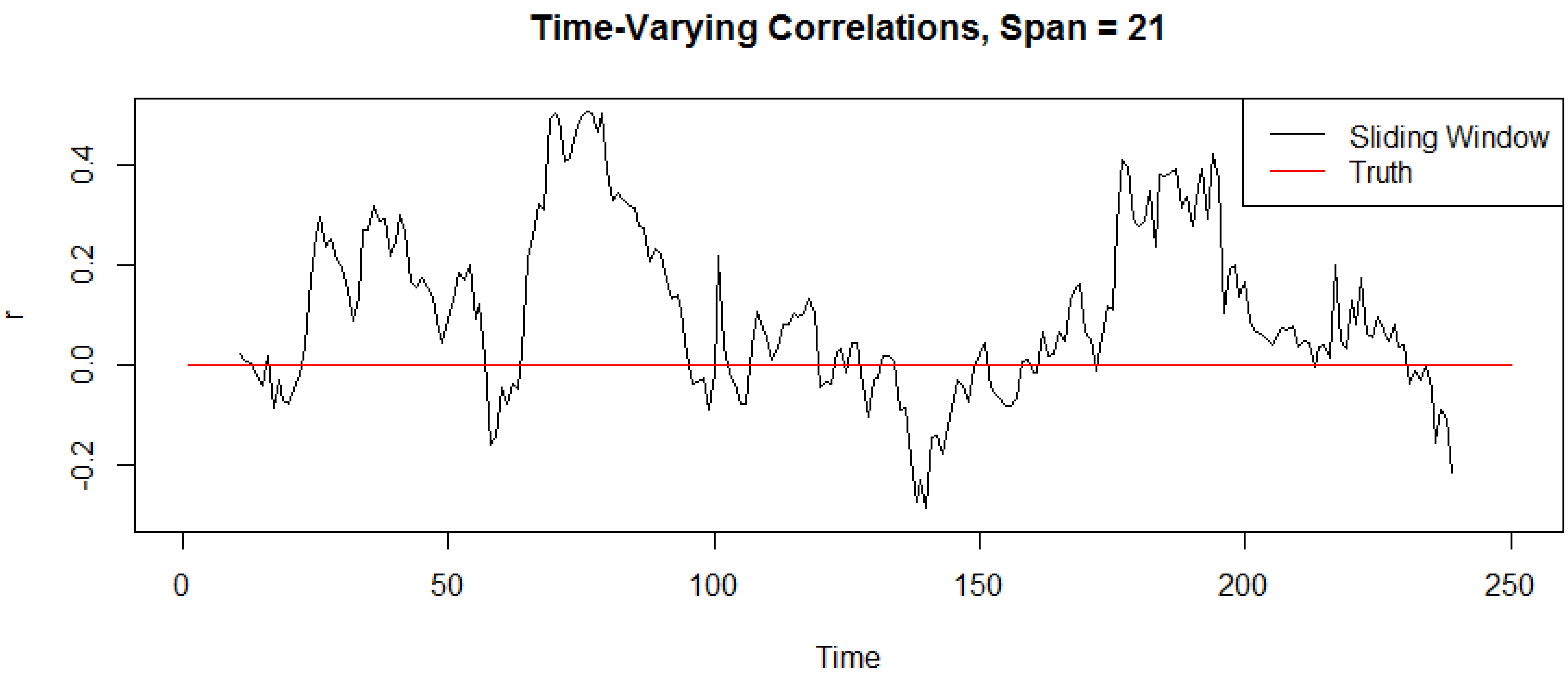
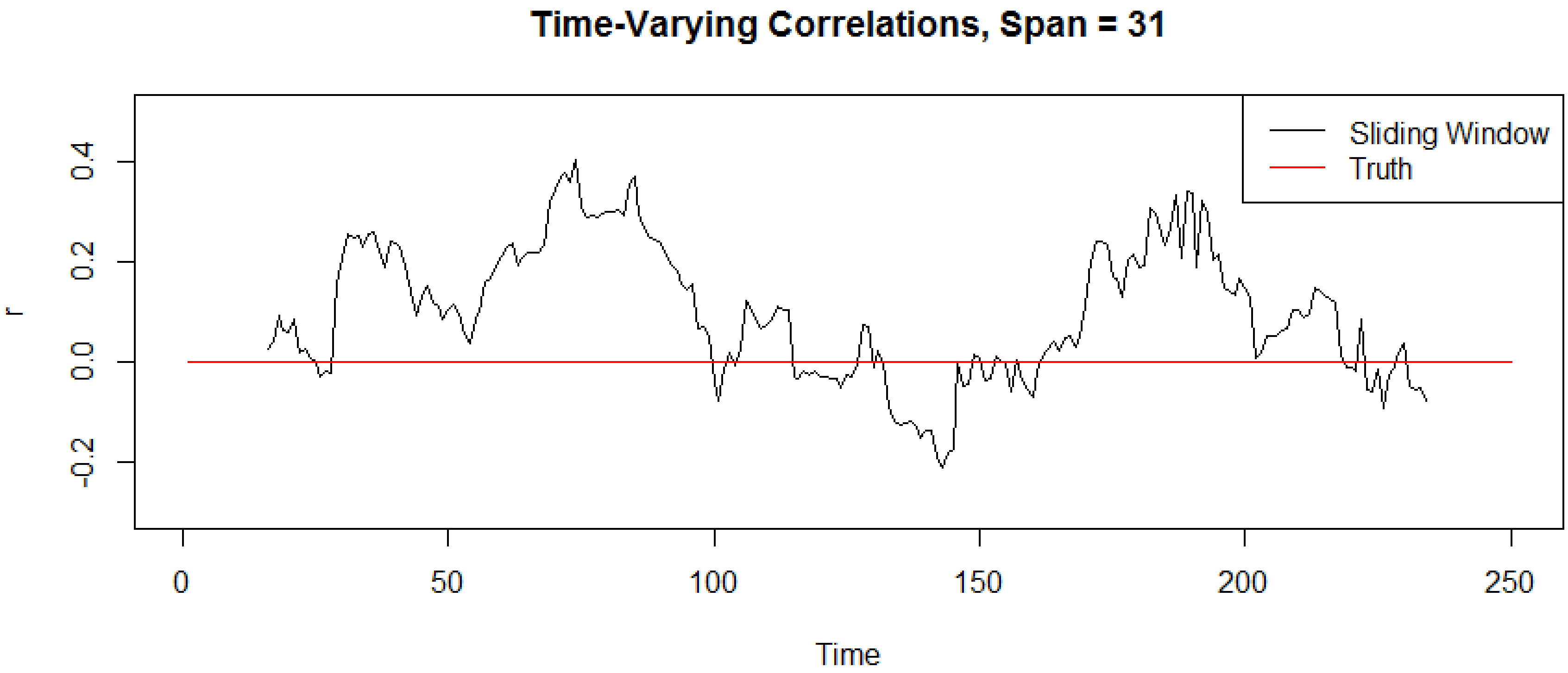
Sliding Window Approach



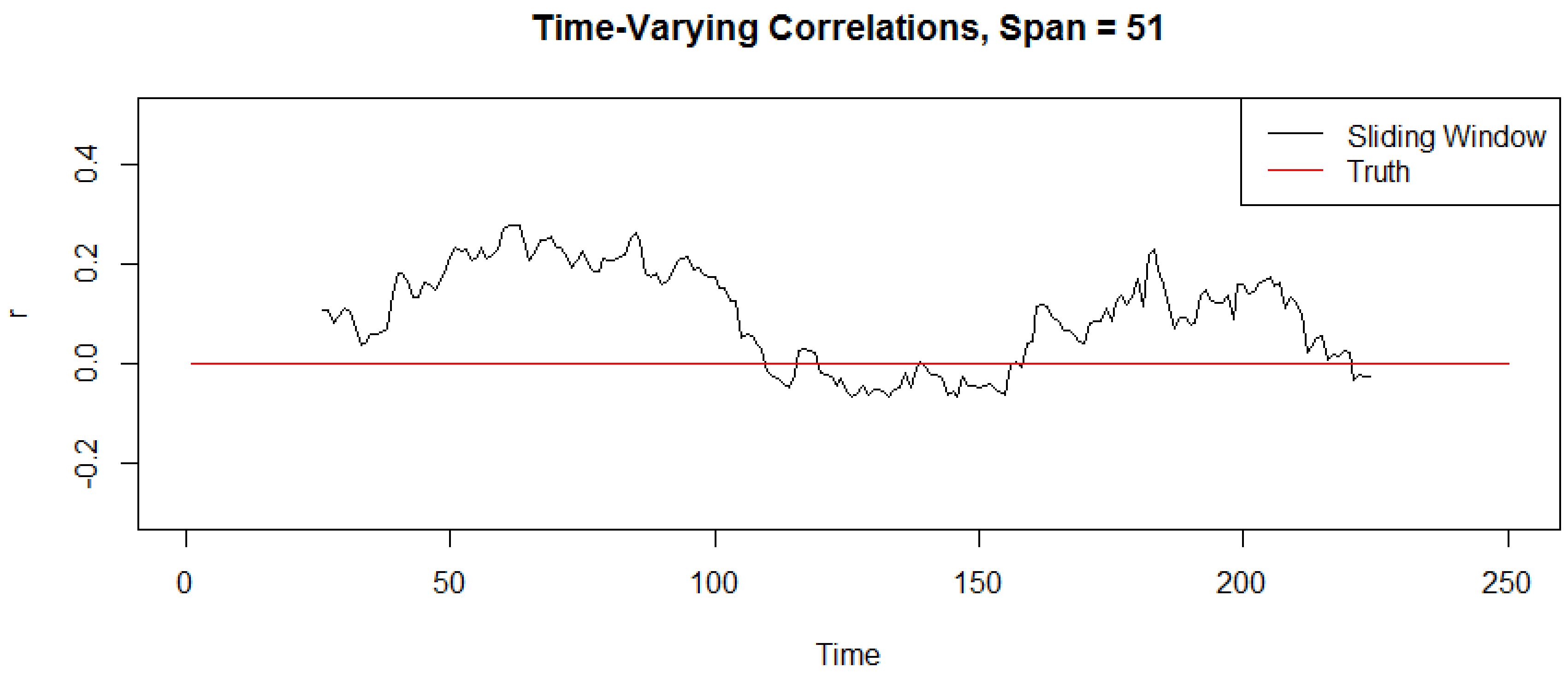
Sliding Window Approach



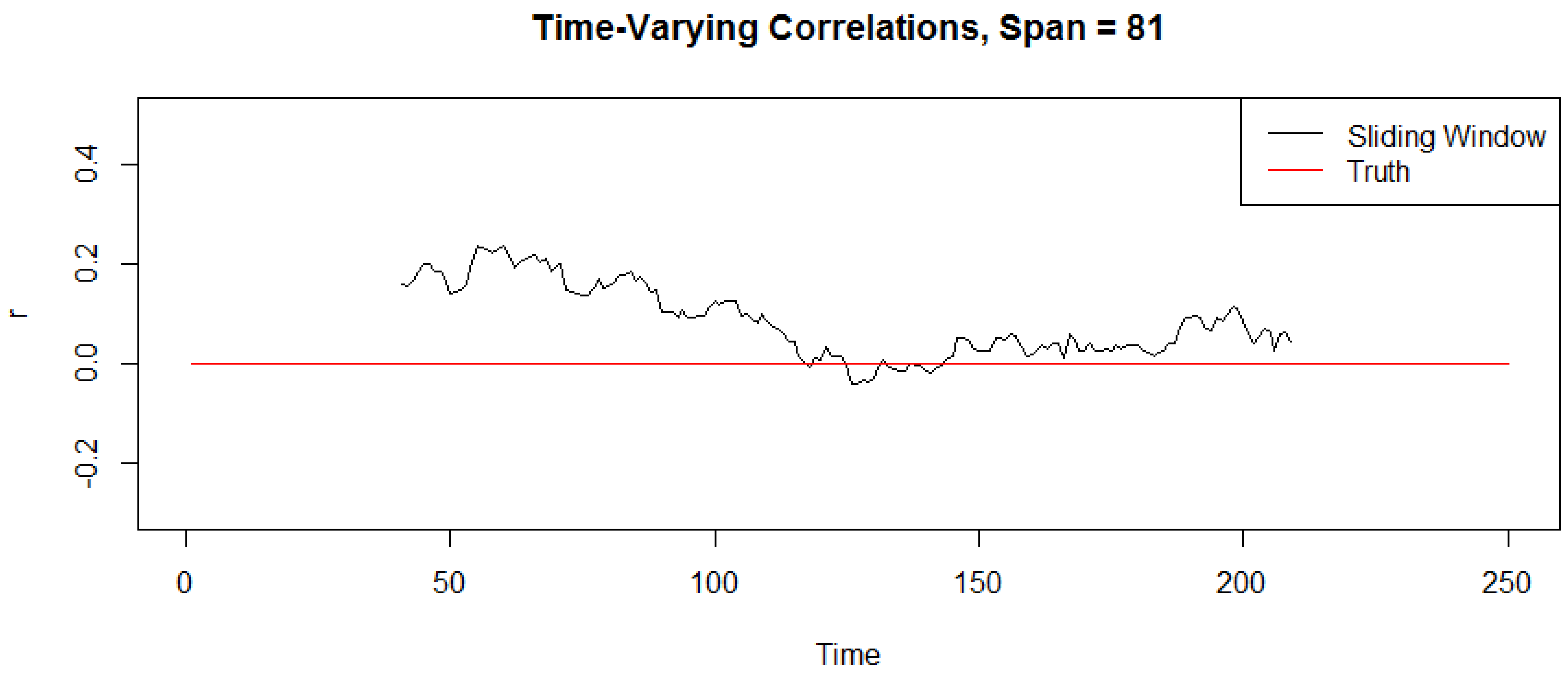
Sliding Window Approach



Sliding Window Approach



Sliding Window Approach



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The Problems

How to choose the smoothing span?

(See Ombao and van Bellegem, (2008) for a data-driven method.)

The Problems

If the smoothing span is too small, estimates have large variance.

If the smoothing span is too big, you will miss transient effects.

Set Up

The set up:

$$\boldsymbol{Y}_t = \boldsymbol{\mu}_t + \boldsymbol{e}_t,$$

Throughout, assume $\boldsymbol{\mu}_t = 0$.

$$Var(\boldsymbol{e}_t) = \Sigma_t = \begin{pmatrix} \sigma_{11,t}^2 \sigma_{12,t} \\ \sigma_{21,t} \sigma_{22,t}^2 \end{pmatrix}$$

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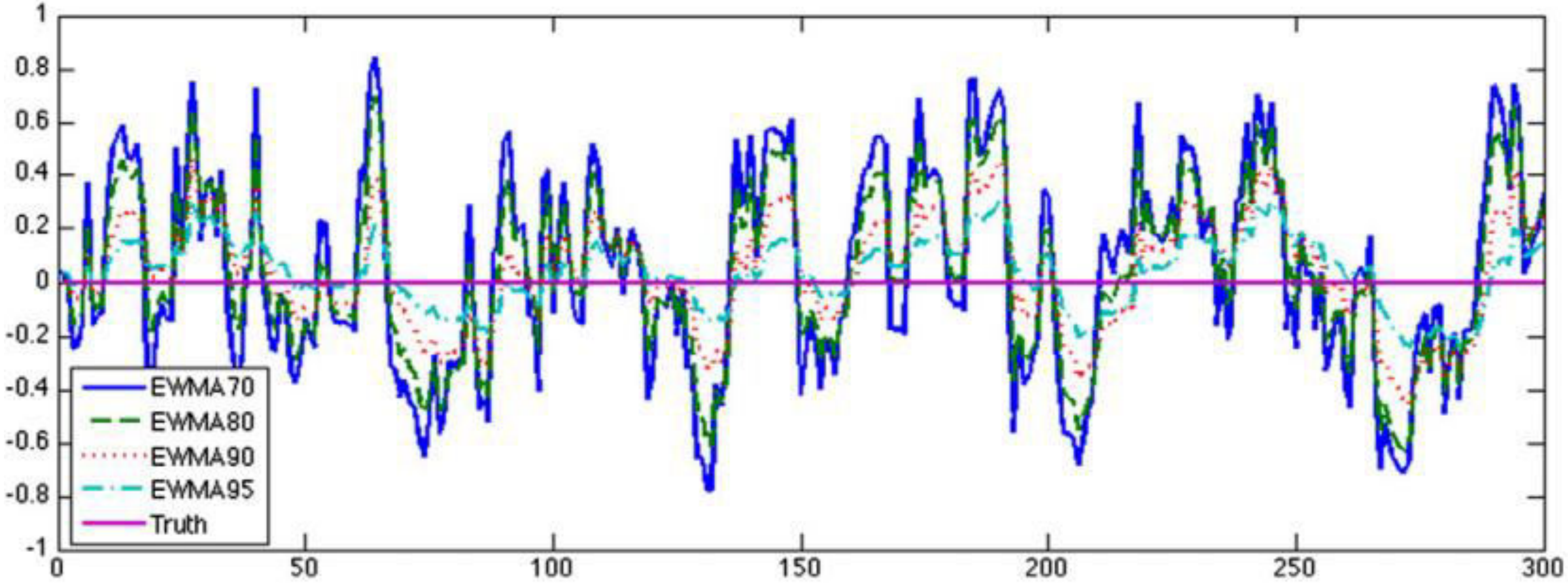
The exponential weighted moving average model

$$\Sigma_t = (1-\lambda)\boldsymbol{e}_{t-1}\boldsymbol{e}'_{t-1} + \lambda\Sigma_{t-1}$$

- A small value of λ gives large weight to recent time points.
- A large value of λ will adjust more slowly to observations from recent time points

The exponential weighted moving average model



Lindquist et al, 2014

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The Dynamic Conditional Correlation Model

Combine the GARCH with the EWMA:

1. Fit a GARCH per dimension, and use the estimated (time-varying) variance to standardize the residuals.
2. Use a EWMA-type estimator to shrink the covariance matrix of the standardized residuals.

The Dynamic Conditional Correlation Model

$$\boldsymbol{Y}_t = \boldsymbol{e}_t$$

$$\sigma_{j,t}^2 = \alpha_{j,0} + \alpha_{j,1} e_{j,t-1} + \beta_{j,1} \sigma_{j,t-1}^2$$

Let $\boldsymbol{D}_t = diag(\sigma_{1,t}, \sigma_{2,t})$

Let $\boldsymbol{\epsilon}_t = \boldsymbol{D}_t^{-1} \boldsymbol{e}_t$

Let $\boldsymbol{Q}_t = \theta_1 \boldsymbol{\epsilon}_{t-1} \boldsymbol{\epsilon}'_{t-1} + \theta_2 \boldsymbol{Q}_{t-1} + (1 - \theta_1 - \theta_2)\boldsymbol{S}$

Let $\boldsymbol{R}_t$ be the time-varying correlation matrix from $\boldsymbol{Q}_t$.

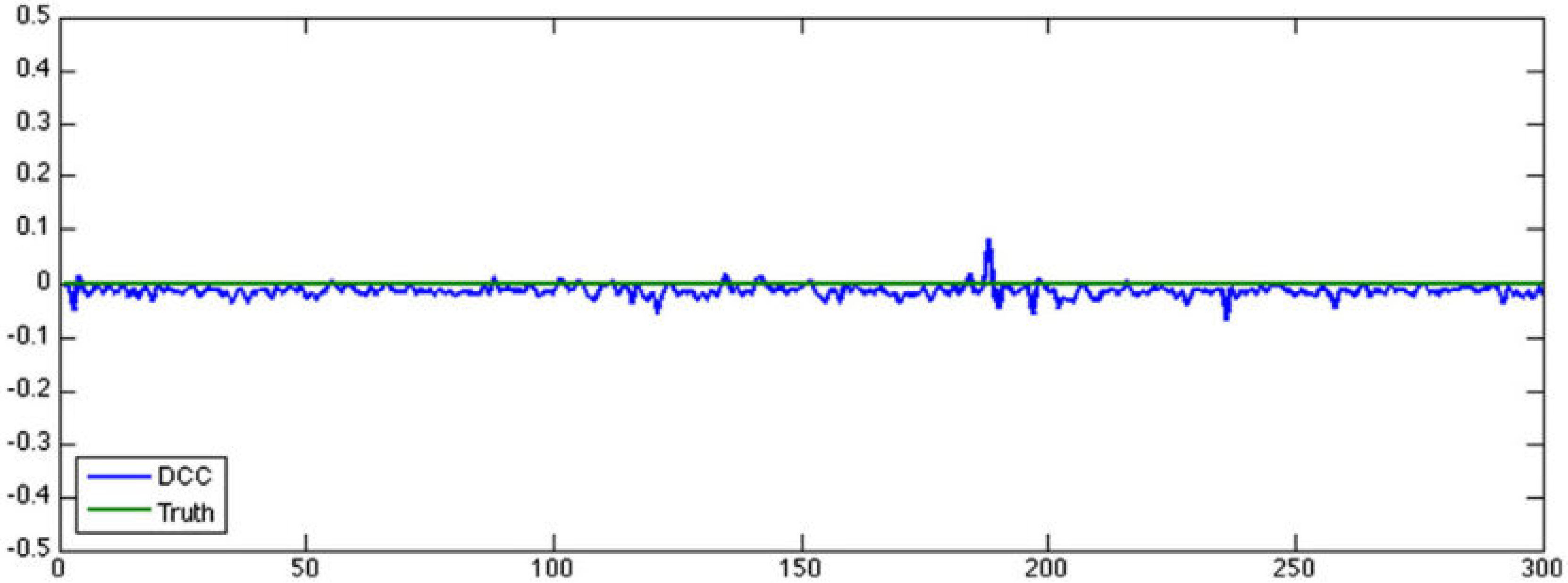
Let $\Sigma_t = \boldsymbol{D}_t \boldsymbol{R}_t \boldsymbol{D}_t$

Estimation

Assume Gaussian noise. Estimate all parameters via maximum likelihood. (Engle (2002) gives thorough details.)

Monte Carlo sampling is used to generate confidence intervals for parameters.

The Dynamic Conditional Correlation Model

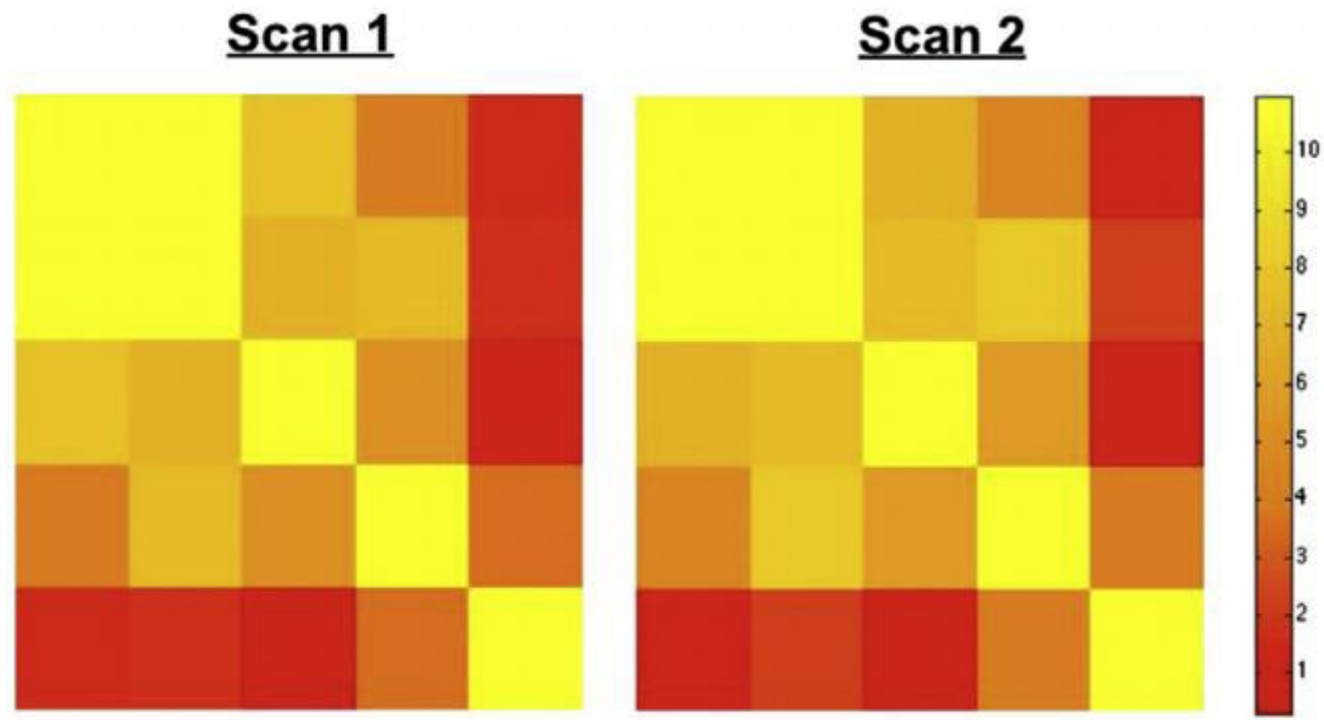


Lindquist et al, 2014

Application to test-retest resting-state fMRI

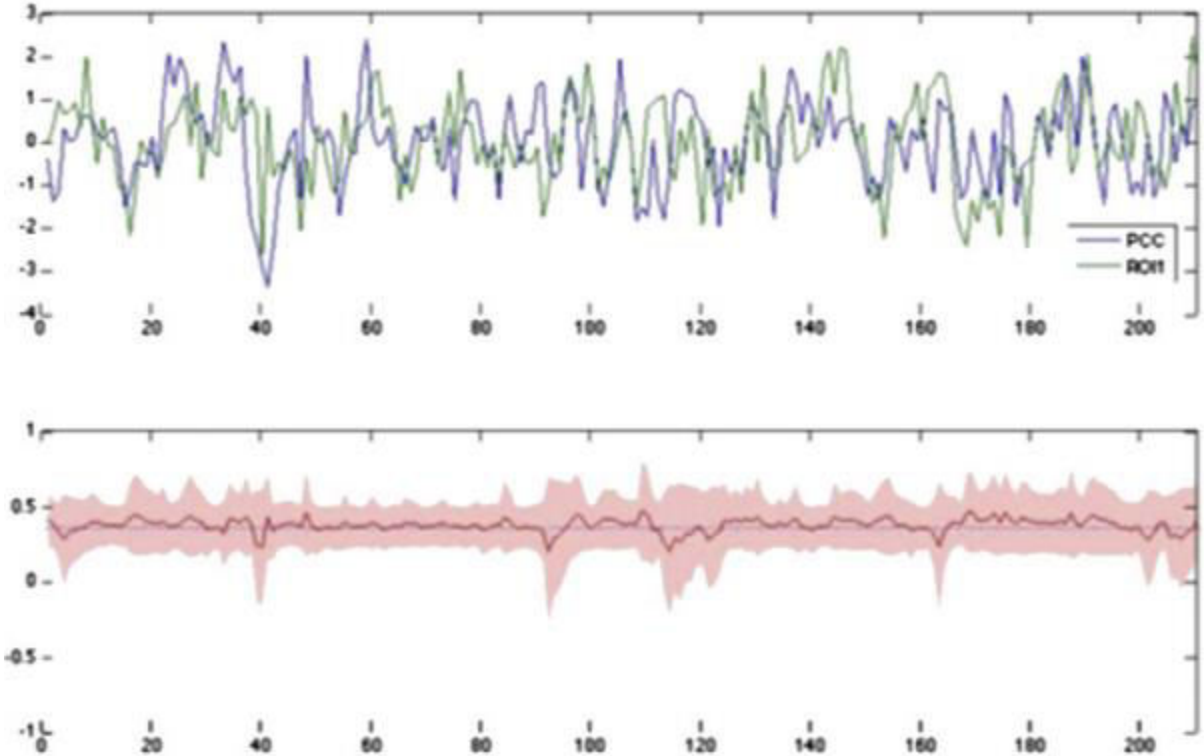
- N = 21 healthy adults (11 male)
- 7 minutes long scan, TR = 2 seconds
- PCC and 5 other ROIs picked

Static Correlations



Lindquist et al, 2014

Dynamic Correlations



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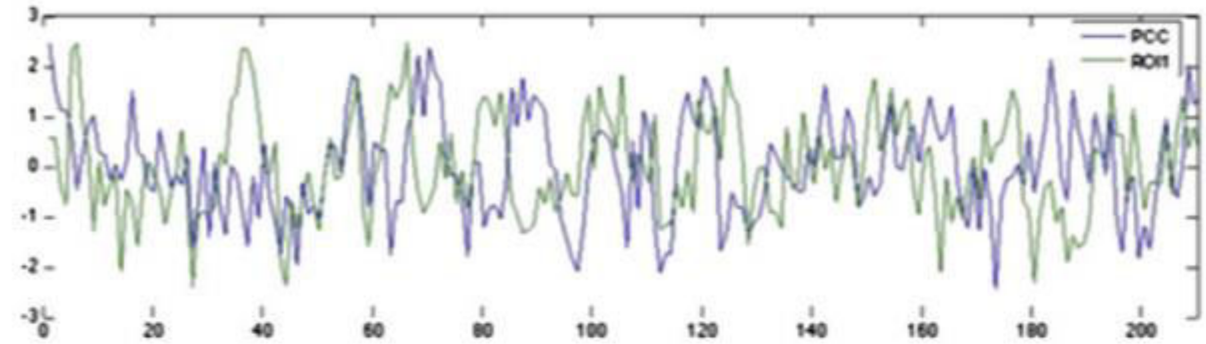
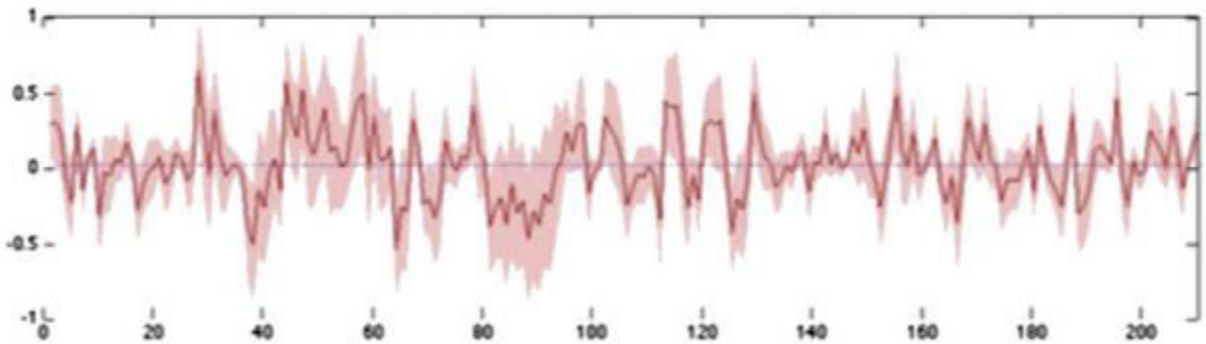
Dynamic Correlations





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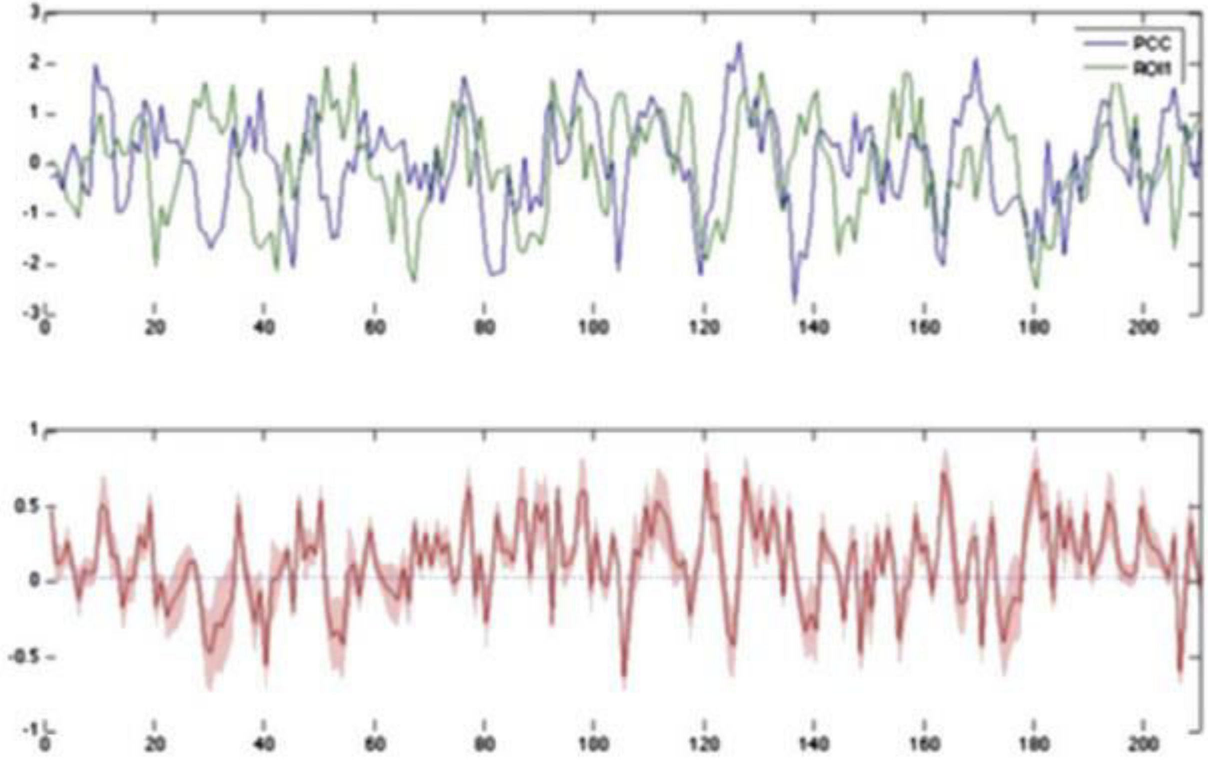
Dynamic Correlations



Lindquist et al, 2014

Conclusions

Dynamic functional connectivity between two ROIs is not reproducible across scanning sessions for the same subject.

SUMMARY AND DISCUSSION

Characterisation of the Data

Failing to account for nonstationarity yields an incorrect characterisation of the data

Summary and Discussion

Validity of comparing dynamic correlation profiles across subjects (or within subject across scanning sessions) in resting-state fMRI?