

# Graph Analysis of Brain Networks

## Time Series Analysis and Pattern Mining of Dynamic Neuroimaging Data

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# Outline

## 1. Vision Restoration

Stimulation-induced Synchronization by rtACS

## 2. Brain Connectivity

## 3. Data Mining

## 4. Model-based Analysis of Dynamic Brain Networks

## 5. Periodic Subgraph Mining

## 6. Conclusions and Future Work

# Visual Loss is the Most Feared Disease in the Elderly



tunnel vision



hemianopia

- 19% of persons  $> 70$  yrs have visual impairments
- causes:
  - age-related macular degeneration (AMD)
  - glaucoma
  - diabetic retinopathy
  - stroke and trauma
  - optic nerve damage
  - retinitis pigmentosa

# Schematic Overview of Visual Field Defects

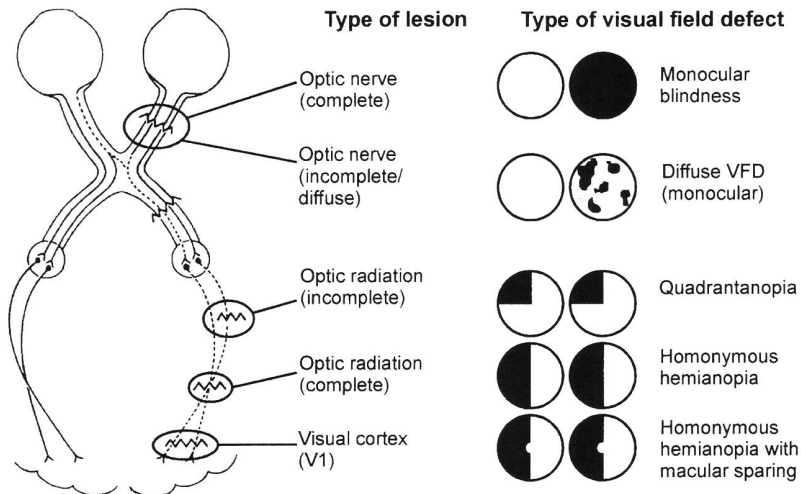
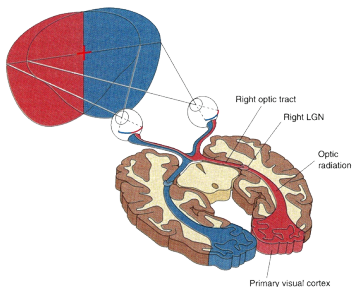
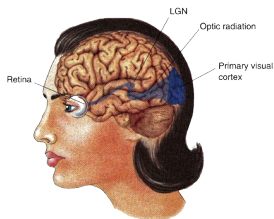


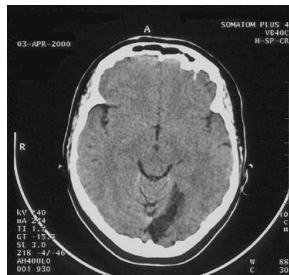
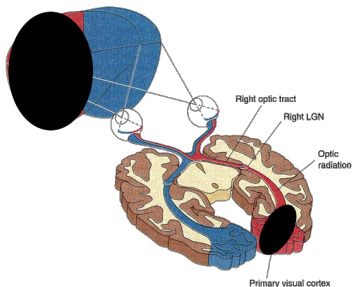
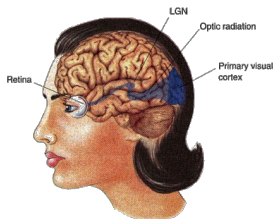
Fig. 1. Schematic overview of visual field defects (white = intact, black = blind areas) which result from lesions at different locations of the visual system.



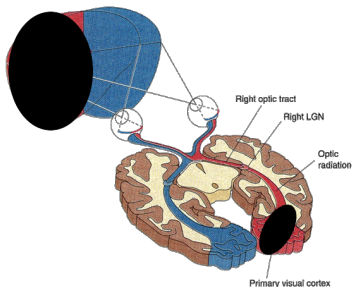
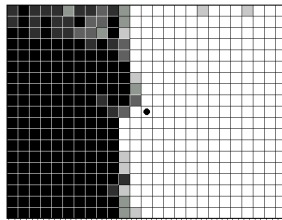
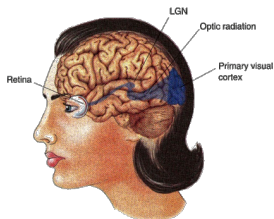
# Visual Pathway



# Low Vision after Brain Damage



## Low Vision after Brain Damage

















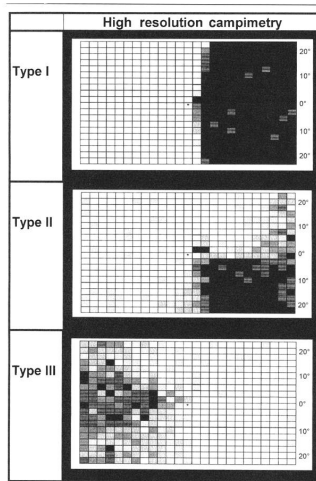
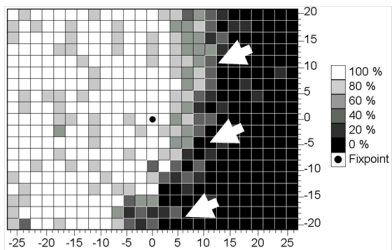
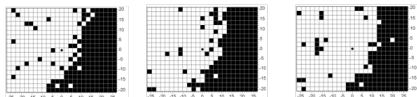






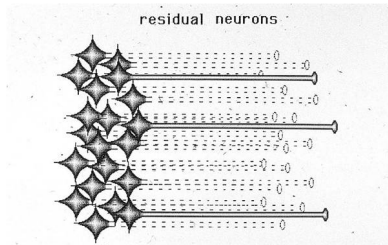
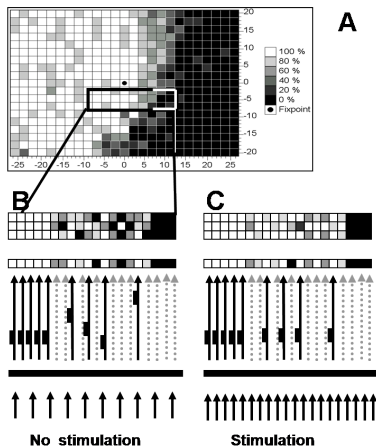


# Visualization of Residual Functions

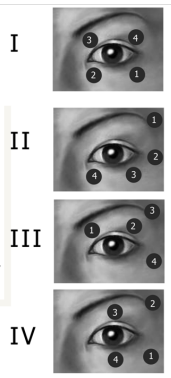
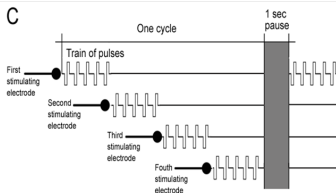
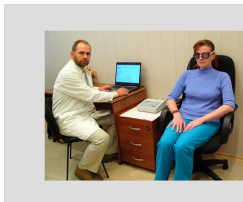


Superimposed evaluations of the central visual field ( $\pm 25^\circ$  eccentricity) using high resolution perimetry. Different types of transition zones have been found. (Upper panel) Sharp visual field border, and, accordingly, a small transition zone. (Middle panel) Transition zone of medium extension. (Lower panel) Fuzzy border, large transition zones, with scattered visual field defects. Black, blind areas; gray, areas of relative defects, i.e. transition zones with residual vision; white, intact.

## Stimulation-induced Synchronization



# Repetitive Transorbital AC Stimulation (rtACS)

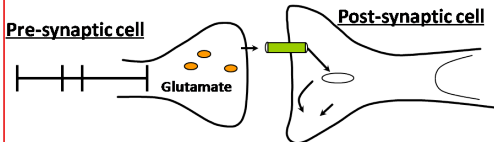
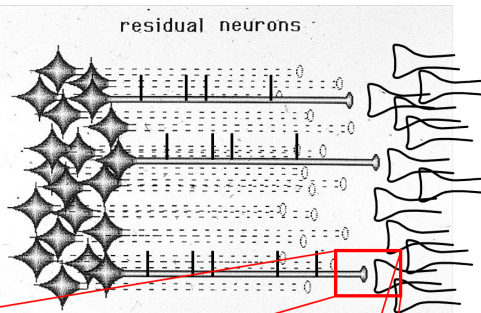
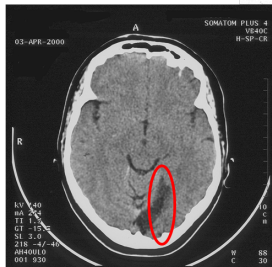


- placing non-invasive electrodes at eye or skull
- rtACS with low current stimulation ( $< 1 \text{ mA}$ ,  $10 - 30 \text{ Hz}$ )
- 20-40 min daily for approx. 10 days

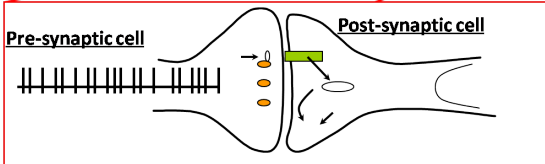
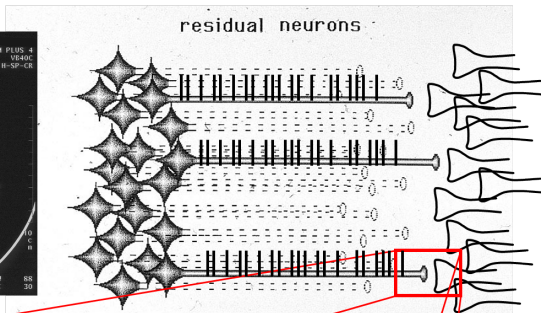
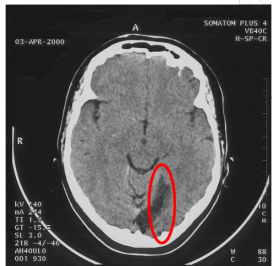


# Synaptic Transmission after Partial Damage

## Before rtACS

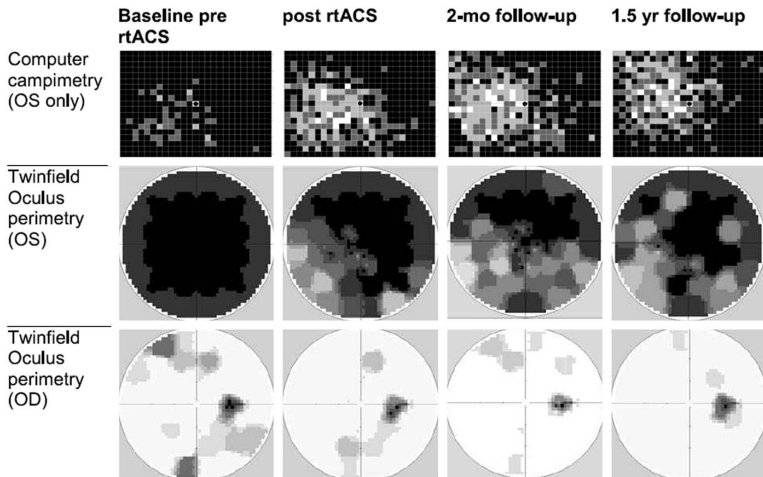


# Synaptic Transmission after Partial Damage After rtACS

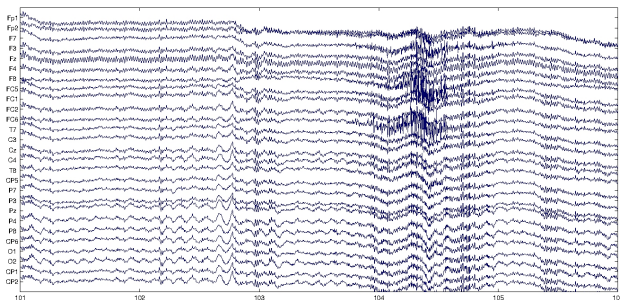


**Goal: strengthening synaptic transmission**

# Visual Fields in Optic Nerve Lesion after rtACS



# Challenge: Electroencephalogram (EEG)



**Figure:** Left: Vision restoration therapy using alternating current.  
Right: Typical raw data (28 EEG channel).

- 25 subjects: each EEG has been filtered by common filters
- **hypothesis:** pairwise channel similarity contains useful information (Sporns 2010)

# Scope and Goal of my Work

- scope: complex networks in real-world applications
- status quo: data mining and network theory studied separately
- research goal: interdisciplinary research by combining techniques
- focus: analysis of dynamic neuroimaging networks
- applications: clinical decision support systems, exploration of dynamic in complex networks

# Outline

1. Vision Restoration

**2. Brain Connectivity**

3. Data Mining

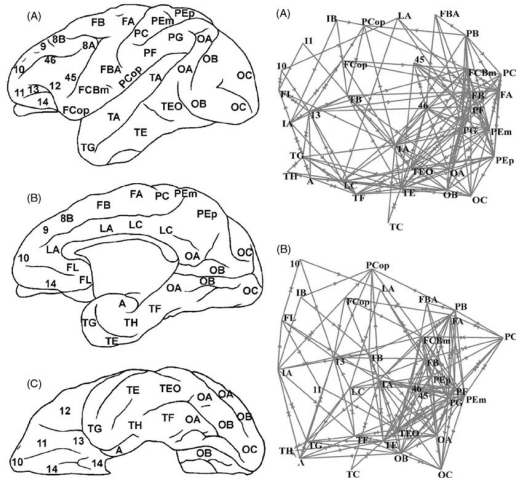
4. Model-based Analysis of Dynamic Brain Networks

5. Periodic Subgraph Mining

6. Conclusions and Future Work

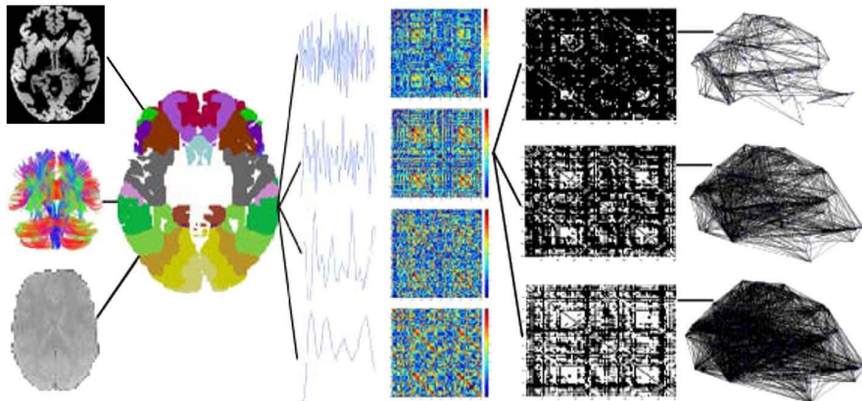
# Cortical Connectivity Maps

Stephan et al. 2000



# fMRI Graphs

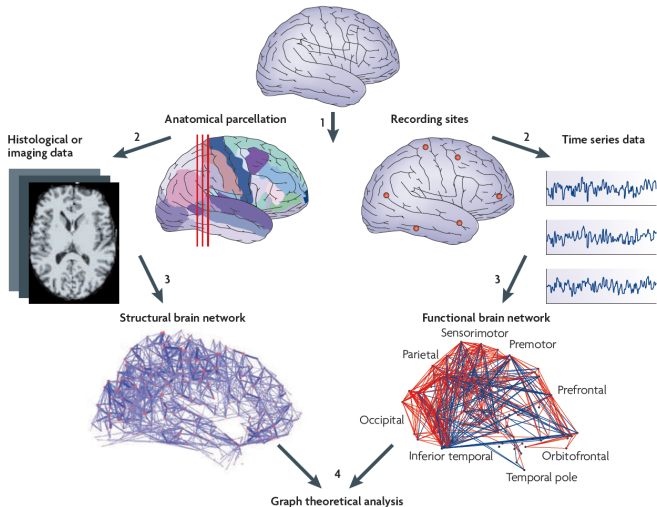
Bullmore, Barnes, et al. 2009





# Brain Network Analysis

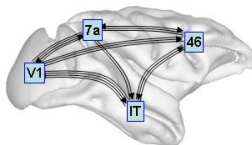
Bullmore and Sporns 2009



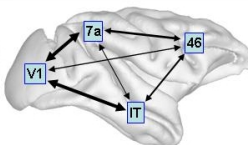
# Brain Connectivity

Sporns 2007

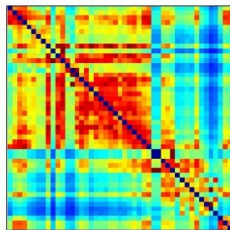
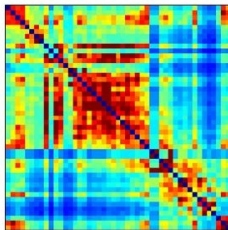
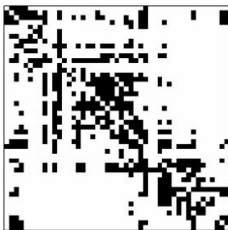
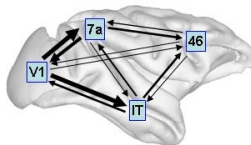
structural connectivity



functional connectivity



effective connectivity



- anatomical links vs. statistical dependencies vs. causal interactions

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## 1. Vision Restoration

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## 3. Data Mining

Knowledge Discovery in Databases

CRISP-DM

## 4. Model-based Analysis of Dynamic Brain Networks

## 5. Periodic Subgraph Mining

## 6. Conclusions and Future Work

# Data

- today: companies/institutes maintain huge databases
- ⇒ gigantic archives of tables, documents, images, sounds
- *“If you have enough data, you can solve any problem!”*
  - in large databases: can't see the wood for the trees
  - patterns, structures, regularities stay undetected
  - finding patterns and exploit information is fairly difficult

*We are drowning in information but starved for  
knowledge.* *[John Naisbitt]*

# Knowledge Discovery in Databases

- actually, abundance of data
  - lack of tools transforming data into knowledge
- ⇒ research area: knowledge discovery in databases (KDD)
- nontrivial process of identifying valid, novel, potentially useful, and ultimately understandable patterns in data
  - one step in KDD: data mining



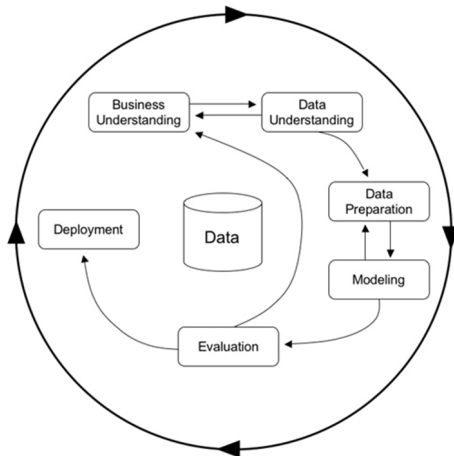
Miner VGA (1989) screenshot

# Data Mining Tasks

- classification  
*Is this patient a responder or non-responder?*
- segmentation, clustering  
*What groups of patients do I have?*
- concept description  
*Which properties characterize verum patients?*
- prediction  
*How much will the patient improve his/her vision?*  
*Which current and frequency must be applied?*
- dependence/association analysis  
*Which EEG waves of verum patients occur together frequently?*

# CRISP-DM

## Cross Industry Standard Process for Data Mining



# Outlook: Find Frequent Patterns in Raw EEG

Which EEG waves occur together frequently?

- every wave = shopping item
- EEG recording = market basket
- frequent patterns = frequent item sets
- association rule learning



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## **4. Model-based Analysis of Dynamic Brain Networks**

From EEG to Dynamic Graphs

Dynamic Graph Analysis

Time Series Model for Graph Measures

Approach using VAR

Experiments

Summary

# EEG Similarity: Synchronization likelihood

Stam and Dijk (2002); Montez et al. (2006)

time-delay embedding:  $X_{i,k} = (x_{i,k}, x_{i+L,k}, x_{i+2 \cdot L,k}, \dots, x_{i+(m-1) \cdot L,k})$

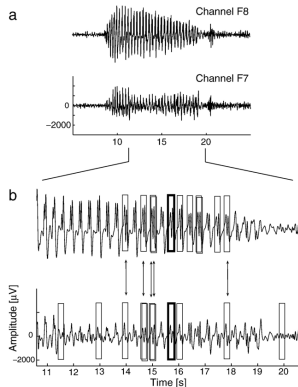
- consider only 2 channels  $A, B$
- probability that  $X_{i,k} \leq \varepsilon$ :

$$P_{i,k}^{\varepsilon} = \frac{1}{2(W_2 - W_1)} \sum_{\substack{j \\ W_1 < |i-j| W_2}}^N \theta(\varepsilon - d(X_{i,k}, X_{j,k}))$$

$$H_{i,j} = \theta(\varepsilon_{i,A} - d(X_{i,A}, X_{j,A})) + \theta(\varepsilon_{i,B} - d(X_{i,B}, X_{j,B}))$$

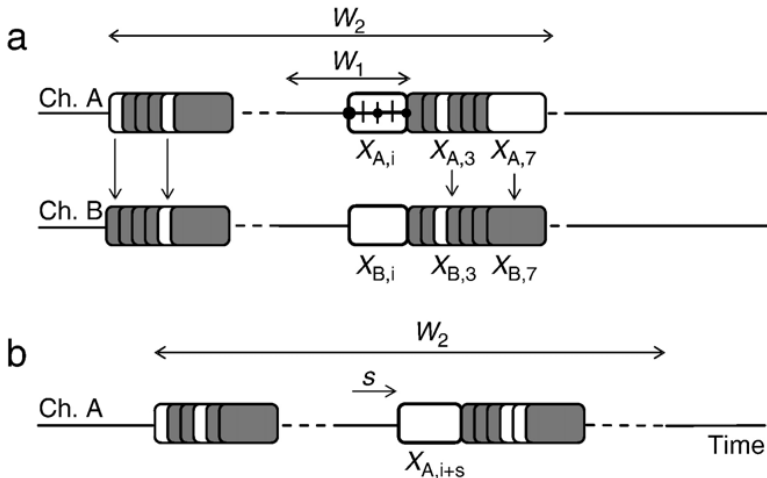
$$SL_i = \frac{1}{2p_{\text{ref}}(W_2 - W_1)} \sum_{\substack{j \\ W_1 < |i-j| W_2}}^N (H_{i,j} - 1)$$

- parameters  $m, L, W_1, W_2, p_{\text{ref}}$  can be estimated



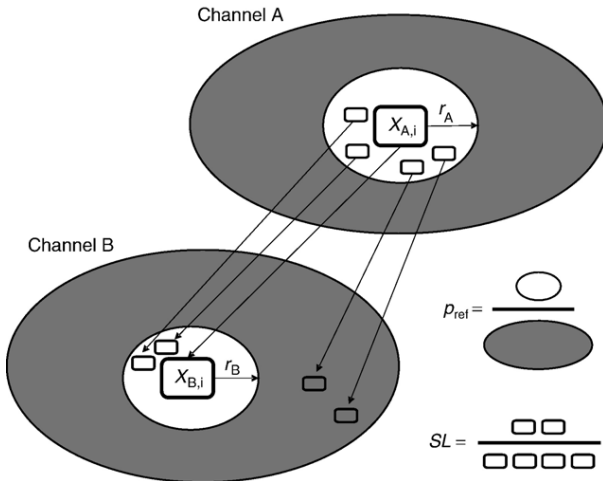
# State Vectors and SL Parameters

Montez et al. (2006)



# SL of 2 Channels

Montez et al. (ibid.)



# From EEG to Dynamic Graphs

$\delta$ : deep sleep     $\theta$ : drowsiness/arousal     $\alpha$ : relaxed/reflecting

$\beta$ : alert/working     $\gamma$ : cognitive functions     $\mu$ : RS motor function

- dynamic graphs of common human EEG frequency bands
- edge width/color represents  $SL \in [0, 1]$

# Dynamic Graphs

Q: What can change over time?

A: Everything ;-)

four categories (Harary and Gupta 1997):

- vertex-dynamic graph: vertices can be added/removed
- edge-dynamic graph: edges can be added/deleted
- vertex weighted dynamic graph: weights on vertices can change
- *edge weighted dynamic graph*: edge weights can change

needed: informative graph measures

# Graph Measures

(Steen 2010)

- *degree* of  $v \in V$ :  $\delta(v) \stackrel{\text{def}}{=} |N(v)|$   
for weighted  $G$ :  $\delta(v) \stackrel{\text{def}}{=} \sum_{u \in N(v)} w(\langle u, v \rangle)$
- $g_{u \leftrightarrow v}$ : shortest path (geodesic) between  $u, v$
- *distance*  $d$  between  $u, v$ :  $d(u, v) \stackrel{\text{def}}{=} \sum_{e \in g_{u \leftrightarrow v}} w(e)$
- *diameter*  $\varnothing(G) = \max_{u, v \in V(G)} d(u, v)$

# Graph Measures

(Latora and Marchiori 2001)

- efficiency of vertex  $u$ :

$$\eta(u) = \sum_{v \in V, v \neq u} 1/d(u,v)$$

- *global efficiency* of  $G$ :

$$\bar{\eta}(G) \stackrel{\text{def}}{=} \frac{1}{|V|} \sum_{u \in V} \eta(u)$$

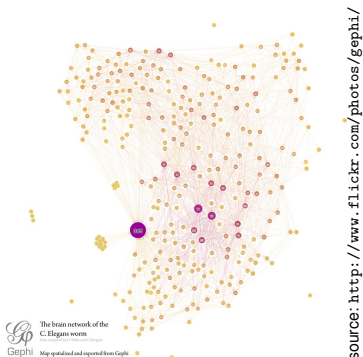
- *local efficiency* of  $G$ :

$$\bar{\eta}_{\text{loc}}(G) \stackrel{\text{def}}{=} \frac{1}{|V|} \sum_{u \in V} \bar{\eta}(G[\{u\} \cup N(u)])$$



# Neural Networks of *C. Elegans*

(Watts and Strogatz 1998)

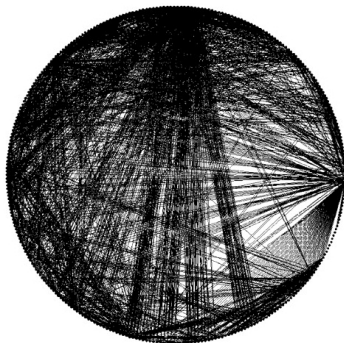


source: <http://blog.neuinfo.org>

- *Caenorhabditis elegans*
- 302 neurons, approx. 7.000 synapses
- Sydney Brenner (Nobel Prize in Medicine 2002)

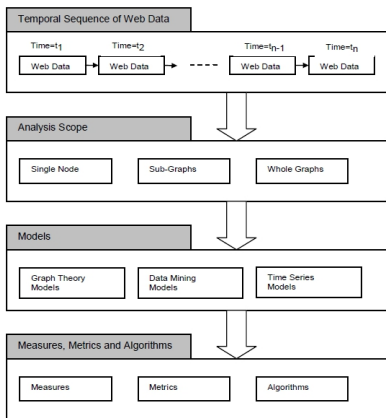
# Example: C. elegans

(ibid.)



	$d_{\text{actual}}$	$d_{\text{random}}$	$c_{\text{actual}}$	$c_{\text{random}}$
C. elegans	2.65	2.25	0.28	0.05

# Dynamic Graph Analysis



source: (Desikan and Srivastava 2004)

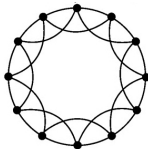
- ARMA models of graphs: anomaly detection (Pincombe 2005), feature selection (Moewes, Kruse, et al. 2012)
- VAR models of graphs: feature selection (Moewes and Kruse 2012)

# Graph Models

(Erdős and Rényi 1960)

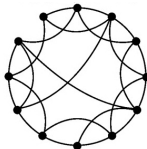
regular

high  $L$ , high  $C$



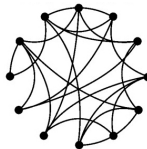
small-world

low  $L$ , high  $C$



random

low  $L$ , low  $C$



increasingly random connectivity

- edge is added with prob.  $p$  independently from other edge
- graphs with  $n$  vertices and  $m$  edges have equal probability of

$$p^m (1 - p)^{\binom{n}{2} - m}$$

- algorithmic models to construct graphs: (Watts and Strogatz 1998) and (Barabási and Albert 1999)

# Time Series Model for Graph Measures

**goal:** find coherence between dynamic functional networks and clinical variables from patients with visual field defects

- networks have been created by synchronization likelihood

⇒ series of weighted networks

- every graph was described by several graph measures

⇒ time series of graph measures

- fitted time series model for each patient
- model parameters have been correlated to clinical variables

# (Vector) Autoregressive Model

Box, Jenkins, Reinsel (2008)

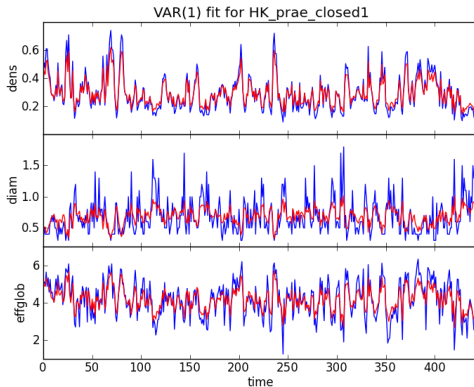
AR( $p$ ) model

$$x_t = \epsilon_t + \sum_{i=1}^p a_i x_{t-i}$$

multivariate case: VAR( $p$ )

$$\vec{x}_t = \vec{c} + \sum_{i=1}^p A_i \vec{x}_{t-i} + \vec{\epsilon}_t$$

# Example: Time Series of Graph Measures



**Figure:** Blue: Original graph measures. Red: Fitted graph measures.

measures for VAR(1) model: density, global efficiency, diameter

# Experiment

given:

- VAR models for each subject (and for each frequency band)
- 6 clinical variables

goal:

- VAR coefficients  $\leftrightarrow$  clinical variables
- *e.g.* linear regression
- here, ridge regression with  $\alpha \in [0.1, 0.2, \dots, 0.9, 1]$
- parameter search: leave-one-out cross-validation

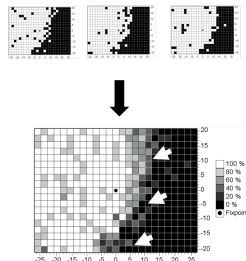


# Results

evaluated by score coefficient

$$R^2 = 1 - \frac{\text{MSE}}{\text{res}}$$

whereas  $\text{MSE} = \sum_{i=1}^n (x_i - x'_i)^2$  and  $\text{res} = \sum_{i=1}^n (x_i - \bar{x})^2$   
best score  $R^2 = 1$  (the lower, the worse)



variable	$\delta$	$\theta$	$\alpha$	$\beta$	$\gamma$	$\mu$
# white	.198	.727	.715	.276	.207	.370
# gray	.193	.101	.156	.240	.273	.189
# black	.226	.605	.692	.328	.269	.400
# white (CMF)	.179	.698	.608	.288	.232	.338
# gray (CMF)	.177	.105	.183	.446	.185	.226
# black (CMF)	.206	.630	.696	.311	.273	.364

# Summary

- still unknown: whether EEG features can describe damages of human visual system
- goal of this study: find suitable network measures and clinical features
- static analysis (Held et al. 2012), dynamic analysis (Moewes, Kruse, et al. 2012)
- most informative frequency bands:  $\delta$  and  $\alpha$  band
- most informative clinical variables: proportion of intact and absolutely defected sectors
- features will be used in future work

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# Periodic Subgraph Mining

Lahiri and Berger-Wolf (2010)

- periodic subgraph mining: discovery of all interactions that occur at regular intervals in dynamic networks
- interactions occur at discrete instances over period of time
- objects of interest: graph edges and how they change over time
- focus: finding periodically occurring interaction patterns in dynamic networks

# Approach

- synthesis of two different data mining problems:
  - frequent pattern mining in transactional DB
  - periodic pattern mining in  $n$ -dimensional sequence
- combination characterizes periodic behavior in dynamic networks

# Some Definitions

- dynamic network  $\mathcal{G}$  of  $T$  points in time
- for arbitrary graph  $F = (V, E)$ , its support set  $S(F)$  in  $\mathcal{G}$  is set of points in time  $t$  in  $\mathcal{G}$  where  $F$  is subgraph of  $G_t$ ,  $F \subseteq G_t$
- *support* of  $F$  is cardinality of its support set,  $|S(F)|$ :

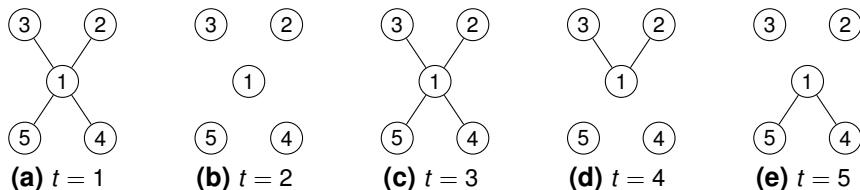
$$S(F) = \{t_i, \dots, t_j\} \text{ s.t. } \forall (t \in S(F) \Leftrightarrow F \subseteq G_t)$$

- $F$  is *frequent* subgraph of  $\mathcal{G}$  if  $|S(F)| \geq \sigma$  where  $1 \leq \sigma \leq T$
- $F(\sigma)$  is set of all frequent subgraphs at minimum support  $\sigma$

# Maximal and Closed Subgraphs

- subgraph is *maximal* if there is no subgraph that can be derived from it
- subgraph  $F \in F(\sigma)$  is *closed* if it is maximal at some support  $\sigma' > \sigma$
- closed and maximal subgraphs reduce size of  $F(\sigma)$

# Frequent and Periodic Subgraphs



**Figure:** using  $\sigma = 3$ ,  
 $\{(1, 2), (1, 3)\}$  is frequent but not periodic while  $\{(1, 4), (1, 5)\}$  is both



# Periodic Subgraph Embedding

- *PSE* of arbitrary subgraph  $F \subseteq \mathcal{G}$  is maximal, ordered set of points in time s.t. difference between points in time is constant

$$S_P(F) = \langle t : F \subseteq G_t \rangle \text{ whereas } \forall i : t_{i+1} - t_i = p$$

- $p$  is period of  $F$  whereas  $F$  is periodic subgraph  $|S_P(F)| \geq \sigma$
- every subgraph can have multiple periodic embeddings in  $\mathcal{G}$  with different positions, supports, etc.
- overlap can exist as long as support set is maximal

# Noisy Subgraphs

- noisy subgraph has some jitter for given period
- given jitter value of  $J \geq 0$

$$S_P(F) = \langle t : F \subseteq G_t \rangle \text{ whereas } \forall i : |t_{i+1} - t_i - p| \leq J$$

# Purity Measure

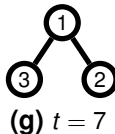
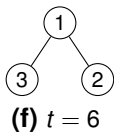
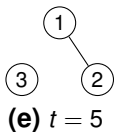
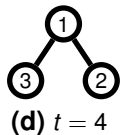
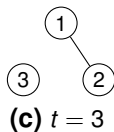
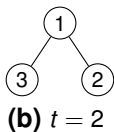
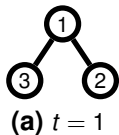
- periodically recurring subgraph does not fully represent interaction pattern that occurs periodically
- purity measure*: how likely does periodic subgraph embedding occur within its periodically predictable point in time
- ratio of periodic support to total support in  $[i, i + p(s - 1)]$

$$\text{purity}(F) = \frac{s}{|\{t : F \subseteq G_t, i \leq t \leq i + p(s - 1)\}|}$$

- given subgraph  $F = (V, E)$ , average purity

$$\text{avgPurity}(F) = \frac{1}{|E|} \sum_{e \in E} \text{purity}(e)$$

# Purity Measure



**Figure: periodic subgraph embedding** with non-periodic occurrences,  
purity =  $3/5$ , average purity =  $1/2(3/7 + 3/5) \approx 0.51$

# The Algorithm

- single-pass, polynomial time and space
- parameterless but accepts following:
  - minimum support threshold  $\sigma \geq 2$  (default: 2)
  - min and max period ( $P_{\min}$  and  $P_{\max}$ )
  - max jitter in period  $J \geq 0$
- natural bound on max period if number of points in time is finite and known beforehand

# Mining PSE Using a Pattern Tree

- crux of algorithm is pattern tree (record of what patterns are periodic and could become periodic)
- pattern tree is updated on-the-fly after each point in time
- anything no longer periodic is removed
- each node in tree contains subgraph and descriptor for each closed PSE
- descriptors are ordered pairs  $D = \langle S = S_P(F), p \rangle$  where  $S$  is periodic support set of embedding of  $F$  and  $p$  the period

# Pattern Tree

- pattern trees are subject to all descendants of node  $N$  representing proper subgraphs of  $F$
- pattern tree is traversed for each new observation
- so, if given node does not have common subgraph with any other nodes, it will be removed

# Subgraph Hash Map

- associates arbitrary subgraph with its node in tree
- utilized by update algorithm
- offers efficient constant look-up time since each node label is unique in each subgraph



# Update Algorithm

- start with empty pattern tree at time  $t$ , read next graph  $G_t$  from input stream
- traverse pattern tree to update nodes with new info
- complete list of periodic subgraphs can be obtained from tree at any point
- breadth first traversal of tree

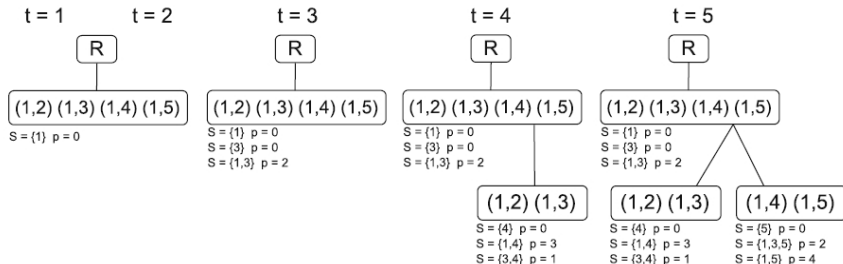
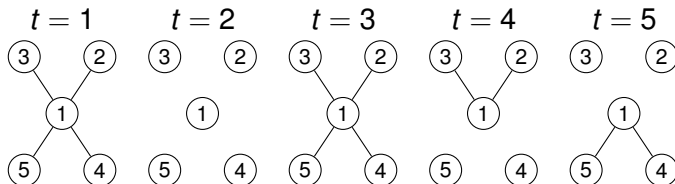
# Details of the Algorithm

- update descriptors: if  $N$  is a subgraph of  $G_t$ , then  $N$  has appeared in its entirety at point  $t$
- for all descriptors  $D$ , if  $\text{next}(D) = t$ , then  $t$  is added to support set
- if  $\text{next}(D) < t$ , descriptor is removed from tree

# Details of the Algorithm

- propagate descriptors: let  $C$  be subgraph of both  $N$  and  $G_t$
- subgraph  $C$  of  $N$  is present at point  $t$ , and if  $N$  has any descriptors  $D$  s.t.  $\text{next}(D) = t$ , then node for  $C$  receives copy of  $D$
- if node for  $C$  already exists, then child is created
- dead subtree: if  $C$  is empty, then  $G_t$  and  $N$  have no common subgraph
- therefore, no child of  $N$  will have any common subgraph with  $G_t$  either
- then, subtree at  $N$  can be removed

# Example: Pattern Tree



# Datasets

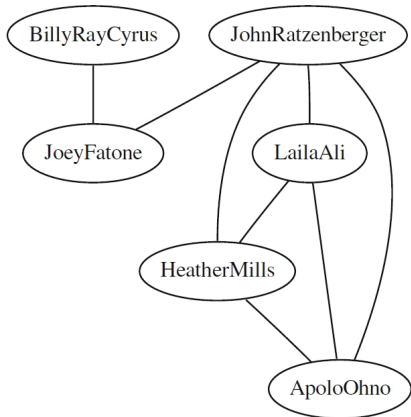
Dataset	Vertices	Length	Avg. Density
Enron	82,614	2,588	$0.028 \pm 0.064$
IMDB	15,011	13,967	$0.22 \pm 0.23$

- Enron e-mails
- IMDB celebs: collect photographs of two or more people on site ((1 d sampling rate)).

# Inherent Periodicity and Algorithm Tractability

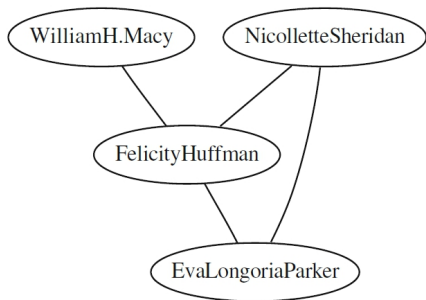
- Enron and IMDB: attention is diverted to patterns with high average purity (patterns which are likely to exhibit truly periodic behavior)
- Enron: peak at 7 (weekly patterns)
- IMDB: peak at 364 (annual events)
- algorithm manages space and execution time easily
- however, unable to mine subgraphs with  $\sigma < 25$  for Enron

# Examples of Interesting Periodic Subgraphs



- complex pattern from IMDB photo database
- repeated approximately every week ( $p = 7 \pm 2$ )
- support is relatively low (3)
- non-trivial grouping of people
- all contestants on weekly reality TV show

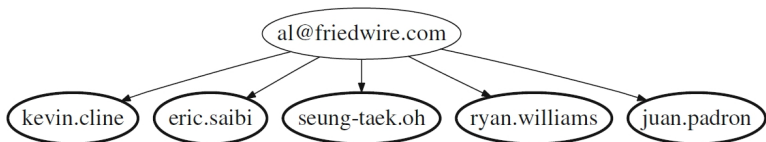
# Examples of Interesting Periodic Subgraphs



- IMDB database: approx. annually repeating pattern
- actresses in popular TV show, fourth vertex is spouse of one of actresses
- low average purity (0.4)
- non-trivial links indicate show's progression other than co-starring



# Examples of Interesting Periodic Subgraphs



- highest periodic support in Enron dataset
- repeating every day for 84 consecutive days, including weekends
- $\exists$  large number of similar periodic patterns in Enron:  
one person emails group of people with periods from 1 – 14 d
- weekly emails very popular
- can be used to infer functional communities

# Summary

- formalized solution for tackling periodic subgraph problem
- One pass, efficient algorithm
- demonstrated effectiveness on two real-world social networks
- all periodic patterns are mined

# Open Research

- probabilistic models of periodicity instead of strictly combinatorial ones
  - weighted edges instead of binary ones
  - change of edge weight must be greater than some threshold
  - application for brain networks
- interestingness of frequent patterns: usually application-dependent

# Outline

1. Vision Restoration

2. Brain Connectivity

3. Data Mining

4. Model-based Analysis of Dynamic Brain Networks

5. Periodic Subgraph Mining

**6. Conclusions and Future Work**

# Conclusions

- complex dynamic networks are ubiquitous
- usually, graphs are treated in static way
- networks typically change their structures in time
- focus: analysis of dynamic brain activity networks from EEG
- global approach: AR model for series of graph measurements
- local approach: periodic subgraph mining of dynamic networks

# Difficulties and Controversies

data preprocessing:

- removal of biological artifacts (electromyographic (EMG), electrocardiograph (EKG))
- frequency bands (parallel graphs)

signal similarity: hundreds of methods possible...

same for graph similarity:

- edit distance
- maximum common subgraph distance
- kernel methods

time series representations:

- symbolic approximations (Moewes and Kruse 2009)
- pattern mining (Moewes and Mörchen 2012)

# Open Research Directions

- *robust* graph measures
- *weighted* subgraph mining
- *association rule learning* based on mined subgraphs
- *rule*-based systems for CDSS
- *other* social networks, e.g. Facebook, Twitter, functional Magnetic Resonance Imaging (fMRI)

# Thank you very much for your indulgence :-)



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