



FAKULTÄT FÜR
INFORMATIK

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

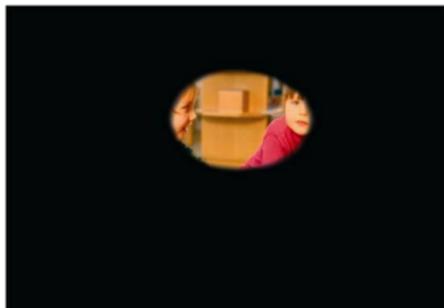
4. Model-based Analysis of Dynamic Brain Networks

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

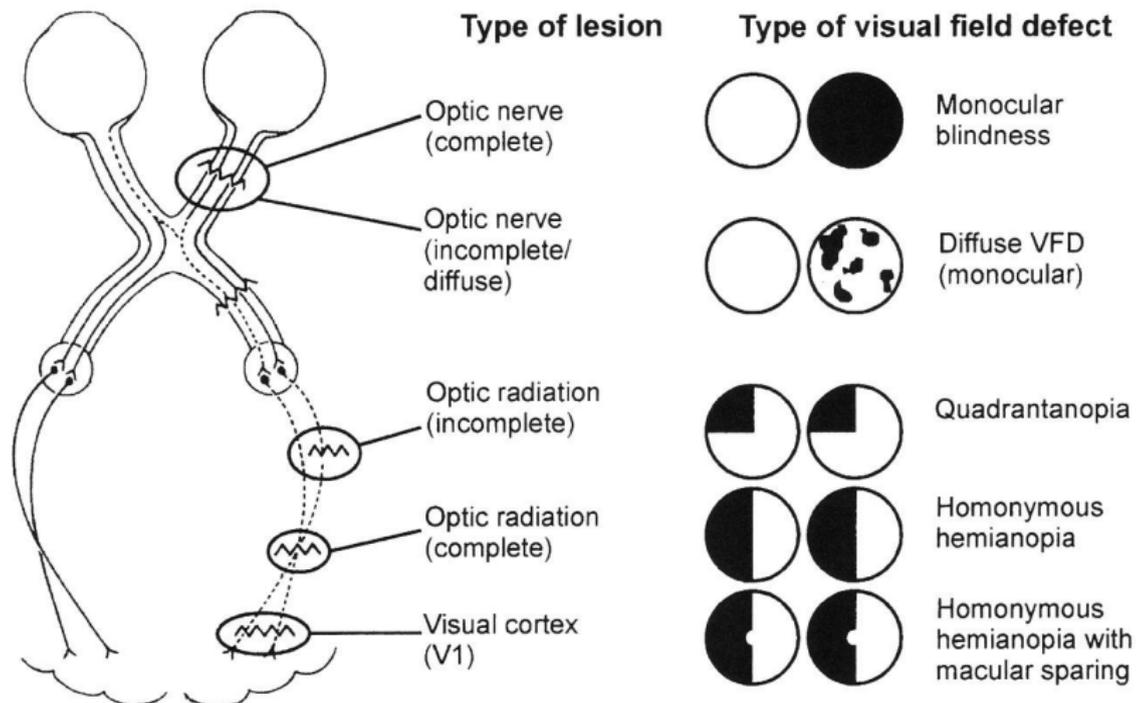
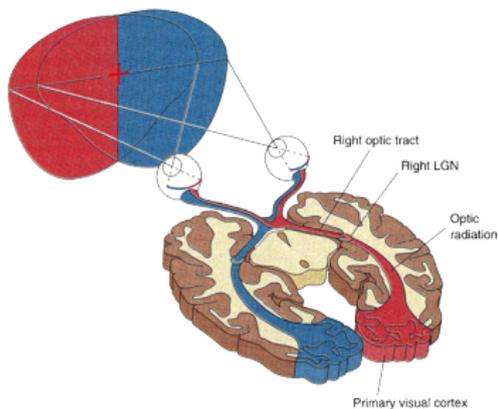
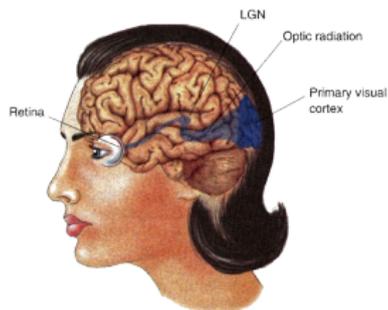
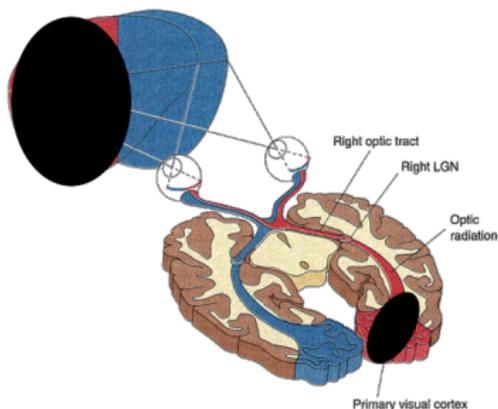
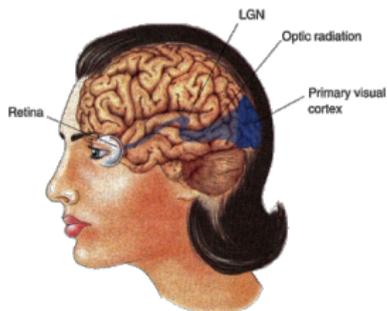


Fig. 1. Schematic overview of visual field defects (white = intact, black = blind areas) which result from lesions at different locations of the visual system.

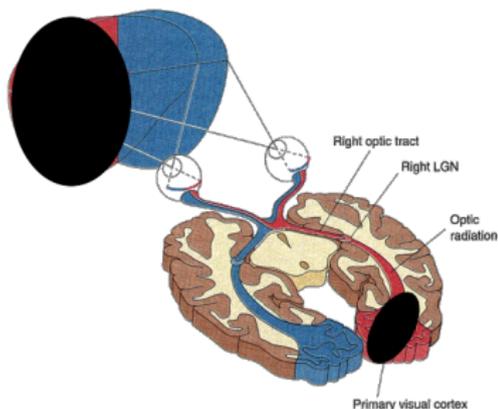
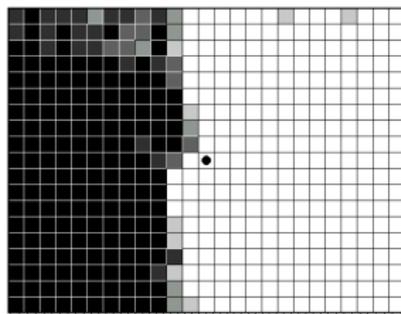
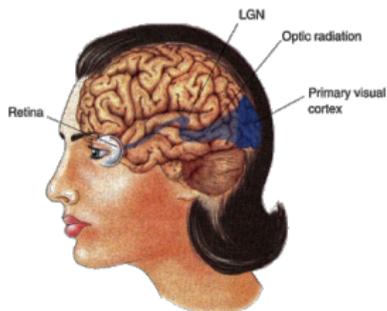
Visual Pathway



Low Vision after Brain Damage



Low Vision after Brain Damage















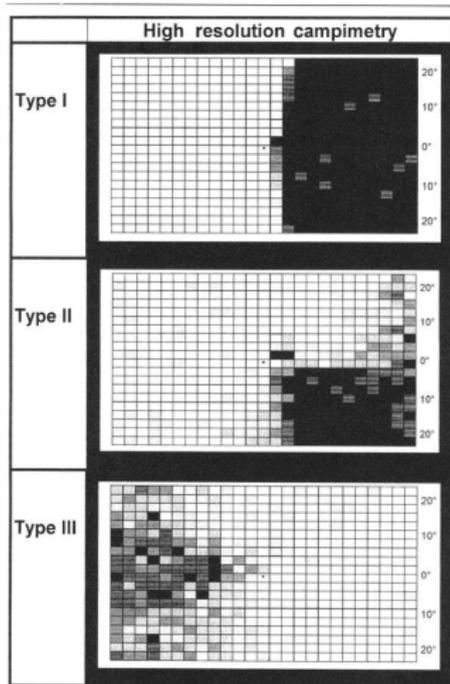
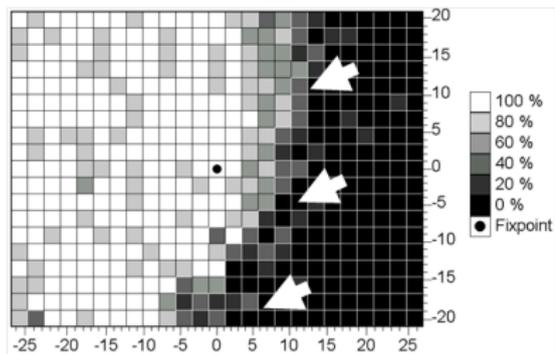
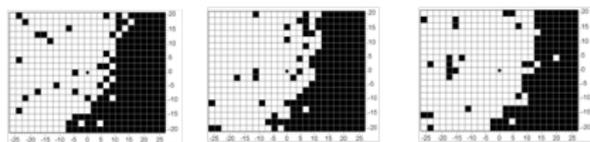






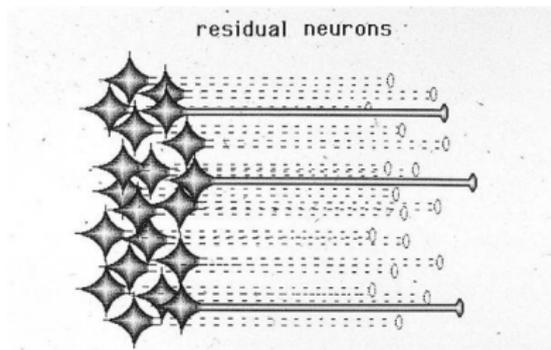
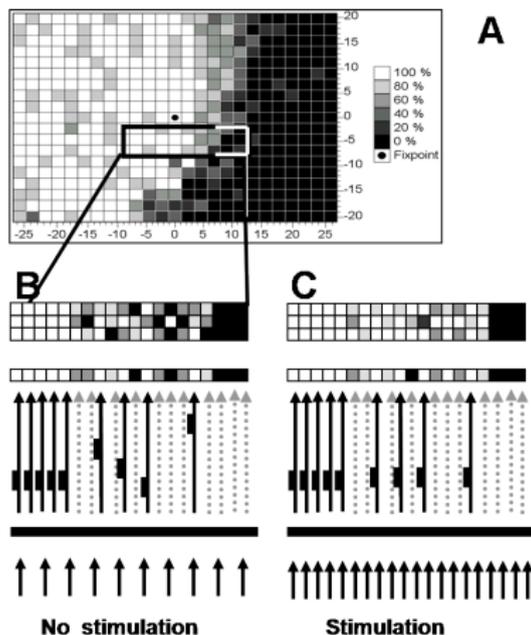


Visualization of Residual Functions

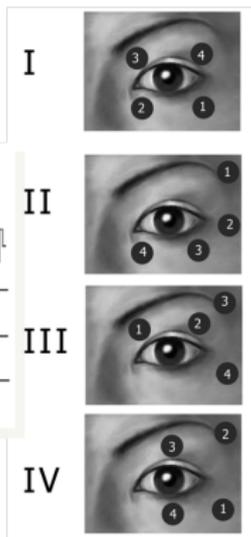
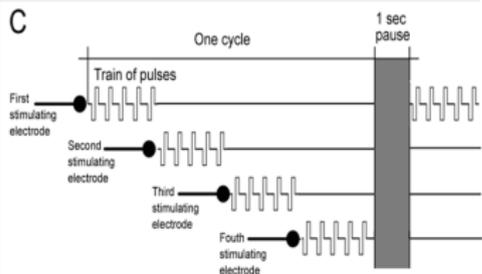
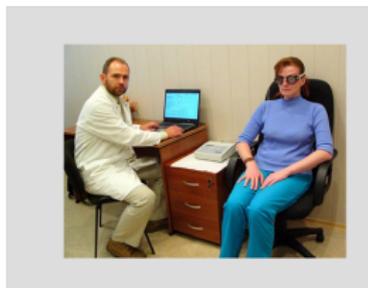


Superimposed evaluations of the central visual field ($\pm 25^\circ$ eccentricity) using high resolution campimetry. Different types of transition zones have been found. (Upper panel) Sharp visual field border, and, accordingly, a small transition zone. (Middle panel) Transition zone of medium extension. (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



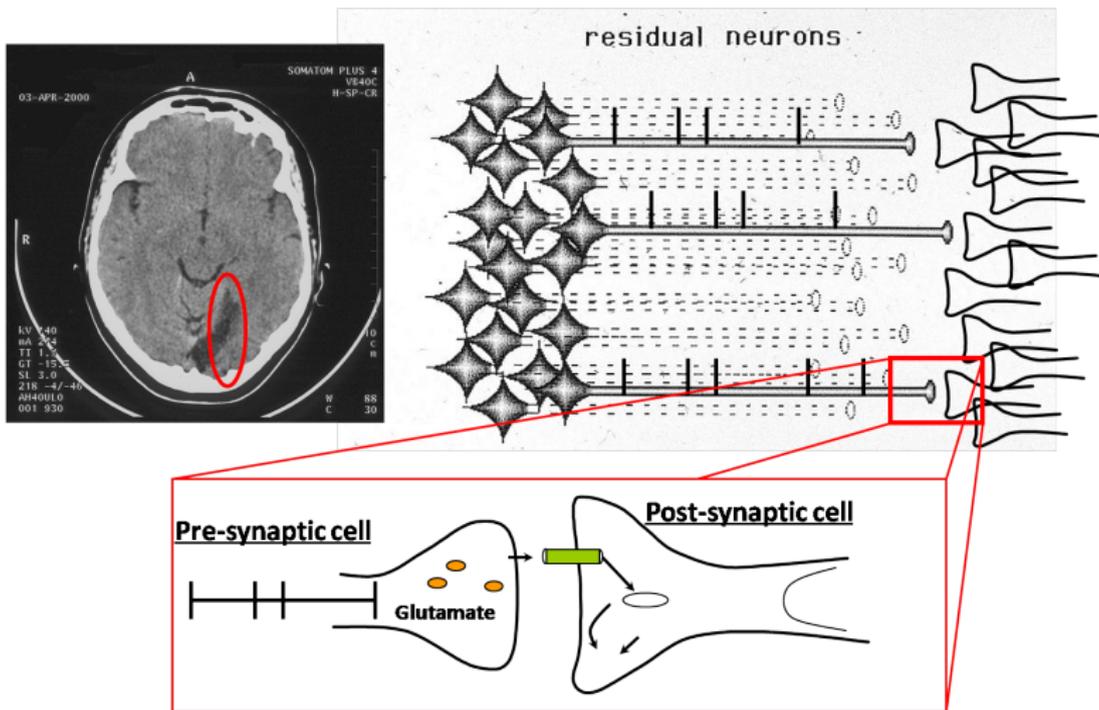
Repetitive Transorbital AC Stimulation (rtACS)



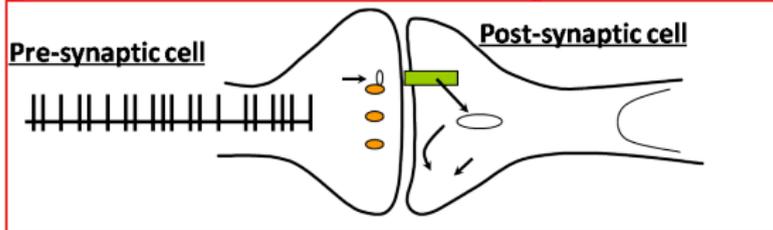
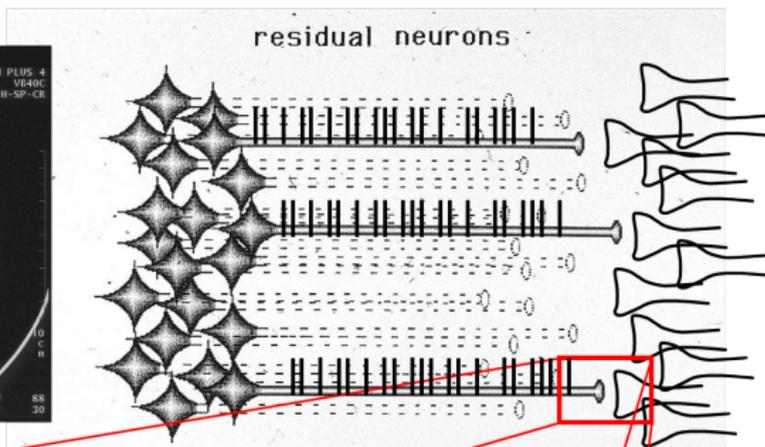
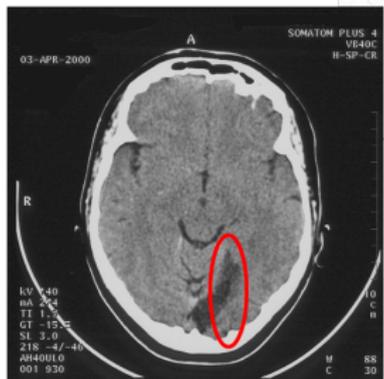
- placing non-invasive electrodes at eye or skull
- rtACS with low current stimulation (< 1 mA, 10 – 30 Hz)
- 20-40 min daily for approx. 10 days

Synaptic Transmission after Partial Damage

Before rtACS

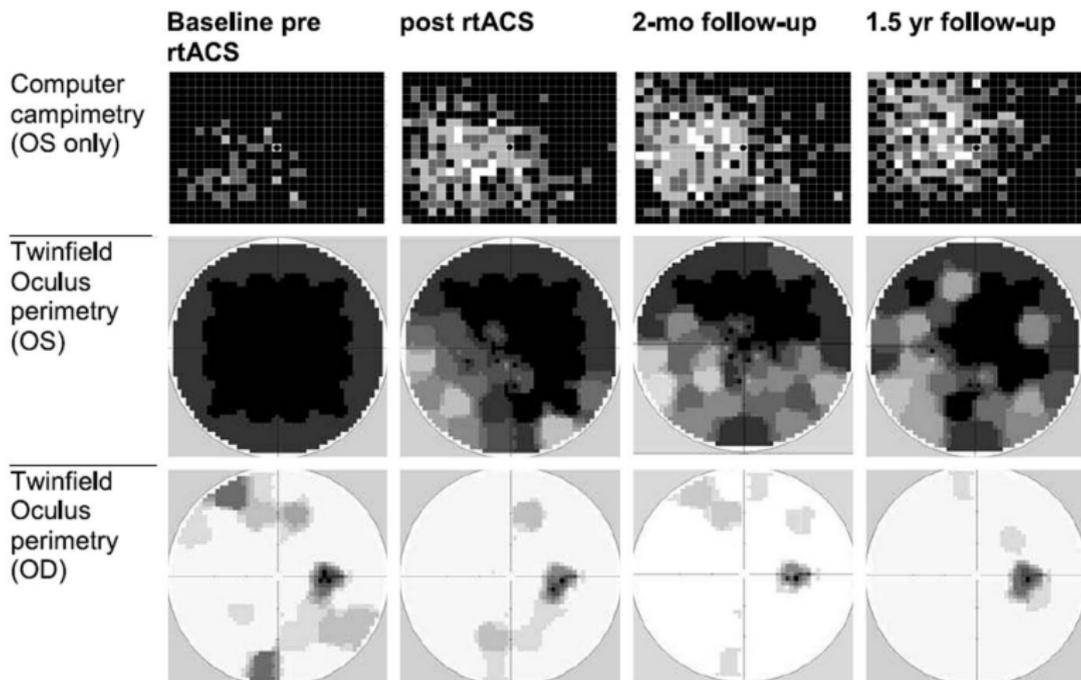


Synaptic Transmission after Partial Damage After rtACS



Goal: strengthening synaptic transmission

Visual Fields in Optic Nerve Lesion after rtACS



Challenge: Electroencephalogram (EEG)

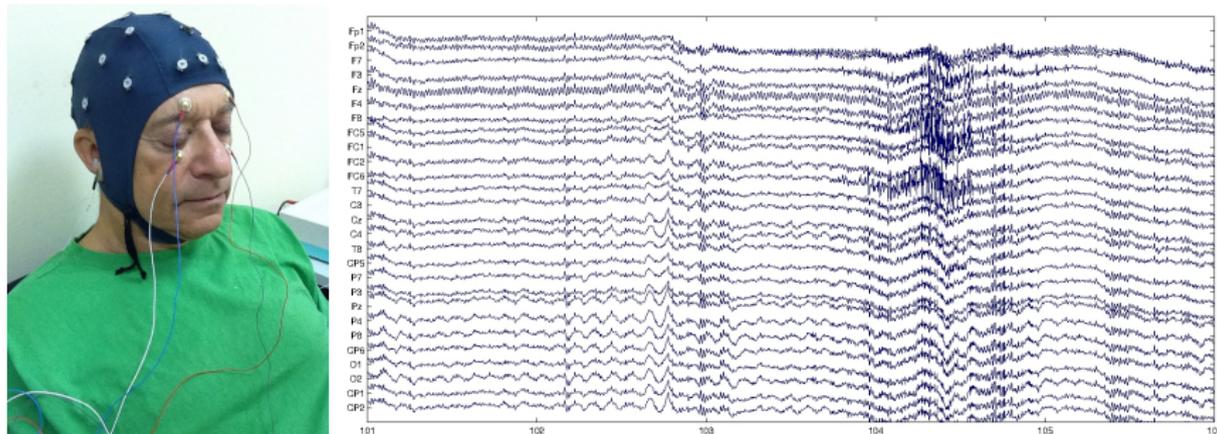


Figure: Left: Vision restoration therapy using alternating current. Right: Typical raw data (28 EEG channel).

- 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

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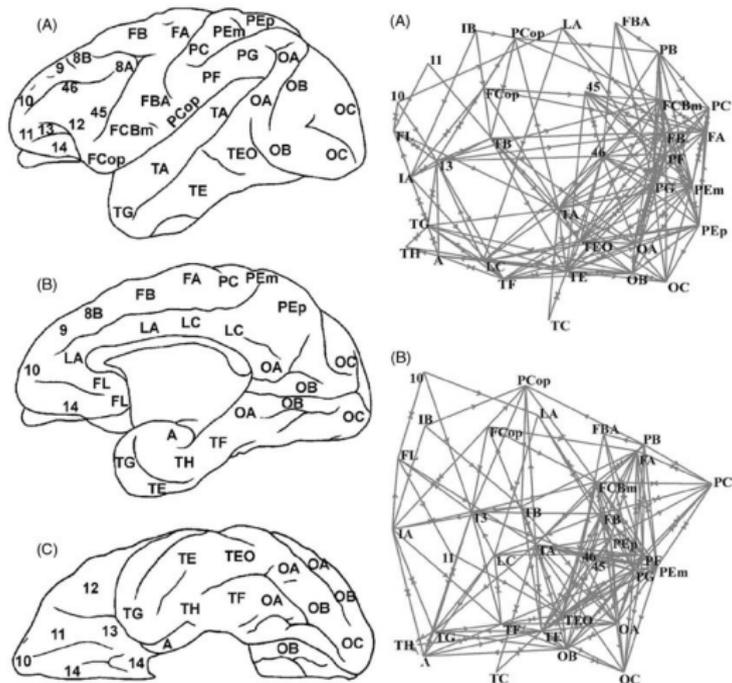
4. Model-based Analysis of Dynamic Brain Networks

5. Periodic Subgraph Mining

6. Conclusions and Future Work

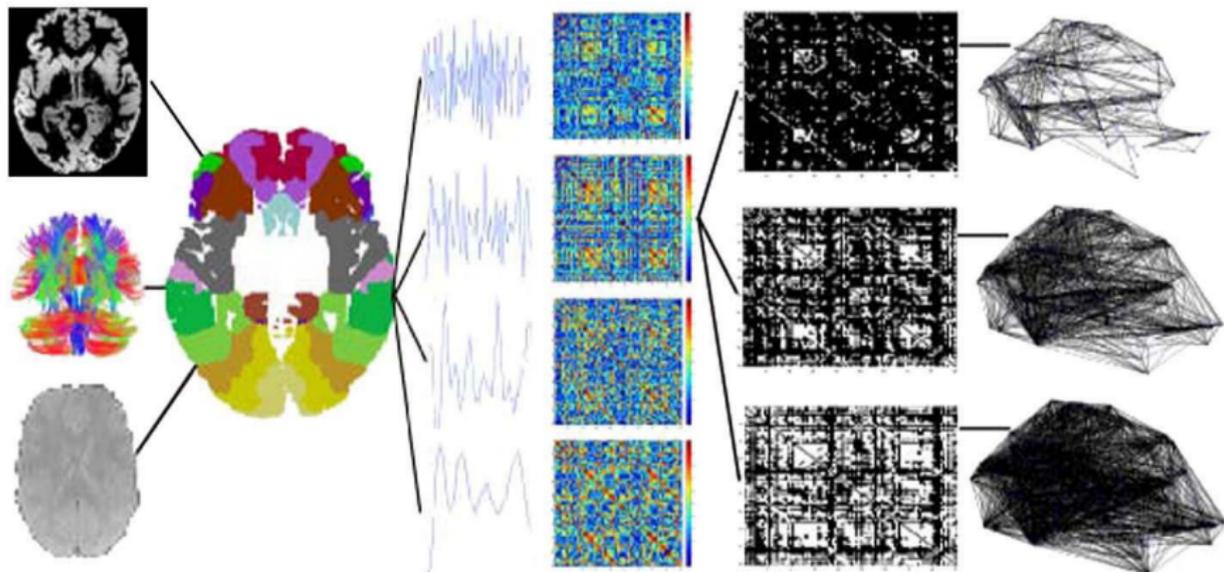
Cortical Connectivity Maps

Stephan et al. 2000



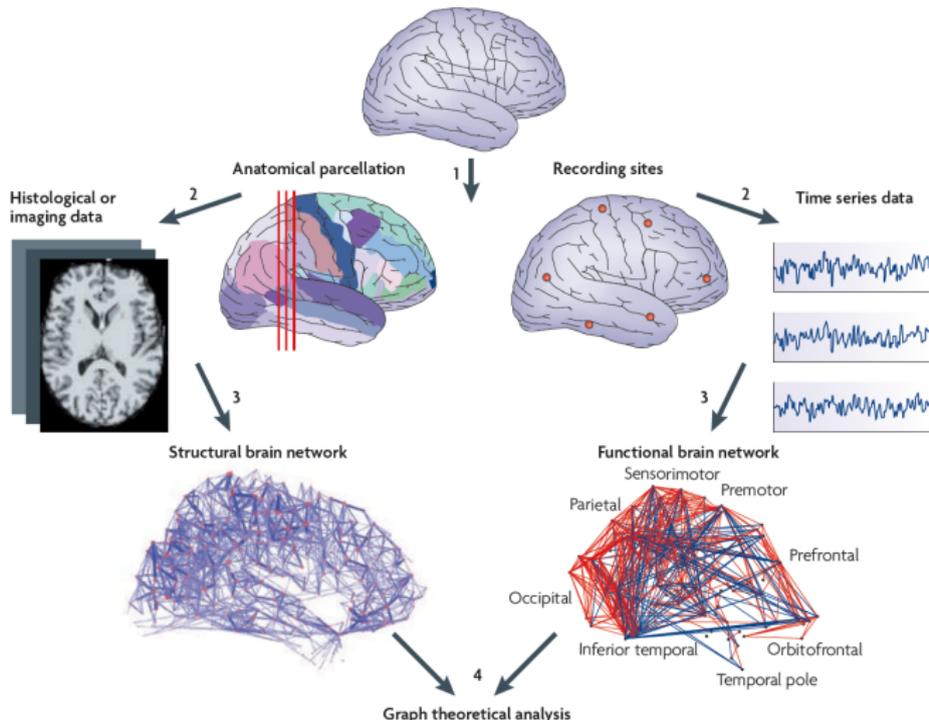
fMRI Graphs

Bullmore, Barnes, et al. 2009



Brain Network Analysis

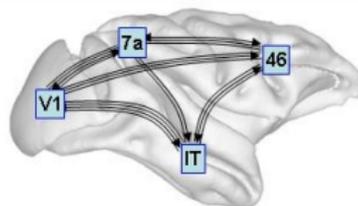
Bullmore and Sporns 2009



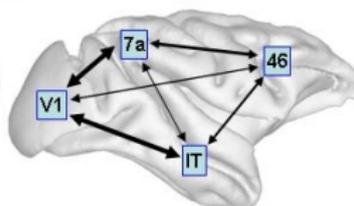
Brain Connectivity

Sporns 2007

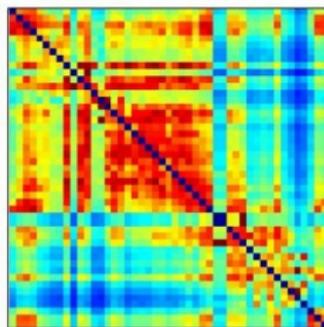
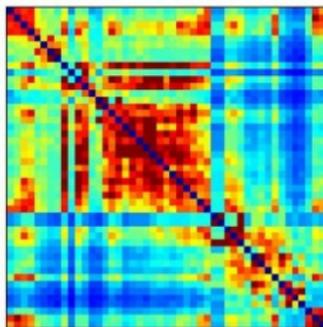
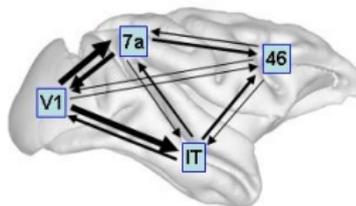
structural connectivity



functional connectivity



effective connectivity



- anatomical links vs. statistical dependencies vs. causal interactions

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Knowledge Discovery in Databases

CRISP-DM

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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



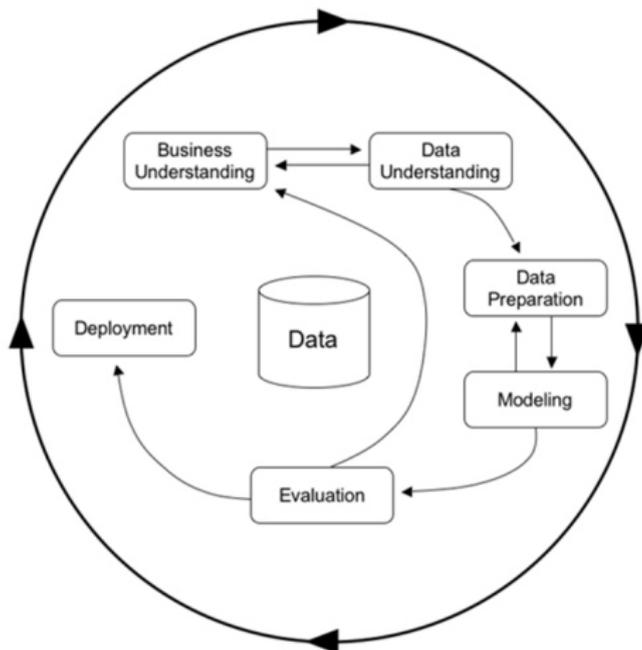
Miner VGA (1989) screenshot

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

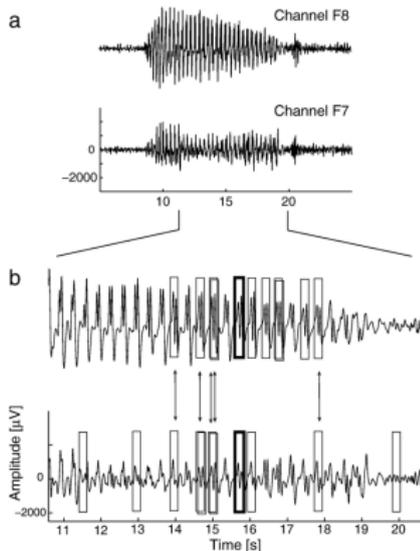
- consider only 2 channels A, B
- probability that $X_{i,k} \leq \varepsilon$:

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

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

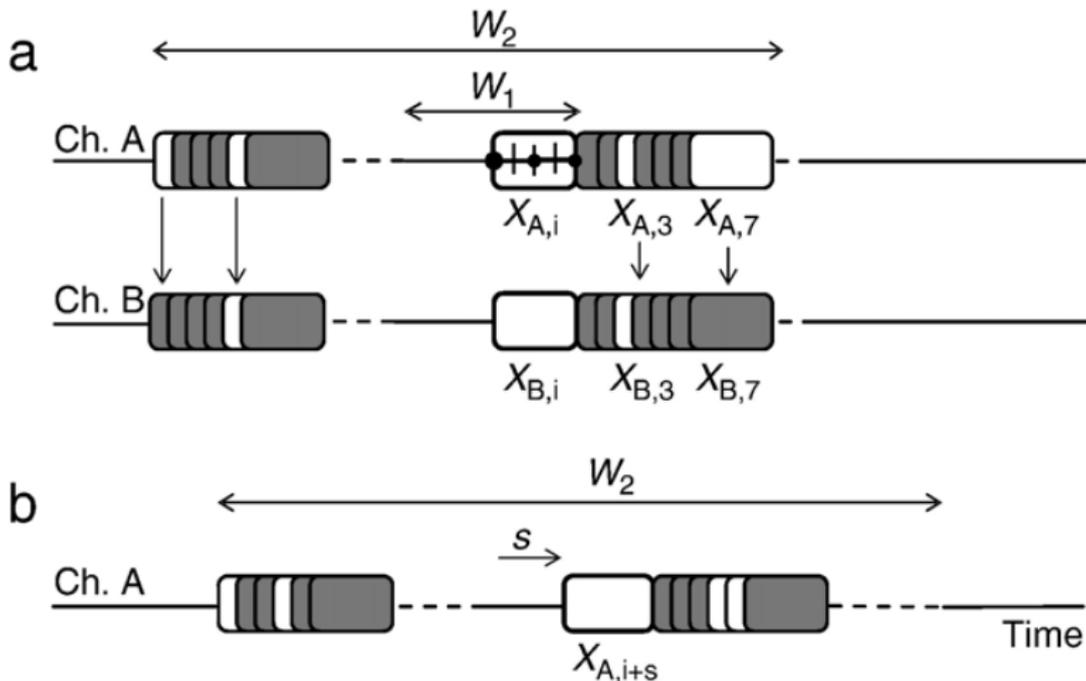
$$SL_i = \frac{1}{2\rho_{\text{ref}}(W_2 - W_1)} \sum_{\substack{j \\ W_1 < |i-j|W_2}}^N (H_{i,j} - 1)$$

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



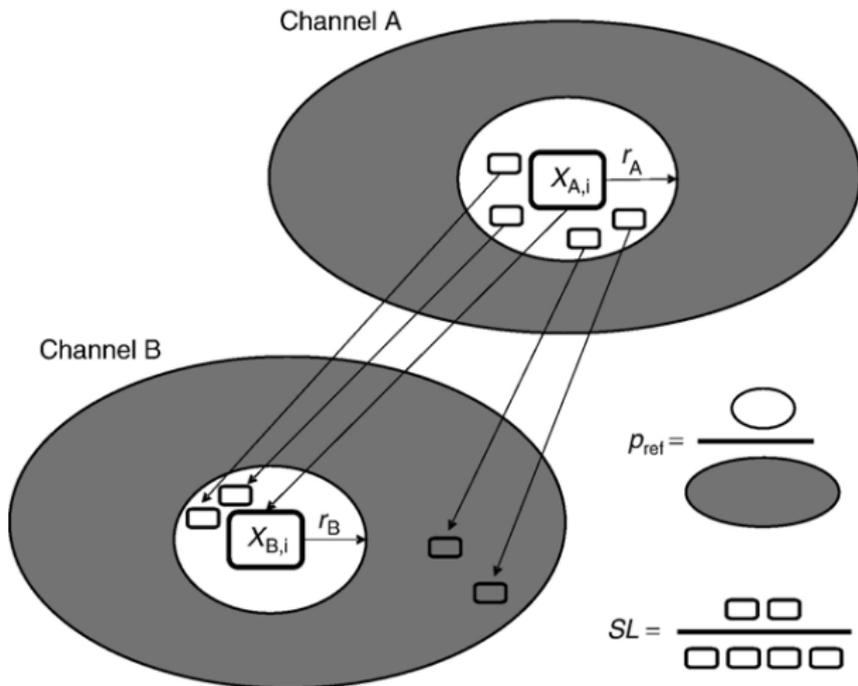
State Vectors and SL Parameters

Montez et al. (2006)



SL of 2 Channels

Montez et al. (ibid.)



From EEG to Dynamic Graphs

δ : deep sleep θ : drowsiness/arousal α : relaxed/reflecting

β : alert/working γ : cognitive functions μ : 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 :

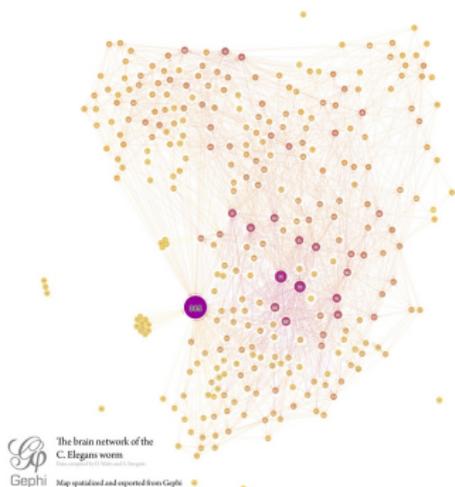
$$\bar{\eta}(G) \stackrel{\text{def}}{=} \frac{1}{|V|} \sum_{u \in V} \eta(u)$$

- *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://www.flickr.com/photos/gephi/>

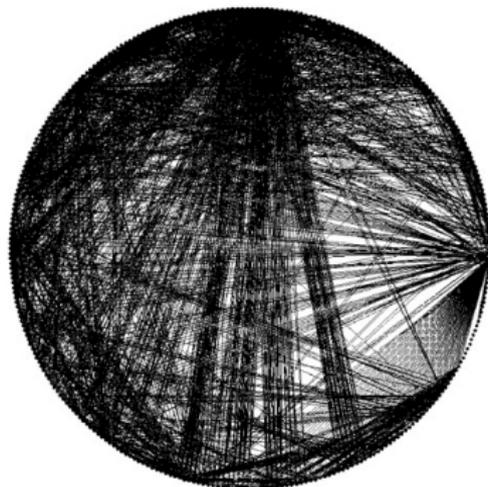


source: <http://blog.neuinfo.org>

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

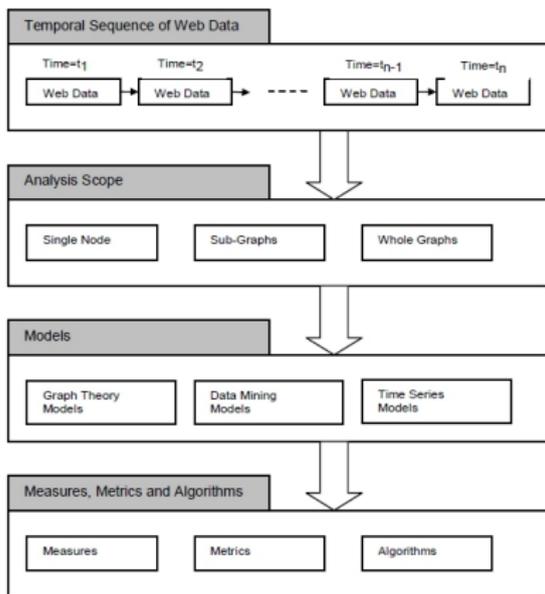
Example: *C. elegans*

(ibid.)



	d_{actual}	d_{random}	C_{actual}	C_{random}
<i>C. elegans</i>	2.65	2.25	0.28	0.05

Dynamic Graph Analysis



source: (Desikan and Srivastava 2004)

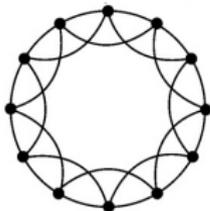
- ARMA models of graphs: anomaly detection (Pincombe 2005), feature selection (Moewes, Kruse, et al. 2012)
- VAR models of graphs: feature selection (Moewes and Kruse 2012)

Graph Models

(Erdős and Rényi 1960)

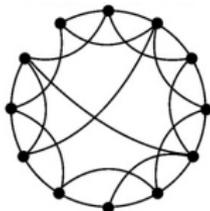
regular

high L , high C



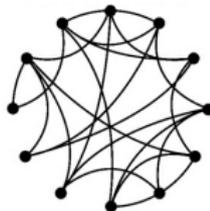
small-world

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

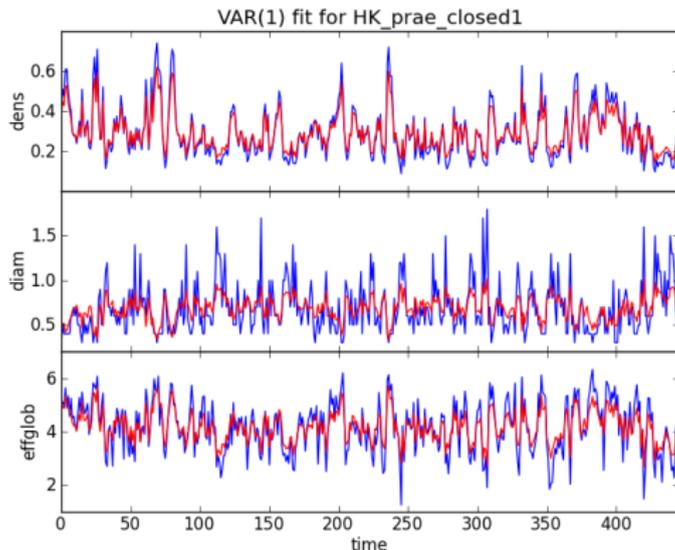


Figure: Blue: Original graph measures. Red: Fitted graph measures.

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:

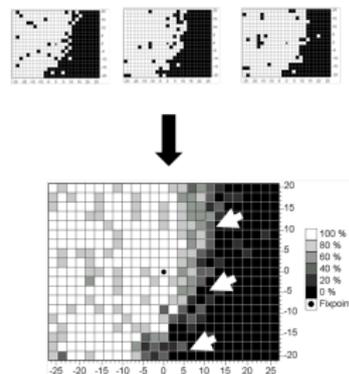
- VAR coefficients \leftrightarrow clinical variables
- *e.g.* linear regression
- here, ridge regression with $\alpha \in [0.1, 0.2, \dots, 0.9, 1]$
- parameter search: leave-one-out cross-validation

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	δ	θ	α	β	γ	μ
# 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: δ and α 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, $|S(F)|$:

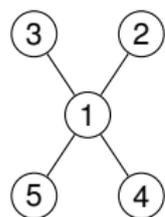
$$S(F) = \{t_i, \dots, t_j\} \text{ s.t. } \forall (t \in S(F) \Leftrightarrow F \subseteq G_t)$$

- 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 σ

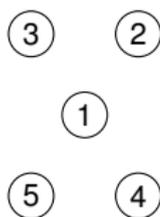
Maximal and Closed Subgraphs

- 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 $F(\sigma)$

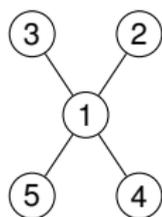
Frequent and Periodic Subgraphs



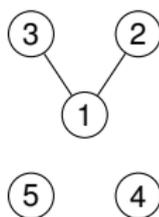
(a) $t = 1$



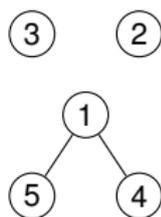
(b) $t = 2$



(c) $t = 3$



(d) $t = 4$



(e) $t = 5$

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 $J \geq 0$

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

Purity Measure

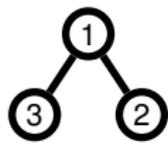
- periodically recurring subgraph does not fully represent interaction pattern that occurs periodically
- *purity measure*: how likely does periodic subgraph embedding occur within its periodically predictable point in time
- ratio of periodic support to total support in $[i, i + p(s - 1)]$

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

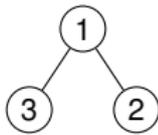
- given subgraph $F = (V, E)$, average purity

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

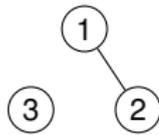
Purity Measure



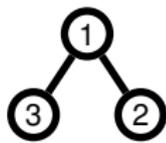
(a) $t = 1$



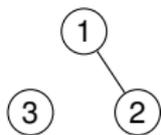
(b) $t = 2$



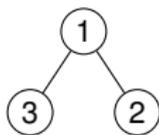
(c) $t = 3$



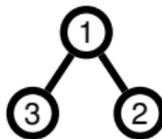
(d) $t = 4$



(e) $t = 5$



(f) $t = 6$



(g) $t = 7$

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

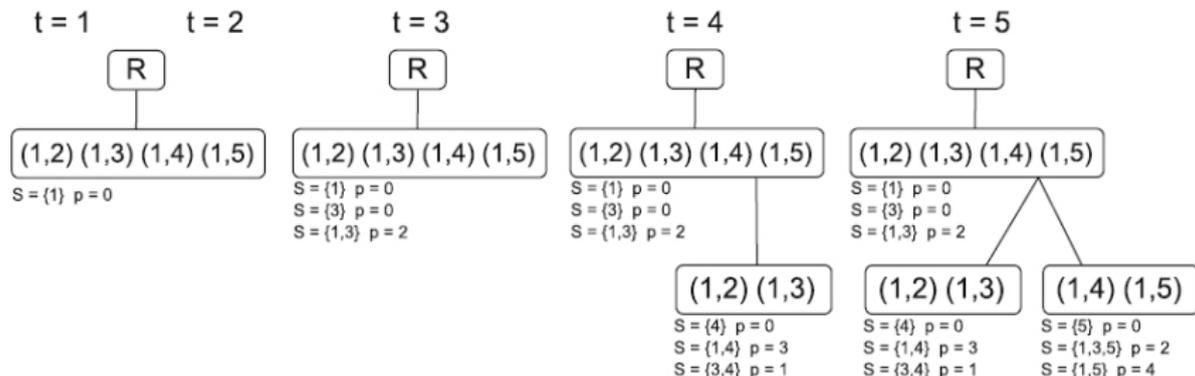
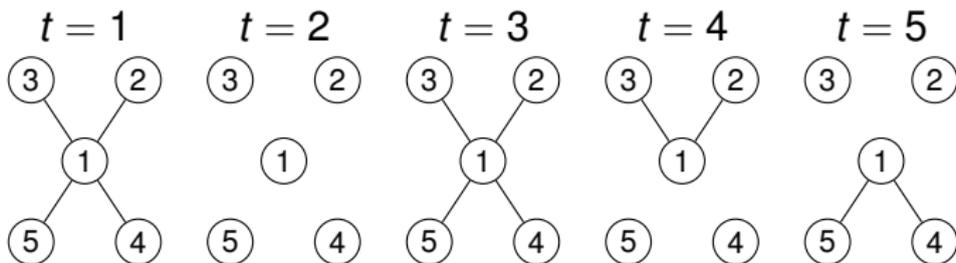
Details of the Algorithm

- 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 ± 0.064
IMDB	15,011	13,967	0.22 ± 0.23

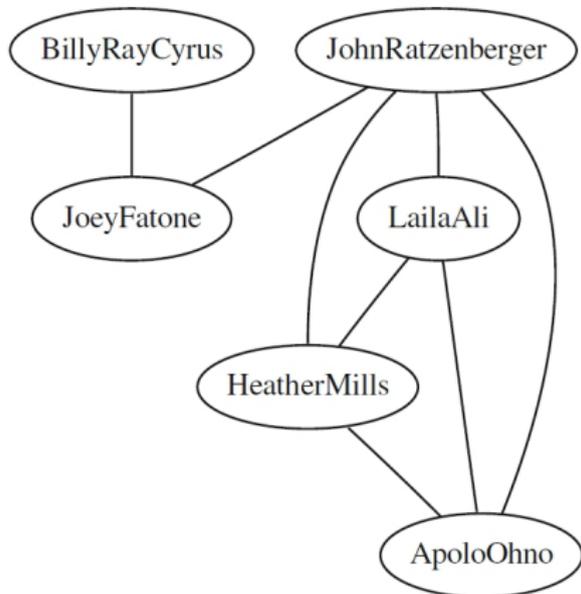
- Enron e-mails
- IMDB celebs: collect photographs of two or more people on site ((1 d sampling rate)).

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)

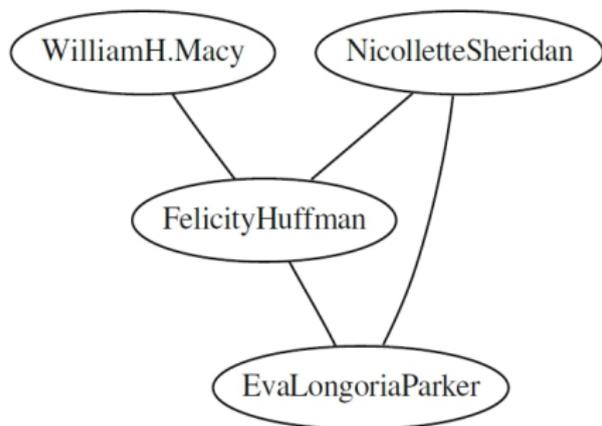
- algorithm manages space and execution time easily
- however, unable to mine subgraphs with $\sigma < 25$ for Enron

Examples of Interesting Periodic Subgraphs



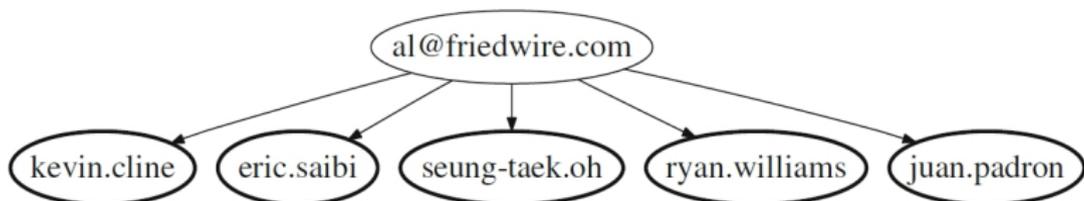
- complex pattern from IMDB photo database
- repeated approximately every week ($p = 7 \pm 2$)
- support is relatively low (3)
- non-trivial grouping of people
- all contestants on weekly reality TV show

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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