



Phenotyping Alzheimer's Disease Workshop

Albert C. Yang, M.D., Ph.D.

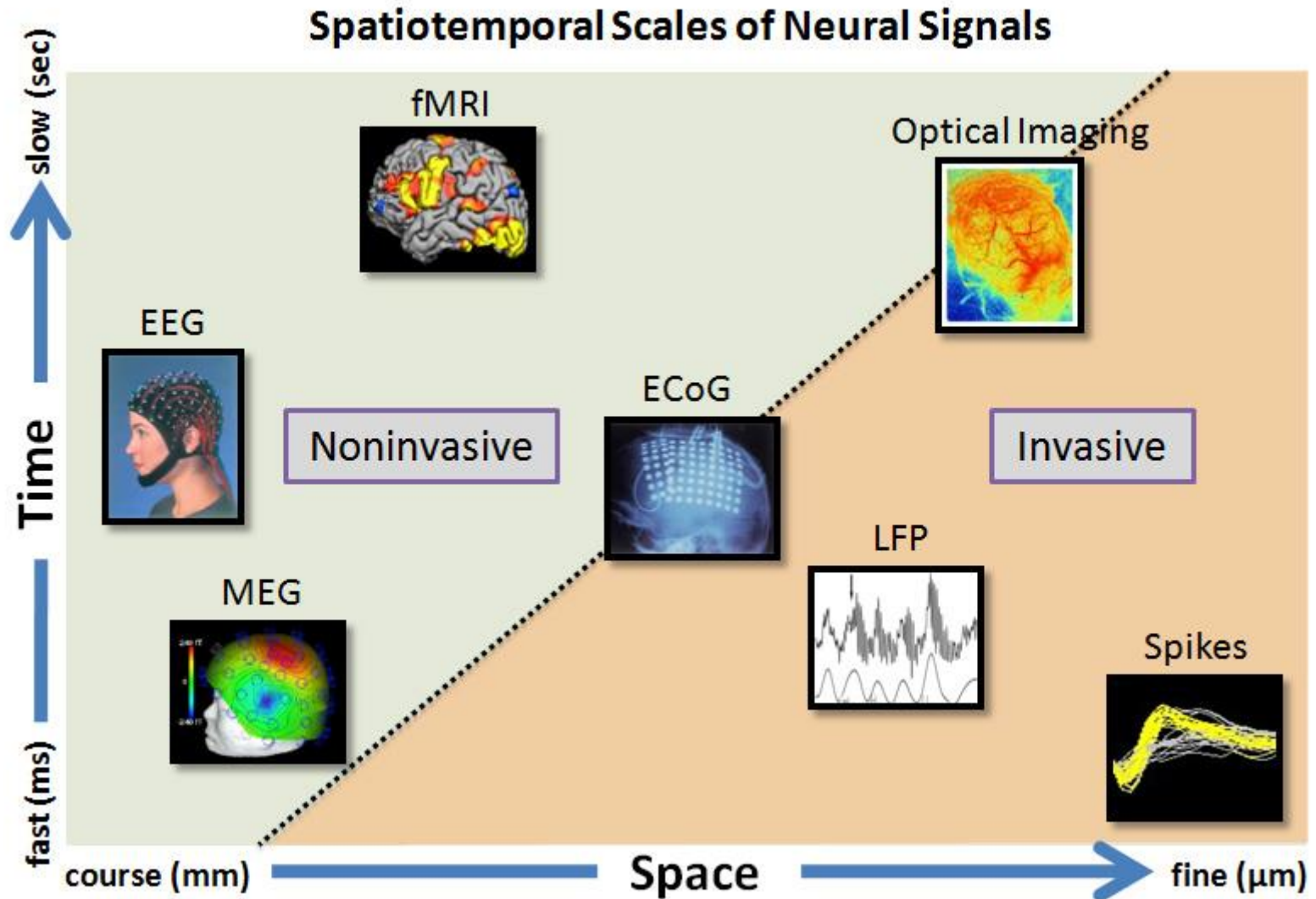
Institutes of Brain Science/Digital Medicine Center
National Yang-Ming University

May 14, 2020

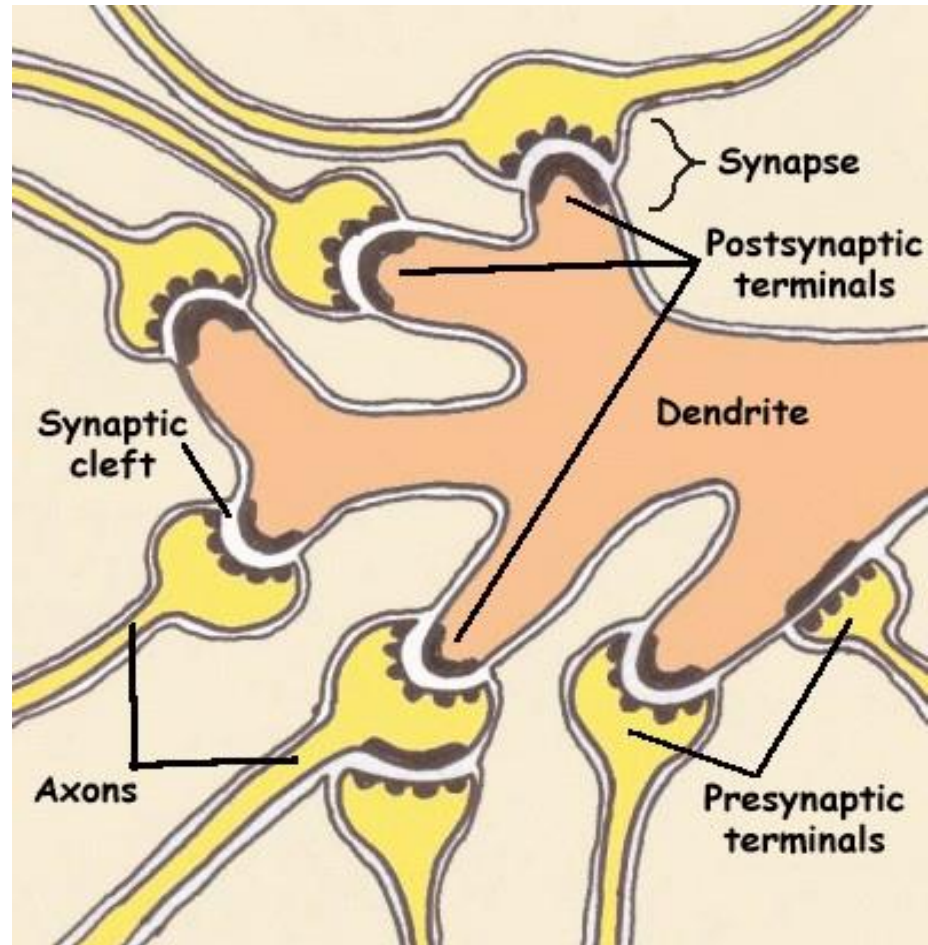
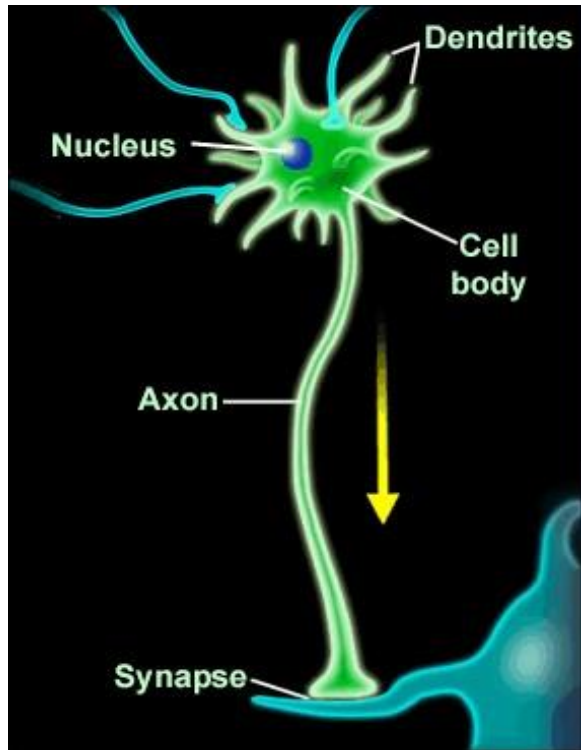
accyang@gmail.com

Brain Signals

Signal sources and corresponded experimental equipment

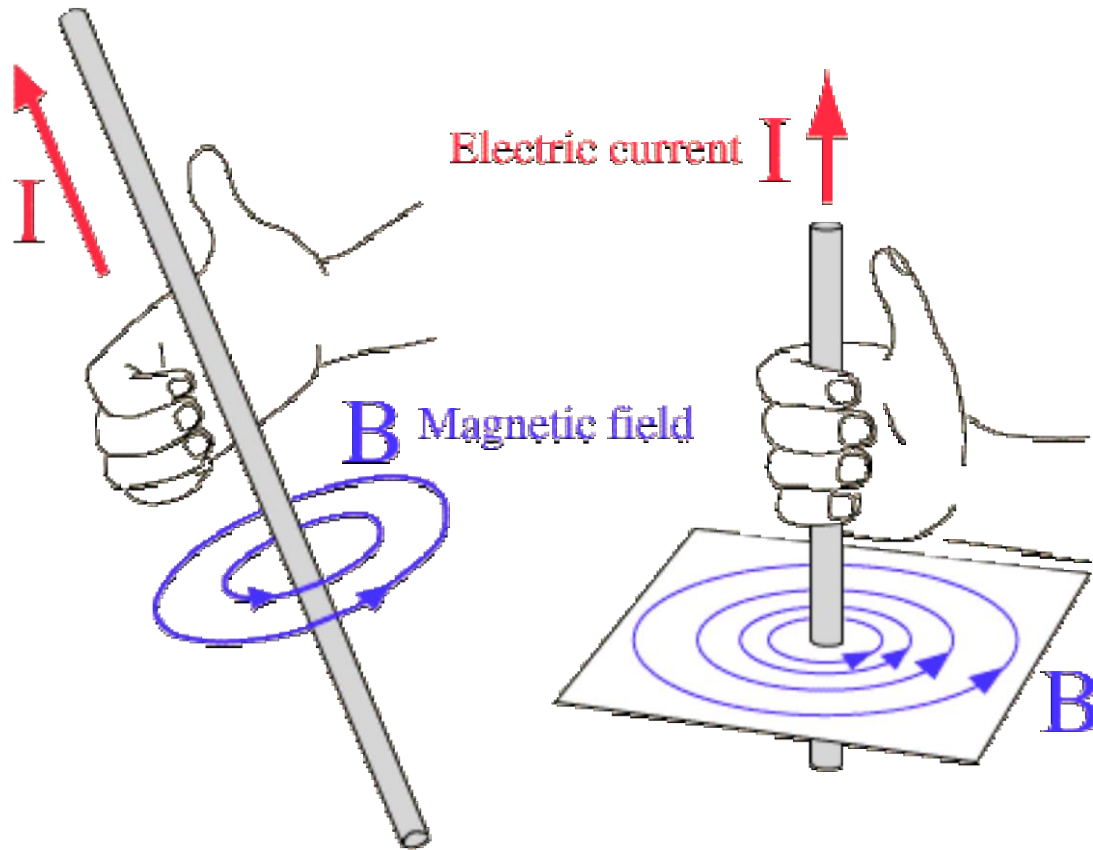


Electrical Activity of Brain Signal

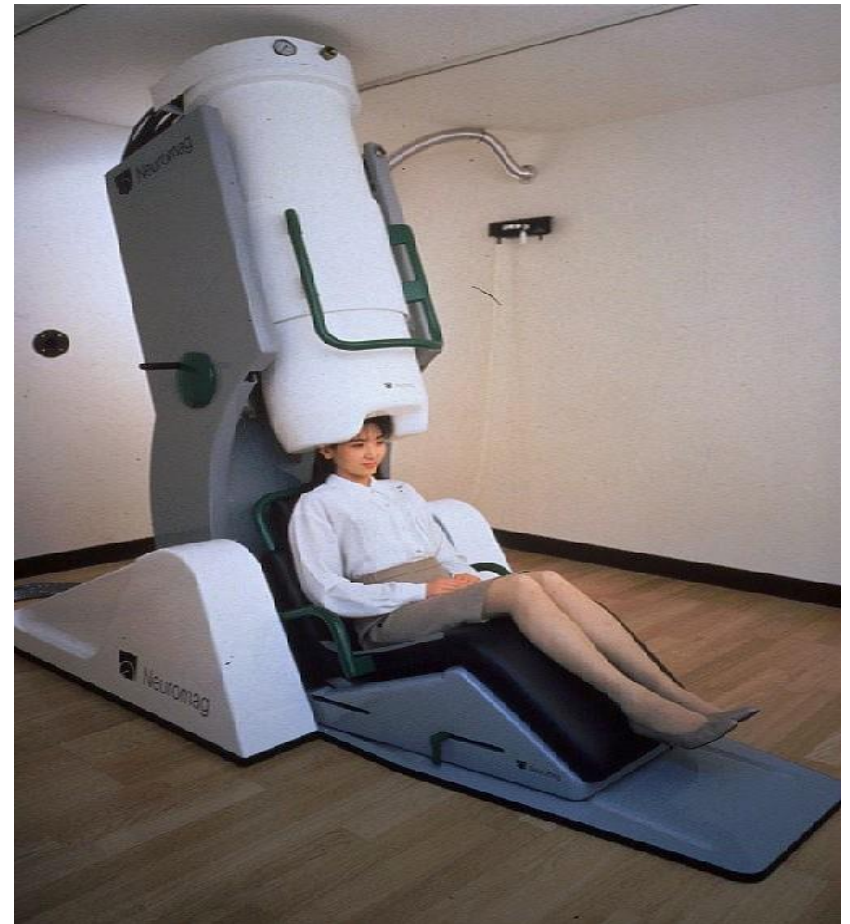


An electric current creates a magnetic field around it.

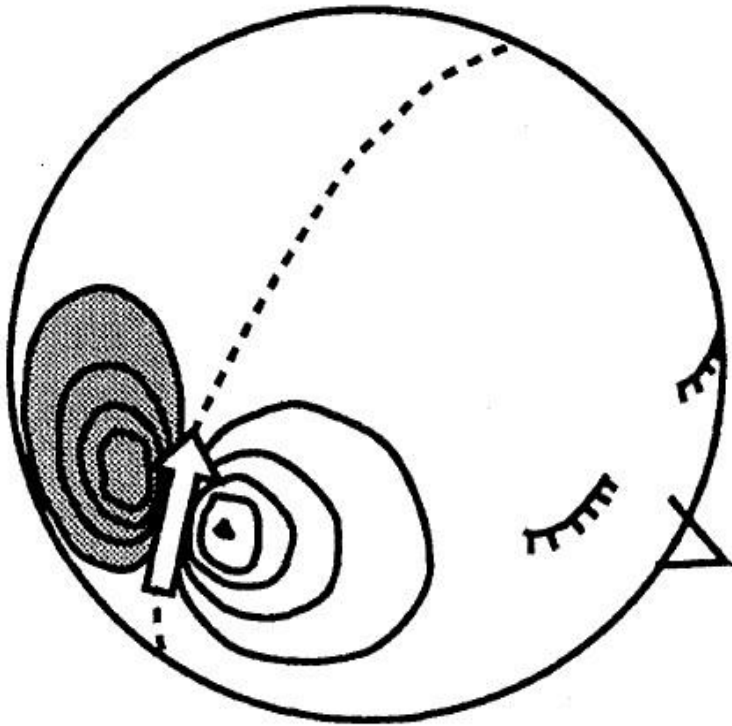
The right-hand rule: When the thumb of the right hand is pointing in the direction of the current, the fingers of the right hand curl in the direction of the magnetic field



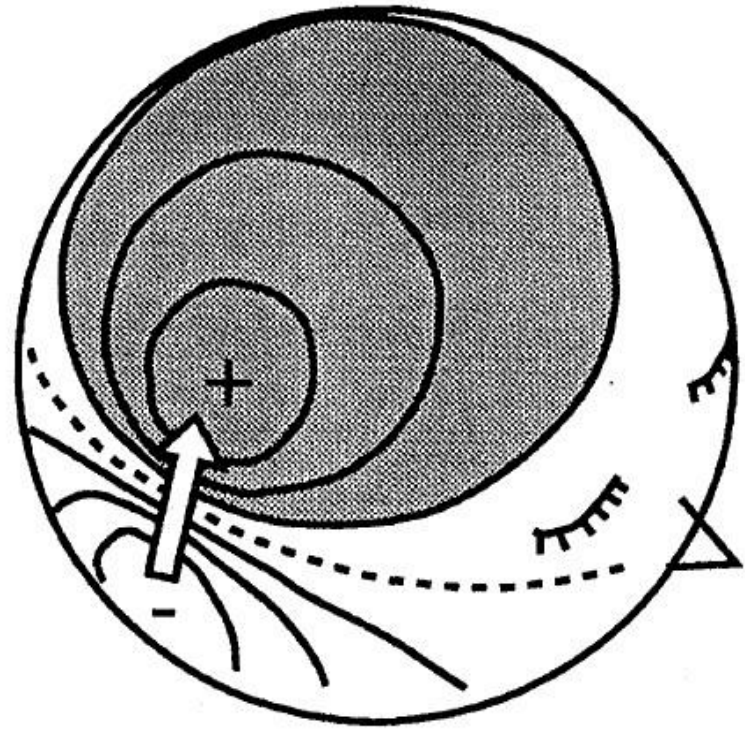
Electroencephalogram Magnetoencephalogram



MEG vs. EEG



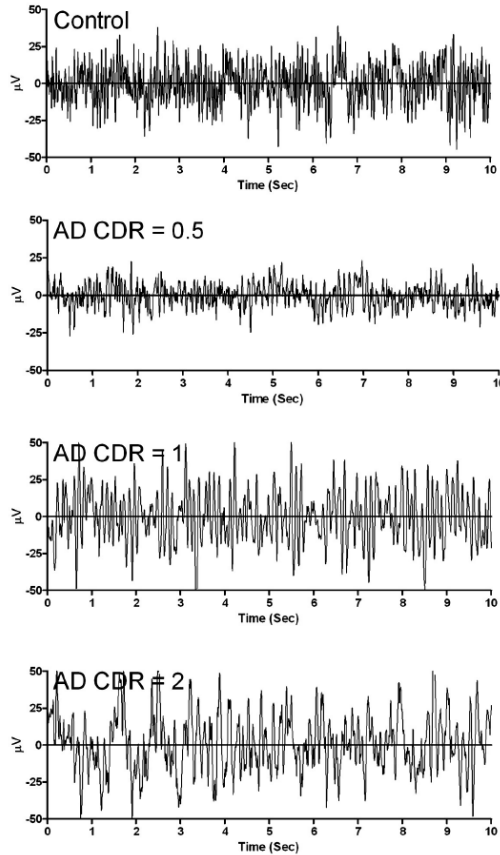
Magnetic field



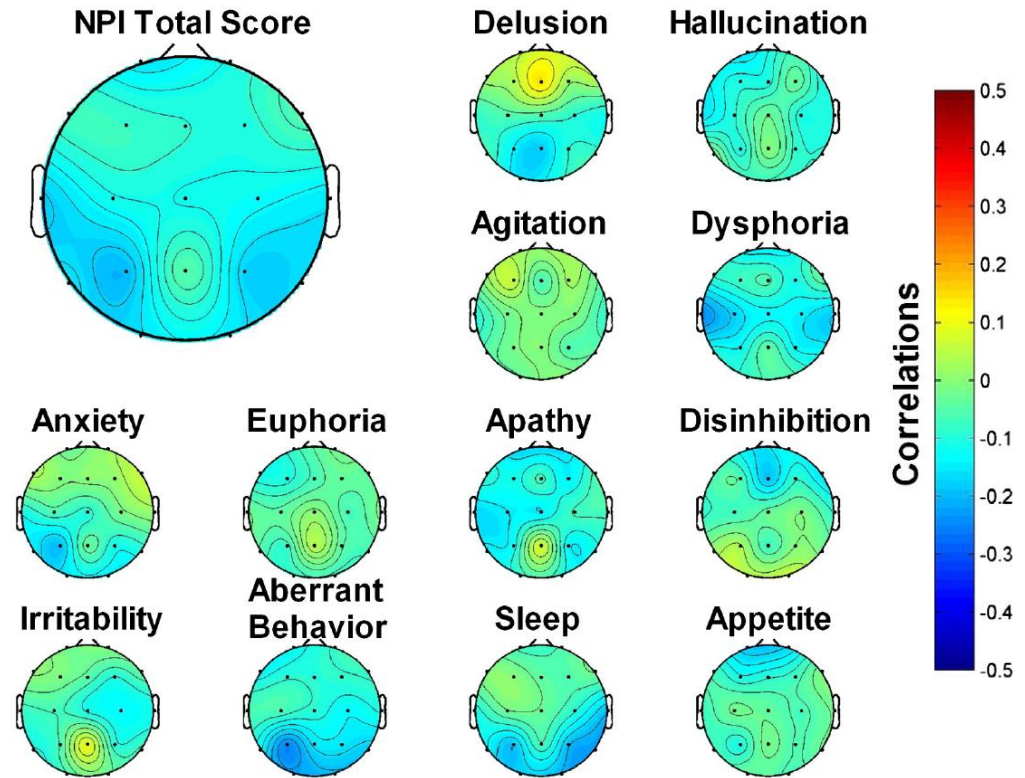
Electric potential

EEG Features in Alzheimer's Disease

Increased Slowing



Multiscale Entropy (Short)



NeuroPsychiatric Inventory

Delusions	Does the patient believe that others are stealing from him or her, or planning to harm him or her in some way?									
Yes	No	Severity: 1	2	3	Distress: 0	1	2	3	4	5
Hallucinations	Does the patient act as if he or she hears voices? Does he or she talk to people who are not there?									
Yes	No	Severity: 1	2	3	Distress: 0	1	2	3	4	5
Agitation or aggression	Is the patient stubborn and resistive to help from others?									
Yes	No	Severity: 1	2	3	Distress: 0	1	2	3	4	5
Depression or dysphoria	Does the patient act as if he or she is sad or in low spirits? Does he or she cry?									
Yes	No	Severity: 1	2	3	Distress: 0	1	2	3	4	5
Anxiety	Does the patient become upset when separated from you? Does he or she have any other signs of nervousness, such as shortness of breath, sighing, being unable to relax, or feeling excessively tense?									
Yes	No	Severity: 1	2	3	Distress: 0	1	2	3	4	5
Elation or euphoria	Does the patient appear to feel too good or act excessively happy?									
Yes	No	Severity: 1	2	3	Distress: 0	1	2	3	4	5
Apathy or indifference	Does the patient seem less interested in his or her usual activities and in the activities and plans of others?									
Yes	No	Severity: 1	2	3	Distress: 0	1	2	3	4	5
Disinhibition	Does the patient seem to act impulsively? For example, does the patient talk to strangers as if he or she knows them, or does the patient say things that may hurt people's feelings?									
Yes	No	Severity: 1	2	3	Distress: 0	1	2	3	4	5
Irritability or lability	Is the patient impatient and cranky? Does he or she have difficulty coping with delays or waiting for planned activities?									
Yes	No	Severity: 1	2	3	Distress: 0	1	2	3	4	5
Motor disturbance	Does the patient engage in repetitive activities, such as pacing around the house, handling buttons, wrapping string, or doing other things repeatedly?									
Yes	No	Severity: 1	2	3	Distress: 0	1	2	3	4	5
Nighttime behaviors	Does the patient awaken you during the night, rise too early in the morning, or take excessive naps during the day?									
Yes	No	Severity: 1	2	3	Distress: 0	1	2	3	4	5
Appetite and eating	Has the patient lost or gained weight, or had a change in the food he or she likes?									
Yes	No	Severity: 1	2	3	Distress: 0	1	2	3	4	5

Adapted with permission from: Kaufer DI, Cummings JL, Ketchel P et al. J Neurosychiatry Clin Neurosci 2000; 12:233-9. 2000 © American Psychiatric Press, Inc.⁵⁷

NPI Dataset from Taipei Veterans General Hospital

A	B	C	D	E	F	G	H	I	J	K	L	M
NPI_T	DEL_T	HAL_T	AG_T	DEP_T	ANX_T	EUP_T	APA_T	DIS_T	IRR_T	ABE_T	NIG_T	APP_T
16	0	0	3	0	1	0	3	1	2	3	3	0
28	2	0	6	0	1	4	2	4	2	0	1	6
0	0	0	0	0	0	0	0	0	0	0	0	0
16	0	0	4	2	0	1	1	1	4	1	1	1
9	0	0	0	0	2	0	0	0	1	0	6	0
1	0	0	0	0	0	0	1	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0
4	1	0	1	1	1	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	8	0
5	0	0	0	1	0	0	1	0	0	0	0	3
9	0	0	1	1	0	0	0	0	0	0	1	6
4	0	0	0	3	1	0	0	0	0	0	0	0
12	0	0	0	0	4	0	0	0	0	0	0	8
28	0	0	3	12	2	0	3	1	6	0	1	0
68	6	1	6	8	12	0	12	6	12	2	3	0
12	0	0	0	2	6	0	0	0	0	0	4	0
0	0	0	0	0	0	0	0	0	0	0	0	0
7	0	1	1	0	0	0	1	0	0	3	1	0
29	8	6	3	3	0	0	0	0	0	3	6	0

**Alzheimer's Disease
Clinical Dementia Rating Scale = 1**

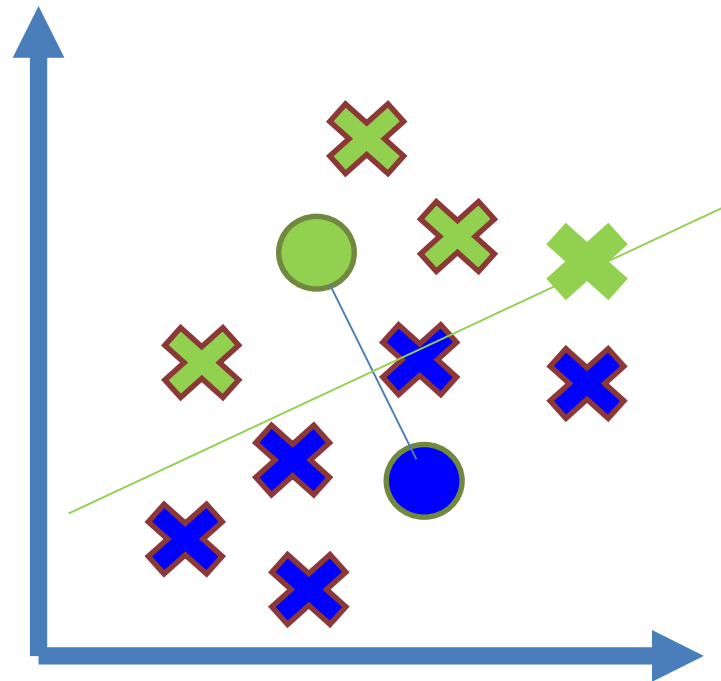
Strictly use within the class!

Read Data into Matlab

- `data=readtable('Dementia_NPI.xlsx');`
- `npi=table2array(data);`

K-means Cluster Analysis

- `idx = kmeans(npi,2)`



K-means Cluster Analysis

Different K

```
>> idx=kmeans(npi,2)
```

```
idx =
```

```
2  
1  
2  
2  
2  
2  
2  
2  
2  
2  
2  
2  
2  
2  
2  
1  
1  
2  
2  
2  
1  
2  
1  
1  
2  
2  
2  
1  
1  
1
```

```
>> idx=kmeans(npi,3)
```

```
idx =
```

```
1  
3  
1  
1  
1  
1  
1  
1  
1  
1  
1  
1  
1  
1  
1  
3  
2  
1  
1  
1  
3  
3  
1  
1  
1  
3  
3  
2
```

```
>> idx=kmeans(npi,4)
```

```
idx =
```

```
1  
2  
3  
1  
1  
3  
3  
3  
3  
3  
1  
3  
3  
1  
2  
1  
3  
3  
2  
3  
2  
1  
1  
1  
2  
2  
4
```

Evaluate Number of Clusters

- Silhouette value

The silhouette value for each point is a measure of how similar that point is to points in its own cluster, when compared to points in other clusters. The silhouette value S_i for the i th point is defined as

$$S_i = (b_i - a_i) / \max(a_i, b_i)$$

where a_i is the average distance from the i th point to the other points in the same cluster as i , and b_i is the minimum average distance from the i th point to points in a different cluster, minimized over clusters.

The silhouette value ranges from -1 to 1 . A high silhouette value indicates that i is well matched to its own cluster, and poorly matched to other clusters. If most points have a high silhouette value, then the clustering solution is appropriate. If many points have a low or negative silhouette value, then the clustering solution might have too many or too few clusters. You can use silhouette values as a clustering evaluation criterion with any distance metric.

Average Silhouette Values Across Different K

- `idx = kmeans(npi,2);`
- `s2=mean(silhouette(npi,idx));`
- `idx = kmeans(npi,3);`
- `s3=mean(silhouette(npi,idx));`
- `idx = kmeans(npi,4);`
- `s4=mean(silhouette(npi,idx));`
- `idx = kmeans(npi,5);`
- `s5=mean(silhouette(npi,idx));`
- `idx = kmeans(npi,6);`
- `s6=mean(silhouette(npi,idx));`
- `idx = kmeans(npi,7);`
- `s7=mean(silhouette(npi,idx));`



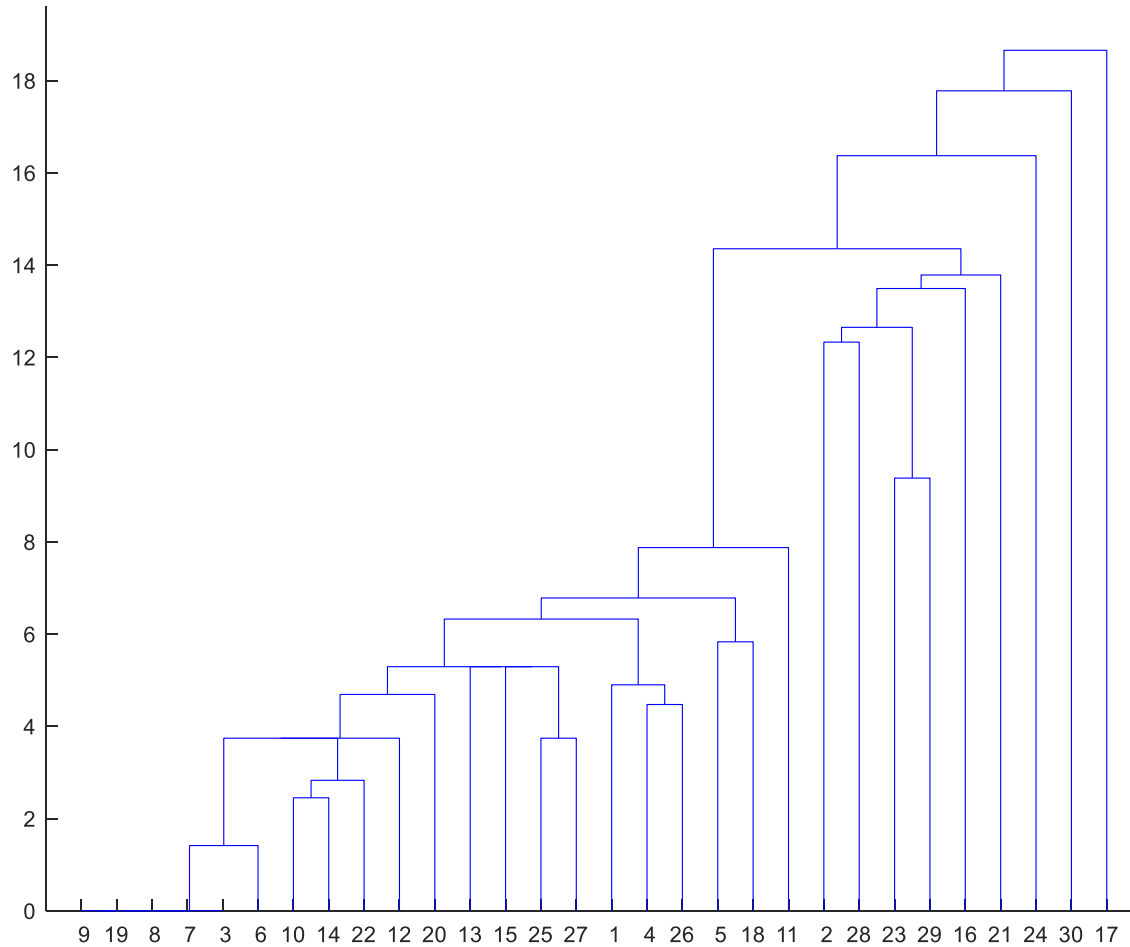
s2
s3
s4
s5
s6
s7

0.7791
0.7593
0.6333
0.5619
0.5341
0.4836

Hierarchical Clustering

- `dist = pdist(npi);`
- `Z = linkage(dist);`
- `dendrogram(Z)`

Hierarchical Clustering





GAP

Generalized Association Plots

GAP is a java-designed software for generalized association plots (Chen, 2002) and exploratory data analysis. It is programmed for the java runtime environment 1.5 (JRE version 1.5.0_04), which is available for most operating systems.

Last Updated: 2012/05/15

Authors:

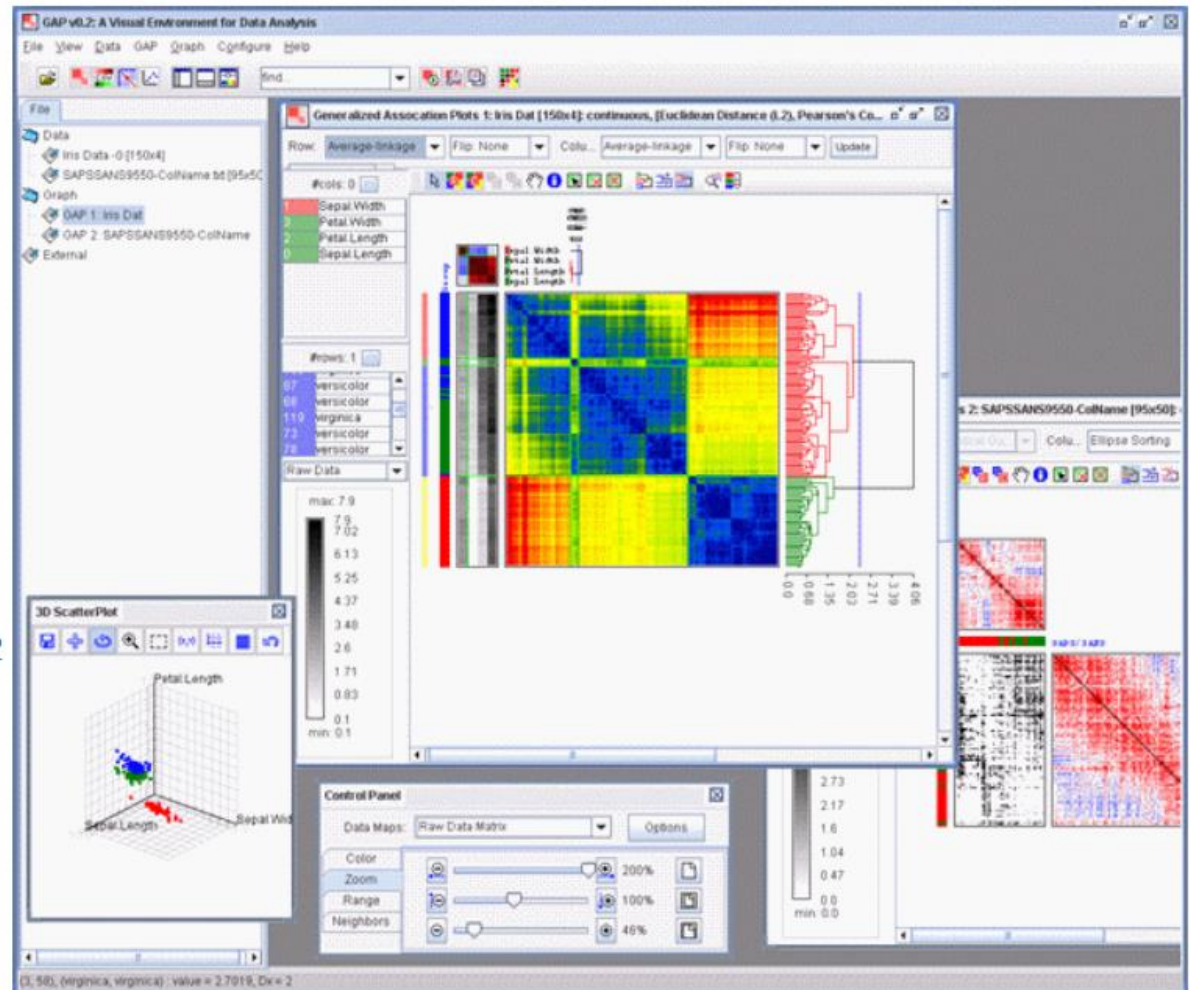
Dr. Han-Ming Wu
 Department of Mathematics,
 Tamkang University
 Tamsui, Taiwan, R.O.C.
 E-mail: hmwu AT mail.tku.edu.tw
 Homepage:
<http://www.hmwu.idv.tw>

Dr. Chun-houh Chen
 Institute of Statistical Science,
 Academia Sinica
 Taipei, Taiwan, R. O. C.
 E-mail: cchen AT stat.sinica.edu.tw
 Homepage:
<http://gap.stat.sinica.edu.tw>

Official Website of GAP Software:
<http://gap.stat.sinica.edu.tw/Software/GAP>

Mirror Website
<http://www.hmwu.idv.tw/GAPSoftware>

Current Version:
 v0.2.7, Build 20110331



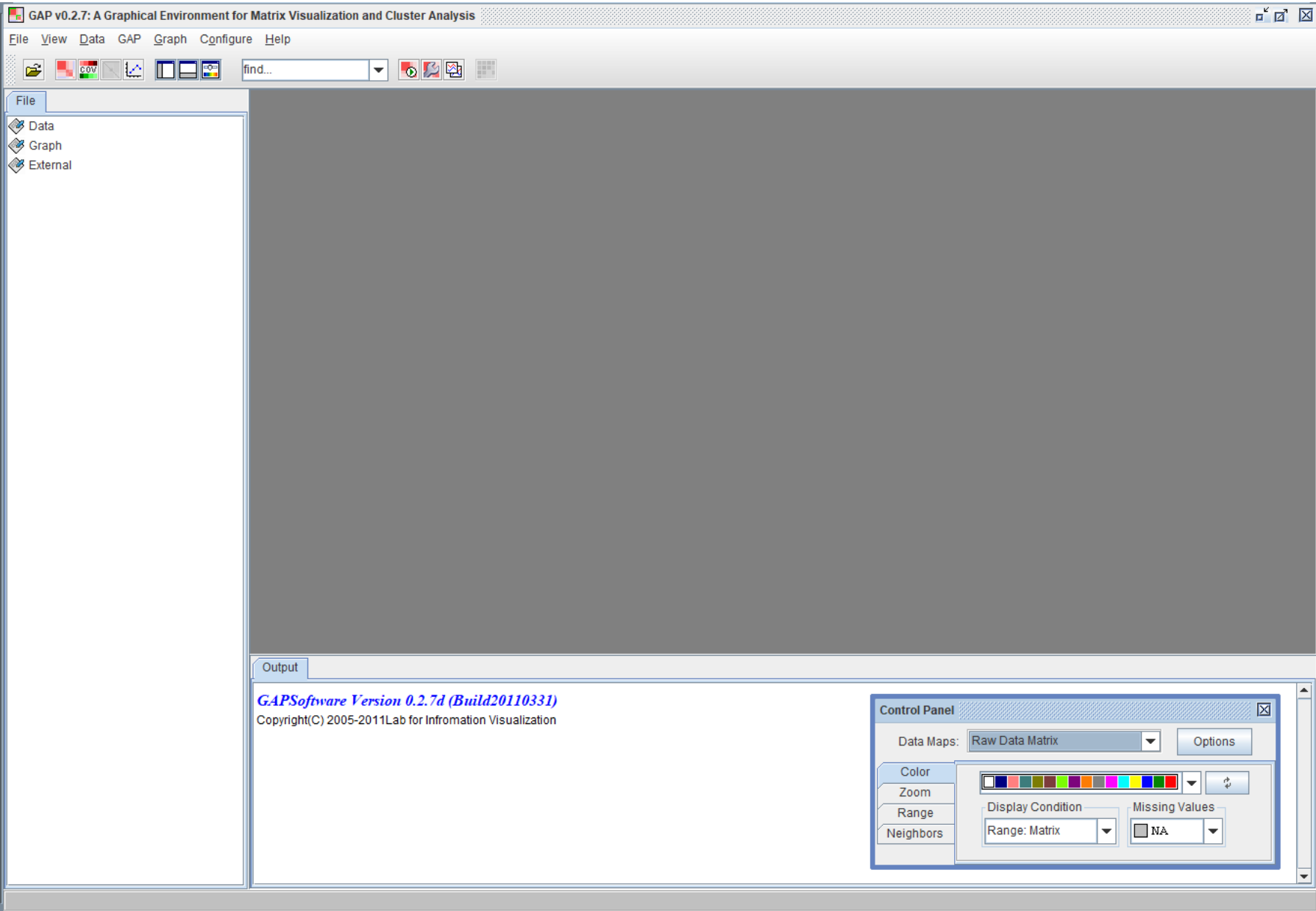
The GAP Main Window [more screenshots...]

Installing GAP

<http://gap.stat.sinica.edu.tw/Software/GAP/>

http://gap.stat.sinica.edu.tw/Software/GAP/downloads/GAPv0.2.7d_win_setup.exe





GAP v0.2.7: A Graphical Environment for Matrix Visualization and Cluster Analysis

File View Data GAP Graph Configure Help

find...

- File
- Data
- Graph
- External

Output

GAPSoftware Version 0.2.7d (Build20110331)
Copyright(C) 2005-2011Lab for Information Visualization

Control Panel

Data Maps: Raw Data Matrix [Options]

Color [Color palette]

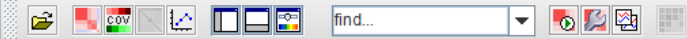
Zoom [Zoom controls]

Range

Neighbors

Display Condition: Range: Matrix

Missing Values: NA



- File
- Data
 - Dementia_NPI.bt [30x13]
- Graph
- External

Dementia_NPI.txt [30x13]

RowN..	NPI_T	DEL_T	HAL_T	AG_T	DEP_T	ANX_T	EUP_T	APA_T	DIS_T
r0	16.0	0.0	0.0	3.0	0.0	1.0	0.0	3.0	1.0
r1	28.0	2.0	0.0	6.0	0.0	1.0	4.0	2.0	4.0
r2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
r3	16.0	0.0	0.0	4.0	2.0	0.0	1.0	1.0	1.0
r4	9.0	0.0	0.0	0.0	0.0	2.0	0.0	0.0	0.0
r5	1.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.0
r6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
r7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
r8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
r9	4.0	1.0	0.0	1.0	1.0	1.0	0.0	0.0	0.0
r10	14.0	0.0	0.0	0.0	0.0	0.0	0.0	6.0	0.0
r11	5.0	0.0	0.0	0.0	1.0	0.0	0.0	1.0	0.0
r12	9.0	0.0	0.0	1.0	1.0	0.0	0.0	0.0	0.0
r13	4.0	0.0	0.0	0.0	3.0	1.0	0.0	0.0	0.0
r14	12.0	0.0	0.0	0.0	0.0	4.0	0.0	0.0	0.0
r15	28.0	0.0	0.0	3.0	12.0	2.0	0.0	3.0	1.0
r16	68.0	6.0	1.0	6.0	8.0	12.0	0.0	12.0	6.0
r17	12.0	0.0	0.0	0.0	2.0	6.0	0.0	0.0	0.0
r18	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
r19	7.0	0.0	1.0	1.0	0.0	0.0	0.0	1.0	0.0
r20	29.0	8.0	6.0	3.0	3.0	0.0	0.0	0.0	0.0
r21	5.0	0.0	0.0	0.0	1.0	2.0	0.0	2.0	0.0
r22	31.0	4.0	2.0	0.0	3.0	8.0	0.0	2.0	0.0
r23	46.0	0.0	0.0	4.0	9.0	0.0	0.0	12.0	0.0
r24	13.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.0
r25	15.0	0.0	0.0	2.0	1.0	3.0	0.0	0.0	1.0
r26	14.0	1.0	0.0	1.0	1.0	0.0	0.0	1.0	1.0
r27	29.0	0.0	0.0	0.0	2.0	2.0	0.0	8.0	2.0
r28	36.0	1.0	1.0	2.0	2.0	6.0	0.0	6.0	0.0
r29	57.0	4.0	0.0	8.0	6.0	2.0	0.0	6.0	9.0

Output

GAPSoftware Version 0.2.7d (Build20110331)
 Copyright(C) 2005-2011Lab for Information Visualization
 D:\Dropbox\Archives\PowerPoint Presentations\Teaching Course\Intelligent Medicine\Dementia_NPI.bt
 #rows: 31
 #columns: 23

Control Panel

Data Maps: Raw Data Matrix [Options]

Color [Color palette]

Zoom [Slider]

Range: Matrix [Display Condition]

Neighbors: NA [Missing Values]



File

- Data
 - Dementia_NPI.txt [30x13]
- Graph
- External

Dementia_NPI.txt [30x13]

RowN...	NPI_T	DEL_T	HAL_T	AG_T	DEP_T	ANX_T	EUP_T	APA_T	DIS_T
r0	16.0	0.0	0.0	3.0	0.0	1.0	0.0	3.0	1.0
r1	28.0	2.0	0.0	6.0	0.0	1.0	4.0	2.0	4.0
r2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
r3	16.0	0.0	0.0	4.0	2.0	0.0	1.0	1.0	1.0
r4	9.0	0.0	0.0	0.0	0.0	2.0	0.0	0.0	0.0
r5	1.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.0
r6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
r7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
r8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
r9	4.0	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
r10	14.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
r11	5.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
r12	9.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
r13	4.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
r14	12.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
r15	28.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0
r16	68.0	6.0	0.0	0.0	0.0	0.0	0.0	0.0	6.0
r17	12.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
r18	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
r19	7.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
r20	29.0	8.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
r21	5.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
r22	31.0	4.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
r23	46.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
r24	13.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
r25	15.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0
r26	14.0	1.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0
r27	29.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.0
r28	36.0	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
r29	57.0	4.0	0.0	0.0	0.0	0.0	0.0	0.0	9.0

Generalized Association Plots

Data Sets
Dementia_NPI.txt

Data Type

Raw Data Matrix: Continuous Binary Nominal Ordinal

Proximity Matrix: Similarity DisSimilarity

Proximity Measure

Row Processing Column Processing

Pearson's Correlation

Extensions

Covariate Adjustment Nonlinear Association

OK Cancel

Output

GAPSoftware Version 0.2.7d (Build20110331)
 Copyright(C) 2005-2011Lab for Information Visualization
 D:\Dropbox\Archives\PowerPoint Presentations\Teaching Course\Intelligent Medicine\Dementia_NPI.txt
 #rows: 31
 #columns: 13

Control Panel

Data Maps: Raw Data Matrix Options

Color

Zoom

Range

Neighbors

Display Condition: Range: Matrix

Missing Values: NA

File

- Data
 - Dementia_NPI.bt [30x13]
- Graph
 - GAP 1: Dementia_NPI
- External

Raw Data

max: 68.0

68.0

57.26

46.53

35.79

25.05

14.32

3.58

0.0

min: 0.0

Dementia_NP...

Generalized Association Plots 1: Dementia_NPI [30x13]: continuous, [Pearson's Correlation, Pearson's Correlation]

Row: Original Order Flip: None Colu... Original Order Flip: None Update Raw Data

#cols: 0

0 NPI_T

1 DEL_T

2 HAL_T

3 AG_T

4 DEP_T

5 ANX_T

6 EUP_T

7 APA_T

8 DIS_T

9 IRR_T

Raw Data

max: 68.0

68.0

57.26

46.53

35.79

25.05

14.32

3.58

0.0

min: 0.0

Dementia_NP...

Output

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D:\Dropbox\Archives\PowerPoint Presentations\Teaching Course\Intelligent Medicine\Dementia_NPI.bt

#rows: 31

#columns: 13

=== Starting GAP Analysis ===

***** Memory and Time Information *****

* Total Memory: 494MB - 494MB = 0MB

* Free Memory: 396MB - 393MB = -3MB

* Use Time: 0.071 seconds.

Control Panel

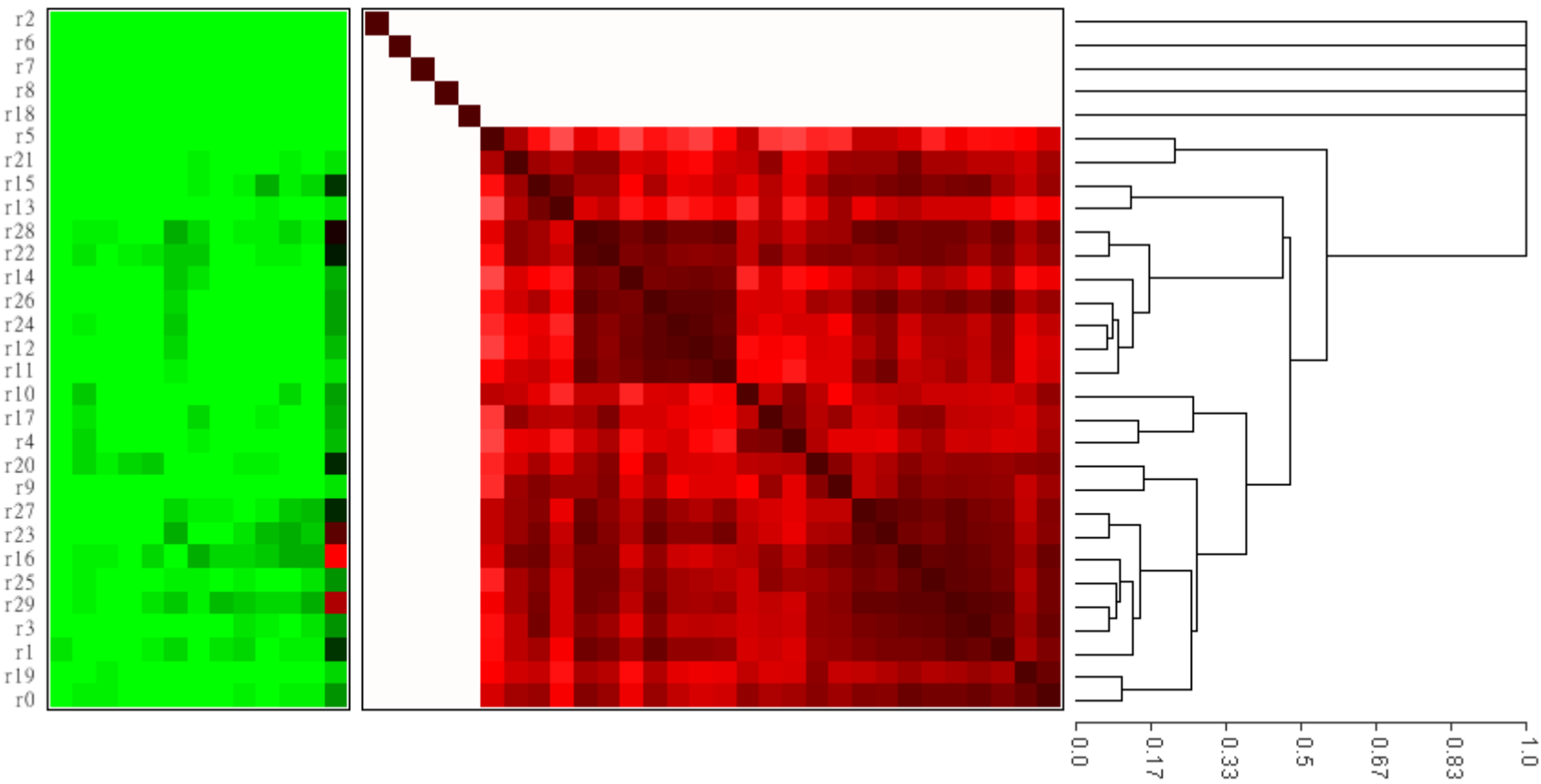
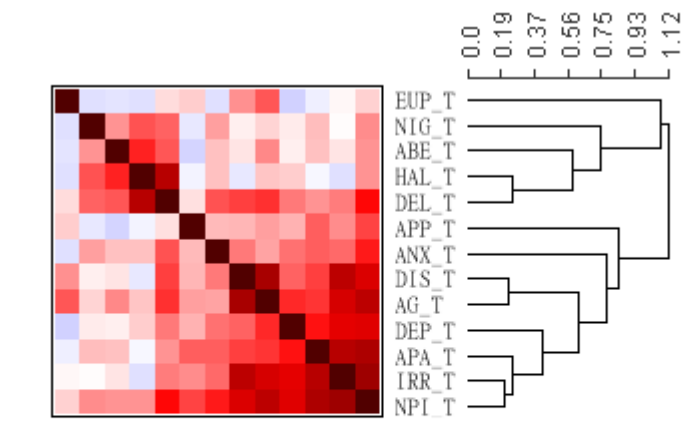
Data Maps: Raw Data Matrix Options

Color

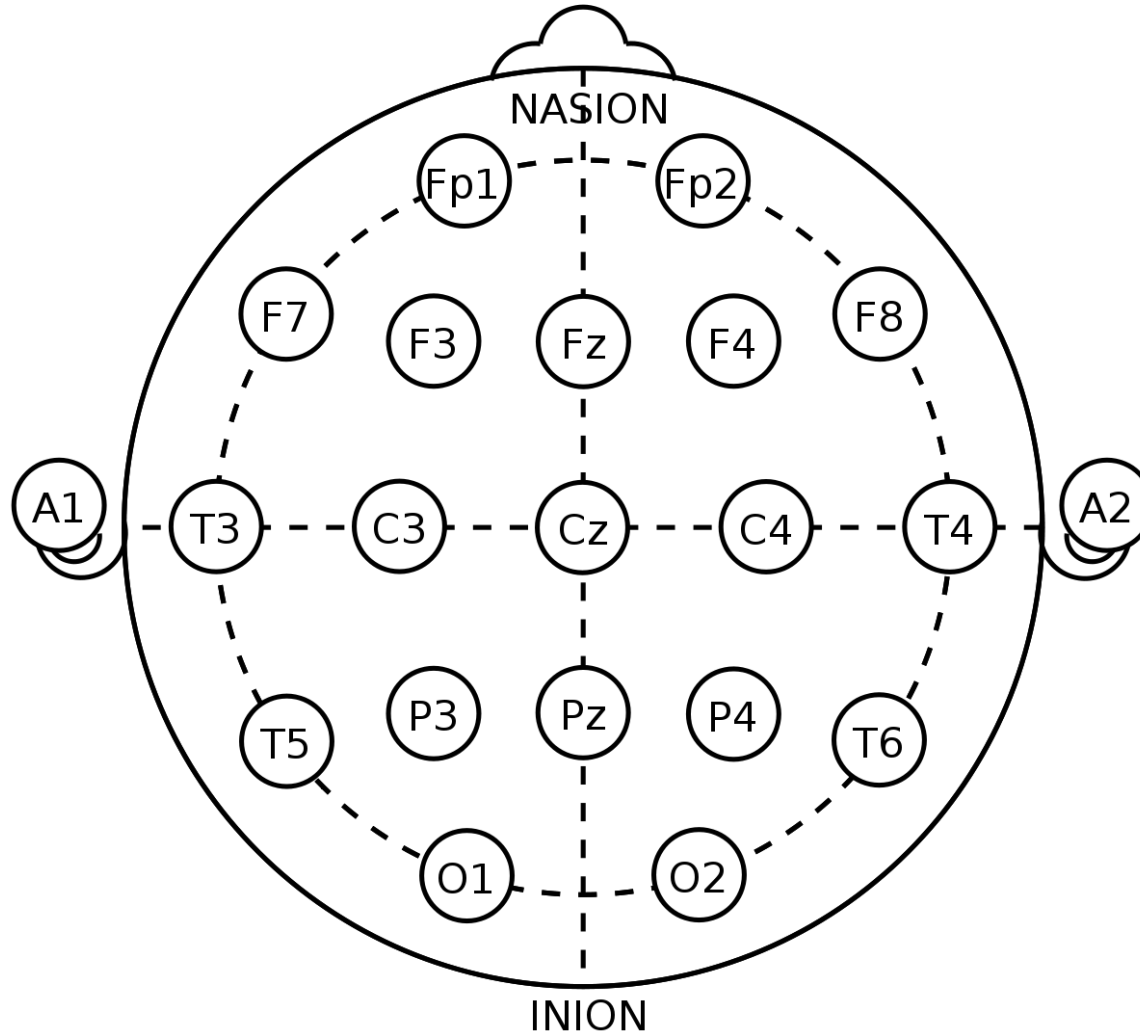
Zoom 200%

Range 100%

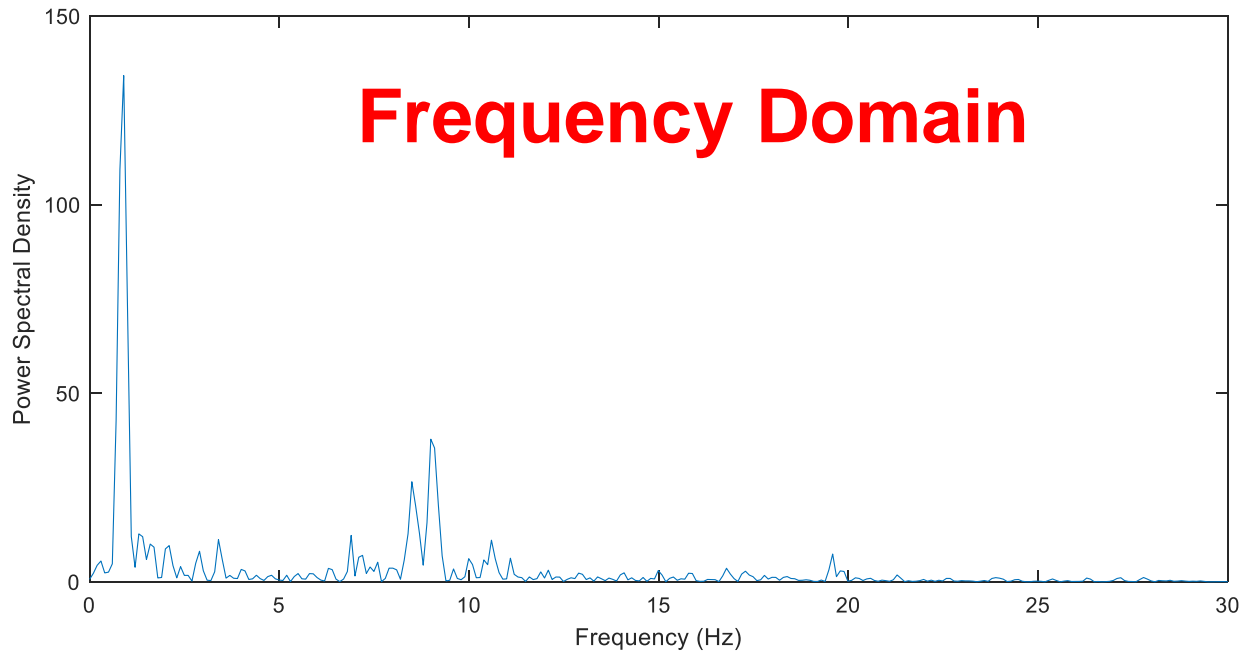
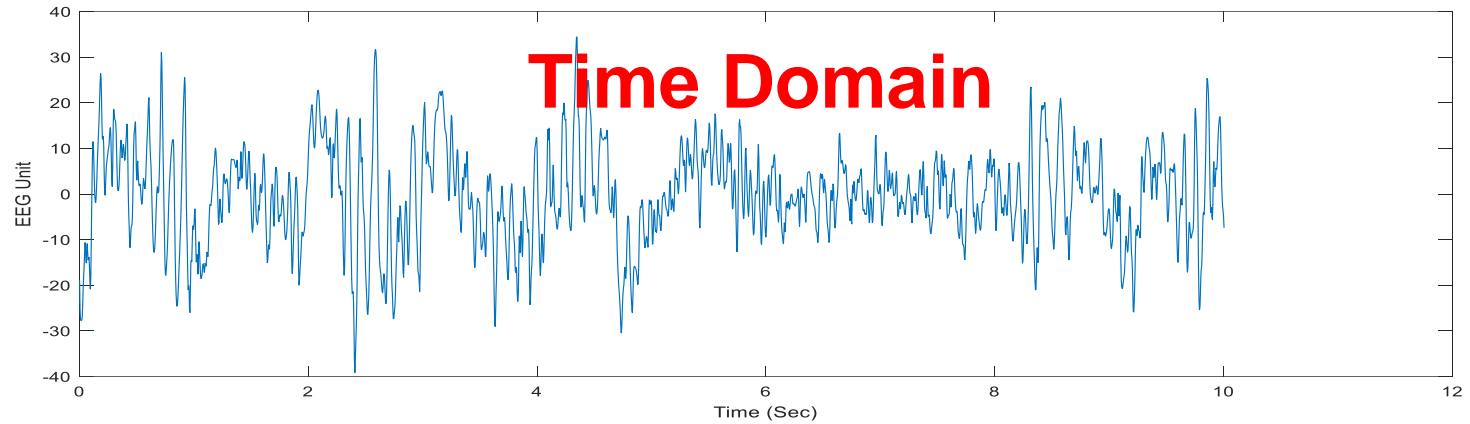
Neighbors 104%



Working on EEG Data...



Working on EEG Data...



EEG Power Dataset from Taipei Veterans General Hospital

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R
0.60	0.70	0.80	0.90	1.00	1.10	1.20	1.30	1.40	1.50	1.60	1.70	1.80	1.90	2.00	2.10	2.20	2.30
4.772268	42.7288	109.237	134.2057	72.83398	12.02012	3.8653	12.70799	11.959	5.921989	10.00712	9.181209	1.027156	1.151498	8.727189	9.600889	4.307525	1.042721
17.44779	9.077563	30.47459	43.43895	14.65272	10.05859	27.92523	34.01321	9.479686	6.3351	6.829078	4.668872	1.485585	17.00385	17.0138	12.60226	5.414003	10.61846
0.122783	0.731211	4.245903	2.761158	26.45982	7.122036	16.83671	14.84089	6.843938	16.77246	8.865251	3.423829	1.527713	0.447893	1.377859	3.431667	8.541264	2.146037
30.67661	19.61354	24.23157	20.43295	7.945283	0.066813	8.094166	2.557659	14.28646	16.40735	1.818496	2.49593	3.129556	1.780533	0.572835	4.136835	7.985638	0.681112
4.217674	0.835116	1.814976	8.235098	12.64343	6.673285	1.203852	11.07234	23.22974	27.22052	1.153593	3.827163	0.329168	0.030645	1.157584	1.697575	0.560194	0.491356
32.69621	9.097504	4.083971	3.287204	6.405678	6.87577	5.228232	5.22564	7.804129	3.370961	2.143753	7.193283	17.99515	6.207295	8.521345	18.31513	4.501235	6.203788
2.570912	4.136851	4.179596	1.90007	4.168743	0.765803	4.225782	1.845419	4.638629	26.19067	23.06942	3.418901	13.41276	9.112344	4.847453	1.251631	0.091183	0.23641
2.812165	4.991649	12.7354	9.226673	13.24596	5.520705	1.199685	0.343871	2.183523	3.641361	3.042871	0.300526	0.011043	2.269092	5.646373	8.988518	3.050006	1.216821
18.54338	8.407034	19.70256	10.63157	2.842853	2.897933	7.758708	2.525452	7.283646	31.98878	27.31104	27.40163	22.29202	8.266734	3.838882	4.852341	1.695692	3.296026
0.871255	7.430406	25.53304	5.194486	6.083051	5.236733	7.28128	4.014	8.2741	0.5562	8.444	4.491	0.36	0.732878	1.766705	6.974483	14.65016	14.49069
74.55017	90.06569	51.95959	164.8729	95.95706	101.3894	84.68497	49.2128	15.2739	56.14229	40.47444	34.3578	27.56455	108.9754	2.778332	20.26662	12.15292	77.28362
1.95562	0.411374	0.179626	3.412617	3.842076	11.98194	32.28935	10.14038	6.62093	0.50171	1.57811	2.22093	1.78713	2.81761	15.2863	5.02412	3.21085	2.237218
9.91643	5.885977	5.273525	5.592037	7.19503	13.1159	2.740397	8.900317	7.90723	0.196221	3.71321	3.25054	1.80519	0.225533	0.50995	1.153875	0.899275	2.238172
33.72619	18.77023	16.3105	58.3692	53.0945	23.97205	4.898463	7.168367	41.17127	12.6211	0.003553	1.004787	8.723724	5.935012	4.439573	0.394742	1.412466	0.791597
39.37171	2.862427	63.04441	104.1739	39.22022	4.777613	20.02056	44.8558	51.65452	35.42794	24.60856	26.88602	12.75645	10.05442	3.320367	6.558742	14.55409	7.817091
264.1489	134.8059	43.03868	12.80866	29.80515	14.37792	6.85928	1.614161	3.336148	0.622645	0.487556	5.918992	2.027131	0.886036	0.984674	0.017916	3.080228	11.76012
106.9223	39.55132	7.216353	3.711951	10.53529	6.6216	9.562213	3.804701	1.152286	9.182741	25.09931	21.69939	6.998326	0.298428	14.71584	1.093296	9.094213	0.241148
0.27513	9.64104	15.77792	34.06076	23.12449	4.632235	6.001405	2.555283	3.232669	4.215873	0.613927	2.451388	3.511696	4.3517	1.997743	1.954508	1.688941	0.882759
47.63441	0.759335	54.10424	80.6067	142.3068	73.18979	7.567681	12.50001	40.05875	7.138165	11.72849	24.17549	21.43297	10.20406	14.54391	15.72521	14.01135	12.34363
1.040302	3.057529	3.338515	4.442098	4.075459	4.986446	2.944733	4.838103	0.001837	3.99017	1.397713	0.485314	0.180414	0.408893	0.262242	1.900535	3.438242	0.224185
146.6562	317.2814	196.8799	107.7961	26.33676	5.552854	84.30163	44.93191	10.85698	36.71533	79.5457	43.21373	18.79511	15.08924	15.38055	16.48044	16.47159	17.6513
8.039877	7.189481	184.2541	223.0374	10.82993	64.91547	87.41572	28.98365	14.53221	12.89301	86.94226	141.8868	106.0159	15.05574	0.197246	13.41605	25.56306	0.441882
1.428694	1.177153	2.327129	1.484481	1.038524	2.414151	0.543384	5.006852	13.26452	19.82395	2.200532	3.299606	2.547027	2.6214	4.705722	1.289838	0.884474	3.315119
83.77203	147.7684	115.076	33.70095	53.43856	107.2531	133.901	65.33051	0.409682	79.01761	101.0143	160.4892	136.8812	138.7506	142.5571	161.6292	33.85023	6.641605
0.121422	0.181742	0.146354	0.124749	0.092158	0.121971	0.001265	0.196737	0.333379	0.041284	0.471808	0.55431	0.346426	0.457098	0.335705	0.257886	2.129856	1.162401
147.9143	316.582	457.3758	456.2142	390.8716	107.7527	14.97224	47.46801	181.7624	66.007	2.285989	14.0435	16.23945	71.49997	41.03732	10.69051	0.042711	23.92931

**Alzheimer's Disease
Clinical Dementia Rating = 1**

Strictly use within the class!