Group ICA: Network Discovery with fMRI
Analytic Choices & Their Implications

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Outline of Talk

• Approaches
  • Seeds vs Components
  • Intro to ICA
  • Group ICA vs single subject

• Processing issues
  • Impact of (micro) motion
  • Autocorrelation
  • Band-pass filtering

• Other issues
  • Task vs Rest
  • Overlap of networks

• Applications
  • Diagnostic
  • Prediction

• Dynamic connectivity

• Summary
Convergence of Methods for Identifying Resting Networks

Seeds vs Components

• Once fixed they are very similar
  • “Seed-based FC measures are shown to be the sum of independent component analysis-derived within network connectivities and between network connectivities” Joel SE, Caffo BS, van Zijl PC, Pekar JJ. On the relationship between seed-based and ICA-based measures of functional connectivity, Magn Reson Med. 2011 Sep;66(3):644-57

• ICA/seed hybrid (use ICA to derive seed regions or maps)

• Spatially constrained approach

Great for artifact cleaning:


\[
\langle \lambda \rangle W = \langle \rho \rangle E\{G_y'(Wx)x^T\} - \frac{1}{2} \langle \mu \rangle E\{g'_y(y : W)x^T\}
\]
Networks and Seeds

- Context determines the meaning and interpretation of the word “network” in brain imaging analysis.
  - **GLM and seed-based methods** define a network as a subset of voxels whose timeseries are significantly correlated with a reference signal.
  - **ICA** defines a network as a subset of voxels whose timeseries are significantly correlated with the estimated ICA timecourse.
  - Using **graph theory**, a network may be defined as a connectivity matrix between nodes, which represent voxels, areas, or components.

“All models are wrong, but some are useful!”
  - “I believe in ignorance-based methods because humans have a lot of ignorance and we should play to our strong suit.”
    - Eric Lander, Whitehead Institute, M.I.T.
Blind Source Separation: The Cocktail Party Problem

Observations → Mixing matrix $A$ → Sources
ICA vs PCA

Uncorrelated: \( E\{y_1, y_2\} = E\{y_1\} E\{y_2\} \)

Independent: \( p(y_1, y_2) = p(y_1) p(y_2) \)

\[ \Rightarrow E\{h(y_1) h(y_2)\} = E\{h(y_1)\} E\{h(y_2)\} \]

PCA finds directions of maximal variance (using second order statistics)

ICA finds directions which maximize independence (using higher order statistics)
General Linear Model

1. Model (1 or more Regressors)
   - $x_i(j)$
   - Regression Results

2. Data
   - $y(j)$

3. Fitting the Model to the Data at each voxel
   \[ y(j) = \hat{\beta}_0 + \sum_{i=1}^{M} \hat{\beta}_i x_i(j) + e(j) \]
Voxels \rightarrow \text{Time} \rightarrow \text{Data}(X) = G \times \hat{\beta}

"Activation maps" Corresponding to columns of G

The GLM is by far the most common approach to analyzing fMRI data. To use this approach, one needs a model for the fMRI time course.

The General Linear Model (GLM)

In spatial ICA, there is no model for the fMRI time course, this is estimated along with the hemodynamic source locations.

Independent Component Analysis (ICA)

In spatial ICA, there is no model for the fMRI time course, this is estimated along with the hemodynamic source locations.
ICA Halloween (Un)Mixer!

\[ X = A \times S \]

- background

→ Time

- candle 1

- candle 2

- candle 3

Candle out
Assessing Task Modulation of Components

- We can evaluate the component timecourses within a standard GLM approach.

<table>
<thead>
<tr>
<th>Comp#</th>
<th>R²</th>
<th>Subject</th>
<th>Reg1</th>
<th>Reg2</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>0.81</td>
<td>1</td>
<td>1.89</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>2.28</td>
<td>0.66</td>
</tr>
<tr>
<td>10</td>
<td>0.79</td>
<td>1</td>
<td>0.28</td>
<td>2.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>0.65</td>
<td>2.03</td>
</tr>
<tr>
<td>4</td>
<td>0.017</td>
<td>1</td>
<td>-0.19</td>
<td>-0.40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>-0.10</td>
<td>0.08</td>
</tr>
</tbody>
</table>
Consistency of ICA Algorithms

Group ICA


ICA (Forward Estimation)

Data

Subject 1

$X$

Subject N

Components

$A_1$

$A_N$

Back-reconstruction (PCA-based, Dual regression, etc)

Subject i

$S_i$

Components

Voxels

$\approx$

$\times$

Sagg

Component Images

Voxel-wise stats
(e.g. one-sample t-test, two-sample t-test, correlation, etc)

Component images
(one per subject)

T-statistic

Task-modulation
(e.g. Fit timecourses to GLM model then test parameter)

Component Timecourses

Model timecourses

Multiple regression fit to ICA timecourses

Beta-weights
(second level model)

Component Images

Voxel-wise stats
(e.g. one-sample t-test, two-sample t-test, correlation, etc)

Component images
(one per subject)

T-statistic

Task-modulation
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Multiple regression fit to ICA timecourses

Beta-weights
(second level model)

Spectra
(e.g. power spectra, fractal parameters, etc)

Functional Network Connectivity
(e.g. inter-component correlation)

Power spectra group differences

Model timecourses

Multiple regression fit to ICA timecourses

Beta-weights
(second level model)
Group ICA

ICA (Forward Estimation)

Data

\[
\begin{align*}
\text{Subject 1} & \quad A_1 \\
\vdots & \quad A \\
\text{Subject N} & \quad A_N
\end{align*}
\]

ICA

\[
A \times S_{\text{agg}} = \text{Data}
\]

Back-reconstruction through inversion\(^1\)

\[
A_i \times \text{Subject i} = S_i
\]


Back-reconstruction through Spatial-temporal (dual) regression\(^2,3\)

1) Regress \(S_{\text{agg}}\) onto each timepoint of Subject i to generate \(A_i\)

2) Regress \(A_i\) onto each image of Subject i to generate \(S_i\)

Iterate steps 1 & 2 until converged

Pushing the Limits of Group ICA (simTB)

- Roughly 30 SMs can be selected through the graphical user interface by clicking on components, or by component number in the batch script.
- For each subject, each selected component can be included or not, be translated and rotated in space, and the spatial spread of the component can be increased or decreased.
- Each SM is normalized to have a peak-to-peak amplitude range of one.


http://mialab.mrn.org/software/simtb

Group ICA of Rest fMRI Data: N=603

Component spatial maps

Functional network connectivity (FNC)

28 labeled components & superset of 75 components
N=603 subjects

http://mialab.mrn.org/data

**univariate models**

(1) $H_0: \beta_1 = 0$

\[ \vdots \]

(v) $H_0: \beta_v = 0$

Is voxel $i$ affected by age?

**multivariate models**

$H_0: \beta_1 = \beta_2 = \ldots \beta_v = 0$

Are any of these voxels affected by age?
Rapid Imaging (multiband EPI)

TR=275ms, 39 subjects
On ICA Model Order: Reconstruction of low model order from high model order

<table>
<thead>
<tr>
<th># Components (var)</th>
<th>X = -0.5 mm</th>
<th>Y = 45.5 mm</th>
<th>Z = 39.5 mm</th>
<th>X = -0.5 mm</th>
<th>Y = 42.5 mm</th>
<th>Z = 44.5 mm</th>
<th>X = -0.5 mm</th>
<th>Y = 44.5 mm</th>
<th>Z = -5.5 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (83%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (81%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 (45%, 21% 11%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 (45%, 21%, 11%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 (41%, 24%, 10%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 (32%, 22%, 17%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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  • Overlap of networks

• Applications
  • Diagnostic
  • Prediction

• Dynamic connectivity

• Summary
We selected 3 sets of subjects (total $N = 199$).

- **Non Movers (NM):** Subject group who had very small framewise micromovements ($\text{FD}_{\text{rms}} < 0.2$ mm in general) ($N1 = 68$)
- **Continuous Movers (CM):** Subject group who had continuous framewise micromovements of 0.2 mm or higher (more micromovements) ($N2 = 66$)
- **Spikey Movers (SM):** Subject group who had reasonable framewise micromovements but with occasional big jerky movements of $\text{FD}_{\text{rms}} > 0.5$ ($N3 = 65$).


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- **Summary**
Result 1: AOD and rest data produced highly similar networks

<table>
<thead>
<tr>
<th>Comp#</th>
<th>Comp#</th>
<th>Description</th>
<th>Corr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oddball</td>
<td>Rest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>19</td>
<td>A: Default mode</td>
<td>0.9577</td>
</tr>
<tr>
<td>11</td>
<td>9</td>
<td>B: Motor</td>
<td>0.9156</td>
</tr>
<tr>
<td>13</td>
<td>12</td>
<td>C: Sup parietal</td>
<td>0.9142</td>
</tr>
<tr>
<td>10</td>
<td>6</td>
<td>D: Medial visual</td>
<td>0.8628</td>
</tr>
<tr>
<td>12</td>
<td>7</td>
<td>E: Left lateral frontoparietal</td>
<td>0.8557</td>
</tr>
<tr>
<td>14</td>
<td>2</td>
<td>F: Lateral Visual</td>
<td>0.8170</td>
</tr>
<tr>
<td>17</td>
<td>13</td>
<td>G: Temporal2</td>
<td>0.8135</td>
</tr>
<tr>
<td>8</td>
<td>11</td>
<td>H: Cerebellum</td>
<td>0.8059</td>
</tr>
<tr>
<td>1</td>
<td>15</td>
<td>I: Temporal1</td>
<td>0.8048</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>J: Frontal</td>
<td>0.7838</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>K: Right lateral frontoparietal</td>
<td>0.8170</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>L: Anterior cingulate</td>
<td>0.035</td>
</tr>
</tbody>
</table>

Result 2: Though similar TCNs were identified for AOD and rest, spatial and temporal task modulation was induced.

<table>
<thead>
<tr>
<th>Description</th>
<th>Tar</th>
<th>Nov</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Default mode</td>
<td>-8.44 (1.4e-9)</td>
<td>-5.79 (5.6e-6)</td>
</tr>
<tr>
<td>B: Motor</td>
<td>4.62 (2.3e-4)</td>
<td>1.11 (1.0)</td>
</tr>
<tr>
<td>C: Sup parietal</td>
<td>2.51 (8.9e-2)</td>
<td>-3.50 (6.5e-3)</td>
</tr>
<tr>
<td>D: Medial visual</td>
<td>1.09 (1.0)</td>
<td>0.12 (1.0)</td>
</tr>
<tr>
<td>E: Left lateral frontoparietal</td>
<td>2.41 (1.1e-1)</td>
<td>1.21 (1.0)</td>
</tr>
<tr>
<td>F: Lateral Visual</td>
<td>-4.34 (5.4e-4)</td>
<td>-3.92 (1.9e-3)</td>
</tr>
<tr>
<td>G: Temporal2</td>
<td>10.29 (6.2e-12)</td>
<td>7.76 (1.1e-8)</td>
</tr>
<tr>
<td>H: Cerebellum</td>
<td>4.09 (1.1e-3)</td>
<td>-2.59 (7.4e-2)</td>
</tr>
<tr>
<td>I: Temporal1</td>
<td>13.67 (1.2e-15)</td>
<td>9.30 (1.1e-10)</td>
</tr>
<tr>
<td>J: Frontal</td>
<td>-2.55 (8.1e-2)</td>
<td>-3.28 (1.2e-2)</td>
</tr>
<tr>
<td>K: Right lateral frontoparietal</td>
<td>-12.00 (6.3e-15)</td>
<td>-3.89 (2.1e-3)</td>
</tr>
</tbody>
</table>

These results suggest that changes in neuronal synchronization as indicated by power fluctuations in high-frequency (>1Hz) EEG rhythms such as posterior alpha are partly mediated by widespread changes in inter-regional low-frequency (<.1Hz) functional activities detected in fMRI. They also indicate that generation of local hemodynamic responses is highly sensitive to global state changes that do not involve changes of mental effort or awareness.
fBIRN SIRP Task

- **Methods**
  - **Subjects & Task**
    - 28 subjects (14 HC/14 SZ) across two sites
    - Three runs of SIRP task preprocessed with SPM2
  - **ICA Analysis**
    - All data entered into group ICA analysis in GIFT
    - ICA time course and image reconstructed for each subject, session, and component
    - Images: sessions averaged together creating single image for each subject and component
    - Time courses: SPM SIRP model regressed against ICA time course
  - **Statistical Analysis:**
    - Images: all subjects entered into voxelwise 1-sample t-test in SPM2 and thresholded at t=4.5
    - Time courses: Goodness of fit to SPM SIRP model computed, beta weights for load 1, 3, 5 entered into Group x Load ANOVA

*fBIRN Phase II Data: www.nbirn.net; NCRR (NIH), 5 MOI RR 000827 (2002-2006) and 1 U24 RR0219921 (2006 onwards)*
Component 1: Bilateral Frontal/Parietal

fBIRN Phase II Data: [www.nbirn.net](http://www.nbirn.net);
NCRR (NIH), 5 MOI RR 000827 (2002-2006) and 1 U24 RR0219921 (2006 onwards)
Component 2: Right Frontal, Left Parietal, Post. Cing.

R2 = 0.257, Group (p < 0.070), Load (p < 0.053), Group X Load (p < 0.541)

fBIRN Phase II Data: [www.nbirn.net](http://www.nbirn.net);
NCRR (NIH), 5 MOI RR 000827 (2002-2006) and 1 U24 RR0219921 (2006 onwards)
Component 3: Temporal Lobe

R² = 0.178, Group (p < 0.000), Load (p < 0.487), Group X Load (p < 0.767)

fBIRN Phase II Data: [www.nbirn.net](http://www.nbirn.net);
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- Summary
Relationship to Disease (N=1140)

Healthy (N=590)
Substance Use (N=469)
Schizo/BP (N=81)
Within network example: anterior DMN
Between network example: precuneus-cerebellar connectivity
Robustness of ‘modes’

3-way Classification of Schizophrenia, Bipolar, Control

1) Remove subjects from each group

2) Identify regions which maximally separate remainder

HC-SZ  HC-BP  SZ-BP

Temporal

Default

3: Develop simple classifier based upon 'distance' between each group:

Classify as cont if $D_{cont,i} > D_{schizo,i}$ and $D_{cont,i} > D_{bipo,i}$,
schizo if $D_{schizo,i} > D_{cont,i}$ and $D_{schizo,i} > D_{bipo,i}$,
bipo if $D_{bipo,i} > D_{cont,i}$ and $D_{bipo,i} > D_{schizo,i}$

4) Classify 'left out' participants

Overall: Sensitivity (90%) Specificity (95%)

Control  Schizo  Bipo

Separate ICAs performed on training/testing sets, 9 RSNs selected

Features are the **temporal correlations** between components

How informative is 5 minutes of resting-state fMRI data?

M. Arbabshirani, K. A. Kiehl, G. Pearlson, and V. D. Calhoun, "Classification of schizophrenia patients based on resting-state functional network connectivity " Frontiers in Brain Imaging Methods, in press.
## Diagnostic Classification: FNC

How informative is 5 minutes of resting-state fMRI data?

<table>
<thead>
<tr>
<th>Method</th>
<th>Overall Error (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear Discriminant</td>
<td>29.17</td>
<td>41.67</td>
<td>100</td>
</tr>
<tr>
<td>SVM (linear)</td>
<td>16.67</td>
<td>75</td>
<td>91.67</td>
</tr>
<tr>
<td>SVM (RBF)</td>
<td>4.17</td>
<td>100</td>
<td>91.67</td>
</tr>
<tr>
<td>K nearest neighbors</td>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Naïve Bayes</td>
<td>20.83</td>
<td>75</td>
<td>83.33</td>
</tr>
<tr>
<td>Neural Net (bp)</td>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

M. Arbabshirani, K. A. Kiehl, G. Pearlson, and V. D. Calhoun, "Classification of schizophrenia patients based on resting-state functional network connectivity " Frontiers in Brain Imaging Methods, in press.
Simulated Driving Paradigm

- Drive
- Watch

* 0 180 360 600
“Our results suggest that simulated driving engages mainly areas concerned with perceptual-motor integration and does not engage areas associated with higher cognitive functions.”

“our study suggests that the main ideas of cognitive psychology used in the design of cars, in the planning of respective behavioral experiments on driving, as well as in traffic related political decision making (i.e. laws on what drivers are supposed to do and not to do during driving) may be inadequate, as it suggests a general limited capacity model of the psyche of the driver which is not supported by our results. If driving deactivates rather than activates a number of brain regions the quests for the adequate design of the man-machine interface as well as for what the driver should and should not do during driving is still widely open.”
Baseline Simulated Driving Results

Higher Order Visual/Motor: Increases during driving; less during watching.

Low Order Visual: Increases during driving; less during watching.

Motor control: Increases only during driving.

Vigilance: Decreases only during driving; amount proportional to speed.

Error Monitoring & Inhibition: Decreases only during driving; rate proportional to speed.

Visual Monitoring: Increases during epoch transitions.


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The windowed FNC approach (dFNC)


Dynamic Connectivity

Concurrent EEG/fMRI, Observations/Conclusions...

- Qualitative replication of previous FC states and temporal trends in a much smaller sample.
- Classification of EEG by FC confirms that different FC states indeed exhibit different electrophysiological signatures.
- Overview of dynamics (greatly simplified):

  - Strong antagonism between DMN and attentional networks corresponds to less low frequency power (delta, theta, and alpha).
  - Partial antagonism corresponds to increased alpha power.
  - Cortical-subcortical antagonism and decreased intra-DMN connectivity corresponds to increased delta/theta power.
  - Hyper-synchronization corresponds to larger increases in delta/theta power and decreases in alpha.

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Static FNC in fBIRN Schizophrenia Data (n~315 HC/SZ)

* Hyper: thalamus-sensorimotor
* Hypo: thalamus-(prefrontal-striatal-cerebellar)

Inverse related (less so in patients)
Sensorimotor region & cortical-subcortical antagonism co-occur with thalamic hyperconnectivity

Spatial Patterns of Connectivity are also Dynamic

- The DMN spatial patterns in patients are more likely to stay linked to the other network spatial patterns.
- The DMN spatial patterns in controls are more dynamic in their links to the other network spatial patterns.

S. Ma, V. D. Calhoun, R. Phlypo, and T. Adalı, "Dynamic changes of spatial functional network connectivity in healthy individuals and schizophrenia patients using independent vector analysis.," NeuroImage, in press
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- **Summary**
A Few ICA Software Packages (RAM?)

  - matlab
  - three different ICA algorithms
  - fMRI specific with demo data

- FMRIB Software Library, which includes the ICA tool MELODIC ([http://www.fmrib.ox.ac.uk/analysis/research/melodic/](http://www.fmrib.ox.ac.uk/analysis/research/melodic/)):
  - C
  - FastICA+
  - Complete Package

- AnalyzeFMRI ([http://www.stats.ox.ac.uk/~marchini/software.html](http://www.stats.ox.ac.uk/~marchini/software.html))
  - R
  - FastICA

  - Commercial
  - FastICA
  - Complete Package

- FMRLAB ([http://www.secn.ucsd.edu/fmrlab/](http://www.secn.ucsd.edu/fmrlab/))
  - matlab
  - infomax algorithm
  - fMRI specific with additional tools

- ICALAB
  - matlab
  - multiple ICA algorithms
  - not fMRI specific although one fMRI example included

- GIFT ([http://icatb.sourceforge.net](http://icatb.sourceforge.net))
  - matlab
  - >14 ICA algorithms (more coming) including infomax and fastICA
  - Constrained ICA algorithms
  - Dynamic FNC algorithms
  - Visualization tools and sorting options.
  - Sample data and a step-by-step walk through

Mialab Software

- http://mialab.mrn.org/software
- freeware, written in MATLAB (also offering compiled versions): over 11,000 unique downloads
- **Group ICA of fMRI Toolbox (GIFT)**
  - Single subject/Group ICA
  - MANCOVA testing framework
  - Source Based Morphometry
  - Model order estimation
  - ICASSO (clustering/stability)
- **Fusion ICA Toolbox (FIT)**
  - Parallel ICA, jICA
  - mCCA+jICA & much more!
- **Simulation Toolbox (SimTB)**
  - Flexible generation of fMRI-like data
- **COINS**
  - http://coins.mrn.org/dx
Speaking of Prediction…..

The IEEE International Workshop on Machine Learning for Signal Processing is proud to announce:

The 2014 Schizophrenia Classification Challenge

This year’s learning task features:

Multi-modal brain imaging data (functional and structural MRI)

We encourage all the participants to identify abnormal functional and structural brain patterns as well as interactions between them to improve diagnosis prediction.

Please visit the website for full details about the competition and submission instructions.


371 teams
Over 400 individuals
Over 2200 submissions

Collection of this dataset was made under an NIH NIGMS Centers of Biomedical Research Excellence (COBRE) grant P20GM103472 to Vince Calhoun (PI).
Application to Animal Work: Resting Connectivity, Behavioral, and Exposure to Phencyclidine

PCP exposure induced a long-term spatial memory deficit, but did not impair subsequent spatial learning.

- PCP exposed animals displayed stronger negative relationships between cortical-hippocampal and cortical-midbrain components and stronger positive relationships within the amygdala/hippocampi components.
- Sub-chronic exposure to PCP caused widespread alterations in FNC.

Prenormalization & Reliability

1) No Normalization (NN), where data is left in its raw intensity units

2) Intensity Normalization (IN), which involves voxel-wise division of the time series mean

3) Variance Normalization (VN), voxel-wise z-scoring of the time series

Functional Normalization (fNORM)

A Overlap comparison (Incidence maps) from subject-specific results

Before ICA-fNORM

SCALE:
- Orange: Active for 28 subjects
- Pink: Active for 8 subjects

A After ICA-fNORM

B Voxels active in all 28 subjects (Orange region from A)

Before ICA-fNORM

After ICA-fNORM
Current Directions

- Individual variability
- Dependencies in space, time, space/time
- Dynamics