Models of Effective Connectivity & Dynamic Causal Modelling

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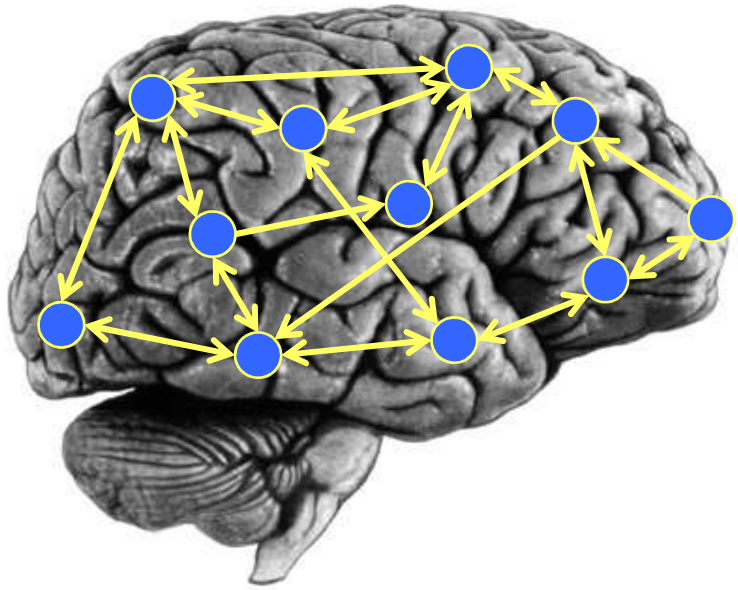
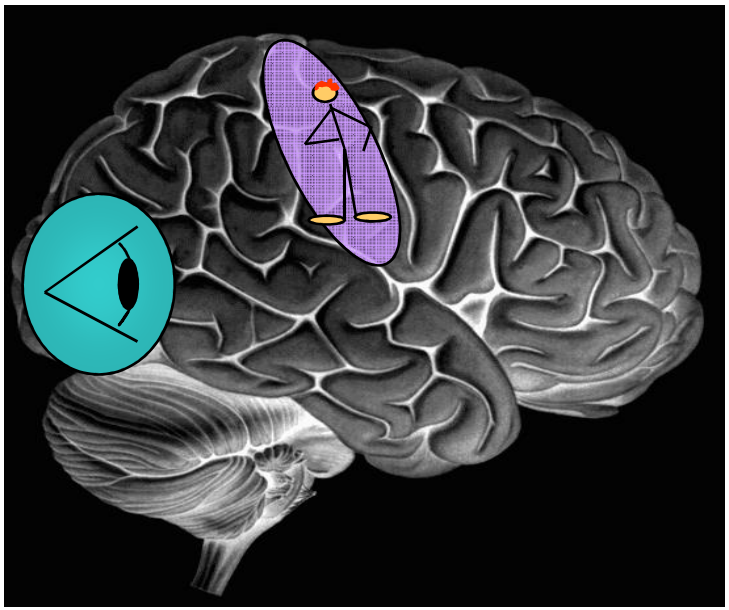


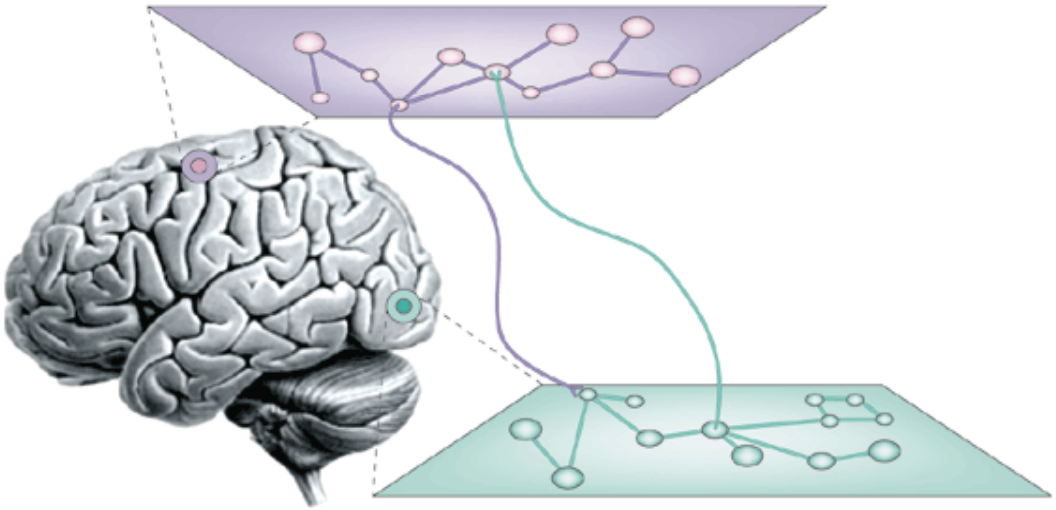
SPM Course, London
13-15 May 2010

Principles of Organisation

Functional specialization



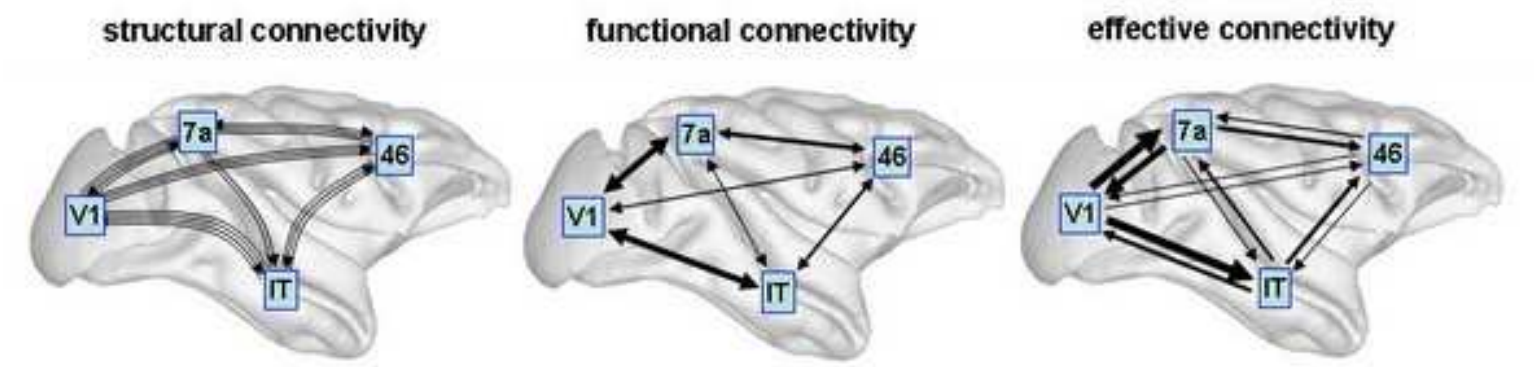
Functional integration



Overview

- Brain connectivity: types & definitions
  - anatomical connectivity
  - functional connectivity
  - effective connectivity
- Functional connectivity
- Psycho-physiological interactions (PPI)
- Dynamic causal models (DCMs)
- Applications of DCM to fMRI data

Structural, functional & effective connectivity



Sporns 2007, *Scholarpedia*

- anatomical/structural connectivity
  = presence of axonal connections

- functional connectivity
  = statistical dependencies between regional time series

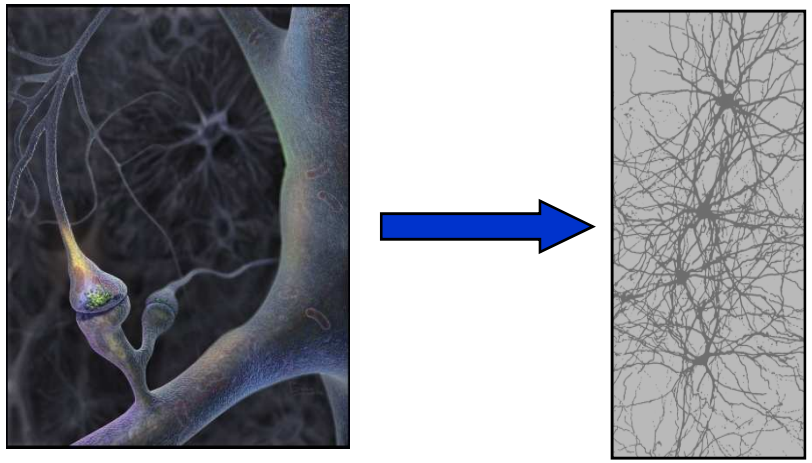
- effective connectivity
  = causal (directed) influences between neurons or neuronal populations

Anatomical connectivity

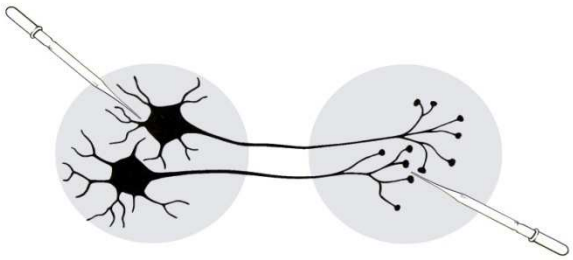
Definition:

presence of axonal connections

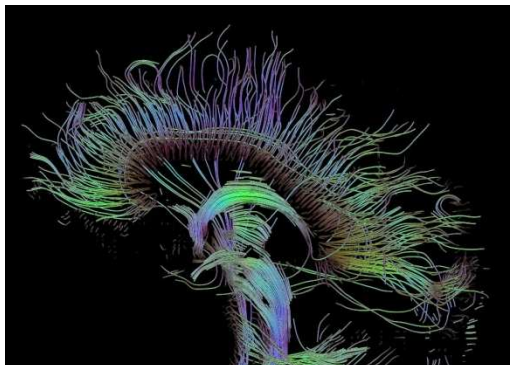
- neuronal communication via synaptic contacts



- Measured with
  - tracing techniques



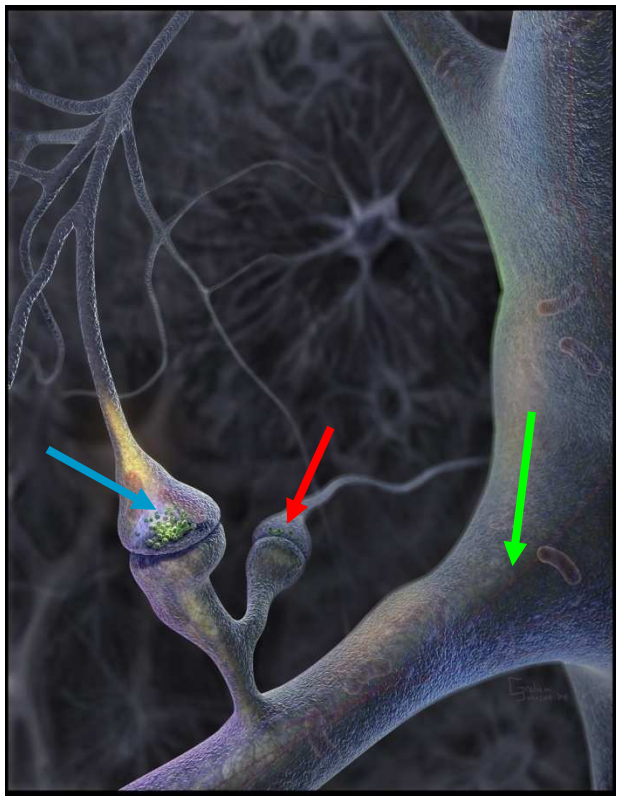
  - diffusion tensor imaging (DTI)



Knowing anatomical connectivity is not enough...

- Context-dependent recruiting of connections :
  - Local functions depend on network activity
- Connections show synaptic plasticity
  - change in the structure and transmission properties of a synapse
  - even at short timescales

→ Look at functional and effective connectivity



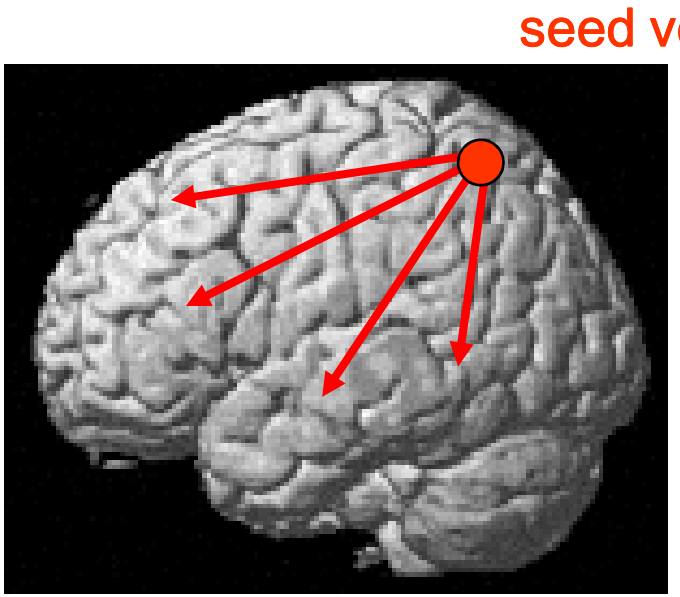
Functional connectivity

Definition: statistical dependencies between regional time series

- Seed voxel correlation analysis 
- Coherence analysis
- Eigen-decomposition (PCA, SVD)
- Independent component analysis (ICA)
- any technique describing statistical dependencies amongst regional time series

Seed-voxel correlation analyses

- hypothesis-driven choice of a seed voxel
- extract reference time series
- voxel-wise correlation with time series from all other voxels in the brain

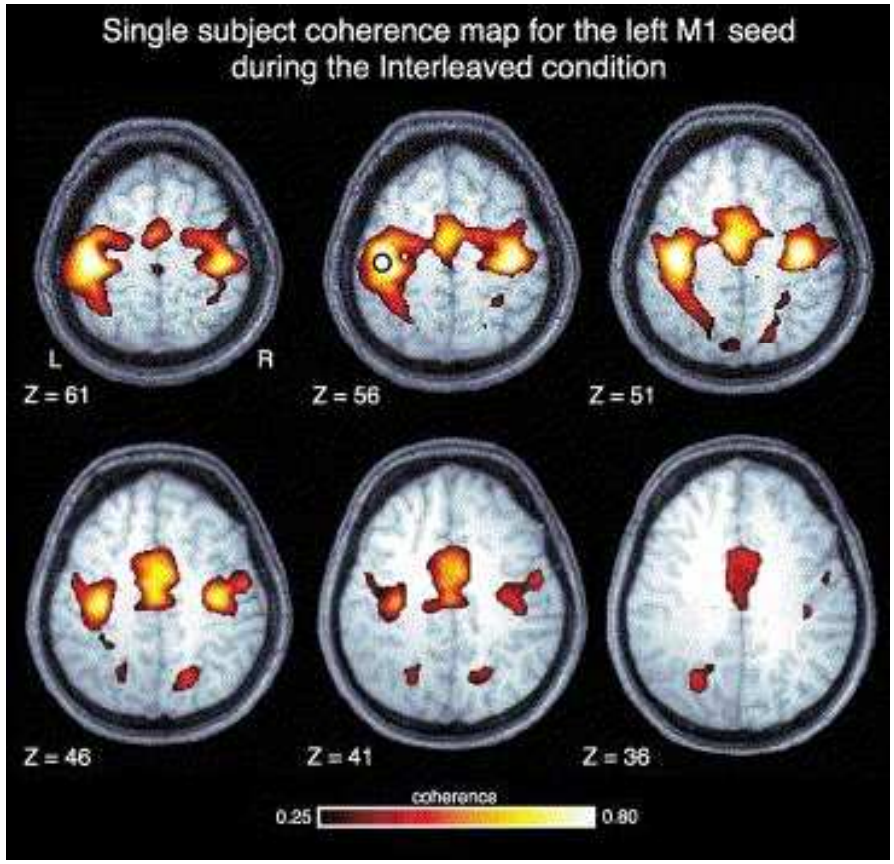


SVCA example:
Task-induced changes in functional connectivity

2 bimanual finger-tapping tasks:

During task that required more bimanual coordination, SMA, PPC, M1 and PM showed increased functional connectivity ($p<0.001$) with left M1

→ No difference in SPMs!



Sun et al. 2003, *Neuroimage*

Does functional connectivity not simply correspond to co-activation in SPMs?

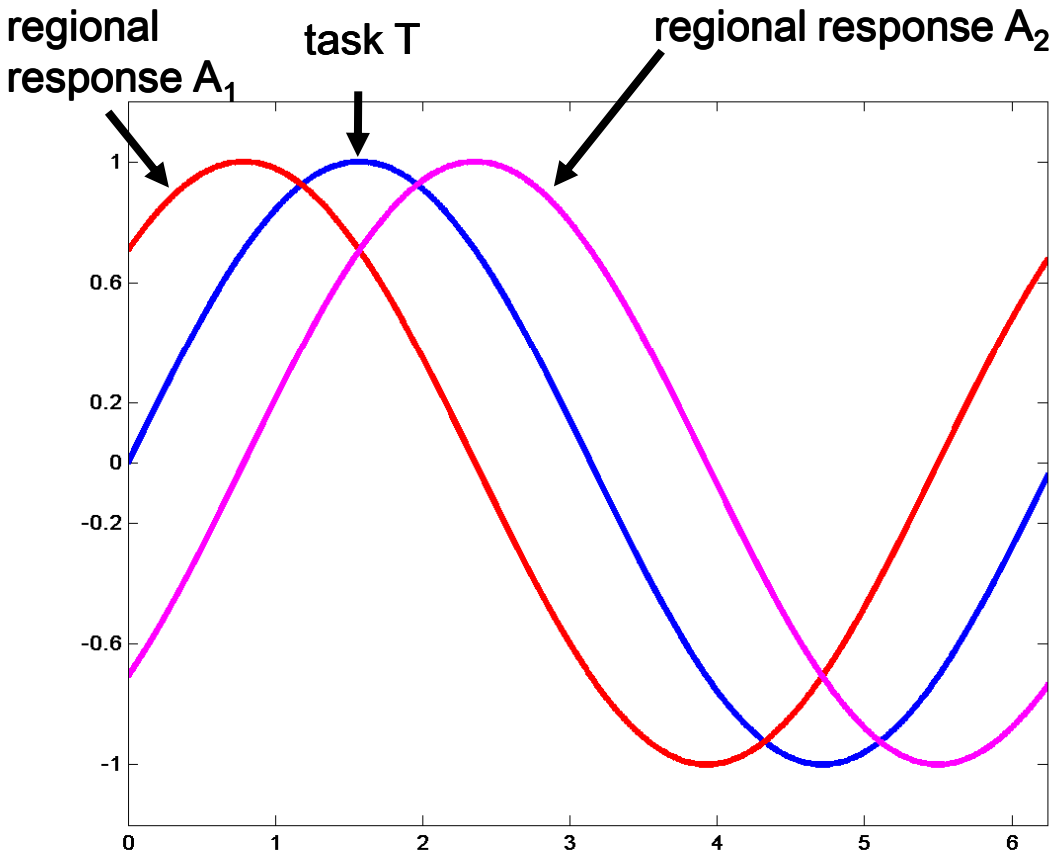
No

Here both areas A_1 and A_2 are correlated identically to task T, yet they have zero correlation among themselves:

$r(A_1,T) = r(A_2,T) = 0.71$

but

$r(A_1,A_2) = 0$!

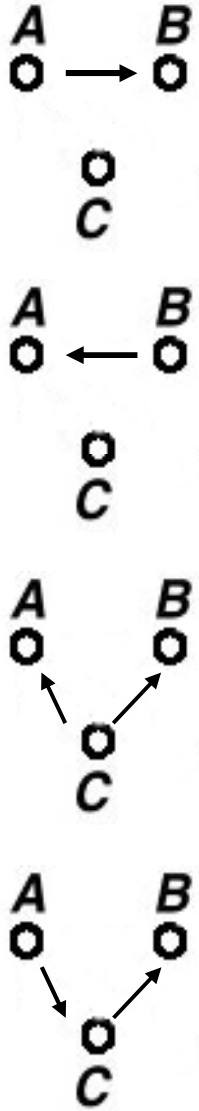


Stephan 2004, *J. Anat.*

Pros & Cons of functional connectivity analysis

- Pros:
  - useful when we have no experimental control over the system of interest and no model of what caused the data (e.g. sleep, hallucinations, etc.)
- Cons:
  - interpretation of resulting patterns is difficult / arbitrary
  - no mechanistic insight
  - usually suboptimal for situations where we have a priori knowledge / experimental control

→ Effective connectivity



Effective connectivity

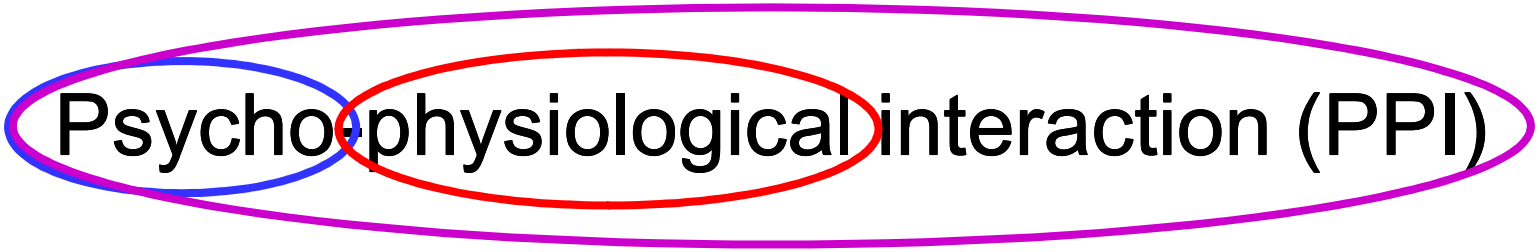
Definition: ***causal*** *(directed) influences between neurons or neuronal populations*

- *In vivo* and *in vitro* stimulation and recording
-
-
-
- Models of causal interactions among neuronal populations
  - explain *regional* effects in terms of *interregional* connectivity

Some models for computing effective connectivity from fMRI data

- Structural Equation Modelling (SEM)
  McIntosh et al. 1991, 1994; Büchel & Friston 1997; Bullmore et al. 2000
- regression models
  (e.g. psycho-physiological interactions, PPIs)
  Friston et al. 1997

- Volterra kernels
  Friston & Büchel 2000
- Time series models (e.g. MAR, Granger causality)
  Harrison et al. 2003, Goebel et al. 2003
- Dynamic Causal Modelling (DCM)
  bilinear: Friston et al. 2003; *nonlinear:* Stephan et al. 2008

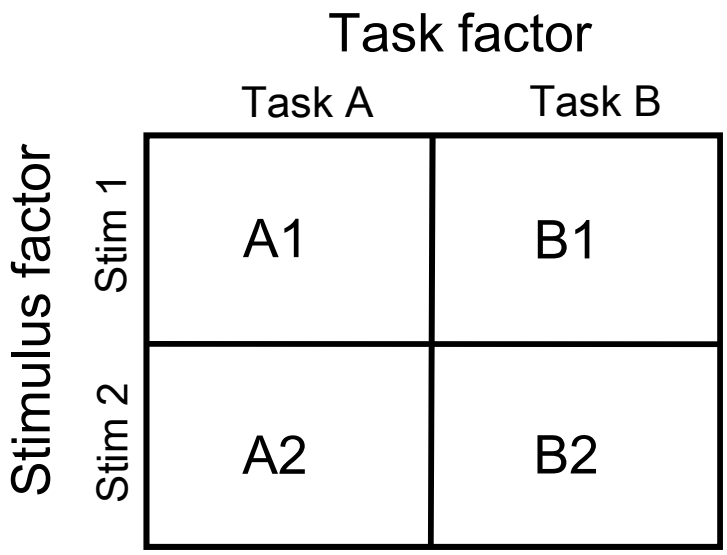


- bilinear model of how the psychological context A changes the influence of area B on area C :

$$B \times A \rightarrow C$$

- A PPI corresponds to differences in regression slopes for different contexts.

Psycho-physiological interaction (PPI)



GLM of a 2x2 factorial design:

$$y = (T_A - T_B)\,\beta_1 + (S_1 - S_2)\beta_2 + (T_A - T_B)(S_1 - S_2)\beta_3 + e$$

main effect of task

main effect of stim. type

interaction

We can replace one main effect in the GLM by the time series of an area that shows this main effect.

$$y = (T_A - T_B)\,\beta_1 + V1\beta_2 + \boxed{(T_A - T_B)\,V1\beta_3} + e$$

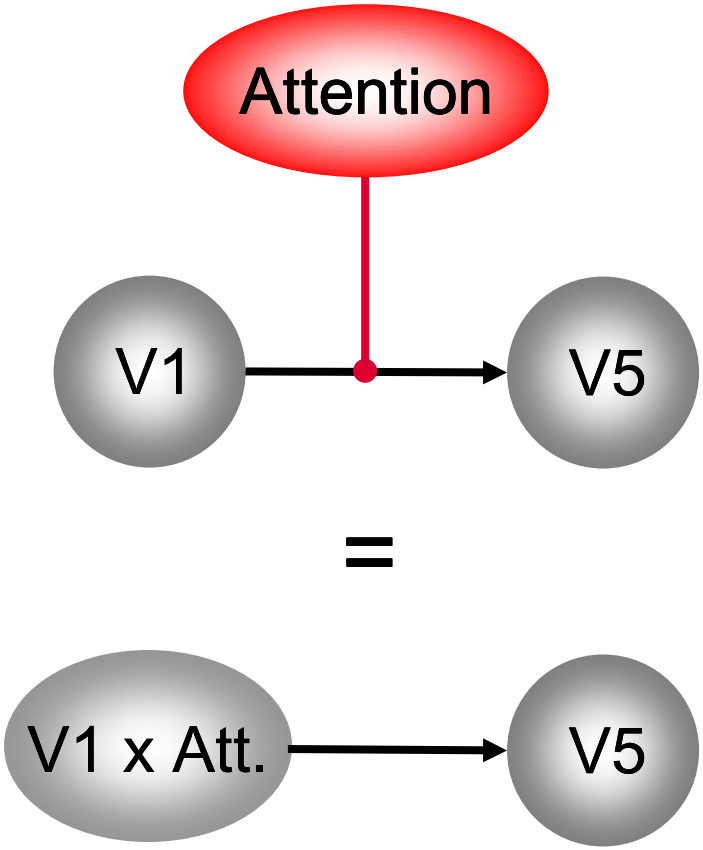
main effect of task

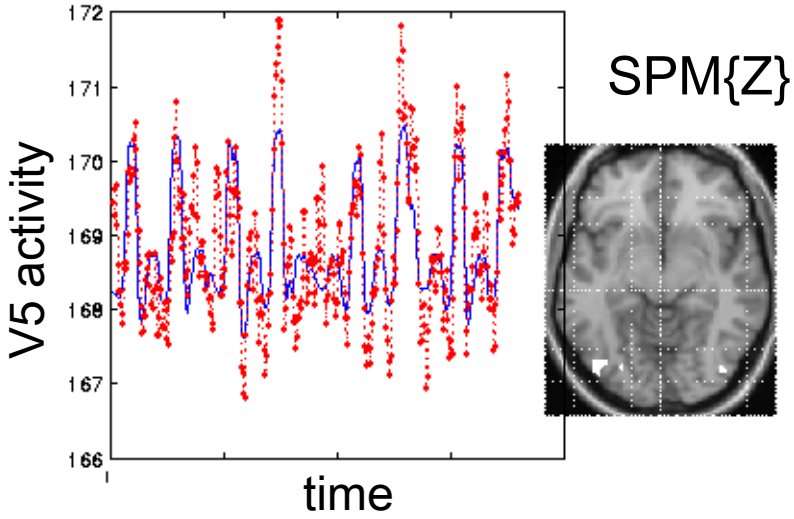
V1 time series ≈ main effect of stim. type

psycho-physiological interaction

Friston et al. 1997, *NeuroImage*

Example PPI: Attentional modulation of V1→V5





Friston et al. 1997, *NeuroImage*
Büchel & Friston 1997, *Cereb. Cortex*

Pros & Cons of PPIs

- Pros:
  - given a single source region, we can test for its context-dependent connectivity across the entire brain
  - easy to implement
- Cons:
  - only allows to model contributions from a single area
  - operates at the level of BOLD time series
  - ignores time-series properties of the data

 Dynamic Causal Models

Overview

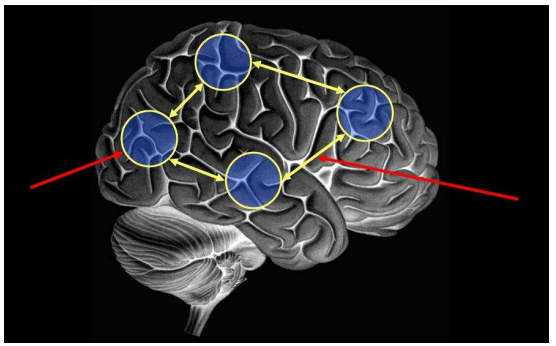
- Brain connectivity: types & definitions
- Functional connectivity
- Psycho-physiological interactions (PPI)
- Dynamic causal models (DCMs)
  - Basic idea
  - Neural level
  - Hemodynamic level
  - Parameter estimation, priors & inference
- Applications of DCM to fMRI data

Basics of Dynamic Causal Modelling

DCM allows us to look at how areas within a network interact:

Investigate functional integration & modulation of specific cortical pathways

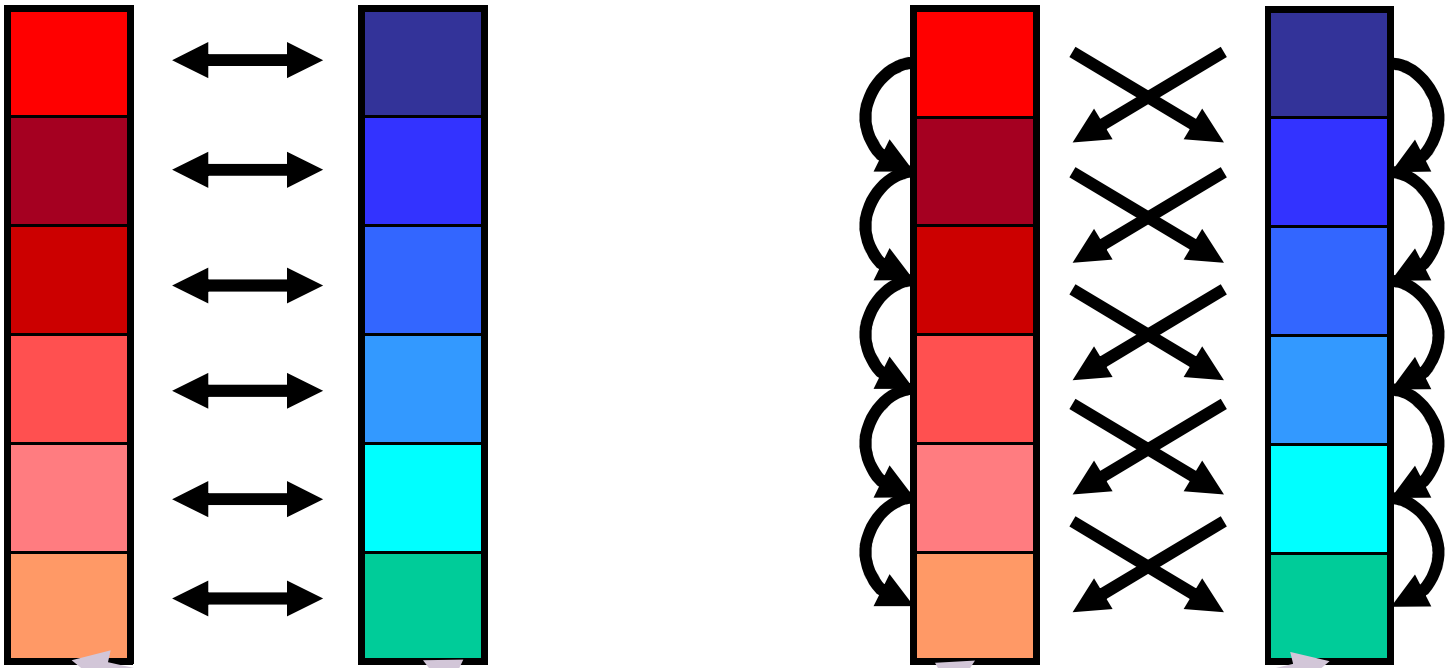
– Temporal dependency of activity within and between areas (causality)



Temporal dependence and causal relations

Seed voxel approach, PPI etc.

Dynamic *Causal* Models



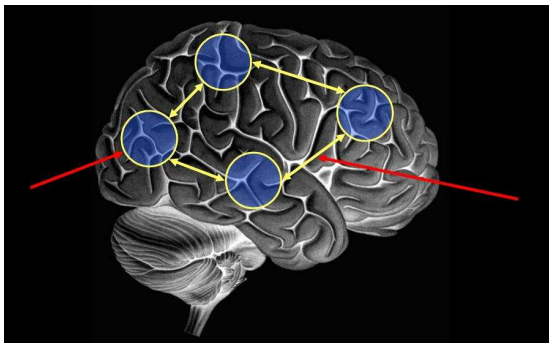
timeseries (neuronal activity)

Basics of Dynamic Causal Modelling

DCM allows us to look at how areas within a network interact:

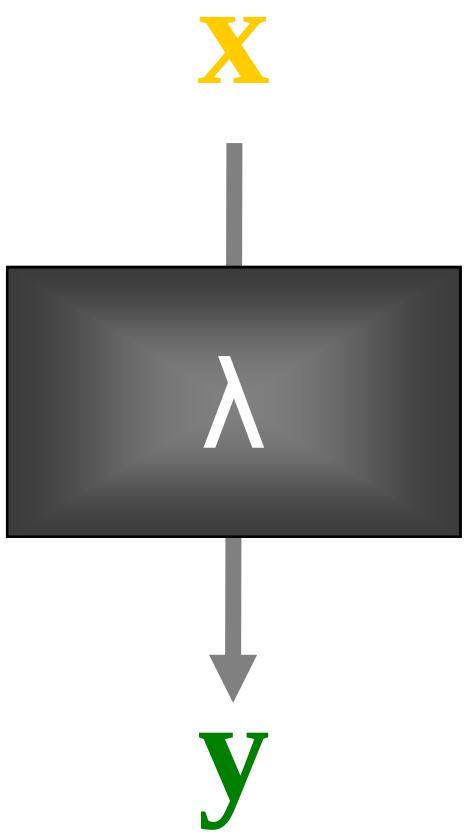
Investigate functional integration & modulation of specific cortical pathways

- Temporal dependency of activity within and between areas (causality)
- Separate neuronal activity from observed BOLD responses



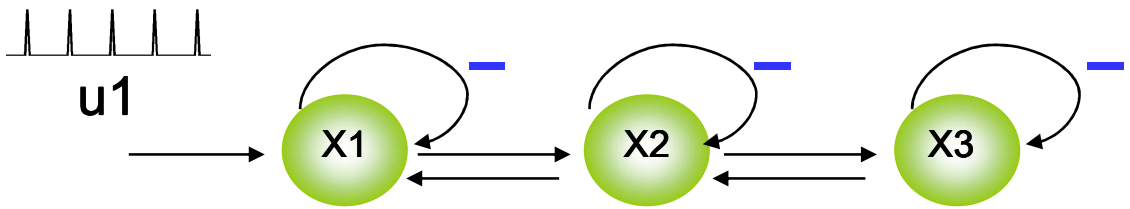
Basics of DCM: Neuronal and BOLD level

- Cognitive system is modelled at its underlying neuronal level (not directly accessible for fMRI).
- The modelled neuronal dynamics (**x**) are transformed into area-specific BOLD signals (**y**) by a hemodynamic model (**λ**).



The aim of DCM is to estimate parameters at the neuronal level such that the modelled and measured BOLD signals are maximally* similar.

DCM: Linear Model



$$\dot{x} = Ax + Cu$$

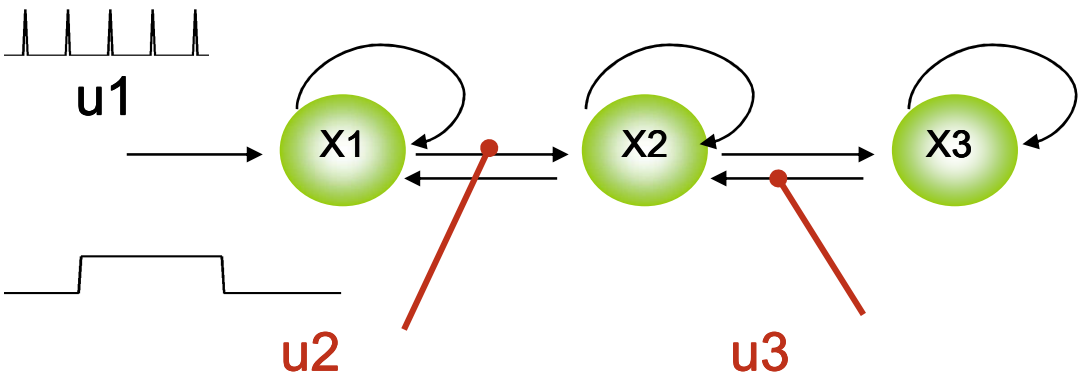
$$\theta = \{A, C\}$$

$$\dot{x}_2 = a_{21}x_1 + a_{22}x_2 + a_{23}x_3$$

state changes | effective connectivity | system state | input parameters | external inputs

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \end{bmatrix} = \begin{bmatrix} a_{11} & a_{12} & 0 \\ a_{21} & a_{22} & a_{23} \\ 0 & a_{32} & a_{33} \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix} + \begin{bmatrix} c_{11} & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} u_1 \\ u_2 \\ u_3 \end{bmatrix}$$

DCM: Bilinear Model



Neural State Equation

$$\dot{x} = \left(A + \sum_{j=1}^{m} u_j B^{(j)} \right) x + Cu$$

$$\theta = \{A, B, C\}$$

$$\dot{x}_1 = a_{11}x_1 + a_{12}x_2 + c_1u_1$$

$$\dot{x}_2 = \left(a_{21} + u_2 b_{21}^{(2)}\right)x_1 + a_{22}x_2 + \left(a_{23} + u_3 b_{23}^{(3)}\right)x_3$$

$$\dot{x}_3 = a_{32}x_2 + a_{33}x_3$$

state changes | fixed effective connectivity | modulatory effective connectivity | system state | input parameters | external inputs

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \end{bmatrix} = \left\{ \begin{bmatrix} a_{11} & a_{12} & 0 \\ a_{21} & a_{22} & a_{23} \\ 0 & a_{32} & a_{33} \end{bmatrix} + u_2 \begin{bmatrix} 0 & 0 & 0 \\ b_{21}^{(2)} & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} + u_3 \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & b_{23}^{(3)} \\ 0 & 0 & 0 \end{bmatrix} \right\} \begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix} + \begin{bmatrix} c_{11} & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} u_1 \\ u_2 \\ u_3 \end{bmatrix}$$

Basics of DCM:
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- Cognitive system is modelled at its underlying neuronal level (not directly accessible for fMRI).

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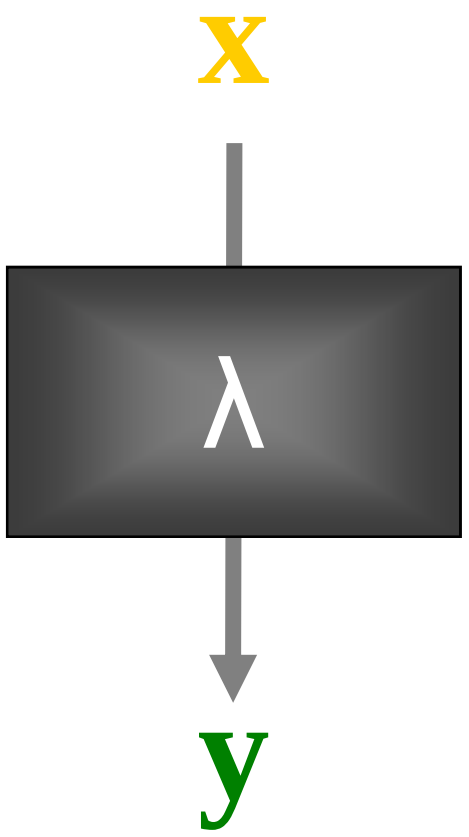


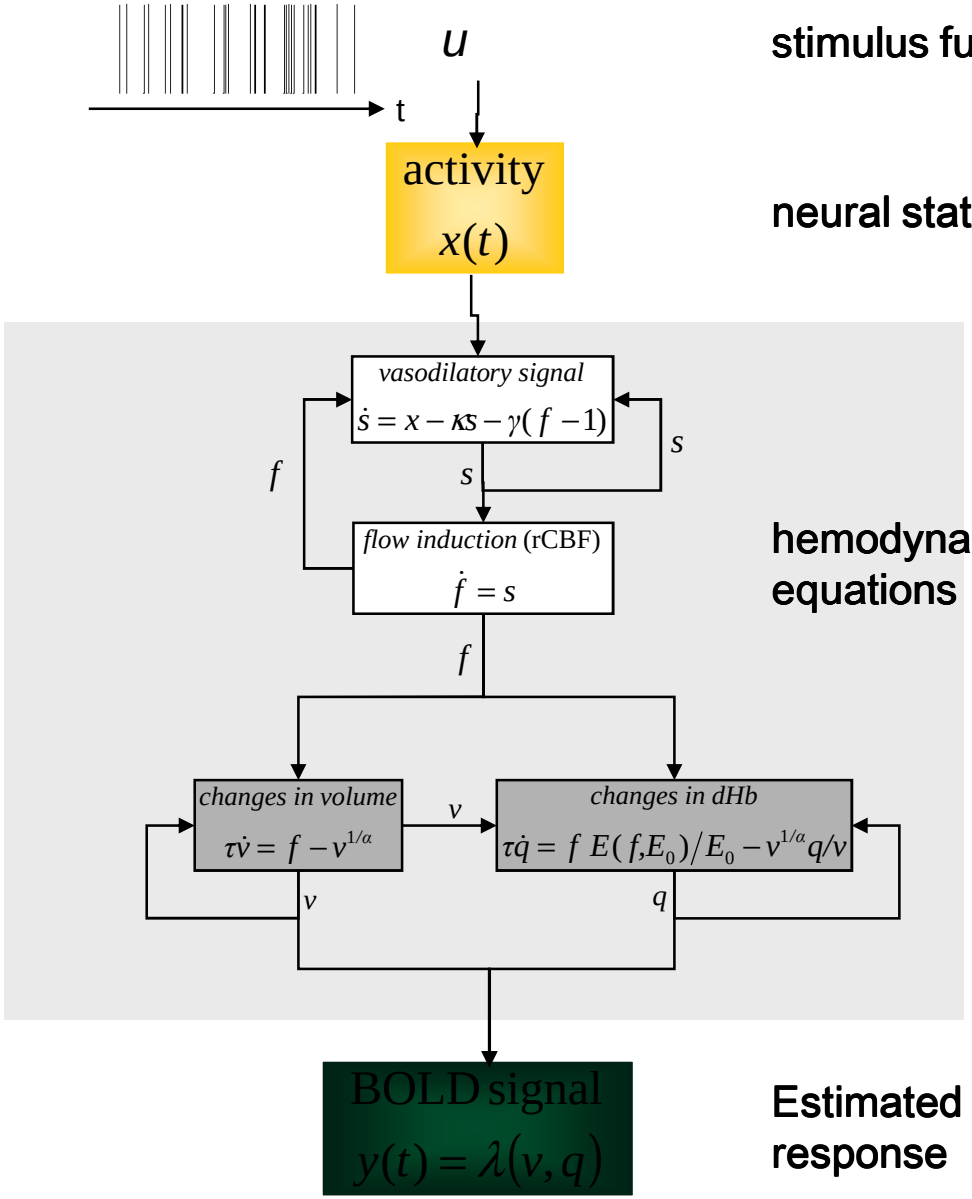
The hemodynamic model

- 6 hemodynamic parameters:

$$\theta^h = \{\kappa, \gamma, \tau, \alpha, \rho, \varepsilon\}$$

important for model fitting, but of no interest for statistical inference

- Computed separately for each area → region-specific HRFs!



stimulus functions

neural state equation

hemodynamic state equations

Estimated BOLD response

Friston et al. 2000, *NeuroImage*
Stephan et al. 2007, *NeuroImage*

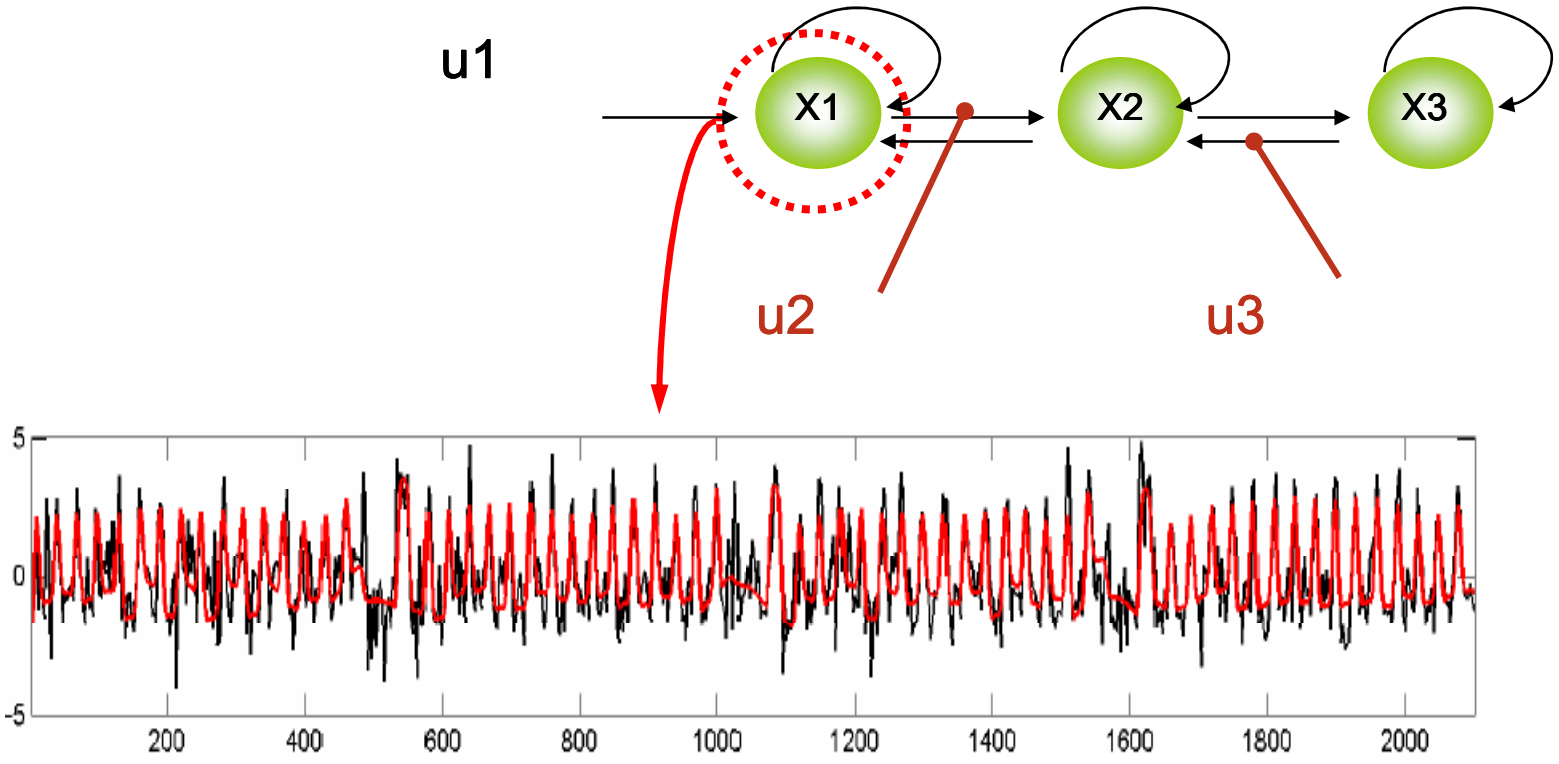
Measured vs Modelled BOLD signal

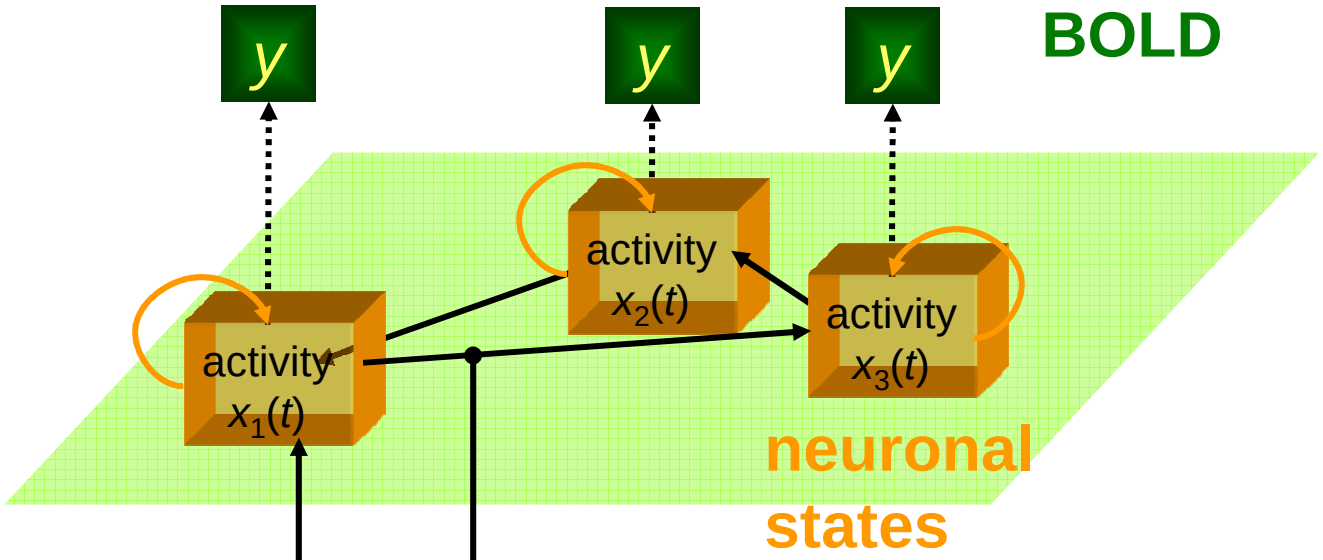
Recap

The aim of DCM is to estimate

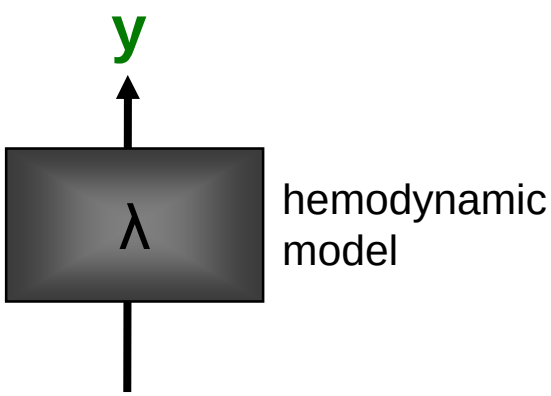
- neural parameters {A, B, C}
- hemodynamic parameters

such that the modelled and **measured** BOLD signals are maximally similar.



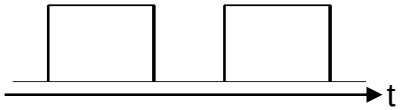


BOLD

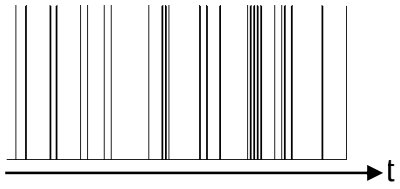


integration

modulatory
input $u_2(t)$



driving
input $u_1(t)$



Neural state equation $\dot{x} = (A + \sum u_j B^{(j)})x + Cu$

endogenous connectivity → $A = \frac{\partial \dot{x}}{\partial x}$

modulation of connectivity → $B^{(j)} = \frac{\partial}{\partial u_j}\frac{\partial \dot{x}}{\partial x}$

direct inputs → $C = \frac{\partial \dot{x}}{\partial u}$

Stephan & Friston (2007),
Handbook of Brain Connectivity

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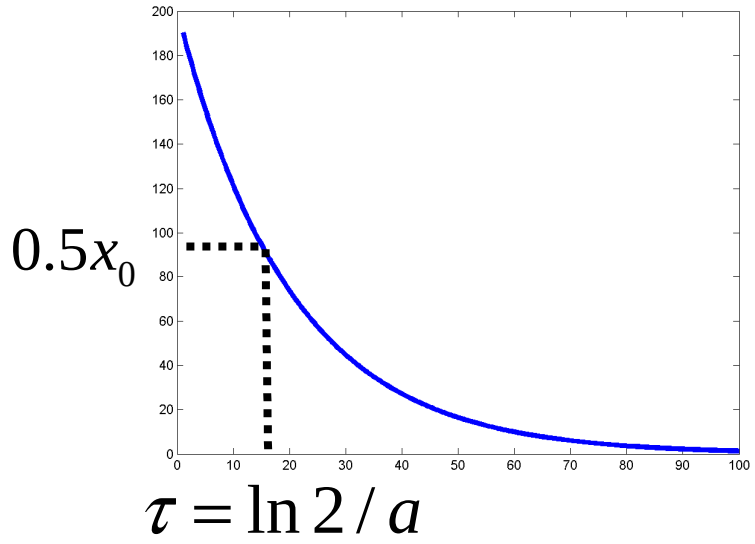
DCM parameters = rate constants

Integration of a first-order linear differential equation gives an exponential function:

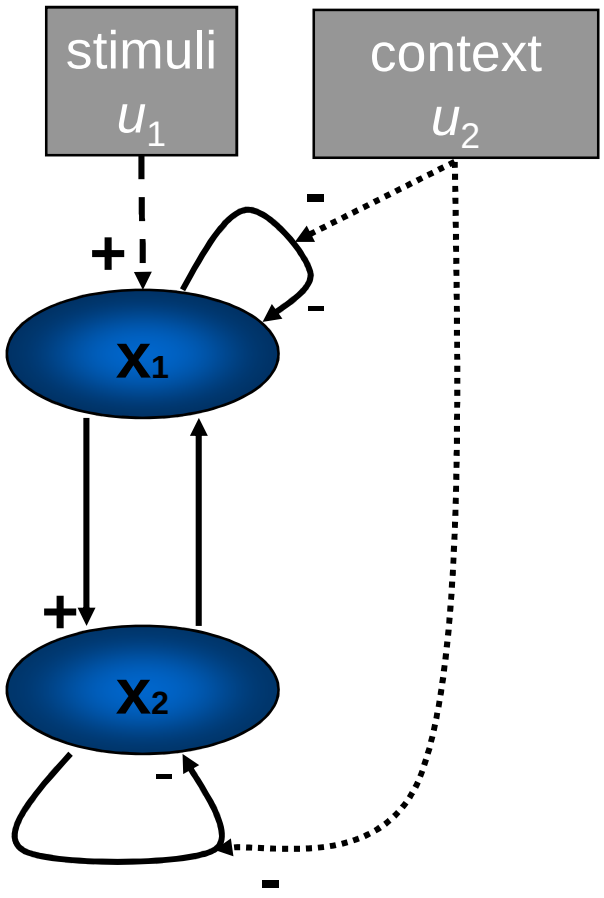
$$\frac{dx}{dt} = ax \longrightarrow x(t) = x_0 \exp(at)$$

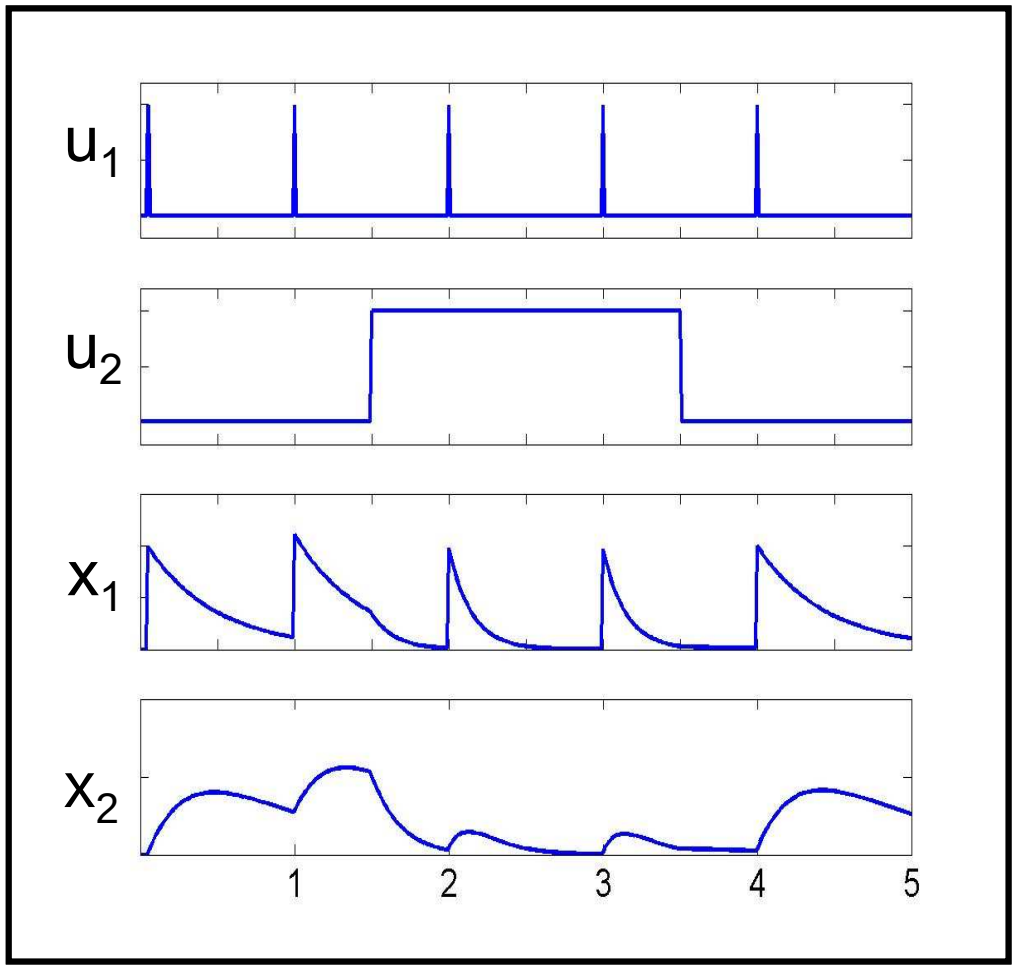
The coupling parameter a determines the half life of $x(t)$, and thus describes the speed of the exponential change



If A→B is 0.10 s^{-1} this means that, per unit time, the increase in activity in B corresponds to 10% of the activity in A

Example: context-dependent decay

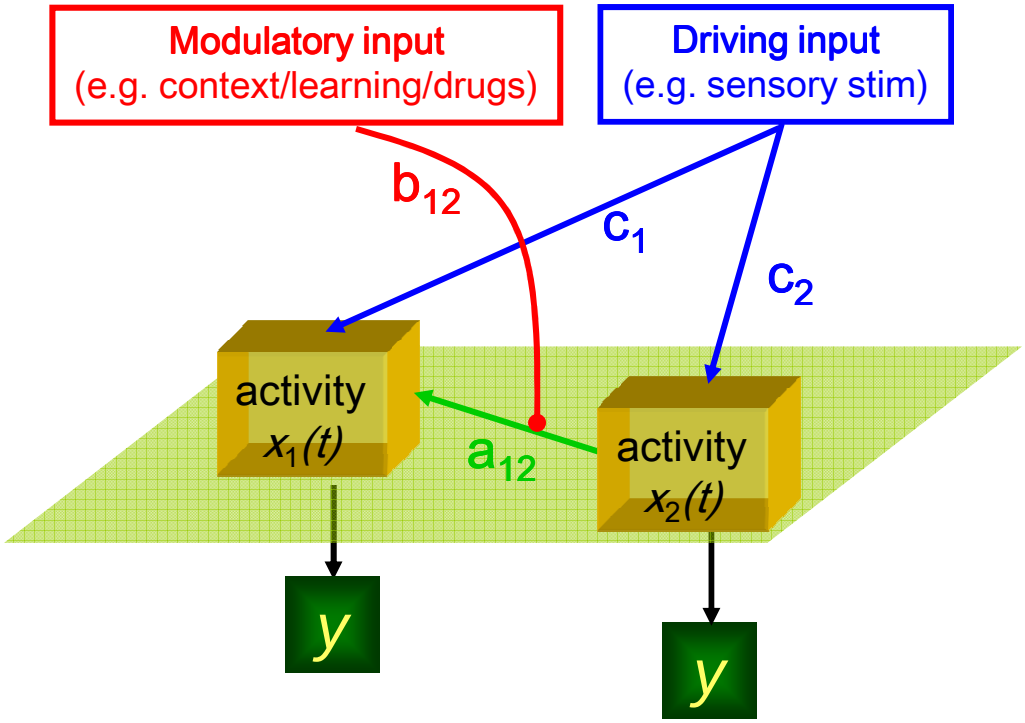




Penny, Stephan, Mechelli, Friston
NeuroImage (2004)

Conceptual overview

Neuronal states



BOLD Response

Parameters are optimised so that the predicted matches the measured BOLD response

→How confident are we about these parameters?

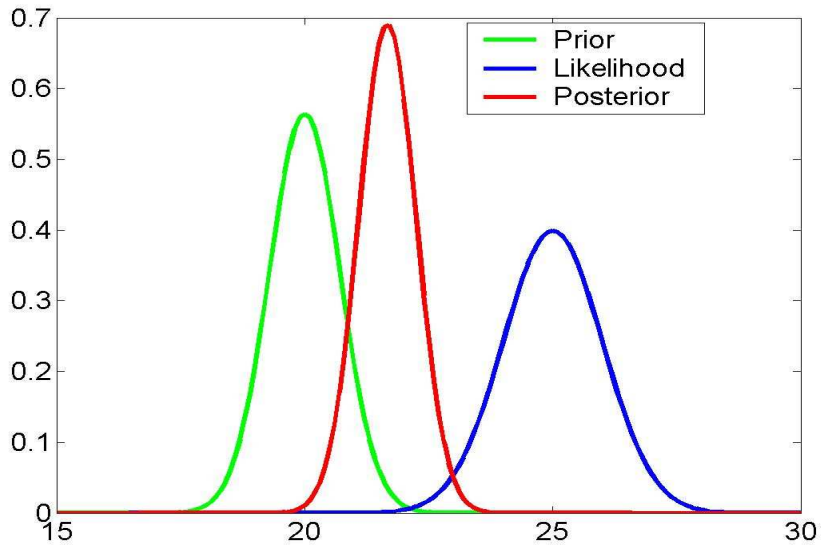
Bayesian statistics

Express our **prior knowledge** or "belief" about parameters of the model

new data prior knowledge

$$p(\theta \mid y) \propto p(y \mid \theta)\, p(\theta)$$

posterior ∝ likelihood • prior



Parameters governing

- Hemodynamics in a single region
- Neuronal interactions

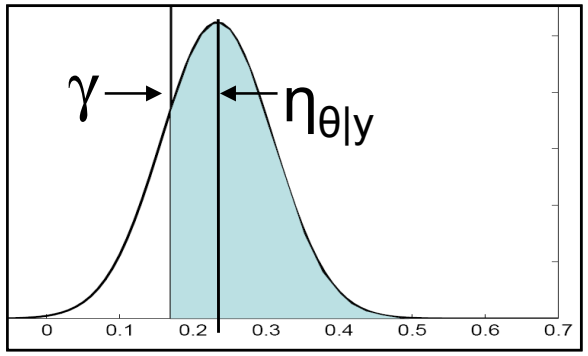
Constraints (priors) on

- Hemodynamic parameters
  - empirical
- Self connections
  -principled
- Other connections
  - shrinkage

Inference about DCM parameters

Bayesian single subject analysis

- The model parameters are distributions that have a mean $\eta_{\theta|y}$ and covariance $C_{\theta|y}$.
  - Use of the cumulative normal distribution to test the probability that a certain parameter is above a chosen threshold γ:



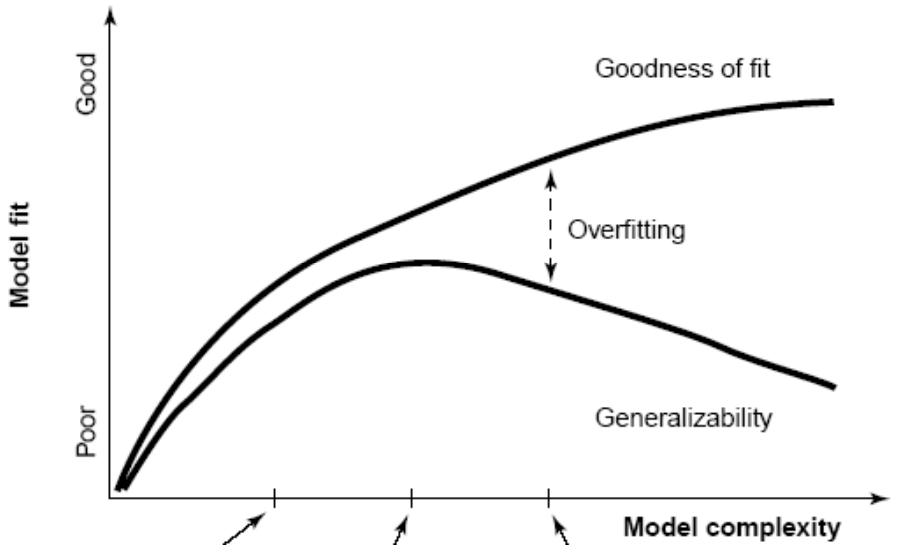
Classical frequentist test across Ss

- Test summary statistic: mean $\eta_{\theta|y}$
  - One-sample t-test: Parameter > 0?
  - Paired t-test:
    parameter 1 > parameter 2?
  - rmANOVA: e.g. in case of multiple sessions per subject

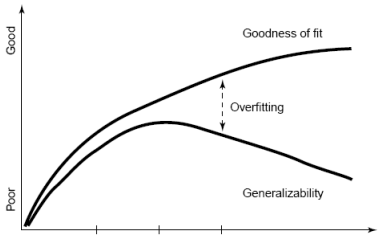
Bayesian model averaging

Inference about model space

Model evidence: The optimal balance of fit and complexity



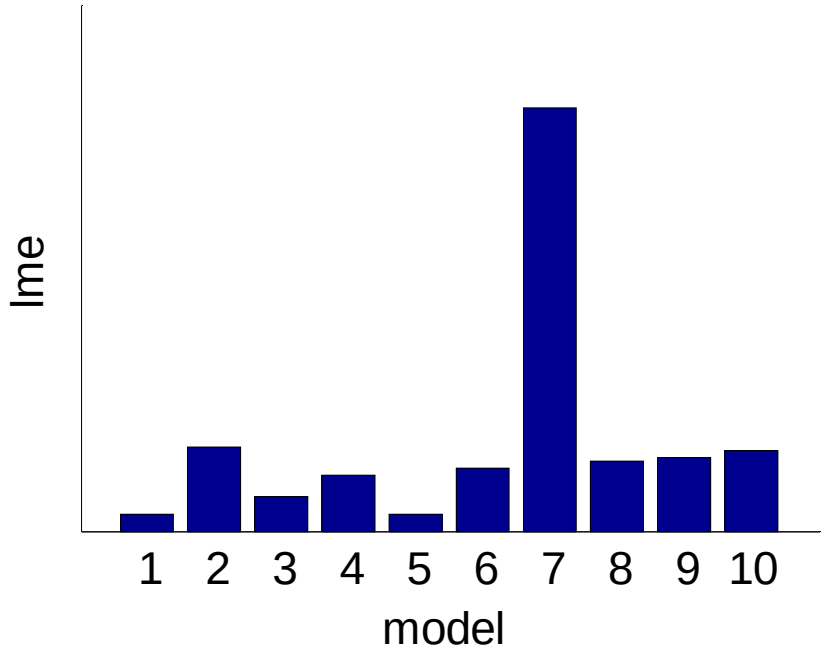
Inference about model space



Model evidence: The optimal balance of fit and complexity

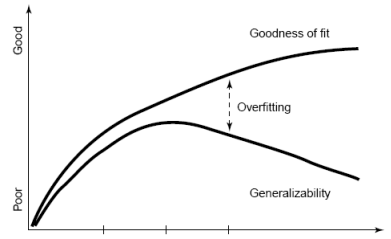
Comparing models

- Which is the best model?



Inference about model space

Model evidence: The optimal balance of fit and complexity



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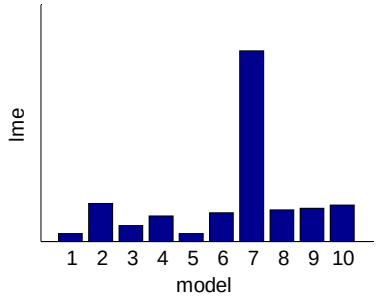
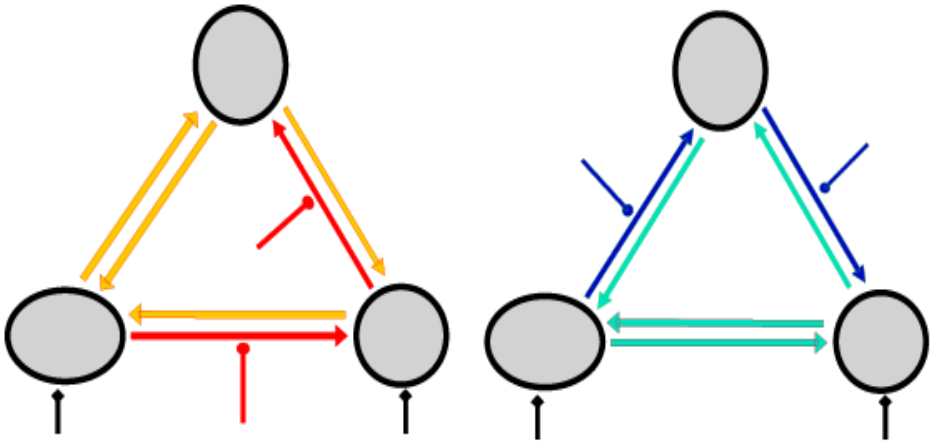


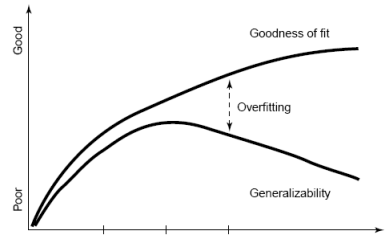
Comparing families of models

- What type of model is best?
  - Feedforward vs feedback
  - Parallel vs sequential processing
  - With or without modulation



Inference about model space

Model evidence: The optimal balance of fit and complexity



Comparing models

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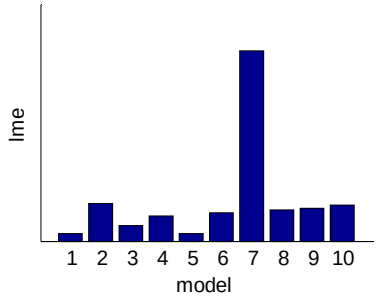

Comparing families of models

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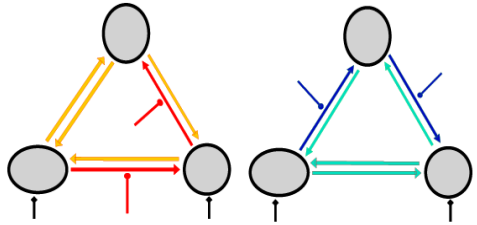
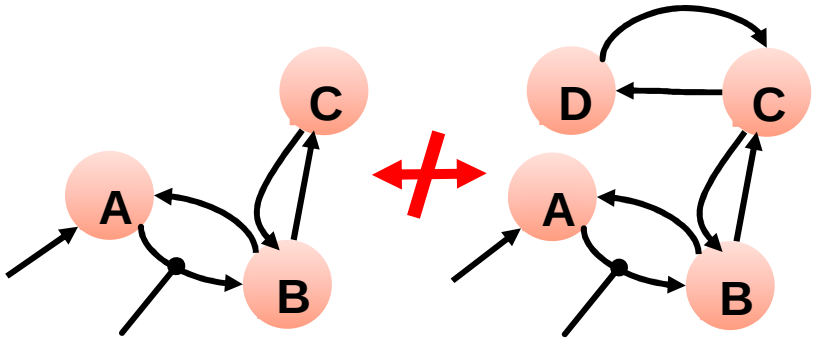


Only compare models with the same data



Overview

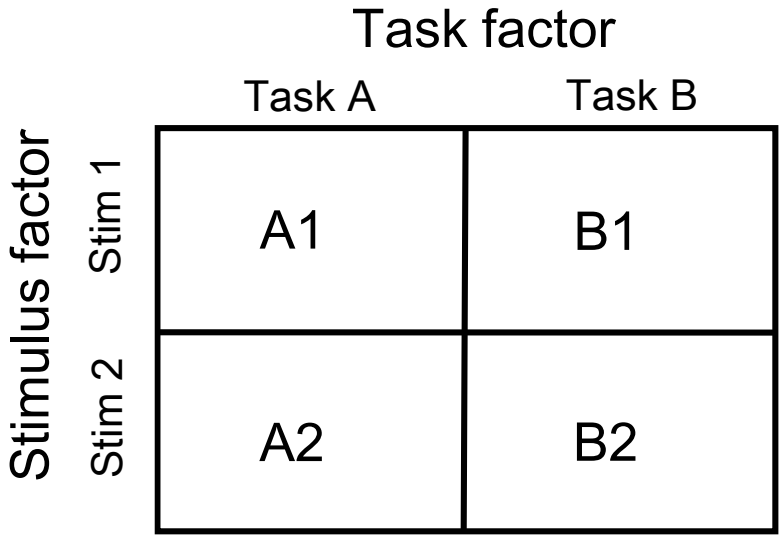
- Brain connectivity: types & definitions
- Functional connectivity
- Psycho-physiological interactions (PPI)
- Dynamic causal models (DCMs)
- Applications of DCM to fMRI data
  - Design of experiments and models
  - Generating data

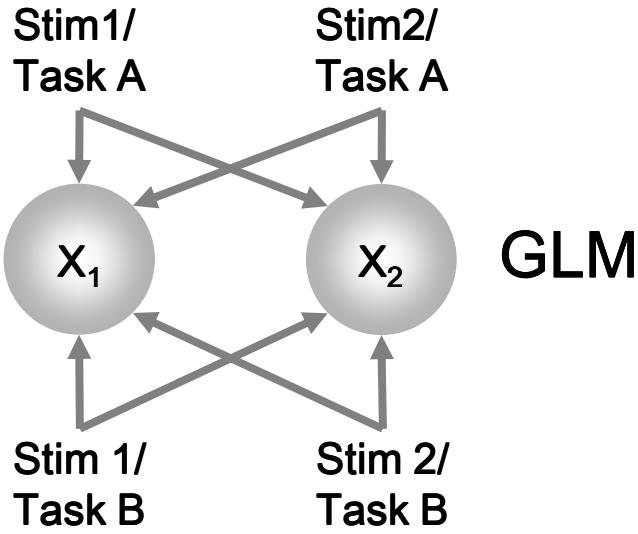
Planning a DCM-compatible study

- Suitable experimental design:
  - any design that is suitable for a GLM
  - preferably multi-factorial (e.g. 2 x 2)
    - e.g. one factor that varies the driving (sensory) input
    - and one factor that varies the contextual input

- Hypothesis and model:
  - Define specific *a priori* hypothesis
  - Which parameters are relevant to test this hypothesis?
  - If you want to verify that intended model is suitable to test this hypothesis, then use simulations
  - Define criteria for inference
  - What are the alternative models to test?

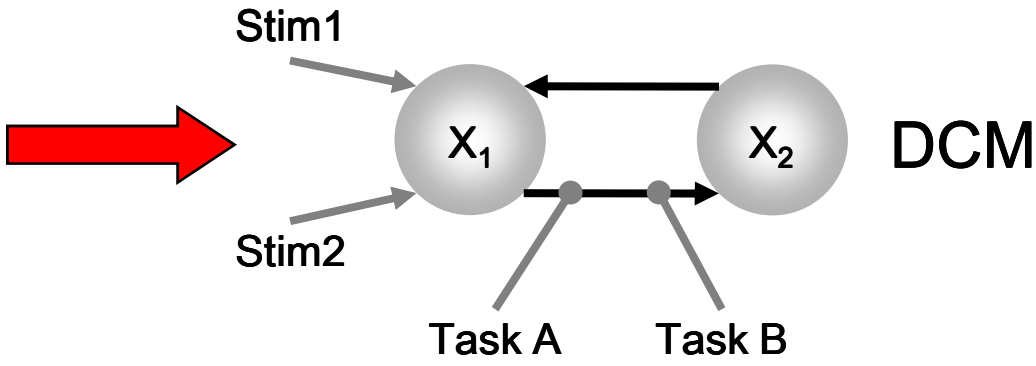
Multifactorial design: explaining interactions with DCM



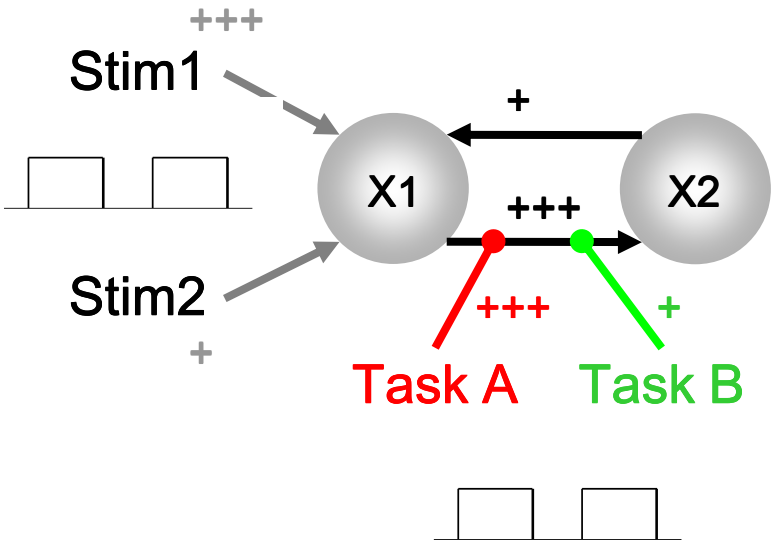


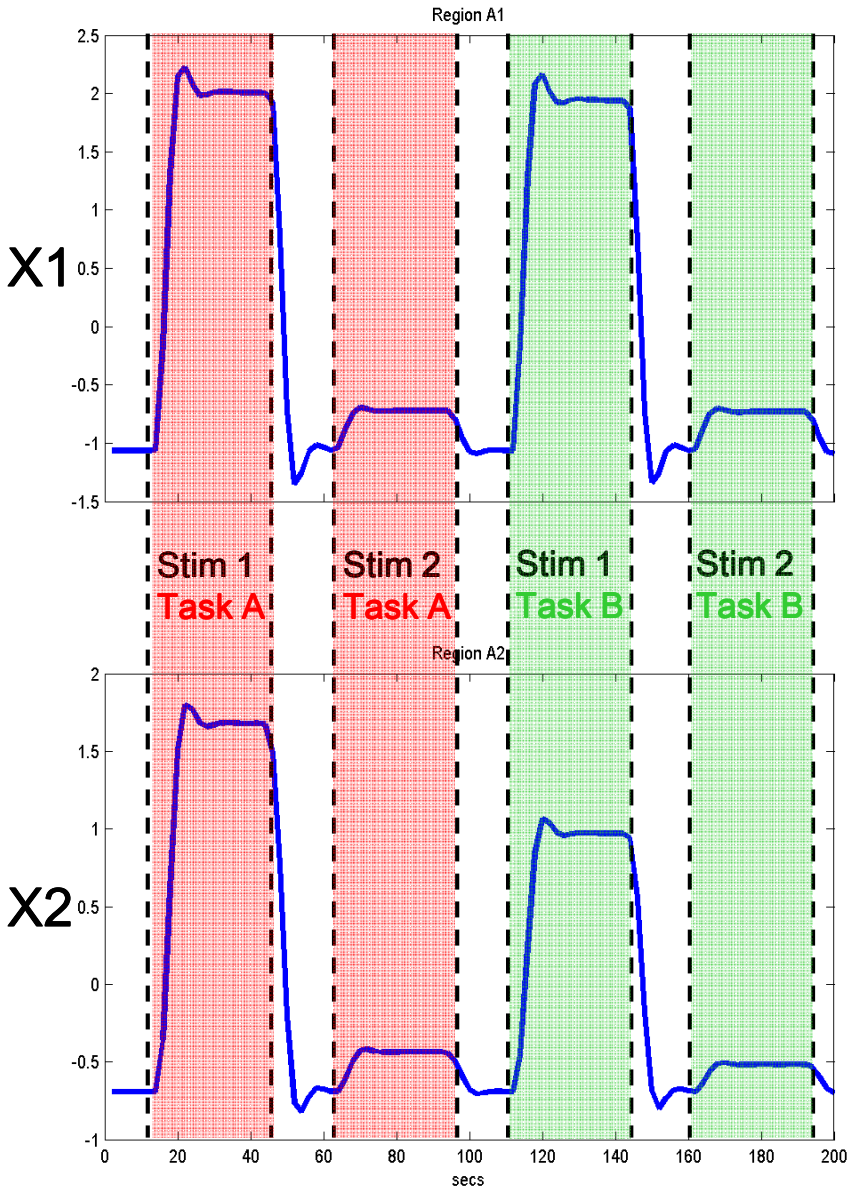
Let's assume that an SPM analysis shows a main effect of stimulus in X_1 and a stimulus × task interaction in X_2.

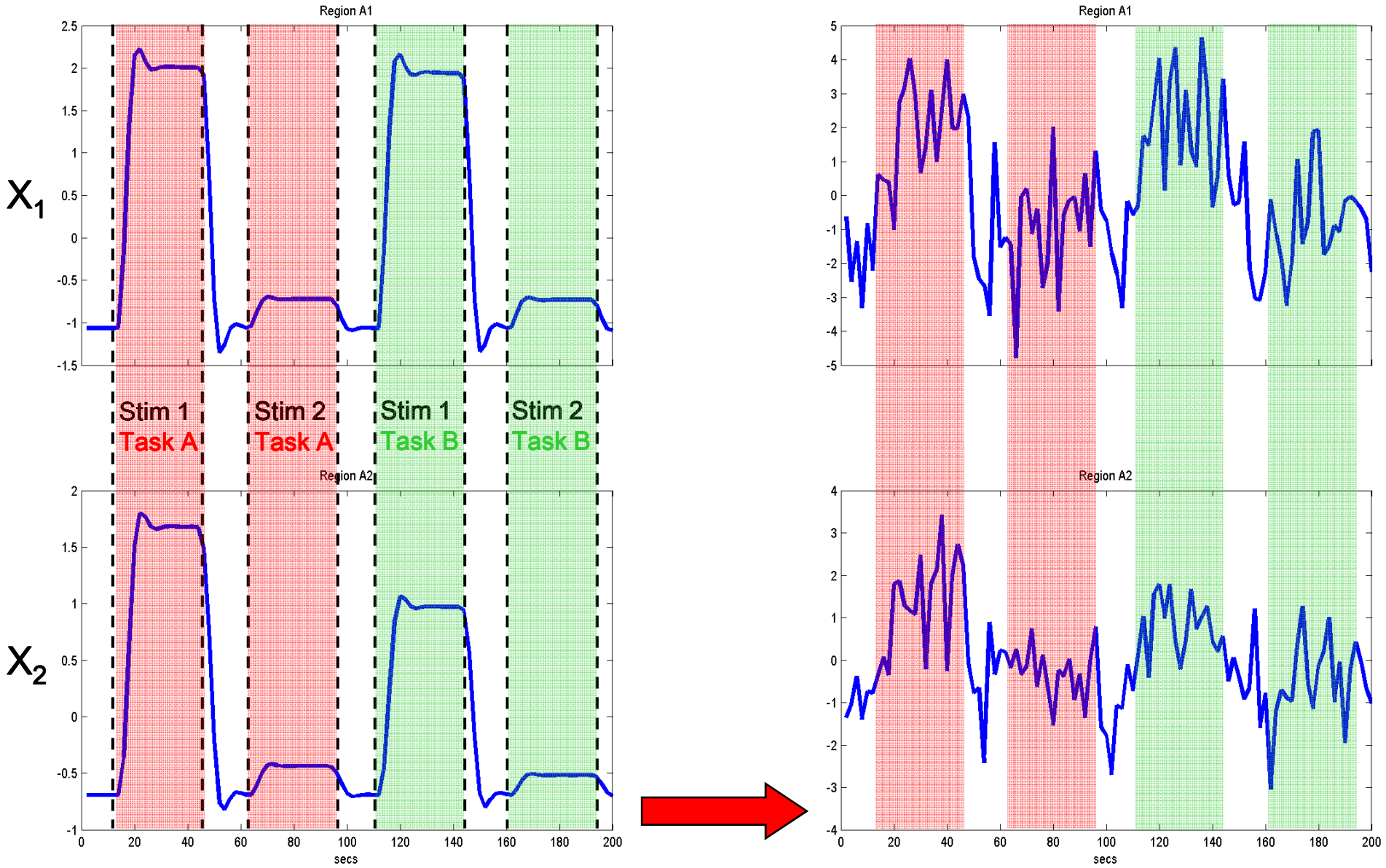
How do we model this using DCM?



Simulated data

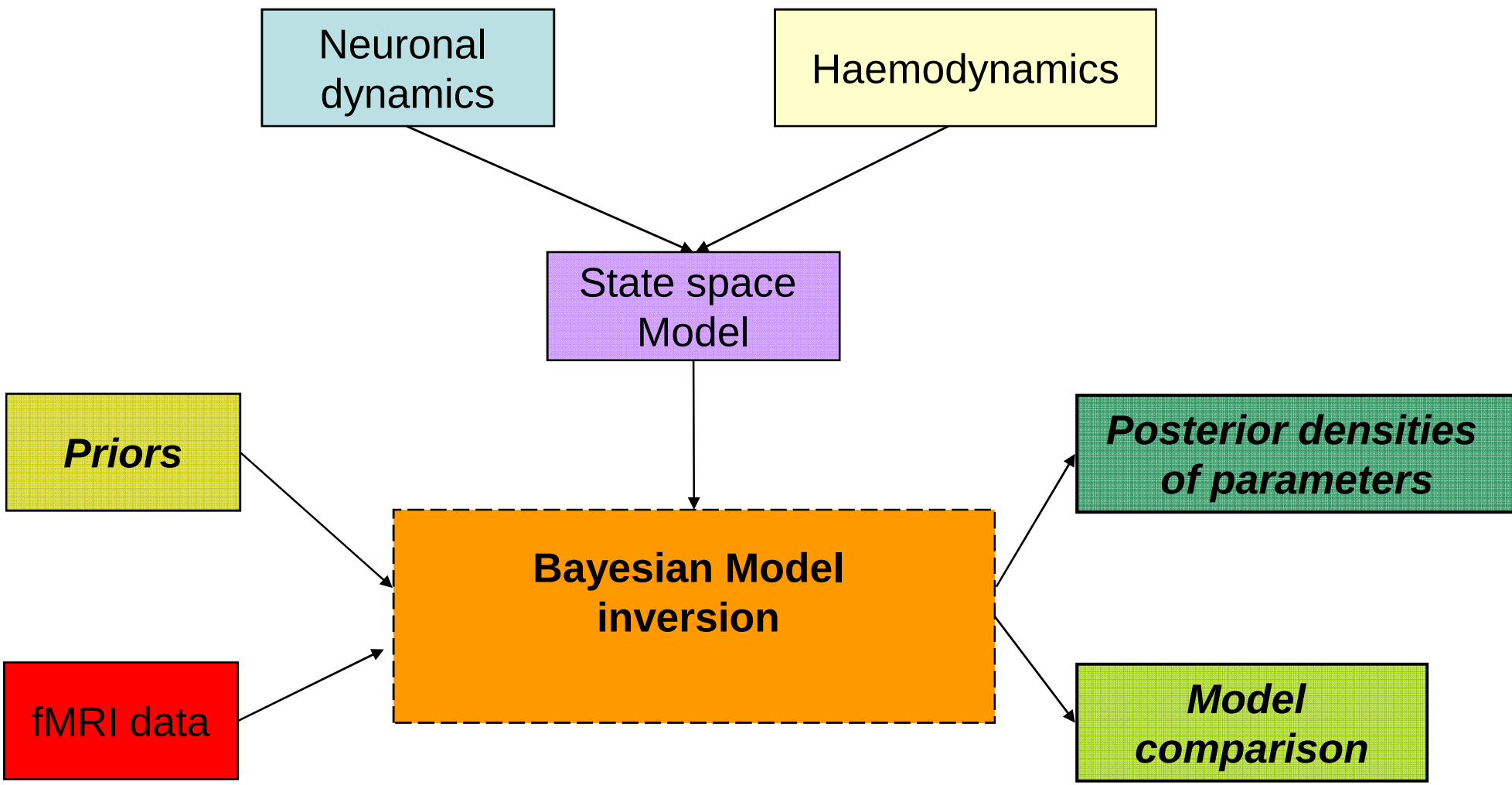






plus added noise (SNR=1)

DCM roadmap


Neuronal dynamics
Haemodynamics
State space Model
Priors
fMRI data
Bayesian Model inversion
Posterior densities of parameters
Model comparison

So, DCM….

- enables one to **infer hidden neuronal processes** from fMRI data
- tries to model the same phenomena as a GLM
  - **explaining experimentally controlled variance** in local responses
  - based on connectivity and its modulation
- allows one to **test mechanistic hypotheses** about observed effects
- is informed by anatomical and physiological principles.
- uses a **Bayesian framework** to estimate model parameters
- is a generic approach to modeling experimentally perturbed dynamic systems.
  - provides an observation model for neuroimaging data, e.g. fMRI, M/EEG
  - DCM is **not model or modality specific** (Models will change and the method extended to other modalities e.g. ERPs)

Some useful references

- **The first DCM paper:** Dynamic Causal Modelling (2003). Friston et al. *NeuroImage* 19:1273-1302.
- **Physiological validation of DCM for fMRI:** Identifying neural drivers with functional MRI: an electrophysiological validation (2008). David et al. *PLoS Biol.* 6 2683–2697
- **Hemodynamic model:** Comparing hemodynamic models with DCM (2007). Stephan et al. *NeuroImage* 38:387-401
- **Nonlinear DCMs:**Nonlinear Dynamic Causal Models for FMRI (2008). Stephan et al. *NeuroImage* 42:649-662
- **Two-state model:** Dynamic causal modelling for fMRI: A two-state model (2008). Marreiros et al. *NeuroImage* 39:269-278
- **Group Bayesian model comparison:** Bayesian model selection for group studies (2009). Stephan et al. *NeuroImage* 46:1004-10174
- **10 Simple Rules for DCM** (2010). Stephan et al. *NeuroImage 52*.

Thank you

Time to do a DCM!

Dynamic Causal Modelling
PRACTICAL

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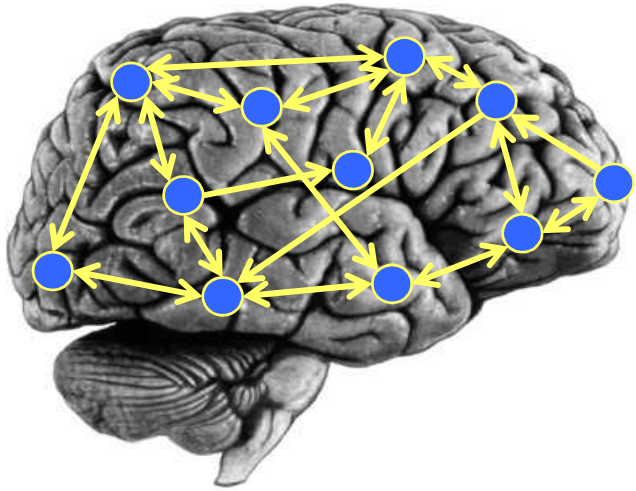


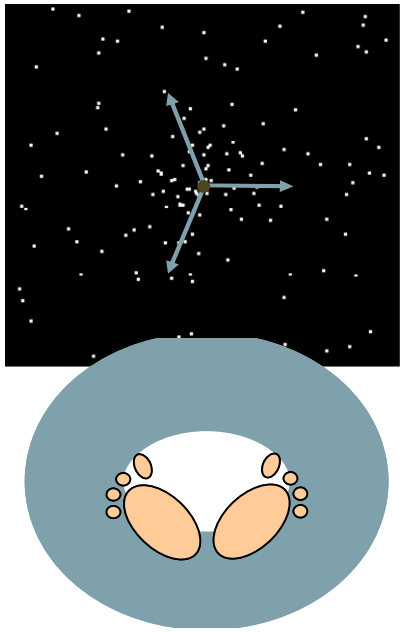
Hanneke den Ouden

Donders Centre for Cognitive Neuroimaging
Radboud University Nijmegen

SPM Course, London
13-15 May 2010

Attention to Motion in the visual system

Paradigm



Stimuli 250 radially moving dots at 4.7 degrees/s

Pre-Scanning

5 x 30s trials with 5 speed changes (reducing to 1%)

Task - detect change in radial velocity

Scanning (no speed changes)

F A F N F A F N S ….

F - fixation

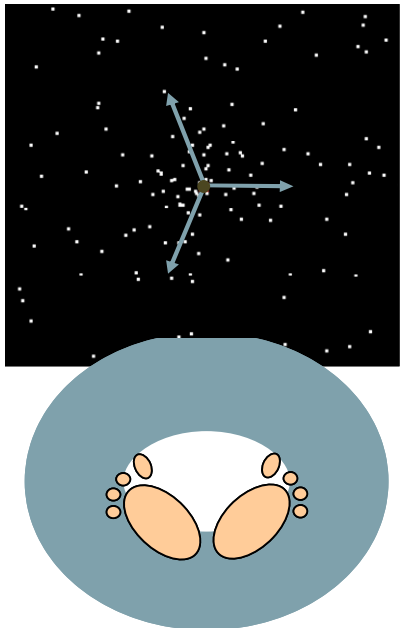
S - observe static dots	+ photic
N - observe moving dots	+ motion
A - attend moving dots	+ attention

Parameters

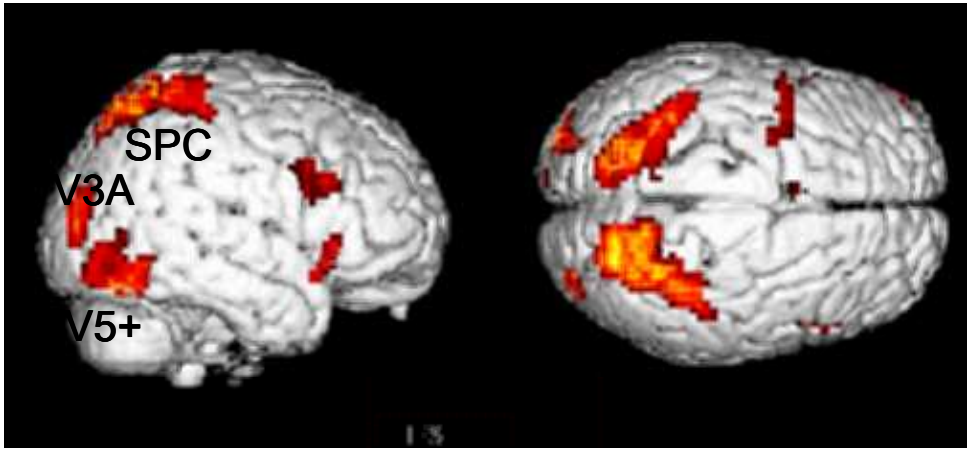
- blocks of 10 scans
- 360 scans total
- TR = 3.22 seconds

Attention to Motion in the visual system

Paradigm



Results

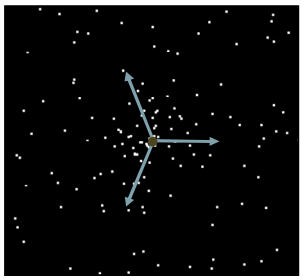


Attention – No attention

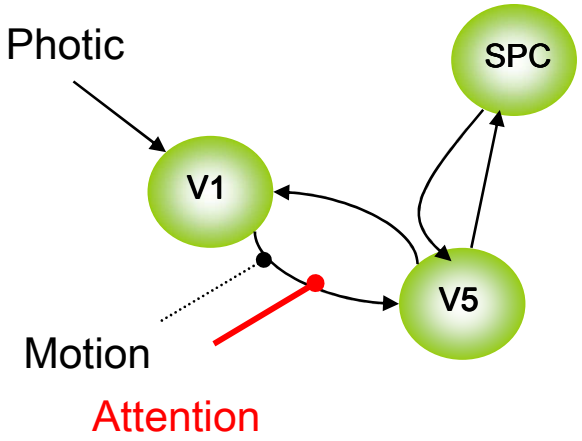
Büchel & Friston 1997, Cereb. Cortex
Büchel et al. 1998, Brain

- fixation only
- observe static dots + photic → V1
- observe moving dots + motion → V5
- task on moving dots + attention → V5 + parietal cortex

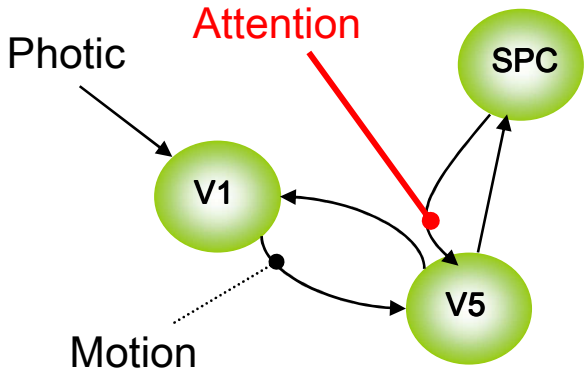
DCM: comparison of 2 models



Model 1
attentional modulation
of V1→V5: forward



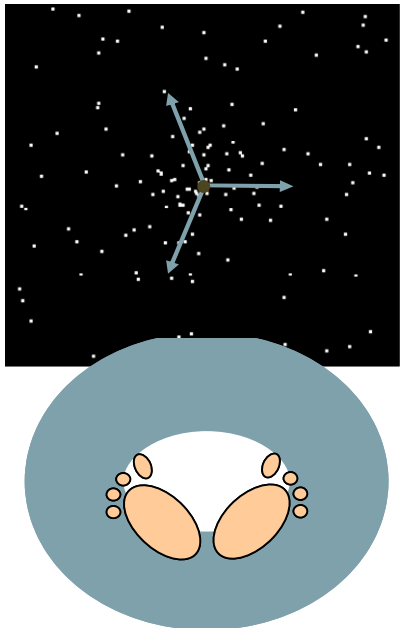
Model 2
attentional modulation
of SPC→V5: backward



Bayesian model selection: Which model is optimal?

Attention to Motion in the visual system

Paradigm



Ingredients for a DCM

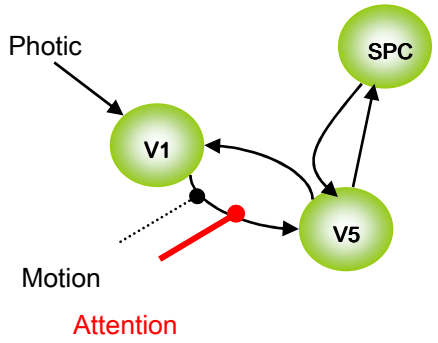
Specific hypothesis/question

Model: based on hypothesis

Timeseries: from the SPM

Inputs: from design matrix

Model 1
attentional modulation
of V1→V5: forward



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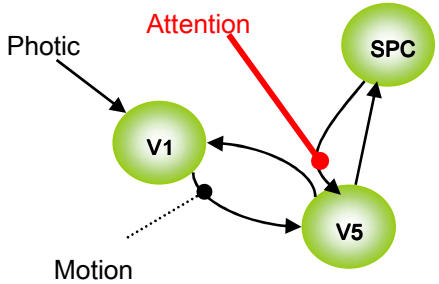
attentional modulation
of SPC→V5: backward



Attention to Motion in the visual system

DCM – GUI basic steps

1 – Extract the time series (from all regions of interest)

2 – Specify the model

3 – Estimate the model

4 – Review the estimated model

5 – Repeat steps 2 and 3 for all models in model space

6 – Compare models