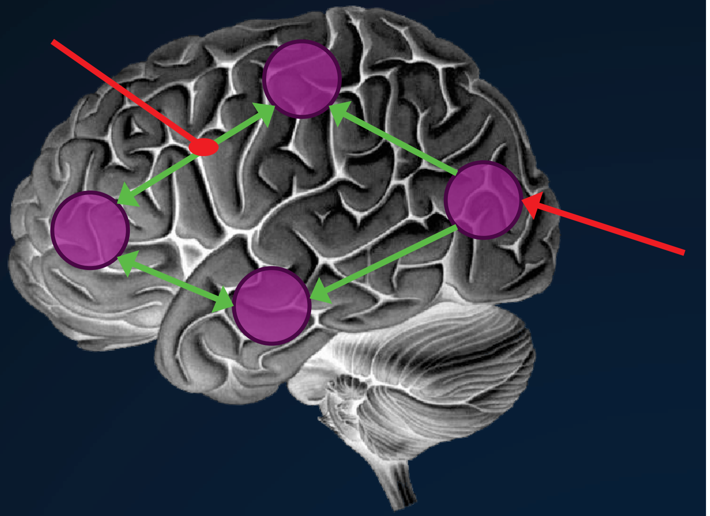
Effective Connectivity & the basics of Dynamic Causal Modelling

Hanneke den Ouden

Center for Neural Science
New York University

Donders Centre for Cognitive Neuroimaging
Radboud University Nijmegen



NYU/CNS
Center for Neural Science

Donders Institute
for Brain, Cognition and Behaviour

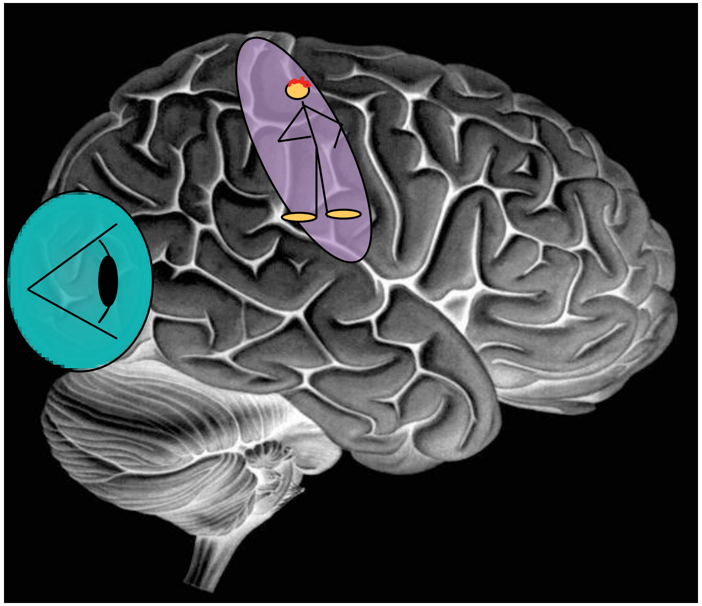
UCL

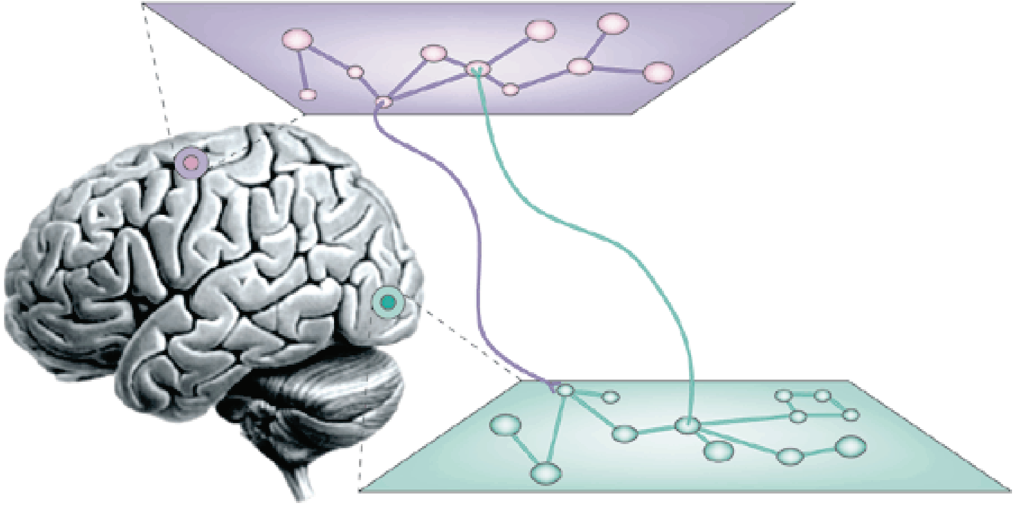
SPM for fMRI beginners, FIL, UCL, October 18-20

Principles of organisation

Functional Specialisation

Functional Integration





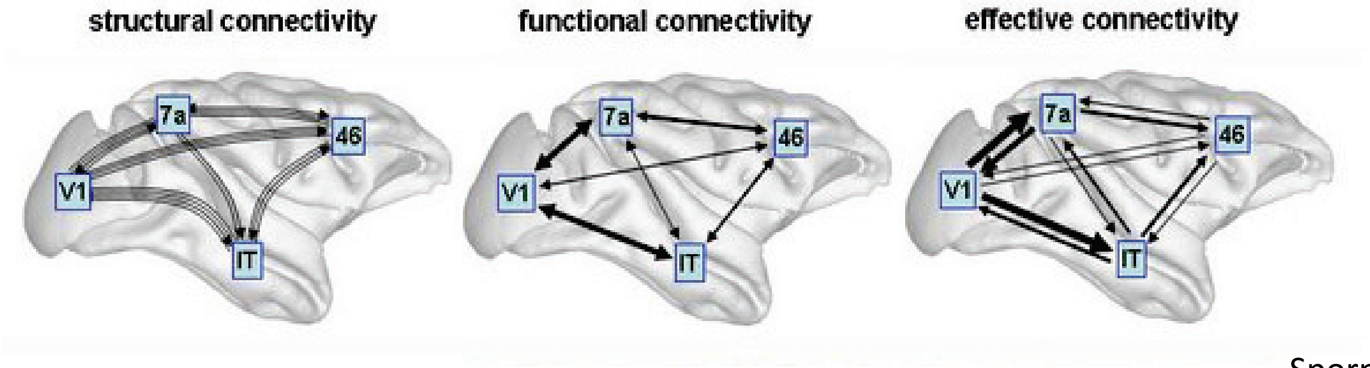
Overview

Brain Connectivity: types & definitions

Dynamic Causal Modelling – in theory

Dynamic Causal Modelling – in practice

Structural, functional & effective connectivity



Sporns 2007, *Scholarpedia*

- **anatomical/structural connectivity**

  presence of axonal connections

- **functional connectivity**

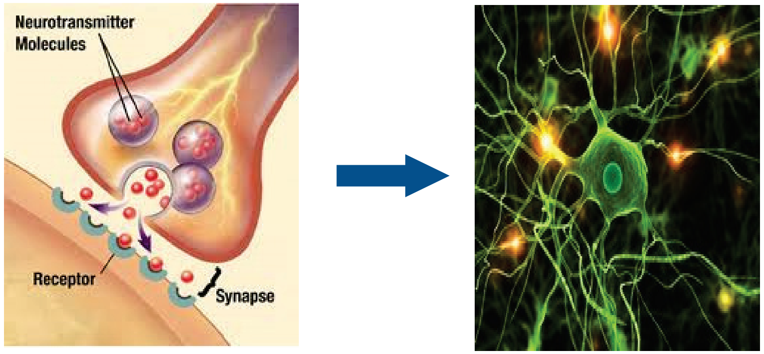
  statistical dependencies between regional time series

- **effective connectivity**

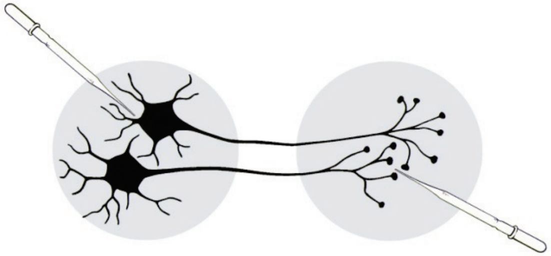
  causal (directed) influences between neurons or neuronal populations

Anatomical connectivity

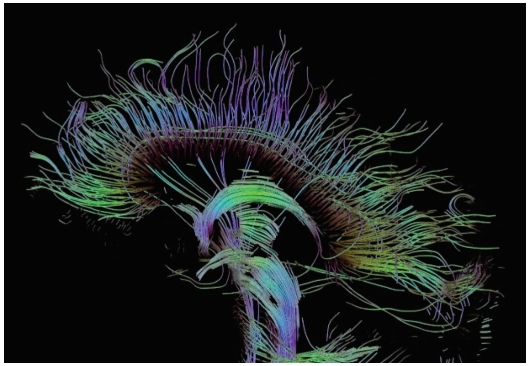
Presence of axonal connections



- neuronal communication via synaptic contacts

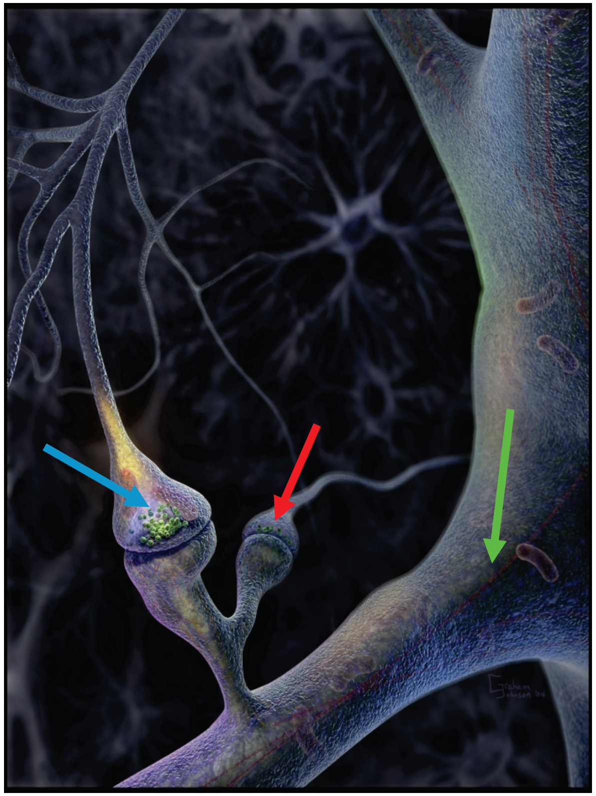


- Measured with
  - tracing techniques
  - diffusion tensor imaging (DTI)



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

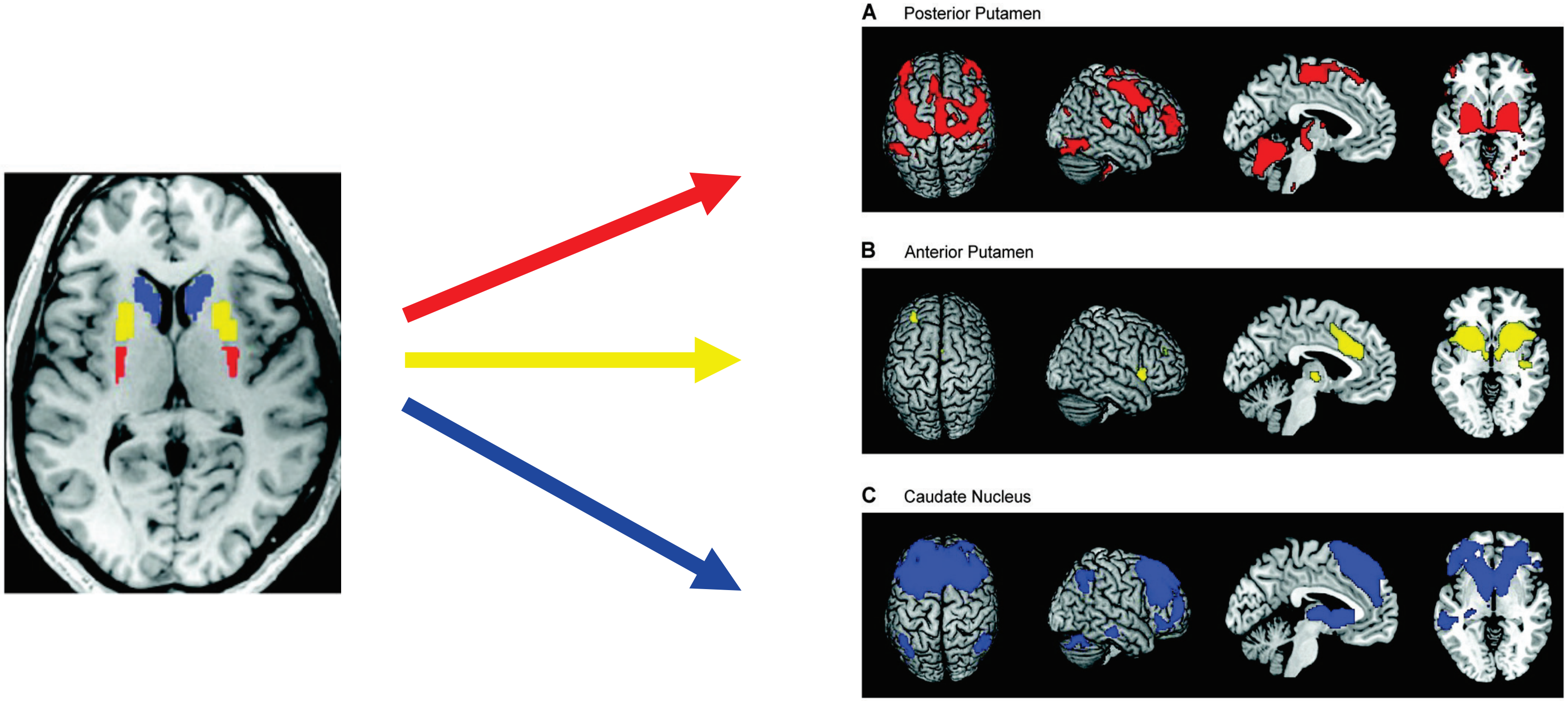
Functional Connectivity

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

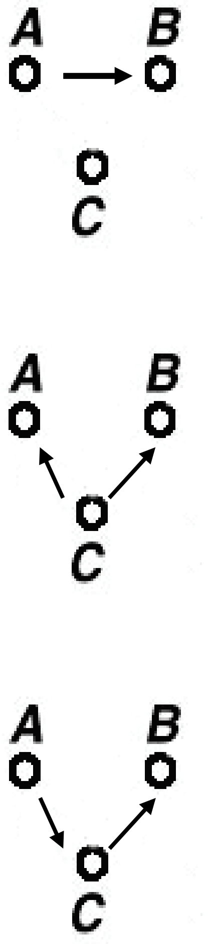


Helmich R C et al. Cereb. Cortex 2009

Functional Connectivity

- Pro
  - 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.)
- Con
  - interpretation of resulting patterns is difficult / arbitrary
  - no mechanistic insight
  - usually suboptimal for situations where we have a priori knowledge / experimental control

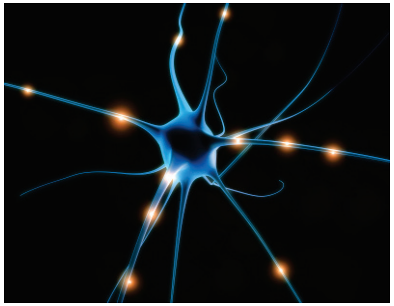
Effective Connectivity



Effective Connectivity

Causal (directed) influences between neurons /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

Models for computing effective connectivity in 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

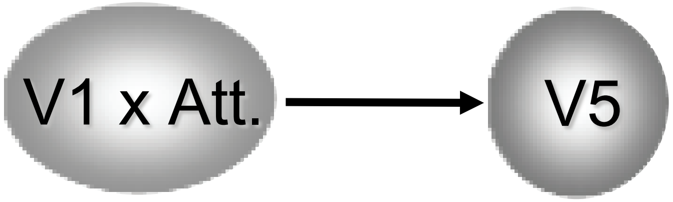
Psycho-physiological interactions (PPI)

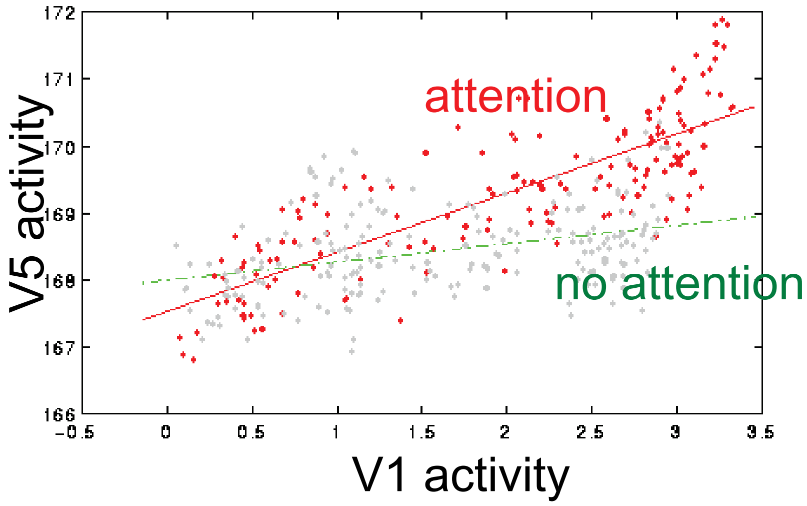
- Bilinear model of how the psychological context A changes the influence of area B on area C :

B x A → C

- Replace a (main) effect with the timeseries of a voxel showing that effect

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





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

Psycho-physiological interactions (PPI)

- Pro
  - given a single source region, we can test for its context-dependent connectivity across the entire brain
  - easy to implement

- Con
  - only allows to model contributions from a single area
  - operates at the level of BOLD time series*
  - ignores time-series properties of the data *

* To be explained ☺

DCM for more robust statements of effective connectivity

Overview

Brain Connectivity: types & definitions

Dynamic Causal Modelling – in theory

- Basic idea
- Neural and hemodynamic levels
- Preview: priors & inference

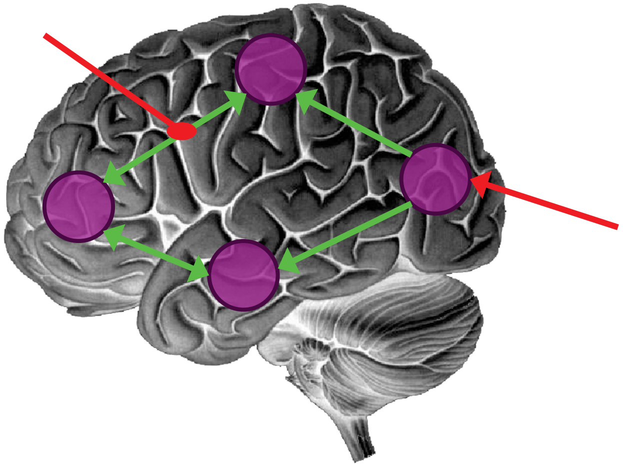
Dynamic Causal Modelling – in practice

DCM: the basics

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)

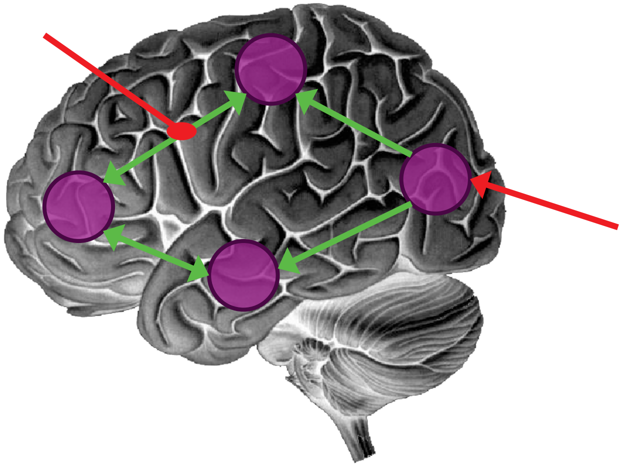


DCM: the basics

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

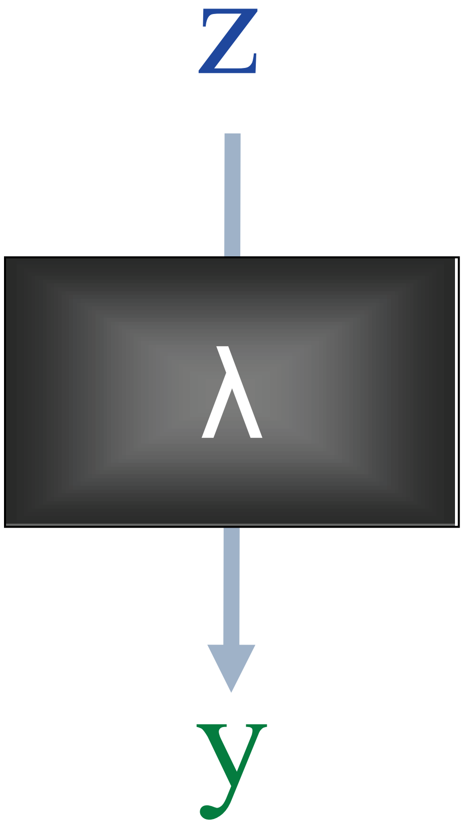


DCM: Neuronal and hemodynamic level

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

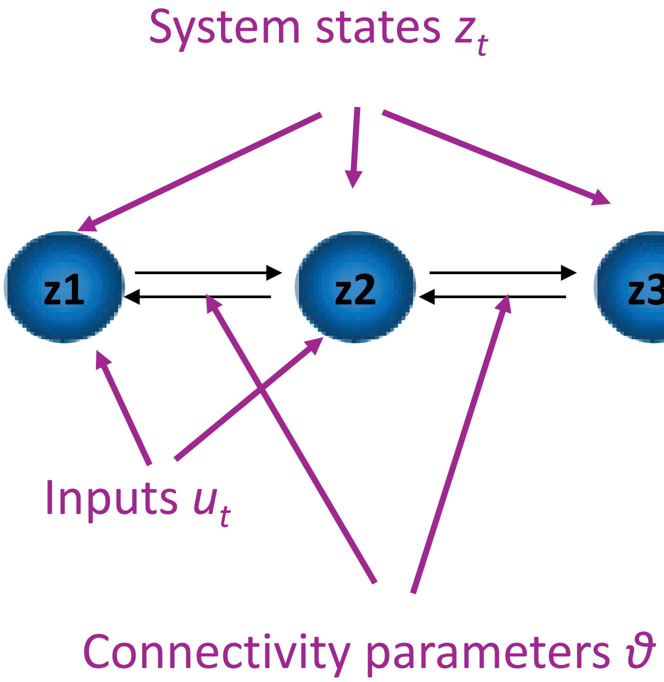
- The modelled neuronal dynamics (**z**) are transformed into area-specific BOLD signals (**y**) by a hemodynamic model (λ).

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



Neuronal model

- Aim: model temporal evolution of a set of neuronal states z_t



System states z_t

Inputs u_t

Connectivity parameters ϑ

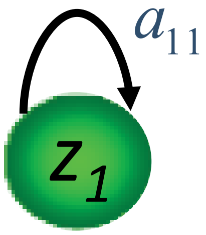
State changes are dependent on:

- the current state z
- external inputs u
- its connectivity ϑ

$$\frac{dz}{dt} = F(z, u, \theta)$$

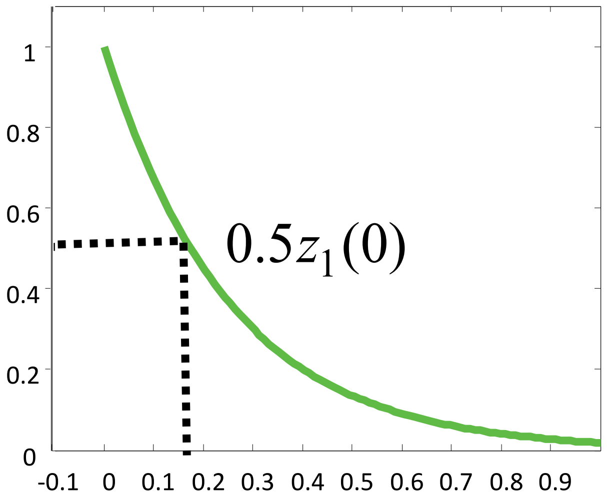
Why are DCM parameters rate constants?

Integration of a 1st order linear differential equation gives an exponential function:



$$= \frac{dz_1}{dt} = a_{11}z_1 \longrightarrow z_1(t) = z_1(0)\exp(a_{11}t)$$

Decay function

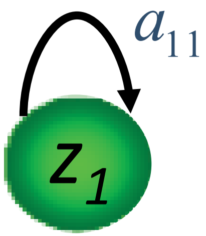


$$\tau = \ln 2 / s$$

If $z_1 \rightarrow z_1$ is -0.10 s^{-1} this means that, per unit time, the decrease in activity in z_1 corresponds to 10% of the current activity in z_1

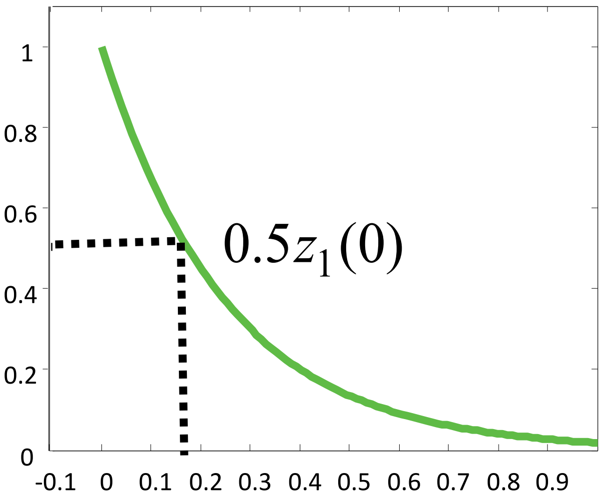
Why are DCM parameters rate constants?

Integration of a 1st order linear differential equation gives an exponential function:

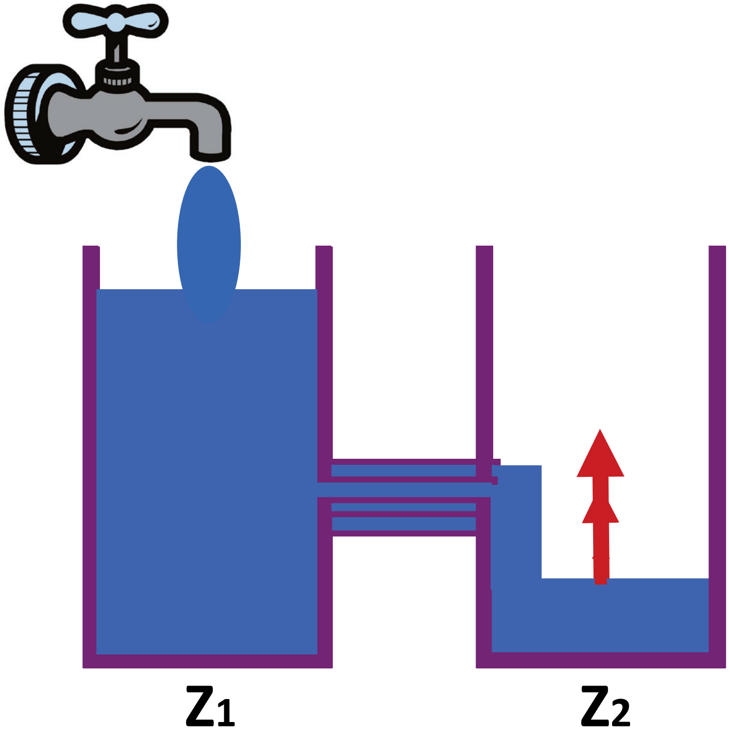


$$= \quad \frac{dz_1}{dt} = a_{11}z_1 \longrightarrow z_1(t) = z_1(0)\exp(a_{11}t)$$

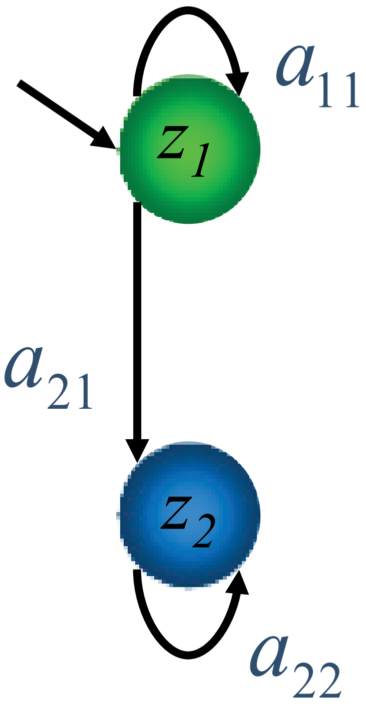
Decay function

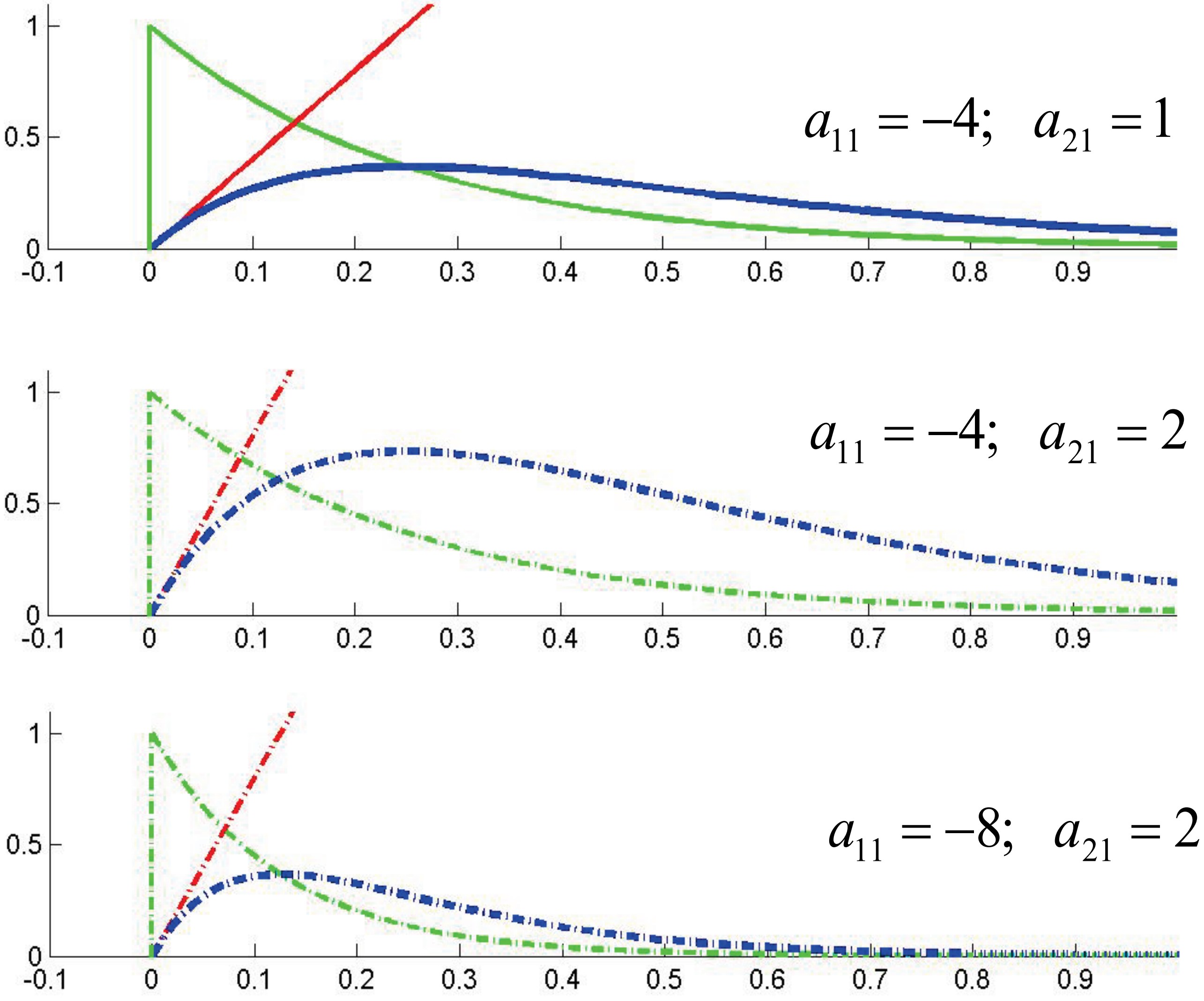


$$\tau = \ln 2 / s$$

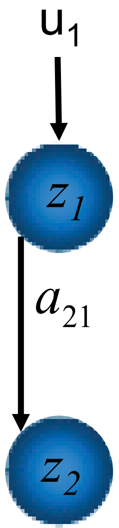


Neurodynamics: 2 nodes with input

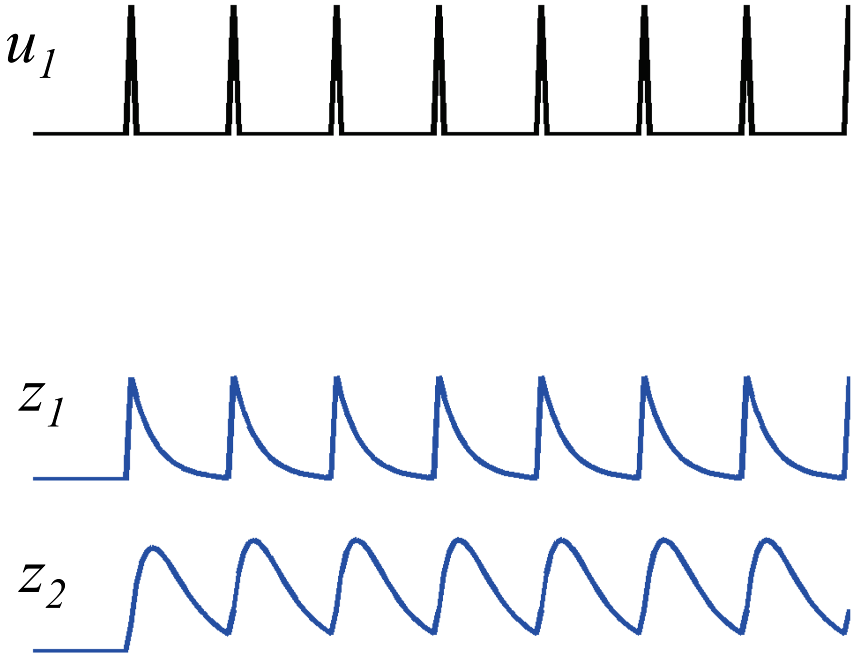




Neurodynamics: 2 nodes with input



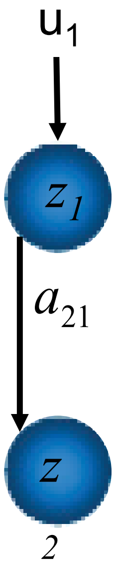
activity in z_2 is coupled to z_1 via coefficient a_{21}



$$\dot{z}_1 = a_{11}z_1 + c_{11}u_1$$
$$\dot{z}_2 = a_{21}z_1 + a_{22}z_2$$

$$\begin{bmatrix} \dot{z}_1 \\ \dot{z}_2 \end{bmatrix} = \begin{bmatrix} a_{11} & 0 \\ \enclose{circle}{a_{21}} & a_{22} \end{bmatrix} \begin{bmatrix} z_1 \\ z_2 \end{bmatrix} + \begin{bmatrix} c_{11} \\ 0 \end{bmatrix} u_1$$

Neurodynamics: 2 nodes with input



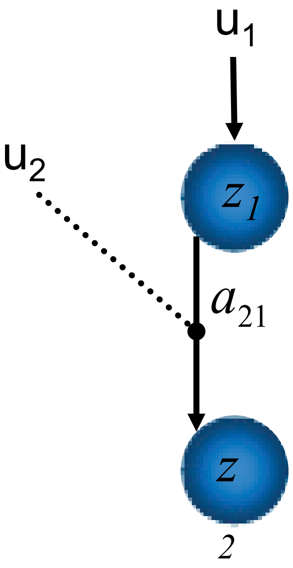
activity in z_2 is coupled to z_1 via coefficient a_{21}

$$\boxed{\begin{array}{l}\dot{z} = Az + Cu \\ \theta = \{A, C\}\end{array}}$$

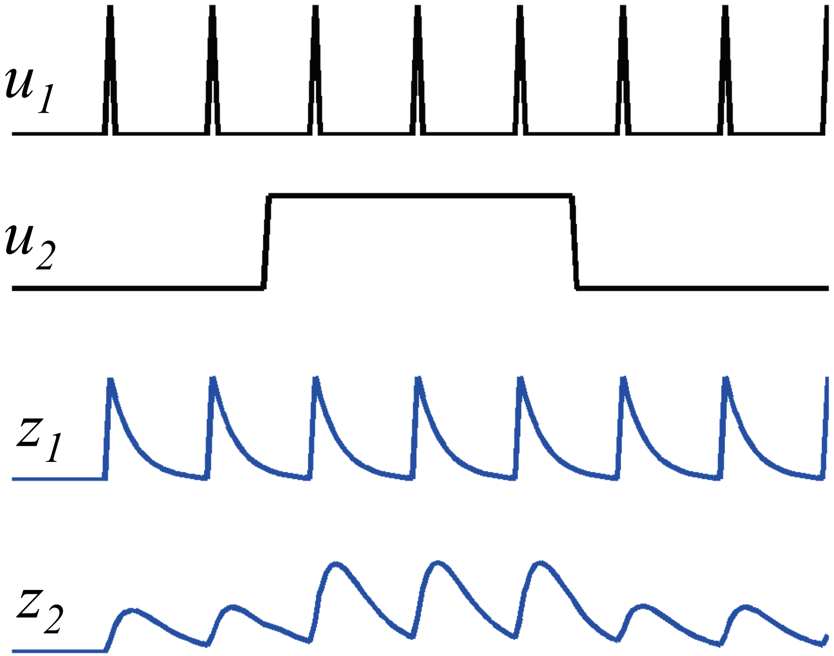
$$\dot{z}_1 = a_{11} z_1 + c_{11} u_1$$
$$\dot{z}_2 = a_{21} z_1 + a_{22} z_2$$

$$\begin{bmatrix} \dot{z}_1 \\ \dot{z}_2 \end{bmatrix} = \begin{bmatrix} a_{11} & 0 \\ \bigcirc\!\!\!\!\!\!\!\; a_{21} & a_{22} \end{bmatrix} \begin{bmatrix} z_1 \\ z_2 \end{bmatrix} + \begin{bmatrix} c_{11} \\ 0 \end{bmatrix} u_1$$

Neurodynamics: modulatory input



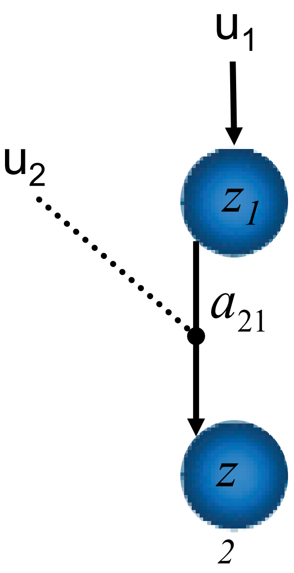
Modulatory input u_2 activity through coefficient a_{21}



$$\dot{z}_1 = a_{11}z_1 + c_{11}u_1$$

$$\dot{z}_2 = (a_{21} + b^2_{21}u_2)z_1 + a_{22}z_2$$

Neurodynamics: modulatory input



Modulatory input u_2 activity through coefficient a_{21}

$$\begin{bmatrix} \dot{z}_1 \\ \dot{z}_2 \end{bmatrix} = \begin{bmatrix} a_{11} & 0 \\ a_{21} & a_{22} \end{bmatrix} \begin{bmatrix} z_1 \\ z_2 \end{bmatrix} + u_2 \begin{bmatrix} 0 & 0 \\ \boxed{b^2_{21}} & 0 \end{bmatrix} \begin{bmatrix} z_1 \\ z_2 \end{bmatrix} + \begin{bmatrix} c_{11} & 0 \\ 0 & 0 \end{bmatrix} \begin{bmatrix} u_1 \\ u_2 \end{bmatrix}$$

$$\dot{z}_1 = a_{11} z_1 + c_{11} u_1$$

$$\dot{z}_2 = (a_{21} + b^2_{21} u_2) z_1 + a_{22} z_2$$

Neurodynamics: bilinear neural state equation

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

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

$$\overset{\substack{\text{state}\\ \text{changes}\\ \downarrow}}{\begin{bmatrix} \dot{z}_1 \\ \vdots \\ \dot{z}_n \end{bmatrix}} = \left\{ \overset{\substack{\text{connectivity}\\ \downarrow}}{\begin{bmatrix} a_{11} & \cdots & a_{1n} \\ \vdots & \ddots & \vdots \\ a_{n1} & \cdots & a_{nn} \end{bmatrix}} + \sum_{j=1}^{m} u_j \overset{\substack{\text{modulation of}\\ \text{connectivity}\\ \downarrow}}{\begin{bmatrix} b_{11}^{j} & \cdots & b_{1n}^{j} \\ \vdots & \ddots & \vdots \\ b_{n1}^{j} & \cdots & b_{nn}^{j} \end{bmatrix}} \right\} \overset{\substack{\text{state}\\ \text{vector}\\ \downarrow}}{\begin{bmatrix} z_1 \\ \vdots \\ z_n \end{bmatrix}} + \overset{\substack{\text{direct}\\ \text{inputs}\\ \downarrow}}{\begin{bmatrix} c_{11} & \cdots & c_{1m} \\ \vdots & \ddots & \vdots \\ c_{n1} & \cdots & c_{nm} \end{bmatrix}} \overset{\substack{\text{external}\\ \text{inputs}\\ \downarrow}}{\begin{bmatrix} u_1 \\ \vdots \\ u_m \end{bmatrix}}$$

n regions

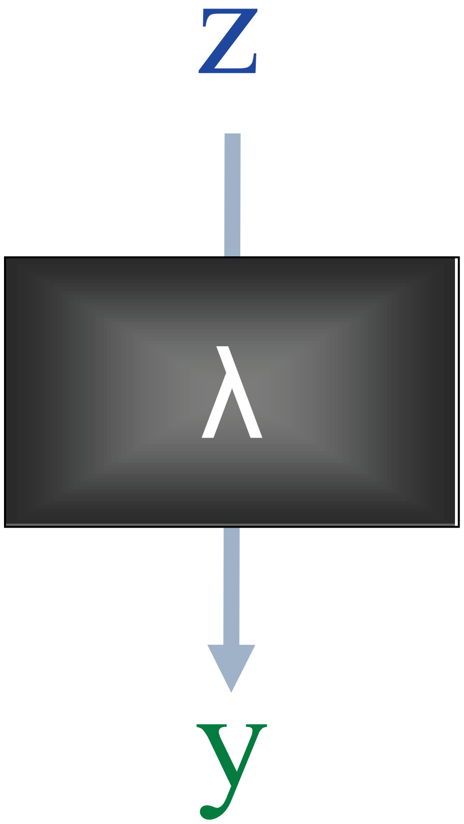
m mod inputs

m direct inputs

DCM: Neuronal and hemodynamic level

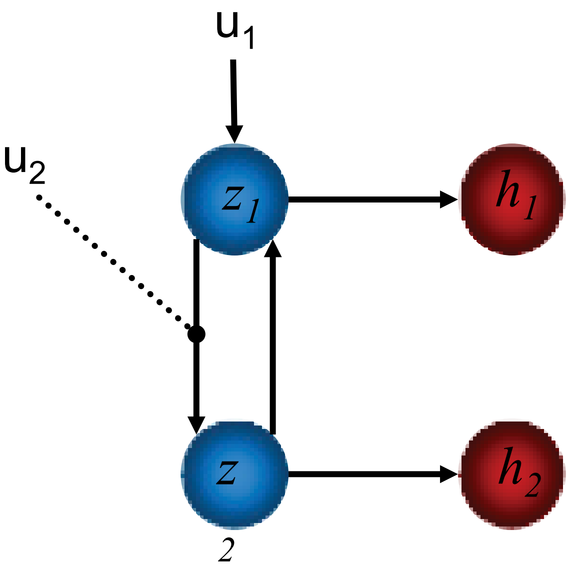
- Cognitive system is modelled at its underlying <u>neuronal level</u> (not directly accessible for fMRI).

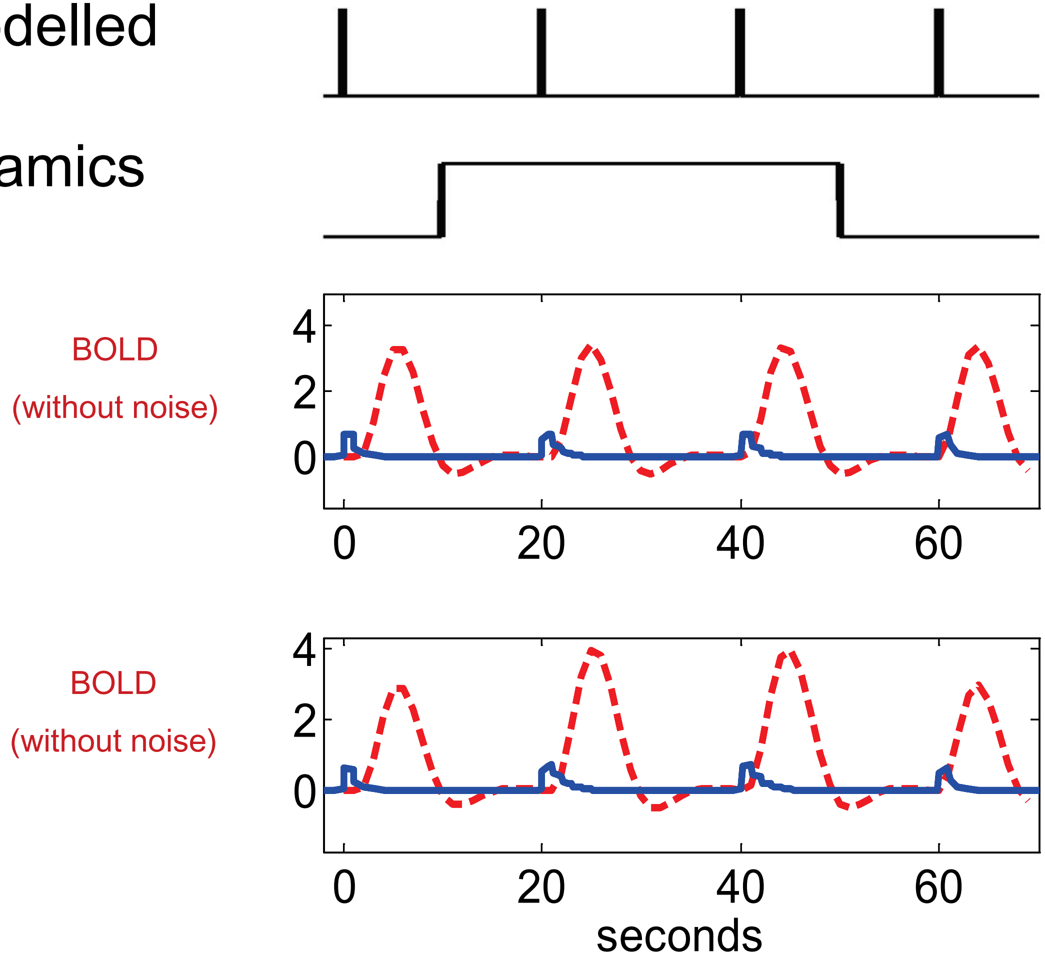
- The modelled neuronal dynamics ($\mathbf{z}$) are transformed into area-specific BOLD signals ($\mathbf{y}$) by a hemodynamic model (λ).



Hemodynamics: reciprocal connections

$h(u,\theta)$ represents the modelled BOLD response (balloon model) to the neural dynamics

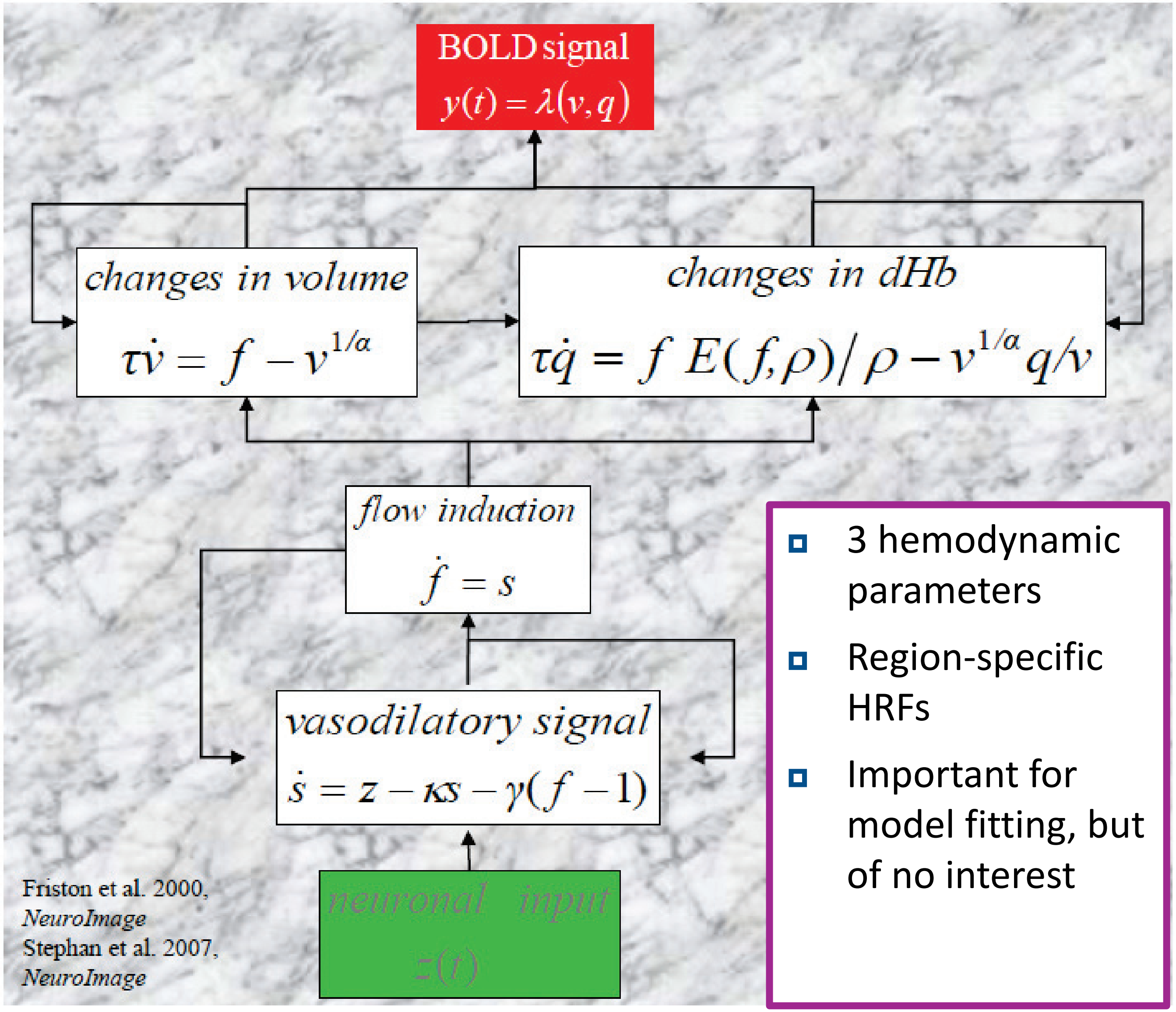




Z: neuronal activity

H: BOLD response

The hemodynamic “Balloon” model



BOLD signal

$$y(t) = \lambda(v, q)$$

changes in volume

$$\tau \dot{v} = f - v^{1/\alpha}$$

changes in dHb

$$\tau \dot{q} = f\, E(f,\rho)/\rho - v^{1/\alpha} q/v$$

flow induction

$$\dot{f} = s$$

vasodilatory signal

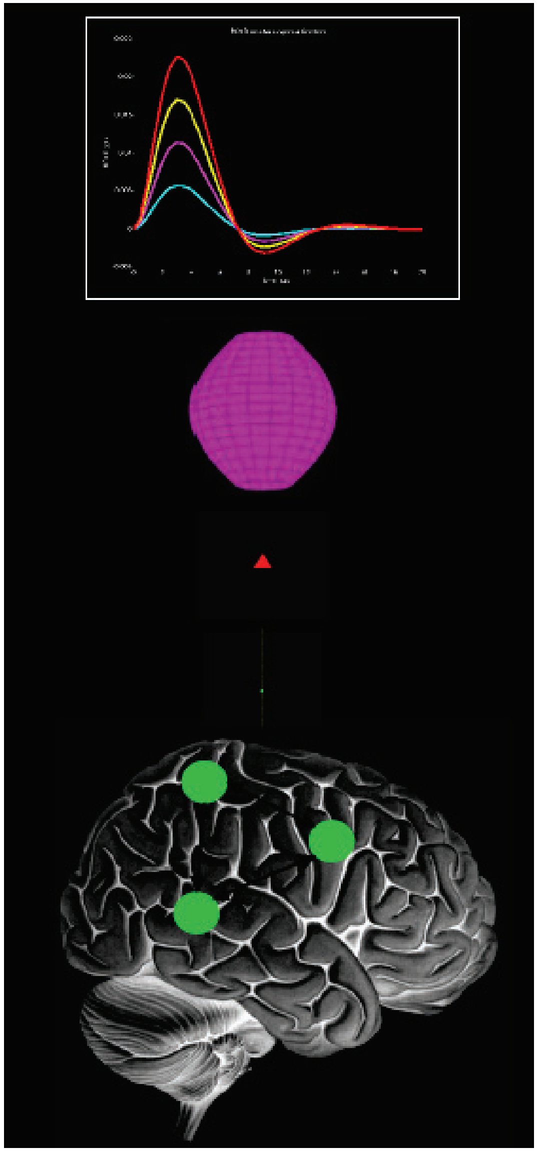
$$\dot{s} = z - \kappa s - \gamma(f - 1)$$

neuronal input

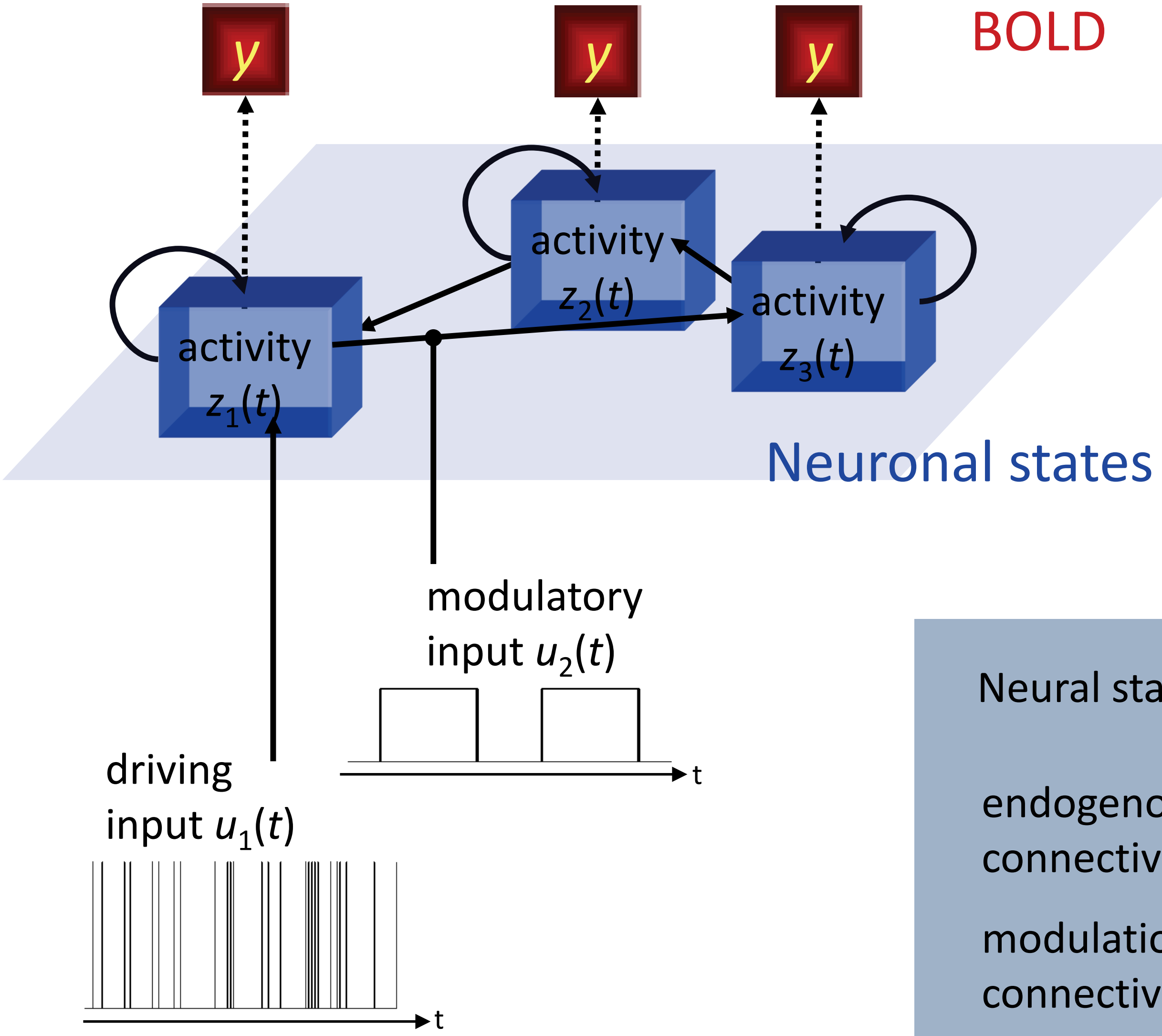
$$z(t)$$

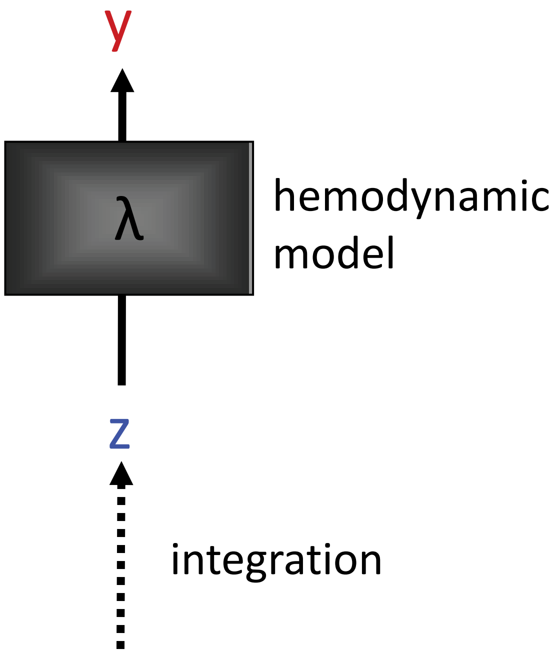
Friston et al. 2000, *NeuroImage*
Stephan et al. 2007, *NeuroImage*

- 3 hemodynamic parameters
- Region-specific HRFs
- Important for model fitting, but of no interest



DCM for fMRI: the full picture





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

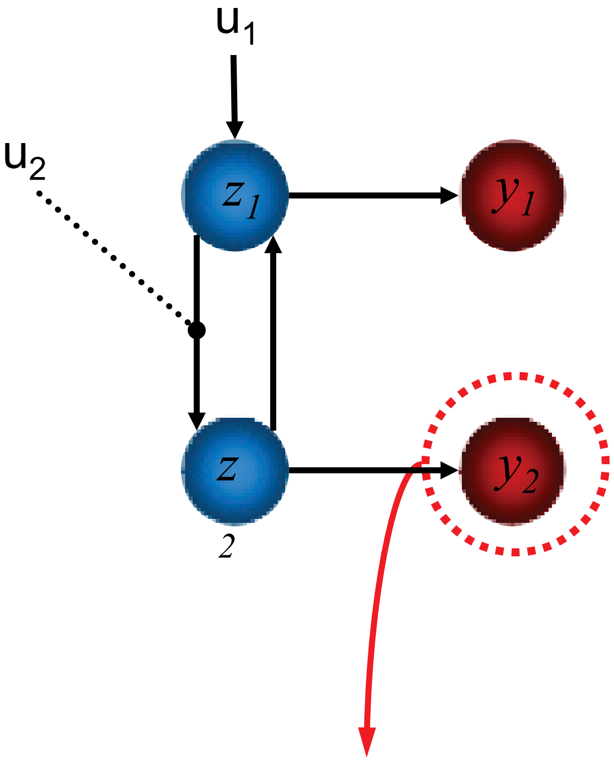
endogenous connectivity $A = \frac{\partial \dot{z}}{\partial z}$

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

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

Stephan & Friston (2007), *Handbook of Brain Connectivity*

Modelled and measured BOLD signal

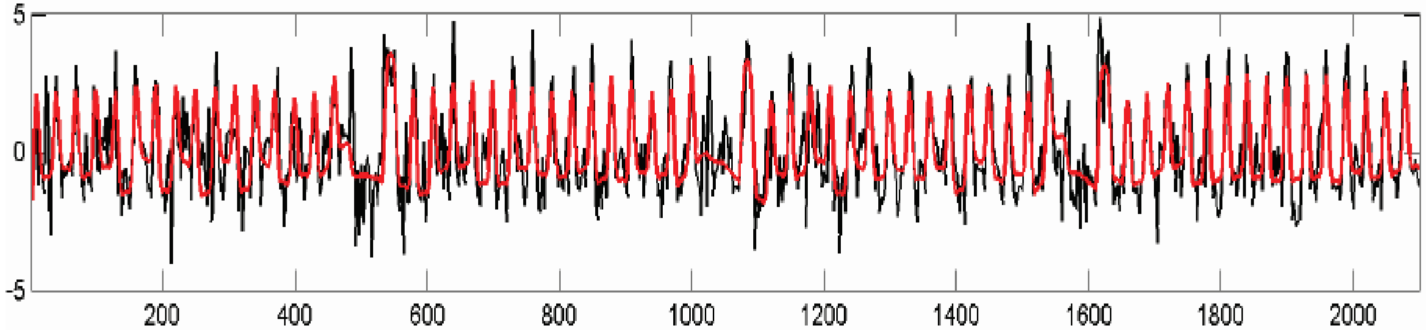


Recap

The aim of DCM is to estimate

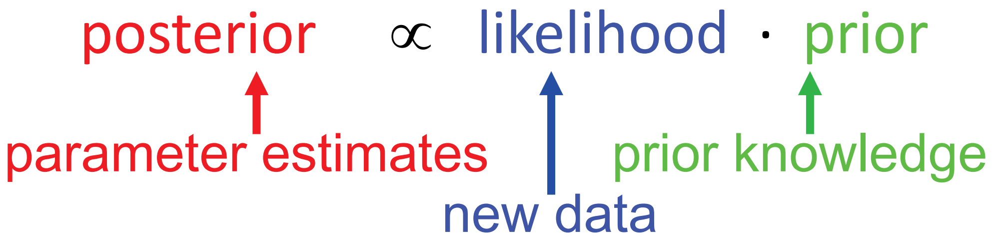
- neural parameters {A, B, C}
- hemodynamic parameters

such that the **MODELLED** and **MEASURED** BOLD signals are maximally



Bayesian statistics: Priors in DCM

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



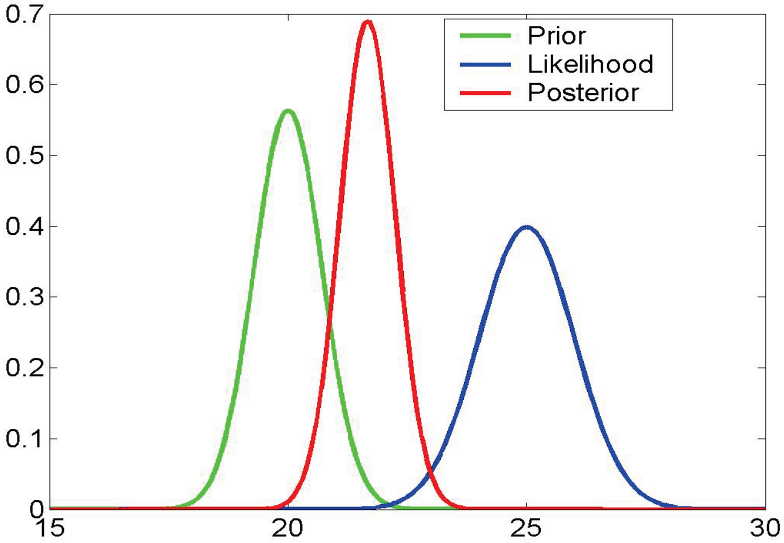
posterior ∝ likelihood · prior

parameter estimates

new data

prior knowledge

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



Parameters governing

- Hemodynamics in a single region
- Neuronal interactions

Constraints (priors) on

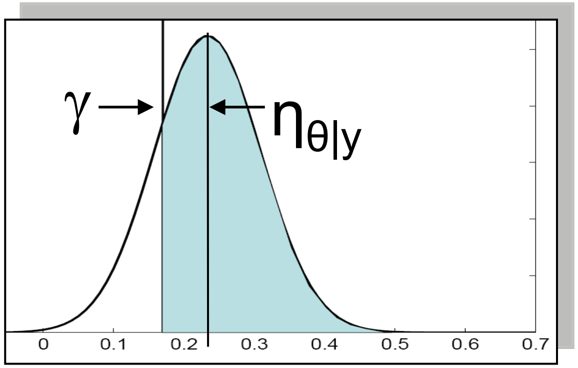
- Hemodynamic parameters
  - Empirical
- Self connections
  - principled
- Other connections
  - shrinkage

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?

Bayesian model averaging

Overview

Brain Connectivity: types & definitions

Dynamic Causal Modelling – in theory

Dynamic Causal Modelling – in practice

- Design of experiments and models
- Simulated data
- Connectivity in synesthesia

Planning a DCM compatible study

Suitable experimental design:

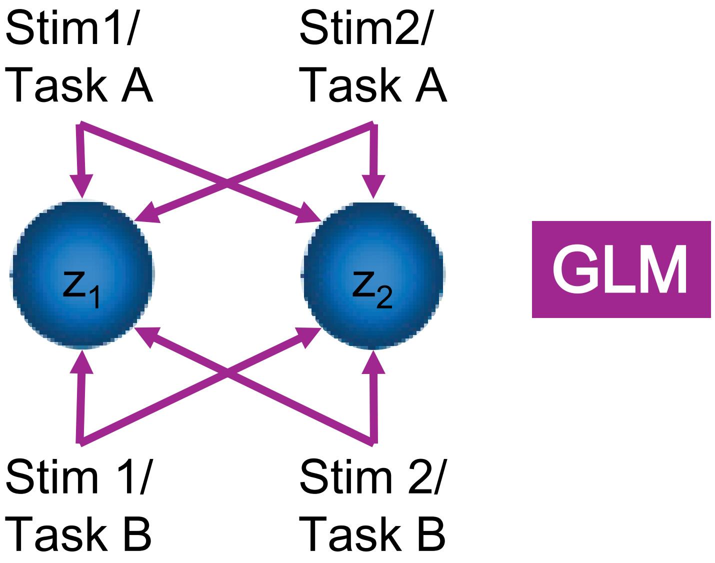
- any design that is suitable for a GLM
- preferably multi-factorial (e.g. 2 x 2)
  - e.g. one factor that varies the driving (sensory) input
  - and one factor that varies the contextual input

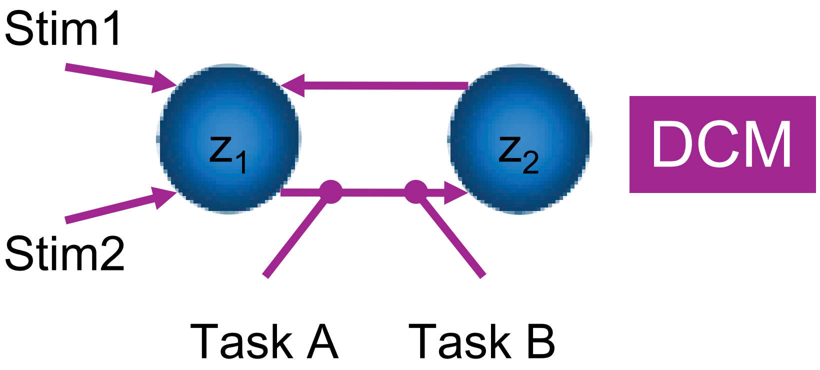
Hypothesis and model:

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

Multifactorial design: explaining interactions with DCM

		Task factor	
		Task A	Task B
Stimulus factor	Stim 1	A1	B1
	Stim 2	A2	B2

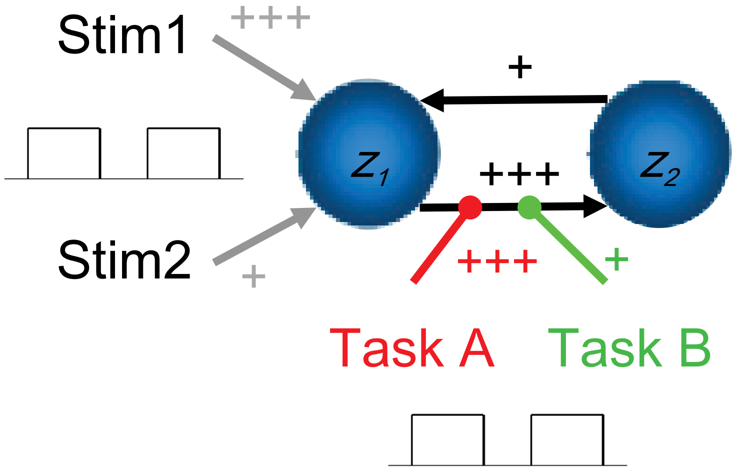


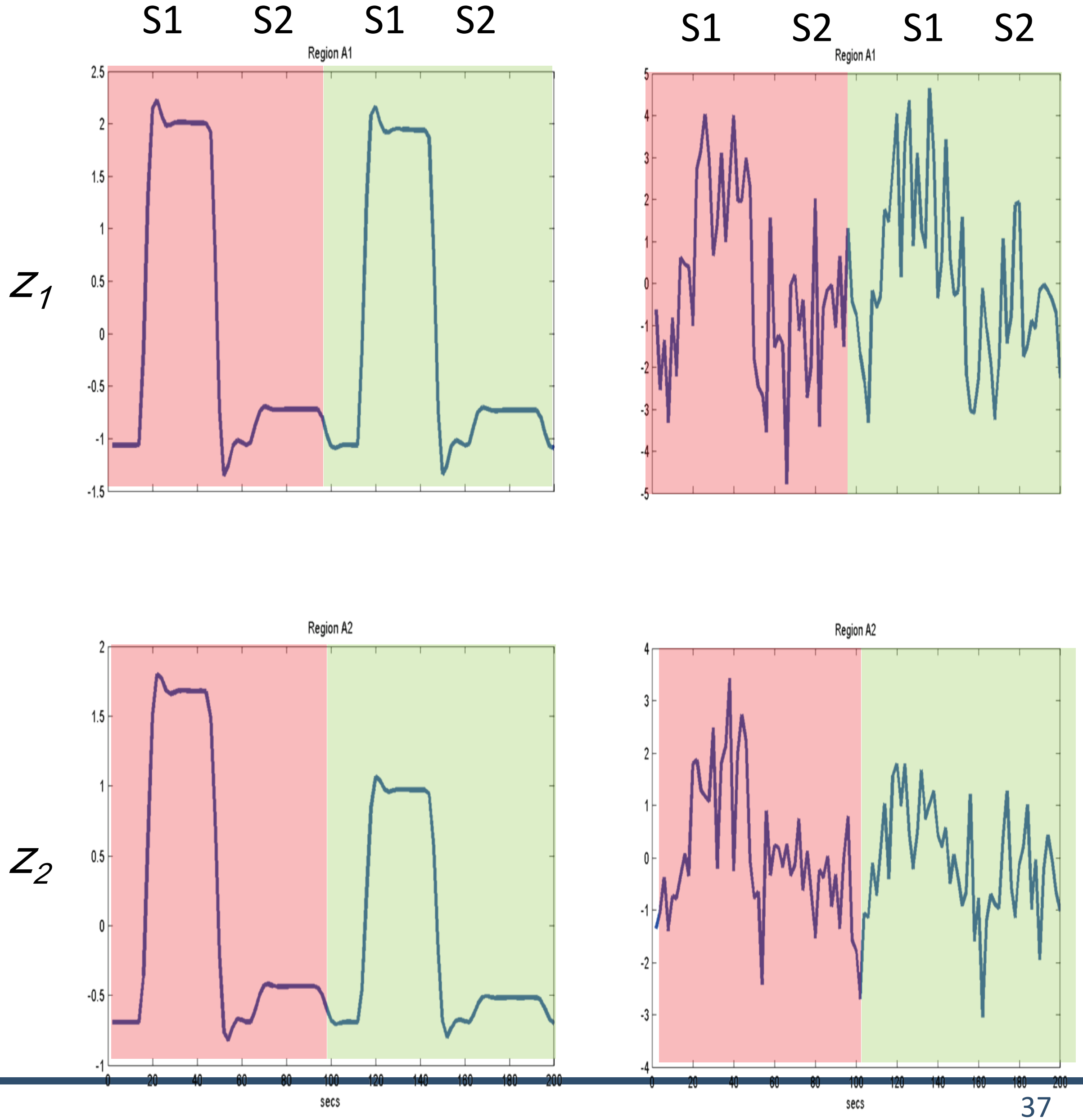


Let's assume that an SPM analysis shows a main effect of stimulus in z_1 and a stimulus × task interaction in z_2.

How do we model this using DCM?

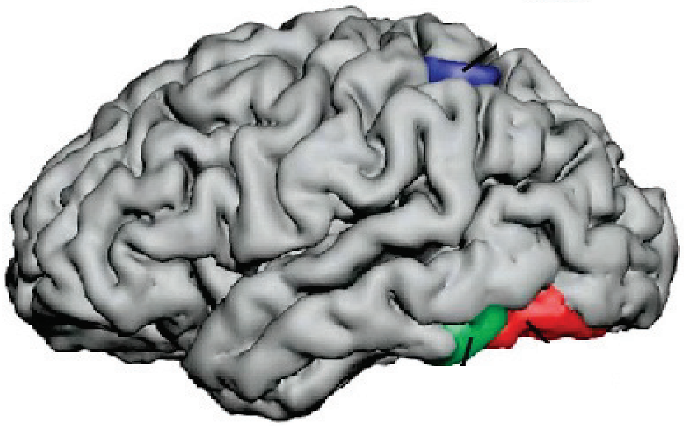
Simulation


Stim1
+++
+
z_1
z_2
+++
Stim2
+
+++
+
Task A
Task B


S1
S2
S1
S2
S1
S2
S1
S2
Region A1
Region A1
z_1
Region A2
Region A2
z_2
2.5
2
1.5
1
0.5
0
-0.5
-1
-1.5
5
4
3
2
1
0
-1
-2
-3
-4
-5
0
20
40
60
80
100
120
140
160
180
200
secs
secs

An Example: Brain Connectivity in Synesthesia

- Specific sensory stimuli lead to unusual, additional experiences
- Grapheme-color synesthesia: color
- Involuntary, automatic; stable over time, prevalence ~4%
- Potential cause: aberrant **cross-activation** between brain areas
    - grapheme encoding area
    - color area V4
    - superior parietal lobule (SPL)



Hubbard, 2007

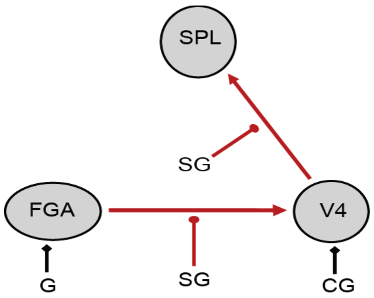
Can changes in effective connectivity explain synesthesia activity in V4?

Van Leeuwen et al. 2011 *JNeurosci*

An Example: Brain Connectivity in Synesthesia

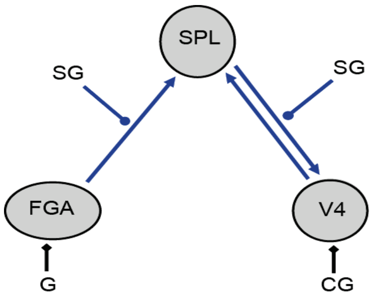
Bottom-up

(*Ramachandran & Hubbard, 2001*)



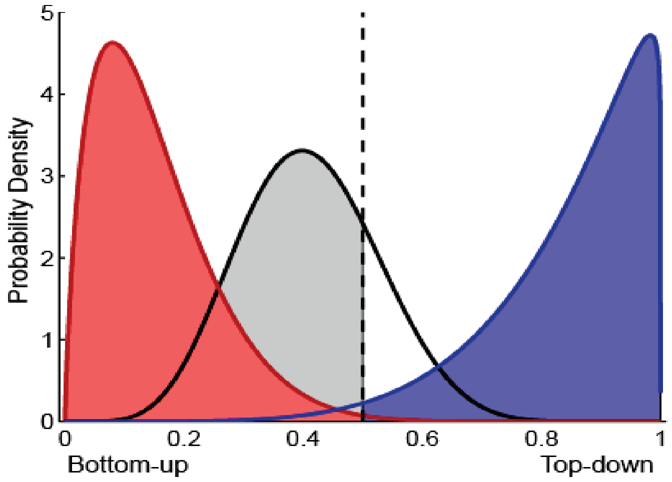
Top-down

(*Grossenbacher & Lovelace, 2001*)

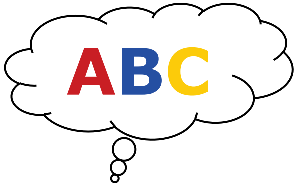


Projectors

ABC



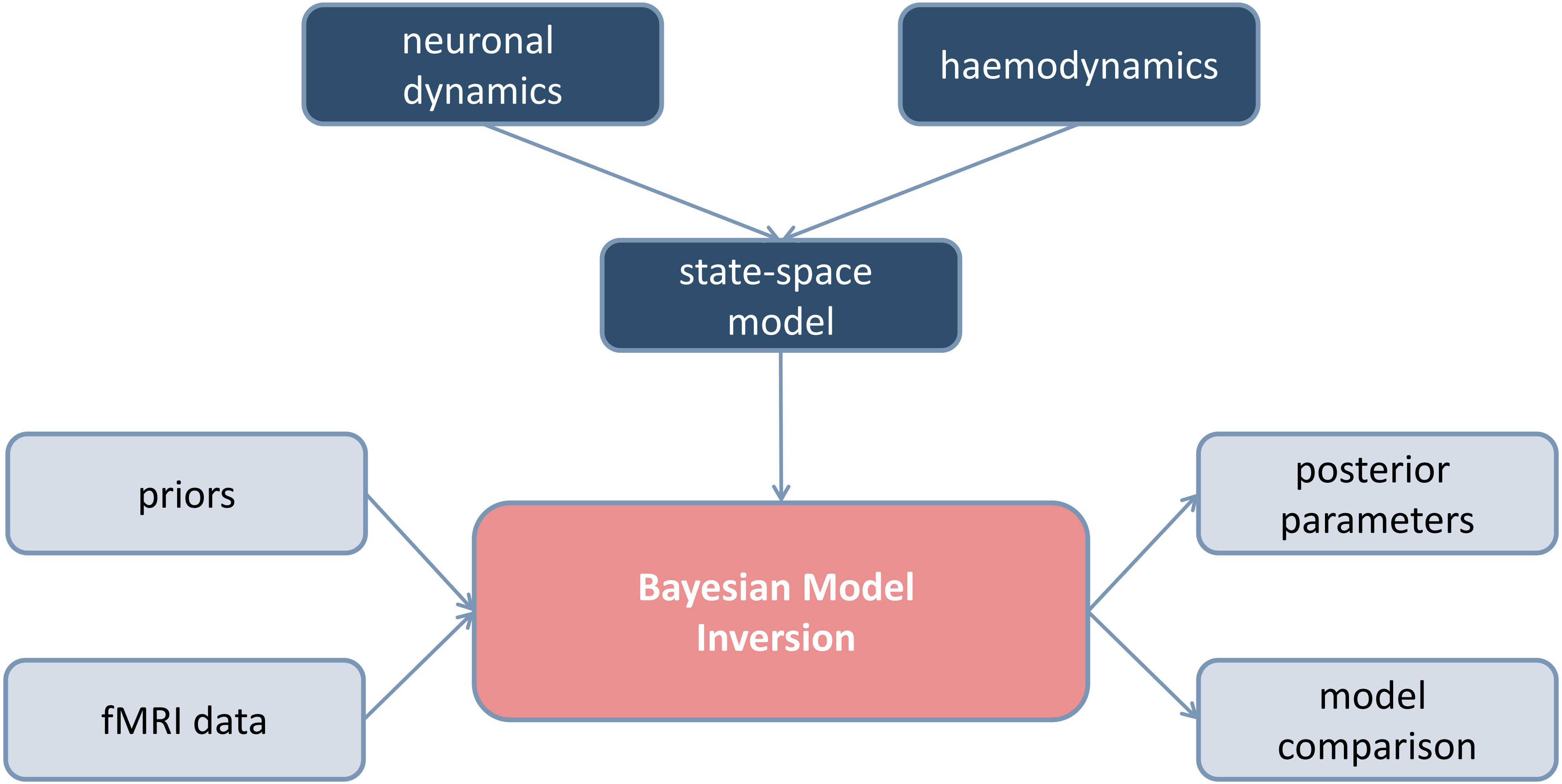
Associators



ABC

Effective connectivity determines conscious experiences…!

DCM Roadmap



neuronal dynamics

haemodynamics

state-space model

priors

fMRI data

Bayesian Model Inversion

posterior parameters

model comparison

Some useful references

- 10 Simple Rules for DCM (2010). Stephan et al. *NeuroImage 52*.
- 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 DCM:Nonlinear Dynamic Causal Models for FMRI (2008). Stephan et al. *NeuroImage* 42:649-662
- Two-state DCM: Dynamic causal modelling for fMRI: A two-state model (2008). Marreiros et al. *NeuroImage* 39:269-278
- Stochastic DCM: Generalised filtering and stochastic DCM for fMRI (2011). Li et al. *NeuroImage* 58:442-457.
- Bayesian model comparison: Comparing families of dynamic causal models (2010). Penny et al. *PLoS Comput Biol.* 6(3):e1000709.