Effective Connectivity & the basics of Dynamic Causal Modelling

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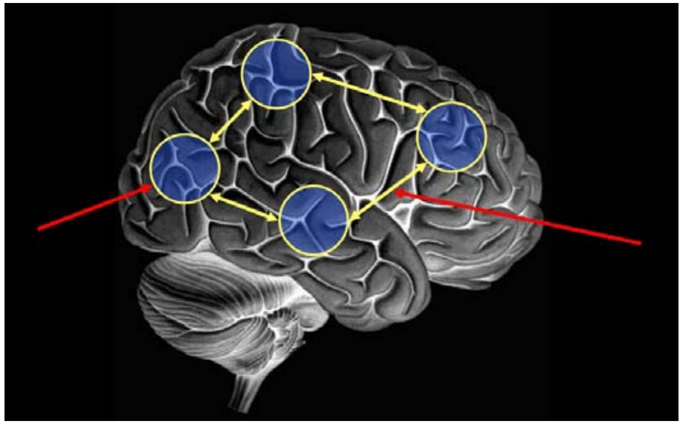


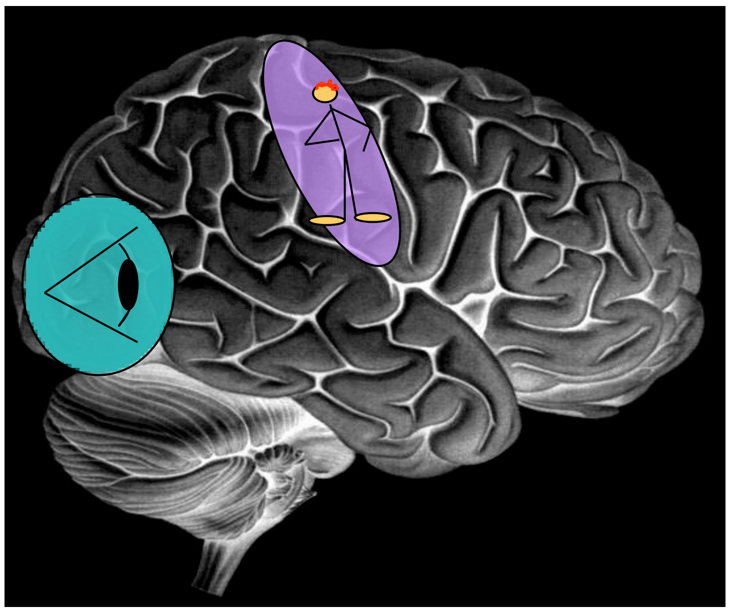
SPM course

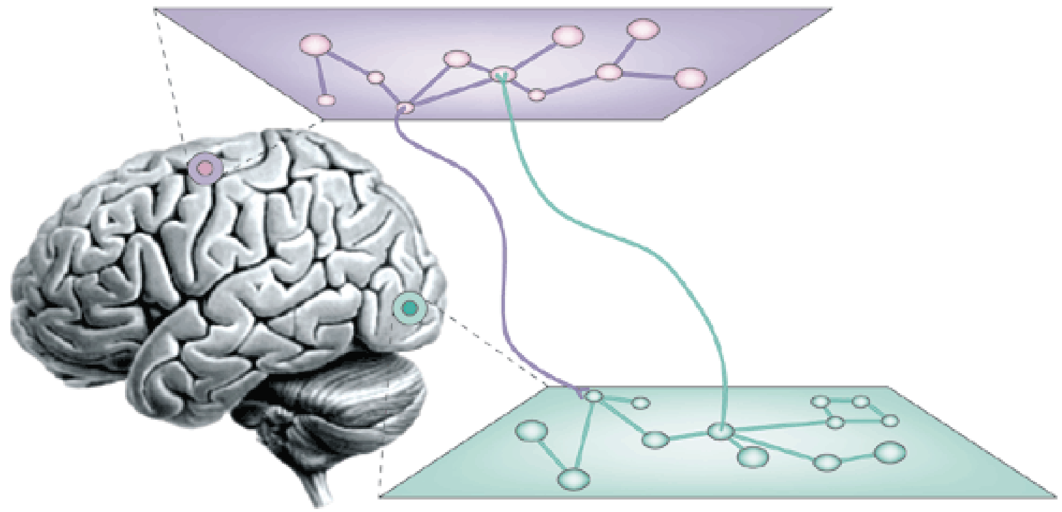
Zurich, February 2011

Principles of Organisation

Functional specialization

Functional integration





Overview

- Brain connectivity: Types & definitions
- Dynamic causal models (DCMs)
- Practical examples

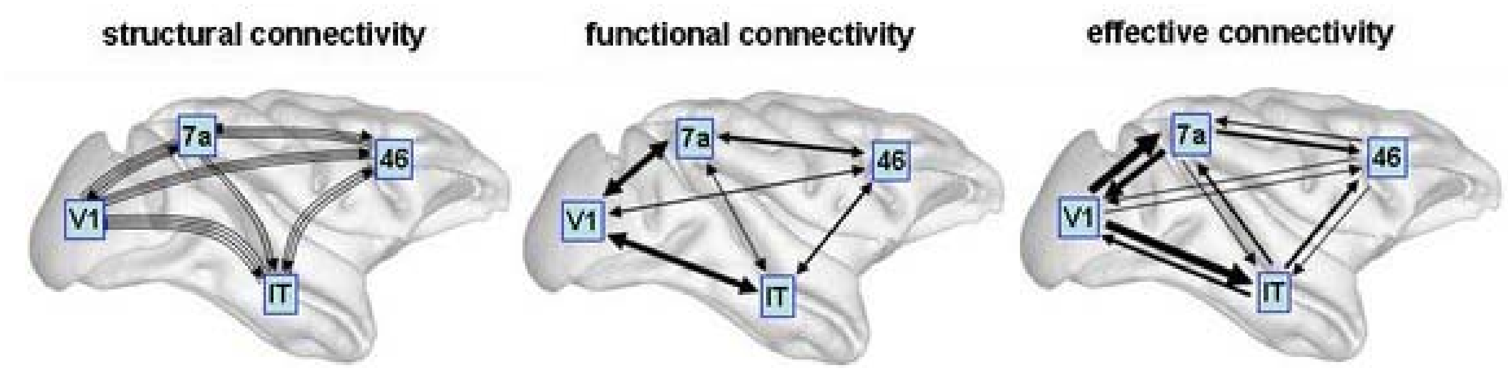
Overview

- Brain connectivity: Types & definitions
  - Anatomical connectivity
  - Functional connectivity
  - Effective Connectivity

- Dynamic causal models (DCMs)

- Practical examples

Structural, functional & effective connectivity



Sporns 2007, *Scholarpedia*

- **anatomical/structural connectivity**
  = presence of axonal connections

- **functional connectivity**
  = statistical dependencies between regional time series

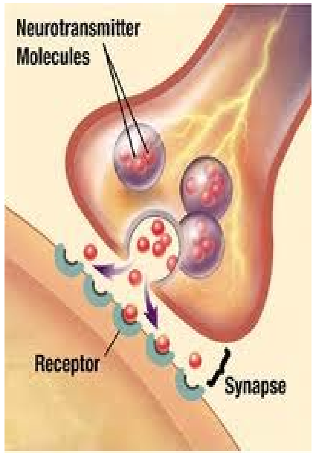
- **effective connectivity**
  = causal (directed) influences between neurons or neuronal populations

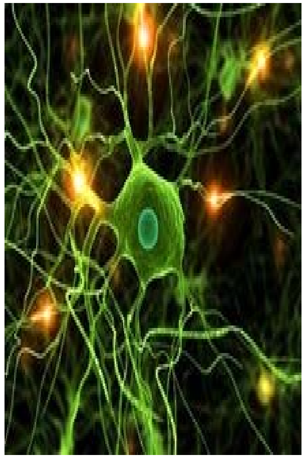
Anatomical connectivity

Definition:

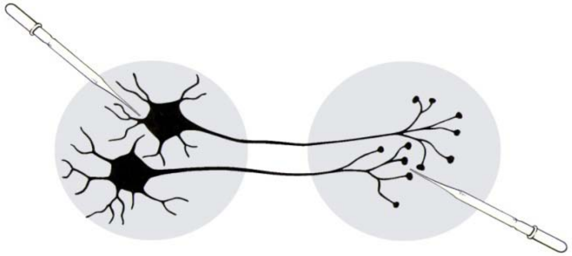
presence of axonal connections

- neuronal communication via synaptic contacts

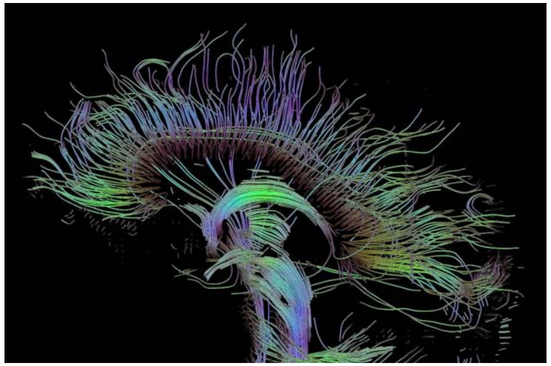




- Measured with
  - tracing techniques



  - diffusion tensor imaging (DTI)

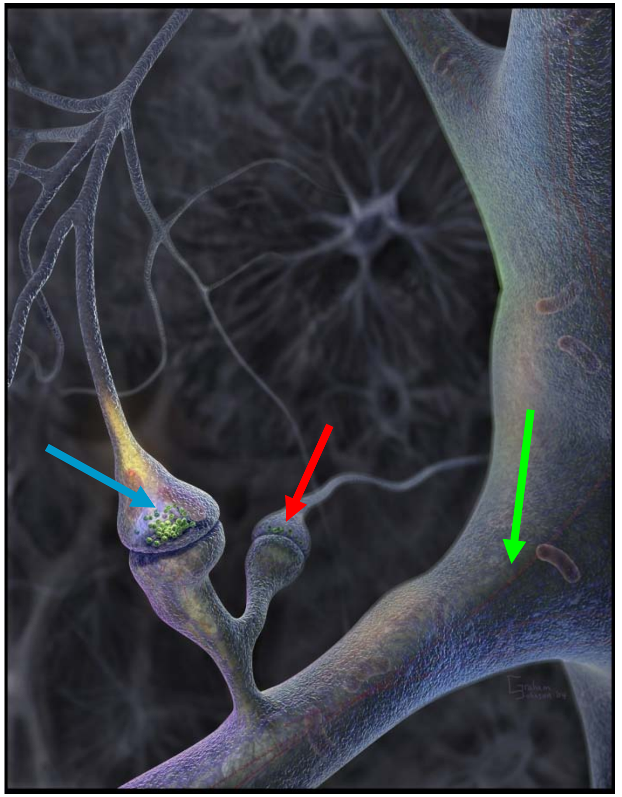


Knowing anatomical connectivity is not enough...

- 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



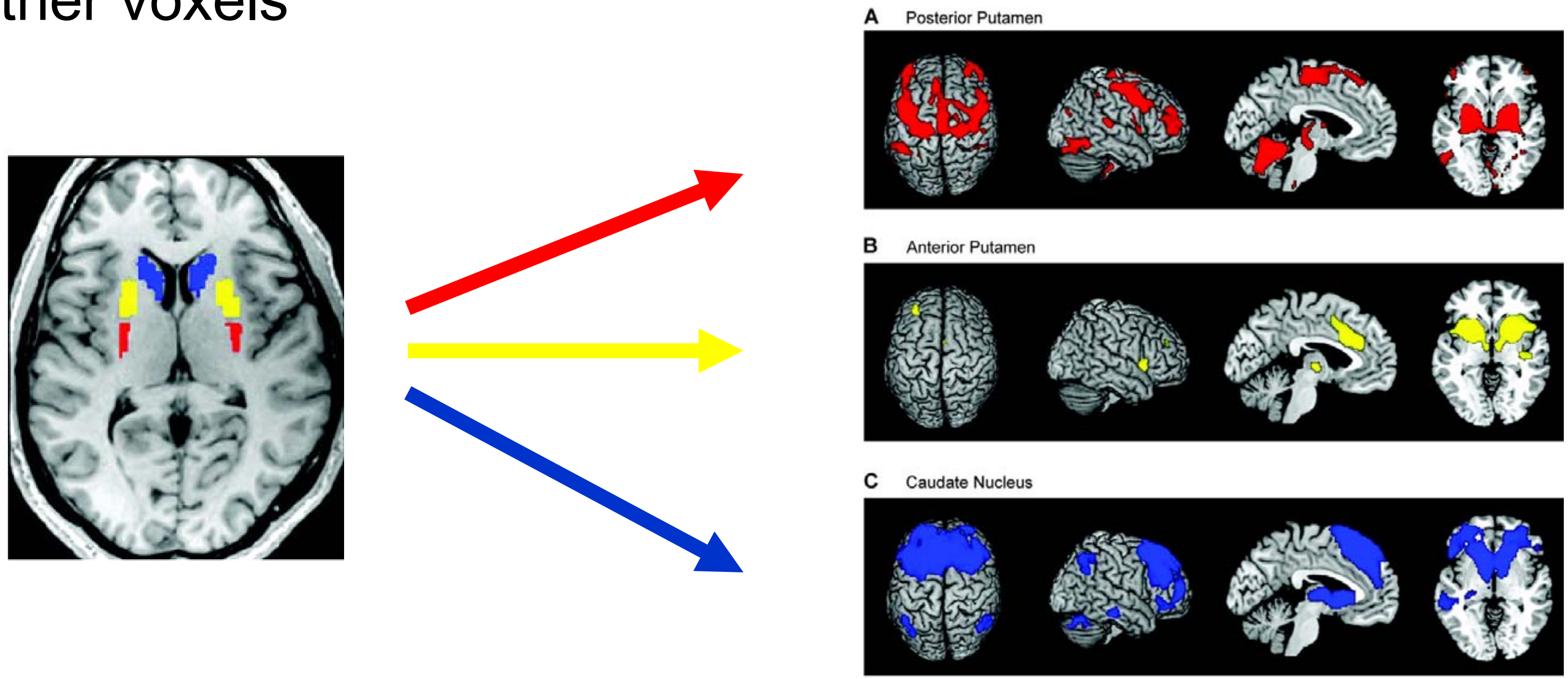
Functional connectivity

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

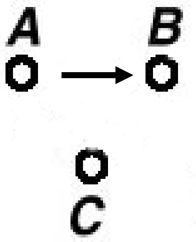
- hypothesis-driven choice of a seed voxel
- extract reference time series
- voxel-wise correlation with time series from all other voxels



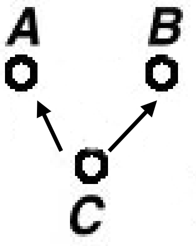
Helmich R C et al. Cereb. Cortex 2009

Pros & Cons of functional connectivity analysis

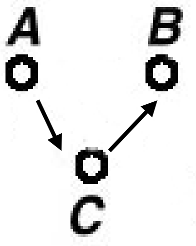
- Pros:
  - useful when we have no experimental control over the system of interest and no model of what caused the data (e.g. sleep, hallucinations, etc.)



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



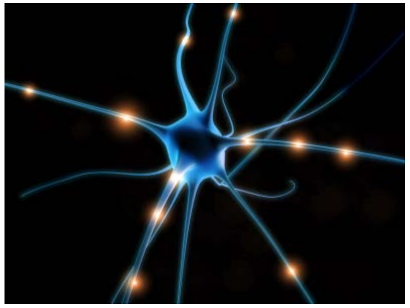
→ Effective connectivity



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

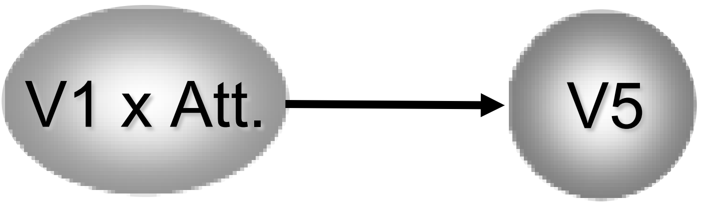
- Dynamic Causal Modelling (DCM)
  bilinear: Friston et al. 2003; *nonlinear:* Stephan et al. 2008

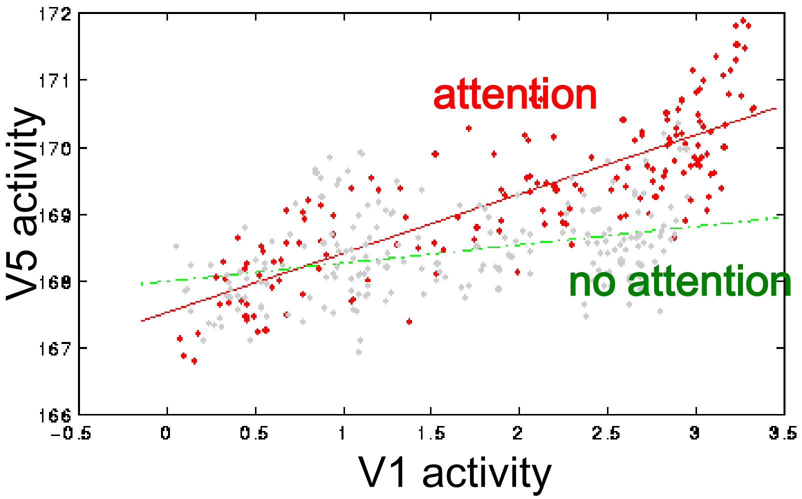
Psycho-physiological interaction (PPI)

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

$$B \times A \rightarrow C$$

- 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*

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

DCM needed for more robust statements of effective connectivity.

Overview

- Brain connectivity: types & definitions

- Dynamic causal models (DCMs)
  - Basic idea
  - Neural level
  - Hemodynamic level
  - Preview: priors & inference on parameters and models

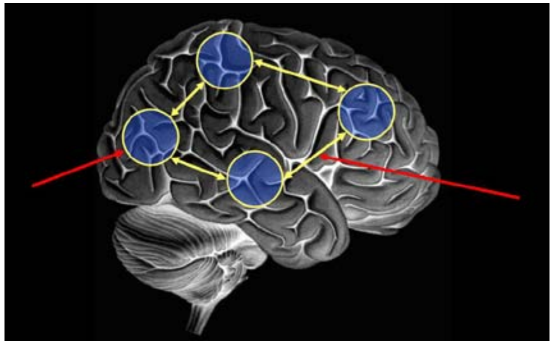
- Practical examples

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

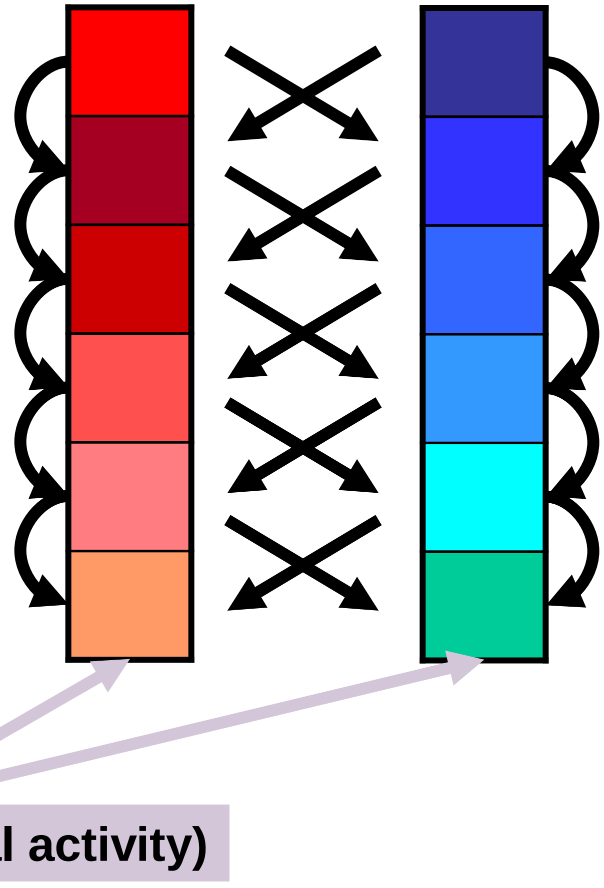
– Temporal dependency of activity within and between areas (causality)



Temporal dependence and causal relations

Seed voxel approach, PPI etc.

Dynamic *Causal* Models

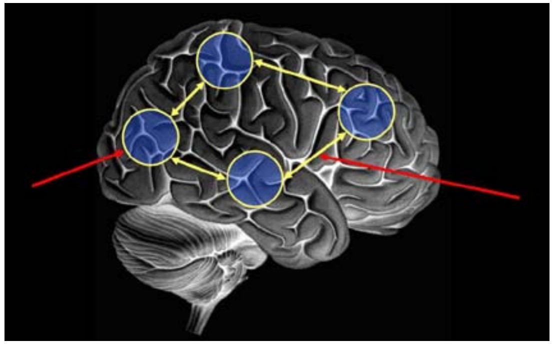


Basics of Dynamic Causal Modelling

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

Investigate functional integration & modulation of specific cortical pathways

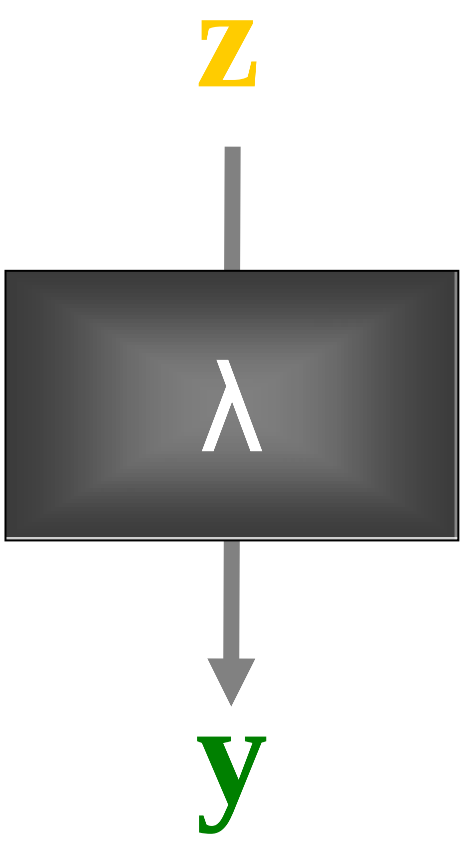
- Temporal dependency of activity within and between areas (causality)
- Separate neuronal activity from observed BOLD responses



Basics of DCM: Neuronal and BOLD level

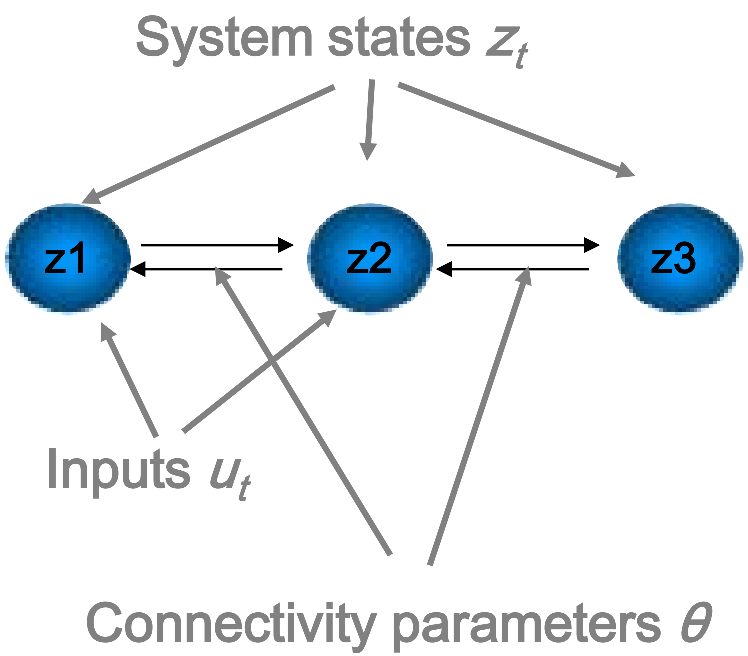
- Cognitive system is modelled at its underlying neuronal level (not directly accessible for fMRI).
- The modelled neuronal dynamics (**z**) are transformed into area-specific BOLD signals (**y**) by a hemodynamic model (λ).

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



The neuronal system

A System is a set of elements $z_n(t)$ which interact in a spatially and temporally specific fashion



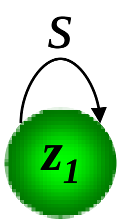
State changes of the system states are dependent on:

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

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

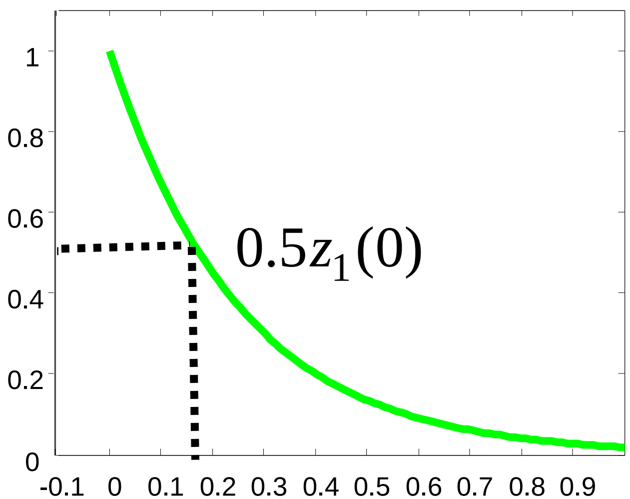
DCM parameters = rate constants

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

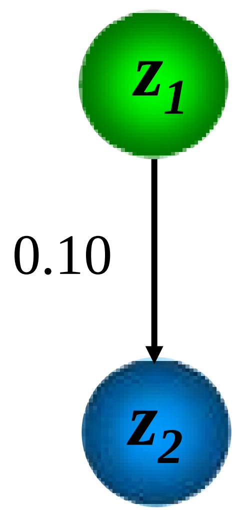


$$\frac{dz_1}{dt} = -sz_1 \quad \longrightarrow \quad z_1(t) = z_1(0)\exp(-st)$$

Decay function

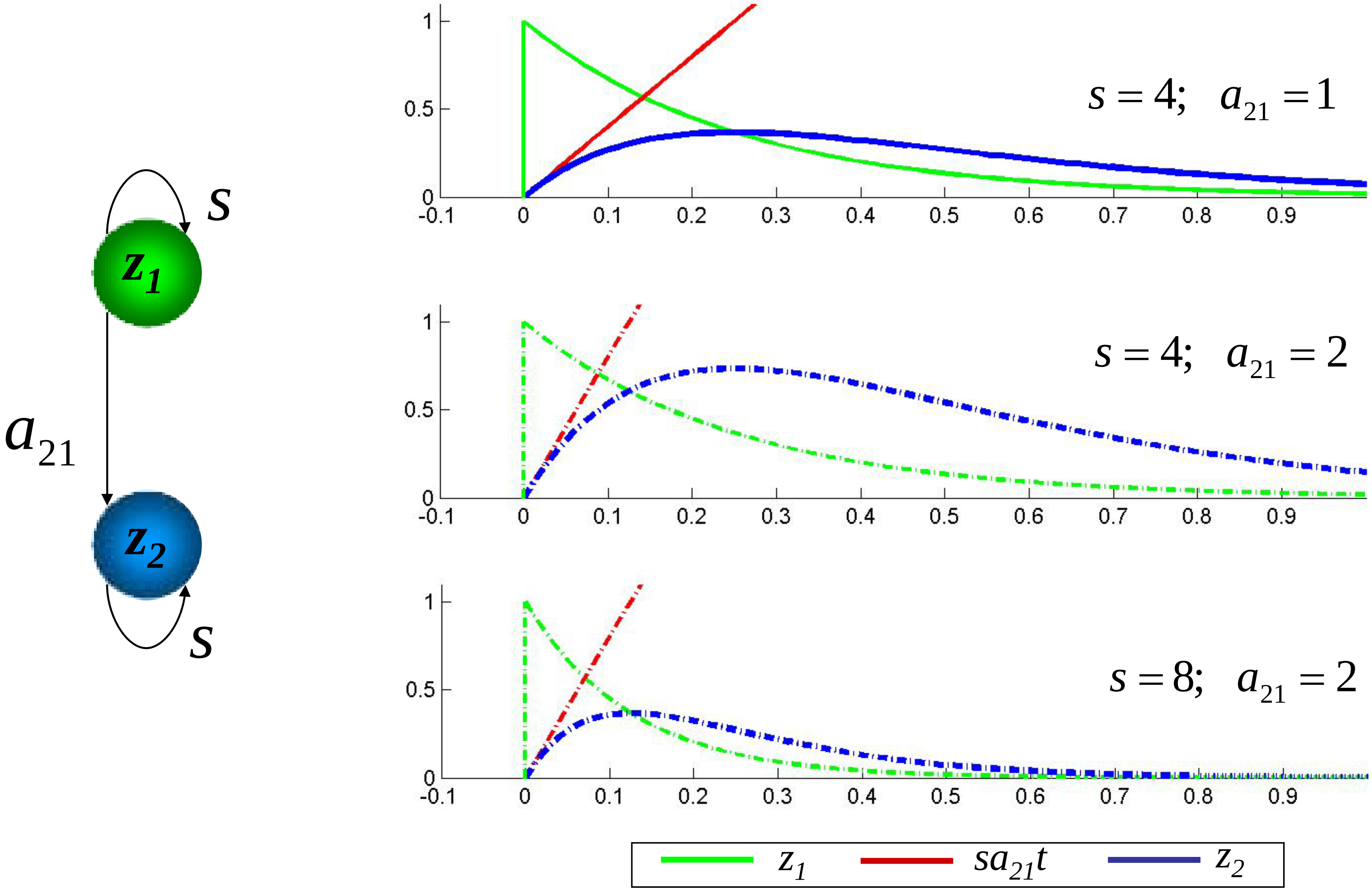


$$\tau = \ln 2 / s$$

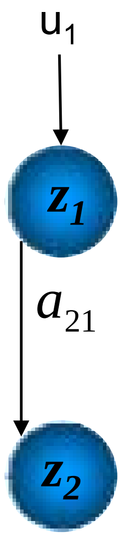


If $z_1 \rightarrow z_2$ is 0.10 s^{-1} this means that, per unit time, the increase in activity in z_2 corresponds to 10% of the activity in z_1

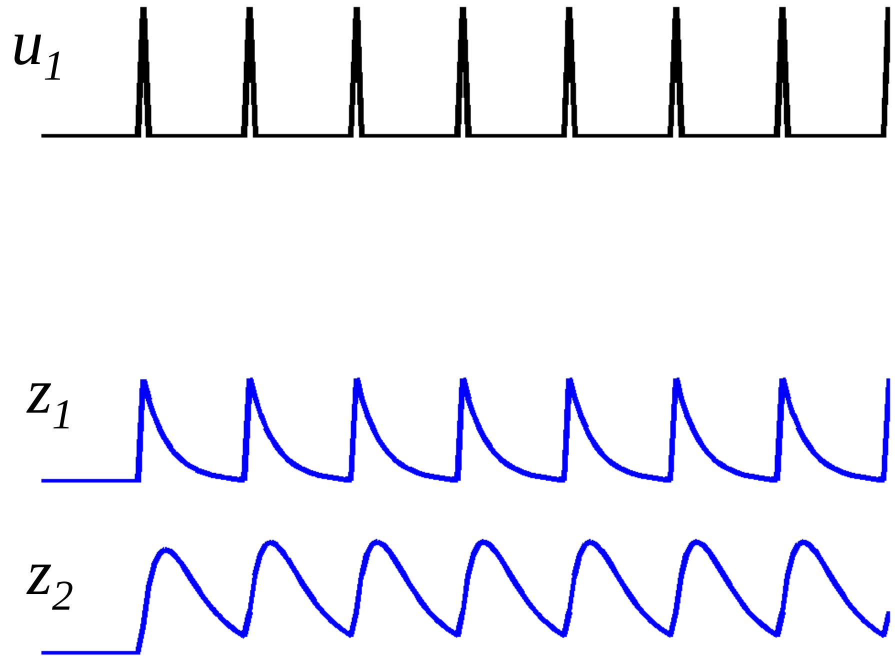
Linear dynamics: 2 nodes



Neurodynamics: 2 nodes with input



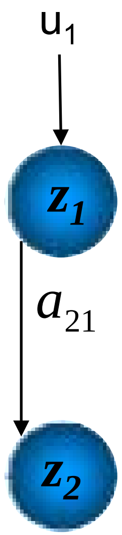
activity in z_2 is coupled to z_1 via coefficient a_{21}



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

$$\begin{bmatrix} \dot{z}_1 \\ \dot{z}_2 \end{bmatrix} = s \begin{bmatrix} -1 & 0 \\ a_{21} & -1 \end{bmatrix} \begin{bmatrix} z_1 \\ z_2 \end{bmatrix} + \begin{bmatrix} c_{11} \\ 0 \end{bmatrix} u_1$$

Neurodynamics: 2 nodes with input



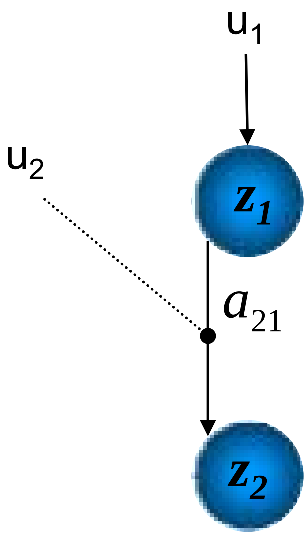
activity in z_2 is coupled to z_1 via coefficient a_{21}

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

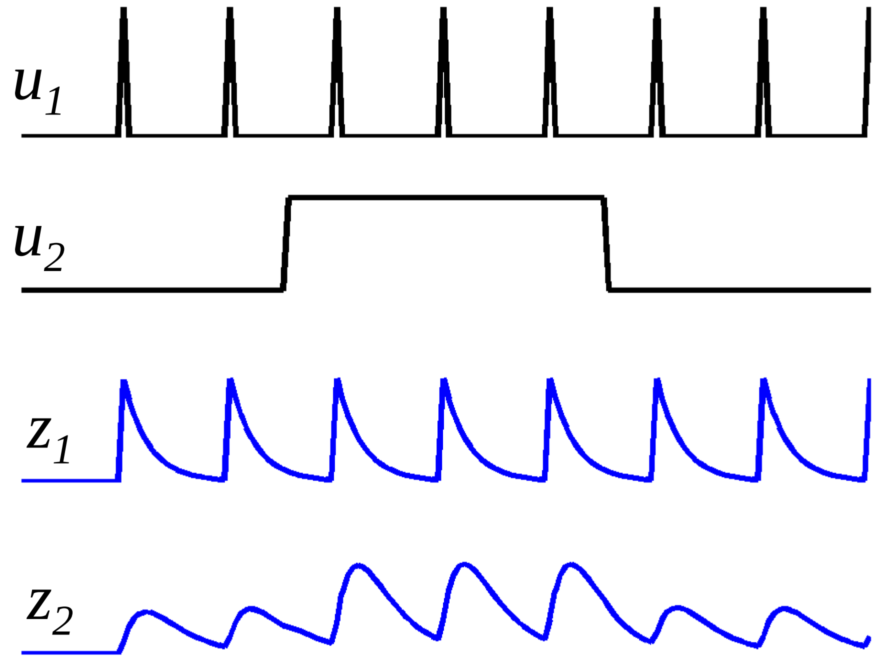
$$\begin{aligned} \dot{z}_1 &= a_{11} z_1 + c_{11} u_1 \\ \dot{z}_2 &= a_{21} z_1 + a_{22} z_2 \end{aligned}$$

$$\begin{bmatrix} \dot{z}_1 \\ \dot{z}_2 \end{bmatrix} = s \begin{bmatrix} -1 & 0 \\ a_{21} & -1 \end{bmatrix} \begin{bmatrix} z_1 \\ z_2 \end{bmatrix} + \begin{bmatrix} c_{11} \\ 0 \end{bmatrix} u_1$$

Neurodynamics: positive modulation



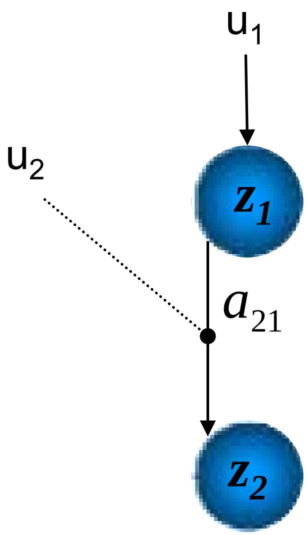
Modulatory input
u_2 activity through
coefficient a_{21}



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

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

Neurodynamics: positive modulation



Modulatory input
u_2 activity through
coefficient a_{21}

$$\begin{bmatrix} \dot{z}_1 \\ \dot{z}_2 \end{bmatrix} = s\begin{bmatrix} -1 & 0 \\ a_{21} & -1 \end{bmatrix}\begin{bmatrix} z_1 \\ z_2 \end{bmatrix} + u_2\begin{bmatrix} 0 & 0 \\ b_{21}^{2} & 0 \end{bmatrix}\begin{bmatrix} z_1 \\ z_2 \end{bmatrix} + \begin{bmatrix} c \\ 0 \end{bmatrix}u_1$$

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

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

Bilinear neural state equation in DCM for fMRI

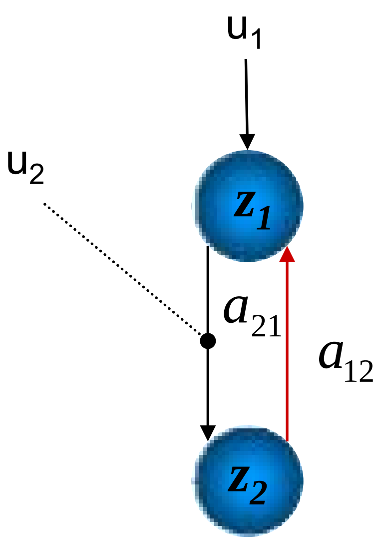
$$\boxed{\begin{aligned}\dot{z} &= \left(A + \sum_{j=1}^{m} u_j B^{(j)}\right) z + Cu \\ \theta &= \{A, B, C\}\end{aligned}}$$

state changes **connectivity** **modulation of connectivity** **state vector** **direct inputs** **external inputs**

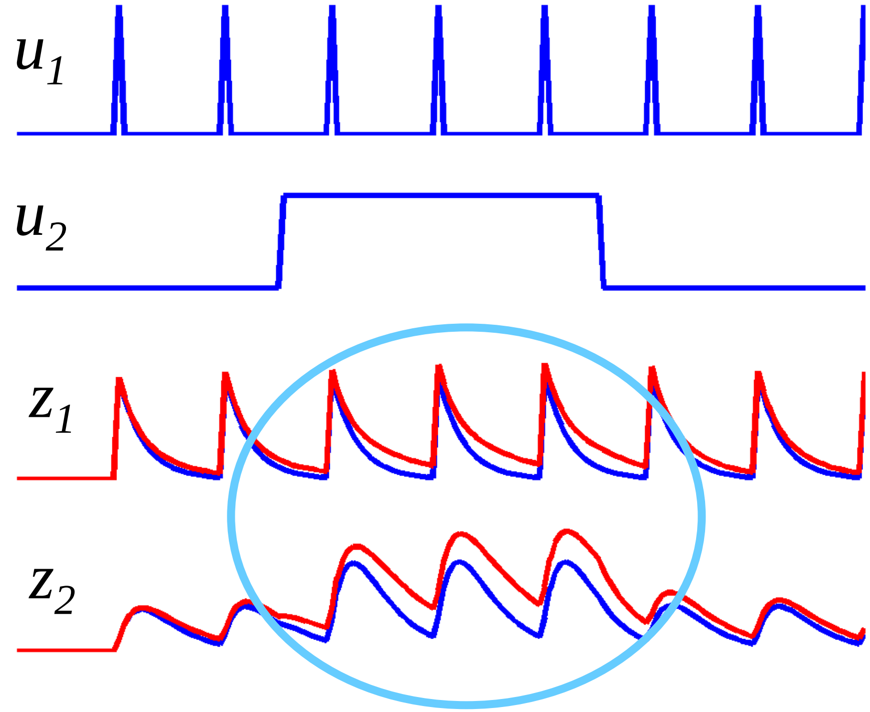
$$\begin{bmatrix} \dot{z}_1 \\ \vdots \\ \dot{z}_n \end{bmatrix} = \left\{ \begin{bmatrix} a_{11} & \cdots & a_{1n} \\ \vdots & \ddots & \vdots \\ a_{n1} & \cdots & a_{nn} \end{bmatrix} + \sum_{j=1}^{m} u_j \begin{bmatrix} b_{11}^{j} & \cdots & b_{1n}^{j} \\ \vdots & \ddots & \vdots \\ b_{n1}^{j} & \cdots & b_{nn}^{j} \end{bmatrix} \right\} \begin{bmatrix} z_1 \\ \vdots \\ z_n \end{bmatrix} + \begin{bmatrix} c_{11} & \cdots & c_{1m} \\ \vdots & \ddots & \vdots \\ c_{n1} & \cdots & c_{nm} \end{bmatrix} \begin{bmatrix} u_1 \\ \vdots \\ u_m \end{bmatrix}$$

n regions *m mod* inputs *m direct* inputs

Neurodynamics: reciprocal connections



reciprocal connection disclosed by u_2

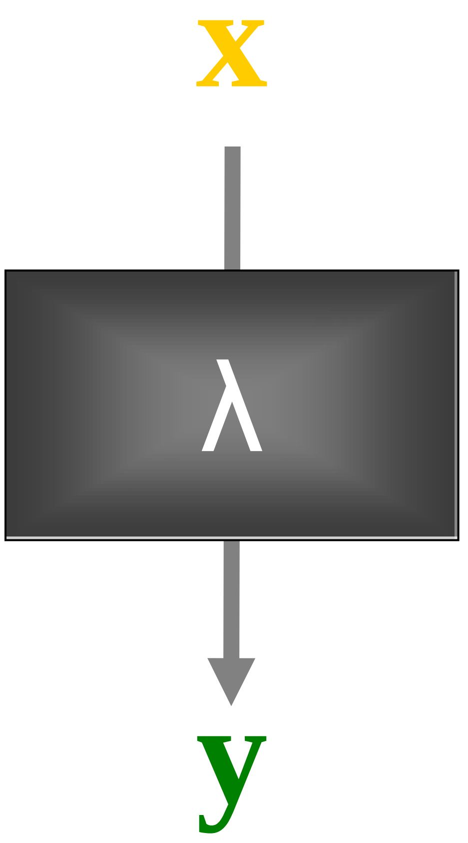


$$\begin{bmatrix} \dot{z}_1 \\ \dot{z}_2 \end{bmatrix} = s\begin{bmatrix} -1 & a_{12} \\ a_{21} & -1 \end{bmatrix}\begin{bmatrix} z_1 \\ z_2 \end{bmatrix} + u_2\begin{bmatrix} 0 & 0 \\ b_{21}^2 & 0 \end{bmatrix}\begin{bmatrix} z_1 \\ z_2 \end{bmatrix} + \begin{bmatrix} c \\ 0 \end{bmatrix}u_1$$

Basics of DCM: Neuronal and BOLD level

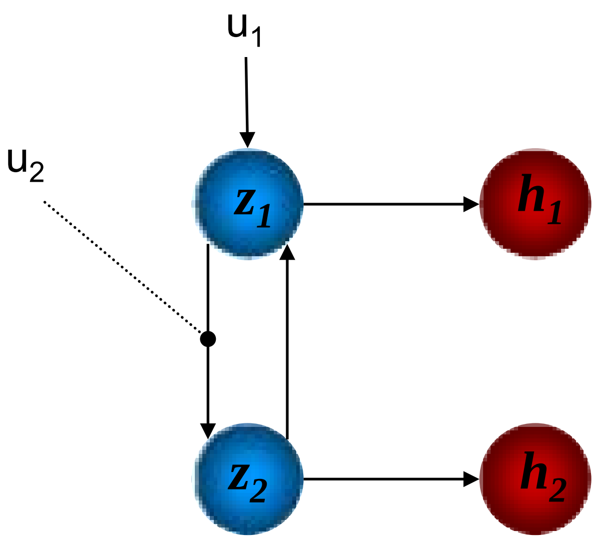
- Cognitive system is modelled at its underlying neuronal level (not directly accessible for fMRI).

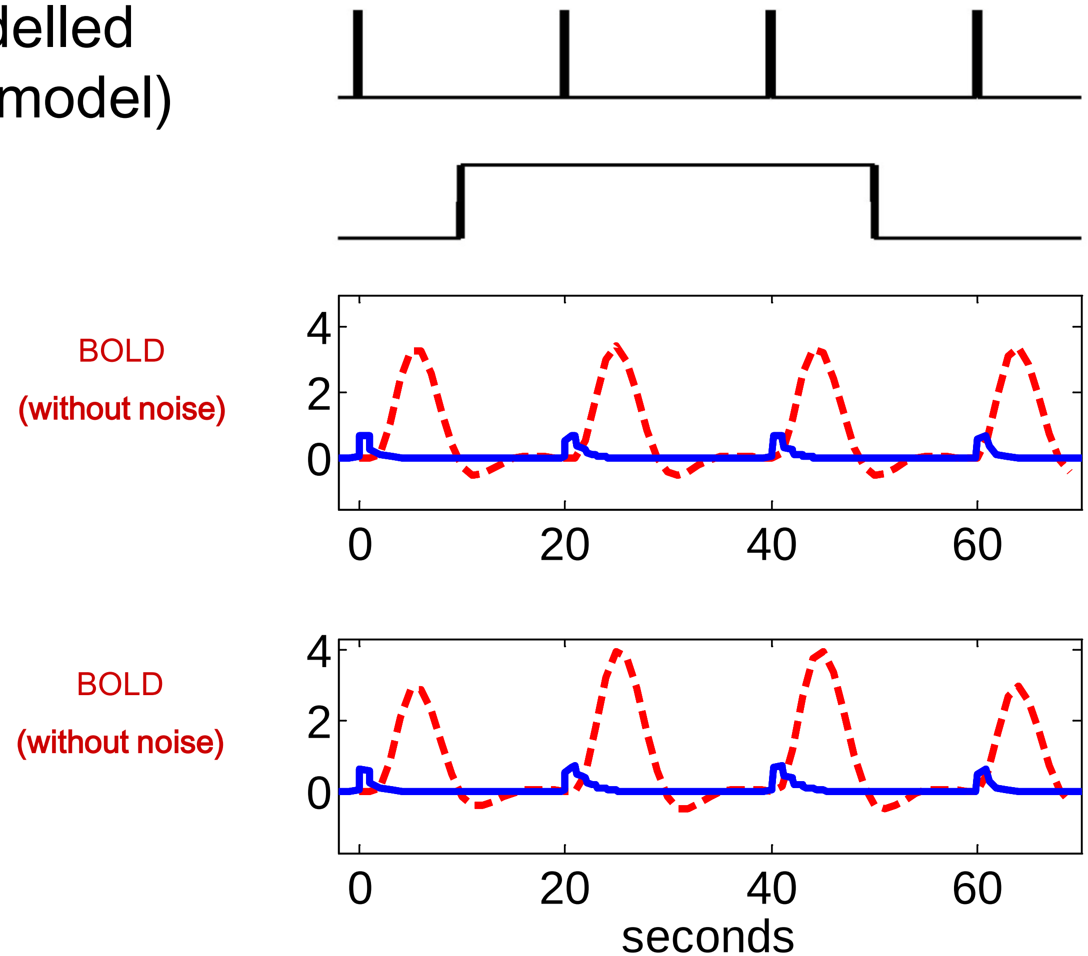
- The modelled neuronal dynamics (x) are transformed into area-specific BOLD signals (y) by a hemodynamic model (λ).



Haemodynamics: reciprocal connections

h(u,θ) represents the modelled BOLD response (balloon model) to inputs in this network

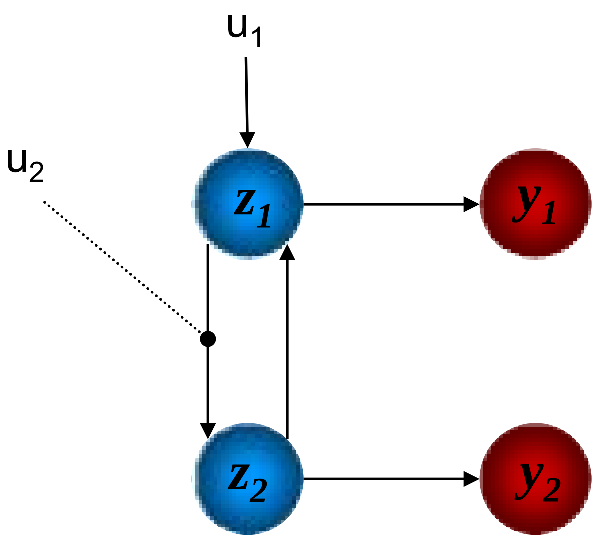


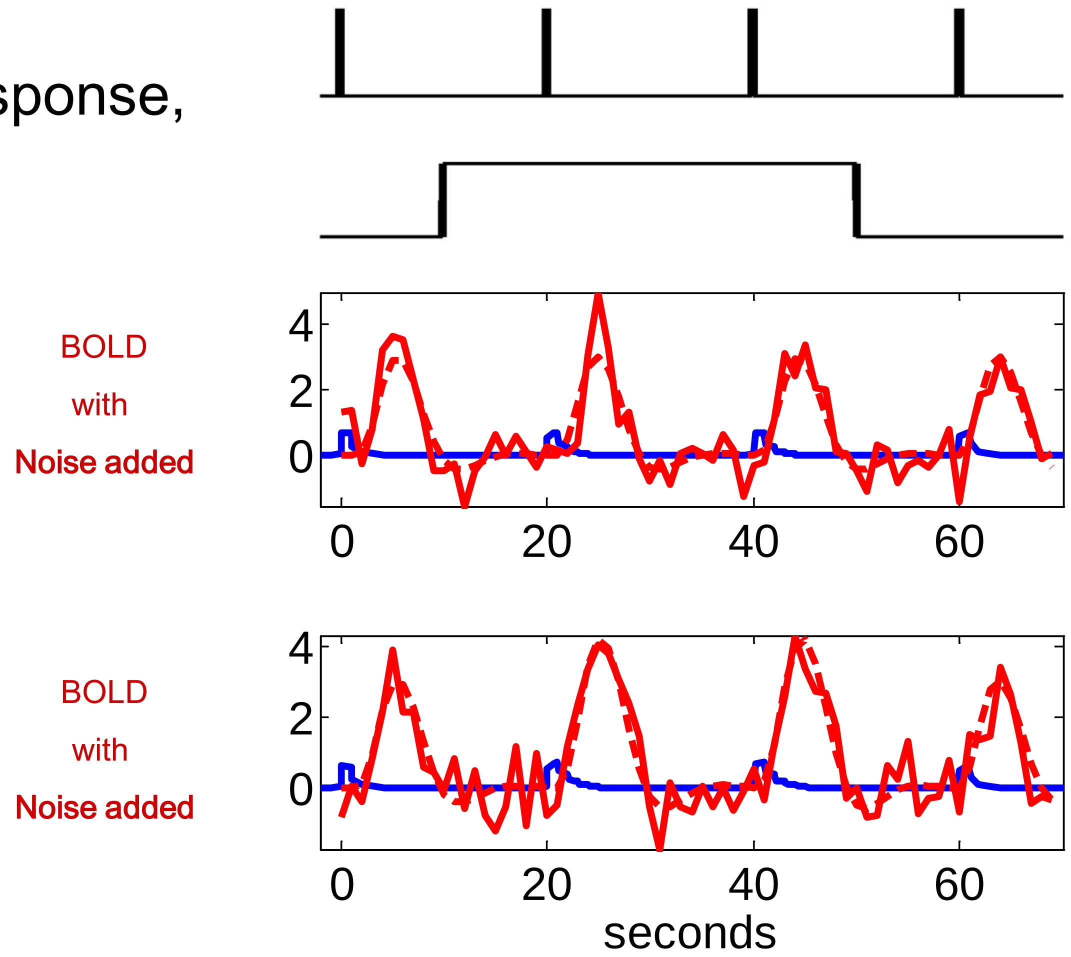


blue: neuronal activity
red: bold response

Haemodynamics: reciprocal connections

y represents simulated observation of BOLD response, i.e. includes noise

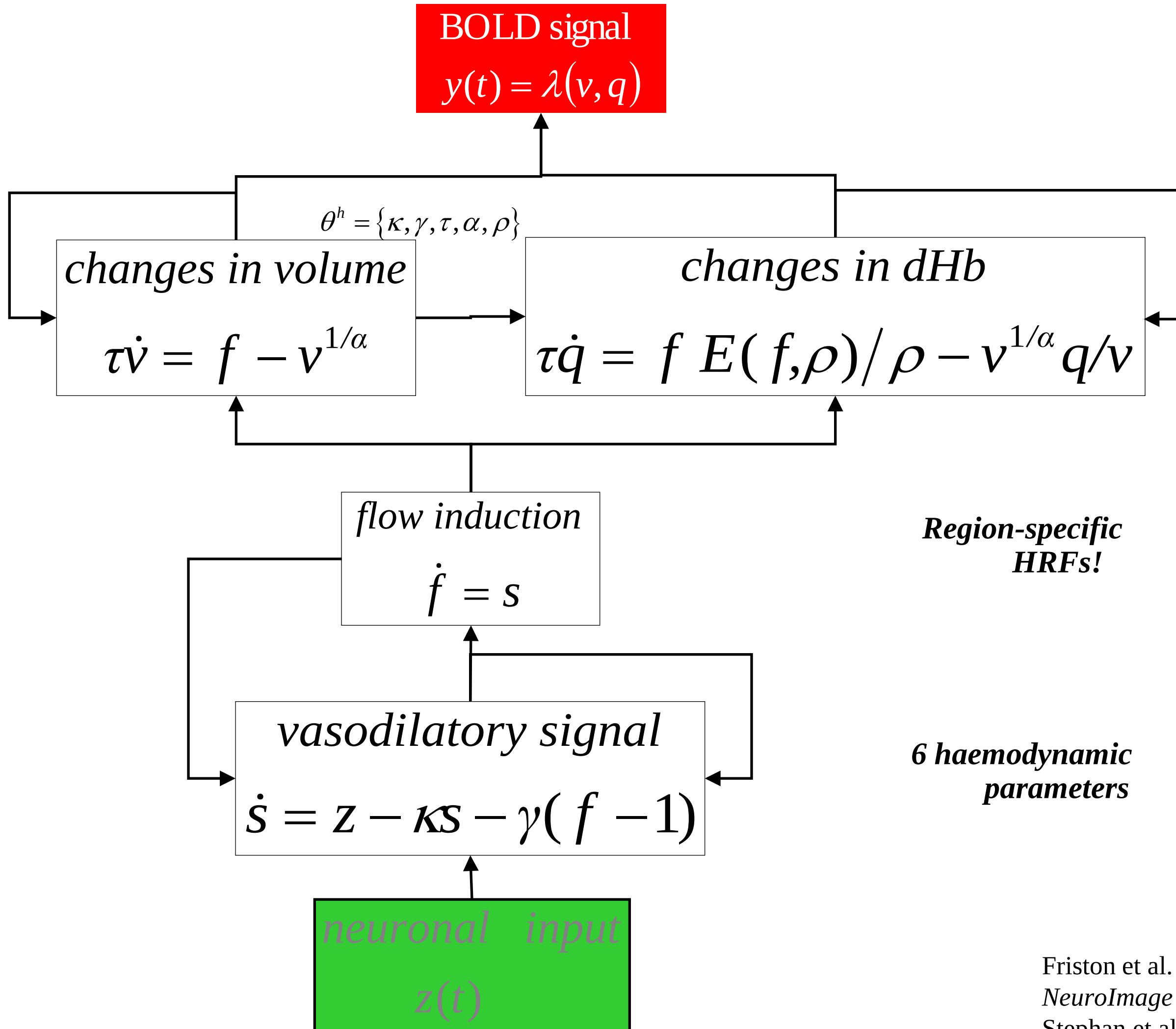




$$y = h(u, \theta) + e$$

The hemodynamic “Balloon” model

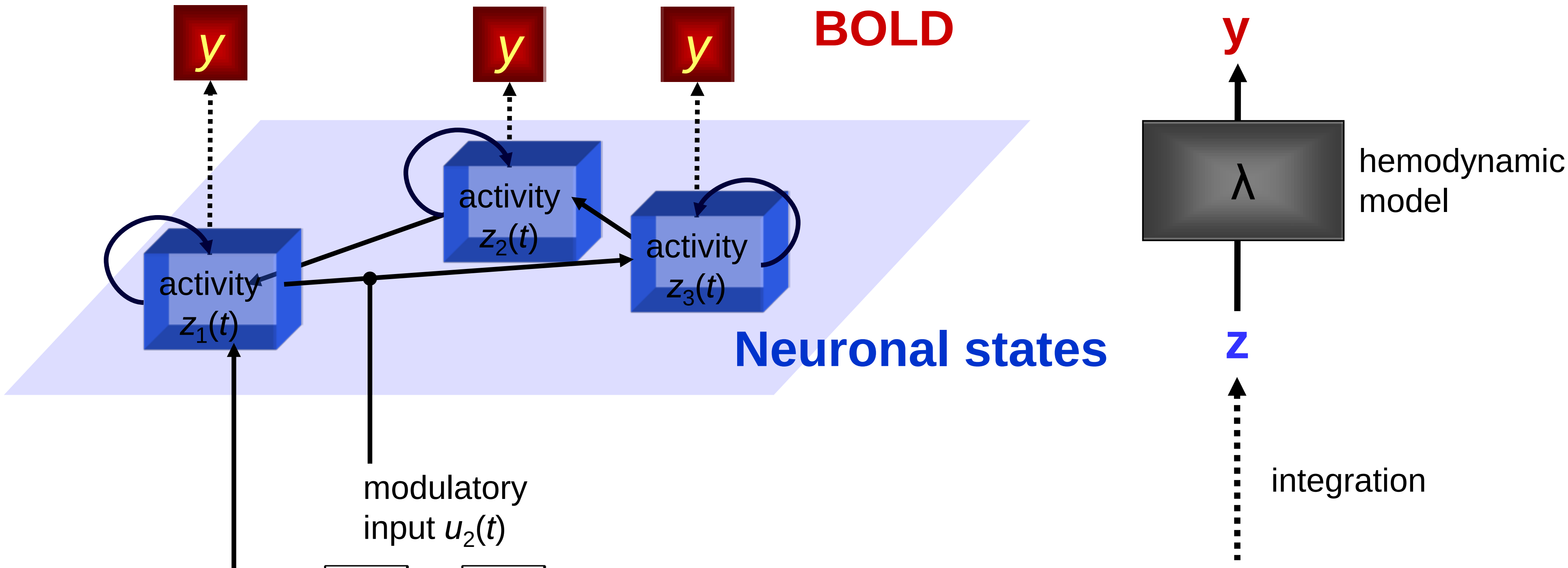
- 3 hemodynamic parameters:
- important for model fitting, but of no interest for statistical inference
- Computed separately for each area → region-specific HRFs!

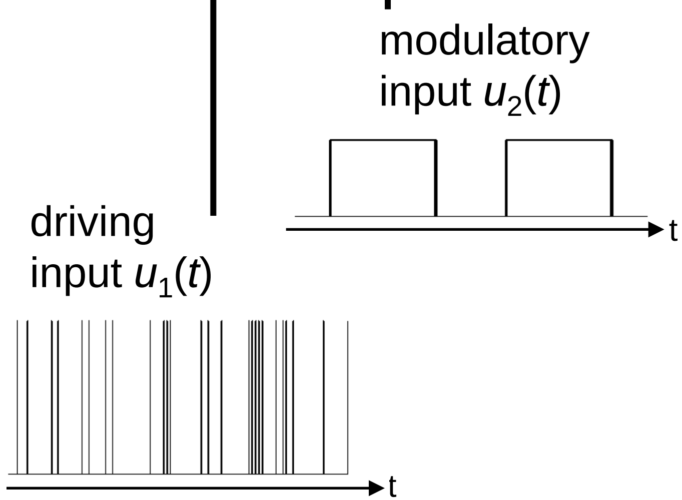


Region-specific HRFs!

6 haemodynamic parameters

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





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

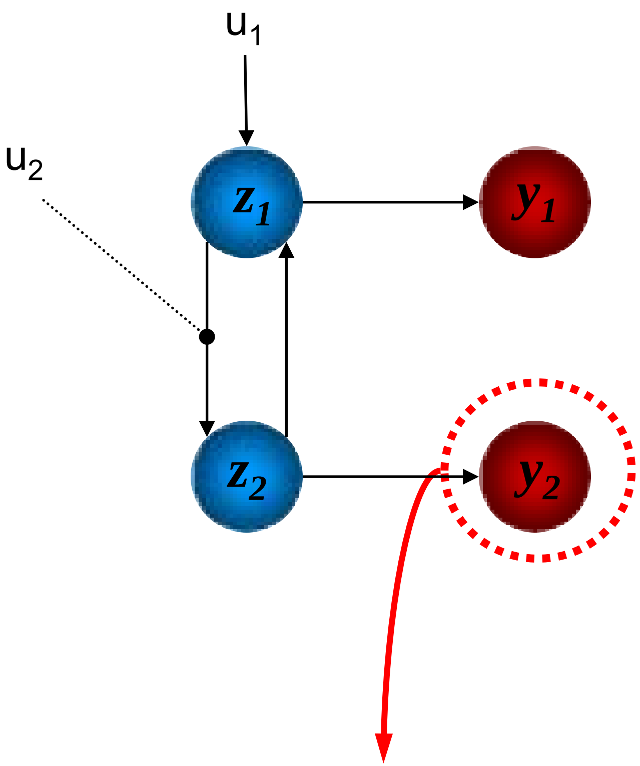
endogenous connectivity → $A = \dfrac{\partial \dot{x}}{\partial x}$

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

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

Stephan & Friston (2007),
Handbook of Brain Connectivity

Measured vs Modelled BOLD signal

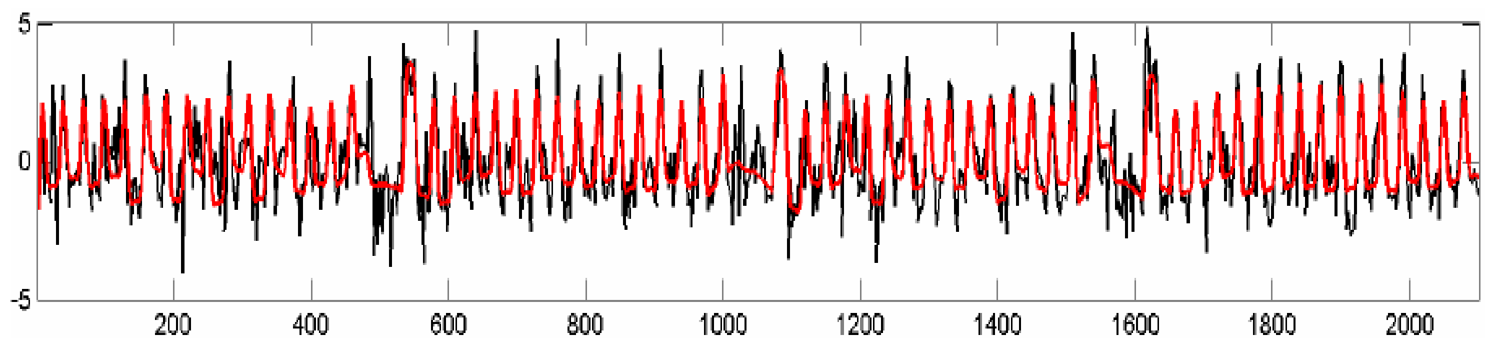


Recap

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.



Overview

- Brain connectivity: types & definitions
- Functional connectivity
- Psycho-physiological interactions (PPI)
- Dynamic causal models (DCMs)
  - Basic idea
  - Neural level
  - Hemodynamic level
  - Preview: priors & inference on parameters and models
- Practical examples

Bayesian statistics

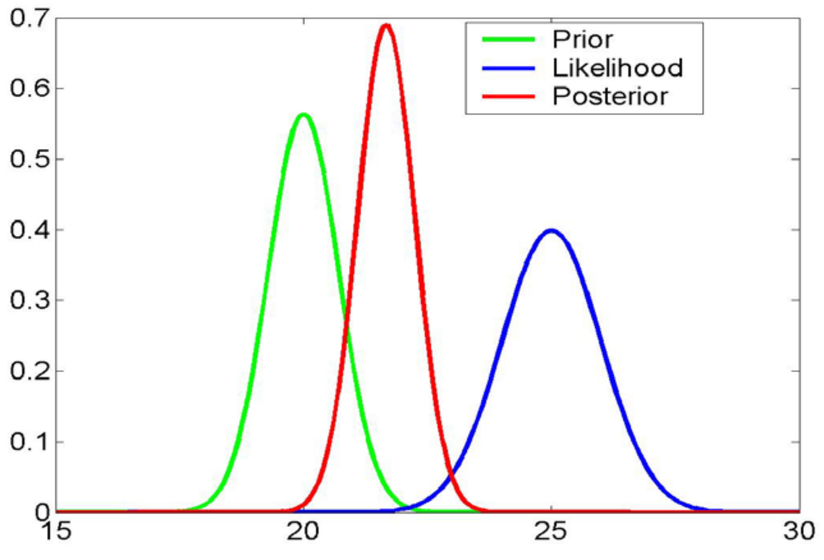
Express our **prior knowledge** or “belief” about parameters of the model

new data $\quad$ prior knowledge

$$\boxed{p(y\,|\,\theta)} \qquad \boxed{p(\theta)}$$

$$\boxed{p(\theta\,|\,y) \propto p(y\,|\,\theta)\,p(\theta)}$$

posterior $\propto$ likelihood • prior



Parameters governing

- Hemodynamics in a single region
- Neuronal interactions

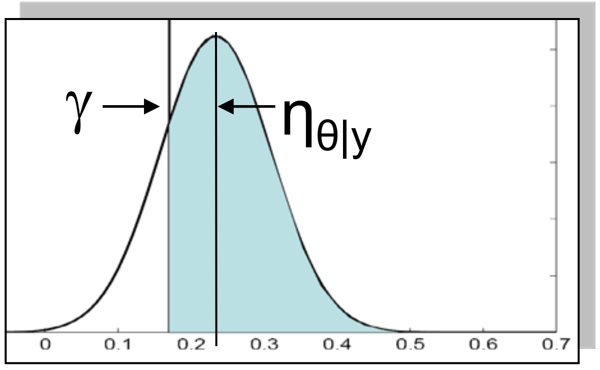
Constraints (priors) on

- 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?

Bayesian model averaging

Overview

- Brain connectivity: types & definitions

- Dynamic causal models (DCMs)

- Practical examples
  - Design of experiments and models
  - Simulating data

Planning a DCM-compatible study

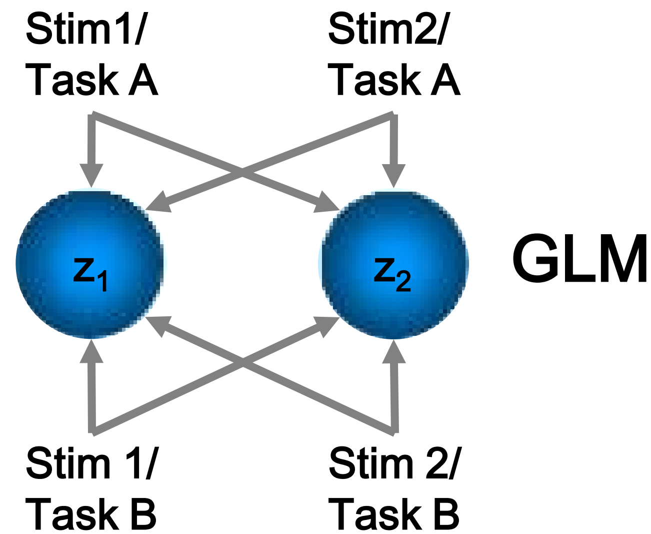
- Suitable experimental design:
  - any design that is suitable for a GLM
  - preferably multi-factorial (e.g. 2 x 2)
    - e.g. one factor that varies the driving (sensory) input
    - and one factor that varies the contextual input

- 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

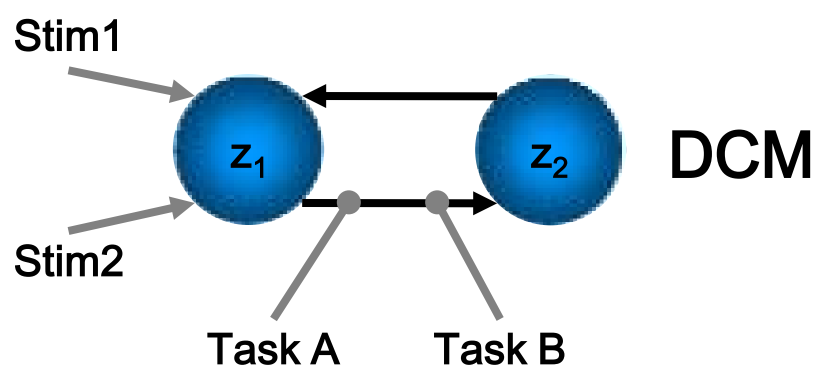
Task factor

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

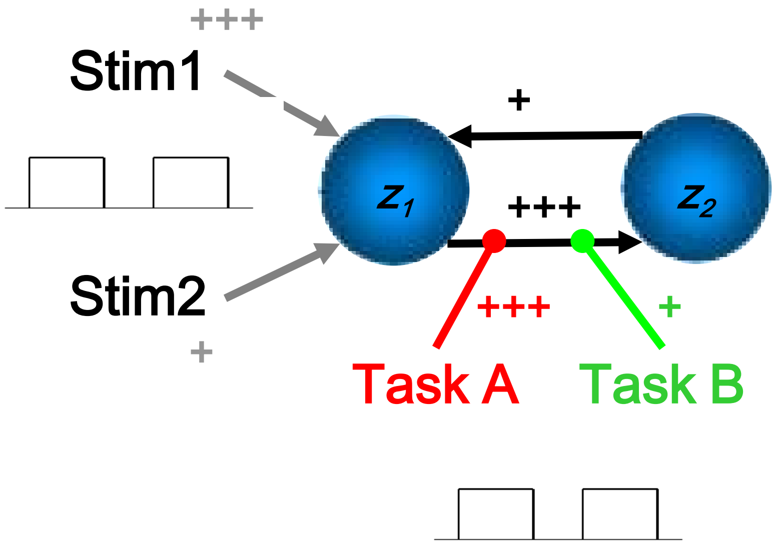


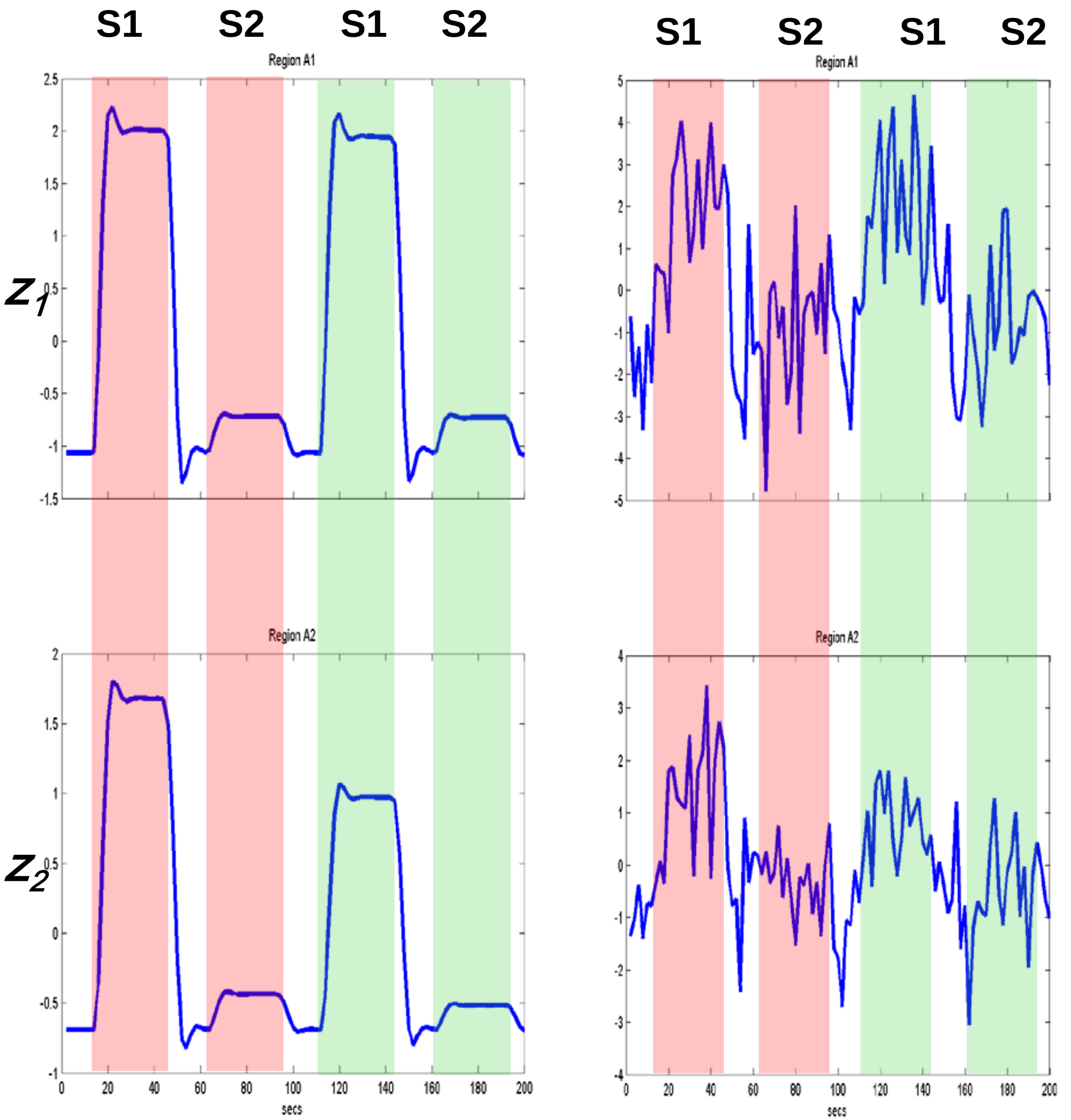
Let's assume that an SPM analysis shows a main effect of stimulus in z_1 and a stimulus $\times$ task interaction in z_2.

How do we model this using DCM?

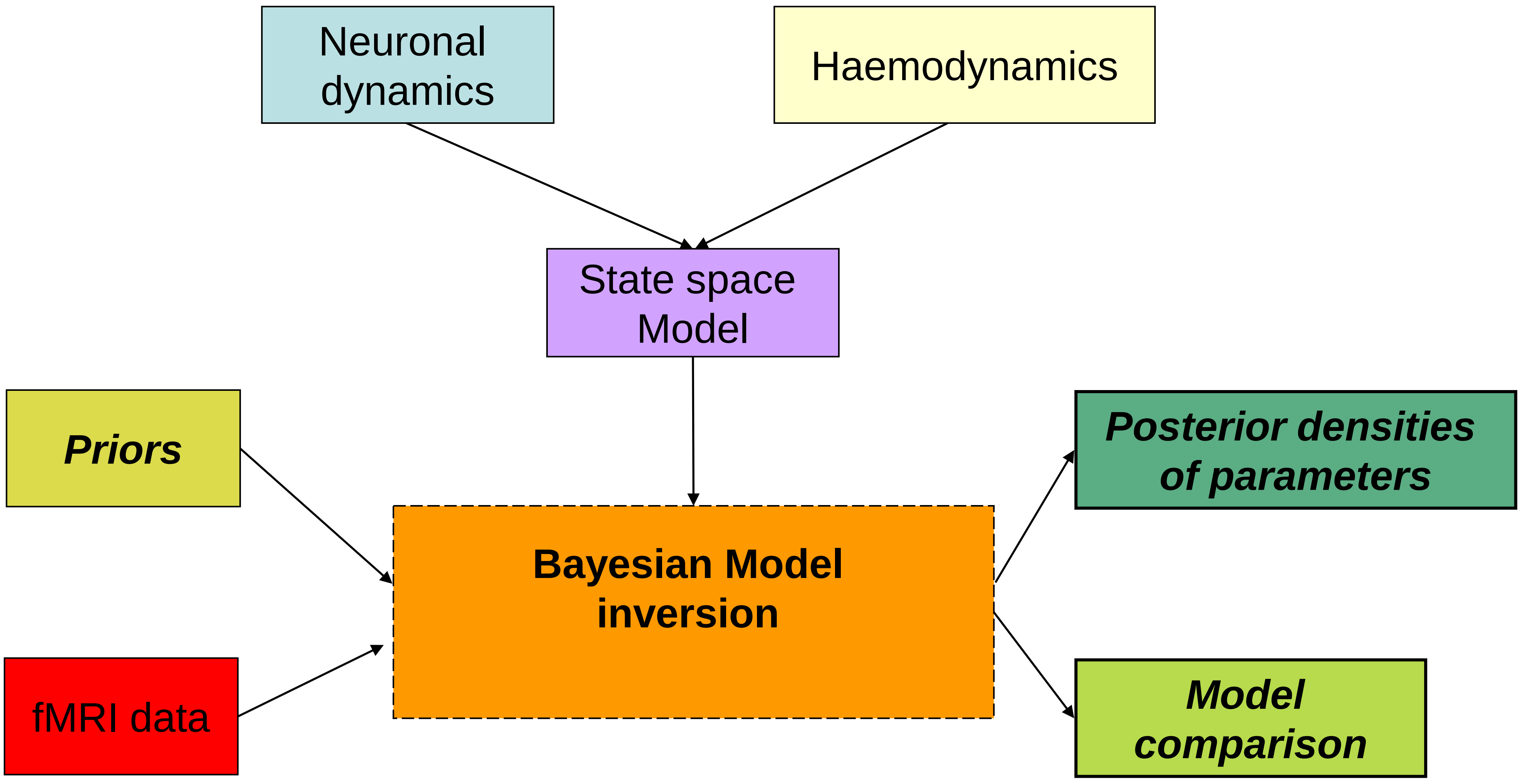


Simulated data





DCM roadmap


Neuronal dynamics
Haemodynamics
State space Model
Priors
Bayesian Model inversion
Posterior densities of parameters
fMRI data
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 for your attention