# Effective Connectivity & Dynamic Causal Modelling

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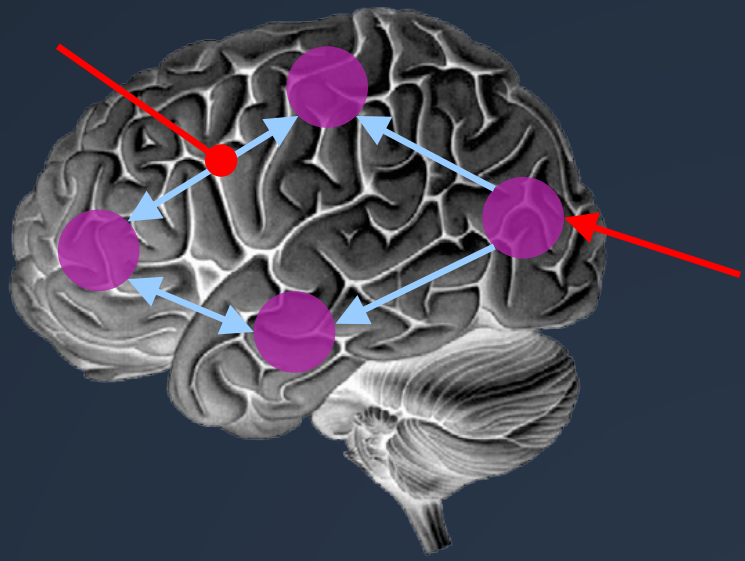
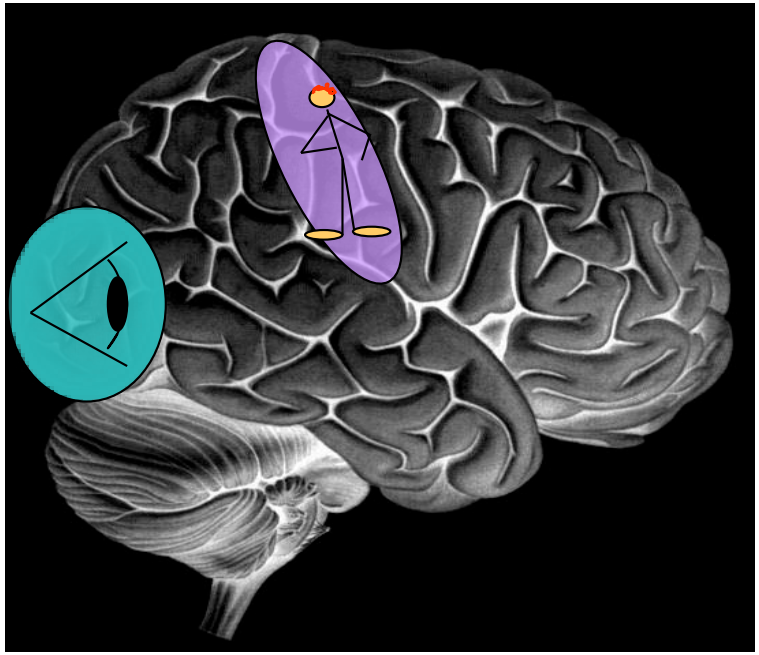
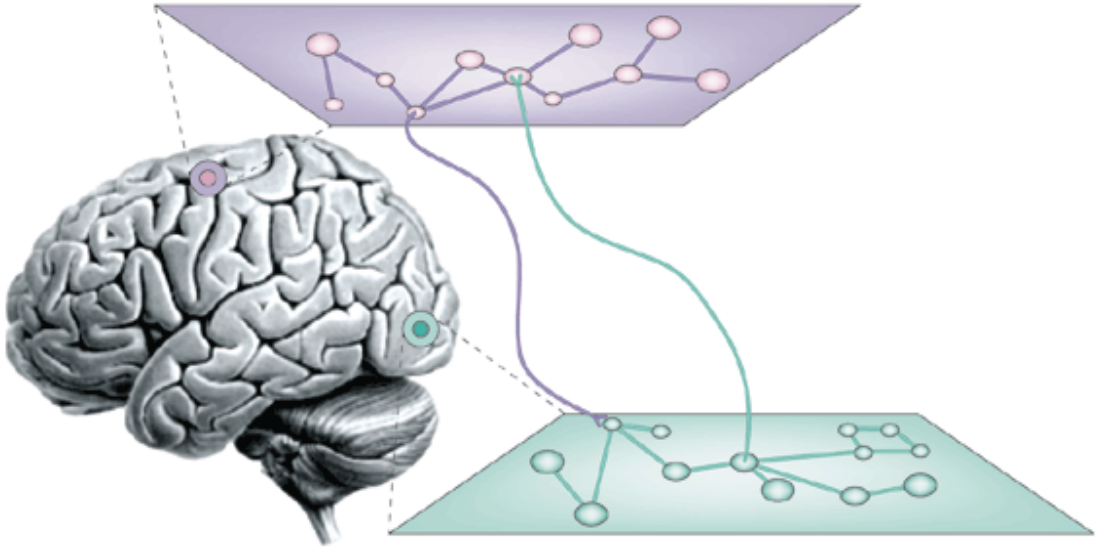


Advanced SPM course Zurich, February 18-19, 2016

## Functional Specialisation



## Functional Integration



# Outline

1 Investigating Connectivity

2 Dynamic causal models (DCMs)

3 Applications of DCM to fMRI data

4 Final remarks and useful references

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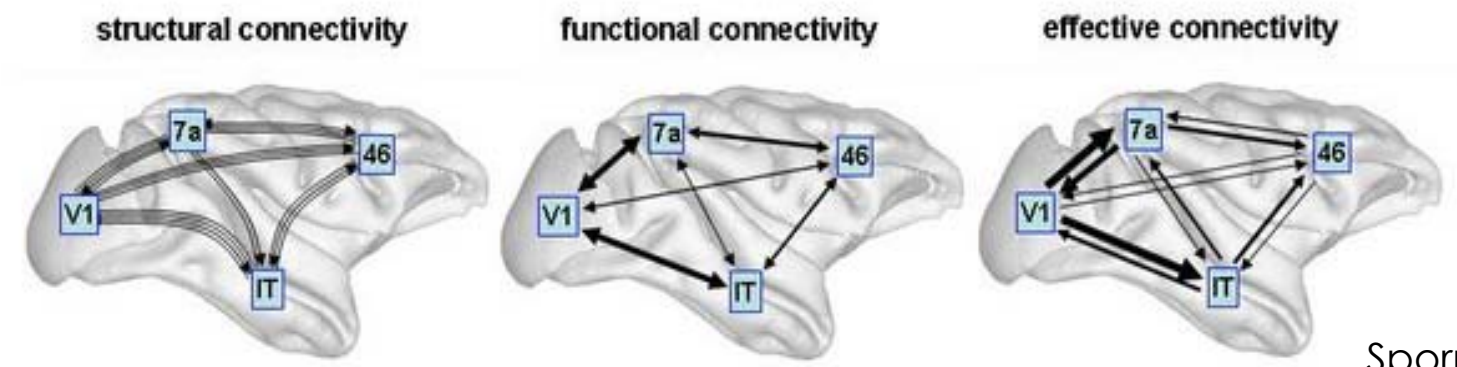
# Structural, functional & effective connectivity




Sporns 2007, *Scholarpedia*

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

  Context-independent

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

  Mechanism - free

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

  Mechanistic

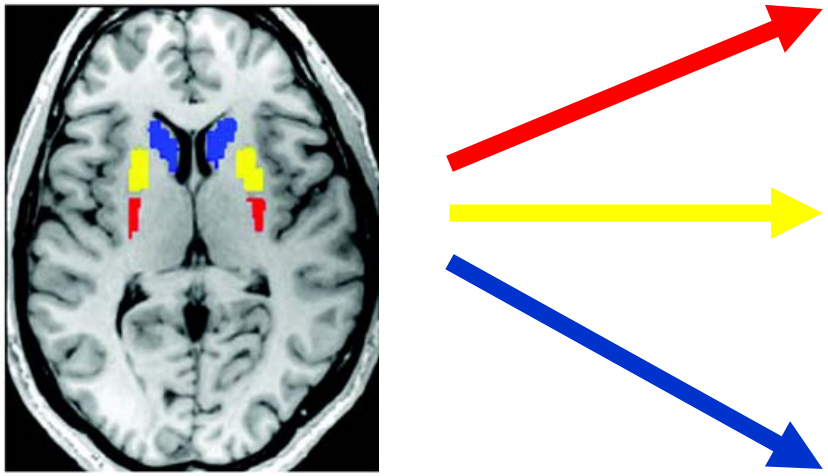
# Functional Connectivity

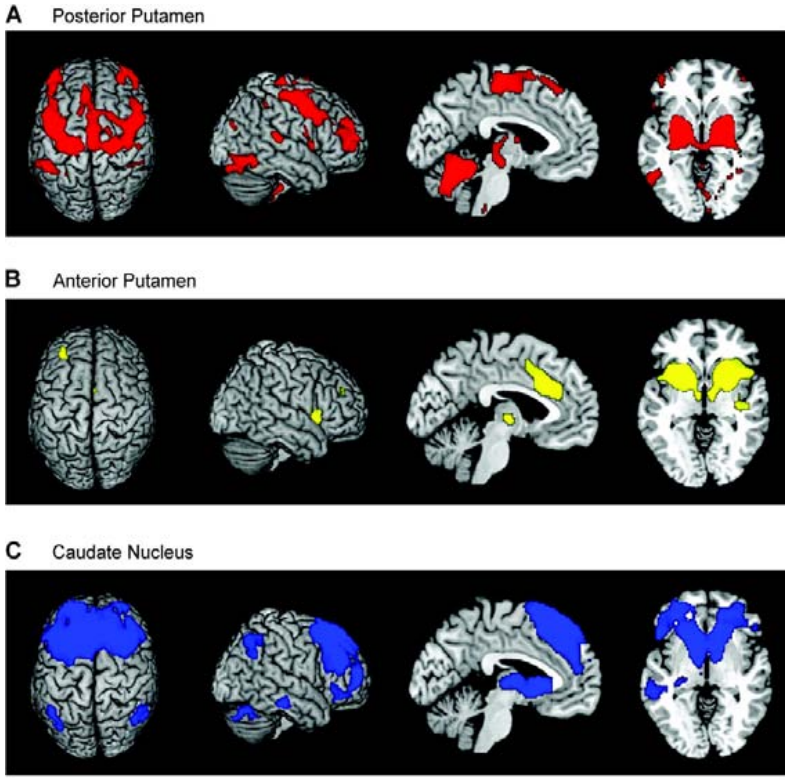
Statistical dependencies between regional time series

- Seed voxel correlation analysis
- Coherence analysis
- Eigen-decomposition (PCA, SVD)
- Independent component analysis (ICA)
- …

# Seed voxel correlation analyses

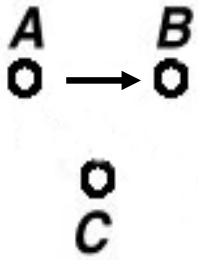
- hypothesis-driven choice of a seed voxel /roi
- extract *reference* time series
- voxel-wise correlation with all other voxels



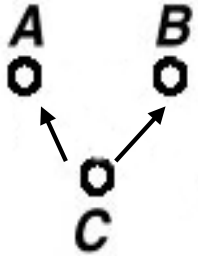


# Functional Connectivity

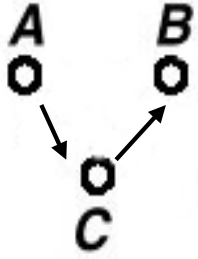
- Pro
  - useful when we have no experimental control over the system of interest and no model of what caused the data (e.g. sleep, hallucinations, etc.)




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



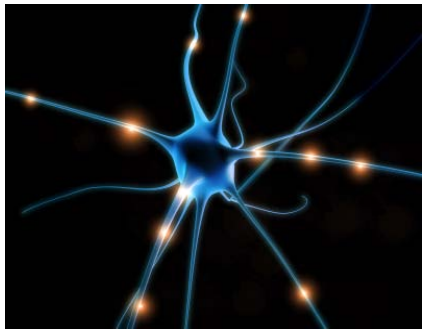

Effective Connectivity



# 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
- Time series models (e.g. MAR, Granger causality)
  Harrison et al. 2003, Goebel et al. 2003, but see Smith et al. 2012
- Ancestral graph theory
  Waldorp et al. 2011
- Dynamic Causal Modelling (DCM)
  *bilinear:* Friston et al. 2003; *nonlinear:* Stephan et al. 2008; *stochastic:* Li et al. 2011

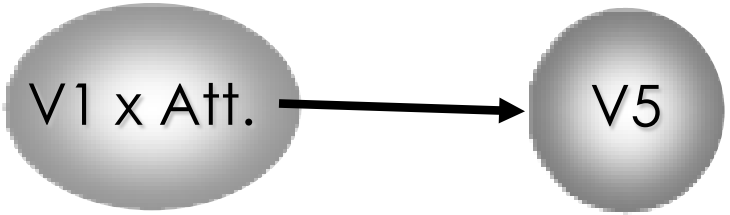
# Psycho-physiological interactions (PPI)

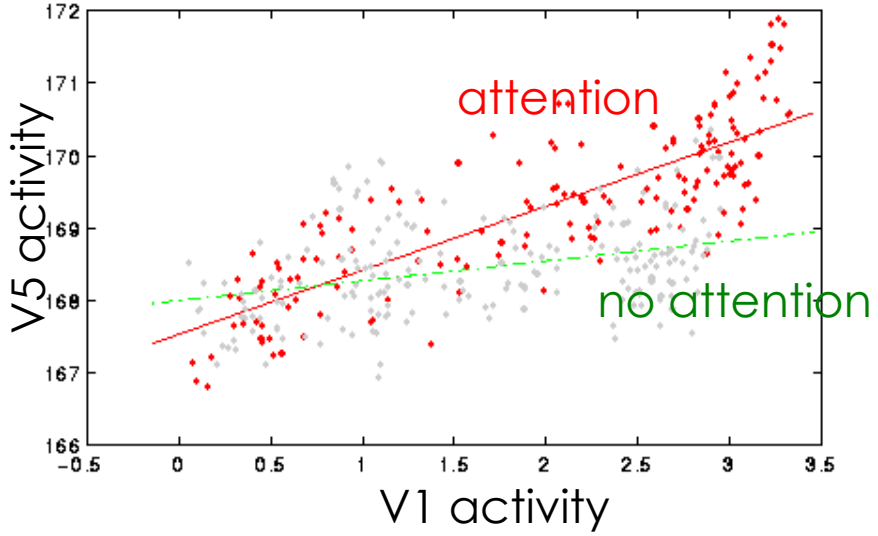
- Bilinear model of how the psychological context **A** changes the influence of area **B** on area **C** :

$$\mathbf{B} \times \mathbf{A} \rightarrow \mathbf{C}$$

- Add regressor to the GLM: the timeseries of VOI x psychological context

- 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
  - Ignores differences in neurovascular coupling in different areas
  - ignores time-series properties of the data

DCM for more robust statements of effective connectivity

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2 Dynamic causal models (DCMs)
- Basic idea
- Neural level
- Hemodynamic level
- Parameter estimation, priors & inference

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4 Final remarks and useful references

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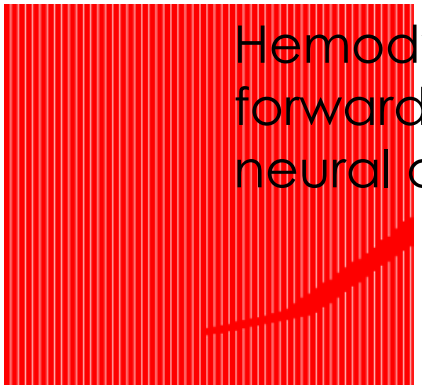
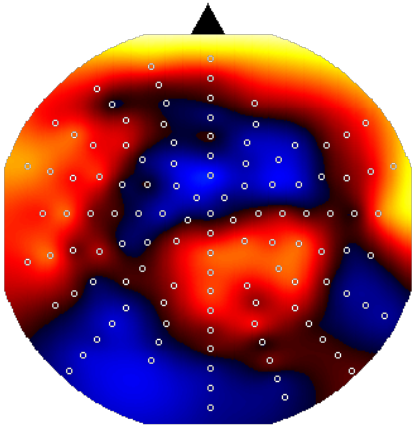
# Dynamic Causal Modelling (DCM)



Hemodynamic
forward model:
neural activity→BOLD

Electromagnetic
forward model:
neural activity→EEG
MEG
LFP



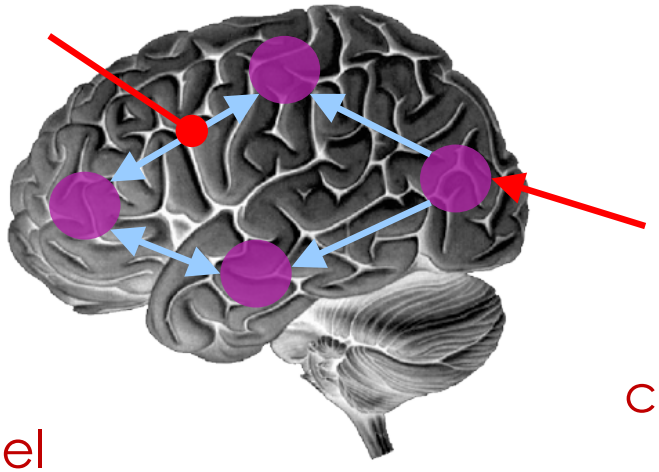
Neural model:

regional interactions →

neural activity:

fMRI

EEG/MEG



simple neuronal model
complicated forward model

complicated neuronal model
simple forward model

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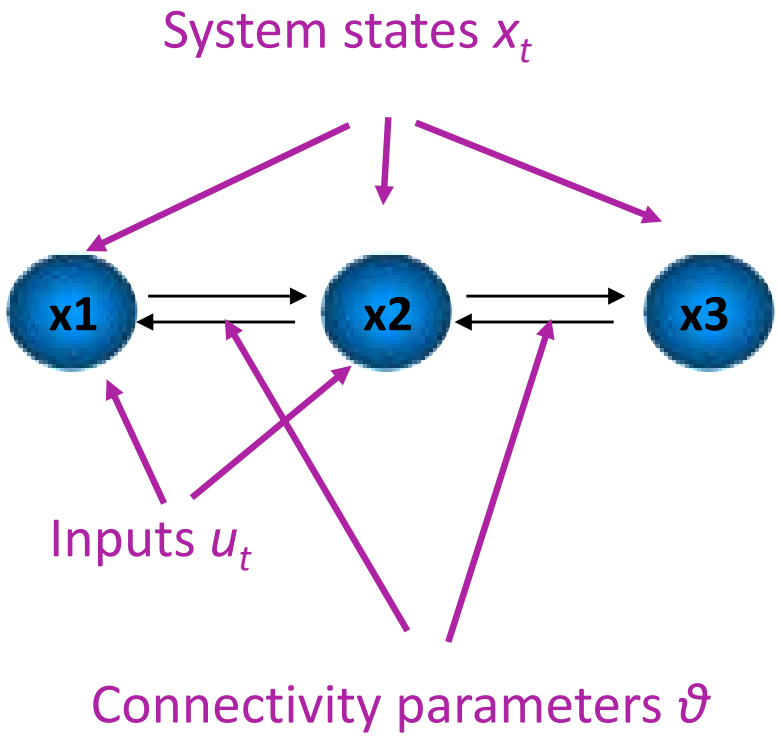
# Neural model

- Aim: model temporal evolution of a set of neuronal states $x_t$

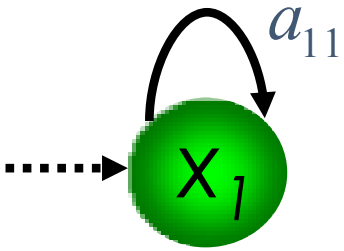



State changes are dependent on:

- the current state x
- external inputs u
- its connectivity $\vartheta$

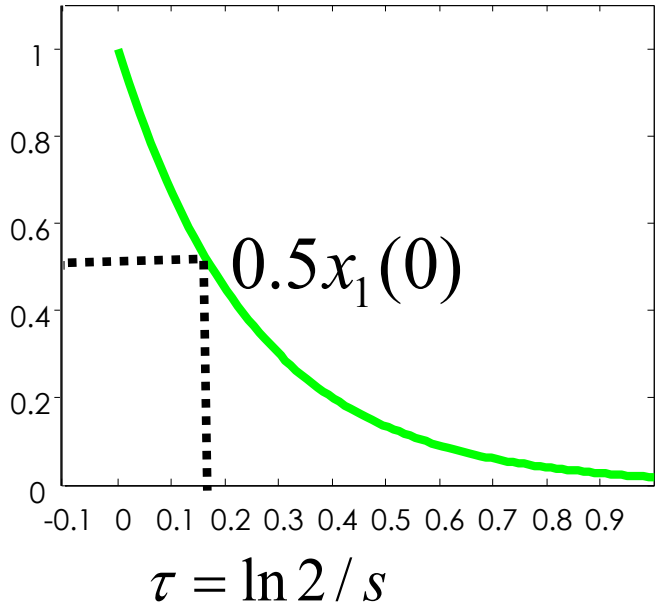
$$\frac{dx}{dt} = F(x, u, \theta)$$

# DCM parameters = rate constant

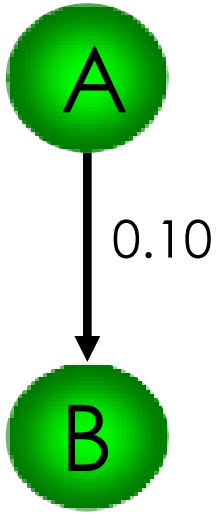



$$=\quad \frac{dx_1}{dt} = a_{11}x_1 \quad \rightarrow \quad x_1(t) = x_1(0)\exp(a_{11}t)$$

*Decay function*

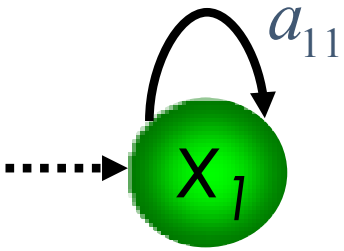



$$\tau = \ln 2 / s$$




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 current activity in A

# DCM parameters = rate constant

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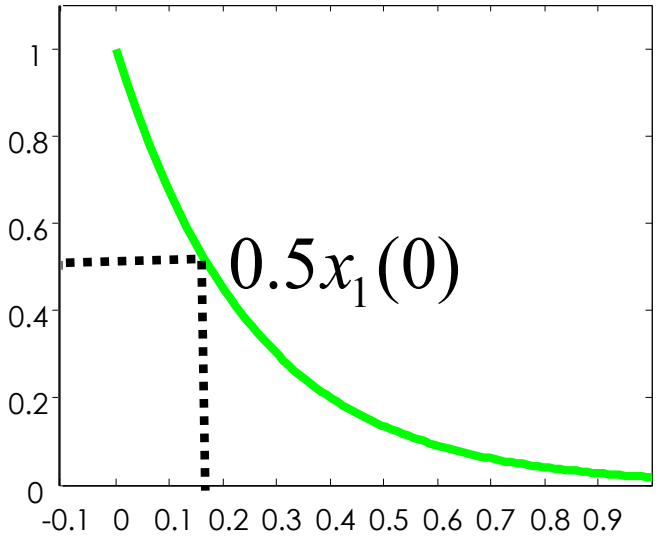
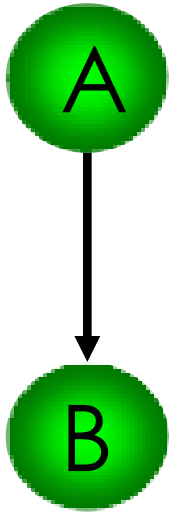
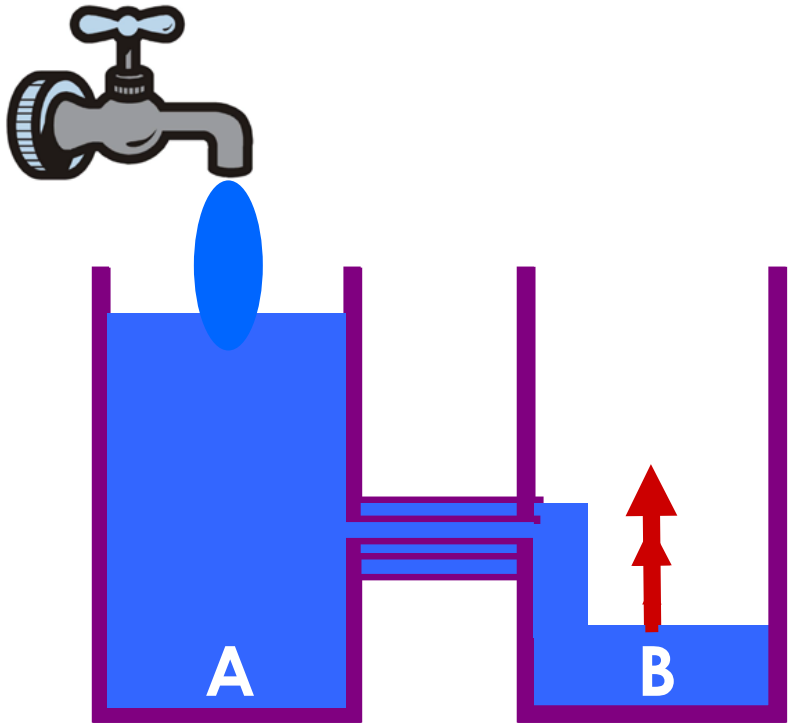
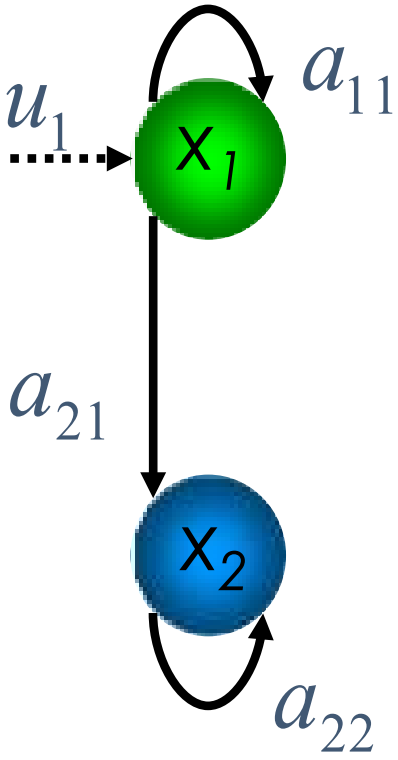


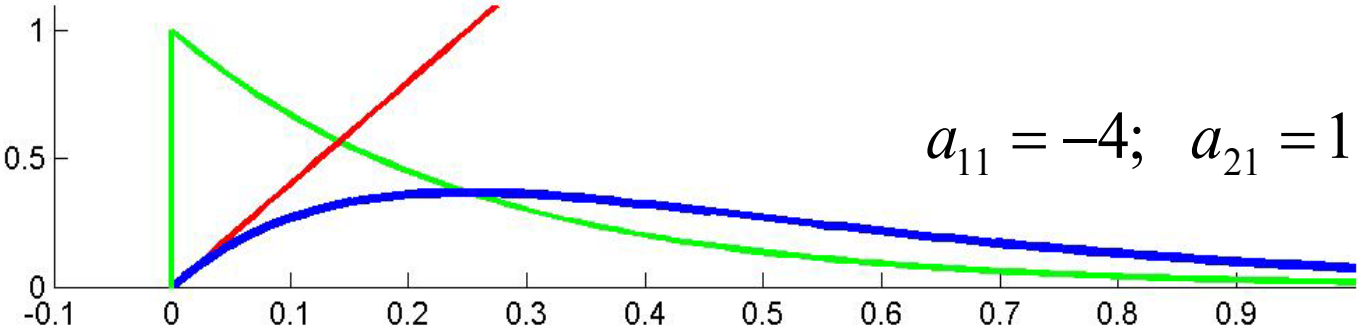

$$\tau = \ln 2 / s$$

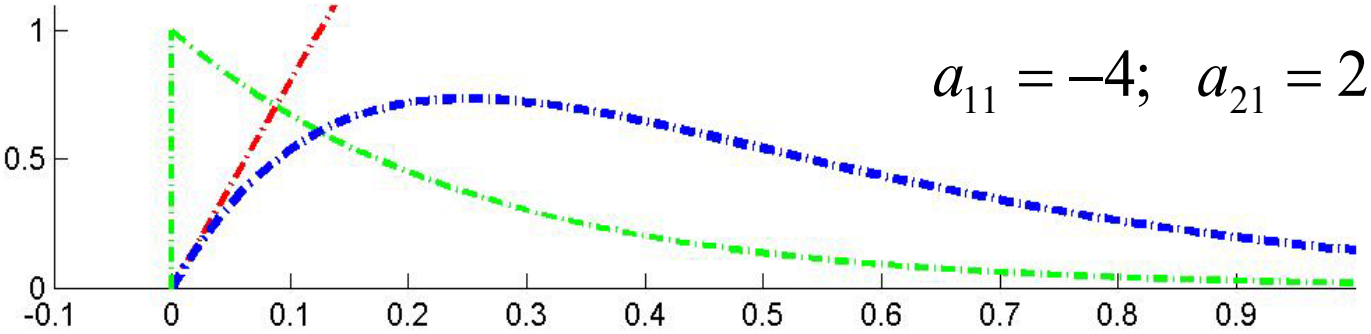


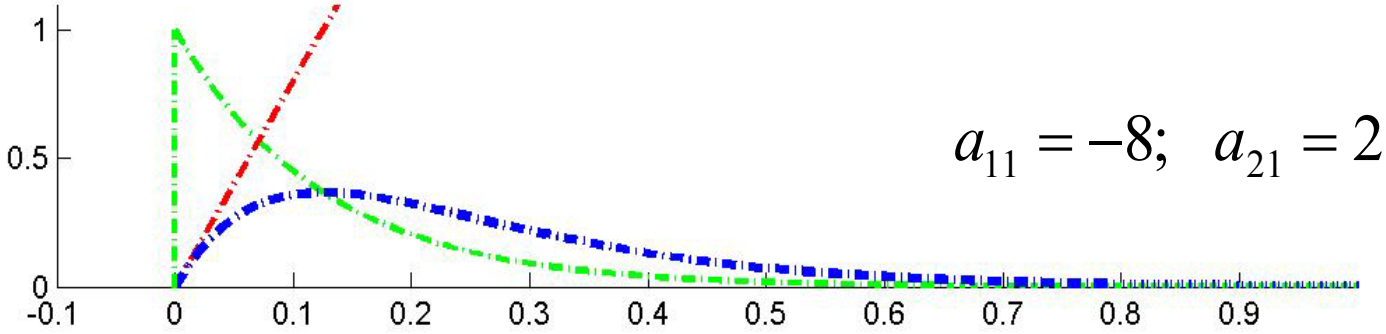



# Neurodynamics: 2 nodes with input

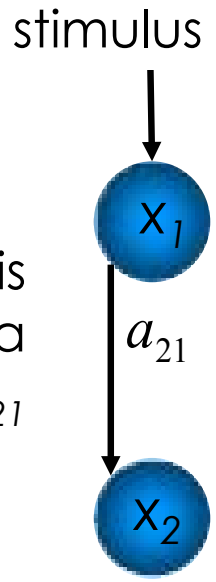


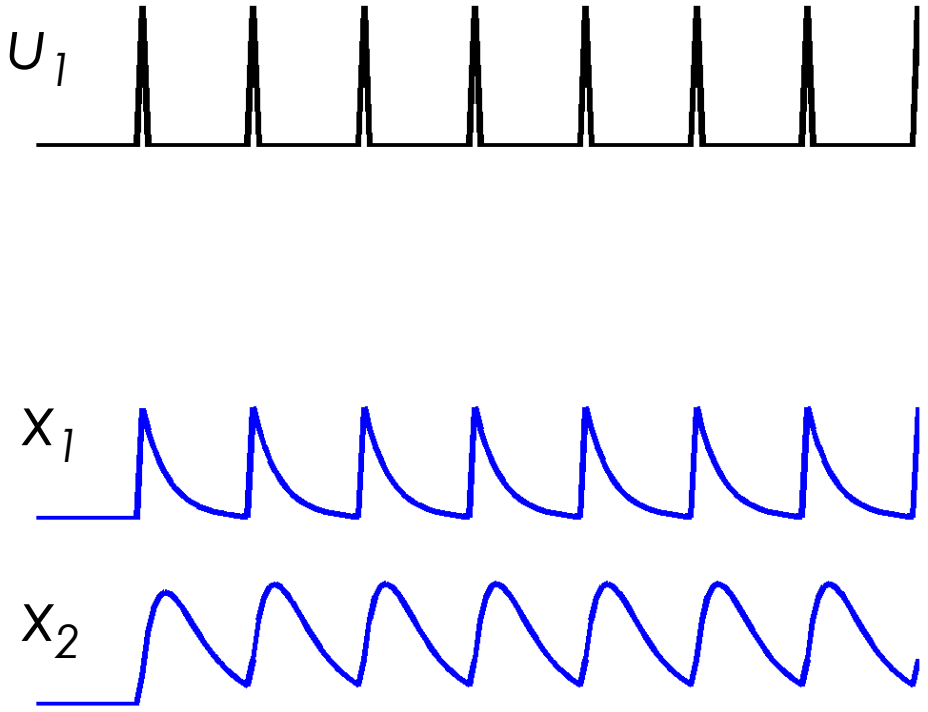



# Example: 2 nodes with input



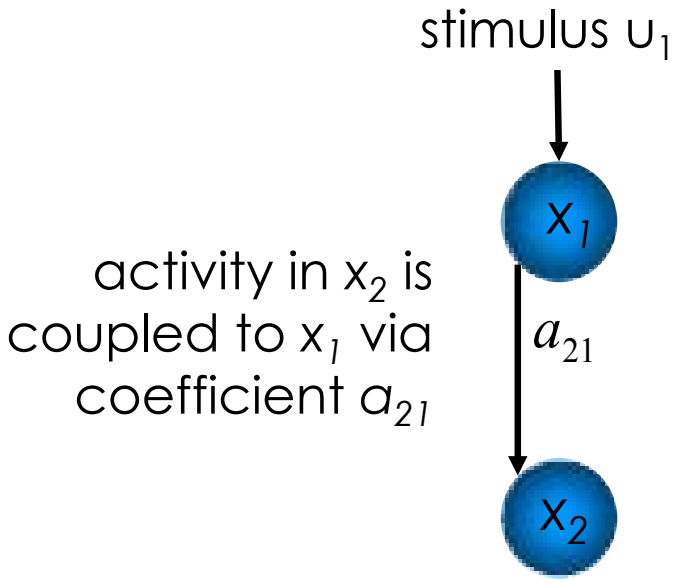

activity in $x_2$ is coupled to $x_1$ via coefficient $a_{21}$




$$\dot{x}_1 = a_{11}x_1 + c_{11}u_1$$
$$\dot{x}_2 = a_{21}x_1 + a_{22}x_2$$

$$\begin{bmatrix}\dot{x}_1\\ \dot{x}_2\end{bmatrix} = \begin{bmatrix}a_{11} & 0\\ a_{21} & a_{22}\end{bmatrix}\begin{bmatrix}x_1\\ x_2\end{bmatrix} + \begin{bmatrix}c_{11}\\ 0\end{bmatrix}u_1$$

# Example: 2 nodes with input

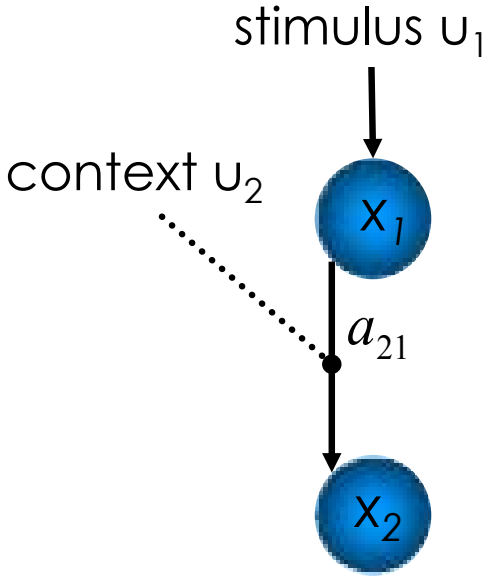


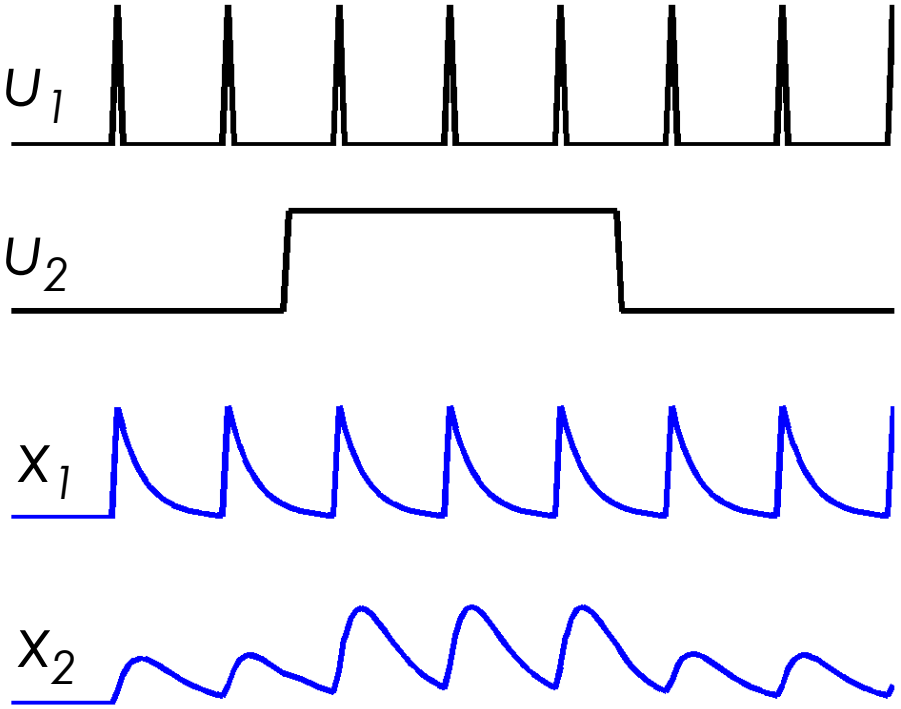

$$\dot{x} = Ax + Cu$$
$$\theta = \{A, C\}$$

$$\dot{x}_1 = a_{11}x_1 + c_{11}u_1$$
$$\dot{x}_2 = a_{21}x_1 + a_{22}x_2$$

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \end{bmatrix} = \begin{bmatrix} a_{11} & 0 \\ a_{21} & a_{22} \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} + \begin{bmatrix} c_{11} \\ 0 \end{bmatrix} u_1$$

# Example: context-dependent enhancement

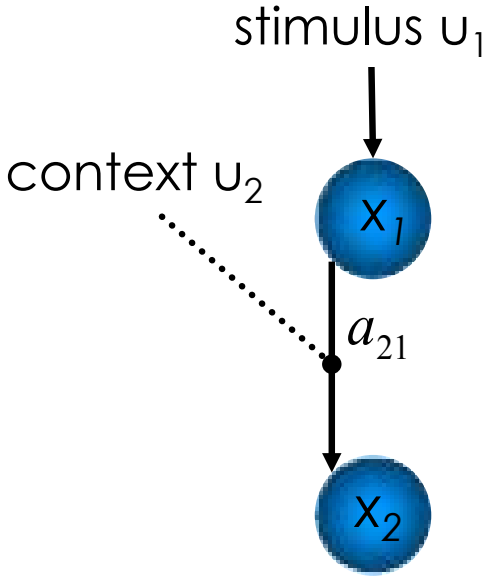


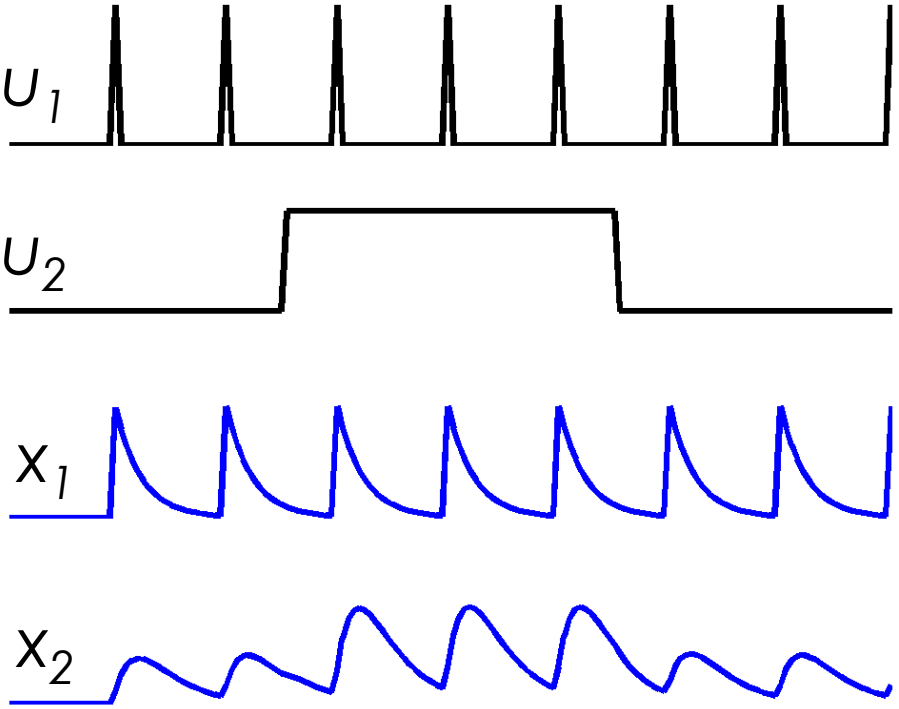




$$\dot{x}_1 = a_{11} \cdot x_1 + c_{11} \cdot u_1$$

$$\dot{x}_2 = a_{21} \cdot x_1 + u_2 \cdot b_{21}^{(2)} \cdot x_1 + a_{22} \cdot x_2$$

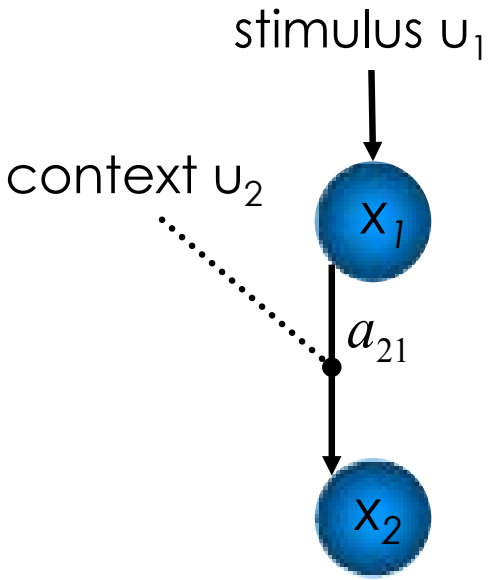
# Example: context-dependent enhancement




$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \end{bmatrix} = \left( \begin{bmatrix} a_{11} & 0 \\ a_{21} & a_{22} \end{bmatrix} + u_2 \begin{bmatrix} 0 & 0 \\ b_{21}^{(2)} & 0 \end{bmatrix} \right) \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} + \begin{bmatrix} c_{11} & 0 \\ 0 & 0 \end{bmatrix} \begin{bmatrix} u_1 \\ u_2 \end{bmatrix}$$

# Neural state equation




state changes

external inputs

current state

external inputs

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

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

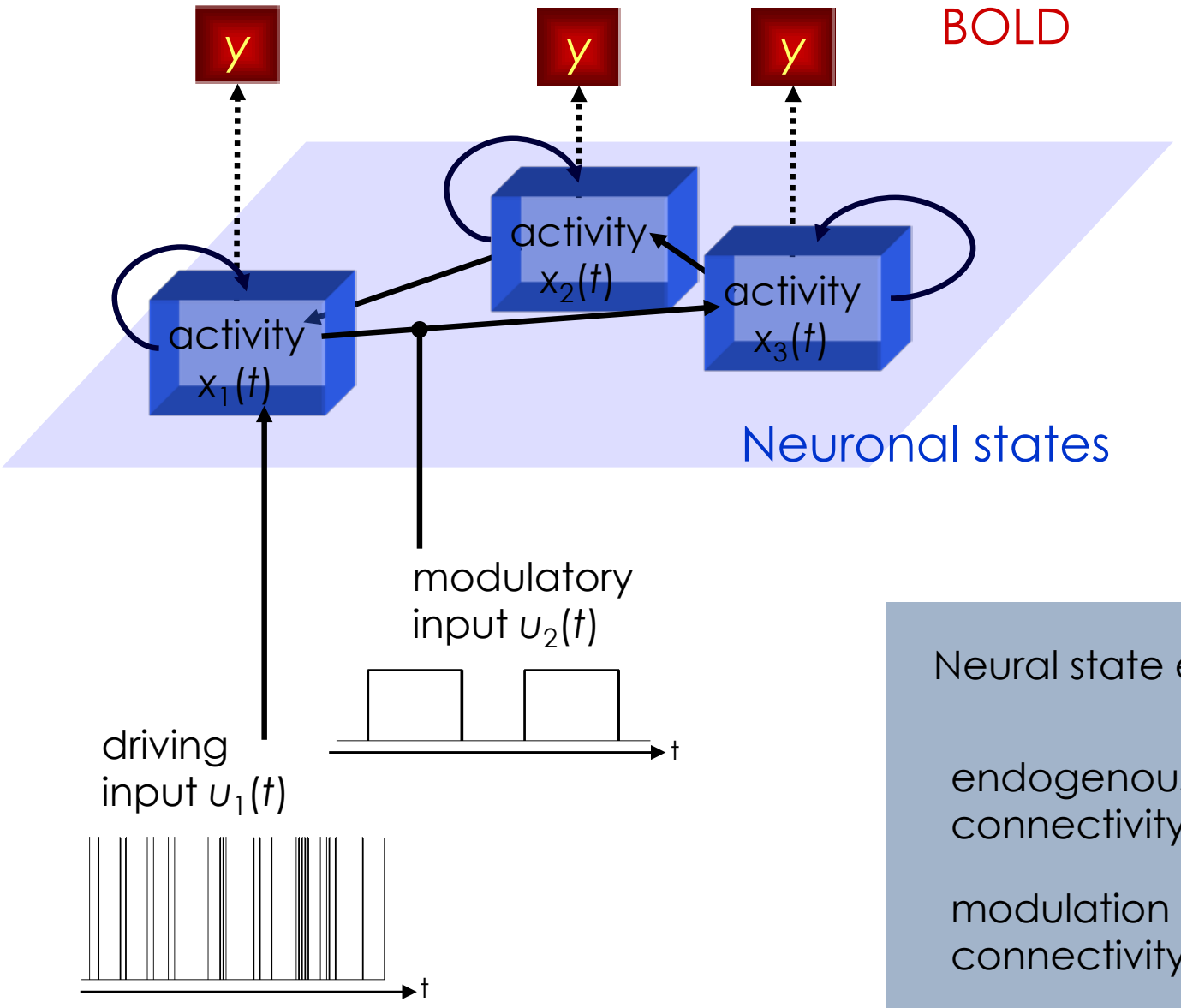
fixed connectivity

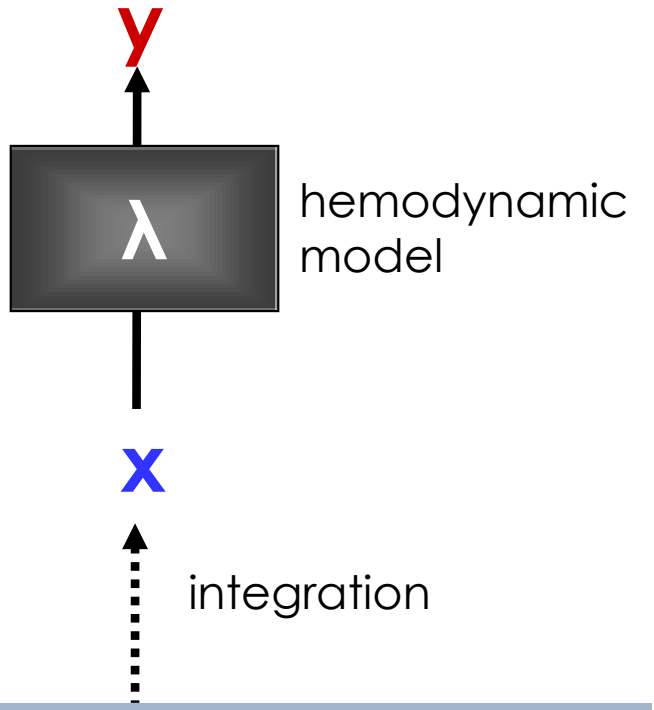
inputs that modulate connectivity

direct inputs drive activity

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \end{bmatrix} = \left( \begin{bmatrix} a_{11} & 0 \\ a_{21} & a_{22} \end{bmatrix} + u_2 \begin{bmatrix} 0 & 0 \\ b_{21}^{(2)} & 0 \end{bmatrix} \right) \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} + \begin{bmatrix} c_{11} & 0 \\ 0 & 0 \end{bmatrix} \begin{bmatrix} u_1 \\ u_2 \end{bmatrix}$$

# DCM for fMRI: the full picture




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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# Validity of 2-level model

OPEN ACCESS Freely available online

PLOS BIOLOGY

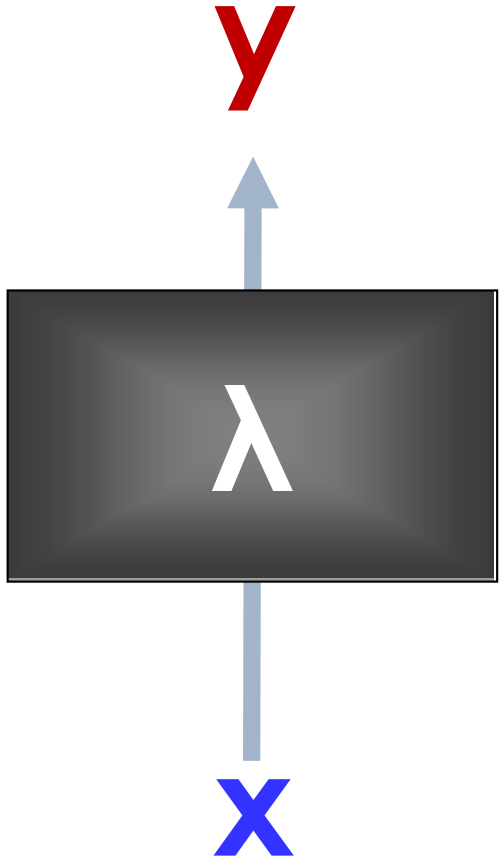
## Identifying Neural Drivers with Functional MRI: An Electrophysiological Validation

Olivier David[1,2*], Isabelle Guillemain[1,2], Sandrine Saillet[1,2], Sebastien Reyt[1,2], Colin Deransart[1,2], Christoph Segebarth[1,2], Antoine Depaulis[1,2]

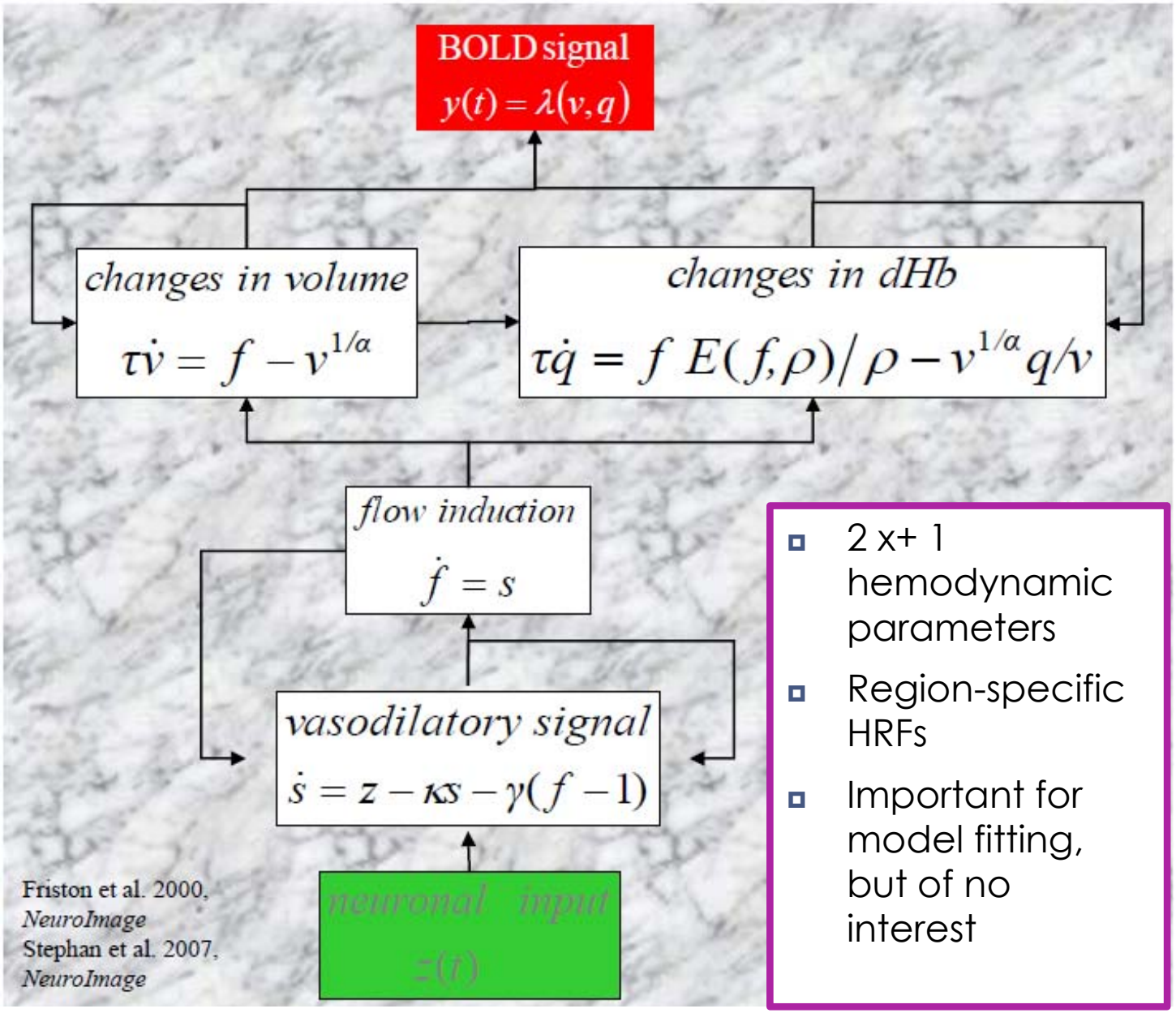
1 INSERM, U836, Grenoble Institut des Neur[illegible]nces, Grenoble, France, 2 Université Joseph Fourier, Grenoble, France

Whether functional magnetic [illegible]ging (fMRI) allows the identification of neural drivers remains an open question of particular importa[illegible]siological and neuropsychological models of the brain, and/or to understand neurophysiopathol[illegible]wing spontaneous spike-and-wave discharges originating from [illegible]eous electroencephalo-graphic (EEG) and f[illegible]egions strongly activated in fM[illegible]irectly and from hidde[illegible]naptic activity[illegible]try in ge[illegible] iEE[illegible] di[illegible] irr[illegible] int[illegible] stu[illegible]

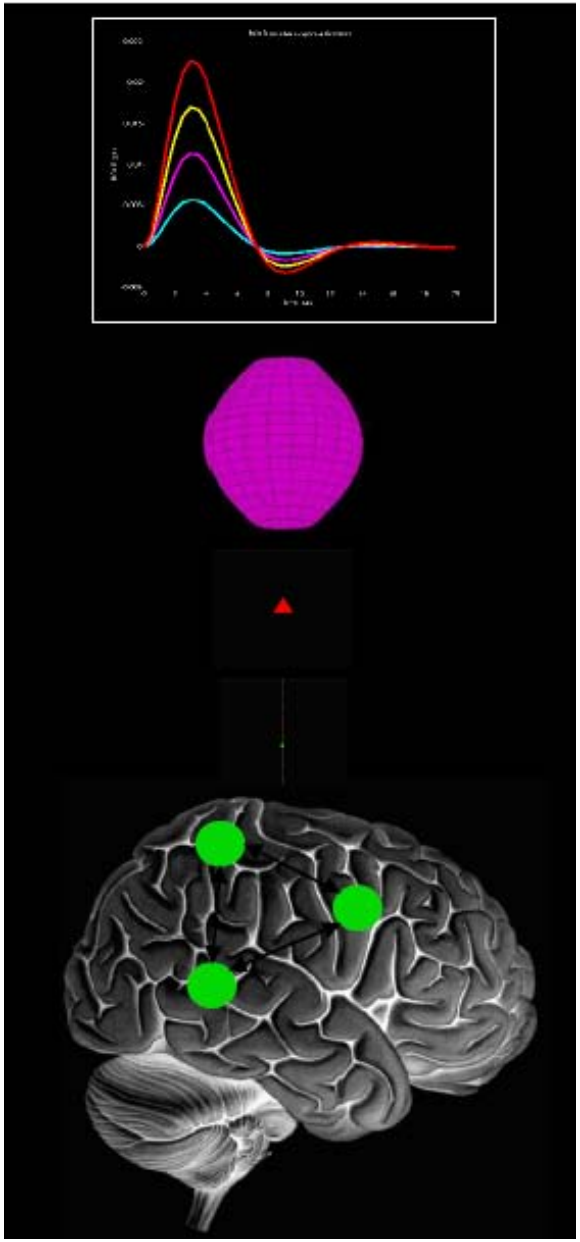
"Connectivity analysis applied directly on fMRI signals failed because hemodynamics varied between regions, rendering temporal precedence irrelevant" ....The neural driver was identified using DCM, where these effects are accounted for...



# The hemodynamic "Balloon" model



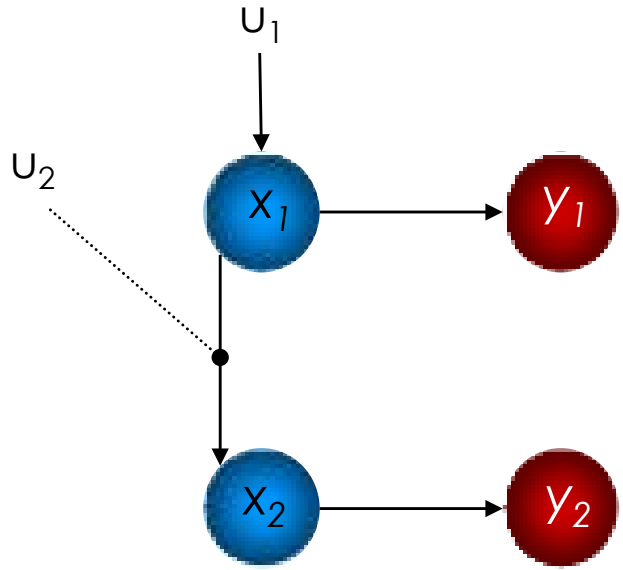

- 2 x+ 1 hemodynamic parameters
- Region-specific HRFs
- Important for model fitting, but of no interest



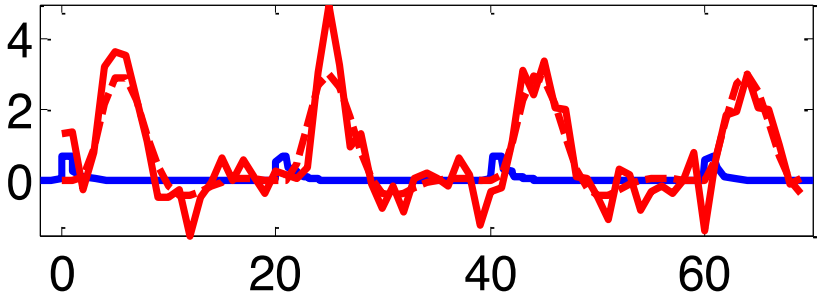
# Hemodynamic model

y represents the simulated observation of the bold response, including noise, i.e.

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




BOLD
(with noise added)




BOLD
(with noise added)

**x: neuronal activity**
**Y: BOLD response**

# Outline

1 Investigating Connectivity

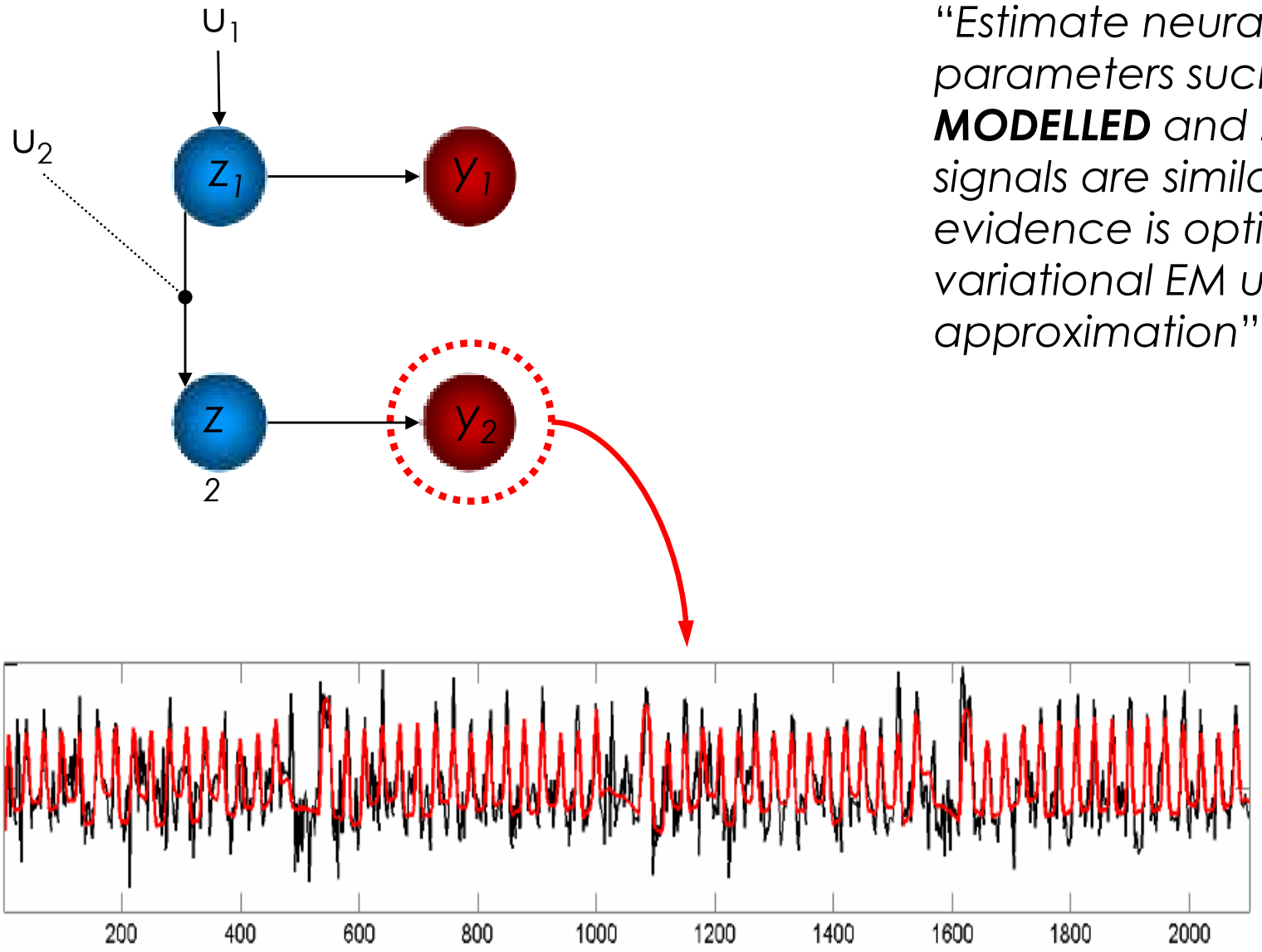
2 Dynamic causal models (DCMs)

- Basic idea
- Neural level
- Hemodynamic level
- Parameter estimation, priors & inference

3 Applications of DCM to fMRI data

4 Final remarks and useful references

# Parameter estimation: Bayesian inversion




*"Estimate neural & hemodynamic parameters such that the **MODELLED** and **MEASURED** BOLD signals are similar (model evidence is optimised), using variational EM under Laplace approximation"*

# Bayesian model inversion

Regional responses

Specify generative forward model
(with prior distributions of parameters)

Variational Expectation-Maximization algorithm

Iterative procedure:

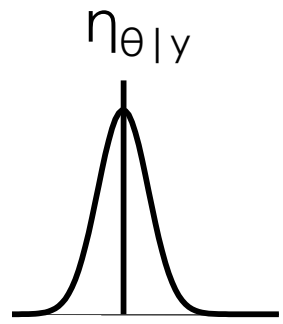
1. Compute model response using current set of parameters
2. Compare model response with data
3. Improve parameters, if possible

1. Gaussian posterior distributions of parameters

2. Model evidence

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

$p(y \mid m)$



# Bayesian model inversion & priors in DCM

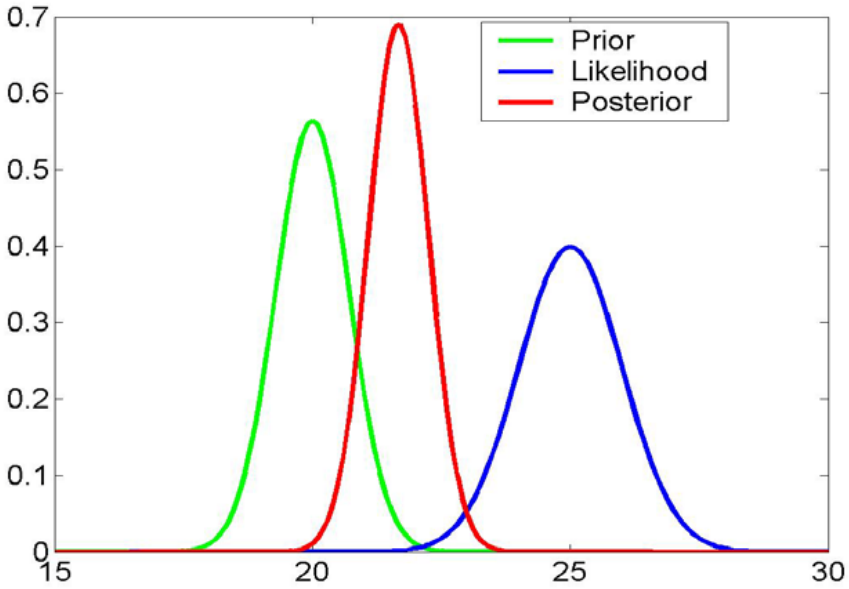
Express our prior knowledge or "belief" about parameters of the model

## Parameters governing

- Hemodynamics in a single region
- Neuronal interactions

## Constraints (priors) on

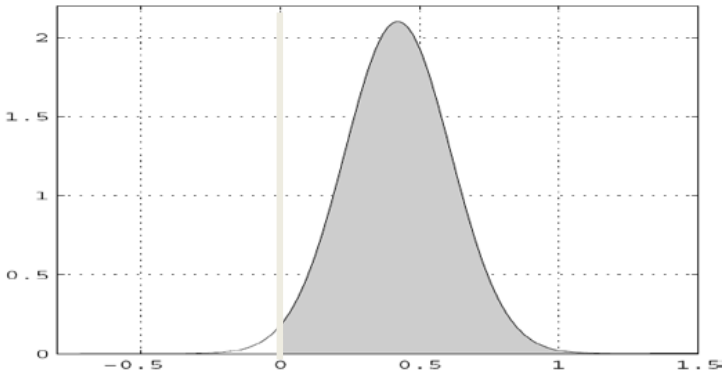
- Hemodynamic parameters
  - Empirical
- Self connections
  - principled
- Other connections
  - shrinkage



# Inference about DCM parameters

## Bayesian single subject analysis

- gaussian assumptions about the posterior distributions of the parameters
- posterior probability that a certain parameter (or contrast of parameters) is above a chosen threshold γ:
- by default, γ is chosen as zero – the prior ("does the effect exist?").




## Classical frequentist test across Ss

test summary statistic:

- one-sample t-test:

  parameter > 0?

- paired t-test:

  parameter 1 > parameter 2?

## Bayesian parameter averaging

## ! Bayesian model comparison !

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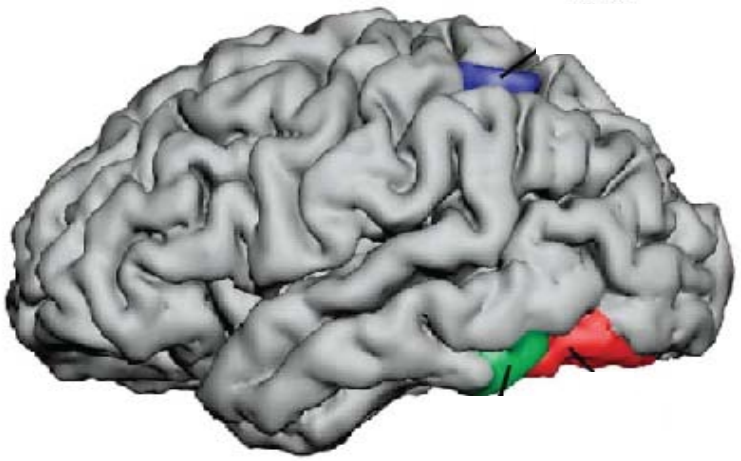
# Example: Brain Connectivity in Synesthesia

- 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)



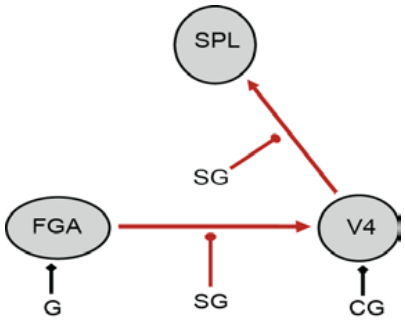
Hubbard, 2007

Can changes in effective connectivity explain synesthesia activity in V4?

# Model Comparison

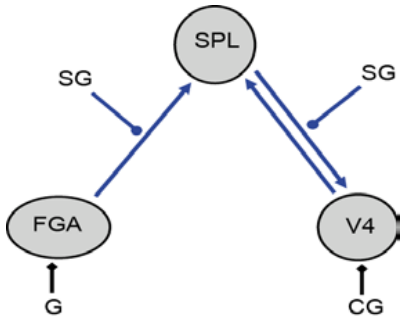
**Bottom-up**

(*Ramachandran & Hubbard, 2001*)



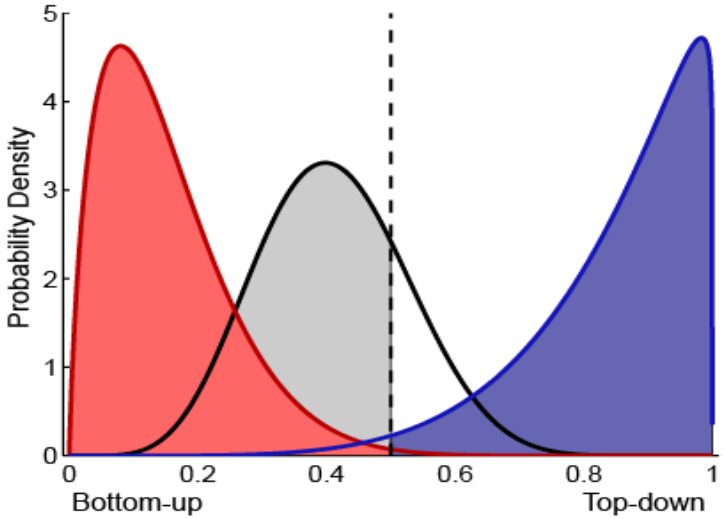

**Top-down**

(*Grossenbacher & Lovelace, 2001*)




**Projectors**

**ABC**

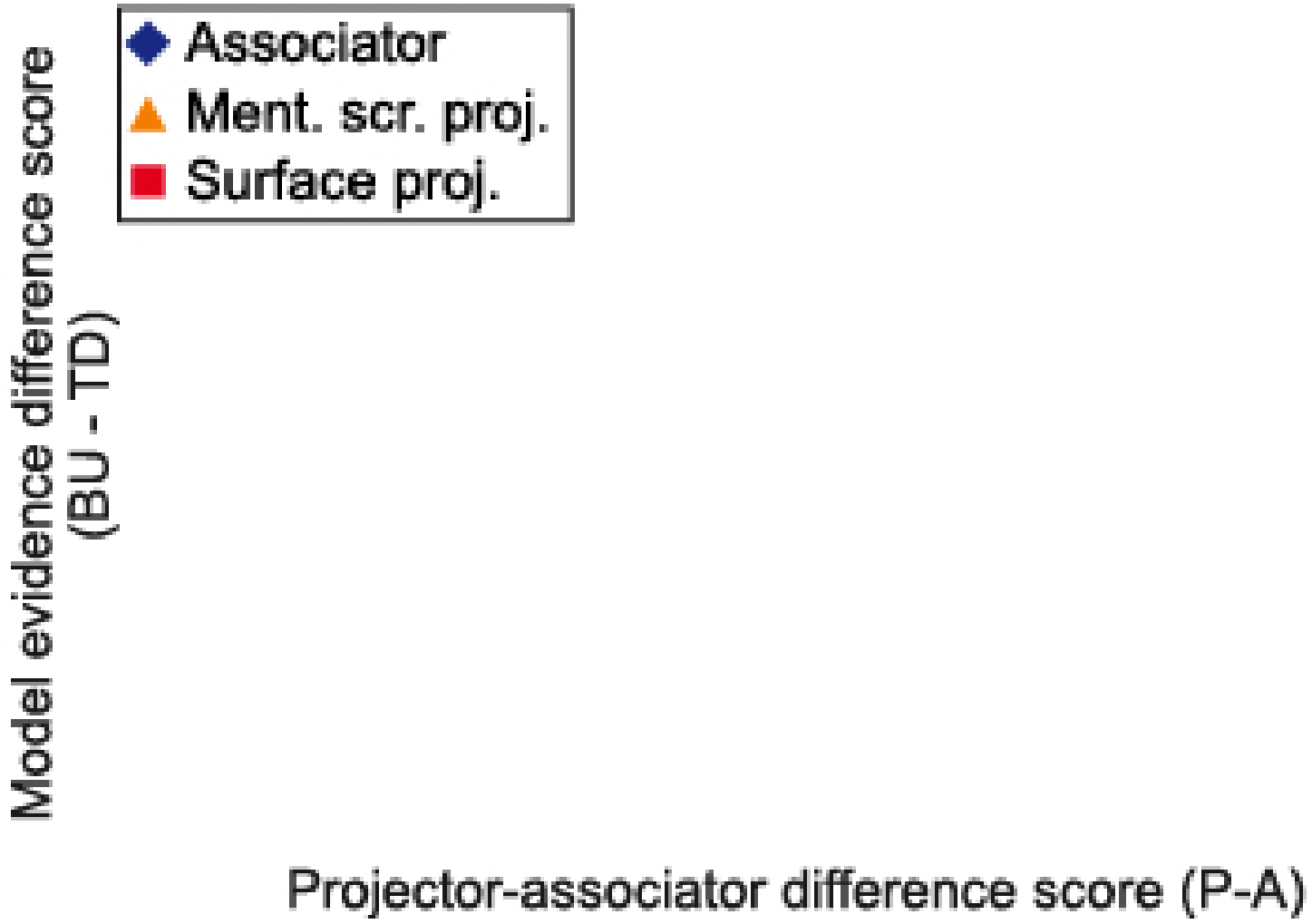



**Associators**

**ABC**

**ABC**

# Effective connectivity reflects sensory experience



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1. Investigating Connectivity
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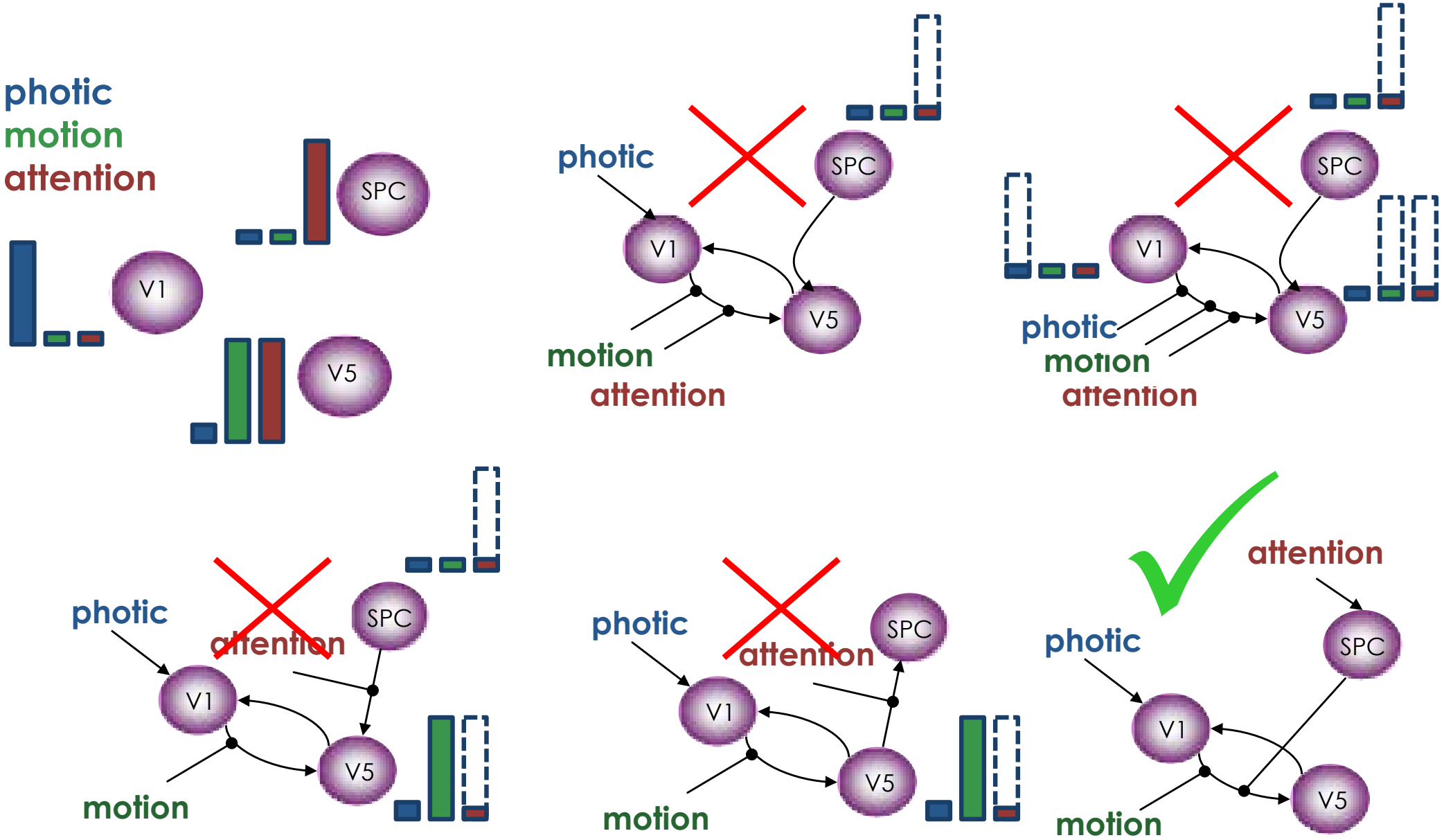
   - Quiz
4. Final remarks and useful references

# Quiz: can this DCM explain your data?



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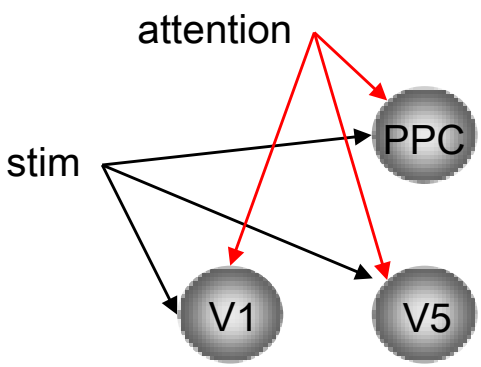
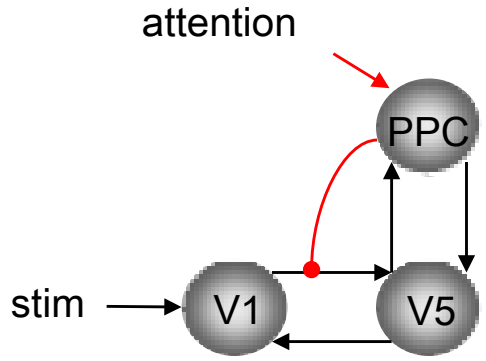
# GLM vs. DCM

DCM tries to model the same phenomena (i.e. local BOLD responses) as a GLM, just in a different way (via connectivity and its modulation).

**no activation detected by a GLM**
**→ no motivation to include this region in a *deterministic* DCM.**

however, a stochastic DCM could be applied despite the absence of a local activation.

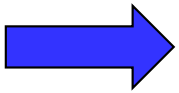



Stephan (2004) *J. Anat.*

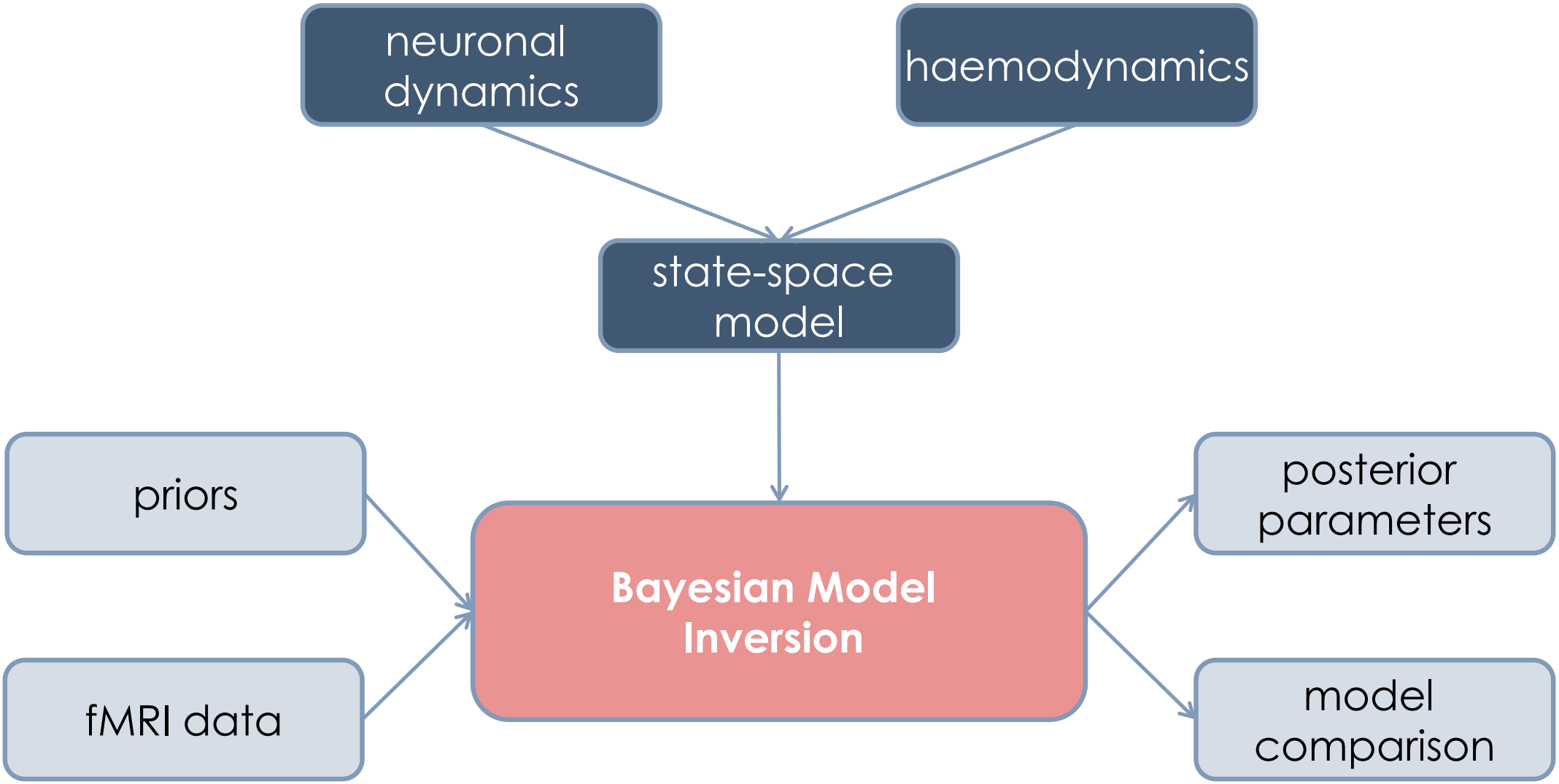
# The evolution of DCM in SPM

- DCM is not one specific model, but a framework for Bayesian inversion of dynamic system models
- The default implementation in SPM is evolving over time
  - better numerical routines for inversion
  - change in priors to cover new variants (e.g., stochastic DCMs, endogenous DCMs etc.)



To enable replication of your results, you should state which SPM version you are using when publishing papers.

# DCM Roadmap


neuronal dynamics
haemodynamics
state-space model
priors
fMRI data
Bayesian Model Inversion
posterior parameters
model comparison

# Exciting extensions in DCM

- Nonlinear DCM for fMRI: *Could connectivity changes be mediated by another region? (Stephan et al. 2008)*
- Embedding computational models in DCMs: *DCM can be used to make inferences on parametric designs like SPM (den Ouden et al. 2010, J Neurosci.)*
- DCM as a summary statistic: clustering and classification: *Classify patients, or even find new sub-categories (Brodersen et al. 2011Neuroimage)*
- Integrating tractography and DCM: *Prior variance is a good way to embed other forms of information, test validity (Stephan et al. 2009, NeuroImage)*
- Stochastic / spectral DCM: *Model resting state studies / background fluctuations (Li et al. 2011 Neuroimage, Daunizeau et al. Physica D 2009)*

# Validation studies of DCM

- reliability (reproducibilty)
  - parameter estimates are highly reliable across sessions (Schuyler et al. 2010)
  - model selection results are highly reliable across sessions (Rowe et al. 2010)
- face validity
  - simulations and empirical studies (Stephan et al. 2007, 2008)
- construct validity
  - comparison with SEM (Penny et al. 2004)
  - comparison with large-scale spiking neuron models (Lee et al. 2006)
- predictive validity:
  - infer correct site of seizure origin (David et al. 2008)
  - infer primary recipient of vagal nerve stimulation (Reyt et al. 2010)
  - infer synaptic changes as predicted from microdialysis (Moran et al. 2008)
  - infer conditioning-induced plasticity in amygdala (Moran et al. 2009)
  - track anaesthesia levels (Moran et al. 2011)
  - predict sensory stimulation (Brodersen et al. 2010)
  - infer DA induced changes in AMPA/NMDA ratio from MEG (Moran et al. 2011)
  - predict presence/absence of remote lesion (Brodersen et al. 2011)

# To get started...

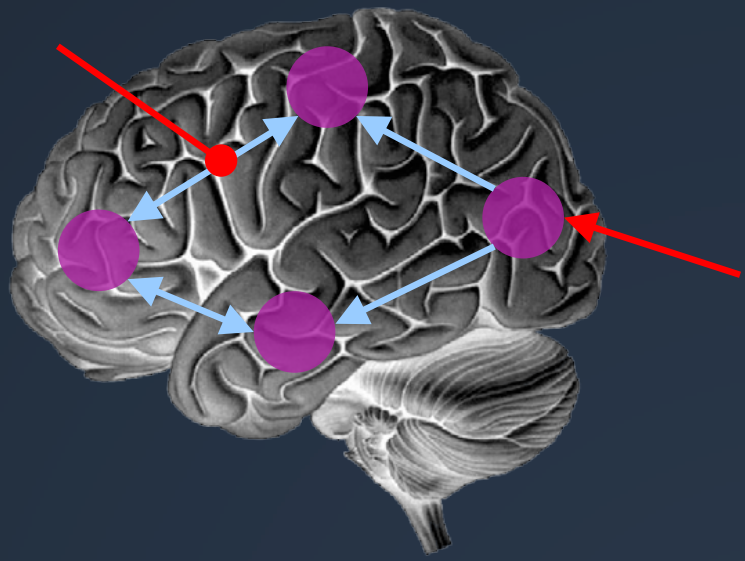
- 10 Simple Rules for DCM (2010). Stephan et al. *NeuroImage 52*
- The first DCM paper: Dynamic Causal Modelling (2003). Friston et al. *NeuroImage* 19:1273-1302.
- Physiological validation of DCM for fMRI: Identifying neural drivers with functional MRI: an electrophysiological validation (2008). David 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

# Thank you

# DCM for fMRIdemo

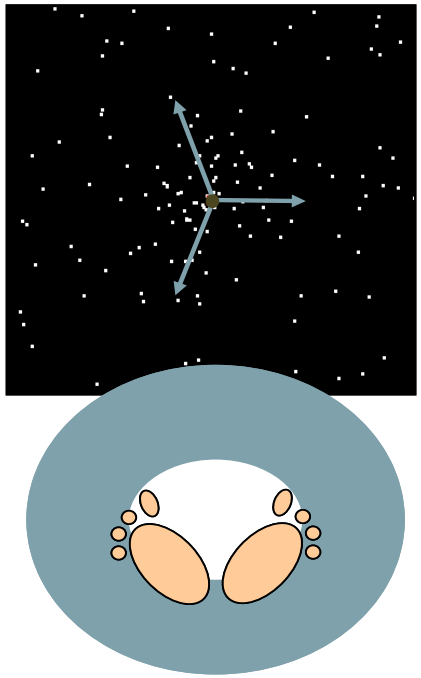
Hanneke den Ouden

Donders Institute for Brain, Cognition and Behaviour
Radboud University Nijmegen



# 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

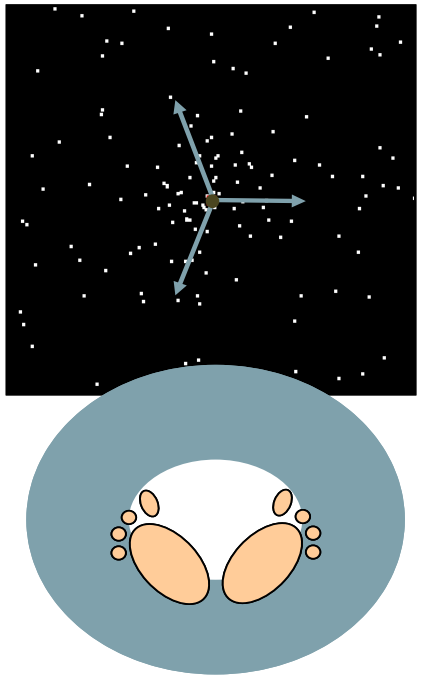
A - attend moving dots + attention

## Parameters

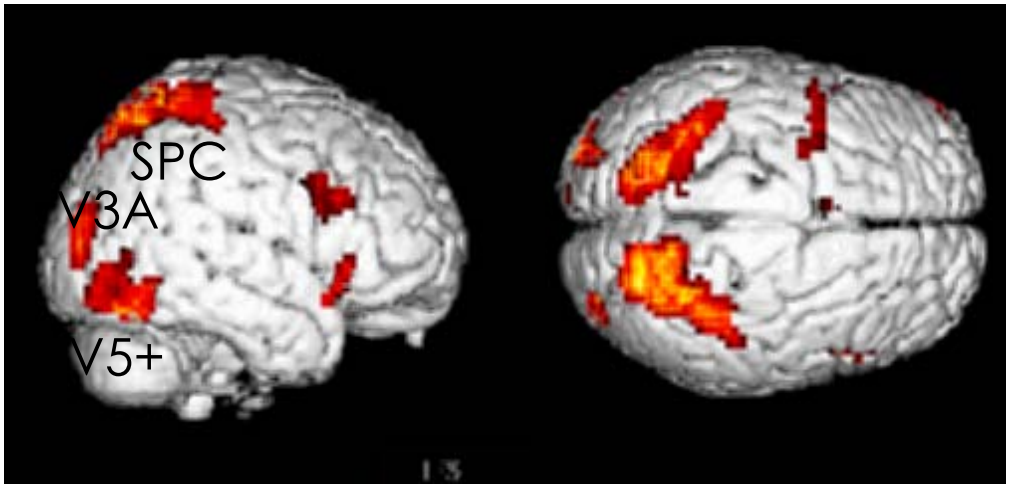
- blocks of 10 scans
- 360 scans total
- TR = 3.22 seconds

# Attention to motion in the visual system

## Paradigm



## Results

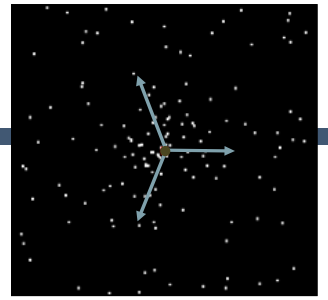



Attention – No attention

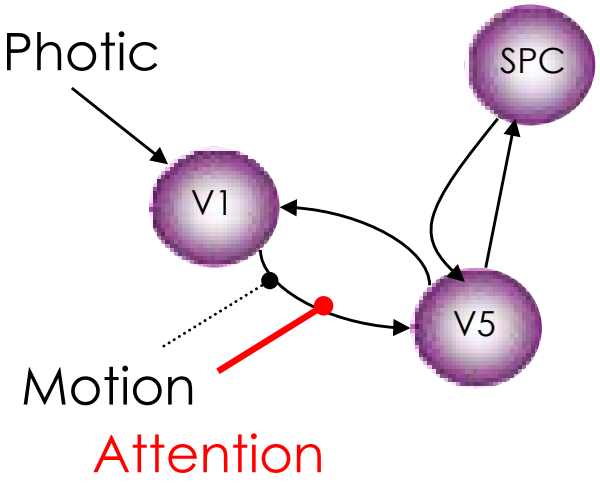
Büchel & Friston 1997, Cereb. Cortex
Büchel et al. 1998, Brain

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

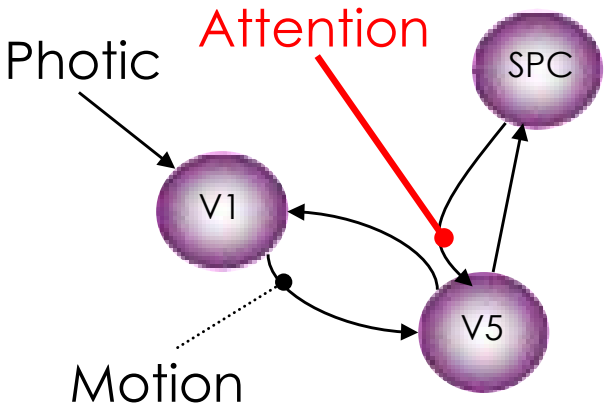
# DCM: comparison of 2 models



Model 1
attentional modulation
of V1→V5: forward



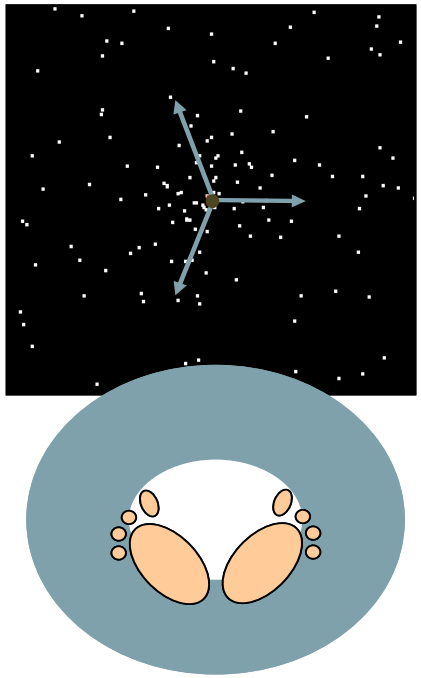

Model 2
attentional modulation
of SPC→V5: backward




Bayesian model selection: Which model is optimal?

# Attention to motion in the visual system

## Paradigm



## Ingredients for a DCM

Specific hypothesis/question

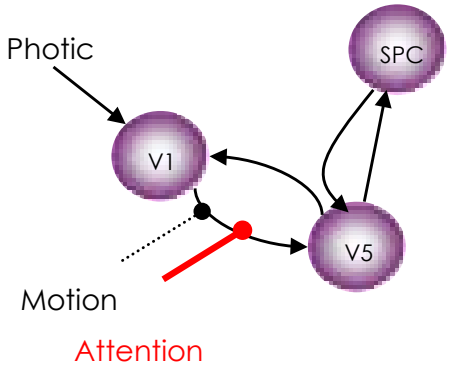
Model: based on hypothesis

Timeseries: from the SPM

Inputs: from design matrix

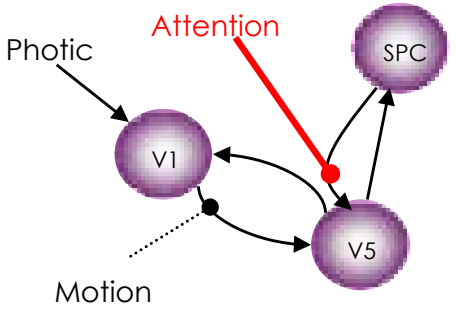
### Model 1

attentional modulation of V1→V5: forward

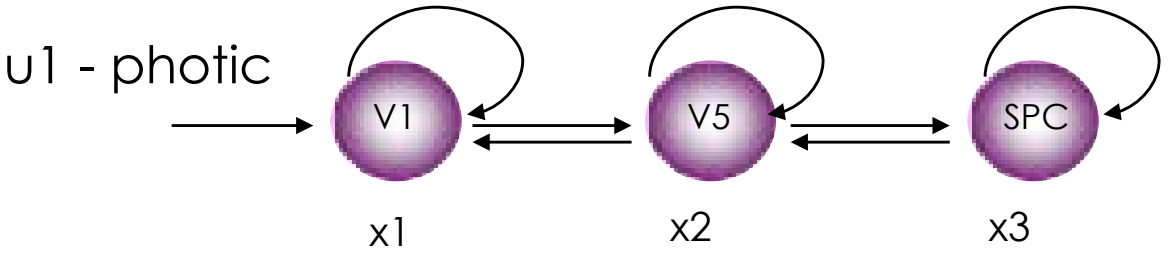



### Model 2

attentional modulation of SPC→V5: backward



# DCM: linear model




$$\dot{x} = Ax + Cu$$
$$\theta = \{A, C\}$$

$$\dot{x}_1 = a_{11}x_1 + a_{12}x_2 + c_1u_1$$
$$\dot{x}_2 = a_{21}x_1 + a_{22}x_2 + a_{23}x_3$$
$$\dot{x}_3 = a_{32}x_2 + a_{33}x_3$$

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \end{bmatrix} = \begin{bmatrix} a_{11} & a_{12} & 0 \\ a_{21} & a_{22} & a_{23} \\ 0 & a_{31} & a_{33} \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix} + \begin{bmatrix} c_{11} & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} u_1 \\ u_2 \\ u_3 \end{bmatrix}$$

## DCM – GUI basic steps

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

2 – Specify the model

3 – Estimate the model

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

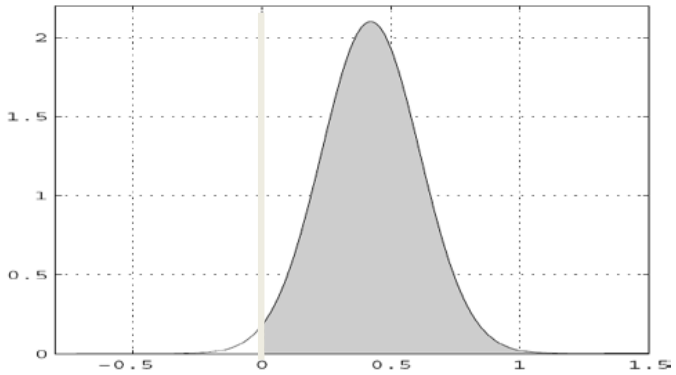
5 – Compare models

6 – OPTIONAL: do parameter inference on optimal model (potentially after model averaging)

# 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 (or contrast of parameters $c^T \eta_{\theta|y}$) is above a chosen threshold γ:




## Classical frequentist test across Ss

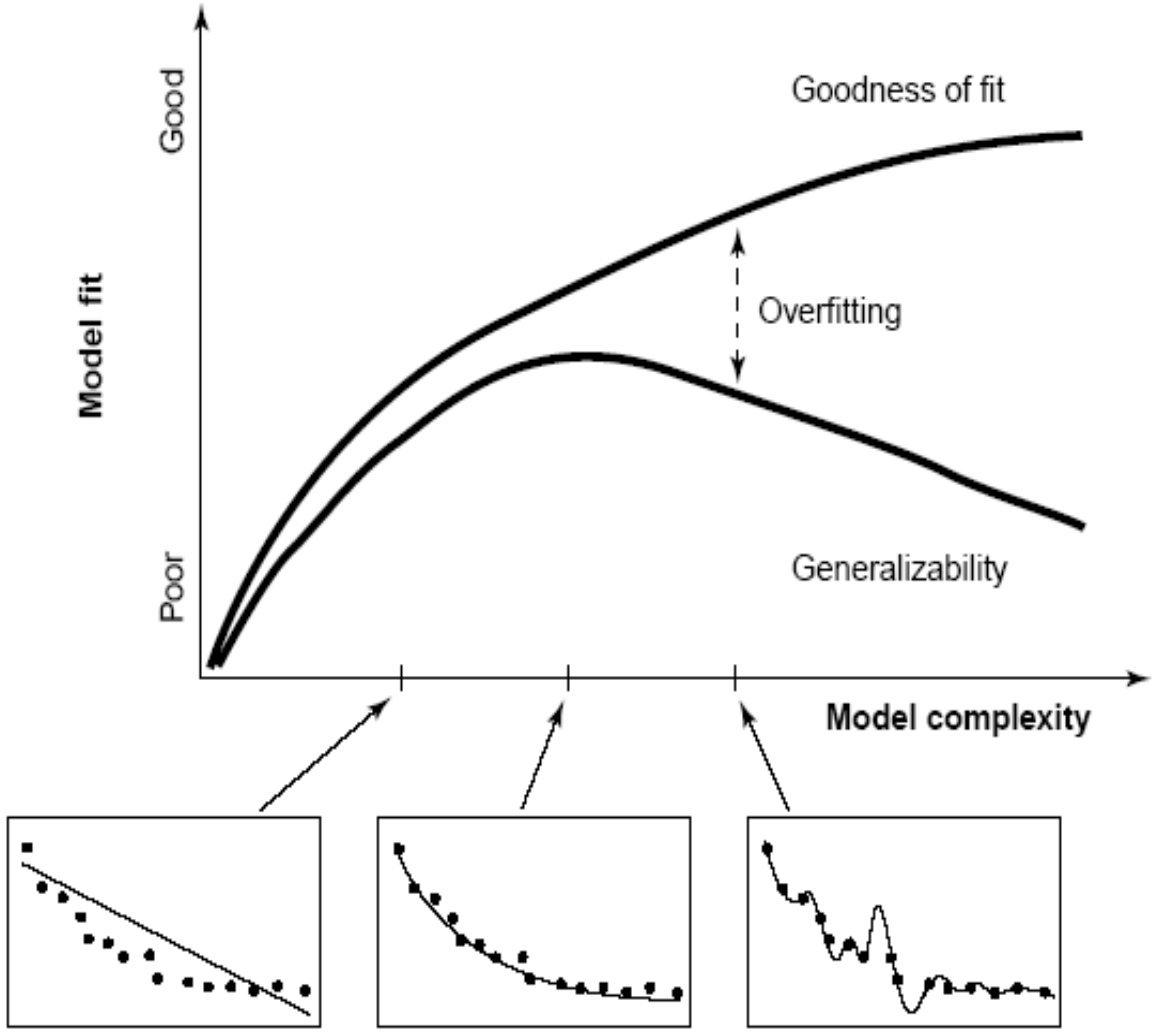
- Test summary statistic: mean $\eta_{\theta|y}$
  - One-sample t-test:
    Parameter > 0?
  - Paired t-test:
    parameter 1 > parameter 2?
  - rmANOVA: e.g. in case of multiple sessions per subject

# Model comparison and selection

Given competing hypotheses on structure & functional mechanisms of a system, which model is the best?

Which model represents the best balance between model fit and model complexity?

For which model *m* does model evidence $p(y \mid m)$ become maximal?




Pitt & Miyung (2002) *TICS*

# Comparing models with Bayes factors

For a given dataset, to compare two models, we compare their evidences.

$$B_{12} = \frac{p(y \mid m_1)}{p(y \mid m_2)}$$

positive value, [0; ∞]

| $B_{12}$ | $p(m_1 \mid y)$ | Evidence |
|---|---|---|
| 1 to 3 | 50-75% | weak |
| 3 to 20 | 75-95% | positive |
| 20 to 150 | 95-99% | strong |
| ≥ 150 | ≥ 99% | Very strong |

or their log evidences

$$\ln(B_{12}) = \ln\left(p\left(y \mid m_1\right)\right) - \ln\left(p\left(y \mid m_2\right)\right) \approx F_1 - F_2$$

Kass & Raftery 1995, *J. Am. Stat. Assoc.*

# Comparing models with Bayes factors

A posteriori

Model evidence

Bayes' rule:

$$p(m \mid y) = \frac{p(y \mid m) \cdot p(m)}{\int p(y \mid m) \cdot p(m) dm}$$

Given flat priors on the models, the posterior and model evidence are equivalent