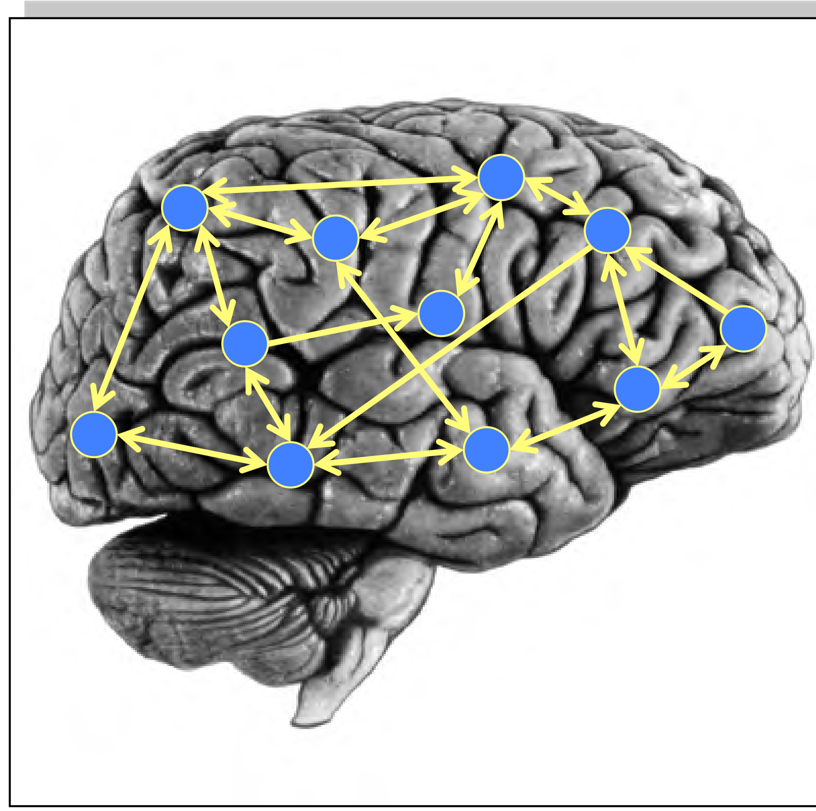
Models of effective connectivity & Dynamic Causal Modelling (DCM)



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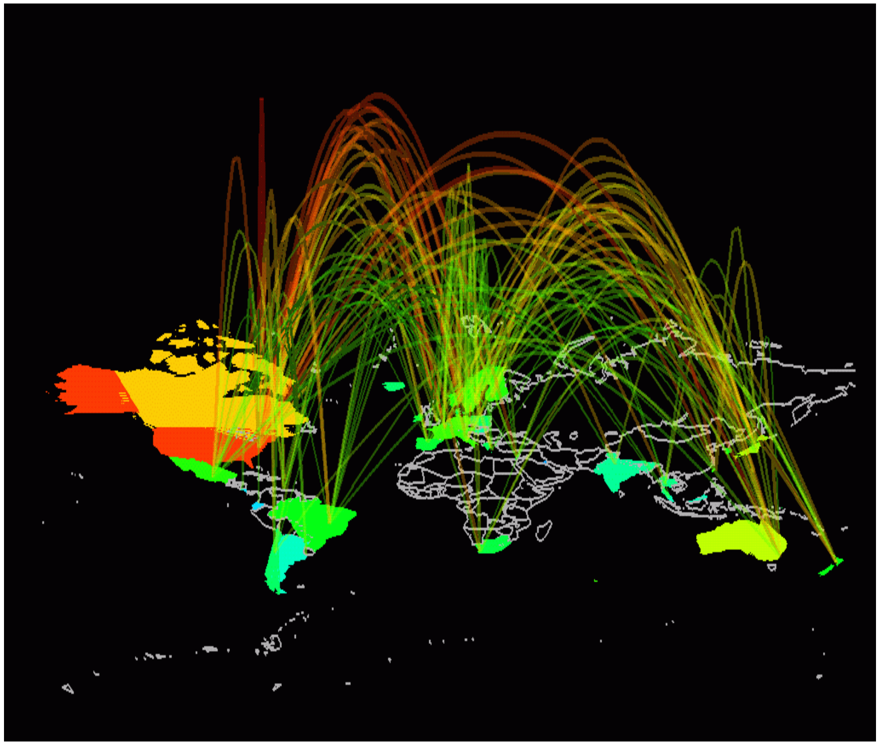
Overview

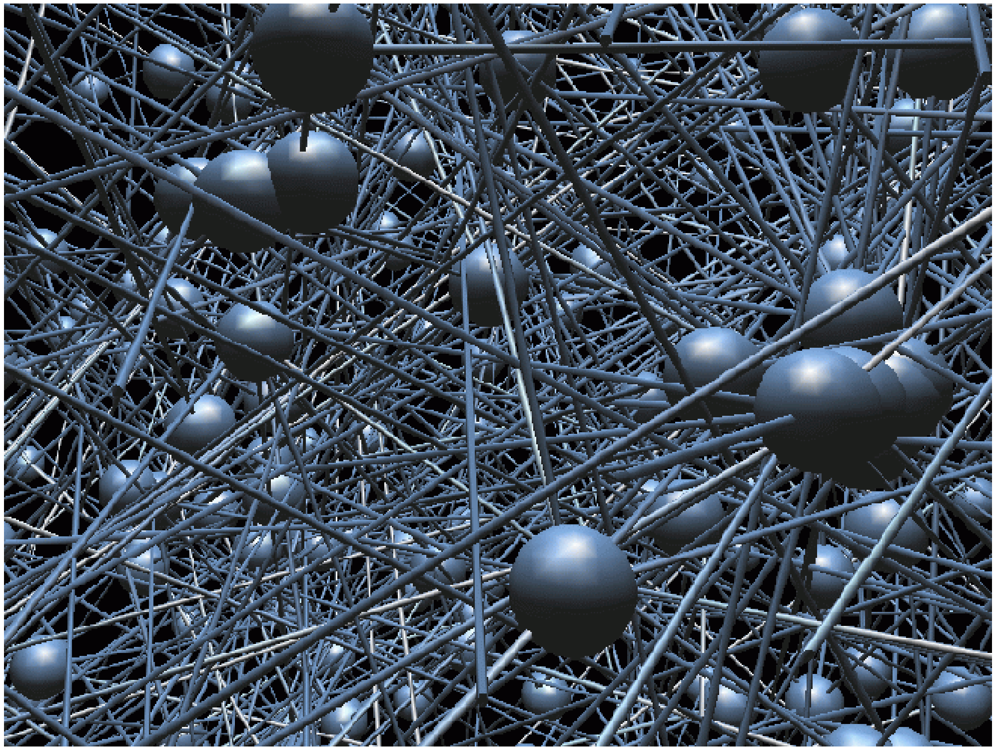
- Brain connectivity: types & definitions
  - anatomical connectivity
  - functional connectivity
  - effective connectivity
- Dynamic causal models (DCMs)
  - DCM for fMRI: Neural and hemodynamic levels
  - Parameter estimation & inference
- Applications of DCM to fMRI data
  - Design of experiments and models
  - Some empirical examples and simulations

Connectivity

A central property of any system



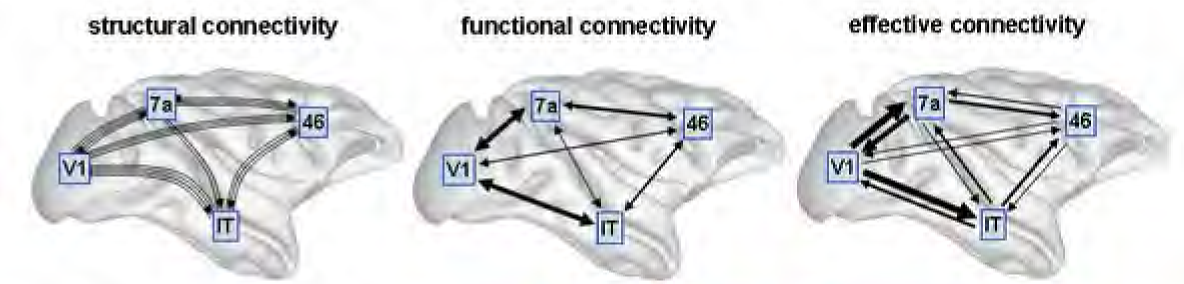
Communication systems
(internet)



Social networks
(Canberra, Australia)

FIgs. by Stephen Eick and A. Klovdahl;
see http://www.nd.edu/~networks/gallery.htm

Structural, functional & effective connectivity

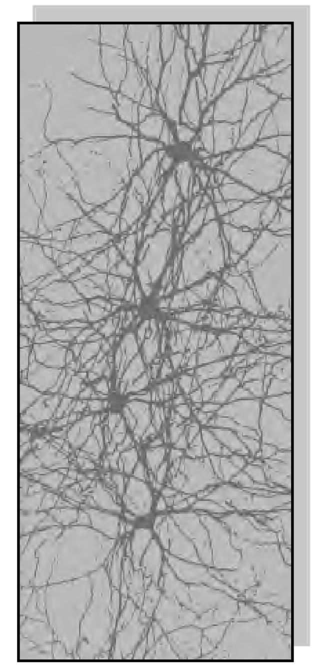


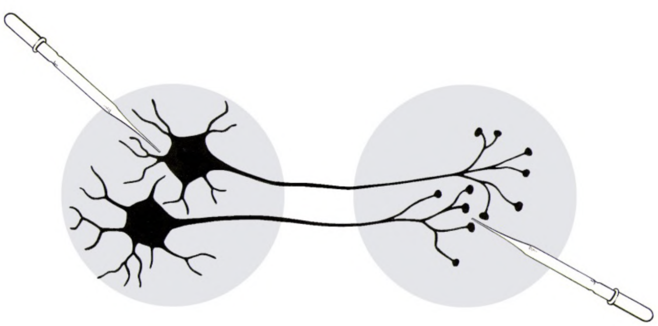
Sporns 2007, *Scholarpedia*

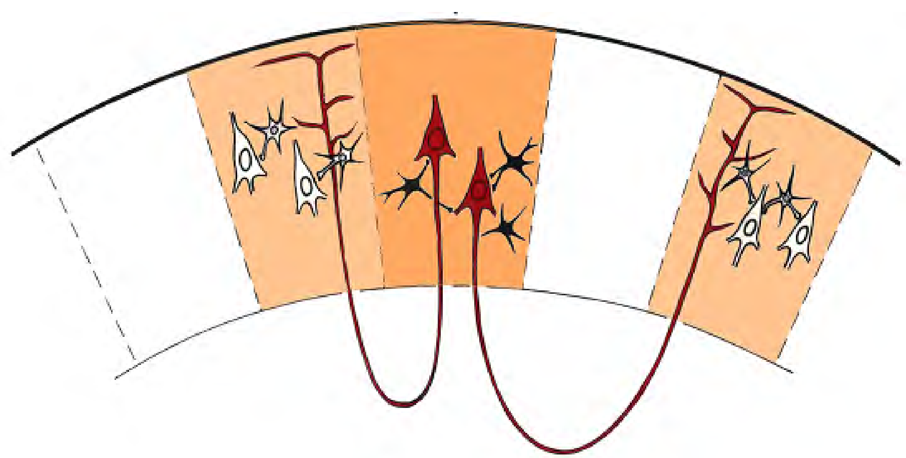
- **anatomical/structural connectivity**
  = presence of axonal connections
- **functional connectivity**
  = statistical dependencies between regional time series
- **effective connectivity**
  = causal (directed) influences between neurons or neuronal populations

Anatomical connectivity

- neuronal communication via synaptic contacts
- visualisation by tracing techniques
- long-range axons → "association fibres"







Different approaches to analysing functional connectivity

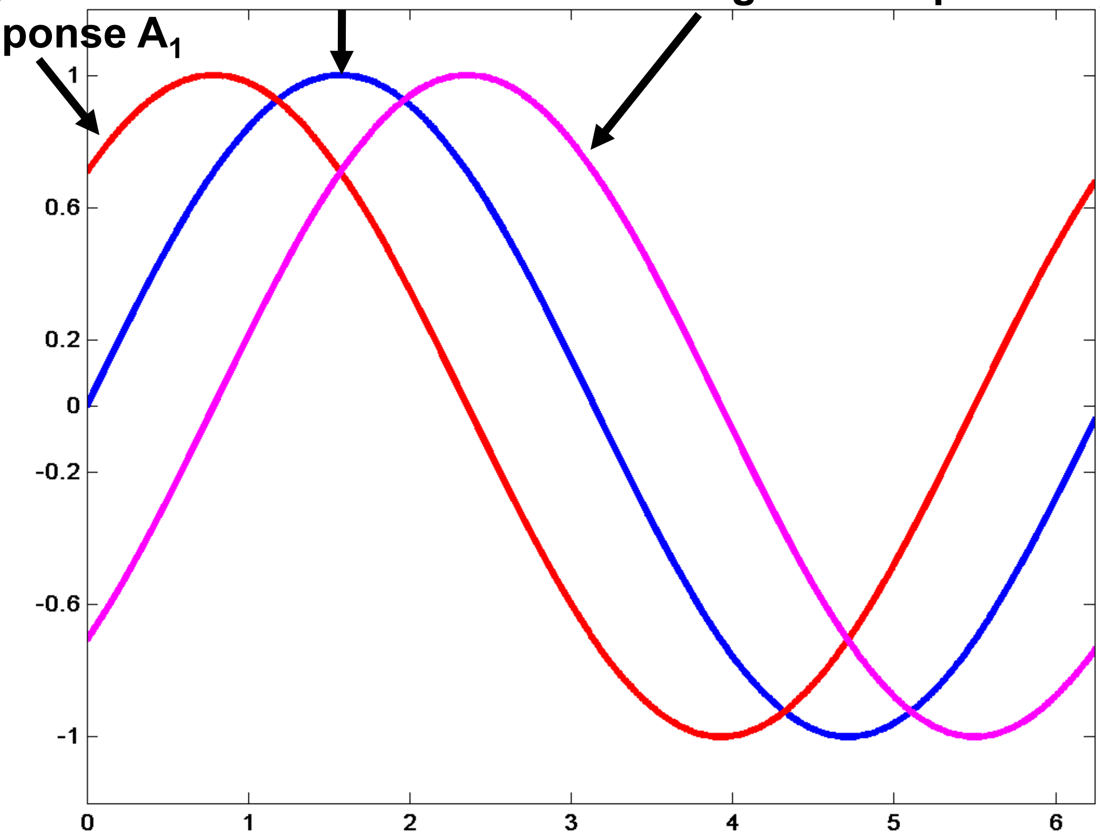
- Seed voxel correlation analysis
- Eigen-decomposition (PCA, SVD)
- Independent component analysis (ICA)
- any other technique describing statistical dependencies amongst regional time series

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

No, it does not - see the fictitious example on the right:

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 analyses

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

- Cons:
  - interpretation of resulting patterns is difficult / arbitrary
  - no mechanistic insight into the neural system of interest
  - usually suboptimal for situations where we have a priori knowledge and experimental control about the system of interest

models of effective connectivity necessary

For understanding brain function mechanistically, we need **models of effective connectivity**, i.e.

models of causal interactions among neuronal populations.

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

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Dynamic causal modelling (DCM)

ACADEMIC PRESS
Available online at www.sciencedirect.com
SCIENCE DIRECT
NeuroImage
NeuroImage 19 (2003) 1273–1302
www.elsevier.com/locate/ynimg

Dynamic causal modelling

K.J. Friston,* L. Harrison, and W. Penny
The Wellcome Department of Imaging Neuroscience, Institute of Neurology, Queen Square, London WC1N 3BG, UK

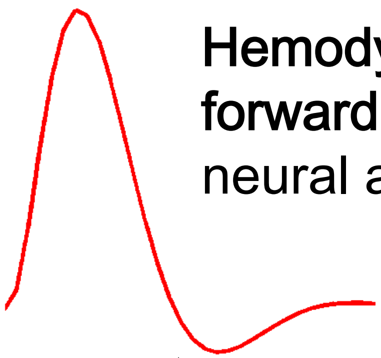
Received 18 October 2002; revised 7 March 2003; accepted 2 April 2003

- DCM framework was introduced in 2003 for fMRI by Karl Friston, Lee Harrison and Will Penny (NeuroImage 19:1273-1302)
- part of the SPM software package
- currently more than 100 published papers on DCM

DCM vs GLM: Cheat Sheet

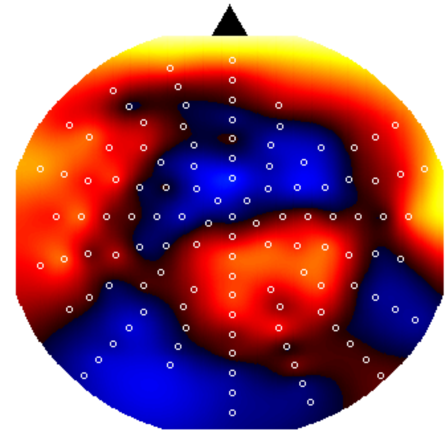
	GLM	DCM
Inference	Within voxels	Among ROIs
On	BOLD signal	Neuronal Activation
Answering	*Where* the stimulus produced activation.	*How* the stimulus activated the system of interconnected ROIs.
Using	Frequentist Estimation	Bayesian Estimation

Dynamic Causal Modeling (DCM)



Hemodynamic forward model:
neural activity, BOLD

Electromagnetic forward model:
neural activity, EEG
MEG
LFP



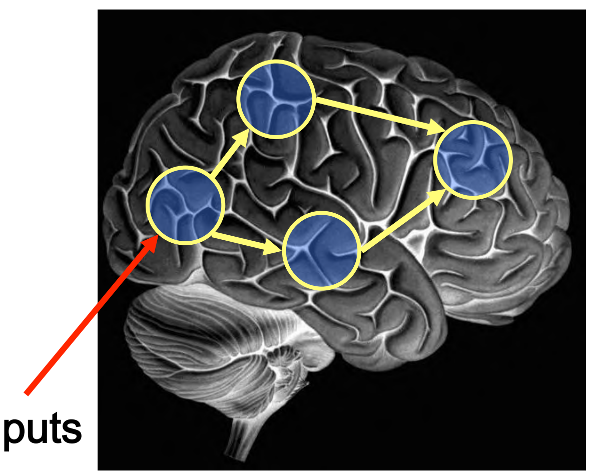
Neural state equation:

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

fMRI

EEG/MEG

simple neuronal model
complicated forward model

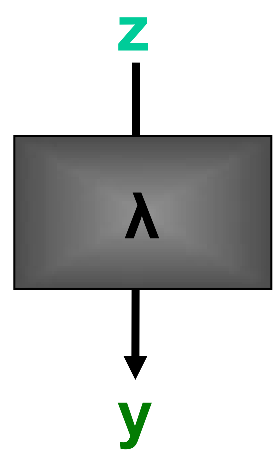


complicated neuronal model
simple forward model

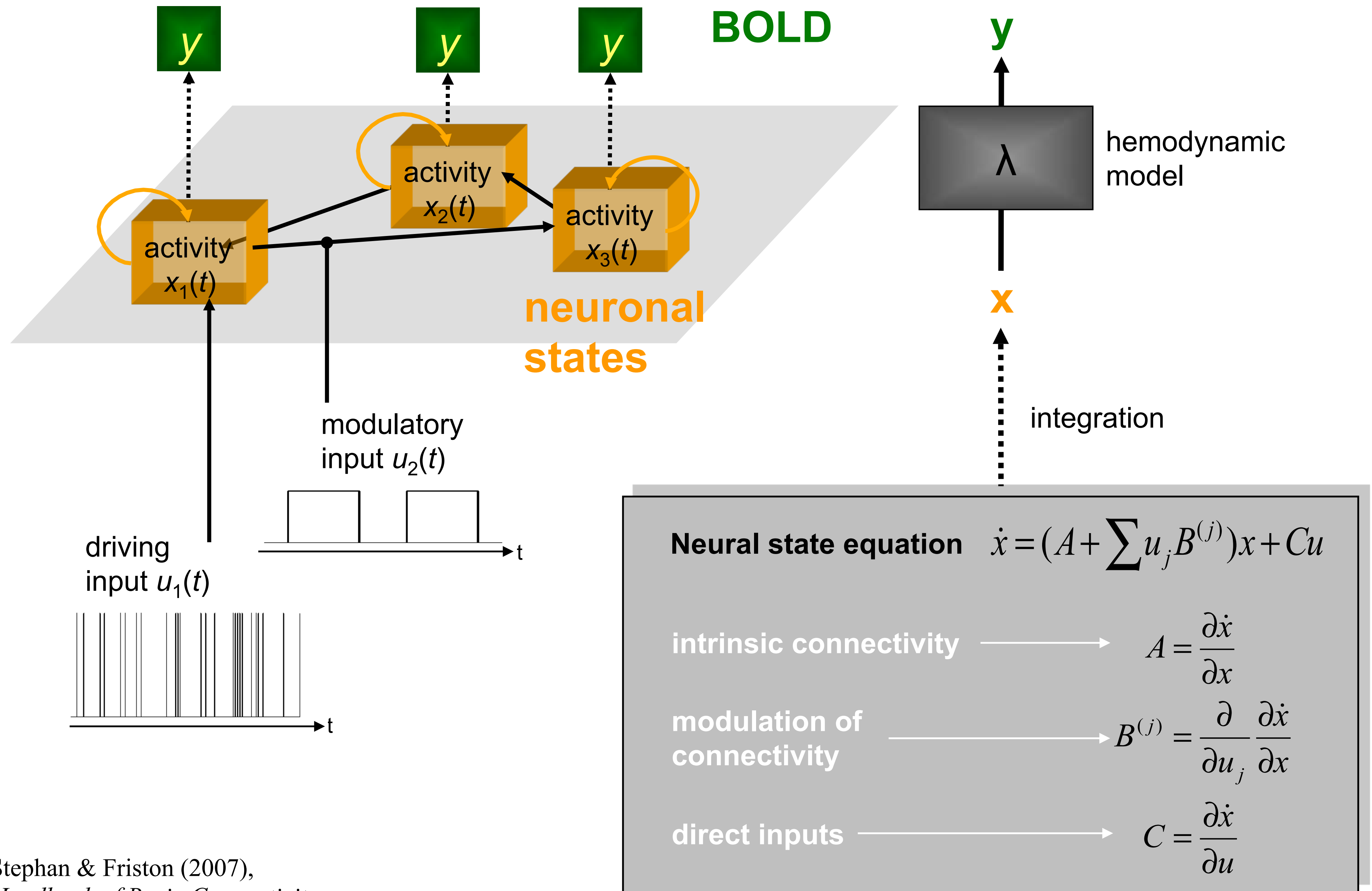
Stephan & Friston 2007,
Handbook of Brain Connectivity

DCM for fMRI: the basic idea

- Using a bilinear state equation, a cognitive system is modelled at its underlying <u>neuronal level</u> (which is not directly accessible for fMRI).
- The modelled neuronal dynamics (x) is transformed into area-specific BOLD signals (y) by a hemodynamic forward model (λ).

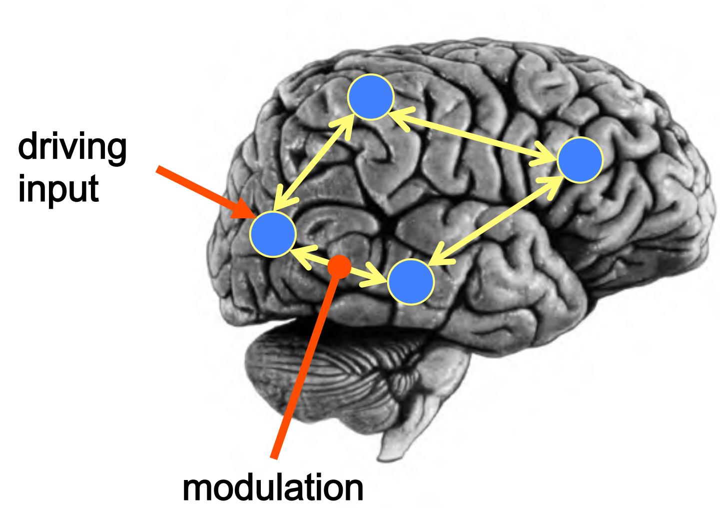


The aim of DCM is to estimate <u>parameters at the neuronal level</u> such that the modelled BOLD signals are maximally similar to the experimentally measured BOLD signals.



Stephan & Friston (2007),
Handbook of Brain Connectivity

Bilinear DCM



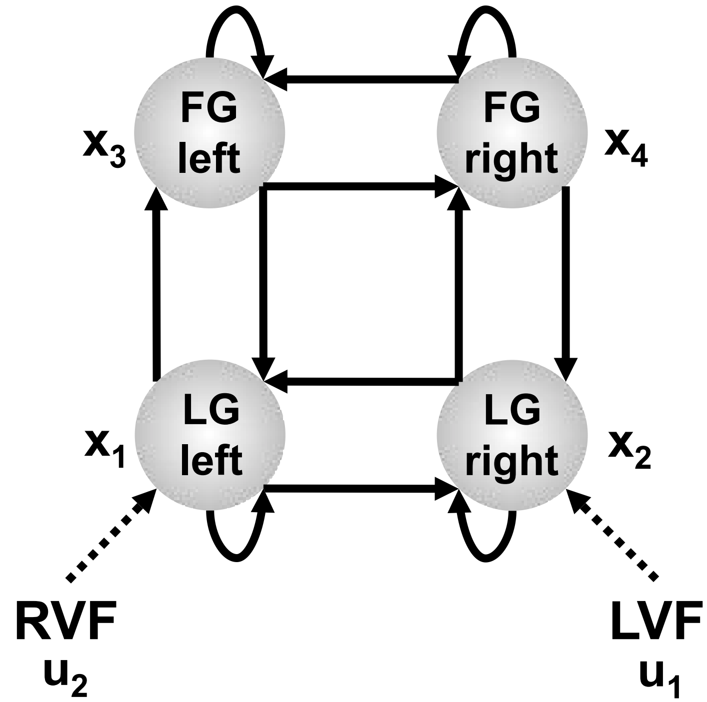
Two-dimensional Taylor series (around x_0=0, u_0=0):

$$\frac{dx}{dt} = f(x,u) \approx f(x_0,0) + \frac{\partial f}{\partial x}x + \frac{\partial f}{\partial u}u + \frac{\partial^2 f}{\partial x \partial u}ux + \ldots$$

Bilinear state equation:

$$\frac{dx}{dt} = \left(A + \sum_{i=1}^{m} u_i B^{(i)} \right) x + Cu$$

Example: a linear system of dynamics in visual cortex



LG = lingual gyrus
FG = fusiform gyrus

Visual input in the
- left (LVF)
- right (RVF)

visual field.

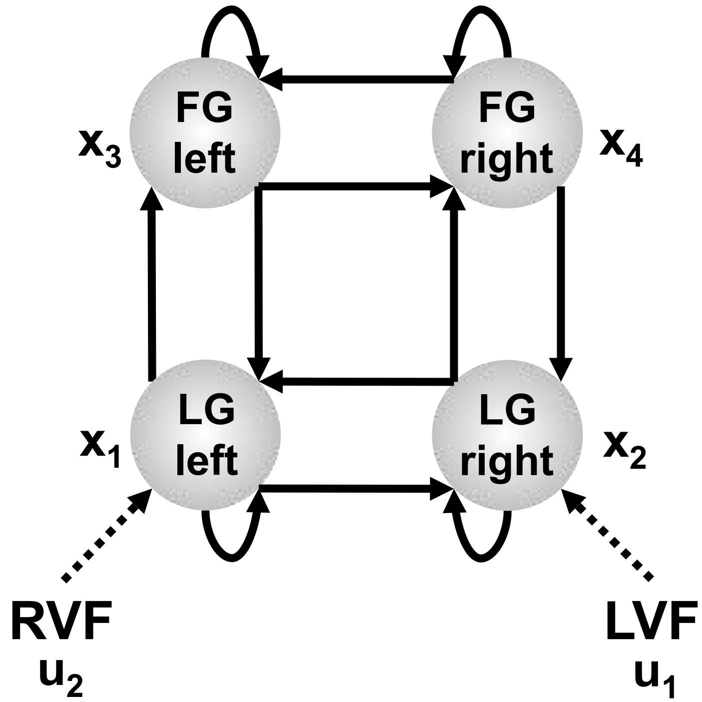
$$\dot{x}_1 = a_{11}x_1 + a_{12}x_2 + a_{13}x_3 + c_{12}u_2$$

$$\dot{x}_2 = a_{21}x_1 + a_{22}x_2 + a_{24}x_4 + c_{21}u_1$$

$$\dot{x}_3 = a_{31}x_1 + a_{33}x_3 + a_{34}x_4$$

$$\dot{x}_4 = a_{42}x_2 + a_{43}x_3 + a_{44}x_4$$

Example: a linear system of dynamics in visual cortex



LG = lingual gyrus
FG = fusiform gyrus

Visual input in the
- left (LVF)
- right (RVF)

visual field.

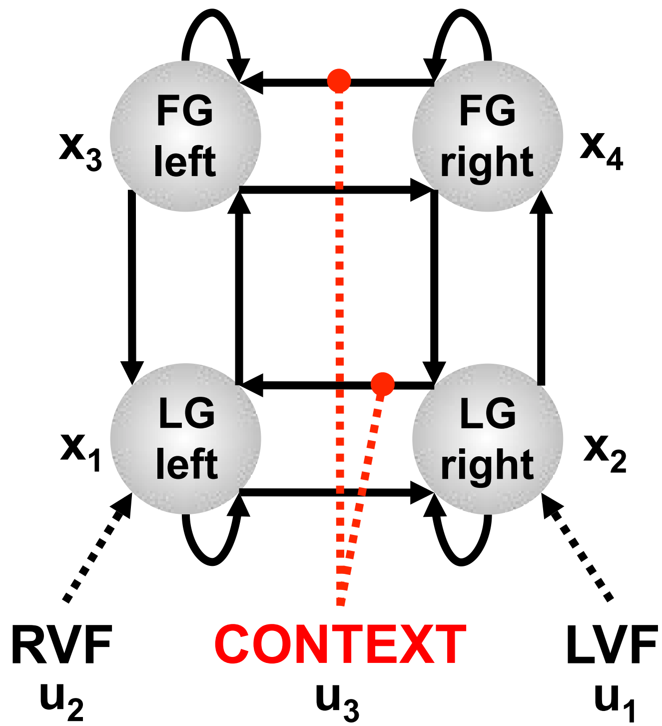
state changes — effective connectivity — system state — input parameters — external inputs

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

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

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \\ \dot{x}_4 \end{bmatrix} = \begin{bmatrix} a_{11} & a_{12} & a_{13} & 0 \\ a_{21} & a_{22} & 0 & a_{24} \\ a_{31} & 0 & a_{33} & a_{34} \\ 0 & a_{42} & a_{43} & a_{44} \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix} + \begin{bmatrix} 0 & c_{12} \\ c_{21} & 0 \\ 0 & 0 \\ 0 & 0 \end{bmatrix} \begin{bmatrix} u_1 \\ u_2 \end{bmatrix}$$

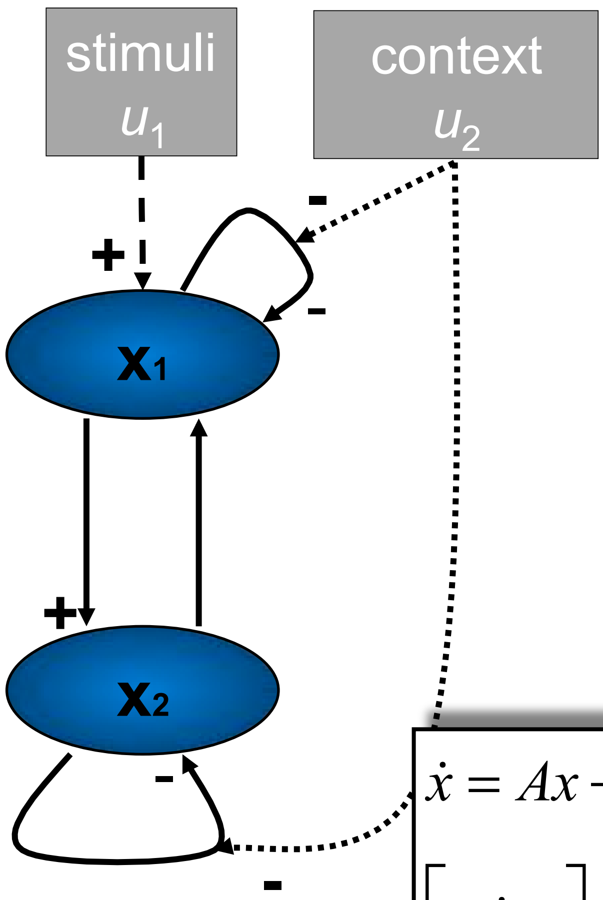
Extension: bilinear dynamic system

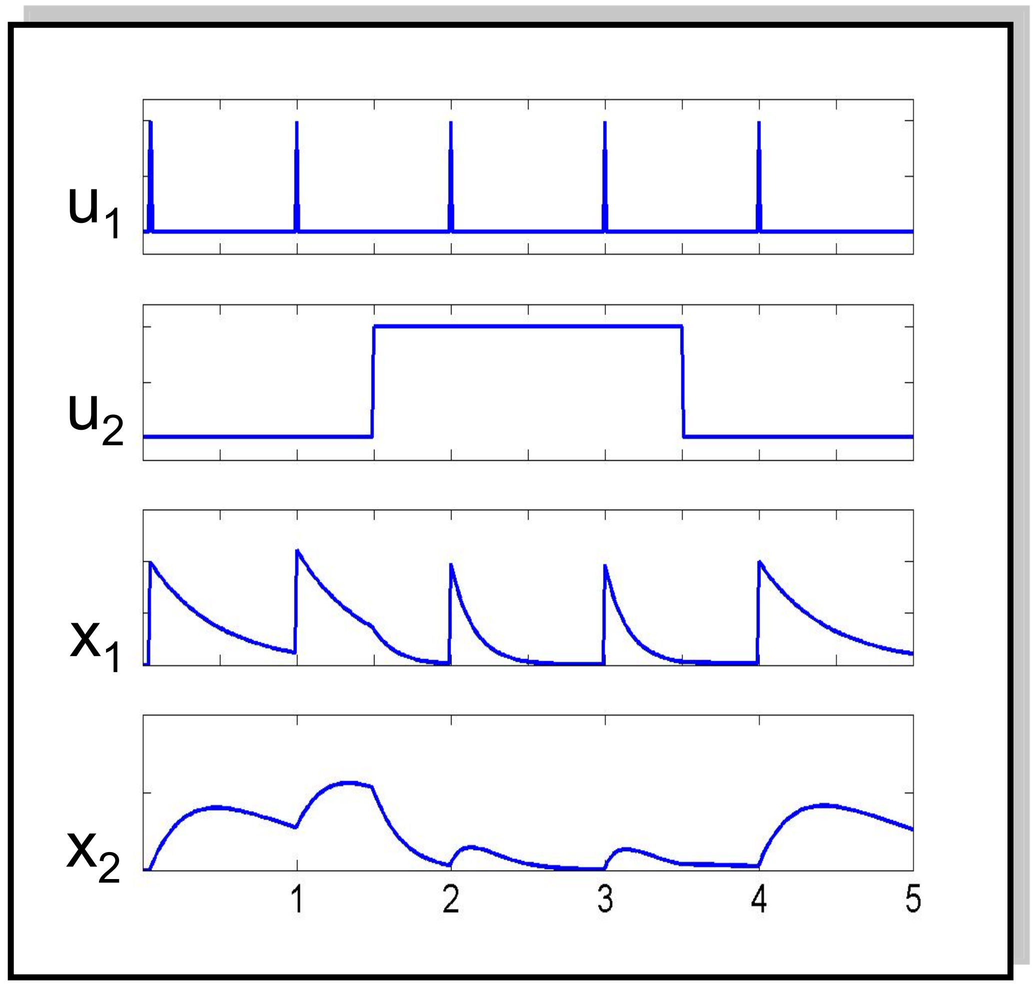


$$\dot{x} = (A + \sum_{j=1}^{m} u_j B^{(j)})x + Cu$$

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \\ \dot{x}_4 \end{bmatrix} = \left\{ \begin{bmatrix} a_{11} & a_{12} & a_{13} & 0 \\ a_{21} & a_{22} & 0 & a_{24} \\ a_{31} & 0 & a_{33} & a_{34} \\ 0 & a_{42} & a_{43} & a_{44} \end{bmatrix} + u_3 \begin{bmatrix} 0 & b_{12}^{(3)} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & b_{34}^{(3)} \\ 0 & 0 & 0 & 0 \end{bmatrix} \right\} \begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix} + \begin{bmatrix} 0 & c_{12} & 0 \\ c_{21} & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} u_1 \\ u_2 \\ u_3 \end{bmatrix}$$

Example:
context-dependent decay





$$\dot{x} = Ax + u_2 B^{(2)} x + C u_1$$

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \end{bmatrix} = \begin{bmatrix} \sigma & a_{12} \\ a_{21} & \sigma \end{bmatrix} x + u_2 \begin{bmatrix} b_{11}^{2} & 0 \\ 0 & b_{22}^{2} \end{bmatrix} x + \begin{bmatrix} c_1 & 0 \\ 0 & 0 \end{bmatrix} \begin{bmatrix} u_1 \\ u_2 \end{bmatrix}$$

Penny, Stephan, Mechelli, Friston
NeuroImage (2004)

What type of design is good for DCM?

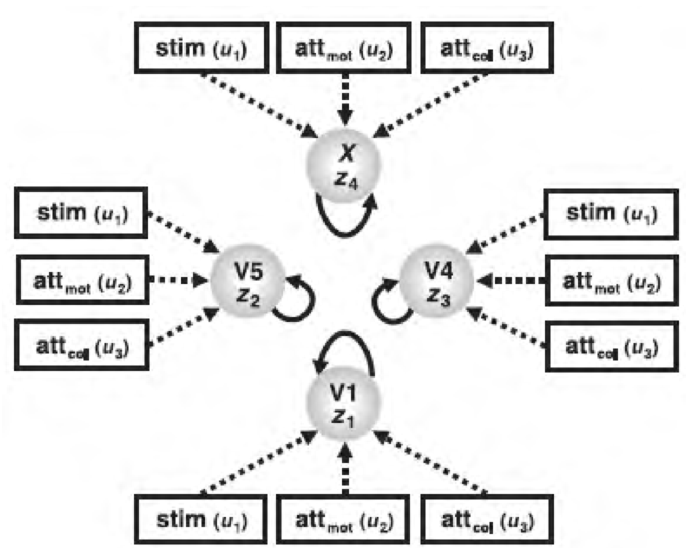
Any design that is good for a GLM of fMRI data.

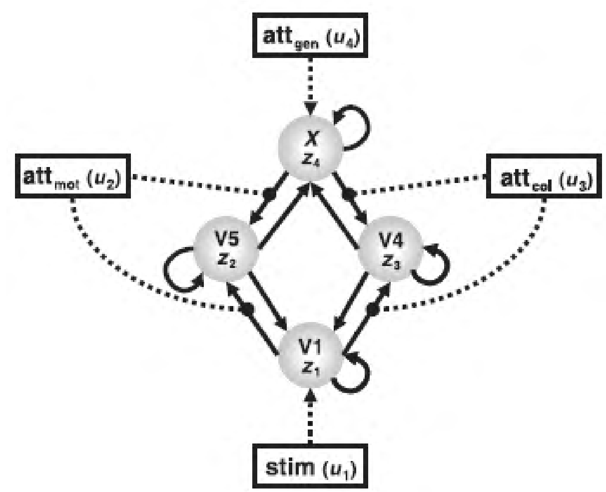
GLM vs. DCM

DCM tries to model the same phenomena as a GLM, just in a different way:

It is a model, based on connectivity and its modulation, for explaining experimentally controlled variance in local responses.

No activation detected by a GLM → inclusion of this region in a DCM is useless!



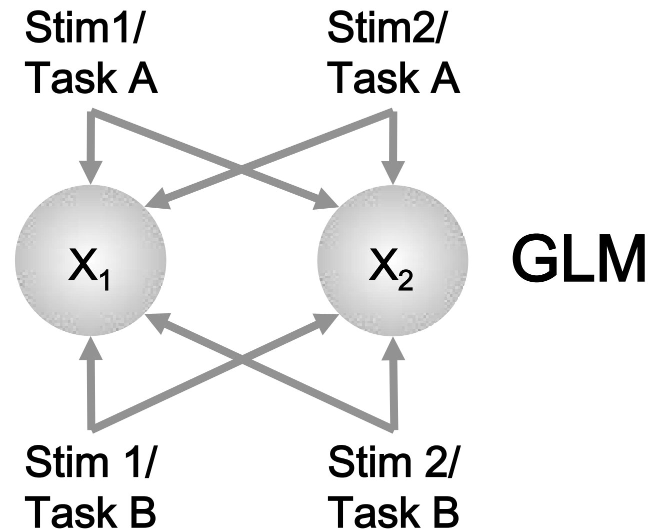


Stephan 2004, *J. Anat.*

Multifactorial design: explaining interactions with DCM

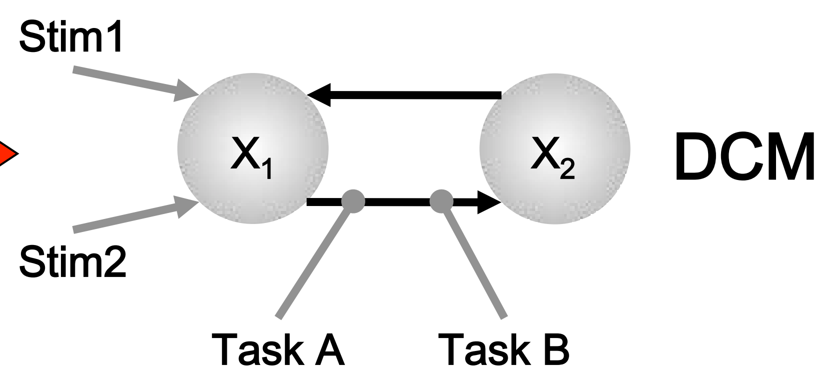
Task factor

		Task A	Task B
Stimulus factor	Stim 1	T_A/S_1	T_B/S_1
	Stim 2	T_A/S_2	T_B/S_2

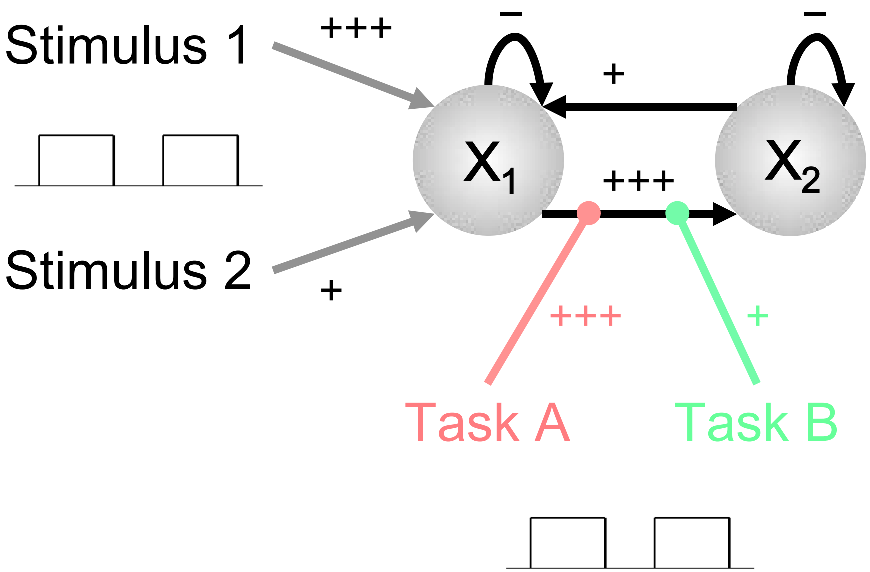


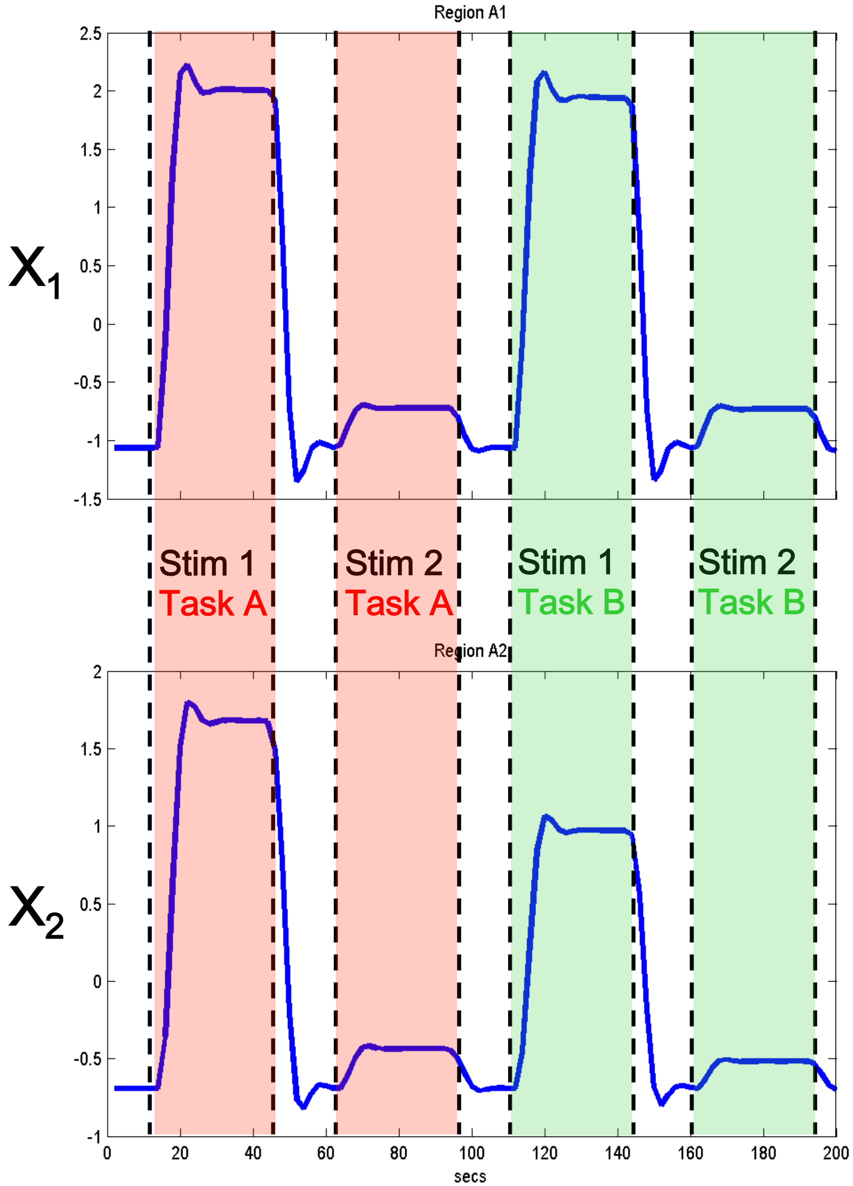
Let's assume that an SPM analysis shows a main effect of stimulus in X_1 and a stimulus * task interaction in X_2.

How do we model this using DCM?

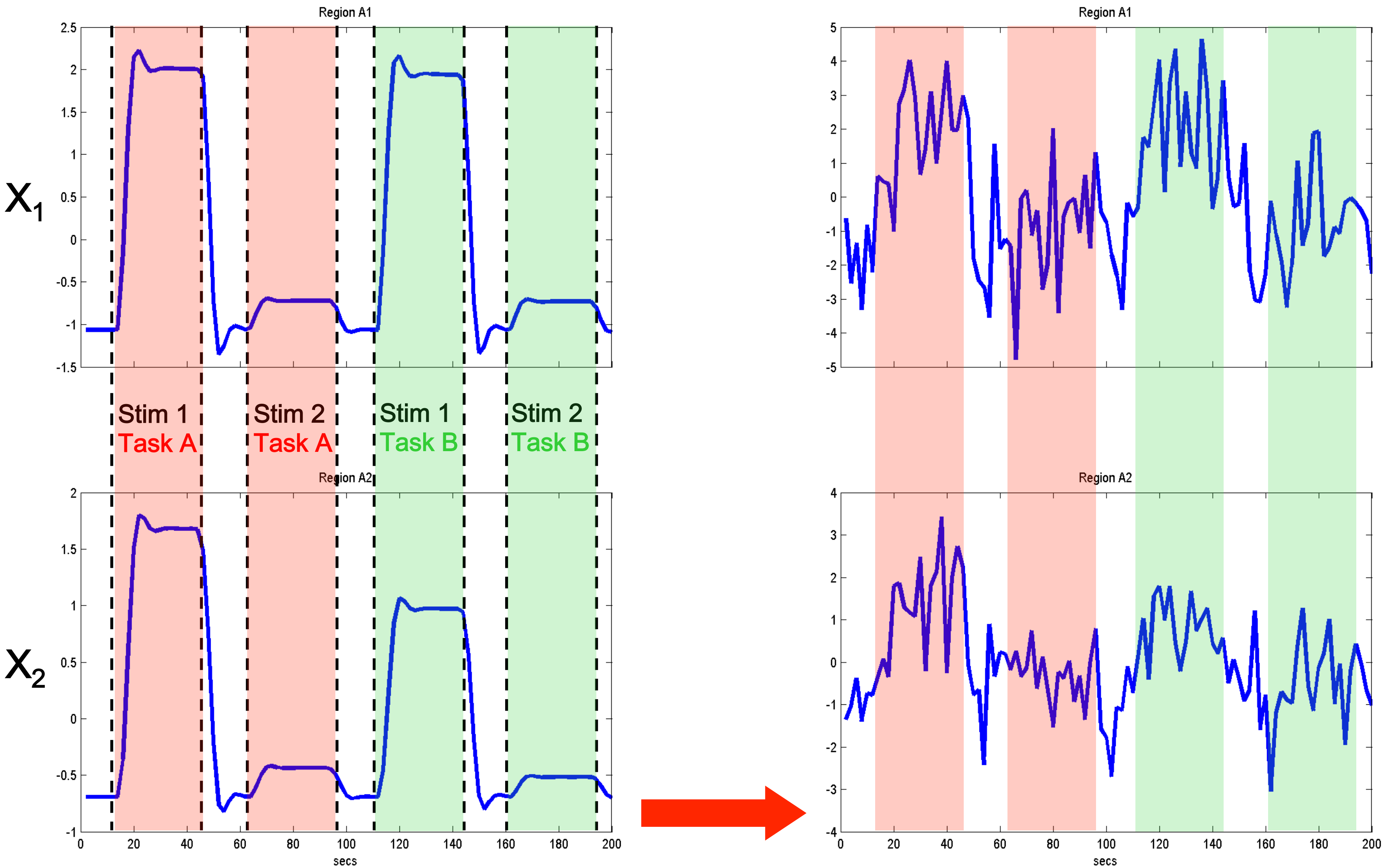


Simulated data





Stephan et al. 2007, *J. Biosci.*



plus added noise (SNR=1)

DCM parameters = rate constants

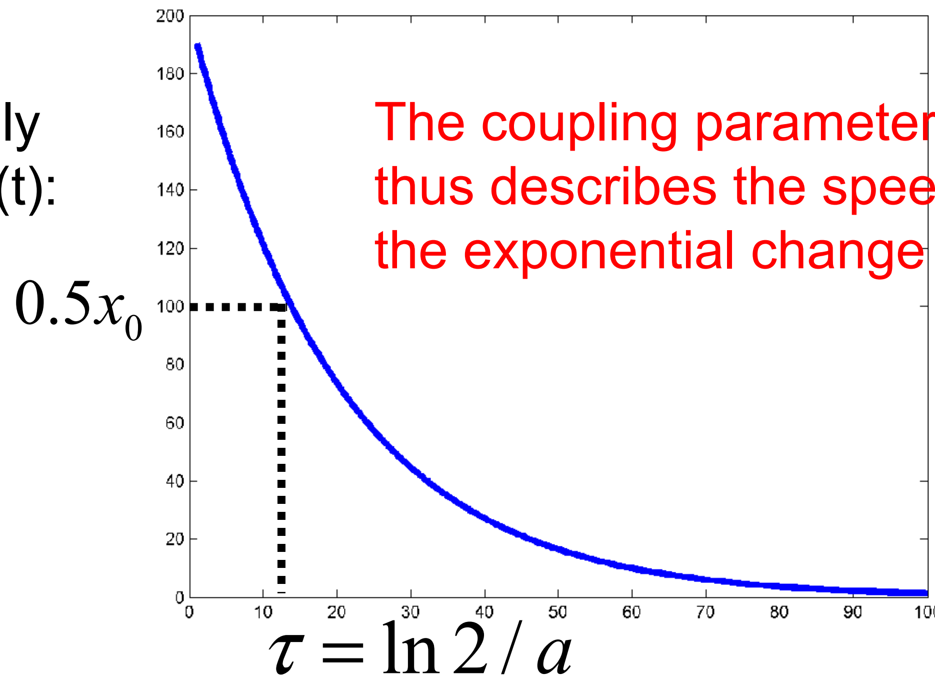
Integration of a first-order linear differential equation gives an exponential function:

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

Coupling parameter a is inversely proportional to the half life τ of z(t):

$$x(\tau) = 0.5x_0$$
$$= x_0 \exp(a\tau)$$

$$\Rightarrow \quad a = \ln 2 / \tau$$



The coupling parameter a thus describes the speed of the exponential change in x(t)

Interpretation of DCM parameters

- **Dynamic model (differential equations)**
  a neural parameters correspond to rate constants (inverse of time constants = Hz!)
  τ speed at which effects take place

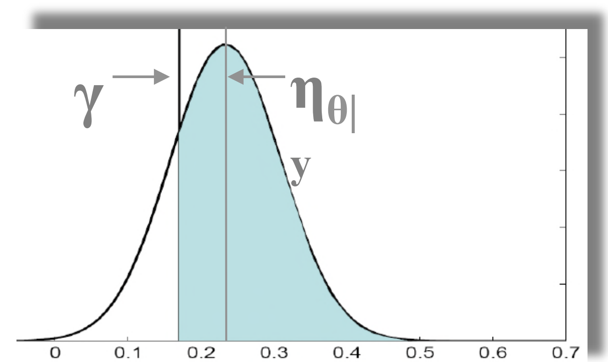
$$\theta^n = \{A, B, C, \sigma\}$$

$$a = \ln 2 / \tau$$

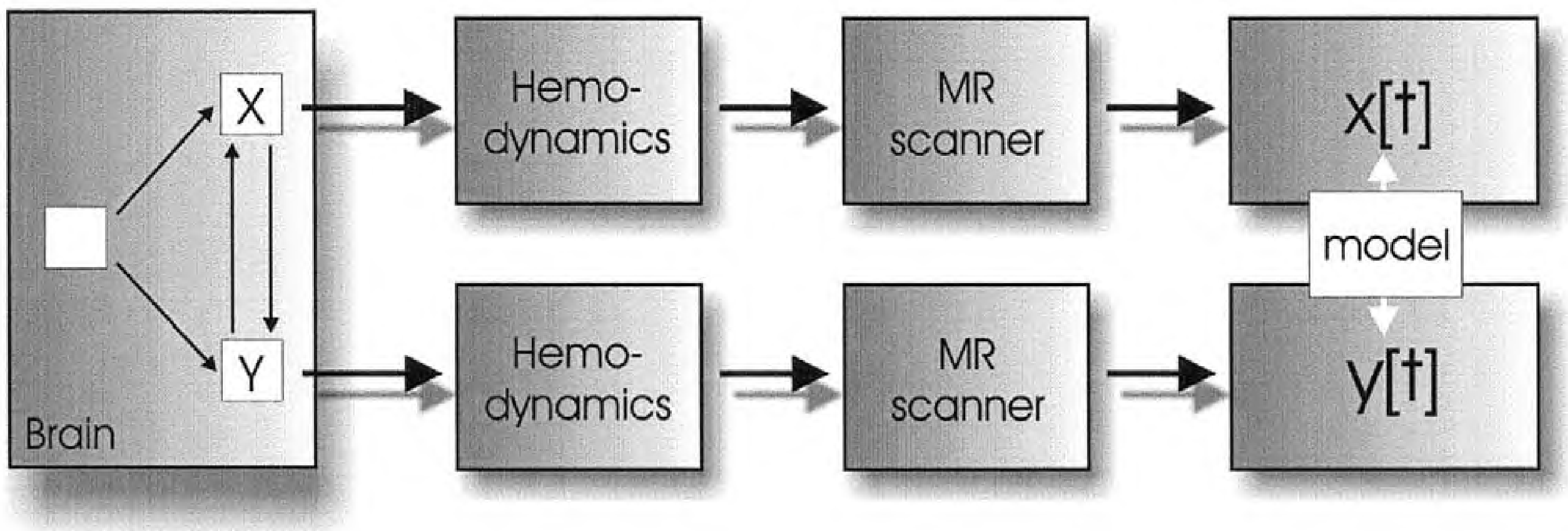
- **Identical temporal scaling in all areas by factorising A and B with σ: all connection strengths are relative to the self-connections.**

$$A \rightarrow \sigma A = \sigma \begin{bmatrix} -1 & a_{12} & \cdots \\ a_{21} & -1 & \\ \vdots & & \ddots \end{bmatrix}$$

- **Each parameter is characterised by the mean ($\eta_{\theta|y}$) and covariance of its *a posteriori* distribution. Its mean can be compared statistically against a chosen threshold *γ*.**



The problem of hemodynamic convolution



Goebel et al. 2003, *Magn. Res. Med.*

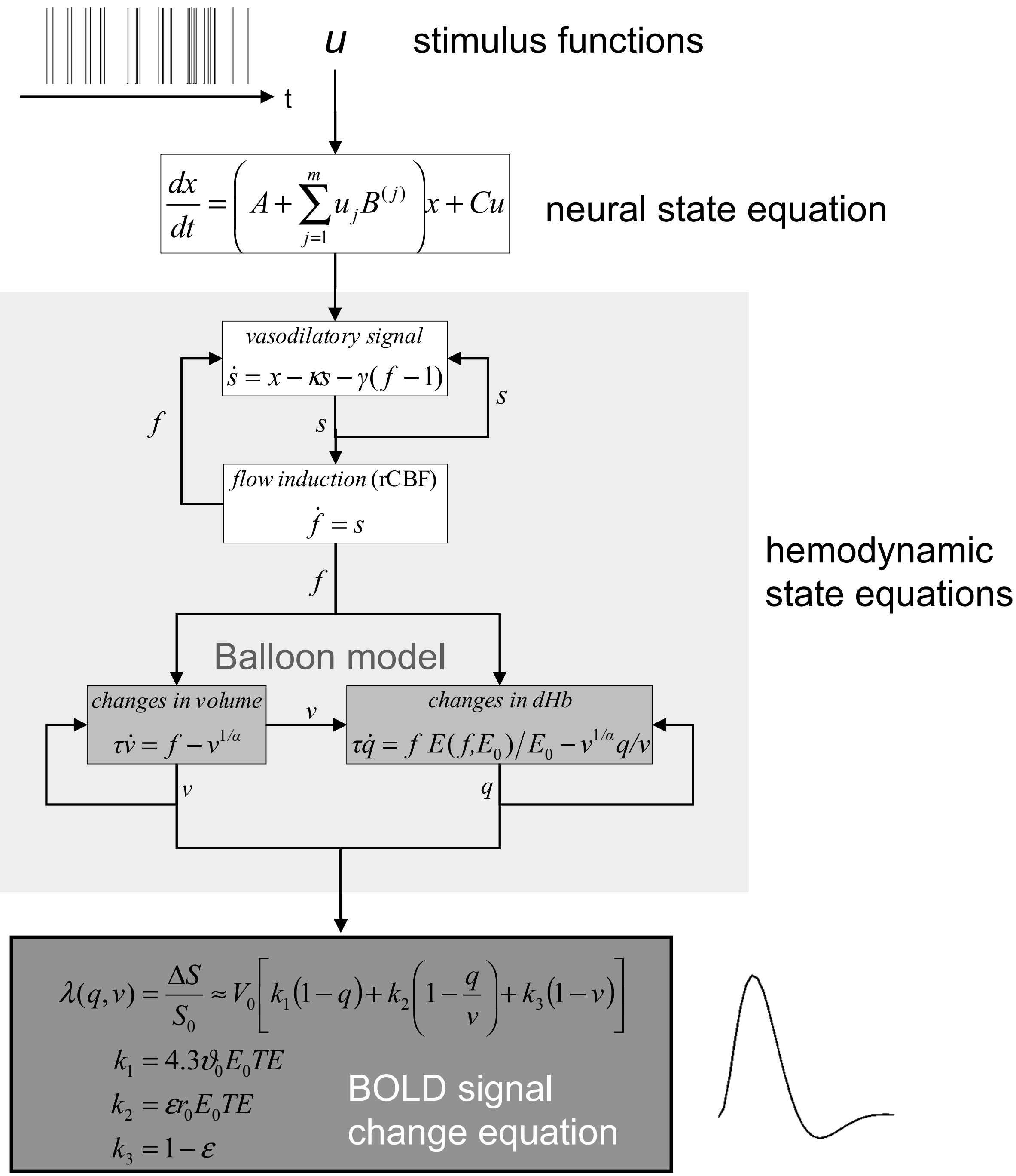
The hemodynamic model in DCM

- 6 hemodynamic parameters:

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

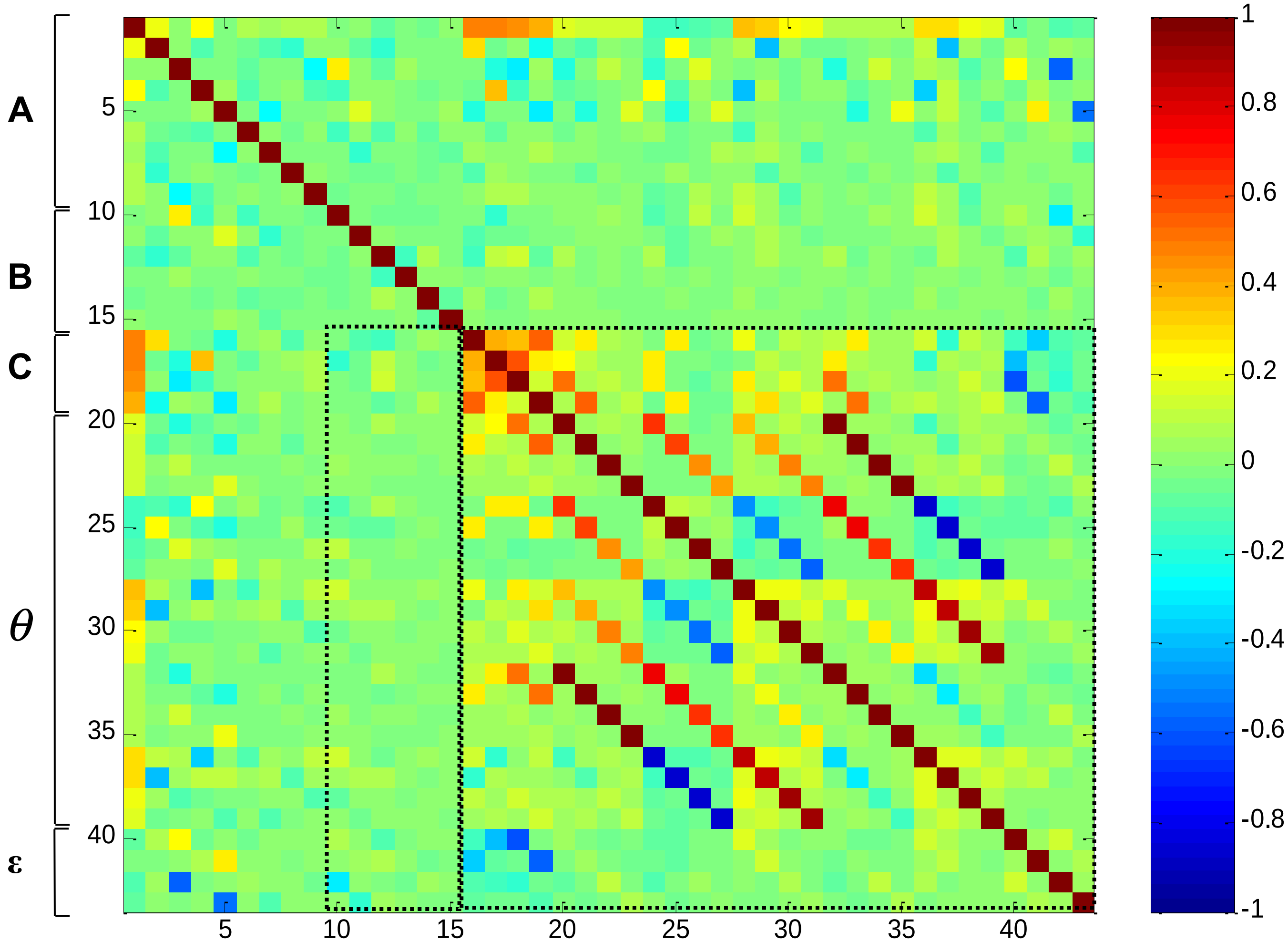
important for model fitting, but (usually) of no interest for statistical inference

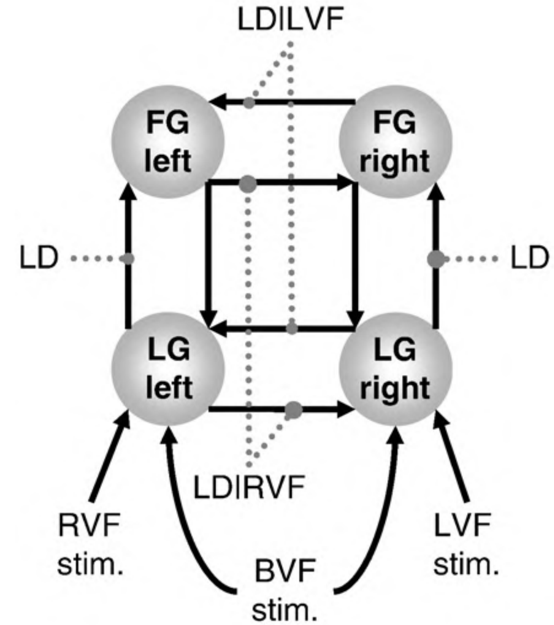
- Computed separately for each area (like the neural parameters)
  ⇒ region-specific HRFs!



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

How interdependent are neural and hemodynamic parameter estimates?

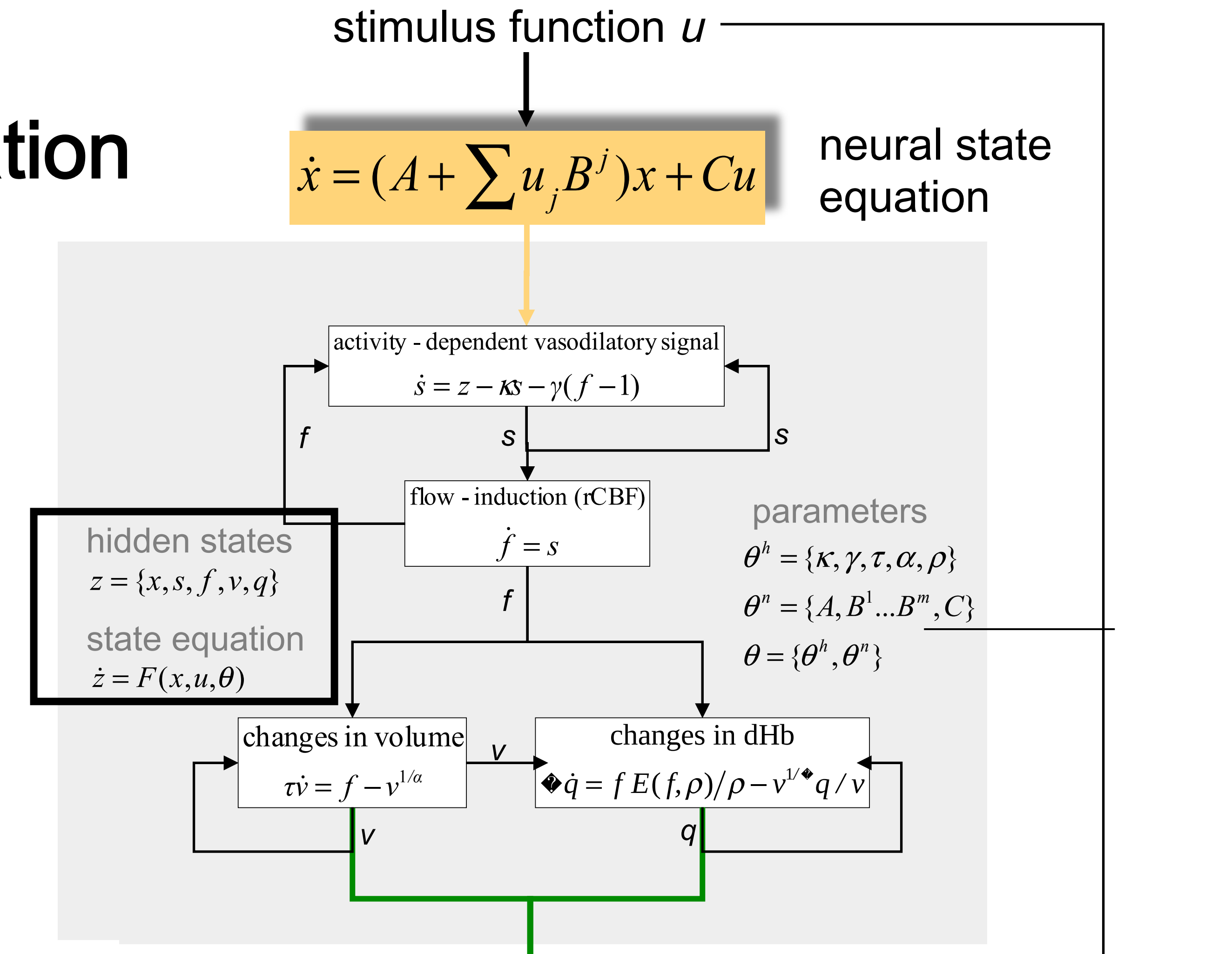


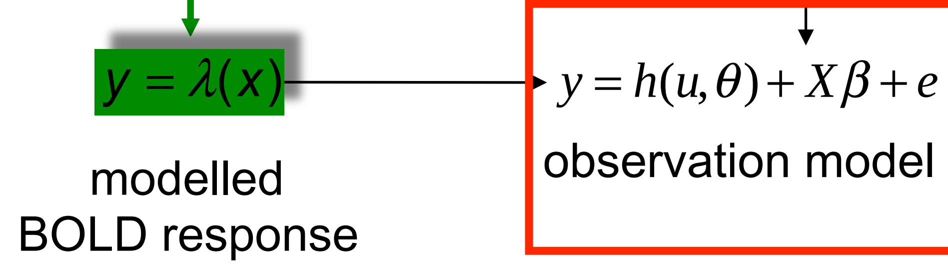


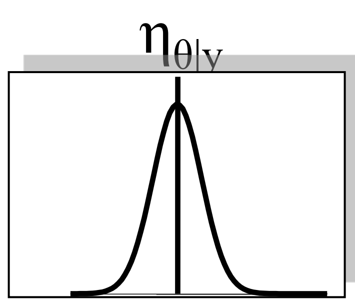
Stephan et al. 2007, *NeuroImage*

Overview: parameter estimation

- Combining the neural and hemodynamic states gives the complete forward model.
- An observation model includes measurement error e and confounds X (e.g. drift).
- Bayesian parameter estimation by means of a Levenberg-Marquardt gradient ascent, embedded into an EM algorithm.
- Result: Gaussian a posteriori parameter distributions, characterised by mean $\eta_{\theta|y}$ and covariance $C_{\theta|y}$.







Problems of classical (frequentist) statistics

p-value: probability of getting the observed data in the effect's absence. If small, reject null hypothesis that there is no effect.

$$H_0 : \theta = 0$$
$$p(y \mid H_0)$$

Probability of observing the data y, given no effect.

Limitations:

⇨ One can never accept the null hypothesis

⇨ Given enough data, one can always demonstrate a significant effect

⇨ Correction for multiple comparisons necessary

Solution: infer **posterior probability** of the **effect**

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

Probability of the effect, given the observed data

Bayes' Theorem

Reverend Thomas Bayes
1702 - 1761

Posterior — Likelihood — Prior

$$P(\theta \mid y) = \frac{p(y \mid \theta)\, p(\theta)}{p(y)}$$

Evidence

"Bayes' Theorem describes, how an ideally rational person processes information."

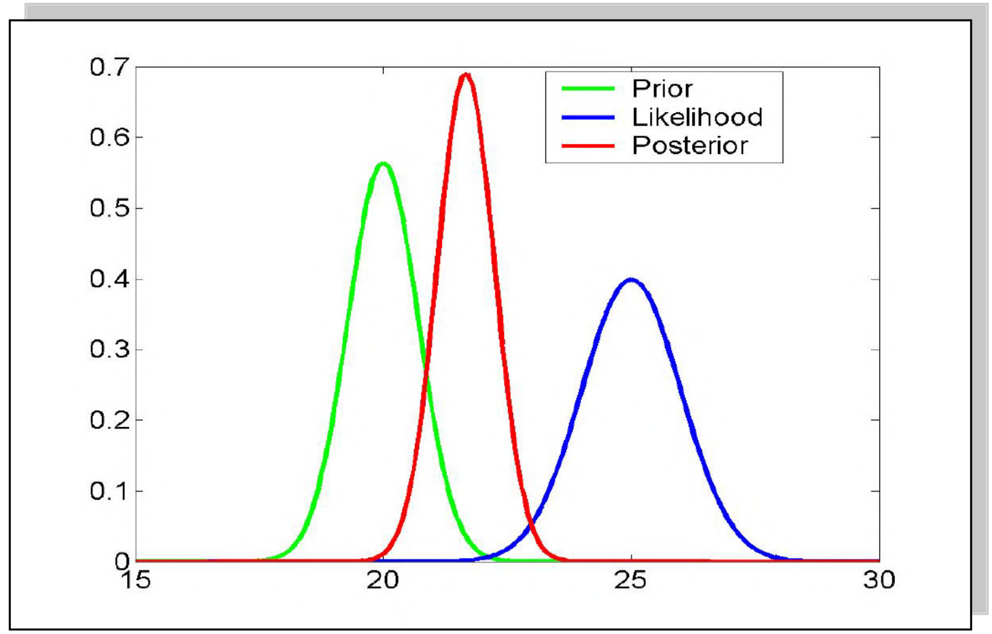
Wikipedia

Bayesian statistics

new data $p(y \mid \theta)$ prior knowledge $p(\theta)$

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

posterior $\propto$ likelihood • prior



Bayes theorem allows one to formally incorporate prior knowledge into computing statistical probabilities.

Priors can be of different sorts: empirical, principled or shrinkage priors.

The “posterior” probability of the parameters given the data is an optimal combination of prior knowledge and new data, weighted by their relative precision.

Principles of Bayesian inference

➩ Formulation of a generative model

Likelihood $p(y \mid \theta)$

prior distribution $p(\theta)$

➩ Observation of data

y

➩ Update of beliefs based upon observations, given a prior state of knowledge

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

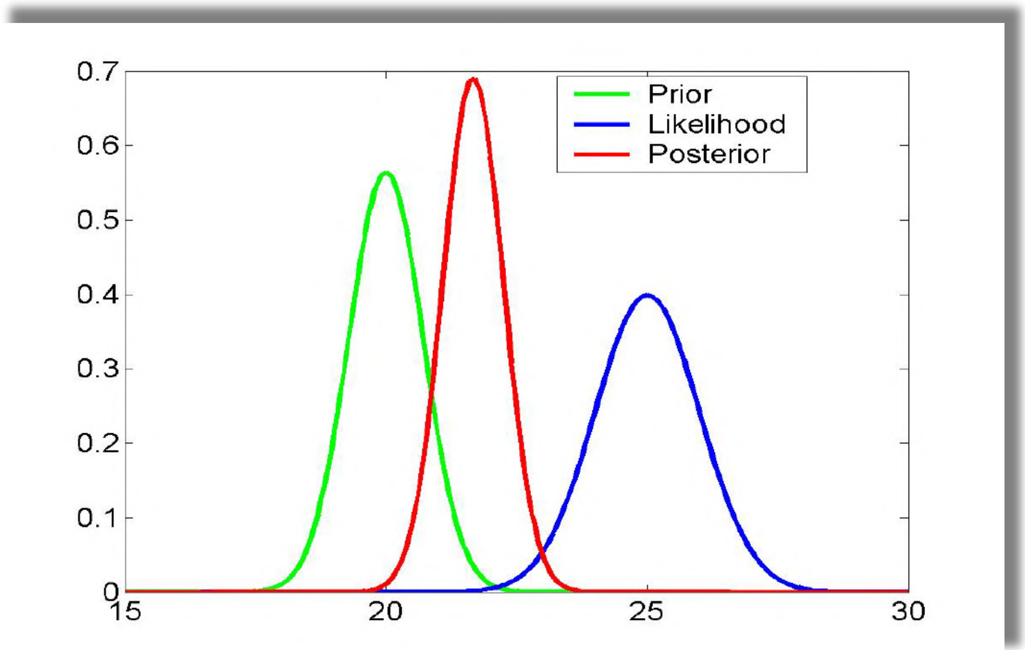
Priors in DCM

- needed for Bayesian estimation, embody constraints on parameter estimation
- express our prior knowledge or "belief" about parameters of the model
- <u>hemodynamic parameters:</u> empirical priors
- <u>temporal scaling:</u> principled prior
- <u>coupling parameters:</u> shrinkage priors

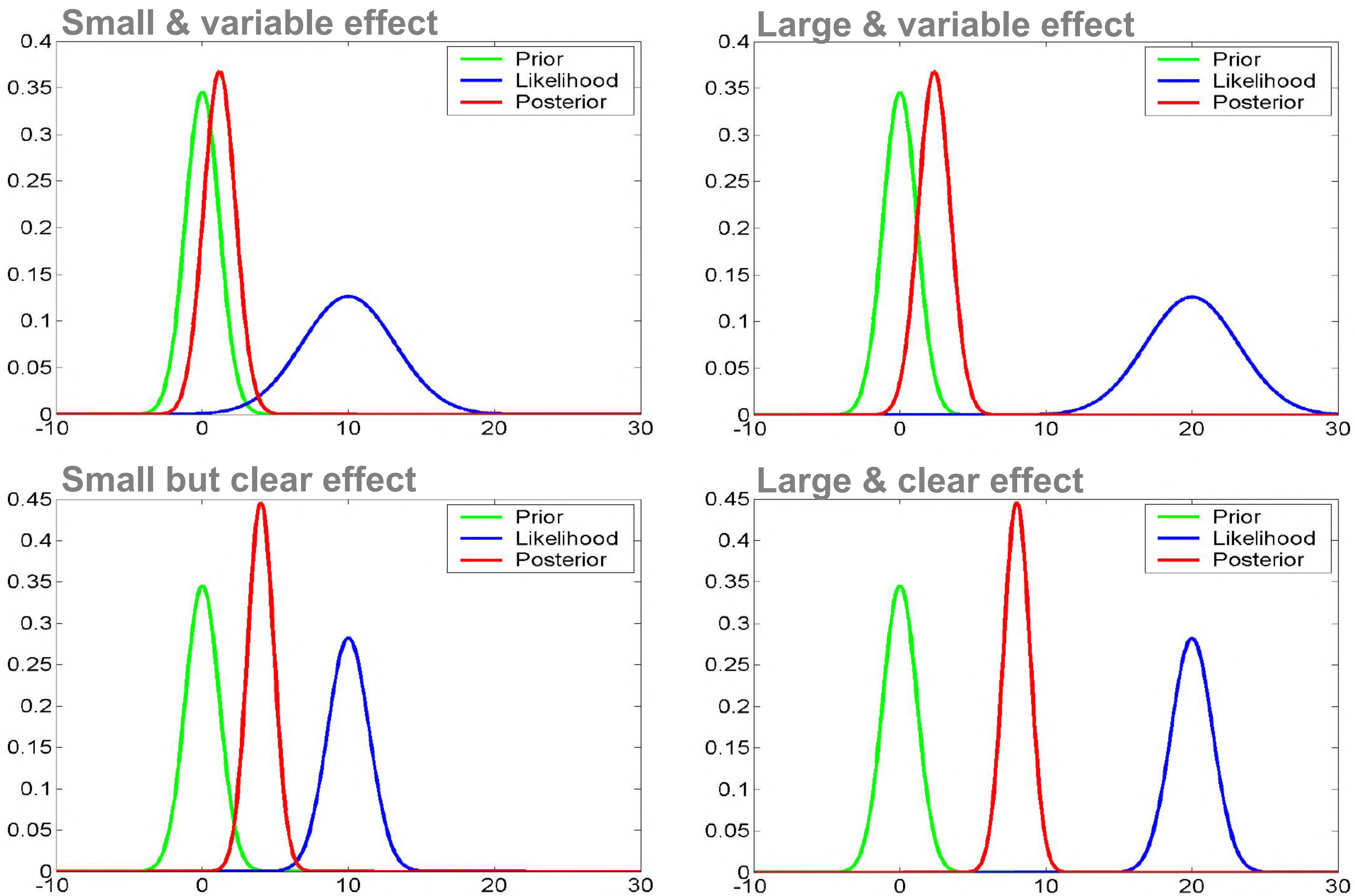
Bayes Theorem

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

posterior ∝ **likelihood** · **prior**



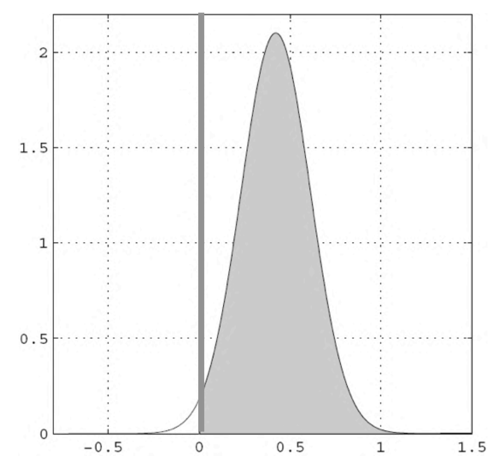
Shrinkage Priors



Inference about DCM parameters: Bayesian single-subject analysis

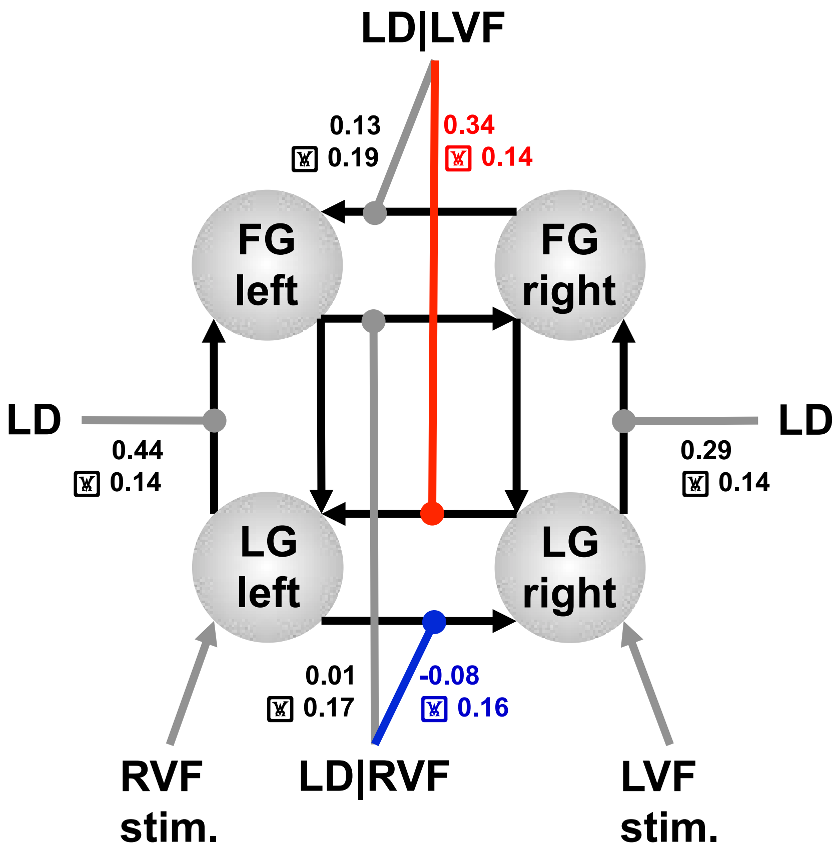
- Gaussian assumptions about the posterior distributions of the parameters
- Use of the cumulative normal distribution to test the probability that a certain parameter (or contrast of parameters $c^T \eta_{\theta|y}$) is above a chosen threshold γ:

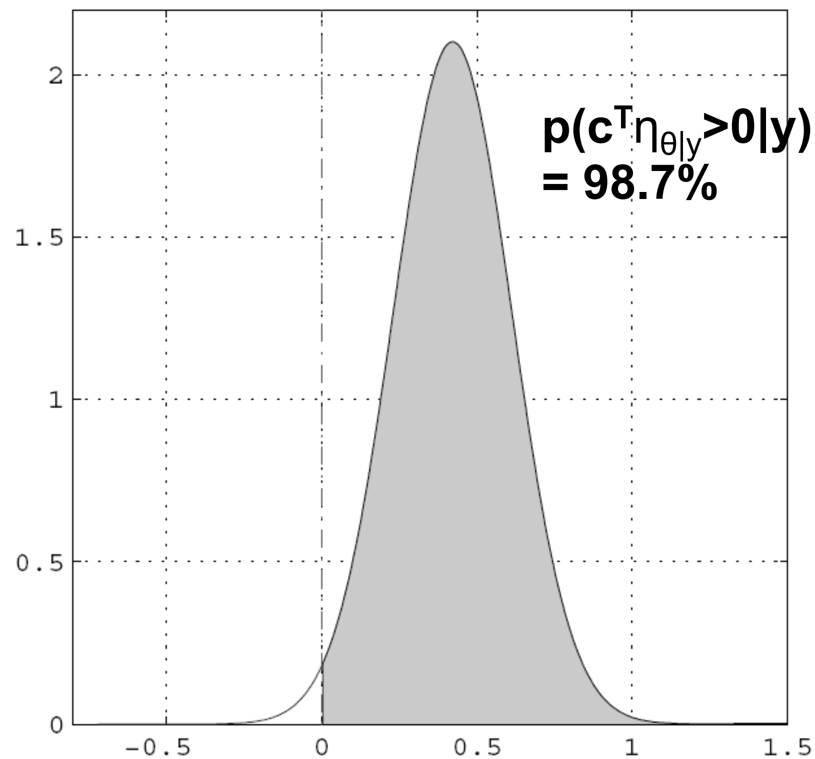
$$p = \phi_N\left(\frac{c^T \eta_{\theta|y} - \gamma}{\sqrt{c^T C_{\theta|y} c}}\right)$$



- By default, γ is chosen as zero ("does the effect exist?").

Bayesian single subject inference





Contrast:
Modulation LG right -> LG links by LD|LVF
vs.
modulation LG left -> LG right by LD|RVF

Stephan et al. 2005,
Ann. N.Y. Acad. Sci.

Inference about DCM parameters: Bayesian fixed-effects group analysis

Because the likelihood distributions from different subjects are independent, one can combine their posterior densities by using the posterior of one subject as the prior for the next:

$$
\begin{aligned}
p(\theta \mid y_1) &\propto p(y_1 \mid \theta)\, p(\theta) \\
p(\theta \mid y_1, y_2) &\propto p(y_2 \mid \theta)\, p(y_1 \mid \theta)\, p(\theta) \\
&\propto p(y_2 \mid \theta)\, p(\theta \mid y_1) \\
&\ldots \\
p(\theta \mid y_1, \ldots, y_N) &\propto p(y_N \mid \theta)\, p(\theta \mid y_{N-1}) \ldots p(\theta \mid y_1)
\end{aligned}
$$

Under Gaussian assumptions this is easy to compute:

$$
C^{-1}_{\theta|y_1,\ldots,y_N} = \sum_{i=1}^{N} C^{-1}_{\theta|y_i}
$$

$$
\eta_{\theta|y_1,\ldots,y_N} = \left(\sum_{i=1}^{N} C^{-1}_{\theta|y_i} \eta_{\theta|y_i} \right) C^{-1}_{\theta|y_1,\ldots,y_N}
$$

group posterior covariance

individual posterior covariances

group posterior mean

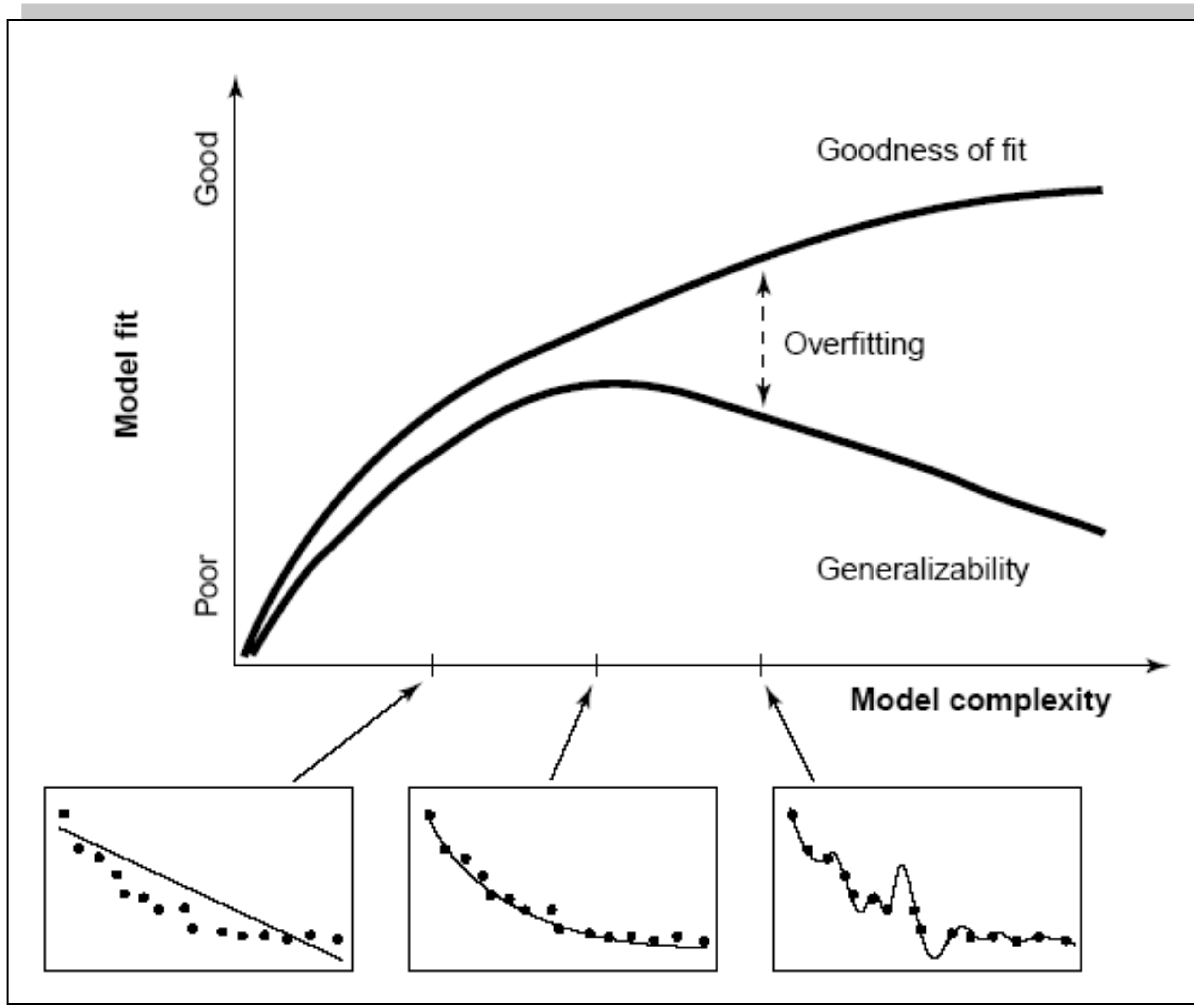
individual posterior covariances and means

Bayesian model selection (BMS)

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 p(y|m) become maximal?



Pitt & Miyung (2002), *TICS*

Bayesian model selection (BMS)

Bayes' rules:

$$p(\theta \mid y, m) = \frac{p(y \mid \theta, m)\, p(\theta \mid m)}{p(y \mid m)}$$

Model evidence:

$$p(y \mid m) = \int p(y \mid \theta, m) \cdot p(\theta \mid m)\, d\theta$$

- accounts for both accuracy and complexity of the model
- allows for inference about structure (generalisability) of the model

Various approximations, e.g.:

- negative free energy
- AIC
- BIC

Model comparison via Bayes factor:

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

Penny et al. (2004) *NeuroImage*

Bayes factors

To compare two models, we can just compare their log evidences.

But: the log evidence is just some number – not very intuitive!

A more intuitive interpretation of model comparisons is made possible by Bayes factors:

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

Kass & Raftery classification:

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

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

Example studies of DCM for fMRI

- DCM now an established tool for fMRI & M/EEG analysis
- >100 studies published, incl. high-profile journals
- combinations of DCM with computational models

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Task and Content Modulate Amygdala-Hippocampal Connectivity in Emotional Retrieval

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2004b), raising the question of how these structures might interact, particularly because they are well interconnected anatomically (Amaral et al., 1992). A recent study by Greenberg and colleagues (2005) reported correlated activity in amygdala and hippocampus during

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Behavioral/Systems/Cognitive

Interhemispheric Integration of Visual Processing during Task-Driven Lateralization

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A Dual Role for Prediction Error in Associative Learning

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Thank you