Dynamic causal modeling for fMRI

Methods and Models for fMRI, HS 2015

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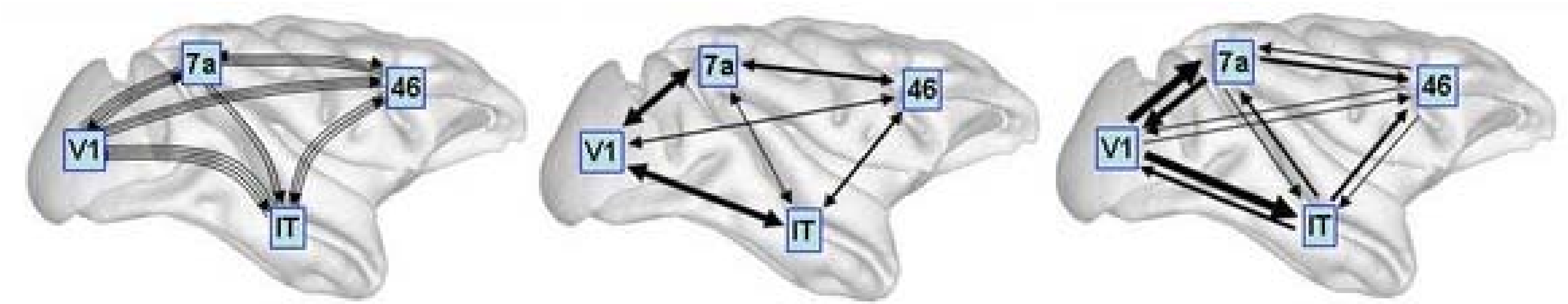
Structural, functional & effective connectivity



Sporns 2007, *Scholarpedia*

anatomical/structural connectivity
- presence of physical connections
- DWI, tractography, tracer studies (monkeys)

functional connectivity
- statistical dependency between regional time series
- correlations, ICA

effective connectivity
- causal (directed) influences between neuronal populations
- DCM

Dynamic causal modelling (DCM) for fMRI

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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

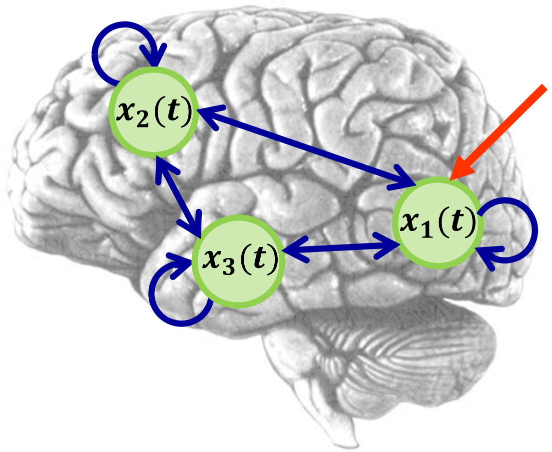
- DCM framework was introduced in 2003 for fMRI by Karl Friston, Lee Harrison and Will Penny (NeuroImage 19:1273-1302)
- part of the SPM software package
- Allows to do an effective connectivity analysis

DCM approach to effective connectivity

A simple model of a neural network …

… described as a dynamical system …

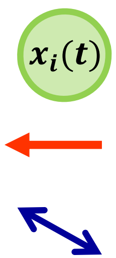
… causes the data (BOLD signal).



$$\dot{x} = f(x, u, \theta_x)$$

$$y = g(x, \theta_y)$$

Let the system run with input (u) and parameters (θ_x, θ_y), and you will get a BOLD signal time course y that you can compare to the measured data.

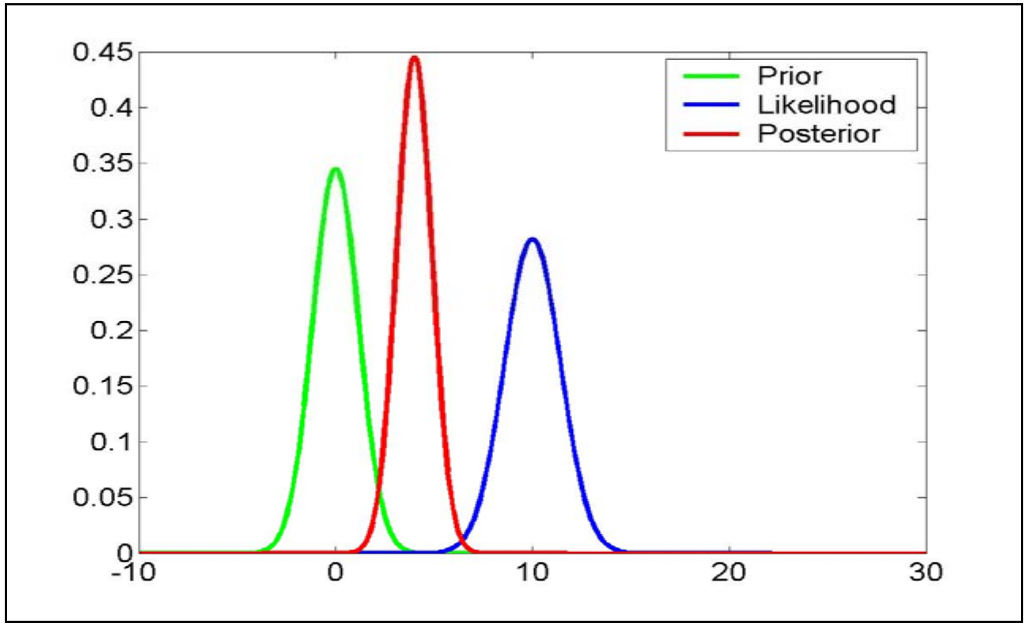


Neural node

Input (u)

Connections (θ)

Bayes' theorem

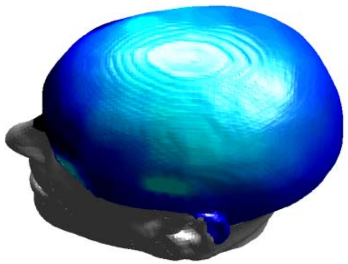


The Reverend Thomas Bayes
(1702-1761)

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

posterior = likelihood • prior / evidence

Generative model

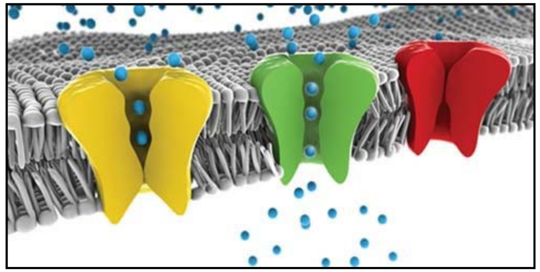


$$p(y \mid \theta, m) \cdot p(\theta \mid m)$$

$$\longleftarrow$$

$$\longrightarrow$$

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

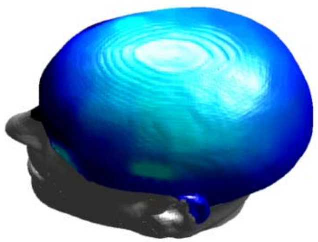


1. enforces mechanistic thinking: how could the data have been caused?
2. generate synthetic data (observations) by sampling from the prior – can model explain certain phenomena at all?
3. inference about model structure: formal approach to disambiguating mechanisms → p(m|y)
4. inference about parameters → p(θ|y)

Dynamic causal modeling (DCM)

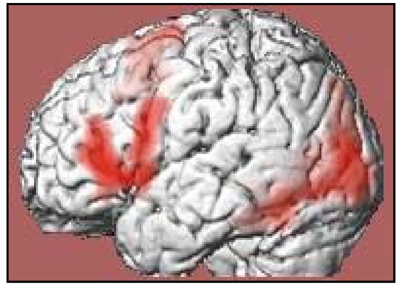
dwMRI

EEG, MEG

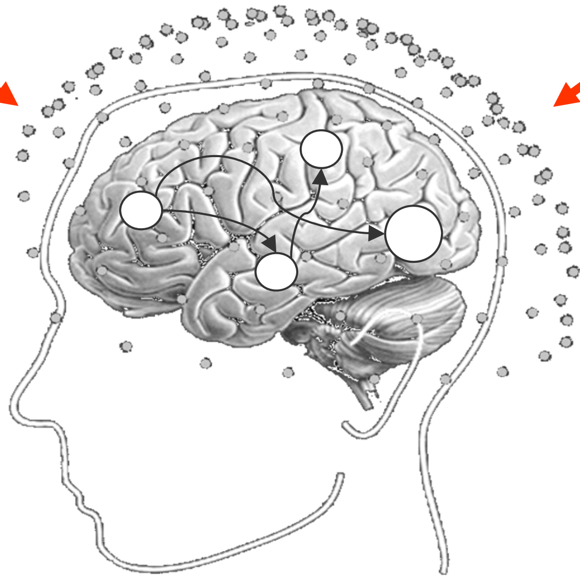


structural priors

fMRI



structural priors



Forward model:
Predicting measured activity

$$y = g(x,\theta) + \varepsilon$$

Model inversion:
Estimating neuronal mechanisms

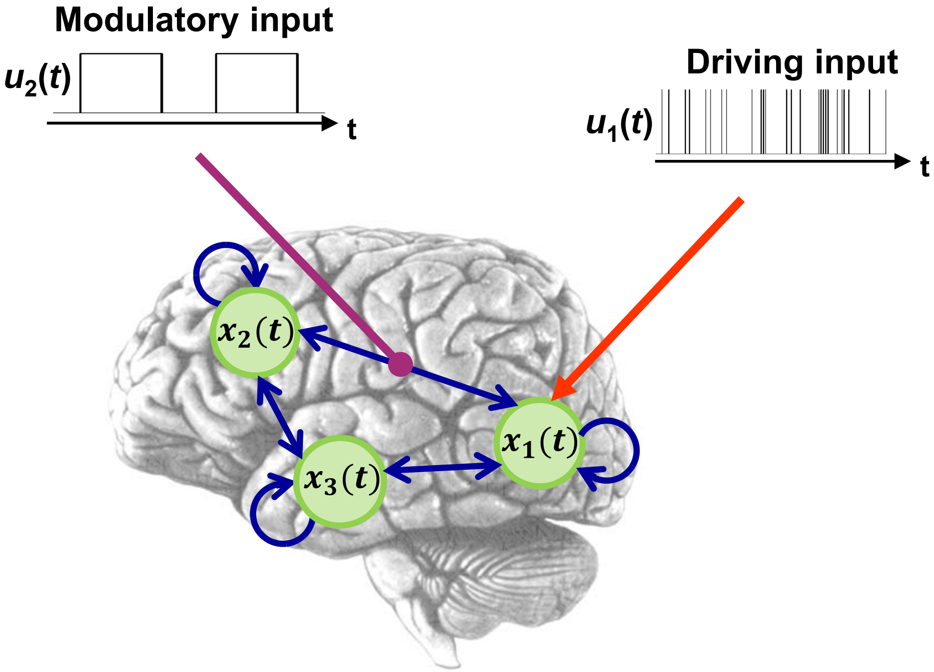
$$\frac{dx}{dt} = f(x,u,\theta) + \omega$$

Friston et al. 2003, *NeuroImage*

Stephan, Tittgemeyer et al. 2009, *NeuroImage*

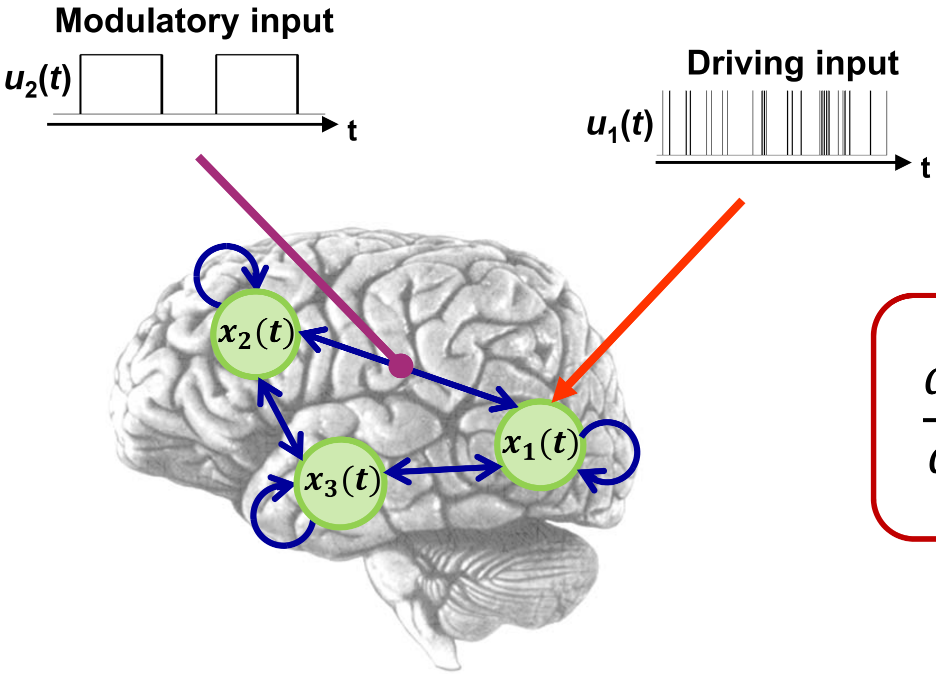
Approximating $f(x, u, \theta)$

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



Non-linear model

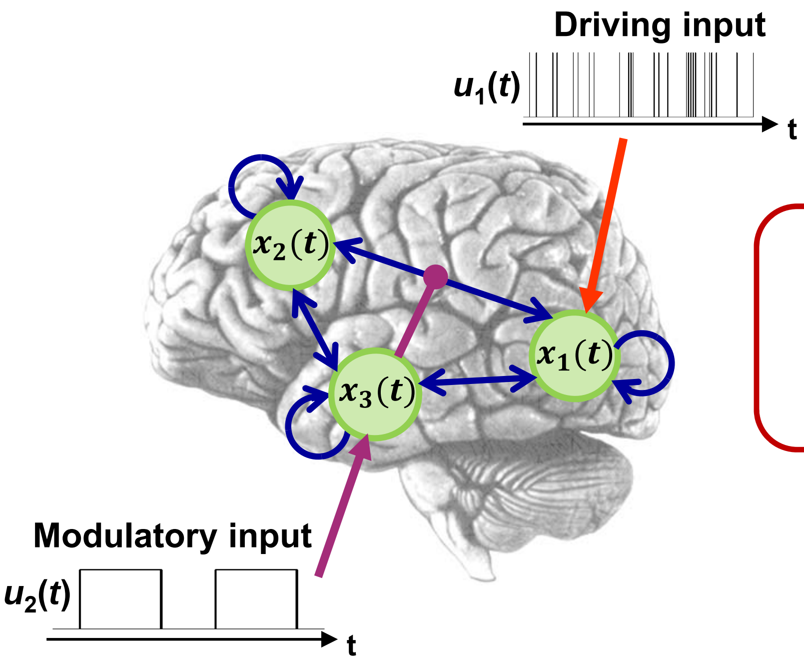
The neural equations – bilinear model



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

Parameters A, B and C define connectivity!

The neural equations – non-linear model



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

Parameters A, B, C and D define connectivity!

The problem of the hemodynamic response

↑ neural activity

⬇

↑ blood flow

⬇

↑ oxyhemoglobin

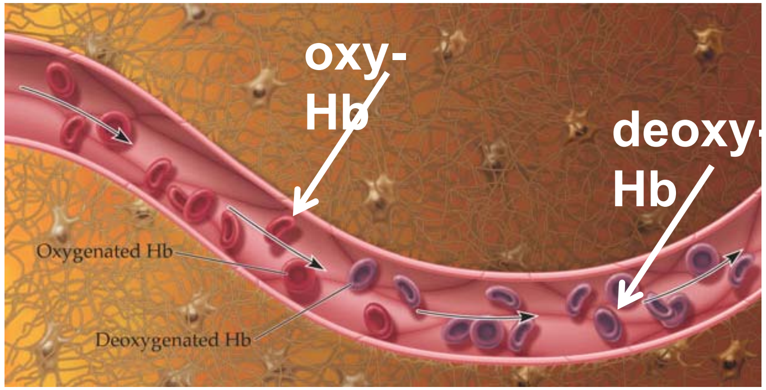
⬇

↑ T2*

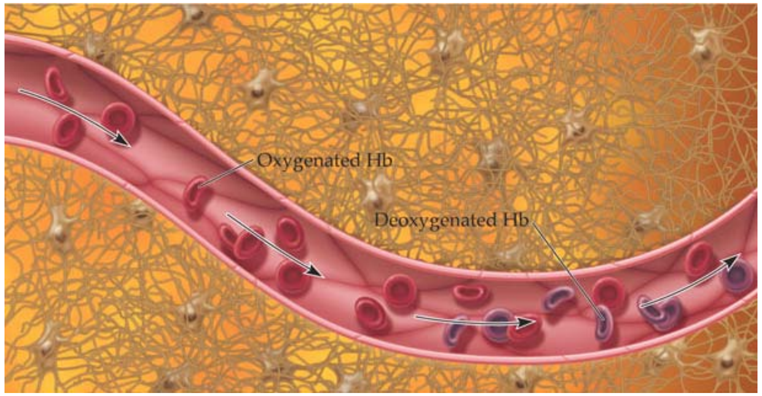
⬇

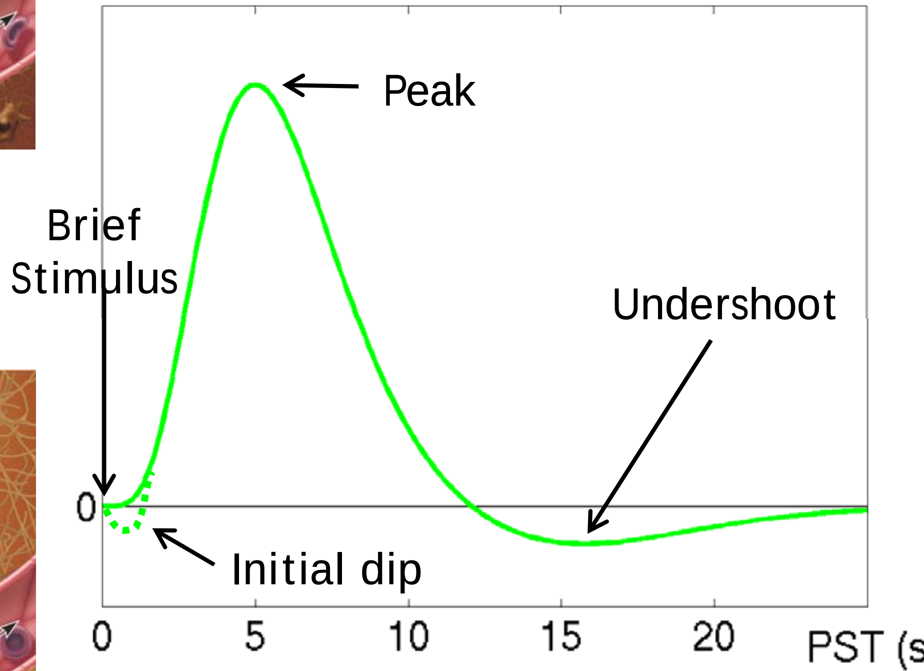
↑ MR signal

Rest



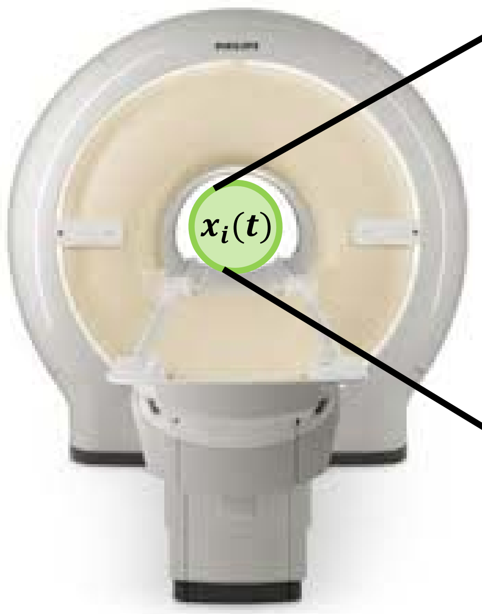
Activity





Source, Huettel et al, 2004, fMRI (Book)

From neural activity to the BOLD signal



Local hemodynamic state equation

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

vasodilatory signal and flow Induction (rCBF)

f

Balloon model

$$\tau\dot{v} = f - v^{1/\alpha}$$
$$\tau\dot{q} = fE(f, E_0)/E_0 - v^{1/\alpha}q/v$$

Changes in volume (v) and dHb (q)

BOLD signal change equation

$$y = \frac{\Delta S}{S_0} \approx V_0\left[k_1(1 - q) + k_2\left(1 - \frac{q}{v}\right) + k_3(1 - v)\right]$$

cf. Simulations in Lecture 1

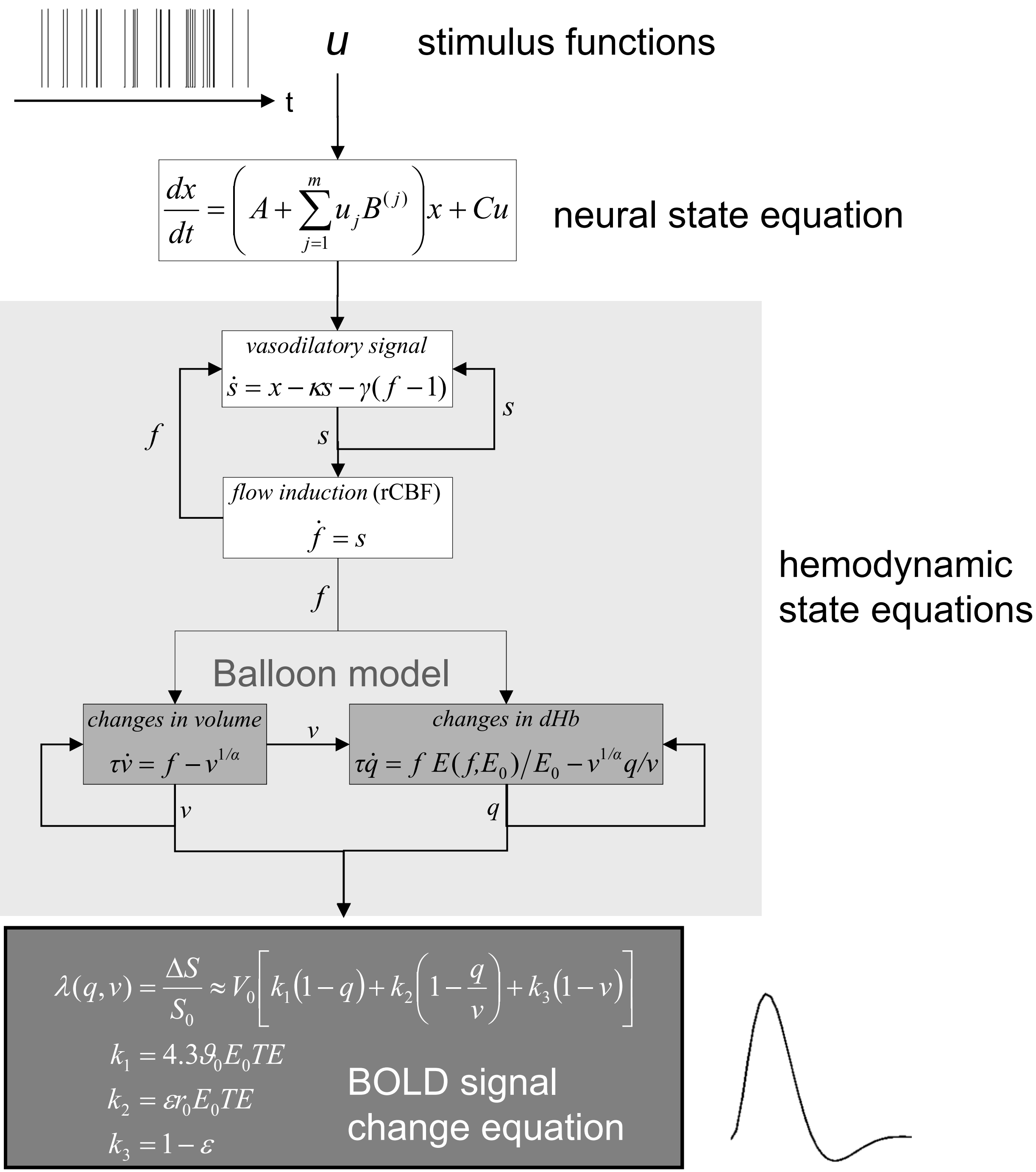
The hemodynamic model in DCM

- 6 hemodynamic parameters:

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

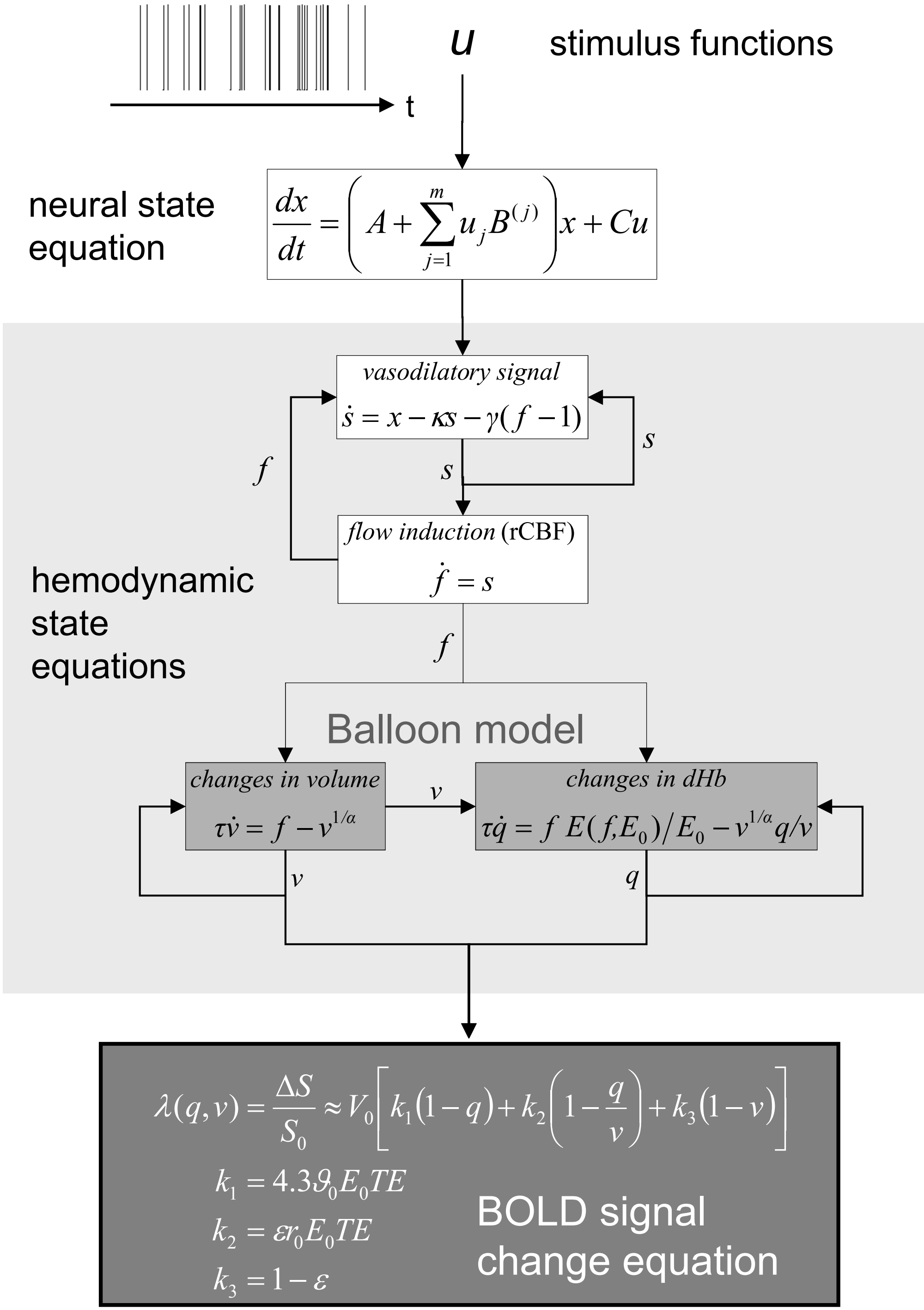
important for model fitting, but of no interest for statistical inference

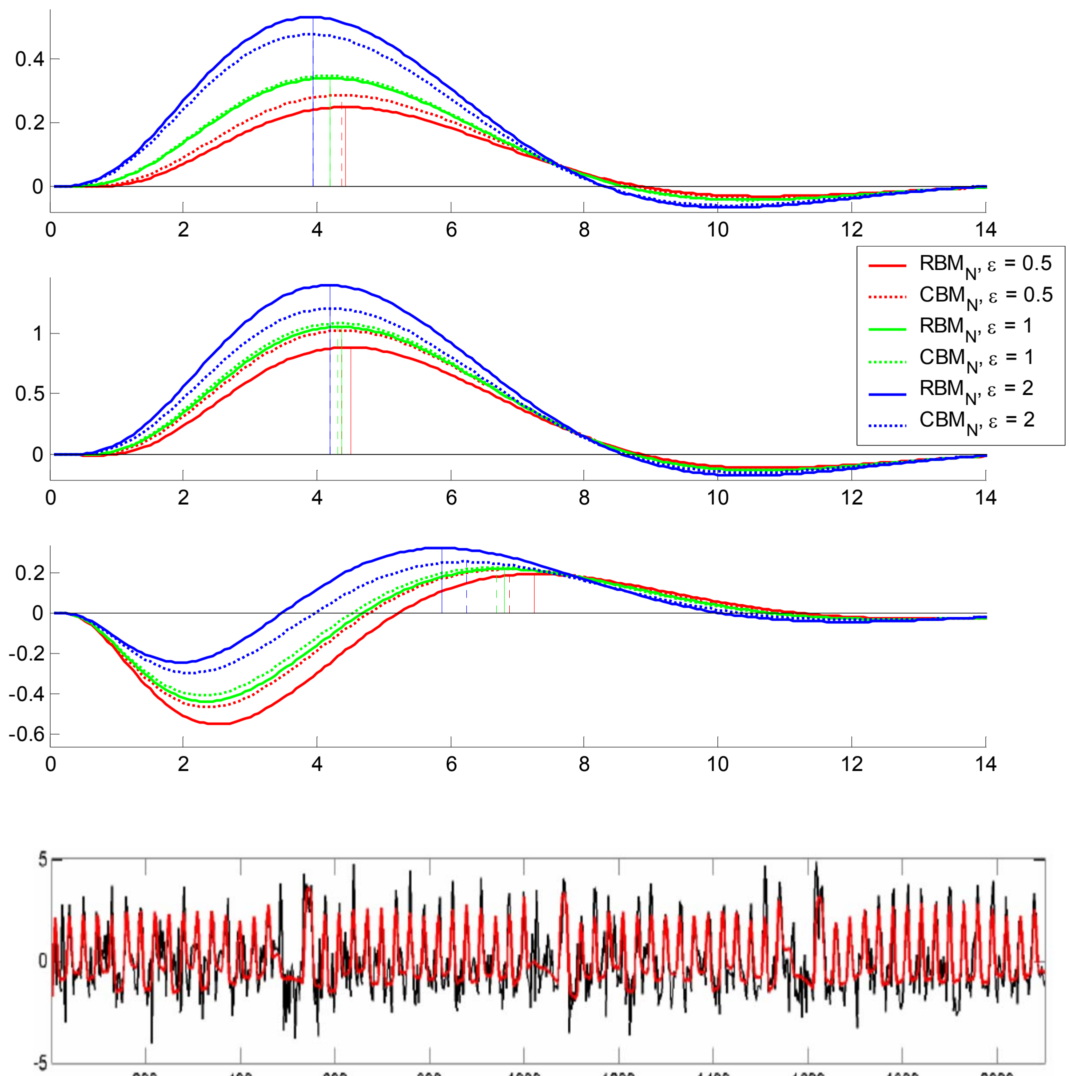
- Computed separately for each area (like the neural parameters)
  $\rightarrow$ region-specific HRFs!



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

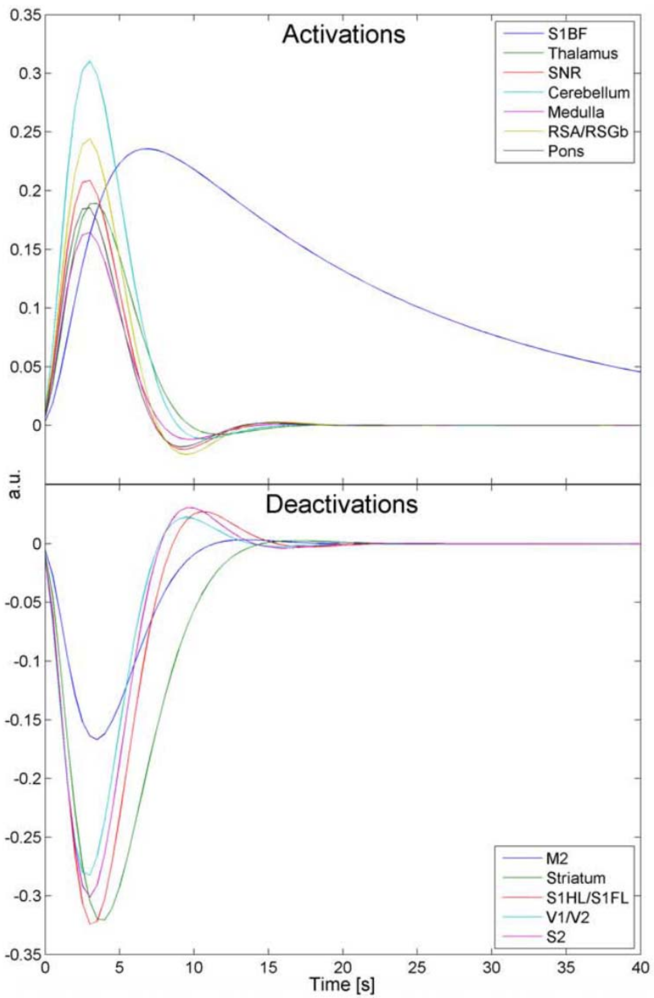
The hemodynamic model in DCM – role of ε



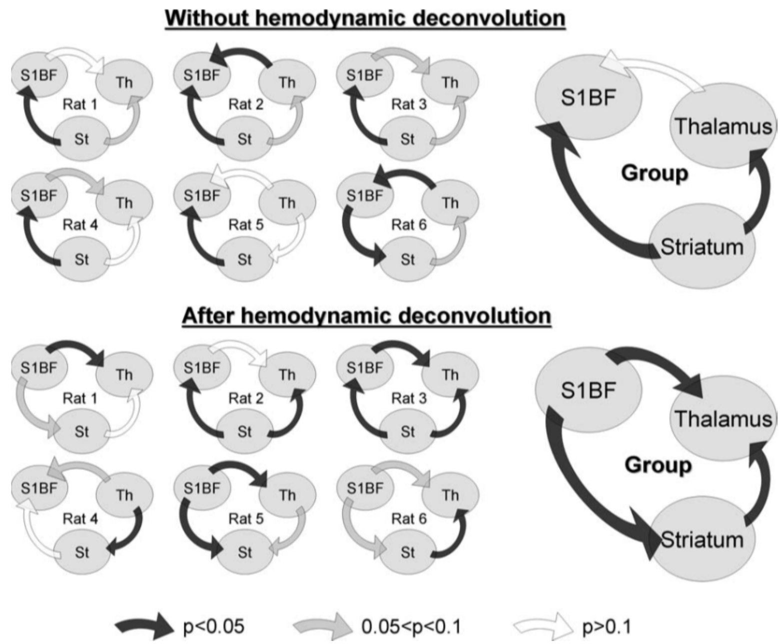


Stephan et al. 2007, *NeuroImage*

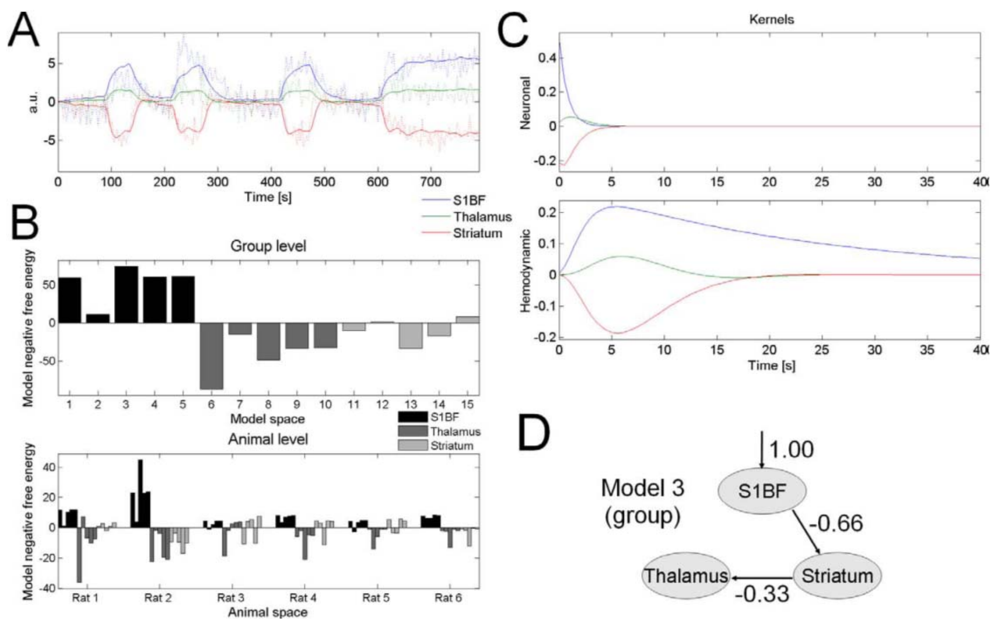
Hemodynamic forward models are important for connectivity analyses of fMRI data



Granger causality

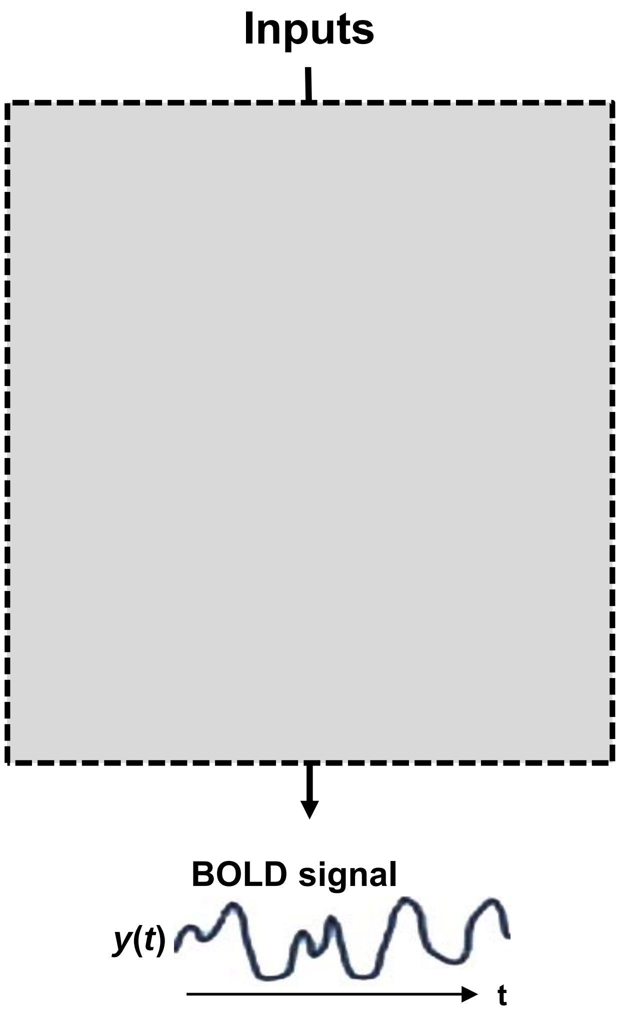


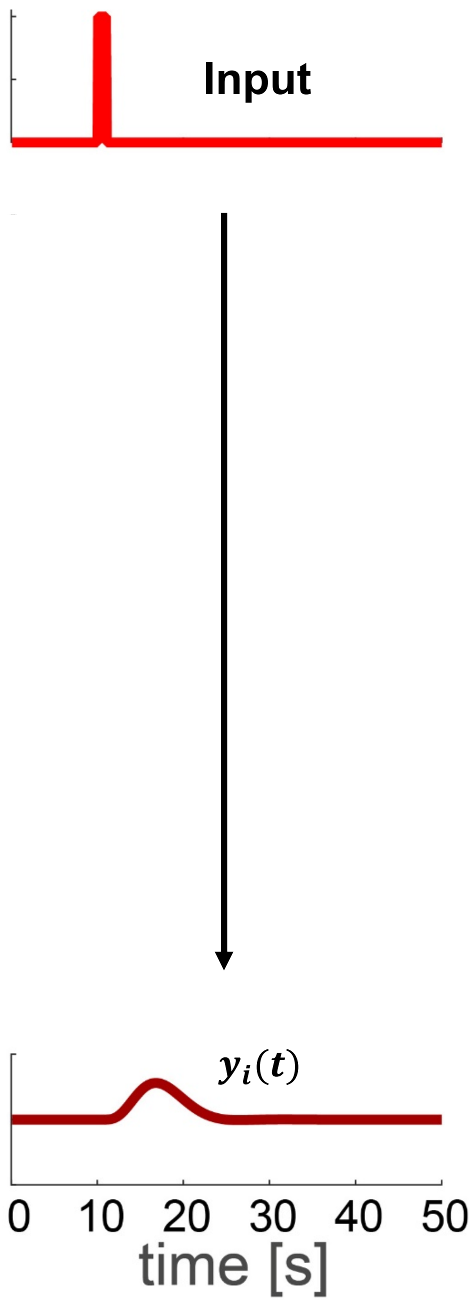
DCM



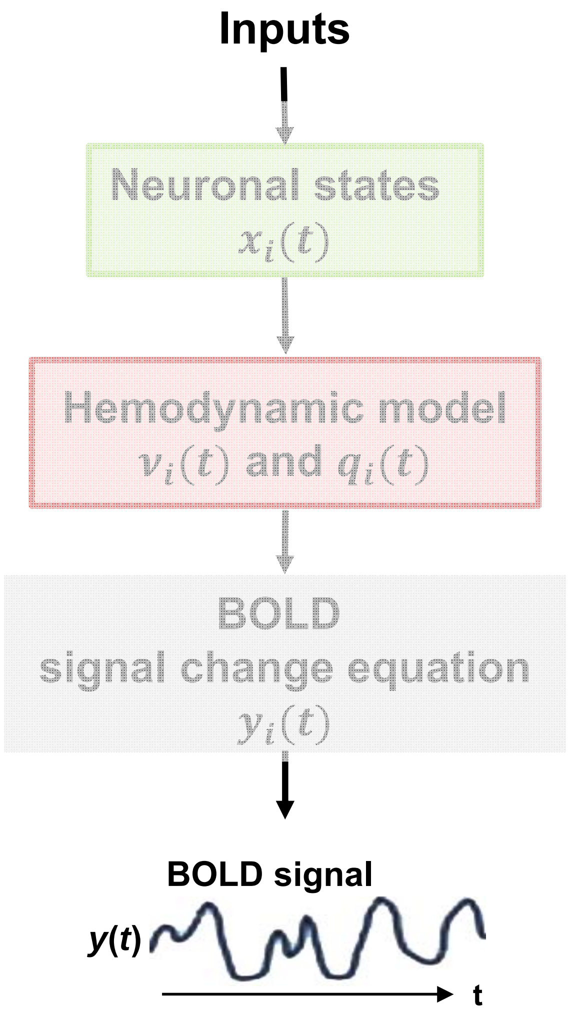
David et al. 2008, *PLoS Biol.*

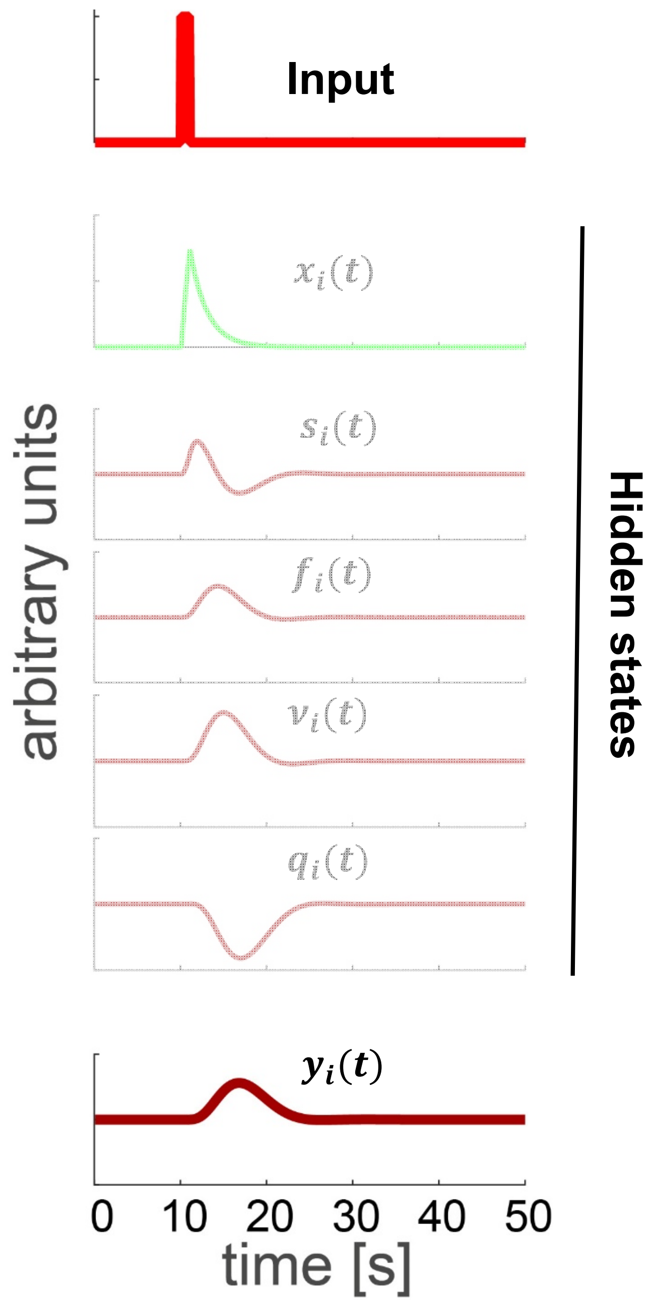
Summary – the full model



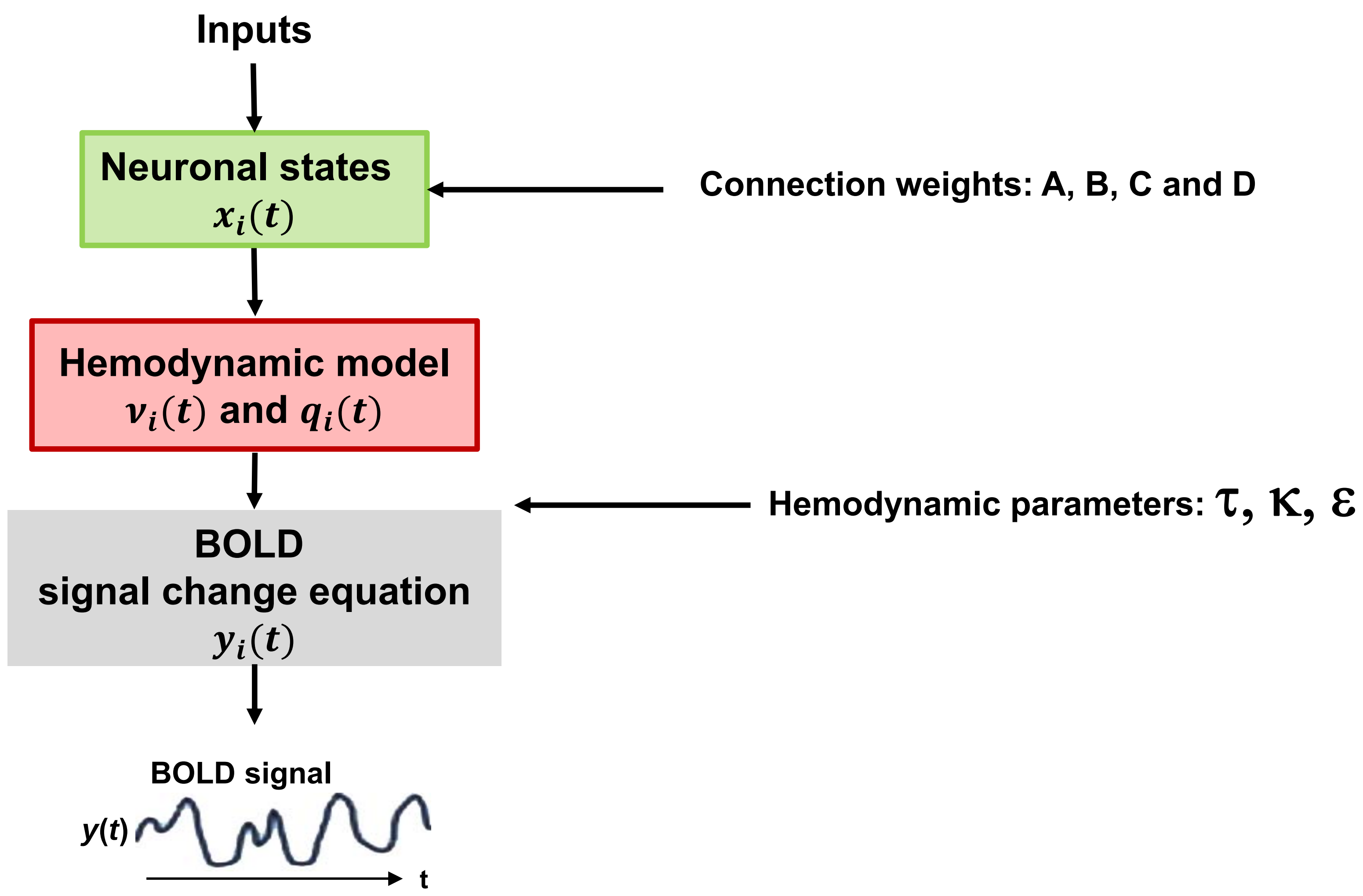


Summary – the full model

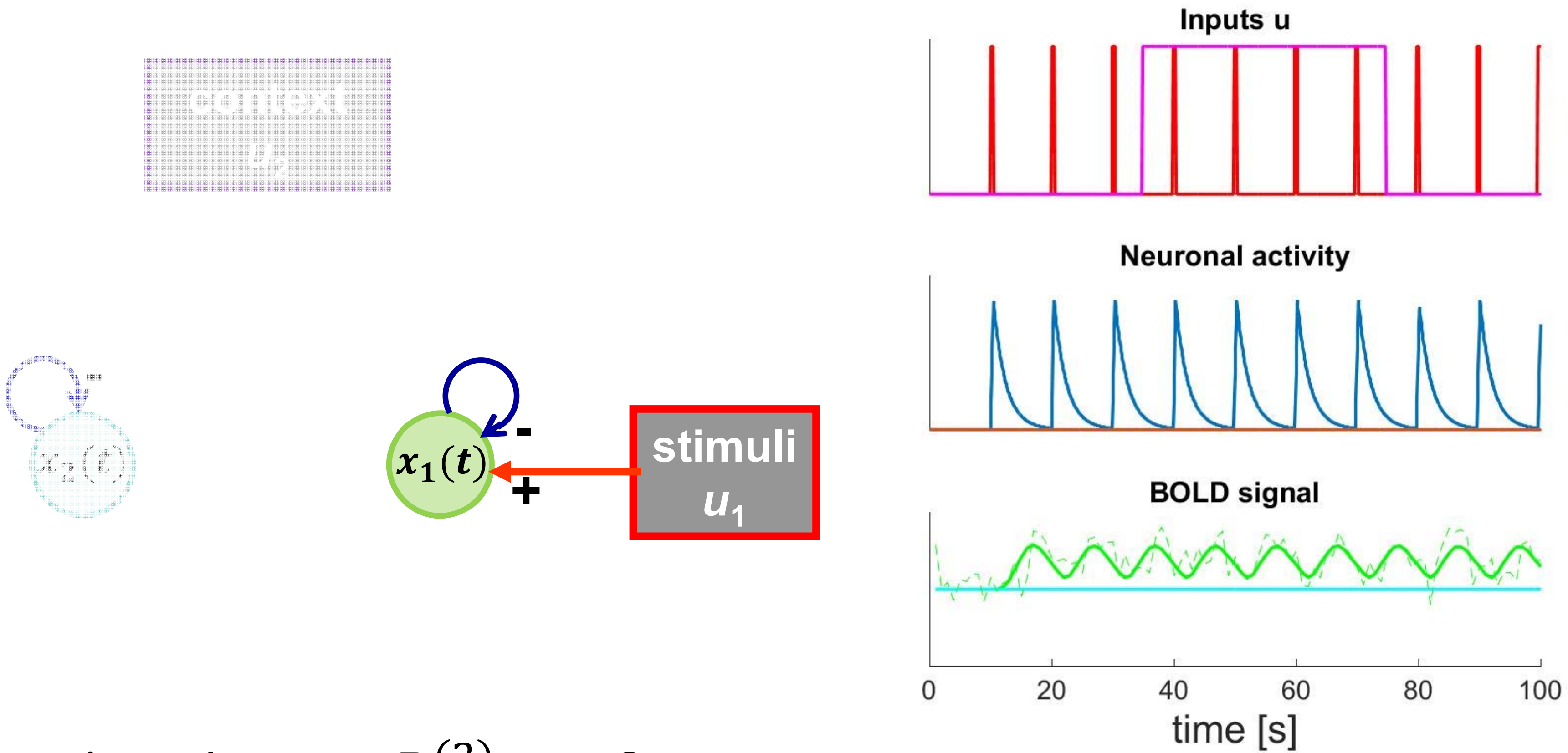




Summary – parameters of interest



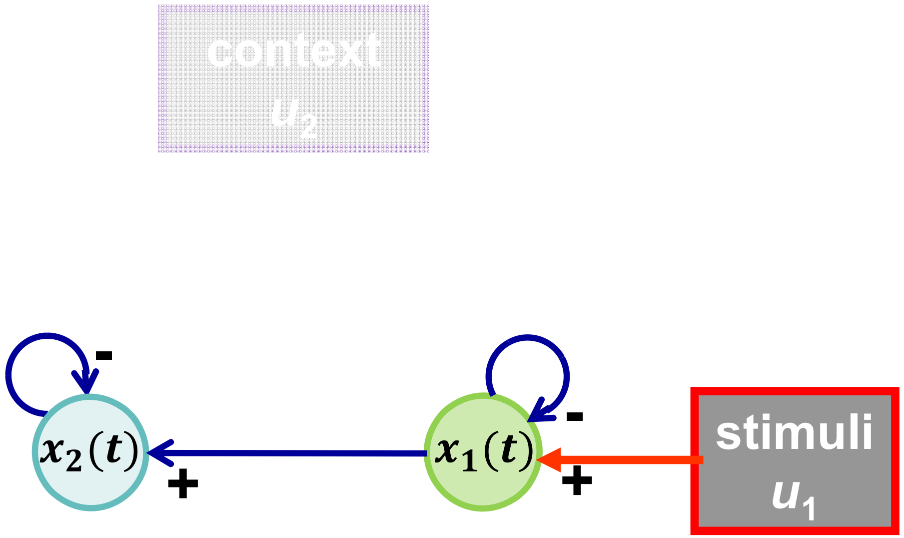
Example traces 1: Single node

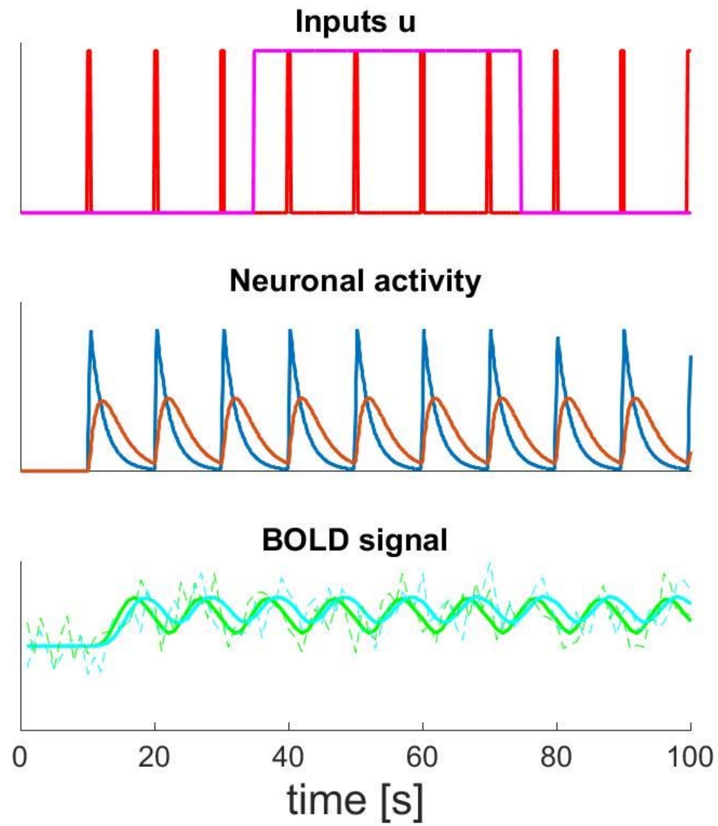


$$\dot{x} = Ax + u_2 B^{(2)} x + C u_1$$

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \end{bmatrix} = \begin{bmatrix} \sigma & 0 \\ 0 & \sigma \end{bmatrix} \cdot \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} + u_2 \begin{bmatrix} 0 & 0 \\ 0 & 0 \end{bmatrix} \cdot \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} + \begin{bmatrix} c_{11} & 0 \\ 0 & 0 \end{bmatrix} \cdot \begin{bmatrix} u_1 \\ u_2 \end{bmatrix}$$

Example traces 2: Connected nodes

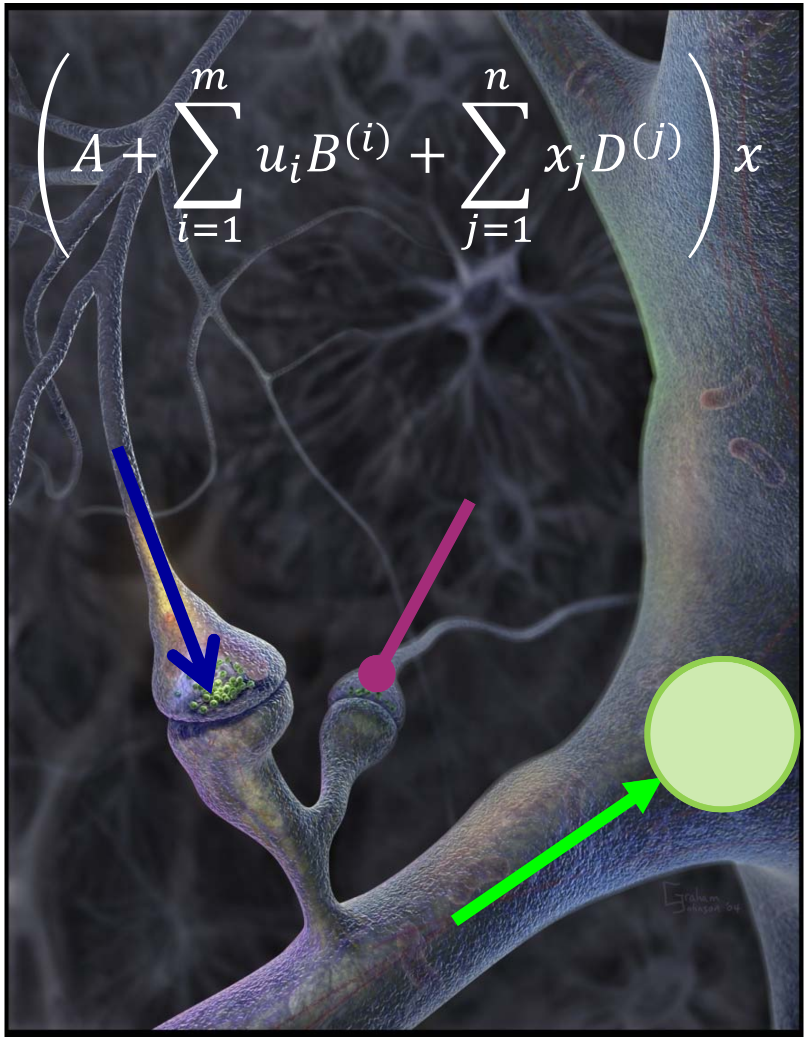


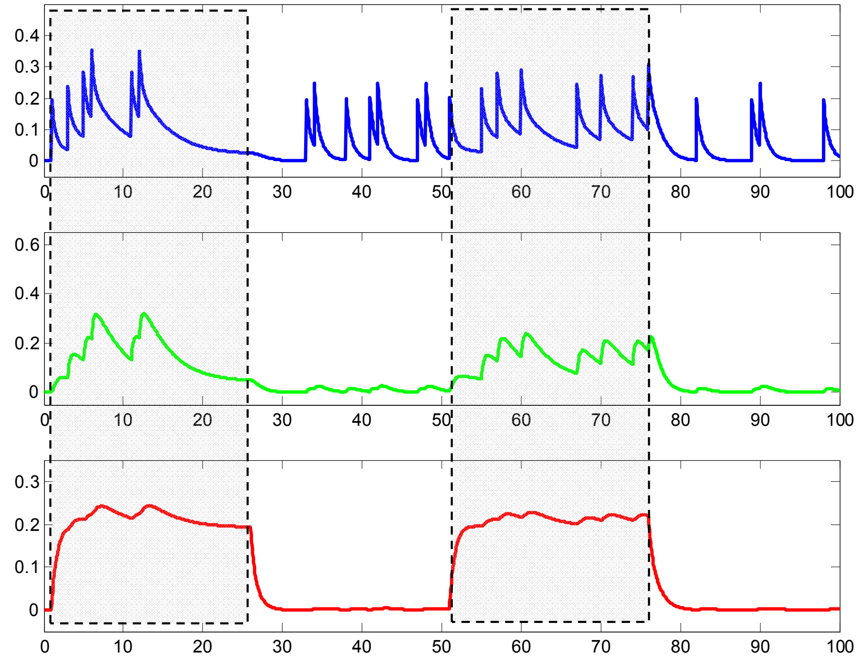


$$\dot{x} = Ax + u_2 B^{(2)} x + C u_1$$

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \end{bmatrix} = \begin{bmatrix} \sigma & 0 \\ a_{12} & \sigma \end{bmatrix} \cdot \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} + u_2 \begin{bmatrix} 0 & 0 \\ 0 & 0 \end{bmatrix} \cdot \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} + \begin{bmatrix} c_{11} & 0 \\ 0 & 0 \end{bmatrix} \cdot \begin{bmatrix} u_1 \\ u_2 \end{bmatrix}$$

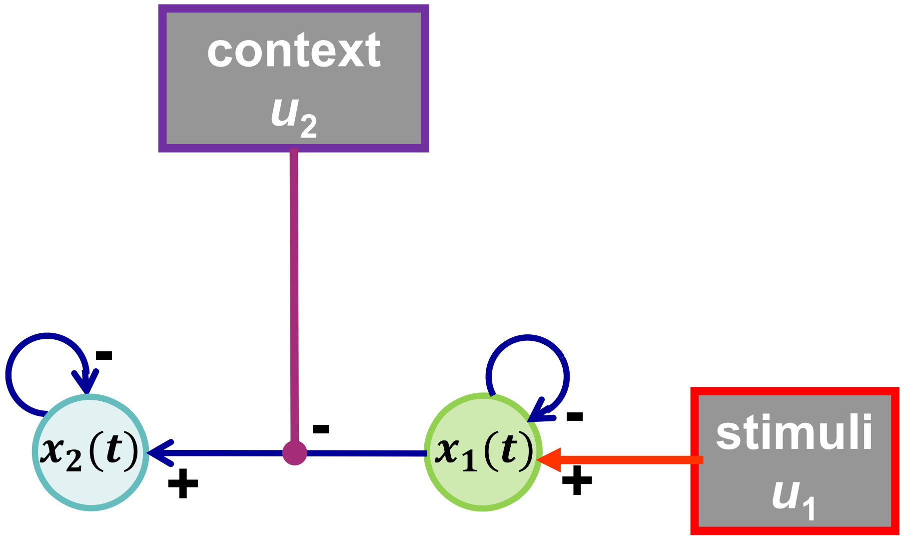
Context specific «neuro»-modulation

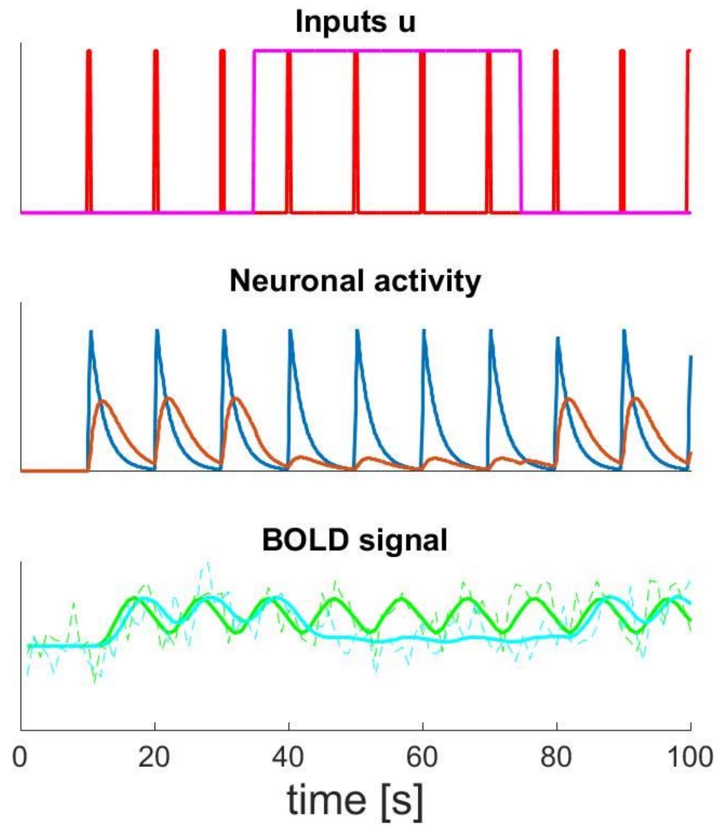




Synaptic strengths are context-sensitive:
They depend on spatio-temporal patterns of network activity.

Example traces 3: Modulation of connection

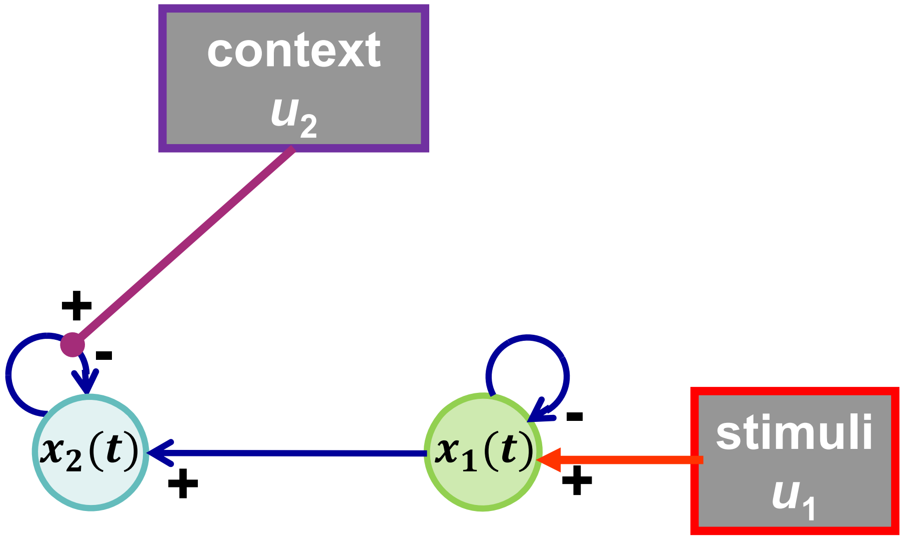


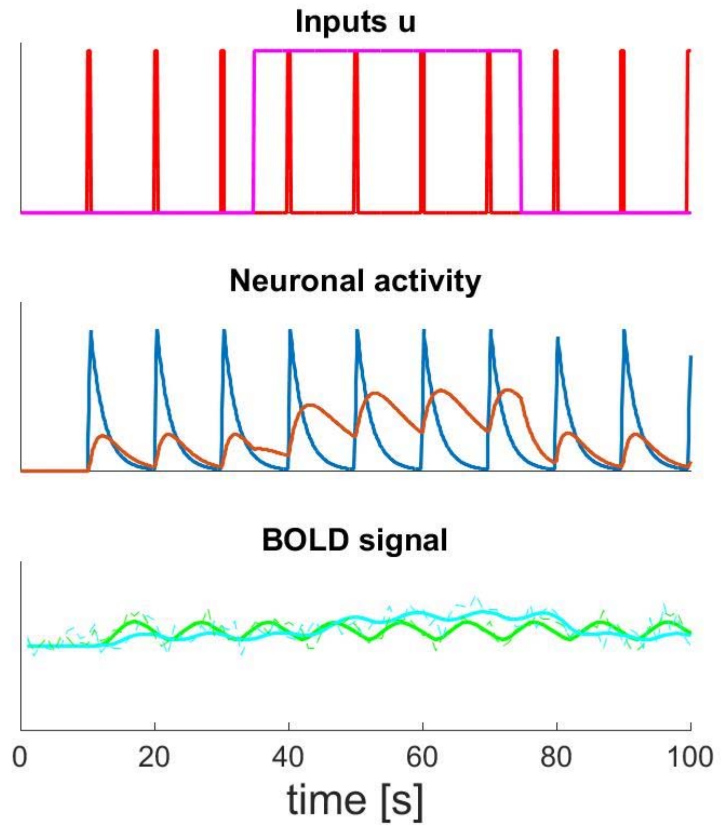


$$\dot{x} = Ax + u_2 B^{(2)} x + C u_1$$

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \end{bmatrix} = \begin{bmatrix} \sigma & 0 \\ a_{12} & \sigma \end{bmatrix} \cdot \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} + u_2 \begin{bmatrix} 0 & 0 \\ b_{12}^{(2)} & 0 \end{bmatrix} \cdot \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} + \begin{bmatrix} c_{11} & 0 \\ 0 & 0 \end{bmatrix} \cdot \begin{bmatrix} u_1 \\ u_2 \end{bmatrix}$$

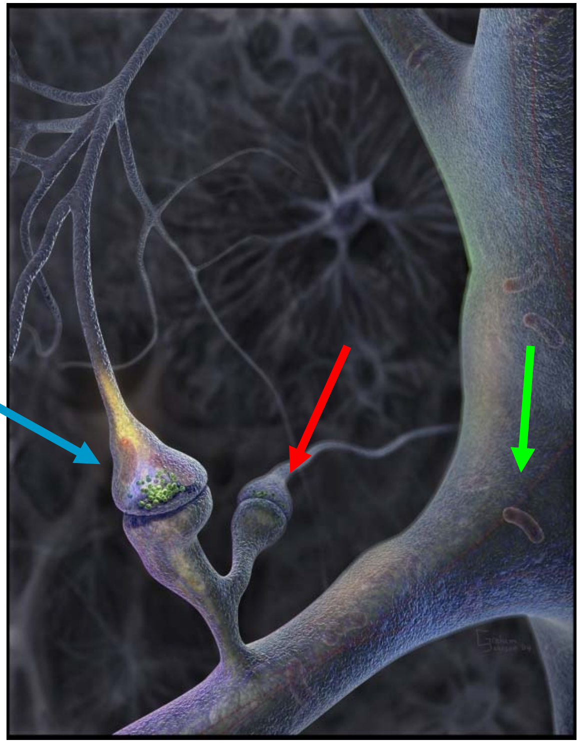
Example traces 4: Modulation of self-connection

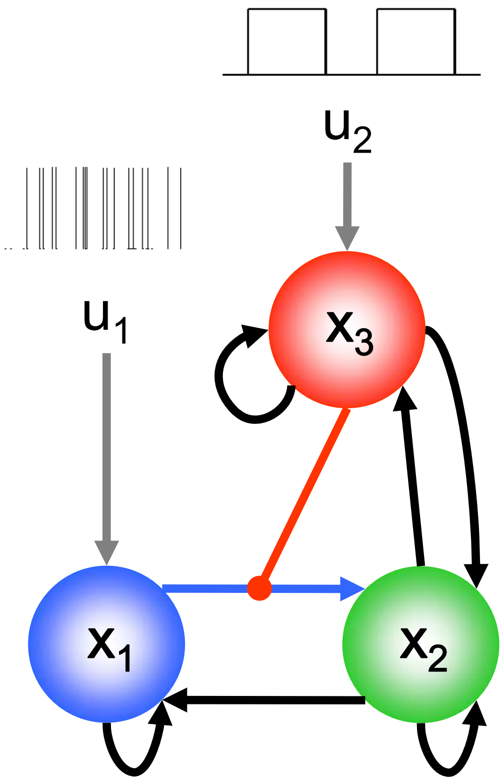


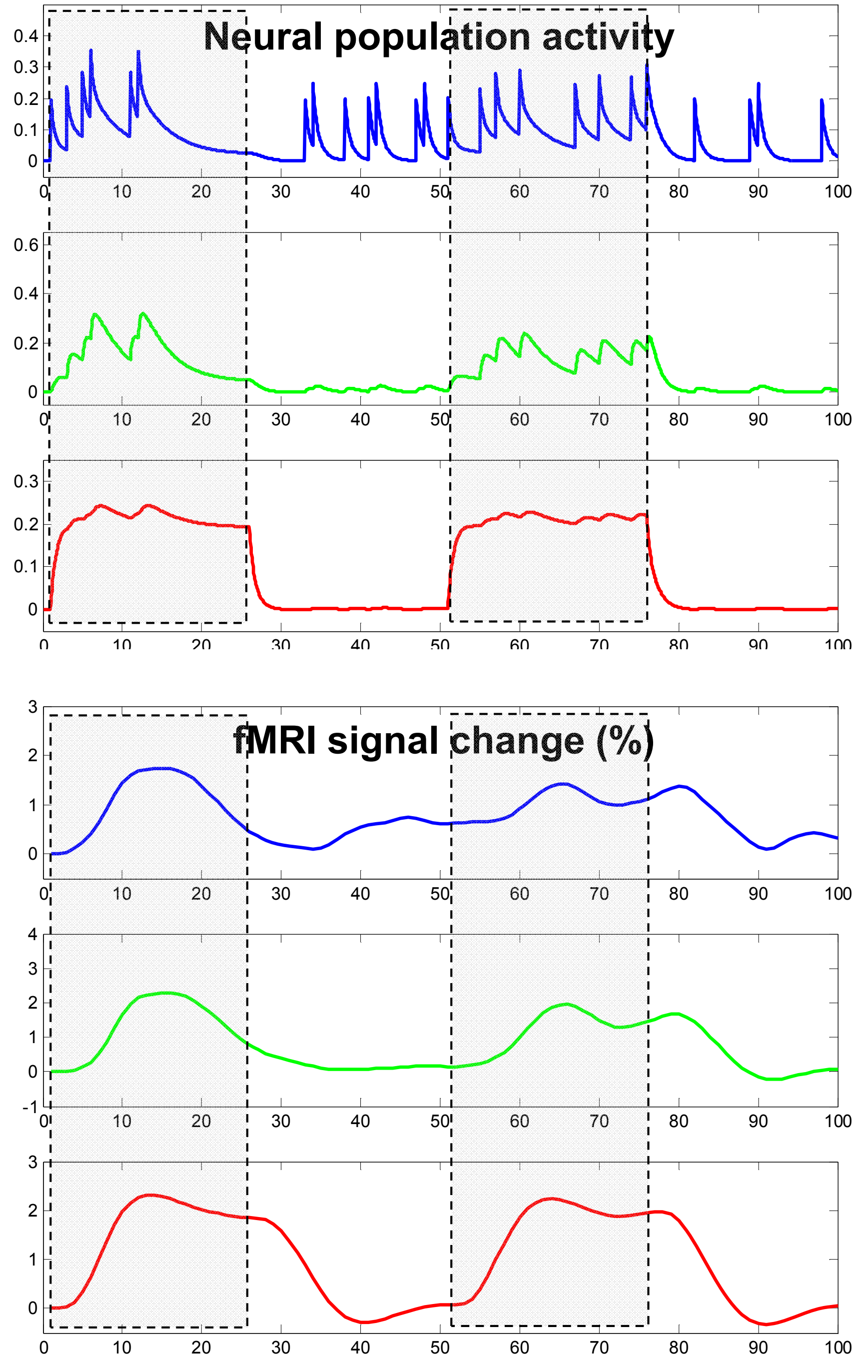


$$\dot{x} = Ax + u_2 B^{(2)} x + C u_1$$

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \end{bmatrix} = \begin{bmatrix} \sigma & 0 \\ a_{12} & \sigma \end{bmatrix} \cdot \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} + u_2 \begin{bmatrix} 0 & 0 \\ 0 & b_{22}^{(2)} \end{bmatrix} \cdot \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} + \begin{bmatrix} c_{11} & 0 \\ 0 & 0 \end{bmatrix} \cdot \begin{bmatrix} u_1 \\ u_2 \end{bmatrix}$$







Nonlinear Dynamic Causal Model for fMRI

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

Stephan et al. 2008, *NeuroImage*

How to introduce dynamical systems in Bayes' world

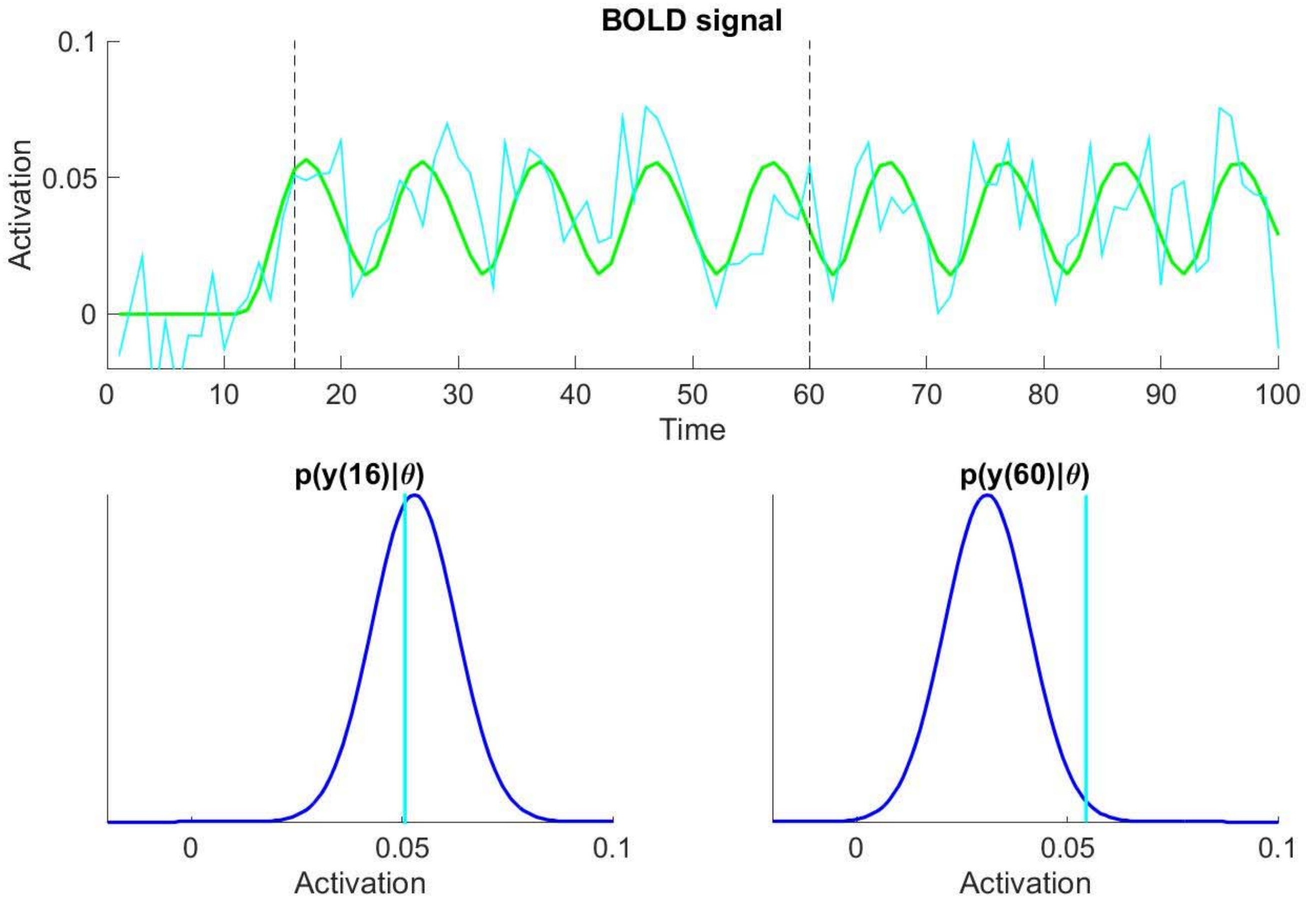
$$p(\theta|y,m) = \frac{\boxed{p(y|\theta,m)}\,p(\theta|m)}{p(y|m)}$$ **Bayes' formula**

Assume data is normally distributed around the prediction from the dynamical model.

$$\Rightarrow \quad p(y(t)|\theta,m) = \mathcal{N}(y(t),\theta_\sigma)$$

Dynamical model defines the likelihood!

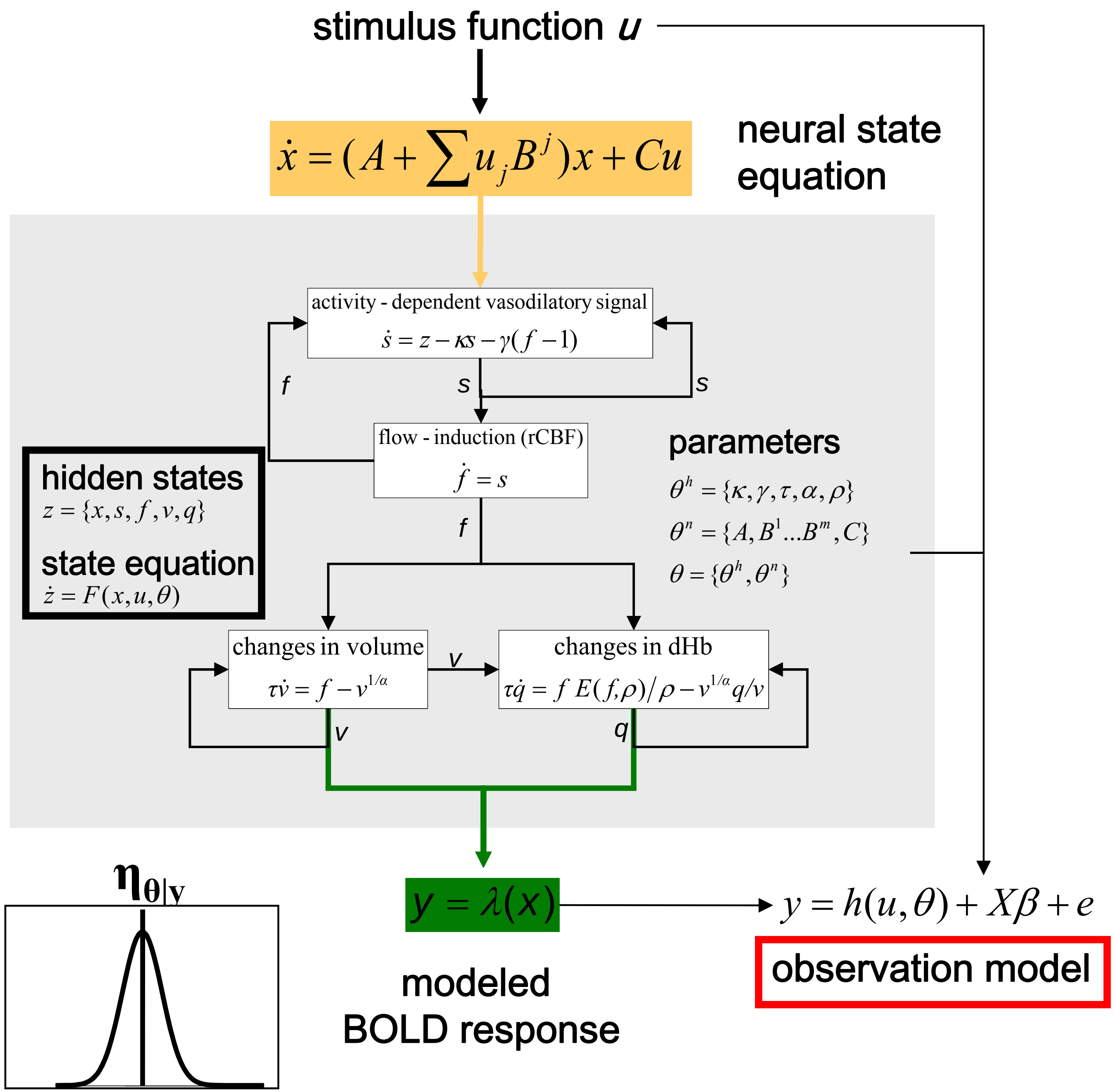
Illustration of likelihood



$$p(y|\theta, m) = \prod_t p(y(t)|\theta, m)$$

One slide summary

- Combining the neural and hemodynamic states gives the complete forward model.
- Observation model includes measurement error *e* and confounds *X* (e.g. drift).
- Bayesian inversion: parameter estimation variational Bayes or MCMC
- Result 1: A posteriori parameter distributions $p(\theta|y,m)$, characterised by mean $\eta_{\theta|y}$ and covariance $C_{\theta|y}$.
- Result 2: Estimate of model evidence $p(y|m)$.



Bayesian system identification

$u(t)$

Neural dynamics

$$dx/dt = f(x,u,\theta)$$

Observer function

$$y = g(x,\theta) + \varepsilon$$

$$p(y \mid \theta, m) = N(g(\theta), \Sigma(\theta))$$

$$p(\theta, m) = N(\mu_\theta, \Sigma_\theta)$$

Inference on model structure

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

Inference on parameters

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

Design experimental inputs

Define likelihood model

Specify priors

Invert model

Make inferences

cf. Lecture 11 on Bayesian Inference

Generative models & model selection

- any DCM = a particular generative model of how the data (may) have been caused

- generative modelling: comparing competing hypotheses about the mechanisms underlying observed data

  $\rightarrow$ a priori definition of hypothesis set (model space) is crucial

  $\rightarrow$ determine the most plausible hypothesis (model), given the data

- model selection $\neq$ model validation!

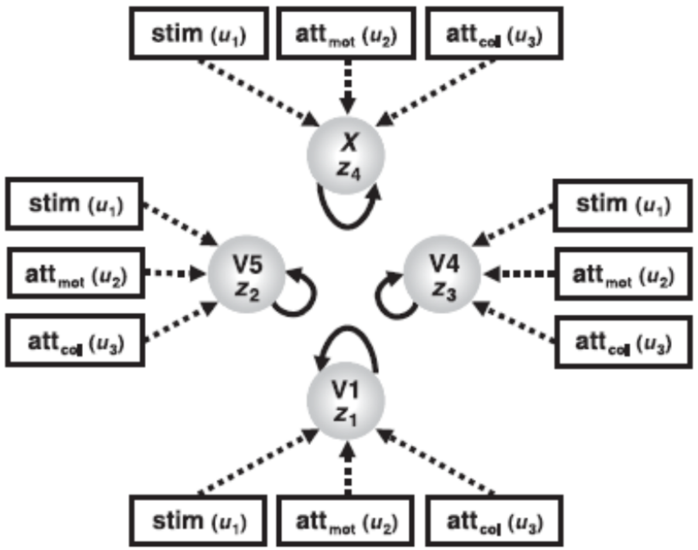
  $\rightarrow$ model validation requires external criteria (external to the measured data)

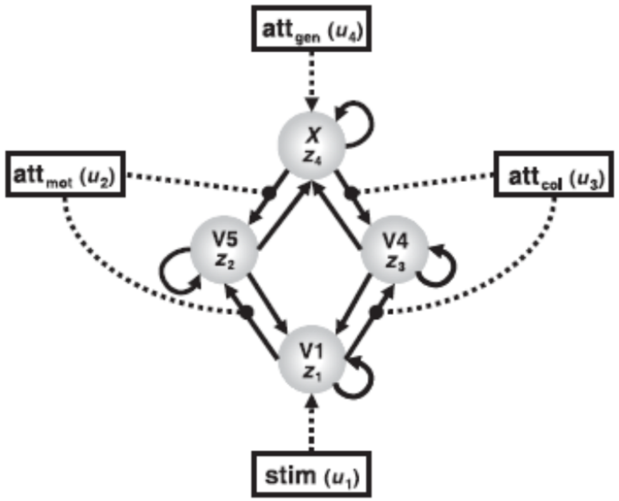
GLM vs. DCM

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.

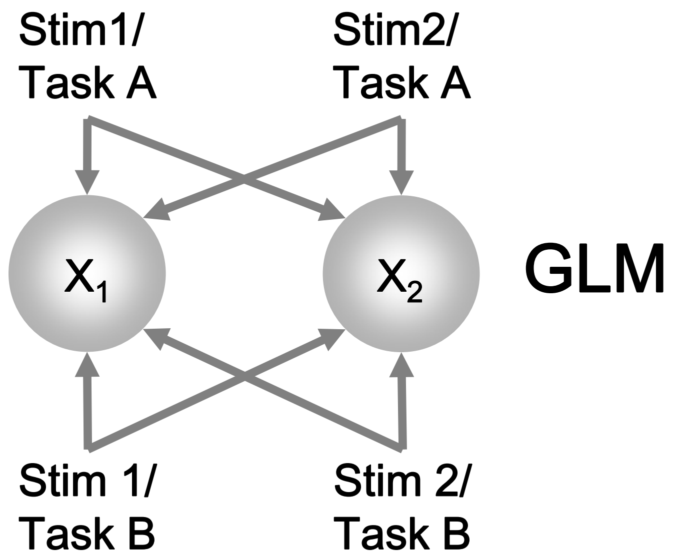




Stephan 2004, *J. Anat.*

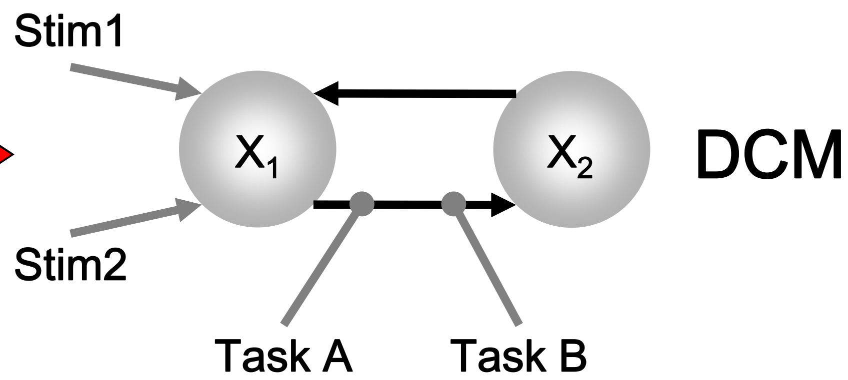
Multifactorial design: explaining interactions with DCM

		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

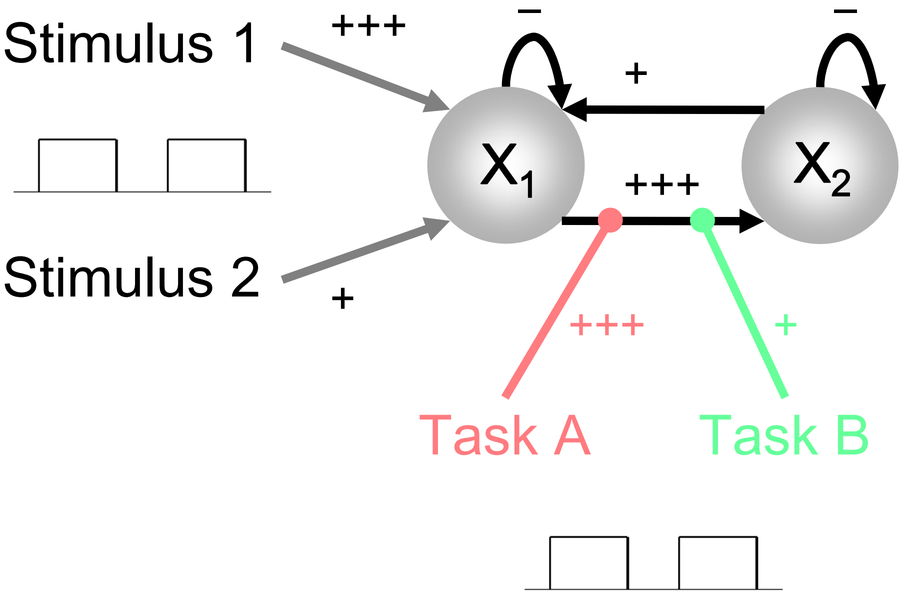


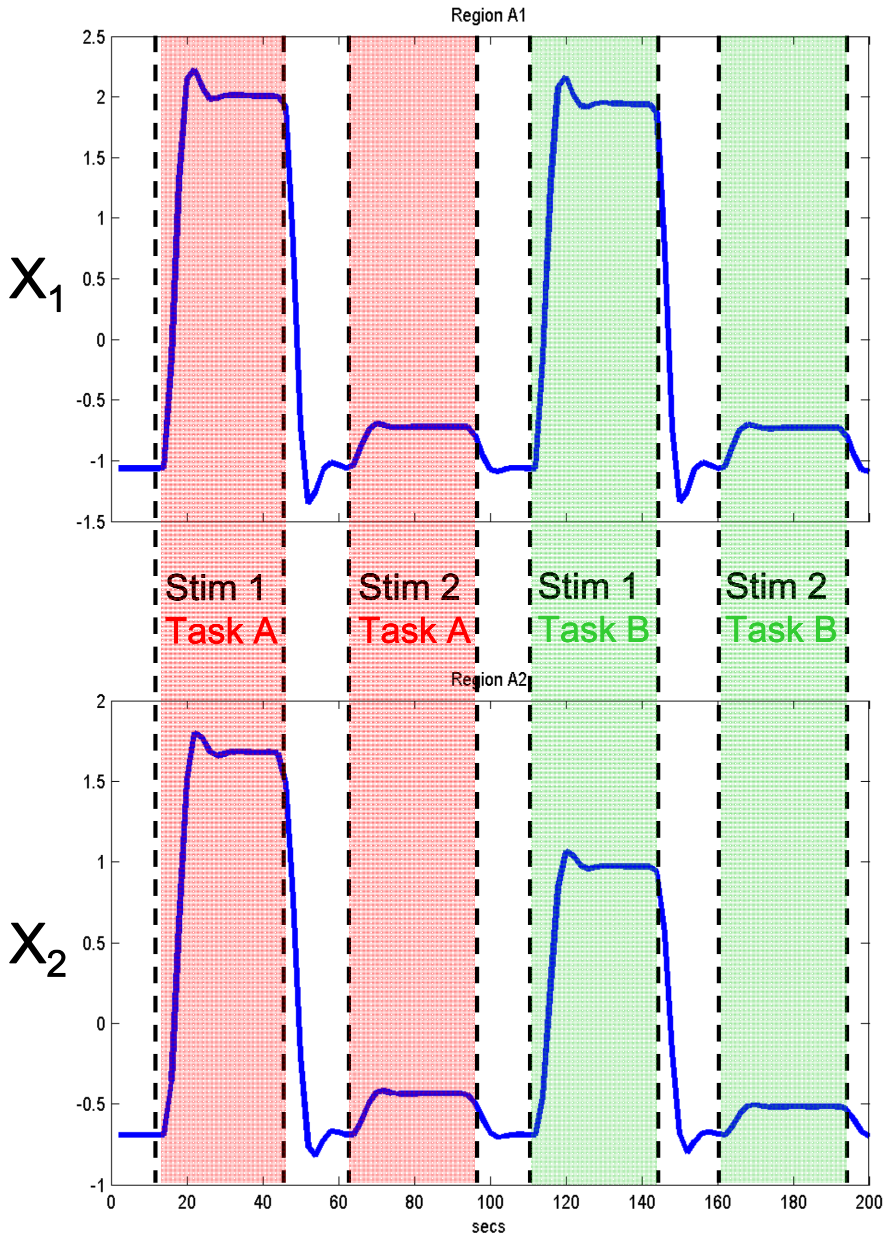
Let's assume that an SPM analysis shows a main effect of stimulus in X_1 and a stimulus $\times$ task interaction in X_2.

How do we model this using DCM?

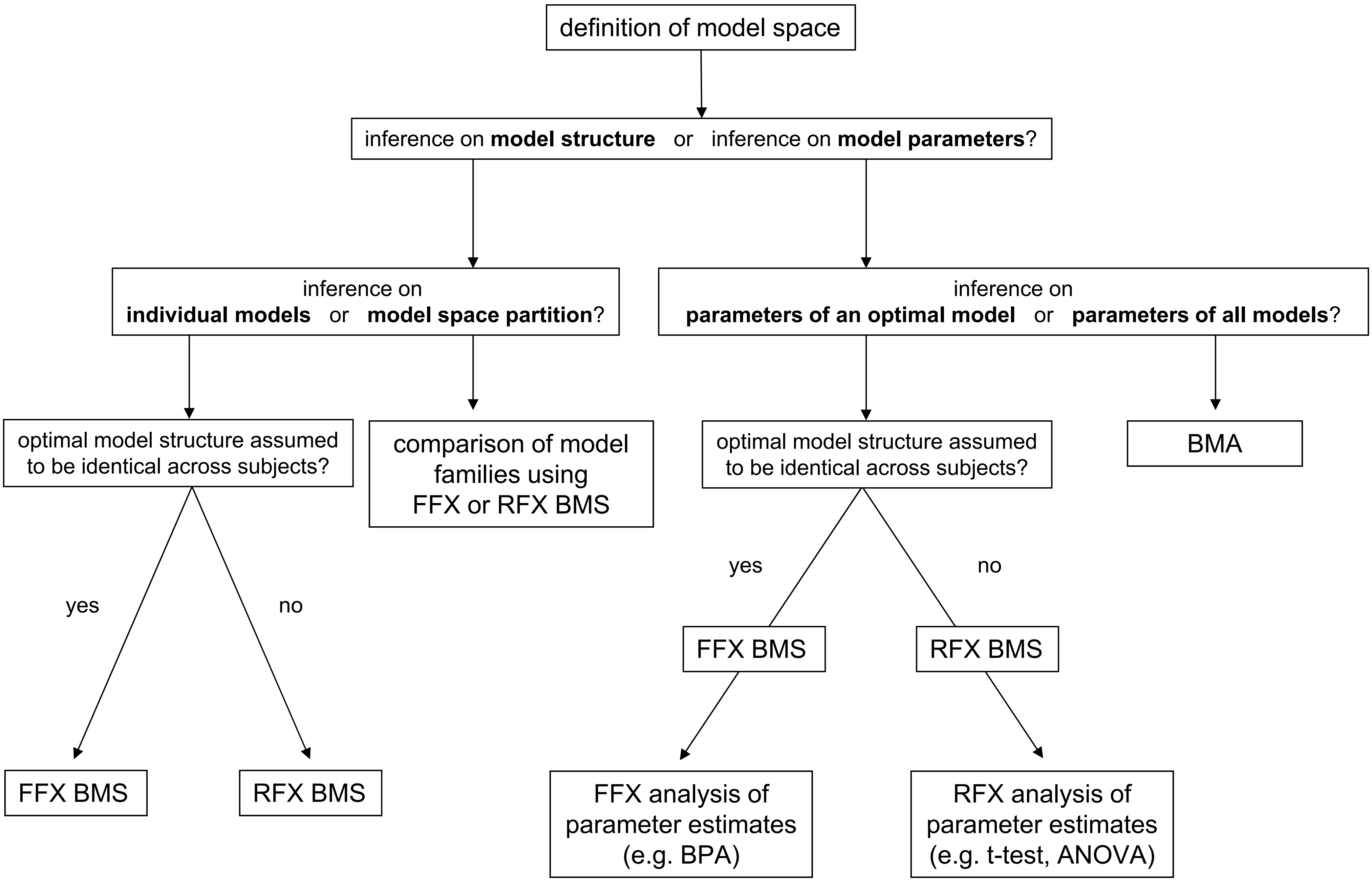


Simulated data





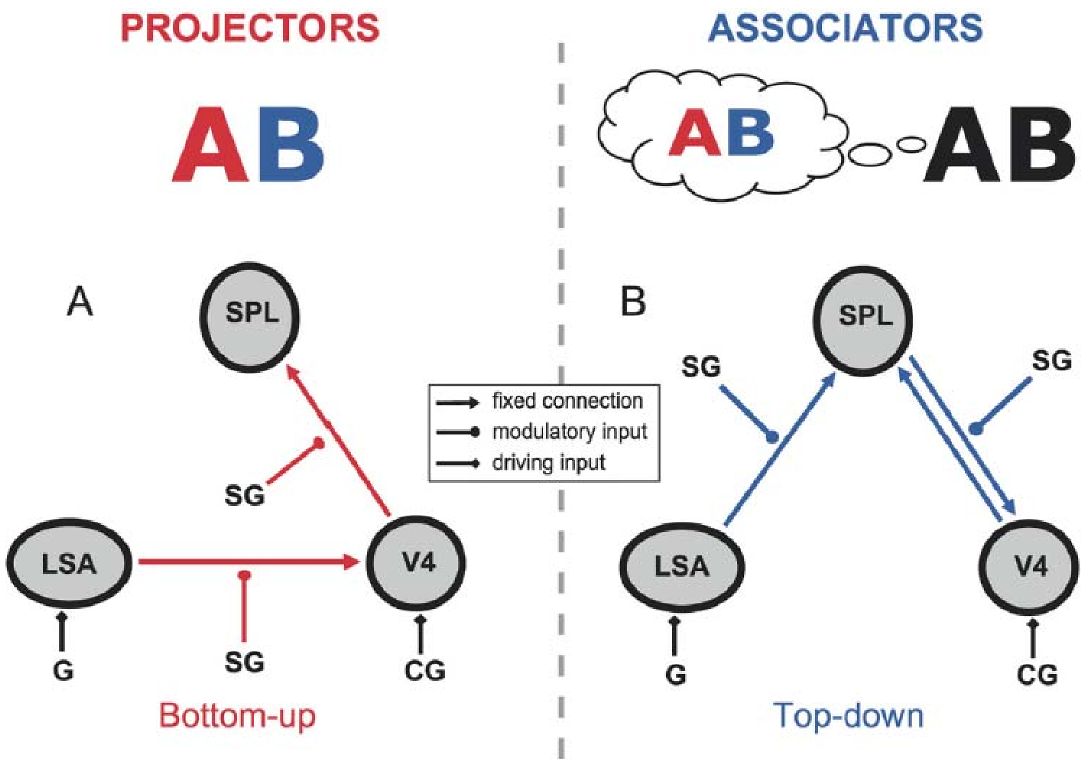
Stephan et al. 2007, *J. Biosci.*



Stephan et al. 2010, *NeuroImage*

Model comparison: Synesthesia

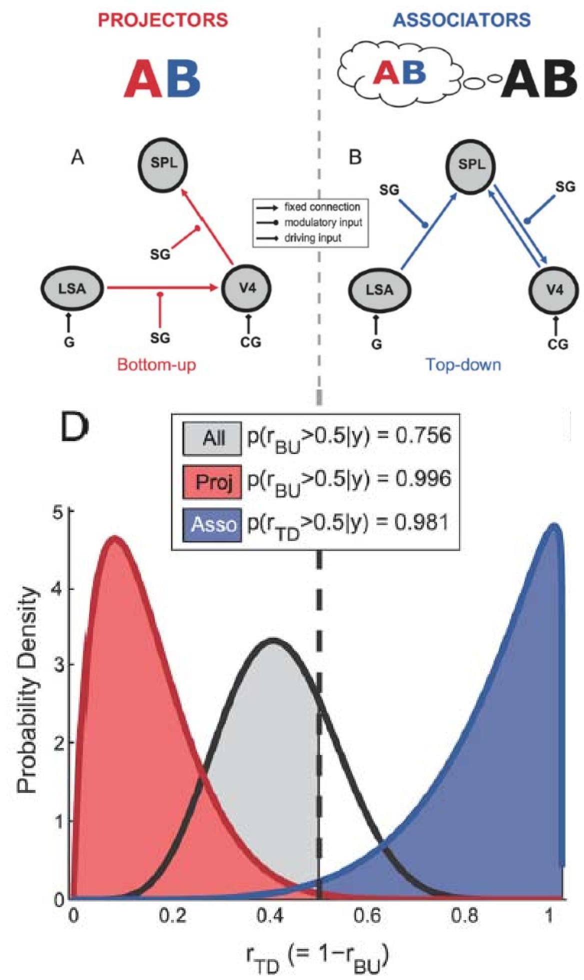
- "projector" synesthetes experience color externally co-localized with a presented grapheme
- "associators" report an internally evoked association



van Leeuwen et al., J Neurosci 2011

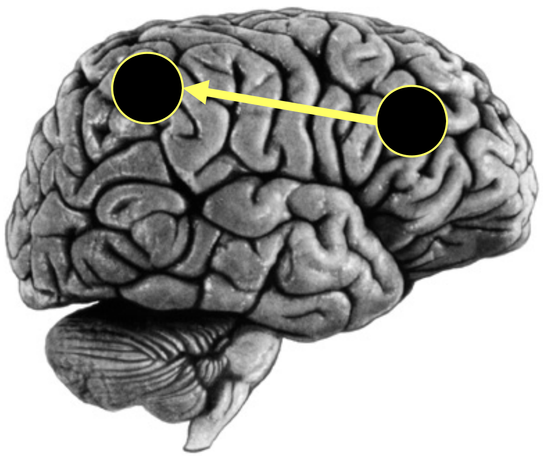
Model comparison: Synesthesia

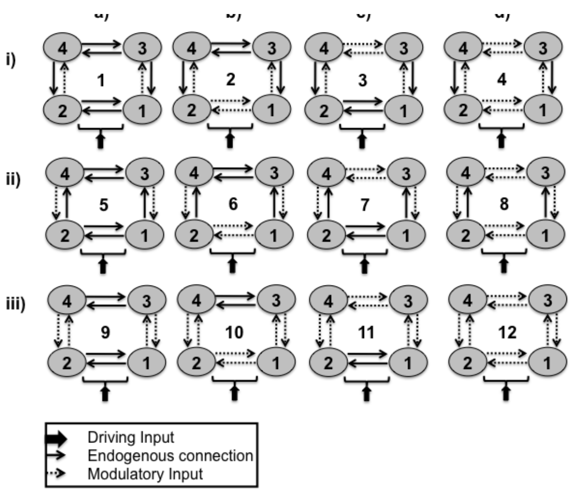
- “projector” synesthetes experience color externally co-localized with a presented grapheme
- “associators” report an internally evoked association
- across all subjects: no evidence for either model
- but splitting into synesthesia types gives very strong evidence for bottom-up (projectors) and top-down (associators) mechanisms, respectively

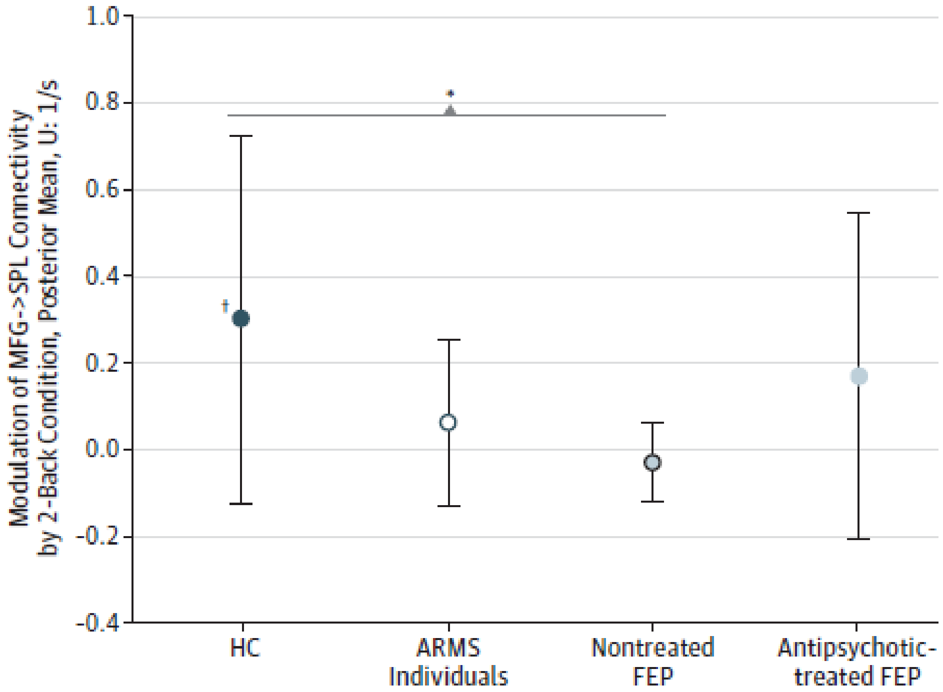


van Leeuwen et al., J Neurosci 2011

Prefrontal-parietal connectivity during working memory in schizophrenia







17 ARMS, 21 first-episode (13 non-treated), 20 controls

Schmidt et al. 2013, *JAMA Psychiatry*

“All models are wrong, but some are useful.”

George E.P. Box (1919-2013)

Hierarchical strategy for model validation

1	in silico	numerical analysis & simulation studies
2	humans	cognitive experiments
3	animals & humans	experimentally controlled system perturbations
4	patients	clinical utility

For DCM: >15 published validation studies (incl. 6 animal studies):

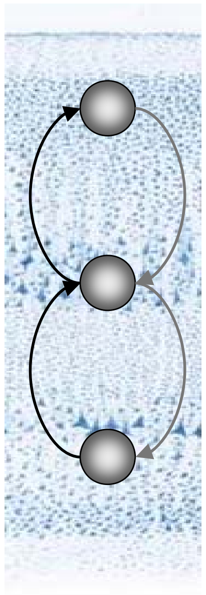
- infers site of seizure origin (David et al. 2008)
- infers primary recipient of vagal nerve stimulation (Reyt et al. 2010)
- infers synaptic changes as predicted by microdialysis (Moran et al. 2008)
- infers fear conditioning induced plasticity in amygdala (Moran et al. 2009)
- tracks anaesthesia levels (Moran et al. 2011)
- predicts sensory stimulation (Brodersen et al. 2010)

Many thanks to
Andreea Diaconescu and Klaas Enno Stephan
for some of the slides!

Thank you!

Validating models: clinical utility

model of neuronal (patho)physiology

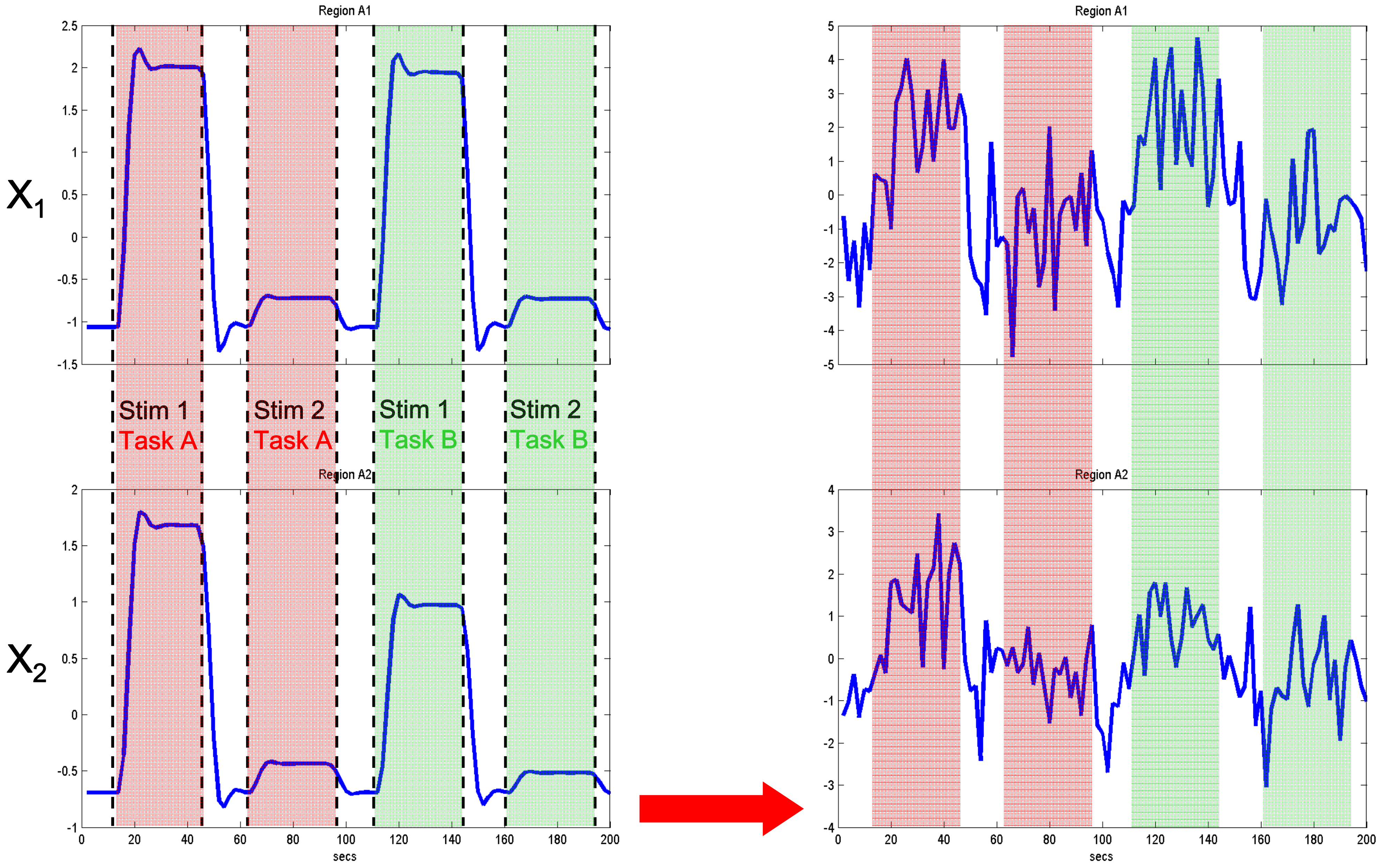


predicting

individual symptoms

individual outcome

individual therapeutic response



plus added noise (SNR=1)

Methods papers: DCM for fMRI and BMS – part 1

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- Stephan KE, Tittgemeyer M, Knösche TR, Moran RJ, Friston KJ (2009b) Tractography-based priors for dynamic causal models. NeuroImage 47: 1628-1638.
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