

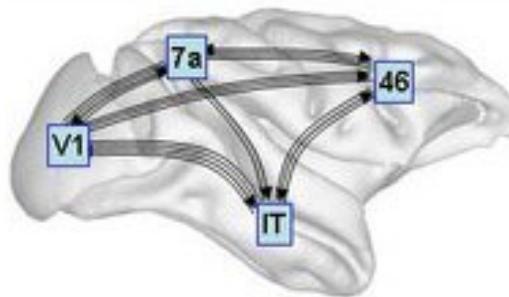
Modeling connectivity: Dynamic Causal Modeling for fMRI

Jakob Heinze

Translational Neuromodeling Unit (TNU),
Institute for Biomedical Engineering
University and ETH Zürich

CP Course 2021, Zürich, Switzerland

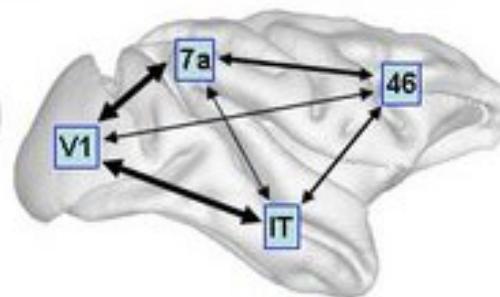
Structural, functional & effective connectivity



anatomical/structural

- presence of physical connections

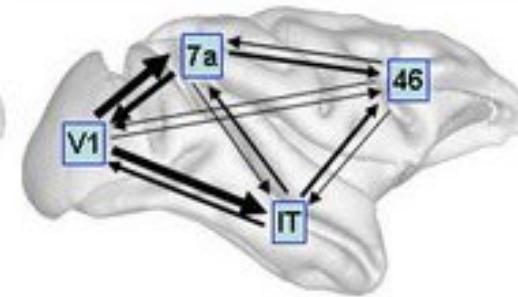
→ *DWI, tractography, tracer studies (animals)*



functional

- statistical dependency between regional time series

→ *correlations, ICA*



Sporns 2007, Scholarpedia

effective

- direct influences between neuronal populations

→ *DCM*

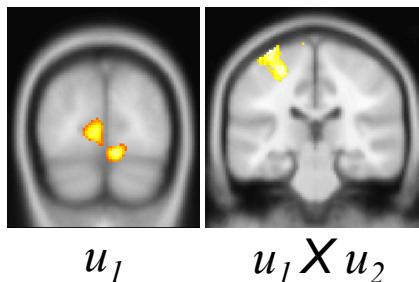
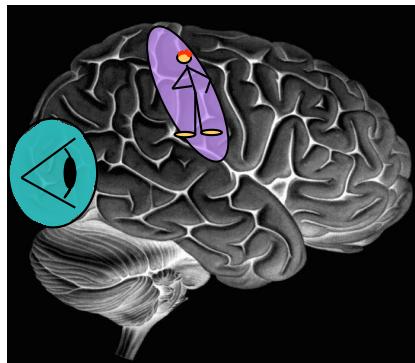
Context-independent

Mechanism - free

Mechanistic

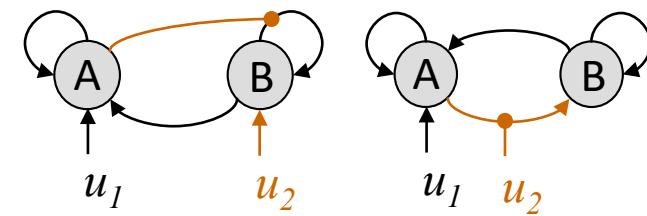
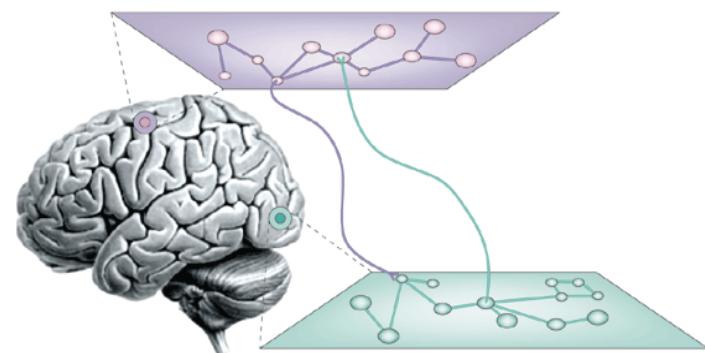
Specialisation vs. Integration

Functional Specialisation



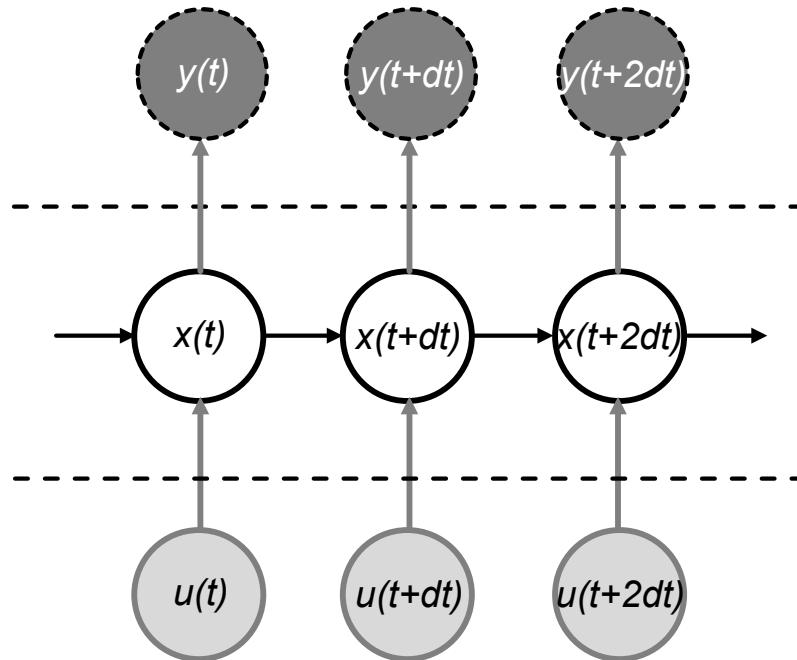
«**Where**, in the brain, did my experimental manipulation have an effect?»

Functional Integration



«**How** did my experimental manipulation propagate through the network?»

A reminder – generative models



Observed data (fMRI)

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

Hidden states (Brain activity)

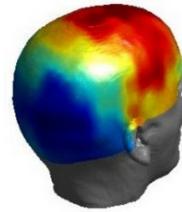
$$\frac{dx}{dt} = f(x, u, \theta) + \omega$$

Inputs (Exp. manipulations)

$$u(t)$$

Dynamic causal modelling

EEG,
MEG



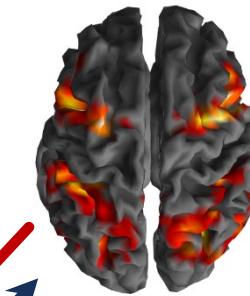
Model inversion:
Estimating
neuronal
mechanisms

Forward model:
Predicting
measured activity

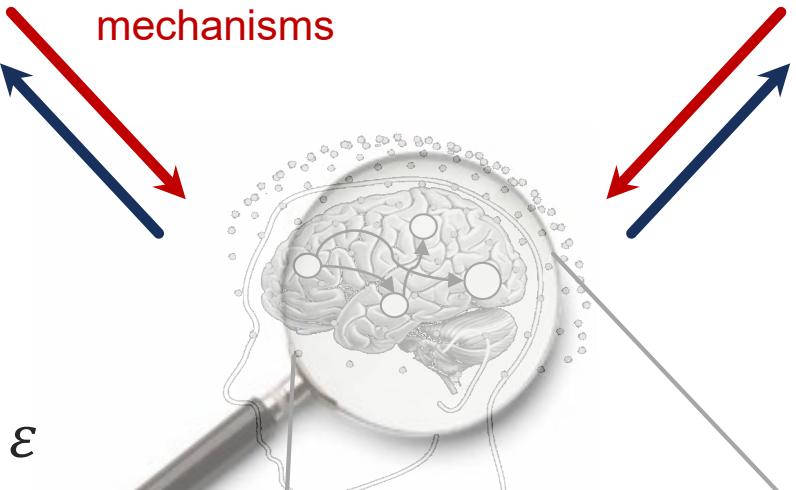
$$y = g(x, \theta) + \varepsilon$$

DCM for EEG
→ later today
→ Rosalyn Moran

fMRI



State equation:
Describing neuronal
dynamics (and
hemodynamics)



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



University of
Zurich^{UZH}



Translational Neuromodeling Unit

ETH zürich

Dynamic causal modelling



ACADEMIC
PRESS

Available online at www.sciencedirect.com



NeuroImage 19 (2003) 1273–1302

NeuroImage

www.elsevier.com/locate/ynimng

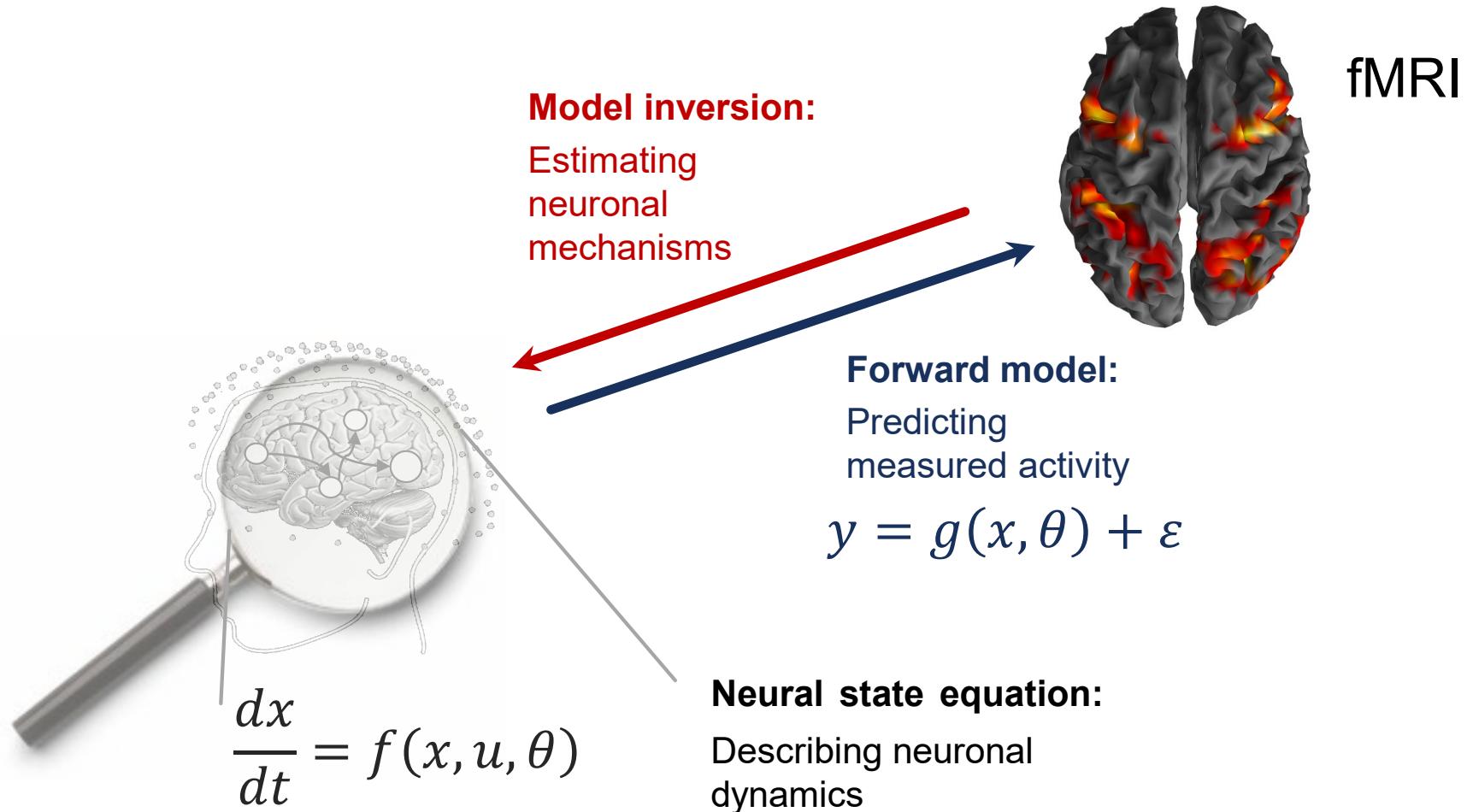
Dynamic causal modelling

K.J. Friston,* L. Harrison, and W. Penny

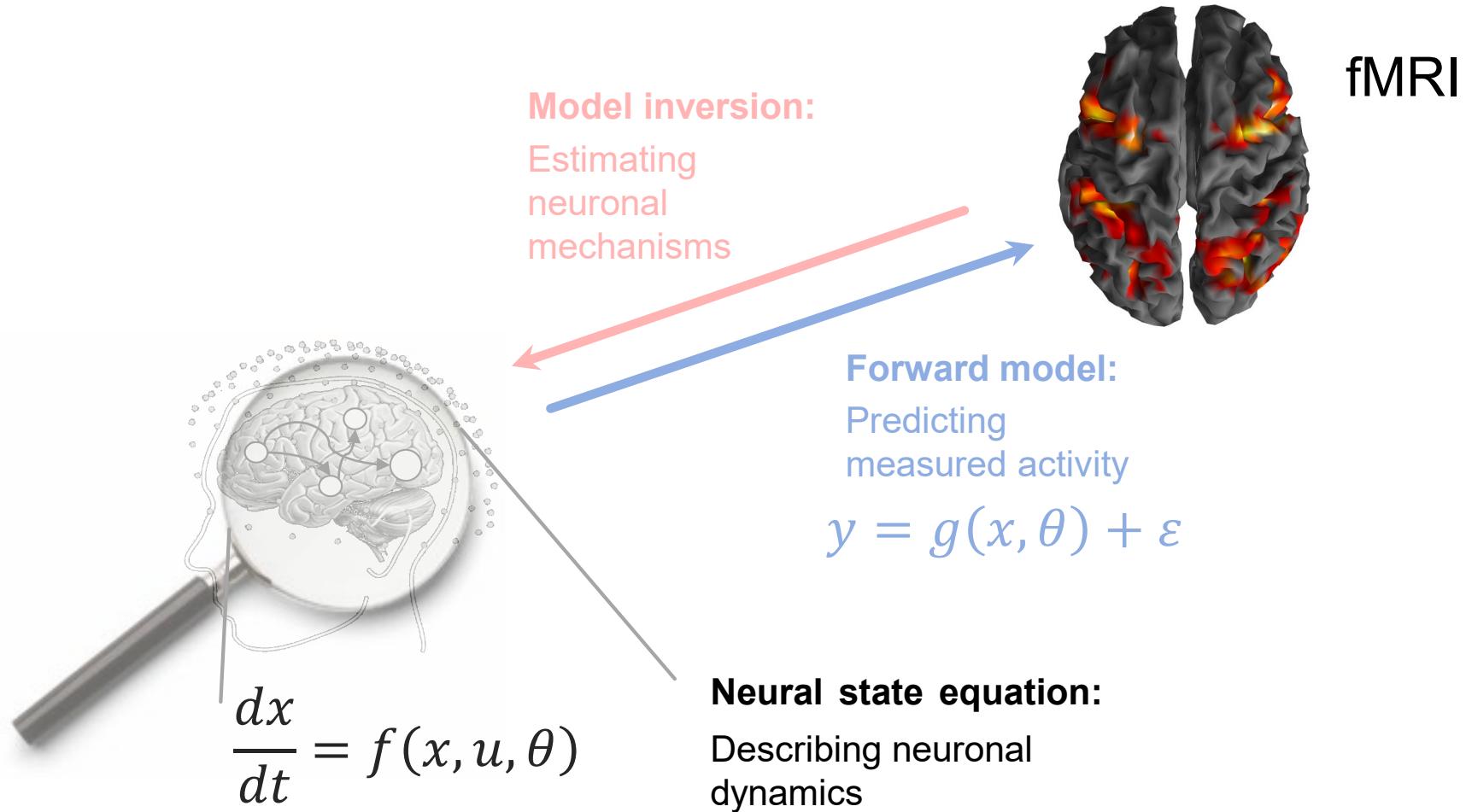
The Wellcome Department of Imaging Neuroscience, Institute of Neurology, Queen Square, London WC1N 3BG, UK

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

DCM for fMRI - overview



DCM for fMRI - overview





Neuronal state equations

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



Neuronal state equations

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

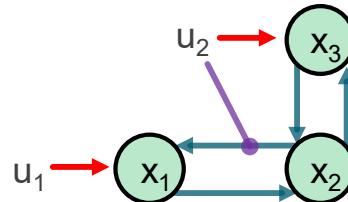
bilinear model

Neuronal state equations

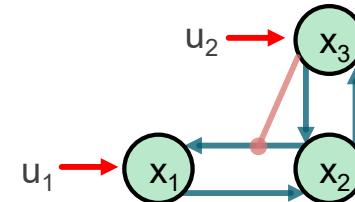
$$\frac{dx}{dt} = f(x, u) \approx f(x_0, 0) + \frac{\partial f}{\partial x} x + \frac{\partial f}{\partial u} u + \frac{\partial^2 f}{\partial x \partial u} u x + \frac{\partial^2 f}{\partial x^2} \frac{x^2}{2} + \dots$$

A C B D

bilinear model

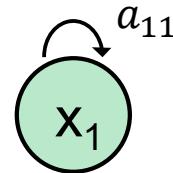


nonlinear model



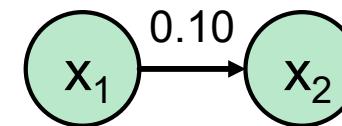
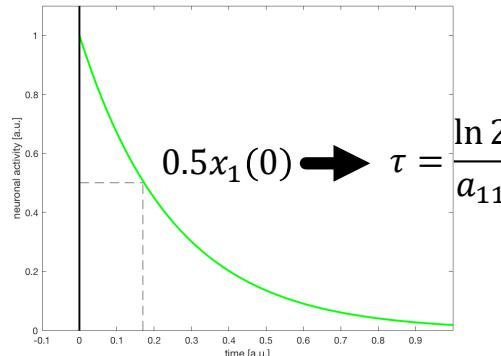
Neuronal state equations

DCM effective connectivity parameters are rate constants



$$\frac{dx_1}{dt} = a_{11}x_1 \longrightarrow$$

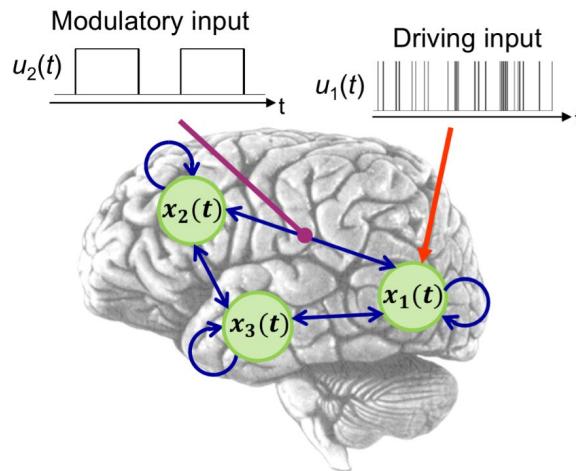
$$x_1(t) = x_1(0) \cdot \exp(a_{11}t)$$



If $x_1 \rightarrow x_2$ is 0.10s^{-1} , this means that, per unit time, the increase in activity in x_2 corresponds to 10% of the current activity in x_1

Neuronal state equations

Interim summary: bilinear neuronal state equation



$$\frac{dx}{dt} = \underbrace{\left(A + \sum_{j=1}^m u_j B^{(j)} \right)}_{\text{connectivity}} x + \underbrace{Cu}_{\text{External inputs}}$$

State change

External inputs

Current state

connectivity

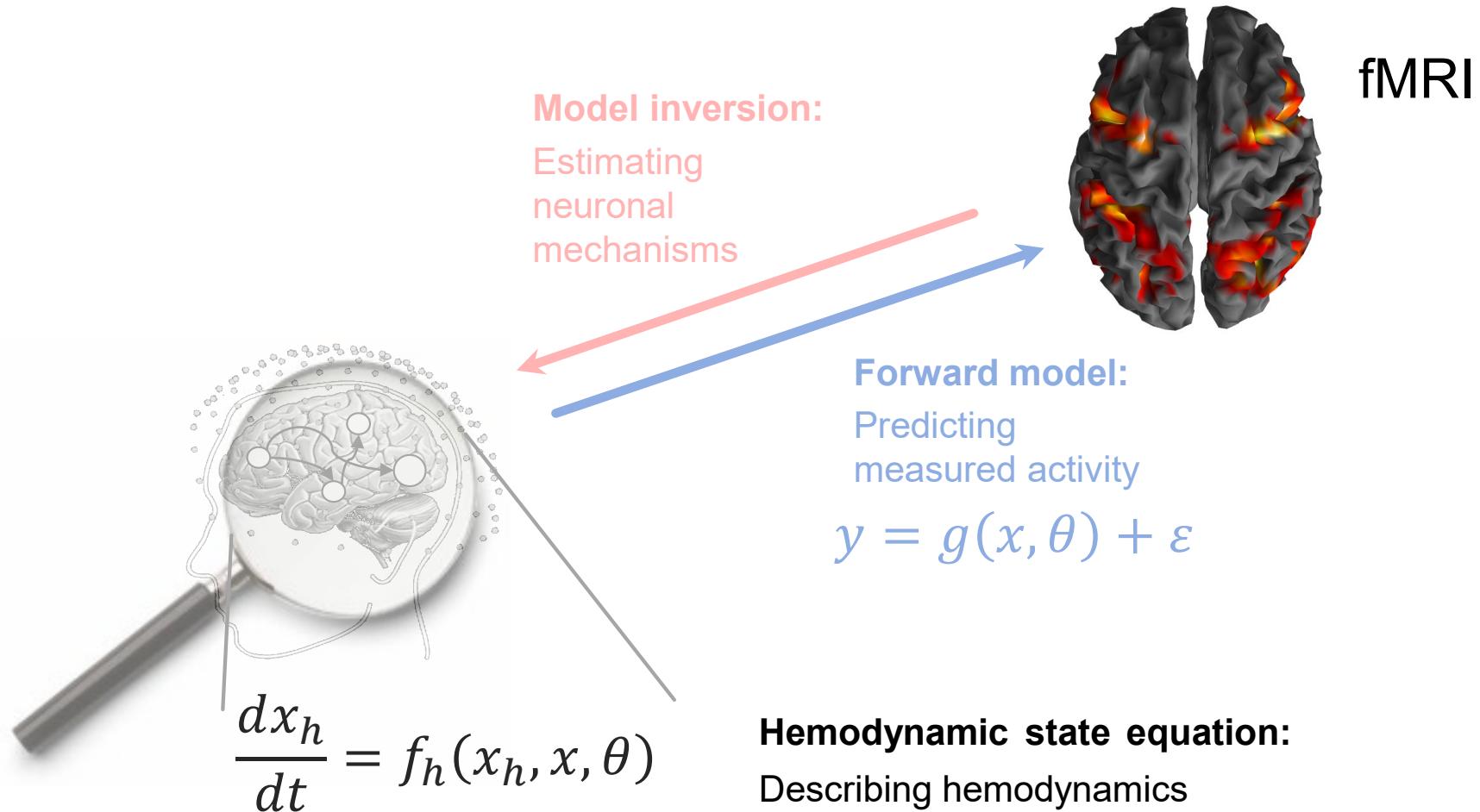
$$\theta = \{A, B^{(1)}, \dots, B^{(m)}, C\}$$

Endogenous connectivity

Modulatory connectivity

Driving inputs

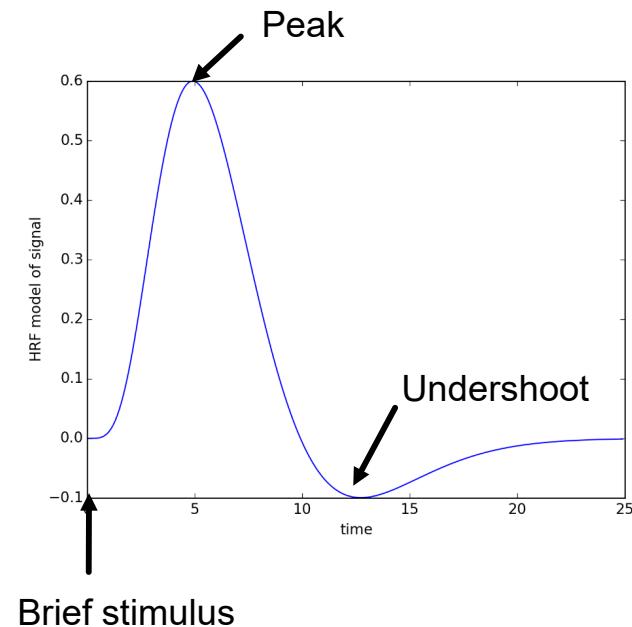
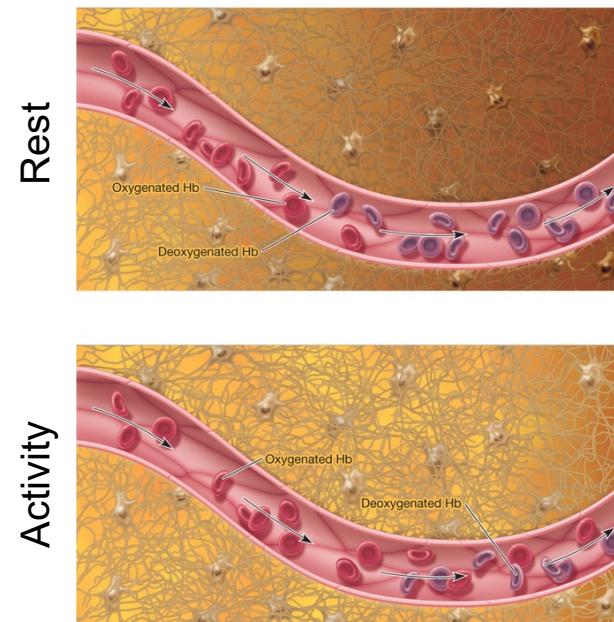
DCM for fMRI - overview



The hemodynamic response

Neuronal dynamics only indirectly observable via hemodynamic response

- ↑ neuronal activity
- ↑ blood flow
- ↑ oxygenated Hb
- ↑ T2*
- ↑ fMRI signal



The hemodynamic model

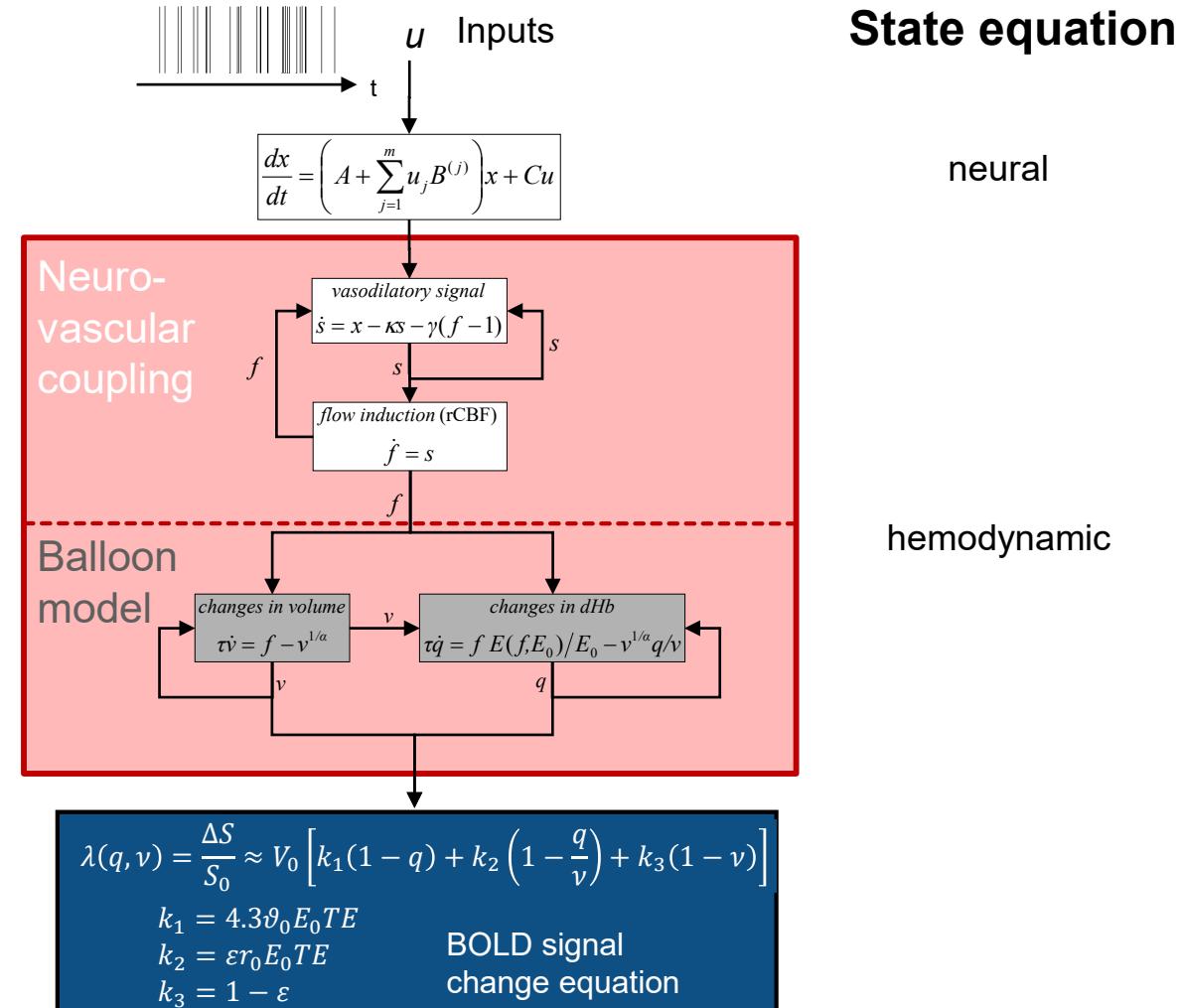
6 parameters:

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

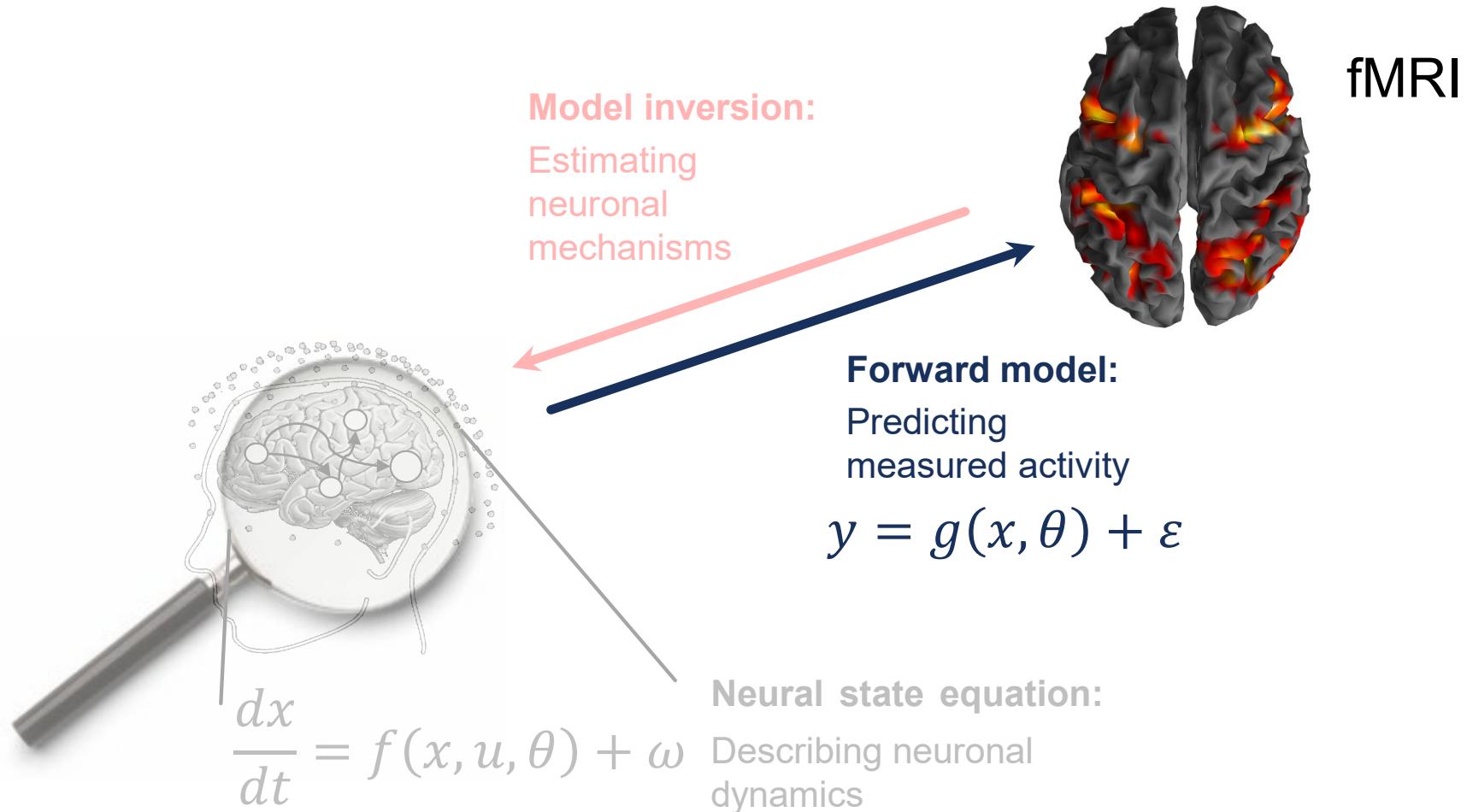
Important for model fitting,
but typically of no interest
for statistical inference.

Region specific HRF

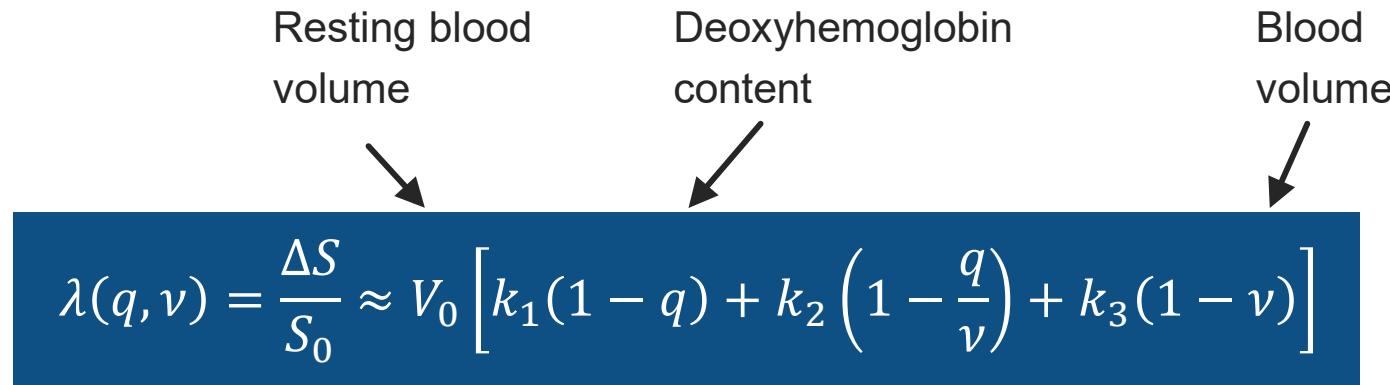
→ Parameters computed
separately for each region



DCM for fMRI - overview



The BOLD signal equation



Resting blood volume Deoxyhemoglobin content Blood volume

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

BOLD-Signal Parameters:

$$k_1 = 4.3\vartheta_0 E_0 TE$$

$$k_2 = \varepsilon r_0 E_0 TE$$

$$k_3 = 1 - \varepsilon$$

$$V_0 = 0.04 \quad E_0 = 0.32 - 0.4$$

At 1.5 Tesla

$$\vartheta_0 \approx 40.3 \text{ s}^{-1}$$

$$r_0 \approx 25 \text{ s}^{-1}$$

$$TE \approx 0.04 \text{ s}$$

$$\varepsilon \approx 1.28$$

At 3 Tesla

$$\vartheta_0 \approx 80.6 \text{ s}^{-1}$$

$$r_0 \approx 110 \text{ s}^{-1}$$

$$TE \approx 0.035 \text{ s}$$

$$\varepsilon \approx 0.47$$

At 7 Tesla

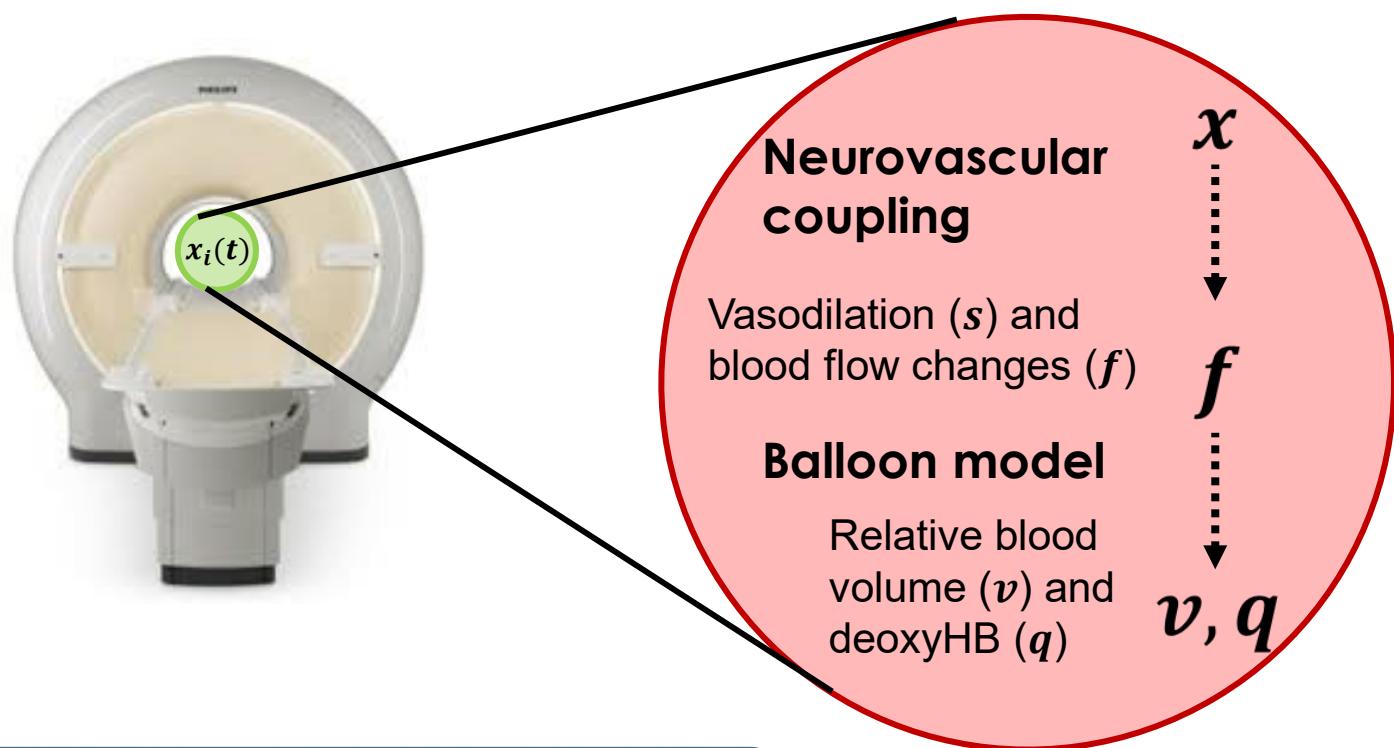
$$\vartheta_0 \approx 188 \text{ s}^{-1}$$

$$r_0 \approx 340 \text{ s}^{-1}$$

$$TE \approx 0.025 \text{ s}$$

$$\varepsilon \approx 0.026$$

From neural activity to the BOLD signal: summary

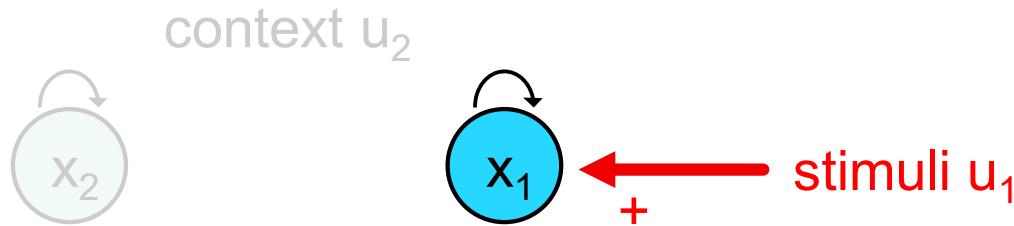
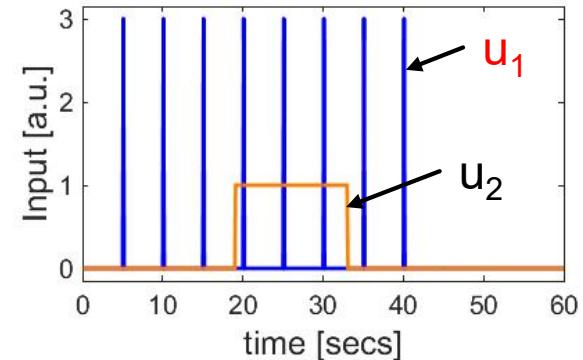


BOLD signal is a **direct function** of v and q

$$y = \frac{\Delta S}{S_0} = g(v, q) + \varepsilon$$

Simulation example: What can DCM explain?

Example: single node

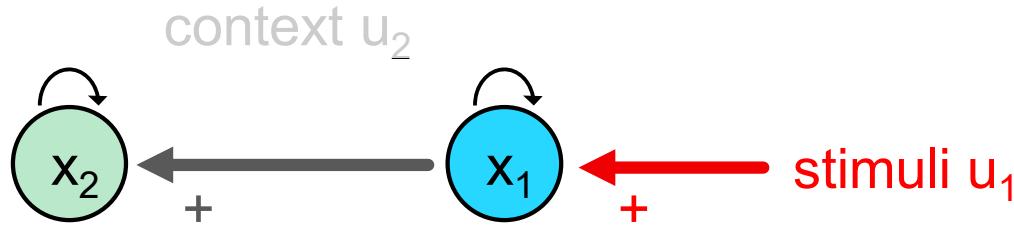


$$\frac{dx}{dt} = (A + u_2 B^{(2)})x + Cu_1$$

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

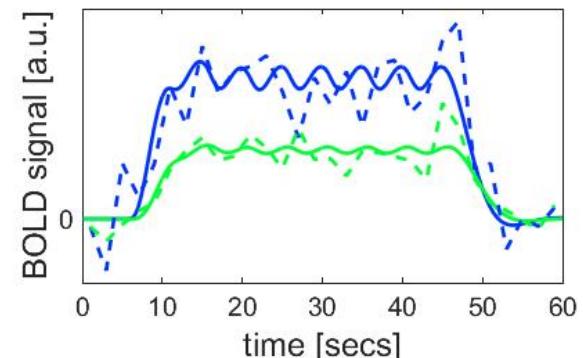
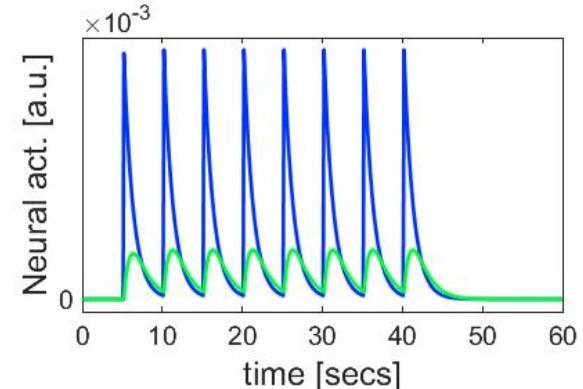
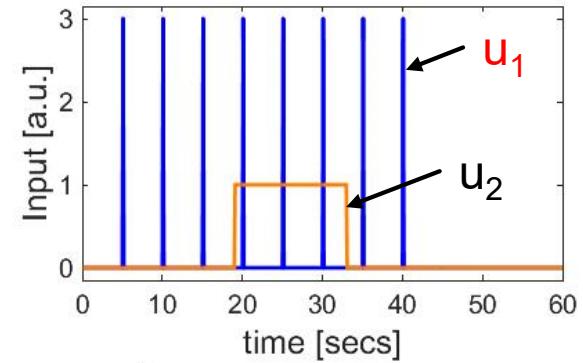
Simulation example: What can DCM explain?

Example: two connected node



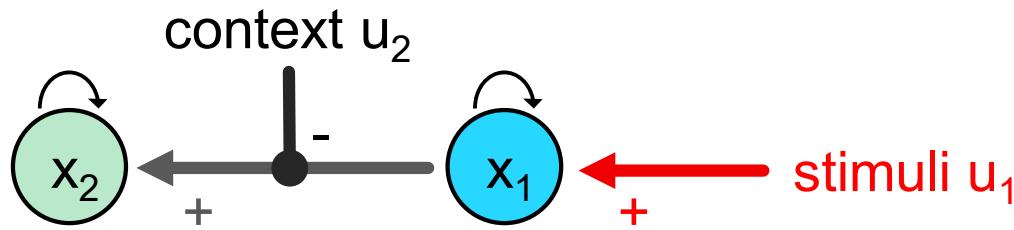
$$\frac{dx}{dt} = (A + u_2 B^{(2)})x + Cu_1$$

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



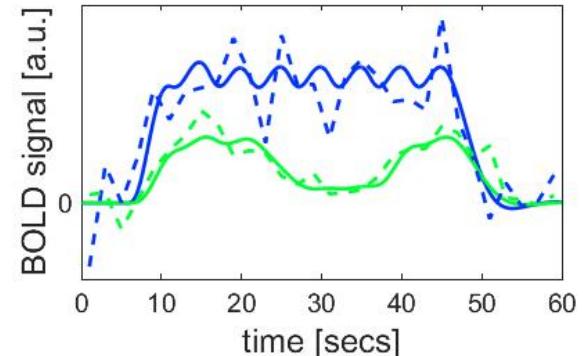
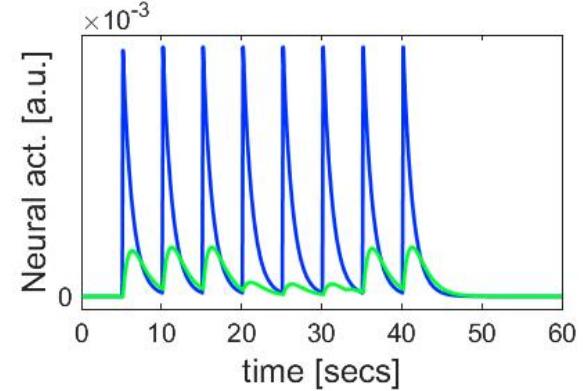
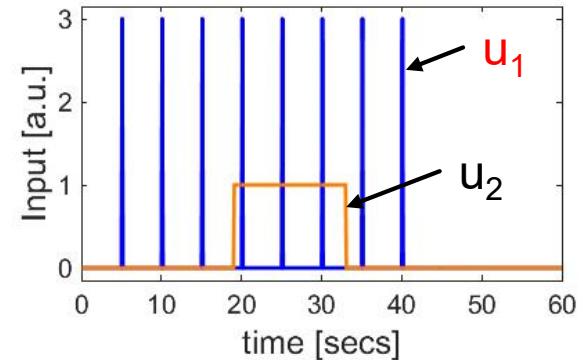
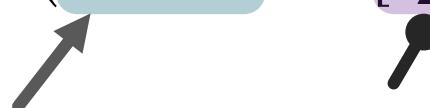
Simulation example: What can DCM explain?

Example: modulation of connection



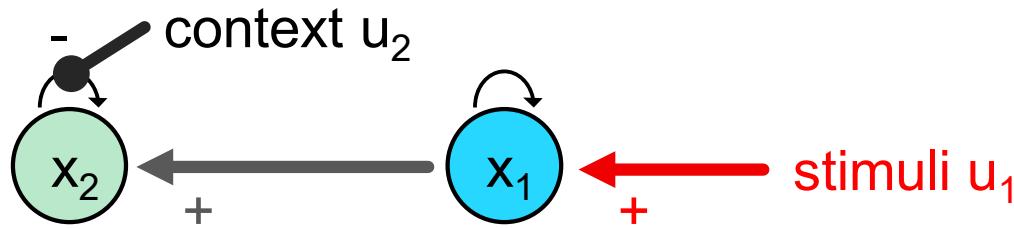
$$\frac{dx}{dt} = (A + u_2 B^{(2)})x + Cu_1$$

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



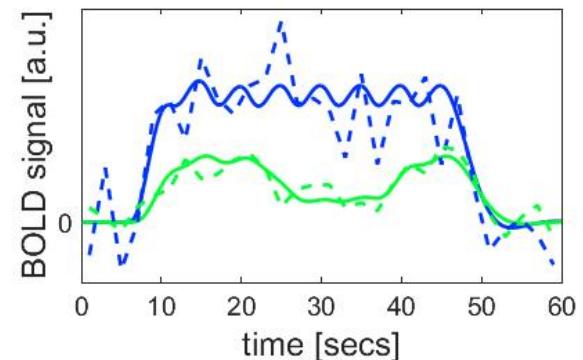
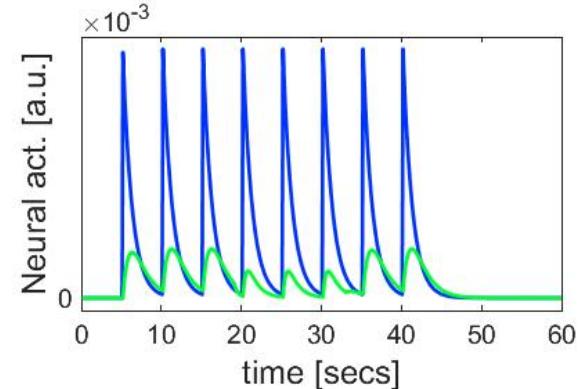
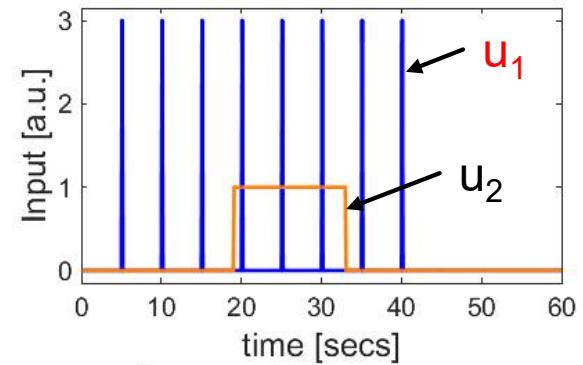
Simulation example: What can DCM explain?

Example: modulation of inhibitory self-connection



$$\frac{dx}{dt} = (A + u_2 B^{(2)})x + Cu_1$$

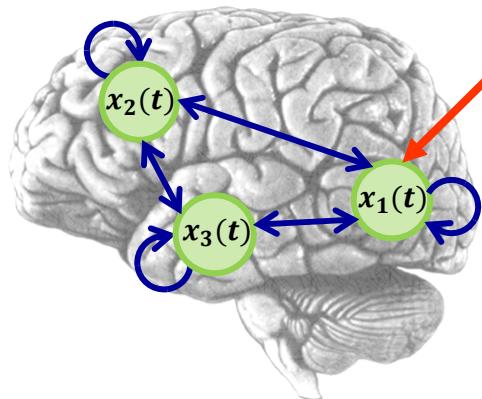
$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \end{bmatrix} = \left(\begin{bmatrix} a_{11} & 0 \\ a_{21} & a_{22} \end{bmatrix} + u_2 \begin{bmatrix} 0 & 0 \\ 0 & b_{22}^{(2)} \end{bmatrix} \right) \cdot \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} + \begin{bmatrix} c_{11} & 0 \\ 0 & 0 \end{bmatrix} \cdot \begin{bmatrix}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



DCM for fMRI

A simple model of
a neural network

...



Neural node



Input



Connections

... described as a
dynamical system

...

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

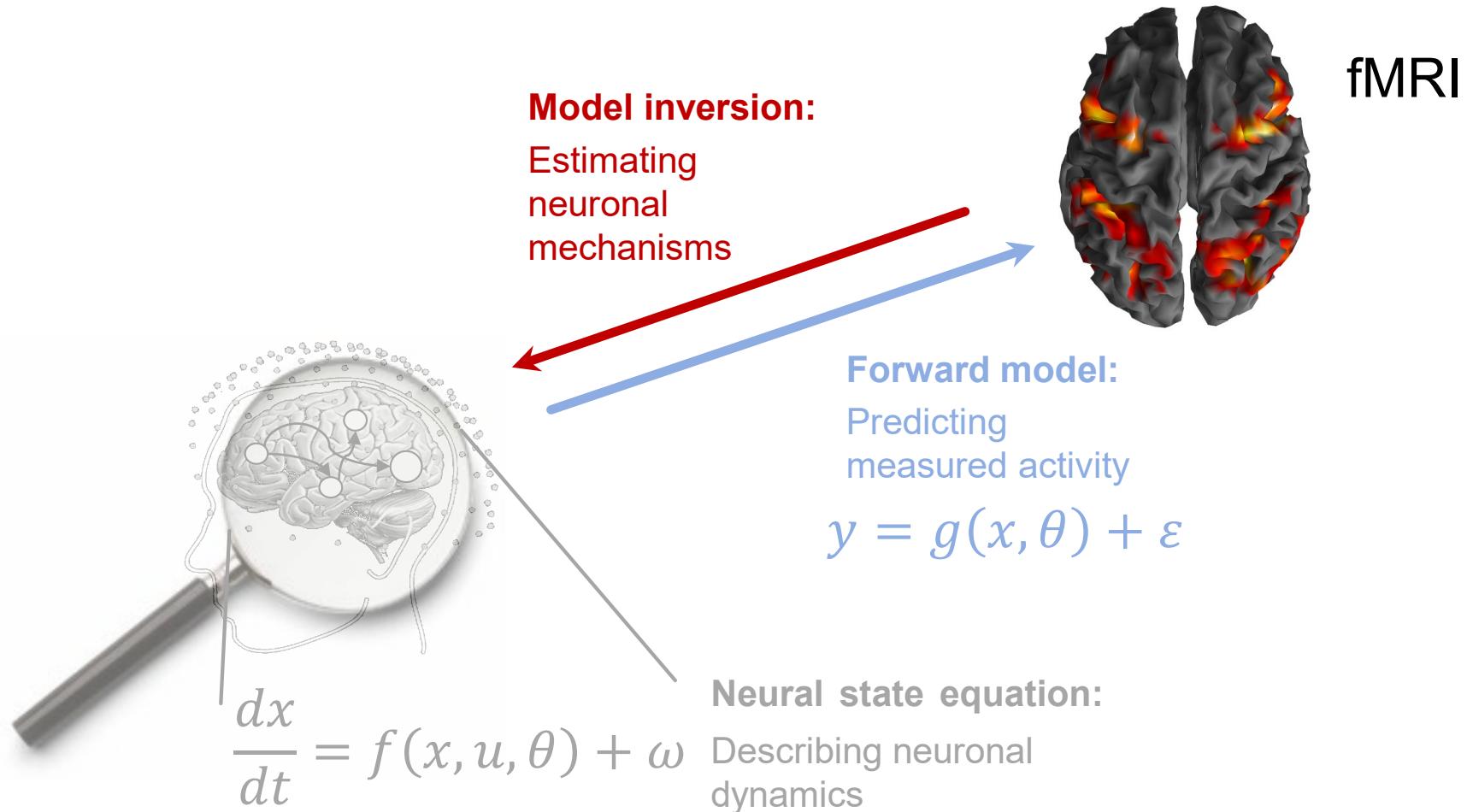
... causes the data
(BOLD signal).

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

Simulate the system with input u and
parameters θ

→ BOLD signal time course y that can be
compared to measured data.

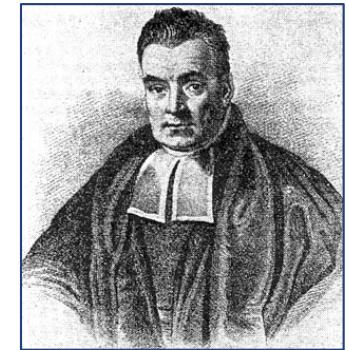
DCM for fMRI - overview



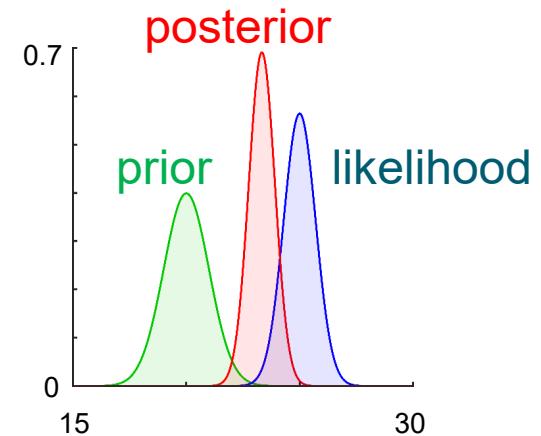


Bayes' theorem

$$\text{posterior } p(\theta|y, m) = \frac{\text{likelihood prior}}{\text{model evidence}} = \frac{p(y|\theta, m)p(\theta|m)}{p(y|m)}$$



Reverend Thomas Bayes
(1702-1761)





The likelihood function for DCM

$$p(y(t)|\theta, m) = \mathcal{N}(y(t); g(\theta^n, \theta^h, u(t)), \theta^\sigma)$$

likelihood

Assume data is normally distributed around the prediction from the dynamical model (Gaussian noise)

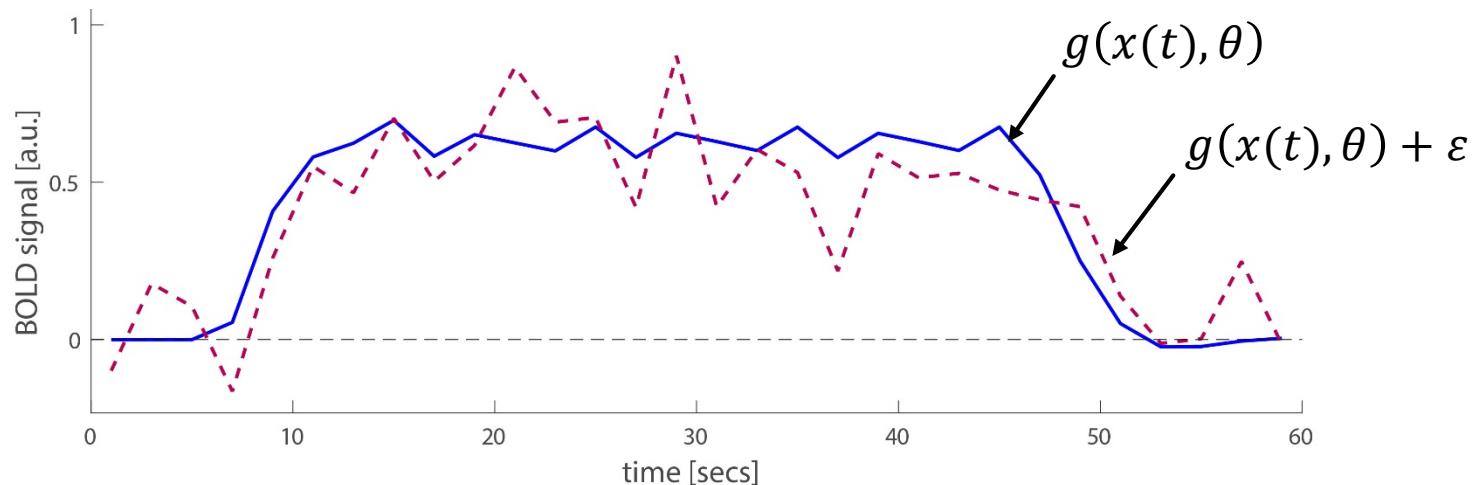
$$y(t) = g(x(t), \theta) + \varepsilon$$
$$\varepsilon \sim \mathcal{N}(0, \sigma^2 I)$$

Data is prediction plus Gaussian noise

The likelihood function for DCM

$$p(y(t)|\theta, m) = \mathcal{N}(y(t); g(\theta^n, \theta^h, u), \theta^\sigma)$$

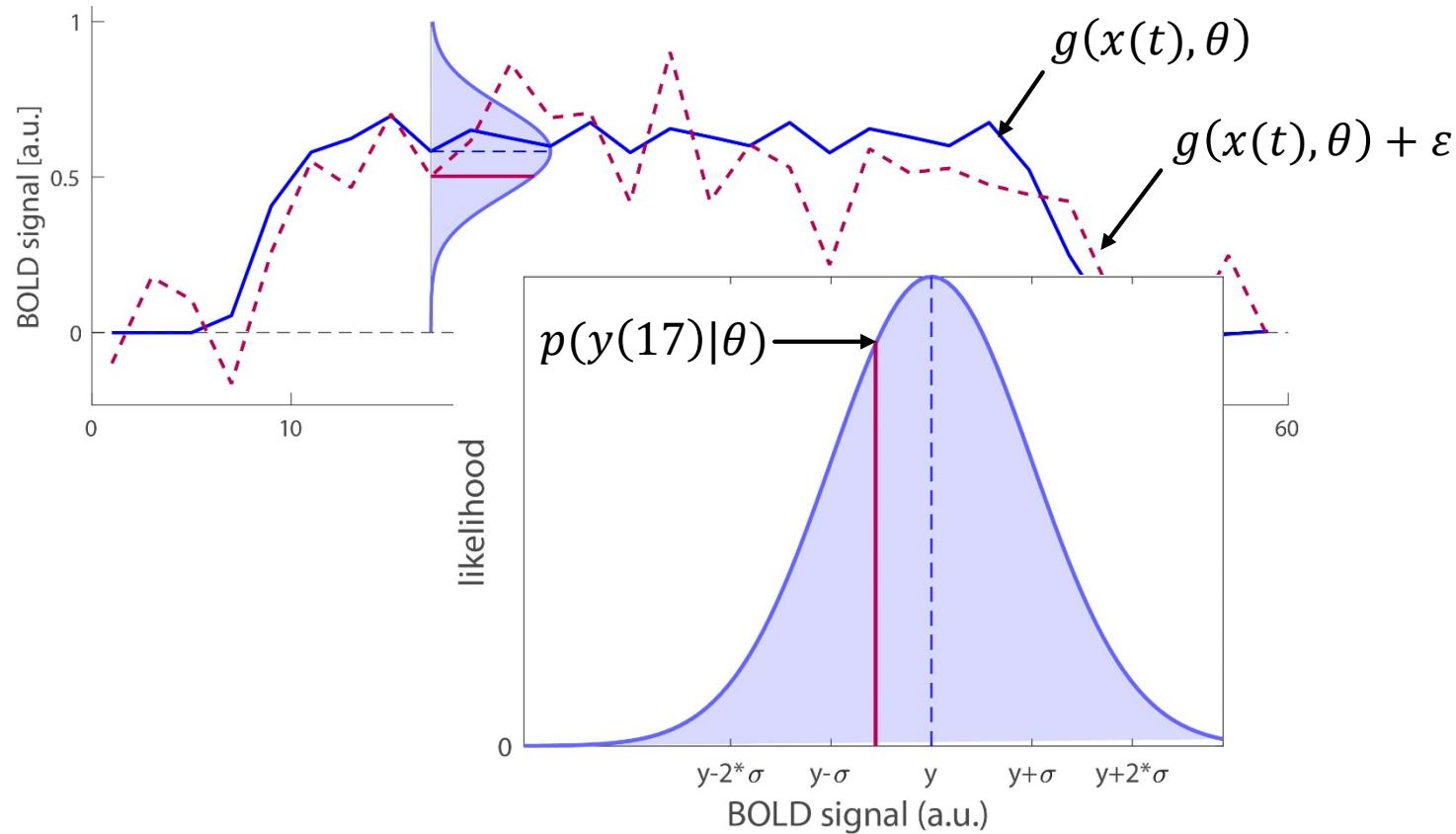
likelihood



The likelihood function for DCM

$$p(y(t)|\theta, m) = \mathcal{N}(y(t); g(\theta^n, \theta^h, u), \theta^\sigma)$$

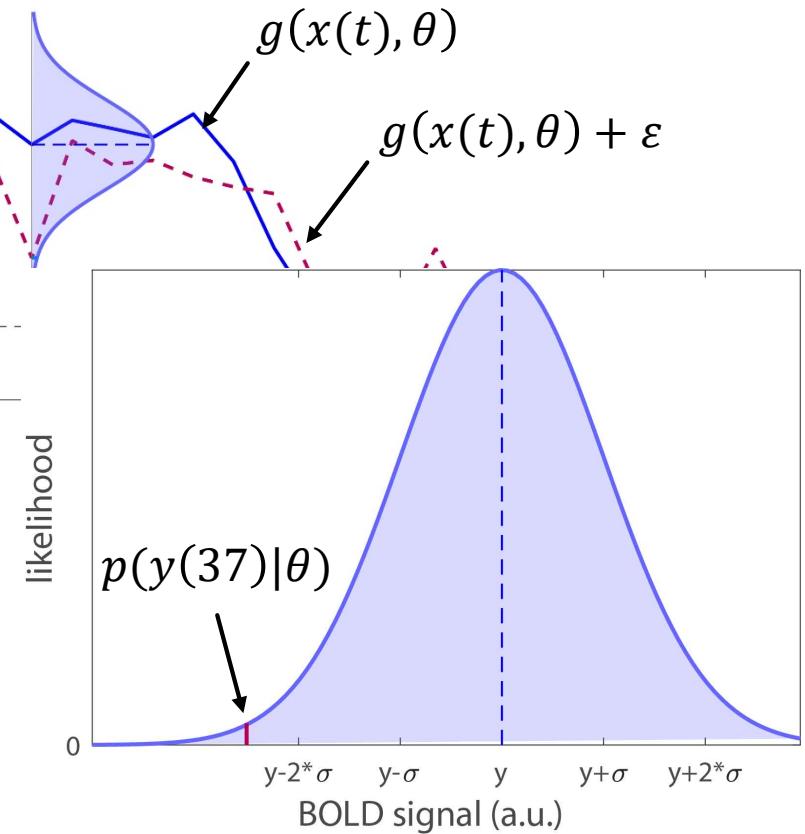
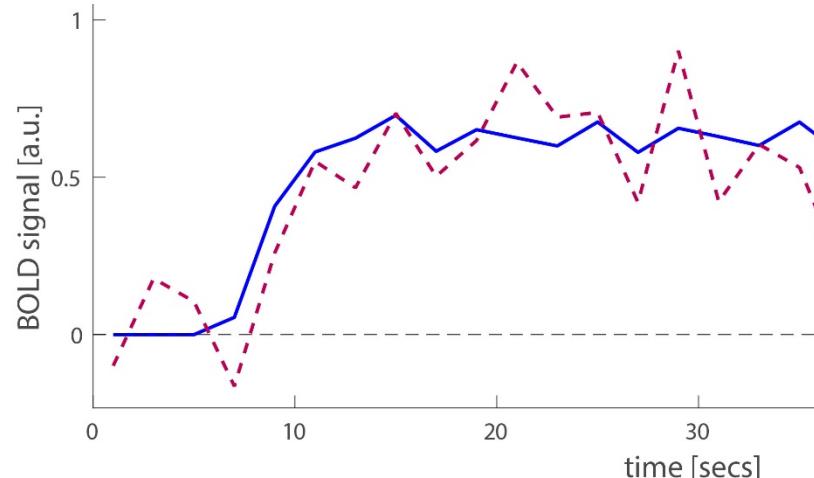
likelihood



The likelihood function for DCM

$$p(y(t)|\theta, m) = \mathcal{N}(y(t); g(\theta^n, \theta^h, u), \theta^\sigma)$$

likelihood





Priors

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

prior

Neuronal parameters:

- self-connections: principled (to “ensure” that the system is stable)
- other parameters (between—region connections, modulation, inputs): shrinkage priors

Hemodynamic parameters:

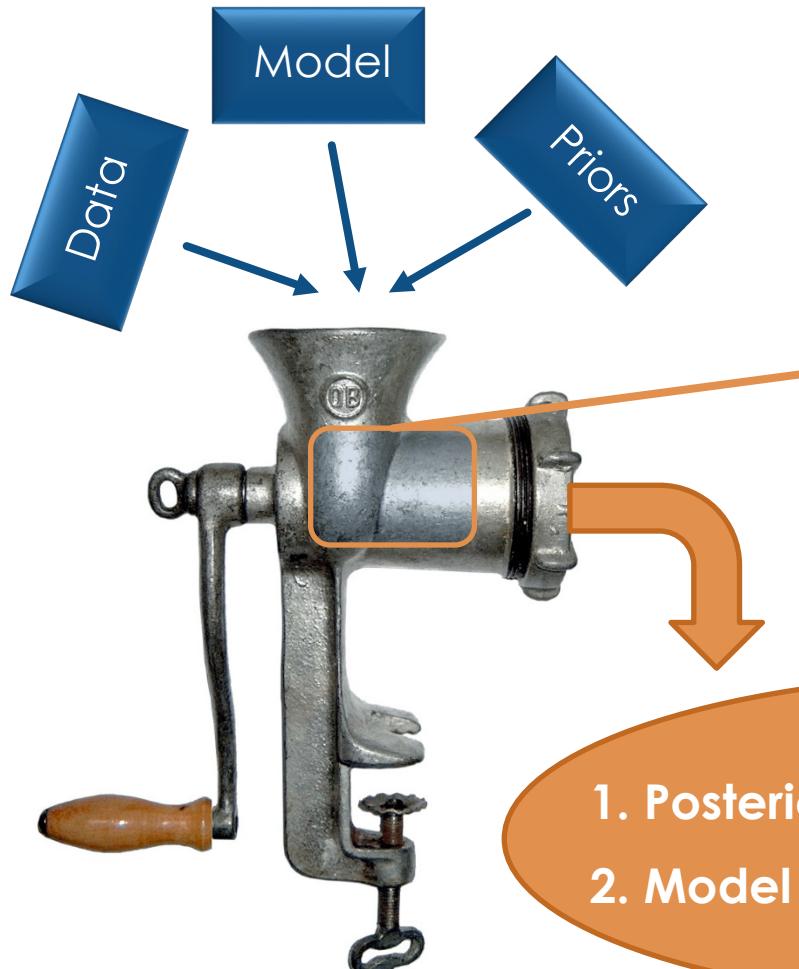
- empirical

Noise prior:

- assume relatively noisy data

(not default in SPM12 → set DCM.options.hE = 0; DCM.options.hC = 1)

Model estimation: running the machinery



Free energy approximation
Variational Bayes

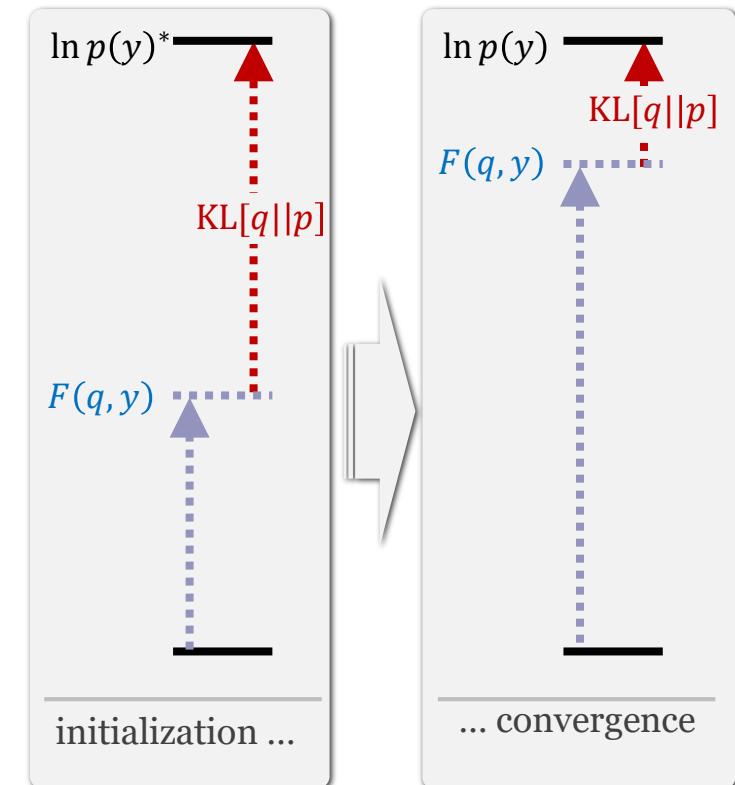
Thermodynamic integration
MCMC

Inversion – variational Free Energy approximation to model evidence

model evidence

$$\ln p(y) = \underbrace{\text{KL}[q||p]}_{\substack{\text{divergence} \\ \geq 0 \\ (\text{unknown})}} + \underbrace{F(q, y)}_{\substack{\text{neg. free energy} \\ (\text{easy to evaluate} \\ \text{for a given } q)}}$$

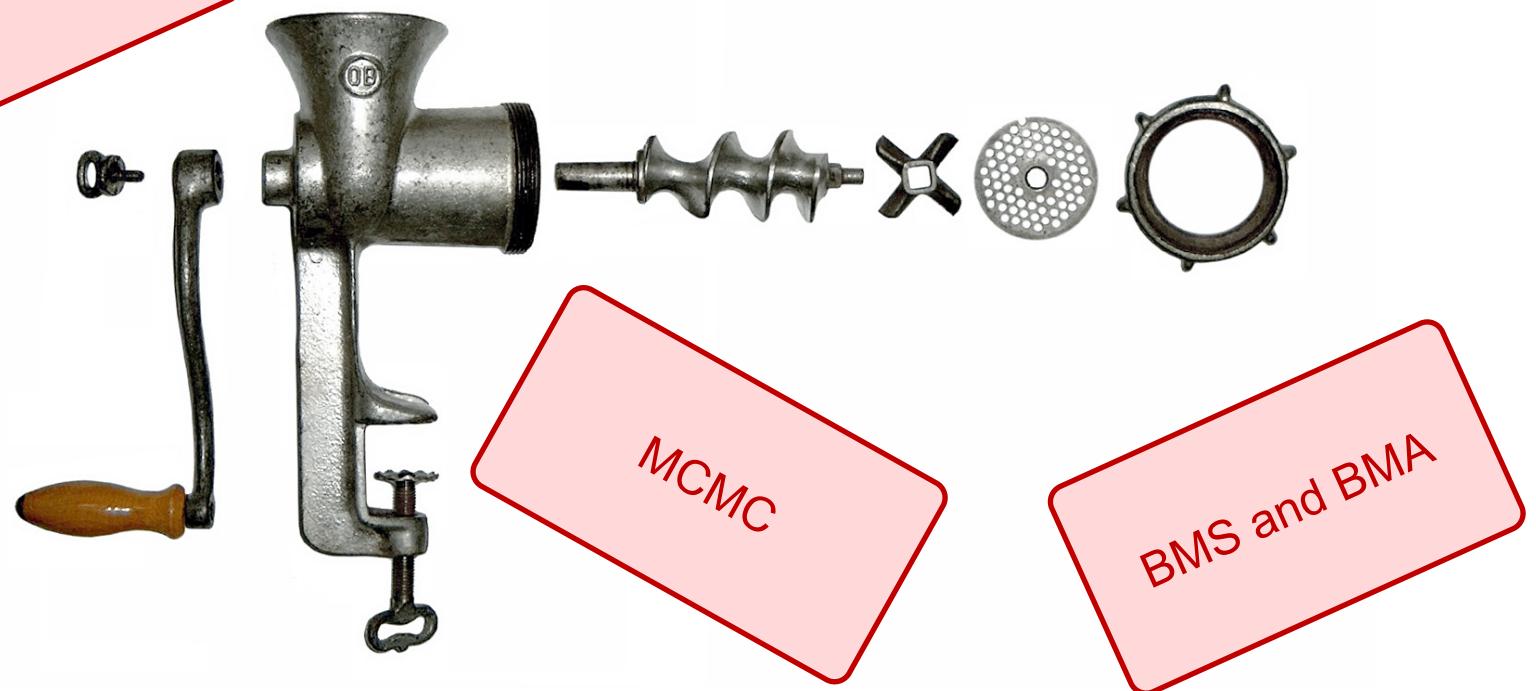
When $F(q, y)$ is maximized, $q(\theta)$ is our best estimate of the true posterior.





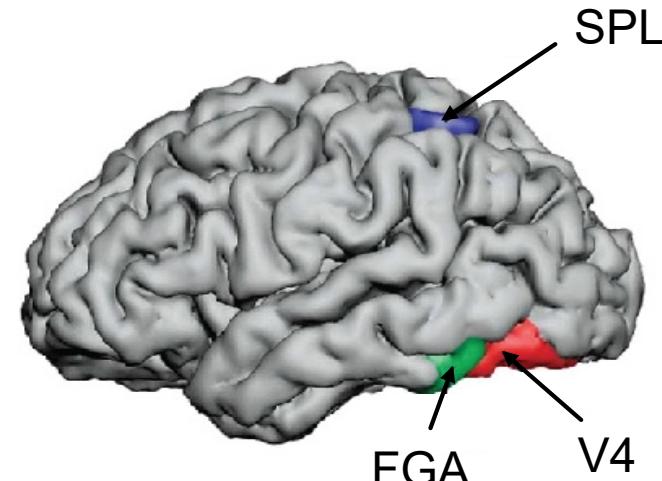
Model estimation: running the machinery

Variational Bayes



Model selection example: 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/coupling** between brain areas
 - grapheme encoding area (FGA)
 - color area (V4)
 - superior parietal lobule (SPL)

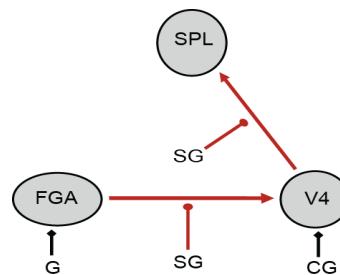


Hubbard, 2007

Bottom-up or Top-down “cross-activation”?

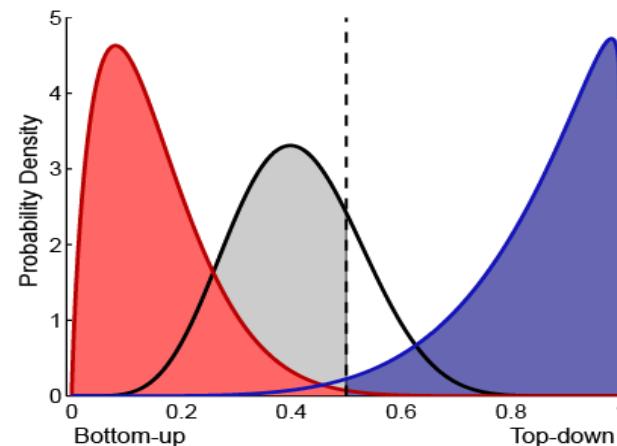
Bottom-up

(Ramachandran & Hubbard, 2001)



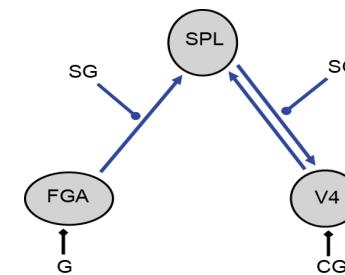
Projectors

ABC

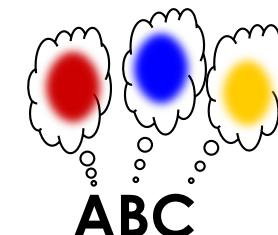


Top-down

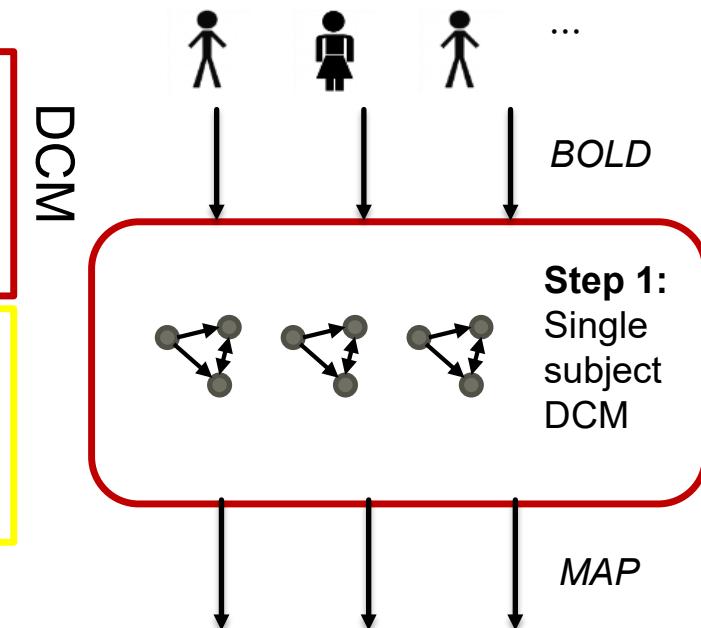
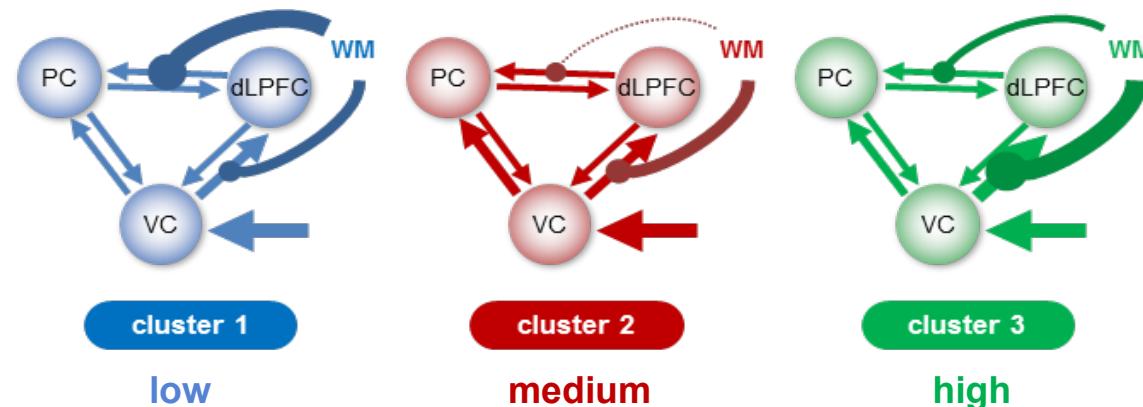
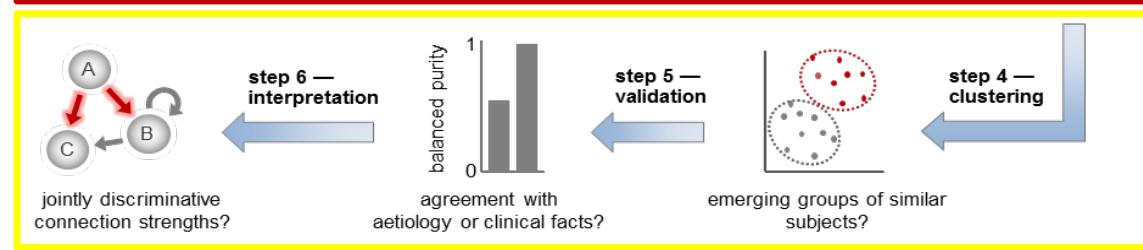
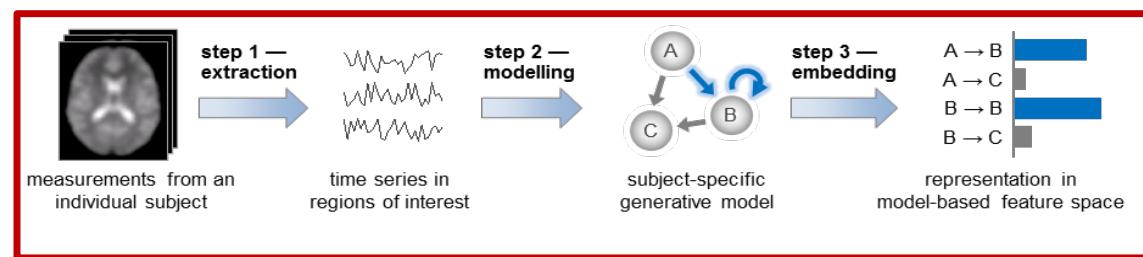
(Grossenbacher & Lovelace, 2001)



Associators



Example: DCM for physiologically plausible feature extraction (generative embedding)





What questions can we answer using DCM?

Model comparison

What is the functional architecture of a network of brain regions?

→ Synesthesia

Are optimal models different between groups?

→ Synesthesia

Which connections are modulated by experimental manipulations?

Parameter inference

Are parameters different between individuals/groups?

Use parameters as physiologically informed summary statistics

→ Generative embedding

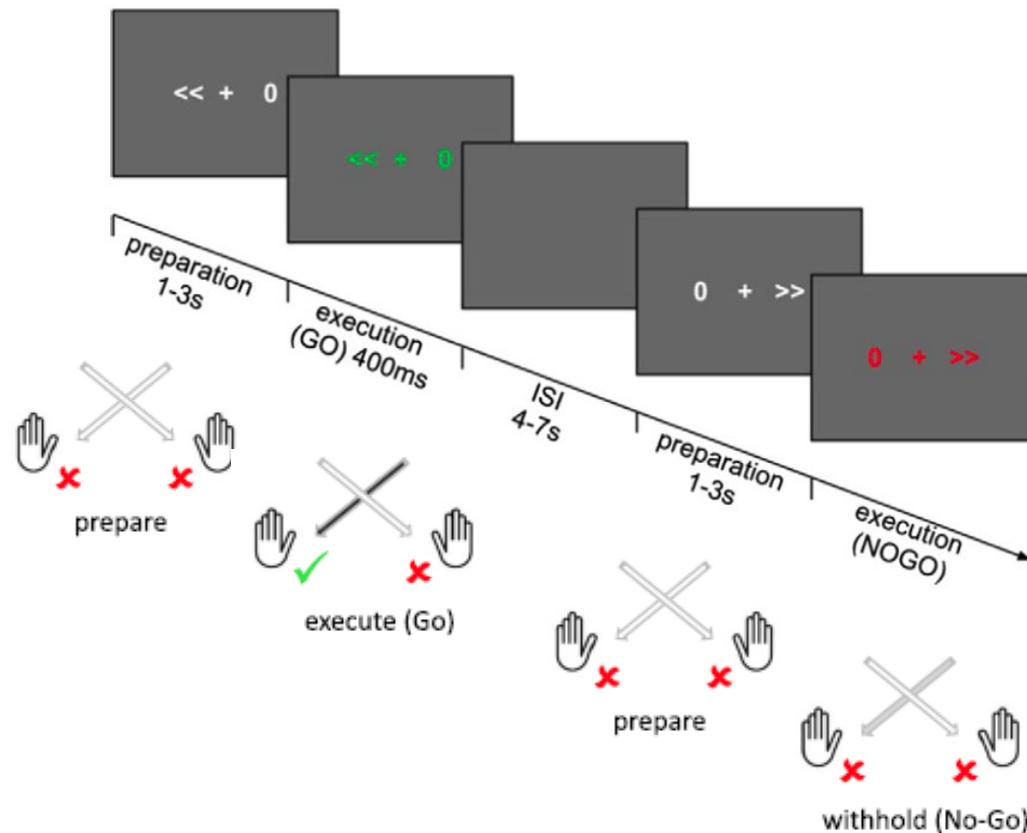
... and of course many more!



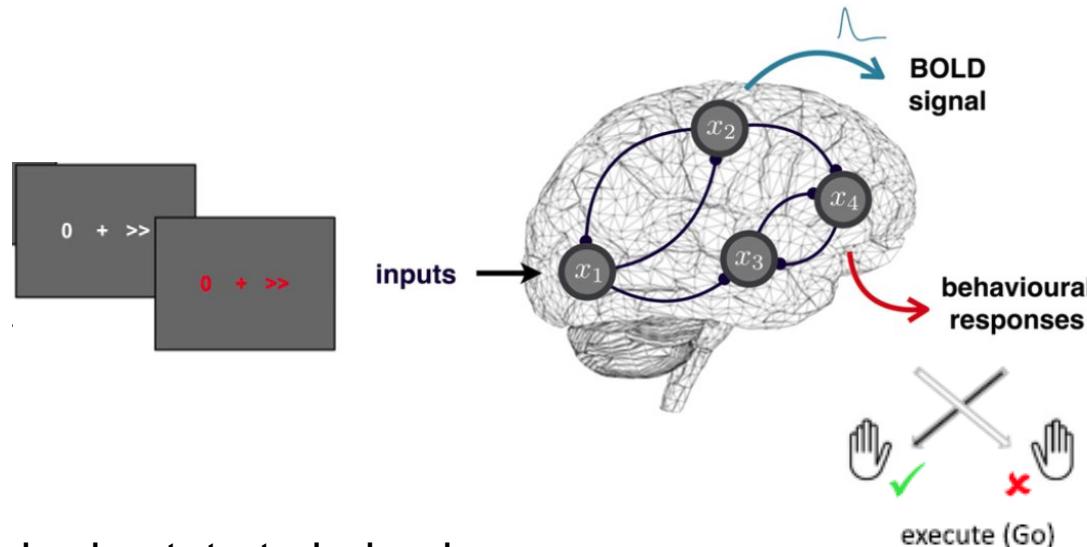
Limitations

- DCMs only have inputs, no outputs
 - Limits the study of behavioral paradigms
- Local minima
 - Variational approximation can get stuck in local minima of free energy
- Size of networks
 - Standard inversion too slow for large networks (>10 nodes).
- Regularization through fixed priors:
 - Regularization based on other data → empirical Bayes.

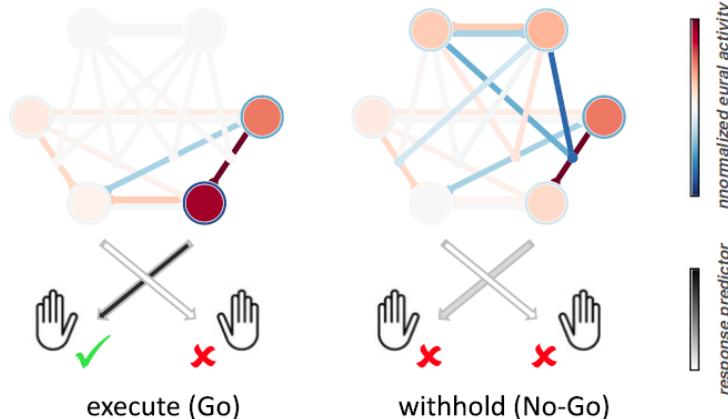
Behavioral DCM – a step towards a neurocomputational model



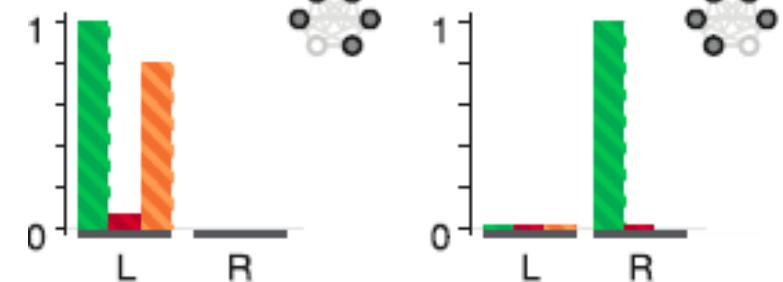
Behavioral DCM – a step towards a neurocomputational model



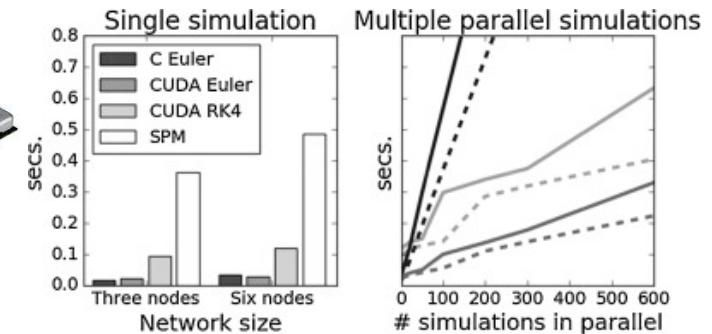
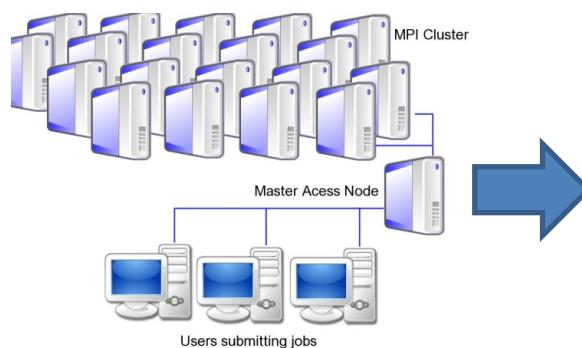
Mapping brain state to behavior



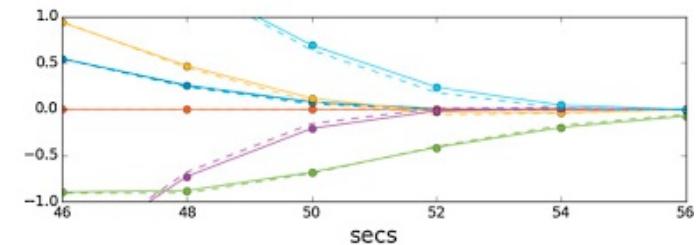
Lesion simulations



MCMC inversion of DCMs: Massively Parallel DCM - mpdcm



$$\begin{aligned} \dot{x} &= f(x, u_1, \theta_1) \\ \dot{x} &= f(x, u_2, \theta_2) \\ &\vdots \\ \dot{x} &= f(x, u_n, \theta_n) \end{aligned} \quad \left. \right\} \text{mpdcm_integrate(dcms)} \quad \begin{bmatrix} y_1 \\ y_2 \\ \vdots \\ y_n \end{bmatrix}$$



- Fast inversion of DCMs
 - MCMC based inversion possible
- **Thermodynamic Integration** (alternative to negative Free Energy)



Recent additions to DCM for fMRI

- Massively parallel dynamic causal modelling
 - **mpdcm** Aponte et al., J Neuroscience Methods, 2016
- Regression dynamic causal modelling
 - **rDCM** Frässle et al., Neuroimage, 2017
- Hierarchical unsupervised generative embedding
 - **HUGE** Yu et al., Neuroimage, 2019

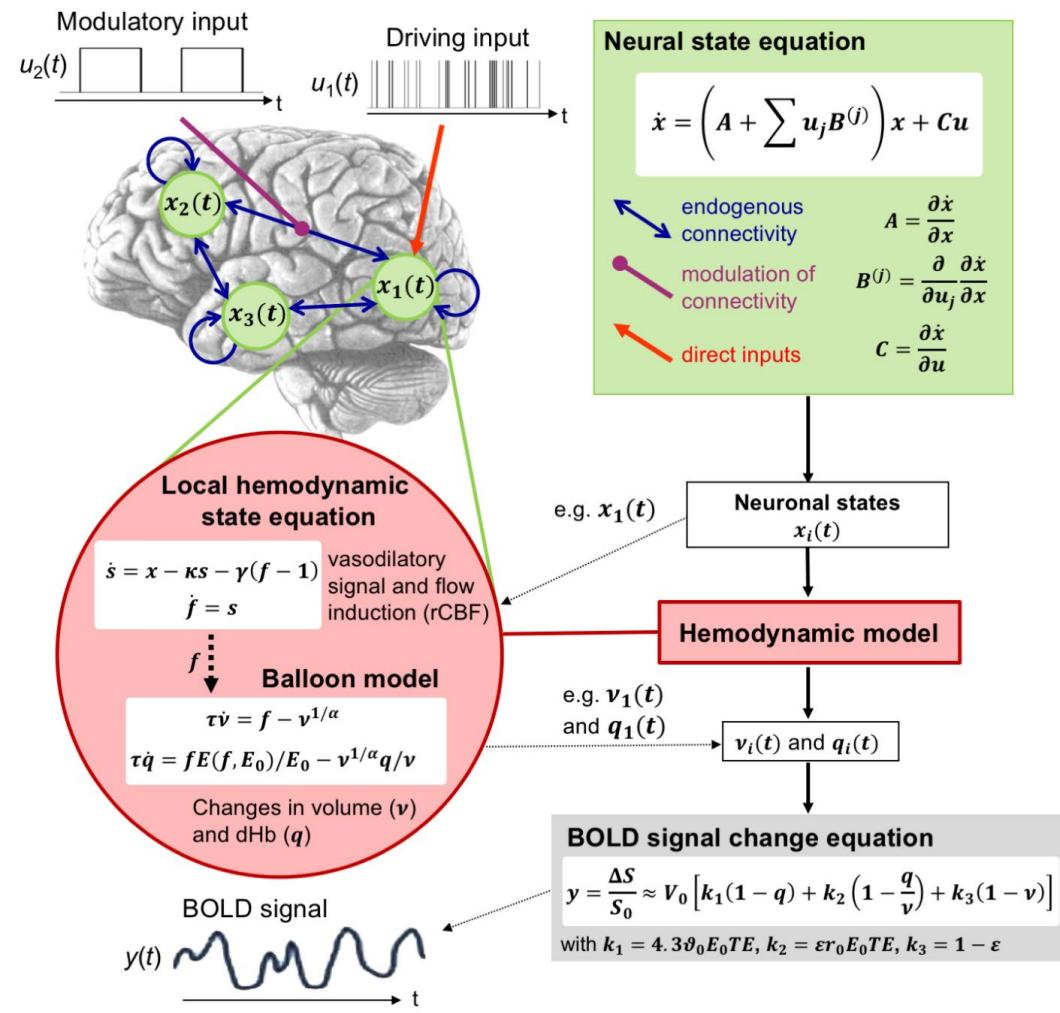
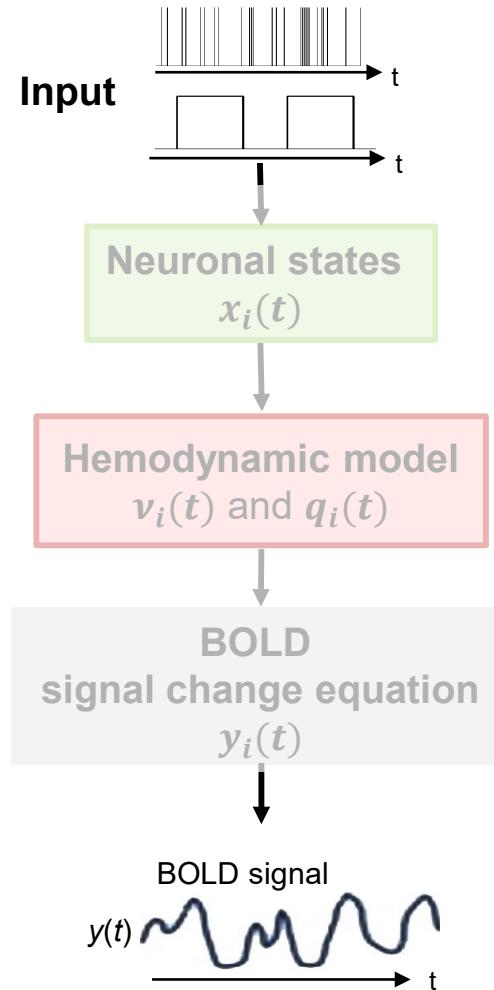
Modeling Connectivity:
Advanced DCM for
fMRI
→ Stefan Frässle

Available in TAPAS:
www.translationalneuromodeling.org/tapas

Summary – generative model



Summary – generative model

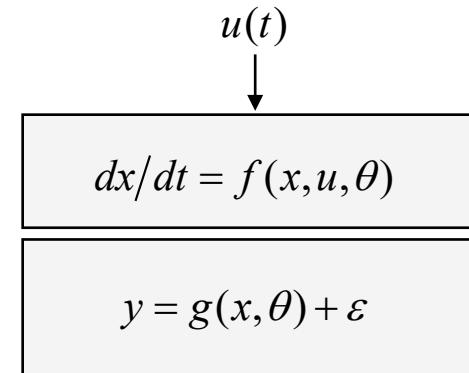


Summary - Bayesian system identification

Neural (and hemo-)
dynamics

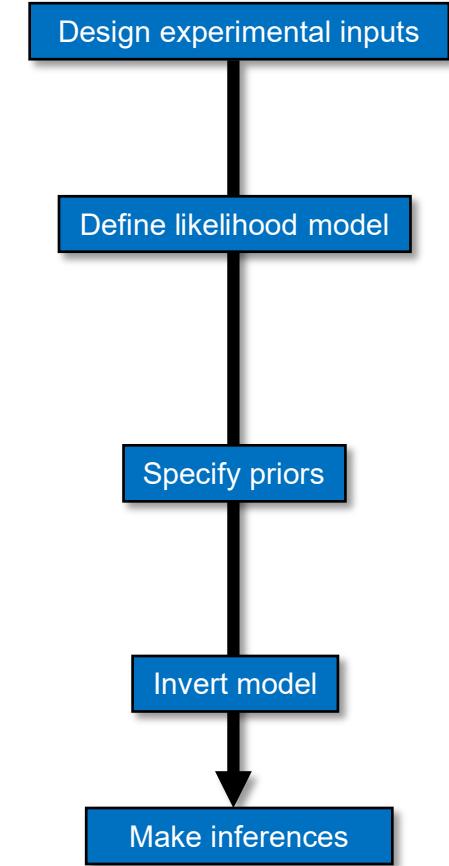
Observer function

Inference on
model structure
Inference on
parameters



$$p(y | \theta, m) = N(g(\theta), \Sigma(\theta))$$
$$p(\theta, m) = N(\mu_\theta, \Sigma_\theta)$$

$$p(y | m) = \int p(y | \theta, m) p(\theta) d\theta$$
$$p(\theta | y, m) = \frac{p(y | \theta, m) p(\theta, m)}{p(y | m)}$$





DCM software note

Basic functionality for DCM for fMRI is provided within

SPM

<https://www.fil.ion.ucl.ac.uk/spm/>



Thank you!

Many thanks to Stefan Frässle,
Klaas Enno Stephan, Hanneke den Ouden
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List with suggested DCM literature in Appendix of this presentation!



DCM literature (1)

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- **Frässle S, Lomakina EI, Razi A, Friston KJ, Buhmann JM, Stephan KE (2017) Regression DCM for fMRI. *NeuroImage* 155:406-421.**



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- Li B, Daunizeau J, Stephan KE, Penny WD, Friston KJ (2011). Stochastic DCM and generalised filtering. *NeuroImage* 58: 442-457
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- **Raman S, Deserno L, Schlagenhauf F, Stephan KE (2016). A hierarchical model for integrating unsupervised generative embedding and empirical Bayes. *Journal of Neuroscience Methods* 269: 6-20.**
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- **Zeidman P, Jafarian A, Seghier ML, Litvak V, Cagnan H, Price CJ, Friston KJ (2019) A guide to group effective connectivity analysis, part 2: Second level analysis with PEB. *NeuroImage*, DOI: 10.1016/j.neuroimage.2019.06.032**