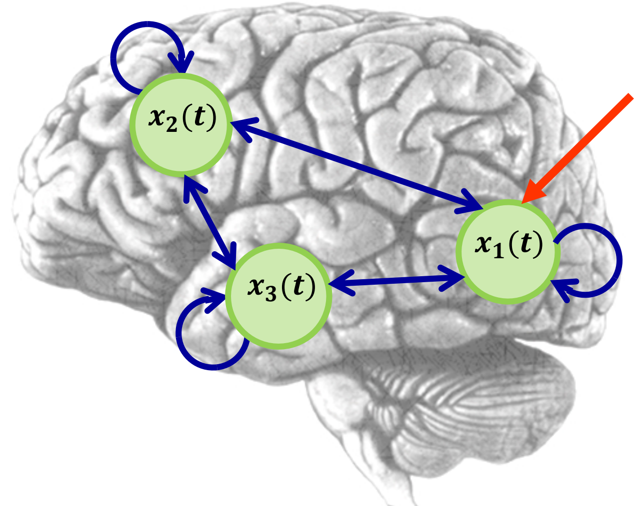
University of Zurich[UZH]

Translational Neuromodeling Unit

ETH zürich



Models of Connectivity: Dynamic Causal Modelling for fMRI

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Translational Neuromodeling Unit (TNU),

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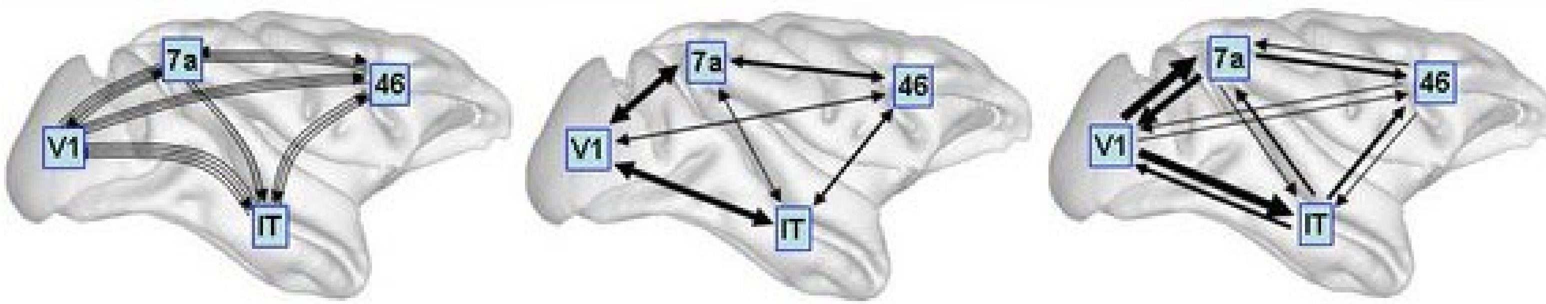
University and ETH Zürich

CP Course 2020, Zürich, Switzerland

Structural, functional & effective connectivity



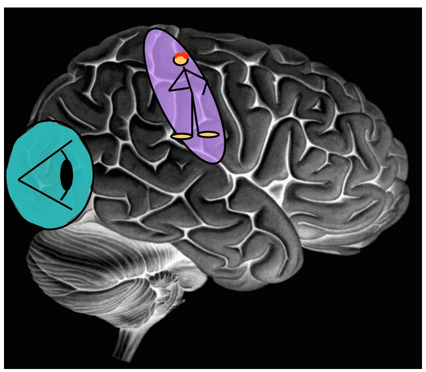
Sporns 2007, *Scholarpedia*

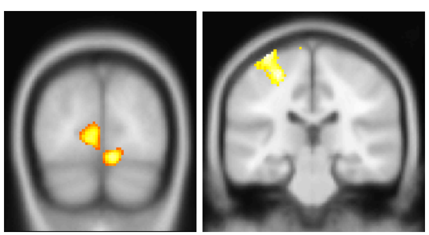
anatomical/structural	**functional**	**effective**
- presence of physical connections	- statistical dependency between regional time series	- direct influences between neuronal populations
→ *DWI, tractography, tracer studies (animals)*	→ *correlations, ICA*	→ *DCM*

Context-independent | Mechanism - free | Mechanistic

Specialisation vs. Integration

Functional Specialisation

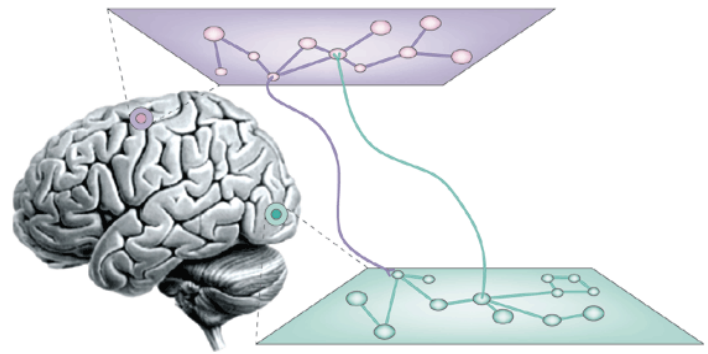


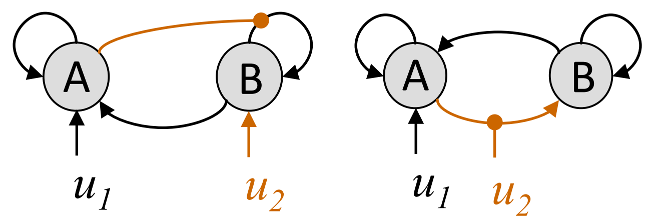


u_1 $u_1 \times u_2$

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

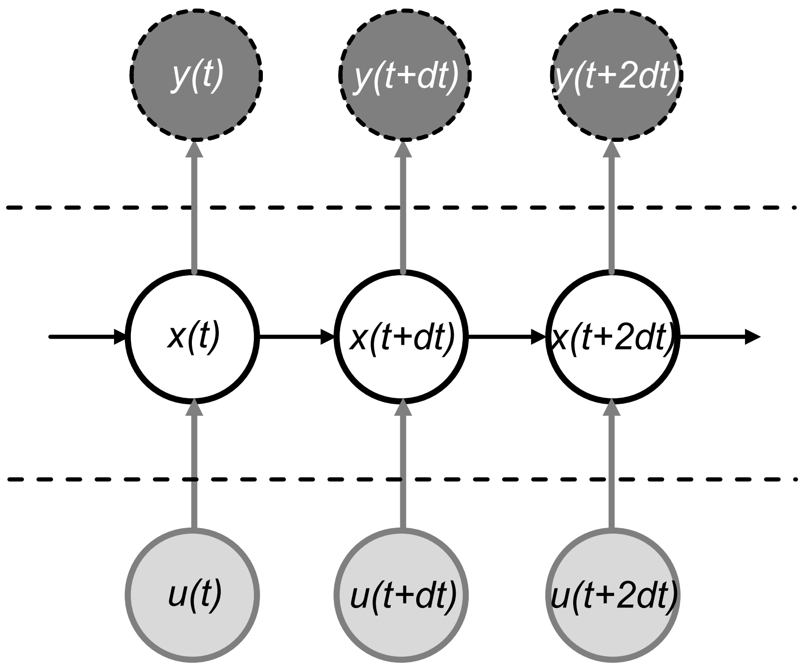
Functional Integration





*«**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)

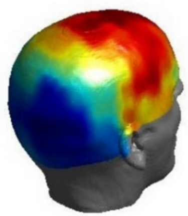
$$\frac{dx}{dt} = f(x, u, \theta) + \omega$$

Inputs (Exp. manipulations)

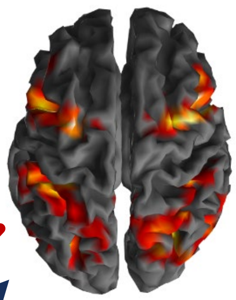
$$u(t)$$

Dynamic causal modelling

EEG, MEG



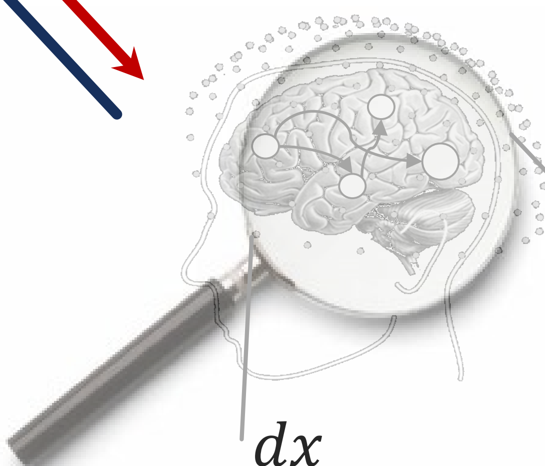
fMRI



Model inversion:
Estimating neuronal mechanisms

Forward model:
Predicting measured activity

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



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

State equation:
Describing neuronal dynamics (and hemodynamics)

DCM for EEG
→ Next lecture
→ Jean Daunizeau

Friston et al., 2003, NeuroImage; David et al., 2006, NeuroImage

Dynamic causal modelling

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NeuroImage

NeuroImage 19 (2003) 1273–1302

www.elsevier.com/locate/ynimg

Dynamic causal modelling

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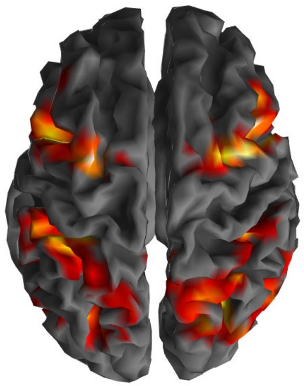
The Wellcome Department of Imaging Neuroscience, Institute of Neurology, Queen Square, London WC1N 3BG, UK

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

DCM for fMRI - Overview

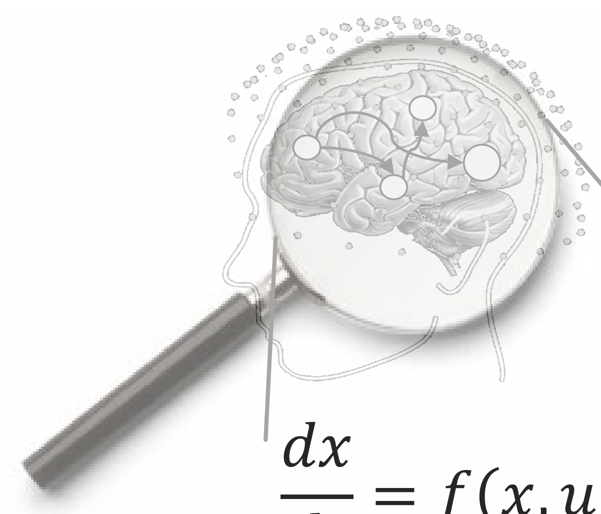


fMRI

Model inversion:
Estimating neuronal mechanisms

Forward model:
Predicting measured activity

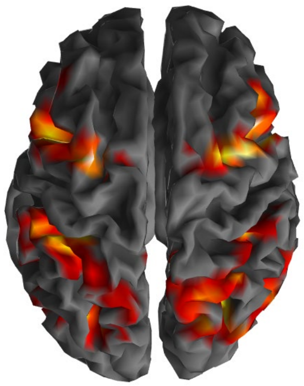
$$y = g(x, \theta) + \varepsilon$$



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

Neural state equation:
Describing neuronal dynamics

DCM for fMRI - Overview



fMRI

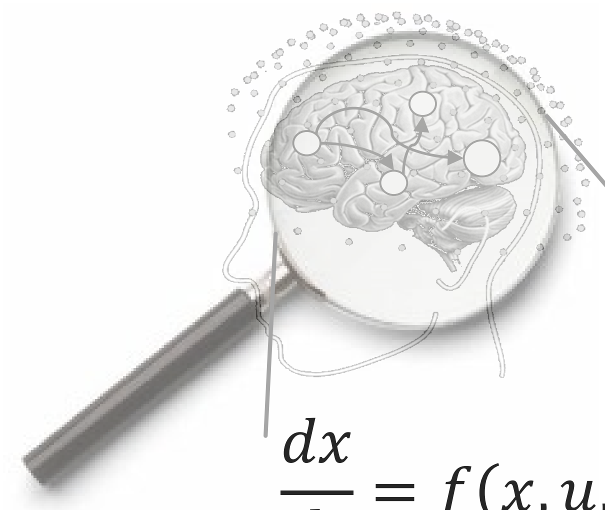
Model inversion:

Estimating neuronal mechanisms

Forward model:

Predicting measured activity

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



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

Neural state equation:

Describing neuronal dynamics

Neuronal state equations

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

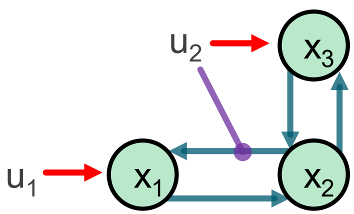
Neuronal state equations

$$\frac{dx}{dt} = f(x,u) \approx \underbrace{\boxed{f(x_0,0) + \frac{\partial f}{\partial x}x + \frac{\partial f}{\partial u}u + \frac{\partial^2 f}{\partial x \partial u}ux}}_{\text{bilinear model}} + \frac{\partial^2 f}{\partial x^2}\frac{x^2}{2} + \cdots$$

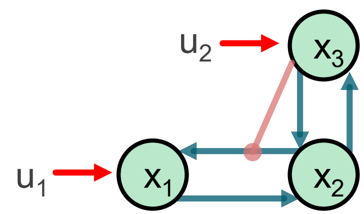
Neuronal state equations

$$\frac{dx}{dt} = f(x,u) \approx \boxed{f(x_0,0) + \overset{A}{\frac{\partial f}{\partial x}}x + \overset{C}{\frac{\partial f}{\partial u}}u + \overset{B}{\frac{\partial^2 f}{\partial x \partial u}}ux} + \overset{D}{\frac{\partial^2 f}{\partial x^2}}\frac{x^2}{2} + \cdots$$

bilinear model



nonlinear model



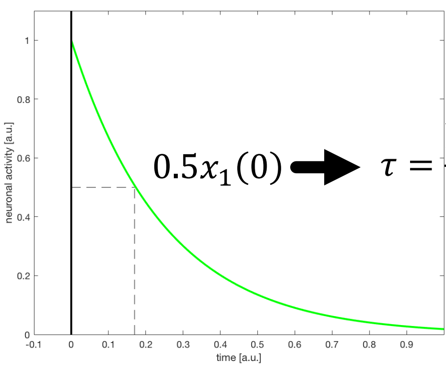
Neuronal state equations

DCM effective connectivity parameters are rate constants

a_{11}

x_1

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



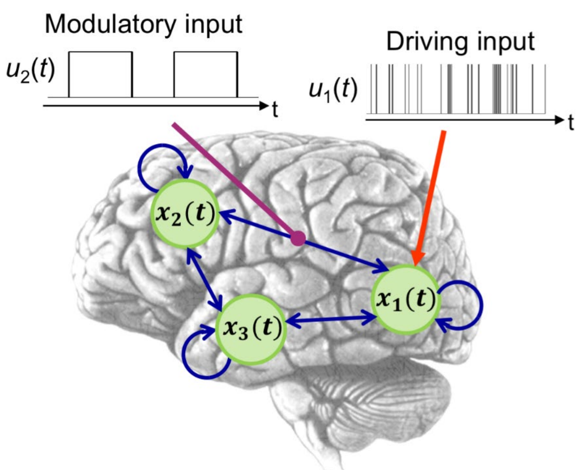
$$0.5x_1(0) \rightarrow \tau = \frac{\ln 2}{a_{11}}$$

$$x_1 \xrightarrow{0.10} x_2$$

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



State change

External inputs

Current state

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

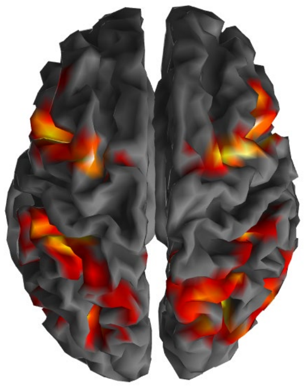
$$\theta = \{A, B^{(1)}, \dots, B^{(m)}, C\}$$

Endogenous connectivity

Modulatory connectivity

Driving inputs

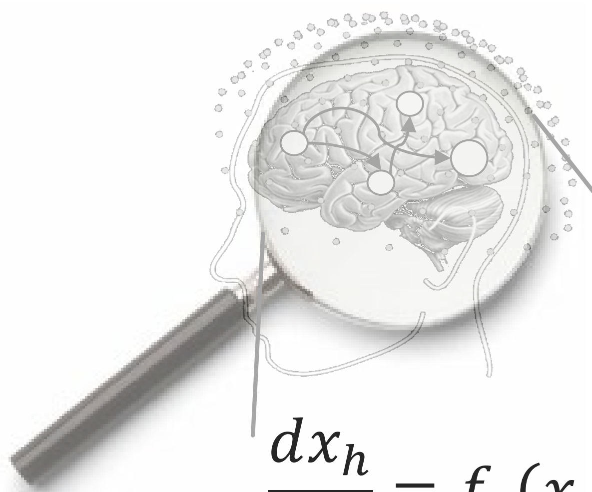
DCM for fMRI - Overview



Model inversion:
Estimating
neuronal
mechanisms

Forward model:
Predicting
measured activity

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



$$\frac{dx_h}{dt} = f_h(x_h, x, \theta)$$

Hemodynamic state equation:
Describing hemodynamics

The hemodynamic response

Neuronal dynamics only indirectly observable via hemodynamic response

↑ neuronal activity

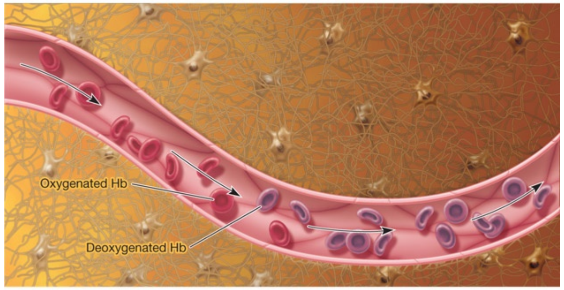
↑ blood flow

↑ oxygenated Hb

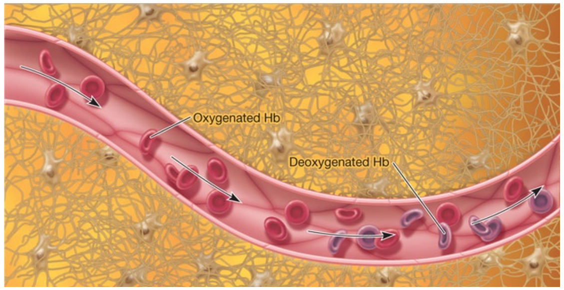
↑ T2*

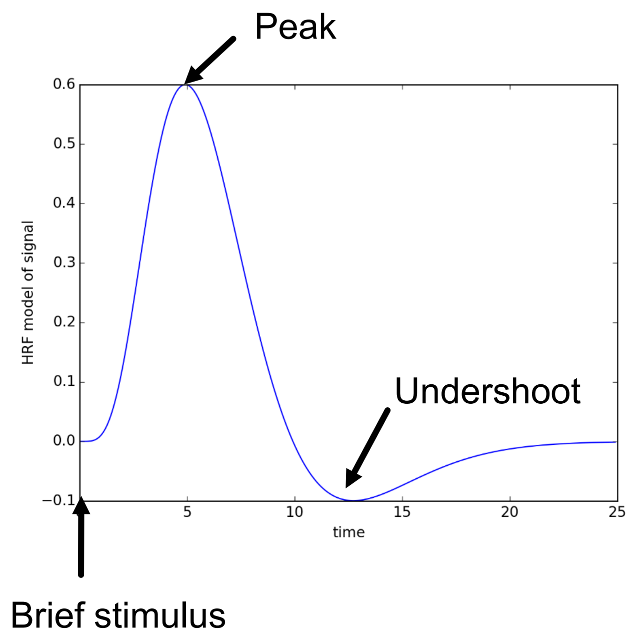
↑ fMRI signal

Rest



Activity





Huettel et al, 2004, fMRI (Book)

The hemodynamic model

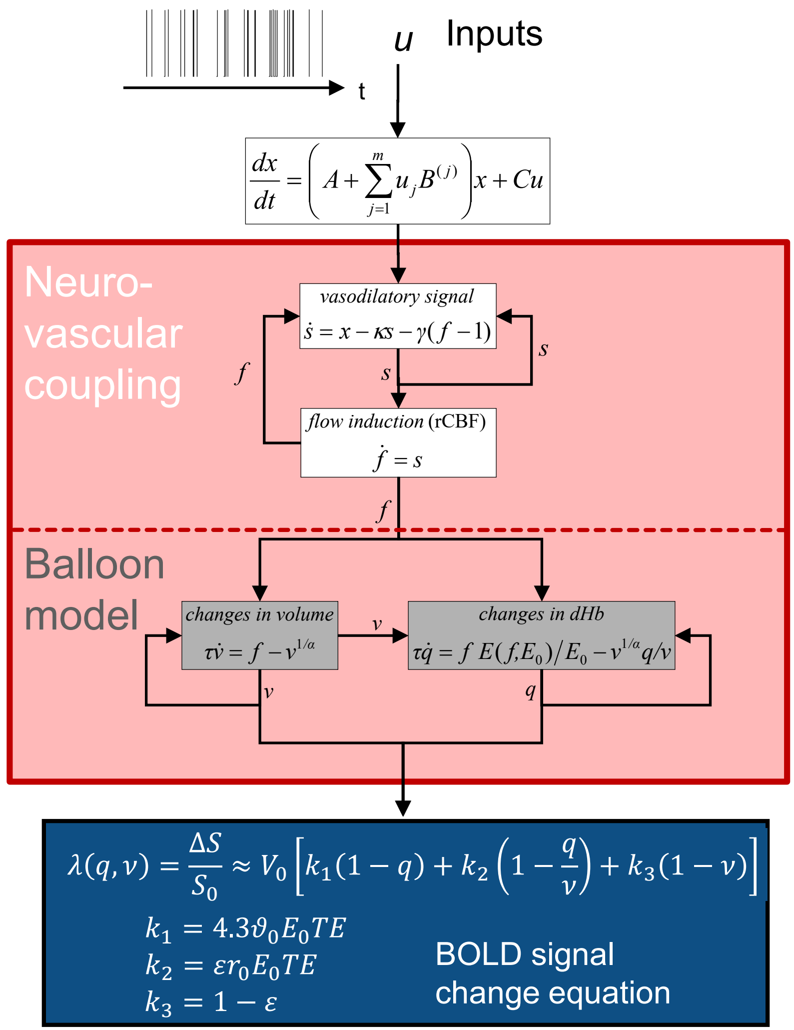
6 parameters:

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

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

Region specific HRF

→ Parameters computed separately for each region



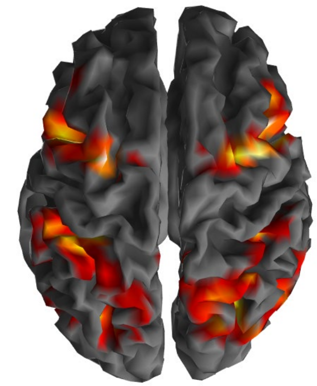
State equation

neural

hemodynamic

Stephan et al., 2007, NeuroImage

DCM for fMRI - Overview



fMRI

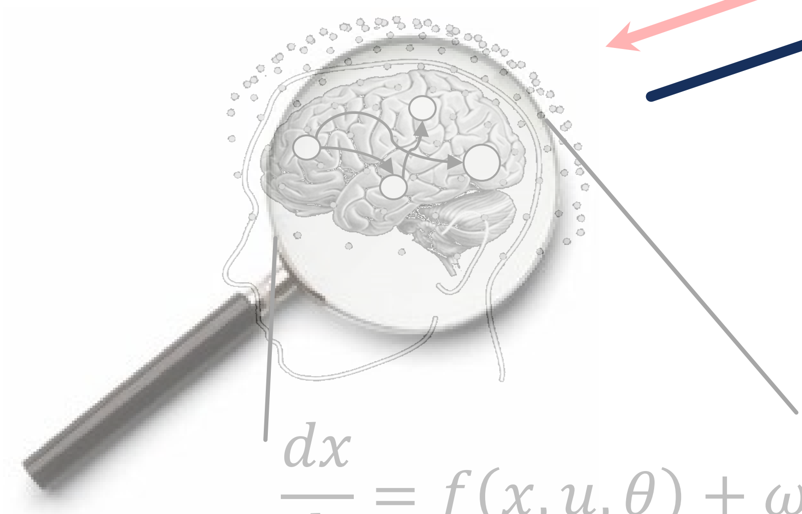
Model inversion:

Estimating neuronal mechanisms

Forward model:

Predicting measured activity

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



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

Neural state equation:

Describing neuronal dynamics

Friston et al., 2003, NeuroImage; David et al., 2006, NeuroImage

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:

$k_1 = 4.3\vartheta_0 E_0 TE$

$k_2 = \varepsilon r_0 E_0 TE$

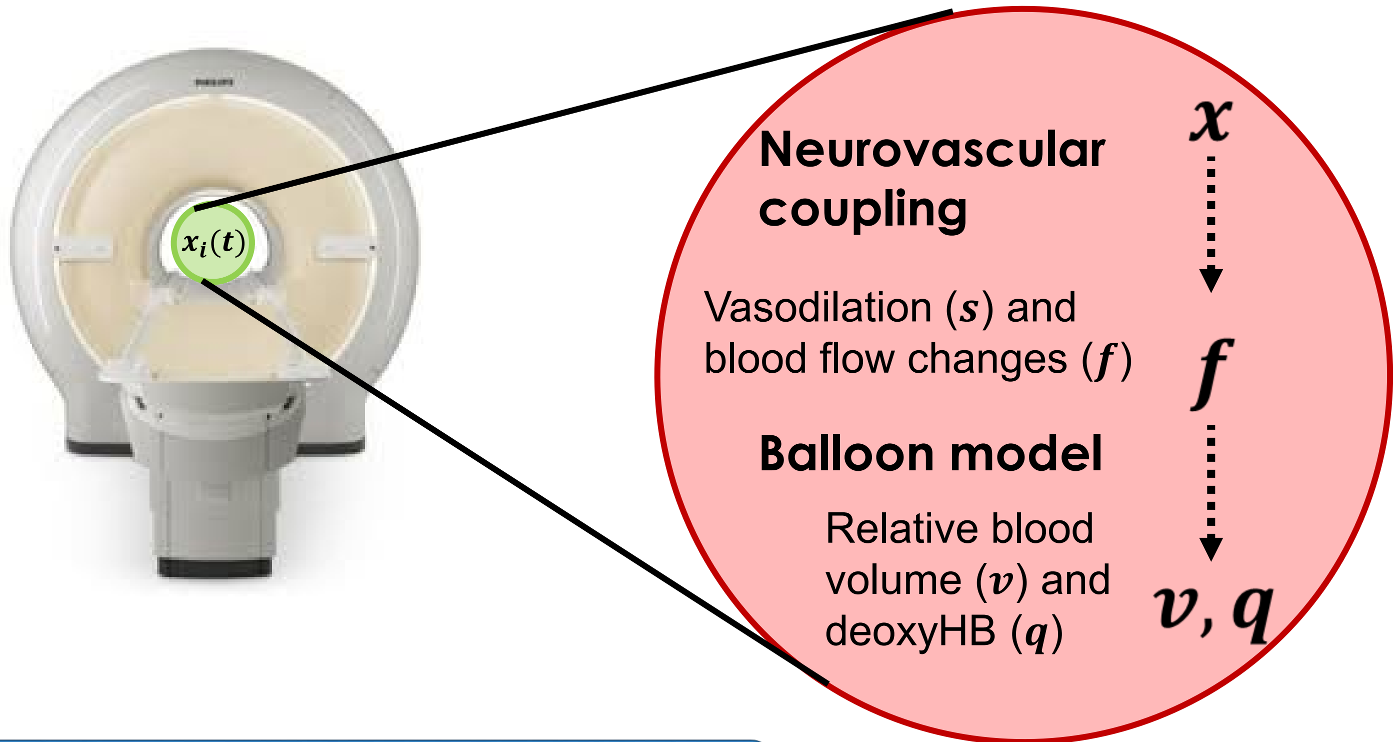
$k_3 = 1 - \varepsilon$

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

At 1.5 Tesla	At 3 Tesla	At 7 Tesla
$\vartheta_0 \approx 40.3\ \mathrm{s}^{-1}$	$\vartheta_0 \approx 80.6\ \mathrm{s}^{-1}$	$\vartheta_0 \approx 188\ \mathrm{s}^{-1}$
$r_0 \approx 25\ \mathrm{s}^{-1}$	$r_0 \approx 110\ \mathrm{s}^{-1}$	$r_0 \approx 340\ \mathrm{s}^{-1}$
$TE \approx 0.04\ s$	$TE \approx 0.035\ s$	$TE \approx 0.025\ s$
$\varepsilon \approx 1.28$	$\varepsilon \approx 0.47$	$\varepsilon \approx 0.026$

Heinzle et al., 2016, NeuroImage

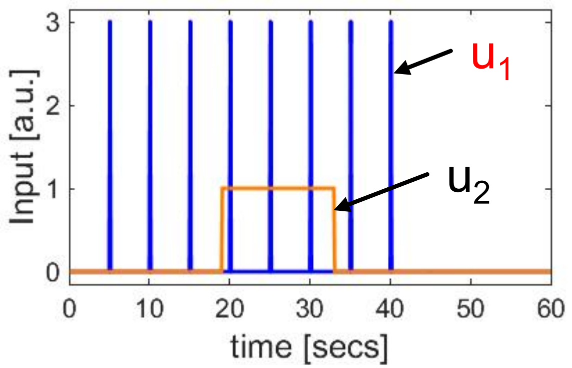
From neural activity to the BOLD signal: Summary



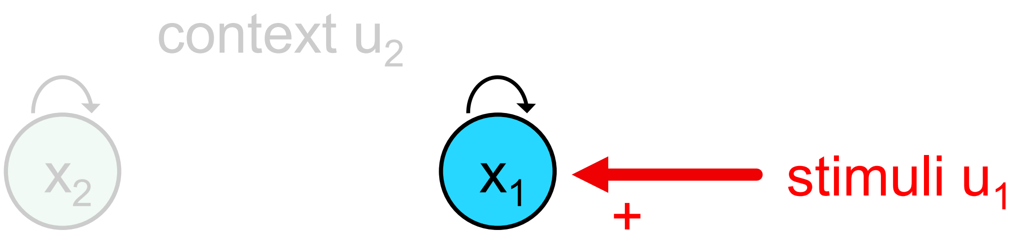
BOLD signal is a **direct function** of v and q

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

Simulation example: What can DCM explain?



Example: single node

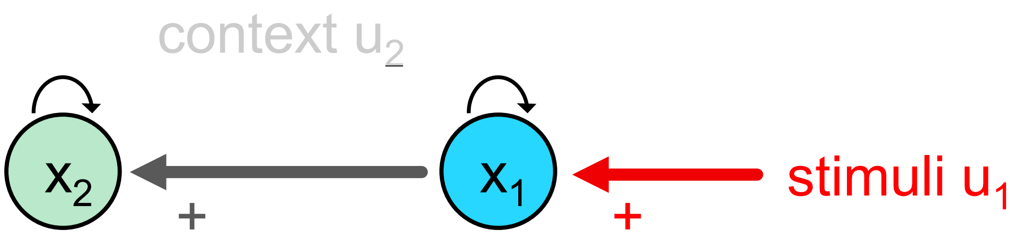


$$\frac{dx}{dt} = Ax + u_2 B^{(2)} x + C u_1$$

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

Simulation example: What can DCM explain?

Example: two connected node



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

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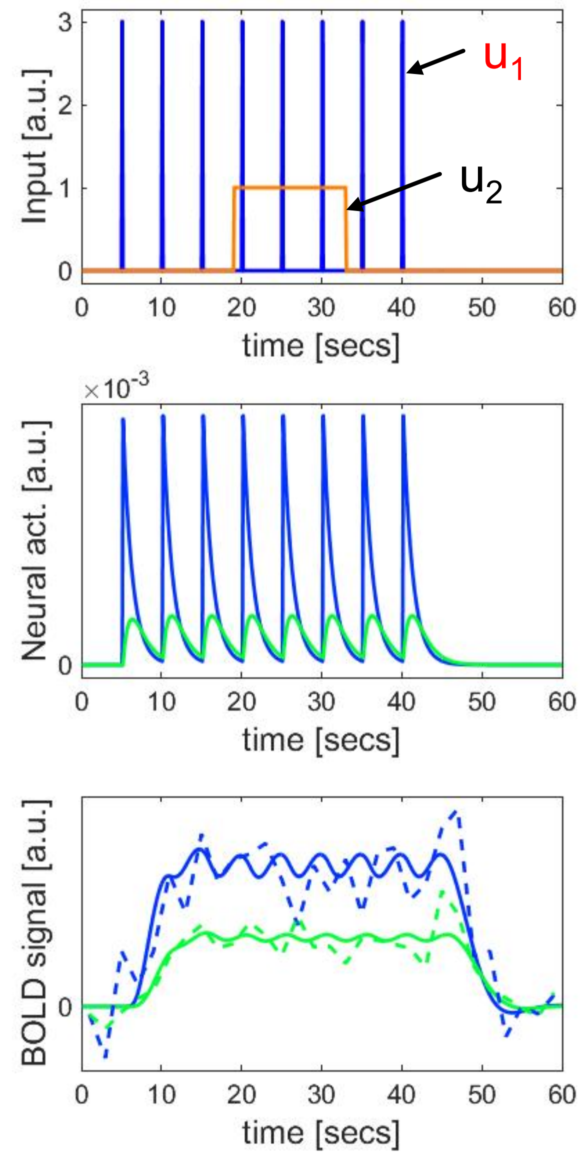
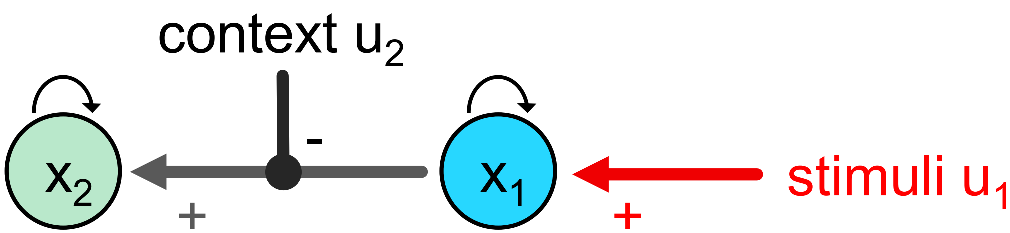


Simulation example: What can DCM explain?

Example: modulation of connection



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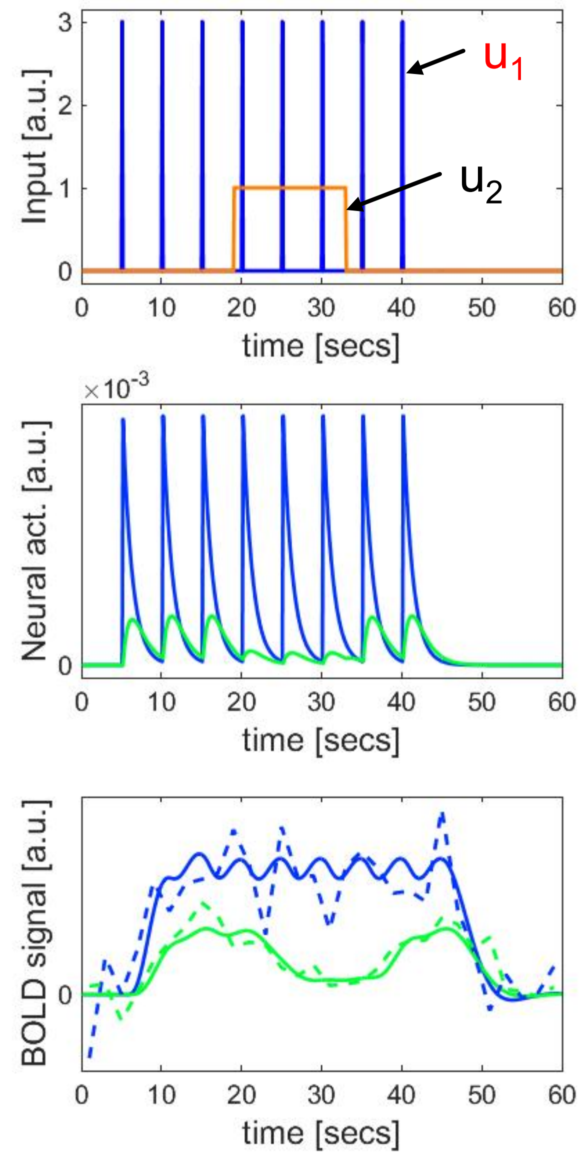
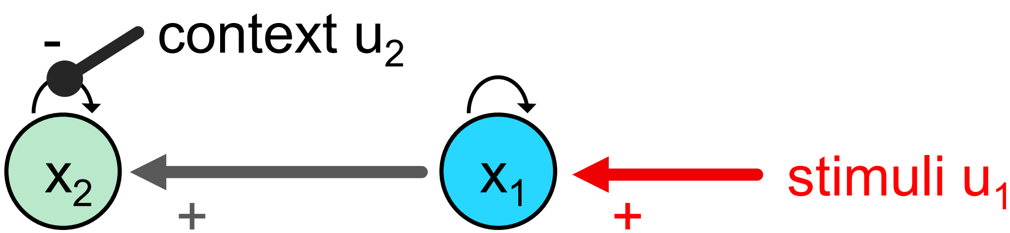


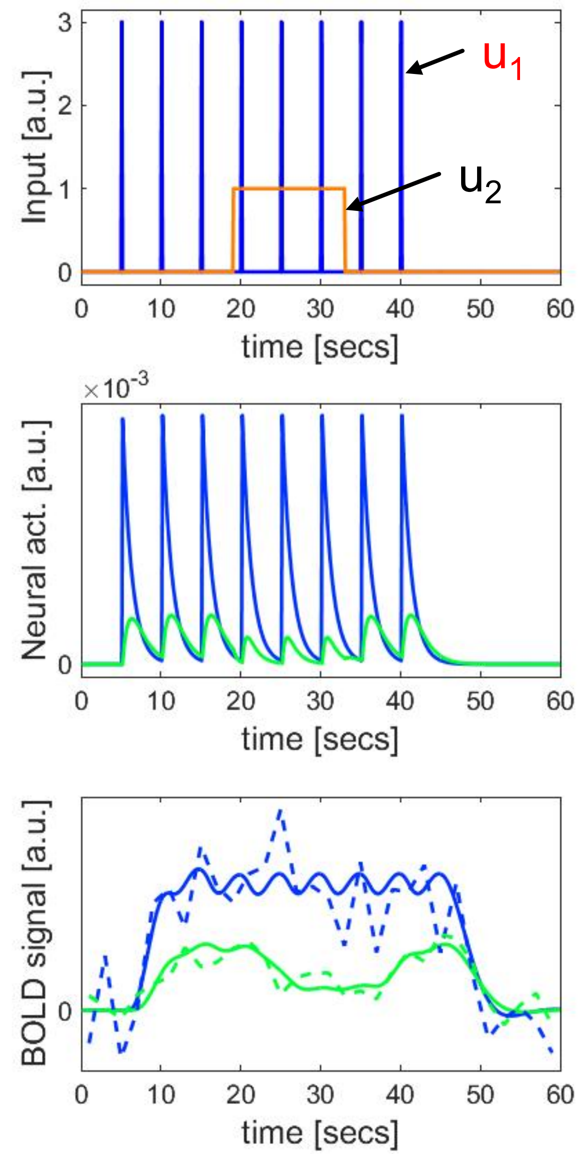
Simulation example: What can DCM explain?

Example: modulation of inhibitory self-connection



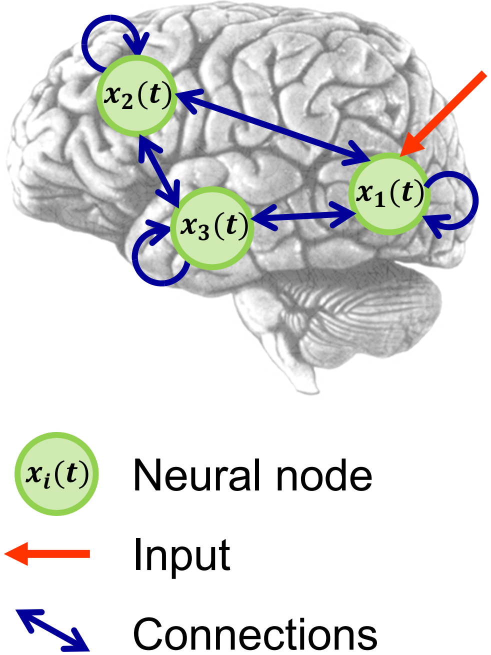
$$\frac{dx}{dt} = Ax + u_2 B^{(2)} x + C u_1$$

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



DCM for fMRI

A simple model of a neural network …



… described as a dynamical system …

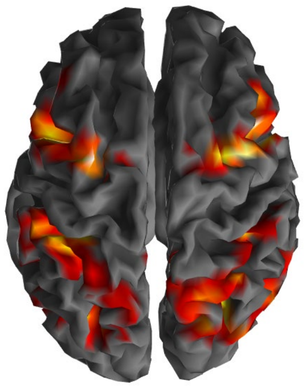
$$\dot{x} = f(x, u, \theta)$$

… causes the data (BOLD signal).

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

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

DCM for fMRI - Overview



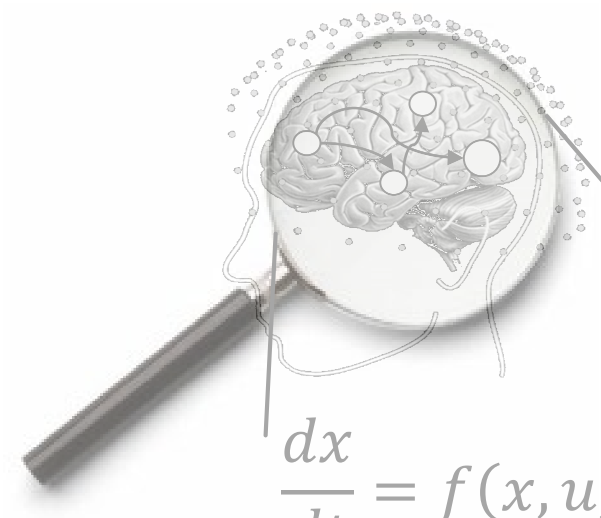
Model inversion:

Estimating neuronal mechanisms

Forward model:

Predicting measured activity

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



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

Neural state equation:

Describing neuronal dynamics

Friston et al., 2003, NeuroImage; David et al., 2006, NeuroImage

Bayes' theorem

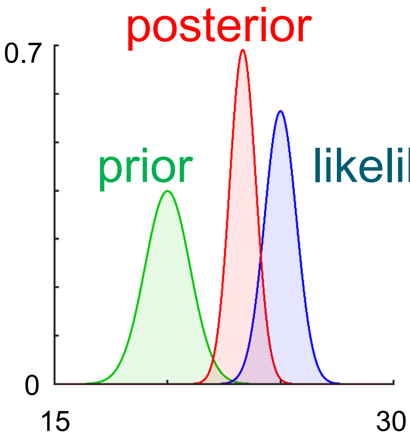
Reverend Thomas Bayes
(1702-1761)

likelihood prior

posterior

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

model evidence



The likelihood function for DCM

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

likelihood

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

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

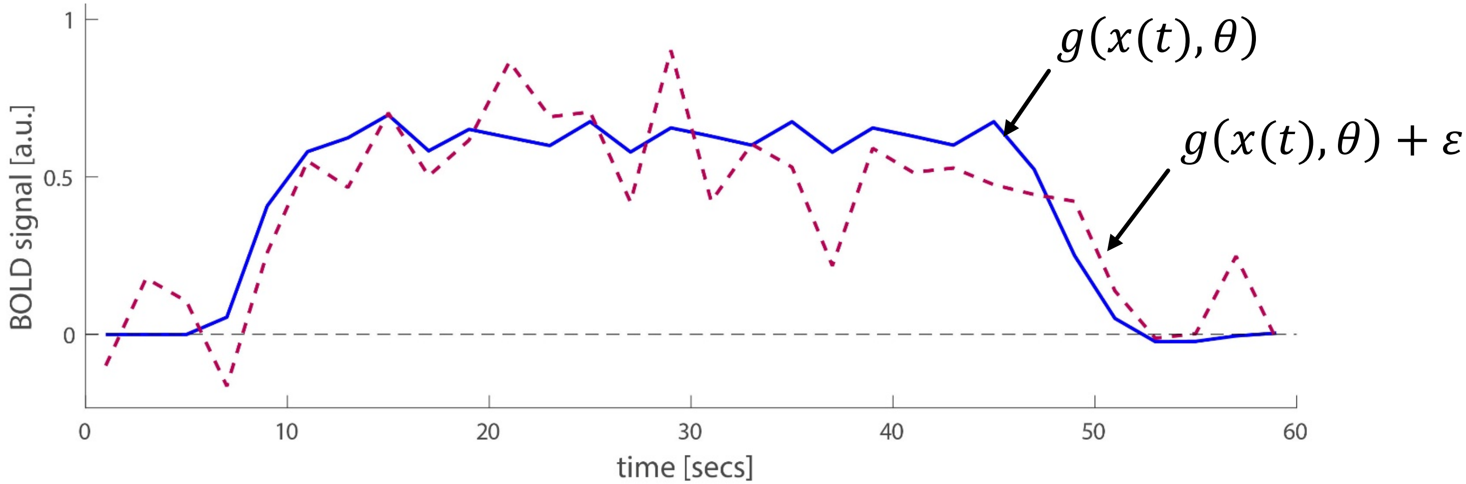
$$\varepsilon \sim \mathcal{N}(0,\sigma^2 I)$$

Data is prediction plus Gaussian noise

The likelihood function for DCM

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

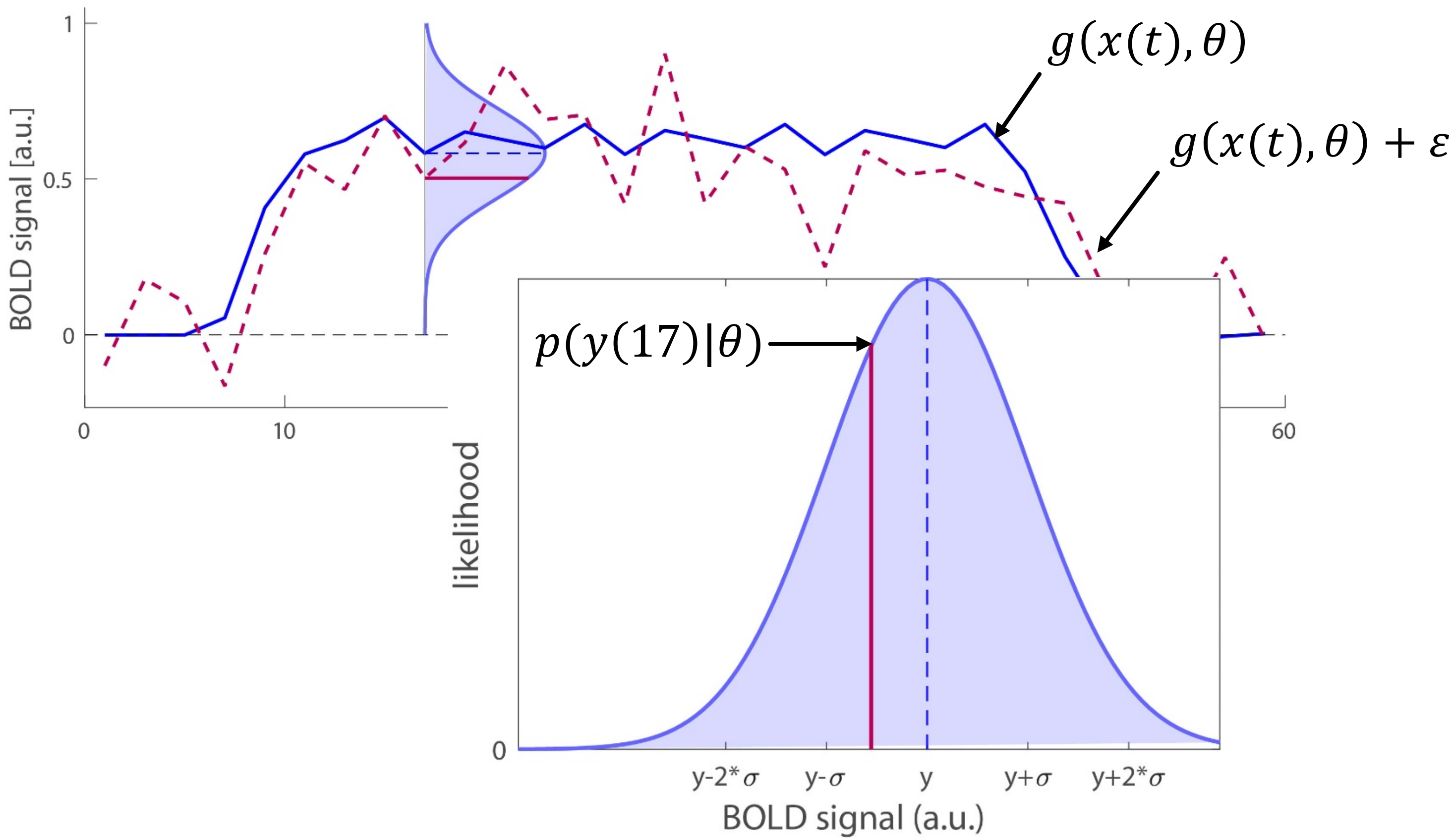
likelihood



The likelihood function for DCM

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

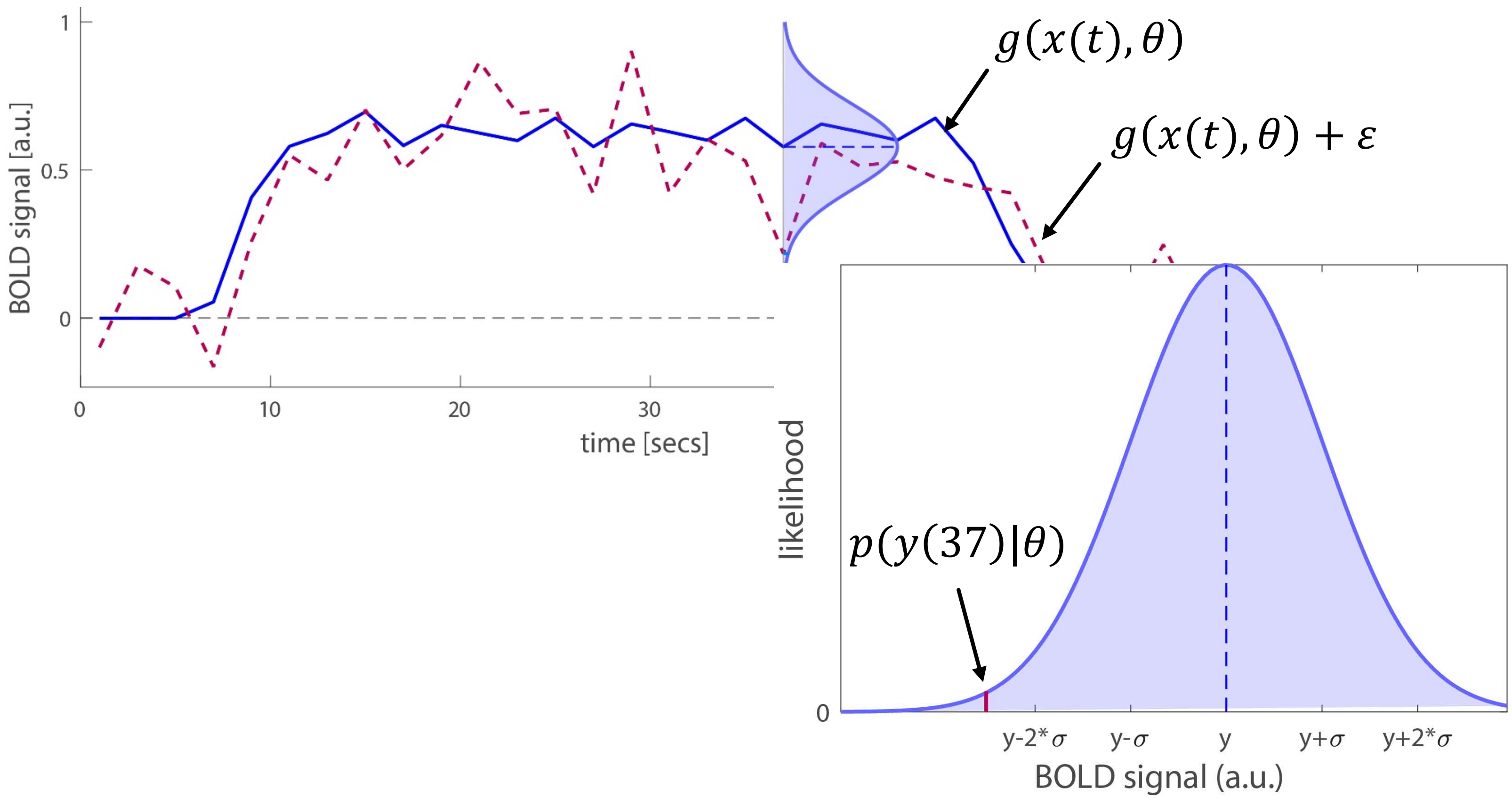
likelihood



The likelihood function for DCM

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

likelihood



Priors

prior

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

Neuronal parameters:

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

Hemodynamic parameters:

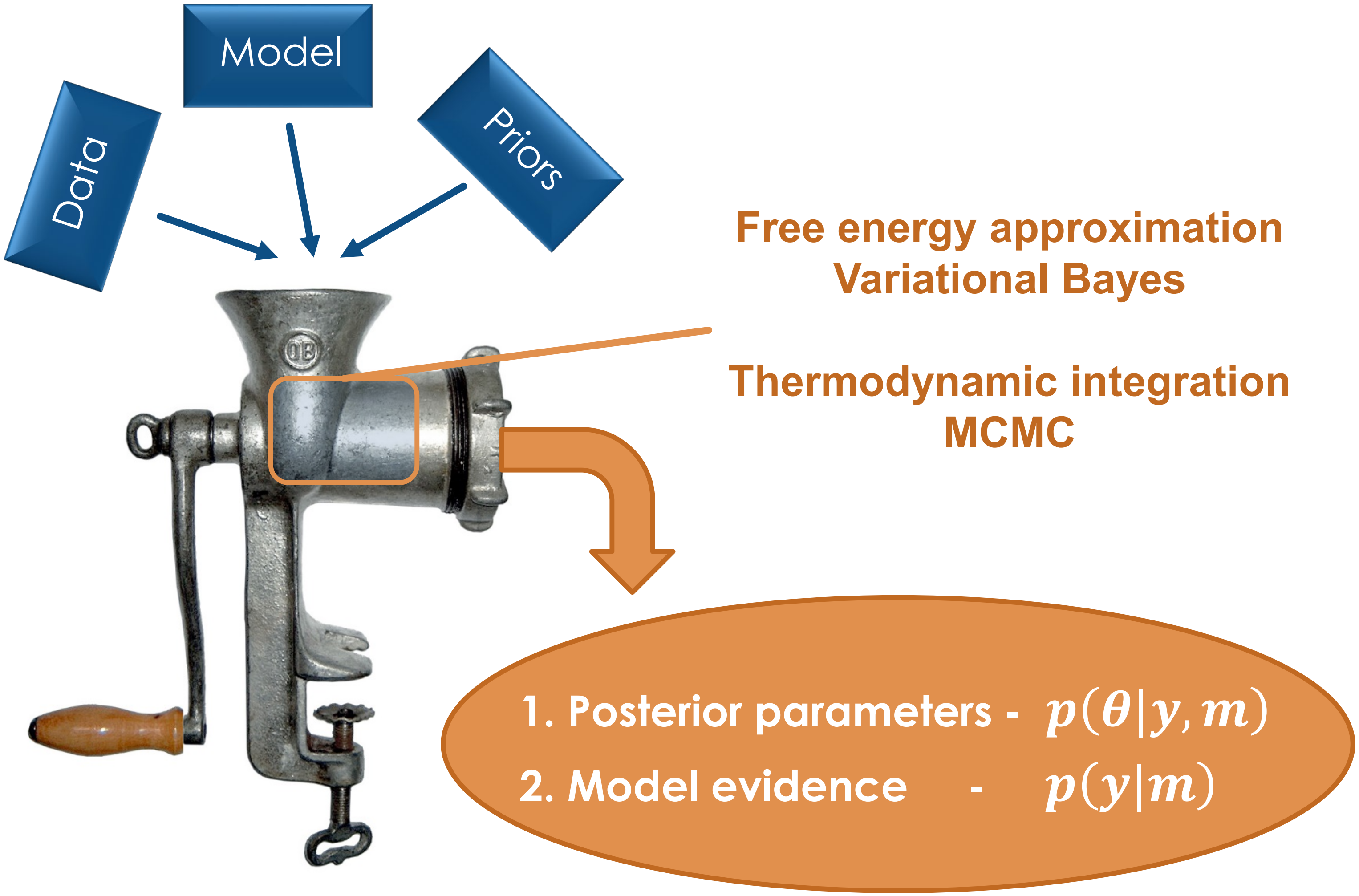
- empirical

Noise prior:

- assume relatively noisy data

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

Model estimation: running the machinery



Inversion – variational Free Energy approximation to model evidence

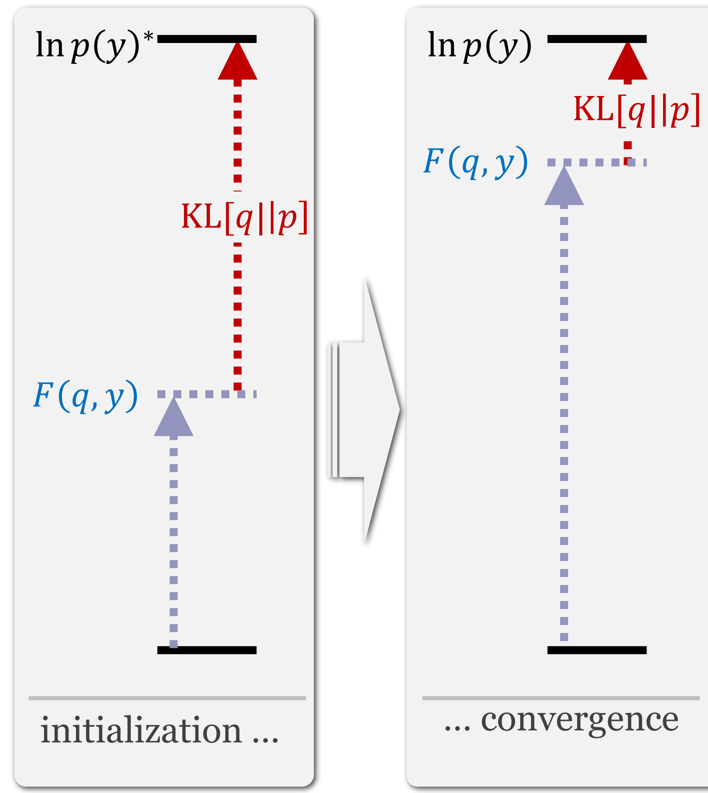
model evidence

$$\ln p(y) = \underbrace{\mathrm{KL}[q||p]} + \underbrace{F(q,y)}$$

divergence
≥ 0
(unknown)

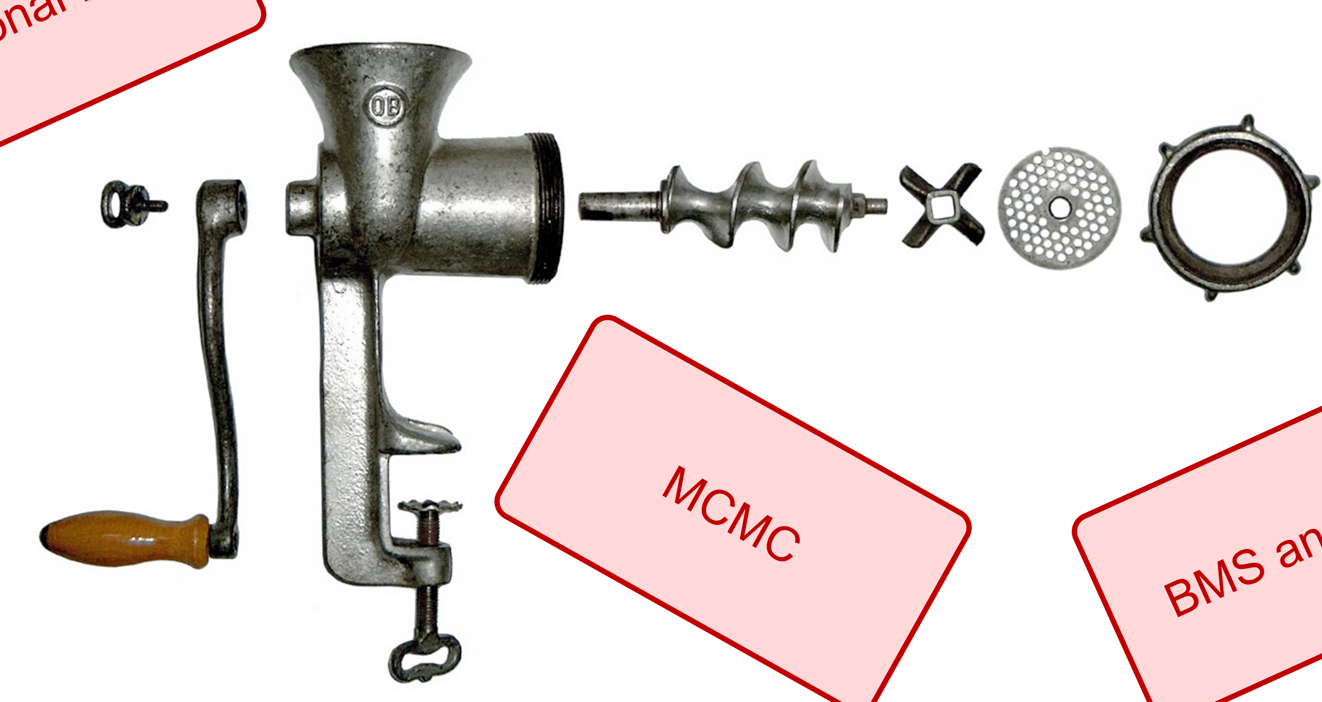
neg. free energy
(easy to evaluate for a given q)

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



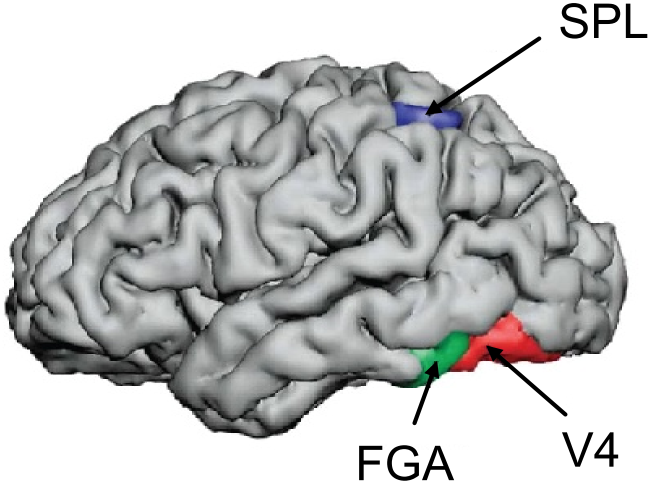
Bishop, 2006; Friston et al., 2007, Neuroimage

Model estimation: running the machinery



Example: Model Selection

- 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)

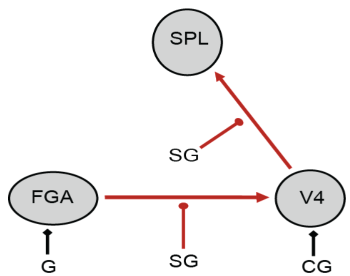


Hubbard, 2007

Bottom-up or Top-down "cross-activation"?

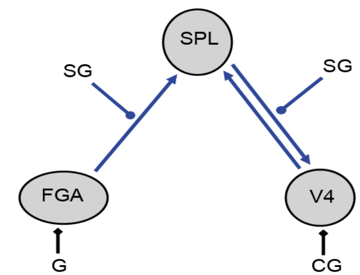
Bottom-up

(*Ramachandran & Hubbard, 2001*)



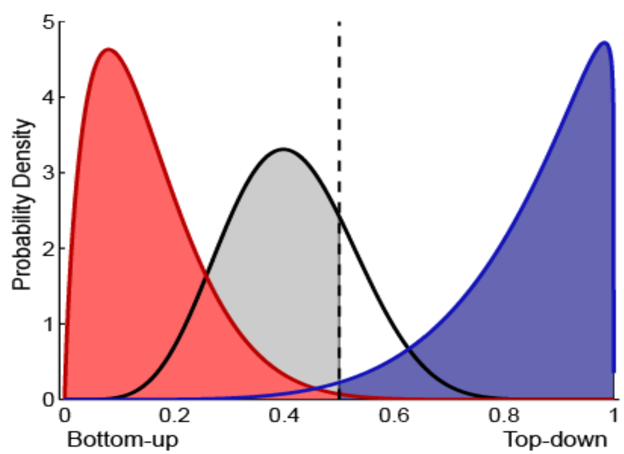
Top-down

(*Grossenbacher & Lovelace, 2001*)

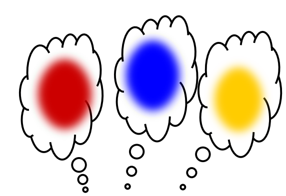


Projectors

ABC



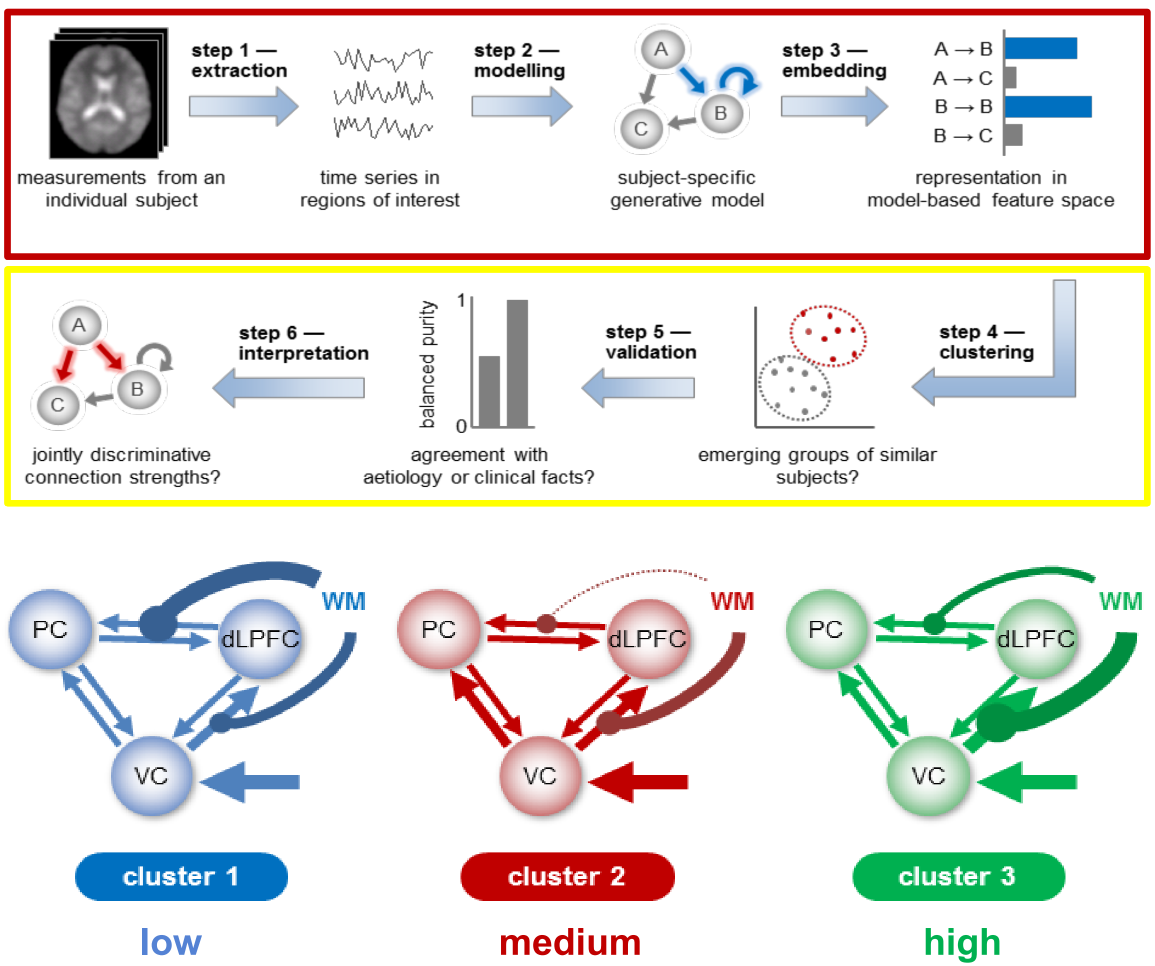
Associators



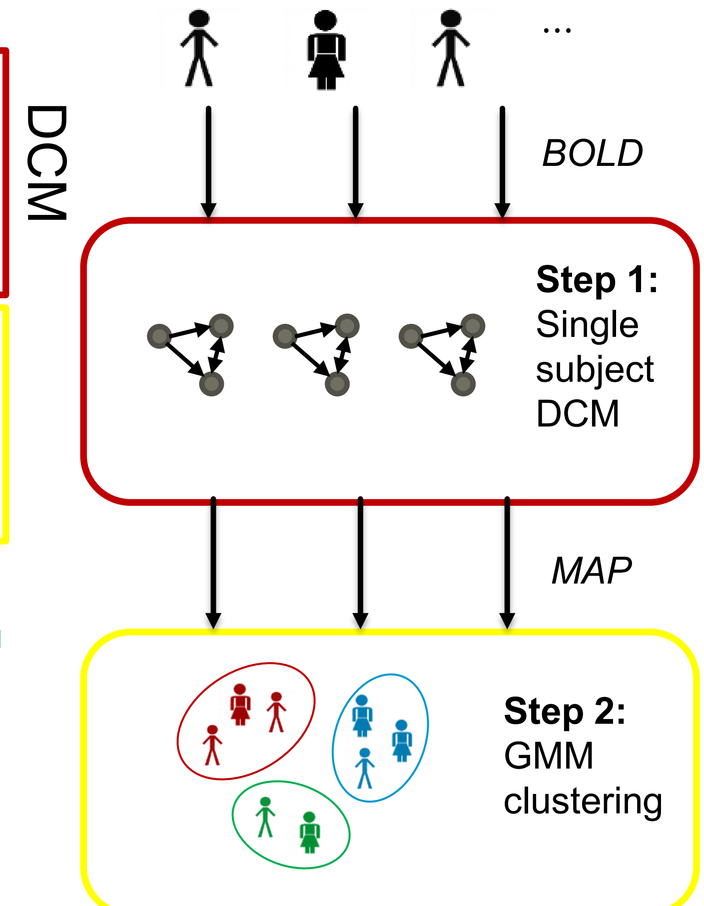
ABC

Van Leeuwen et al., JNeurosci, 2011

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



negative symptoms (NS) subscale of the PANSS score



Brodersen et al., NeuroImage: Clinical, 2014

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

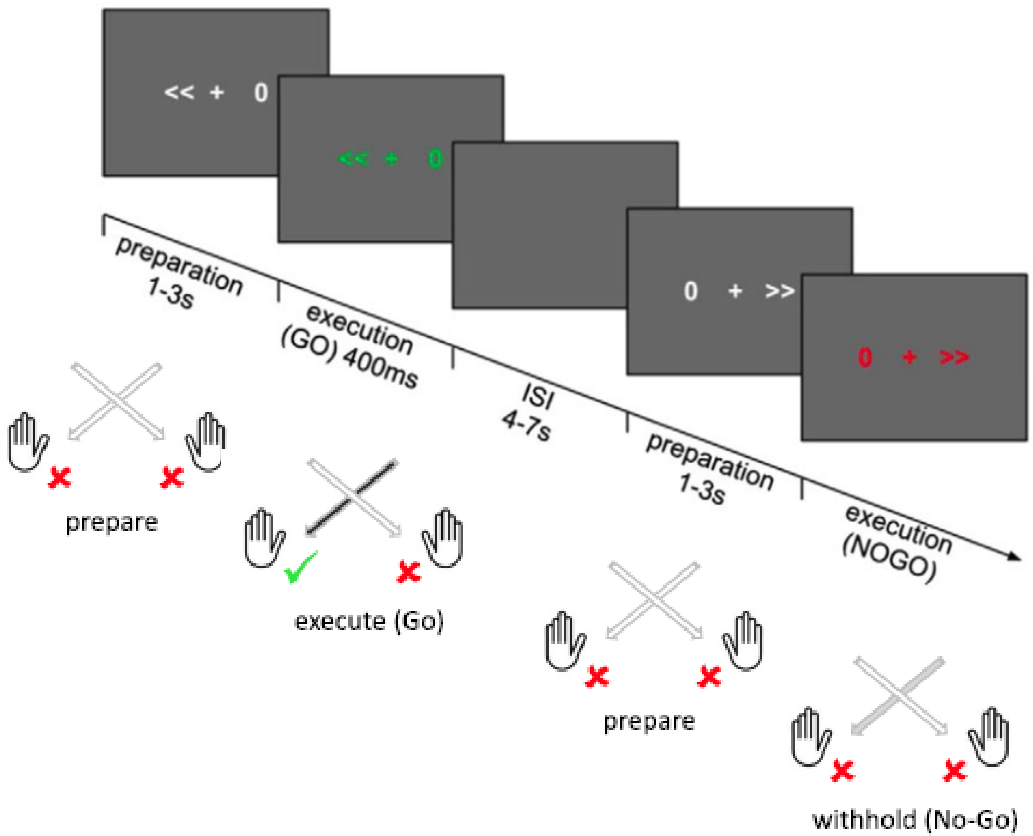
→ Generative embedding

... and of course many more!

Limitations

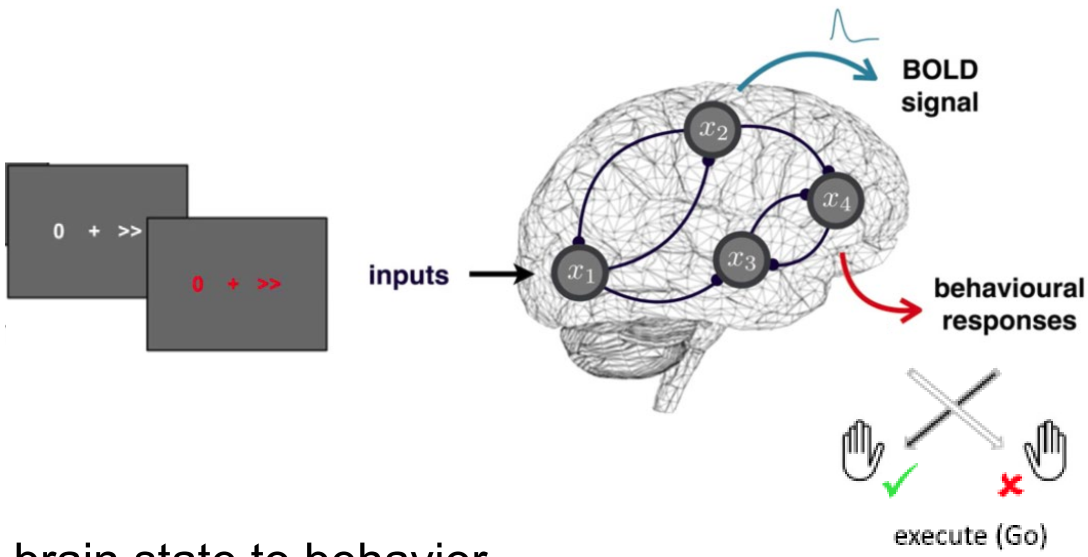
- DCMs only have inputs, no outputs
  - Limits the study of behavioral paradigms
- Local minima
  - Variational approximation can get stuck in local minima of free energy
- Size of networks
  - Standard inversion too slow for large networks (>10 nodes).
- Regularization through fixed priors:
  - Regularization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

Behavioral DCM – A step towards a neurocomputational model

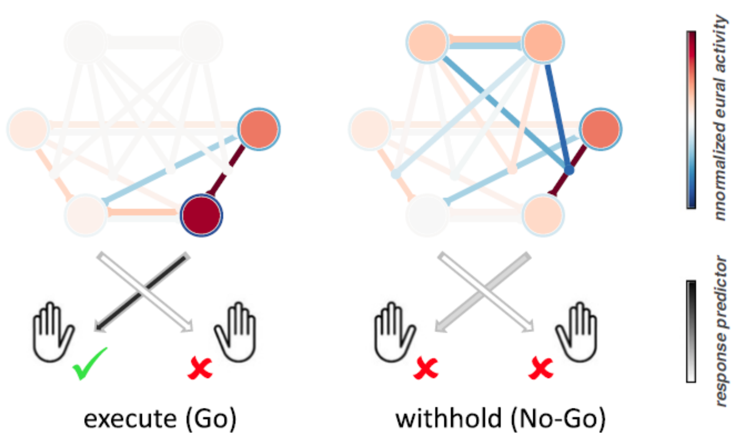


Rigoux and Daunizeau, Neuroimage, 2015

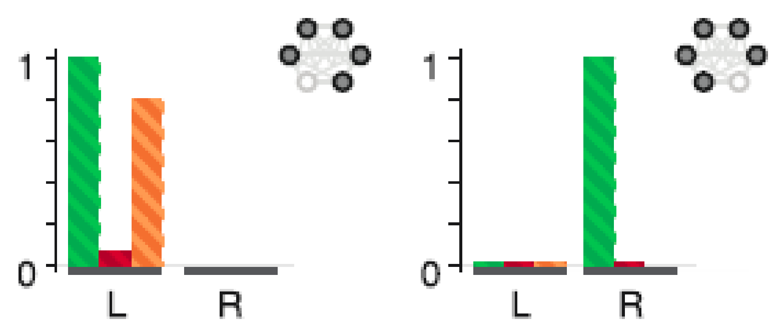
Behavioral DCM – A step towards a neurocomputational model



Mapping brain state to behavior

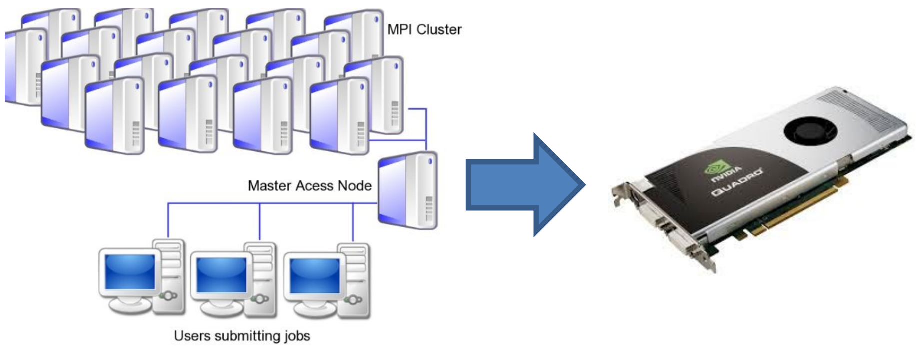


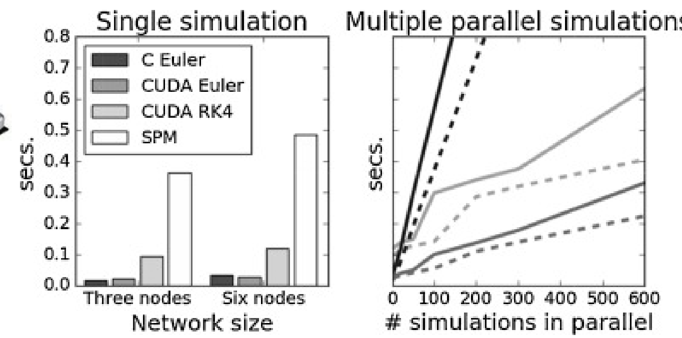
Lesion simulations



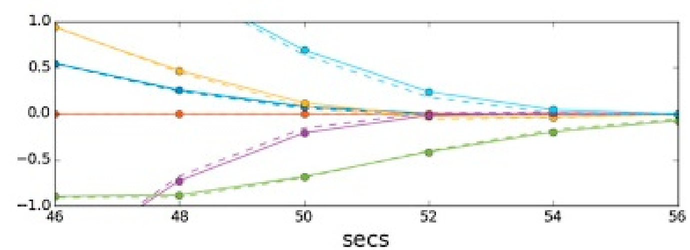
Rigoux and Daunizeau, Neuroimage, 2015

MCMC inversion of DCMs: Massively parallel DCM - mpdcm





$$
\begin{rcases}
\dot{x} = f(x, u_1, \theta_1) \\
\dot{x} = f(x, u_2, \theta_2) \\
\vdots \\
\dot{x} = f(x, u_1, \theta_1)
\end{rcases}
\text{mpdcm\_integrate(dcms)}
\begin{cases}
y_1 \\
y_2 \\
\vdots \\
y_3
\end{cases}
$$



- Fast inversion of DCMs
- MCMC based inversion possible

→ **Thermodynamic Integration** (alternative to Free Energy)

Aponte et al. , J. Neurosci. Meth., 2015

Recent additions to DCM for fMRI

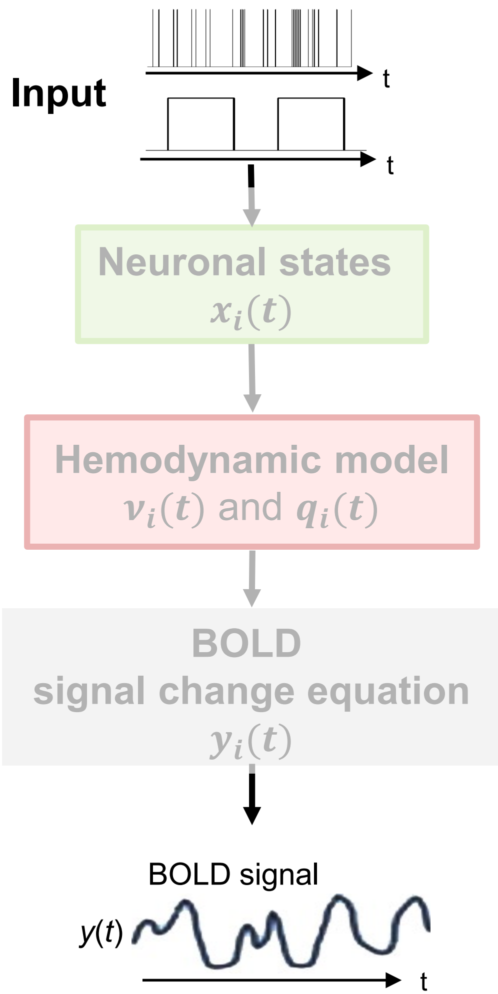
- Massively parallel dynamic causal modelling
  - ➢ mpdcm Aponte et al., J Neuroscience Methods, 2016
- Regression dynamic causal modelling
  - ➢ rDCM Frässle et al., Neuroimage, 2017
- Hierarchical unsupervised generative embedding
  - ➢ HUGE Yu et al., Neuroimage, 2019

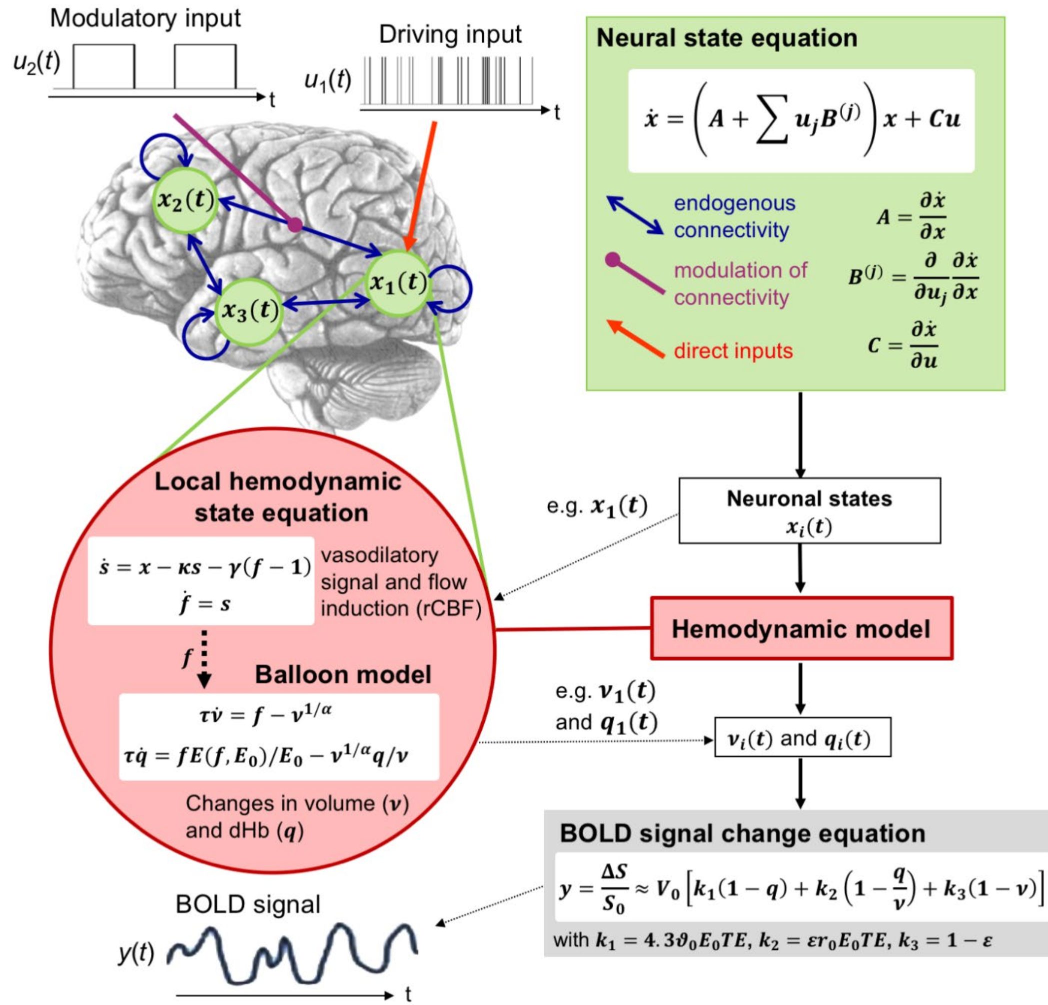
Models of Connectivity: Advanced
→ Today, 10:50
→ Stefan Frässle and Yu Yao

Available in TAPAS:
www.translationalneuromodeling.org/tapas

Summary – Generative model

Summary – Generative Model





Stephan et al., 2015, Neuron

Summary - Bayesian System Identification

$$u(t)$$

Neural (and hemo-) dynamics

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

Observer function

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

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

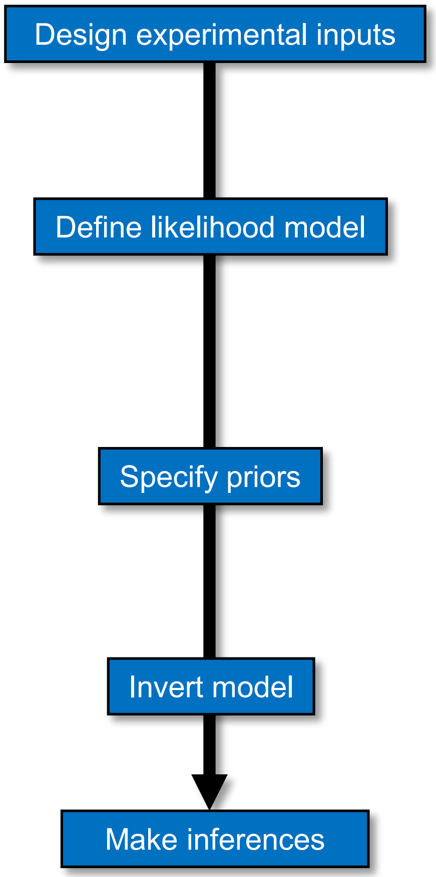
$$p(\theta, m) = N(\mu_\theta, \Sigma_\theta)$$

Inference on model structure

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

Inference on parameters

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



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

and Jean Daunizeau for many of the slides!

List with suggested DCM literature in Appendix of this presentation!

DCM literature (1)

- **Aponte EA, Raman S, Sengupta B, Penny WD, Stephan KE, Heinzle J (2016). mpdcm: A Toolbox for Massively Parallel Dynamic Causal Modeling. Journal of Neuroscience Methods 257: 7-16.**
- Brodersen KH, Schofield TM, Leff AP, Ong CS, Lomakina EI, Buhmann JM, Stephan KE (2011) Generative embedding for model-based classification of fMRI data. PLoS Computational Biology 7: e1002079.
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- Friston KJ, Mattout J, Trujill-Barreto, Ashburner J, Penny W (2007) Variational free energy and the Laplace approximation. NeuroImage 34: 220-234.
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- Friston KJ, Kahan J, Biswal B, Razi A (2014) A DCM for resting state fMRI. Neuroimage 94:396-407.
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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.**

DCM literature (2)

- Kiebel SJ, Kloppel S, Weiskopf N, Friston KJ (2007) Dynamic causal modeling: a generative model of slice timing in fMRI. NeuroImage 34:1487-1496.
- Li B, Daunizeau J, Stephan KE, Penny WD, Friston KJ (2011). Stochastic DCM and generalised filtering. NeuroImage 58: 442-457
- Marreiros AC, Kiebel SJ, Friston KJ (2008) Dynamic causal modelling for fMRI: a two-state model. NeuroImage 39:269-278.
- Penny WD, Stephan KE, Mechelli A, Friston KJ (2004a) Comparing dynamic causal models. NeuroImage 22:1157-1172.
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- Penny WD, Stephan KE, Daunizeau J, Joao M, Friston K, Schofield T, Leff AP (2010) Comparing Families of Dynamic Causal Models. PLoS Computational Biology 6: e1000709.
- Penny WD (2012) Comparing dynamic causal models using AIC, BIC and free energy. Neuroimage 59: 319-330
- **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.**
- Rigoux L, Stephan KE, Friston KJ, Daunizeau J (2014). Bayesian model selection for group studies – revisited. NeuroImage 84: 971-985.
- **Rigoux L and Daunizeau J (2015). Dynamic causal modelling of brain–behaviour relationships. NeuroImage 117:202-221**
- Stephan KE, Harrison LM, Penny WD, Friston KJ (2004) Biophysical models of fMRI responses. Curr Opin Neurobiol 14:629-635.
- Stephan KE, Weiskopf N, Drysdale PM, Robinson PA, Friston KJ (2007) Comparing hemodynamic models with DCM. NeuroImage 38:387-401.
- Stephan KE, Harrison LM, Kiebel SJ, David O, Penny WD, Friston KJ (2007) Dynamic causal models of neural system dynamics: current state and future extensions. J Biosci 32:129-144.

DCM literature (3)

- Stephan KE, Weiskopf N, Drysdale PM, Robinson PA, Friston KJ (2007) Comparing hemodynamic models with DCM. NeuroImage 38:387-401.
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- **Yao Y, Raman SS, Schiek M, Leff A, Frässle S, Stephan KE (2018). Variational Bayesian Inversion for Hierarchical Unsupervised Generative Embedding (HUGE). NeuroImage, 179: 604-619**