

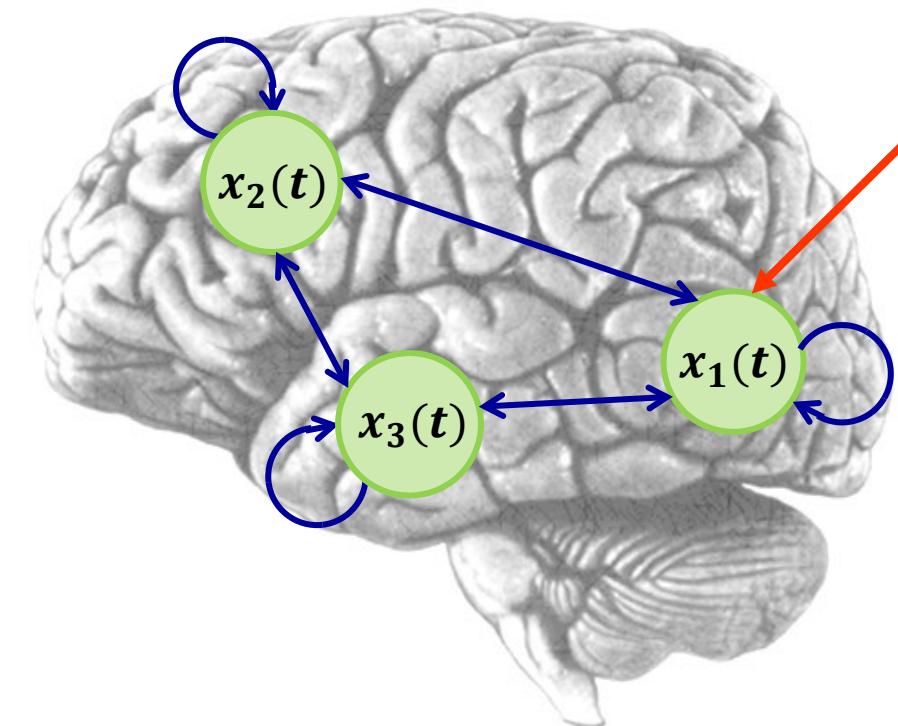
# Modeling connectivity: Dynamic Causal Modeling for fMRI



**Jakob Heinze**

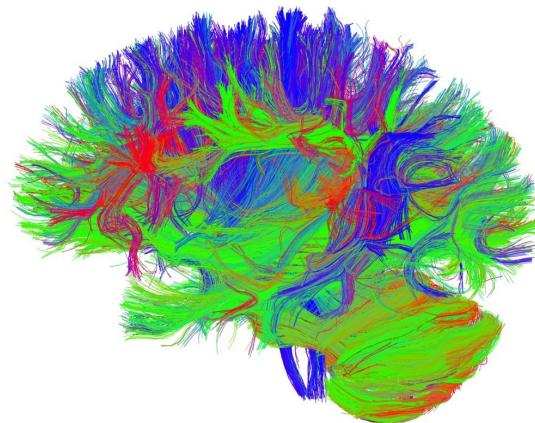
Translational Neuromodeling Unit (TNU),  
Institute for Biomedical Engineering  
University and ETH Zürich

CP Course 2025, Zürich, Switzerland



# Structural, functional & effective connectivity

anatomical/structural

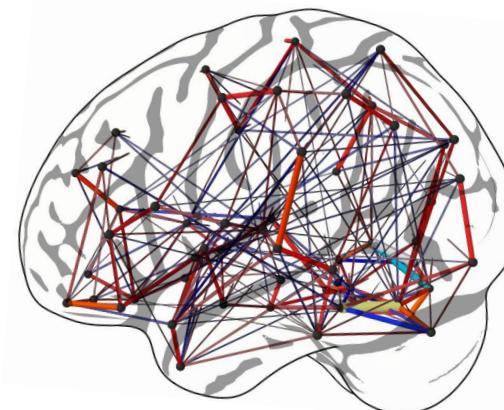


<https://optimalsurgerytle.weebly.com/imaging-and-dataset.html>

- presence of physical connections  
→ DWI, tractography, tracer studies (animals)

Context - independent

functional

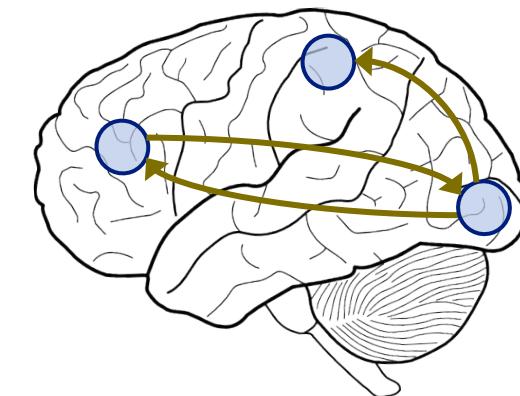


[https://team.inria.fr/parietal/files/2013/02/pc\\_dag.jpg](https://team.inria.fr/parietal/files/2013/02/pc_dag.jpg)

- statistical dependency between regional time series  
→ correlations, ICA

Mechanism - free

effective



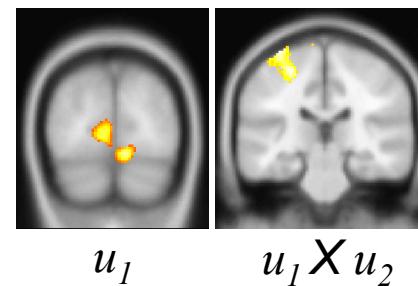
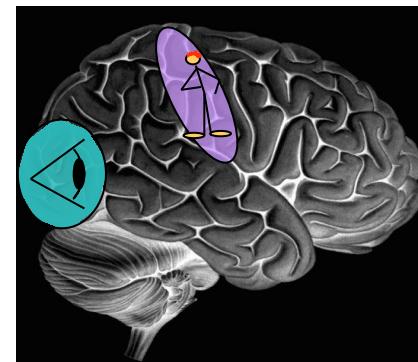
<http://www.clker.com/cliparts/e/5/Q/i/e/o/brain-line-drawing-md.png>

- direct influences between neuronal populations  
→ DCM

Mechanistic

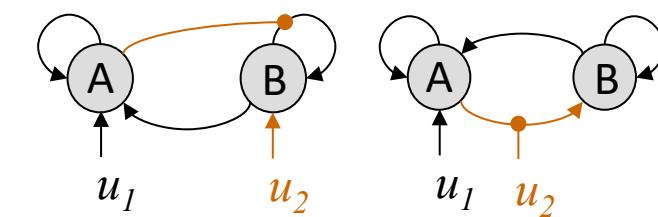
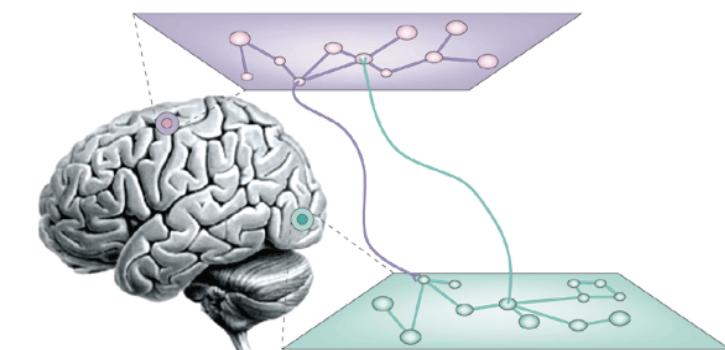
## Specialisation vs. Integration

### Functional Specialisation



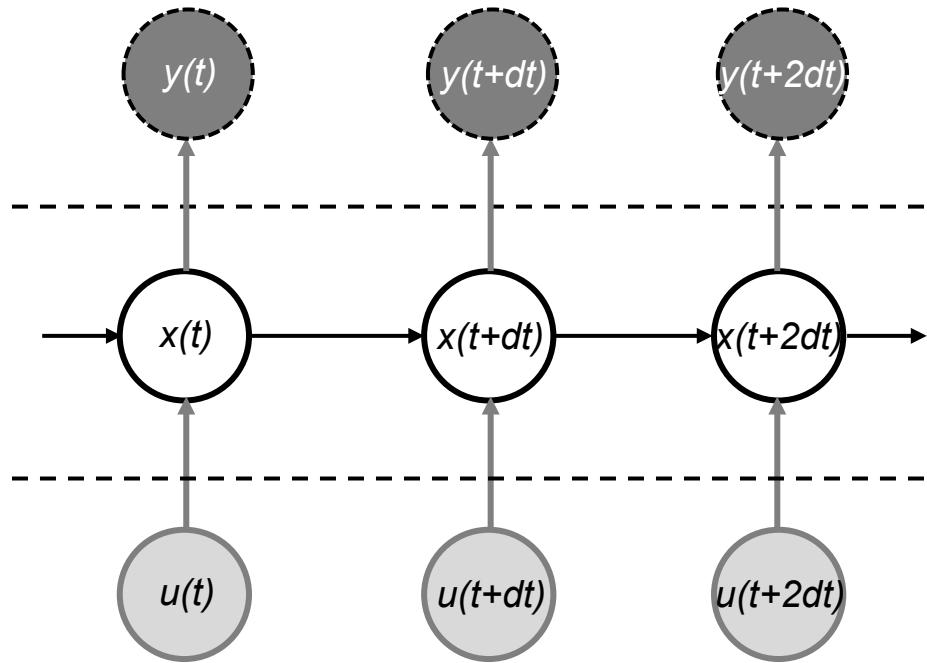
«**Where, in the brain, did my experimental manipulation have an effect?**»

### Functional Integration



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

## A reminder – generative models



Observed data (fMRI)

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

Hidden states (Brain activity)

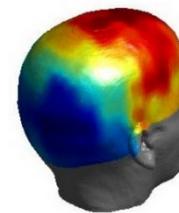
$$\frac{dx}{dt} = f(x, u, \theta_f) + \omega$$

Inputs (Exp. manipulations)

$$u(t)$$

## Dynamic causal modelling

EEG,  
MEG



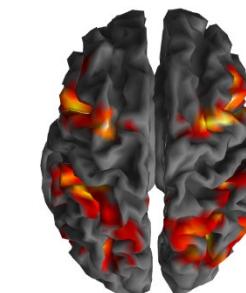
**Forward model:**  
Predicting  
measured activity

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

DCM for EEG  
→ later today

**Model inversion:**  
Estimating  
neuronal  
mechanisms

fMRI



**State equation:**  
Describing neuronal  
dynamics (and  
hemodynamics)



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

# Dynamic causal modelling



ACADEMIC  
PRESS

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)



NeuroImage 19 (2003) 1273–1302

---

NeuroImage

---

[www.elsevier.com/locate/ynimng](http://www.elsevier.com/locate/ynimng)

---

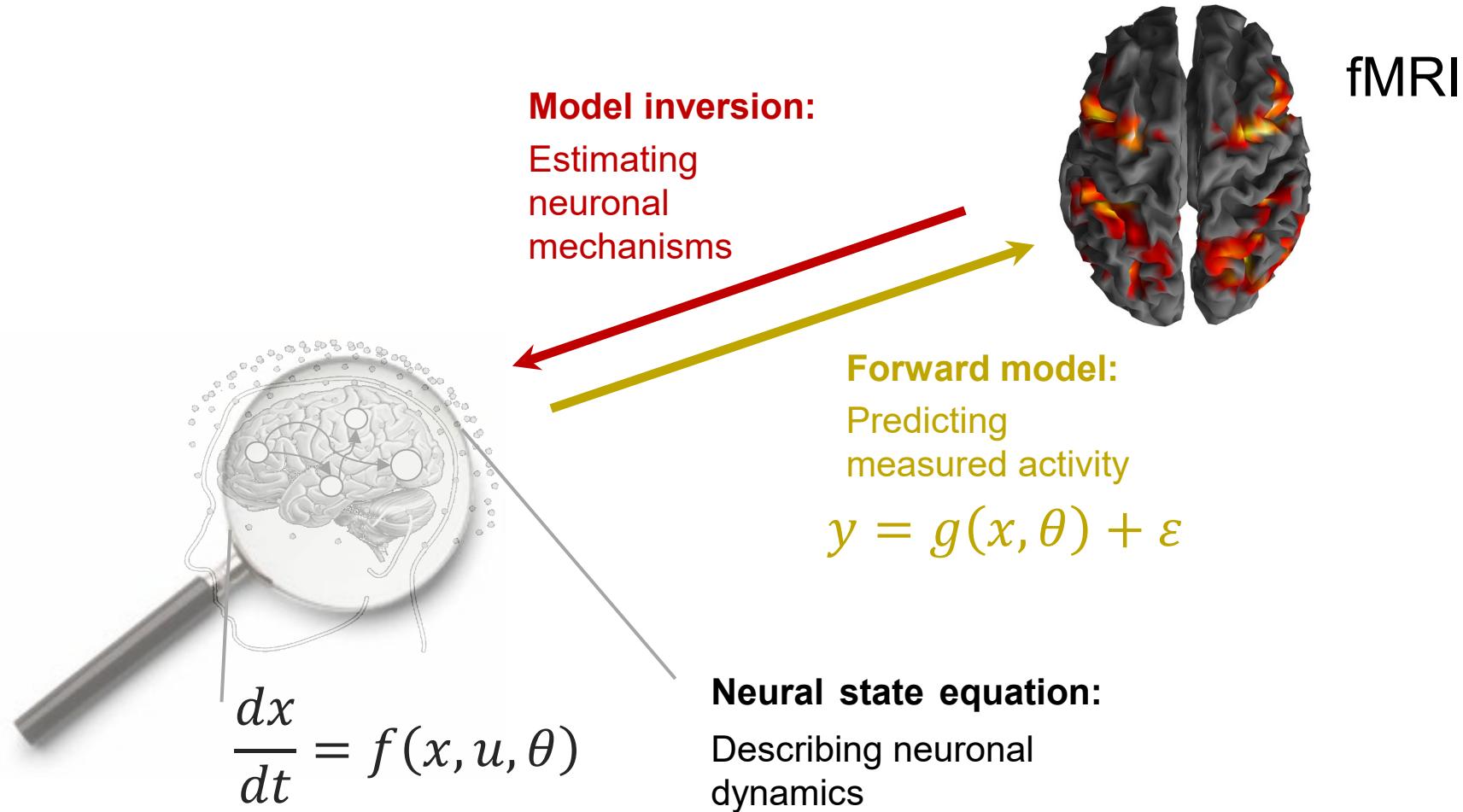
## Dynamic causal modelling

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

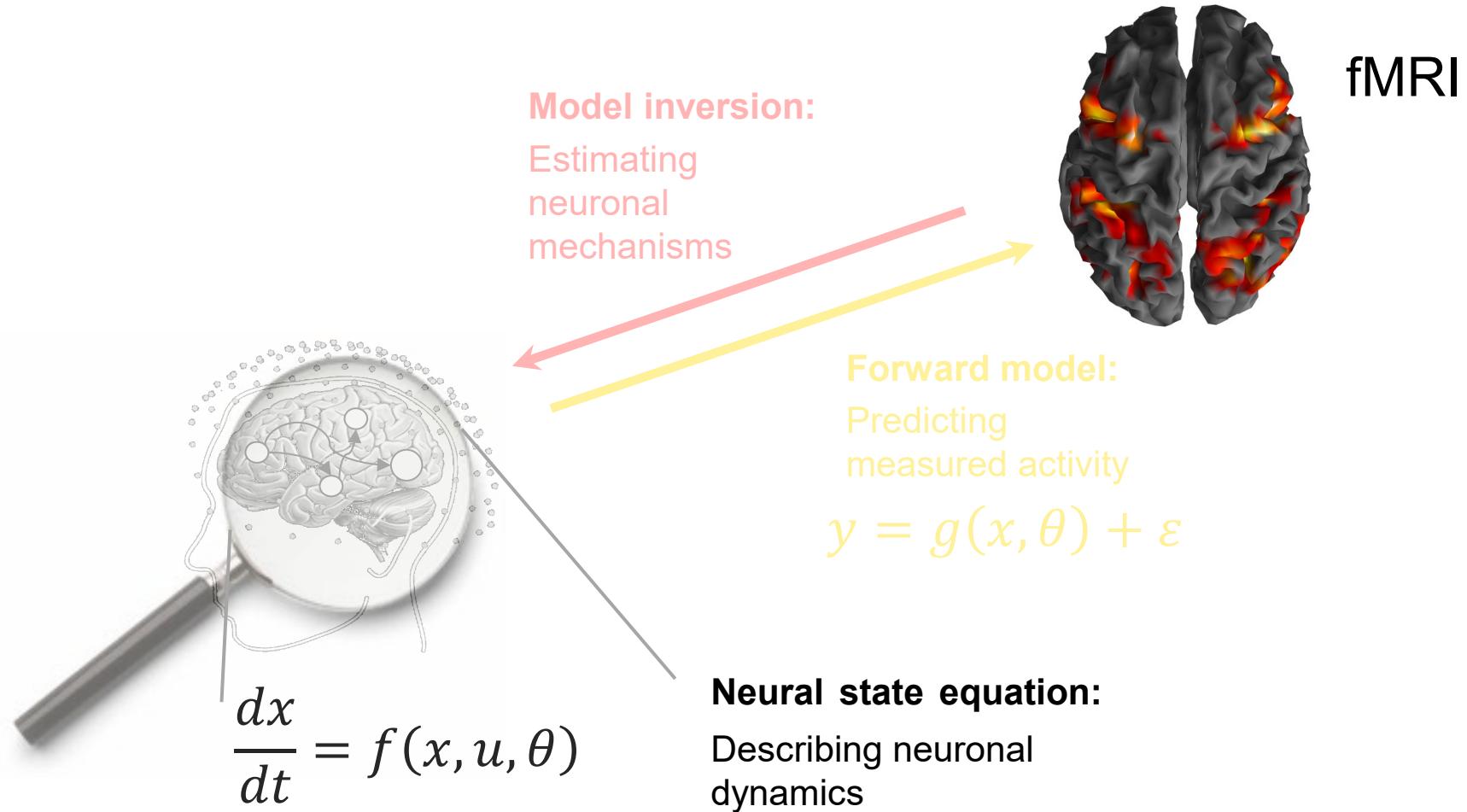
*The Wellcome Department of Imaging Neuroscience, Institute of Neurology, Queen Square, London WC1N 3BG, UK*

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

## DCM for fMRI - overview



## DCM for fMRI - overview





University of  
Zurich

ETH zürich



Translational Neuromodeling Unit

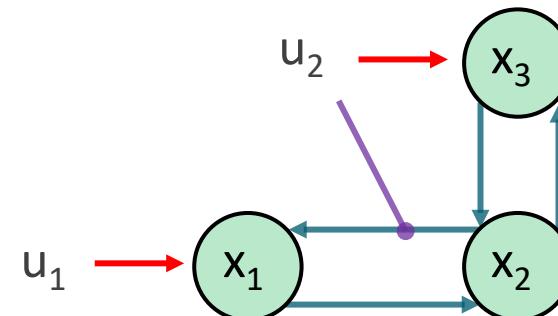
## Neuronal state equations

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

## Neuronal state equations

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

A    C    B



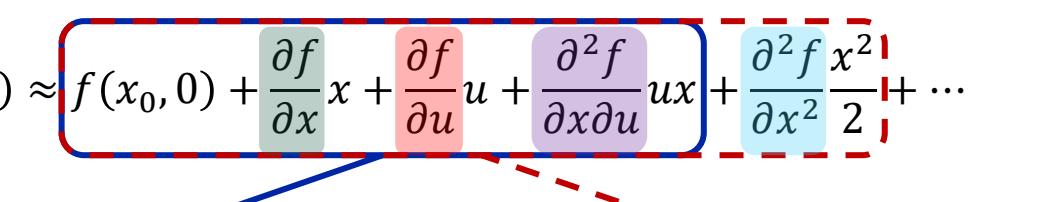
## Neuronal state equations

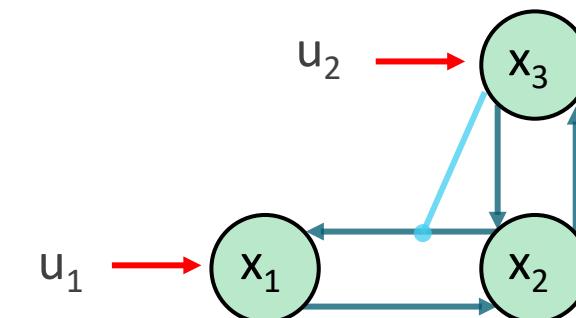
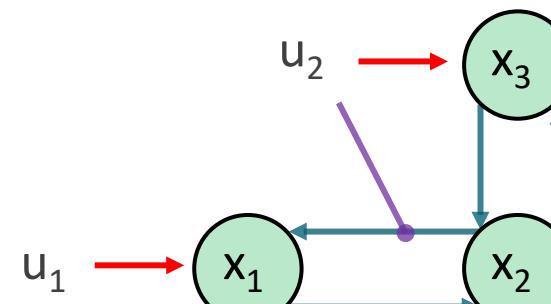
$$\frac{dx}{dt} = f(x, u) \approx f(x_0, 0) + \frac{\partial f}{\partial x} x + \frac{\partial f}{\partial u} u + \frac{\partial^2 f}{\partial x \partial u} ux + \frac{\partial^2 f}{\partial x^2} \frac{x^2}{2} + \dots$$

A    C    B    D

bilinear model

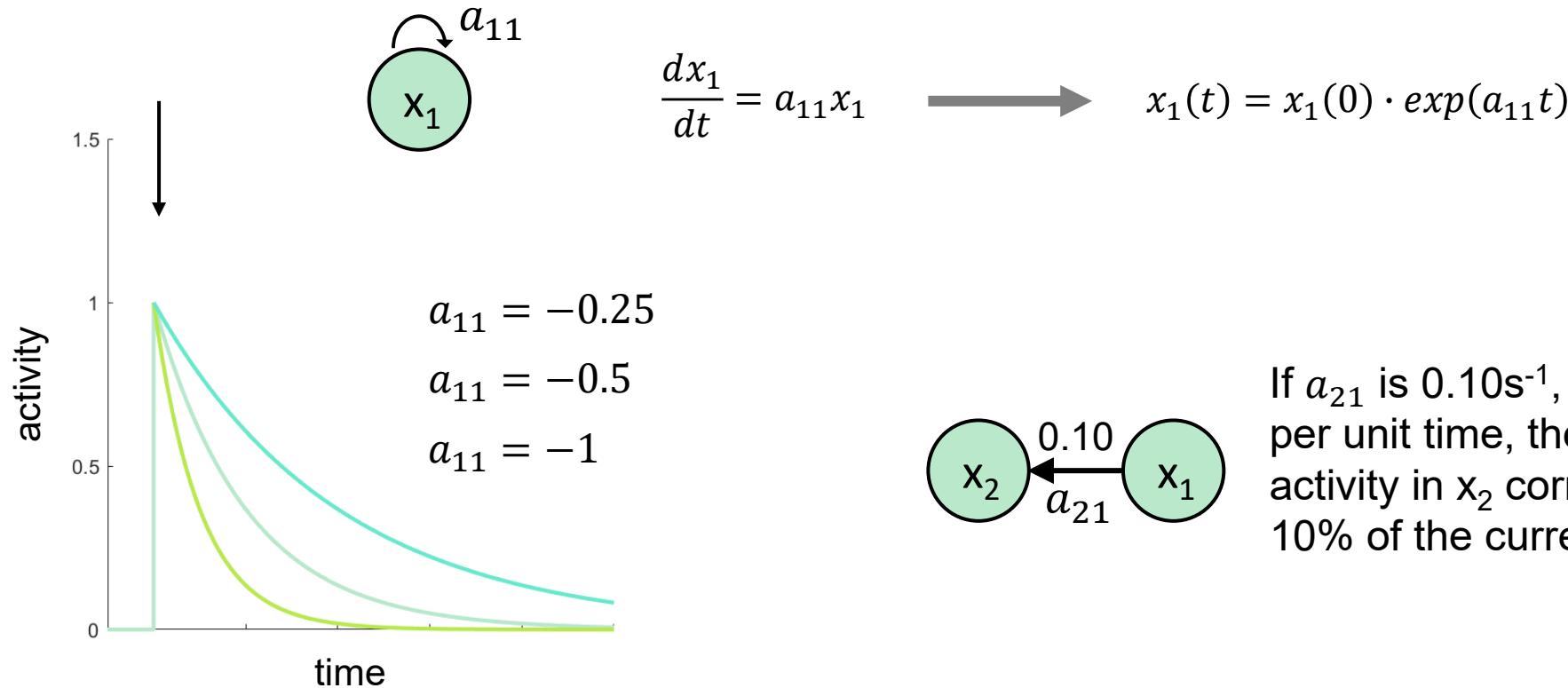
nonlinear model





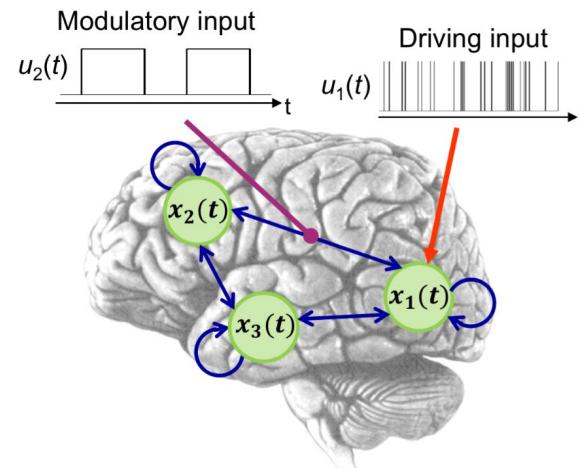
## Neuronal state equations

DCM effective connectivity parameters are rate constants



# Neuronal state equations

Interim summary: bilinear neuronal state equation



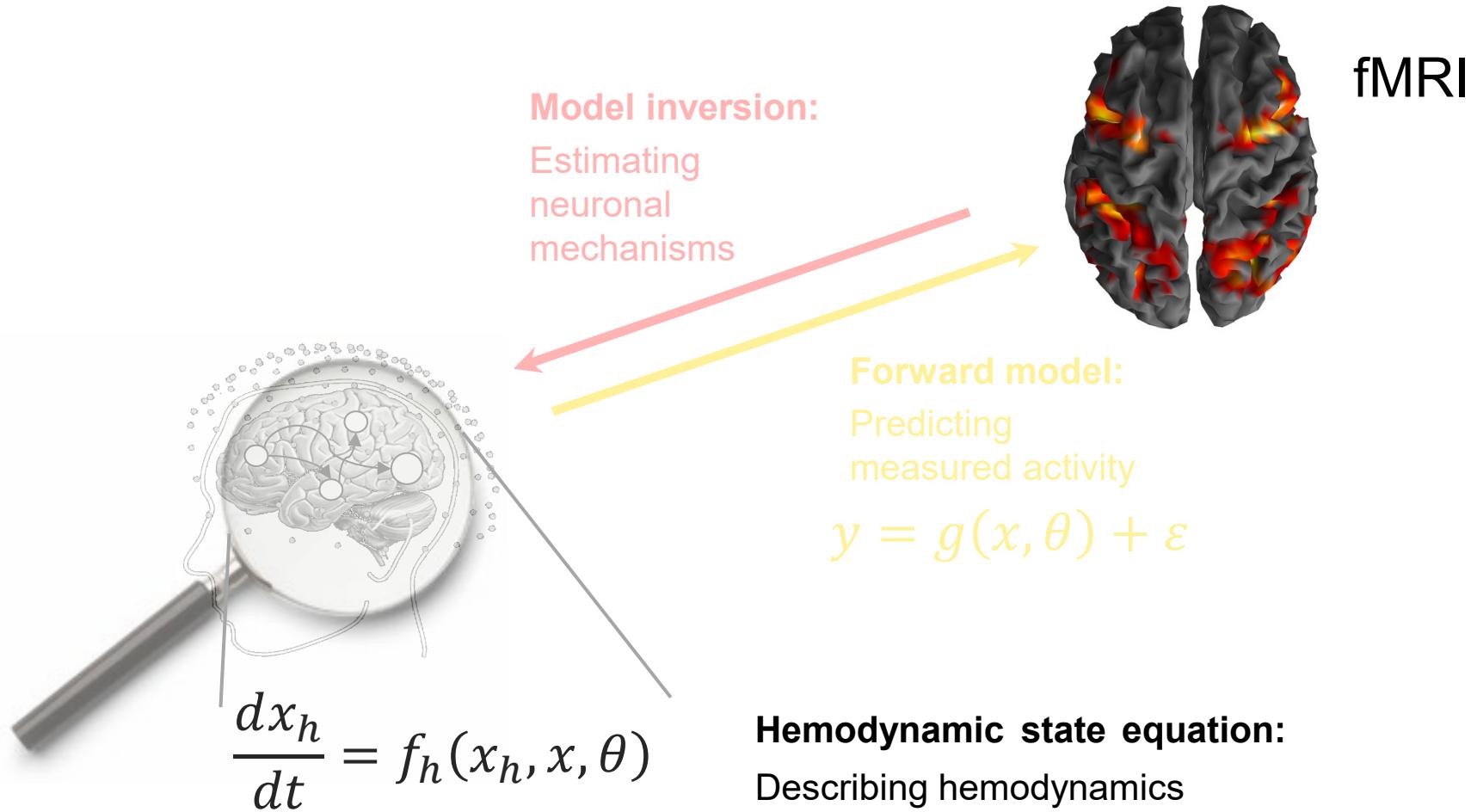
$$\frac{dx}{dt} = \underbrace{\left( A + \sum_{j=1}^m u_j B^{(j)} \right)}_{\text{connectivity}} x + Cu$$

State change      External inputs      Current state

Endogenous connectivity      Modulatory connectivity      Driving input weights

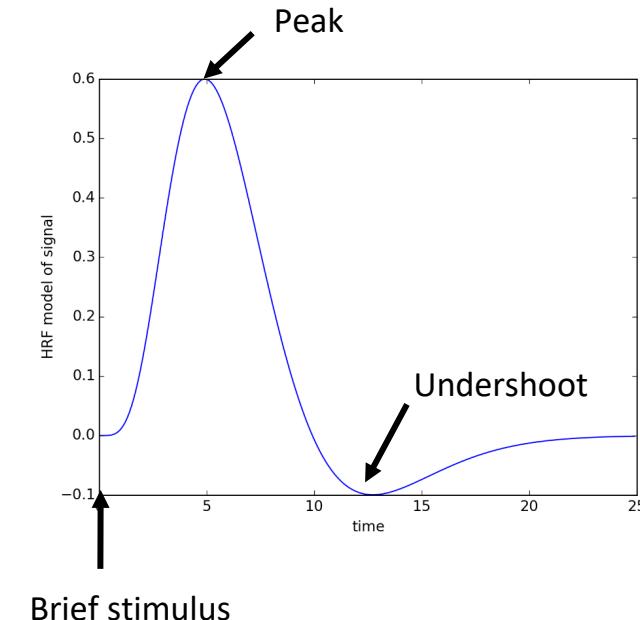
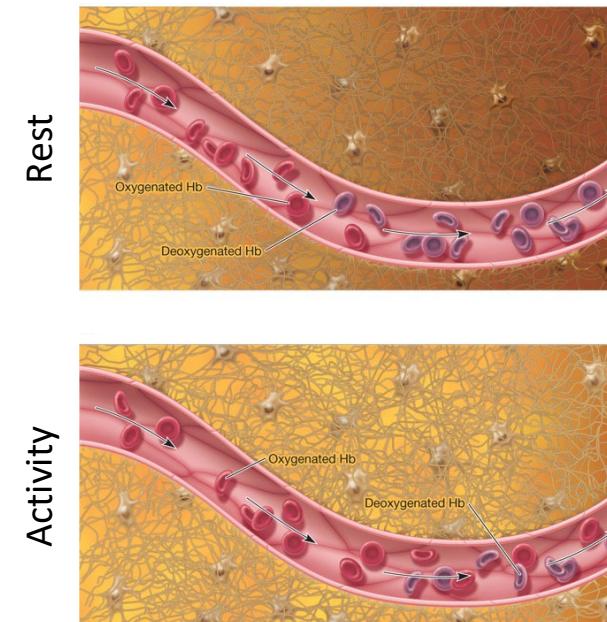
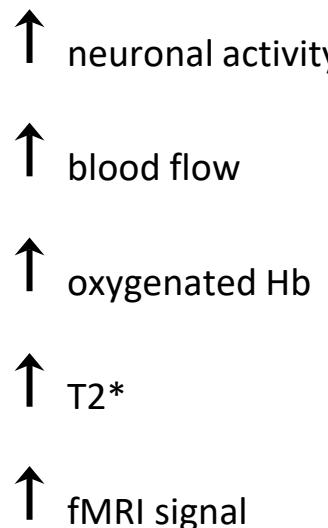
$\theta = \{A, B^{(1)}, \dots, B^{(m)}, C\}$

## DCM for fMRI - overview



# The hemodynamic response

Neuronal dynamics only indirectly observable via hemodynamic response



# The hemodynamic model

**6 parameters:**

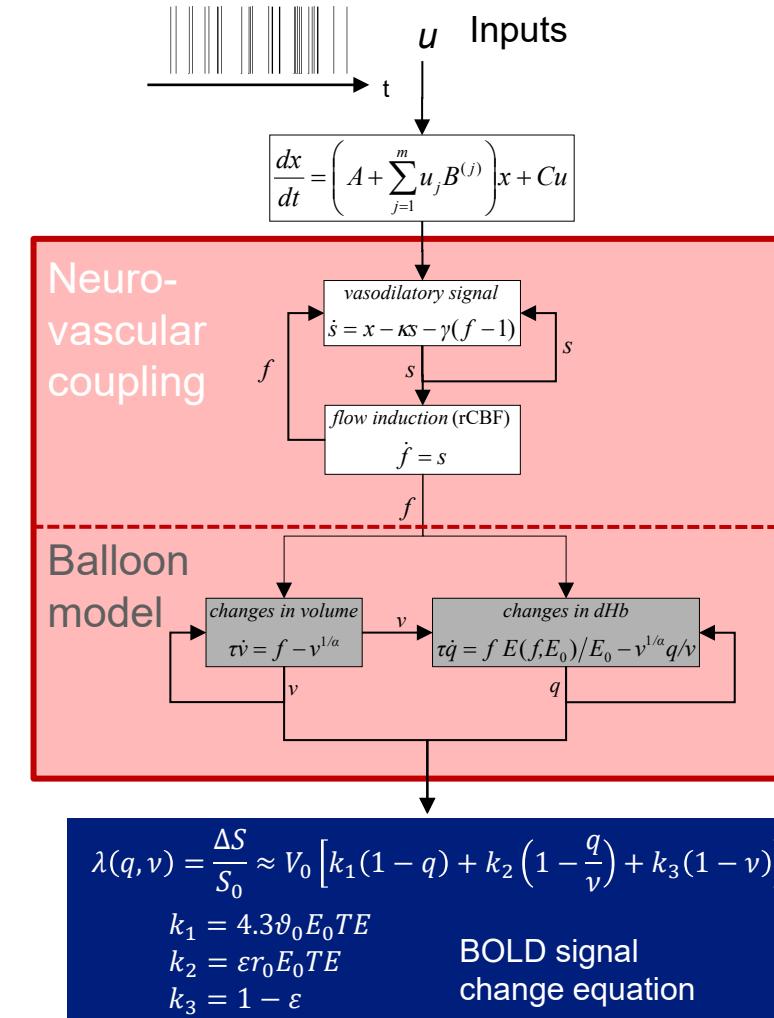
$$\theta^h = \{\kappa, \gamma, \tau, \alpha, \rho, \varepsilon\}$$

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

**Region specific HRF**

→ Parameters computed  
separately for each region

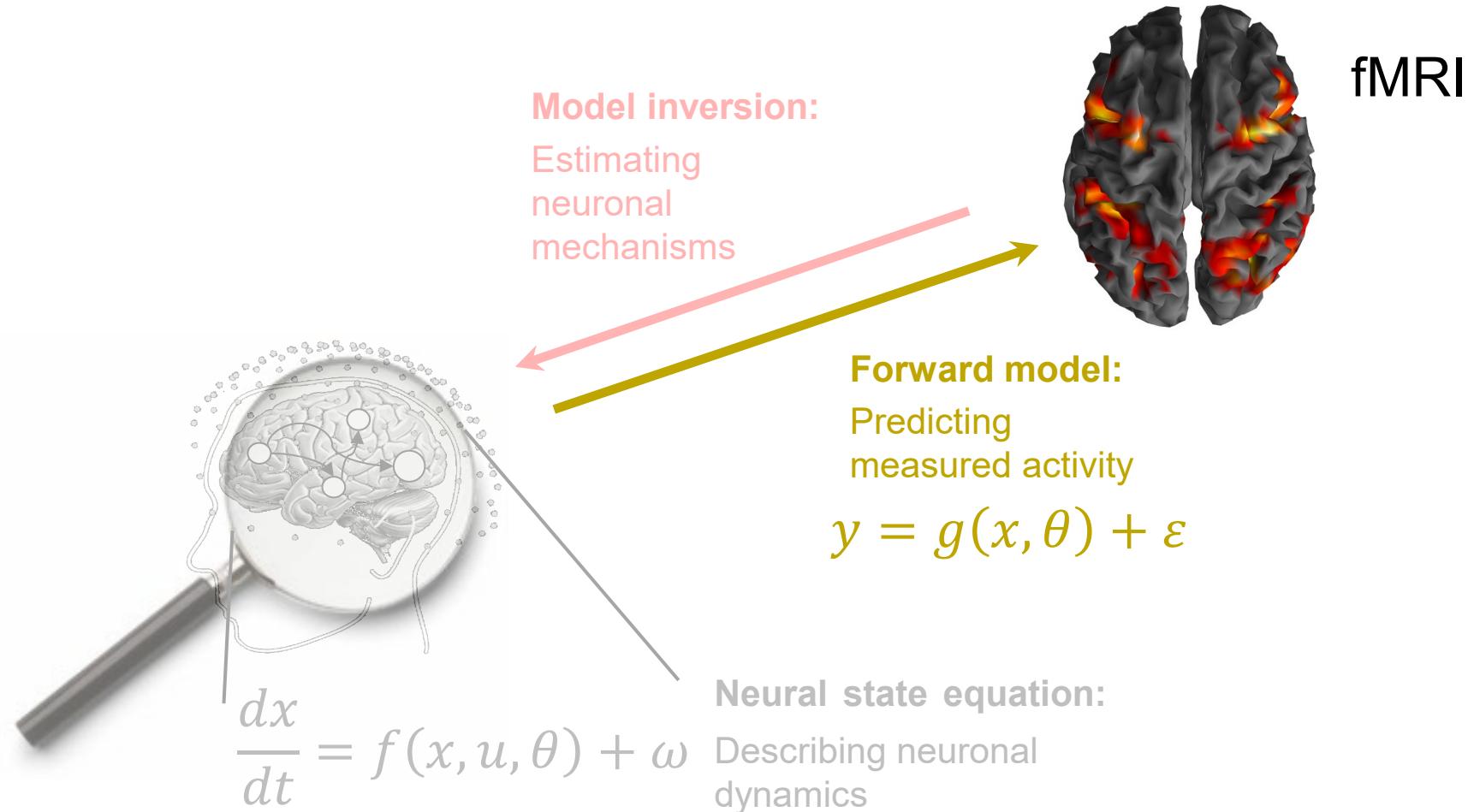
neural  
hemodynamic



Vasodilation ( $s$ ) and  
blood flow changes ( $f$ )

Relative blood  
volume ( $v$ ) and  
deoxyHB ( $q$ )

## DCM for fMRI - overview





## The BOLD signal equation

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

Resting blood volume      Deoxyhemoglobin content      Blood volume

```
graph TD; A[Resting blood volume] --> E; B[Deoxyhemoglobin content] --> E; C[Blood volume] --> E;
```

BOLD-Signal Parameters:

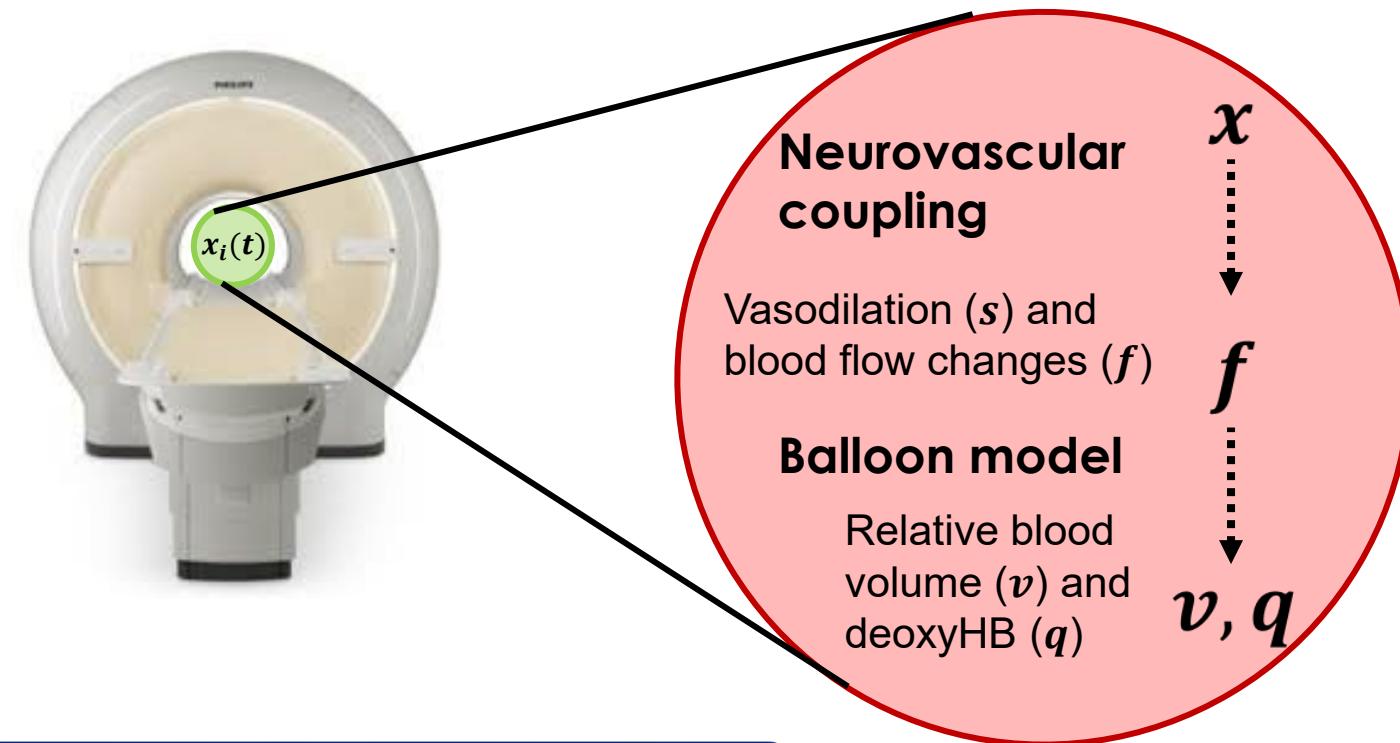
$$k_1 = 4.3\vartheta_0 E_0 TE$$

$$k_2 = \varepsilon r_0 E_0 TE$$

$$k_3 = 1 - \varepsilon$$

$V_0 = 0.04$	$E_0 = 0.32 - 0.4$	
At 1.5 Tesla	At 3 Tesla	At 7 Tesla
$\vartheta_0 \approx 40.3 \text{ s}^{-1}$	$\vartheta_0 \approx 80.6 \text{ s}^{-1}$	$\vartheta_0 \approx 188 \text{ s}^{-1}$
$r_0 \approx 25 \text{ s}^{-1}$	$r_0 \approx 110 \text{ s}^{-1}$	$r_0 \approx 340 \text{ s}^{-1}$
$TE \approx 0.04 \text{ s}$	$TE \approx 0.035 \text{ s}$	$TE \approx 0.025 \text{ s}$
$\varepsilon \approx 1.28$	$\varepsilon \approx 0.47$	$\varepsilon \approx 0.026$

## From neural activity to the BOLD signal: summary

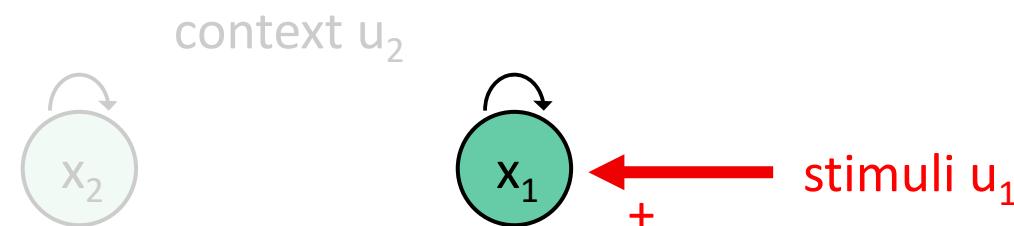


BOLD signal is a direct function of  $v$  and  $q$

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

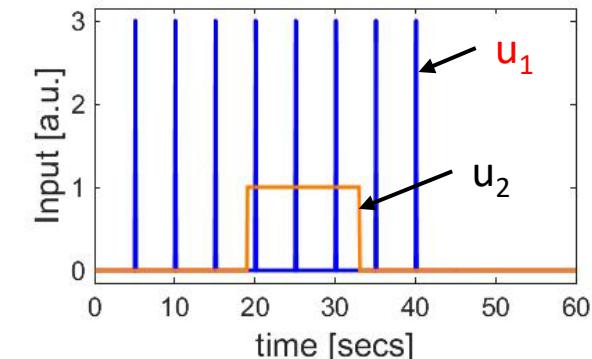
## Simulation example: What can DCM explain?

Example: single node



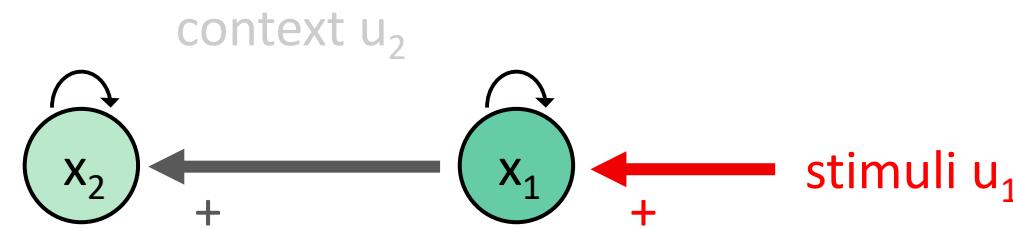
$$\frac{dx}{dt} = (A + u_2 B^{(2)})x + Cu_1$$

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



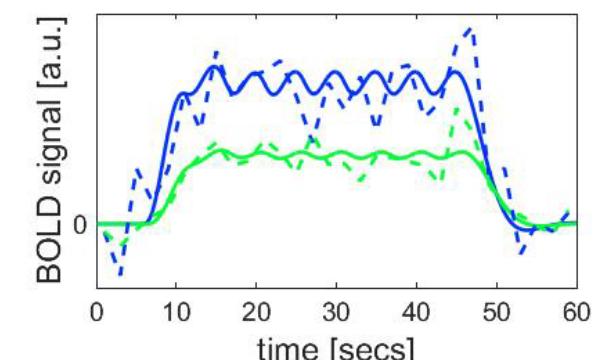
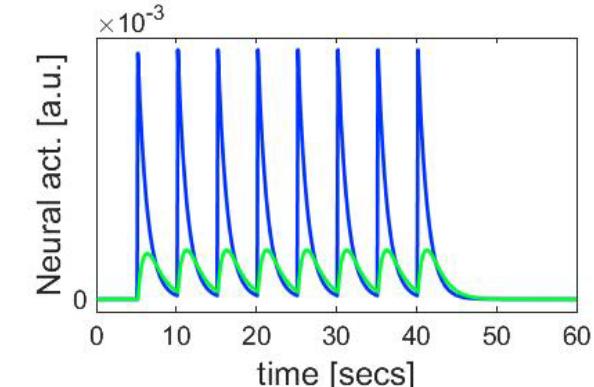
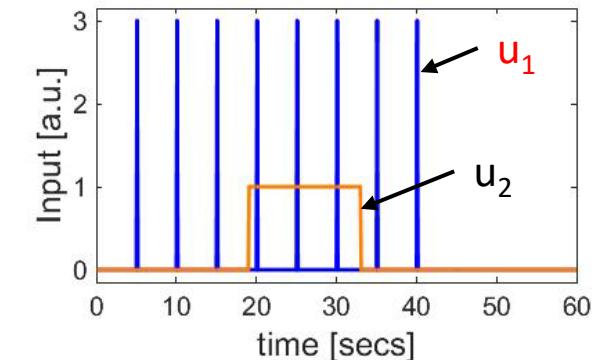
## Simulation example: What can DCM explain?

Example: two connected node



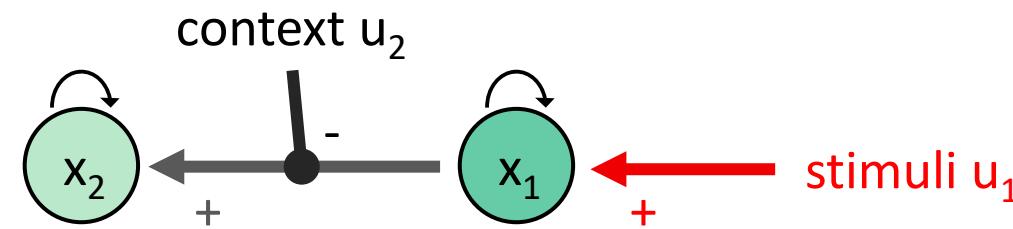
$$\frac{dx}{dt} = (A + u_2 B^{(2)})x + Cu_1$$

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



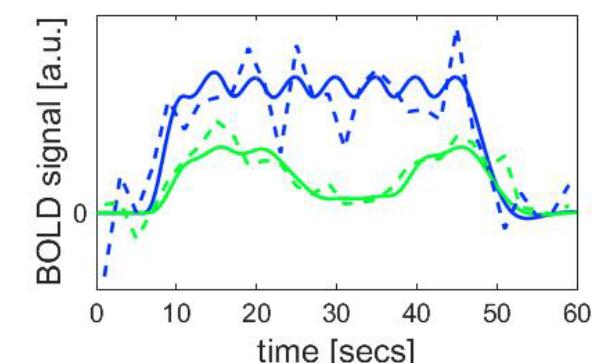
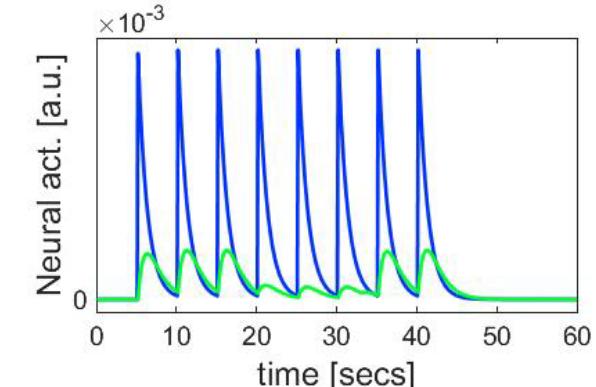
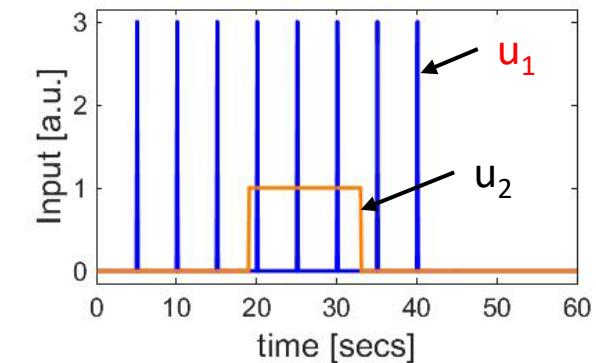
## Simulation example: What can DCM explain?

Example: modulation of connection



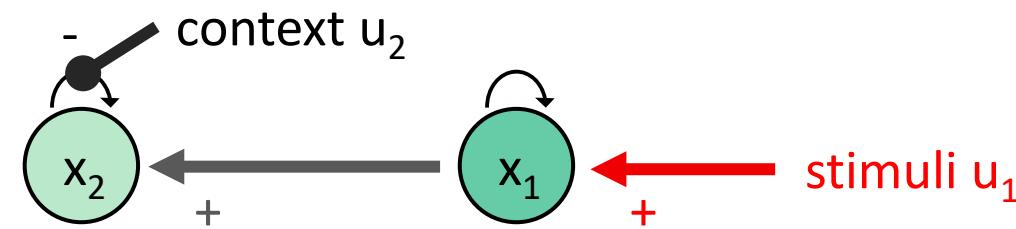
$$\frac{dx}{dt} = (A + u_2 B^{(2)})x + Cu_1$$

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



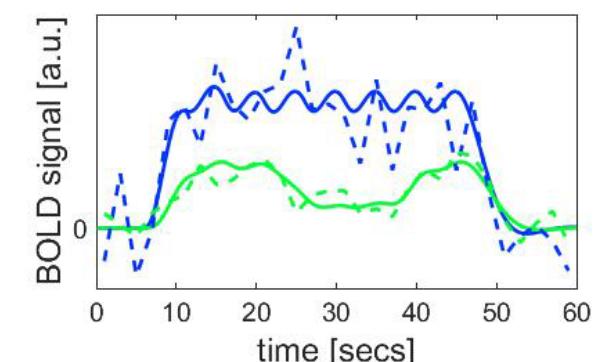
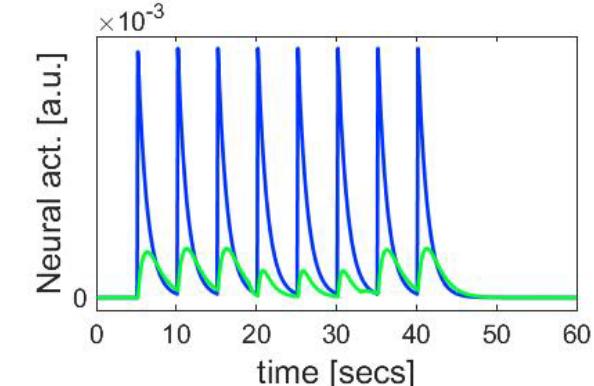
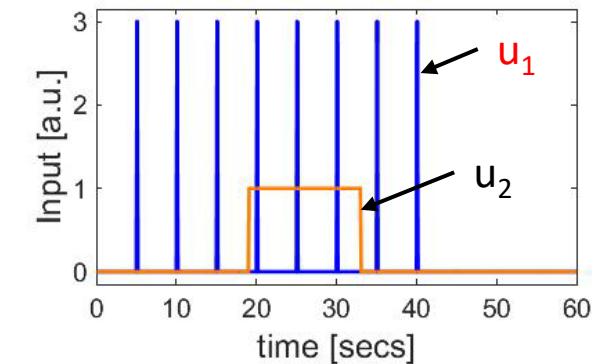
## Simulation example: What can DCM explain?

Example: modulation of inhibitory self-connection



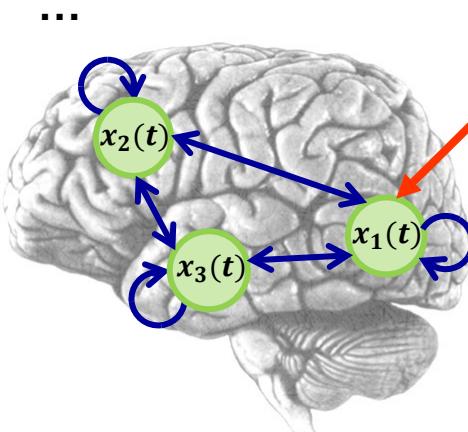
$$\frac{dx}{dt} = (A + u_2 B^{(2)})x + Cu_1$$

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



## 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).

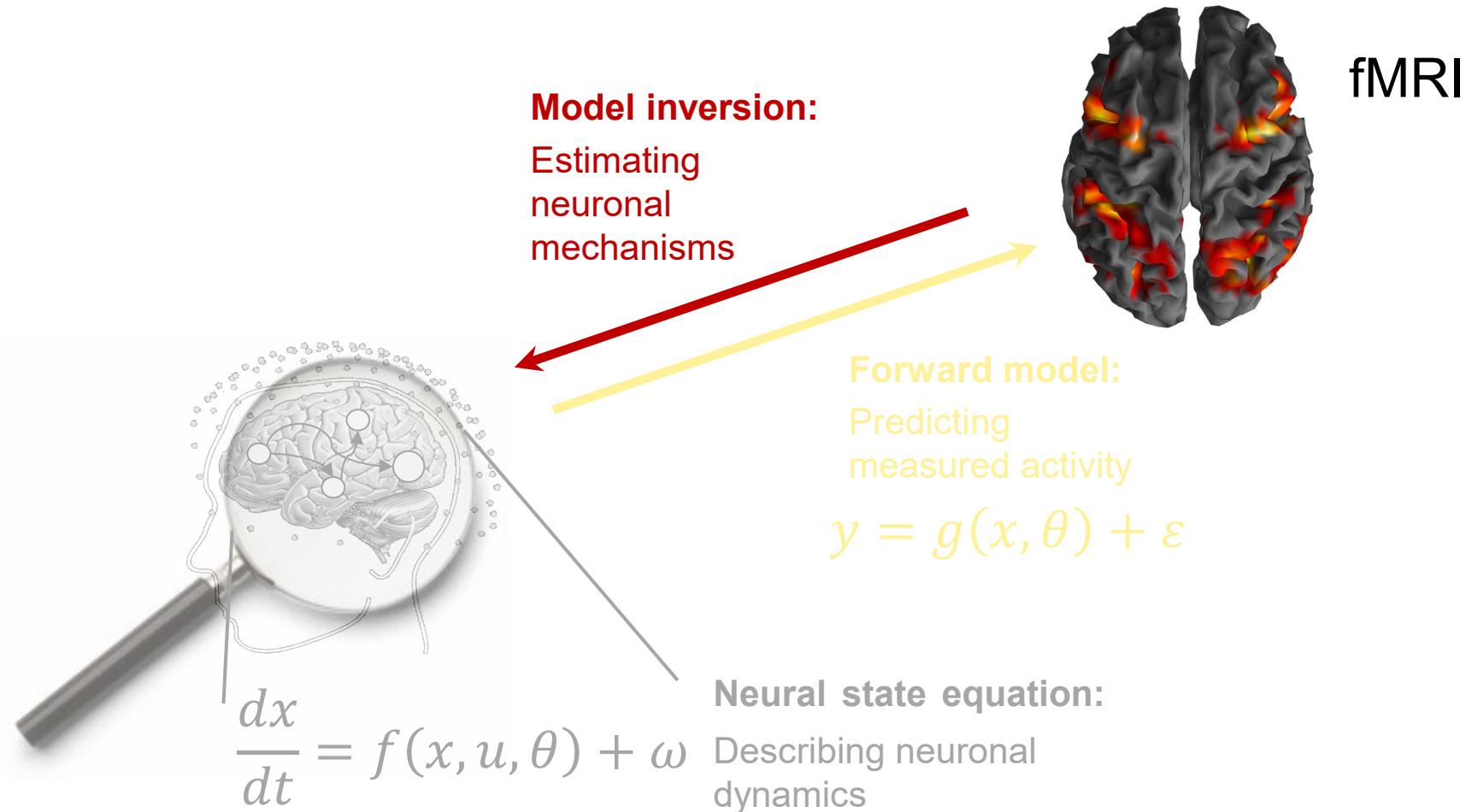
...

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

Simulate the system with input  $u$  and parameters  $\theta$

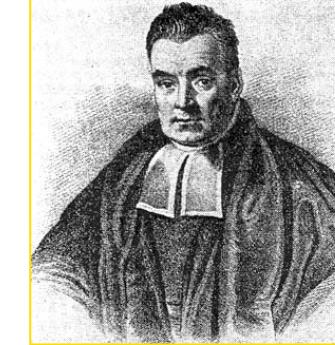
→ BOLD signal time course  $y$  that can be  
compared to measured data.

## DCM for fMRI - overview

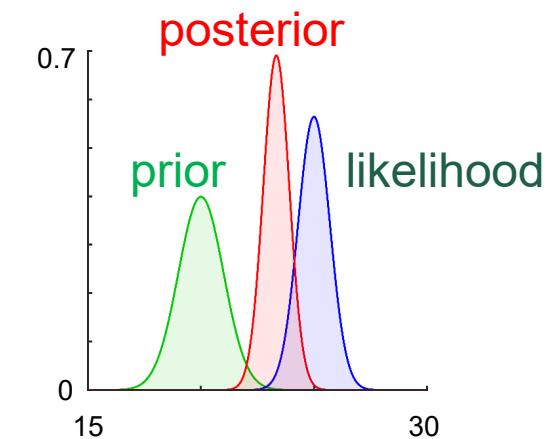


## Bayes' theorem

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



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)

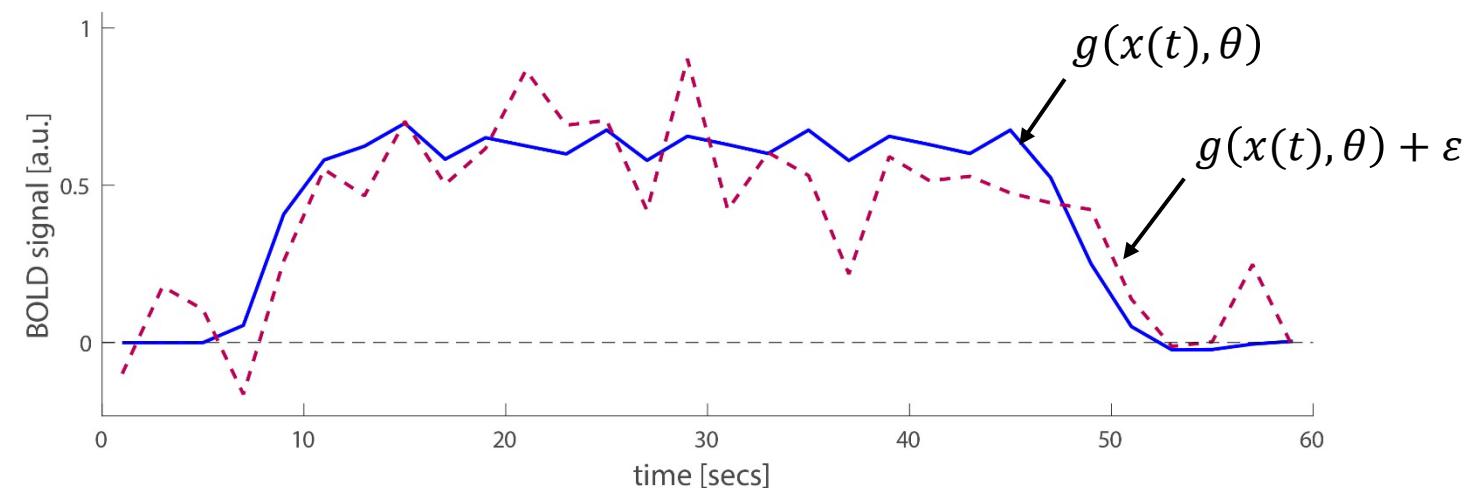
$$y(t) = g(x(t), \theta) + \varepsilon$$
$$\varepsilon \sim \mathcal{N}(0, \sigma^2 I)$$

Data is prediction plus  
Gaussian noise

## The likelihood function for DCM

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

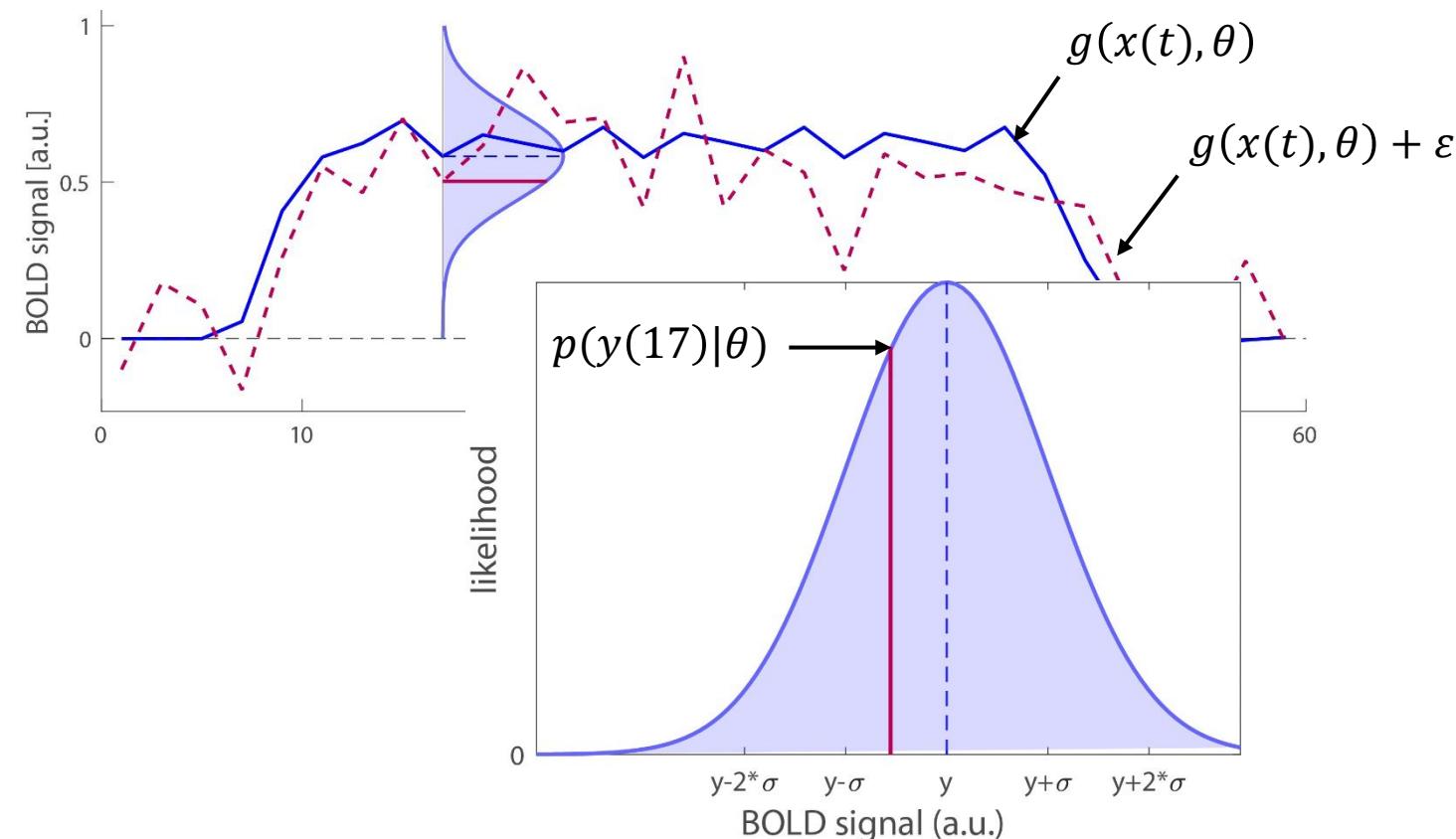
likelihood



## The likelihood function for DCM

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

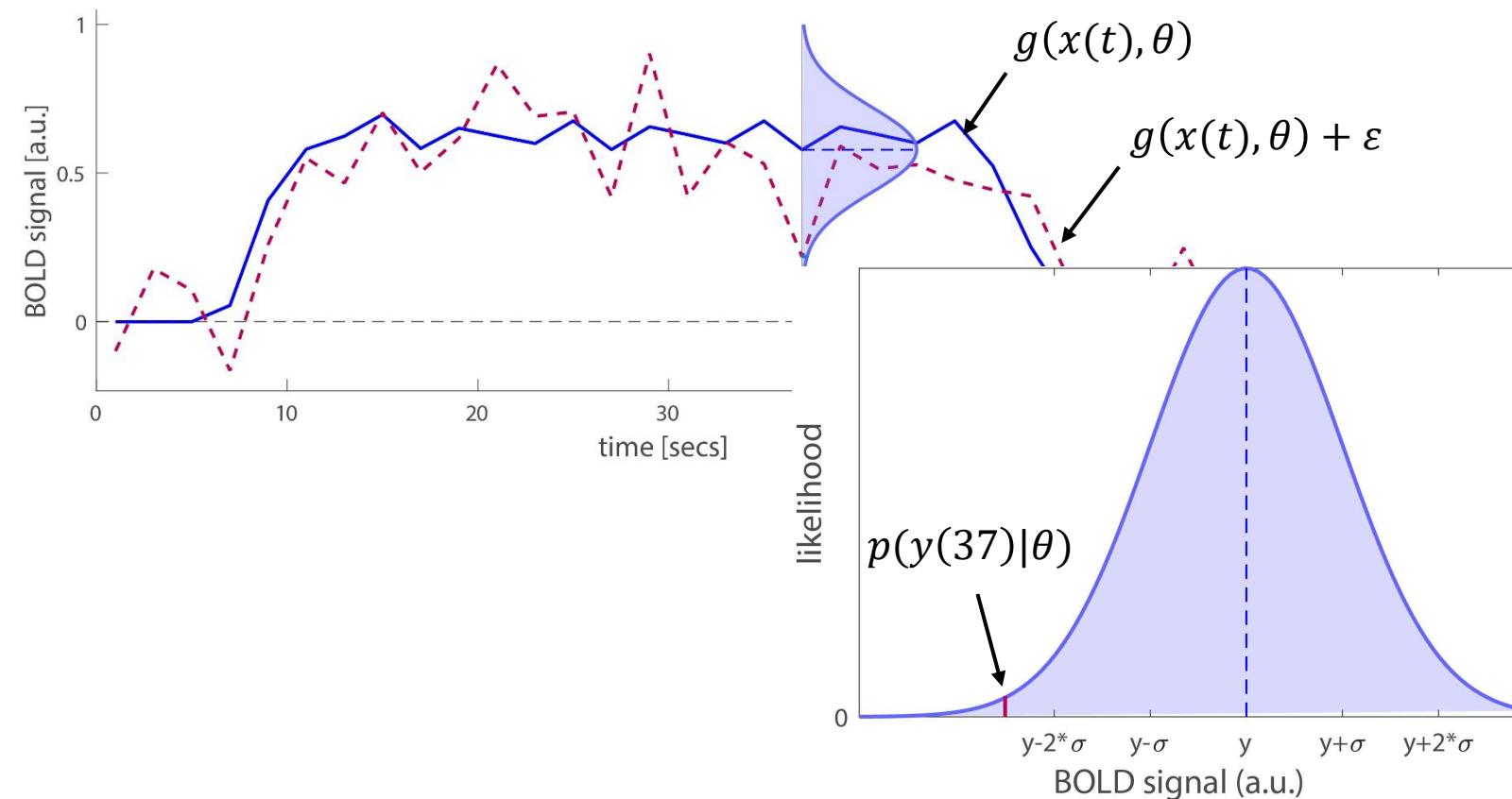
likelihood



## 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:

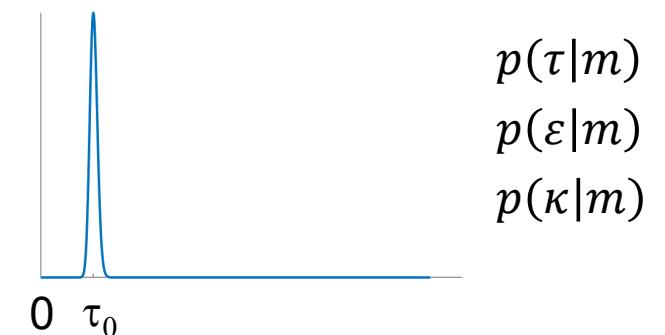
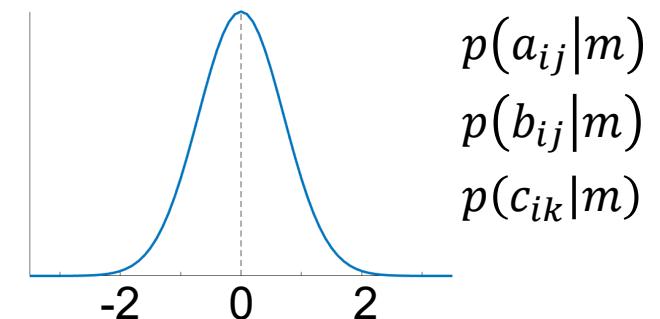
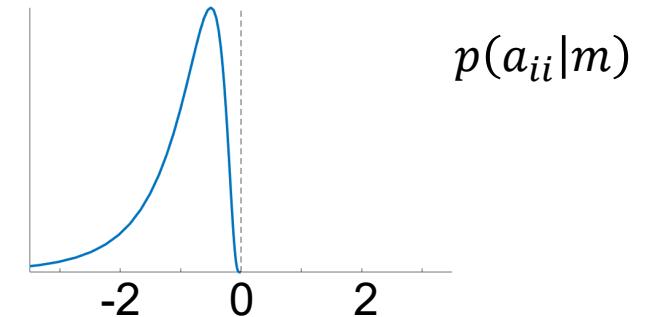
- self-connections: principled (to “ensure” that the system is stable)
- other parameters (between—region connections, modulation, inputs): shrinkage priors

### Hemodynamic parameters:

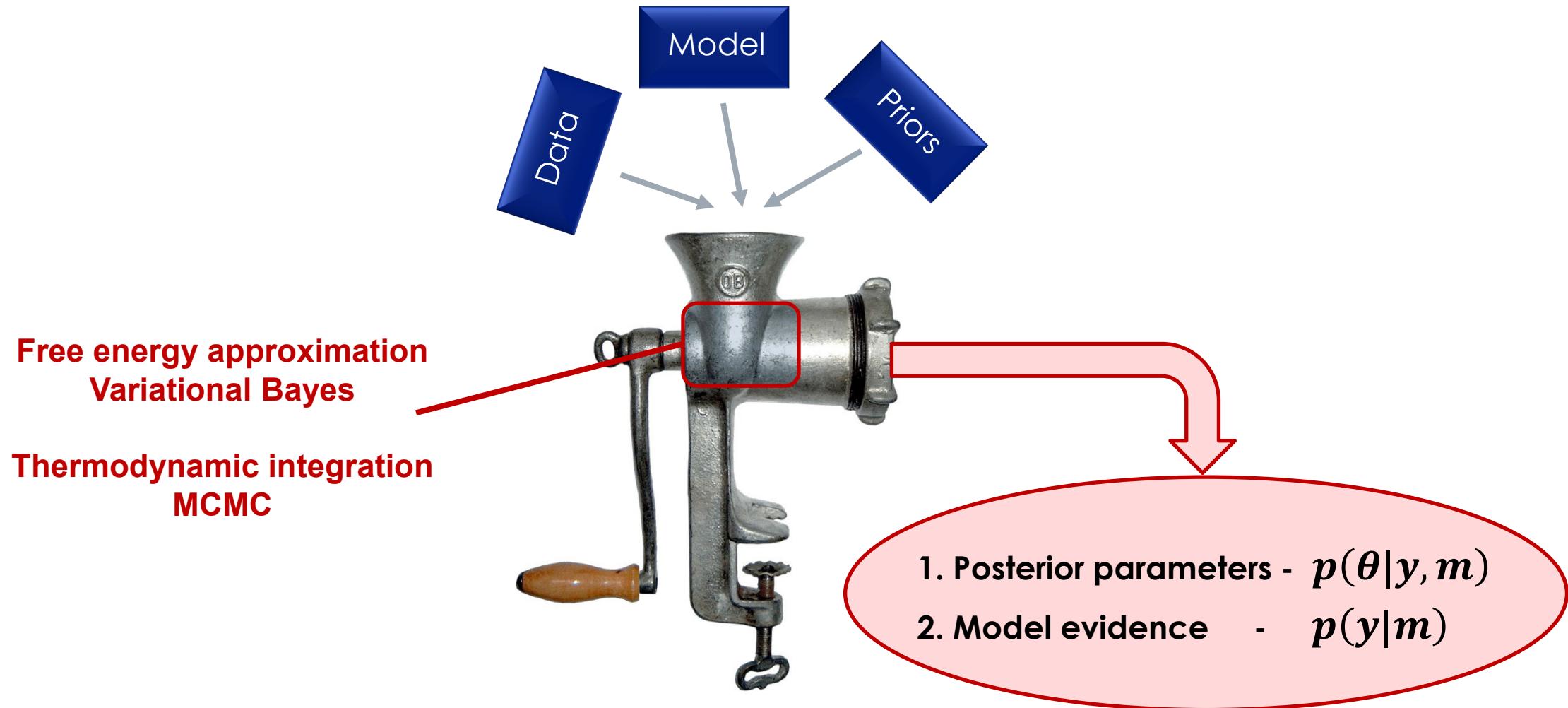
- empirical

### Noise prior (hyperparameter):

- assume relatively noisy data  
(not default in SPM12 → set DCM.options.hE = 0; DCM.options.hC = 1)



## Model estimation: running the machinery

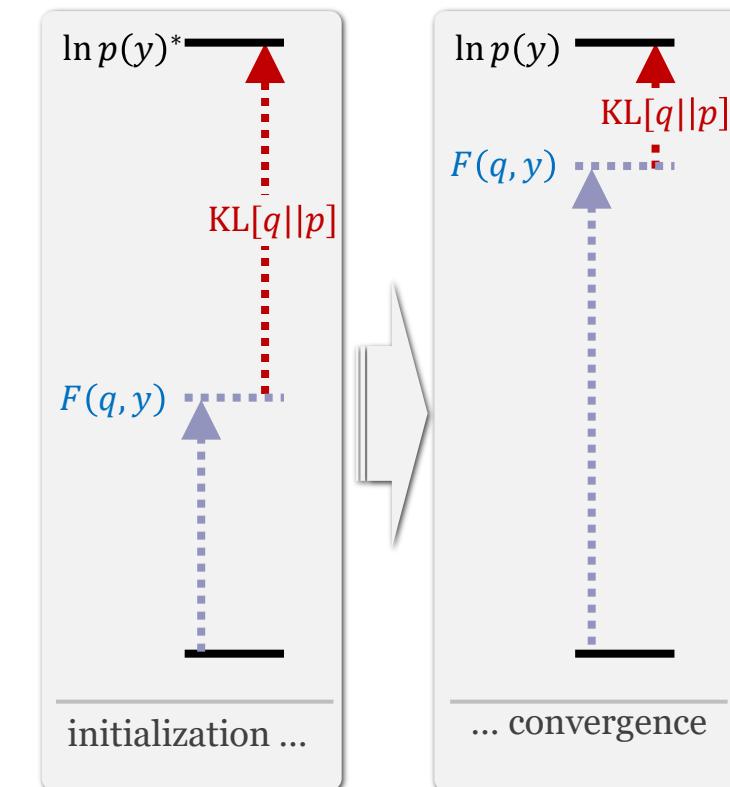


## Inversion – variational Free Energy approximation to model evidence

model evidence

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

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



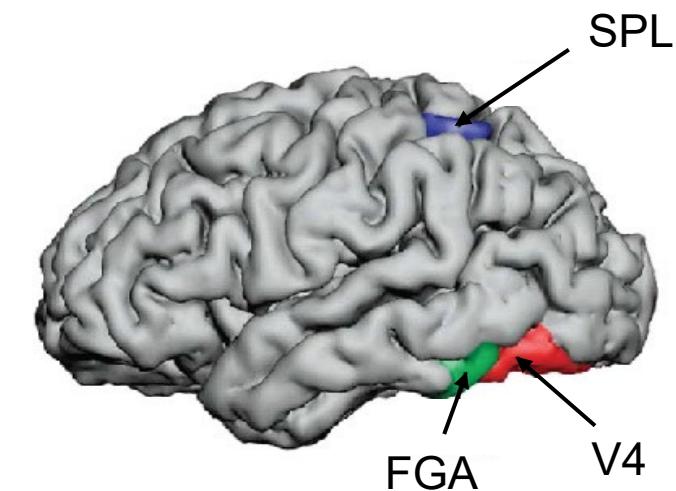


## Model estimation: running the machinery



## 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)

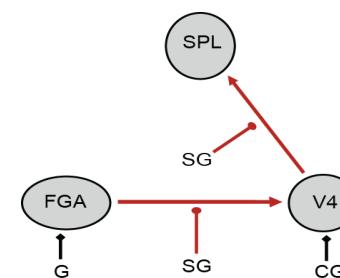


Hubbard, 2007

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

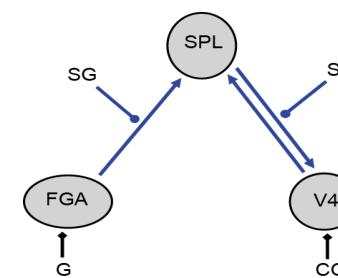
## Bottom-up

(Ramachandran & Hubbard, 2001)



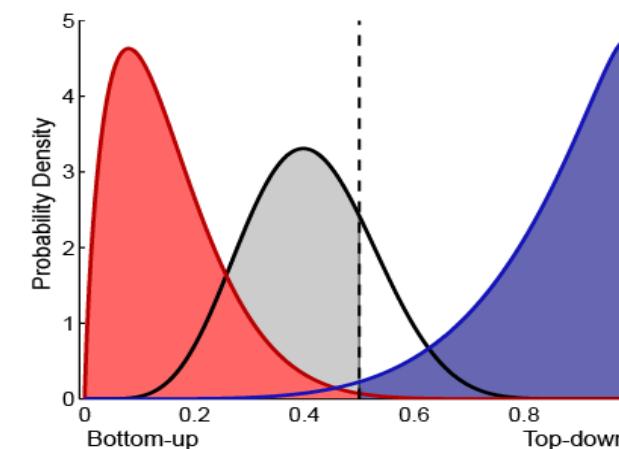
## Top-down

(Grossenbacher & Lovelace, 2001)

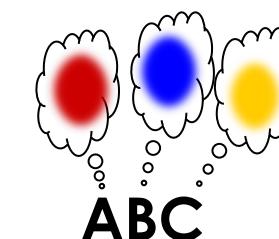


## Projectors

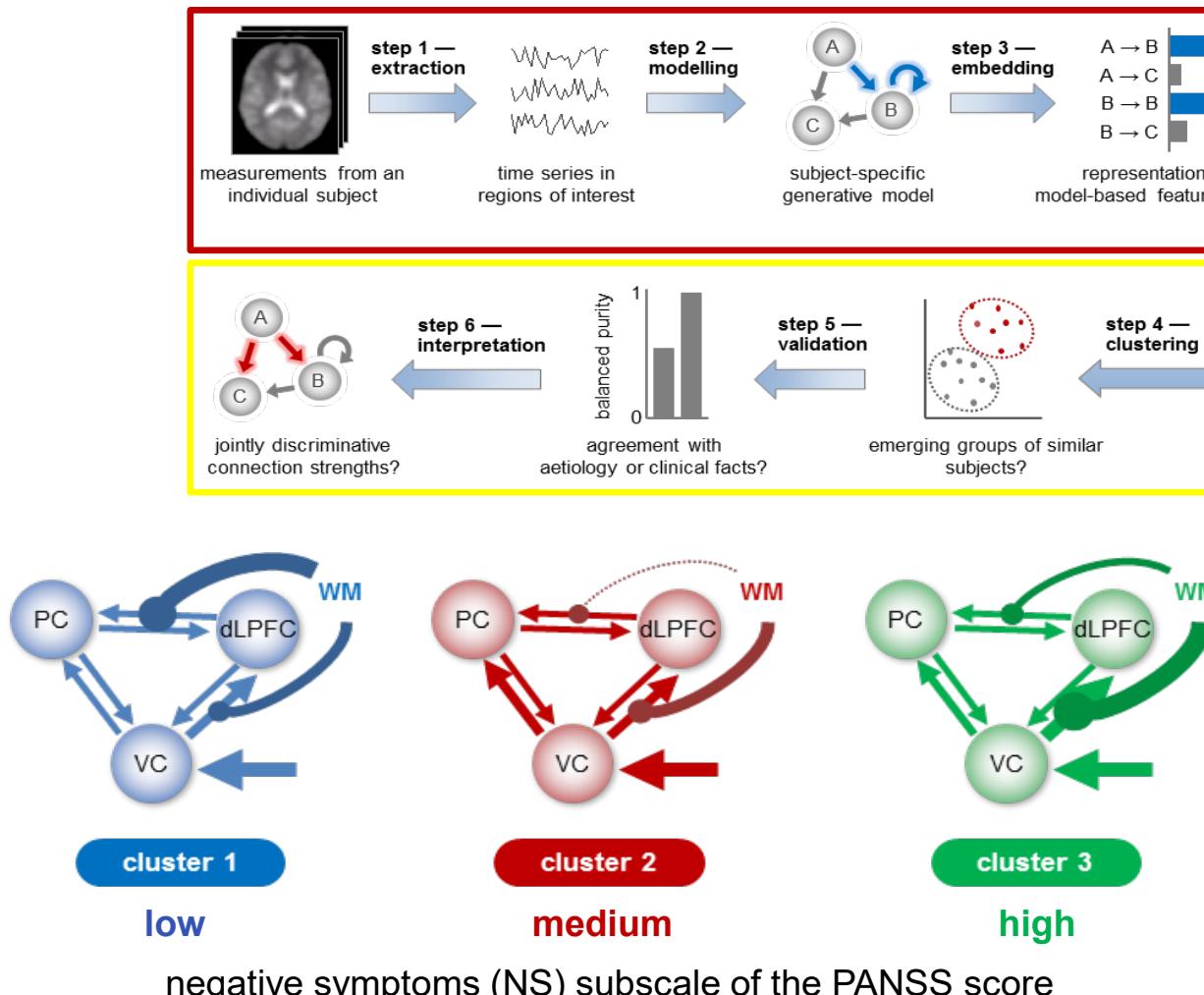
**ABC**



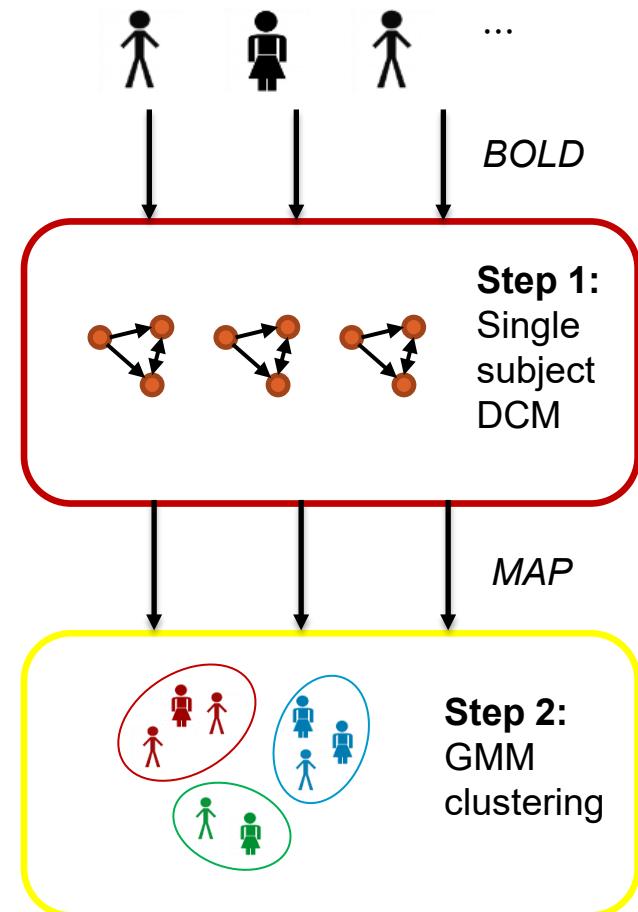
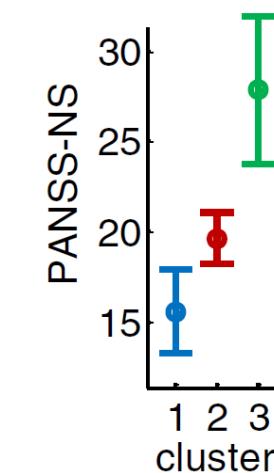
## Associators



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



DCM





## 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

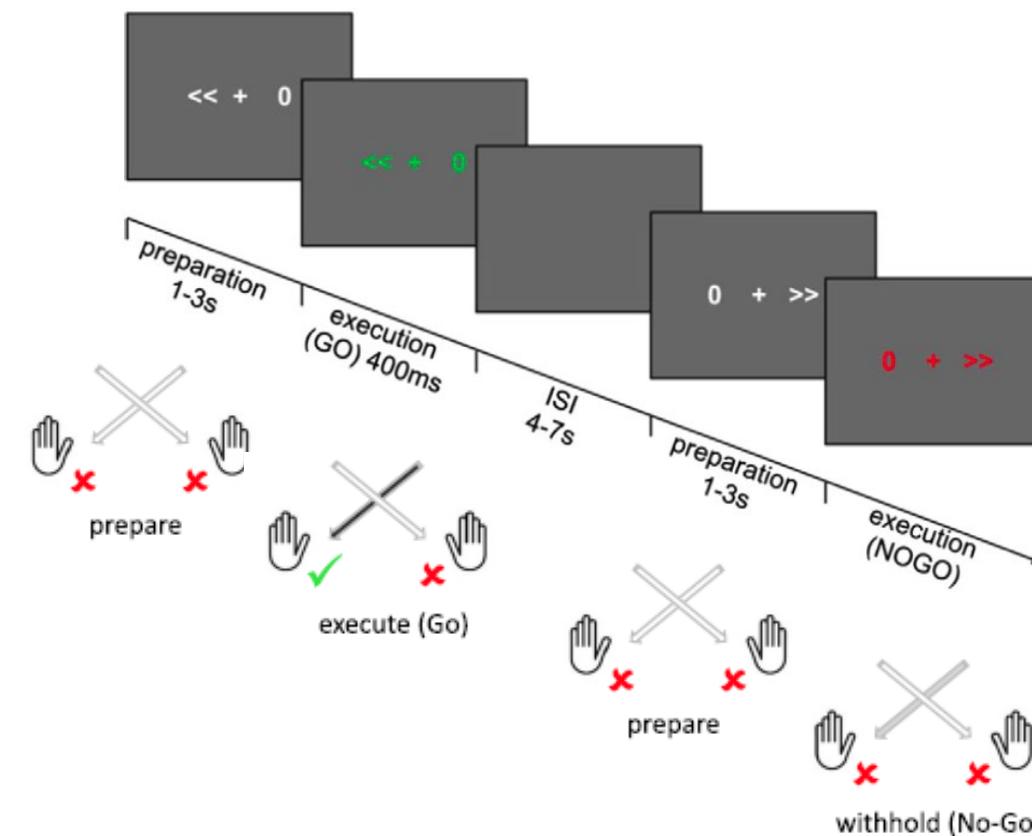
**... and of course many more!**

## Limitations

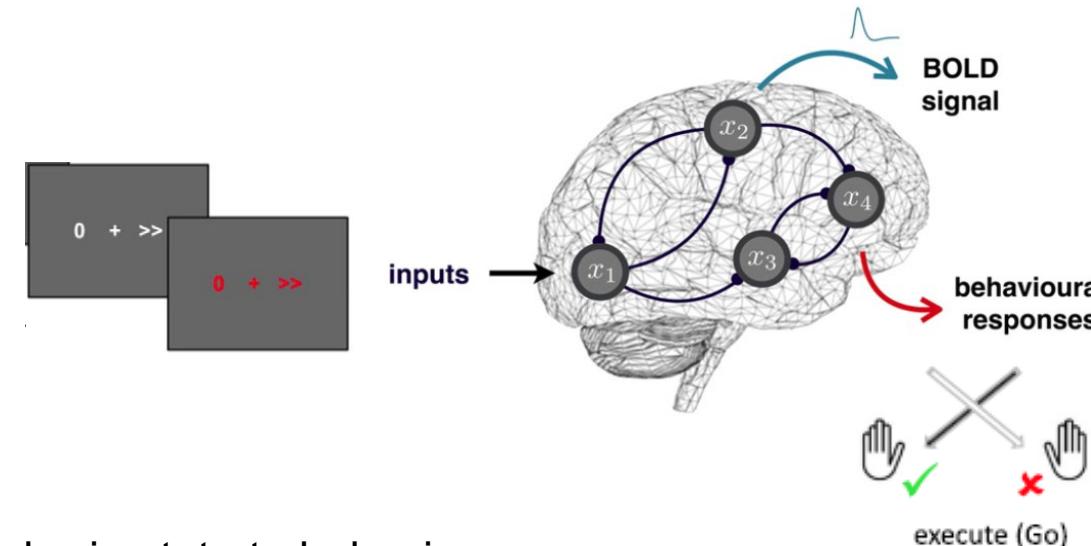
- DCMs only have inputs, no outputs
  - Limits the study of behavioral paradigms
- Local minima
  - Variational approximation can get stuck in local minima of free energy
- Size of networks
  - Standard inversion too slow for large networks (>10 nodes).



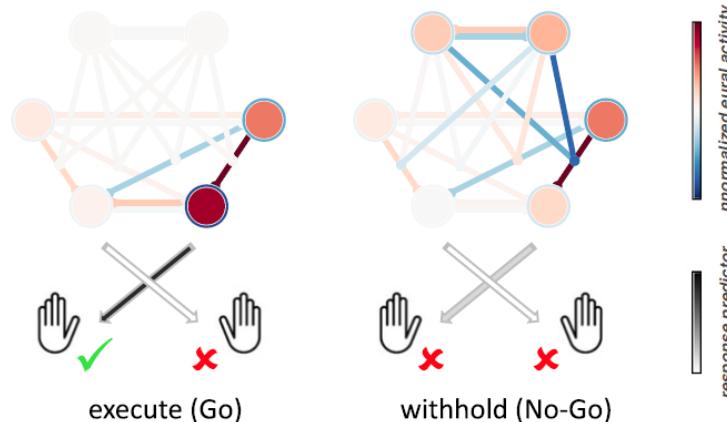
## Behavioral DCM – a step towards a neurocomputational model



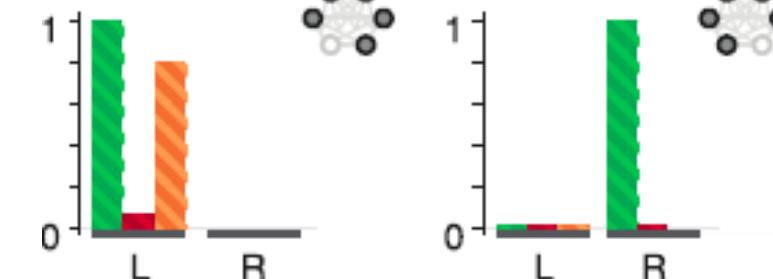
# Behavioral DCM – a step towards a neurocomputational model



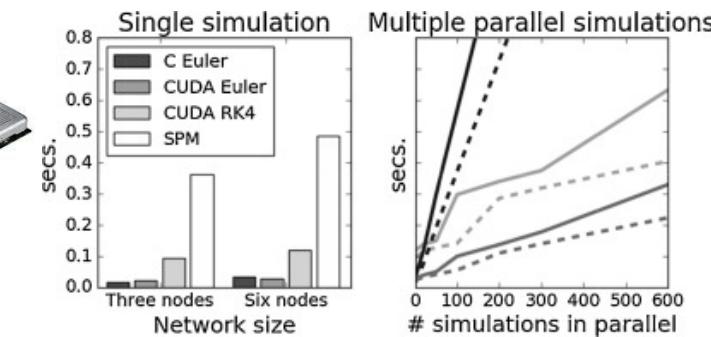
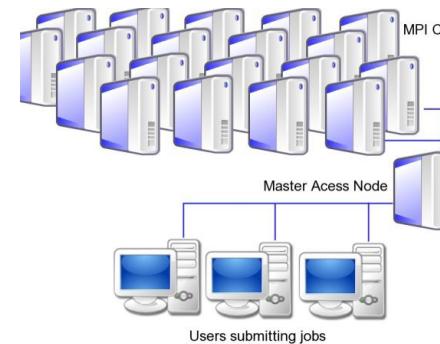
Mapping brain state to behavior



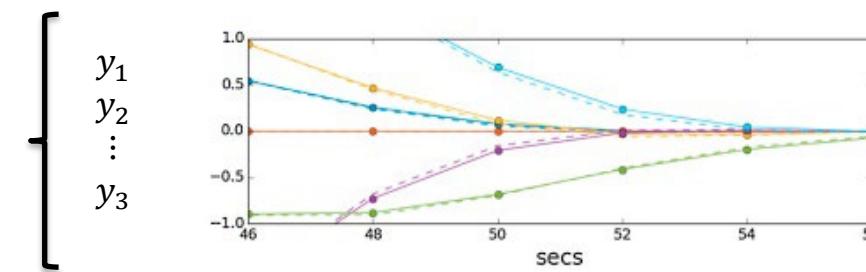
Lesion simulations



## MCMC inversion of DCMs: Massively Parallel DCM - mpdcm

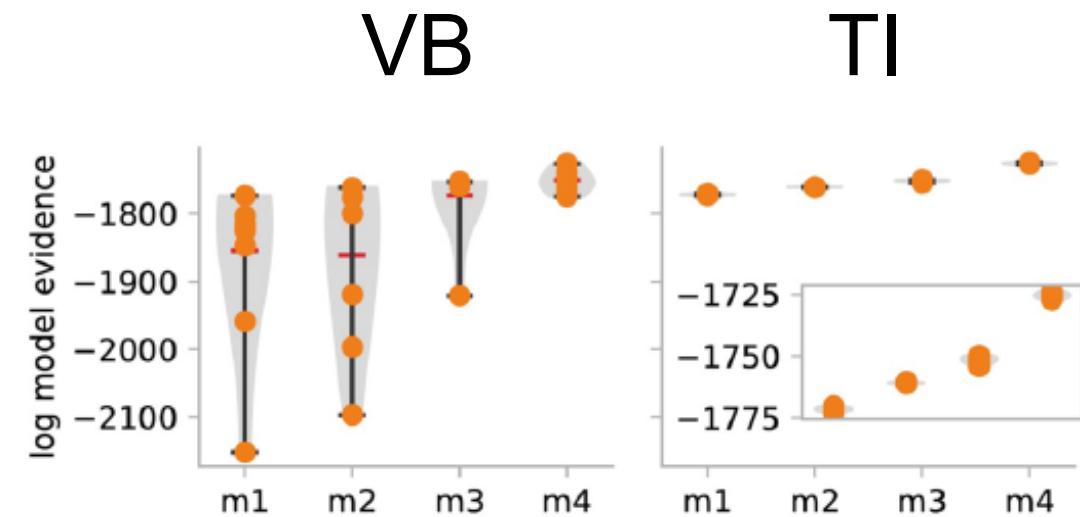
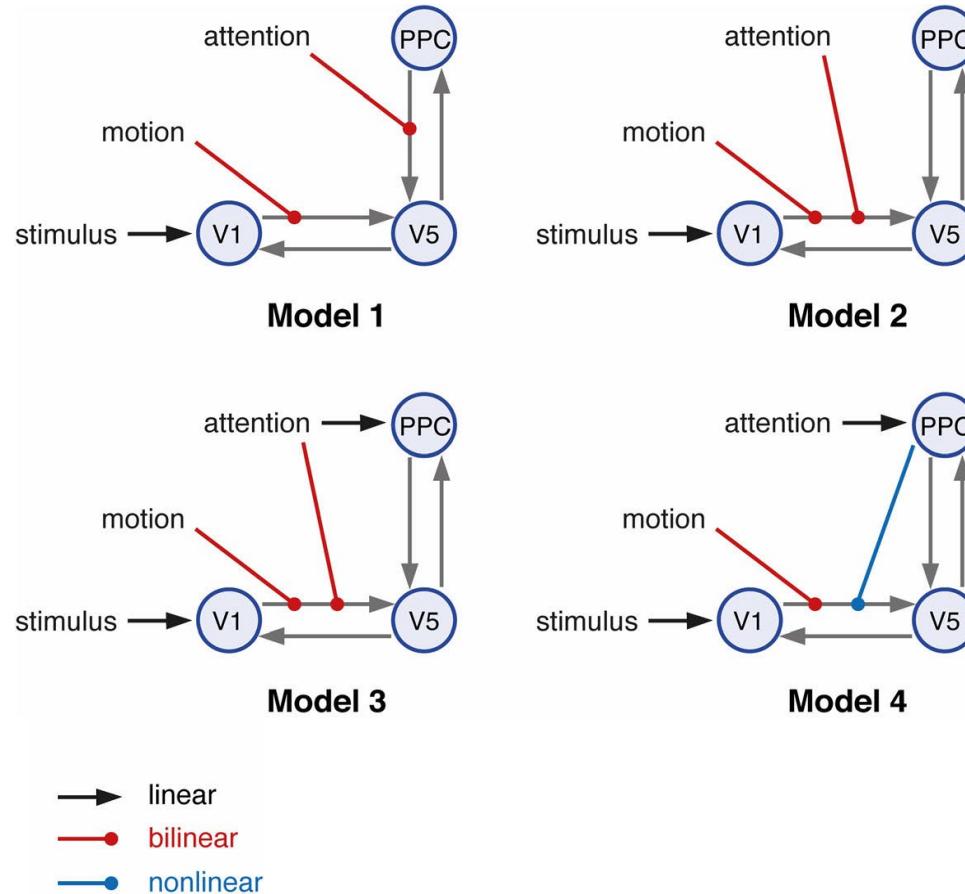


$$\begin{aligned} \dot{x} &= f(x, u_1, \theta_1) \\ \dot{x} &= f(x, u_2, \theta_2) \\ &\vdots \\ \dot{x} &= f(x, u_n, \theta_n) \end{aligned} \quad \left. \right\} \text{mpdcm\_integrate(dcms)}$$



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

## Variational Bayes (VB) vs. Thermodynamic Integration (TI)



## Extensions of 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

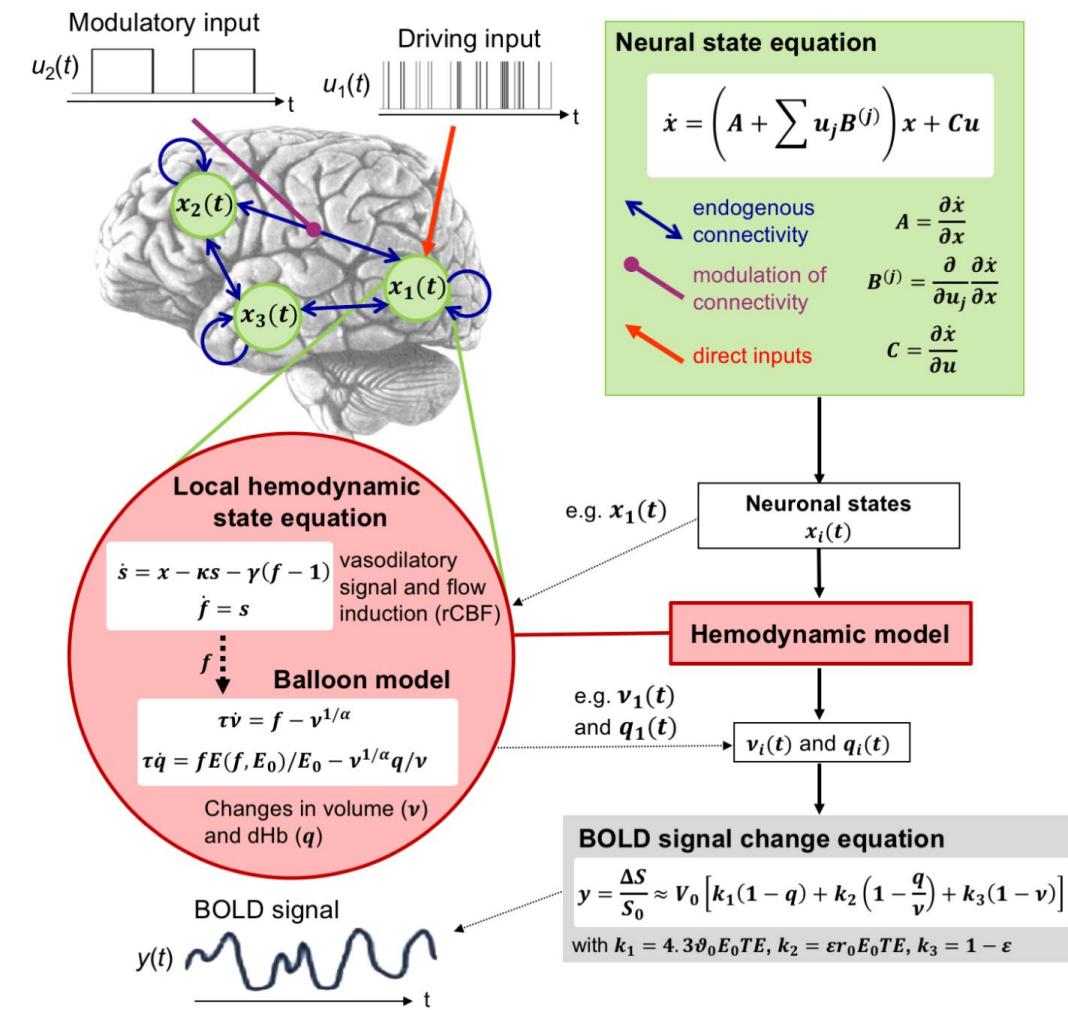
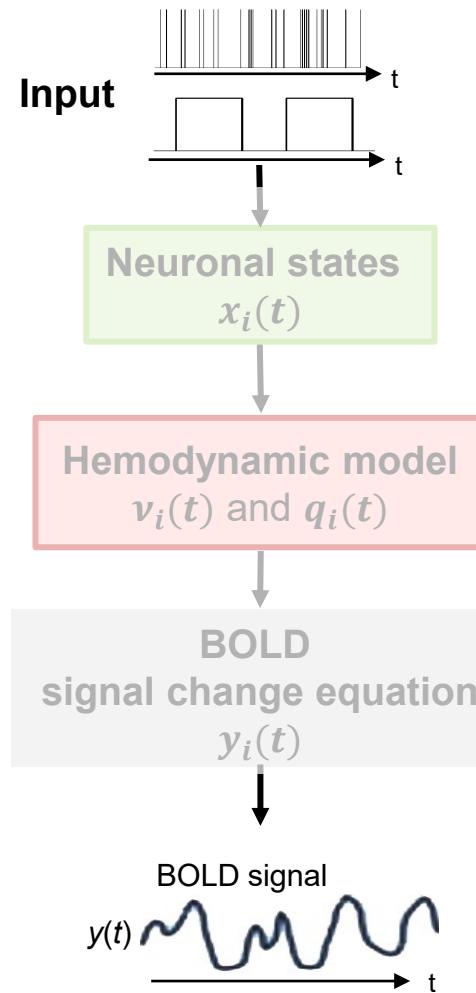
Modeling Connectivity:  
Regression DCM for fMRI

Available in TAPAS:  
[www.translationalneuromodeling.org/tapas](http://www.translationalneuromodeling.org/tapas)

## Summary – generative model



## Summary – generative model



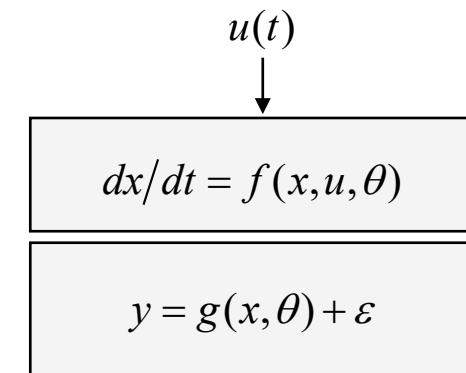
# Summary - Bayesian system identification

Neural (and hemo-)  
dynamics

Observer function

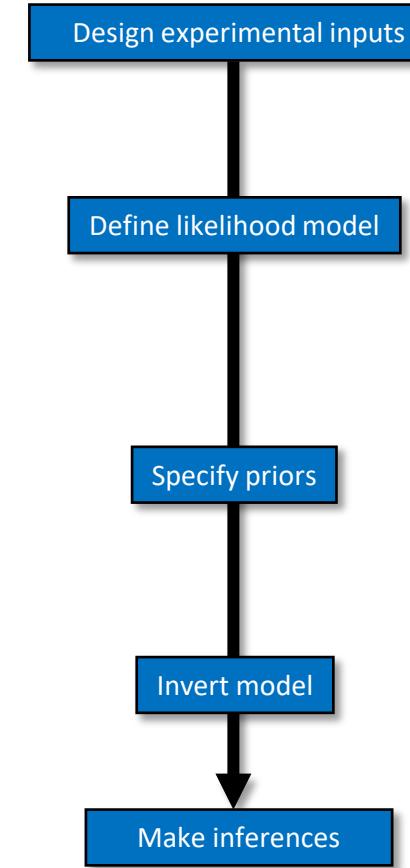
Inference on model  
structure

Inference on  
parameters



$$\begin{aligned} p(y | \theta, m) &= N(g(\theta), \Sigma(\theta)) \\ p(\theta, m) &= N(\mu_\theta, \Sigma_\theta) \end{aligned}$$

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





## DCM software note

Basic functionality for DCM for fMRI is provided within

SPM

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

<https://github.com/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, Heinze J (2016). mpdcm: A Toolbox for Massively Parallel Dynamic Causal Modeling. *Journal of Neuroscience Methods* 257: 7-16.
- Aponte EA, Yao Y, Raman S, Frässle S, Heinze J, Penny WD, Stephan KE (2021). An introduction to thermodynamic integration and application to dynamic causal models. *Cognitive Neurodynamics* 16: 1-15.
- 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.
- Brodersen KH, Deserno L, Schlagenauf F, Lin Z, Penny WD, Buhmann JM, Stephan KE (2014) Dissecting psychiatric spectrum disorders by generative embedding. *NeuroImage: Clinical* 4: 98-111
- Daunizeau J, David, O, Stephan KE (2011) Dynamic Causal Modelling: A critical review of the biophysical and statistical foundations. *NeuroImage* 58: 312-322.
- Daunizeau J, Stephan KE, Friston KJ (2012) Stochastic Dynamic Causal Modelling of fMRI data: Should we care about neural noise? *NeuroImage* 62: 464-481.
- **Friston KJ, Harrison L, Penny W (2003) Dynamic causal modelling. *NeuroImage* 19:1273-1302.**
- Friston KJ, Mattout J, Trujill-Barreto, Ashburner J, Penny W (2007) Variational free energy and the Laplace approximation. *NeuroImage* 34: 220-234.
- Friston K, Stephan KE, Li B, Daunizeau J (2010) Generalised filtering. *Mathematical Problems in Engineering* 2010: 621670.
- Friston KJ, Li B, Daunizeau J, Stephan KE (2011) Network discovery with DCM. *NeuroImage* 56: 1202–1221.
- Friston K, Penny W (2011) Post hoc Bayesian model selection. *Neuroimage* 56: 2089-2099.
- Friston KJ, Kahan J, Biswal B, Razi A (2014) A DCM for resting state fMRI. *Neuroimage* 94:396-407.
- Friston KJ, Preller KH, Mathys C, Cagnan H, Heinze J, Razi A, Zeidman P (2017) Dynamic causal modelling revisited. *NeuroImage*. 199:730-744.

## DCM literature (2)

- Frässle S, Yao Y, Schöbi S, Aponte EA, Heinze J, Stephan KE (in press) Generative models for clinical applications in computational psychiatry. Wiley Interdisciplinary Reviews: Cognitive Science.
- **Frässle S, Lomakina EI, Razi A, Friston KJ, Buhmann JM, Stephan KE (2017) Regression DCM for fMRI. NeuroImage 155:406-421.**
- 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.
- Penny WD, Stephan KE, Mechelli A, Friston KJ (2004b) Modelling functional integration: a comparison of structural equation and dynamic causal models. NeuroImage 23 Suppl 1:S264-274.
- 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**

## DCM literature (3)

- 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.
- Stephan KE, Weiskopf N, Drysdale PM, Robinson PA, Friston KJ (2007) Comparing hemodynamic models with DCM. *NeuroImage* 38:387-401.
- Stephan KE, Kasper L, Harrison LM, Daunizeau J, den Ouden HE, Breakspear M, Friston KJ (2008) Nonlinear dynamic causal models for fMRI. *NeuroImage* 42:649-662.
- Stephan KE, Penny WD, Daunizeau J, Moran RJ, Friston KJ (2009a) Bayesian model selection for group studies. *NeuroImage* 46:1004-1017.
- Stephan KE, Tittgemeyer M, Knösche TR, Moran RJ, Friston KJ (2009b) Tractography-based priors for dynamic causal models. *NeuroImage* 47: 1628-1638.
- **Stephan KE, Penny WD, Moran RJ, den Ouden HEM, Daunizeau J, Friston KJ (2010) Ten simple rules for Dynamic Causal Modelling. *NeuroImage* 49: 3099-3109.**
- Stephan KE, Mathys C (2014). Computational approaches to psychiatry. *Current Opinion in Neurobiology* 25: 85-92.
- 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
- **Zeidman P, Jafarian A, Corbin N, Seghier ML, Razi A, Price CJ, Friston KJ (2019) A guide to group effective connectivity analysis, part 1: First level analysis with DCM for fMRI. *NeuroImage*, DOI: 10.1016/j.neuroimage.2019.06.031**
- **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**