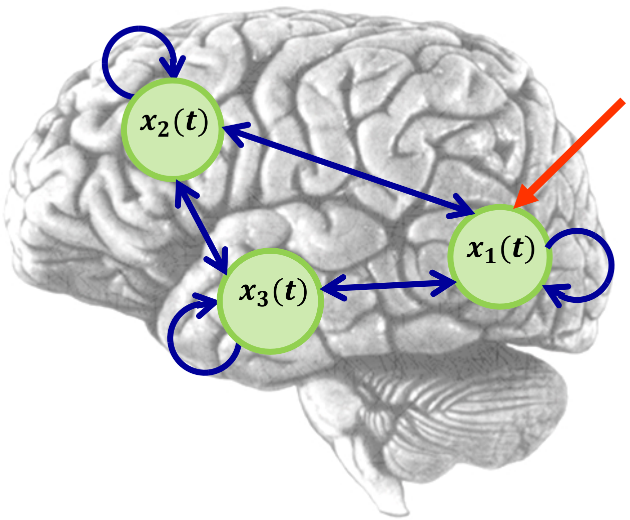


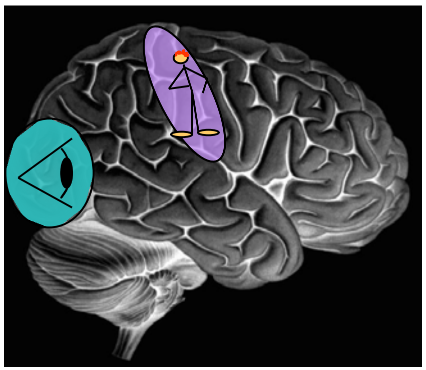
Dynamic causal modelling for fMRI

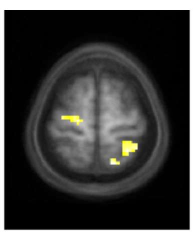
Jakob Heinzle
Translational Neuromodeling Unit (TNU),
Institute for Biomedical Engineering
University and ETH Zürich

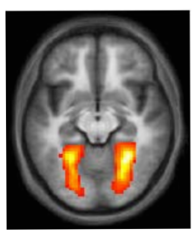
CPC 2018, Zürich, Switzerland

Specialisation vs. Integration

Functional Specialisation



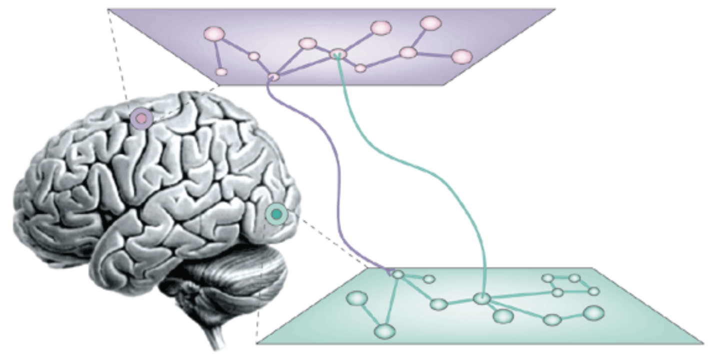


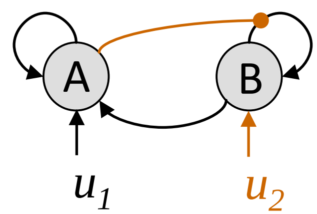


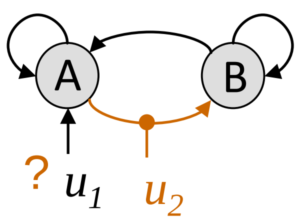
u_1 $u_1 \, X \, u_2$

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

Functional Integration

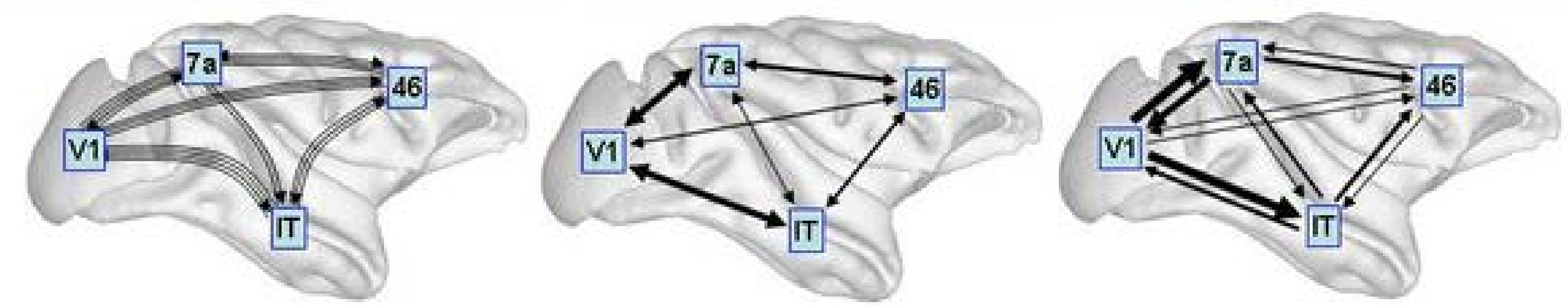






*«**How** did my experimental manipulation **propagate through the network**?»*

Structural, functional & effective connectivity



Sporns 2007, *Scholarpedia*

anatomical/structural

- presence of physical connections

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

functional

- statistical dependency between regional time series

→ *correlations, ICA*

effective

- direct influences between neuronal populations

→ *DCM*

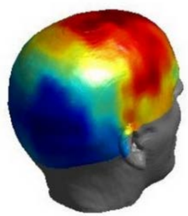
Context-independent

Mechanism - free

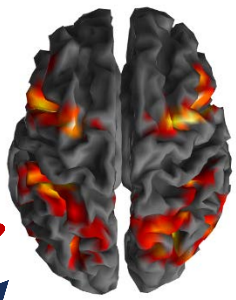
Mechanistic

Dynamic causal modelling

EEG,
MEG



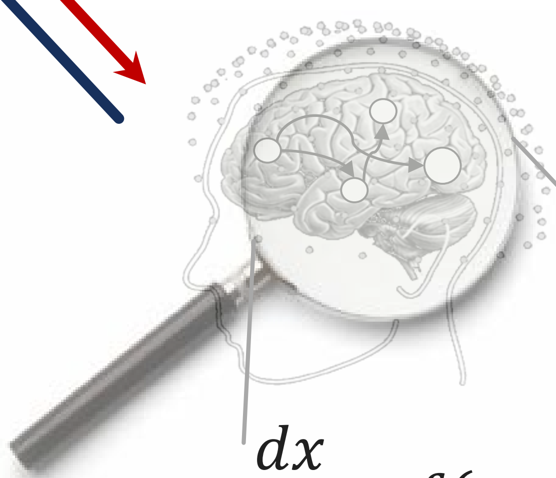
Model inversion:
Estimating
neuronal
mechanisms



fMRI

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
→ Dario Schöbi

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

Dynamic causal modelling

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NeuroImage
NeuroImage 19 (2003) 1273–1302
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Dynamic causal modelling

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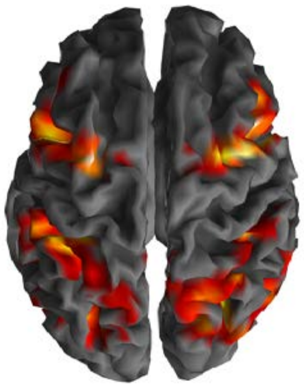
Received 18 October 2002; revised 7 March 2003; accepted 2 April 2003

DCM for fMRI - Overview

Model inversion:

Estimating neuronal mechanisms

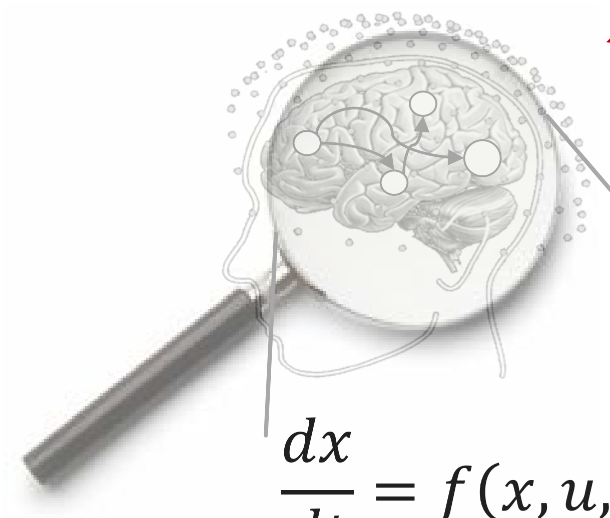


fMRI

Forward model:

Predicting measured activity

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

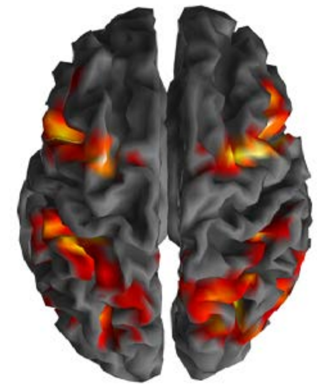


$$\frac{dx}{dt} = f(x, u, \theta)$$

Neural state equation:

Describing neuronal dynamics

DCM for fMRI - Overview



fMRI

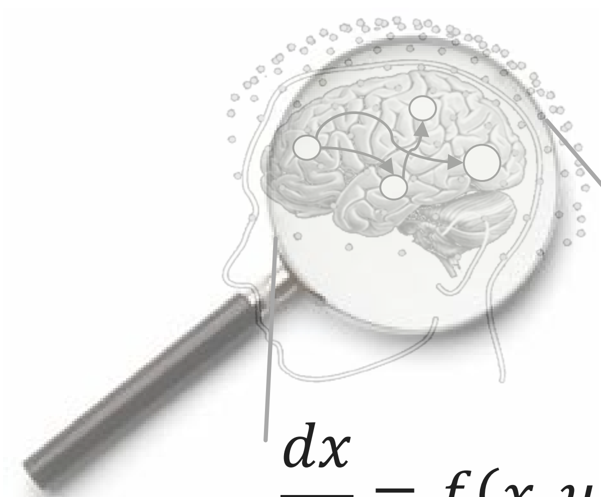
Model inversion:

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

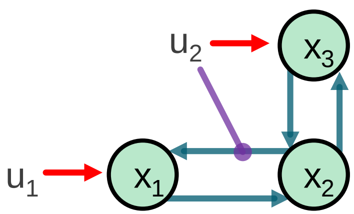
$$\frac{dx}{dt} = f(x,u) \approx \boxed{f(x_0,0) + \frac{\partial f}{\partial x}x + \frac{\partial f}{\partial u}u + \frac{\partial^2 f}{\partial x \partial u}ux} + \frac{\partial^2 f}{\partial x^2}\frac{x^2}{2} + \cdots$$

bilinear model

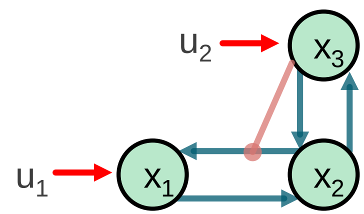
Neuronal state equations

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

bilinear model

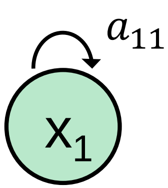


nonlinear model

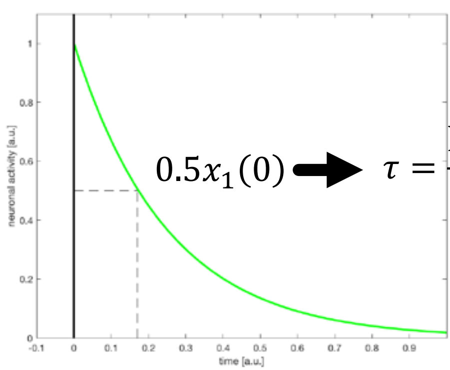


Neuronal state equations

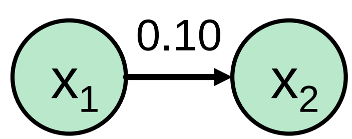
DCM effective connectivity parameters are rate constants



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



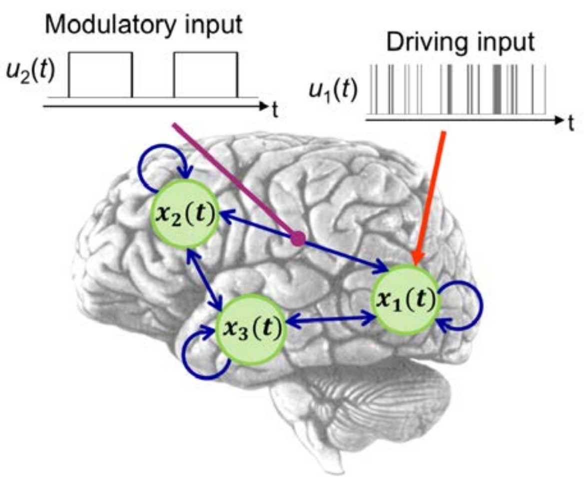
$$0.5x_1(0) \longrightarrow \tau = \frac{\ln 2}{a_{11}}$$



If region$_1$ → region$_2$ is 0.10s^{-1}, this means that, per unit time, the increase in activity in region$_2$ corresponds to 10% of the current activity in region$_1$

Neuronal state equations

Interim summary: bilinear neuronal state equation



State change

External inputs

Current state

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

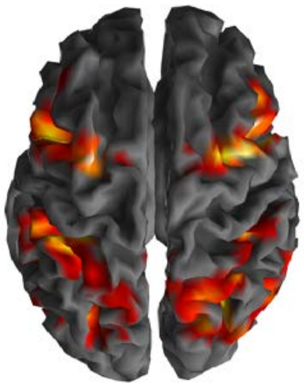
$$\theta = \{A, B^{(1)}, \ldots, B^{(m)}, C\}$$

Endogenous connectivity

Modulatory connectivity

Driving inputs

DCM for fMRI - Overview



fMRI

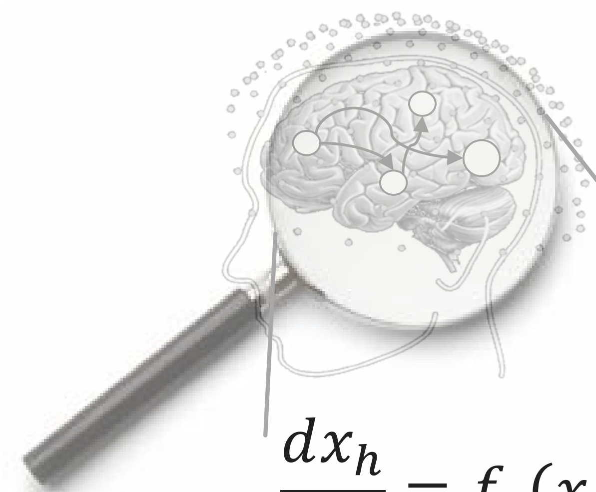
Model inversion:

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

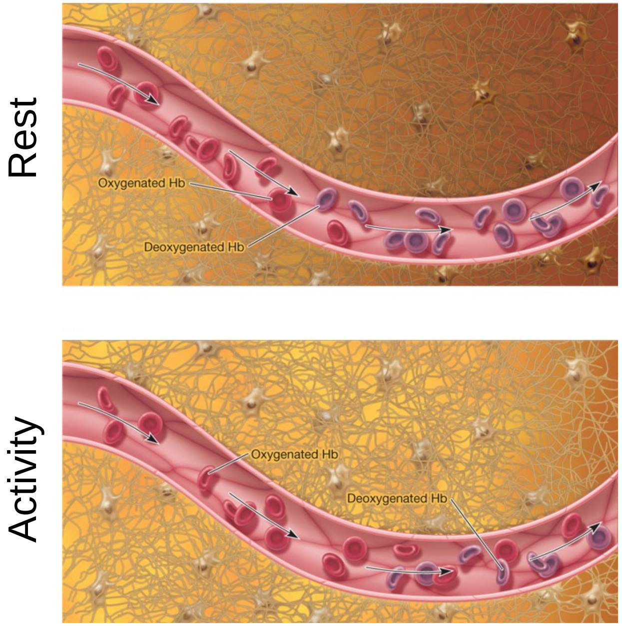
↑ neuronal activity

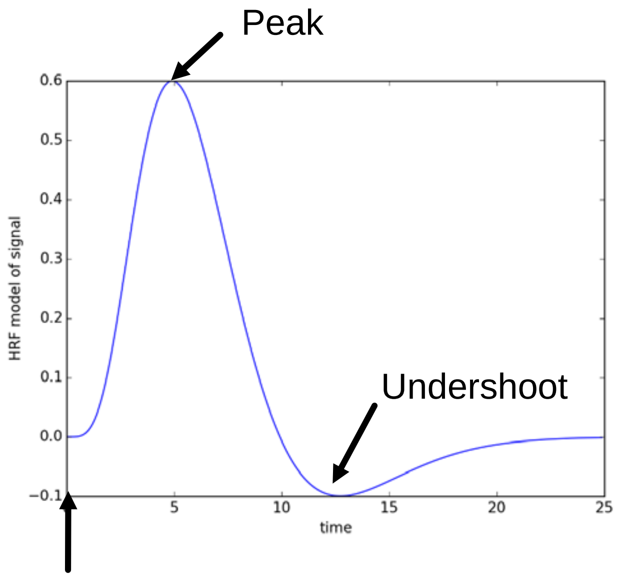
↑ blood flow

↑ oxygenated Hb

↑ T2*

↑ fMRI signal





Huettel et al, 2004, fMRI (Book)

The hemodynamic model

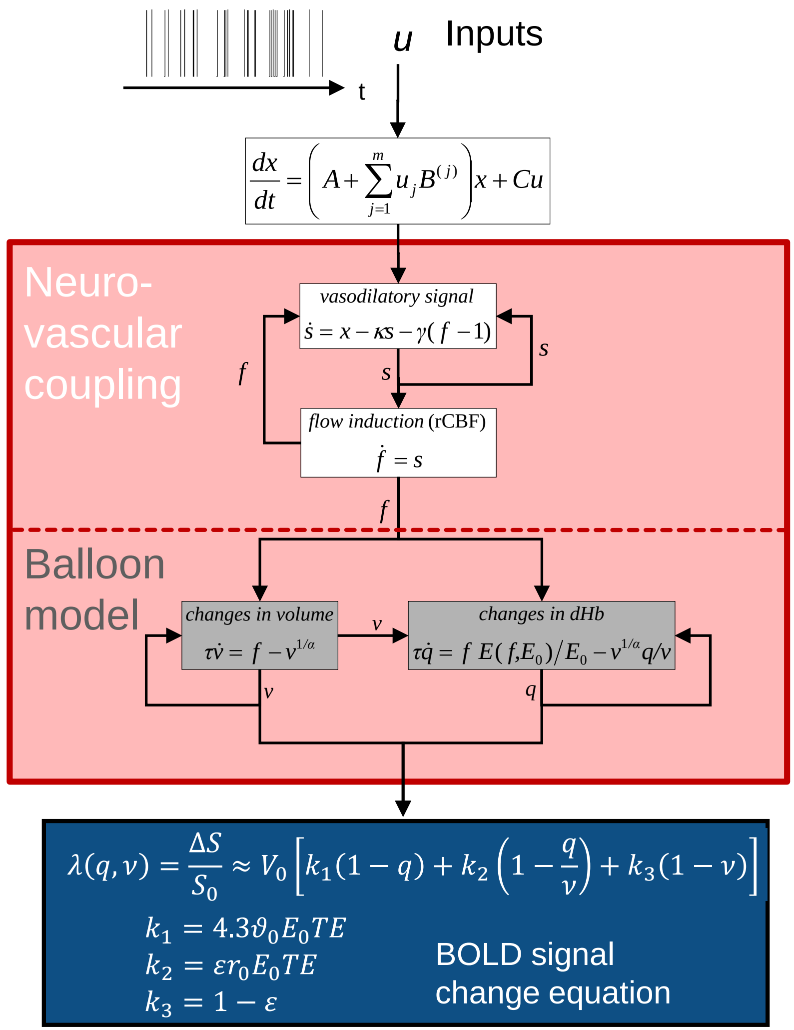
6 parameters:

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

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

Region specific HRF

→ Parameters computed separately for each region



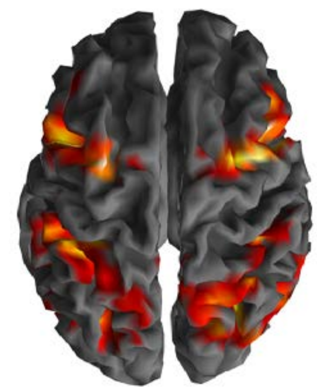
State equation

neural

hemodynamic

Stephan et al., 2007, NeuroImage

DCM for fMRI - Overview



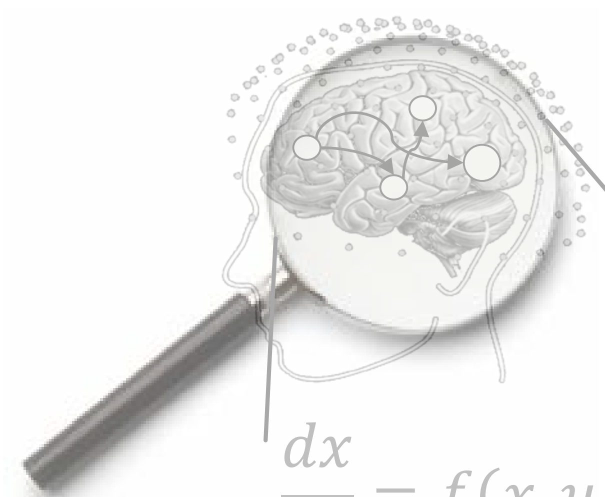
Model inversion:

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

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

BOLD-Signal Parameters:

$$k_1 = 4.3\vartheta_0 E_0 TE$$

$$k_2 = \varepsilon r_0 E_0 TE$$

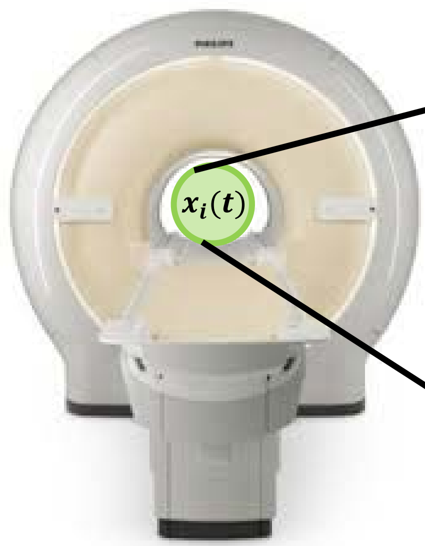
$$k_3 = 1 - \varepsilon$$

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

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



Neurovascular coupling

Changes in volume ($\boldsymbol{v}$) and dHb ($\boldsymbol{q}$)

Balloon model

Changes in volume ($\boldsymbol{v}$) and dHb ($\boldsymbol{q}$)

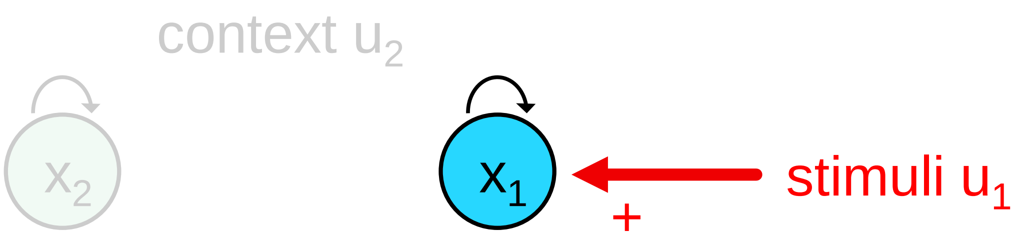
$$\boldsymbol{x} \rightarrow \boldsymbol{f} \rightarrow \boldsymbol{v}, \boldsymbol{q}$$

BOLD signal is a **direct function** of $\boldsymbol{v}$ and $\boldsymbol{q}$

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

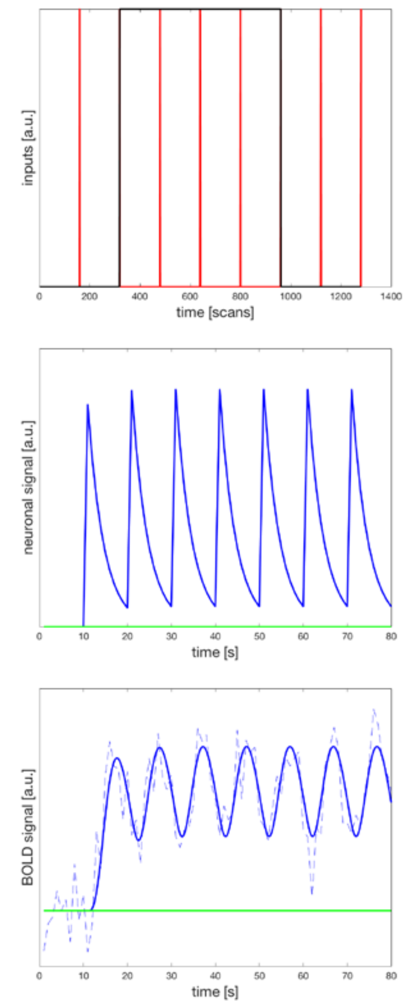
Simulation example: What can DCM explain?

Example: single node



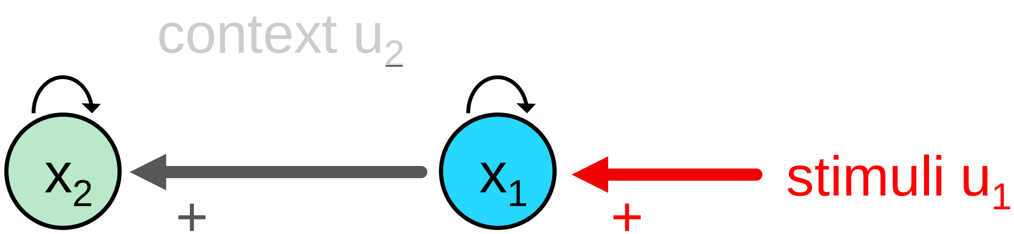
$$\frac{dx}{dt} = Ax + u_2 B^{(2)} x + C u_1$$

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



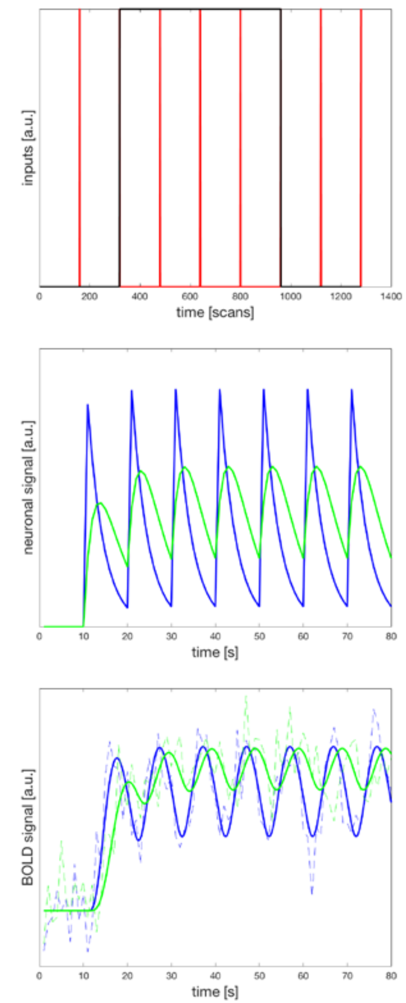
Simulation example: What can DCM explain?

Example: two connected node



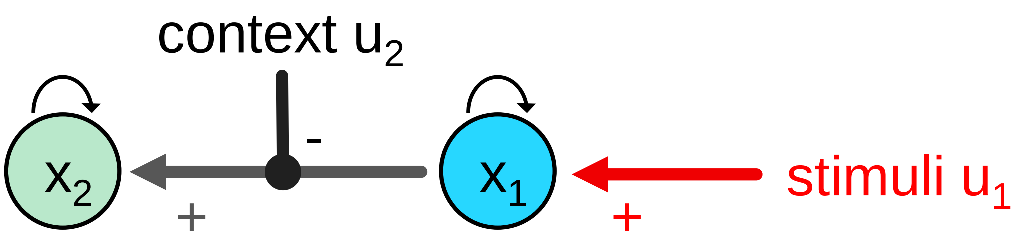
$$\frac{dx}{dt} = Ax + u_2 B^{(2)} x + C u_1$$

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



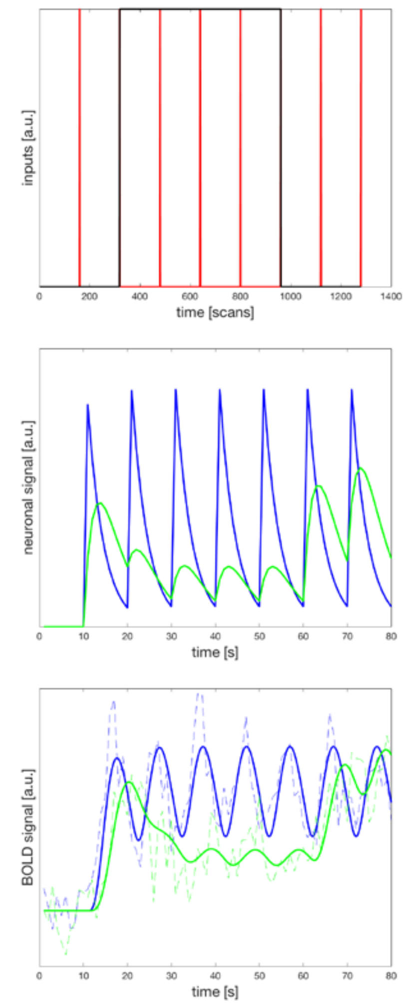
Simulation example: What can DCM explain?

Example: modulation of connection



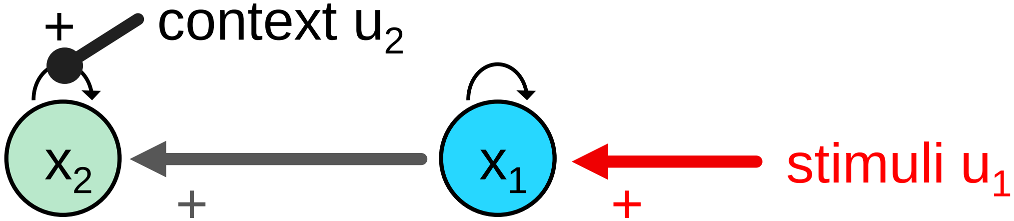
$$\frac{dx}{dt} = Ax + u_2 B^{(2)} x + C u_1$$

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



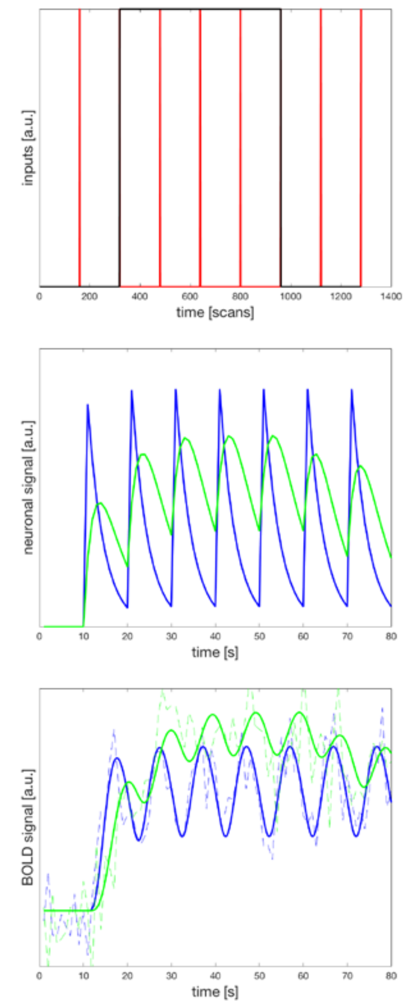
Simulation example: What can DCM explain?

Example: modulation of inhibitory self-connection



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

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

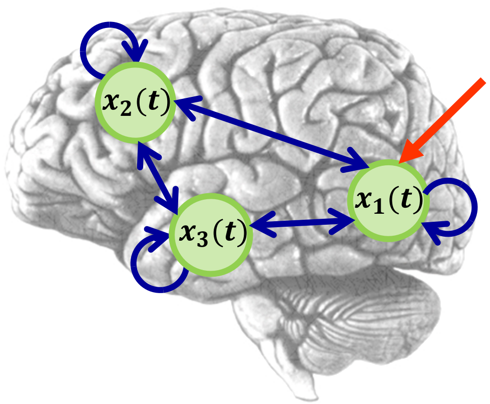


DCM for fMRI

A simple model of a neural network …

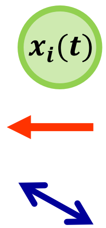
… described as a dynamical system …

… causes the data (BOLD signal).



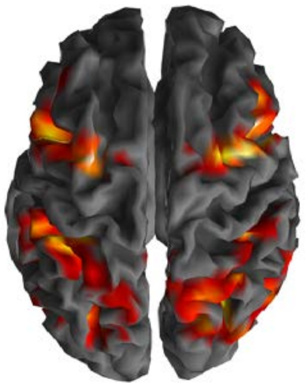
$$\dot{x} = f(x, u, \theta)$$

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



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



fMRI

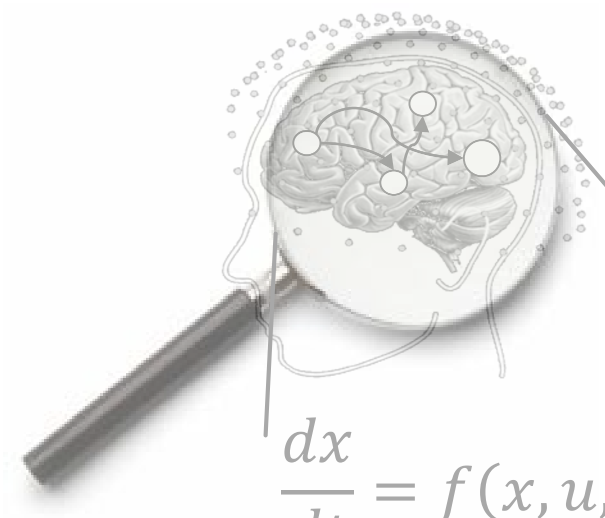
Model inversion:

Estimating neuronal mechanisms

Forward model:

Predicting measured activity

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



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

Neural state equation:

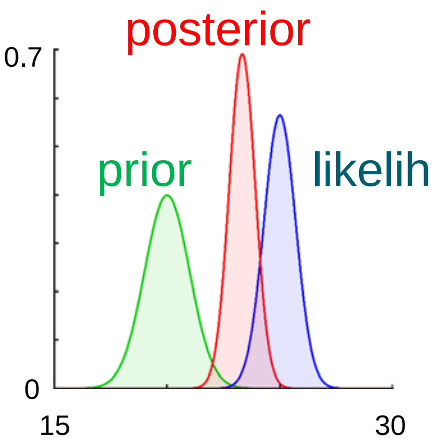
Describing neuronal dynamics

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

Bayes’ theorem

Reverend Thomas Bayes
(1702-1761)

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



The likelihood function for DCM

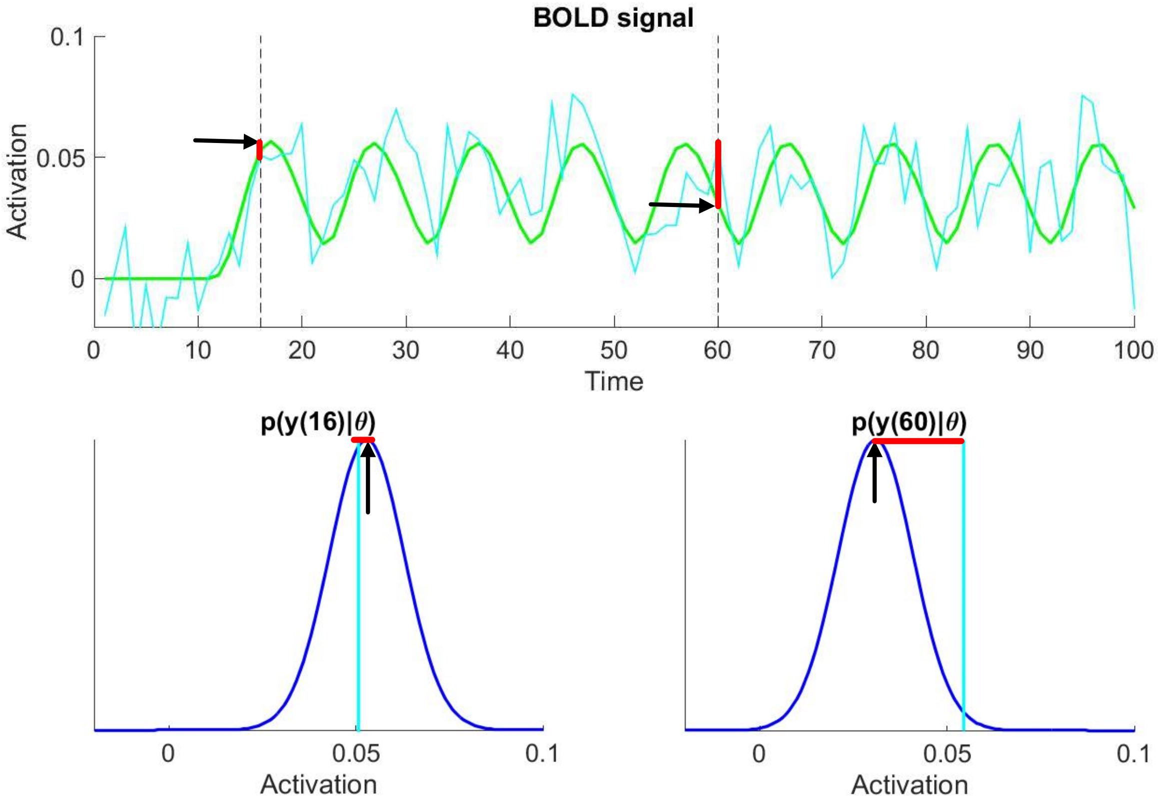
$$\underbrace{p(y(t)|\theta, m)}_{\text{likelihood}} = \mathcal{N}\left(y(t); g\left(\theta^{n}, \theta^{h}, u\right), \theta^{\sigma}\right)$$

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



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

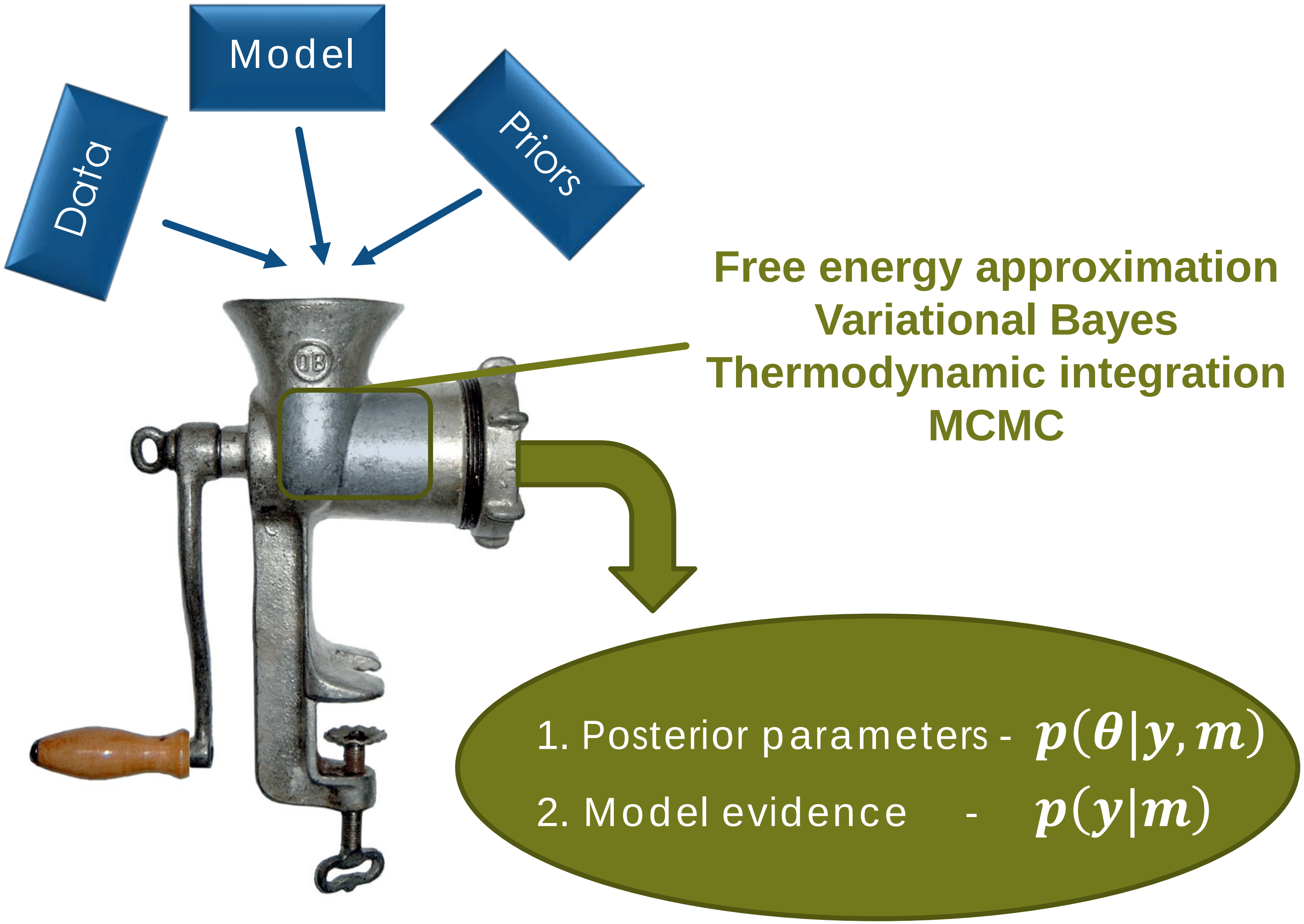
Hemodynamic parameters:

- empirical

Noise prior:

- assume relatively noisy data

Model estimation: running the machinery

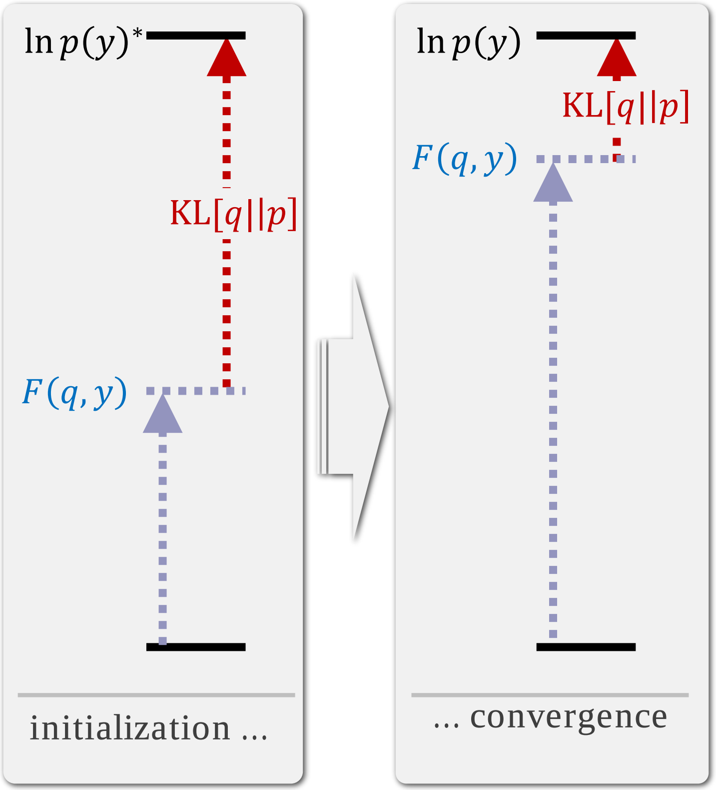


Inversion – variational Free Energy approximation to model evidence

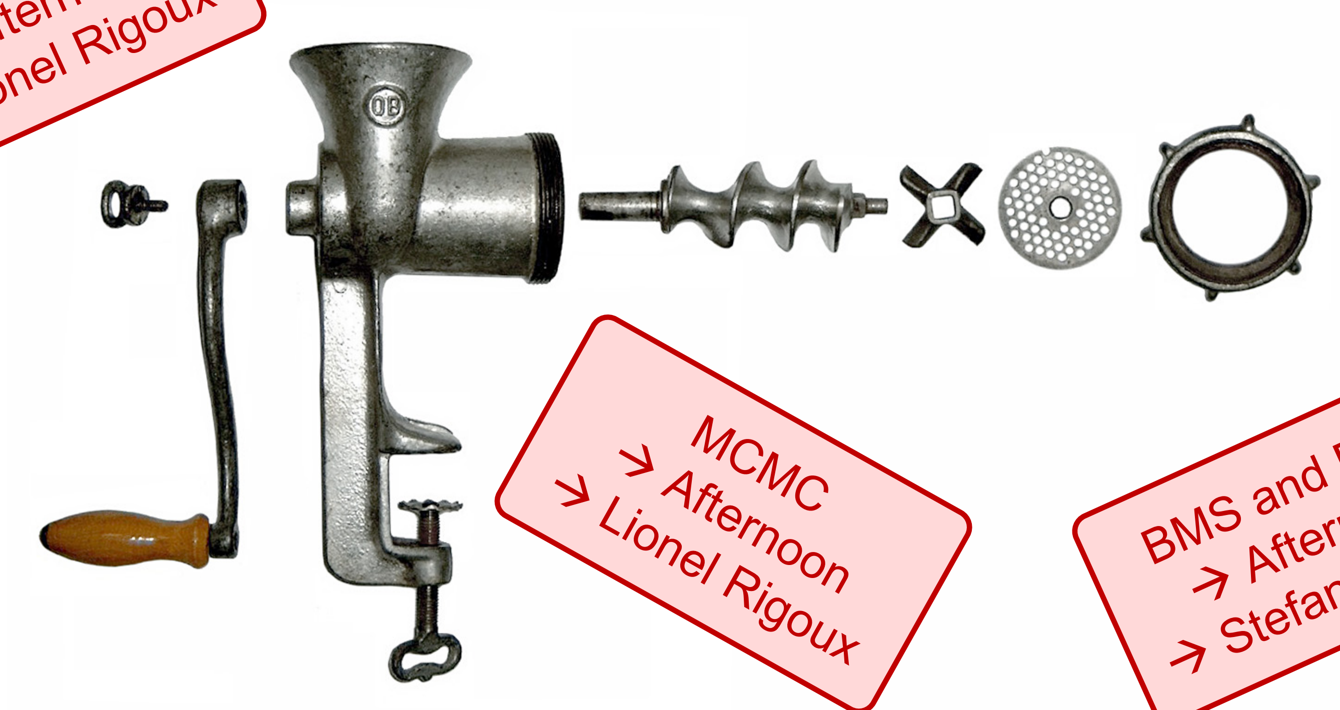
model evidence

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

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



Model estimation: running the machinery



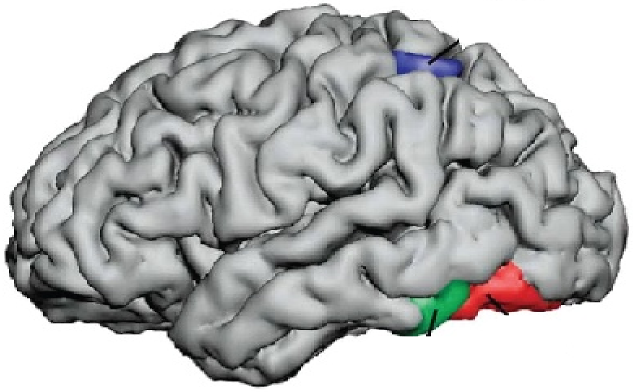
Variational Bayes
→ Afternoon
→ Lionel Rigoux

MCMC
→ Afternoon
→ Lionel Rigoux

BMS and BMA
→ Afternoon
→ Stefan Frässle

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)

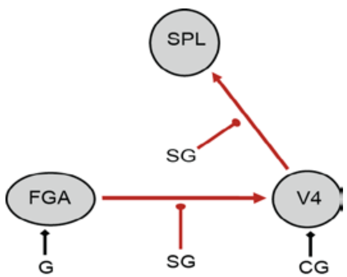


Hubbard, 2007

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

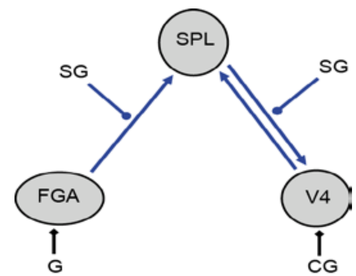
Bottom-up

(*Ramachandran & Hubbard, 2001*)



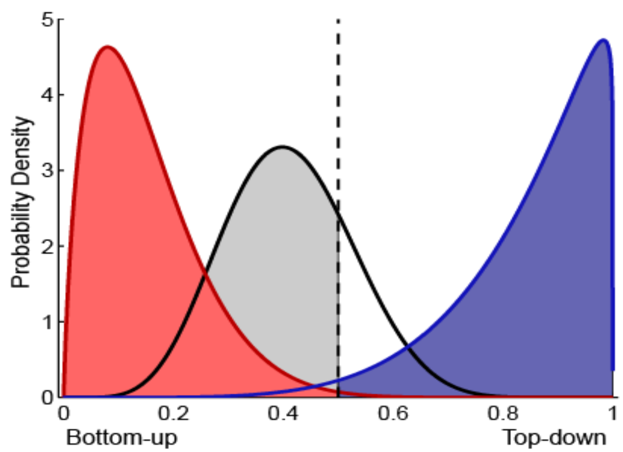
Top-down

(*Grossenbacher & Lovelace, 2001*)

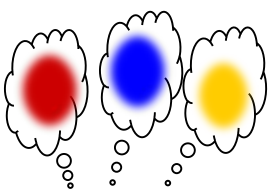


Projectors

ABC



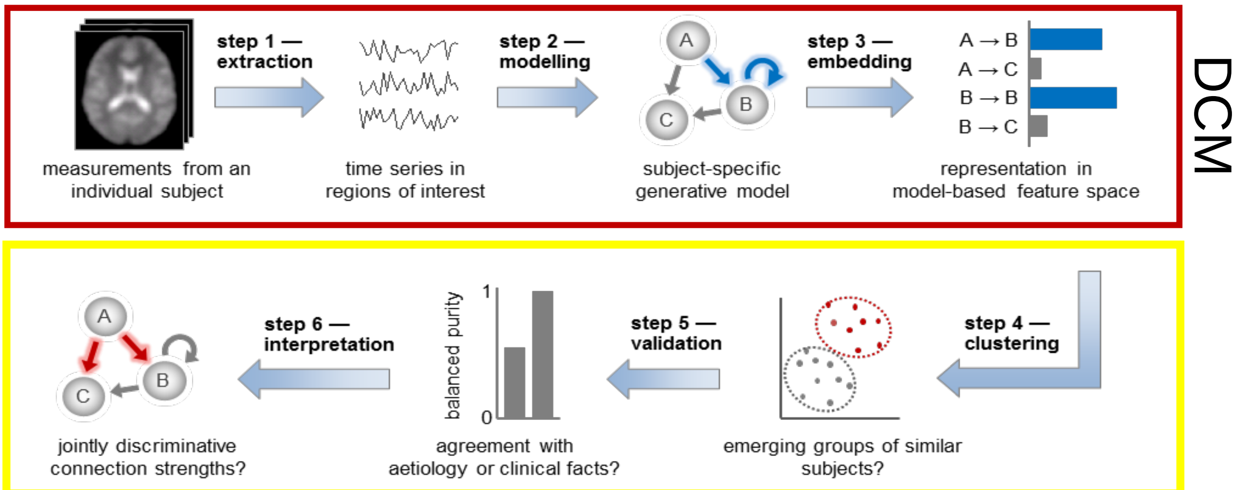
Associators

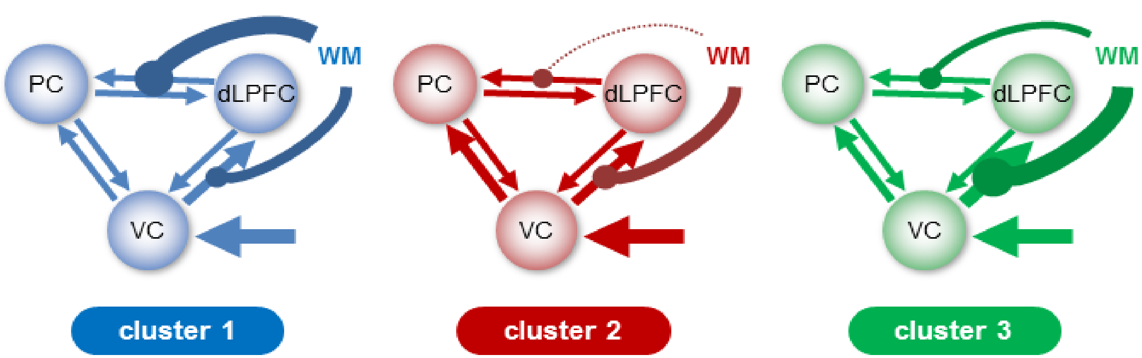


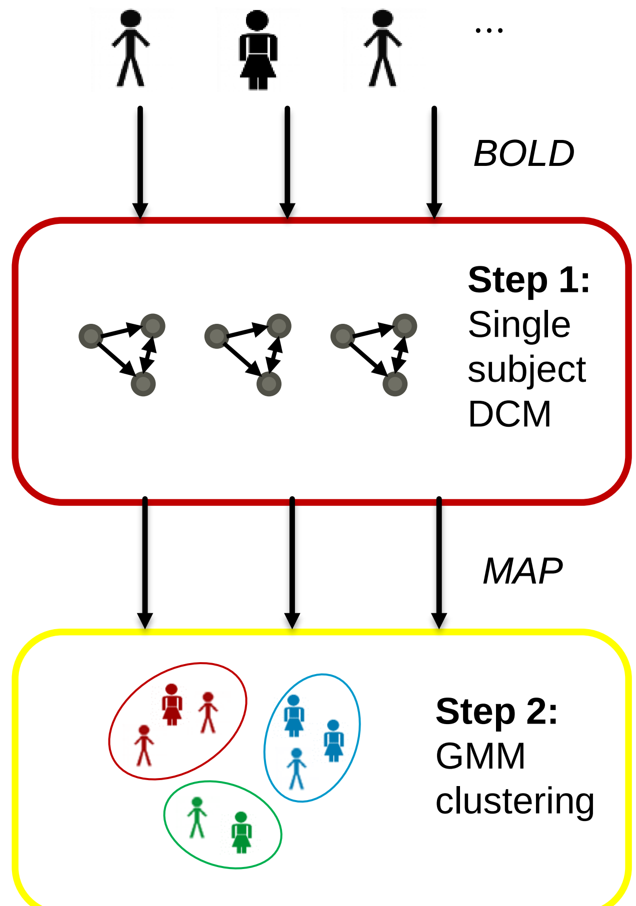
ABC

Van Leeuwen et al., JNeurosci, 2011

Example: DCM for physiologically plausible feature extraction







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!

DCM software note

Basic functionality for DCM for fMRI is provided within

SPM
https://www.fil.ion.ucl.ac.uk/spm/

Limitations

- Local minima:
  - Variational approximation can get stuck in local minima of free energy
- Size of networks:
  - Standard inversion gets prohibitively slow for large networks (more than 10 nodes).
- Regularization through fixed priors:
  - Current regularization depends on priors only. Regularization based on group (all subjects) would be better → empirical Bayes.

Recent additions to DCM for fMRI

- Massively parallel dynamic causal modelling
  - ➢ mpdcm

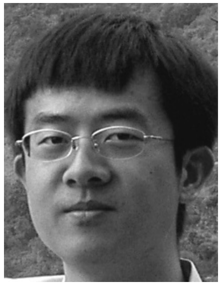
Eduardo Aponte

- Regression dynamic causal modelling
  - ➢ rDCM

Stefan Frässle

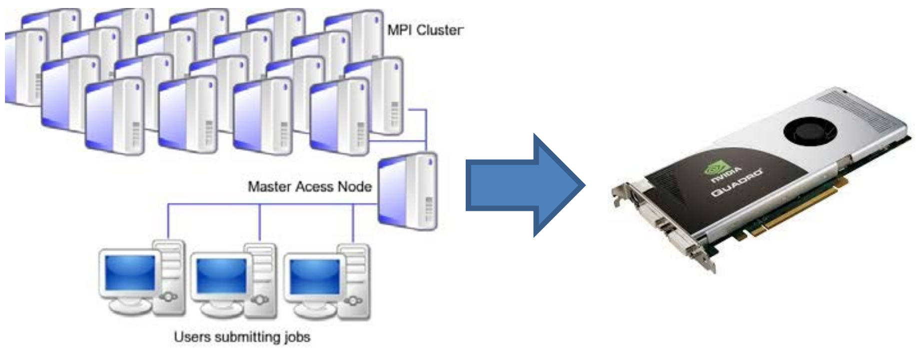
- Hierarchical unsupervised generative embedding
  - ➢ HUGE

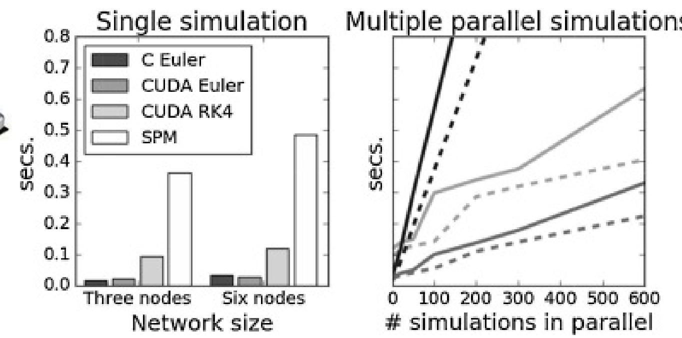
Yu Yao



Available in TAPAS:
www.translationalneuromodeling.org/tapas

Massively parallel DCM - mpdcm

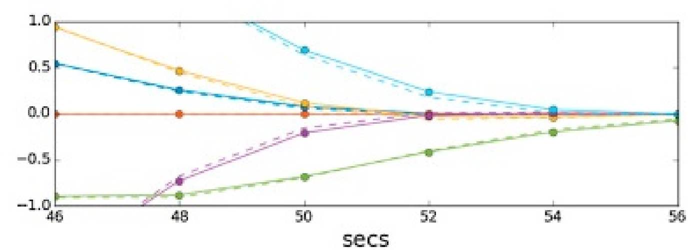




$$\left.\begin{array}{l}\dot{x} = f(x, u_1, \theta_1) \\ \dot{x} = f(x, u_2, \theta_2) \\ \vdots \\ \dot{x} = f(x, u_1, \theta_1)\end{array}\right\}$$

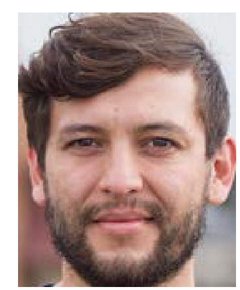
mpdcm_integrate(dcms)

$$\left\{\begin{array}{l}y_1 \\ y_2 \\ \vdots \\ y_3\end{array}\right.$$



- Fast inversion of DCMs
- MCMC based inversion possible

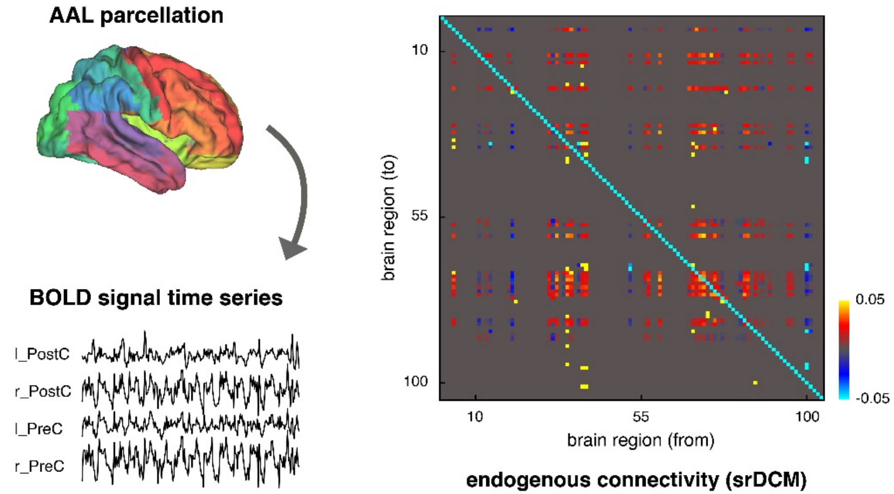
→ **Thermodynamic Integration** (alternative to Free Energy)

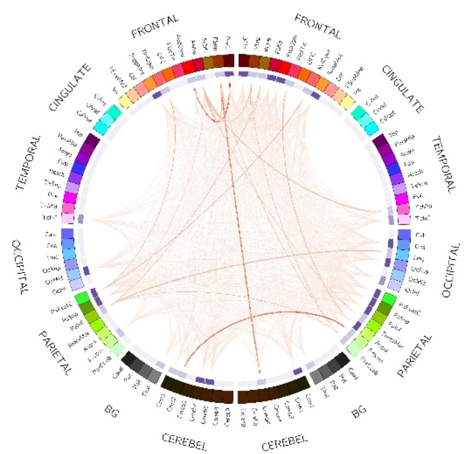


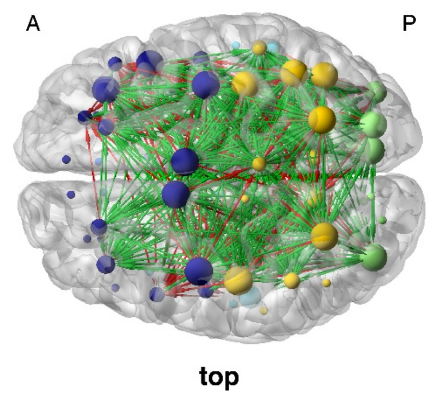
Aponte et al., 2015, J. Neurosci. Meth.

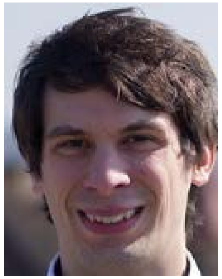
Regression DCM - rDCM

- Extremely efficient model inversion
- Graceful scaling to large networks
- Network pruning as part of model inversion (sparsity constraints)
- **Inference of whole-brain connectogram** (~100 nodes and 10000 connections)



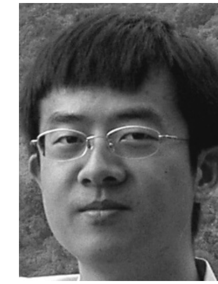




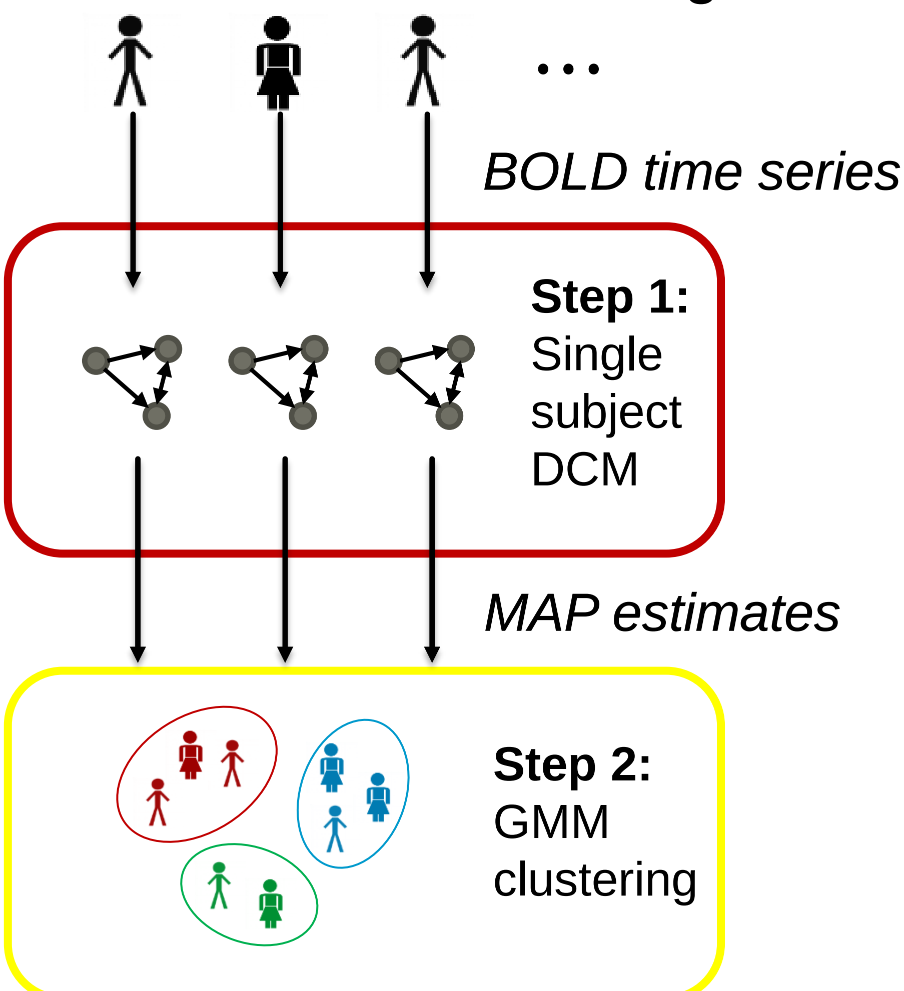


Frässle et al., 2017, NeuroImage; Frässle et al., 2018, NeuroImage

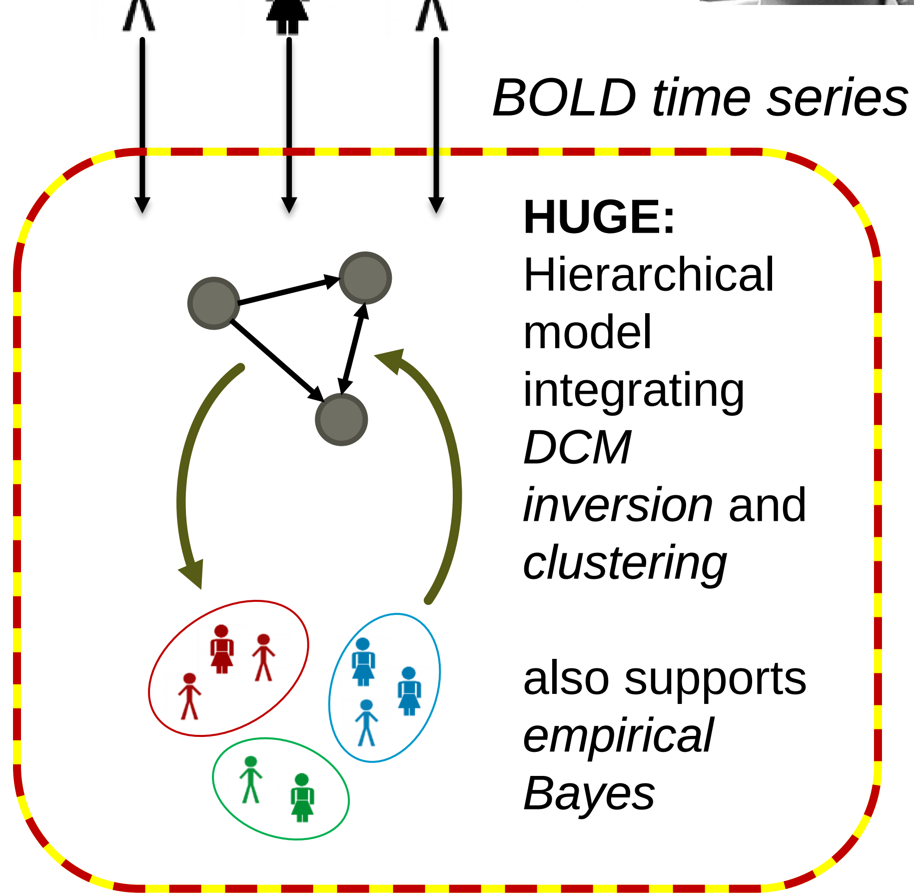
Hierarchical Unsupervised Generative Embedding (HUGE)



Generative Embedding

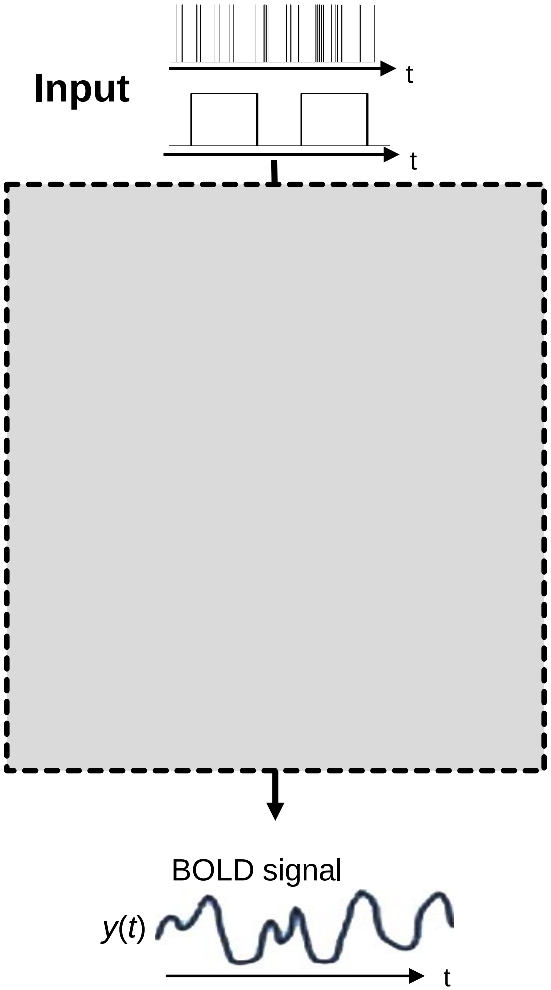


HUGE

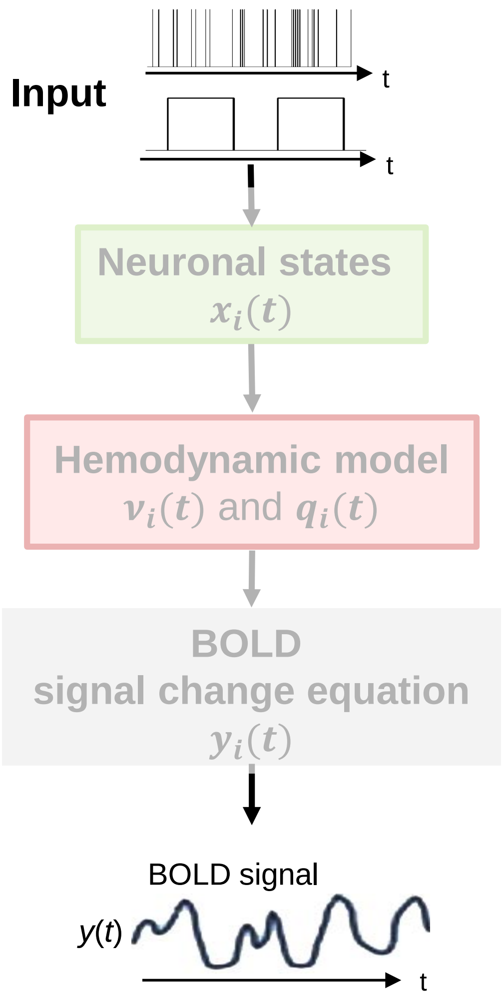


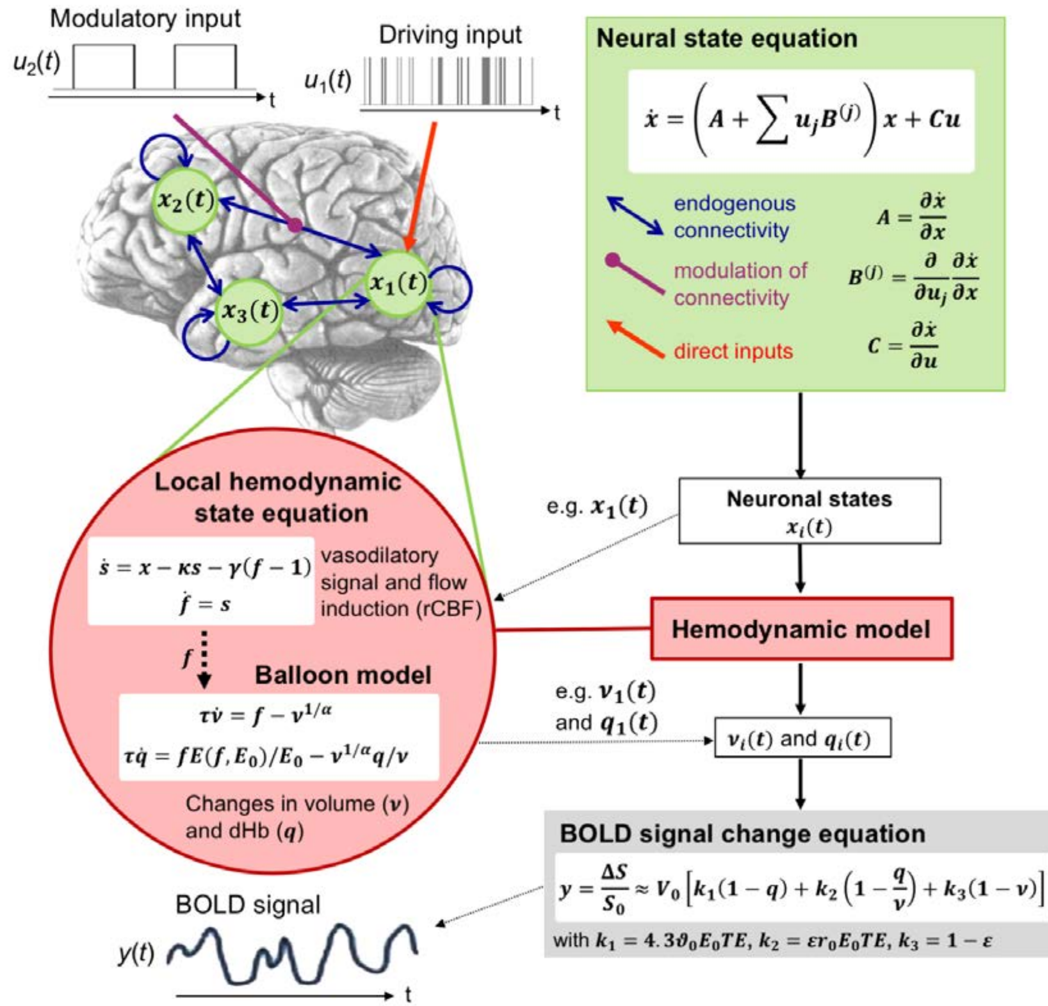
Raman et al., 2018, J Neurosci Meth; Yao et al., 2018, NeuroImage

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

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

Design experimental inputs

Define likelihood model

Specify priors

Invert model

Make inferences

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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- 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.
- Frässle S, Yao Y, Schöbi S, Aponte EA, Heinzle 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.**

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.
- 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.
- 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.
- 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.
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- **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**