Translational Neuromodeling Unit

University of Zurich UZH

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Eidgenössische Technische Hochschule Zürich
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DYNAMIC CAUSAL MODELING

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Methods and Models for fMRI Analysis (HS 2017)

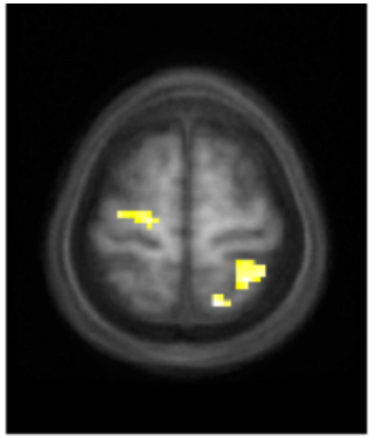
Theoretical Session

Zurich, December 12, 2017

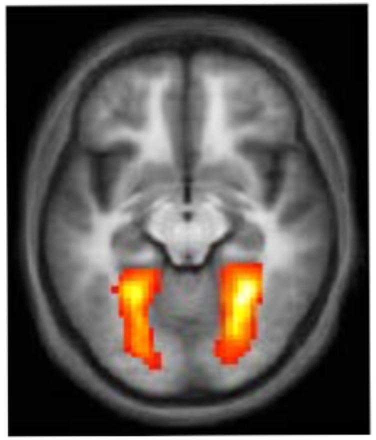
FROM FUNCTIONAL SEGREGATION TO FUNCTIONAL INTEGRATION

localization of brain activity

functional segregation



u_1

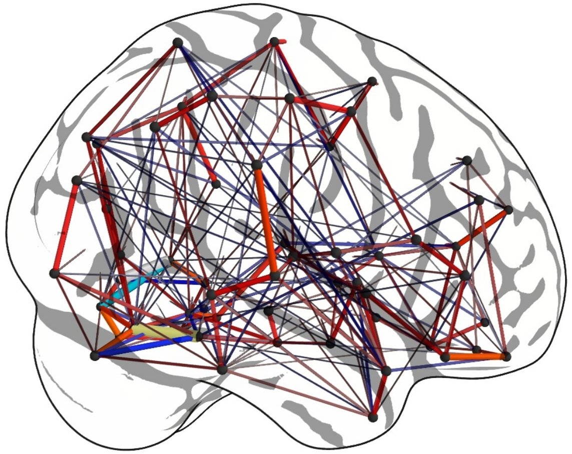


$u_1 \times u_2$

"Where in the brain did my experimental manipulation have an effect?"

analysis of brain connectivity

functional integration

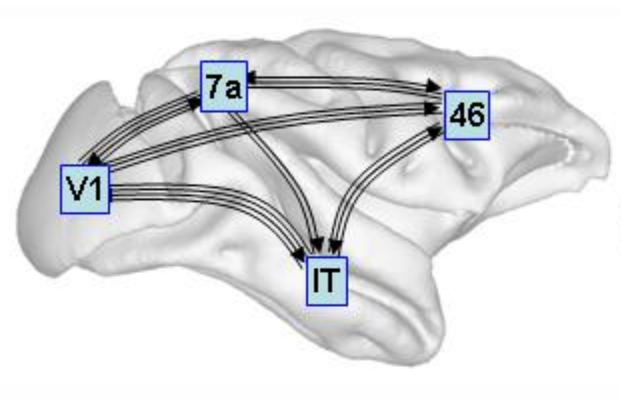


https://team.inria.fr/parietal/files/2013/02/pc_dag.jpg

"How did brain regions interact with each other? How did my experimental manipulation propagate through the network?"

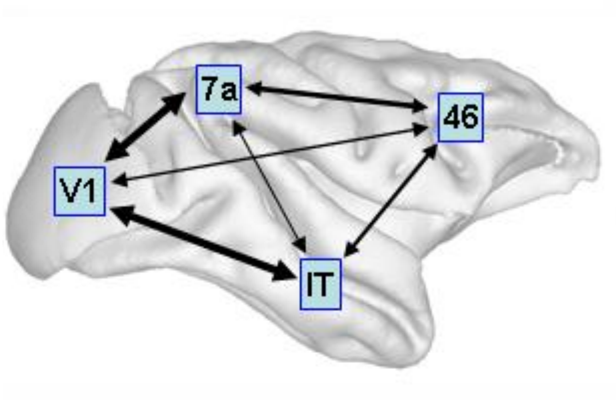
DIFFERENT FORMS OF BRAIN CONNECTIVITY

structural connectivity



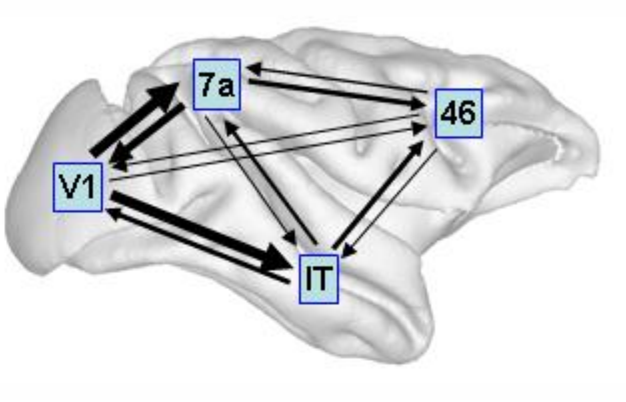
- presence of physical connections
- Diffusion weighted imaging (DWI), tractography, tracer studies

functional connectivity



- statistical dependencies between regional time series
- correlations, Independent Component Analysis (ICA)

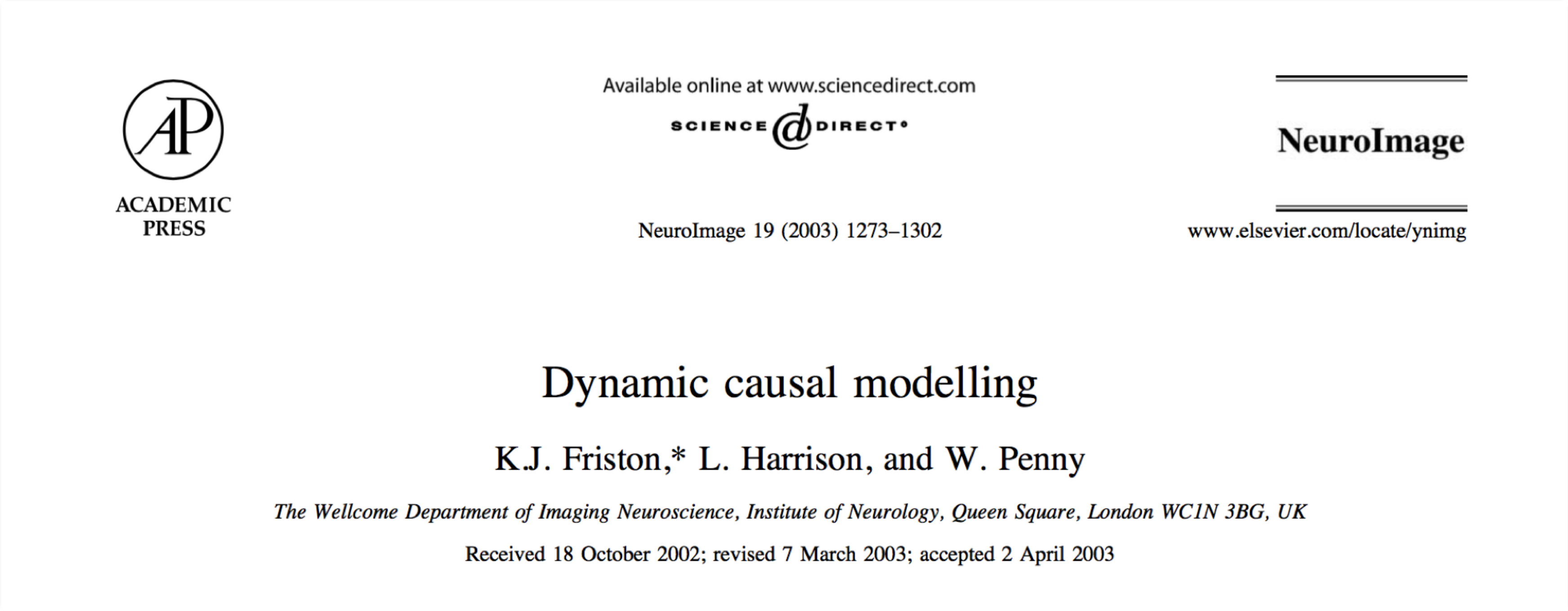
effective connectivity



- causal (directed) influences between neuronal populations
- Dynamic causal modeling (DCM)

Sporns, 2007, *Scholarpedia*

DYNAMIC CAUSAL MODELING



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NeuroImage 19 (2003) 1273–1302

NeuroImage

www.elsevier.com/locate/ynimg

Dynamic causal modelling

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

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

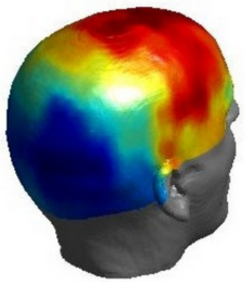
Received 18 October 2002; revised 7 March 2003; accepted 2 April 2003

- Dynamic causal modeling (DCM) for functional magnetic resonance imaging (fMRI) data was introduced in 2003 by Karl Friston, Lee Harrison and Will Penny (NeuroImage 19:1273-1302)
- Allows effective connectivity analyses based on fMRI data

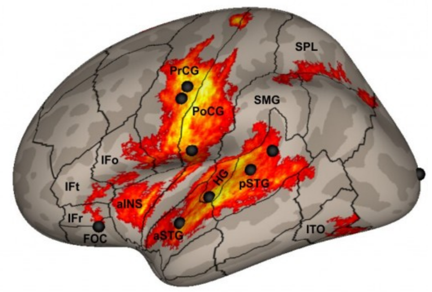
Friston et al., 2003, *NeuroImage*

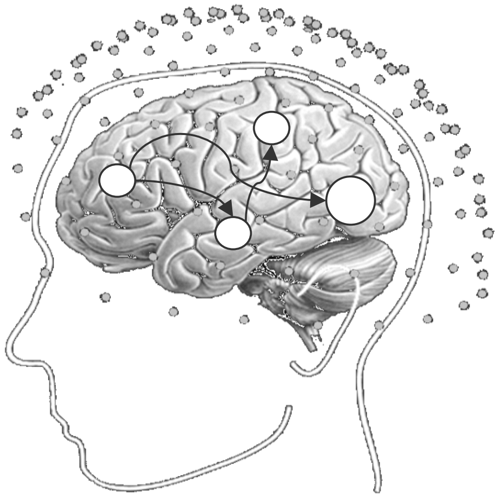
DYNAMIC CAUSAL MODELING

EEG, MEG



fMRT





Forward model:

Predicting measured activity

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

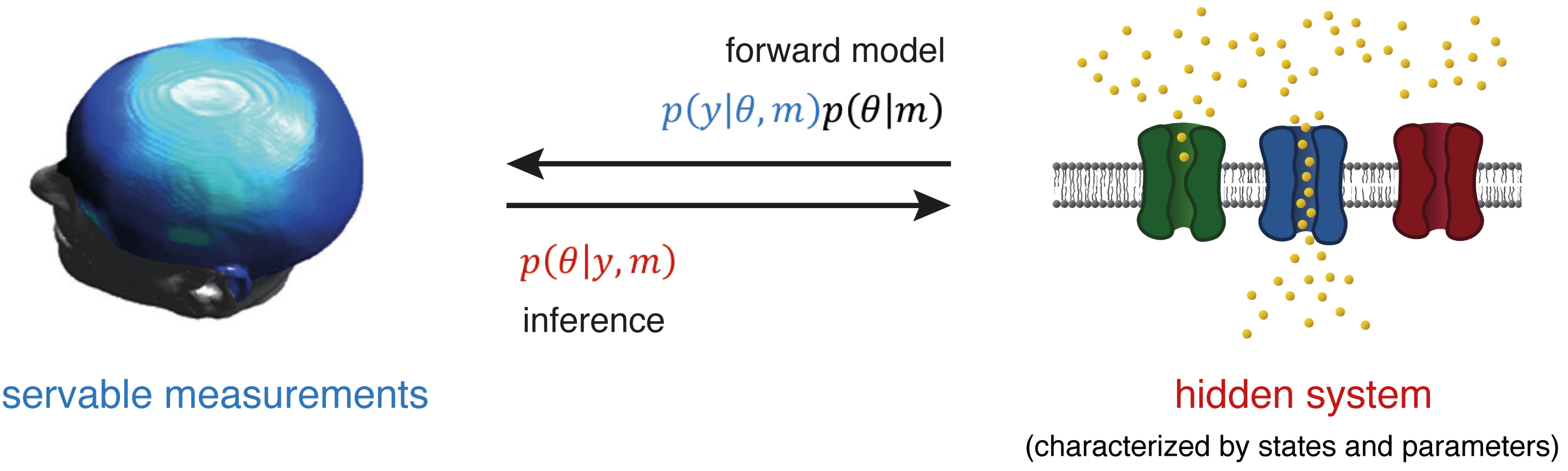
Model inversion:

Estimating neuronal mechanisms

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

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

GENERATIVE MODEL



forward model

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

$p(\theta|y,m)$

inference

observable measurements

hidden system

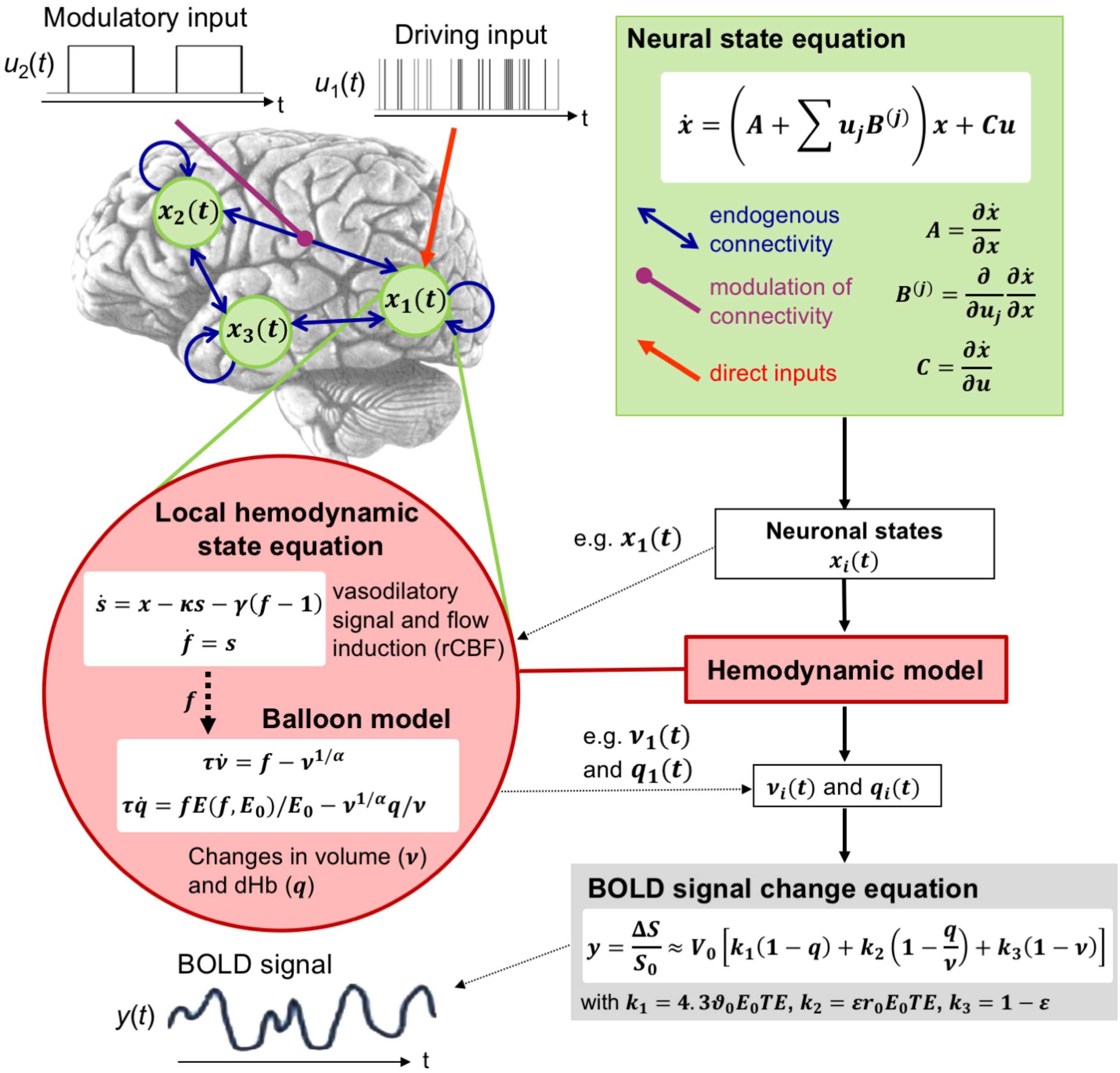
(characterized by states and parameters)

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

Stephan et al., 2016, *Front. Hum. Neurosci.*; Frässle et al., in press, *Wiley Interdiscip. Rev. Cogn. Sci.*

THEORY

DCM FOR FMRI (OVERVIEW)



Neural state equation

$$\dot{x} = \left(A + \sum u_j B^{(j)}\right) x + Cu$$

endogenous connectivity $A = \frac{\partial \dot{x}}{\partial x}$

modulation of connectivity $B^{(j)} = \frac{\partial}{\partial u_j}\frac{\partial \dot{x}}{\partial x}$

direct inputs $C = \frac{\partial \dot{x}}{\partial u}$

Neuronal states
$x_i(t)$

Hemodynamic model

Local hemodynamic state equation

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

vasodilatory signal and flow induction (rCBF)

f

Balloon model

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

Changes in volume (v) and dHb (q)

$v_i(t)$ and $q_i(t)$

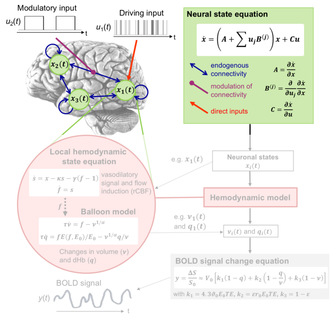
BOLD signal change equation

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

with $k_1 = 4.3\vartheta_0 E_0 TE$, $k_2 = \varepsilon r_0 E_0 TE$, $k_3 = 1 - \varepsilon$

Friston et al., 2003, *NeuroImage*; Stephan et al., 2015, *Neuron*

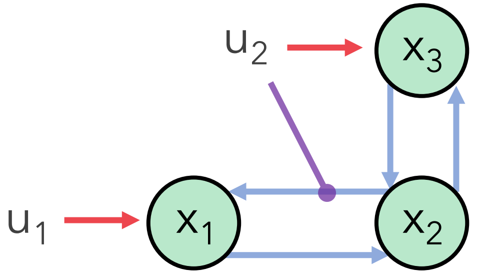
NEURONAL STATE EQUATION

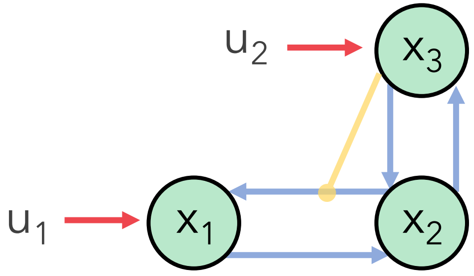


$$\frac{dx}{dt} = f(x,u) \approx f(x_0,0) + \overset{A}{\frac{\partial f}{\partial x}} x + \overset{C}{\frac{\partial f}{\partial u}} u + \overset{B}{\frac{\partial^2 f}{\partial x \partial u}} ux + \overset{D}{\frac{\partial^2 f}{\partial x^2}} \frac{x^2}{2} + \cdots$$

bilinear model

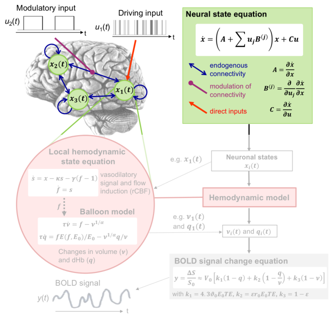
nonlinear model



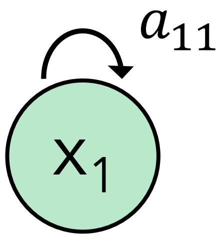


Friston et al., 2003, *NeuroImage*; Stephan et al., 2008, *NeuroImage*

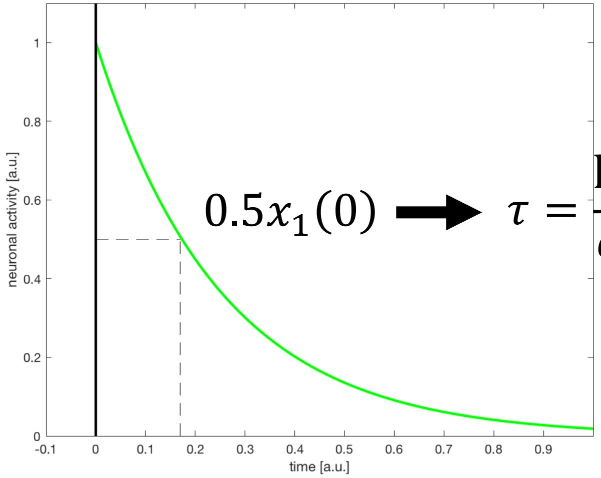
NEURONAL STATE EQUATION



DCM effective connectivity parameters are rate constants

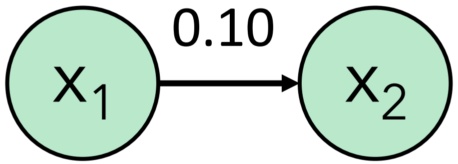


$$\frac{dx_1}{dt} = a_{11}x_1 \longrightarrow x_1(t) = x_1(0) \cdot exp(a_{11}t)$$



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

Friston et al., 2003, *NeuroImage*



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$_1$

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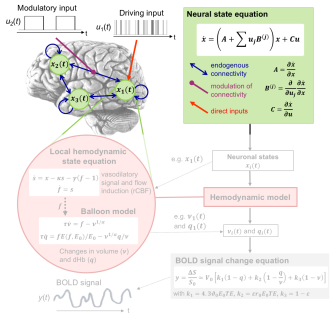
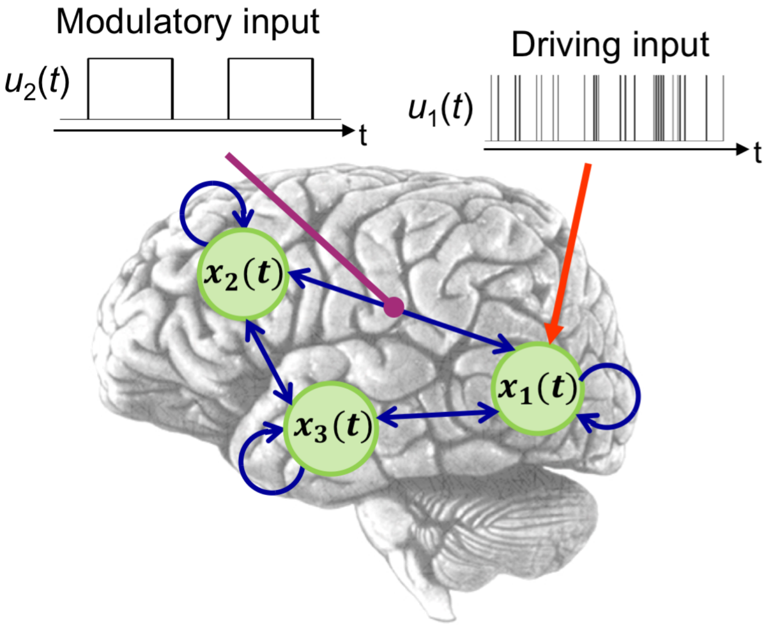


NEURONAL STATE EQUATION

Interim summary: bilinear neuronal state equation



Friston et al., 2003, *NeuroImage*

State change

External inputs

Current state

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

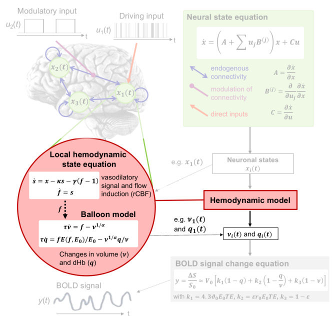
$$\theta = \{A, B^{(1)}, \dots, B^{(m)}, C\}$$

Endogenous connectivity

Modulatory connectivity

Driving inputs

HEMODYNAMIC MODEL



Neuronal dynamics only indirectly observable via hemodynamic response

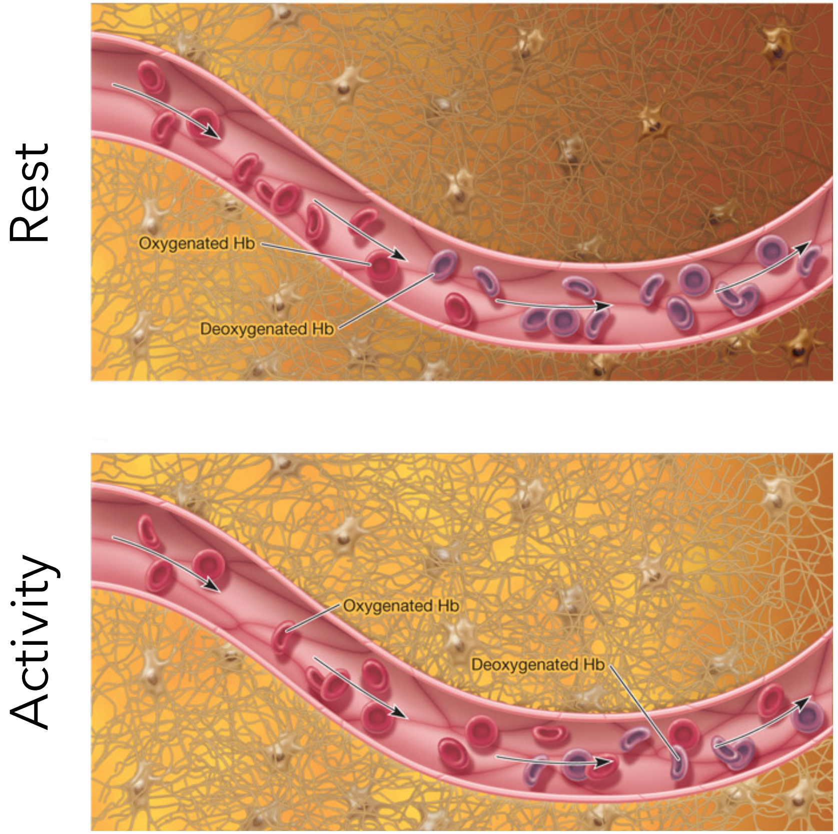
↑ neuronal activity

↑ blood flow

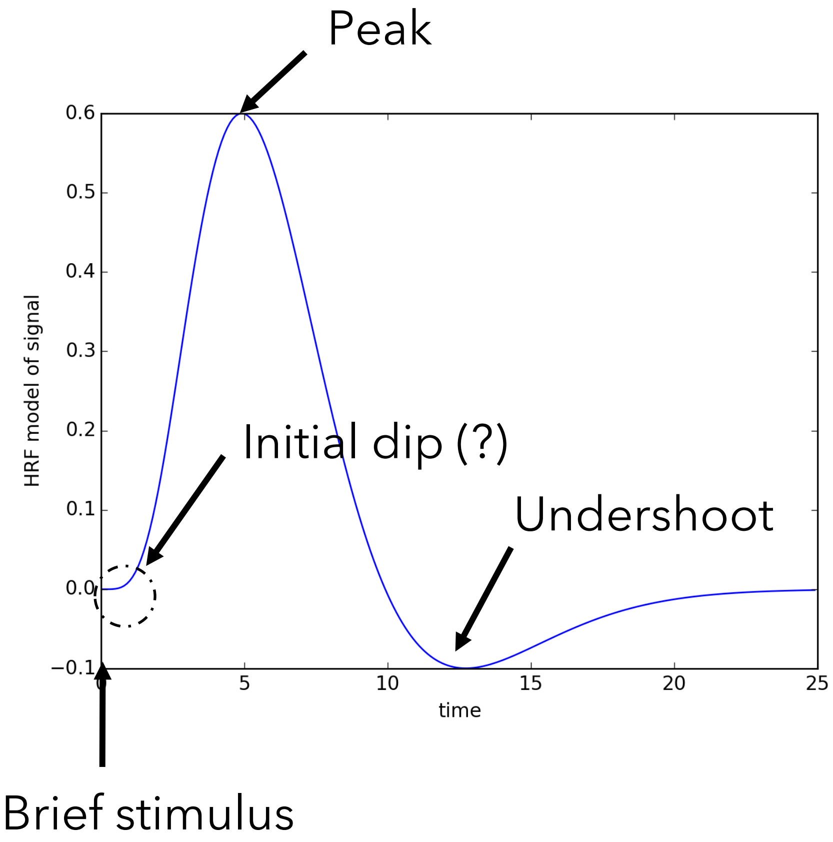
↑ oxygenated Hb

↑ T2*

↑ fMRI signal



Huettel et al., 2004, *NeuroImage*



HEMODYNAMIC MODEL

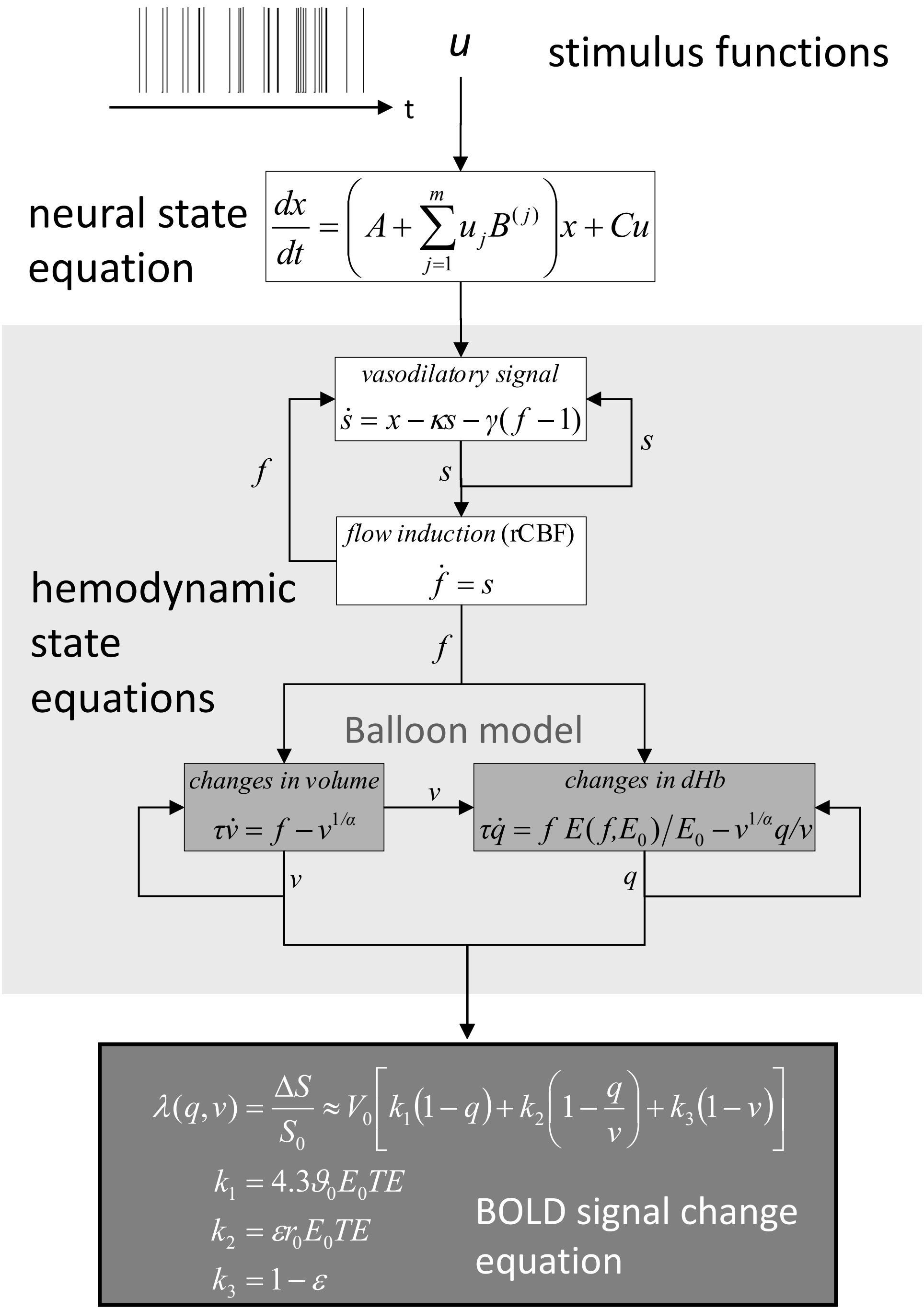
6 hemodynamic parameters:

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

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

Hemodynamic parameters are compute separately for each region → region specific HRFs!

Friston et al., 2003, *NeuroImage*; Stephan et al., 2007, *NeuroImage*



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

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

$$\dot{f} = s$$

$$\tau \dot{v} = f - v^{1/\alpha}$$

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

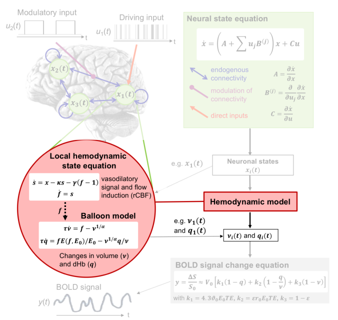
$$\lambda(q,v) = \frac{\Delta S}{S_0} \approx V_0 \left[k_1(1-q) + k_2\left(1 - \frac{q}{v}\right) + k_3(1-v) \right]$$

$$k_1 = 4.3\vartheta_0 E_0 TE$$

$$k_2 = \varepsilon r_0 E_0 TE$$

$$k_3 = 1 - \varepsilon$$

BOLD signal change equation



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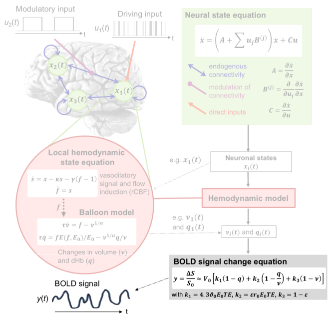
BOLD SIGNAL CHANGE EQUATION



Resting blood volume

Deoxyhemoglobin content

Blood volume

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

$$k_1 = 4.3\vartheta_0 E_0 TE$$

$$k_2 = \varepsilon r_0 E_0 TE$$

$$k_3 = 1-\varepsilon$$

$$V_0 = 0.04$$

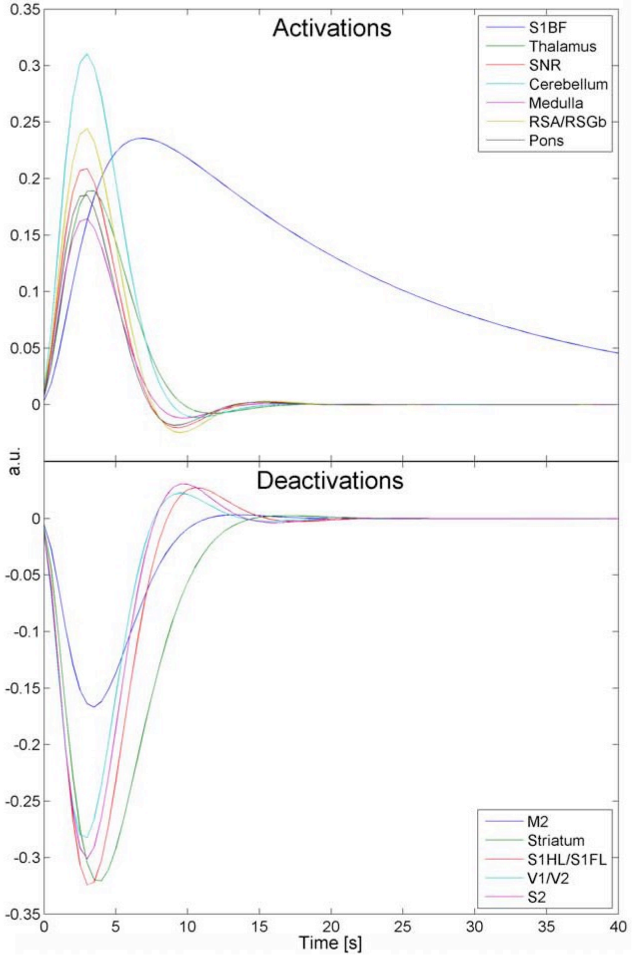
$$\vartheta_0 = 40.3\ \mathrm{s}^{-1}$$

$$E_0 = 0.4$$

$$r_0 = 25\ \mathrm{s}^{-1}$$

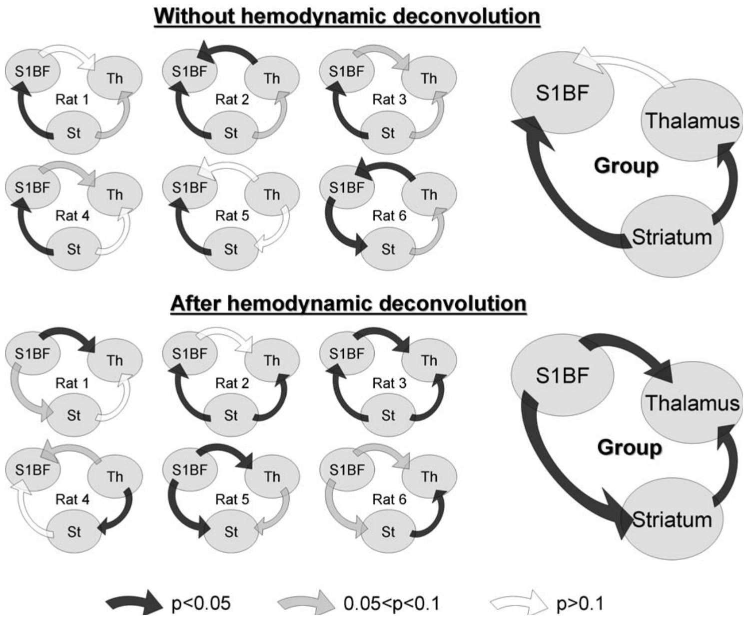
Friston et al., 2003, *NeuroImage*; Stephan et al., 2007, *NeuroImage*

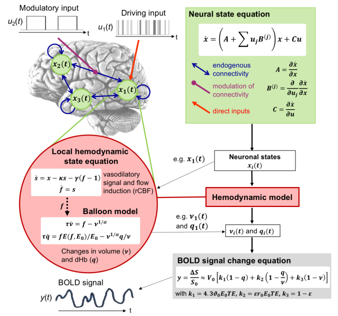
HEMODYNAMICS ARE IMPORTANT



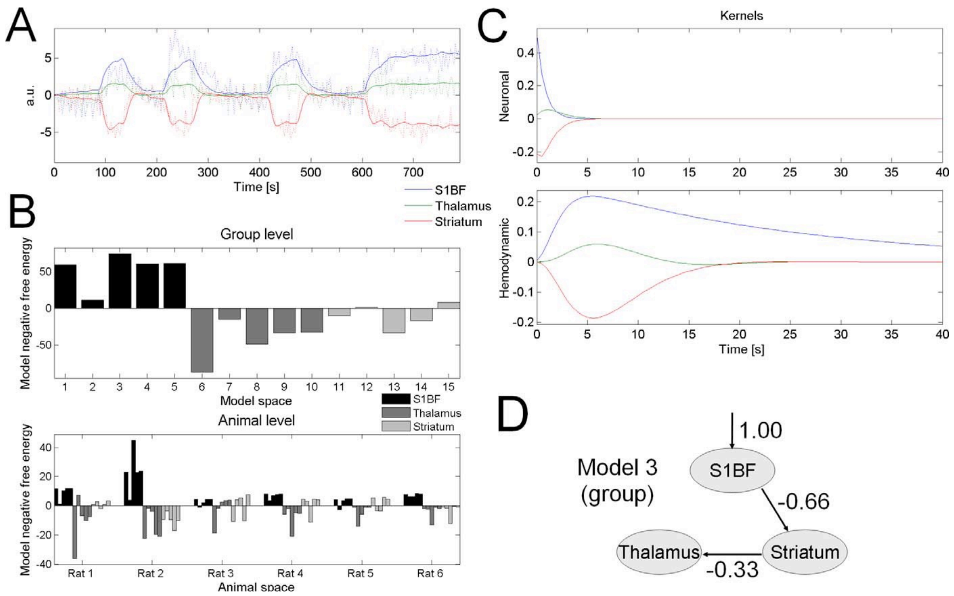
David et al., 2008, *PLoS Biol.*

Granger causality





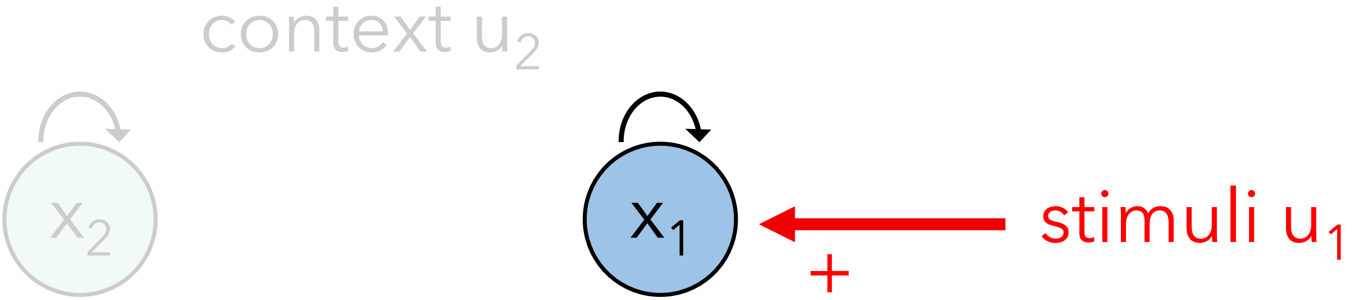
DCM



SIMULATIONS

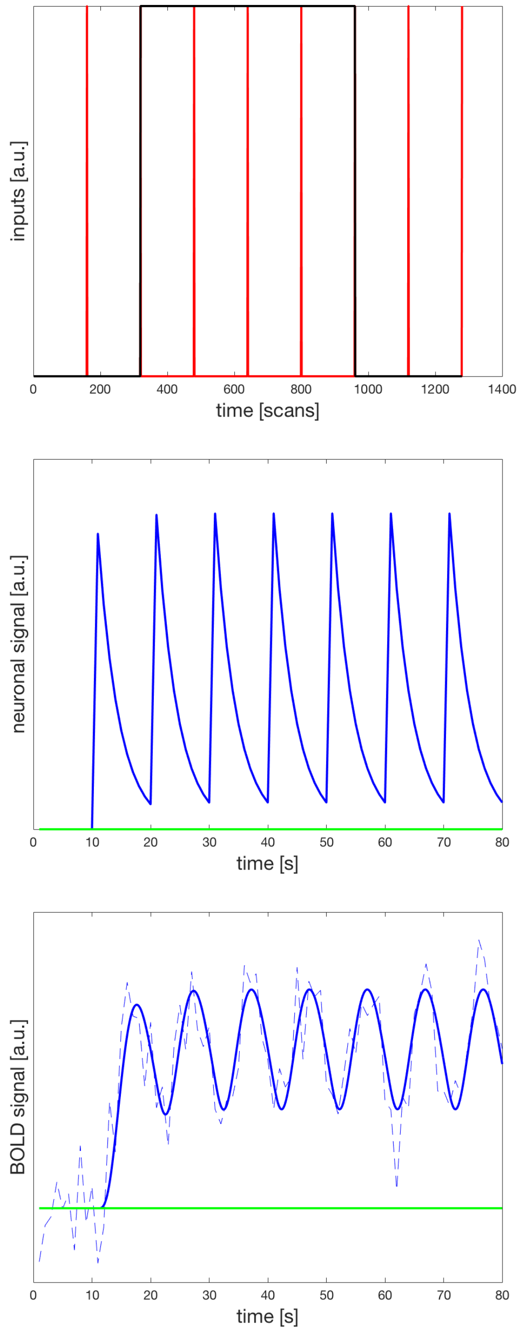
WHAT CAN DCM EXPLAIN?

Example: single node



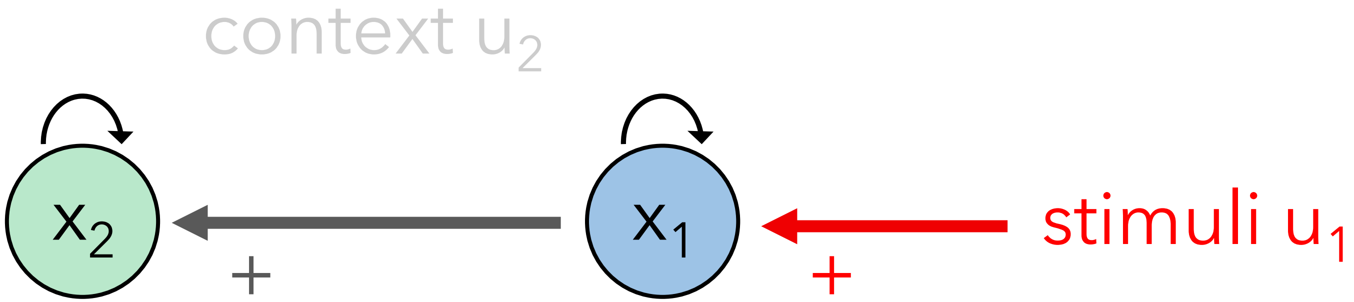
$$\frac{dx}{dt} = Ax + u_2 B^{(2)} x + Cu_1$$

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



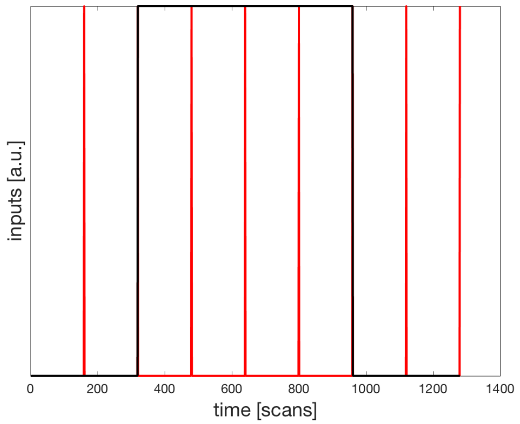
WHAT CAN DCM EXPLAIN?

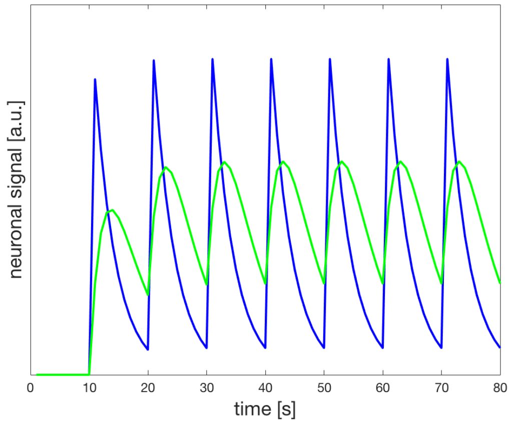
Example: two connected node

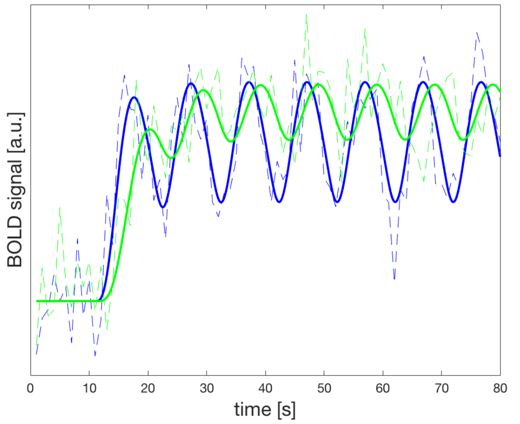


$$\frac{dx}{dt} = Ax + u_2 B^{(2)} x + Cu_1$$

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

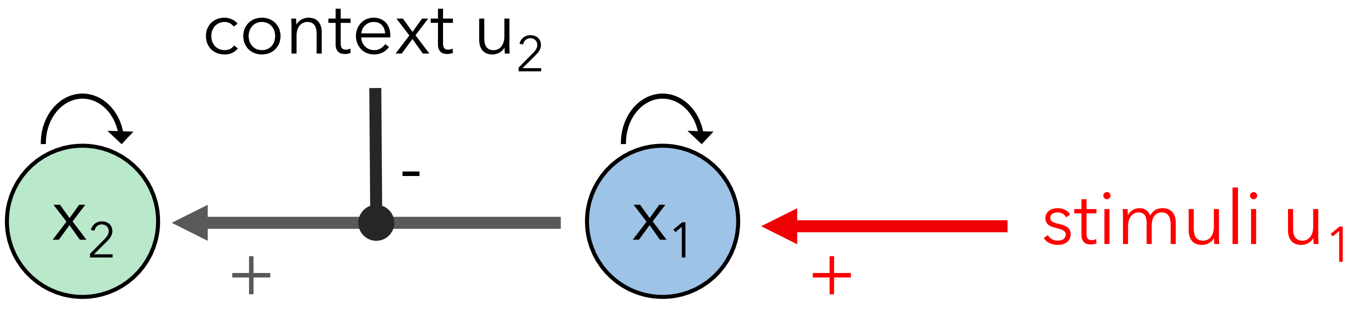






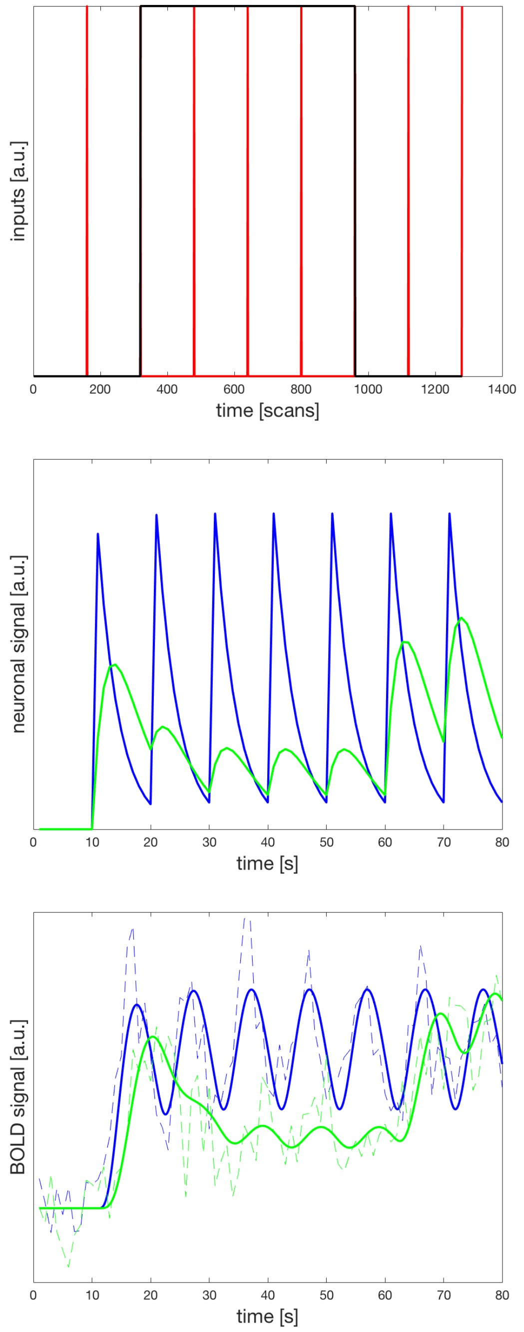
WHAT CAN DCM EXPLAIN?

Example: modulation of connection



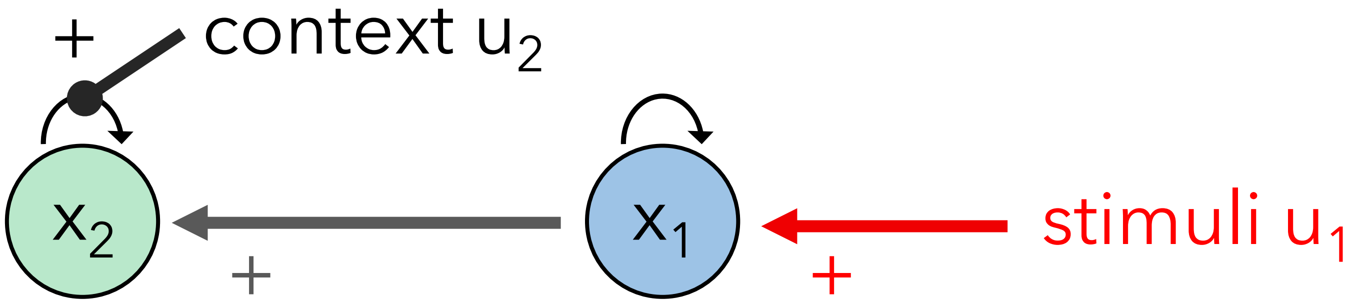
$$\frac{dx}{dt} = Ax + u_2 B^{(2)} x + C u_1$$

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



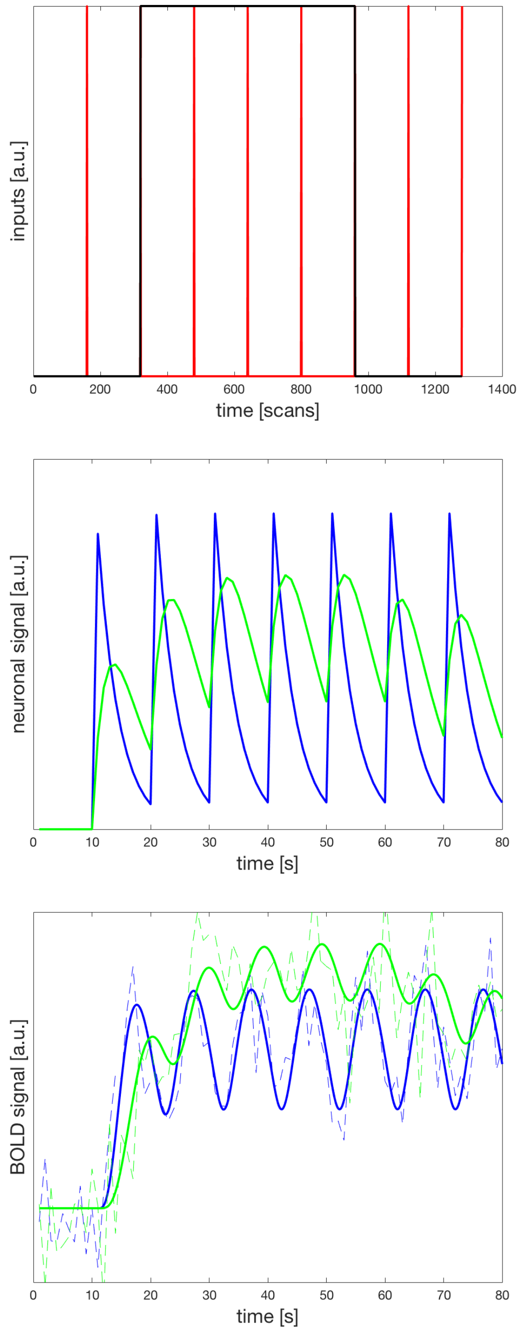
WHAT CAN DCM EXPLAIN?

Example: modulation of inhibitory self-connection



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

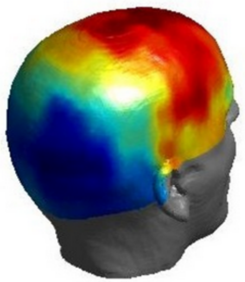
$$\begin{bmatrix}\dot{x}_1\\ \dot{x}_2\end{bmatrix} = \begin{bmatrix}a_{11} & 0\\ a_{21} & a_{22}\end{bmatrix}\cdot\begin{bmatrix}x_1\\ x_2\end{bmatrix} + u_2\begin{bmatrix}0 & 0\\ 0 & b_{22}^{(2)}\end{bmatrix}\cdot\begin{bmatrix}x_1\\ x_2\end{bmatrix} + \begin{bmatrix}c_{11} & 0\\ 0 & 0\end{bmatrix}\cdot\begin{bmatrix}u_1\\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



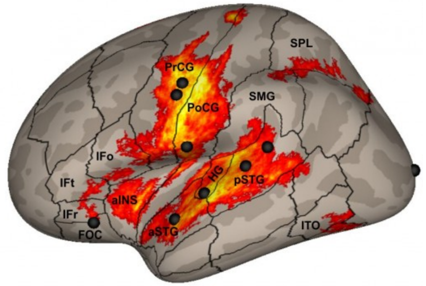
MODEL INVERSION / INFERENCE

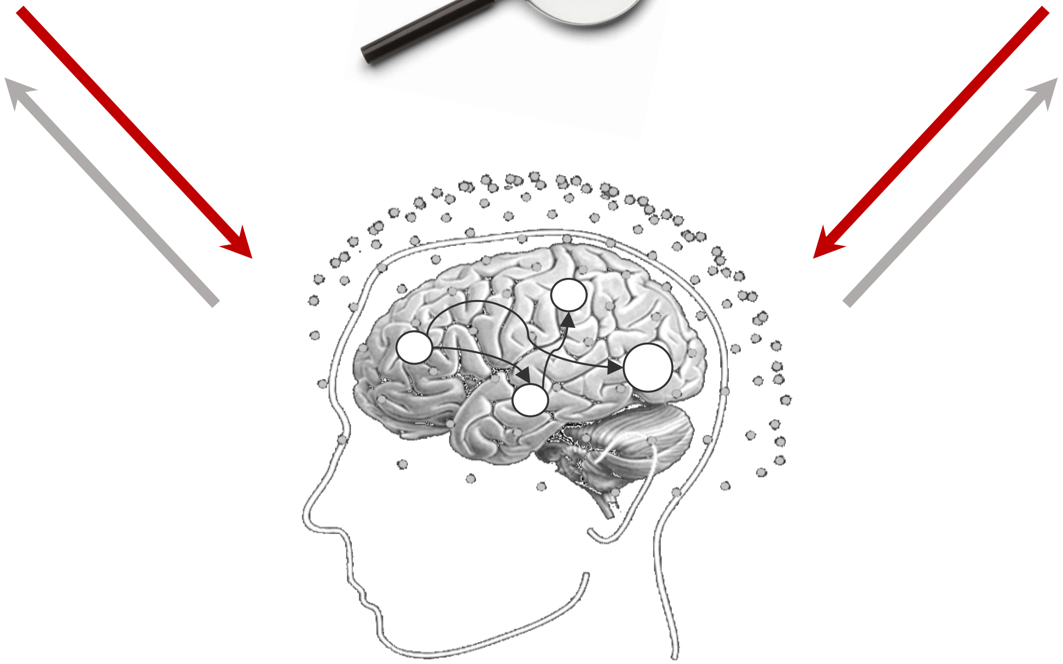
DYNAMIC CAUSAL MODELING

EEG, MEG



fMRT





Forward model:

Predicting measured activity

$$p(y|\vartheta,m)$$

likelihood

Model inversion:

Estimating neuronal mechanisms

$$p(\vartheta|y,m)$$

posterior

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

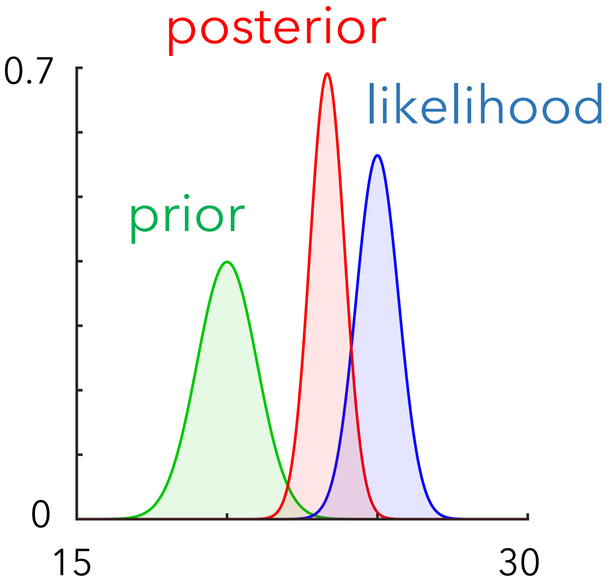
BAYES THEOREM

Reverend Thomas Bayes
(1702-1761)

Bayes theorem gives a recipe for evaluating the posterior density by combining new data (likelihood) and prior knowledge

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

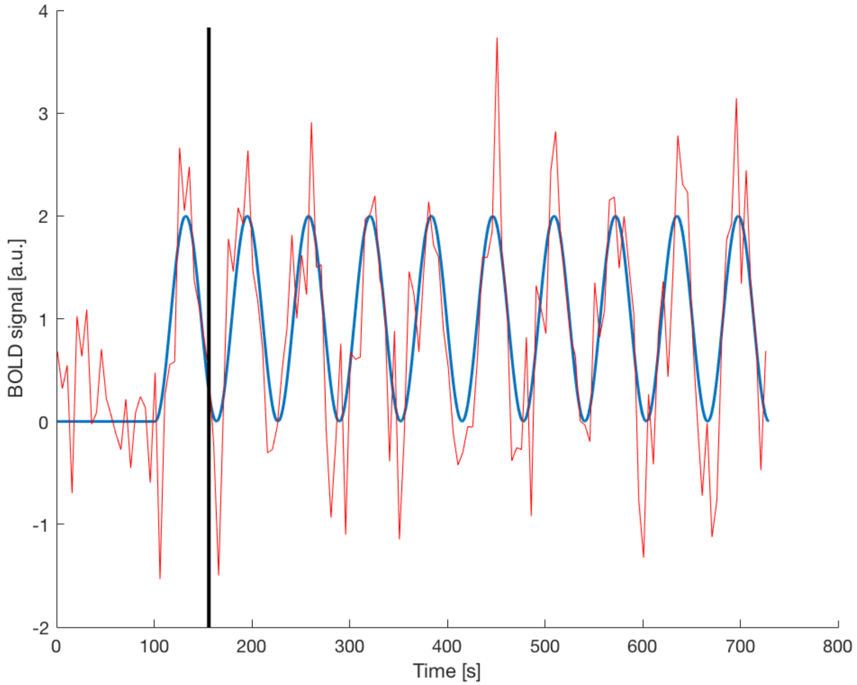
The posterior probability of the parameters is an optimal combination of our prior knowledge and the new data that we have acquired

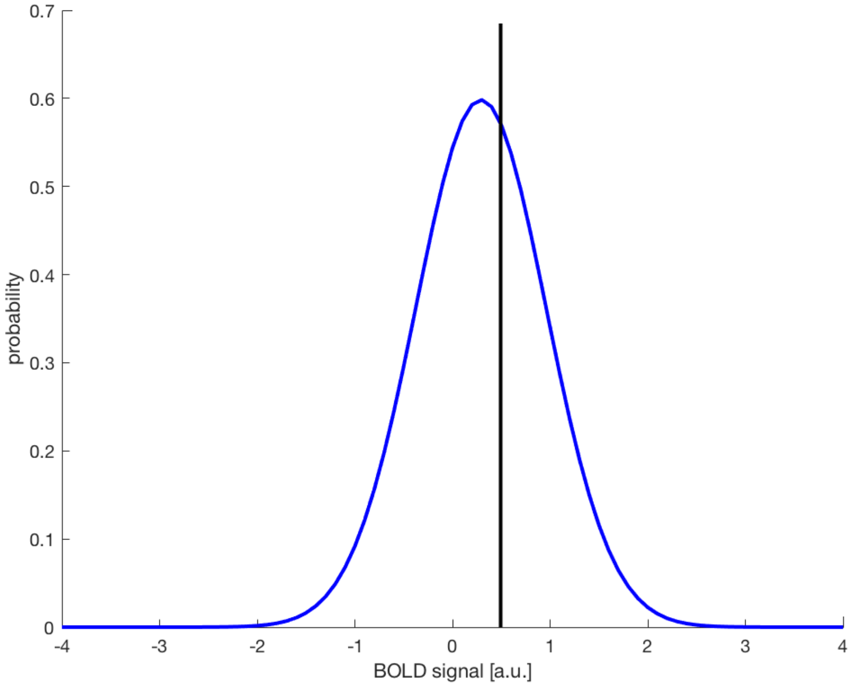


LIKELIHOOD FUNCTION

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

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





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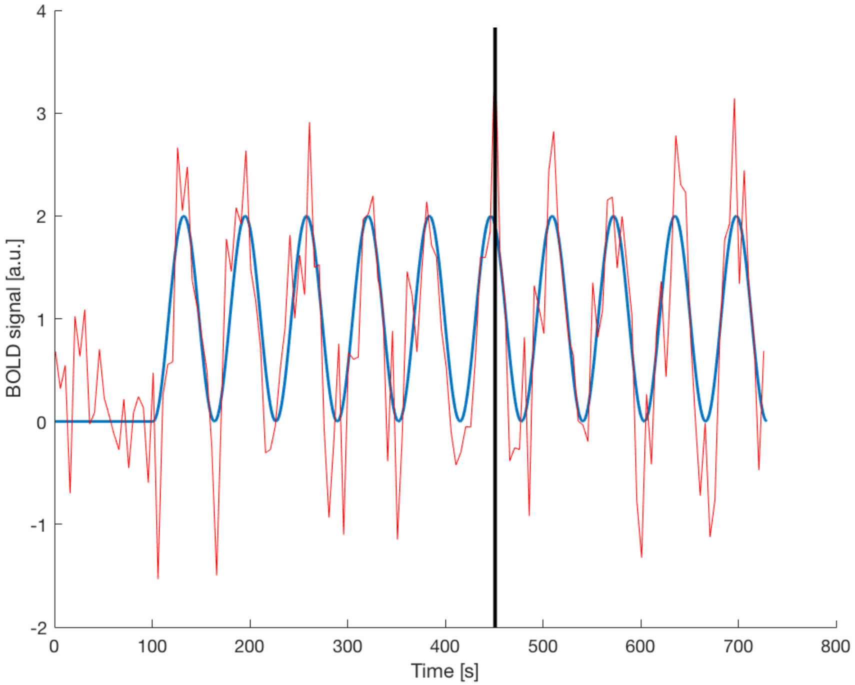
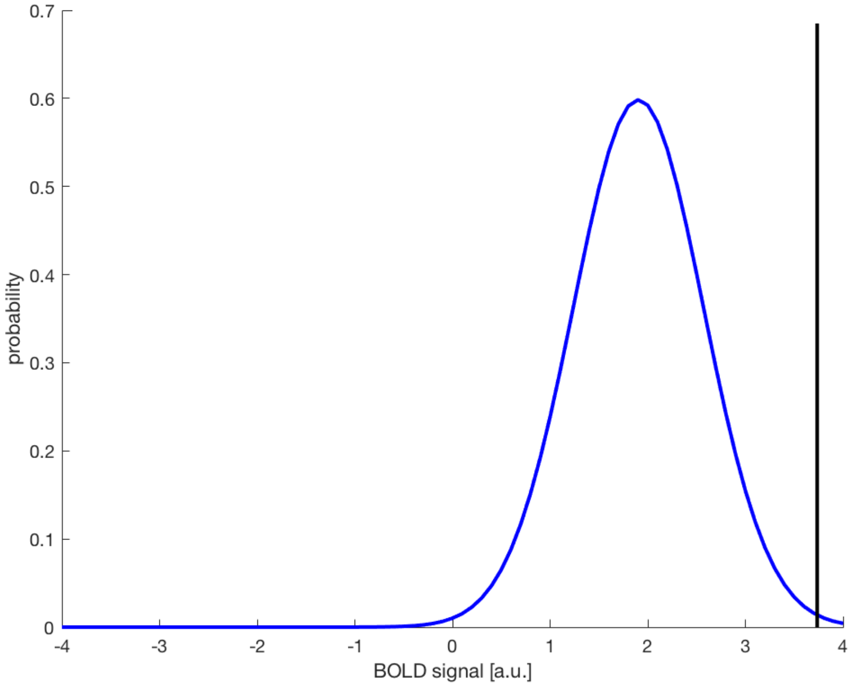




PRIORS

Bayes theorem gives a recipe for evaluating the posterior density by combining new data (likelihood) and prior knowledge

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

Neuronal parameters:

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

Hemodynamic parameters:

- empirical

PRIORS

Types of priors:

- Explicit priors on *model parameters* (e.g., connection strengths)
- Implicit priors on *model functional form* (e.g., system dynamics)
- Choice of "interesting" *data features* (e.g., regional time-series vs. ICA analysis)

Role of priors (on model parameters):

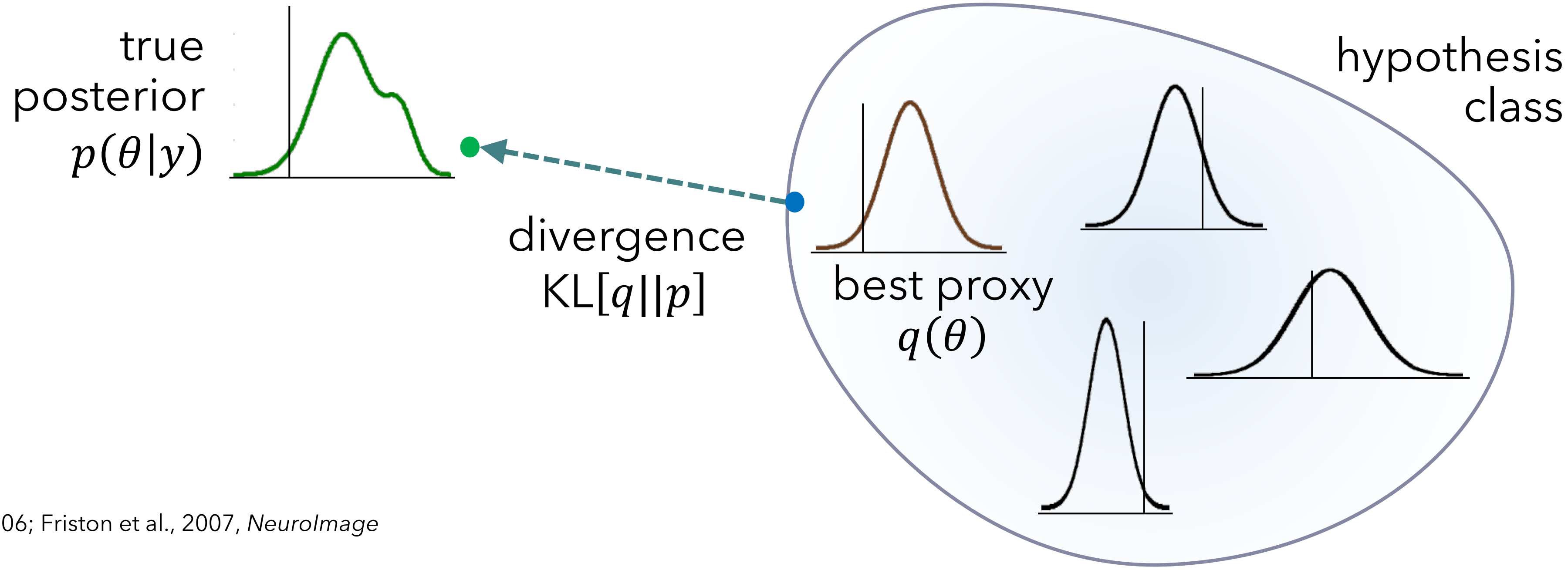
- Resolving the *ill-posedness* of the inverse problem
- Avoiding *overfitting* (cf. generalization error)

Impact of priors:

- On parameter posterior distributions (cf. "shrinkage to the mean" effect)
- On model evidence (cf. "Occam's razor")
- On free-energy landscape (cf. Laplace approximation)

VARIATIONAL BAYES (VB)

Idea: find an approximate density $q(\theta)$ that is maximally similar to the true posterior $p(\theta|y)$. This is often done by assuming a particular form for q (fixed form VB) and then optimizing its sufficient statistics.



true posterior $p(\theta|y)$

divergence KL$[q||p]$

hypothesis class

best proxy $q(\theta)$

Bishop, 2006; Friston et al., 2007, *NeuroImage*

NEGATIVE FREE ENERGY

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

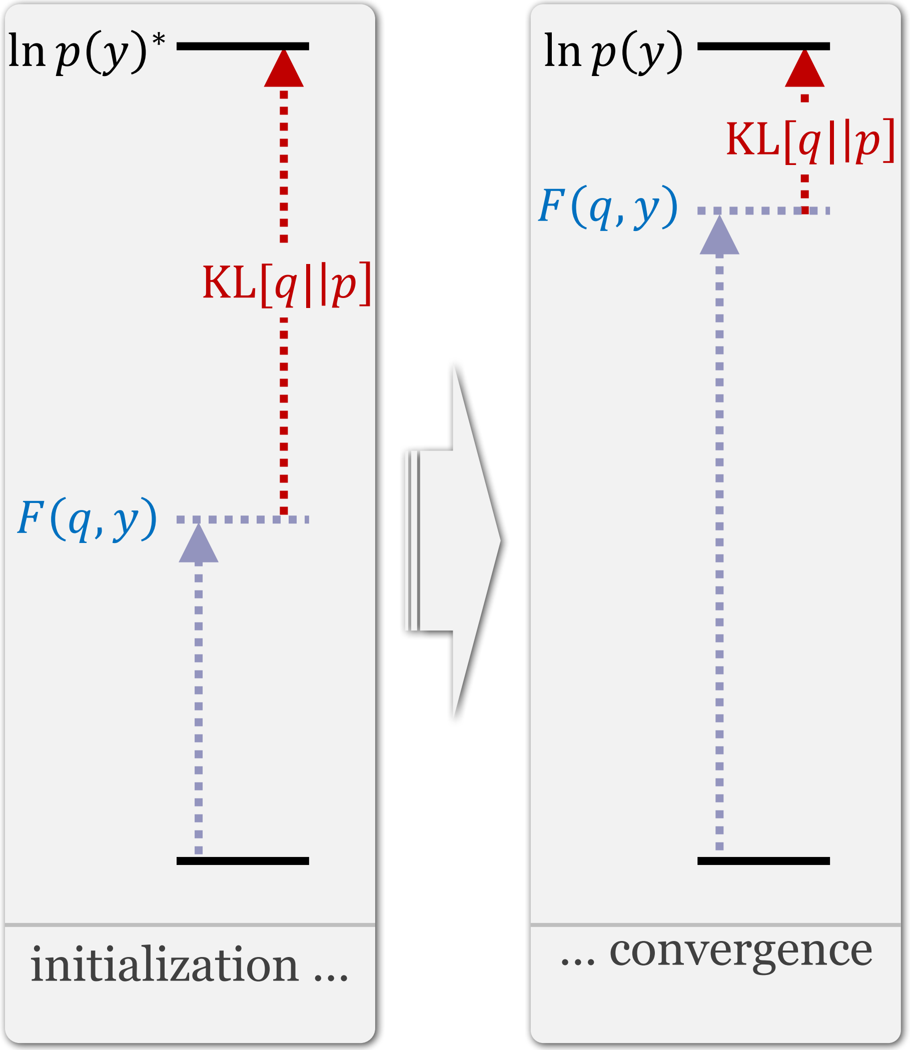
$F(q,y)$ is a functional with respect to the approximate posterior $q(\theta)$.

Maximizing $F(q,y)$ is equivalent to:

- minimizing $KL[q||p]$
- tightening $F(q,y)$ as a lower bound on the log model evidence

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

Bishop, 2006; Friston et al., 2007, *NeuroImage*



NEGATIVE FREE ENERGY – A CLOSER LOOK

The **negative free energy** represents a trade-off between the accuracy and complexity of a model:

$$F = \underbrace{\langle \log p(y|\theta, m)\rangle_q}_{\text{accuracy}} - \underbrace{KL[q(\theta)||p(\theta|m)]}_{\text{complexity}}$$

accuracy
(expected log likelihood)

complexity
(KL divergence between
approximate posterior and prior)

Bishop, 2006; Friston et al., 2007, *NeuroImage*

NEGATIVE FREE ENERGY – A CLOSER LOOK

The **negative free energy** represents a trade-off between the accuracy and complexity of a model:

$$F = \langle \log p(y|\theta,m) \rangle_q - KL[q(\theta) \| p(\theta|m)]$$

In contrast to “simple” criteria (e.g., AIC & BIC), the complexity term of the negative free energy accounts for parameter interdependencies and is a much richer description:

$$KL[q(\theta) \| p(\theta|m)] = \frac{1}{2}\ln|C_\theta| - \frac{1}{2}\ln|C_{\theta|y}| + \frac{1}{2}\left(\mu_{\theta|y} - \mu_\theta\right)^T C_\theta^{-1}\left(\mu_{\theta|y} - \mu_\theta\right)$$

complexity **higher** the more independent prior parameters

Bishop, 2006; Friston et al., 2007, *NeuroImage*

NEGATIVE FREE ENERGY – A CLOSER LOOK

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NEGATIVE FREE ENERGY – A CLOSER LOOK

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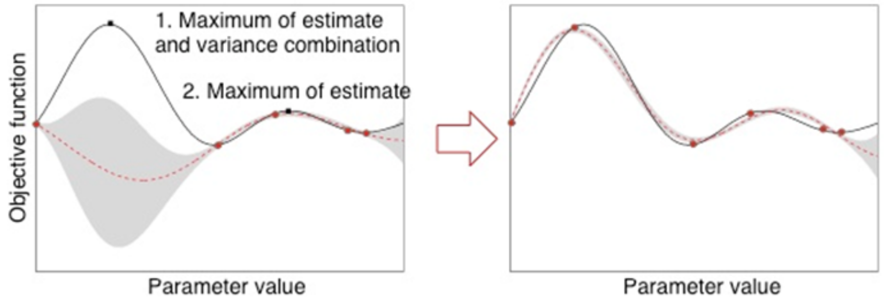
complexity **higher** the more posterior deviates from prior mean

Bishop, 2006; Friston et al., 2007, *NeuroImage*

METHODOLOGICAL DEVELOPMENTS OF DCM

Global optimization schemes for model inversion

- Markov Chain Monte Carlo (MCMC) sampling (Sengupta et al., 2015, *NeuroImage*)
- Gaussian process (GP) regression (Lomakina et al., 2015, *NeuroImage*)

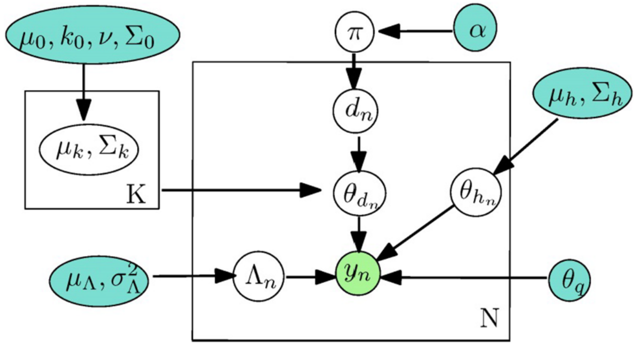


Sampling-based estimates of model evidence

- Aponte et al. 2015, *J. Neurosci. Meth.*
- Raman et al., 2016, *J. Neurosci. Meth.*

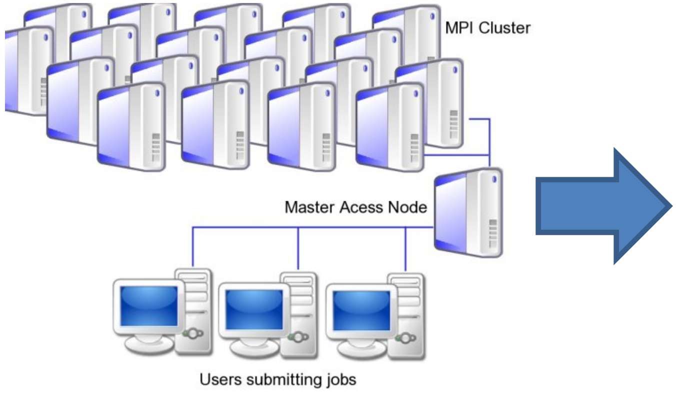
Choice of priors → empirical Bayes

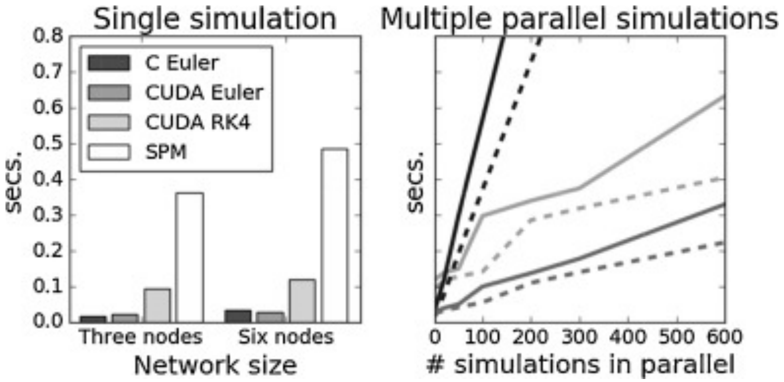
- Friston et al. 2016, *NeuroImage*
- Raman et al. 2016, *J. Neurosci. Meth.*



Sengupta et al, 2015, *NeuroImage*; Lomakina et al., 2015, *NeuroImage*; Aponte et al., 2015, *J. Neurosci. Meth.*; Friston et al., 2016, *NeuroImage*; Raman et al., 2016, *J. Neurosci. Meth.*

MASSIVELY PARALLEL DCM (MPDCM)

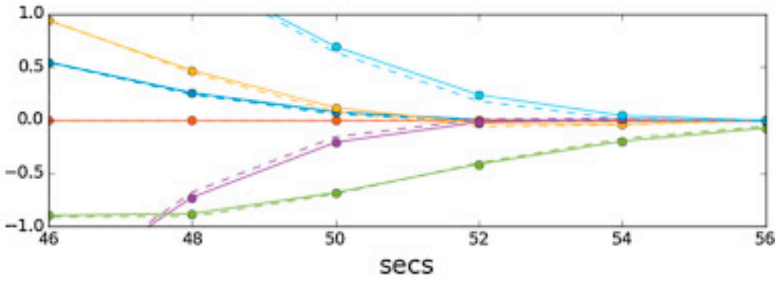




$$\left.\begin{aligned} \dot{x} &= f(x,u_1,\theta_1) \\ \dot{x} &= f(x,u_2,\theta_2) \\ &\vdots \\ \dot{x} &= f(x,u_1,\theta_1) \end{aligned}\right\}$$

mpdcm_integrate(dcms)

$$\left\{\begin{aligned} &y_1 \\ &y_2 \\ &\vdots \\ &y_3 \end{aligned}\right.$$



www.translationalneuromodeling.org/tapas

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

BAYESIAN SYSTEM IDENTIFICATION

$$u(t)$$

Neural dynamics

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

Observer function

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

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

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

Inference on model structure

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

Inference on parameters

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

Design experimental inputs

Define likelihood model

Specify priors

Invert model

Make inferences

BAYESIAN MODEL SELECTION (BMS)

The **negative free energy** as a lower bound approximation to the log model evidence is the current gold standard for Bayesian model selection (BMS).

Generative modeling: comparing competing hypotheses about the mechanisms underlying observed data.

- *a priori* definition of hypothesis set (model space) is crucial
- determine the most plausible hypothesis (model), given the data

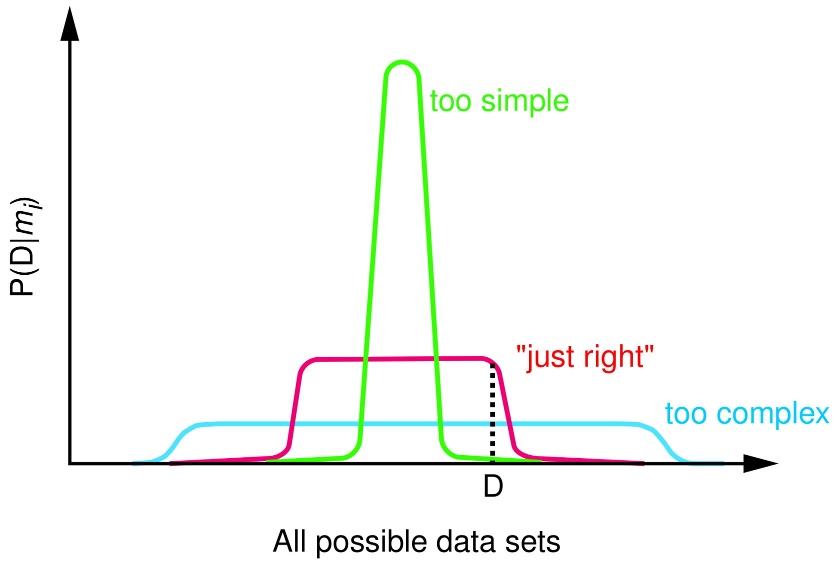
Note: **Model selection is not equal to model validation** and only allows to compare the relative goodness of competing hypotheses within the pre-specified model space!

→ Model validation requires external criteria (external to the measured data).

OVERFITTING AT THE LEVEL OF MODELS

But: There is an infinite number of possible models for a given dataset. Wouldn't we need to search the entire model space and test all possible models?

No! With more models included in the model space, the risk of overfitting (at the level of models) increases, too.



Ghahramani, 2004

OVERFITTING AT THE LEVEL OF MODELS

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No! With more models included in the model space, the risk of overfitting (at the level of models) increases, too.

Solutions:

- regularization: definition of model space (i.e., specify priors $p(m)$ over models)
- family-level Bayesian model selection
- Bayesian model averaging (BMA)

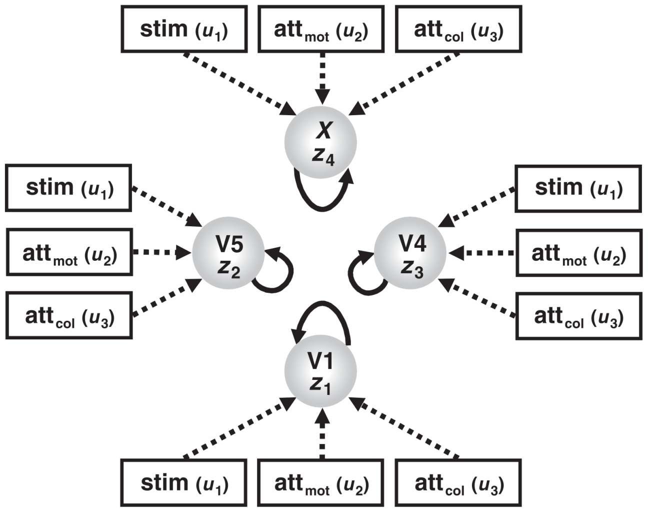
Ghahramani, 2004

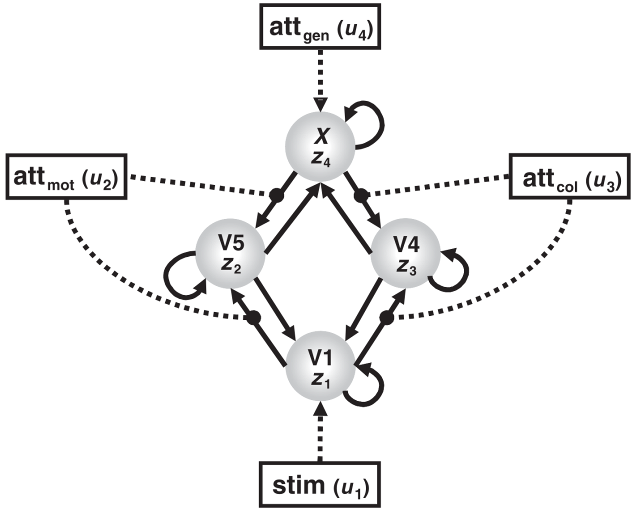
NOTE: GLM VS. DCM

DCM tries to model the same phenomena (i.e., local BOLD responses) as a GLM, just in a different way (via connectivity and its modulations).

No activation detected by a GLM → no motivation to include this region in a deterministic DCM.

However, a stochastic DCM (that accounts for fluctuations at the neuronal level) could be applied despite the absence of a local activation.





Stephan, 2004, *J. Anat.*

APPLICATIONS

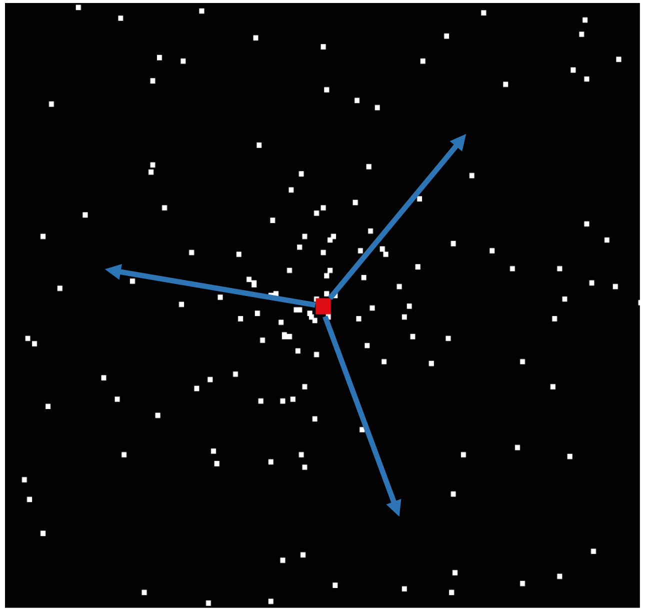
SIMPLE EXAMPLE: ATTENTION TO MOTION

Stimuli: radially moving dots were presented.

Pre-scanning: 5x30s trials with 5 speed changes. Subjects were asked to detect the change in radial velocity.

Scanning: No actual speed changes. Conditions:

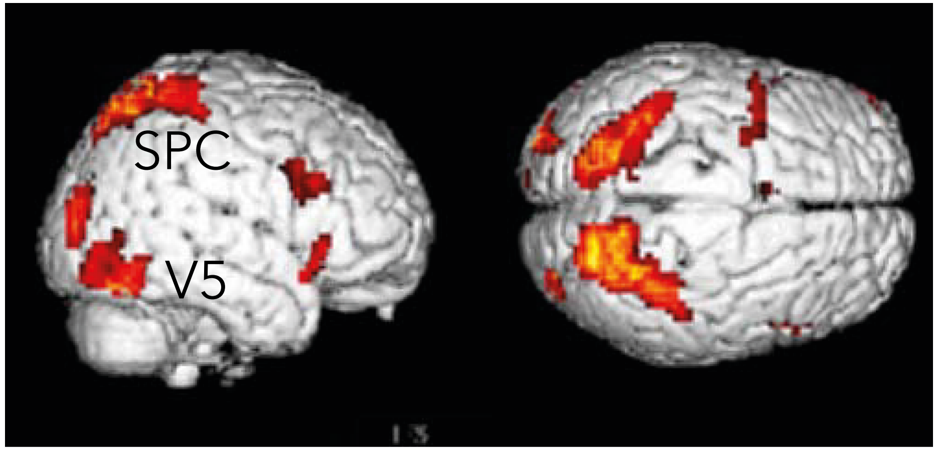
- F: fixation
- S: static dots
- M: moving dots
- A: attend moving dots



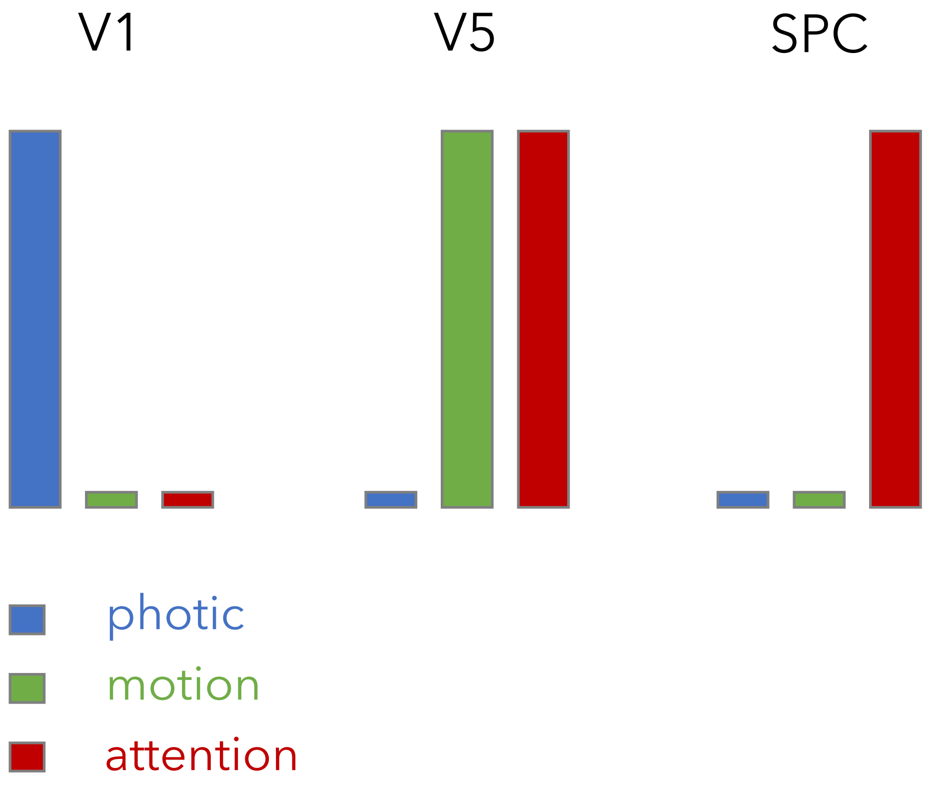
Büchel and Friston, 1997, *Cerebral Cortex*; Friston et al., 2003, *NeuroImage*

SIMPLE EXAMPLE: ATTENTION TO MOTION

Single-subject results: BOLD activation patterns



Linear contrast: attention > no attention



Büchel and Friston, 1997, *Cerebral Cortex*; Friston et al., 2003, *NeuroImage*

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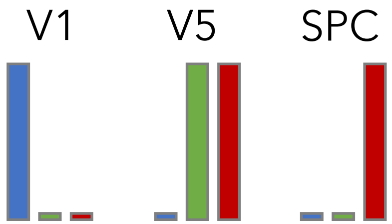
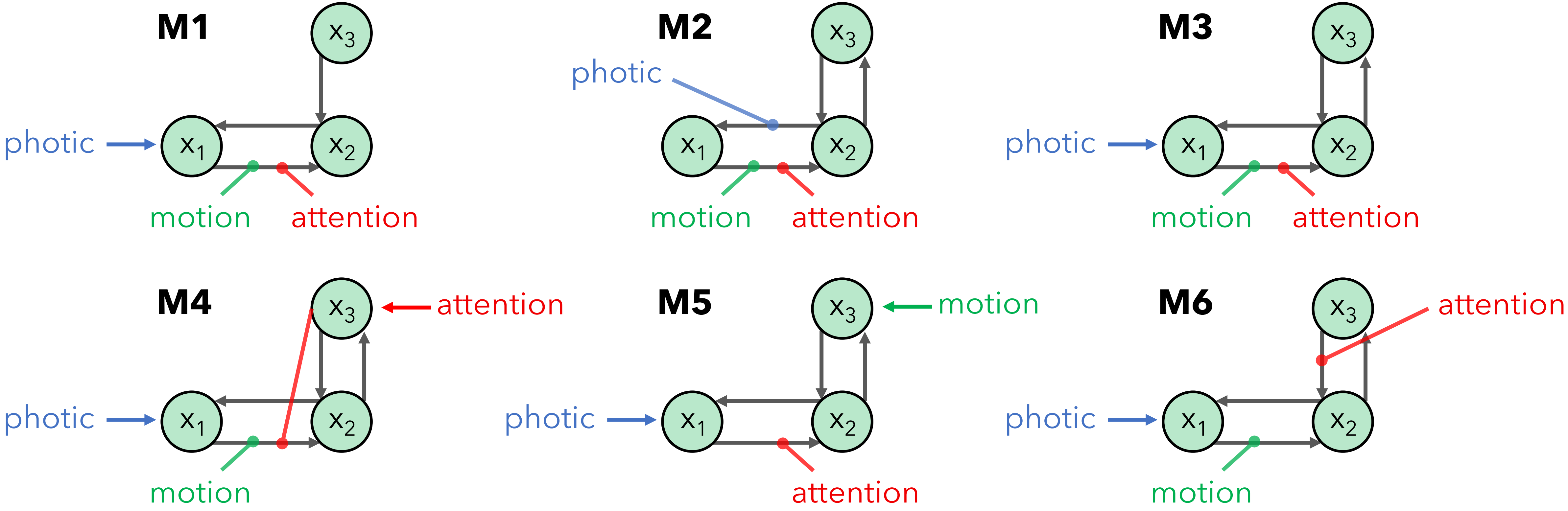


Model space definition – which models can explain the data (Quiz)?



Büchel and Friston, 1997, *Cerebral Cortex*; Friston et al., 2003, *NeuroImage*

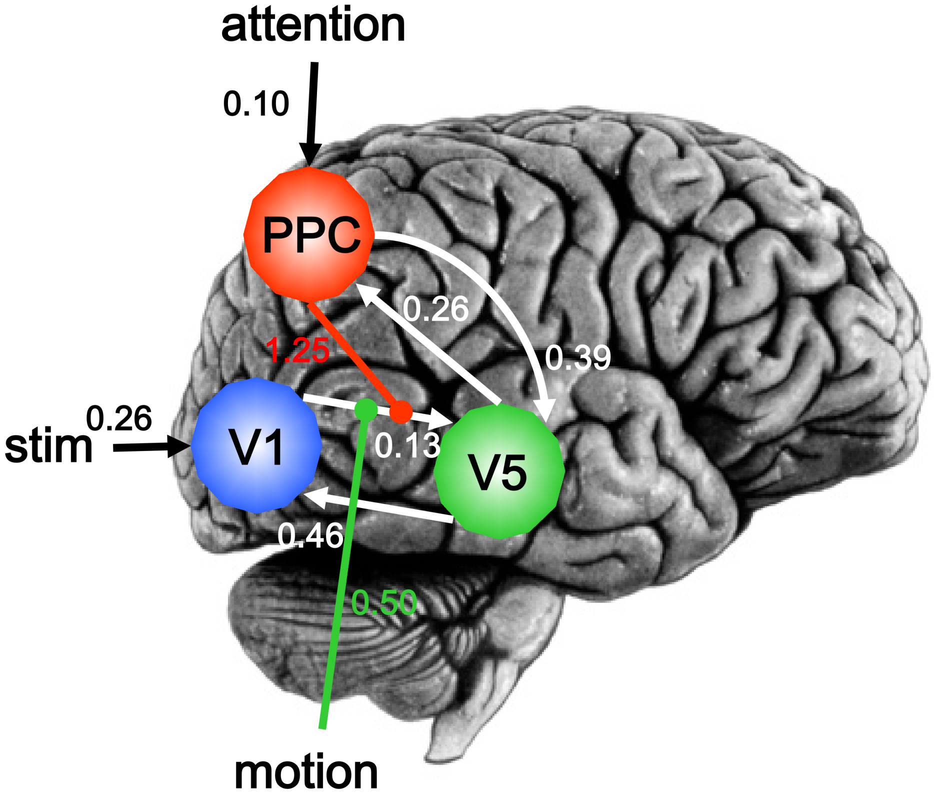
Translational Neuromodeling Unit

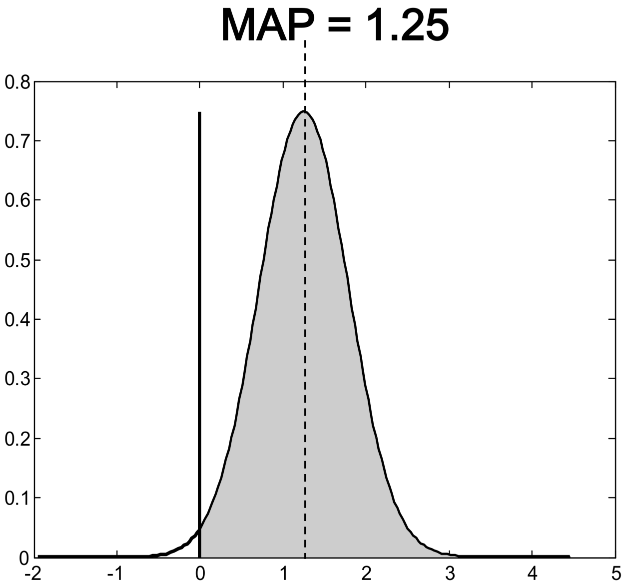
University of Zurich^{UZH}

ETH Eidgenössische Technische Hochschule Zürich Swiss Federal Institute of Technology Zurich

SIMPLE EXAMPLE: ATTENTION TO MOTION

Single-subject results: DCM effective connectivity





$$p(D^{PPC}_{V5,V1} > 0 \mid y) = 99.1\%$$

Büchel and Friston, 1997, *Cerebral Cortex*; Friston et al., 2003, *NeuroImage*; Stephan et al., 2008, *NeuroImage*

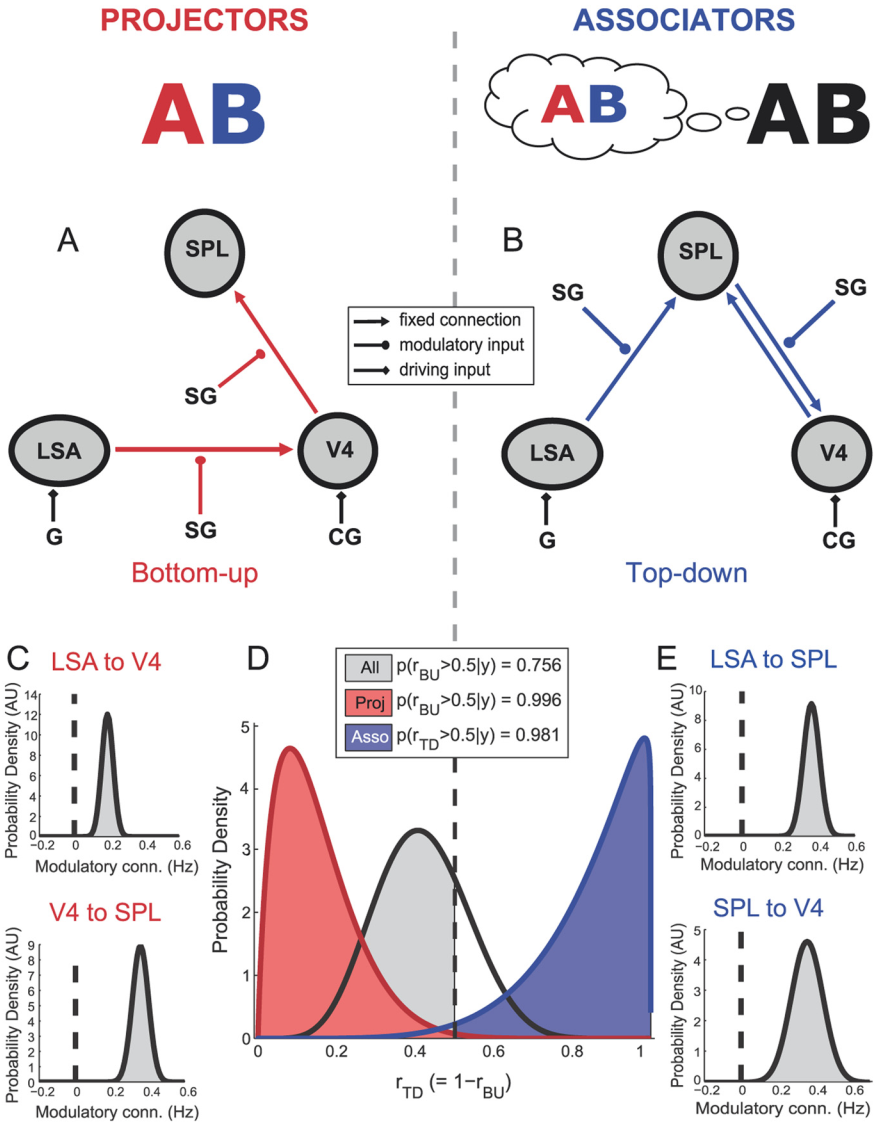
BAYESIAN MODEL SELECTION: SYNESTHESIA

Individuals with different forms of color-grapheme synesthesia were tested and effective connectivity in the relevant neural circuits was assessed using DCM.

Bayesian model selection (BMS) as a formal approach to differential diagnosis in clinical applications

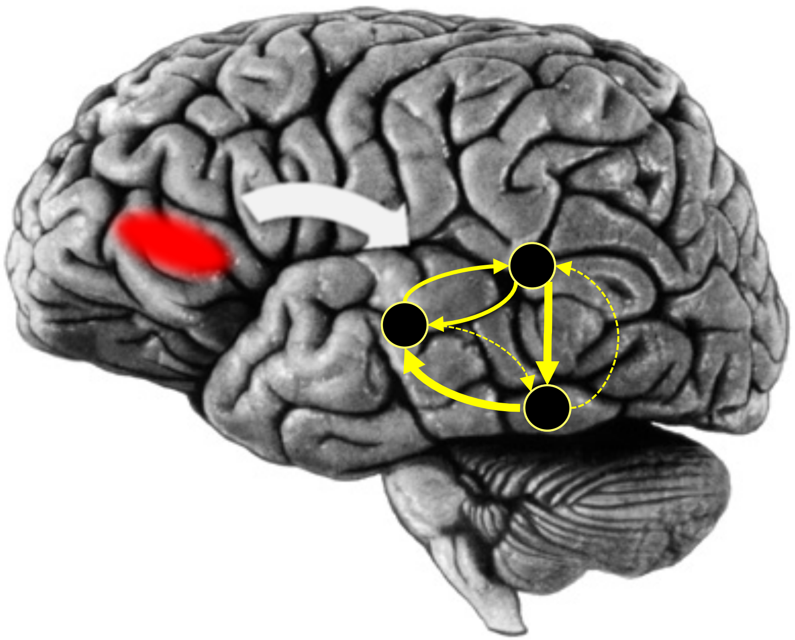
(Note: Here, different forms of synesthesia were tested. This is not a clinical condition, but simply a specific cognitive trait)

Van Leeuwen et al., 2011, *J. Neurosci.*



GENERATIVE EMBEDDING: APHASIA

Dissociating aphasic patients (N=11) and healthy controls (N=26)



Schofield et al., 2012, *J. Neurosci.*; Brodersen et al., 2011, *PLoS Comp. Biol.*

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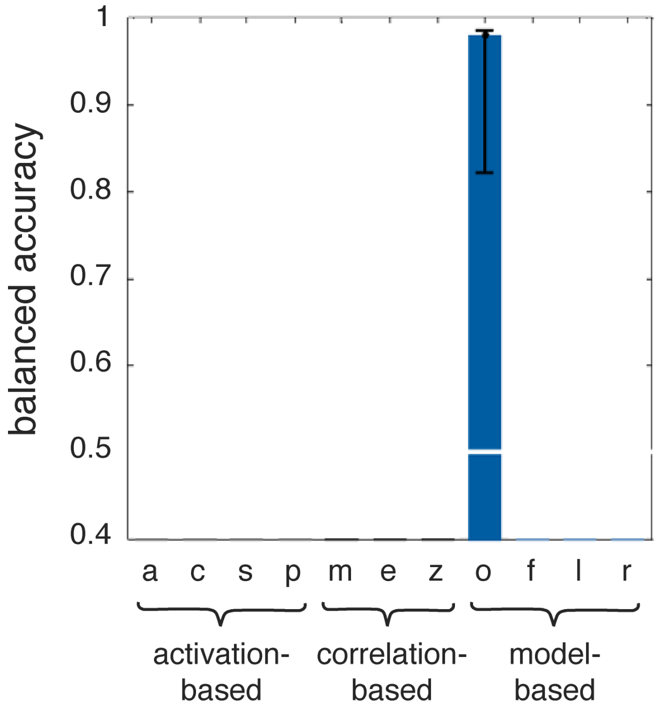
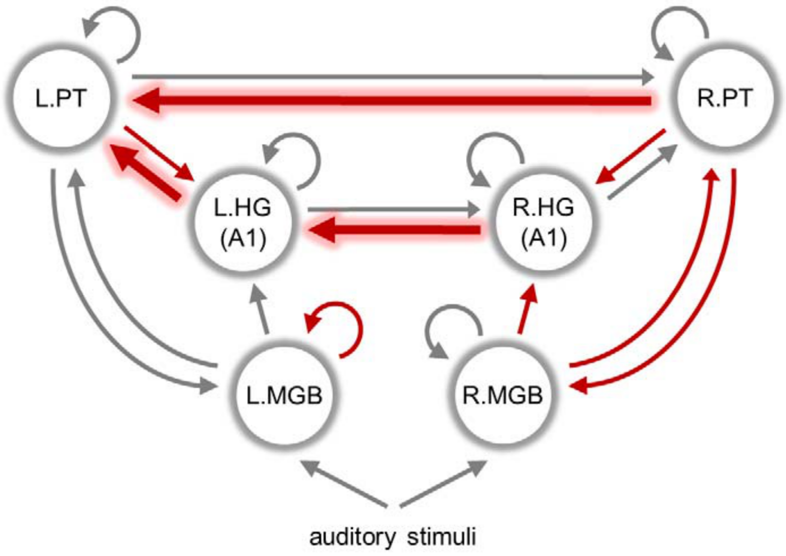
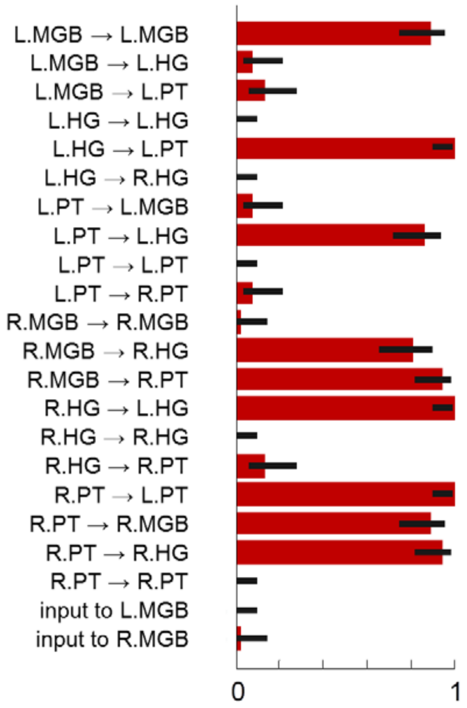


support vectors



frequency



Schofield et al., 2012, *J. Neurosci.*; Brodersen et al., 2011, *PLoS Comp. Biol.*

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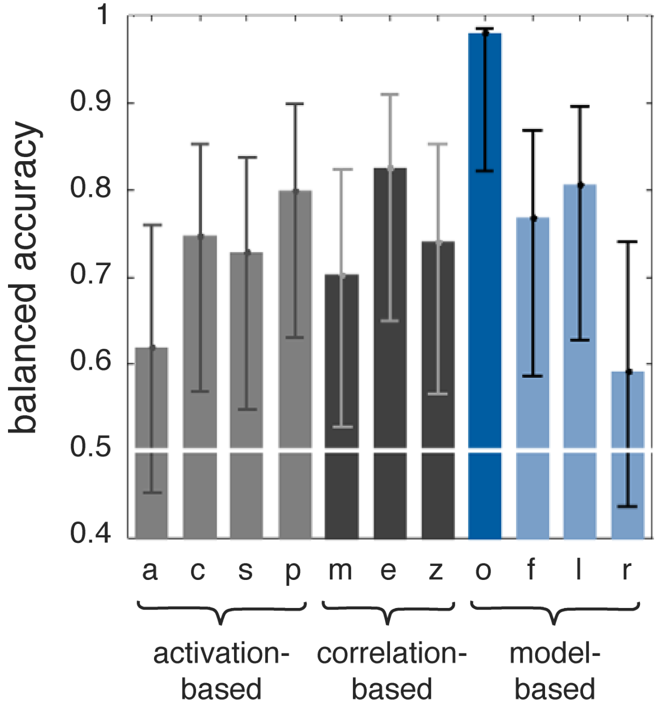
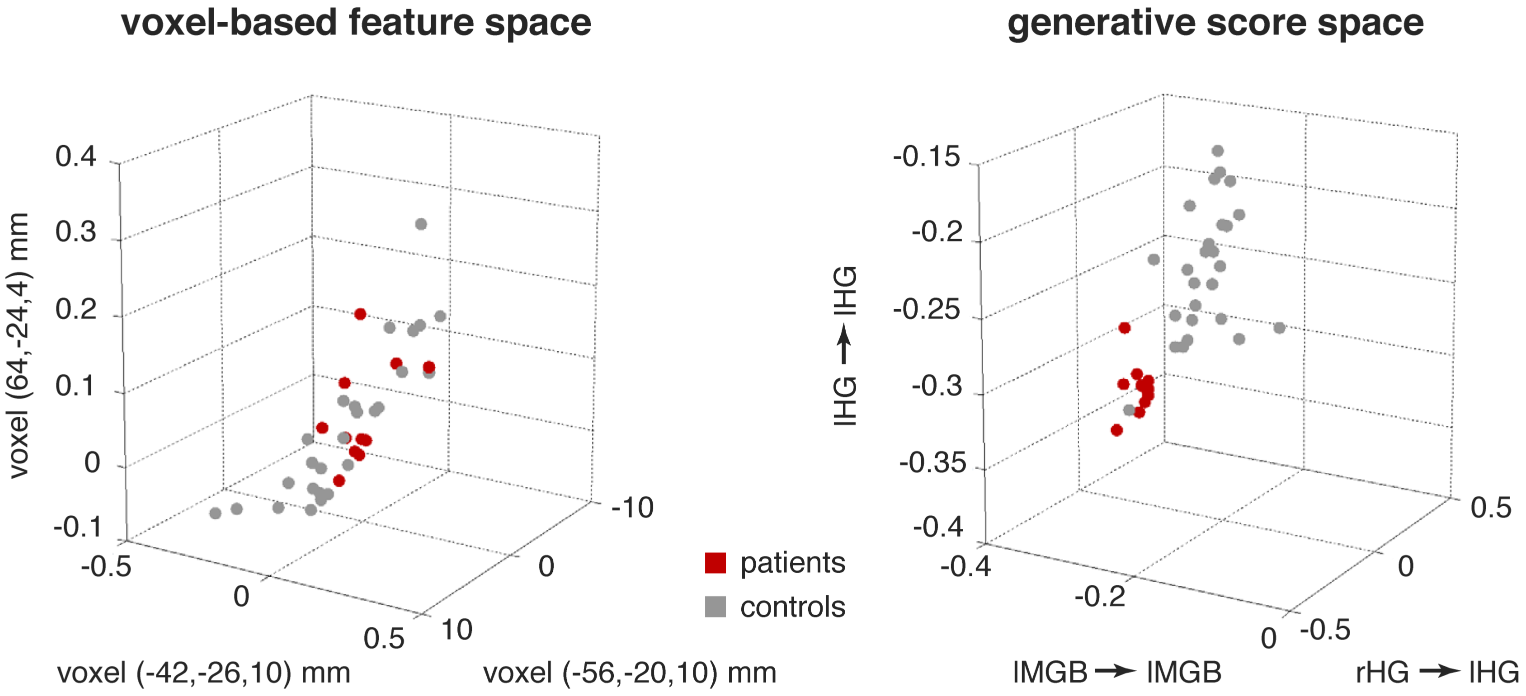


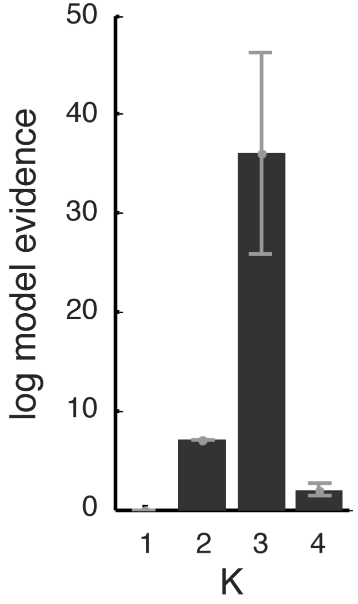


Schofield et al., 2012, *J. Neurosci.*; Brodersen et al., 2011, *PLoS Comp. Biol.*

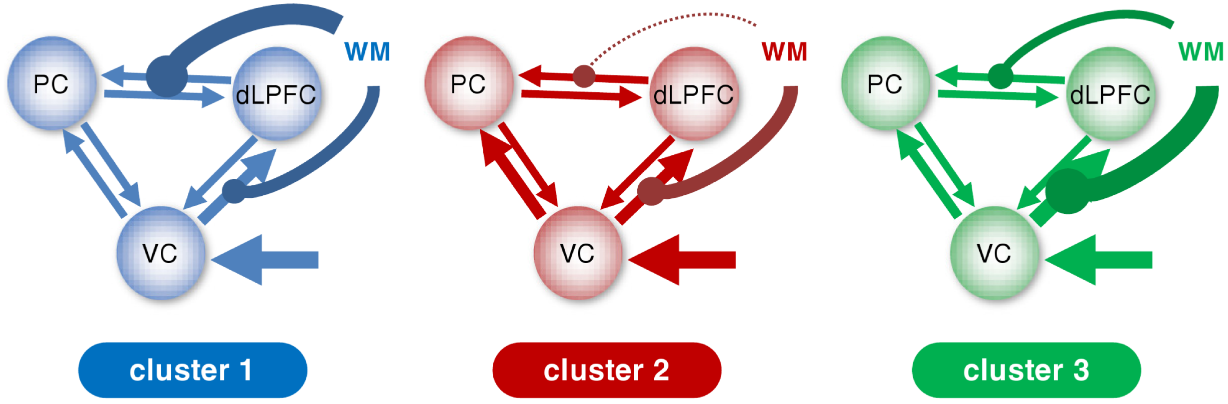
Generative embedding: Schizophrenia

Detecting subgroups of patients in schizophrenia (N=41)

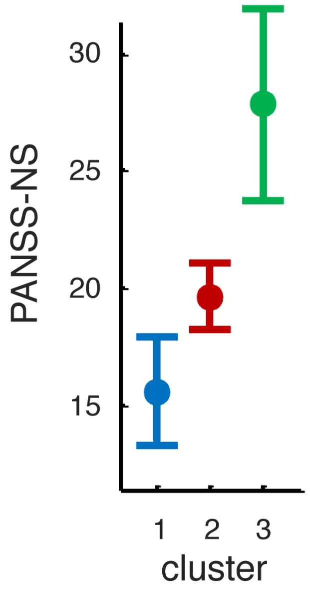
model selection



neurophysiological characterisation



validation

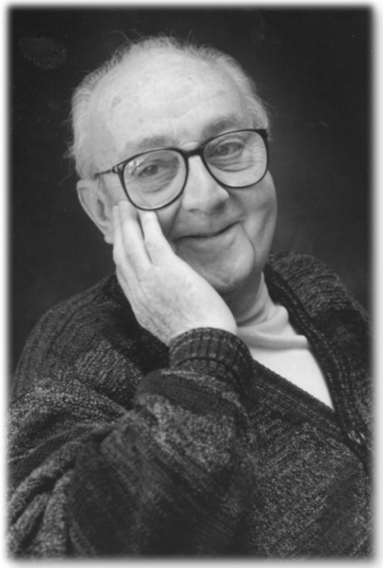


Deserno et al., 2012, *J. Neurosci.*; Brodersen et al., 2014, *NeuroImage: Clinical*

ALL MODELS ARE WRONG

BUT SOME ARE USEFUL

George Edward Pelham Box
(1919-2013)



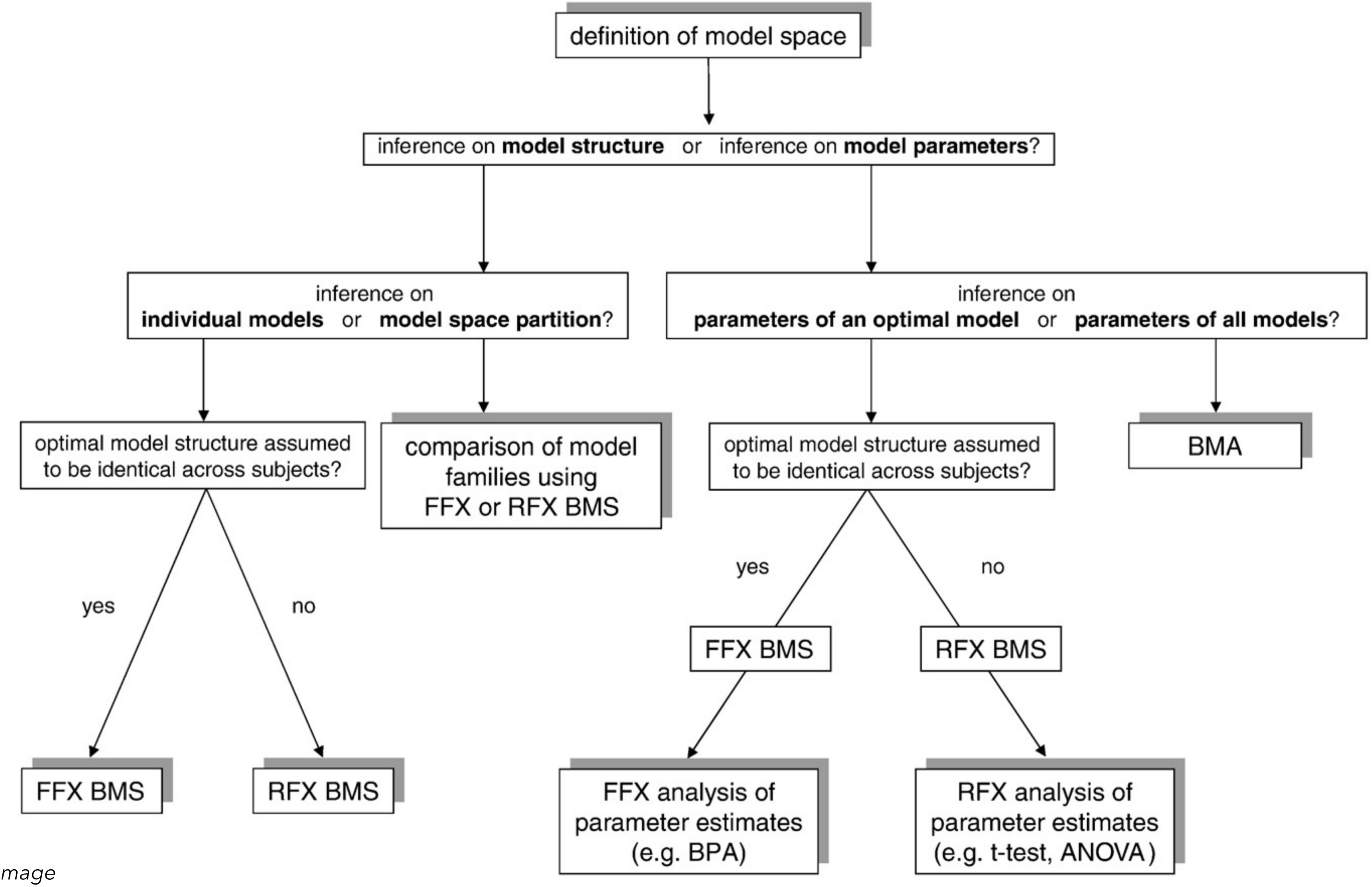
HIERARCHICAL STRATEGY FOR MODEL VALIDATION

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

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

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

SCHEMATIC OVERVIEW



definition of model space

inference on **model structure** or inference on **model parameters**?

inference on
individual models or **model space partition**?

inference on
parameters of an optimal model or **parameters of all models**?

optimal model structure assumed to be identical across subjects?

yes

no

FFX BMS

RFX BMS

comparison of model families using FFX or RFX BMS

optimal model structure assumed to be identical across subjects?

yes

no

FFX BMS

RFX BMS

FFX analysis of parameter estimates (e.g. BPA)

RFX analysis of parameter estimates (e.g. t-test, ANOVA)

BMA

Stephan et al., 2010, *NeuroImage*

FURTHER READINGS (1)

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DYNAMIC CAUSAL MODELING

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Methods and Models for fMRI Analysis (HS 2017)

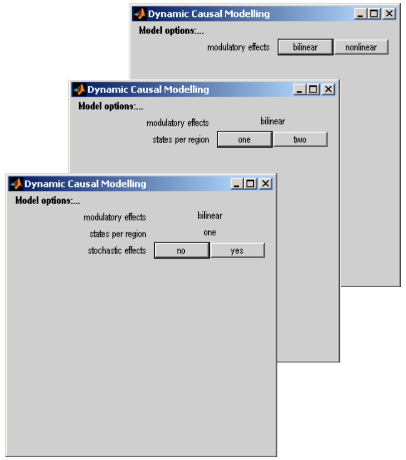
Practical Session

Zurich, December 12, 2017

EVOLUTION OF DCM

Different variants and extensions **within** SPM

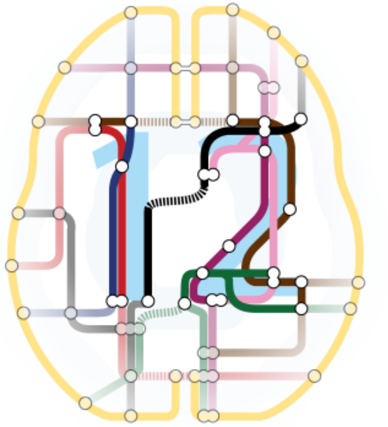
- bilinear vs. nonlinear
- single-state vs. two-state (per region)
- deterministic vs. stochastic
- time-series vs. cross-spectra



Dynamic Causal Modelling
Model options:...
modulatory effects: bilinear | nonlinear

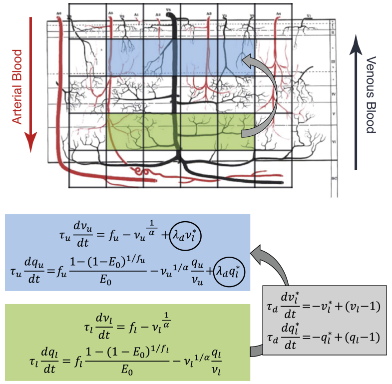
Dynamic Causal Modelling
Model options:...
modulatory effects: bilinear
states per region: one | two

Dynamic Causal Modelling
Model options:...
modulatory effects: bilinear
states per region: one
stochastic effects: no | yes



Different variants and extensions **outside** SPM

- biologically plausible hemodynamic models
- DCM for layered BOLD
- regression DCM (rDCM)



$$\tau_u \frac{d\nu_u}{dt} = f_u - \nu_u{}^{\frac{1}{\alpha}} + \boxed{\lambda_d \nu_l^*}$$

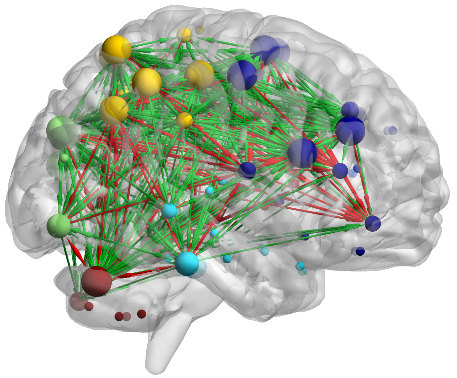
$$\tau_u \frac{dq_u}{dt} = f_u \frac{1-(1-E_0)^{1/f_u}}{E_0} - \nu_u{}^{1/\alpha}\frac{q_u}{\nu_u} + \boxed{\lambda_d q_l^*}$$

$$\tau_l \frac{d\nu_l}{dt} = f_l - \nu_l{}^{\frac{1}{\alpha}}$$

$$\tau_l \frac{dq_l}{dt} = f_l \frac{1-(1-E_0)^{1/f_l}}{E_0} - \nu_l{}^{1/\alpha}\frac{q_l}{\nu_l}$$

$$\tau_d \frac{dv_l^*}{dt} = -v_l^* + (v_l - 1)$$

$$\tau_d \frac{dq_l^*}{dt} = -q_l^* + (q_l - 1)$$



Friston et al., 2003, *NeuroImage*; Stephan et al., 2009, *NeuroImage*; Marreiros et al., 2008, *NeuroImage*; Daunizeau et al., 2009, *NeuroImage*; Friston et al., 2014, *NeuroImage*; Havlicek et al., 2017, *NeuroImage*; Heinzle et al., 2016, *NeuroImage*; Frässle et al., 2017, *NeuroImage*

DATASET: BUTTON PRESSES

Experimental Paradigm:

Stimuli: Arrows pointing to the left or right.

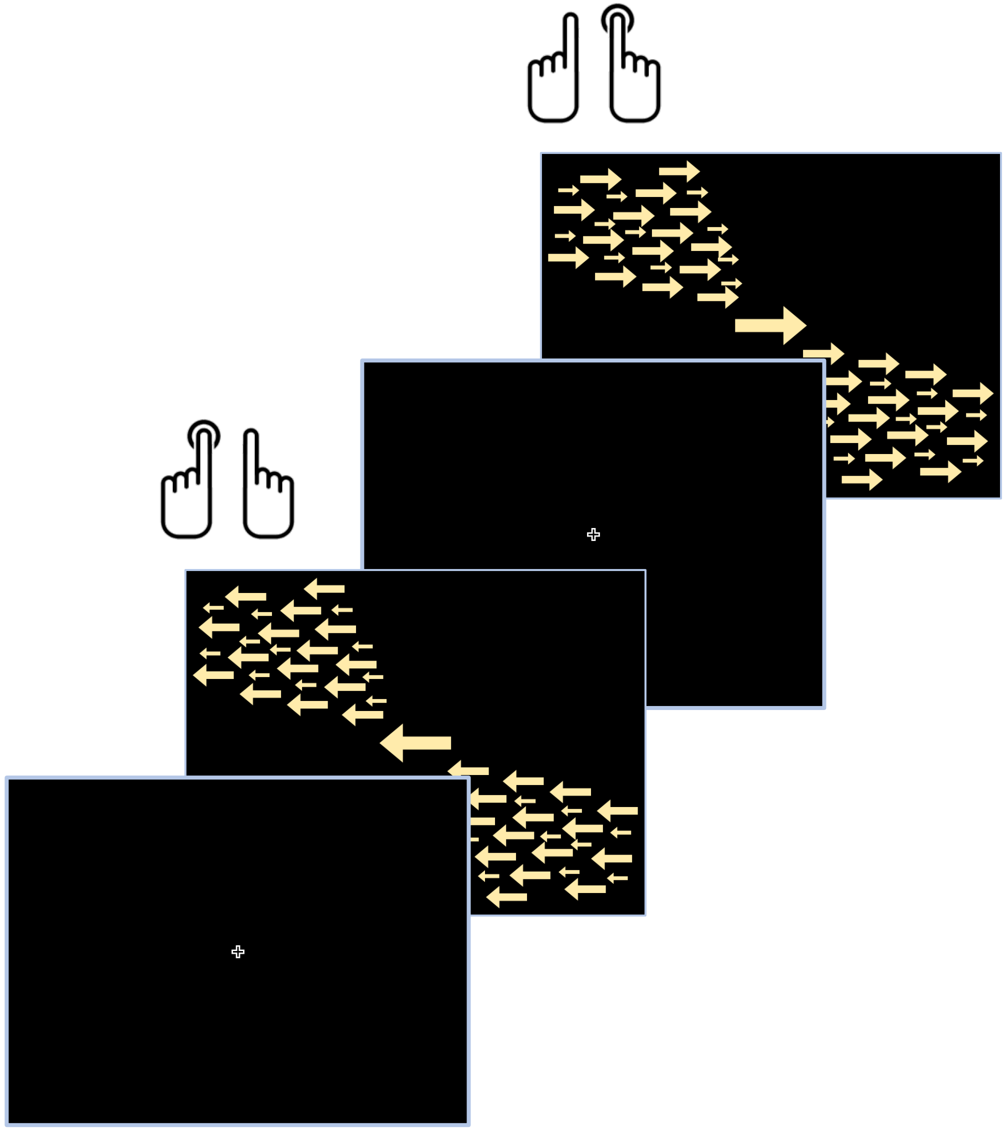
Scanning: Button presses with respective hand.

- F: fixation
- LH: button press with left hand
- RH: button press with right hand

6 LH- and 6 RH-blocks (10 button presses per block)

Each block lasted roughly 14 s

TR = 2.2 s, TE = 36 ms

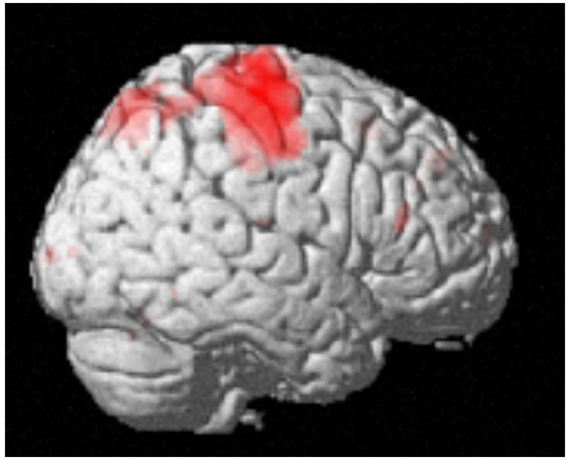


RESULTS: BOLD ACTIVITY

Exemplary single-subject (*Sub003*) results:

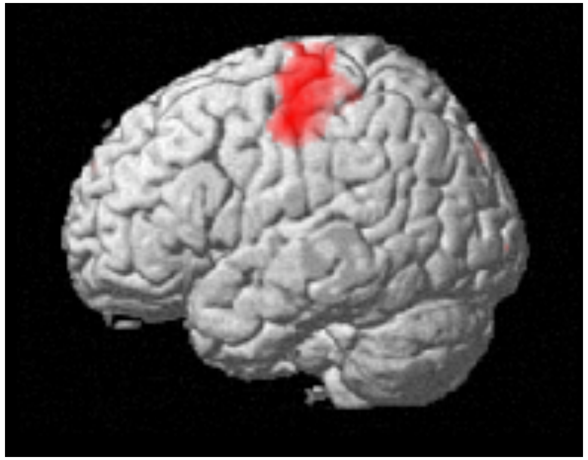
right M1

(left hand > right hand)



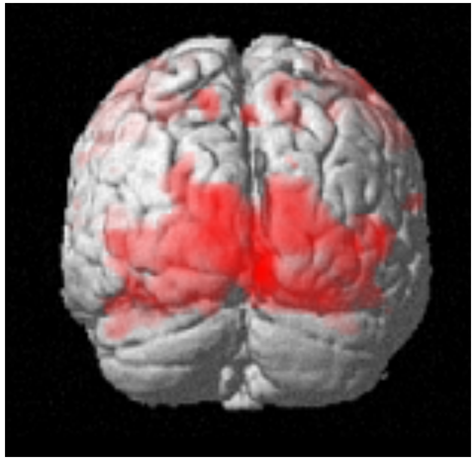
left M1

(right hand > left hand)



V1

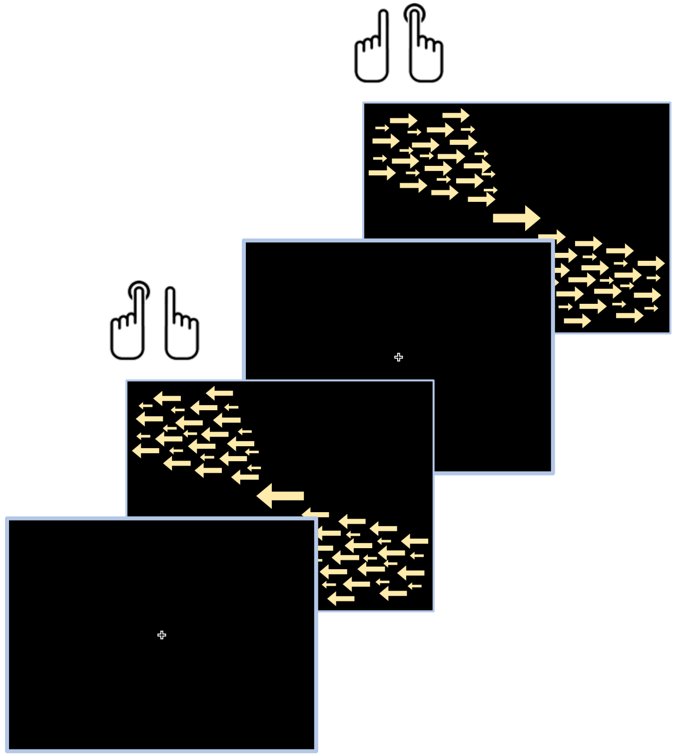
(left + right hand > baseline)



$p < 0.001$, *uncorrected*

DYNAMIC CAUSAL MODELING

Ingredients for DCM analysis:



- Specific hypothesis/question
- Model: based on hypothesis
- Time-series: extract from the SPM
- Inputs: experimental conditions from the design matrix

DYNAMIC CAUSAL MODELING

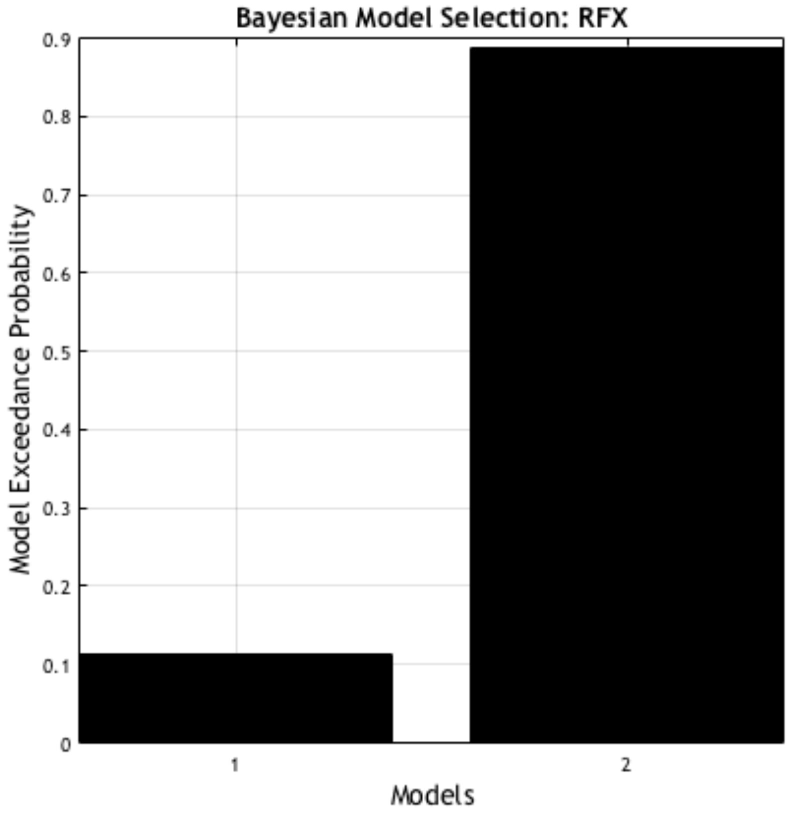
Recipe for DCM analysis (using the GUI in SPM):

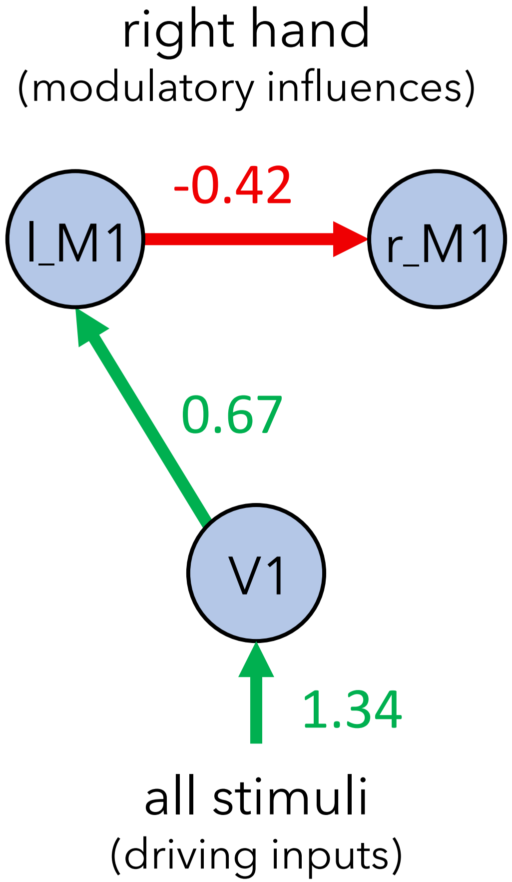
1. extract the time series from all regions of interest (eigenvariate of all voxels in the regions of interest)
2. specify the model according to your hypotheses about the underlying network architecture
3. estimate the model
4. repeat steps 2 and 3 for all models in your model space

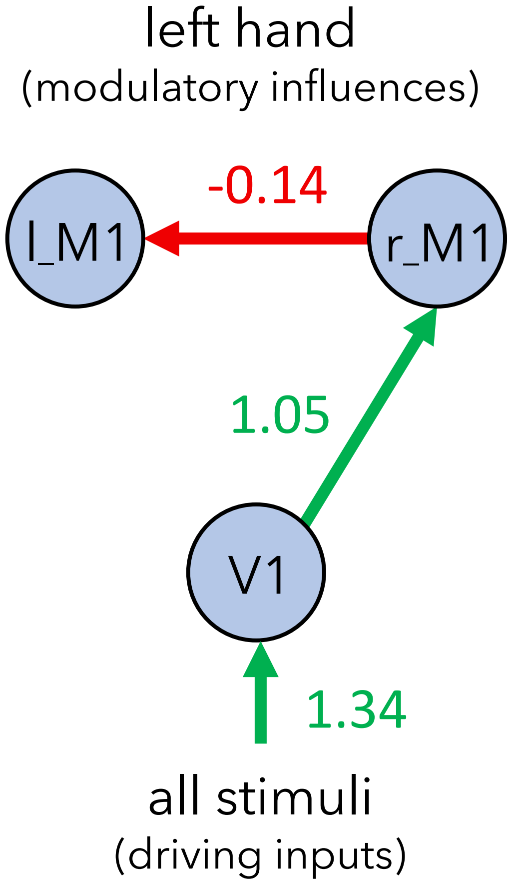
5. perform Bayesian model selection (BMS) or Bayesian model averaging (BMA)
6. inspect posterior parameter estimates of effective connectivity parameters (A, B, and C-matrix)

DYNAMIC CAUSAL MODELING

Bayesian model selection and Bayesian model averaging results:







THANK YOU FOR YOUR ATTENTION !

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