PPIs and DYNAMIC CAUSAL MODELING FOR fMRI

Based on slides from: Klaas Stephan, Hanneke den Ouden, & Andre Marreiros

Darren Gitelman, MD

Associate Professor of Neurology and Radiology

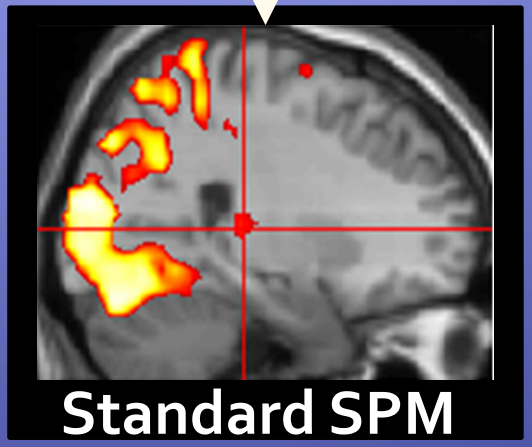
Northwestern University, Feinberg School of Medicine

d-gitelman@northwestern.edu

Systems analysis in functional neuroimaging

Functional specialisation

- Analyses of regionally specific effects
- Which regions are specialized for a particular task?)
- Univariate analysis



Functional integration

- Analyses of inter-regional effects
- What are the interactions between the elements of a neuronal system?
- Univariate & Multivariate analysis

Functional connectivity

Effective connectivity

Systems analysis in functional neuroimaging

Functional integration

Functional connectivity

- Temporal correlations between spatially remote areas
- **MODEL-FREE**
- **Exploratory**
- **Data Driven**
- **No Causation**
- **Whole brain connectivity**

Effective connectivity

- The influence that one neuronal system exerts over another
- **MODEL-DEPENDENT**
- **Confirmatory**
- **Hypothesis driven**
- **Causal (based on a model)**
- **Reduced set of regions**

Connectivity Analysis Methods

- Functional Connectivity
  - ICA (independent component analyses)
  - Pairwise ROI Correlations
  - Whole brain seed driven connectivity
  - Graph analyses
- Effective Connectivity
  - PPI (psycho-physiological interactions)
  - SEM (structural equation models)
  - MAR (multivariate autoregressive models)
  - Granger Causality
  - DCM (dynamic causal models)

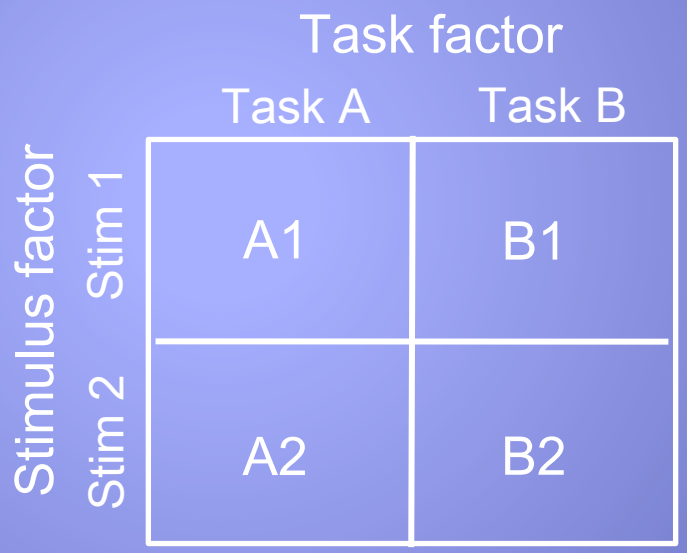
Psycho-physiological interaction (PPI)

- Bilinear model of how the psychological context A changes the influence of area B on area C :

$$B \times A \rightarrow C$$

- A PPI corresponds to differences in regression slopes for different contexts.

Psycho-physiological interaction (PPI)



GLM of a 2x2 factorial design:

$$y = (T_A - T_B)\beta_1 + (S_1 - S_2)\beta_2 + (T_A - T_B)(S_1 - S_2)\beta_3 + e$$

- $(T_A - T_B)\beta_1$: main effect of task
- $(S_1 - S_2)\beta_2$: main effect of stim. type
- $(T_A - T_B)(S_1 - S_2)\beta_3$: interaction

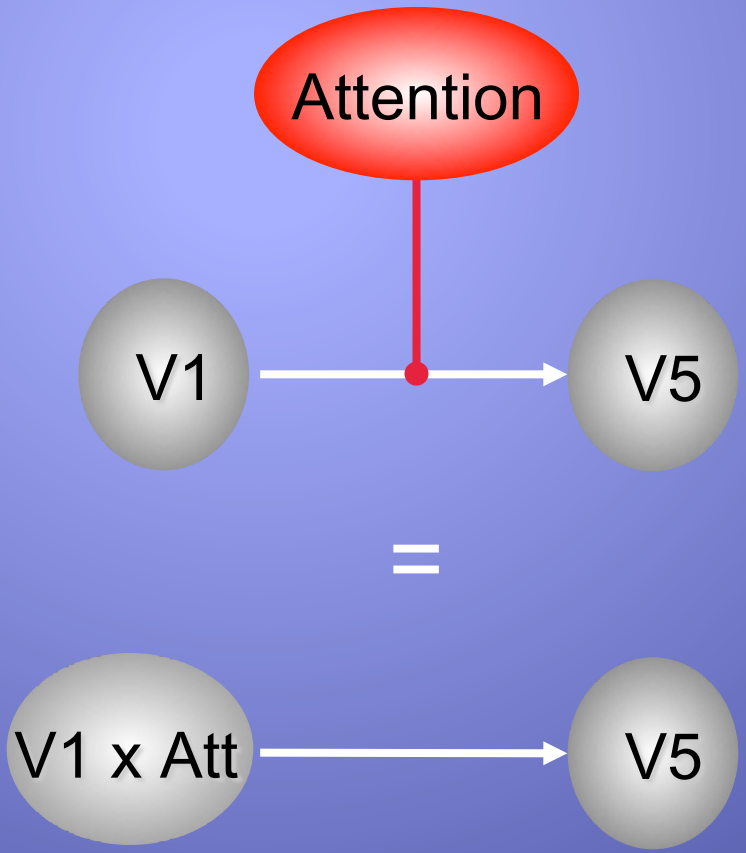
We can replace one main effect in the GLM by the time series of an area that shows this main effect.

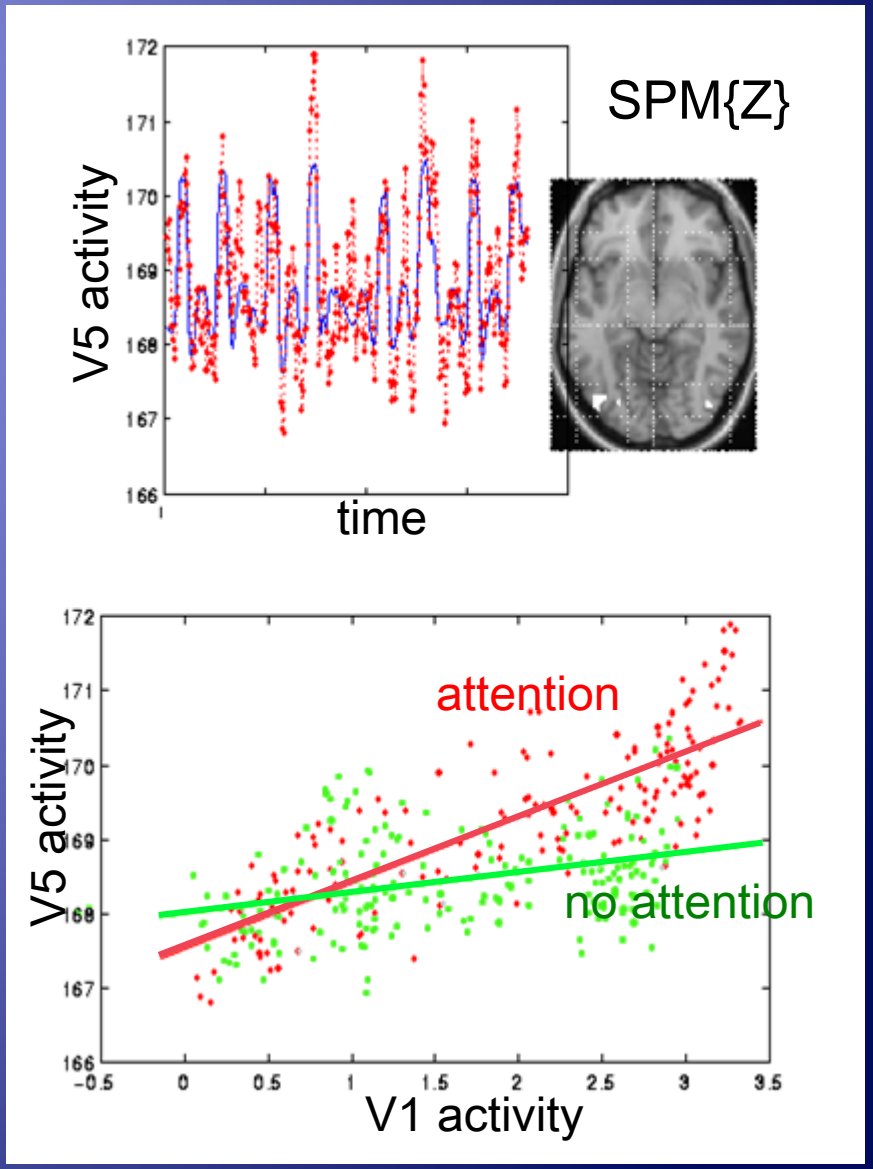
$$y = (T_A - T_B)\beta_1 + V1\beta_2 + (T_A - T_B)V1\beta_3 + e$$

- $(T_A - T_B)\beta_1$: main effect of task
- $V1\beta_2$: V1 time series ≈ main effect of stim. type
- $(T_A - T_B)V1\beta_3$: psycho-physiological interaction

Friston et al. NeuroImage, 1997

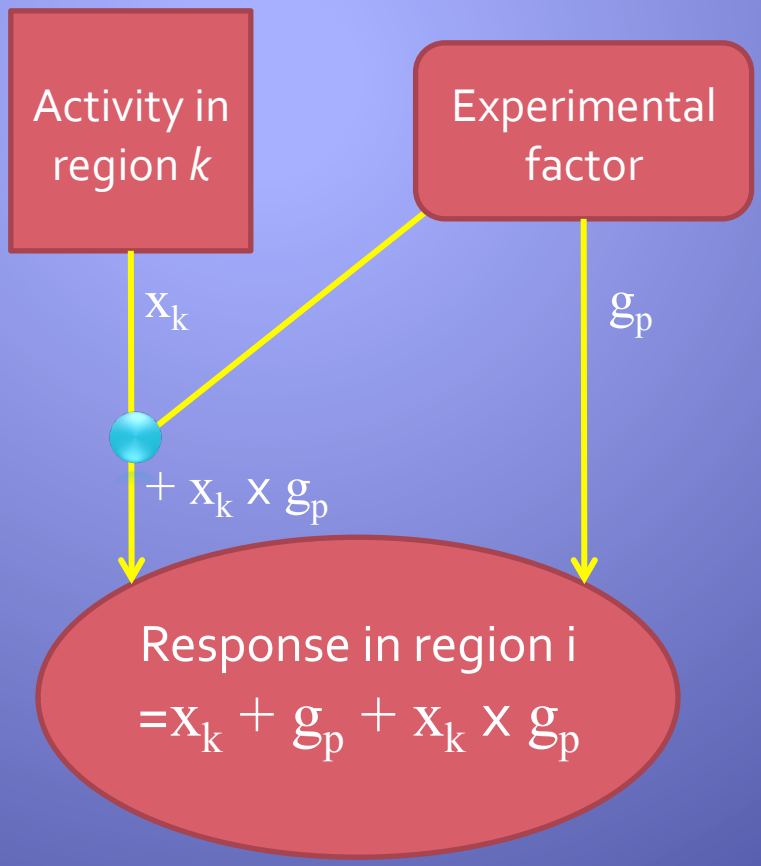
Attentional modulation of V1→V5



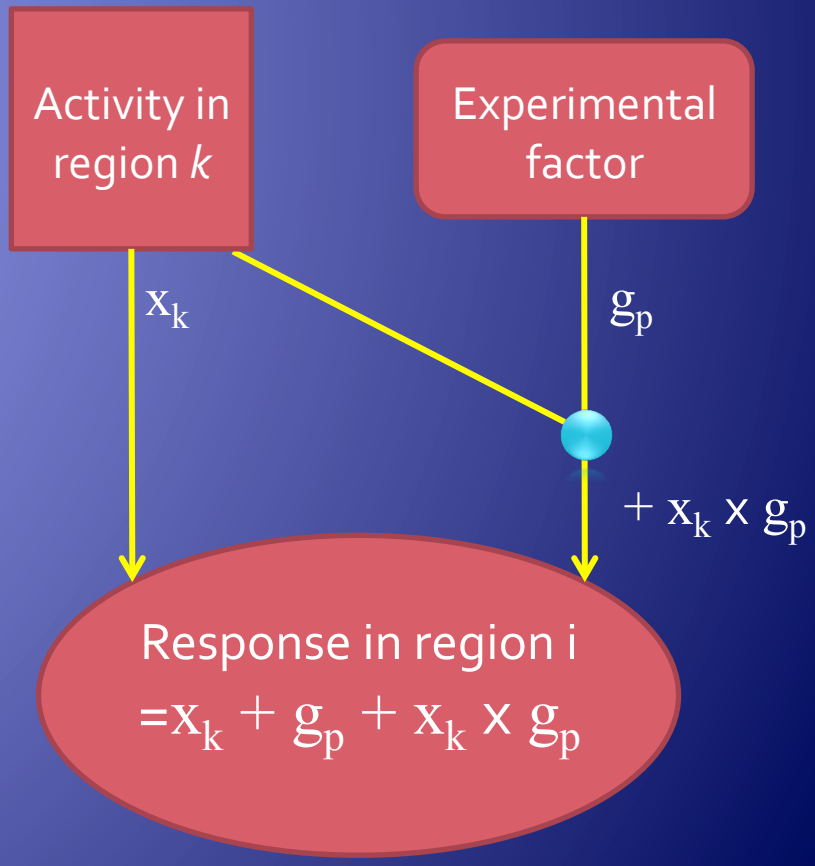


Friston et al. 1997, *NeuroImage*
Büchel & Friston 1997, *Cereb. Cortex*

Two mechanistic interpretations of PPI's.



Context specific modulation of responses to stimulus



Stimulus related modulation of responses to context (attention)

Friston et al, Neuroimage, 1997

PPI directionality

- Although PPIs select a source and find target regions, they cannot determine the directionality of connectivity.
- The regression equations are reversible. The slope of A → B is the reciprocal of B → A.
- Directionality should be pre-specified and based on knowledge of anatomy or other experimental results.

PPI vs. correlation

- Are PPI's the same as correlations?
  - No
    - PPI's are based on regressions and assume a dependent and an independent variable
    - PPI's explicitly discount main effects

PPI vs. correlation

- Kim and Horwitz investigated connectivity using correlations vs. PPI regression applied to a biologically plausible neural model.
- PPI results were similar to those based on integrated synaptic activity (gold standard)
- Results from correlations were not significant for many of the [true] functional connections.
- A change in influence between 2 regions may not involve a change in signal correlation

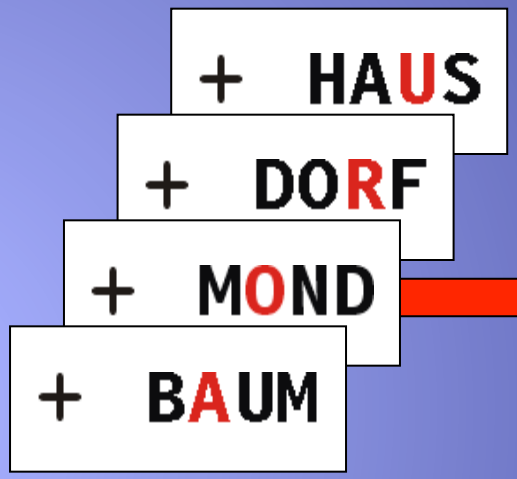
Kim & Horwitz, Mag Res Med, 2008

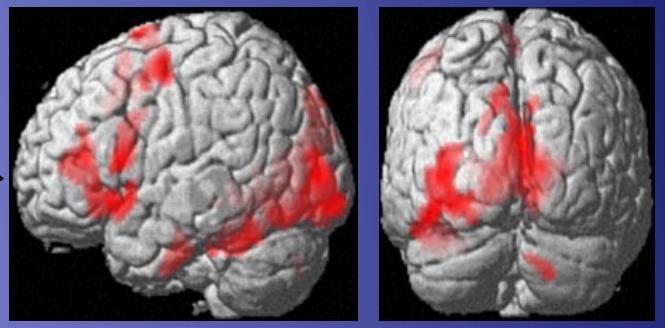
PPI: summary

- Psychological interaction
  - Change in regression slope due to the differential response to a stimulus under the influence of different experimental contexts.
- Physiophysiological interaction
  - Change in regression slope due to the differential response to the signal from one region under the influence of another (region).
- Psychophysiological interaction
  - Change in regression slope due to the differential response to the signal from one region under the influence of different experimental contexts.

Task-driven lateralisation

Does the word contain the letter A or not?

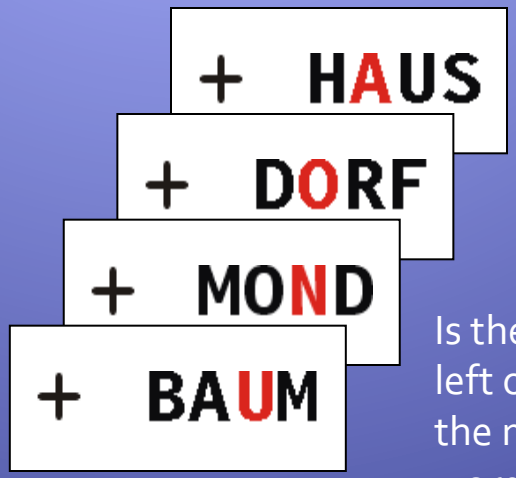




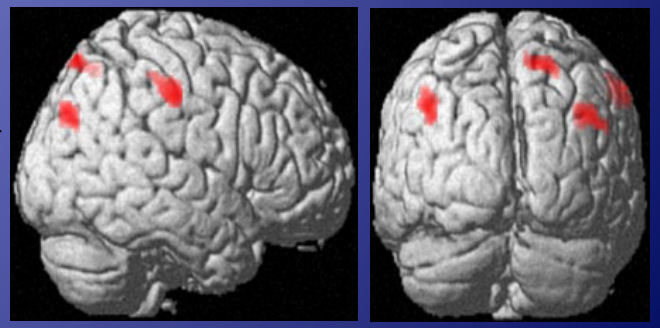
letter decisions > spatial decisions

time

group analysis (random effects), n=16, p<0.05 corrected analysis with SPM2



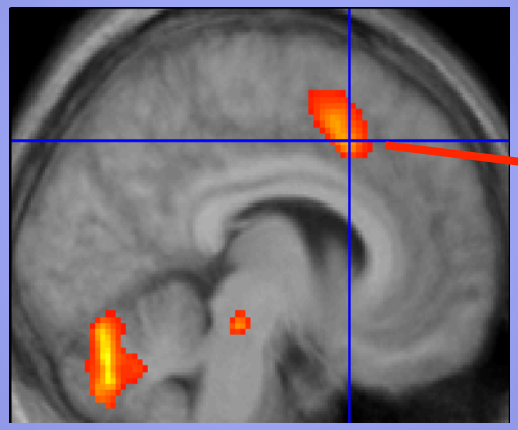
Is the red letter left or right from the midline of the word?



spatial decisions > letter decisions

Stephan et al, Science, 2003

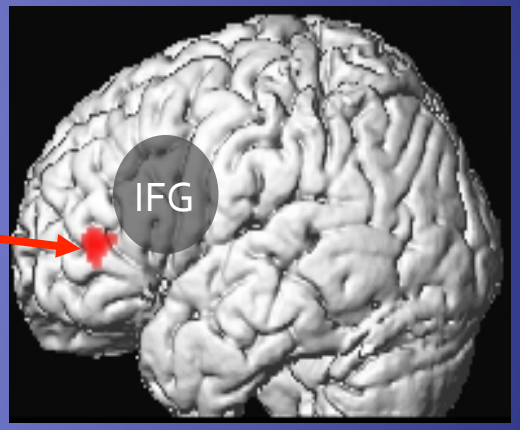
Bilateral ACC activation in both tasks – but asymmetric connectivity !



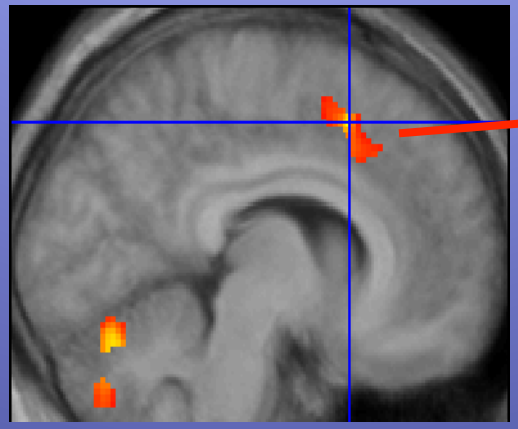
left ACC (-6, 16, 42)

group analysis
random effects (n=15)
p<0.05, corrected (SVC)

letter vs spatial decisions

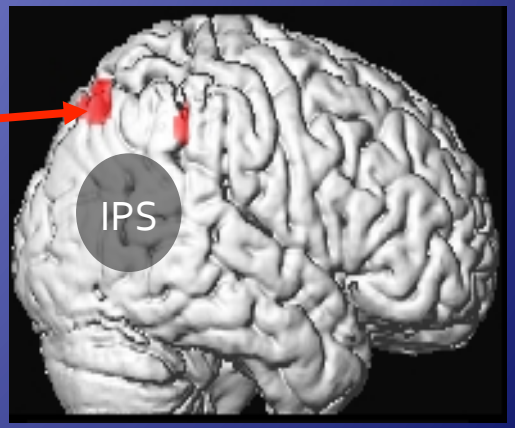


Left ACC → left inf. frontal gyrus (IFG): increase during letter decisions.



right ACC (8, 16, 48)

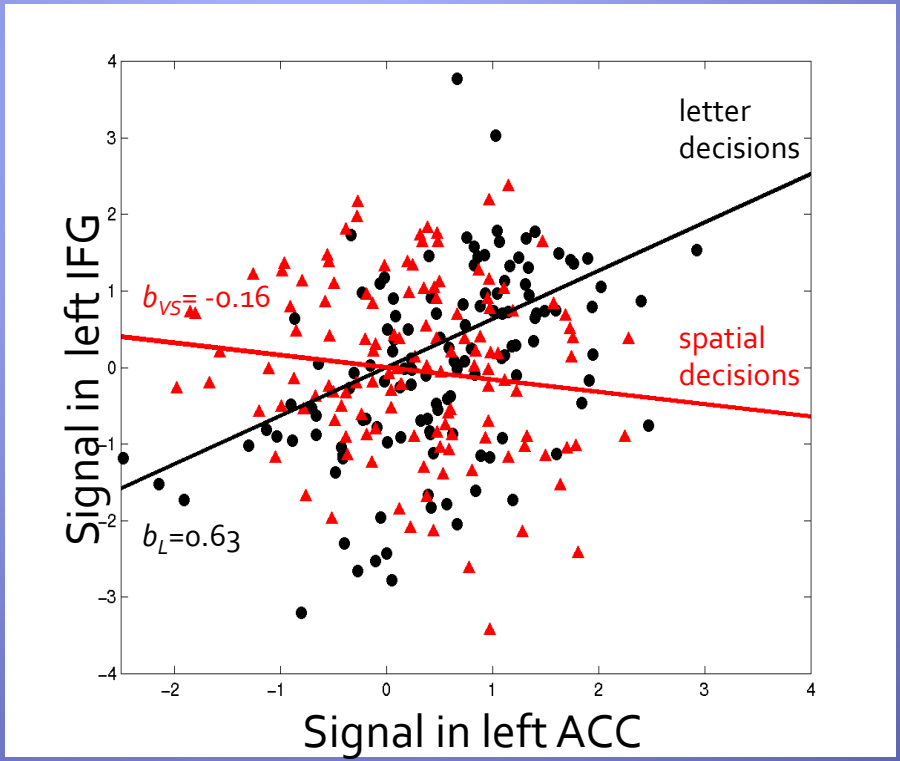
spatial vs letter decisions



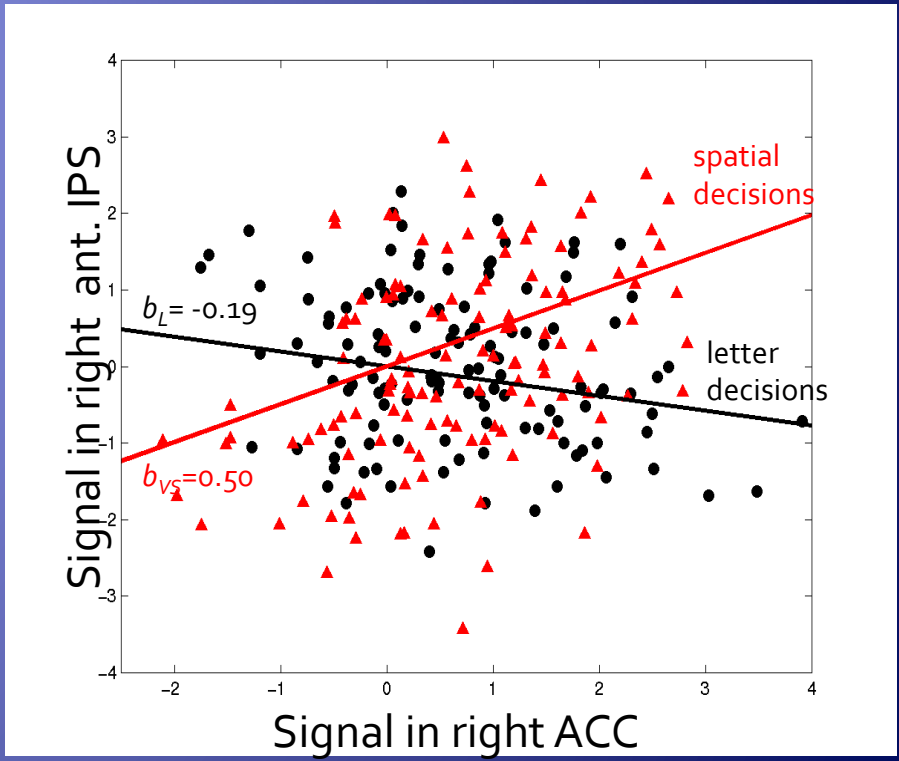
Right ACC → right IPS: increase during spatial decisions.

Stephan et al., *Science*, 2003

PPI single-subject example



Left ACC signal plotted against left IFG



Right ACC signal plotted against right IPS

Stephan et al, Science, 2003

PPI: Pros

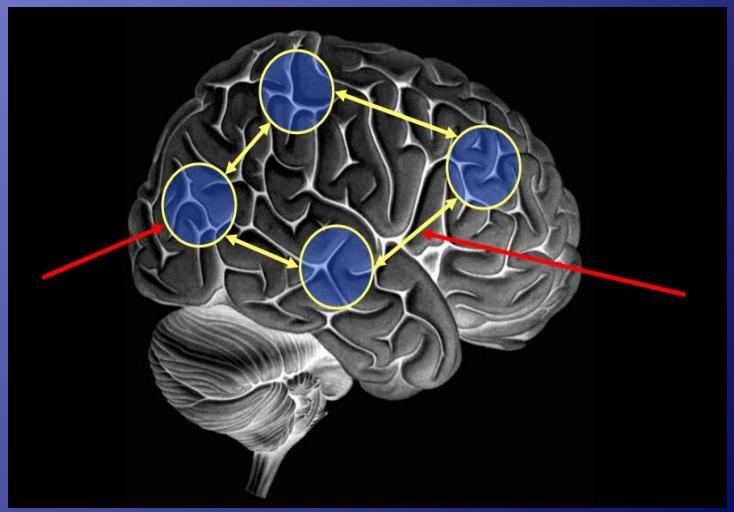
- Pros:
  - Given a single source region, we can test for its context-dependent connectivity across the entire brain
  - Easy to implement

PPI: Pros / Cons

- Cons:
  - Depend on factorial designs. If the interaction and main effects are not orthogonal, the sensitivity will be low.
  - Analysis can be overly sensitive to the choice of region.
  - Very simplistic model: i.e., contributions from a single area
  - Ignores time-series properties of data
  - Operates at the level of BOLD time series (spm99/2). SPM 5/8 deconvolves the BOLD signal to form the proper interaction term, and then reconvolves it.
- Need DCM for to make robust statements about effective connectivity and causality.

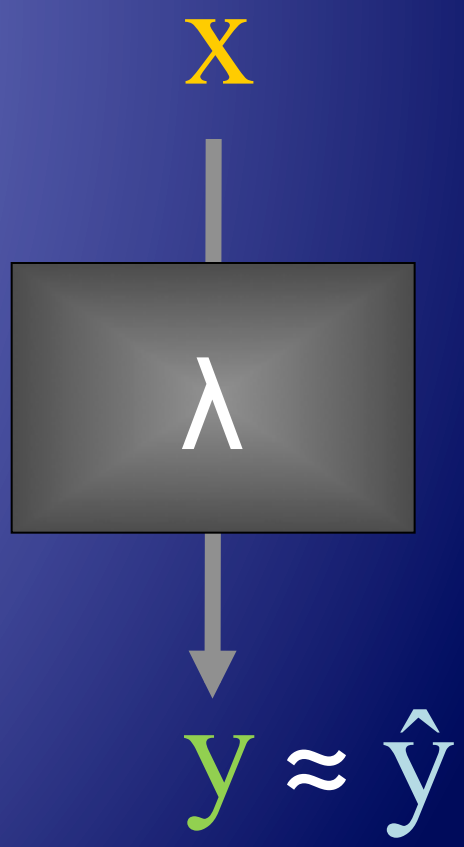
Dynamic Causal Modeling

- DCM allows us to look at how areas within a network interact:
- Investigate functional integration & modulation of specific cortical pathways



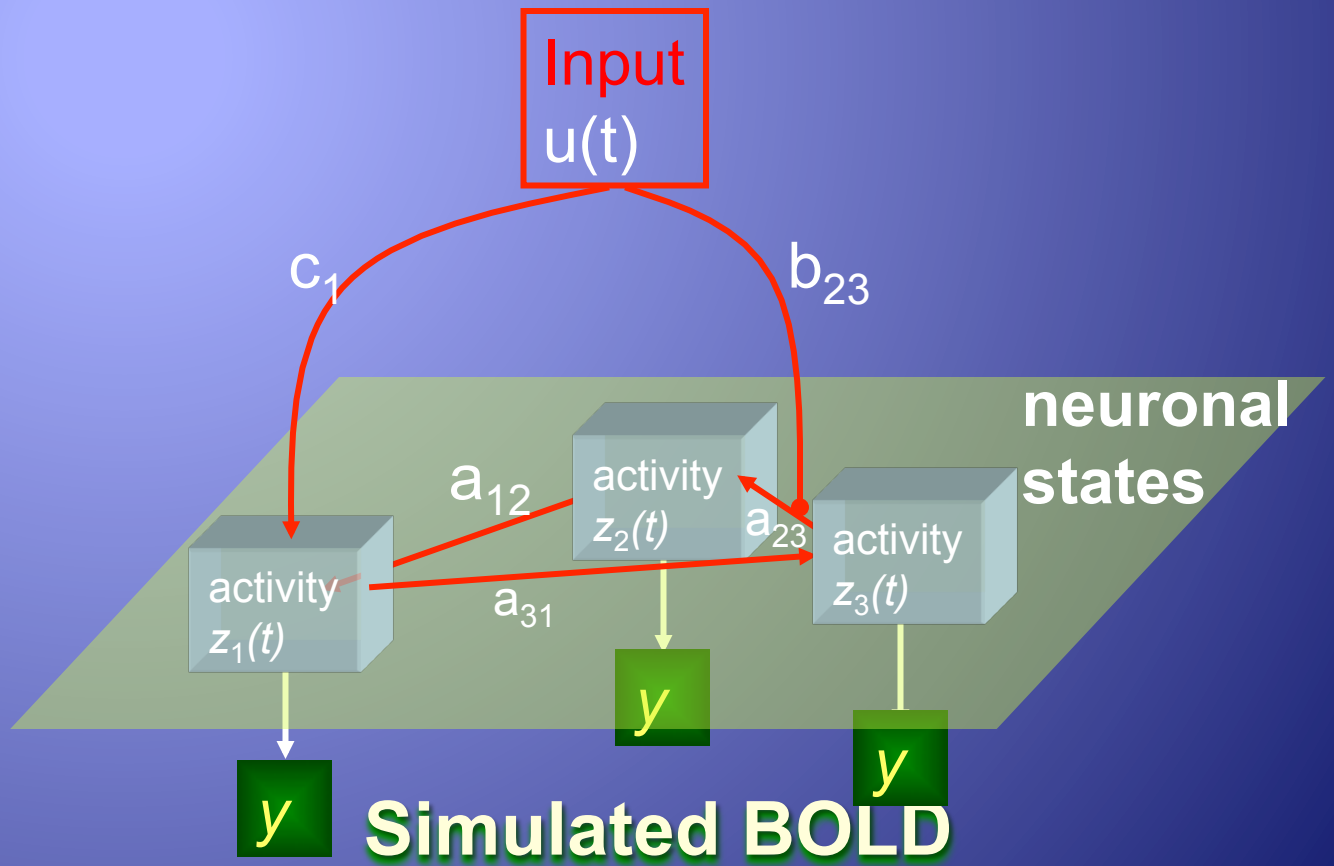
Principles of DCM:

- Investigate functional integration & modulation of specific cortical pathways
- Using a bilinear state equation, a cognitive system is modeled at its underlying neuronal level (which is not directly accessible to fMRI).
- The modeled neuronal dynamics (x) are transformed into area-specific 'simulated' BOLD signals (y) by a hemodynamic model (λ).



The aim of DCM is to estimate parameters at the "neuronal level" such that the modeled and measured BOLD signals are maximally* similar.

Conceptual overview



Use differential equations to represent a neuronal system

- ***State vector***
  - Changes with time
- ***Rate of change of state vector***
  - Interactions between elements
  - External inputs, *u*
- ***System parameters θ***

$$z(t) = \begin{bmatrix} z_1(t) \\ \vdots \\ z_n(t) \end{bmatrix}$$

system represented by state variables

$$\begin{bmatrix} \dot{z}_1 \\ \vdots \\ \dot{z}_n \end{bmatrix} = \begin{bmatrix} f_1(z_1 \ldots z_n, u, \theta_1) \\ \vdots \\ f_n(z_1 \ldots z_n, u, \theta_n) \end{bmatrix}$$

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

DCM parameters = rate constants

Generic solution to the ODEs in DCM:

$$\frac{dz}{dt} = az \rightarrow z(t) = z_0 \exp(at)$$

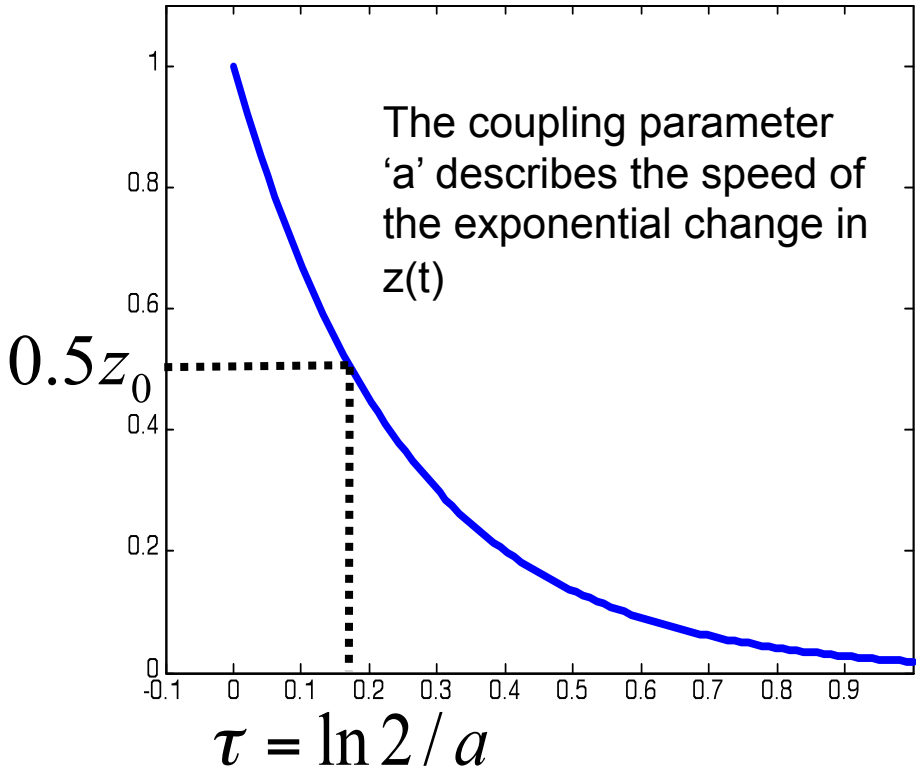
Coupling parameter 'a' is inversely proportional to the half life τ of z(t):

Half-life τ:

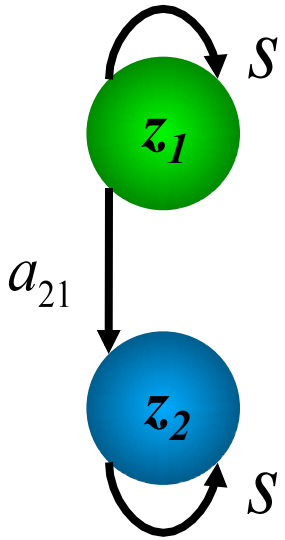
$$z(\tau) = 0.5 z_0$$

$$= z_0 \exp(a\tau)$$

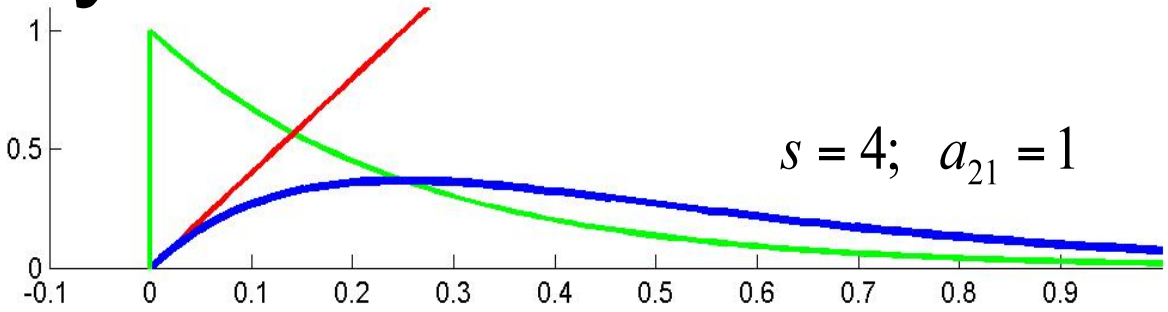
$$\rightarrow \boxed{a = \ln 2 / \tau}$$

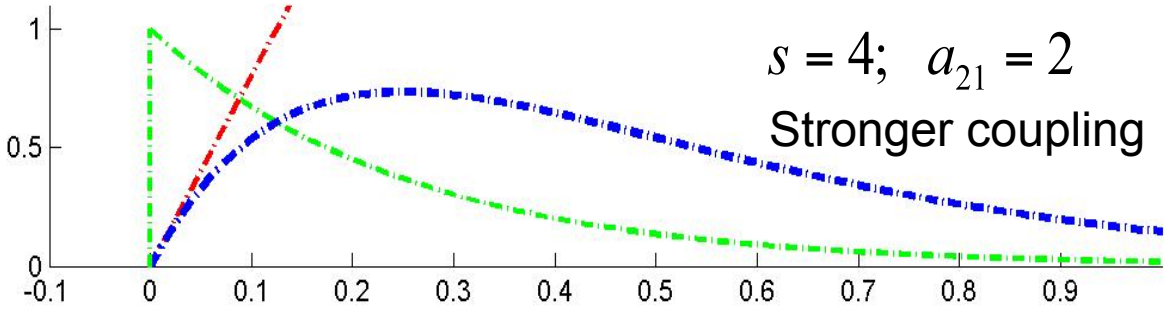


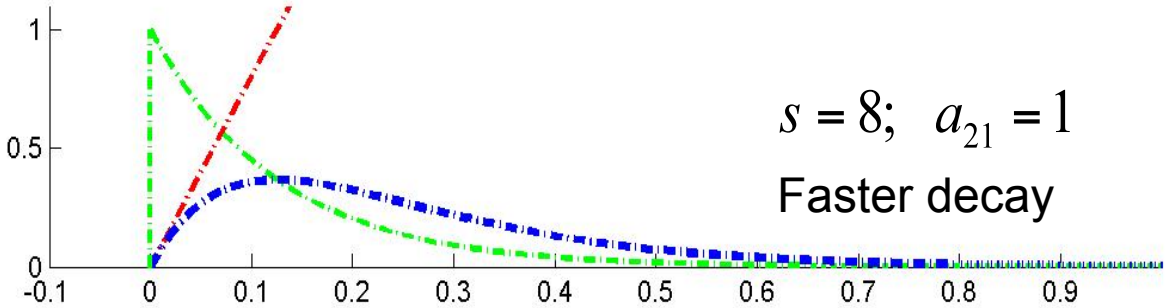
Linear dynamics: 2 nodes



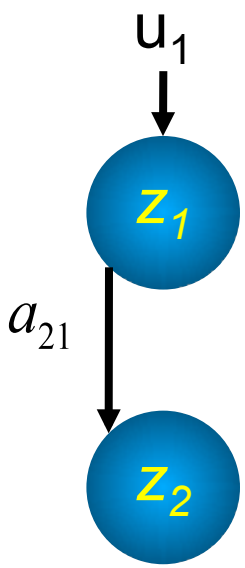
$$\dot{z}_1 = -sz_1$$
$$\dot{z}_2 = s(a_{21}z_1 - z_2)$$
$$z_1(0) = 1$$
$$z_2(0) = 0$$
$$z_1(t) = \exp(-st)$$
$$z_2(t) = sa_{21}t\exp(-st)$$
$$a_{21} > 0$$

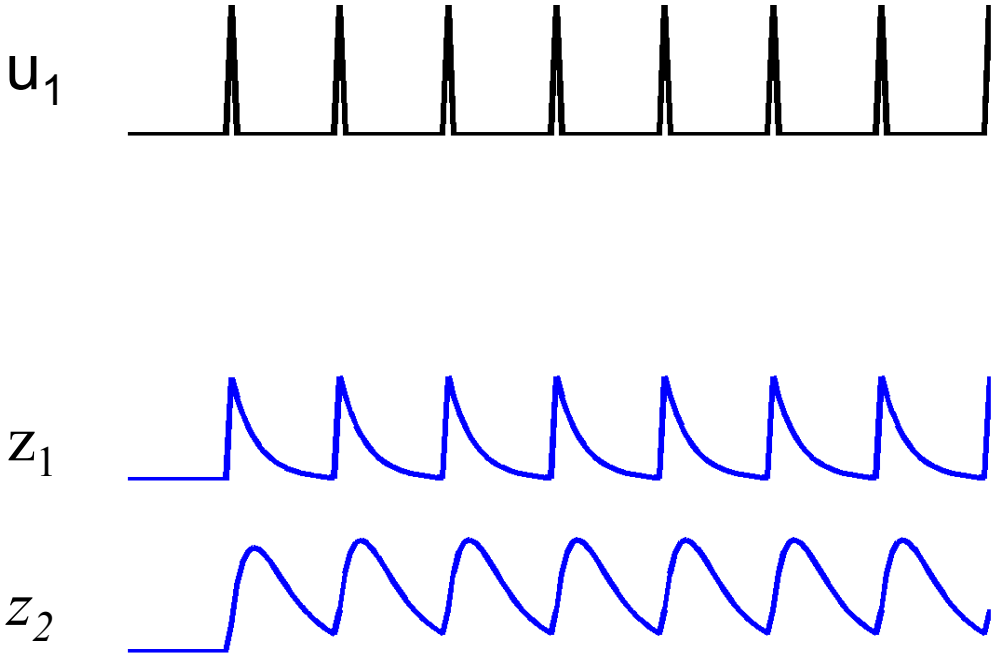






Neurodynamics: 2 nodes with input

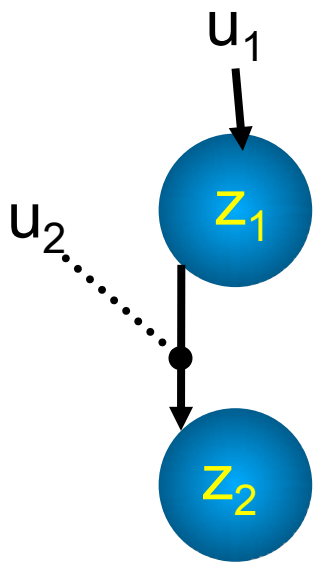


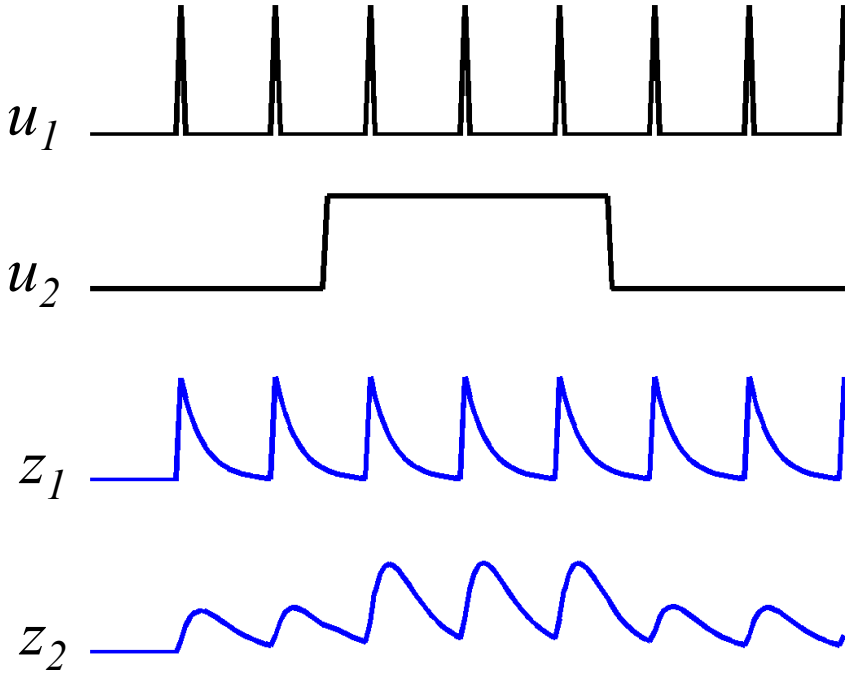


$$\begin{bmatrix} \dot{z}_1 \\ \dot{z}_2 \end{bmatrix} = s \begin{bmatrix} -1 & 0 \\ a_{21} & -1 \end{bmatrix} \begin{bmatrix} z_1 \\ z_2 \end{bmatrix} + \begin{bmatrix} c \\ 0 \end{bmatrix} u_1 \qquad a_{21} > 0$$

activity in z_2 is coupled to z_1 via coefficient a_{21}

Neurodynamics: positive modulation





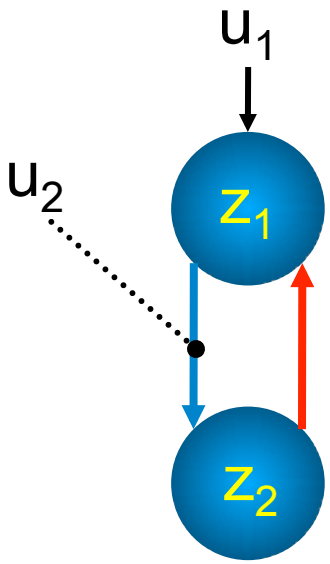
$$\begin{bmatrix} \dot{z}_1 \\ \dot{z}_2 \end{bmatrix} = s \begin{bmatrix} -1 & 0 \\ a_{21} & -1 \end{bmatrix} \begin{bmatrix} z_1 \\ z_2 \end{bmatrix} + u_2 \begin{bmatrix} 0 & 0 \\ b_{21}^2 & 0 \end{bmatrix} \begin{bmatrix} z_1 \\ z_2 \end{bmatrix} + \begin{bmatrix} c \\ 0 \end{bmatrix} u_1$$

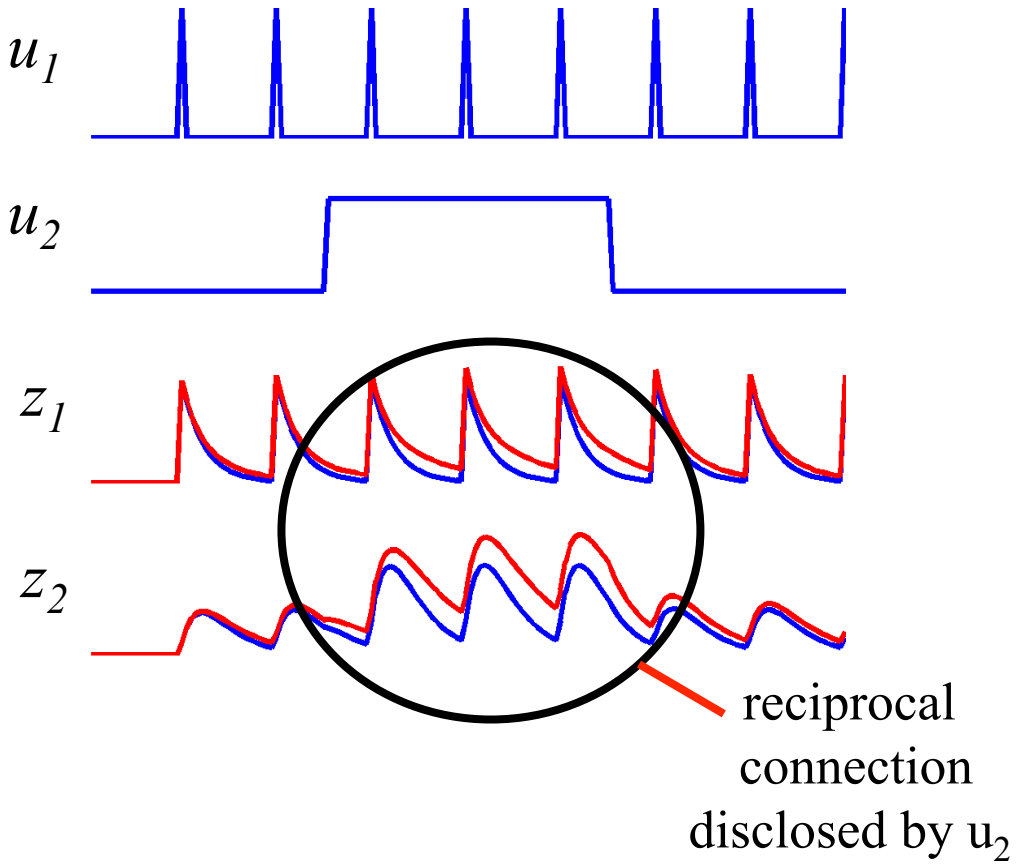
index, not squared

$$b_{21}^2 > 0$$

modulatory input u_2 activity through the coupling a_{21}

Neurodynamics: reciprocal connections

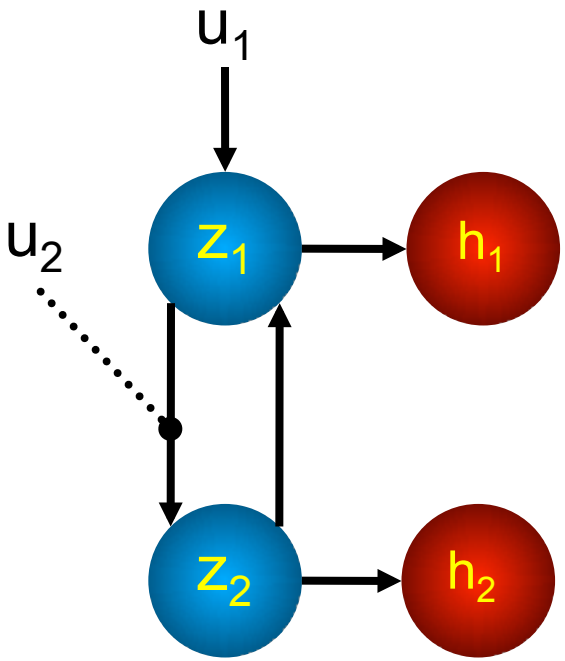


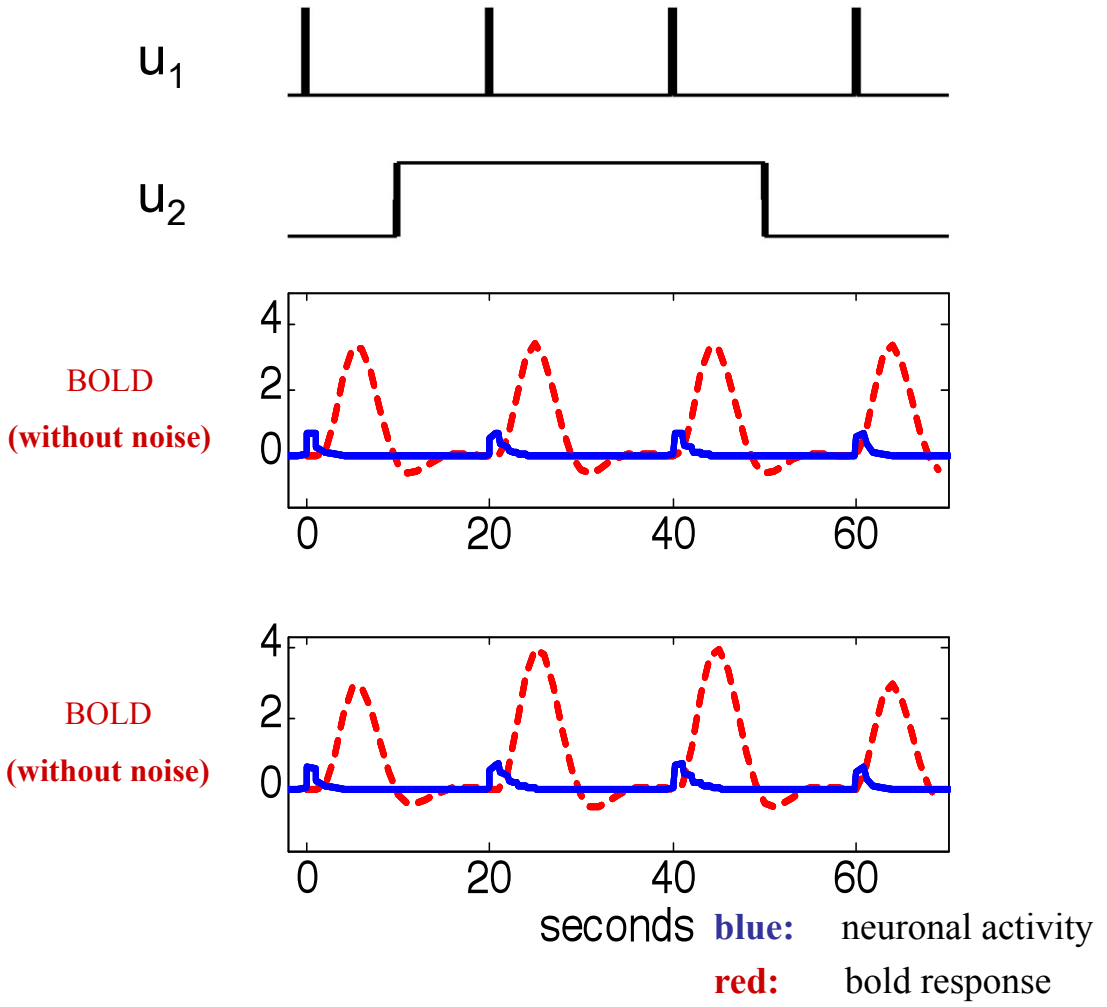


$$\begin{bmatrix}\dot{z}_1\\ \dot{z}_2\end{bmatrix} = s\begin{bmatrix}-1 & a_{12}\\ a_{21} & -1\end{bmatrix}\begin{bmatrix}z_1\\ z_2\end{bmatrix} + u_2\begin{bmatrix}0 & 0\\ b_{21}^2 & 0\end{bmatrix}\begin{bmatrix}z_1\\ z_2\end{bmatrix} + \begin{bmatrix}c\\ 0\end{bmatrix}u_1$$

$$a_{12}, a_{21}, b_{21}^2 > 0$$

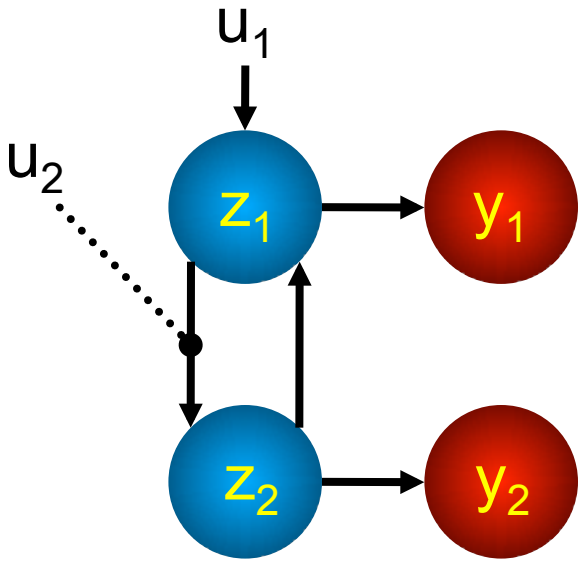
Hemodynamics: reciprocal connections

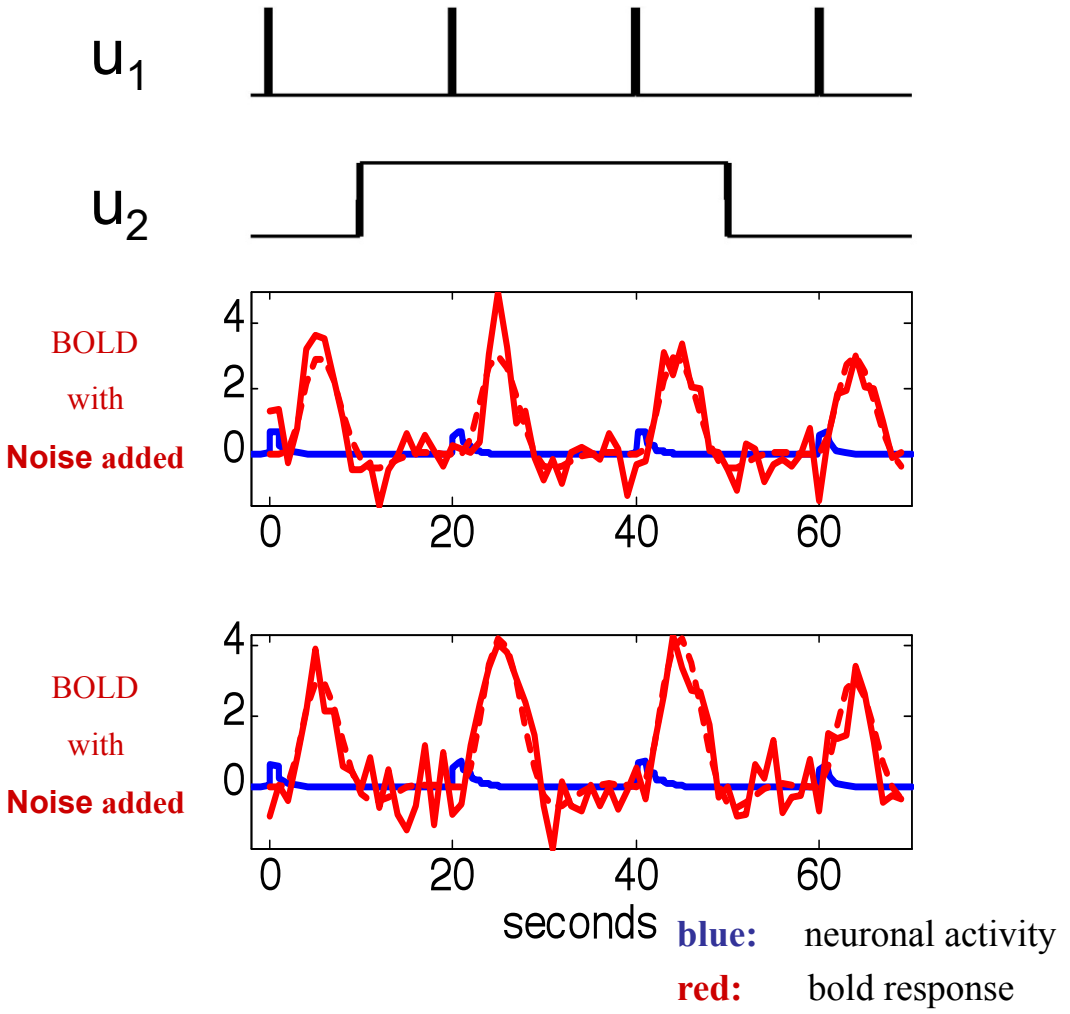




h(u,θ) represents the BOLD response (balloon model) to input

Hemodynamics: reciprocal connections





y represents simulated observation of BOLD response, i.e. includes noise

$$y = h(u,\theta) + e$$

Bilinear state equation in DCM for fMRI

state changes | **connectivity** | **modulation of connectivity** | **state vector** | **direct inputs** | **external inputs**

$$\begin{bmatrix} \dot{z}_1 \\ \vdots \\ \dot{z}_n \end{bmatrix} = \left\{ \begin{bmatrix} a_{11} & \cdots & a_{1n} \\ \vdots & \ddots & \vdots \\ a_{n1} & \cdots & a_{nn} \end{bmatrix} + \sum_{j=1}^{m} u_j \begin{bmatrix} b_{11}^j & \cdots & b_{1n}^j \\ \vdots & \ddots & \vdots \\ b_{n1}^j & \cdots & b_{nn}^j \end{bmatrix} \right\} \begin{bmatrix} z_1 \\ \vdots \\ z_n \end{bmatrix} + \begin{bmatrix} c_{11} & \cdots & c_{1m} \\ \vdots & \ddots & \vdots \\ c_{n1} & \cdots & c_{nm} \end{bmatrix} \begin{bmatrix} u_1 \\ \vdots \\ u_m \end{bmatrix}$$

n regions | *m mod* inputs | *m drv* inputs

$$\dot{z} = (A + \sum_{j=1}^{m} u_j B^j) z + Cu$$

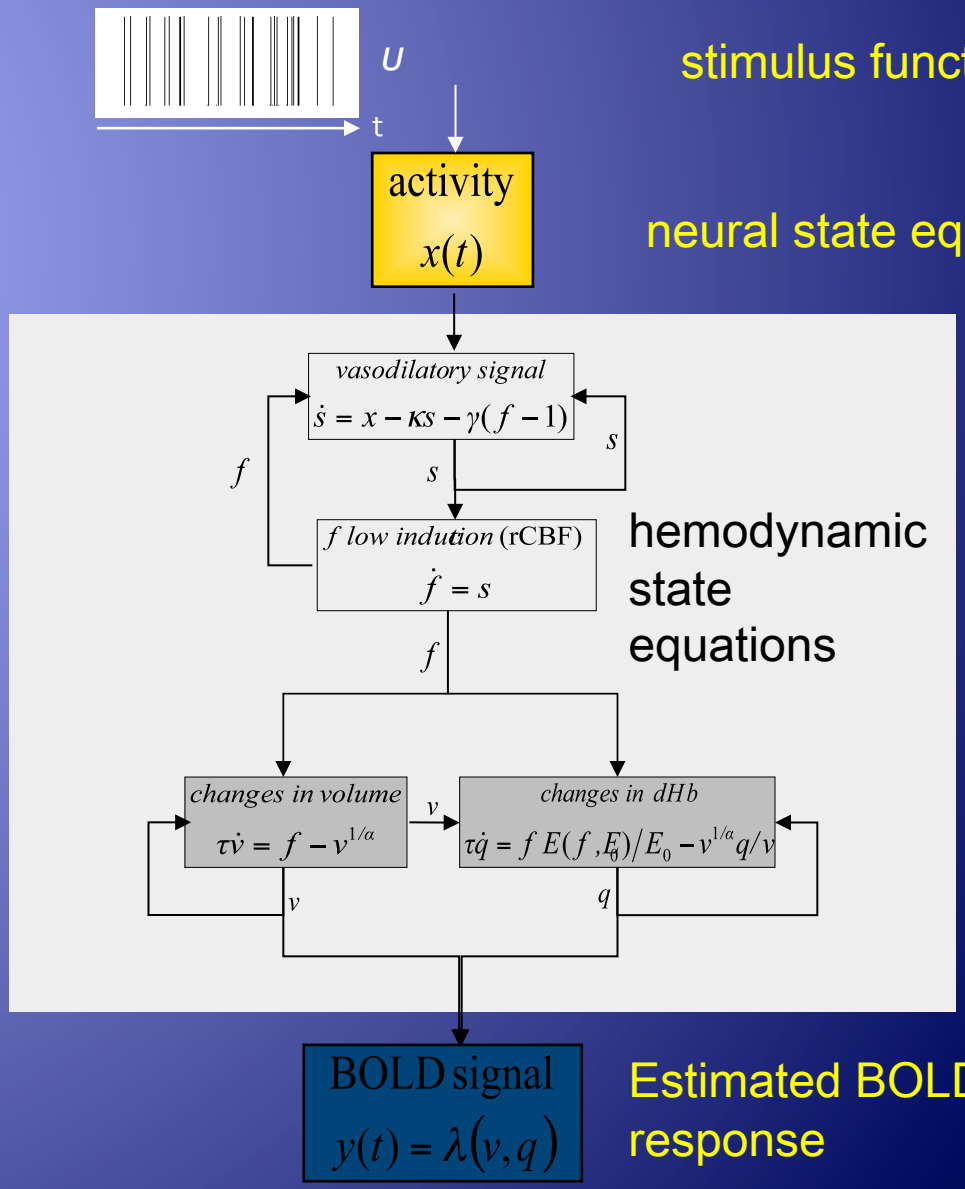
The hemodynamic model

6 hemodynamic parameters:

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

important for model fitting, but of no interest for statistical inference

Computed separately for each area → region-specific HRFs!



Friston et al. NeuroImage, 2000; Stephan et al, NeuroImage, 2007

Conceptual overview

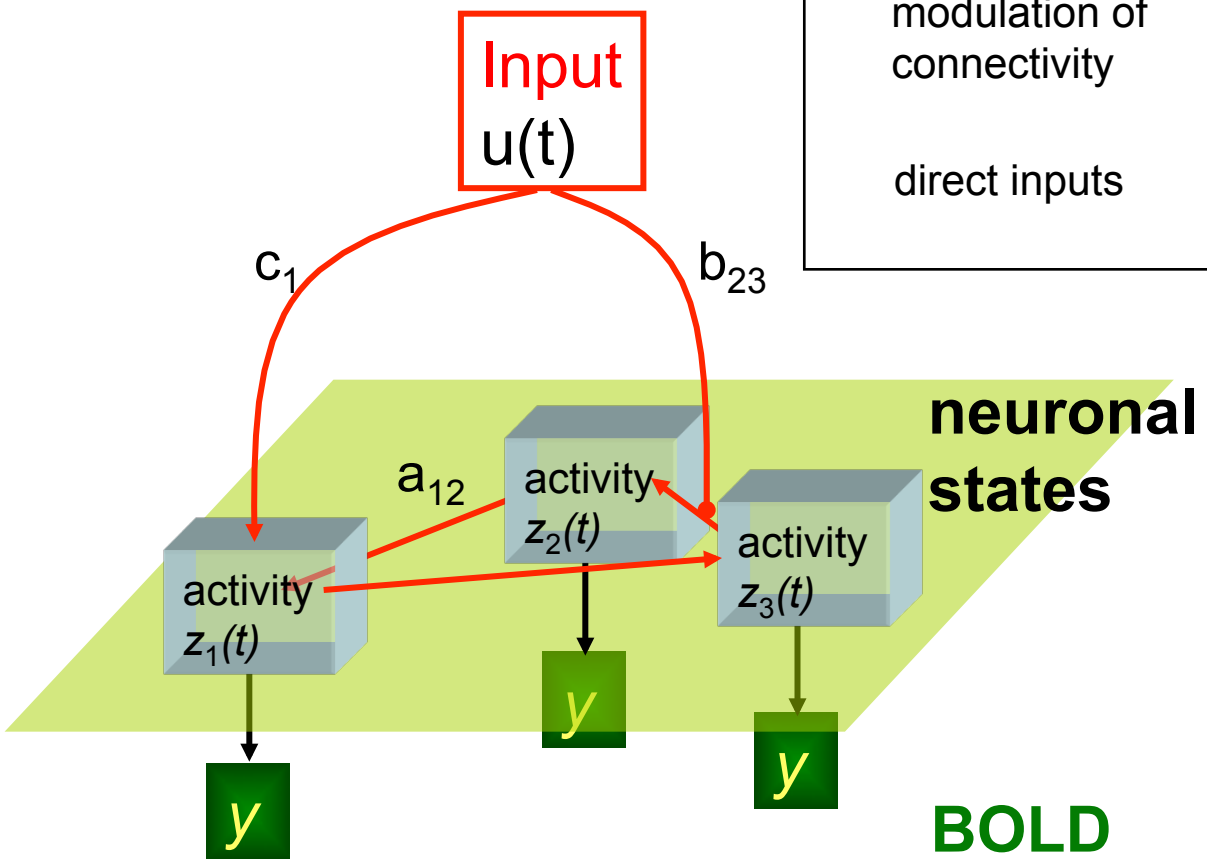
Neuronal state equation $\dot{z} = F(z, u, \theta^n)$

The bilinear model $\dot{z} = (A + \sum u_j B^j)z + Cu$

effective connectivity $A = \frac{\partial F}{\partial z} = \frac{\partial \dot{z}}{\partial z}$

modulation of connectivity $B^j = \frac{\partial^2 F}{\partial z \partial u_j} = \frac{\partial}{\partial u_j}\frac{\partial \dot{z}}{\partial z}$

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



integration

z

λ

haemodynamic model

y

Friston et al., *NeuroImage* 2003

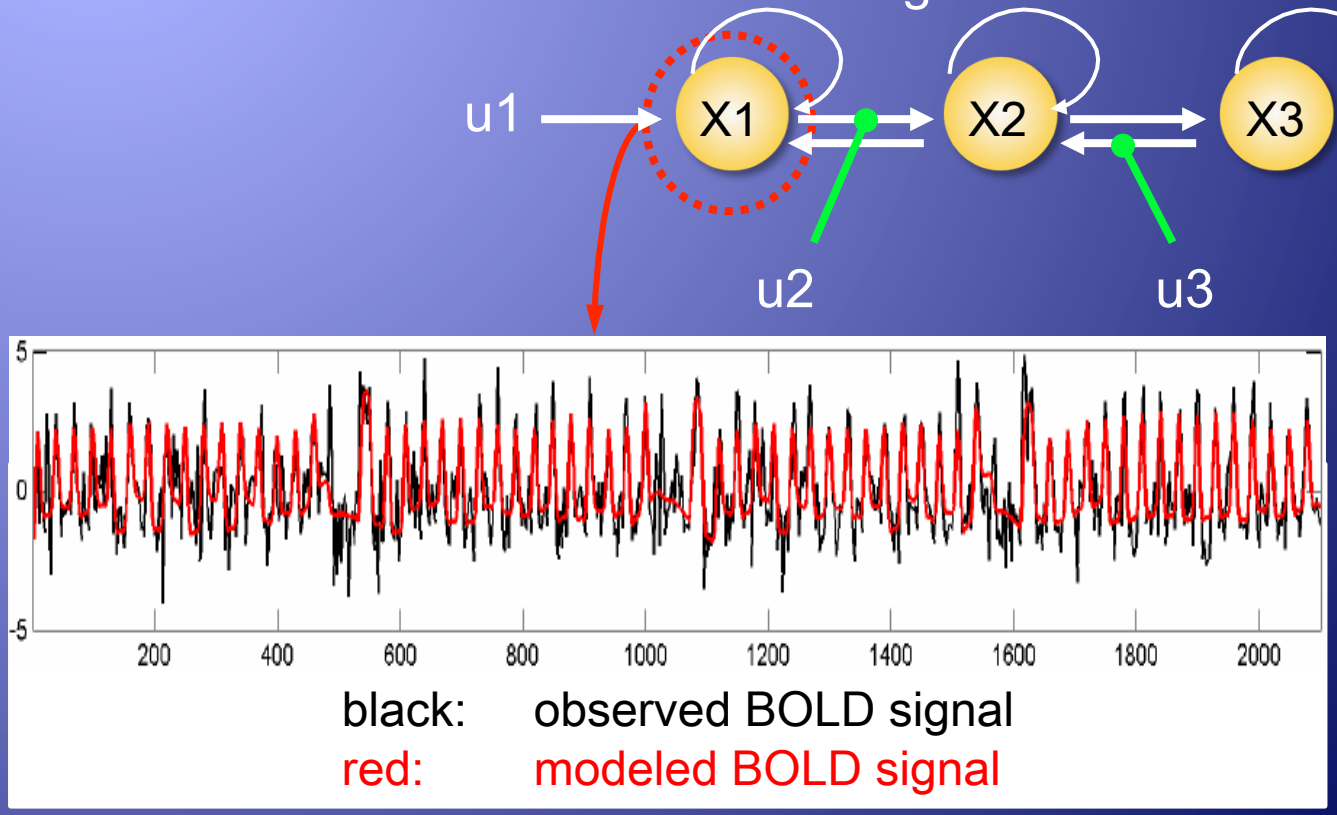
Measured vs Modeled BOLD signal

Recap

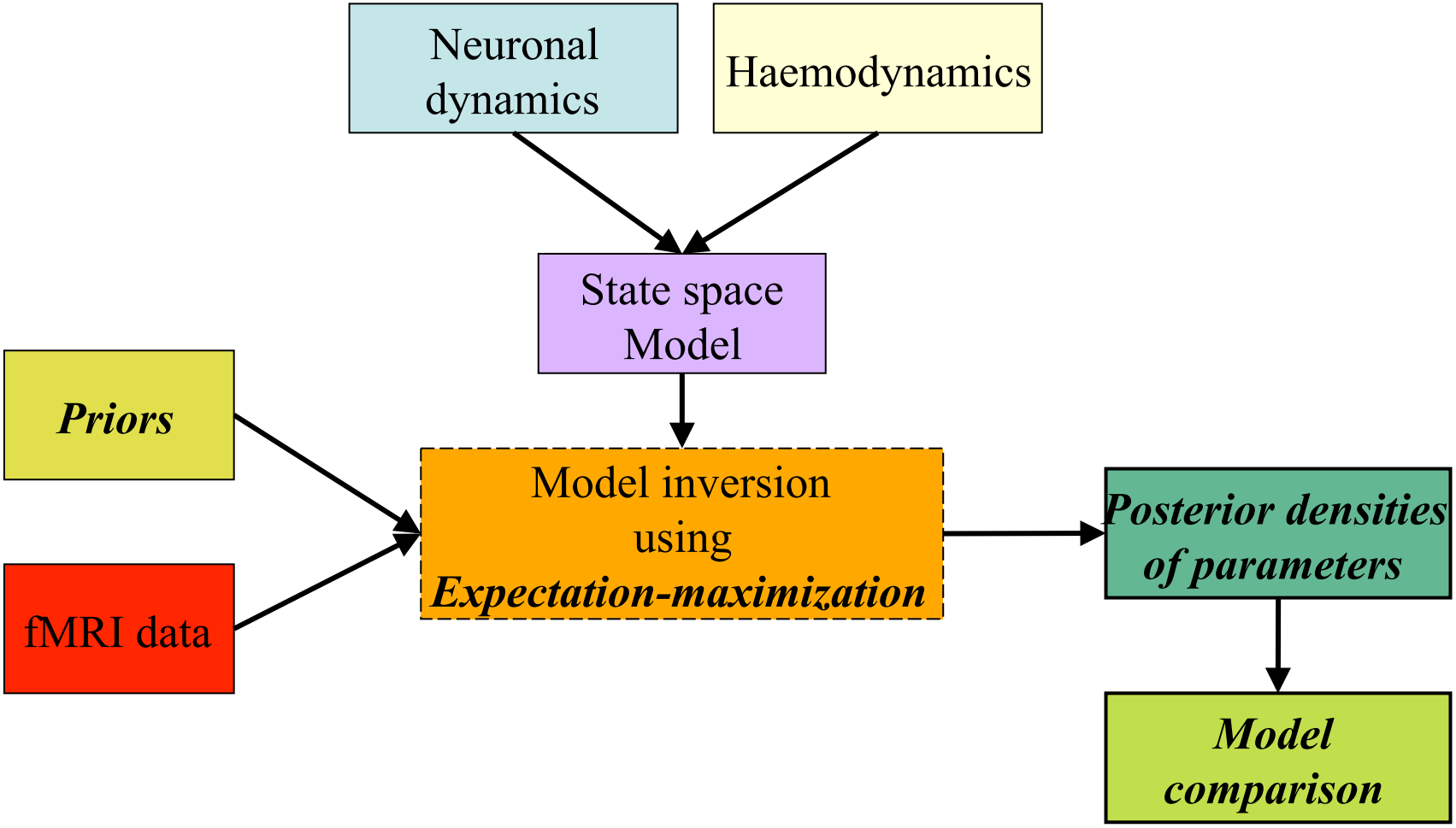
The aim of DCM is to estimate

- neural parameters {A, B, C}
- hemodynamic parameters

such that the modeled and measured BOLD signals are maximally similar.



DCM roadmap


Neuronal dynamics
Haemodynamics
State space Model
Priors
fMRI data
Model inversion using Expectation-maximization
Posterior densities of parameters
Model comparison

Estimation: Bayesian framework

Models of
- Hemodynamics
- Neuronal dynamics

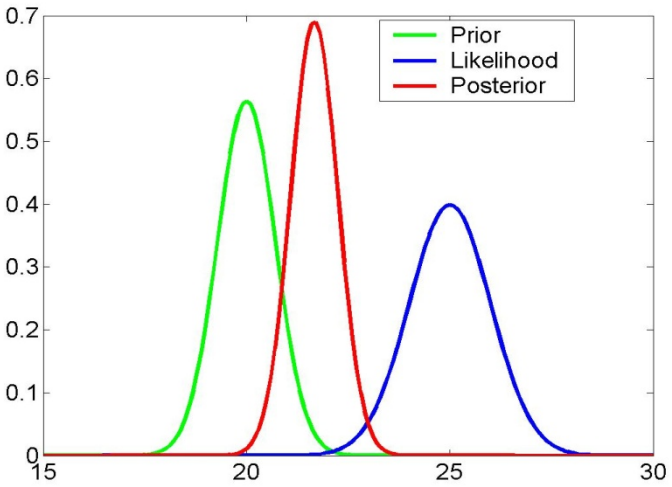
Constraints on
- Hemodynamic parameters
- Connections

likelihood term $p(y \mid \theta)$

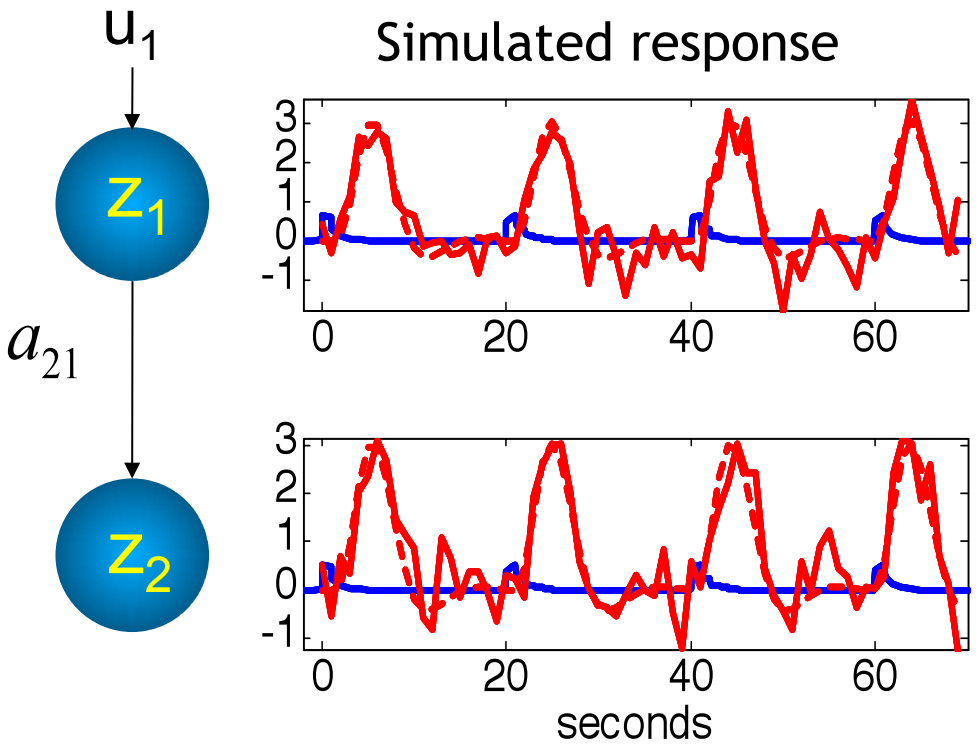
$p(\theta)$ prior

posterior $p(\theta \mid y) \propto p(y \mid \theta) p(\theta)$

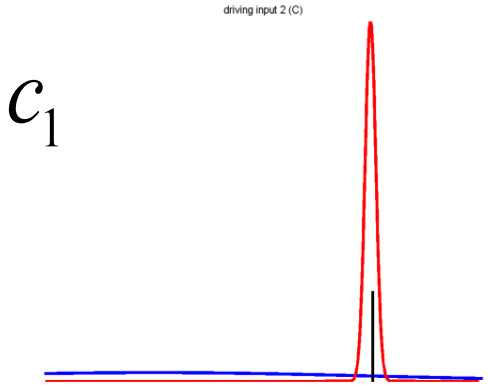
Bayesian estimation



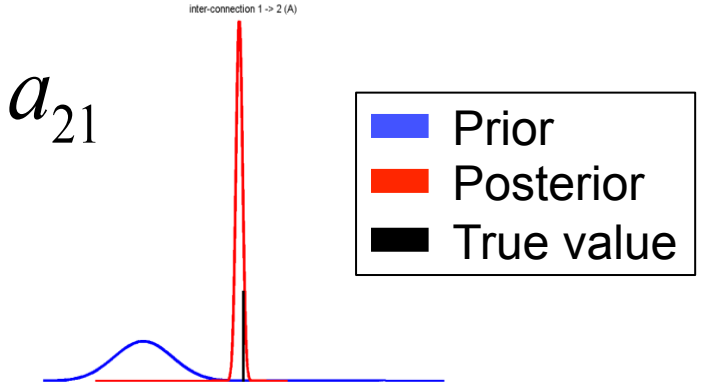
Parameter estimation: an example



Input coupling, c_1

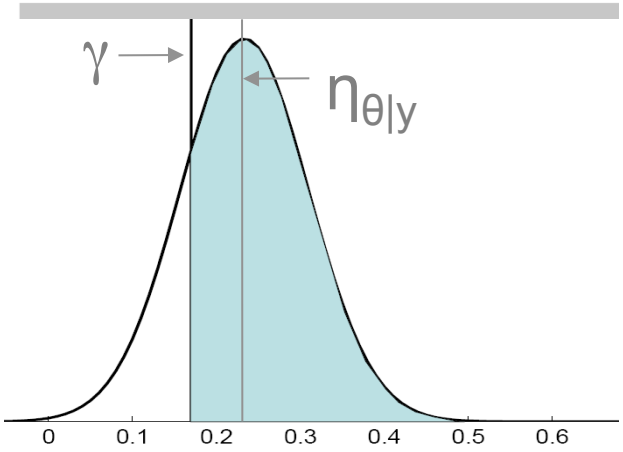


Forward coupling, a_{21}



Inference about DCM parameters: single-subject analysis

- Bayesian parameter estimation in DCM: Gaussian assumptions about the posterior distributions of the parameters
- Quantify the probability that a parameter (or contrast of parameters $c^T \eta_{\theta|y}$) is above a chosen threshold γ:

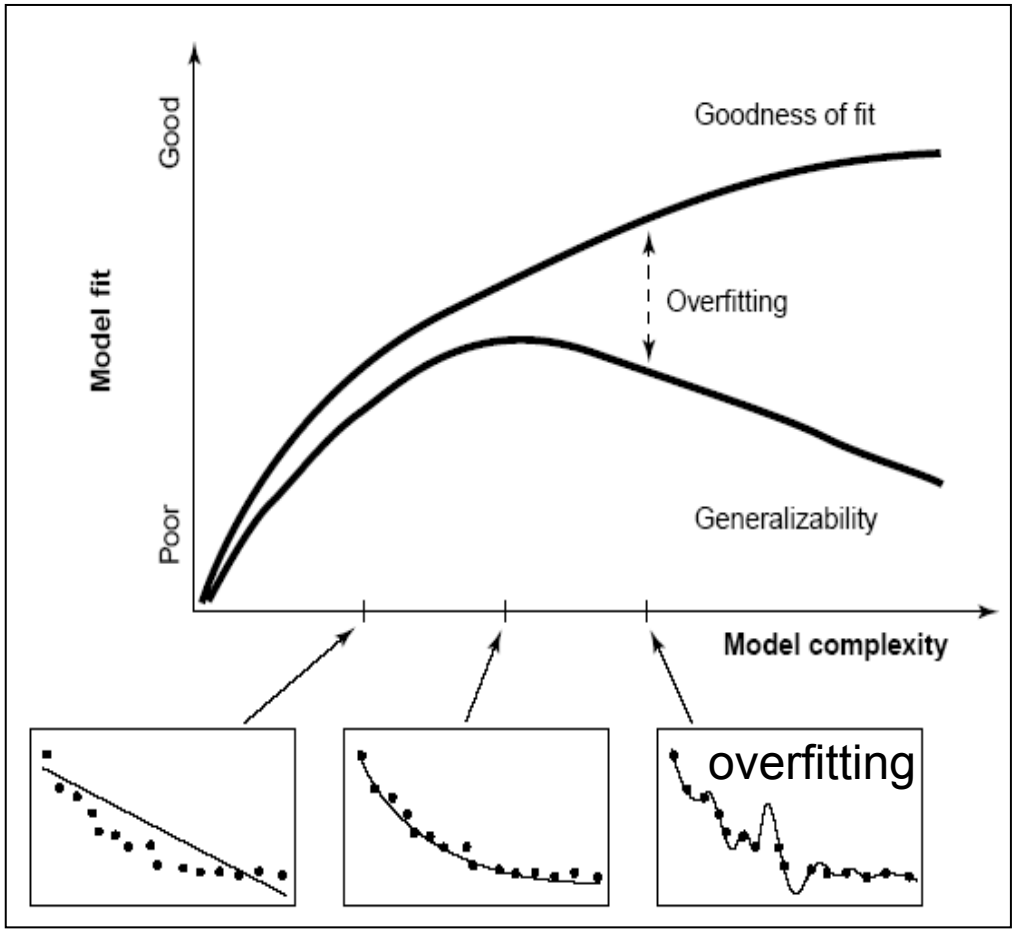


Model comparison and selection

Given competing hypotheses, which model is the best?

$$\log p(y \mid m) = accuracy(m) - complexity(m)$$

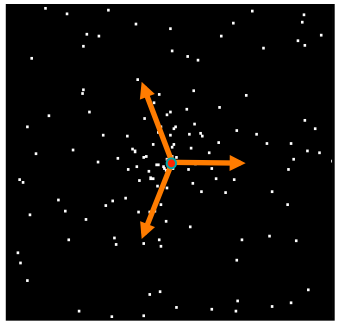
$$B_{ij} = \frac{p(y \mid m = i)}{p(y \mid m = j)}$$

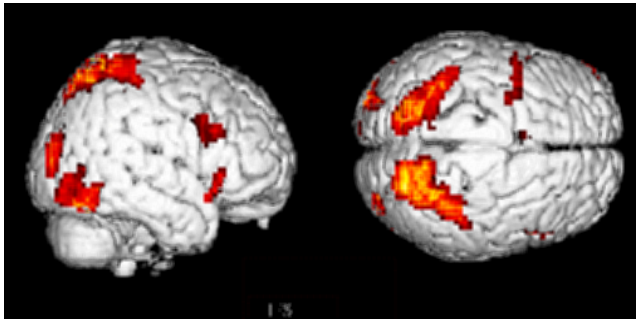


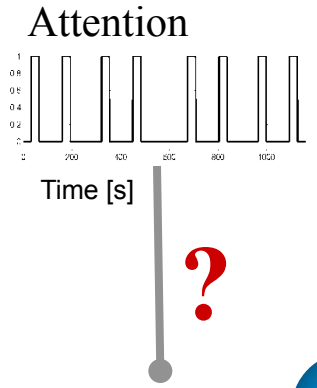
Pitt & Miyung (2002), *TICS*

Attention to motion in the visual system

We used this model to assess the site of ***attention modulation*** during *visual motion processing* in an fMRI paradigm reported by *Büchel & Friston.*





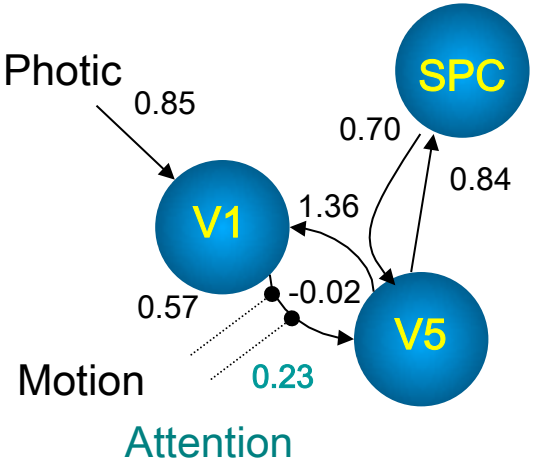


- fixation only
- observe static dots + photic → V1
- observe moving dots + motion → V5
- task on moving dots + attention → V5 + parietal cortex

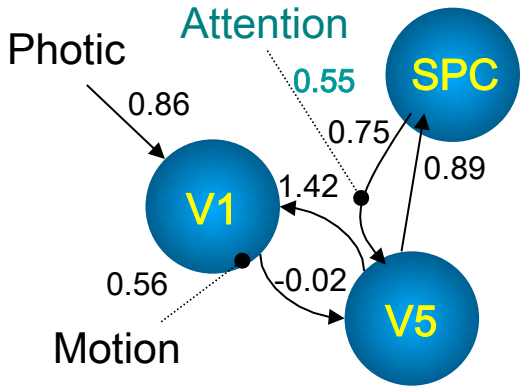
Friston et al., NeuroImage, 2003

Comparison of two simple models

Model 1:
attentional modulation
of V1→V5



Model 2:
attentional modulation
of SPC→V5



Bayesian model selection: Model 1 better than model 2

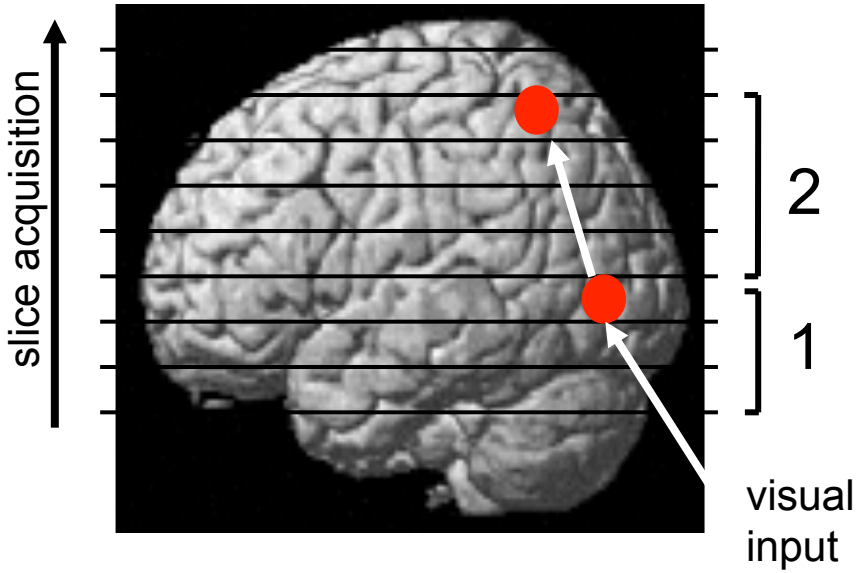
$$\log p(y \mid m_1) >> \log p(y \mid m_2)$$

→ Decision for model 1: in this experiment, attention primarily modulates V1→V5

Extension I: Slice timing model

- potential timing problem in DCM:

  temporal shift between regional time series because of multi-slice acquisition



- Solution:
  - Modeling of (known) slice timing of each area.

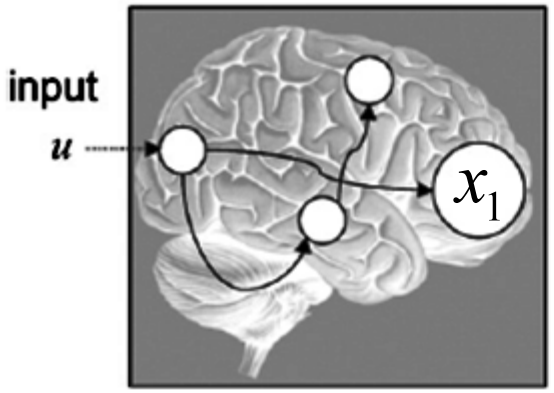
    Slice timing extension now allows for any slice timing differences! (only works for sequential acquisitions)

    Long TRs (> 2 sec) no longer a limitation.

Kiebel et al., Neuroimage, 2007

Extension II: Two-state model

Single-state DCM

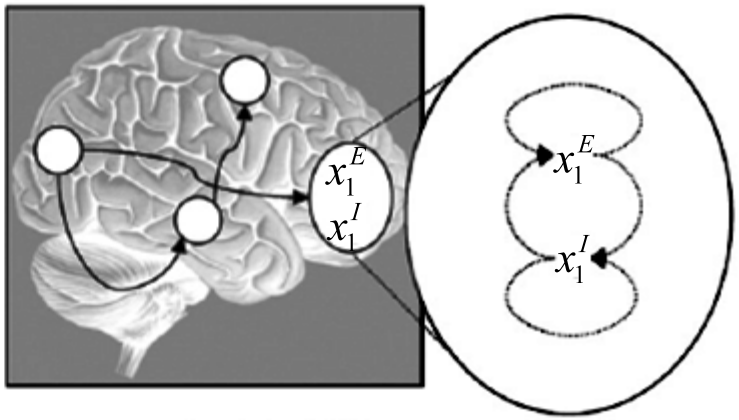


$$\dot{x} = \Im x + Cu$$

$$\Im_{ij} = A_{ij} + uB_{ij}$$

$$\Im = \begin{bmatrix} \Im_{11} & \cdots & \Im_{1N} \\ \vdots & \ddots & \vdots \\ \Im_{N1} & \cdots & \Im_{NN} \end{bmatrix} \quad x = \begin{bmatrix} x_1 \\ \vdots \\ x_N \end{bmatrix}$$

Two-state DCM



$$\dot{x} = \Im x + Cu$$

$$\Im_{ij}^{\bullet\bullet} = \mu_{ij}^{\bullet\bullet} \exp(A_{ij}^{\bullet\bullet} + uB_{ij}^{\bullet\bullet})$$

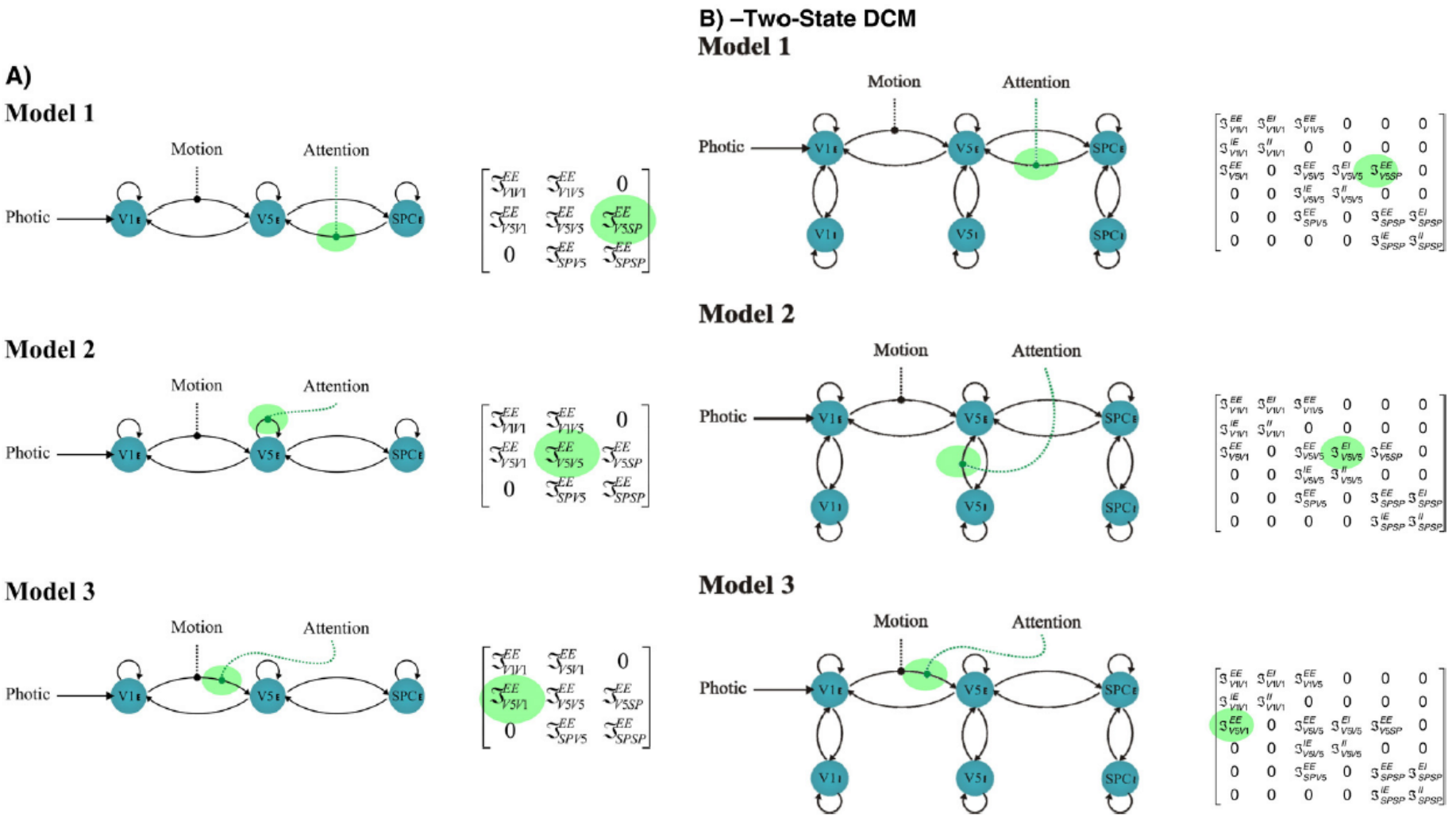
$$\Im = \begin{bmatrix} \Im_{11}^{EE} & \Im_{11}^{EI} & \cdots & \Im_{1N}^{EE} & 0 \\ \Im_{11}^{IE} & \Im_{11}^{II} & & 0 & 0 \\ \vdots & & \ddots & & \vdots \\ \Im_{N1}^{EE} & 0 & & \Im_{NN}^{EE} & \Im_{NN}^{EI} \\ 0 & 0 & \cdots & \Im_{NN}^{IE} & \Im_{NN}^{II} \end{bmatrix} \quad x = \begin{bmatrix} x_1^E \\ x_1^I \\ \vdots \\ x_N^E \\ x_N^I \end{bmatrix}$$

Extrinsic (between-region) coupling

Intrinsic (within-region) coupling

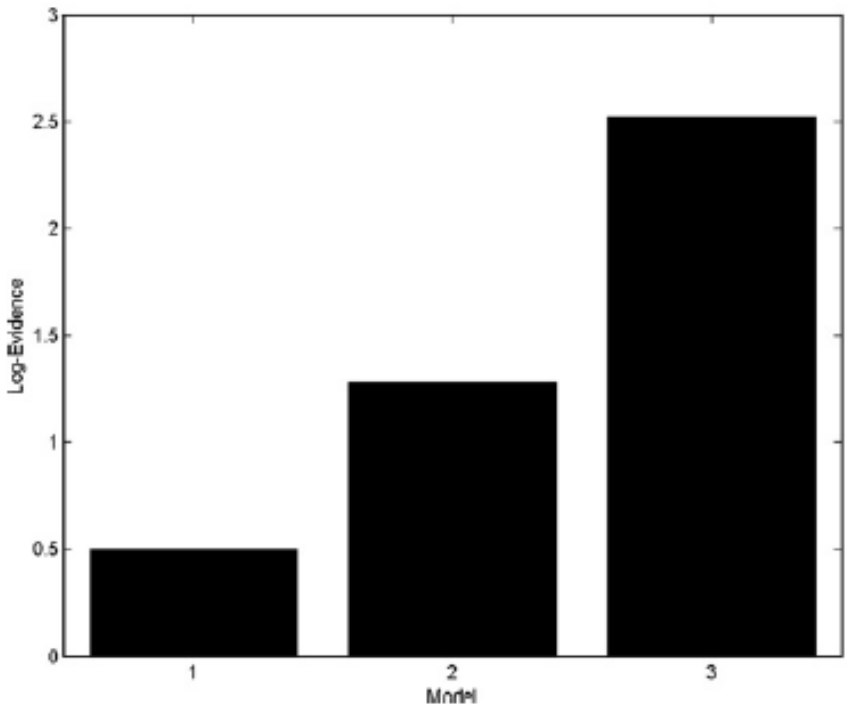
Marreiros et al., Neuroimage, 2008

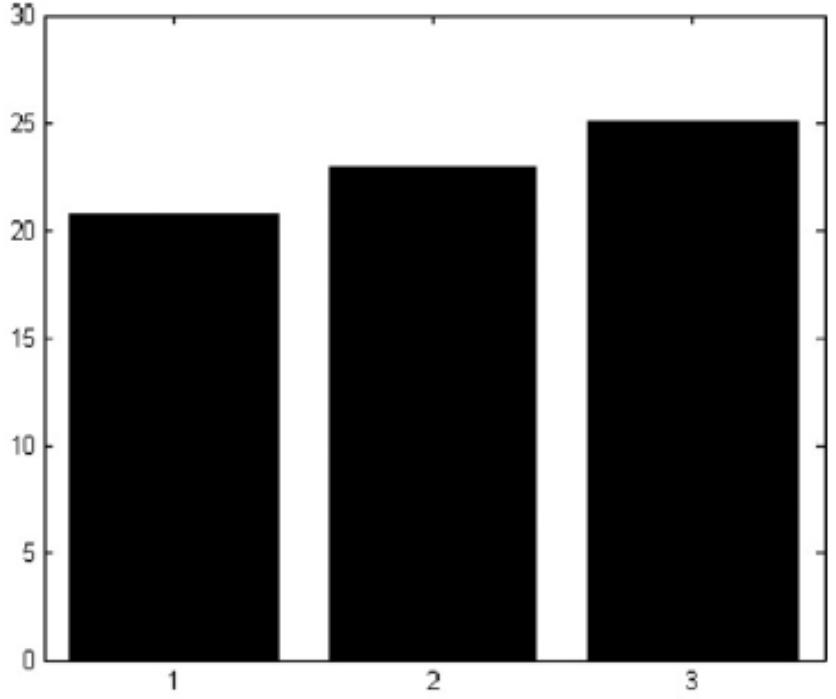
1 vs. 2-state DCM of attention to motion



Marreiros et al., Neuroimage, 2008

BMC: 1 vs. 2-state DCM of attention to motion

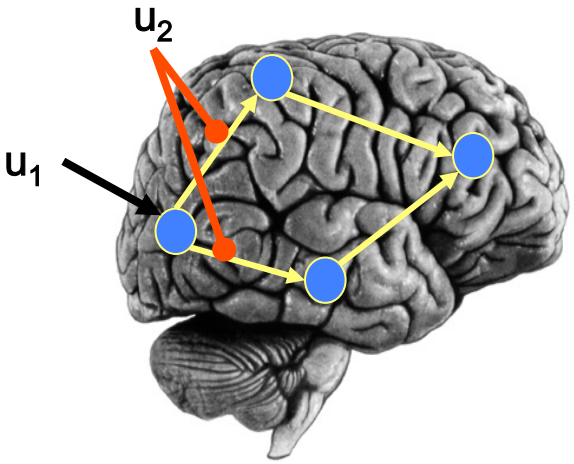




Marreiros et al., Neuroimage, 2008

Extension III: Nonlinear DCM for fMRI

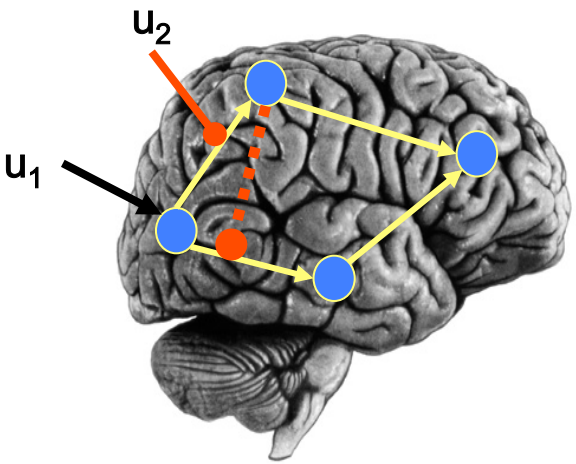
bilinear DCM



Bilinear state equation

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

nonlinear DCM



Nonlinear state equation

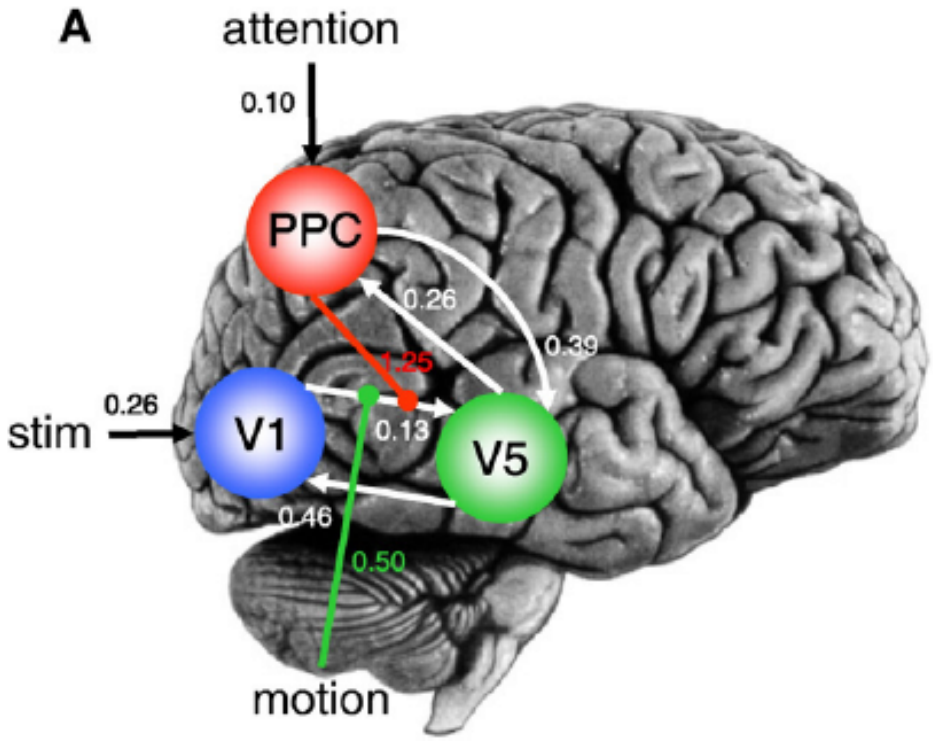
$$\frac{dx}{dt} = \left(A + \sum_{i=1}^{m} u_i B^{(i)} + \sum_{j=1}^{n} x_j D^{(j)} \right) x + Cu$$

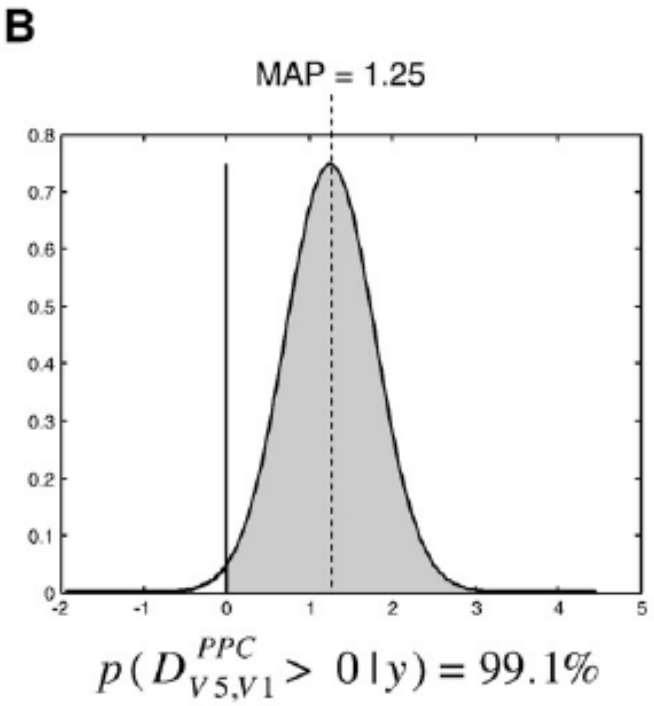
DCM can model activity-dependent changes in connectivity; connections can be enabled or gated by activity in one or more areas.

Stephan et al., Neuroimage, 2009

Extension III: Nonlinear DCM for fMRI

Can V5 activity during attention to motion be explained by allowing activity in SPC to modulate the V1-to-V5 connection?





Conclusions

Dynamic Causal Modeling (DCM) of fMRI is mechanistic model that is informed by anatomical and physiological principles.

DCM uses a deterministic differential equation to model neuro-dynamics (represented by matrices A,B and C)

DCM uses a Bayesian framework to estimate model parameters

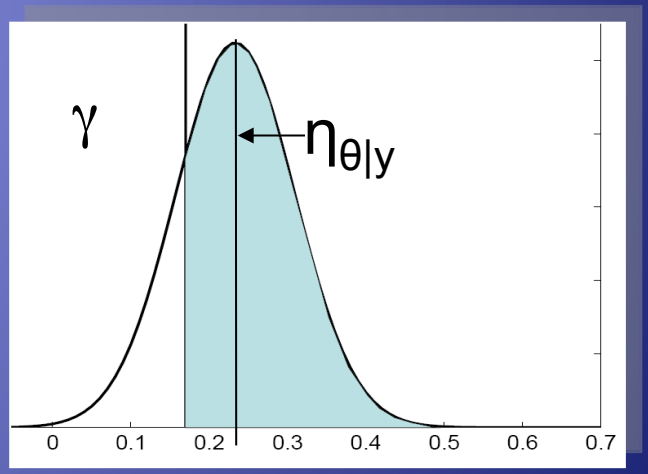
DCM provides an observation model for neuroimaging data, e.g. fMRI, M/EEG

DCM is not model or modality specific (Models will change and the method extended to other modalities e.g. ERPs)

Inference about DCM parameters:

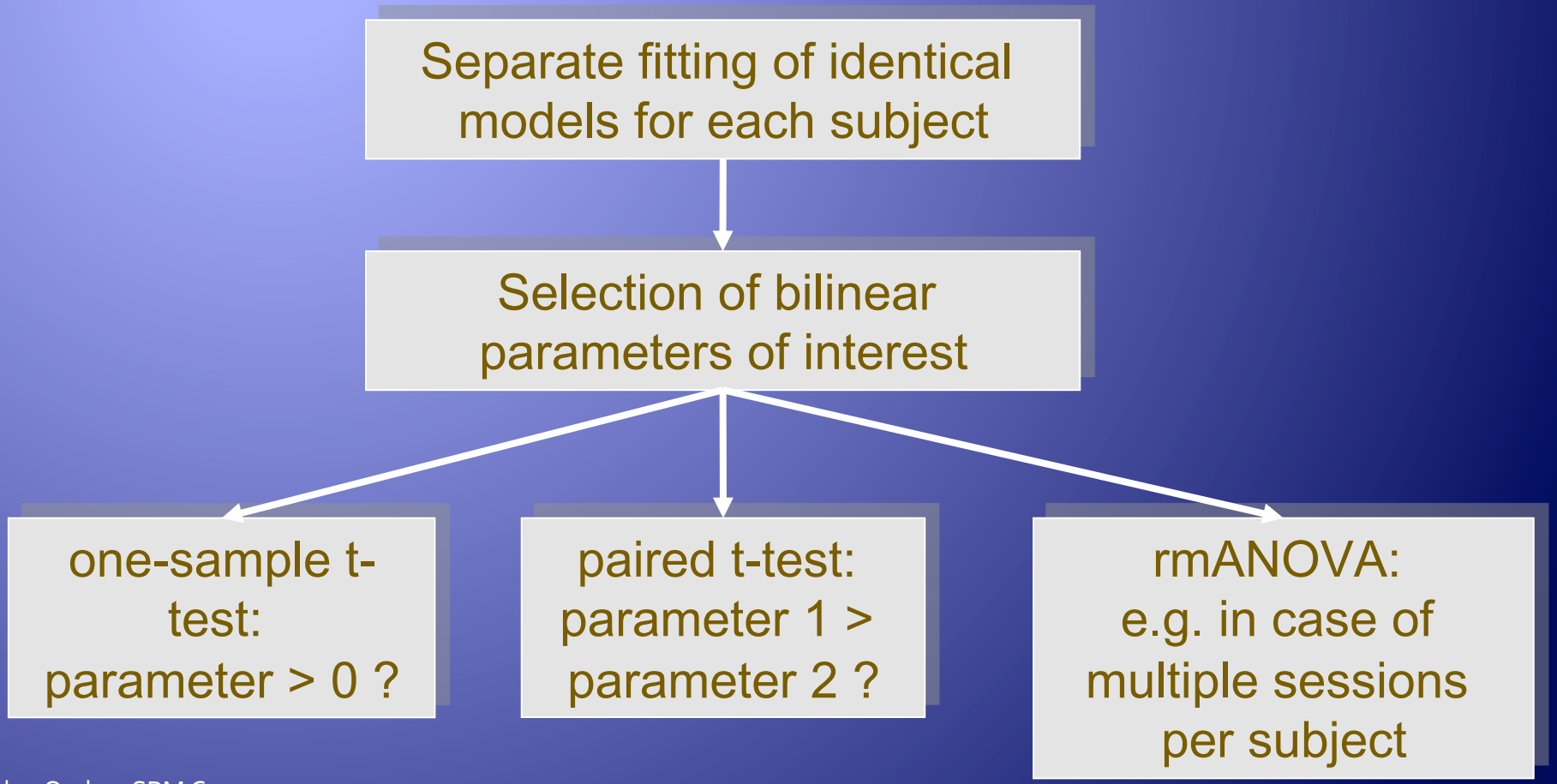
Bayesian single subject analysis

- The model parameters are distributions that have a mean $\eta_{\theta|y}$ and covariance $C_{\theta|y}$.
  - Use of the cumulative normal distribution to test the probability that a certain parameter is above a chosen threshold γ.
  - By default, γ is chosen as zero ("does the effect exist?").



Inference about DCM parameters: group analysis (classical)

- In analogy to "random effects" analyses in SPM, 2nd level analyses can be applied to DCM parameters:



GLM vs. DCM

- DCM tries to model the same phenomena as a GLM, just in a different way:
  - It is a model, based on connectivity and its modulation, for explaining experimentally controlled variance in local responses.
  - If there is no evidence for an experimental effect (no activation detected by a GLM) → inclusion of this region in a DCM is not meaningful.
  - Analysing an experiment using the GLM followed by DCM is not double dipping!

Planning a DCM-compatible study

- Suitable experimental design:
  - any design that is suitable for a GLM
  - preferably multi-factorial (e.g. 2 x 2)
    - e.g. one factor that varies the driving (sensory) input
    - and one factor that varies the contextual input

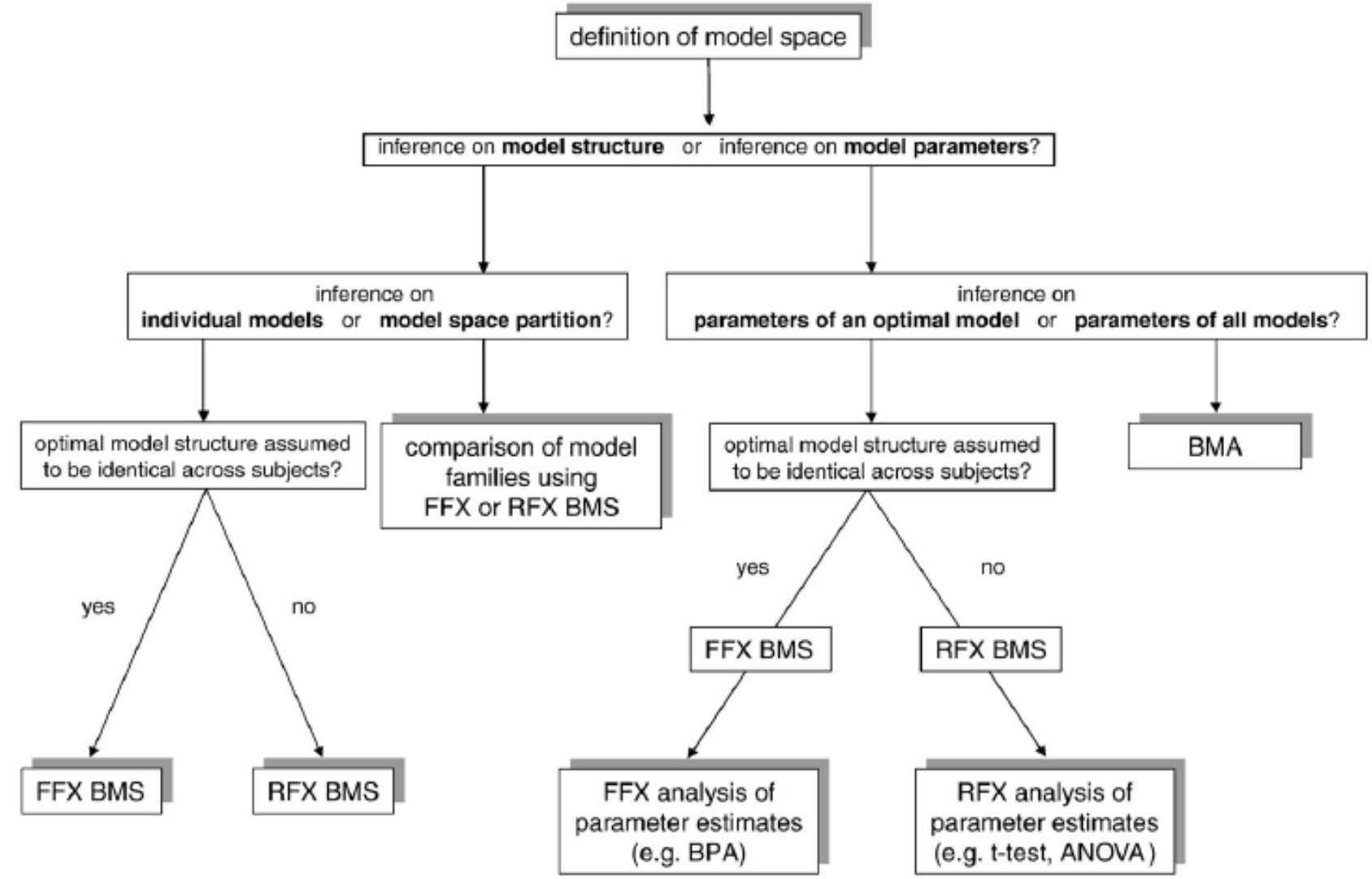
- Hypothesis and model:
  - Define specific *a priori* hypothesis
  - Which parameters are relevant to test this hypothesis?
  - If you want to verify that intended model is suitable to test this hypothesis, then use simulations
  - Define criteria for inference
  - What are the alternative models to test?

10 simple rules for DCM

1. Know what is causal about DCM.
   - The present state of one neuronal population causes dynamics in another via synaptic connections
   - External perturbations and/or neuronal activity can affect these interactions
   - Causality in DCM does not rely on temporal precedence.
2. Know your hypothesis and how to test it.
   - Tests of models vs. tests of parameters.
3. Use Bayesian model selection as a first step.
4. Motivate model space carefully.
   - E.g., permutations of a particular model or other data.

Stephan et al., Neuroimage, 2010

10 simple rules for DCM



Stephan et al., Neuroimage, 2010

10 simple rules for DCM

5. Choose an appropriate method for group-level inference on model structure
   - FFX – similar model across subjects
   - RFX – heterogeneous model across subjects
7. Know what you can and cannot do with Bayesian model selection.
   - E.g., can only compare models in fMRI with equivalent data.
9. Choose an appropriate method for group-level inference on parameters
10. Optimize experimental design and data acquisition
    - Factorial designs
    - Contiguous acquisition of slices vs. interleaved.
    - DCM for slice timing.

Stephan et al., Neuroimage, 2010

10 simple rules for DCM

9. Use anatomical information and computational models to refine DCMs
10. Report modeling approach and results in detail

Stephan et al., Neuroimage, 2010

The end