Effective Connectivity & Dynamic Causal Modelling (DCM)

SPM course at CRC, ULg, 2009

Based on slides from: K. Stephan

The Where, How and What of brain function

- *Where* in the brain is a certain cognitive process implemented?
  → **GLM analyses (e.g. SPM)**
- *How* does this implementation work (in terms of functional principles)?
  → **models of effective connectivity**
- *What* does this process mean (in computational terms)?
  → **models of neural coding**

Structure of this talk

- **Connectivity: concepts & definitions**
- Warming up:
  Psycho-physiological interactions (PPI)
  Structural Equation Modelling (SEM)
- **Dynamic Causal Modelling (DCM):**
  - Conceptual basis
  - The bilinear model at the neural level
  - The hemodynamic model
  - Priors & parameters
  - Planning a DCM-compatible fMRI study
  - Practical steps in SPM5
  - Example: Attention to motion in the visual system

Concepts of brain function

Functional specialisation
analyses of regionally specific effects: which areas constitute a neuronal system?

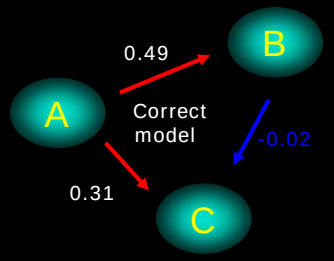
Functional integration
analyses of inter-regional effects: what are the interactions between the components of a given neuronal system?

Functional connectivity
= "the temporal correlation between spatially remote neurophysiological events"
MODEL-FREE

Effective connectivity
= "the influence one neuronal system exerts over another"
MODEL-DEPENDENT

Effective vs. functional connectivity

Model:
A = V1 fMRI time-series
B = 0.5 * A + e1
C = 0.3 * A + e2



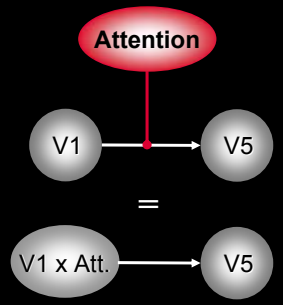
Correlations:

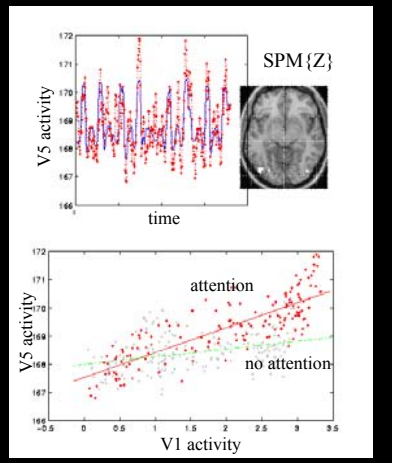
A	B	C
1		
0.49	1	
0.30	0.12	1

Psycho-physiological interactions (PPI)

- bilinear model of the change in coupling between regions A and B, depending on the psychological context C: **A x C → B**
- C can be a contrast of two conditions (C_1=1, C_2= -1, 0 else) or a parametric variable.
- A PPI corresponds to a context-dependent difference in the slope of the regression between two regional time series.

PPI example: attentional modulation of V1→V5



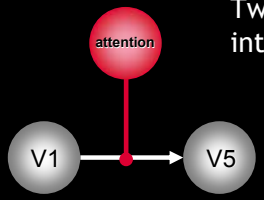


Friston et al. 1997, NeuroImage 6:218-229
Büchel & Friston 1997, Cereb. Cortex 7:768-778

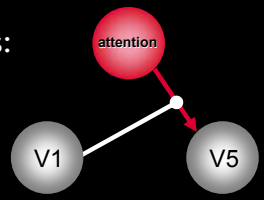
PPI: the statistical model and its interpretation

$$y = [V1 \times C] \cdot \beta_1 + V1 \cdot \beta_2 + C \cdot \beta_3 + G \cdot \beta_G + e$$

Two possible interpretations:



Modulation of V1→V5 by attention



Modulation of the impact of attention on V5 by V1.

PPI: problem…

PPI = mean of identifying regions whose responses can be explained in terms of an interaction between :

- Activity in a specified area (x_n, physiological factor)
- Some experimental effect (C, psychological factor)

Problem:

measured signal x (BOLD signal) is the neuronal activity convolved with the hrf !

$$\text{Conv}(x_n, \text{hrf}) = x$$

One cannot simply convolve the psychological variable C with the hrf and multiply the signal x.

$$\text{Conv}(C, \text{hrf}) * x \neq \text{conv}((C * x_n), \text{hrf})$$

PPI: problem… and solution

PPI = mean of identifying regions whose responses can be explained in terms of an interaction between :

- Activity in a specified area (x_n, physiological factor)
- Some experimental effect (C, psychological factor)

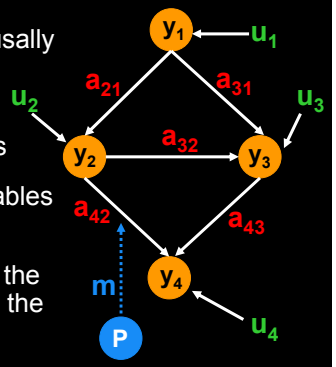
Practically :

1. V1 bold time series x has to be decorelated to estimate the neuronal time series x_n.
2. Multiply x_n and C, then convolve with hrf → ppi
3. Convolve C with hrf → Ch
4. Enter in design matrix:
   - ppi as covariate of interest,
   - x and Ch as covariate of no interest.

Points 1 to 3 are done with spm_peb_ppi, called by the 'PPIs button'.

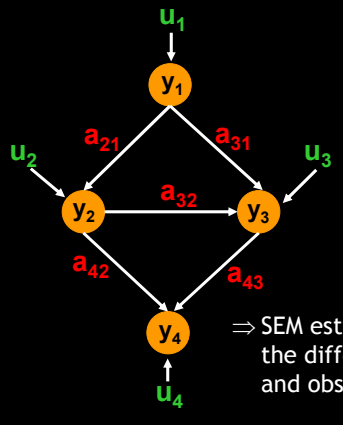
Structural Equation Modeling (SEM)

- SEM tests a hypothesis how several variables interact with each other causally
- in the context of fMRI:
  variables = time series of areas
  interactions = anatomical connections
- strength of interactions between variables is quantified by „path coeffcients"
- modulatory variables allow to assess the influence of a psychological factor on the strength of specific connections



Mathematical example of a structural model

$$\begin{bmatrix} y_1 \\ y_2 \\ y_3 \\ y_4 \end{bmatrix} = \begin{bmatrix} 0 & 0 & 0 & 0 \\ a_{21} & 0 & 0 & 0 \\ a_{31} & a_{32} & 0 & 0 \\ 0 & a_{42} & a_{43} & 0 \end{bmatrix} \begin{bmatrix} y_1 \\ y_2 \\ y_3 \\ y_4 \end{bmatrix} + \begin{bmatrix} u_1 \\ u_2 \\ u_3 \\ u_4 \end{bmatrix}$$



$$y = Ay + u \quad \leftarrow \text{structural model}$$

$$y = (I - A)^{-1}u \quad \leftarrow \text{generative model}$$

$$\Sigma = yy^T \quad \leftarrow \text{modelled covariance } \Sigma$$

$$= (I - A)^{-1}u((I - A)^{-1}u)^T$$

$$= (I - A)^{-1}uu^T(I - A)^{-1^T}$$

⇒ SEM estimates path coefficients in A such that the difference between modelled covariance Σ and observed covariance S becomes minimal

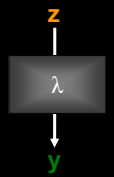
Limitations of PPIs and SEM

- PPIs:
  - very simple model: only allows for contributions from a single area
- SEM:
  - complex models easily become unidentifiable
- both:
  - not easily used with event-related data
  - operate at the level of BOLD time series

→ **limited causal interpretability in neural terms!**

DCM – conceptual overview

- DCM allows to model a cognitive system at the neuronal level (which is not directly accessible for fMRI).
- The modelled neuronal dynamics (z) is transformed into area-specific BOLD signals (y) by a hemodynamic forward model (λ).



The aim of DCM is to estimate parameters at the neuronal level such that the modelled BOLD signals are maximally similar to the experimentally measured BOLD signals.

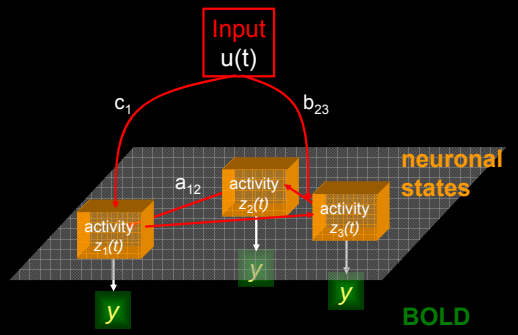
DCM: the neuronal level

- What does DCM model at the neuronal level?
  - For each area, DCM models the change of an abstract neuronal "state" in time.
  - This neuronal state is represented by a single state variable (z).
  - NB: z has no direct biophysical correlate.
- DCM treats the brain as a non-linear, deterministic system whose state changes in time entirely depend on:
  - the current state (z),
  - external inputs into the system (u) = perturbation,
  - intrinsic system structure & properties (parameters θ^n).

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

- Which parameters does θ^n contain and which mechanisms do they concern?

Conceptual overview:
Neural state equations



Friston et al. 2003

Use differential equations to represent a neuronal system

- ***State vector***
  - Changes with time

$$z(t) = \begin{bmatrix} z_1(t) \\ \vdots \\ z_n(t) \end{bmatrix}$$ system represented by state variables

- ***Rate of change of state vector***
  - Interactions between elements
  - External inputs, u

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

- ***System parameters θ***

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

DCM parameters = rate constants

Generic solution to the ODEs in DCM:

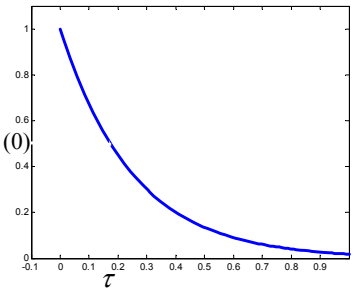
$$\frac{dz_1}{dt} = -sz_1 \Rightarrow z_1(t) = z_1(0)\exp(-st), \qquad z_1(0) = 1$$

Decay function:

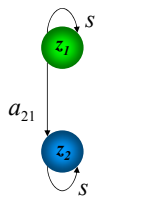
$$z_1(t) = z_1(0)\exp(-at)$$

Half-life τ:

$$z_1(\tau) = 0.5 z_1(0)$$
$$= z_1(0)\exp(-s\tau)$$
$$\Rightarrow \boxed{s = \ln 2 / \tau}$$



Linear dynamics: 2 nodes

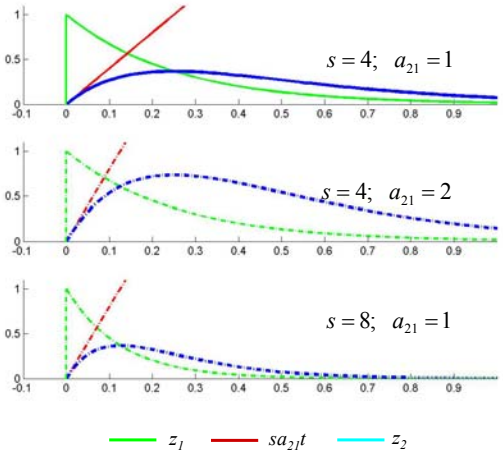


$$\dot{z}_1 = -sz_1$$
$$\dot{z}_2 = s(a_{21}z_1 - z_2)$$

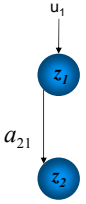
$$z_1(0) = 1$$
$$z_2(0) = 0$$

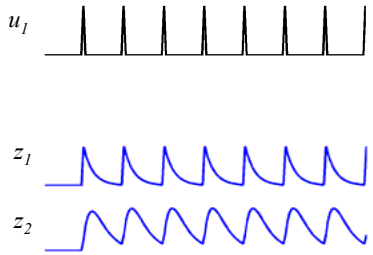
$$z_1(t) = \exp(-st)$$
$$z_2(t) = sa_{21}t\exp(-st)$$

$$a_{21} > 0$$



Neurodynamics: 2 nodes with input

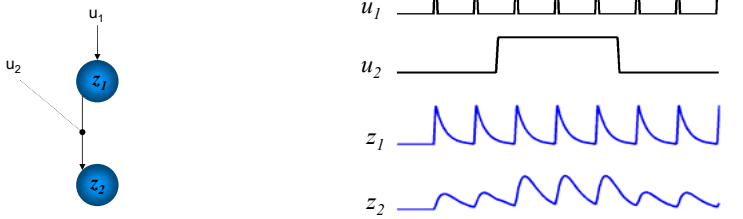




$$\begin{bmatrix} \dot{z}_1 \\ \dot{z}_2 \end{bmatrix} = s\begin{bmatrix} -1 & 0 \\ a_{21} & -1 \end{bmatrix}\begin{bmatrix} z_1 \\ z_2 \end{bmatrix} + \begin{bmatrix} c \\ 0 \end{bmatrix}u_1 \qquad a_{21} > 0$$

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

Neurodynamics: positive modulation



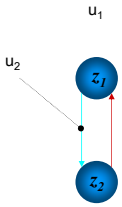
$$\begin{bmatrix}\dot{z}_1\\ \dot{z}_2\end{bmatrix} = s\begin{bmatrix}-1 & 0\\ a_{21} & -1\end{bmatrix}\begin{bmatrix}z_1\\ z_2\end{bmatrix} + u_2\begin{bmatrix}0 & 0\\ b_{21}^2 & 0\end{bmatrix}\begin{bmatrix}z_1\\ z_2\end{bmatrix} + \begin{bmatrix}c\\ 0\end{bmatrix}u_1$$

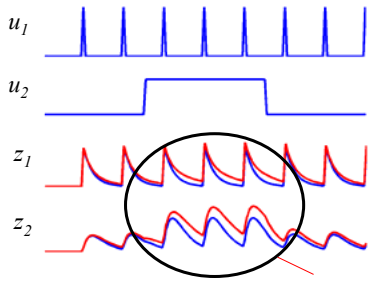
index, not squared

$b_{21}^2 > 0$

modulatory input u_2 activity through the coupling a_{21}

Neurodynamics: reciprocal connections



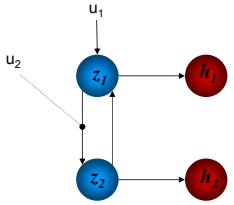


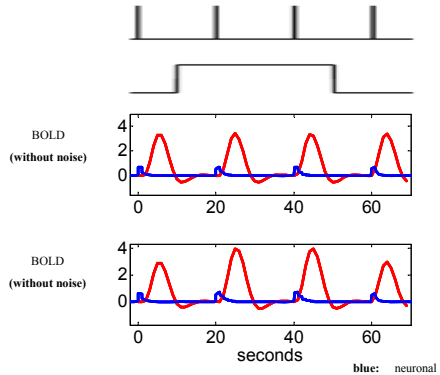
reciprocal connection disclosed by u_2

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

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

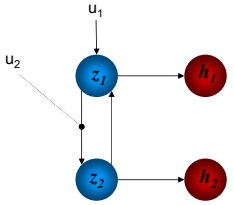
Haemodynamics: reciprocal connections

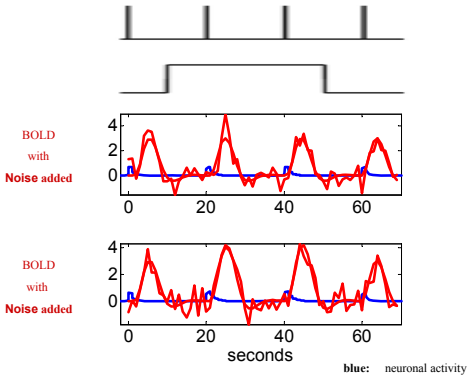




$h(u,\theta)$ represents the BOLD response (balloon model) to input

Haemodynamics: reciprocal connections





$h(u,\theta)$ represents the BOLD response (balloon model) to input

Bilinear state equation in DCM for fMRI

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

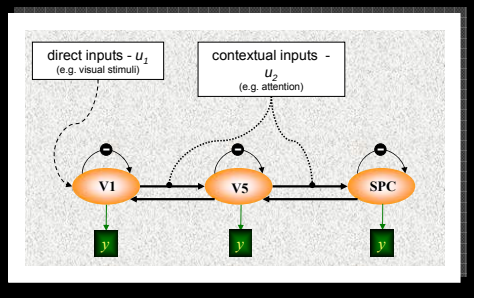
$$\begin{bmatrix} \dot{z}_1 \\ \vdots \\ \dot{z}_n \end{bmatrix} = \left\{ \begin{bmatrix} a_{11} & \cdots & a_{1n} \\ \vdots & \ddots & \vdots \\ a_{n1} & \cdots & a_{nn} \end{bmatrix} + \sum_{j=1}^{m} u_j \begin{bmatrix} b_{11}^j & \cdots & b_{1n}^j \\ \vdots & \ddots & \vdots \\ b_{n1}^j & \cdots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

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

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

- In DCM, the neural dynamics of the modelled system depends on 4 parameters θ^n={A,B,C,σ}:
  - intrinsic connectivity → determines, which areas can influence each other → **A**
  - contextual inputs → change connection strengths → **B**
  - direct (e.g. sensory) inputs → inject activity into the model → **C**
  - area-intrinsic inhibition → decay of induced activity → **σ**

  (θ^n)
- Activity in the system is only induced by direct inputs (C)
  → no spontaneous activity of the areas
- θ^n is determined by a Bayesian estimation scheme (see below).



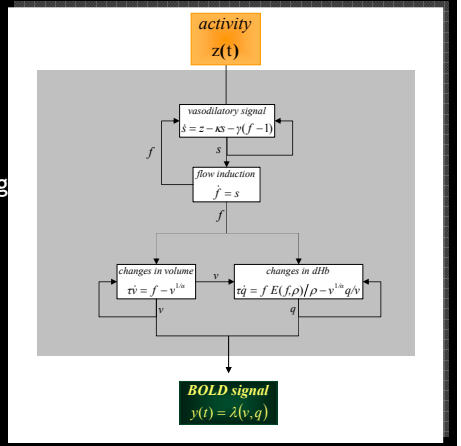
The hemodynamic "Balloon" model

- 5 hemodynamic parameters:

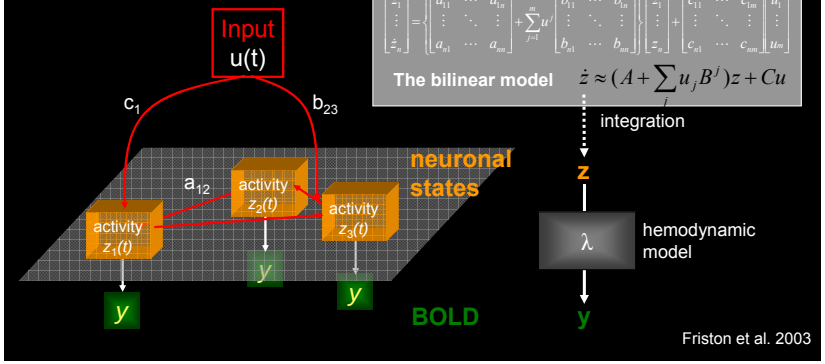
$$\theta^h = \{\kappa, \gamma, \tau, \alpha, \rho\}$$

important for model fitting but of no interest for statistical inference

- Empirically determined *a priori* distributions.
- Computed separately for each area (like the neural parameters).

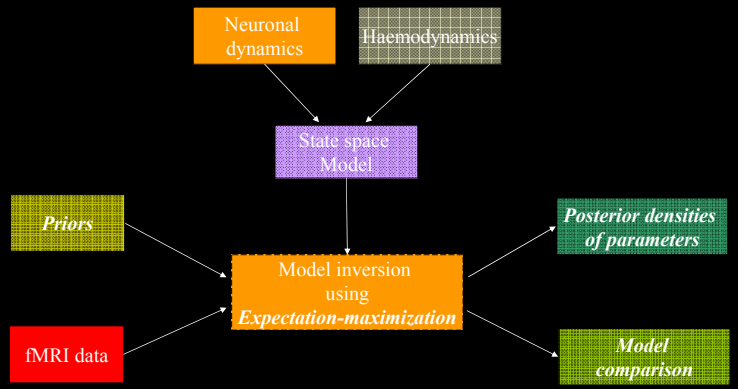


Neural state equations



Friston et al. 2003

DCM roadmap



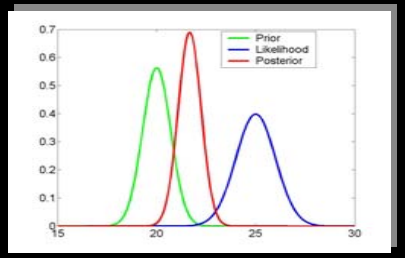
Priors in DCM

- needed for Bayesian estimation, embody constraints on parameter estimation
- express our prior knowledge or "belief" about parameters of the model
- hemodynamic parameters: empirical priors
- temporal scaling: principled prior
- coupling parameters: shrinkage priors

Bayes Theorem

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

posterior ∝ likelihood · prior



Gaussian

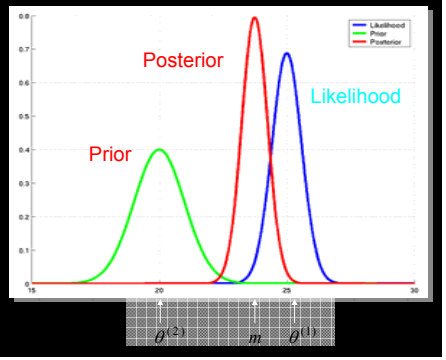
Likelihood and Prior

$$p\left(y \mid \theta^{(1)}\right) = N\left(\theta^{(1)}, \lambda_{(1)}^{-1}\right)$$
$$p\left(\theta^{(1)}\right) = N\left(\theta^{(2)}, \lambda_{(2)}^{-1}\right)$$

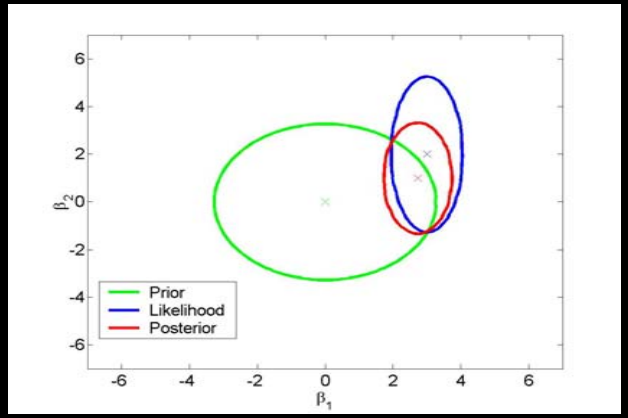
Posterior

$$p\left(\theta^{(1)} \mid y\right) = N\left(m, p^{-1}\right)$$
$$p = \lambda_{(1)} + \lambda_{(2)}$$
$$m = \frac{\lambda_{(1)}}{p}\theta^{(1)} + \frac{\lambda_{(2)}}{p}\theta^{(2)}$$

Relative Precision Weighting



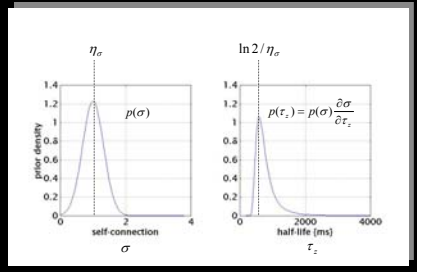
Bivariate Gaussian



Priors in DCM

- system stability:
  in the absence of input, the neuronal states return to a stable mode
  → largest real eigenvalue of the intrinsic coupling matrix (principal Lyapunov exponent) must be negative
  → constraints on prior variance of intrinsic connections (A)
- shrinkage priors
  for coupling parameters (η=0)
  → conservative estimates!
- self-inhibition:
  ensured by priors on σ (η_σ=1, C_σ=0.105)
  → these allow for neural transients with a half life in the range of 300 ms to 2 seconds
  → probability of negative Lyapunov exponent 0.001

$$\theta = \begin{bmatrix} \sigma \\ a_{ij} \\ b_{ij}^k \\ c_{ik} \\ \theta^h \end{bmatrix}, \quad \eta_\theta = \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \\ \eta_\theta^h \end{bmatrix}, \quad C_\theta = \begin{bmatrix} 0.105 & & & & \\ & C_A & & & \\ & & C_B & & \\ & & & C_C & \\ & & & & C_h \end{bmatrix}$$



Parameter estimation

- Combining the neural and hemodynamic states gives the complete forward model:

$$x = \{z, s, f, v, q\}$$
$$\theta = \theta^n + \theta^h$$
$$\dot{x} = f(x, u, \theta)$$
$$y = \lambda(x) = h(u, \theta)$$

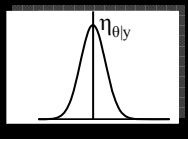
- The observation model includes measurement error ε and confounds X (e.g. drift):

$$y = h(u, \theta) + X\beta + \varepsilon$$

- Bayesian parameter estimation under Gaussian assumptions by means of the EM algorithm (expectation maximisation).

$$y - h(u, \eta_{\theta|y}) \rightarrow \min$$

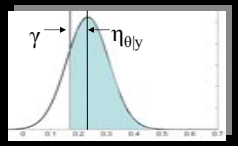
- Result:
  Gaussian *a posteriori* parameter distributions, characterised by mean $\eta_{\theta|y}$ and covariance $C_{\theta|y}$.



Inference about DCM parameters: single-subject analysis

- Bayesian parameter estimation in DCM: Gaussian assumptions about the *a posteriori* distributions of the parameters
- Use of the cumulative normal distribution to test the probability by which a certain parameter (or contrast of parameters $c^T\eta_{\theta|y}$) is above a chosen threshold γ:

$$p = \phi_N\left(\frac{c^T\eta_{\theta|y} - \gamma}{\sqrt{c^T C_{\theta|y} c}}\right)$$



- γ can be chosen as a function of the expected half life of the neural process, e.g. $\gamma = \ln 2 / \tau$

Bayesian model selection

- Bayes theorem in a slightly extended fashion:

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

- Model evidence is computed by

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

- Log of the model evidence can be expressed as

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

- Bayes factors:

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

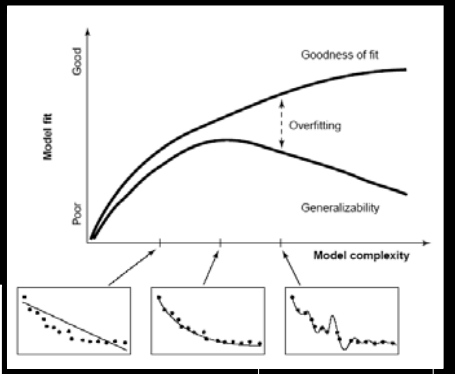
Model comparison and selection

Given competing hypotheses, which model is the best?

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

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

B_{12}	$p(m_1 \mid Y)$	Evidence
1 to 3	50-75	Weak
3 to 20	75-95	Positive
20 to 150	95-99	Strong
≥ 150	≥ 99	Very strong



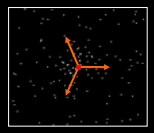
Pitt & Miyung (2002), *TICS*

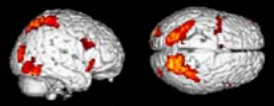
Planning a DCM-compatible study

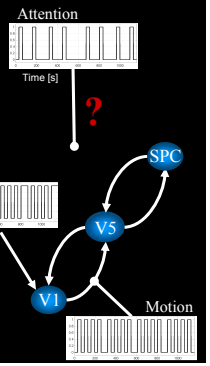
- Suitable experimental design:
  - preferably multi-factorial (e.g. 2 x 2)
  - at least one factor that varies the sensory input
  - at least one factor that varies the contextual input
- TR:
  - as short as possible (optimal: < 2 s)
- Hypothesis and model:
  - define specific *a priori* hypothesis
  - which parameters are relevant?
  - ensure that intended model is suitable to test this hypothesis → initial simulation
  - define criteria for inference

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
- observe moving dots
- task on moving dots

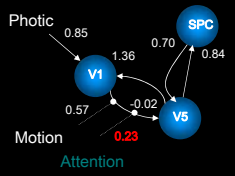
+ photic
+ motion
+ attention

→ V1
→ V5
→ V5 + parietal cortex

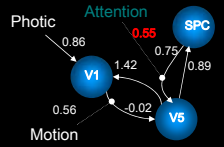
Friston et al. 2003, *NeuroImage*

Comparison of two simple models

Model 1:
attentional modulation of V1→V5



Model 2:
attentional modulation of SPC→V5



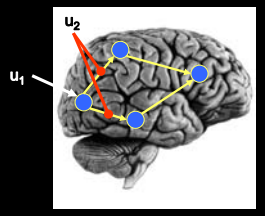
Bayesian model selection: Model 1 better than model 2

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

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

Extension : Nonlinear DCM for fMRI

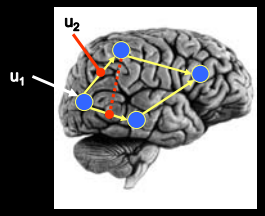
bilinear DCM



Bilinear state equation

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

nonlinear DCM



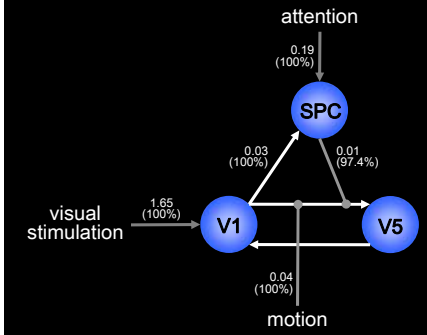
Nonlinear state equation

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

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

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?

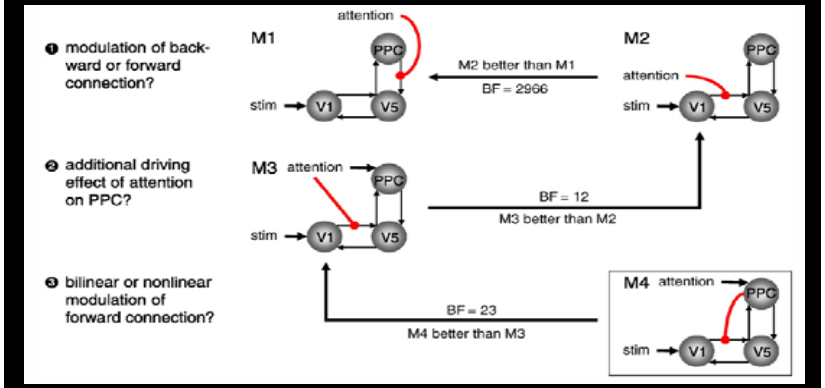


The posterior density of indicates that this gating existed with 97.4% confidence.

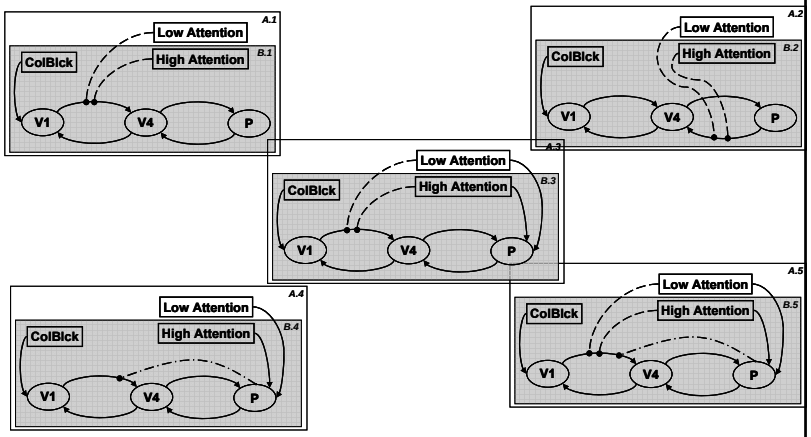
(The *D* matrix encodes which of the *n* neural units gate which connections in the system)

Attentional model comparison

Stephan et al., NeuroImage, 2008

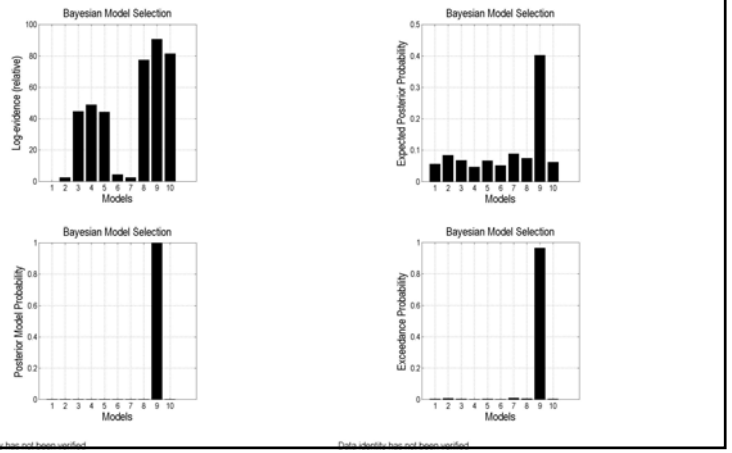


Go for MANY models !



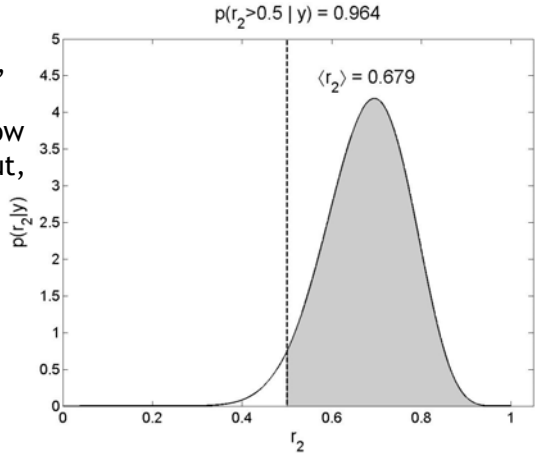
All 10 models fitted on data from 14 subjects ⇒ 140 model fitting !

Group model selection: FFX or RFX?



Model space partitioning

Type ‘A’ or ‘B’, i.e with or without the “low attention” input, as model ?



Conclusions

- Dynamic Causal Modelling (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
- Express hypothesis as “concurrent” models which can be compared, at the individual and/or group level