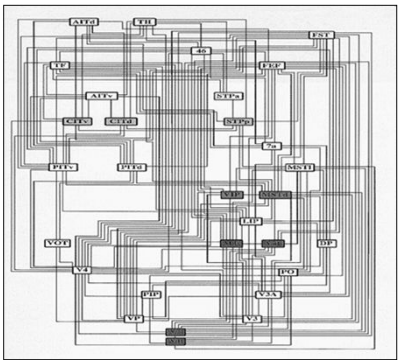
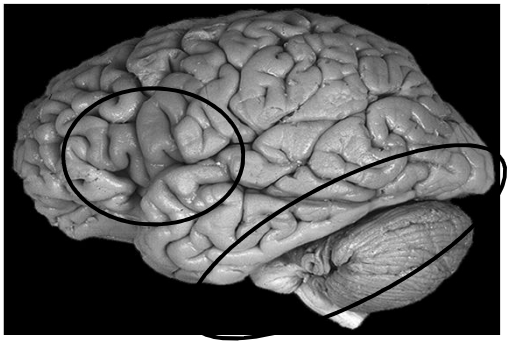
Connectivity in fMRI:
a brief overview



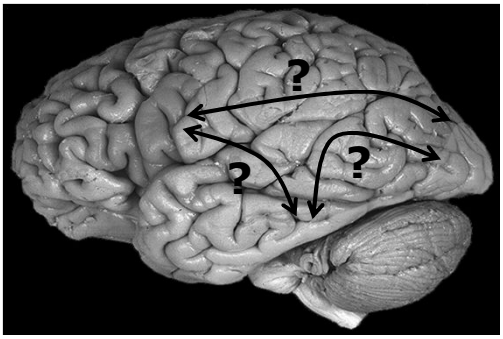
Mohamed Seghier

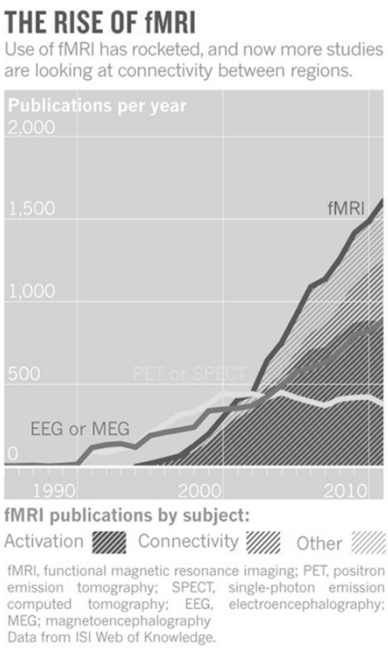
Wellcome Trust Centre for Neuroimaging,
University College London, UK

Functional segregation:
What regions respond to a particular experimental input?



Functional integration:
How do regions influence each other?
➔ Brain Connectivity





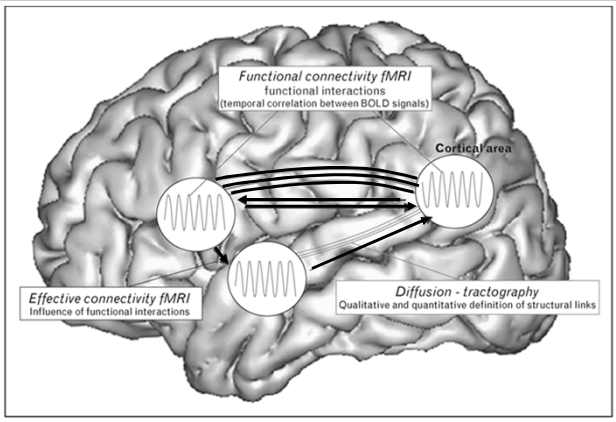
[Smith 2012 Nature]

-**Connectivity is an important facet of brain function:**

**** Regions don't operate in isolation ****

Neurodegenerative and psychiatric *disorders* = a disorder of brain connectivity.

E.g.: Schizophrenia and autism



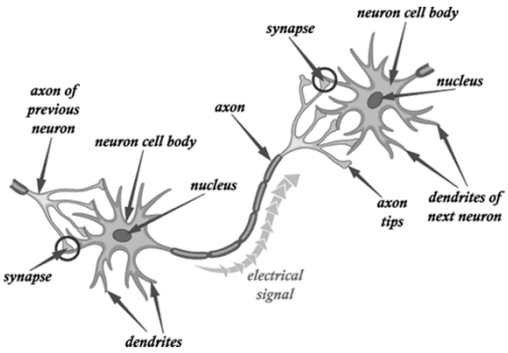
[Sporns 2007, *Scholarpedia*]

- **anatomical/structural connectivity**
  = presence of axonal connections.
- **functional connectivity**
  = statistical dependencies between regional time series.
- **effective connectivity**
  = causal (directed) influences between neurons or neuronal populations.

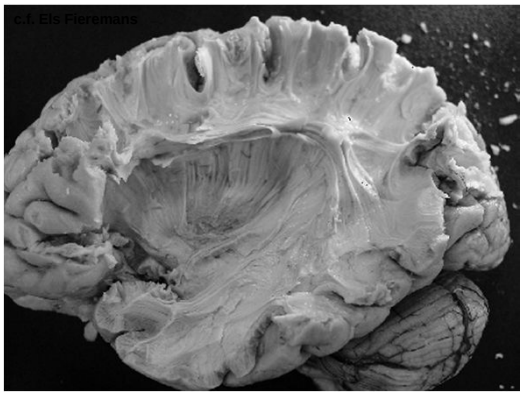
Structural connectivity

- Presence of axonal connections:

The function of the axon is to transmit information to different neurons



➔ relay and coordinate communication between different brain regions



Dissected white matter

- E.g. measured with tracing techniques or diffusion tensor/spectrum imaging (DTI/DSI)

Structural connectivity

DTI: diffusion tensor imaging

-Anisotropy analyses on RA or FA images;
[Basser and Pierpaoli 1996 JMR]
+ in SPM: - correlations with behaviour
- group comparisons.

-Tractography techniques:
(e.g. seed/target/crossing regions)
+ deterministic
[Mori et al. 1999 Ann Neurol]

+ probabilistic
[Parker et al. 2002 IEEE TMI]

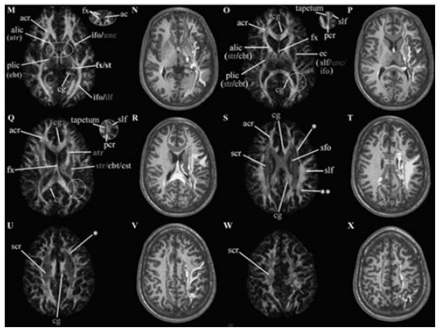
DSI: diffusion spectrum imaging

-Fibers orientation at high definition;
+ Resolving fibers intersections
[Wedeen et al. 2005 MRM]

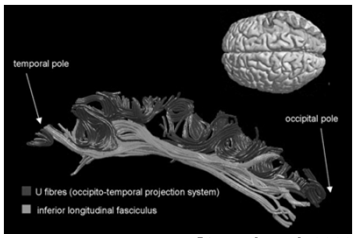
-Identify structural connector hubs;
[Hagmann et al. 2008 PLoS Biol]

Structural connectivity

DTI: diffusion tensor imaging

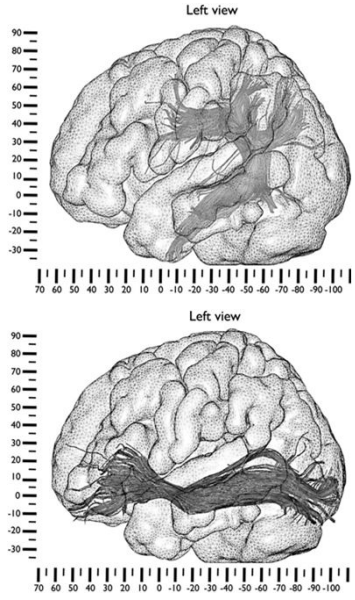


[Wakana et al. 2004 Radiology]



[Catani et al. 2003 Brain]

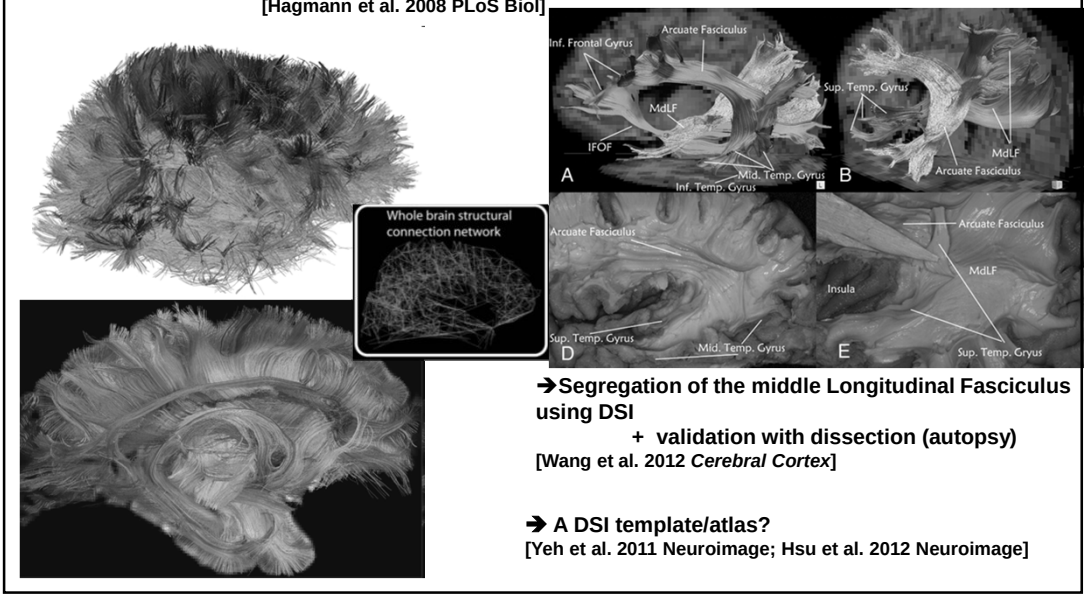
➔ An atlas of white matter tracts in MNI
[Catani and Thiebaut de Schotten 2008 Cortex]



Structural connectivity

DSI: diffusion spectrum imaging

[Hagmann et al. 2008 PLoS Biol]



➔Segregation of the middle Longitudinal Fasciculus using DSI
+ validation with dissection (autopsy)
[Wang et al. 2012 *Cerebral Cortex*]

➔ A DSI template/atlas?
[Yeh et al. 2011 Neuroimage; Hsu et al. 2012 Neuroimage]

But:

Knowing anatomical connectivity is not enough...

- Connections are recruited in a context-dependent fashion:
  - Local functions depend on network activity
- Connections show synaptic plasticity
  - Critical for learning
  - Can occur both rapidly and slowly

→ Need to look at functional/effective connectivity.

**** Anatomo-functional connectivity: combine functional with structural connectivity.**

Functional connectivity

= statistical dependencies (temporal correlations) between activations. [Friston et al. 1993 *JCBFM*]

- Seed-based correlation analysis (in SPM)
- Eigen-decomposition (e.g. PCA, SVD)
- Independent component analysis (ICA)
- Coherence analysis
- Clustering (e.g. FCM)

[Li et al. 2009 *CMGI*]

♣ Task-related connectivity

- ♦ Controlled stimulations (known inputs)
- ♦ Uncontrolled conditions (free-model inputs)

♣ Intrinsic/endogenous task-unrelated connectivity

- ♦ "rest" (external stim. = 0)
- ♦ passive fixation.

[Cordes et al. 2000 AJNR] [McKeown et al. 1998 HBM]

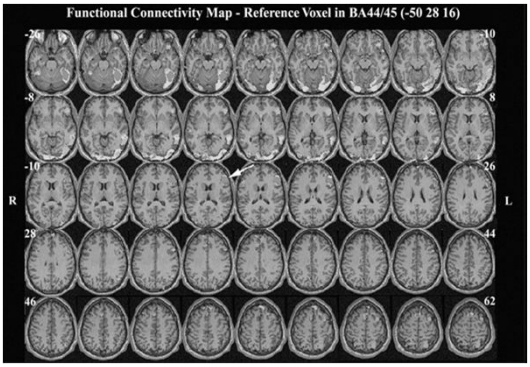
- ♦ Hypothesis-driven, using seed regions; [Biswal et al. 1995 MRM]
- ♦ Data-driven (ICA, FCM), over all voxels; [Damoiseaux et al. 2006 PNAS]

- ♦ Within-subject: inter-regional temporal dependencies;
- ♦ Across-subject: second-level covariance or inter-subject synchronisation.

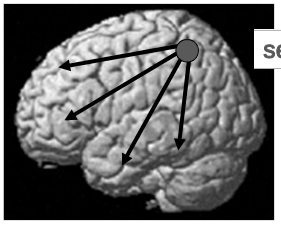
[Hasson et al. 2004 *Science*; Seghier et al. 2008 *Neuroimage*]

♣ **Whole-brain regression with seed regions:**
➔ **functional connectivity maps**

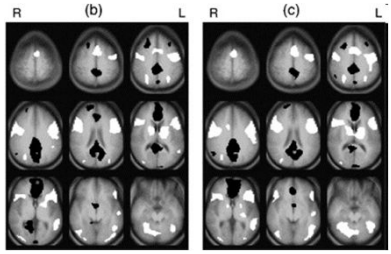
♦ **Controlled task:**
reading words, pseudowords, letter strings.
[Bokde et al. 2001 *Neuron*]



Seed ROI = left inferior frontal gyrus.
Functional connectivity maps vary with word type.



♦ **Uncontrolled task (= unlocked onsets):**
continuous sentence reading.
[Hampson et al. 2006 *Neuroimage*]



Seed ROI = left angular gyrus.
Functional connectivity maps vary during (natural) reading of sentences.

E.g. watching movies / sleep / hallucinations

Does functional connectivity not simply correspond to co-activation in SPMs?

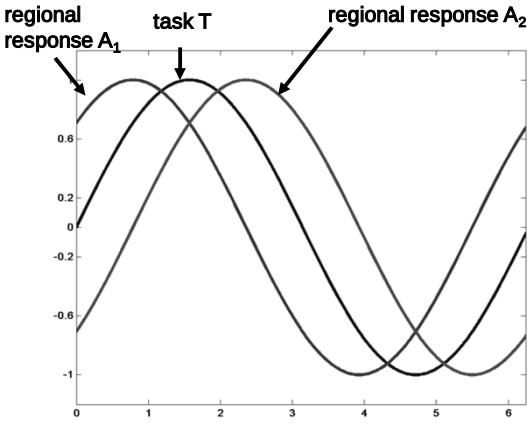
(for task-related functional connectivity)

Seed ROI A1 selected from task T

No !

Here both areas A_1 and A_2 are correlated identically to task T, yet they have zero correlation among themselves:

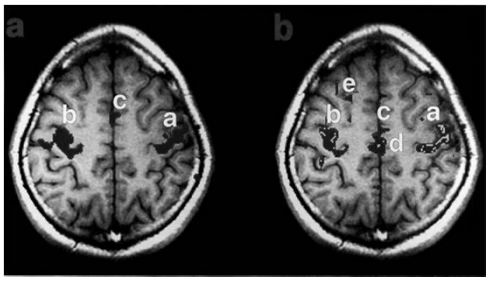
$r(A_1,T) = r(A_2,T) = 0.71$
but
$r(A_1,A_2) = 0$!



[Stephan 2004 *J. Anat.*]

♣ **Intrinsic (resting-state) networks**
➔ **fMRI during "rest" or passive fixation.**
➔ **Spontaneous fluctuations of fMRI signal (LF: 0.01-0.1 Hz)**

[Biswal et al. 1995 MRM]

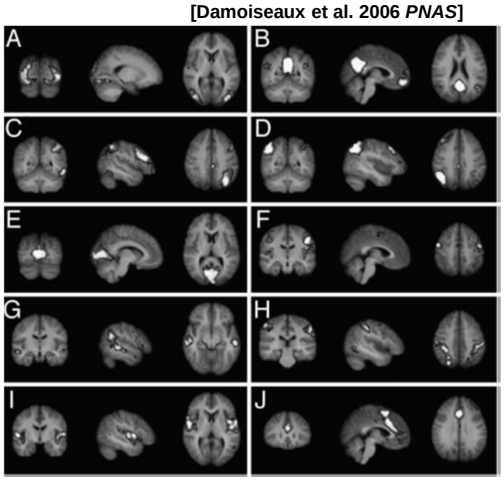


With seed ROIs (hypothesis-driven)

- Widely used in normal subjects and patients: e.g. looking for abnormal/altered intrinsic connectivity in diseased populations.

[Broyd et al. 2009 *Neurosci Biobehav Rev*]
[Fox and Greicius 2010 *Front Syst Neurosci*]

[Damoiseaux et al. 2006 *PNAS*]

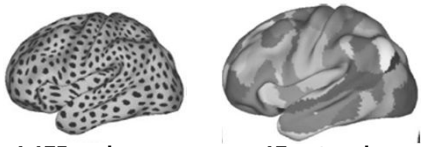


Data-driven, using ICA.
e.g. see Calhoun et al. // Smith et al.

Large-scale network analysis:

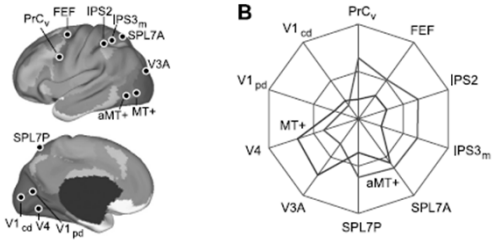
[Yeo et al. 2011 *J Neurophysiol*]

Resting-state fMRI data from 1000 subjects.



1,175 regions **17 networks**

➔ **Functional connectivity profile as a fingerprint**

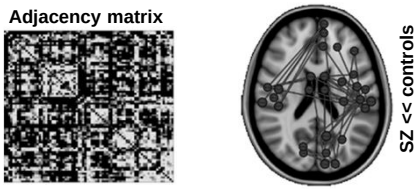


Examine local vs. distributed networks.
➔ **Dissociate different brain areas.**

[Fornito et al. 2012 *Neuroimage*]

Schizophrenia = a disorder of brain connectivity.

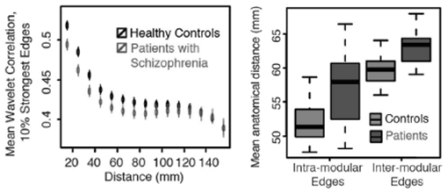
Adjacency matrix



SZ << controls

The use of graph theory:
Local/global statistics on edges and nodes
➔ **Define topological measures of connectivity**

See Sporns and Bullmore work.

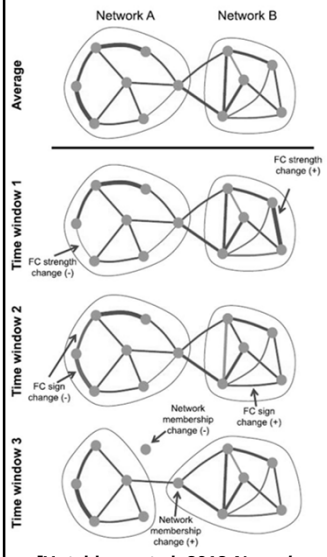


[Alexander-Bloch et al. 2013 *Cereb Cortex*]

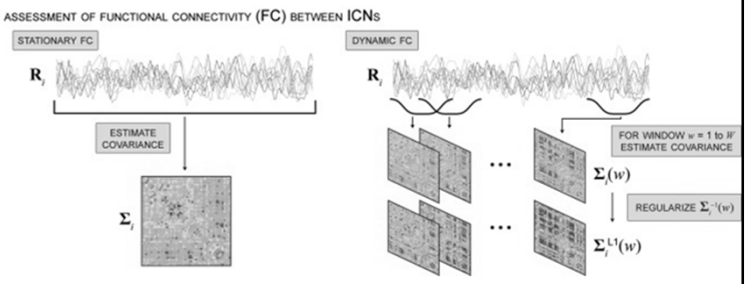
Dynamic functional connectivity:

FC: far from being completely static!

➔ **Characterise/quantify how FC changes over time.**



[Hutchison et al. 2013 *Neuroimage*]



[Allen et al. 2014 *Cereb Cortex*]

A new field, potentially useful for:

- **Monitoring dynamic cognitive processes,**
- **Detecting changes in mood,**
- **Tracking adaptive and learning processes,**
- **Characterising abnormal/atypical behaviour.**

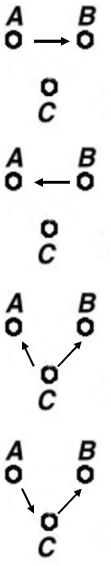
Pros & Cons of functional connectivity analysis

**** Pros:**

- Easy to compute;
- useful when we have no experimental control over the system of interest (e.g. sleep, natural stimulation).
- Useful for large-scale connectivity analyses.

**** Cons:**

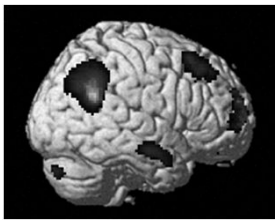
- interpretation of resulting patterns is difficult / arbitrary;
- no mechanistic insight.
- operates at the level of BOLD time series;



➔ **Effective connectivity**

Effective connectivity

fMRI experiment; task contrasts

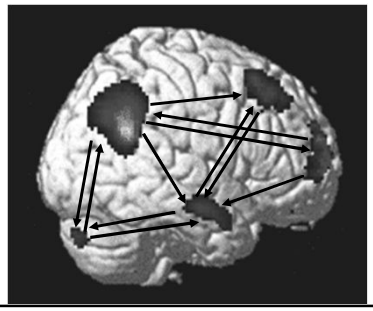


Can we go beyond this "static" picture?
➔ Dynamics or interactions between regions…

For understanding brain function **mechanistically**, we need **models of effective connectivity**,

= causal (directed) influences between neurons or neuronal populations.

➔ explain *regional* effects in terms of *interregional* connectivity.



Some models for computing effective connectivity:

Structural Equation Modelling (SEM)
[McIntosh and Gonzalez-Lima 1991, 1994]

Psycho-Physiological Interactions (PPI)
[Friston et al. 1997]

Dynamic Causal Modelling (DCM)
[Friston et al. 2003]

Multivariate Autoregressive Model (MAR)
[Harrison et al. 2003]

Granger causality
[Goebel et al. 2003]

Dynamic Bayesian networks (DBN)
[Rajapakse and Zhou 2007]

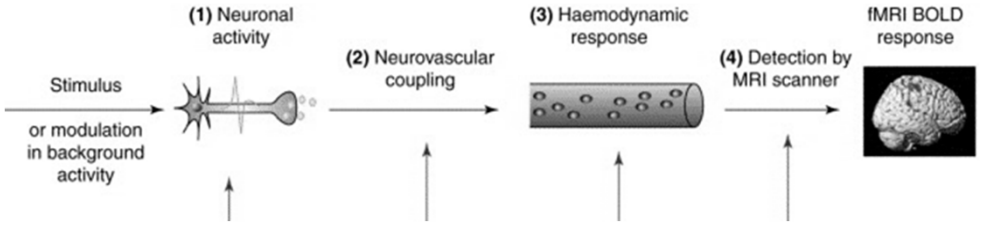
Nonlinear system identification
[Li et al. 2010]

Switching Linear Dynamic System (SLDS)
[Smith et al. 2010]

Each method has its advantages and weaknesses and its use should be motivated by the question of interest, level of inference, paradigm design, data acquisition and analysis.

➔ An alternative method = DCM.

FMRI response = indirect + slow



[Arthurs & Boniface 2002 *TINS*]

→ **parameterise effective connectivity in terms of coupling among unobserved brain states (e.g., neuronal activity in different regions).**

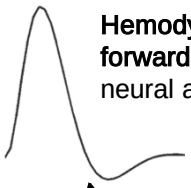
Neuronal:
Unobserved interactions

DCM

BOLD:
Measured responses

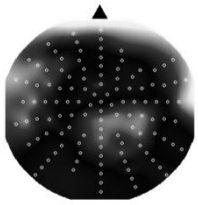
** simple neuronal model;
** complicated hemodynamic forward model (neural activity → BOLD).

DCM: other modalities



Hemodynamic forward model:
neural activity→BOLD

Electromagnetic forward model:
neural activity→EEG
MEG
LFP



Neural state equation:

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

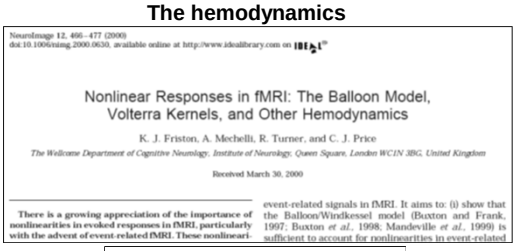
fMRI

EEG/MEG

simple neuronal model
complicated forward model

complicated neuronal model
simple forward model

The hemodynamics



NeuroImage 12, 466–477 (2000)
doi:10.1006/nimg.2000.0630, available online at http://www.idealibrary.com on IDEAL®

Nonlinear Responses in fMRI: The Balloon Model, Volterra Kernels, and Other Hemodynamics

K. J. Friston, A. Mechelli, R. Turner, and C. J. Price

The Wellcome Department of Cognitive Neurology, Institute of Neurology, Queen Square, London WC1N 3BG, United Kingdom

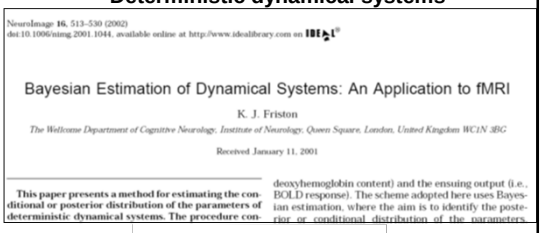
Received March 30, 2000

There is a growing appreciation of the importance of nonlinearities in evoked responses in fMRI, particularly with the advent of event-related fMRI. These nonlineari-

event-related signals in fMRI. It aims to: (i) show that the Balloon/Windkessel model (Buxton and Frank, 1997; Buxton *et al.*, 1998; Mandeville *et al.*, 1999) is sufficient to account for nonlinearities in event-related

[Friston et al. 2000 *Neuroimage*]

Deterministic dynamical systems



NeuroImage **16**, 513–530 (2002)
doi:10.1006/nimg.2001.1044, available online at http://www.idealibrary.com on IDEAL®

Bayesian Estimation of Dynamical Systems: An Application to fMRI

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The Wellcome Department of Cognitive Neurology, Institute of Neurology, Queen Square, London, United Kingdom WC1N 3BG

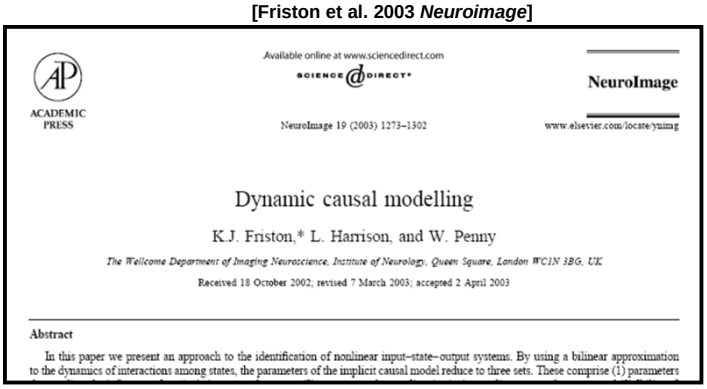
Received January 11, 2001

This paper presents a method for estimating the conditional or posterior distribution of the parameters of deterministic dynamical systems. The procedure con-

deoxyhemoglobin content) and the ensuing output (i.e., BOLD response). The scheme adopted here uses Bayesian estimation, where the aim is to identify the posterior or conditional distribution of the parameters

[Friston 2002 *Neuroimage*]

[Friston et al. 2003 *Neuroimage*]



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NeuroImage 19 (2003) 1273–1302

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Dynamic causal modelling

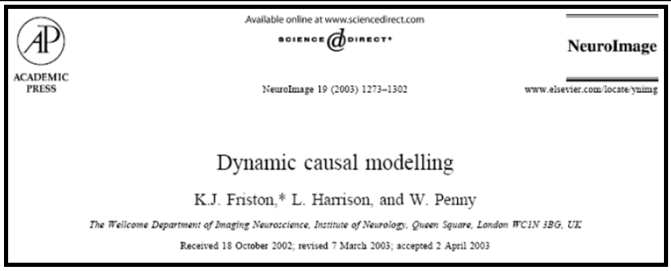
K.J. Friston,* L. Harrison, and W. Penny

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

Abstract

In this paper we present an approach to the identification of nonlinear input–state–output systems. By using a bilinear approximation to the dynamics of interactions among states, the parameters of the implicit causal model reduce to three sets. These comprise (1) parameters



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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

The central idea behind dynamic causal modelling (DCM) is to treat the brain as a deterministic nonlinear dynamic system that is subject to inputs and produces outputs. Effective connectivity is parameterised in terms of

tion, dynamic causal models assume the responses are driven by designed changes in inputs. An important con-

DCM is used to test the specific hypothesis that motivated the experimental design. It is not an exploratory technique; as with all analyses of effective connectivity the

DCM is a <u>generative model</u>

= a quantitative / mechanistic description of how observed data are generated.

<u>Key features:</u>

1- Dynamic
2- Causal
3- Neuro-physiologically motivated
4- Operate at hidden neuronal interactions
5- Bayesian in all aspects
6- Hypothesis-driven
7- Inference at multiple levels.

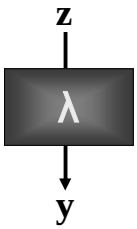
<u>DCM [default] implementation:</u>

Deterministic	**Stochastic [Daunizeau et al. 2009]**
Bilinear	**Nonlinear [Stephan et al. 2008]**
The one-state neuronal	**The two-state [Marreiros et al. 2008]**
Time-series	**Spectral [Friston et al. 2014]**

Basic idea of DCM for fMRI

♣ A cognitive system is modelled at the neuronal level (not directly accessible for fMRI).

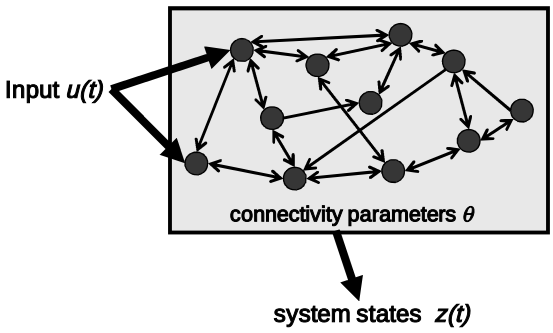
♣ The modelled neuronal dynamics (z) is transformed into area-specific BOLD signals (y) by a hemodynamic forward model (λ).



<u>Aim:</u> to estimate the parameters of a reasonably realistic neural model such that the predicted/modelled BOLD responses correspond as closely as possible to the observed/measured BOLD responses.

What is a system?

System =
a set of elements which interact in a spatially and temporally specific fashion



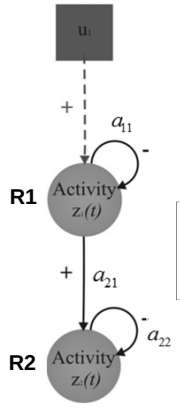
State changes of a system are dependent on:

- the current state **z**
- external inputs **u**
- its connectivity **θ**

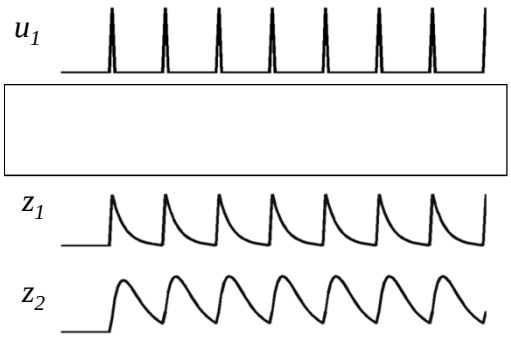
$$\frac{dz}{dt} = F(z,u,\theta)$$

(evolution equation)

Neurodynamics: 2 nodes with input



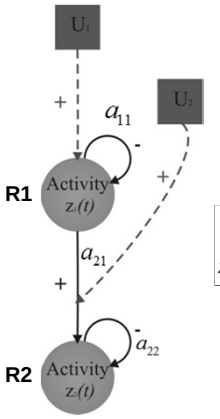
$$\dot{z}_1 = a_{11}z_1 + cu_1$$
$$\dot{z}_2 = a_{22}z_2 + a_{21}z_1$$



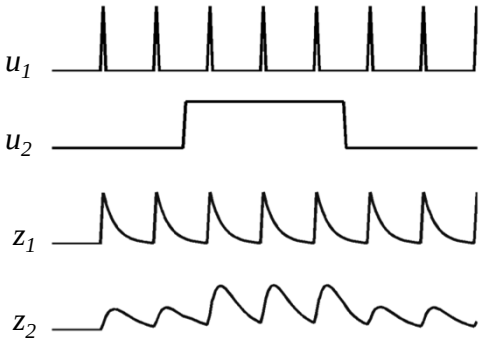
$$\begin{bmatrix}\dot{z}_1\\ \dot{z}_2\end{bmatrix} = \begin{bmatrix}a_{11} & 0\\ a_{21} & a_{22}\end{bmatrix}\begin{bmatrix}z_1\\ z_2\end{bmatrix} + \begin{bmatrix}c\\ 0\end{bmatrix}u_1 \qquad a_{21} > 0$$

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

Neurodynamics: positive modulation



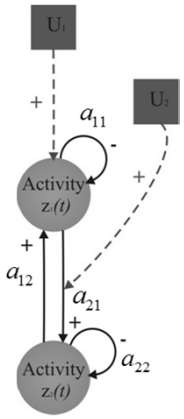
$$\dot{z}_1 = a_{11} z_1 + c u_1$$
$$\dot{z}_2 = a_{22} z_2 + a_{21} z_1 + b_{21}^2 u_2 z_1$$

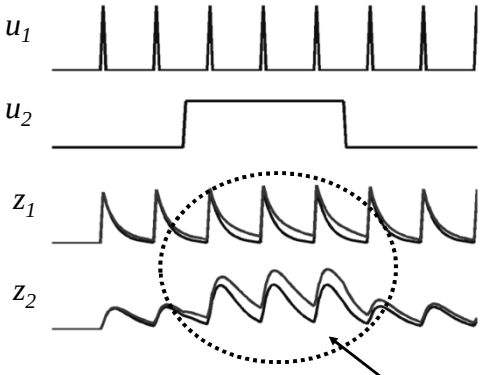


$$\begin{bmatrix} \dot{z}_1 \\ \dot{z}_2 \end{bmatrix} = \begin{bmatrix} a_{11} & 0 \\ a_{21} & a_{22} \end{bmatrix} \begin{bmatrix} z_1 \\ z_2 \end{bmatrix} + u_2 \begin{bmatrix} 0 & 0 \\ b_{21}^2 & 0 \end{bmatrix} \begin{bmatrix} z_1 \\ z_2 \end{bmatrix} + \begin{bmatrix} c \\ 0 \end{bmatrix} u_1 \qquad b_{21}^2 > 0$$

modulatory input u_2 activity through the coupling a_{21}

Neurodynamics: reciprocal connections

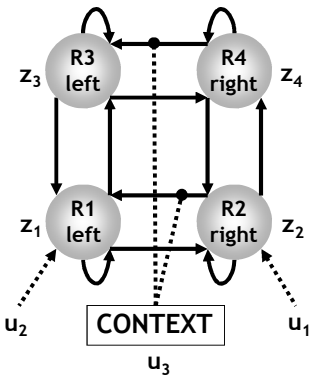




$$\begin{bmatrix} \dot{z}_1 \\ \dot{z}_2 \end{bmatrix} = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix} \begin{bmatrix} z_1 \\ z_2 \end{bmatrix} + u_2 \begin{bmatrix} 0 & 0 \\ b_{21}^2 & 0 \end{bmatrix} \begin{bmatrix} z_1 \\ z_2 \end{bmatrix} + \begin{bmatrix} c \\ 0 \end{bmatrix} u_1 \qquad a_{21} > 0 \quad a_{12} > 0 \quad b_{21}^2 > 0$$

reciprocal connection disclosed by u_2

bilinear dynamic system



$$\begin{bmatrix}\dot{z}_1\\ \dot{z}_2\\ \dot{z}_3\\ \dot{z}_4\end{bmatrix} = \left\{\begin{bmatrix}a_{11} & a_{12} & a_{13} & 0\\ a_{21} & a_{22} & 0 & a_{24}\\ a_{31} & 0 & a_{33} & a_{34}\\ 0 & a_{42} & a_{43} & a_{44}\end{bmatrix} + u_3\begin{bmatrix}0 & b^3_{12} & 0 & 0\\ 0 & 0 & 0 & 0\\ 0 & 0 & 0 & b^3_{34}\\ 0 & 0 & 0 & 0\end{bmatrix}\right\}\begin{bmatrix}z_1\\ z_2\\ z_3\\ z_4\end{bmatrix} + \begin{bmatrix}0 & c_{12} & 0\\ c_{21} & 0 & 0\\ 0 & 0 & 0\\ 0 & 0 & 0\end{bmatrix}\begin{bmatrix}u_1\\ u_2\\ u_3\end{bmatrix}$$

Bilinear state equation in DCM for fMRI

The neural state equation

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

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

n regions | *m* inputs (mod.) | *m* inputs (driv.)

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

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

"C", the direct or driving effects:
- extrinsic influences of inputs on neuronal activity.

"A", the endogenous coupling or the latent connectivity:
- fixed or intrinsic effective connectivity;
- first order connectivity among the regions in the absence of input;
- average/baseline connectivity in the system (DCM10/DCM8).

"B", the bilinear term, modulatory effects, or the induced connectivity:
- context-dependent change in connectivity;
- eq. a second-order interaction between the input and activity in a source region when causing a response in a target region.

[Units]: rates, [Hz];
Strong connection = an effect that is influenced quickly or with a small time constant.

DCM parameters = rate constants

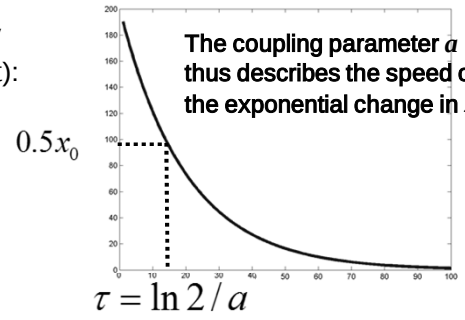
Integration of a first-order linear differential equation gives an exponential function:

$$\frac{dx}{dt} = ax \quad \Rightarrow \quad x(t) = x_0 \exp(at)$$

Coupling parameter a is inversely proportional to the half life τ of x(t):

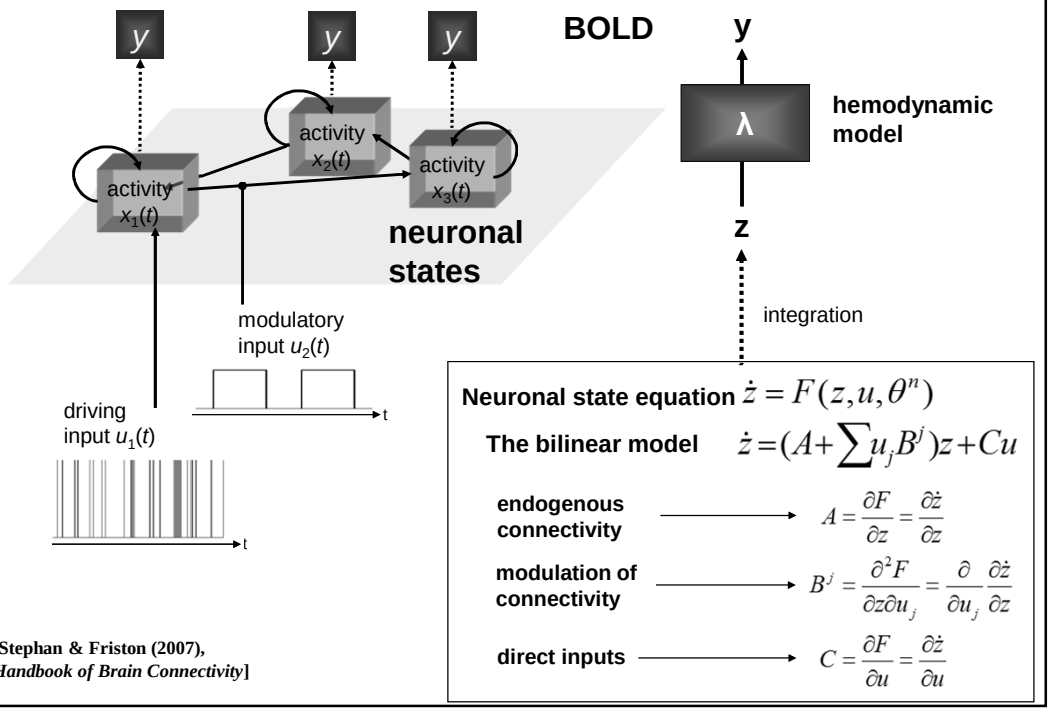
$$x(\tau) = 0.5x_0$$
$$= x_0 \exp(a\tau)$$

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

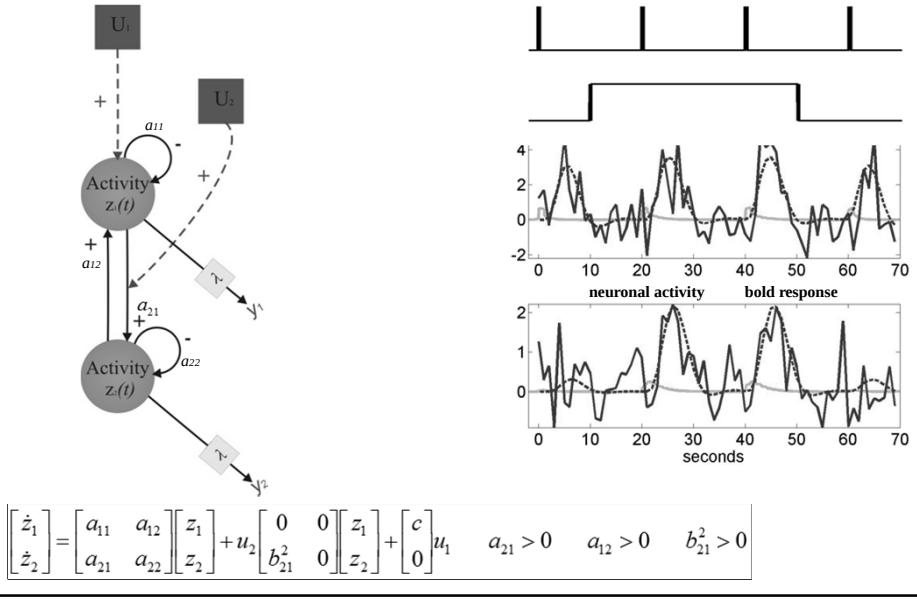


The coupling parameter *a* thus describes the speed of the exponential change in *x*(*t*)

If A→B is 0.10 s^{-1} this means that, per unit time, the increase in activity in B corresponds to 10% of the activity in A



[Stephan & Friston (2007), *Handbook of Brain Connectivity*]



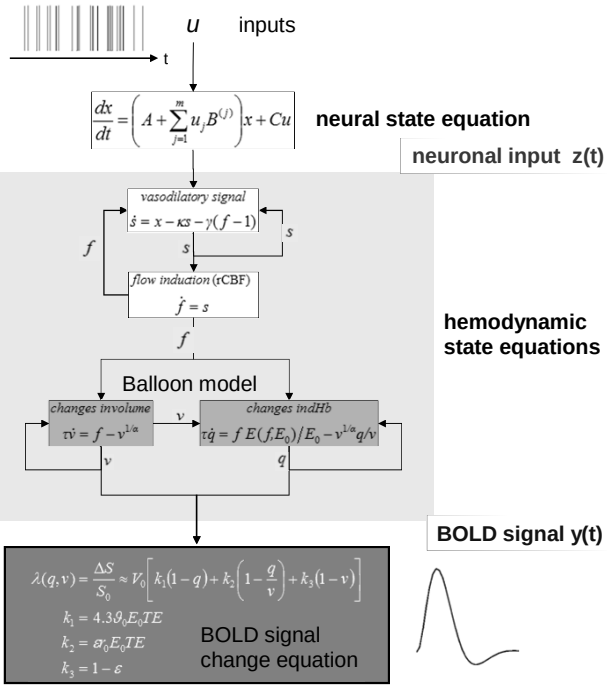
$$\begin{bmatrix}\dot{z}_1\\ \dot{z}_2\end{bmatrix} = \begin{bmatrix}a_{11} & a_{12}\\ a_{21} & a_{22}\end{bmatrix}\begin{bmatrix}z_1\\ z_2\end{bmatrix} + u_2\begin{bmatrix}0 & 0\\ b_{21}^2 & 0\end{bmatrix}\begin{bmatrix}z_1\\ z_2\end{bmatrix} + \begin{bmatrix}c\\ 0\end{bmatrix}u_1 \qquad a_{21} > 0 \qquad a_{12} > 0 \qquad b_{21}^2 > 0$$

The hemodynamic model

- Hemodynamic parameters:

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

- Empirically determined *a priori* distributions.
- Area-specific estimates (like neural parameters) → region-specific HRFs !!

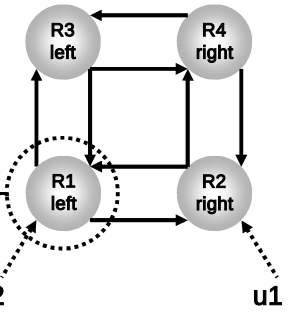


[Friston et al. 2000, *NeuroImage*]
[Stephan et al. 2007, *NeuroImage*]

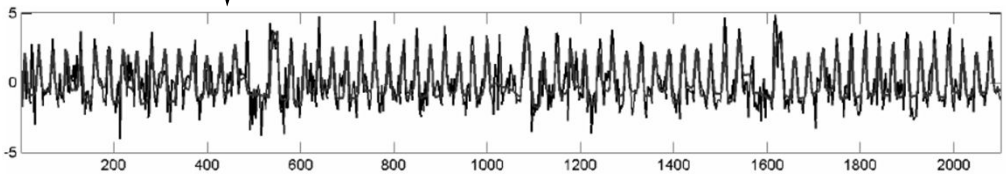
Example: modelled BOLD signal

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

Multiple-input multiple-output system



Recap:
The aim of DCM is to estimate:
-Neuronal parameters [A, B, C];
-Hemodynamic parameters;
Such that modelled/predicted and measured/observed BOLD signals are maximally similar.



black: observed BOLD signal **red:** modelled BOLD signal

Priors & parameter estimation

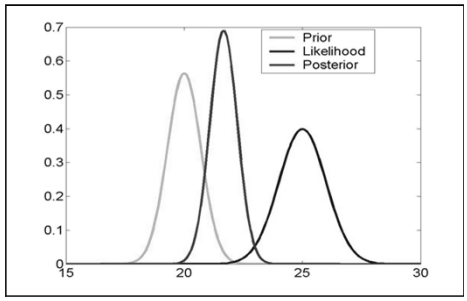
Based on a Bayesian framework.

Bayes theorem allows us to express our **prior knowledge** or "belief" about parameters of the model.

new data $p(y \mid \theta)$ prior knowledge $p(\theta)$

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

posterior ∝ likelihood • prior



The **posterior** probability of the parameters given the data is an optimal combination of prior knowledge and new data, weighted by their relative precision.

Priors in DCM

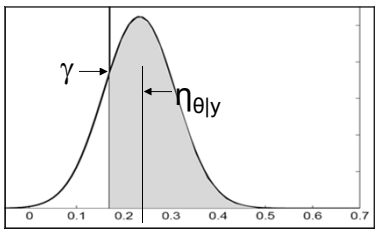
Constraints on parameter estimation:

- hemodynamic parameters: **empirical priors**
- coupling parameters other connections: **shrinkage priors**

Inference about DCM parameters: Bayesian inversion

- Gaussian assumptions about the posterior distributions of the parameters (mean $\eta_{\theta|y}$ and covariance $C_{\theta|y}$).
- Use of the cumulative normal distribution to test the probability that a certain parameter (or contrast of parameters $c^T \eta_{\theta|y}$) is above a chosen threshold γ:

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



- By default, γ is chosen as zero ("does the effect exist?").

**** Parameter estimation by means of Variational Bayes under the Laplace approximation scheme (VL).**

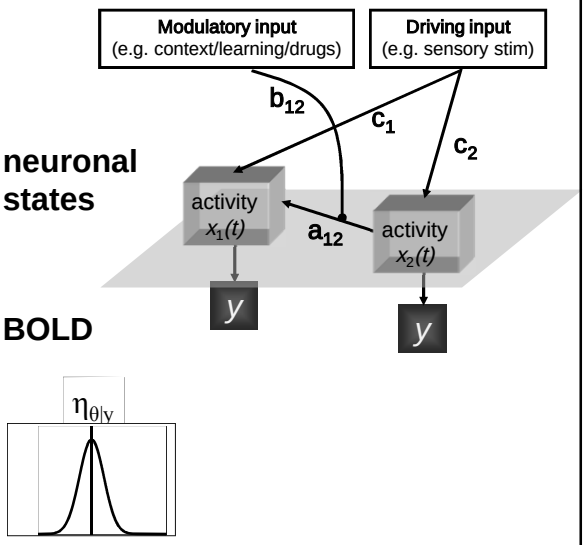
[Friston et al. 2007 *Neuroimage*]

DCM: practical steps

Select areas you want to model

- Extract timeseries of these areas (x(t))
- Specify at neuronal level
  - what drives areas (c)
  - how areas interact (a)
  - what modulates interactions (b)
- State-space model with 2 levels:
  - Hidden neural dynamics
  - Predicted BOLD response
- Estimate model parameters:

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



Attention to motion in the visual system

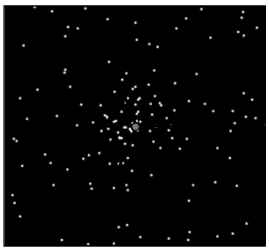
Stimuli 250 radially moving dots at 4.7 degrees/s

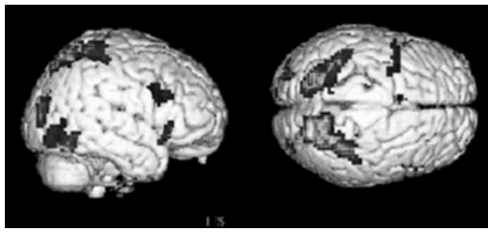
Pre-Scanning
5 x 30s trials with 5 speed changes (reducing to 1%)
Task - detect change in radial velocity

Scanning (no speed changes)
6 normal subjects, 4 x 100 scan sessions;
each session comprising 10 scans of 4 different conditions

F A F N F A F N S .....

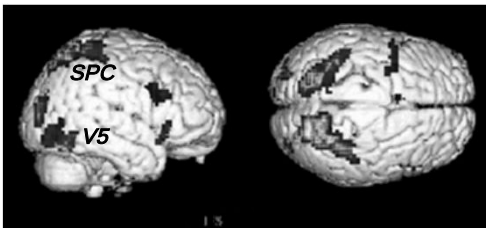
F - fixation point only
A - motion stimuli with attention (detect changes)
N - motion stimuli without attention
S - no motion





[Büchel & Friston 1997, *Cereb. Cortex*]
[Büchel et al. 1998, *Brain*]

How we can interpret, mechanistically, the increase in activity of area V5 by attention when motion is physically unchanged.



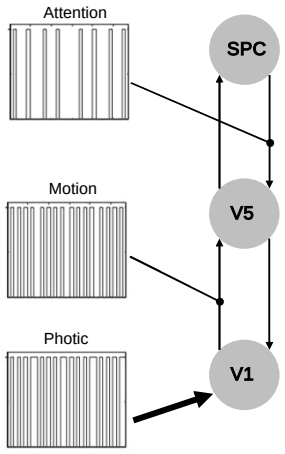
Choice of areas and time series extraction.
➔ Three ROIs: V1, V5, and SPC.

Definition of driving inputs.
➔ All visual stimuli/conditions (photic: A N S)

Definition of modulatory inputs.
➔ The effects of motion and attention (A N)

Building the model:
1- how to connect regions (intrinsic connections "A");
2- how the driving inputs enter the system (extrinsic effects "C");
3- define the context-dependent connections (modulatory effects "B").

- Visual inputs drive V1.
- Activity then spreads to hierarchically arranged visual areas.
- Motion modulates the strength of the V1→V5 forward connection.
- Attention modualtes the strength of the SPC→V5 backward connection.

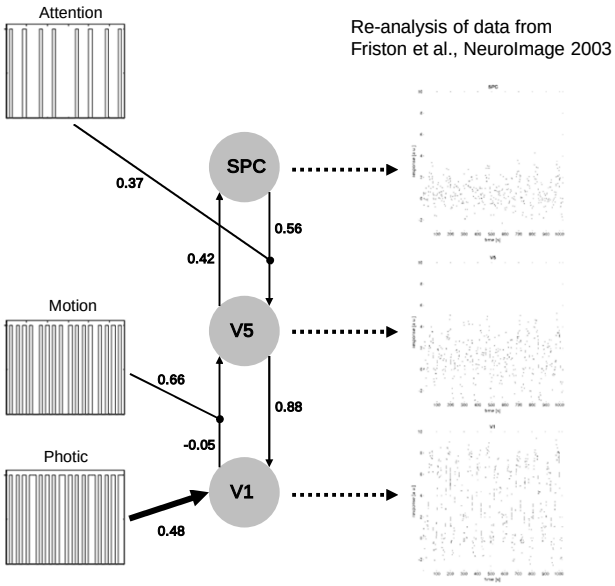


Re-analysis of data from
[Friston et al., 2003 *NeuroImage*]

After DCM estimation:

- Motion modulates the strength of the V1→V5 forward connection.
- Attention increases the backward-connection SPC→V5.

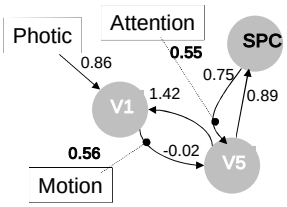
Are there other plausible/alternative models?



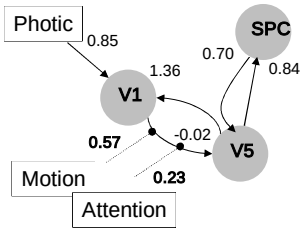
Re-analysis of data from Friston et al., NeuroImage 2003

Alternative models (hypothesis-driven approach):

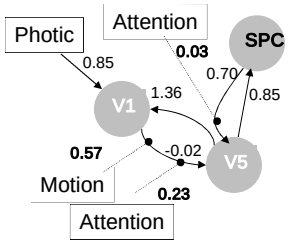
Model 1:
attentional modulation of V1→V5



Model 2:
attentional modulation of SPC→V5



Model 3:
attentional modulation of V1→V5 and SPC→V5



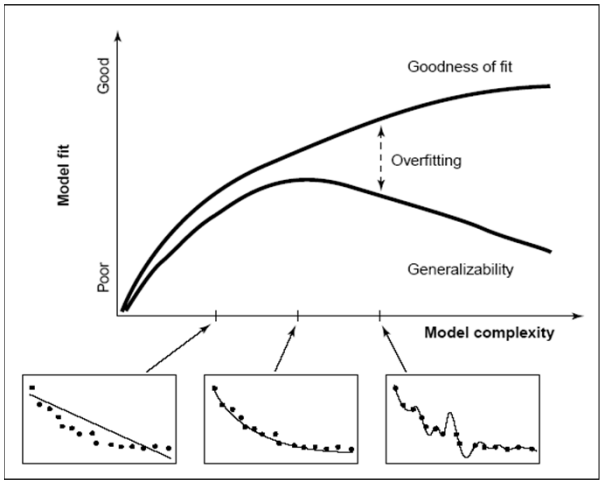
How we can compare between competing hypotheses?
➔ BMS (Bayesian Model Selection)

Model evidence and selection

Given competing hypotheses on functional mechanisms of a system, which model is the best?

Which model represents the best balance between model fit and model complexity?

For which model m does $p(y|m)$ become maximal?



[Pitt and Miyung 2002 *TICS*]

Approximations to the model evidence in DCM

Logarithm is a monotonic function → Maximizing log model evidence = Maximizing model evidence

Log model evidence = balance between fit and complexity

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

[Penny 2012 *NeuroImage*]

The negative variational free energy (F) approximation

Under Gaussian assumptions about the posterior (Laplace approximation), the negative free energy F is a lower bound on the log model evidence:

$$\Rightarrow F = \log p(y \mid m) - KL[q(\theta), p(\theta \mid y, m)]$$

Kullback-Leibler (KL) divergence

The complexity term in *F*

- The negative free energy *F* accounts for parameter interdependencies.

$$Complexity(m) = \frac{1}{2}\log|C_\theta| - \frac{1}{2}\log|C_{\theta|y}| + \frac{1}{2}\left(\mu_{\theta|y} - \mu_\theta\right)^T C_\theta^{-1}\left(\mu_{\theta|y} - \mu_\theta\right)$$

[Penny et al. 2004 *Neuroimage*]
[Stephan et al. 2009 *Neuroimage*]

- The complexity term of *F* is higher:
  - the more independent the prior parameters (↑ effective DFs);
  - the more dependent the posterior parameters;
  - the more the posterior mean deviates from the prior mean.

**** All recent DCM versions use F for model selection !**

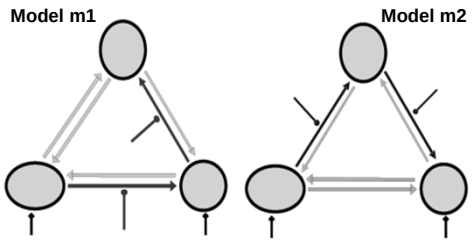
[Penny 2012, *NeuroImage*]

Inference on model space

BMS (Bayesian Model Selection)

An intuitive interpretation of model comparisons is made possible by Bayes factors:

$$BF_{12} = \frac{p(y \mid m_1)}{p(y \mid m_2)}$$



$$BF_{12} = \exp(F_1 - F_2)$$ positive value, [0; ∞[

[Kass & Raftery 1995, *J. Am. Stat. Assoc.*]

BF_{12}	$p(m_1\|y)$	Evidence
1 to 3	50-75%	weak
3 to 20	75-95%	positive
20 to 150	95-99%	strong
≥ 150	≥ 99%	Very strong

!!# Only compare models with the same data #!!

Levels of inference: **Group level**

-- Family level --
-- System/model level --
-- Parameter/connection level --

[Penny et al. 2010, *PLoS Comp Biol*]
[Seghier et al. 2010, *Front Syst Neurosci*]

FFX: subjects assumed to use similar systems.
RFX: best models vary across subjects.

♣ **Family level:**
- Useful when no clear winning model // models have common characteristics.
Models assigned to subsets (families) with shared features.
➔**Inference: a class/type of models that best explains the data.**

♣ **Model level:**
- Useful when a clear winning model can be identified (BMS).
➔**Inference: a useful model structure (inputs & connections) that explains the data.**

♣ **Connection level:**
- Useful when connectivity parameters are of interest (e.g. modulations).
➔**Inference: Bayesian parameters averaging (BPA) or t-test on DCM parameters.**
➔**Inference: BMA on the winning family (or over the whole model space).**

[Stephan *et al.* 2010 *NeuroImage*]

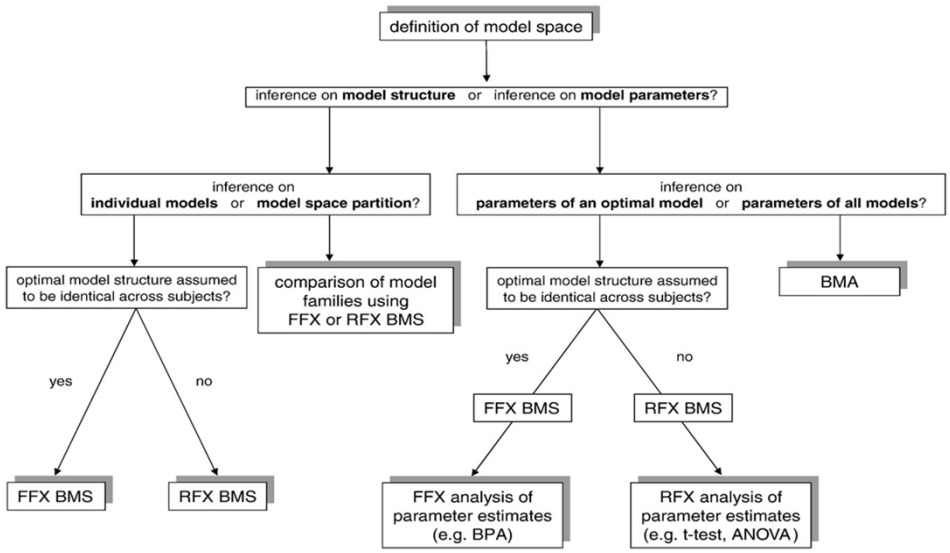


Fig. 1. This schematic summarizes the typical sequence of analysis in DCM, depending on the question of interest. Abbreviations: FFX=fixed effects, RFX=random effects, BMS=Bayesian model selection, BPA=Bayesian parameter averaging, BMA=Bayesian model averaging, ANOVA=analysis of variance.

<u>BMS has nothing to say about the "true" model(s)</u>.
find the most useful model, form a set of alternatives, given the data.
Best model = best balance between accuracy and complexity.

model selection with BMS ≠ model validation!

<u>DCM model space:</u> Compatibility // Size // Plausibility.

BMS cannot be applied to models fitted to different data!
(Only models with the same ROIs can be compared using BMS).

It is helpful to constrain your DCM model space.
(e.g., 6 ROIs, fully connected, 1 Billion alternative modulations!).

(if possible) **Define sets of models that are plausible**, in a systematic way, given prior knowledge (e.g. anatomical, TMS, previous studies).

for group comparison (e.g. patients vs. controls) **make inferences over the same DCM model space.**

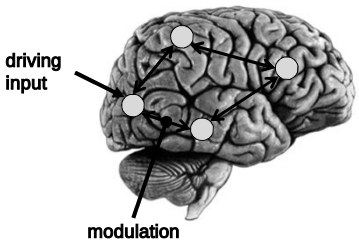
Which DCM version? DCM5 || DCM8 || DCM10 || DCM12.
- **Use the latest version (= DCM12).**
- **Keep the same DCM version for your project (over models, sessions, and subjects).**
- **Indicate the DCM version in your papers.**

Extensions in DCM for fMRI:

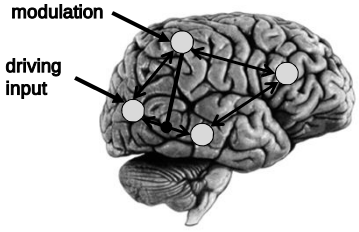
• **Bayesian Model Selection BMS**	**[Penny et al. 2004 *Neuroimage*].**
• **Slice specific sampling**	**[Kiebel et al. 2007 *Neuroimage*].**
• **Refined hemodynamic model**	**[Stephan et al. 2007 *Neuroimage*].**
• **The two-state DCM**	**[Marreiros et al. 2008 *Neuroimage*].**
• **The non-linear DCM**	**[Stephan et al. 2008 *Neuroimage*].**
• **Random-effects BMS**	**[Stephan et al. 2009 *Neuroimage*].**
• **Stochastic DCM**	**[Daunizeau et al. 2009 *Physica D*].**
• **Anatomical-based priors for DCM**	**[Stephan et al. 2009 *Neuroimage*].**
• **Bayesian model averaging BMA**	**[Penny et al. 2010 *PLoS Comp Biol*].**
• **Post-hoc Bayesian optimisation**	**[Friston et al. 2011 *Neuroimage*].**
• **Stochastic DCM (random fluctuations)**	**[Li et al. 2011 *Neuroimage*].**
• **Network discovery for large DCMs**	**[Seghier & Friston et al. 2013 *Neuroimage*].**
• **Spectral DCM for resting-state fMRI**	**[Razi et al. 2015 *Neuroimage*].**

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

bilinear DCM



nonlinear DCM



[Stephan et al. 2008, *NeuroImage*]

Two-dimensional Taylor series (around $z_0=0$, $u_0=0$):

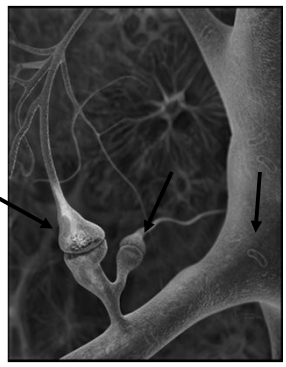
$$\frac{dz}{dt} = f(z,u) \approx f(z_0,0) + \frac{\partial f}{\partial z} z + \frac{\partial f}{\partial u} u + \frac{\partial^2 f}{\partial z \partial u} uz + \frac{\partial^2 f}{\partial z^2} \frac{z^2}{2} + \ldots$$

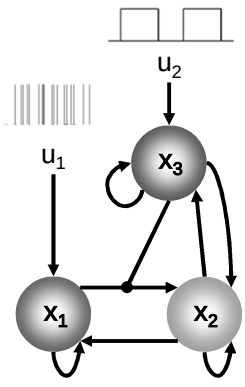
Bilinear state equation:

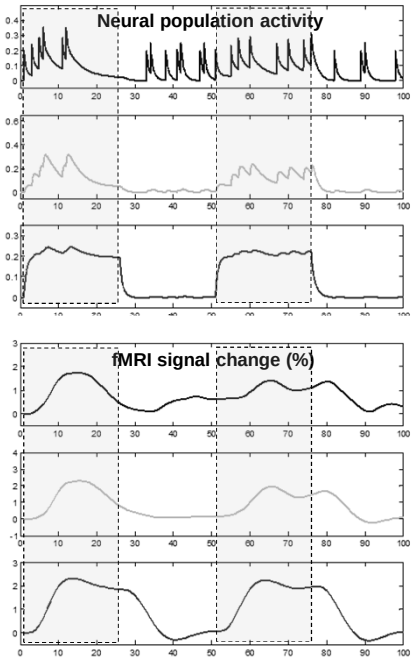
$$\dot{z} = \left(A + \sum_{i=1}^{m} u_i B^{(i)} \right) z + Cu$$

Nonlinear state equation:

$$\dot{z} = \left(A + \sum_{i=1}^{m} u_i B^{(i)} + \sum_{j=1}^{n} z_j D^{(j)} \right) z + Cu$$



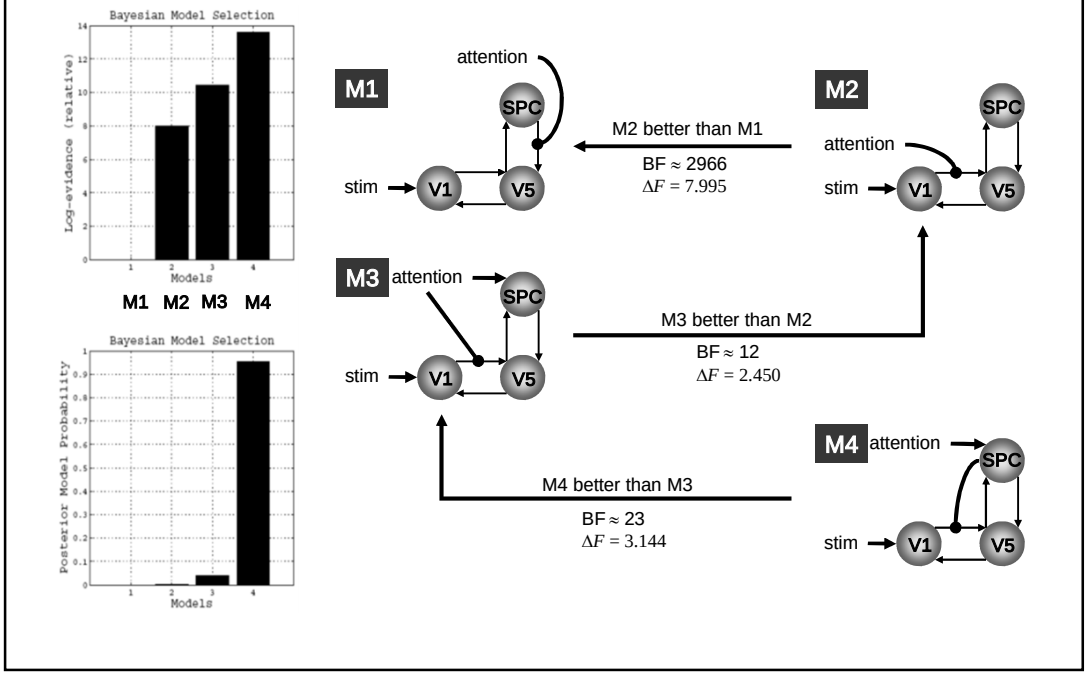


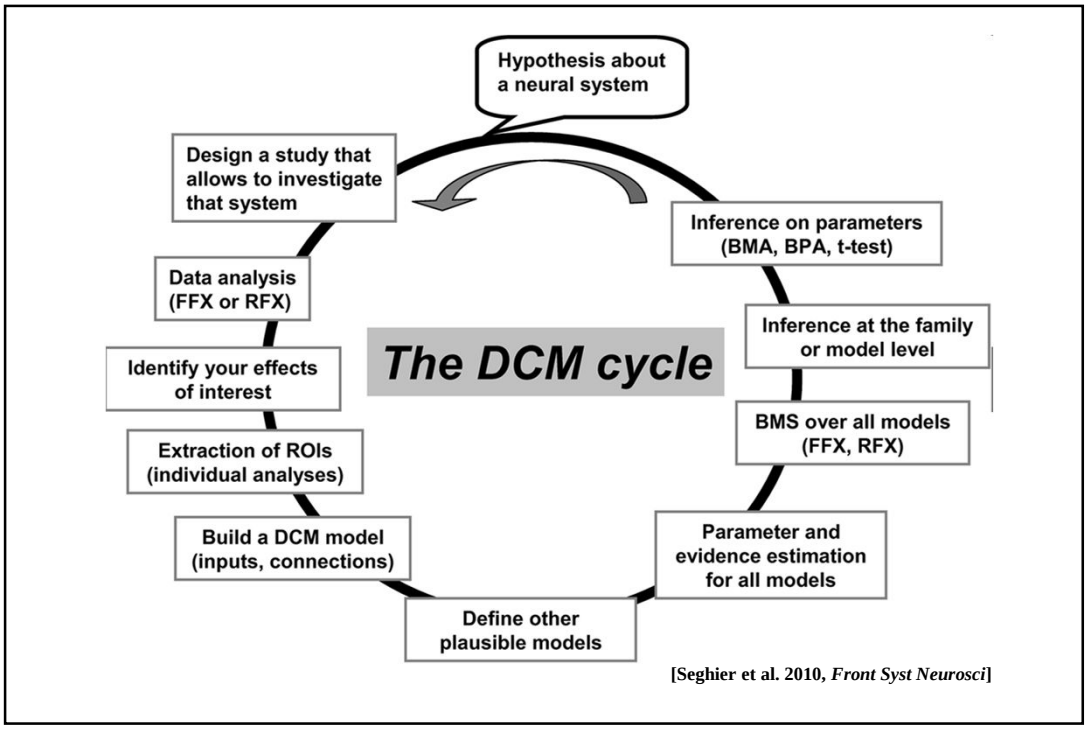


Nonlinear dynamic causal model (DCM):

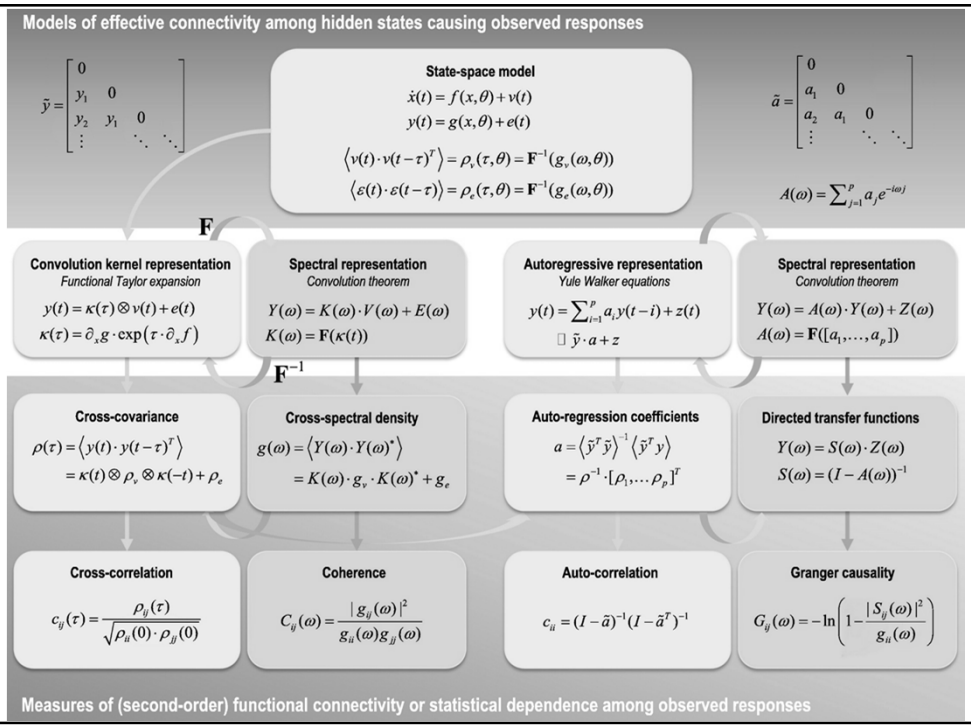
$$\dot{z} = \left(A + \sum_{i=1}^{m} u_i B^{(i)} + \sum_{j=1}^{n} z_j D^{(j)} \right) z + Cu$$

[Stephan et al. 2008, *NeuroImage*]





[Seghier et al. 2010, *Front Syst Neurosci*]



[Friston et al. 2014, *Neuroimage*]

Reviews:

Stephan *et al.* (2010). Ten simple rules for DCM**.** ***NeuroImage.***

Daunizeau et al. (2010). DCM: a critical review of the biophysical and statistical foundations**.** ***NeuroImage.***

Seghier et al. (2010). Identifying abnormal connectivity in patients using dynamic causal modeling of fMRI responses **.** ***Front Syst Neurosci.***

Friston (2011). Functional and effective connectivity: A review. ***Brain Connectivity.***

Practical examples: (DCM-fMRI at the FIL)

- Prediction error and putamen:
den Ouden et al. (2010) *J Neurosci.*

- Inter-hemispheric interactions and laterality for words and pictures:
Seghier et al. (2011) *Cerebral Cortex*.

- Top-down effects on form perception:
Cardin et al. (2011) *Cerebral Cortex.*

- Multilingual vs. Monlingual monitoring of speech production:
Parker-Jones et al. (2013) *J Neurosci.*

http://www.fil.ion.ucl.ac.uk/spm/data/