Dynamic causal modeling for fMRI

Methods and Models for fMRI, HS 2015

Jakob Heinzle
Structural, functional & effective connectivity

anatomical/structural connectivity
- presence of physical connections
- DWI, tractography, tracer studies (monkeys)

functional connectivity
- statistical dependency between regional time series
- correlations, ICA

effective connectivity
- causal (directed) influences between neuronal populations
- DCM

Sporns 2007, Scholarpedia
Dynamic causal modelling (DCM) for fMRI

- DCM framework was introduced in 2003 for fMRI by Karl Friston, Lee Harrison and Will Penny (NeuroImage 19:1273-1302)
- part of the SPM software package
- Allows to do an effective connectivity analysis
DCM approach to effective connectivity

A simple model of a neural network …

… described as a dynamical system …

… causes the data (BOLD signal).

\[
\dot{x} = f(x, u, \theta_x) \quad y = g(x, \theta_y)
\]

Let the system run with input \((u)\) and parameters \((\theta_x, \theta_y)\), and you will get a BOLD signal time course \(y\) that you can compare to the measured data.
Bayes' theorem

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

posterior = likelihood \cdot prior / evidence

The Reverend Thomas Bayes (1702-1761)
Generative model

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

\[ y = g(x, \theta) + \varepsilon \]

Forward model: Predicting measured activity

Model inversion: Estimating neuronal mechanisms

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

Friston et al. 2003, *NeuroImage*

Stephan, Tittgemeyer et al. 2009, *NeuroImage*
Approximating $f(x, u, \theta)$

\[
\frac{dx}{dt} = f(x, u) \approx f(x_0, 0) + \frac{\partial f}{\partial x} x + \frac{\partial f}{\partial u} u + \frac{\partial^2 f}{\partial x \partial u} xu + \frac{\partial^2 f}{\partial x^2} x^2 + \ldots
\]
The neural equations – bilinear model

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

Parameters A, B and C define connectivity!
The neural equations – non-linear model

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

Parameters A, B, C and D define connectivity!
The problem of the hemodynamic response

- ↑ neural activity
- ↓ blood flow
- ↑ oxyhemoglobin
- ↓ T2*
- ↑ MR signal

Rest

Activity

Source, Huettel et al, 2004, fMRI (Book)
From neural activity to the BOLD signal

Local hemodynamic state equation:

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

Balloon model:

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

Changes in volume \( (v) \) and dHb \( (q) \)

BOLD signal change equation:

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

cf. Simulations in Lecture 1
The hemodynamic model in DCM

- 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 (like the neural parameters)
  \[\rightarrow\] region-specific HRFs!

Friston et al. 2000, *NeuroImage*
Stephan et al. 2007, *NeuroImage*
The hemodynamic model in DCM – role of $\epsilon$

The hemodynamic model in DCM – role of $\epsilon$

\[
\frac{dx}{dt} = \left( A + \sum_{j=1}^{m} u_j B^{(j)} \right) x + C u
\]

RBM, $\epsilon = 0.5$

CBMN, $\epsilon = 0.5$

RBM, $\epsilon = 1$

CBMN, $\epsilon = 1$

RBM, $\epsilon = 2$

CBMN, $\epsilon = 2$

\[
\dot{s} = x - KS - \gamma(f - 1)
\]

\[
\dot{f} = s
\]

vasodilatory signal

flow induction (rCBF)

Balloon model

changes in volume

\[
\tau \dot{v} = f - v \dot{v}
\]

changes in dHB

\[
\tau \dot{q} = f \frac{E(f,E_0)}{E_0} - v \dot{v} q / v
\]

BOLD signal change equation

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

$k_1 = 4.3 S_0 E_0 T E$

$k_2 = \varepsilon S_0 E_0 T E$

$k_3 = 1 - \varepsilon$

Stephan et al. 2007, NeuroImage
Hemodynamic forward models are important for connectivity analyses of fMRI data

Granger causality

DCM

Summary – the full model

\[ y(t) \]

Inputs

\[ y_i(t) \]

BOLD signal

\[ t \]

Time [s]
Summary – the full model

Inputs

Neuronal states $x_i(t)$

Hemodynamic model $v_i(t)$ and $q_i(t)$

BOLD signal change equation $y_i(t)$

BOLD signal $y(t)$

Inputs

$y(t)$

$y_i(t)$

Hidden states

arbitrary units

Input

$x_i(t)$

$s_i(t)$

$f_i(t)$

$v_i(t)$

$q_i(t)$

$y_i(t)$

Time [s]
Summary – parameters of interest

Inputs

Neuronal states $x_i(t)$

Hemodynamic model $v_i(t)$ and $q_i(t)$

BOLD signal change equation $y_i(t)$

BOLD signal $y(t)$

Connection weights: A, B, C and D

Hemodynamic parameters: $\tau$, $K$, $\varepsilon$
Example traces 1: Single node

\[
\dot{x} = Ax + u_2 B^{(2)} x + C u_1 \\
\begin{bmatrix}
\dot{x}_1 \\
\dot{x}_2
\end{bmatrix} = \begin{bmatrix}
\sigma & 0 \\
0 & \sigma
\end{bmatrix} \begin{bmatrix}
x_1 \\
x_2
\end{bmatrix} + u_2 \begin{bmatrix}
0 & 0 \\
0 & 0
\end{bmatrix} \begin{bmatrix}
x_1 \\
x_2
\end{bmatrix} + \begin{bmatrix}
c_{11} & 0 \\
0 & 0
\end{bmatrix} \begin{bmatrix}
u_1 \\
u_2
\end{bmatrix}
\]
Example traces 2: Connected nodes

\[
\dot{x} = Ax + u_2 B^{(2)} x + Cu_1
\]

\[
\begin{bmatrix}
\dot{x}_1 \\
\dot{x}_2
\end{bmatrix} = \begin{bmatrix}
\sigma & 0 \\
0 & \sigma
\end{bmatrix} \begin{bmatrix}
x_1 \\
x_2
\end{bmatrix} + u_2 \begin{bmatrix}
0 & 0 \\
0 & 0
\end{bmatrix} \begin{bmatrix}
x_1 \\
x_2
\end{bmatrix} + \begin{bmatrix}
c_{11} & 0 \\
0 & 0
\end{bmatrix} \begin{bmatrix}
u_1 \\
u_2
\end{bmatrix}
\]
Context specific «neuro»-modulation

\[
(A + \sum_{i=1}^{m} u_i B^{(i)} + \sum_{j=1}^{n} x_j D^{(j)}) x
\]

Synaptic strengths are context-sensitive: They depend on spatio-temporal patterns of network activity.
Example traces 3: Modulation of connection

\[ \dot{x} = Ax + u_2 B^{(2)} x + C u_1 \]

\[
\begin{bmatrix}
\dot{x}_1 \\
\dot{x}_2 \\
\end{bmatrix} =
\begin{bmatrix}
\sigma & 0 \\
0 & \sigma \\
\end{bmatrix} \cdot \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} + u_2 \begin{bmatrix} 0 & 0 \\
b^{(2)}_{12} & 0 \\
0 & 0 \\
\end{bmatrix} \cdot \begin{bmatrix} x_1 \\ x_2 \\ 0 \end{bmatrix} + \begin{bmatrix} c_{11} & 0 \\
0 & 0 \\
0 & 0 \\
\end{bmatrix} \cdot \begin{bmatrix} u_1 \\ u_2 \end{bmatrix}
\]
Example traces 4: Modulation of self-connection

\[
\dot{x} =Ax + u_2 B^{(2)} x + Cu_1
\]

\[
\begin{bmatrix}
\dot{x}_1 \\
\dot{x}_2 \\
\end{bmatrix} =
\begin{bmatrix}
\sigma & 0 \\
a_{12} & \sigma \\
\end{bmatrix}
\begin{bmatrix}
x_1 \\
x_2 \\
\end{bmatrix} + u_2
\begin{bmatrix}
0 & 0 \\
0 & b_{22}^{(2)} \\
\end{bmatrix}
\begin{bmatrix}
x_1 \\
x_2 \\
\end{bmatrix} +
\begin{bmatrix}
c_{11} & 0 \\
0 & 0 \\
\end{bmatrix}
\begin{bmatrix}
u_1 \\
u_2 \\
\end{bmatrix}
\]
Nonlinear Dynamic Causal Model for fMRI

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

Stephan et al. 2008, *NeuroImage*
How to introduce dynamical systems in Bayes’ world

Bayes’ formula

\[ p(\theta|y, m) = \frac{p(y|\theta, m)p(\theta|m)}{p(y|m)} \]

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

\[ p(y(t)|\theta, m) = \mathcal{N}(y(t), \theta_\sigma) \]

Dynamical model defines the likelihood!
Illustration of likelihood

\[ p(y|\theta, m) = \prod_t p(y(t)|\theta, m) \]
Combining the neural and hemodynamic states gives the complete forward model.

Observation model includes measurement error \( e \) and confounds \( X \) (e.g. drift).

Bayesian inversion: parameter estimation variational Bayes or MCMC

Result 1: A posteriori parameter distributions \( p(\theta|y, m) \), characterised by mean \( n_{\theta|y} \) and covariance \( C_{\theta|y} \)

Result 2: Estimate of model evidence \( p(y|m) \).
Bayesian system identification

Neural dynamics

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

Observer function

\[ y = g(x,\theta) + \varepsilon \]

\[ p(y \mid \theta,m) = N(g(\theta),\Sigma(\theta)) \]
\[ p(\theta,m) = N(\mu_\theta,\Sigma_\theta) \]

Inference on model structure

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

Inference on parameters

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

cf. Lecture 11 on Bayesian Inference
Generative models & model selection

- any DCM = a particular generative model of how the data (may) have been caused

- generative modelling: comparing competing hypotheses about the mechanisms underlying observed data
  → a priori definition of hypothesis set (model space) is crucial
  → determine the most plausible hypothesis (model), given the data

- model selection ≠ model validation!
  → model validation requires external criteria (external to the measured data)
GLM vs. DCM

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

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

However, a stochastic DCM could be applied despite the absence of a local activation.

Multifactorial design: explaining interactions with DCM

Let’s assume that an SPM analysis shows a main effect of stimulus in $X_1$ and a stimulus $\times$ task interaction in $X_2$.

How do we model this using DCM?
Simulated data

Stephan et al. 2007, J. Biosci.
inference on model structure or inference on model parameters?

inference on individual models or model space partition?

optimal model structure assumed to be identical across subjects?

yes

FFX BMS

no

RFX BMS

comparison of model families using FFX or RFX BMS

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

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

optimal model structure assumed to be identical across subjects?

yes

FFX BMS

no

RFX BMS

parameters of an optimal model or parameters of all models?

BMA

Stephan et al. 2010, NeuroImage
Model comparison: Synesthesia

- “projector” synesthetes experience color externally co-localized with a presented grapheme
- “associators” report an internally evoked association

van Leeuwen et al., J Neurosci 2011
Model comparison: Synesthesia

- “projector” synesthetes experience color externally co-localized with a presented grapheme

- “associators” report an internally evoked association

- across all subjects: no evidence for either model

- but splitting into synesthesia types gives very strong evidence for bottom-up (projectors) and top-down (associators) mechanisms, respectively

van Leeuwen et al., J Neurosci 2011
Prefrontal-parietal connectivity during working memory in schizophrenia

17 ARMS, 21 first-episode (13 non-treated), 20 controls

Schmidt et al. 2013, *JAMA Psychiatry*
“All models are wrong, but some are useful.”

George E.P. Box (1919-2013)
# Hierarchical strategy for model validation

<table>
<thead>
<tr>
<th>Step</th>
<th>Type</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
</table>
| 1    | in silico | numerical analysis & simulation studies | - For DCM: >15 published validation studies (incl. 6 animal studies):  
  - infers site of seizure origin (David et al. 2008)  
  - infers primary recipient of vagal nerve stimulation (Reyt et al. 2010)  
  - infers synaptic changes as predicted by microdialysis (Moran et al. 2008)  
  - infers fear conditioning induced plasticity in amygdala (Moran et al. 2009)  
  - tracks anaesthesia levels (Moran et al. 2011)  
  - predicts sensory stimulation (Brodersen et al. 2010) |
| 2    | humans | cognitive experiments | |
| 3    | animals & humans | experimentally controlled system perturbations | |
| 4    | patients | clinical utility | |
Many thanks to Andreea Diaconescu and Klaas Enno Stephan for some of the slides!

Thank you!
Validating models: clinical utility

model of neuronal (patho)physiology

predicting

individual symptoms

individual outcome

individual therapeutic response
plus added noise (SNR=1)
Methods papers: DCM for fMRI and BMS – part 1

Methods papers: DCM for fMRI and BMS – part 2