Anatomical Background of Dynamic Causal Modeling and Effective Connectivity Analyses

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Outline

• Relation between structure and function
• Effective connectivity
• Dynamic causal modeling (DCM)

Connectional fingerprints determine local function

• Unique anatomical connectivity patterns (connectional fingerprints) for cortical areas
• “Families” of cortical areas (clusters) with similar patterns
• Analogous results for electrophysiological response patterns

Anatomical connectivity is the major determinant for the response profile of neuronal ensembles.

Passingham et al., Nat Rev Neurosci, 2002
Anatomical connections define processing hierarchies

Literature based database:
http://cocomac.g-node.org/
Stephan et al., Phil. Trans. B, 2001;
Kötter, Neuroinformatics, 2004

Anatomical Background for DCM

Weighted and directed connectivity matrix in macaque

Fraction of labeled neurons per area → weight
Markov et al., Cereb Cortex, 2012; J Comp Neurol 2014;

From area
To area

Anatomical Background for DCM

Activation, intrinsic functional connectivity and anatomy

Spontaneous correlation pattern
Evoked response pattern: eye movement task
Anatomical connectivity pattern


Anatomical Background for DCM
Tight link between functional and anatomical connectivity - human fMRI

Intrinsic functional connectivity in humans is visuotopically organized → matches monkey anatomy!

Heinze et al., Neuroimage, 2011

Some naming conventions

• Anatomical connectivity
  - Fibre bundles, Close Contacts, Synapses
• Functional connectivity
  - Statistical relation, e.g. Correlation, Mutual information
• Effective connectivity
  - Directed influence, e.g. DCM, Transfer Entropy, Granger Causality

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Why effective connectivity?

Anatomical connectivity is critical for understanding brain function …
… but not sufficient on its own.

Functional connections → synapses

Context dependent modulation of connection strengths, synaptic plasticity, neuronal adaptation mechanisms, etc. …

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Synaptic connections show plasticity

- Numerous mechanisms at different time scales (ms to days) → incl. very rapid changes!
- Regulated in several ways (e.g. modulatory effects of DA)

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Connections are recruited in a context-dependent fashion

Synaptic strengths are context-sensitive: They depend on the spatio-temporal distribution of presynaptic inputs and post-synaptic events.
To understand brain (dys)function...

... we need models of effective connectivity that:

- incorporate anatomical and physiological principles
- connect these to computational mechanisms
- allow for inference on neuronal mechanisms (e.g., synaptic plasticity) from measured brain responses

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Dynamic causal modeling (DCM)

\[
\begin{align*}
\frac{dx}{dt} &= f(x, u; \theta) + \varepsilon \\
y &= g(x, \theta) + \zeta
\end{align*}
\]

EEG, MEG

Forward model:
Predicting measured activity given a putative neuronal state

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

FMRI

Model inversion:
Estimating neuronal mechanisms from brain activity measures

\[\frac{dx}{dt} = f(x, u; \theta) + \varepsilon\]
Nonlinear DCM for fMRI – neural model

Hemodynamics DCM – forward model

Conductance-based DCMs (for EEG)
Conductance-based DCMs (for EEG)

Weights are constrained by anatomy

Generative models, model selection and model validation

Any given DCM = a particular generative model of how the measured data (may) have been caused

Model selection = hypothesis testing = comparing competing models (i.e. different ideas about mechanisms underlying observed data)

→ Evaluate the relative plausibility of competing explanations for an established effect (e.g., activation)

→ Careful definition of model (hypothesis) space crucial!

Model selection ≠ model validation!

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

Bayesian model selection (BMS)

Model evidence:

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

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

\[ -KL[q(\theta), p(\theta|m)] \]

\[ +KL[q(\theta), p(\theta|y,m)] \]

accounts for both accuracy and complexity of the model

a measure of how well the model generalizes

Various approximations, e.g.:

- negative free energy, AIC, BIC

Gharamani, 2004

McKay, Neural Comp, 1992

Penny et al., Neuroimage, 2004
Examples for the use of DCM

- Anatomical priors for DCM for fMRI
- Modulation of connectivity by prediction errors
- Conductance based DCM
- if time permits: DCM validation in patients or layered DCM

Bayes Factor >10^9

priors were clearly superior:

Posterior model probabilities

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Errors

Examples for the use of DCM

Anatomically informed priors

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Errors
Prediction errors drive synaptic plasticity

\[ W_j = W_{ij} + \alpha \sum_{i=1}^{k} PE_i \]

\[ W_j = a_0 + \alpha \int_0^{t} PE(t) d\tau \]

Synaptic plasticity during learning = \(f\) (prediction error)

Learning of dynamic audio-visual associations

Model behavior with a hierarchical Bayesian Model \(\rightarrow\) estimate of prediction errors PE

\[ \text{Den Ouden et al., J Neurosci, 2010} \]

Prediction error (PE) activity in the putamen

PE during active sensory learning

PE during incidental sensory learning

PE during RF learning

PE = "teaching signal" for synaptic plasticity during learning

Could the putamen be regulating trial-by-trial changes of task-relevant connections?
**PE control plasticity during adaptive cognition**

- Influence of visual areas on premotor cortex:
  - stronger for surprising stimuli
  - weaker for expected stimuli

[Image: den Ouden et al., J Neurosci, 2010]

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**What is a good model?**

“... essentially, all models are wrong, but some are useful.”
George E.P. Box

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**Strategies for model validation**

| 1 | in silico | numerical analysis & simulation studies |
| 2 | humans | experiments of known cognitive/neurphys. processes |
| 3 | animals & humans | experimentally controlled system perturbations |
| 4 | patients | clinical facts |

Examples: Validation of DCM in animal studies:
- infers site of seizure origin (David et al. 2008)
- infers primary recipient of vagal nerve stimulation (Keyl 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 anesthetic levels (Moran et al. 2011)
- predicts sensory stimulation (Brodersen et al. 2010)
Dopaminergic modulation of AMPA/NMDA receptors

- ↓ exogenous inputs to layer IV
- ↑ NMDA inputs to layer III pyramidal cells and interneurons

Estimates of AMPA/NMDA correlate with behaviour

Validating models against clinical facts

Summary

• Anatomical connectivity information is important, but not everything
• Models of effective connectivity → neural system mechanisms can be inferred from neuroimaging data
• DCM is one (not the only) method for this:
  – Neuronal interactions are modeled at the hidden neuronal level
  – Bayesian system identification method
  – Key role for model selection
  – Can be integrated with measures of anatomical connectivity
  – Can be integrated with computational models
• Validation is critical (for any modeling approach)

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