Causal modeling of fMRI: temporal precedence and spatial exploration

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Overview

• **Intro: What is…**
  – Brain Connectivity
  – Causality

• **Problems, solutions, applications**
  – The missing region problem
    – Solution: structural model exploration
    – Application: Task switching
  – The missing time problem
    – Solution: generative model inversion
    – Application: Epileptic seizures
  – The missing model problem
    – Solution: Don’t throw away the less-parametric models
    – Application: Social communication

• **Summary & Conclusions**
Connectivity

- **Anatomical connectivity**
  - A direct anatomical connection
  - Tracer studies, DTI

- **Functional connectivity**
  - Correlation between activities
  - ICA, PCA

- **Effective connectivity**
  - Influence one neural system exerts over another (Friston et al., 1993)
  - Covariance Structural Equation Modeling, Dynamic Causal Modeling, Granger Causality
Functional & Effective Connectivity

- **Functional connectivity**
  - Association (mutual information)
  - Localization of whole networks

- **Effective connectivity**
  - Uncover network mechanisms (causal influence)
  - Directed vs. undirected
  - Direct vs. indirect
  - Generative model
Causality investigation: 
Associative & Interventional

‘Naturally’ working system
Unnaturally ‘perturbed’ system
Naturally ‘perturbed’ system
Effective connectivity

brain -> data

measurement

Effective connectivity modeling

Structural model & priors -> Mathematical model & priors

Inferred model
Effective connectivity

Structural model & priors
- ROI selection
- Graph selection

Dynamical model & priors
- Deterministic vs. stochastic models
- Linear vs. non-linear
- Forward observation models

$A_i \left[ x_{t-i} \right] + e_{xy} \text{ cov} e_{jx} = \left( \sigma_{xy}^2 \sigma_{xy}^2 \right) = \Sigma$

How does it interact: signal model

Roebroeck et al., NI, 2012
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• Summary & Conclusions
Missing region problem

- Danger of strong structural models: Missing region problem
- When important regions are ‘left out’ (of the anatomical model), ANY correct method will give ‘wrong’ answers
- Spurious inference on connections
Granger causality mapping (GCM)

Random effects level GCMs

Roebroeck, NI 2005; Goebel, MRI 2004
Granger causality (G-causality, GC)

- If we can predict $x[t]$ better using $\{X-, Y-\}$ than using $\{X-\}$ alone, then we say that $y$ Granger causes $x$.
- If we can predict $x[t]$ better using $\{X-, Y-, y[t]\}$ than using $\{X-, Y-\}$, then we say that there is instantaneous correlation between $y$ and $x$. 
Application: task switching

Goebel et al., MRI (2003), Roebroeck et al., NI (2005)
Granger causality mapping (GCM)

Experimental modulation:
- Functional assignment
- Avoid HRF confound

Roebroeck, NI 2005; Goebel, MRI 2004
• **Structural model exploration is important**
• **By a mapping approach**
  – Psycho-Physiological Interaction mapping
    • PPI (Friston et al., 1997)
  – GCM
• **By post-hoc network discovery**
  – (Friston et al., 2012)
• **By large G-causality models**
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• **Summary & Conclusions**
Missing time problem

• **Part 1**
  – fMRI: Slowly sampling fast-changing (and interacting) processes

• **Part 2a**
  – Hemodynamics: sampling low-pass filtered processes

• **Part 2b**
  – *Variable* Hemodynamics in different brain areas

![Graph showing Neural Activity, HRF, and BOLD signal with Corr Coef - 0.52]
Part 1: Slow sampling

\[ dX = AXdt + d\omega \]

\[ X[k\Delta t] = BX[(k-1)\Delta t] + e \]

Spurious Direct Connections

Slow sampling

- **When modeling slowly sampled dynamics...**
- **...with a discrete multivariate (D>2) model**
- **Spurious direct causalities can appear**
  - Even if no regions are missing
- **Having said this:**
  - Bi-variate (D=2) models are exempt
  - Causal direction is maintained
  - ‘Just’ a parametrization problem

\[
X[k\Delta t] = \exp(\Delta tA)X[(k-1)\Delta t] + e
\]

Sampling & Hemodynamics

Granger causality analysis

Roebroeck, NI 2005
Part 2: *Variable* Hemodynamics

- **Caution needed in applying and interpreting temporal precedence based causality**

- **Tools:**
  - Studying temporally integrated signals for slow processes (e.g. fatigue; Deshpande, HBM, 2009)
  - Finding experimental modulation of causality (intervention!)
  - Combining fMRI with EEG or MEG
  - Hemodynamic deconvolution by inverting generative models
Dynamic Causal Modeling (DCM)

Input (u) controlled

Neurodynamics
\[ u \rightarrow z \]
\[ \dot{z} = (A + \sum_j u_j B^j)z + Cu \]

Hemodynamics
\[ z \rightarrow y \]

Output (y)
Observed + noise

Simulation

Model inversion

Friston et al., NI (2003)
Hemodynamic deconvolution

Much of DCM for fMRI is concerned with statistical inversion of the complex hemodynamic model.
Application: epilepsy

- An animal study of neural drivers in epilepsy
  - 6 rats
  - Simultaneous EEG and fMRI
  - Intracranial iEEG in 3 areas

David et al., PLoS Biology, 2008
Application: epilepsy

- Rat study of epilepsy
- Simultaneous fMRI/EEG
- Gold standard model =>

Granger without deconvolution

\[ \text{DCM} \]

\[ \begin{align*}
\text{S1BF} & \rightarrow \text{Thalamus} \\
\text{Thalamus} & \rightarrow \text{S1BF} \\
\text{S1BF} & \rightarrow \text{Striatum} \\
\text{Striatum} & \rightarrow \text{S1BF} \\
\end{align*} \]

Granger using deconvolution

David et al., PLoS Biology, 2008
Missing time: solutions

• **Part 1**
  – Bi-variate discrete-time modeling (GCM)
  – Parametrizing the model for missing time (continuous-time models)

• **Part 2**
  – Deconvolution by inverting a generative model of hemodynamics (DCM)
  – Experimental modulation of interactions
  – Independent data (e.g. EEG/MEG)
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• Summary & Conclusions
Missing model problem

• We do not have an appropriate generative model for many interacting processes
  – Or, when we do, we cannot invert it: it is not identifiable
Neurodynamics model

- **Neurodynamics model**
  - Which one is realistic enough and identifiable?
  - 1-state, 2-state, 3-state,…

- **Hemodynamics model**
  - Observation model for fMRI
  - Other ones for EEG/MEG
Application: Social communication

Mapping the information flow from one brain to another during gestural communication

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Schippers et al, PNAS, 2010
• Hard to specify a generative model for the full causal chain between brains
• Less-parametric G-causality can still be applied
Application: Social communication

- Mapping influence between brains

Schippers et al, PNAS, 2010
Application: Social communication

- Mapping influence between brains

Schippers et al, PNAS, 2010
Missing models: solutions

- Find and use more realistic (& complex) neurodynamics models and the data to identify them from
- But don’t throw out less-parametric models that can capture largely unknown mechanisms…
Summary & Conclusion

- **Causality in fMRI: Yes!**
  - Intervention: task design
  - Temporal precedence: signal dynamics
  - Good stochastic dynamic models use **both**

- **Missing regions**
  - Structural model exploration ✓

- **Missing time**
  - Bi-variate mapping
  - Inversion of hemodynamic models ✓

- **Missing models**
  - Think about more parametric…
  - …and less-parametric neuronal models ✓
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