Causal modeling of fMRI:
temporal precedence and spatial exploration

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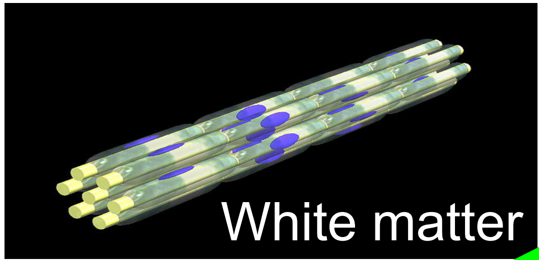
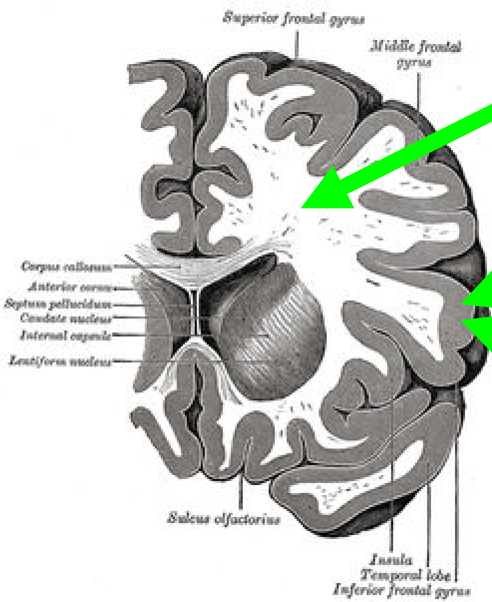
Overview

- **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



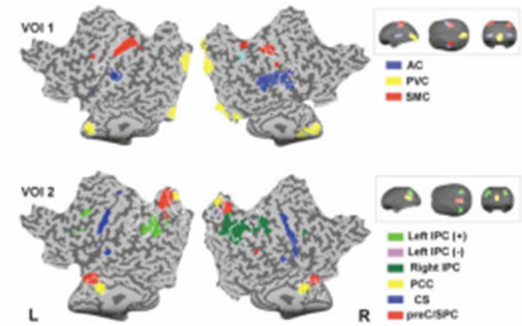


Grey matter

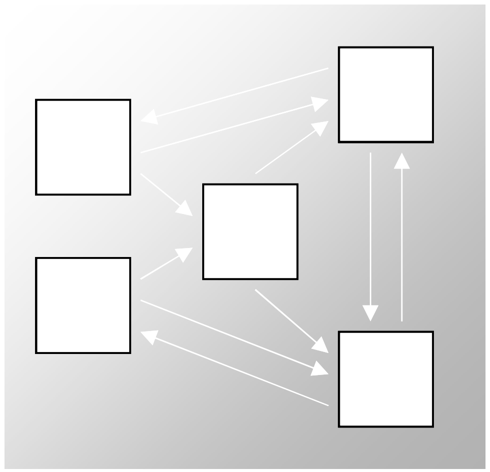
- **Anatomical connectivity**
  - A direct anatomical connection
  - Tracer studies, DTI
- **Functional connectivity**
  - Correlation between activities
  - ICA, PCA
- **Effective connectivity**
  - Influence one neural system exerts over another (Friston et al., 1993)
  - Covariance Structural Equation Modeling, Dynamic Causal Modeling, Granger Causality

Functional & Effective Connectivity

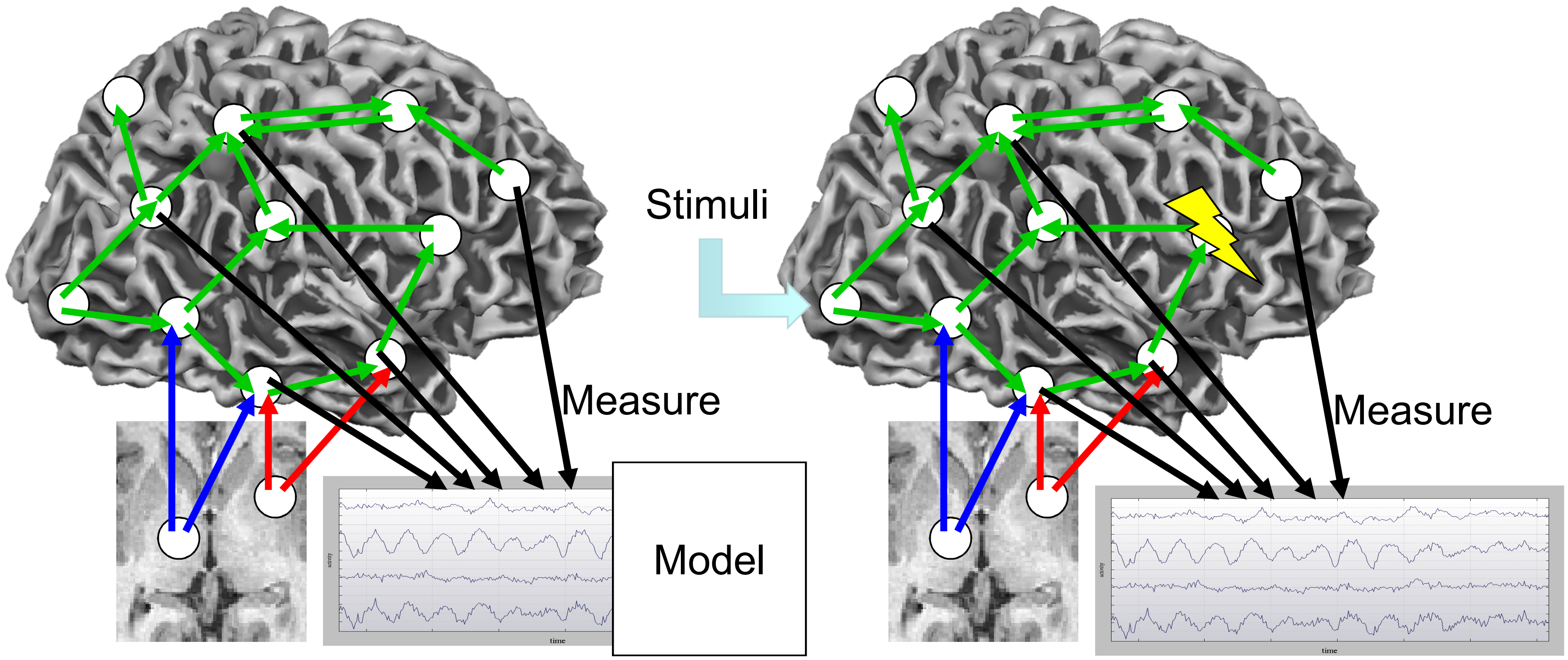
- **Functional connectivity**
  - Association (mutual information)
  - Localization of whole networks



- **Effective connectivity**
  - Uncover network mechanisms (causal influence)
  - Directed vs. undirected
  - Direct vs. indirect
  - Generative model



Causality investigation: Associative & Interventional

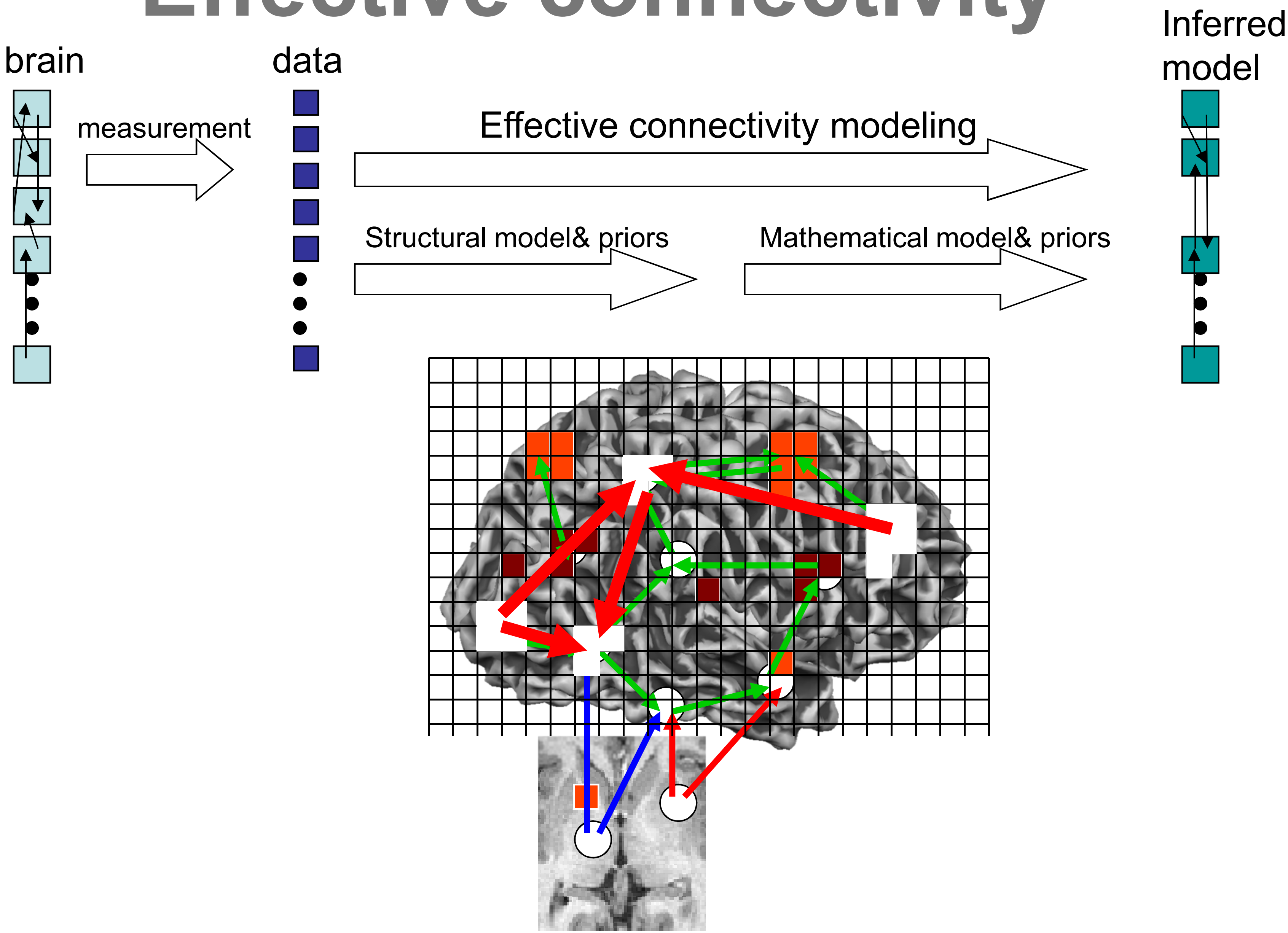


'Naturally' working system

Unnaturally 'perturbed' system

Naturally 'perturbed' system

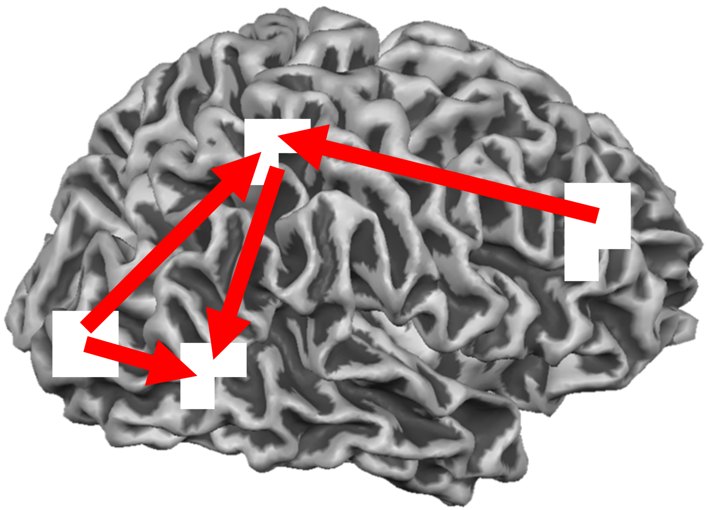
Effective connectivity



Effective connectivity

Structural model& priors

- **ROI selection**
- **Graph selection**



What interacts

Dynamical model& priors

- **Deterministic vs. stochastic models**
- **Linear vs. non-linear**
- **Forward observation models**

$$\begin{pmatrix} x[t] \\ y[t] \end{pmatrix} = \sum_{i=1}^{p} \mathbf{A}_i \begin{pmatrix} x[t-i] \\ y[t-i] \end{pmatrix} + \begin{pmatrix} e_{x|y} \\ e_{y|x} \end{pmatrix} \qquad \mathrm{cov}\begin{pmatrix} e_{x|y} \\ e_{y|x} \end{pmatrix} = \begin{pmatrix} \sigma_{x|y}^2 & \sigma_{xy} \\ \sigma_{xy} & \sigma_{y|x}^2 \end{pmatrix} = \Sigma$$

How does it interact: signal model

Roebroeck et al., NI, 2012

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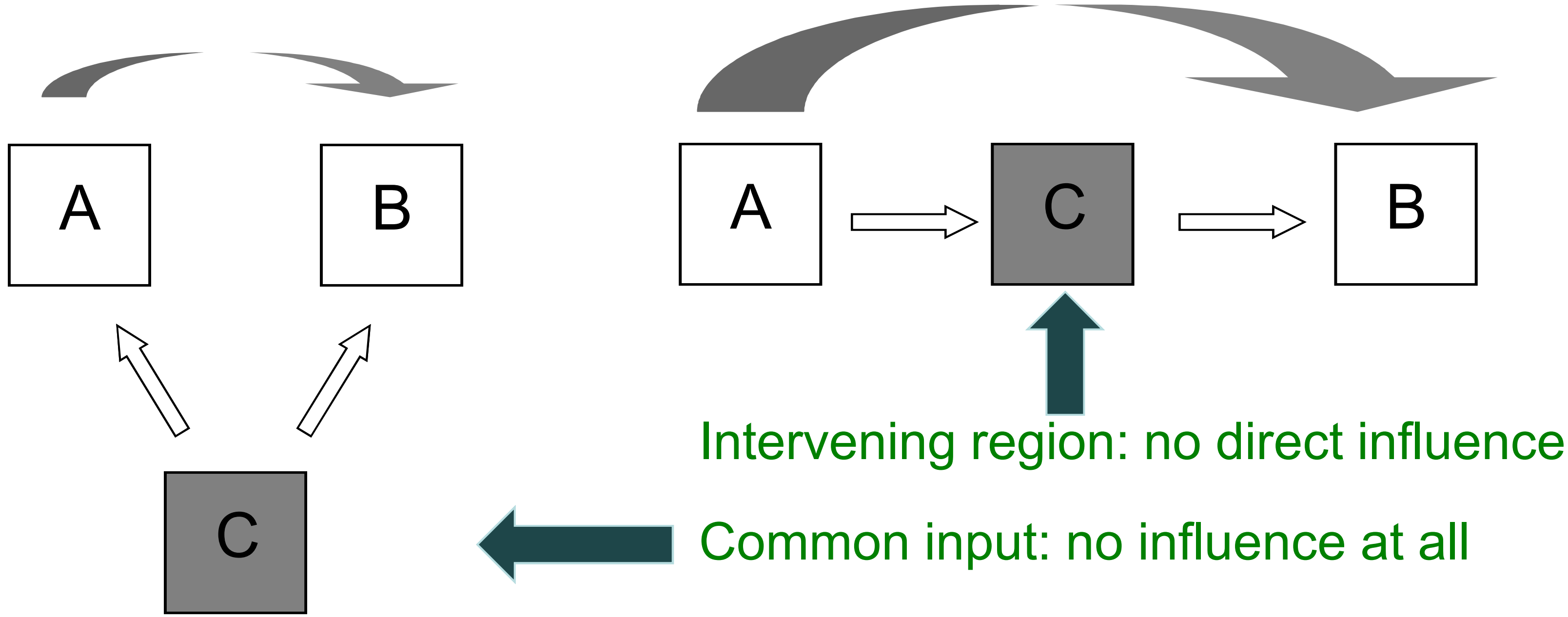
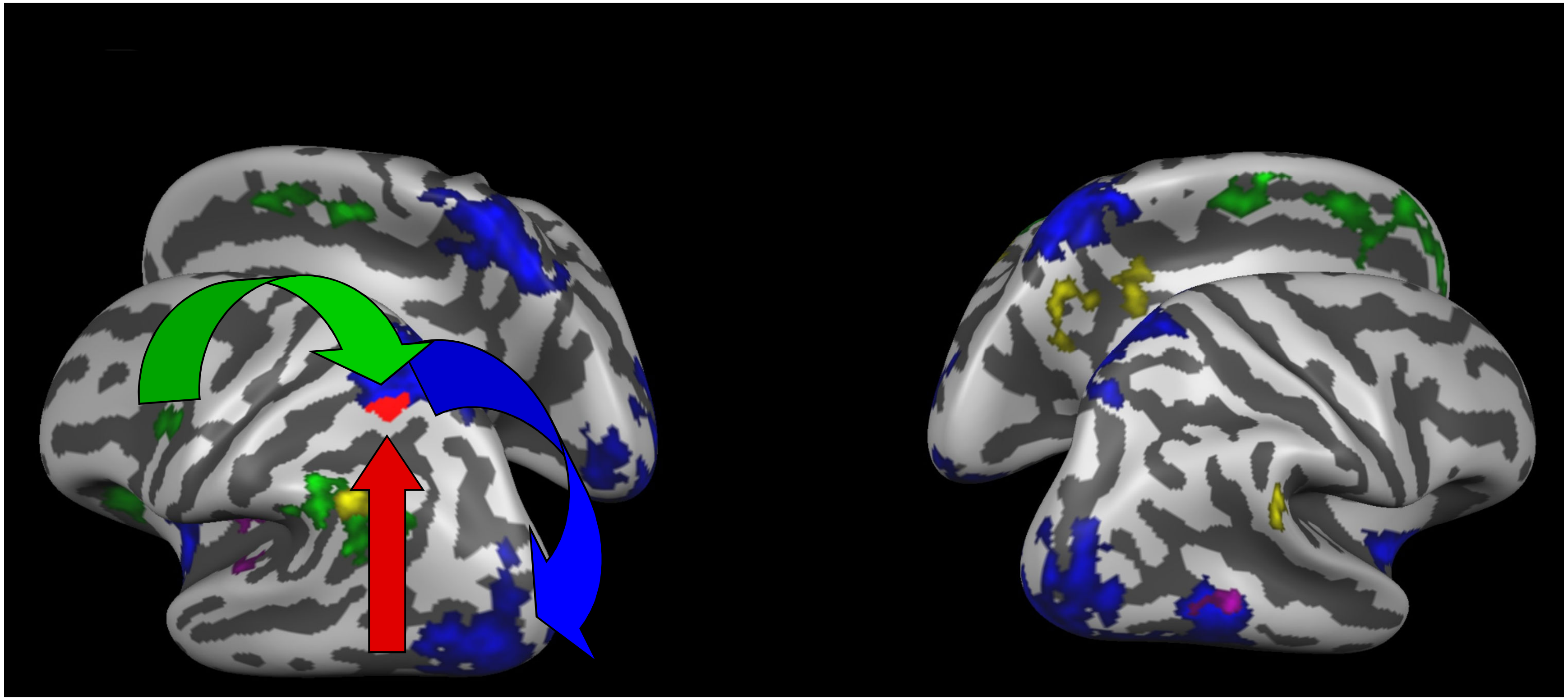
Missing region problem



- **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**

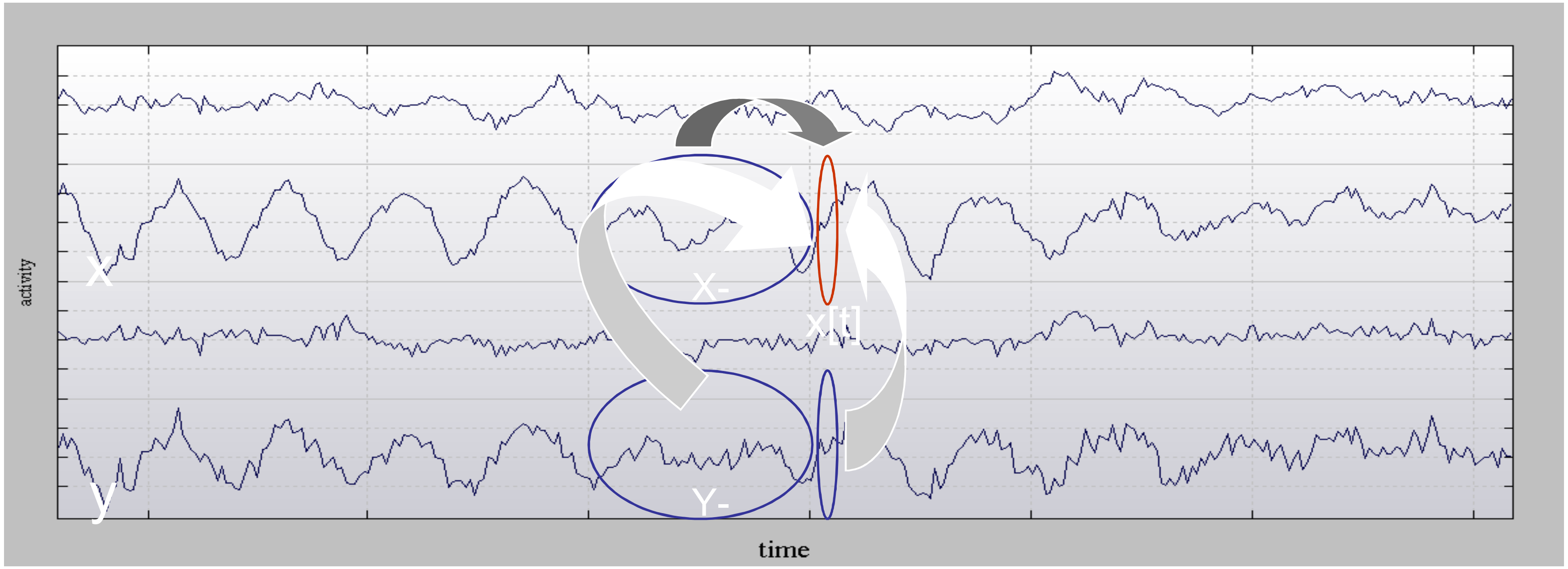
Granger causality mapping (GCM)



Random effects level GCMs

Roebroeck, NI 2005; Goebel, MRI 2004

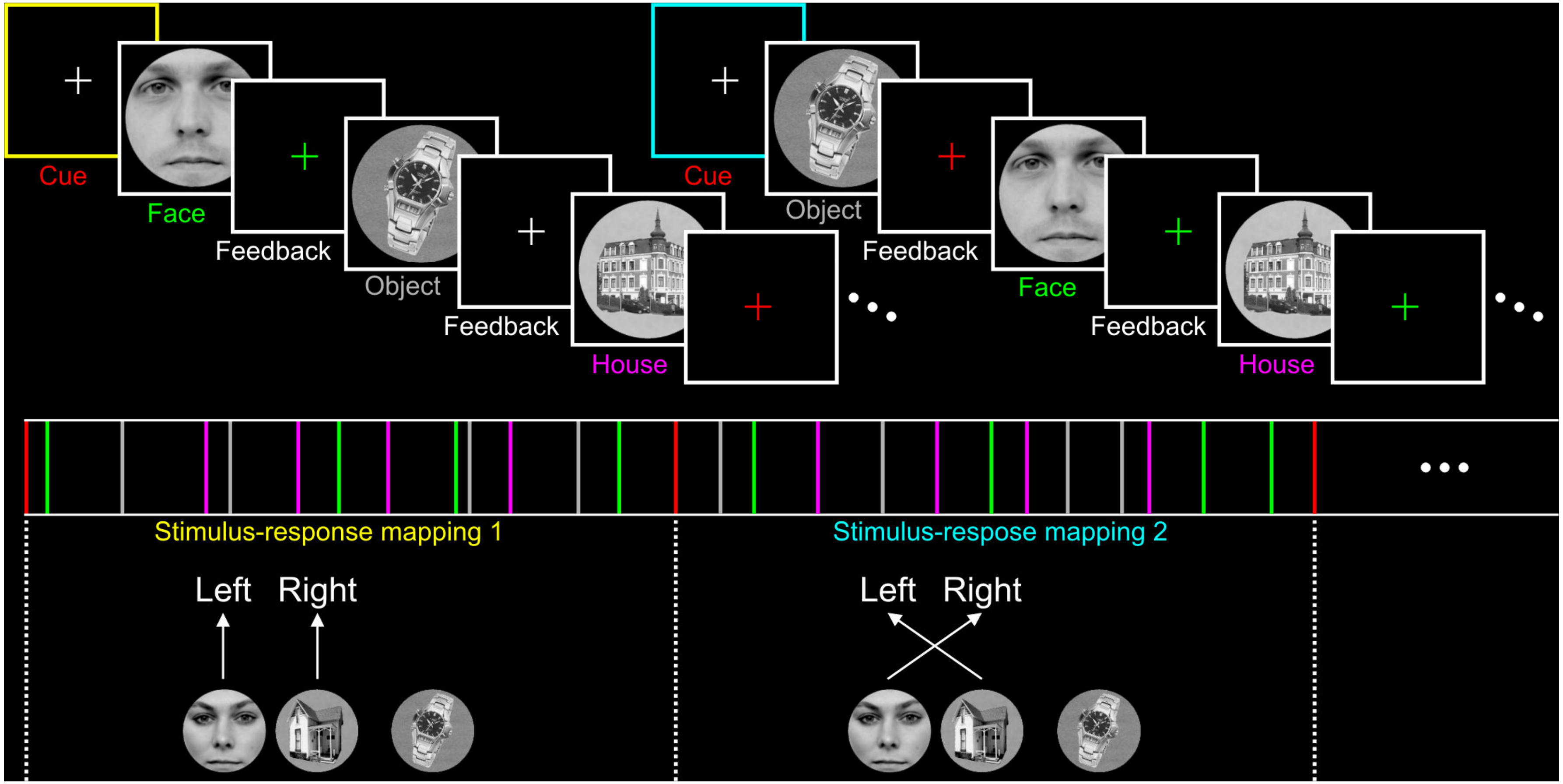
Granger causality (G-causality, GC)



• If we can predict x[t] better using {X-, Y-} than using {X-} alone, then we say that *y Granger causes x*

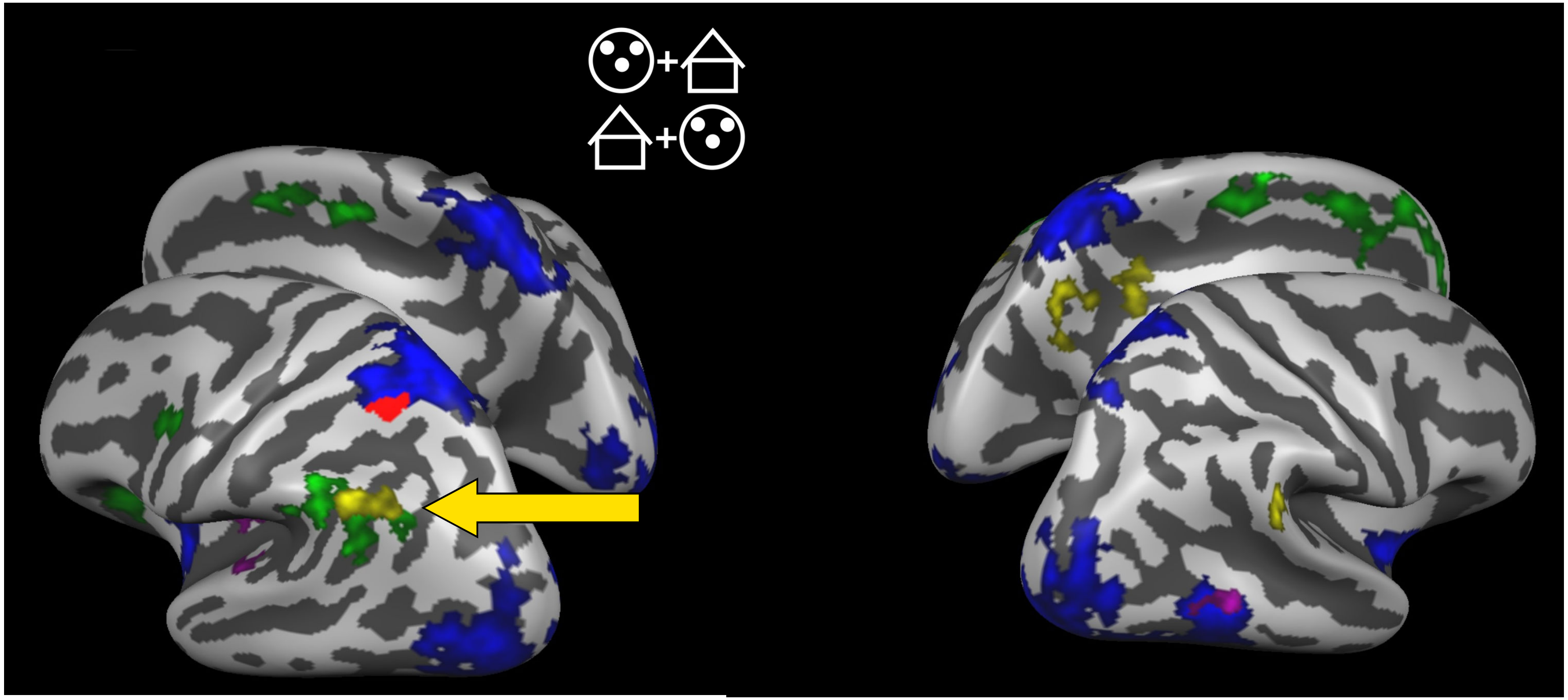
• If we can predict x[t] better using {X-, Y-, y[t]} than using {X-, Y-}, then we say that there is *instantaneous correlation between y and x*

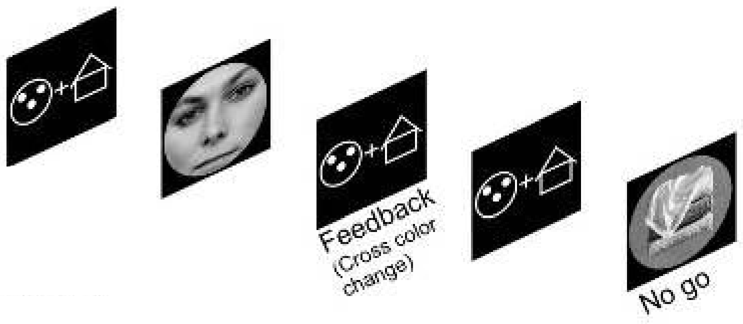
Application: task switching



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

Missing regions: Solutions

- **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**
  - Valdes-Sosa et al. (2004, 2005), Tang et al. (2012)

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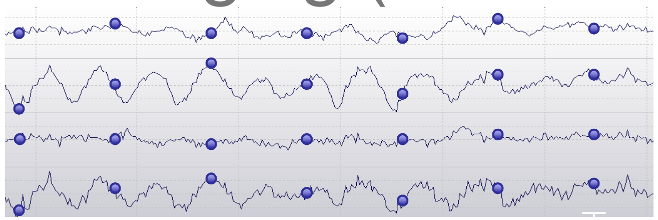
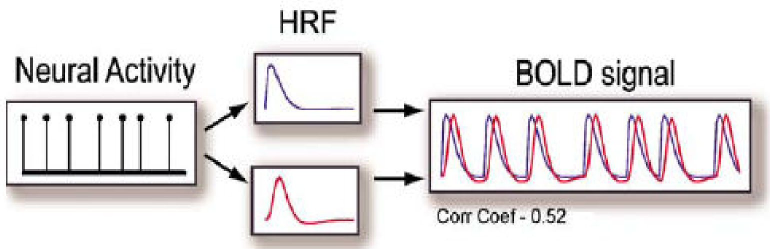
Missing time problem

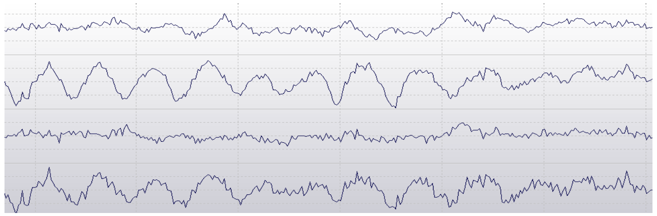
- **Part1**
  - fMRI: Slowly sampling fast-changing (and interacting) processes

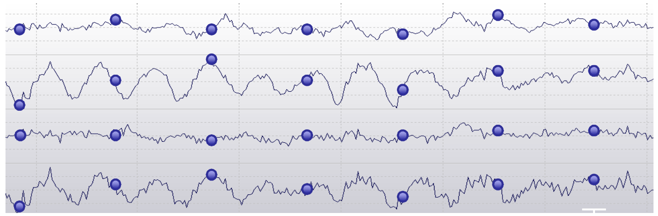


- **Part2a**
  - Hemodynamics: sampling low-pass filtered processes
- **Part2b**
  - *Variable* Hemodynamics in different brain areas



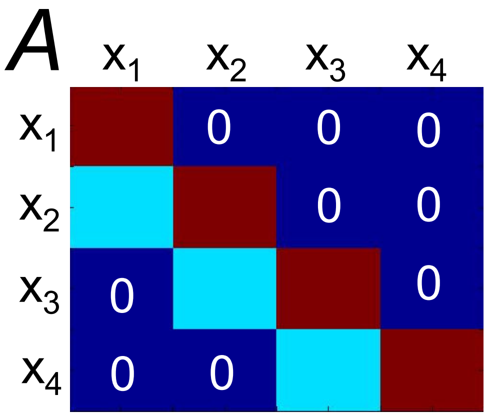
Part1: Slow sampling



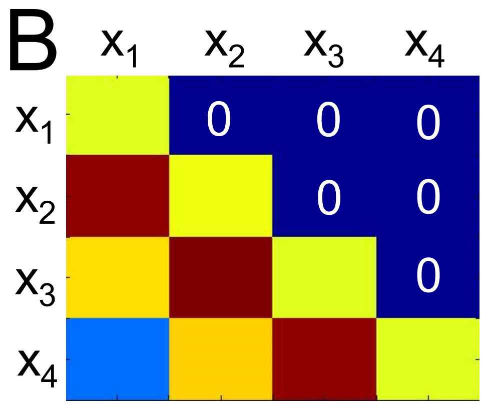


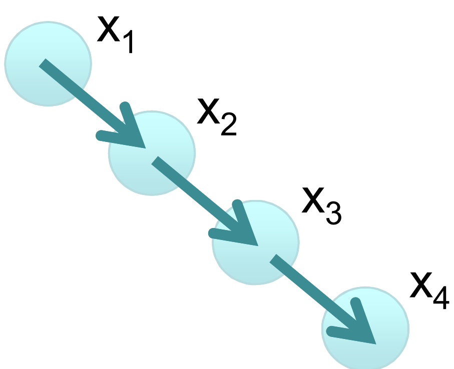
$dX = AXdt + d\omega$

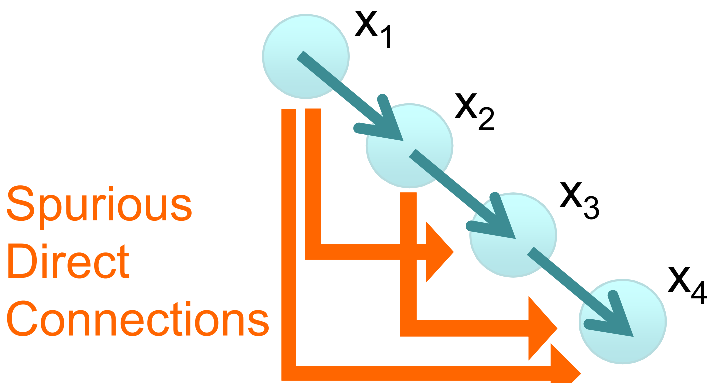
$X[k\Delta t] = BX[(k-1)\Delta t] + e$



$$B = \exp(\Delta t A) = \sum_{i=0}^{\infty} \frac{\Delta t^i}{i!} A^i$$



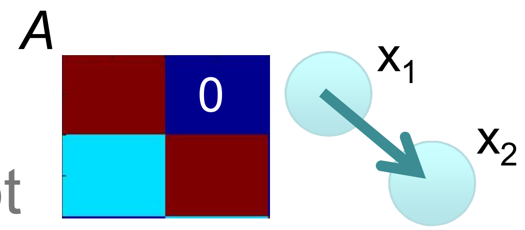


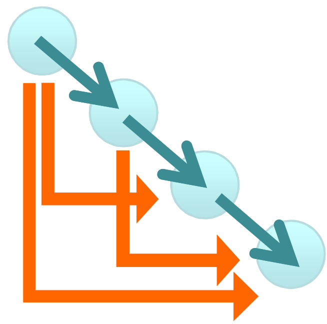


http://jmlr.csail.mit.edu/proceedings/papers/v12/roebroeck11/roebroeck11.pdf

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

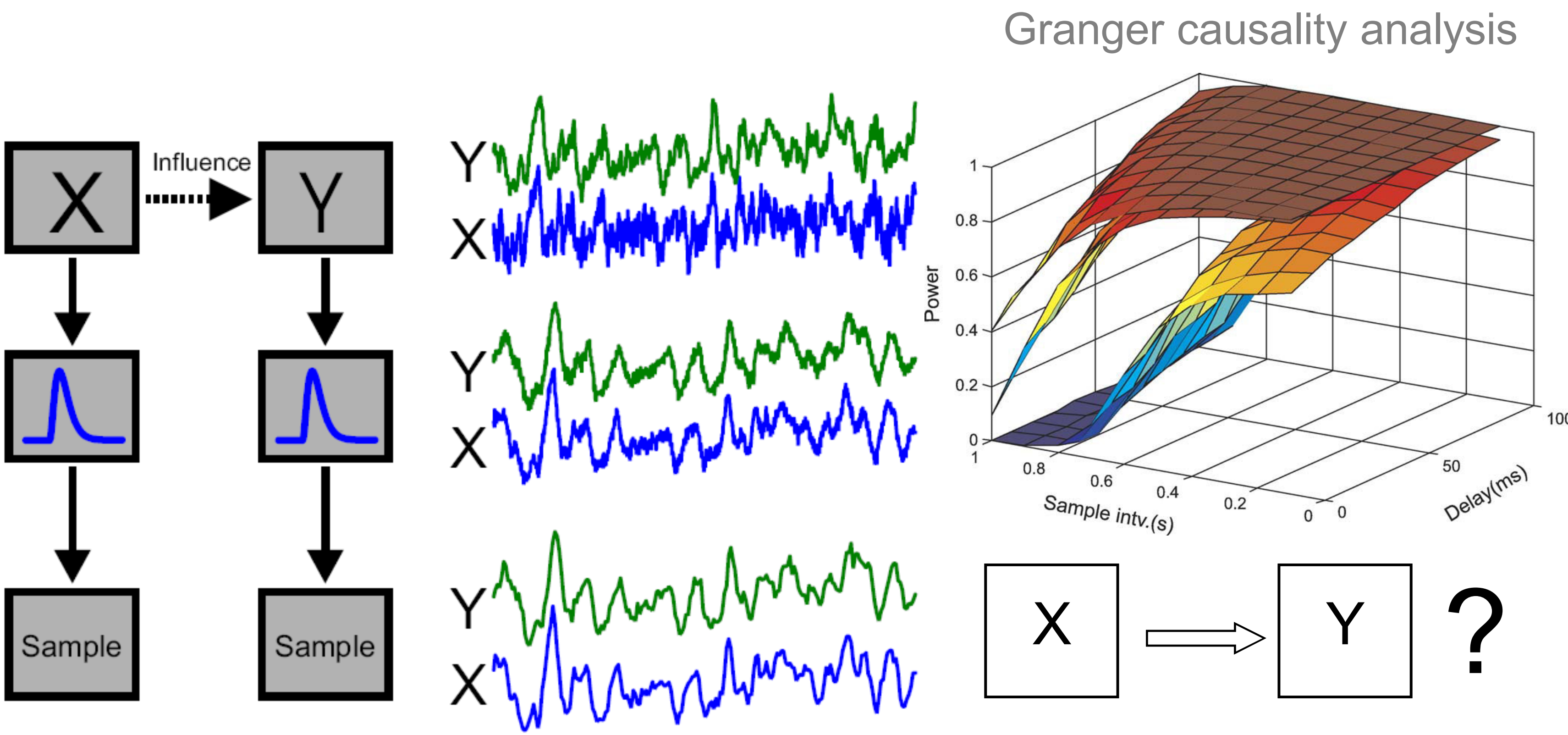




$$X[k\Delta t] = \exp(\Delta t A) X[(k-1)\Delta t] + e$$

http://jmlr.csail.mit.edu/proceedings/papers/v12/roebroeck11/roebroeck11.pdf

Sampling & Hemodynamics



Roebroeck, NI 2005

Part2: *Variable* Hemodynamics

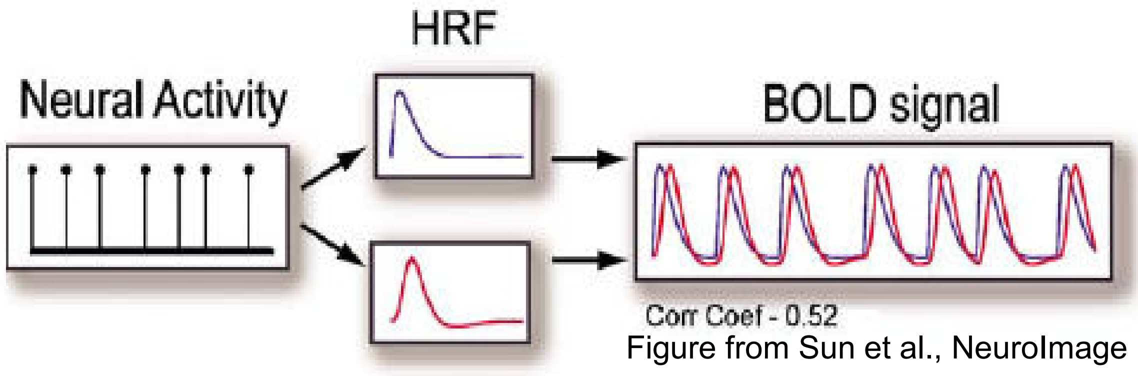


Figure from Sun et al., NeuroImage

- **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)

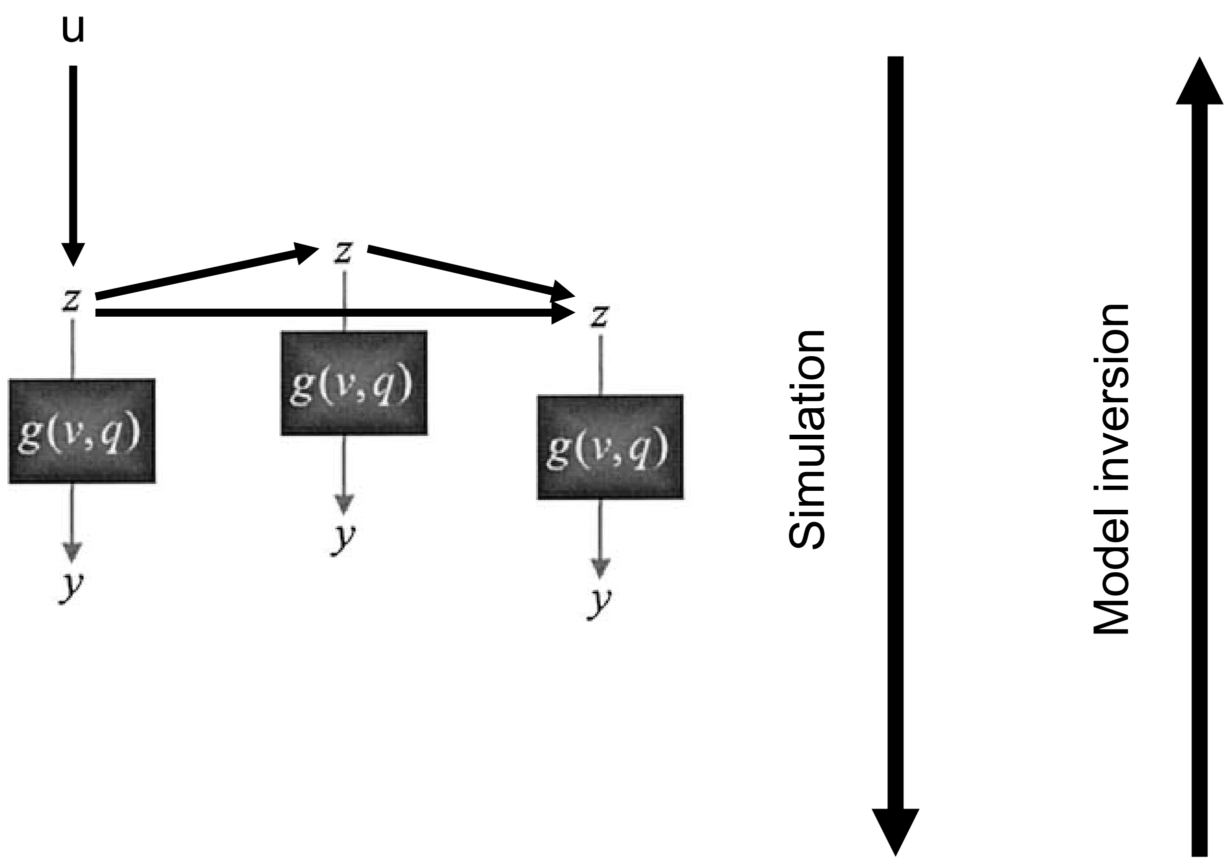
Input (u)
controlled

Neurodynamics
u -> z

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

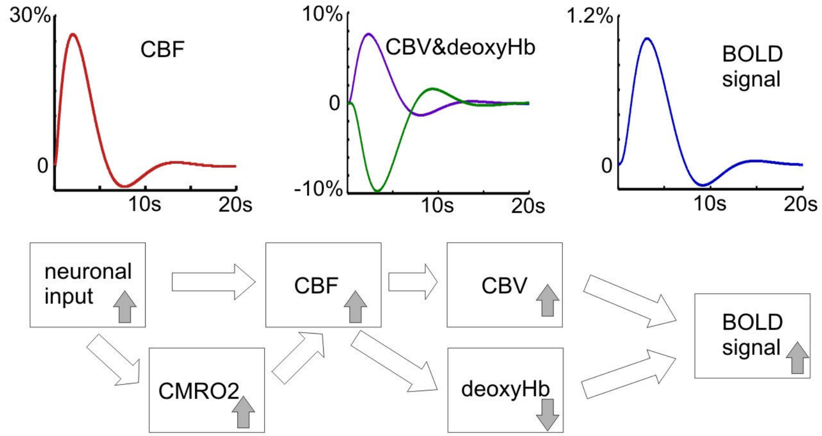
Hemodynamics
z -> y

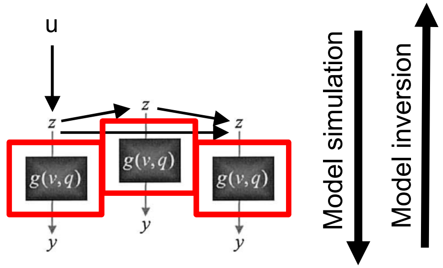
Output (y)
Observed + noise

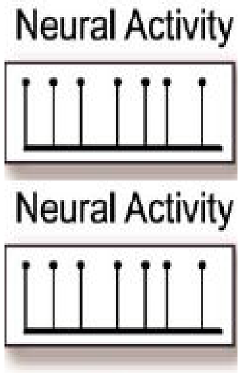


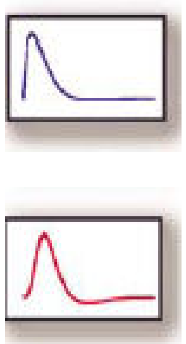
Friston et al., NI (2003)

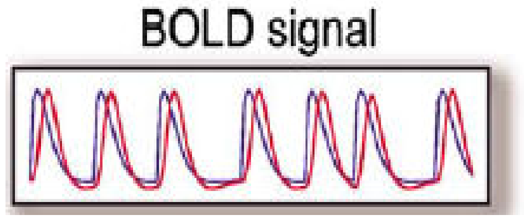
Hemodynamic deconvolution









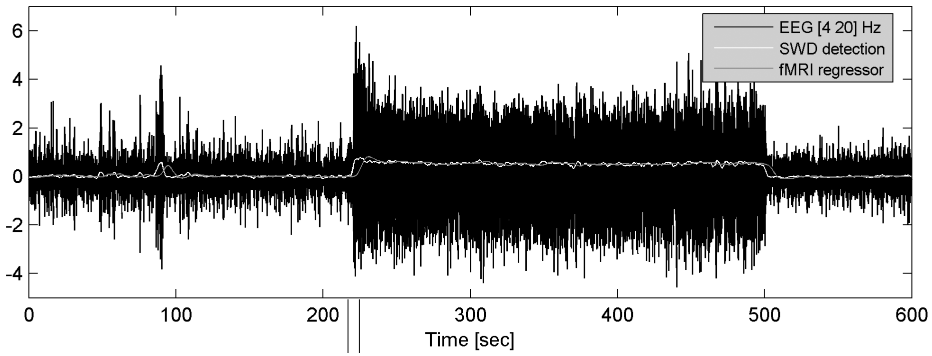


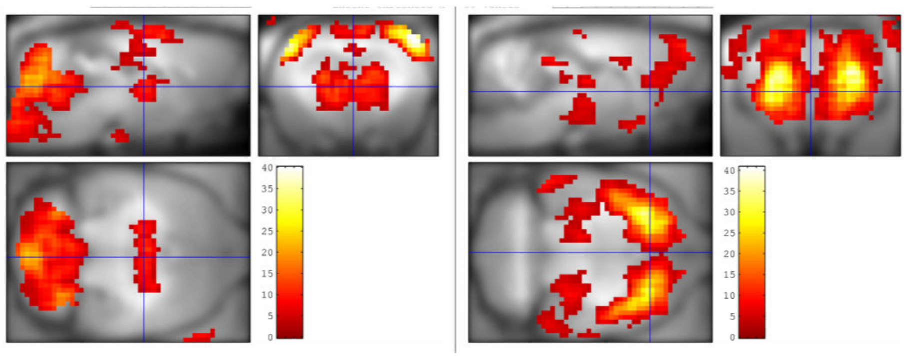
Deconvolution

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

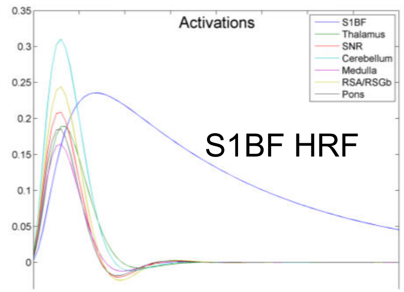




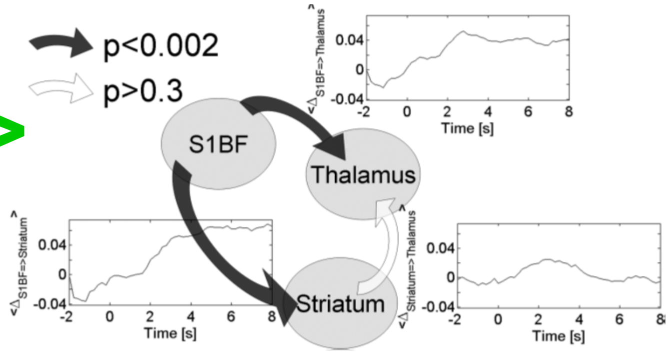
David et al., PLoS Biology, 2008

Application: epilepsy

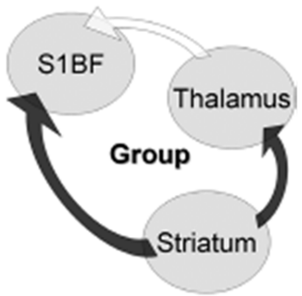
- **Rat study of epilepsy**
- **Simultaneous fMRI/EEG**



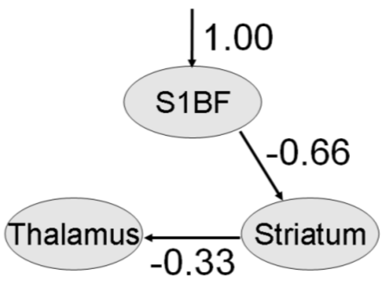
- **Gold standard model =>**



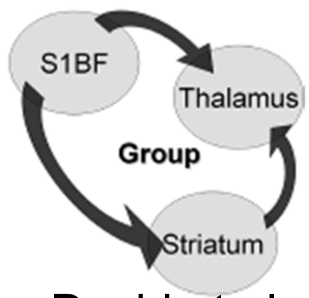
Granger without deconvolution



DCM



Granger using deconvolution



David et al., PLoS Biology, 2008

Missing time: solutions

- **Part1**
  - Bi-variate discrete-time modeling (GCM)
  - Parametrizing the model for missing time (continuous-time models)
- **Part2**
  - Deconvolution by inverting a generative model of hemodynamics (DCM)
  - Experimental modulation of interactions
  - Independent data (e.g. EEG/MEG)

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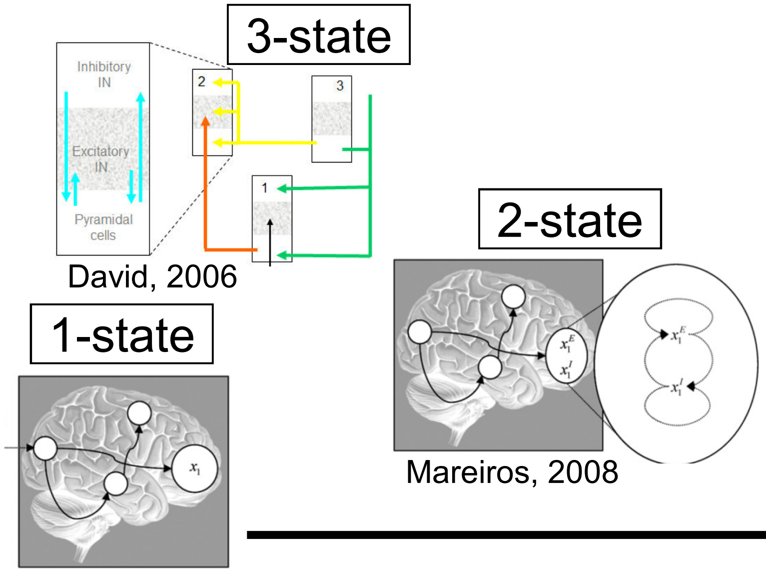
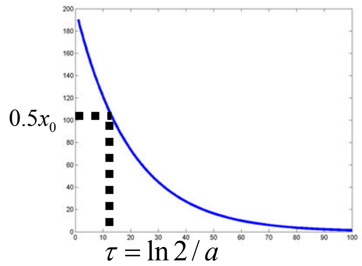
Missing model problem

- **We do not have an appropriate generative model for many interacting procesess**
  - Or, when we do, we can not invert it: it is not identifiable

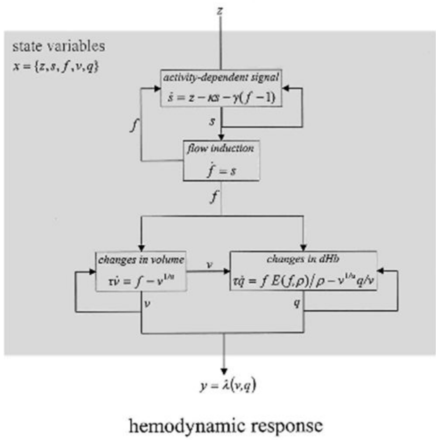
Neurodynamics model



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



Model inversion



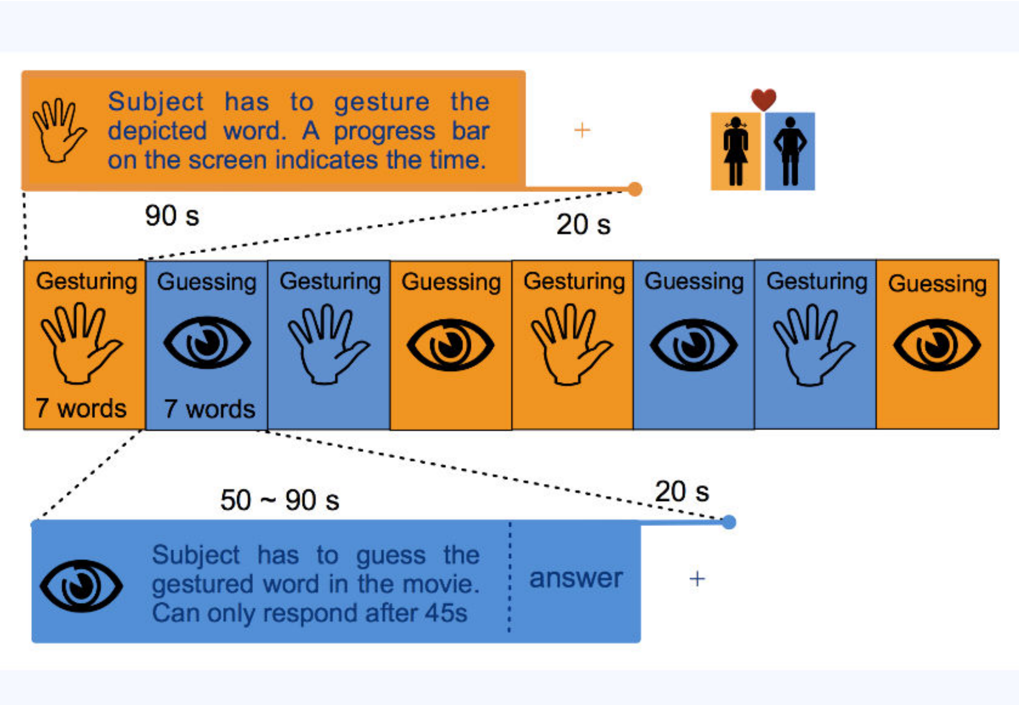
- **Hemodynamics model**
  - Observation model for fMRI
  - Other ones for EEG/MEG

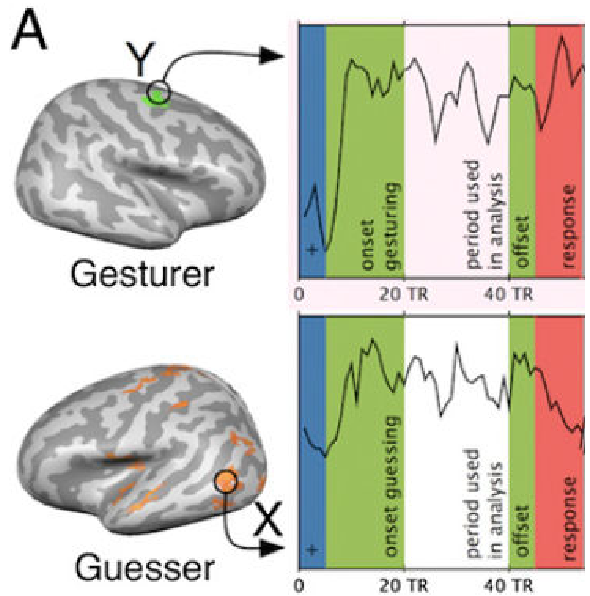
Application: Social communication

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

Marleen B. Schippers[a], Alard Roebroeck[b], Remco Renken[a], Luca Nanetti[a], and Christian Keysers[a,c,1]

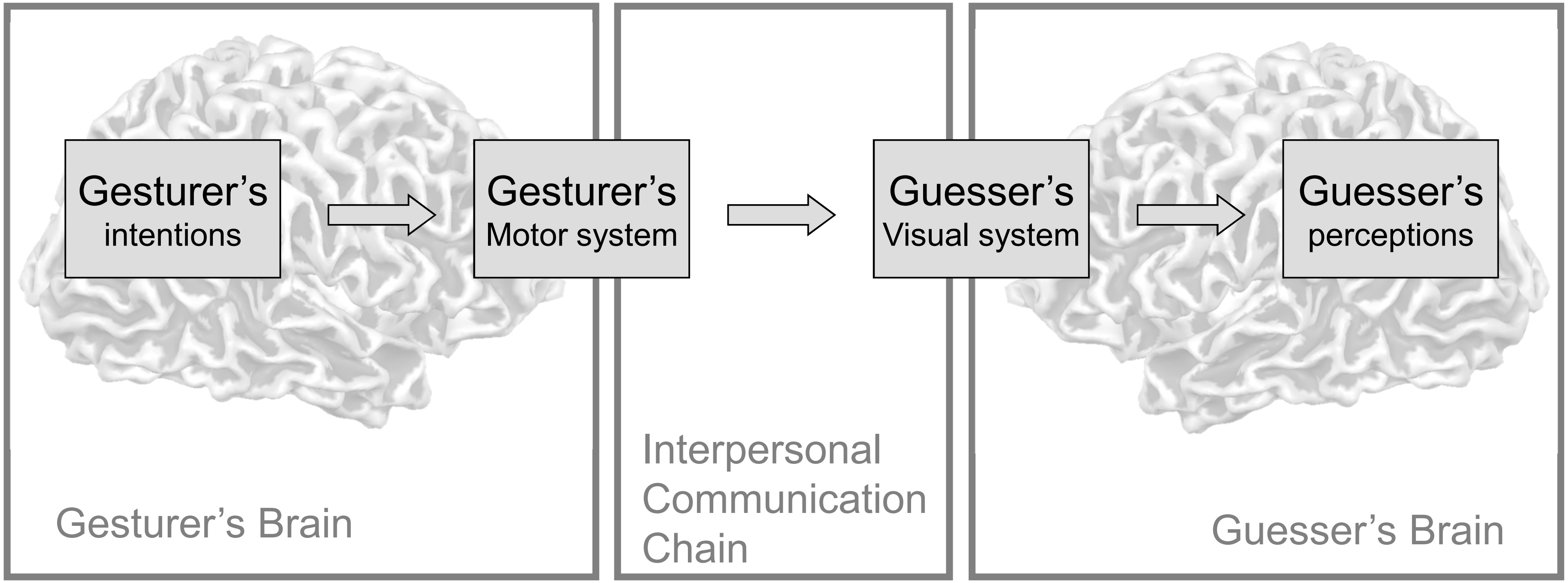
[a]Social Brain Laboratory, Department of Neuroscience, University Medical Center Groningen, University of Groningen, 9713 AW, Groningen, The Netherlands; [b]Department of Cognitive Neuroscience, Faculty of Psychology, University of Maastricht, 6229 ER, Maastricht, The Netherlands; and [c]Social Brain Laboratory, Netherlands Institute for Neurosciences, Royal Netherlands Academy of Arts and Sciences (KNAW), 1105 BA, Amsterdam, The Netherlands





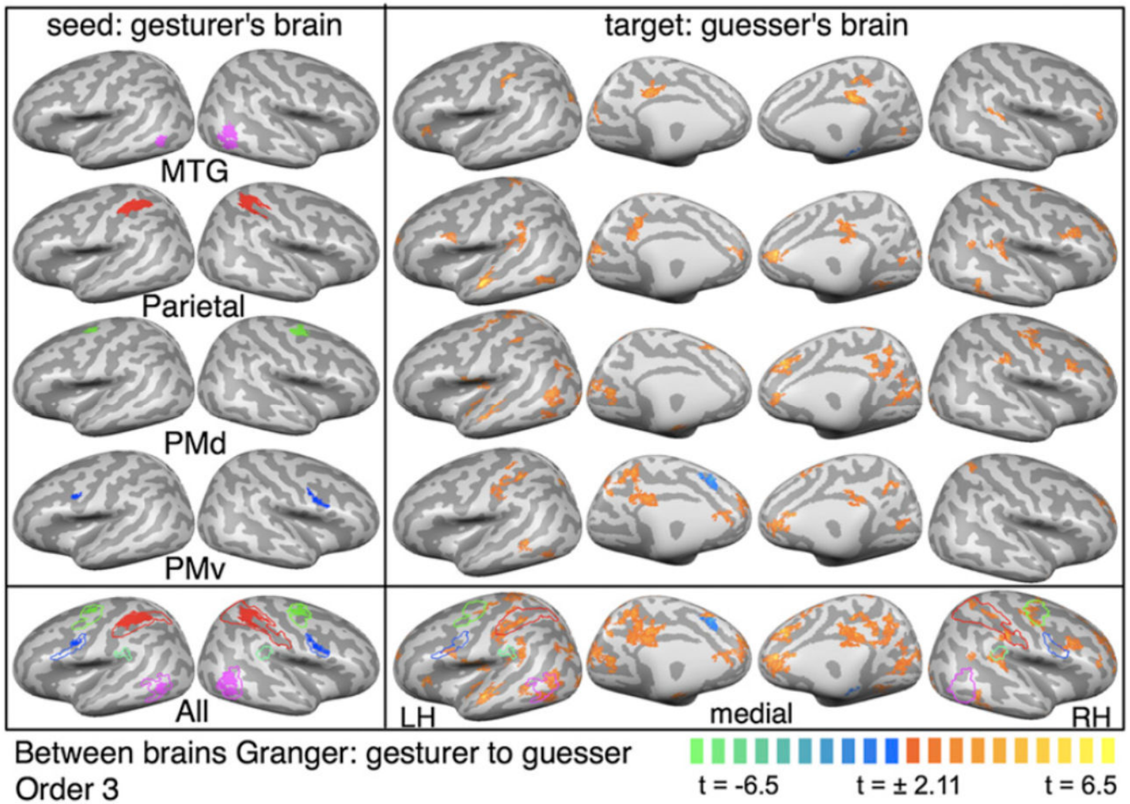
Schippers et al, PNAS, 2010

Missing model problem



- **Hard to specify a generative model for the full causal chain between brains**
- **Less-parametric G-causality can still be applied**

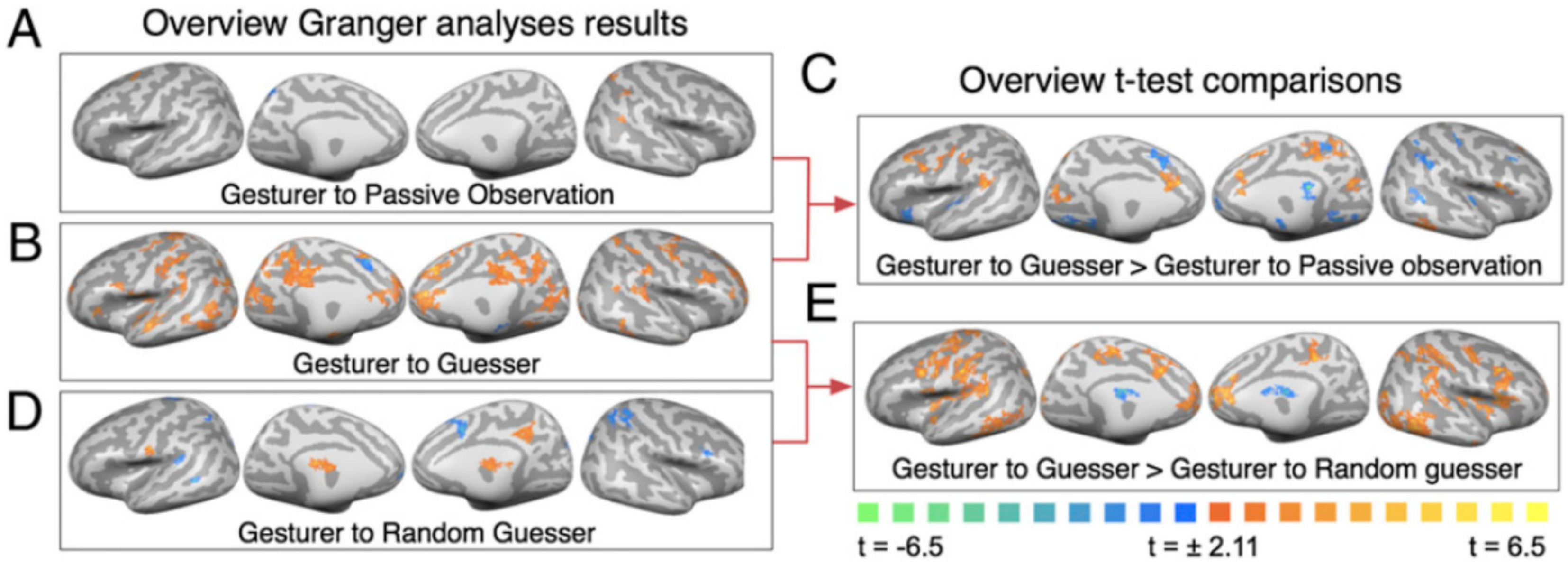
Application: Social communication



- **Mapping influence between brains**

Schippers et al, PNAS, 2010

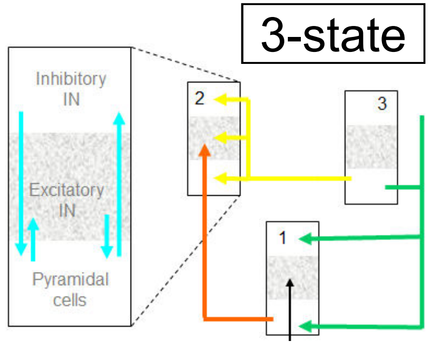
Application: Social communication



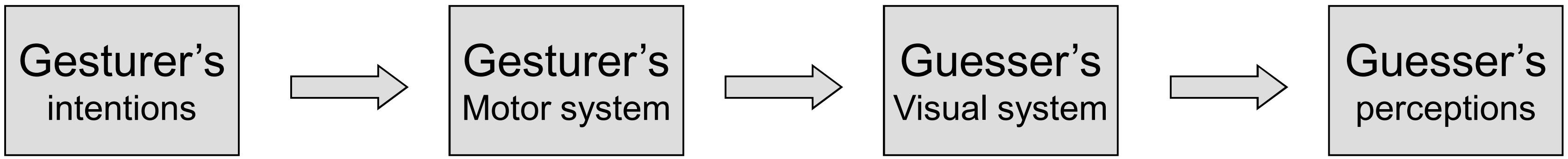
- **Mapping influence between brains**

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 ✓

Thanks for collaboration & discussion

- **Maastricht**
  - Rainer Goebel
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  - Karl Friston
  - Jean Daunizeau
- **Groningen / Amsterdam**
  - Christian Keysers
  - Marleen Schippers
- **Brighton**
  - Anil Seth
- **Grenoble**
  - Olivier David
- **Oxford**
  - Steve Smith