Connectivity Analysis in AFNI

File: Connectivity.pdf

Gang Chen

SSCC/NIMH/NIH/HHS

Why connectivity?

- Understanding communications in brain networks
  - More interesting than regional activations
  - May indicate some abnormal situations (ASD, schizophrenia)
  - Connectome!!!
- Many connectivity methods
  - People try to squeeze the data as hard as possible
  - Unlike activation detection, connectivity analysis methods are usually controversial
    - Two aspects: poor data and poor models
    - Publication bias
  - Only a few introduced here
  - Focus more on understanding methods than recommending

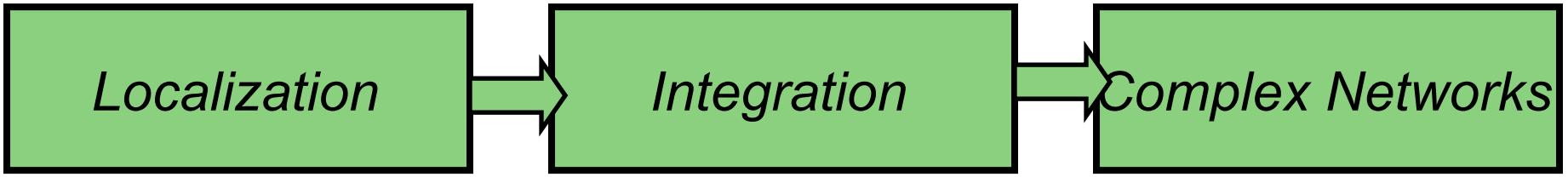
Structure of this lecture

- Two categories of connectivity analysis
  - Seed-based (vs. functional connectivity)
  - Network-based (vs. effective connectivity)
- Seed-based analysis
  - Simple correlation
  - Context-dependent correlation (PPI)
  - Seed-based bivariate autoregression (Granger)
- Network-based analysis
  - Structural equation modeling (SEM)
  - Vector autoregression (VAR) (aka Granger causality)
  - Structural vector autogression (SVAR)

Overview: Connectivity analysis

- Typical FMRI data analysis
  - Massively univariate (voxel-wise) regression: $y = X\beta + \varepsilon$
  - Relatively robust and reliable
  - May infer regions involved in a task/state, but can't say much about the details of a network
- Network analysis
  - Information
    - Seed region, some or all regions in a network
    - Neuroimaging data (FMRI, MEG, EEG): regional time series
  - Inferring interregional communications
    - Inverse problem: infer neural processes from BOLD signal
    - Based on response similarity (and sequence)
    - Difficult and usually not so reliable

FMRI Methods and Measures



- **Methods:** Data driven
  - Subject: voxel-wise regression
  - Group : *t*, GLM, ANOVA
- **Measures**:
  - Signal change,
  - Activation clusters

Methods: *(Data driven/ Hypotheses driven)*

Seed Based

Functional connectivity: cross-correlation
PPI: task-related connectivity
VAR: Granger causality

ROIs/Networks

(Hypotheses driven)
SEM, VAR (Granger Causality), SVAR, DCM

Measures:

Connectivity strength
Connectivity structural

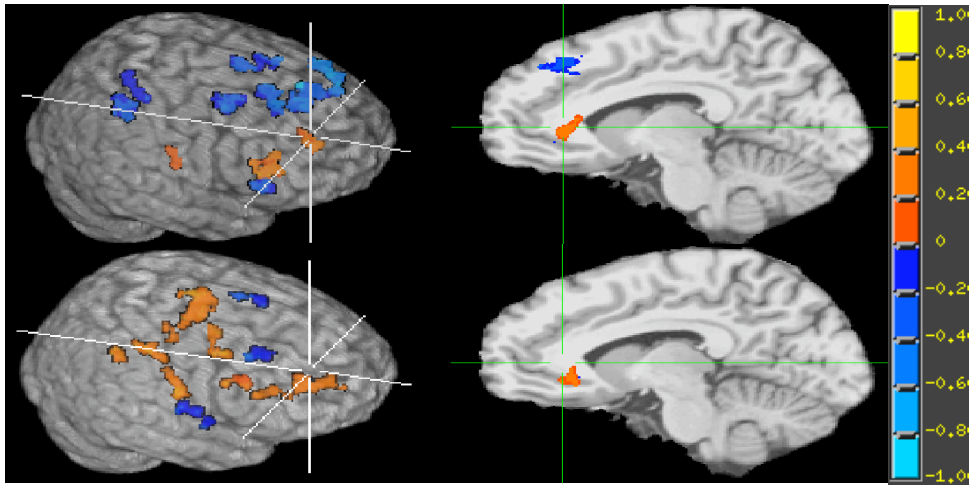
- **Methods**: (Hypotheses driven)
  - Graph theory
- **Measures:**
  - Node degree, degree distribution and assortativity
  - Clustering coefficient and motifs
  - Path length and efficiency
  - Connection or cost
  - Hubs, centrality and robustness
  - Modularity

Overview: Connectivity analysis

- Two types of network analysis
  - Not sure about ALL the regions involved
    - Seed-based: use a seed region to search for other ROIs
  - If all regions in a network known
    - Prior knowledge
    - Network-based: A network with all relevant regions known
    - Everything is relative: No network is fully self-contained
- Currently most methods are crude
  - Models: underlying assumptions not met
  - Data quality: temporal resolution, low signal-to-noise ratio, poor understanding of FMRI signal

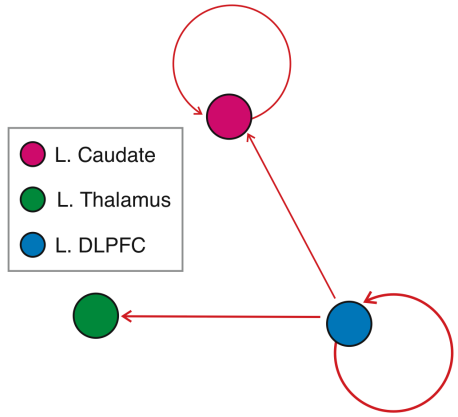
Seed-based analysis: ROI search

- Regions involved in a network are unknown
  - Bi-regional (seed vs. whole brain) (**`3d*`**): brain volume as input
  - Mainly for ROI search
  - Popular name: functional connectivity
  - Basic, coarse, exploratory with weak assumptions
  - Methodologies: simple correlation, PPI, bivariate autoregression
  - Weak interpretation: may or may not indicate directionality/causality



Network-based analysis

- Regions in a network are known
  - Multi-regional (**`1d*`**): ROI data as input
  - Model strategy
    - Model validation + connectivity strength testing
    - Data driven
  - Popular name: effective or structural connectivity
  - Strong assumptions: specific, but with high risk
  - Methodologies: SEM, VAR, SVAR, DCM
  - Directionality, causality (?)
- Graph Theory: neither



Common Preparatory Steps

- Warp brain to standard space
  - **`Uber_subject.py, uber_align_test.py, adwarp, @auto-tlrc, align_epi_anat.py`**
- Create ROI
  - Peak voxel or sphere around a peak voxel: **`3dUndump –master … –srad …`**
  - Activation cluster-based (biased unless from independent data?)
  - Anatomical database or manual drawing
- Extract ROI time series
  - Average over ROI: **`3dmaskave –quiet –mask`**, or **`3dROIstats -quiet –mask`**
  - Principal component among voxels within ROI: **`3dmaskdump`**, then **`1dsvd`**
  - Seed voxel with peak activation: **`3dmaskdump -noijk -dbox`**
- Remove effects of no interest
  - **`3dSynthesize`** (effects of no interest) and **`3dcalc`** (effects of interest)
  - **`3dDetrend –polort`** (trend removal)
  - **`RETROICORR/RetroTS.m`** (physiological confounds)
  - **`3dBandpass`** (bandpass filtering)
  - **`@ANATICOR`** (resting state data)

Simple Correlation Analysis

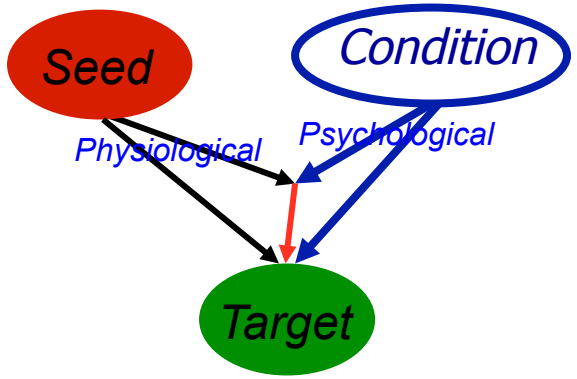
- Resting state data analysis: seed vs. rest of brain
- ROI search based on response similarity
  - Looking for regions with similar signal to seed: spontaneous fluctuations
- **Correlation** at individual subject level
  - Usually have to control for effects of no interest: drift, head motion, physiological variables, censored time points, tasks of no interest, *etc.*
- Applying to experiment types
  - Straightforward for resting state experiment: default mode network (DMN)
  - With tasks: correlation under a specific condition or resting state?
- Program: **`3dDeconvolve`** or **`afni_proc.py`**
  - Original regression: $y = X \beta + \varepsilon(t)$
  - New model: $y = [X\ S(t)]\ \beta + \varepsilon(t)$
  - r: **linear** correlation; slope for standardized Y and X
  - β: slope, amount of **linear** change in Y when X increases by 1 unit
  - **Example 9** in **`afni_proc.py -help`**

Simple Correlation Analysis

- Group analysis
  - Run Fisher-transformation of *r* to *Z*-score and *t*-test: **`3dttest++`**
- Interactive tools in AFNI and SUMA: **`uber_subj.py`**, **`InstaCor`**, **`GroupInstaCor`**
- **Report effect size: convert z-score back to r**
- **Caveats**: don't over-interpret
  - Correlation: crude measurement at the presence of significant noise
    - Only linearity relationship
  - Correlation does not necessarily mean causation: no proof for anatomical connectivity (*e.g.*, more than two regions in a network)
  - No golden standard procedure and so many versions in analysis: seed region selection, confounds, head motions, **preprocessing steps**, …
  - Measurement error problem: underestimation, attenuated bias

Context-Dependent Correlation

- Popular name: Psycho-Physiological Interaction (PPI)
- Regression analysis at individual level
  - Brain response varies in magnitude across multiple trials (repetitions)
    - Habituations, random fluctuations, …
  - Regresson only accounts for the AVERAGE response across trials
    - Trial-to-trial fluctuations treated as noise (residuals)
    - Do the fluctuations provide some information about the brain network?
- Image three components
  - Main effect of condition (or contrast): $C(t)$
  - Main effect of seed on target: $S(t)$
  - Interaction between the two effects: $I(C(t), S(t))$
    - **Implicit directionality assumption** here!



Context-Dependent Correlation

- Model for each subject
  - Original regression: $y(t) = [C(t)\ \text{Others}]W + W(t)$
  - New model: $y(t) = [C(t)\ S(t)\ I(C(t), S(t))\ \text{Others}]W + W(t)$
    - $C(t)$ and $S(t)$: like main effects in a two-way ANOVA
    - $I(C(t), S(t))$: interaction (regressor of interest)
  - 2 more regressors than original model: $S(t)$, $I(C(t), S(t))$
  - Should effects of no interest be included in the model?
    - Others NOT included in SPM
  - What we care for: β for $I(C(t), S(t))$
  - $I(C(t), S(t))$ accounts for the variability in addition to $C(t)$ and $S(t)$
    - Symmetrical modulation

Context-Dependent Correlation

- How to formulate interaction $I(C(t), S(t))$?
  - Interaction at neuronal, not BOLD (an indirect measure), level
  - **Deconvolution**: derive neuronal response from BOLD response
    - Assuming standard (fixed) impulse response
    - **`3dTfitter`**: Impulse ⊗ Neural events = BOLD response; Gamma ⊗ $NE(t) = S(t)$
    - 3dTfitter –RHS … -FALTUNG … 012 -2 –l2lasso -6
    - Deconvolution matters more for event-related than block experiments
  - Interaction at neuronal level – **`3dcalc`**: $NE(t) \times C(t) = NI(t)$
    - **`timing_tool.py`** converts stimulus timing into 0s and 1s
    - 1s and -1s for contrast, and 1s and 0s for condition vs. baseline

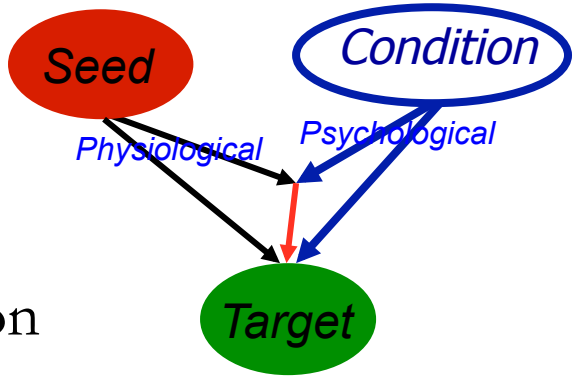
Context-Dependent Correlation

- How to formulate interaction $I(C(t), S(t))$?
  - Interaction at BOLD level - convolution – **`waver`**: Gamma ⊗ $NI(t) = I(C(t), S(t))$
  - If stimuli presented in a higher resolution than TR – not TR-locked
    - Up-sample first: use **`1dUpsample n`** to interpolate $S(t)$ n ⊗ finer before deconvolution **`3dTffiter`**
    - Down-sample interaction $I(C(t), S(t))$ back to original TR: **`1dcat`** with selector '{0..$(n)}'
  - Regression: $y(t) = [C(t)\ S(t)\ I(C(t), S(t))$ Others$]$ ⊗ $+$ ⊗ $(t) +$ **`3dDeconvolve`**
  - Website: http://afni.nimh.nih.gov/sscc/gangc/CD-CorrAna.html
- Group analysis: Take β $(+t)$: **`3dttest`** (**`3dMEMA`**)

Generalized PPI

- Conventional PPI
  - One interaction regressor + seed regressor
  - Student's *t*-test at the group level
- gPPI at the individual subject level
  - For each condition, create one interaction regressor
  - Difference: no more contrast
  - # regressors of interest in original individual subject analysis: *N*
  - *N* interaction regressors in gPPI + seed regressor
- gPPI at the Group analysis
  - AN(C)OVA

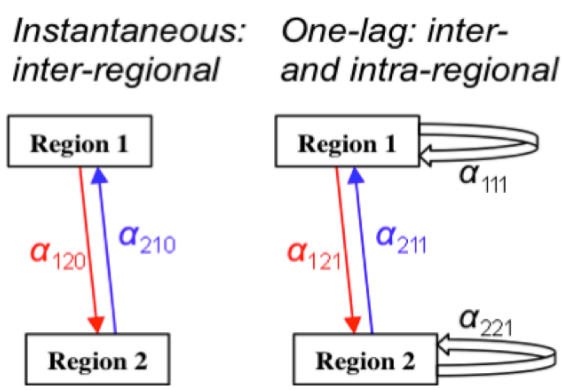
PPI Caveats

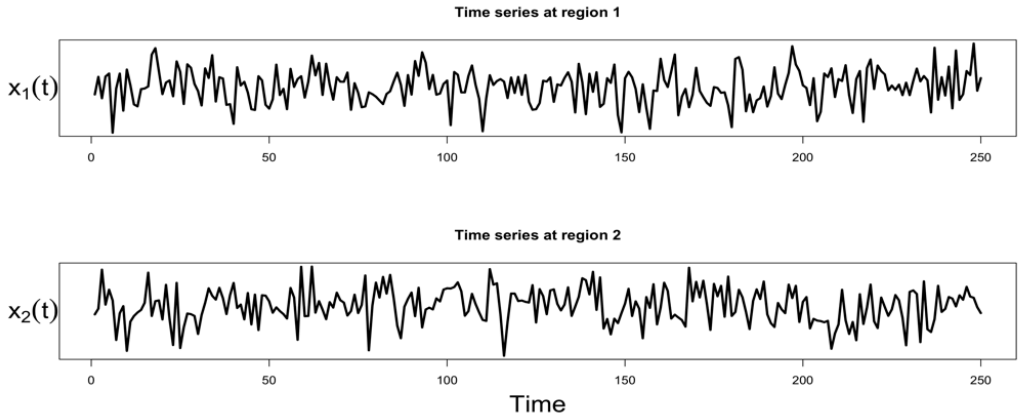


- No proof for anatomical connectivity
  - Correlation does not necessarily mean causation
  - Only modeling interactions between two regions
- Big noise: measurement error in regression
  - Poor understanding of BOLD
  - Neural response hard to decode: Deconvolution is not so reliable, with assumption of a fixed-shape HRF, same across trials/conditions/regions/subjects/groups
  - Noisy seed time series: attenuation or regression dilution
- Directionality presumption
- No information about interaction between condition and target on seed
- No differentiation whether modulation is
  - Condition on neuronal connectivity from seed to target, or
  - Neural connectivity from seed to target on condition effect

Network-Based Modeling: a toy example

- A network with two regions: both contemporaneous and delayed





  - Within-region effects: lagged correlation
  - Cross-regions effects: both instantaneous and lagged

$$x_1(t) = c_1 + \alpha_{120}x_2(t) + \alpha_{111}x_1(t-1) + \alpha_{121}x_2(t-1) + \varepsilon_1(t)$$

$$x_2(t) = c_2 + \alpha_{210}x_1(t) + \alpha_{211}x_1(t-1) + \alpha_{221}x_2(t-1) + \varepsilon_2(t)$$

- If we have time series data from the two regions
  - Can we evaluate the above model?
  - Estimate and make inferences about the connections (α values)?

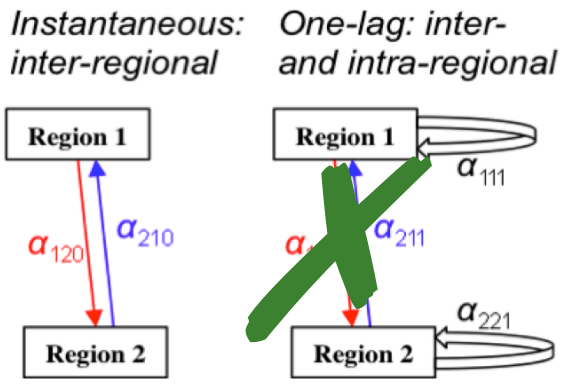
Structure Equation Modeling (SEM): a toy example

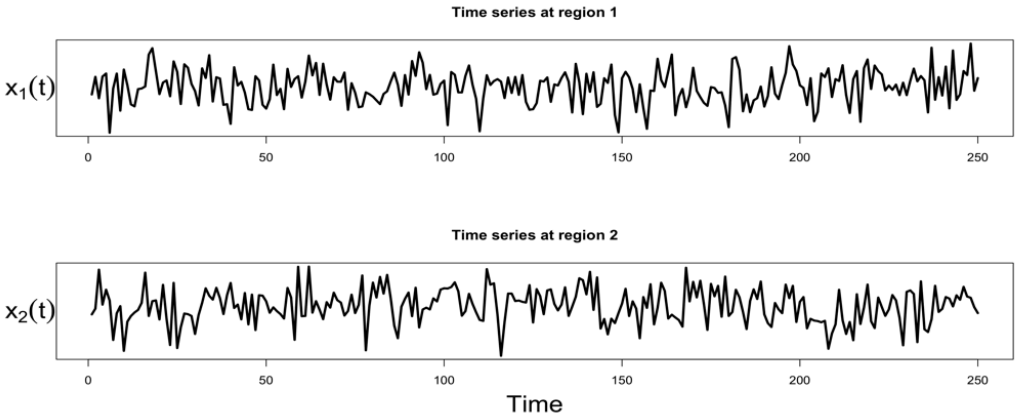
- A network with two regions: no delayed effects
  - No within-region effects: no lagged effects – no temporal correlation!
  - Cross-region effects: instantaneous correlation only; no lagged effects

$$x_1(t) = c_1 + \alpha_{120} x_2(t) + \varepsilon_1(t)$$

$$x_2(t) = c_2 + \alpha_{210} x_1(t) + \varepsilon_2(t)$$

- If we have time series data from the two regions
  - Can we evaluate the above model?
  - Estimate and make inferences about the α values?





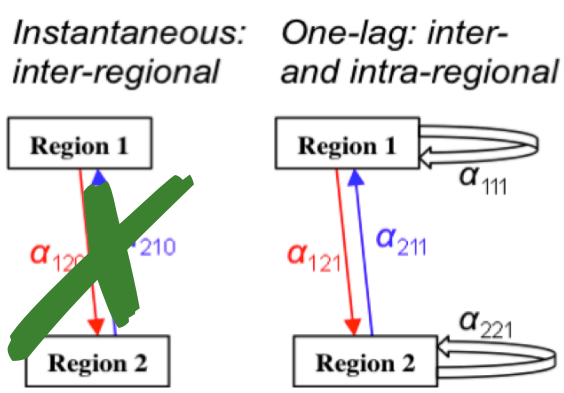
Vector Autoregressive (VAR) Modeling: a toy example

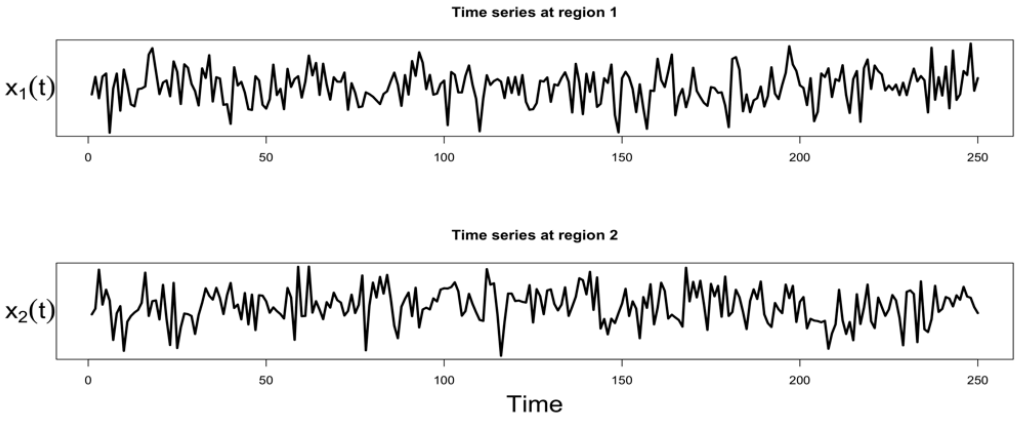
- A network with two regions: no contemporaneous effects
  - Within-region effects: lagged effects
  - Cross-regions effects: lagged effects only; no instantaneous effects

$$x_1(t) = c_1 + \alpha_{111}x_1(t-1) + \alpha_{121}x_2(t-1) + \varepsilon_1(t)$$

$$x_2(t) = c_2 + \alpha_{211}x_1(t-1) + \alpha_{221}x_2(t-1) + \varepsilon_2(t)$$

- If we have time series data from the two regions
  - Can we evaluate the above model?
  - Estimate and make inferences about the α values?



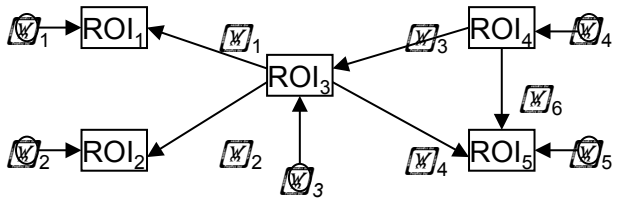


Structure Equation Modeling (SEM) or Path Analysis

- General model for a network of *n* regions $X^*(t) = A_0 X^*(t) + \varepsilon(t)$
  - Only consider instantaneous effects; assumes no delayed effects
  - Data centered around mean; if possible, remove all confounding effects
  - Parameters in A_0 code for cross-region path strength; zero diagonals
  - $\varepsilon(t) \sim N(0, \Psi)$, Ψ: diagonal matrix (interregional correlations: A_0)
- Solving SEM: guess directional connections based on correlations
  - Compare covariance matrix from data,, X'X, with the one from the model

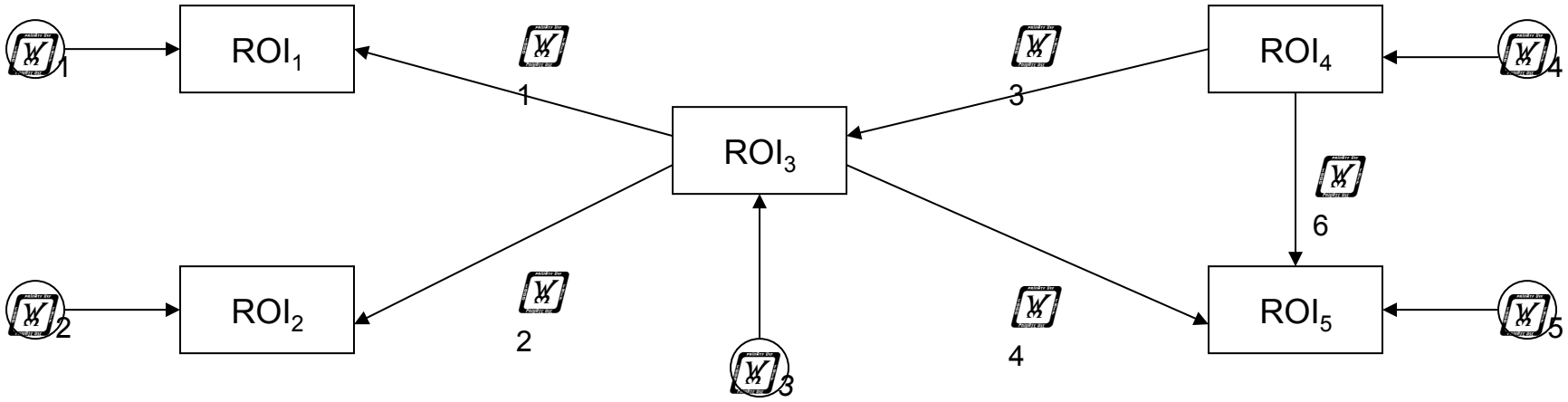
$$\Sigma = (I - A_0)^{-1} \varepsilon \varepsilon^T (I - A_0)^{-T} = (I - A_0)^{-1} \Psi (I - A_0)^{-T}$$

  - One problem: can't solve SEM if all parameters in A_0 are unknown!
    - Totally $n(n+1)/2$ simultaneous equations; $n(n-1)+n=n^2$ unknowns!
    - Can only allow at most $n(n-1)/2$ paths, half of the off-diagonals
    - Fix the rest paths (at least $n(n-1)/2$) to 0 or known values



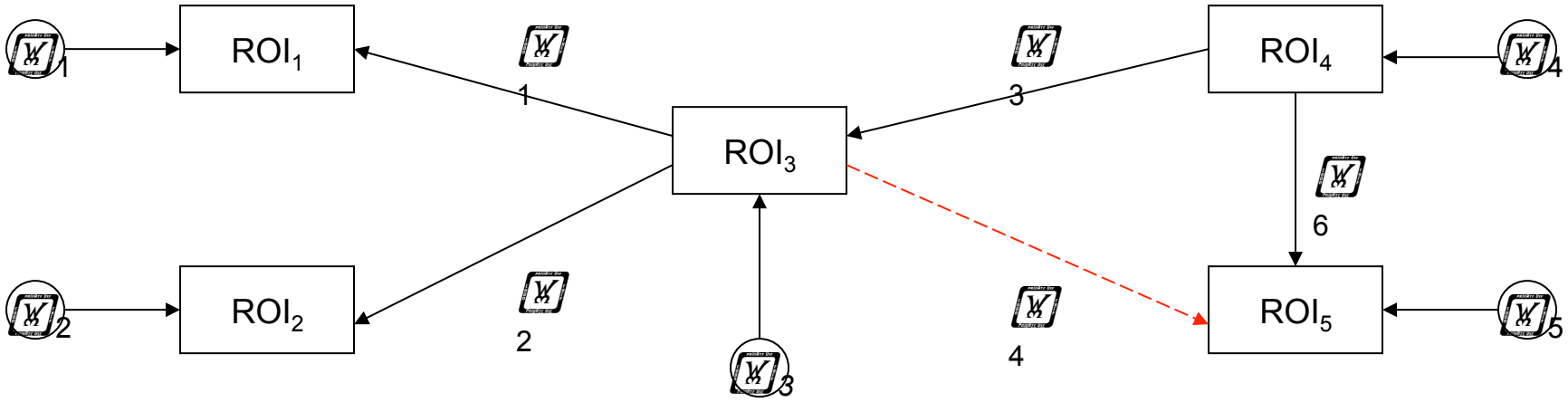
SEM: Model Validation

- Null hypothesis H_0: It's a good model about instantaneous network
  - Knowing directional connectivity btw ROIs, does data support model?
  - Want to see model (H_0) not rejected
    - $\chi^2(n(n\text{-}1)/2\text{-}k)$-test: badness-of-fit
    - Fit indices (AIC, CFI, GFI,): balance between optimization and model complexity
  - Input: model specification, covariance/correlation matrix, *etc.*
  - If H_0 is **not** rejected, estimate path strengths



SEM: Model Comparison and Search

- Comparing two nested models through $\chi^2(1)$-test
  - For example, not sure about one specific path
- Search all possible models
  - Sounds appealing: often seen in literature
  - Problematic: data-driven vs. theory-based
  - **Learn from data, and don't let data be your master!**



SEM: Serious Problems

- Aaron Levenstein: Models are like bikini!
- Correlations as input in SEM: popular practice
  - Usually practiced in social science studies for scaling issues
  - Save DFs in FMRI data analysis
  - Path coefficients not interpretable
  - Can't make statistical inferences: *t*-stat and CI, if provided, are incorrect
- Assumption of no delayed effects
  - Within-region temporal correlations ignored
  - Cross-regions: delayed interactions ignored
- Data preprocessing: Have to remove all confounding effects
- Individual subjects vs. group
  - How to combine multiple multiple subjects
  - Fixed vs. random-effects analysis

Vector Autoregression (VAR)

- General model for a network of n regions VAR(p)
  - $X(t) = A_1X(t\text{-}1)+\ldots+A_pX(t\text{-}p)+\mathbf{c}_1z_1(t)+\ \ldots+\mathbf{c}_qz_q\ (t)+\ \varepsilon\ (t)$
  - Only focus on lagged effects: Current state depends linearly on history
  - Instantaneous effects modeled, but left in residuals as effects of no interest
  - Confounding (exogenous) effects can be incorporated as part of the model
    - Slow drift, head motion, physiological confounds, **time breaks**, conditions of no interest
    - Unlike SEM, only minimal pre-processing needed (slice timing + motion correction)
  - Parameters in A_i code for cross-region path strength: Meaning of path coefficients
  - Assumptions
    - Linearity; Stationarity/invariance: mean, variance, and auto-covariance
    - $\varepsilon\ (t) \sim N(0,\ \Psi)$, Ψ: not diagonal matrix (positive definite contemporaneous covariance); no serial correlation in individual residual time series
- Rationale for VAR(p)
  - Response to stimuli does not occur simultaneously across brain: latency
  - However, is data time resolution fine enough with TR = 2 sec???

Solving VAR

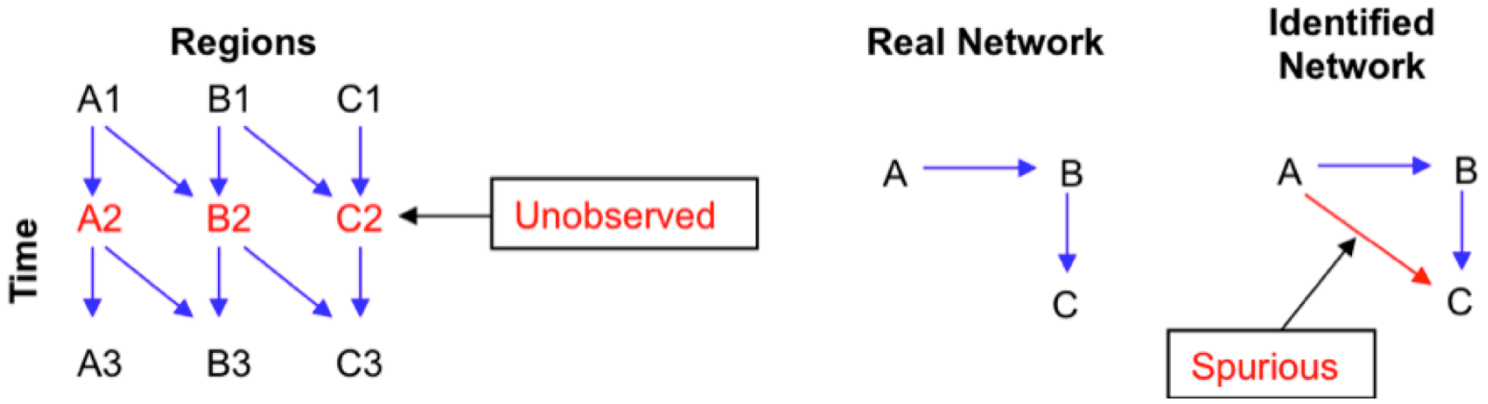
- Model $X(t) = A_1X(t\text{-}1)+\ldots+A_pX(t\text{-}p)+\mathbf{c}_1z_1(t)+\ \ldots+\mathbf{c}_qz_q\ (t)+\ \varepsilon\ (t)$
  - Order selection with 4 criteria (1st two tend to overestimate)
    - AIC: Akaike Information Criterion
    - FPE: Final Prediction Error
    - HQ: Hannan-Quinn
    - SC: Schwartz Criterion
- Solve VAR with OLS
  - No need to specify connections as in SEM
  - Obtain estimates of all elements in A_i, and make statistical inferences based on *t*-statistic for each path
  - **Data driven** instead of model validation?
  - Model tuning when some covariates are not significant
- VAR as a seed-based analysis
  - Bivariate autogression: use seed to search for regions that may form a network with the seed
  - **3dGC** (vs. 1dGC): should have been called 3dVAR (vs. 1dVAR)

VAR Model Quality Check

- Stationarity: VAR(p) $Y(t) = \alpha + A_1 Y(t\text{-}1) + \ldots + A_p Y(t\text{-}p) + \varepsilon(t)$
  - Check characteristic polynomial $\det(I_n - A_1 z - \ldots - A_p z^p) \neq 0$ for $|z| \leq 1$
- Residuals normality test
  - Gaussian process: Jarque-Bera test (dependent on variable order)
  - Skewness (symmetric or tilted?)
  - Kurtosis (leptokurtic or spread-out?)
- Residual autocorrelation
  - Portmanteau test (asymptotic and adjusted)
  - Breusch-Godfrey LM test
  - Edgerton-Shukur F test
- Autoregressive conditional heteroskedasticity (ARCH)
  - Time-varying volatility
- Structural stability/stationarity detection
  - Is there any structural change in the data?
  - Based on residuals or path coefficients

VAR: Serious Problems

- Data sampling rate: time resolution
  - Cross-region interactions occur probably at ms level, but usually TR = 2s in FMRI time series (TR could be 100-200 ms with single-slice scanning)
  - Will VAR(1) catch the real lagged effects across regions???



  - With coarse sampling, the instantaneous effects will more likely reveal the real network than the lagged effects
- Endogeneity problem or over-fitting: data driven

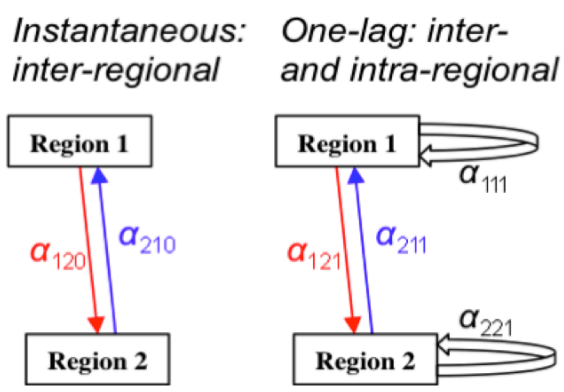
Network-Based Modeling: a toy example

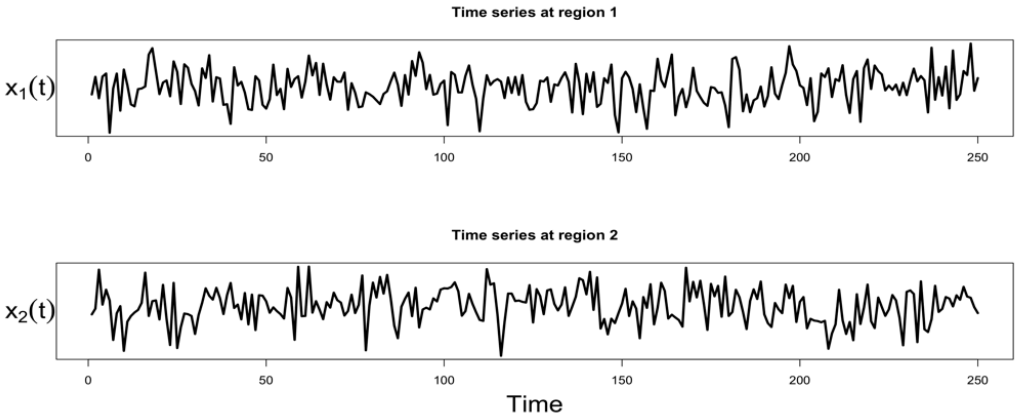
- A network with two regions: both contemporaneous and delayed
  - Within-region effects: lagged correlation
  - Cross-regions effects: both instantaneous and lagged

$$x_1(t) = c_1 + \alpha_{120}x_2(t) + \alpha_{111}x_1(t-1) + \alpha_{121}x_2(t-1) + \varepsilon_1(t)$$

$$x_2(t) = c_2 + \alpha_{210}x_1(t) + \alpha_{211}x_1(t-1) + \alpha_{221}x_2(t-1) + \varepsilon_2(t)$$

- If we have time series data from the two regions
  - Can we evaluate the above model?
  - Estimate and make inferences about the α values?





One World United Under One Flag!

- Why don't we just combine SEM and VAR?
  - No reason we shouldn't or cannot
  - Called Structural Vector Autoregression (SVAR)!
  - Accounts for variability from both instantaneous and lagged effects
  - Improves model quality and statistical power
  - Incorporates covariates, and involves minimum pre-processing
- General SVAR(p) model
  - $X(t)=A_0X(t)+A_1X(t-1)+\ldots+A_pX(t-p)+\mathbf{c}_1z_1(t)+\ldots+\mathbf{c}_qz_q(t)+B\,\boldsymbol{\varepsilon}(t)$
  - A_0 represents the cross-region instantaneous effects
    - Diagonals are 0
  - A_i represents both within-region and cross-region lagged effects
  - B is a diagonal matrix so that $\boldsymbol{\varepsilon}(t) \sim N(0, I)$
    - All the cross-region instantaneous effects are contained in A_0

Solving SVAR

- $X(t)=A_0X(t)+A_1X(t\text{-}1)+\ldots+A_pX(t\text{-}p)+\mathbf{c}_1z_1(t)+\ldots+\mathbf{c}_qz_q(t)+B\,\boldsymbol{\varepsilon}(t)$
  - Equivalence to a reduced VAR(p) model

$$X(t) = A_1^*X(t-1) + \ldots + A_p^*X(t-p) + \mathbf{c}_1^*z_1(t) + \ldots + \mathbf{c}_q^*z_q(t) + \varepsilon^*(t)$$

$A_i^* = (I\text{-}A_0)^{-1}A_i$, $\mathbf{c}_j^*=(I\text{-}A_0)^{-1}\mathbf{c}_j$, $\boldsymbol{\varepsilon}^*(t) = (I\text{-}A_0)^{-1}B\,\boldsymbol{\varepsilon}(t)$

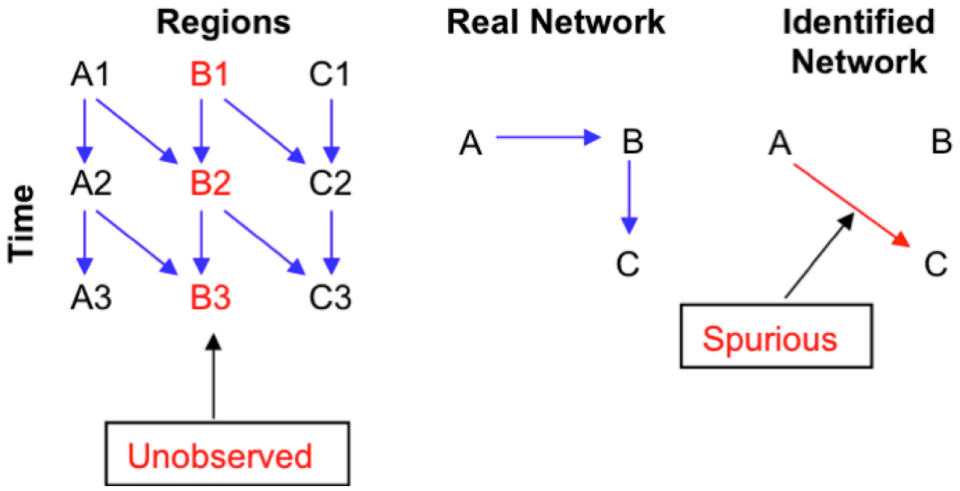
  - Solve the reduced VAR(p), obtain estimates of A_i^*, $\mathbf{c}_j^*$, and residual covariance Σ_{ε^*}
  - Solve $(I\text{-}A_0)^{-1}BB(I\text{-}A_0)^{-T} = \Sigma_{\varepsilon^*}$ through ML. Similar to SEM:
    - Totally $n(n+1)/2$ simultaneous equations; $n(n\text{-}1)+n=n^2$ unknowns!
    - Can only allow at most $n(n\text{-}1)/2$ paths in A_0, half of the off-diagonals
    - Have to fix the rest paths (at least $n(n\text{-}1)/2$) to 0 or known values
    - Model validation, comparison, and search for the instantaneous network A_0
  - Finally update A_i (and $\mathbf{c}_j$) for the lagged effects
- AFNI program 1dSVAR.R

What can we do with 1dSVAR

- If time resolution is too coarse (*e.g.*, FMRI): Model validation/ comparison/search of the instantaneous network while accounting for the lagged effects
  - Knowing directional connectivity btw ROIs, does data support model?
  - Want to see model (H_0) not rejected
    - $\chi^2(n(n\text{-}1)/2\text{-}k)$-test: badness-of-fit
    - Fit indices (AIC, CFI, GFI,): balance between optimization and model complexity
  - If H_0 is **not** rejected, what are the path strengths?
- If time resolution is good (*e.g.*, MEG/EEG)
  - Both instantaneous and lagged effects are of interest?
- SEM+VAR
  - Lagged effects: data-driven; safe but inefficient (over-fitting)
  - Instantaneous effects: theory/hypothesis-based; powerful but risky
  - Various possibilities: *e.g.*, borrow DFs for instantaneous effects from lagged effects?
- Group analysis: MEMA

SVAR: caveats

- Assumptions (stationarity, linearity, Gaussian residuals, no serial correlations in residuals, etc.)
- Accurate ROI selection: If an essential region is missing



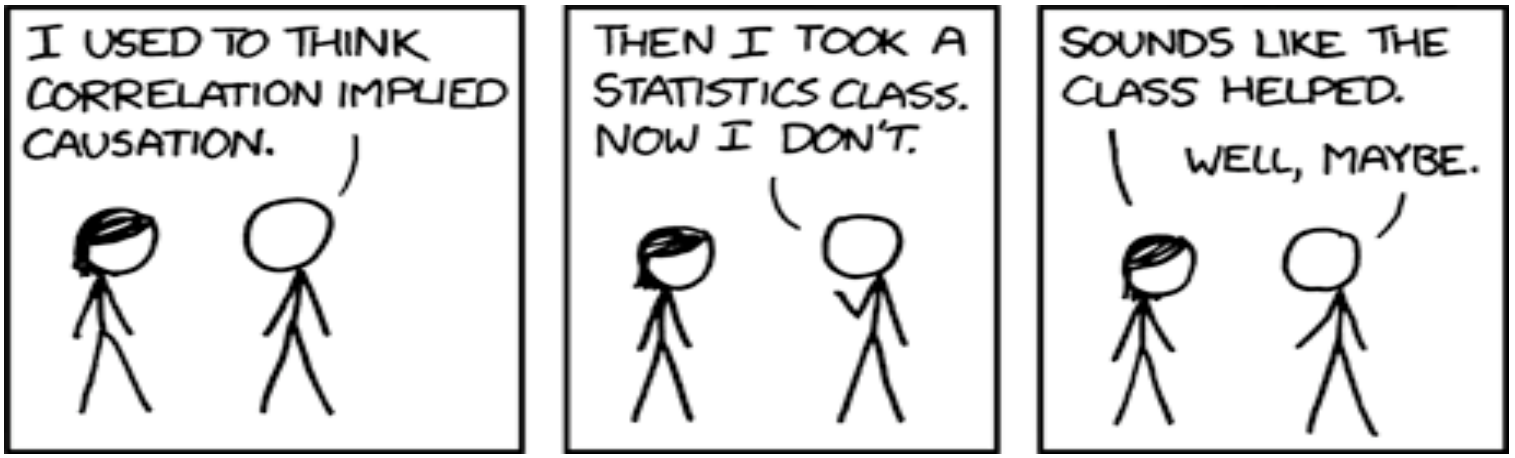
- Sensitive to lags
- Confounding latency due to HDR variability and vascular confounds
- Overfitting
- Model comparison/search
  - **Learn from data, but don't let data be your teacher!**

SVAR applied to FMRI

- Resting state
  - Ideal situation: no cut and paste involved
  - Physiological data maybe essential?
- Block experiments
  - Duration ≥ 5 seconds?
  - Extraction via cut and paste
    - Important especially when handling confounding effects
    - Tricky: where to cut especially when blocks not well-separated?
- Event-related design
  - With rapid event-related, might not need to cut and paste (at least impractical)
  - Other tasks/conditions as confounding effects

SVAR: Why not Granger Causality

- Causality: philosophical and physiological/anatomical; effective?
- Granger causality: A Granger causes B if time series at A provides statistically significant information about time series at B at some time delays (order)
  - Causes must temporally precede effects
  - Causality can be inferred from an *F*- or χ^2-test that shows the amount of variability of overall lagged effects each connection accounts for
- Both instantaneous and lagged effects are modeled in SVAR



Network-based Analysis in AFNI

- Exploratory: ROI searching with **`3dGC`**
  - Seed vs. rest of brain
  - Bivariate model
  - 3 paths: seed to target, target to seed, and self-effect
  - Group analysis with **`3dMEMA`** or **`3dttest`**
- Path strength significance testing in network: **`1dSVAR`**
  - Pre-selected ROIs
  - SVAR model
  - Multiple comparisons issue
  - Group analysis
    - path coefficients only
    - path coefficients + standard error
    - *F*-statistic (BrainVoyager)

Linear Dynamic System for fMRI (LDSf)

- Features: Further development from DCM
  - Deterministic vs stochastic system: capture variability across trials
  - Constant vs varying across time
  - One vs mixture of models
- Literature
  - Smith et al., Front. Syst. Neurosci. (2012) Vol 5:104
  - Smith et al., NeuroImage 52 (2010) 1027-1040
- Regarding Matlab package LDSf (Jason Smith), contact
  - Barry Horwitz (horwitzb@mail.nih.gov)

Keep in mind

- Statisticians, like artists, have the bad habit of falling in love with their models. (George Box)
- If you torture the data enough, nature will always confess. (Ronald Coase)
- **Models are bikinis!**