Connectivity Analysis in AFNI

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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
- Network-based analysis
  - Structural equation modeling (SEM)
  - Vector autoregression (VAR) (aka Granger causality)
  - Structural vector autogression (SVAR)

Overview: Connectivity analysis

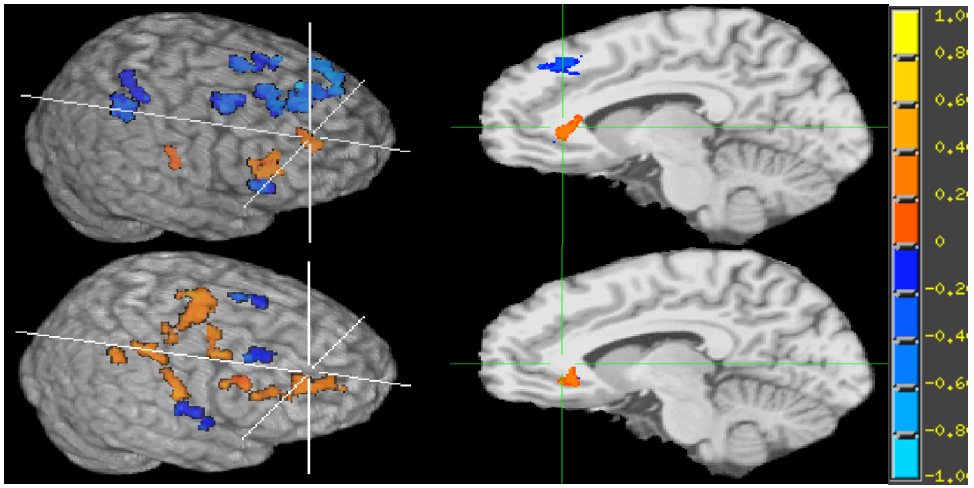
- Typical FMRI data analysis
  - Massively univariate (voxel-wise) regression: $y = X\beta + \varepsilon$
  - Relatively robust and reliable
  - May infer regions involved in a task/state, but can't say much about the details of a network
- Network analysis
  - Information
    - Seed region, some or 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 unreliable

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
- Data types
  - Mainly FMRI
  - Some methodologies may work for MEG, EEG
  - Not for DTI

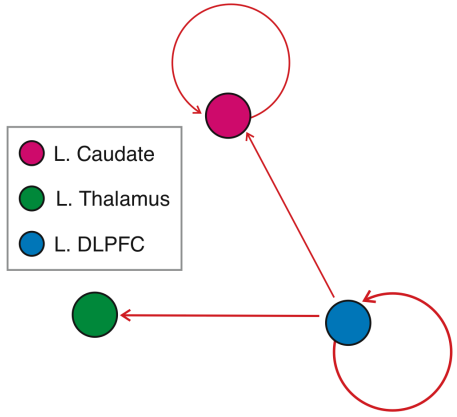
Seed-based analysis: ROI search

- 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 validation, connectivity strength testing
  - Popular name: effective or structural connectivity
  - Strong assumptions: specific, but with high risk
  - Methodologies: SEM, VAR, SVAR, DCM
  - Directionality, causality (?)



Common Preparatory Steps

- Warp brain to standard space
  - **adwarp, @auto-tlrc, align_epi_anat.py**
- Create ROI
  - Peak voxel
  - Sphere around a peak activation voxel: **3dUndump –master … –srad …**
  - Activation cluster-based (biased unless from independent data?)
  - Anatomical database
  - 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** and **3dcalc**
  - **3dDetrend –polort**
  - **RETROICORR/RetroTS.m**
  - **3dBandpass**

Simple Correlation Analysis

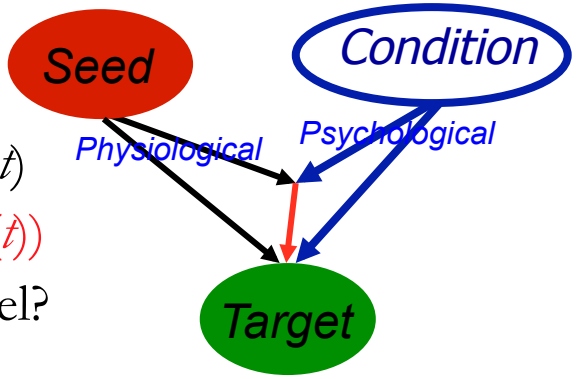
- Seed vs. rest of brain
- ROI search based on response similarity
  - Looking for regions with similar signal to seed
- **Correlation** at individual subject level
  - Usually have to control for effects of no interest: drift, head motion, physiological variables, censored time points, tasks of no interest, *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: **`3dfim+`** or **`3dDeconvolve`**
  - 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

Simple Correlation Analysis

- Group analysis
  - Run Fisher-transformation of *r* to *Z*-score and *t*-test: **`3dttest`**
  - Take β and run *t*-test (pseudo random-effects analysis): **`3dttest`**
  - Take β + *t*-statistic and run random-effects model: **`3dMEMA`**
- **Caveats**: don't over-interpret
  - 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, covariates, r (Z)/β, bandpass filtering, …
  - Measurement error problem: underestimation, attenuated bias
- Website: http://afni.nimh.nih.gov/sscc/gangc/SimCorrAna.html
- Interactive tools in AFNI and SUMA: **`InstaCor`**, **`GroupInstaCor`**

Context-Dependent Correlation

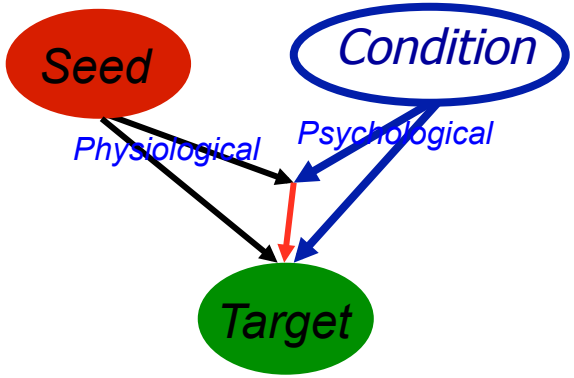
- Popular name: Psycho-Physiological Interaction (PPI)
- 3 explanatory variables
  - Condition (or contrast) effect: $C(t)$
  - Seed effect on rest of brain: $S(t)$
  - Interaction between seed and condition (or contrast): $I(C(t), S(t))$
    - **Directionality** here!
- Model for each subject
  - Original regression: $y(t) = [C(t)\ \text{Others}]\beta + \varepsilon(t)$
  - New model: $y(t) = [C(t)\ S(t)\ I(C(t), S(t))\ \text{Others}]\beta + \varepsilon(t)$
  - 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: r or β for $I(C(t), S(t))$
  - $I(C(t), S(t))$: the variability in addition to $C(t)$ and $S(t)$
    - Symmetrical modulation



Context-Dependent Correlation

- How to formulate $I(C(t), S(t))$?
  - Interaction occurs at neuronal, not BOLD (an indirect measure) level
  - **Deconvolution**: derive "neuronal response" at seed based on BOLD response
    - **`3dTfitter`**: Impulse ⊗ Neuronal events = BOLD response; Gamma ⊗ NE(t) = $S(t)$
    - Deconvolution matters more for event-related than block experiments
  - Interaction at neuronal level – **`3dcalc`**: NE(t) × $C(t)$ = NI(t)
    - Useful tool for $C(t)$: **`timing_tool.py`** converts stimulus timing into 0s and 1s
  - Interaction at BOLD level - convolution – **`waver`**: Gamma ⊗ NI(t) = $I(C(t), S(t))$
  - If stimuli were presented in a resolution finer than TR – not TR-locked
    - **`1dUpsample n`**: interpolate $S(t)$ n × finer before deconvolution **`3dTffiter`**
    - Downsample interaction $I(C(t), S(t))$ back to original TR: **`1dcat`** with selector '{0..$(n)}'
  - Solving $y(t) = [C(t)\ S(t)\ I(C(t), S(t))\ \text{Others}]\beta + \varepsilon(t)$ – **`3dDeconvolve`**
- Group analysis
  - Run Fisher-transformation of r to Z-score and t-test: **`3dttest`**
  - Take β ($+t$): **`3dttest`** (**`3dMEMA`**)

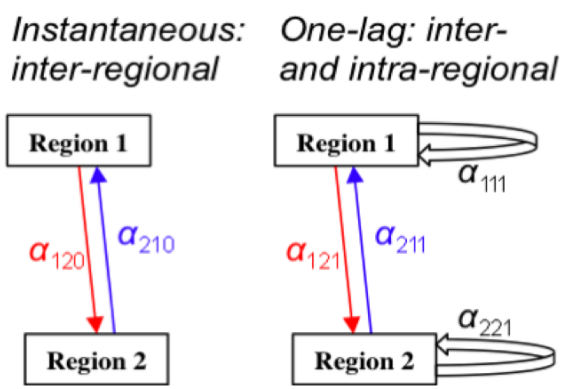
PPI Caveats

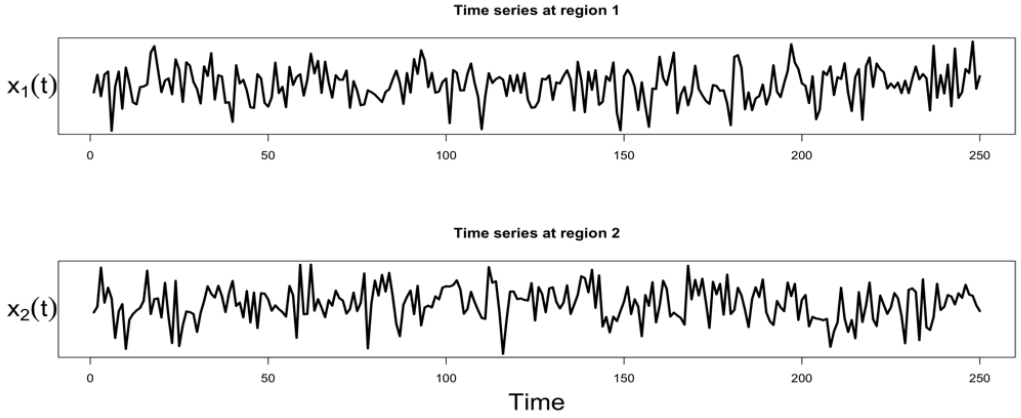


- No proof for anatomical connectivity
  - Correlation does not necessarily mean causation
  - If other regions involved in the network
- Measurement error in regression
  - Noisy seed time series
  - Neuronal response hard to decode: Deconvolution is very far from reliable, and we have to assume a shape-fixed HRF, same shape across conditions/regions/subjects
  - The errors lead to attenuation or regression dilution
- Doesn't say anything about interaction between condition and target on seed
- Doesn't differentiate whether modulation is
  - Condition on neuronal connectivity from seed to target, or
  - Neuronal connectivity from seed to target on condition effect
- Website: http://afni.nimh.nih.gov/sscc/gangc/CD-CorrAna.html

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?

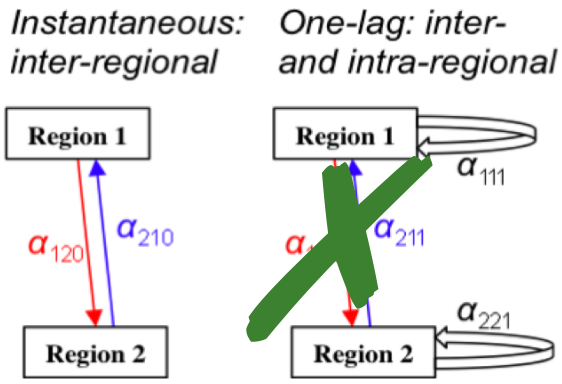
Structure Equation Modeling (SEM): a toy example

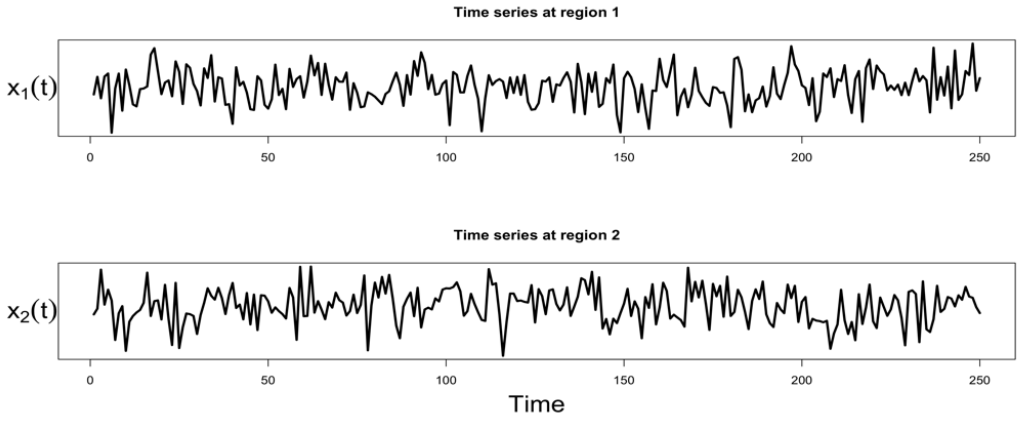
- A network with two regions: no delayed effects
  - No within-region effects: no lagged effects – no temporal correlation!
  - Cross-region effects: instantaneous correlation only; no lagged effects

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

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

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





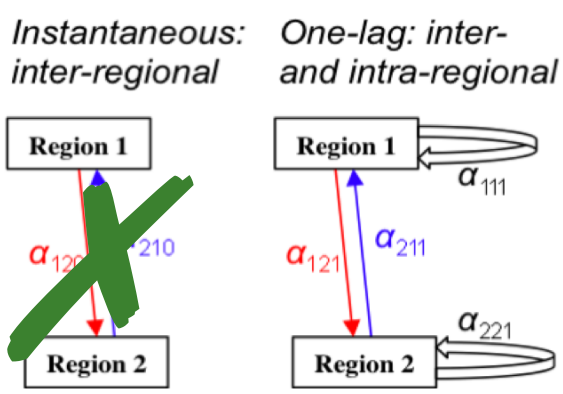
Vector Autoregressive (VAR) Modeling: a toy example

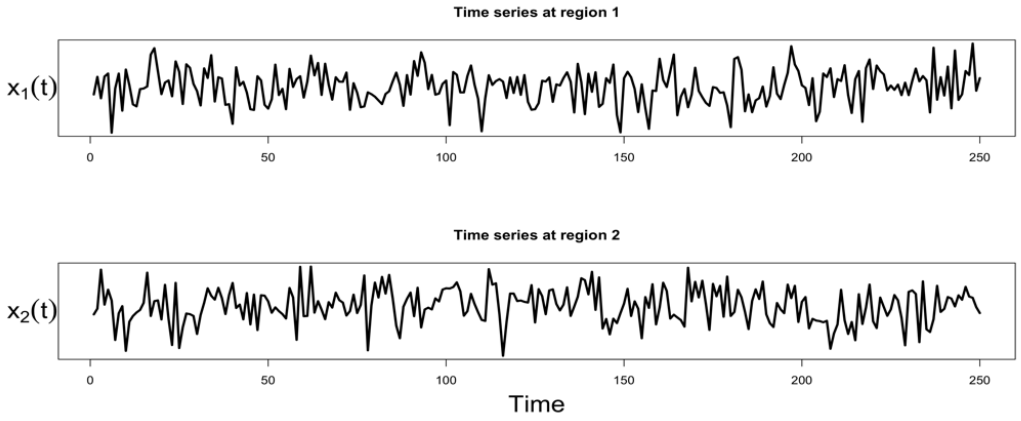
- A network with two regions: no contemporaneous effects
  - Within-region effects: lagged effects
  - Cross-regions effects: lagged effects only; no instantaneous effects

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

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

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



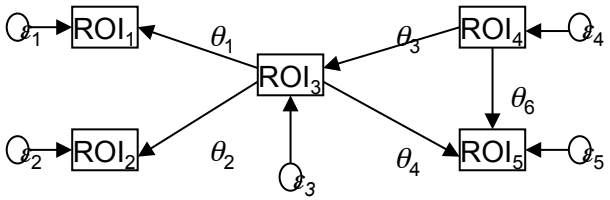


Structure Equation Modeling (SEM) or Path Analysis

- 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
  - Compare covariance matrix from data with the one from the model

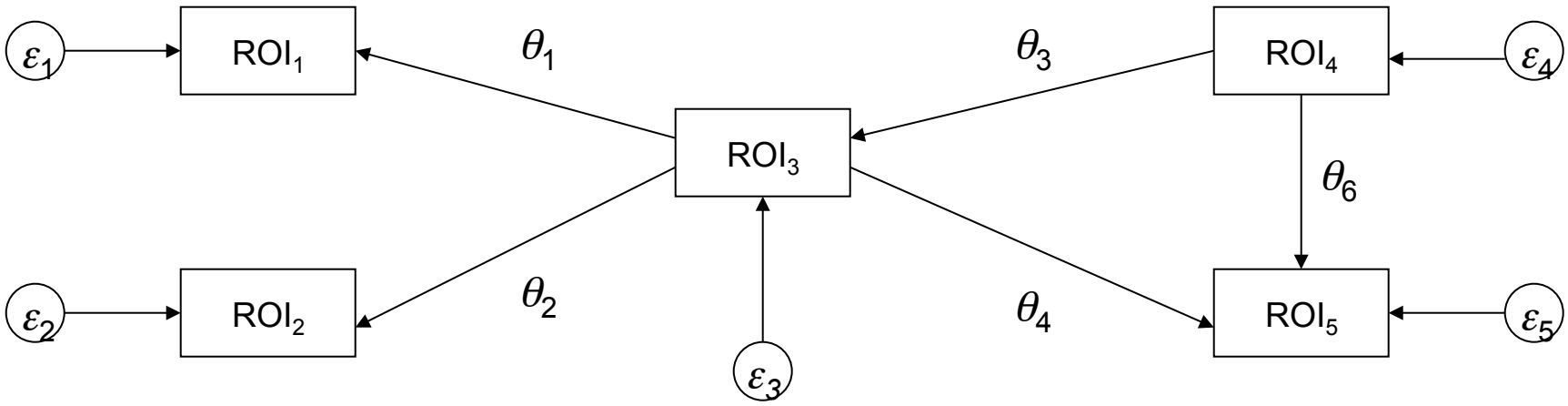
$$\Sigma = (I - A_0)^{-1} \varepsilon \varepsilon^T (I - A_0)^{-T} = (I - A_0)^{-1} \Psi (I - A_0)^{-T}$$

  - One problem: we 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
    - Have to fix the rest paths (at least $n(n-1)/2$) to 0 or known values



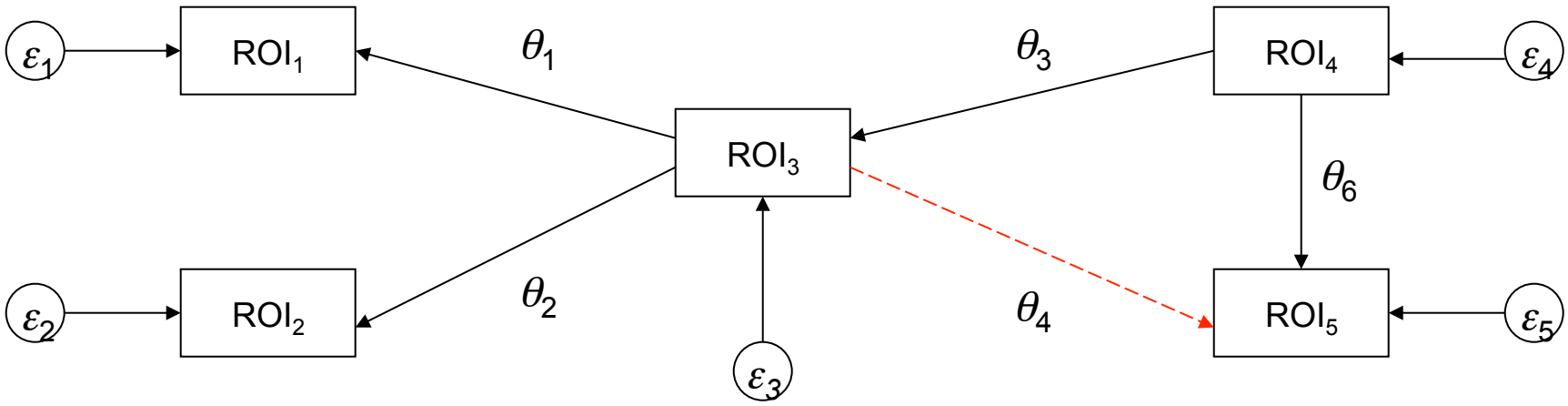
SEM: Model Validation

- 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, what are the path strengths?



SEM: Model Comparison and Search

- Comparing two nested models through $\chi^2(1)$-test
  - For example, not sure about a pth
- 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: More Serious Problems

- 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
- Assumptions
  - 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 = 1-2 sec???

Solving VAR

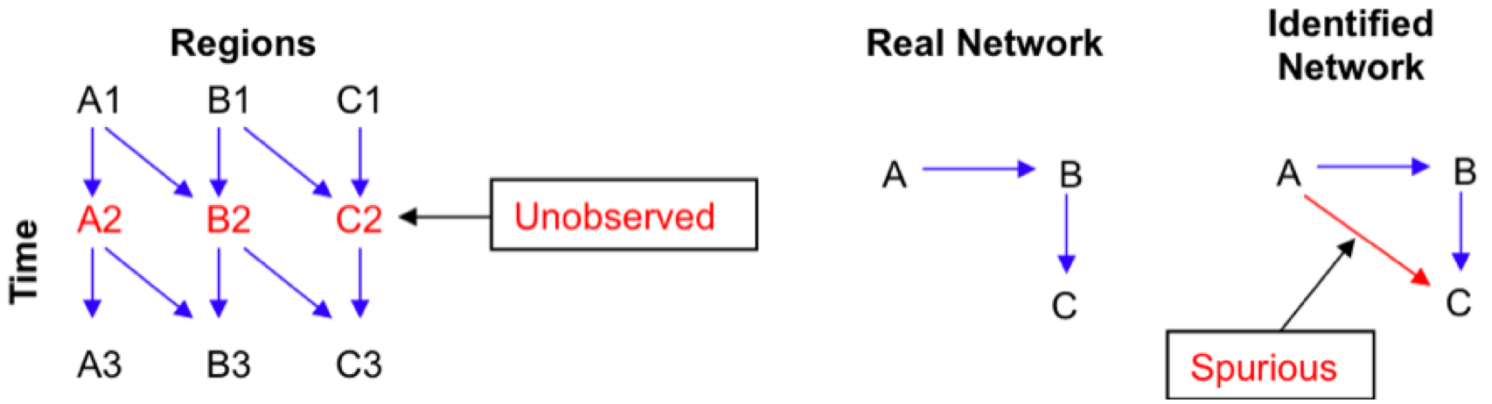
- Model $X(t) = A_1X(t\text{-}1)+\ldots+A_pX(t\text{-}p)+\mathbf{c}_1z_1(t)+\ \ldots+\mathbf{c}_qz_q\ (t)+\varepsilon(t)$
  - Order selection with 4 criteria (1st two tend to overestimate)
    - AIC: Akaike Information Criterion
    - FPE: Final Prediction Error
    - HQ: Hannan-Quinn
    - SC: Schwartz 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)

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 = 1~2 seconds 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
- Over-fitting: data driven

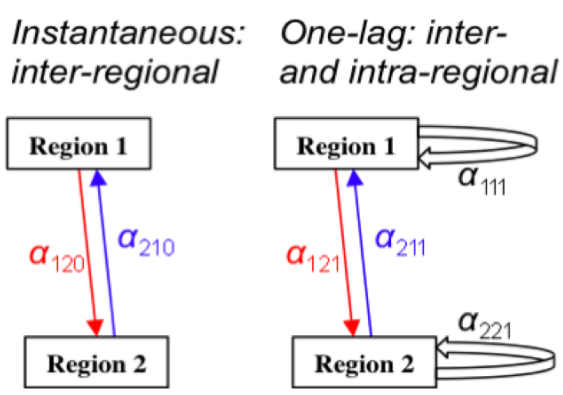
Network-Based Modeling: a toy example

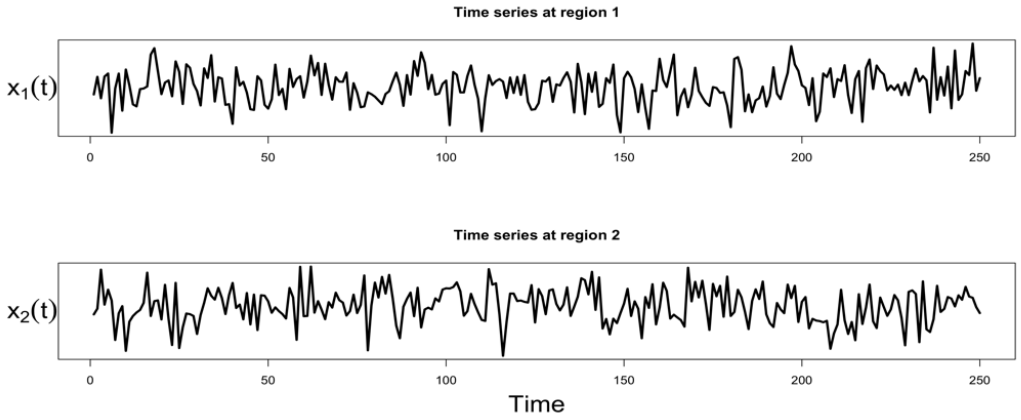
- A network with two regions: both contemporaneous and delayed
  - Within-region effects: lagged correlation
  - Cross-regions effects: both instantaneous and lagged

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

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

- 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
  - $X(t)=A_0X(t)+A_1X(t\text{-}1)+\ldots+A_pX(t\text{-}p)+\mathbf{c}_1z_1(t)+\ldots+\mathbf{c}_qz_q(t)+B\boldsymbol{\varepsilon}(t)$
  - 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 $\boldsymbol{\varepsilon}(t) \sim \mathrm{N}(0, I)$
    - 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

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

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

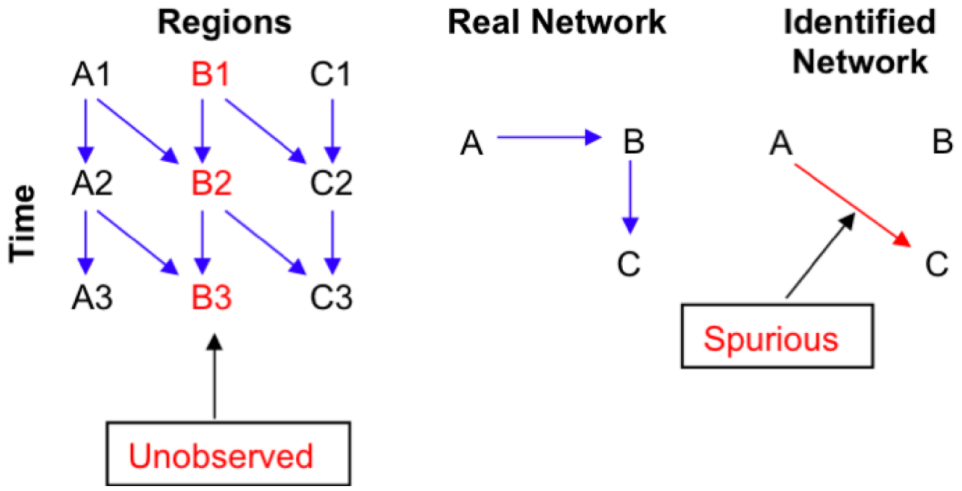
  - Solve the reduced VAR(p), obtain estimates of A_i^*, $\mathbf{c}_j^*$, and residual covariance $\boldsymbol{\Sigma}_{\varepsilon^*}$
  - Solve $(I\text{-}A_0)^{-1}BB(I\text{-}A_0)^{-T} = \boldsymbol{\Sigma}_{\varepsilon^*}$ through ML. Similar to SEM:
    - Totally $n(n+1)/2$ simultaneous equations; $n(n\text{-}1)+n=n^2$ 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

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



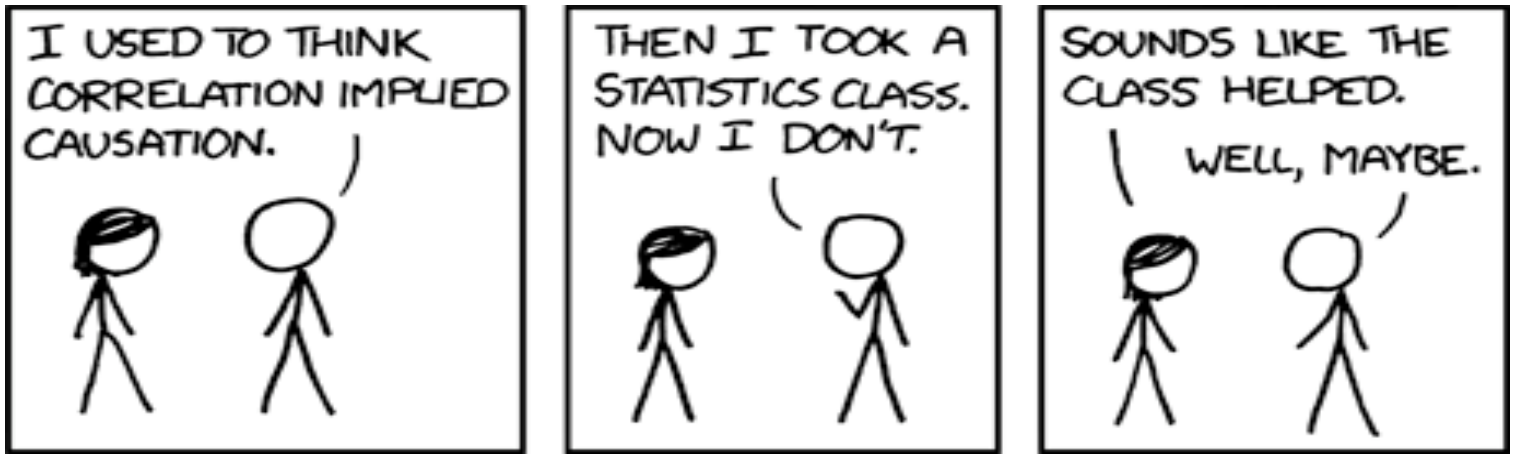
- Sensitive to lags
- Confounding latency due to HDR variability and vascular confounds
- Overfitting
- Model comparison/search
  - **Learn from data, but don't let data be your teacher!**

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)