Statistical challenges in the study of aging and dementia

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Some challenges for statistics…

- ***Change*** is key
- ***Measurement*** is tough
  - Errors
  - Multidimensional constructs
  - Indirect; maybe differential

  → **biases**
- Sicker people refuse, ***drop out***, skip, die
- Aging is ***complex***

…leads to statistical challenges

- ***Longitudinal*** data analysis
- ***Measurement*** modeling
  - Errors-in-variables
  - Data reduction techniques, e.g., principal components
  - Latent variable modeling
- ***Missing data, competing risks*** analysis
- Mathematical ***modeling***

Objective

For you to walk away with specific, useful information on at least one of the challenges:

…leads to statistical challenges

- ***Longitudinal*** data analysis
- ***Measurement*** modeling
  - Errors-in-variables
  - Data reduction techniques, e.g., principal components
  - Latent variable modeling
- ***Missing data, competing risks*** analysis
- Mathematical ***modeling***

Why longitudinal data analysis (LDA)?

- Top ten reasons

10. Because it will make me look so cool

9. Because a grant reviewer will call my application "unsophisticated" if not

(I'm only creative enough to come up with two of these….)

Why LDA?

- Top four reasons
  4. To inform policy
     – Changes in disability prevalence over time
  3. To study natural histories
     – Functional trajectories and their etiologies
  2. To make prognoses, incorporating history
     – Cognitive status transitions
  1. To progress from "association" toward "cause"
     – Intervention A or risk adoption B changes outcomes

What I Hope You'll Get Out of This

- The basic longitudinal modeling methods
- How one implements those methods
  - Key models
  - Software
- Heads up on the primary challenges

An Example
Emotional vitality and mobility

- Study: Women's Health & Aging *(n=1002; Guralnik et al., 1995)*
- Question: Does emotional vitality affect mobility trajectory?
  - Emotional vitality (X: 1 if vital; 0 ow)
    - High mastery, being happy, few depressive/anxious symptoms

Penninx et al., 2000

  - Mobility (Y)
    - Usual walking speed (max 2 trials)
    - Indicator of severe walking difficulty (1 if yes; 0 ow)
  - Time (T)
    - Study rounds 0-6

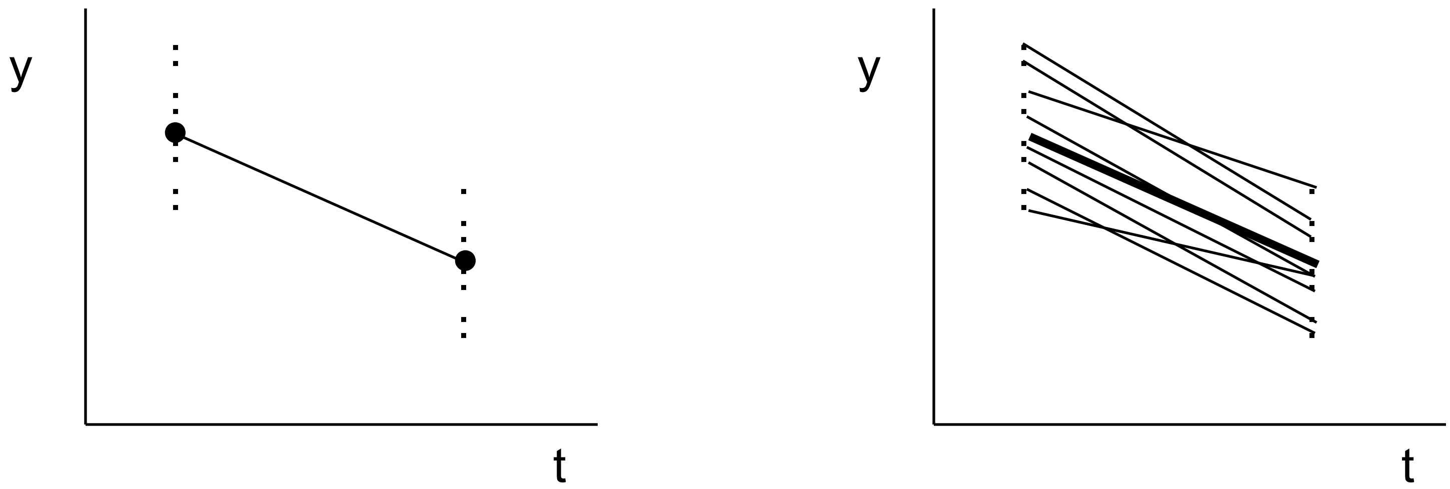
The basic longitudinal methods

Diggle, Heagerty, Liang & Zeger, 2001

- Top four reasons

4. To inform policy
   – Population average (marginal models; GEE)
3. To study natural histories
   – Subject-specific (random effects; growth curves)
2. To make prognoses, incorporating history
   – Transitions (autoregressive & Markov models)
1. To progress from “association” toward “cause”
   – Time-varying covariates (with complexities)

Population average v. Subject-Specific



- PA: Compare populations over time
  - (Fixed) time effect = ***slope of the averages***
- SS: Compare women **to selves** over time
  - (Fixed) time effect = ***average of the slopes***
- Subtle point: These are equal
  - with continuous outcomes Y (linear regression); NOT otherwise
  - provided that within-person correlation is explicitly accounted for

Population-average models

- Keywords
  - Marginal models
  - GEE (Generalized Estimating Equations)

    Liang & Zeger, 1986
  - Panel analysis
- Sound bites
  - Focus usually on averages (their trajectories)
  - Serial correlation often a “nuisance”
  - “Robust”

Population-average models
Description of average trajectories

- Model—time-invariant covariates:

$$Y_{i1} = \beta_0 + \beta_1 x_i + \beta_2 t_{i1} + \beta_3 x_i \cdot t_{i1} + e_{i1}$$

$$Y_{ij} = \beta_0 + \beta_1 x_i + \beta_2 t_{ij} + \beta_3 x_i \cdot t_{ij} + e_{ij}$$

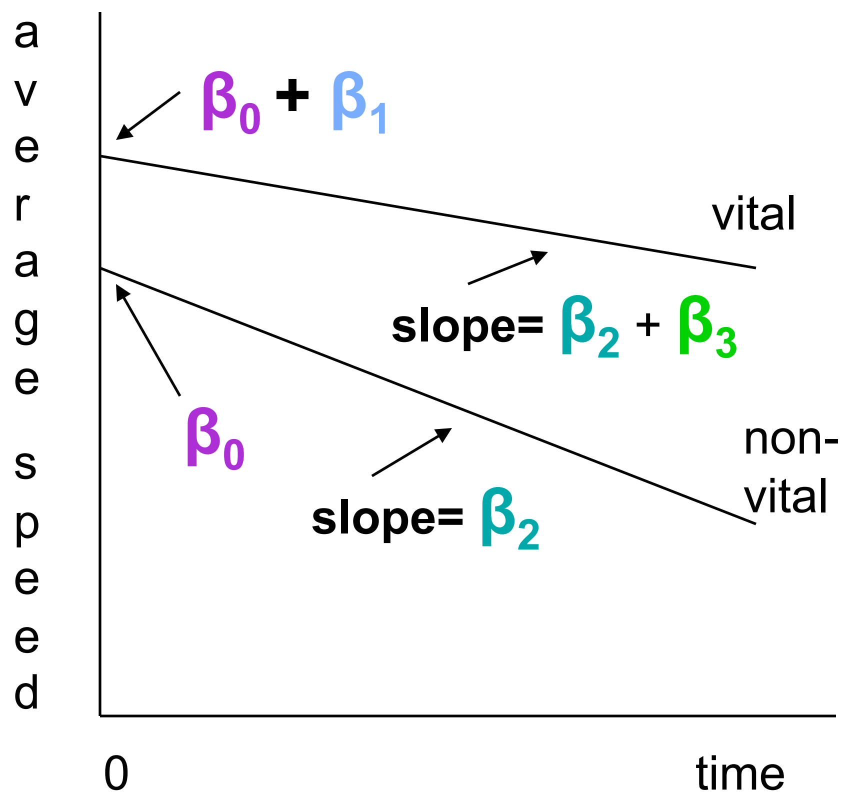
$$Y_{i7} = \beta_0 + \beta_1 x_i + \beta_2 t_{i7} + \beta_3 x_i \cdot t_{i7} + e_{i7}$$

rate of change in average walk speed of non-vital persons (β_2)

amount rate of change in average walk speed differs between vital & non-vital persons (β_3)

- Key points
  - Greek = "fixed"; Roman = variable
  - "ANCOVA" model
    - **Coding: main effects for "treatment," time; interaction**
    - Note contrast viz "change scores": more powerful

Population-average models
Pictures



- Data displays
  - Side-by-side box plots (by time, "treatment")
  - Connect-the-means plots (over time, by treatment)
  - Y versus t smoothed scatterplot, per x

$$Y_{ij} = \beta_0 + \beta_1 x_i + \beta_2 t_{ij} + \beta_3 x_i \cdot t_{ij} + e_{ij}$$

Population-average models
Treatment of serial correlation

$$Y_{i1} = \beta_0 + \beta_1 x_i + \beta_2 t_{i1} + \beta_3 x_i \cdot t_{i1} + e_{i1}$$

$$Y_{ij} = \beta_0 + \beta_1 x_i + \beta_2 t_{ij} + \beta_3 x_i \cdot t_{ij} + e_{ij}$$

$$Y_{i7} = \beta_0 + \beta_1 x_i + \beta_2 t_{i7} + \beta_3 x_i \cdot t_{i7} + e_{i7}$$

error: amount that speed of woman "i" differs from population average at time 7

- Key points
  - Errors are correlated within persons
  - Most software: you choose the correlation "structure"
    - "Exchangeable" – all measures equally strongly correlated
    - "Autoregressive," "banded" – measures closer in time more strongly correlated
    - "Unstructured" – as it sounds (here: 7 choose 2 = 21 ρs)
    - "Independence" – all correlations assumed = 0

Population-average models: Fitting

- Software
  - SAS: GENMOD (GEE); MIXED, repeated (MLE)
  - SPSS: Advanced model package
  - Stata: xtgee (GEE); xtreg (MLE)
- GEE versus MLE (maximum likelihood est.)
  - Both: accurate coefficient estimates whether or not correlation structure choice is correct
  - GEE: standard errors also accurate, regardless
  - MLE: More valid handling of missing data

Subject-specific models

- Keywords
  - Mixed effects, growth curves, multi-level
  - Mixed model; hierarchical (linear) model GEE

    Laird & Ware, 1982; Raudenbush & Bryk, 1986
  - Random coefficient model
- Sound bites
  - Focus usually on individual trajectories
  - “Heterogeneity”: variability of trajectories
  - Assumptions are made, and may matter

Subject-specific models
Average & individual trajectories

- Model—time-invariant covariates:

$$Y_{i1} = \beta_0 + b_{0i} + \beta_1 x_i + \beta_2 t_{i1} + b_{2i} t_{i1} + \beta_3 x_i \cdot t_{i1} + e_{i1}$$

$$Y_{ij} = \beta_0 + b_{0i} + \beta_1 x_i + \dot{\beta}_2 t_{ij} + b_{2i} t_{ij} + \beta_3 x_i \cdot t_{ij} + e_{ij}$$

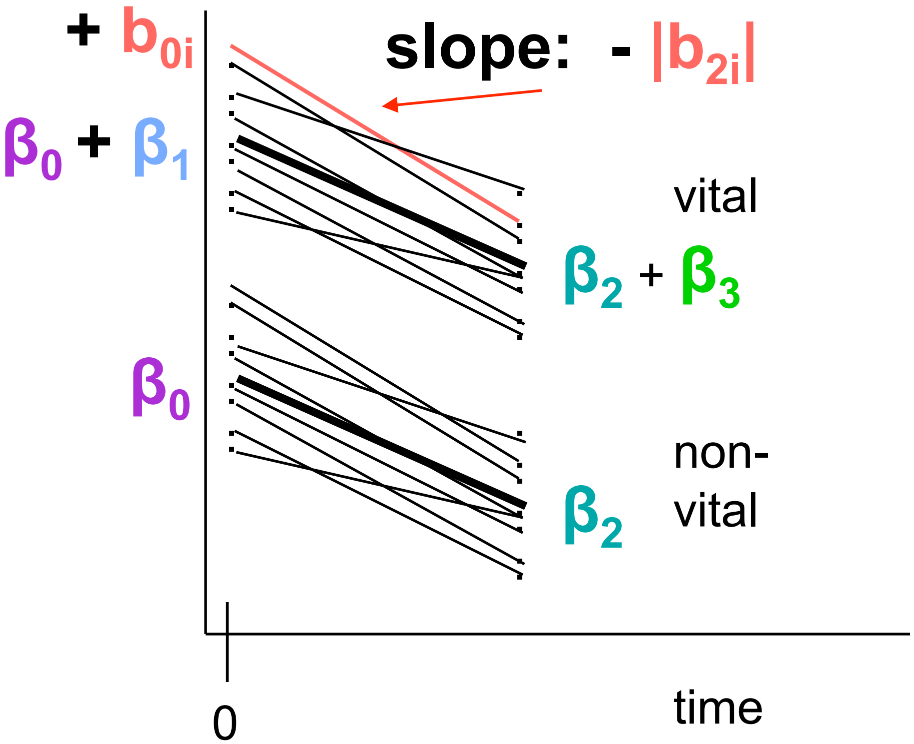
$$Y_{i7} = \beta_0 + \boxed{b_{0i}} + \beta_1 x_i + \dot{\beta}_2 t_{i7} + \boxed{b_{2i}} t_{ij} + \beta_3 x_i \cdot t_{i7} + e_{i7}$$

amount baseline speed for person i exceeds or falls short of the average

amount speed trajectory for person i differs from average

- Key points:
  - The additional coefficients are random
  - Modeling assumes a distribution: usually normal
    - Distribution variance characterizes "heterogeneity"
    - Heterogeneity results in within-person correlation
  - One may define correlation structure for e_{ij}s too

Subject-specific models
Pictures



- b_{0i} = random intercept
  b_{2i} = random slope
  (could define more)
- heterogeneity ⟺ spread in intercepts, slopes
- Sentinel data display: spaghetti plot
  (Ferrucci et al., 1996)

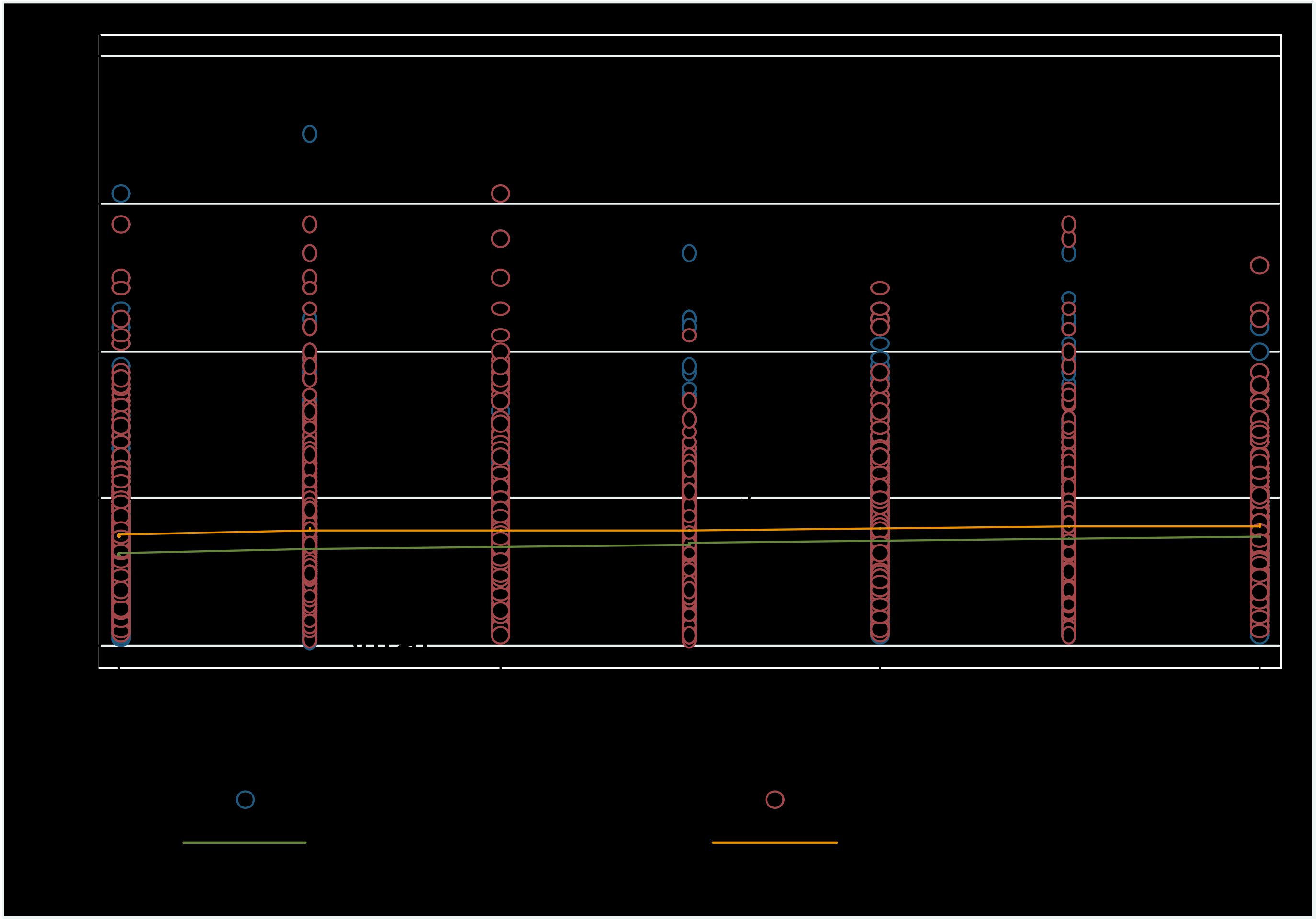
$$Y_{ij} = \beta_0 + b_{0i} + \beta_1 x_i + \beta_2 t_{ij} + b_{2i} t_{ij} + \beta_3 x_i \cdot t_{ij} + e_{ij}$$

Subject-specific models: Fitting

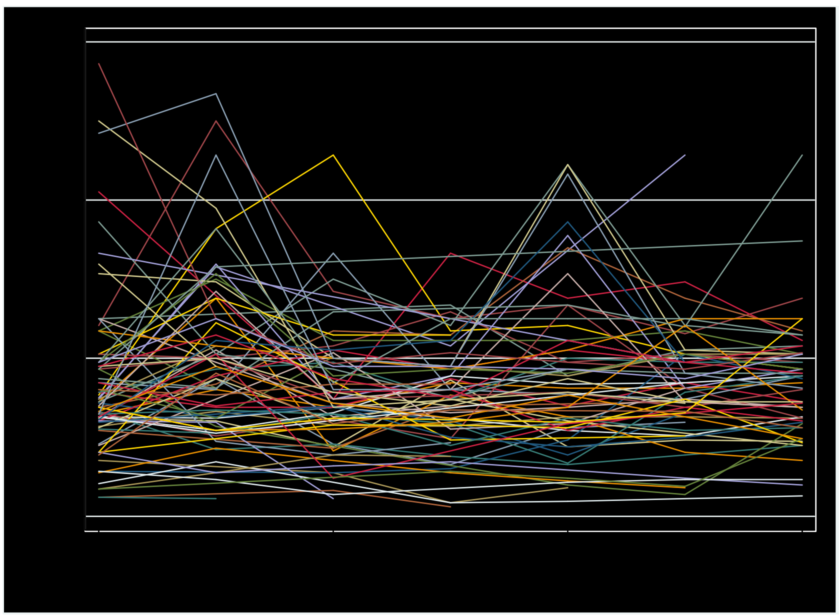
- Software
  - SAS: MIXED, random; GLIMMIX (macro); NLMIXED
  - SPSS: Advanced model package
  - Stata: xt… sequence
  - Other: HLM, MLWIN, Splus, R, winbugs
- Sister formulation: latent growth curve

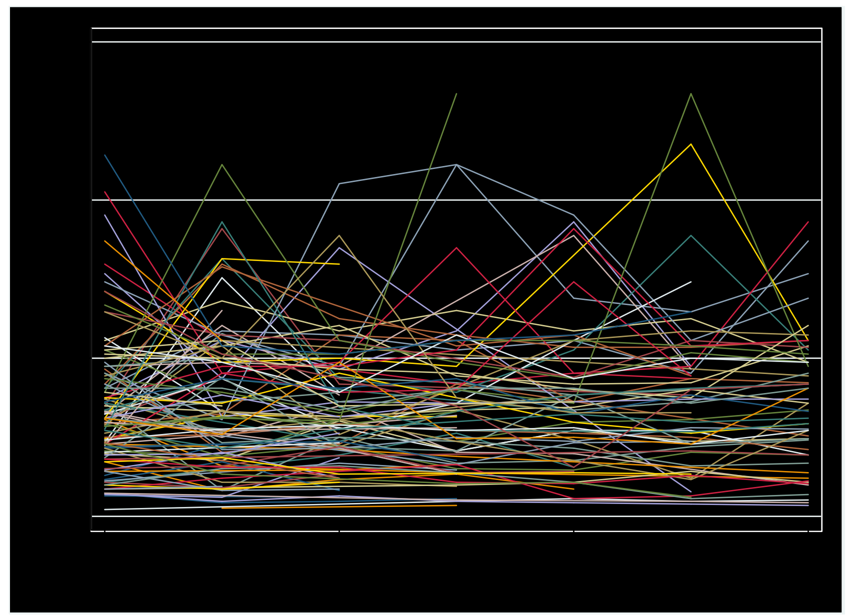
Data

Usual Walking Speed in WHAS Panel Plot



Usual Walking Speed in WHAS Spaghetti Plots





Emotionally vital

Emotionally non-vital

Usual Walking Speed in WHAS
Does vitality affect walking speed?

Parameter	ML: Independent	GEE: exchangeable	ML: unstructured	ML: Random b_0 & b_1
Intercept	.58 (.010)	.63 (.035)	.57 (.012)	.58 (.012)
Vitality	**.10 (.017)**	***.075 (.050)***	**.10 (.020)**	**.10 (.020)**
Time	.0026 (.003)	**-.031 (.012)**	**-.012 (.0022)**	**-.012 (.002)**
Vit*time	-.0015 (.005)	.017 (.018)	**.0068 (.0035)**	***.0062 (.0034)***
Main effects model: Intercept, vitality results very similar to above				
Time	.0020 (.0024)	**-.0058 (.002)**	**-.0091 (.002)**	**-.0094 (.002)**

wrong

Usual Walking Speed in WHAS Heterogeneity

- Residual SD, variance: 0.167, .0280
  - Represents variability of a woman's speeds "about" her own regression line
- Intercept SD, variance: 0.276, .0762
  - "Test-retest" estimate = .076/(.076+.028)=.73
- Slope SD, variance: 0.031, .00094
  - 95% of slopes estimated within +/-.06 of ~-.01
- Intercept, slope covariance: .0020
  - Correlation=.23: better trajectories for better starters
- Unstructured correlations: .6 - >.99
  - Highest late in the study

Vitality & Walking Speed in WHAS
Summary

- Beneficial association with emotional vitality
  - Begin better by ~.1; 95% CI ~ [.06,.14]
  - Moderate evidence: Decline rate ~ halved
- Remarkable stability evidenced
  - Modest average decline
  - Heterogeneity: moderate ↓ to modest ↑
  - Stability increased with duration in study
- To advance toward "causation": much needed
  - Control for confounders
  - Change on change

Population average v. Subject-Specific
How to choose?

- Science
- Advantages of subject-specific models
  - Characterization of heterogeneity–estimates
  - May well embody mechanisms
- Advantages of marginal models
  - More robust
    - Standard errors valid if correlation model wrong (GEE)
    - Fixed effect estimates distribution-insensitive
  - Computationally faster, more transportable (GEE)
- An MLE advantage: Missing data treatment

Why LDA?

- Top four reasons

4. To inform public policy
   – Changes in disability prevalence over time
3. To study natural histories
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Transition Models

- Basic idea: control model for current outcome on all past outcomes
  - "Autoregressive" errors
  - Modify marginal model to include past "Y"s as predictors in model for Y_{it}
- Often assumed: current outcome only depends on the one most immediately past
  - Model for Y_{it} includes Y_{it-1} but no other Ys
  - "First order Markov"

Beckett et al.,1996

Some important LDA Challenges

- Feedback, endogeneity
  - Decline in speed may erode emotional vitality… or, the vital may try harder at the measured walk test

- Dropout, missing data
  - Key distinction: ignorable, non-ignorable

- Nonlinear & clustered trajectories
  - Thresholds, changepoints, trajectory classes

Take home points

- If you're out to save Millions at a Time©
  - Population average (marginal) model
    - Choice 1: GEE (corr-robust) vs. MLE (missing-robust)
    - Choice 2: Association structure to fit?
  - Mean trajectory estimates not sensitive

- If one at a time, or seeking to target
  - Subject-specific (random effect) model
  - Benefit if model correct: heterogeneity characterization, missing-robust, MLE: precise

- Prognosis based on history: transitions

An Introduction to Latent Variable Models

LATENT VARIABLES: TRUTH, LIES, AND EVERYTHING BETWEEN

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December 11, 2007

Objectives
For you to leave here knowing…

- What is a latent variable?
- What are some common latent variable models?
- What is the role of assumptions in latent variable models?
- Why should I consider using—or decide against using—latent variable models?

ALATENT@

1. *Present or potential but not evident or active: latent talent.*
2. *Pathology. In a dormant or hidden stage: a latent infection.*
3. *Biology. Undeveloped but capable of normal growth under the proper conditions: a latent bud.*
4. *Psychology. Present and accessible in the unconscious mind but not consciously expressed.*

<u>The American Heritage7 Dictionary of the English Language</u>, Fourth Edition, 2000

Aexisting in hidden or dormant form but usually capable of being brought to light@

<u>Merriam-Webster's Dictionary of Law</u>, 1996

“LATENT”

“…concepts in their purest form….‘unobserved’ or ‘unmeasured’… ‘hypothetical’”

Bollen KA, Structural Equations with Latent Variables p. 11, 1989

“…in principle or practice, cannot be observed”

Bartholomew DJ, The Statistical Approach to Social Measurement, p. 12, 1996

“Underlying: not directly measurable. Existing in hidden form but usually capable of being measured indirectly by observables”

Bandeen-Roche K, Synthesis, 2006

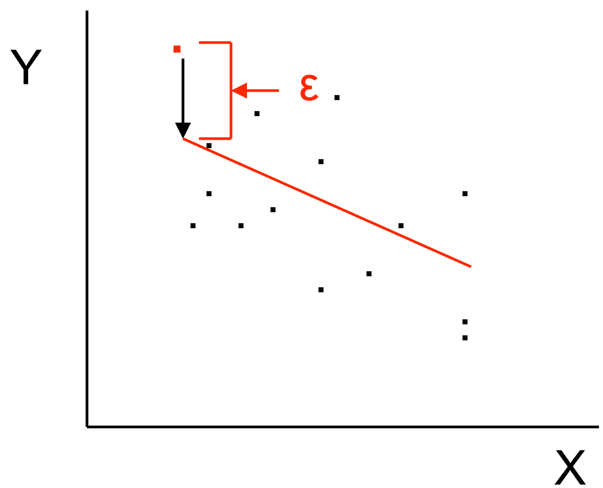
ALATENT VARIABLES@

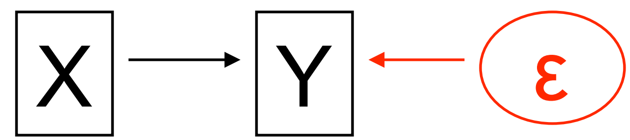
Ordinary linear regression model:

Y_i = outcome (measured)
$\underline{X}_i$ = covariate vector (measured)
ε_i = residual (unobserved)

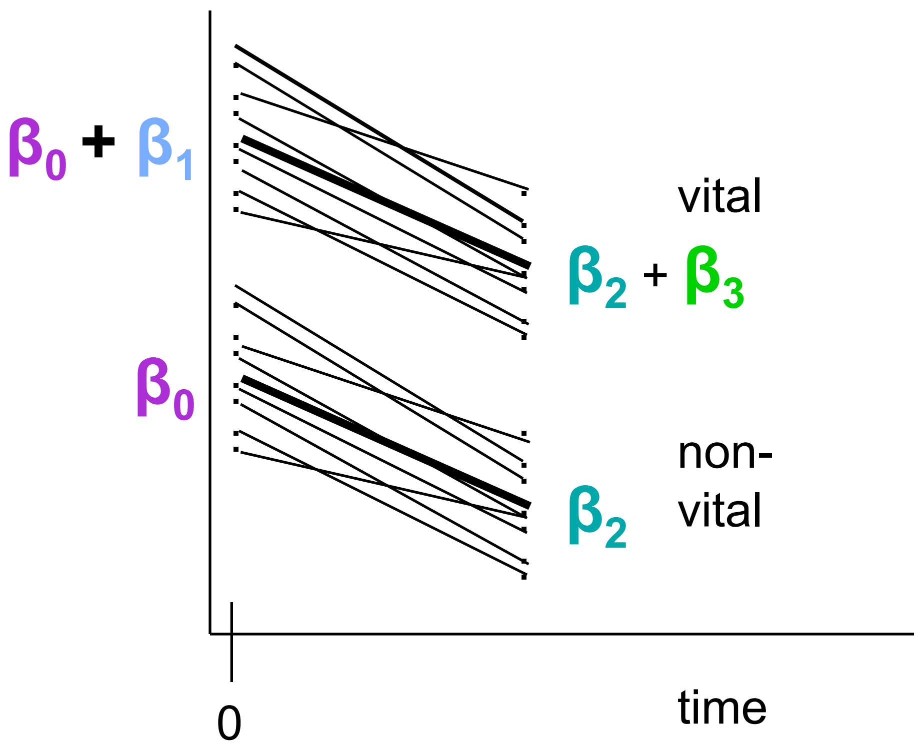
$$Y_i = \underline{X}_i^T \underline{\beta} + \varepsilon_i$$

Ordinary Linear Regression
Residual as Latent Variable



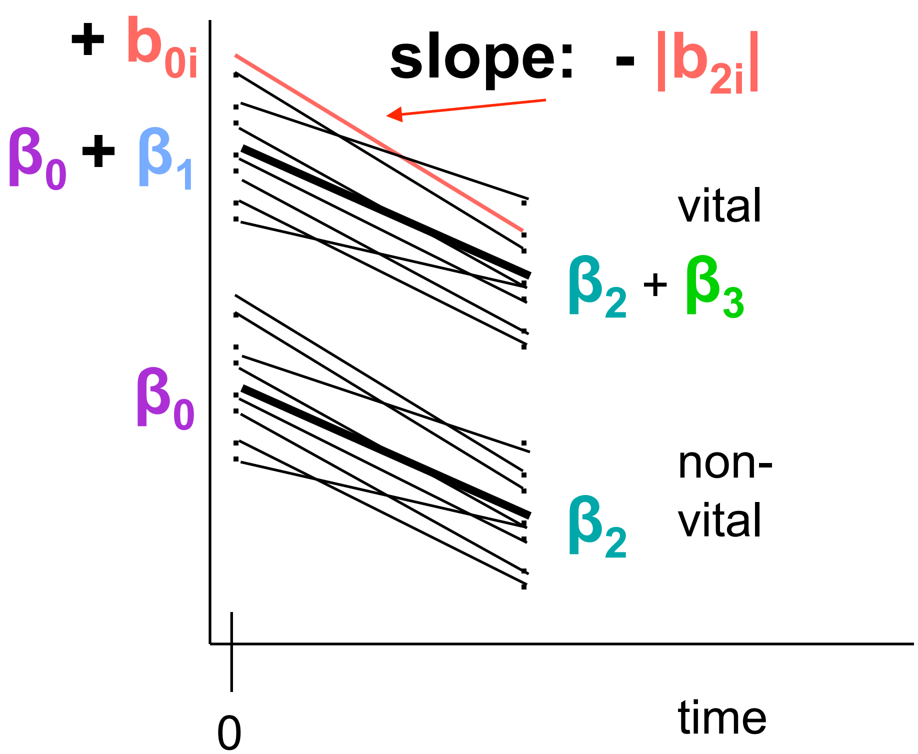


Mixed effect / Multi-level models
Random effects as Latent Variables



$$Y_{ij} = \beta_0 + \beta_1 x_i + \beta_2 t_{ij} + \beta_3 x_i \cdot t_{ij} + e_{ij}$$

Mixed effect / Multi-level models
Random effects as Latent Variables



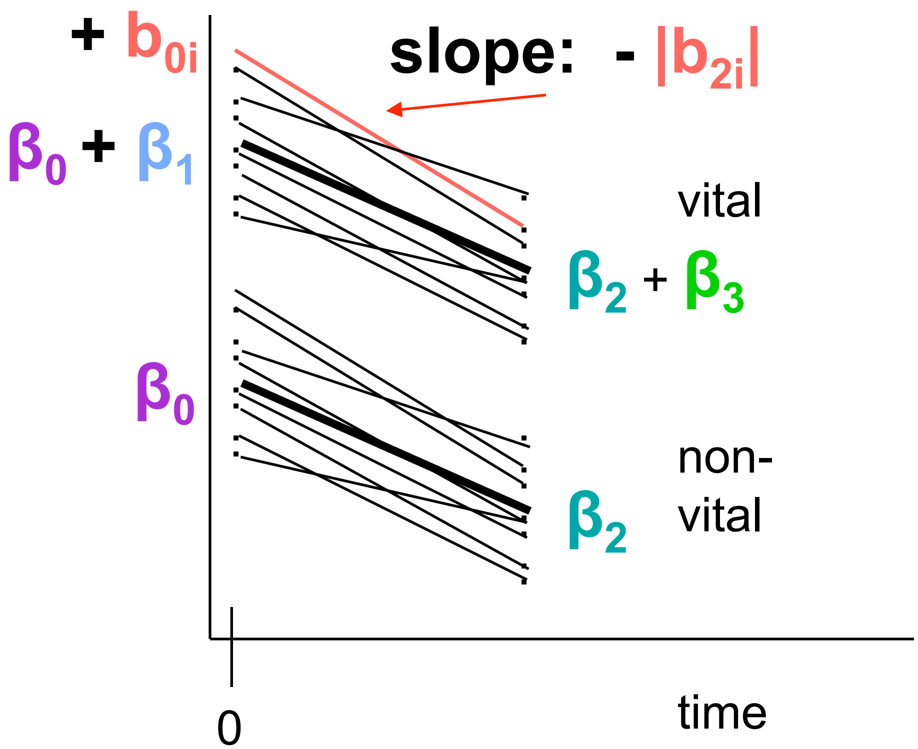
- b_{0i} = random intercept

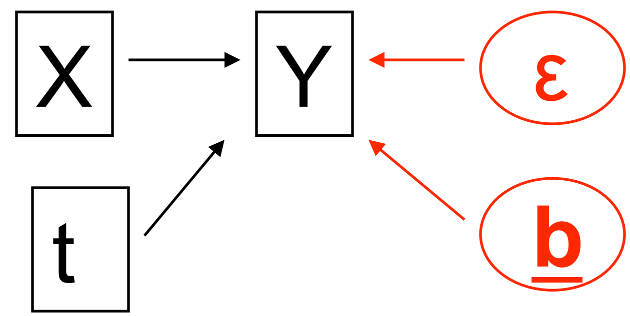
  b_{2i} = random slope

  (could define more)
- Population heterogeneity captured by spread in intercepts, slopes

$$Y_{ij} = \beta_0 + b_{0i} + \beta_1 x_i + \beta_2 t_{ij} + b_{2i} t_{ij} + \beta_3 x_i \cdot t_{ij} + e_{ij}$$

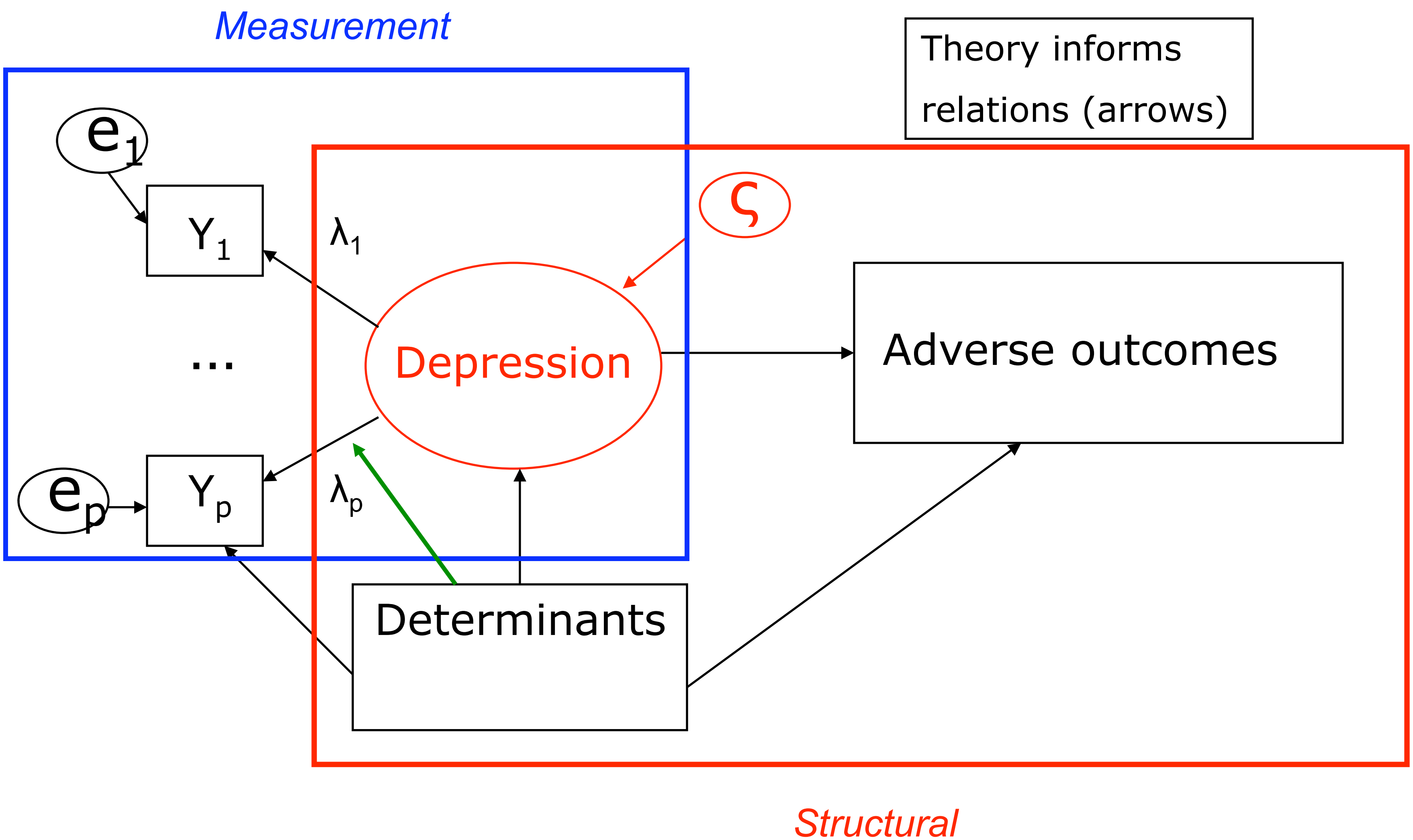
Mixed effect / Multi-level models
Random effects as Latent Variables





$$Y_{ij} = \beta_0 + b_{0i} + \beta_1 x_i + \beta_2 t_{ij} + b_{2i} t_{ij} + \beta_3 x_i \cdot t_{ij} + e_{ij}$$

Depression
Latent Variable Illustration



Why do people use latent variable models?

- The complexity of my problem demands it
- NIH wants me to be sophisticated
- Reveal underlying truth (e.g. “discover” latent types)
- Operationalize and test theory
- Sensitivity analyses
- Acknowledge, study issues with measurement; correct attenuation; etc.

Well-used latent variable models

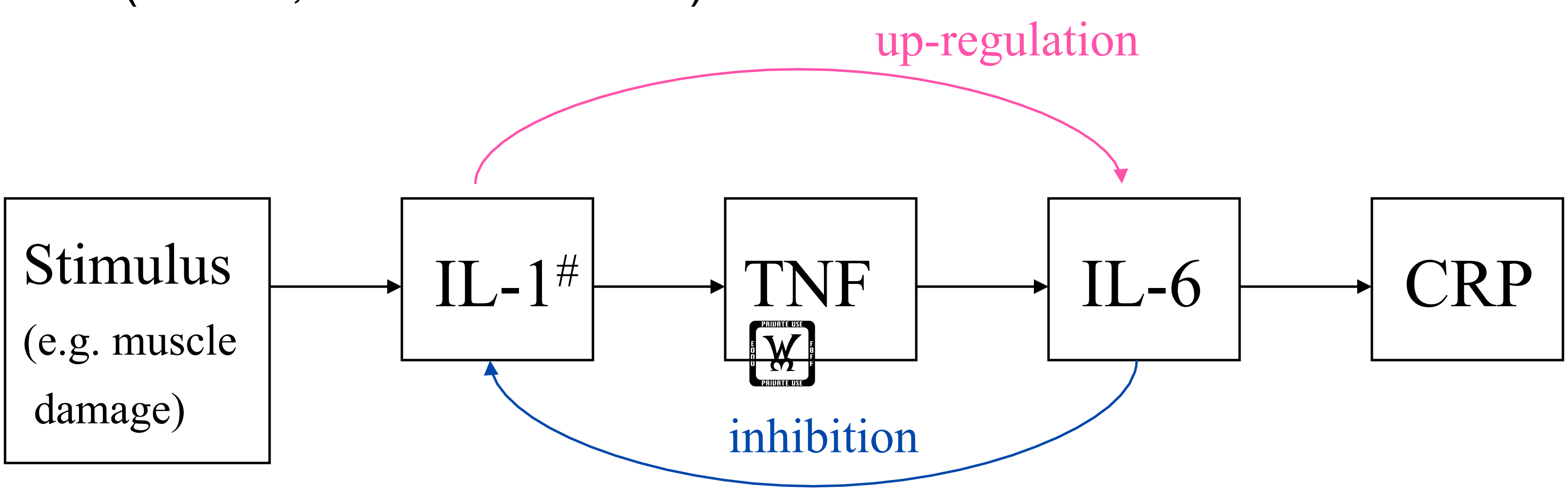
Latent variable scale	Observed variable scale	
	Continuous	Discrete
Continuous	Factor analysis LISREL	Discrete FA IRT (item response)
Discrete	Latent profile Growth mixture	Latent class analysis, regression

General software: MPlus, Latent Gold, WinBugs (Bayesian), NLMIXED (SAS)

LISREL software: LISREL, AMOS, CALIS (SAS)

Example: Theory Infusion

- Inflammation: central in cellular repair
- Hypothesis: dysregulation=key in accel. aging
  - Muscle wasting (*Ferrucci et al., JAGS 50:1947-54; Cappola et al, J Clin Endocrinol Metab 88:2019-25*)
  - Receptor inhibition: erythropoetin production / anemia (*Ershler, JAGS 51:S18-21*)

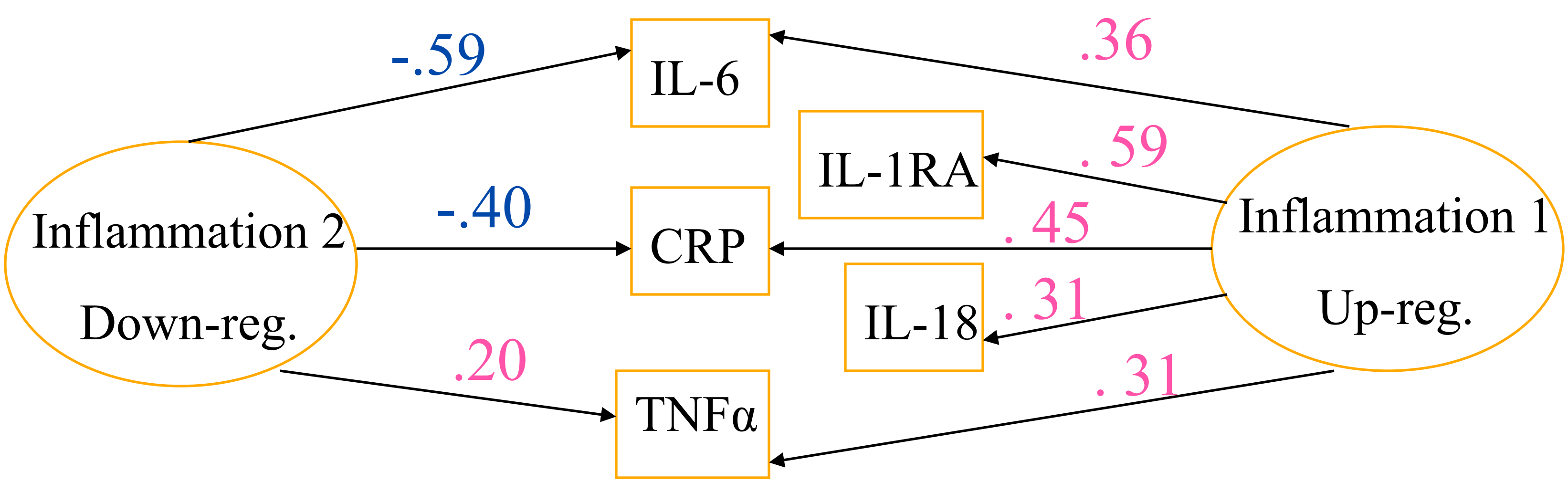


Difficult to measure. IL-1RA = proxy

Theory infusion

InCHIANTI data (*Ferrucci et al., JAGS, 48:1618-25*)

- LV method: factor analysis model
  - two independent underlying variables
  - down-regulation IL-1RA path=0
  - conditional independence



Application: Post-traumatic Stress Disorder Ascertainment

! PTSD

C Follows a qualifying traumatic event

> ***This study***: ***<u>personal assault</u>, <u>other personal injury/trauma</u>, <u>trauma to loved one</u>, <u>sudden death of loved one</u>***
= Ax@, along with gender

C Criterion endorsement of symptoms related to the event diagnosis

> Binary report on 17 symptoms = AY@

! A recent study (Chilcoat & Breslau, *Arch Gen Psych*, 1998)

C Telephone interview in metropolitan Detroit

C n=1827 with a qualifying event

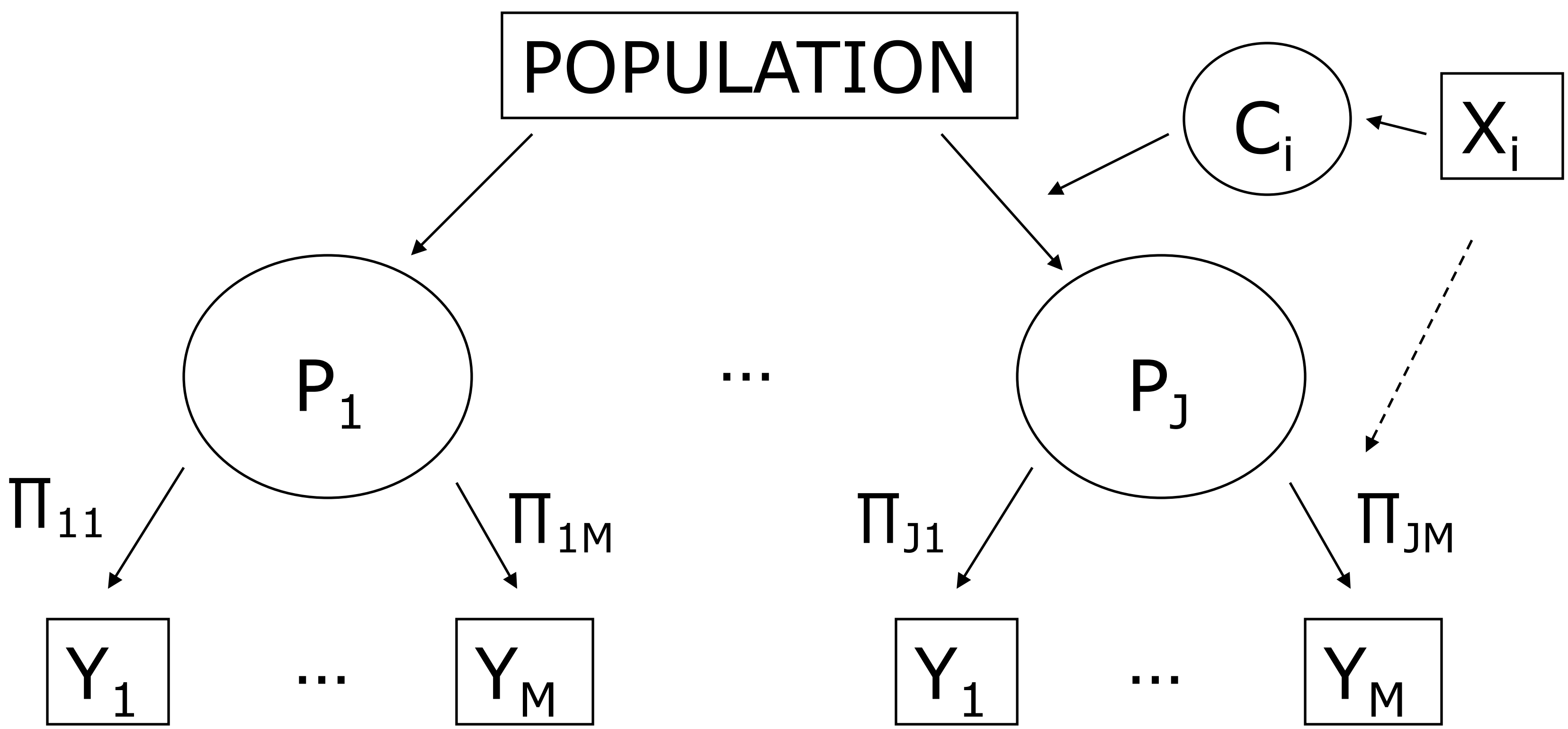
C Analytic issues

> Nosology

> Does diagnosis differ by trauma type or gender?

> *Are female assault victims particularly at risk?*

Analysis of underlying subpopulations
Latent class analysis / regression



19-Goodman, 1974; 27-McCutcheon, 1987

Analysis of underlying subpopulations
Method: Latent class analysis/ regression

- Seeks homogeneous subpopulations
  - **Assumption:** *reporting heterogeneity unrelated to measured or unmeasured characteristics*
  - *conditional independence, non differential measurement by covariates of responses within latent groups :* ***partially determine features***
- Features that characterize latent groups
  - Prevalence in overall population
  - Proportion reporting each symptom
  - Number of them

PTSD Study: Descriptive Statistics

Gender	**Trauma Type: percentage distribution**				**n**
	Personal Assault	*Other Injury*	*Trauma to loved one*	*Sudden death*	
Male	14.2	**37.7**	26.9	21.3	964
Female	14.3	26.3	**32.2**	**27.2**	863
Total	14.2	32.3	29.4	24.1	1827

! PTSD symptom criteria met: 11.8% (n=215)

- C <u>By gender</u>: 8.3% of men, 15.6% of women
- C <u>By trauma</u>: *assault (26.9%), sudden death (14.8%),other injury (8.1%), trauma to loved one (6.0%)*
- C <u>Interactions</u>: female x assault (▯), female x other (▯)
- C <u>Criterion issue</u>? 60% reported symptoms short of diagnosis

Latent Class Model for PTSD: 9 items

SYMPTOM CLASS	SYMPTOM (prevalence)	SYMPTOM PROBABILITY (π)		
		Class 1 - NO PTSD	Class 2 - SOME SYMPTOMS	Class 3 - PTSD
RE-EXPERIENCE	Recurrent thoughts (.49)	.20	**.74**	.96
	Distress to event cues (.42)	.12	**.68**	.88
	Reactivity to cues (.31)	.05	**.51**	.77
AVOIDANCE/ NUMBING	Avoid related thoughts (.28)	.08	.37	.75
	Avoid activities (.24)	.05	.34	.66
	Detachment (.15)	**.01**	**.14**	**.64**
INCREASED AROUSAL	Difficulty sleeping (.19)	.02	.18	.78
	Irritability (.21)	.02	.22	.83
	Difficulty concentrating (.25)	.03	.30	.89
MEAN PREVALENCE-BASELINE		.52	.33	.14

[Omitted: nightmares, flashback; **amnesia, ▯interest, ▯affect, short future;** hypervigilance, startle]

PTSD: DIAGNOSIS, LCR MEASUREMENT MODEL

! Method: Regress item responses on covariates Acontrolling@ for class
  C For simplicity: non-assaultive traumas merged into Aother trauma@

Variable	Odds Ratio or Interaction Ratio (CI)	By-item Odds Ratio MODEL 2
Female	1.07 (0.93,1.22)	1.07 (0.93,1.22)
Trauma =other than assault (recur.)	**3.19 (1.89,5.40)**	**3.19 (1.89,5.40)**
Cue distress x other trauma	**0.18 (0.09,0.38)**	**0.58 (0.36,0.92)**
Cue reactivity x other trauma	**0.14 (0.07,0.28)**	**0.44 (0.27,0.72)**
Avoid thoughts x other trauma	**0.21 (0.11,0.41)**	***0.68 (0.44,1.05)***
Avoid activities x other trauma	**0.11 (0.05,0.22)**	**0.35 (0.21,0.58)**
Detachment x other trauma	**0.27 (0.13,0.58)**	0.88 (0.51,1.49)
Difficulty sleep x other trauma	**0.43 (0.21,0.90)**	1.37 (0.78,2.42)
Irritability x other trauma	**0.28 (0.13,0.61)**	0.91 (0.52,1.59)
Concentration x other trauma	0.73 (0.36,1.47)	**2.33 (1.35,4.03)**

Summary
PTSD Analysis

- The analysis hypothesizes that PTSD is
  - a syndrome comprising **unaffected**, **subclinically affected**, and **diseased** subpopulations of those suffering traumas
  - reported homogeneously within subpopulations
- The hypotheses are consistent with current diagnostic criteria
- Gender x type interactions: are strongly indicated
  - Female assault victims at particular risk
  - ... given the subpopulations defined by the model

Summary
PTSD Analysis

! Symptoms appeared differentially sensitive to different traumas

Within classes: those who had a non-assaultive trauma were

C **less prone** to report distress to cues, reactivity to cues, avoiding thoughts, & avoiding activities

C **more prone** to report recurrent thoughts & difficulty concentrating

! Concern: Current criteria may better detect psychiatric sequelae to assault than to traumas other than assault

Objectives
For you to leave here knowing…

- What is a latent variable?
- What are some common latent variable models?
- What is the role of assumptions in latent variable models?
- Why should I consider using—or decide against using—latent variable models?

DISCUSSION
The Debate over Latent Variable Models

! **In favor**: they
- C acknowledge **measurement problems:** errors, differential reporting
- C **summarize** multiple measures **parsimoniously**
- C operationalize **theory**
- C describe population **heterogeneity**

! **Against**: their
- C **modeling assumptions** may determine scientific conclusions

- C **interpretation** may be ambiguous
  - > Nature of latent variables (*existence*)?
  - > Unique (***identif iability***)?
  - > Comparable fit of very different models (*estimability*)?
  - > Seeing is believing (*can the model be checked*)?

Some closing thoughts

- Useful information?
  - Enrichment for reading the literature
  - A sense of what's possible
  - Priming for thinking about study design
- Something to build on
  - Courses
  - Seminars
  - Mentoring