

**Prevention Models for Alcoholism: Implications for
Assessing Treatment Effects That Vary Across
Surrogate Endpoint Trajectory Classes**

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Presentation at the NIH Workshop Research Needs for the
Design and Analysis of Surrogate Endpoints in Clinical Trials
December 1-2, 1998, Potomac, Maryland

This work has benefitted from comments and assistance from
Hendricks Brown, Jason Liao, Linda Muthén, David Francis,
Tom Harford, Kerby Shedden, Damir Spisic, Siek-Toon
Khoo, Booil Jo, Noah Yang, Christy Kim Boscardin, Jin-Ok
Kim and others. The research was supported by an
Independent Scientist award from NIAAA.

Overview

- Introduction to general growth mixture modeling
 - Avoiding measurement error and accounting for heterogeneity using continuous and categorical latent variables
- Alcohol research example
 - Predicting alcohol dependence at age 30 from trajectories of heavy drinking development ages 18-25
- Unemployment/depression prevention trial example
 - Modeling intervention effects with non-compliance
- Implications for clinical trials with repeated measures of surrogate endpoint biomarkers
 - Two simulation studies

Mixtures and Latent Trajectory Classes

Modeling motivated by substantive theories of:

- Multiple Disease Processes: Prostate cancer (Pearson et al.)
- Multiple Pathways of Development: Adolescent-limited and life-course persistent antisocial behavior (Moffitt), crime curves (Nagin), alcohol development (Zucker, Schulenberg)
- Subtypes: Subtypes of alcoholism (Cloninger, Zucker)

EXAMPLE: Mixed-effects Regression Models for Studying the Natural History of Prostate Disease.

Pearson, Morrell, Landis, and Carter (1994).
Statistics in Medicine

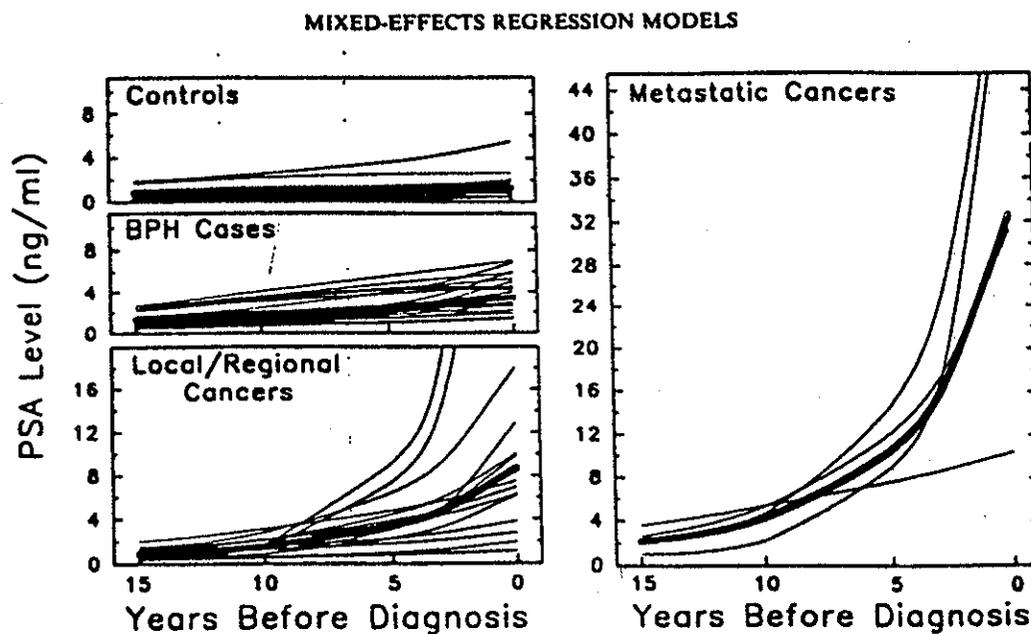
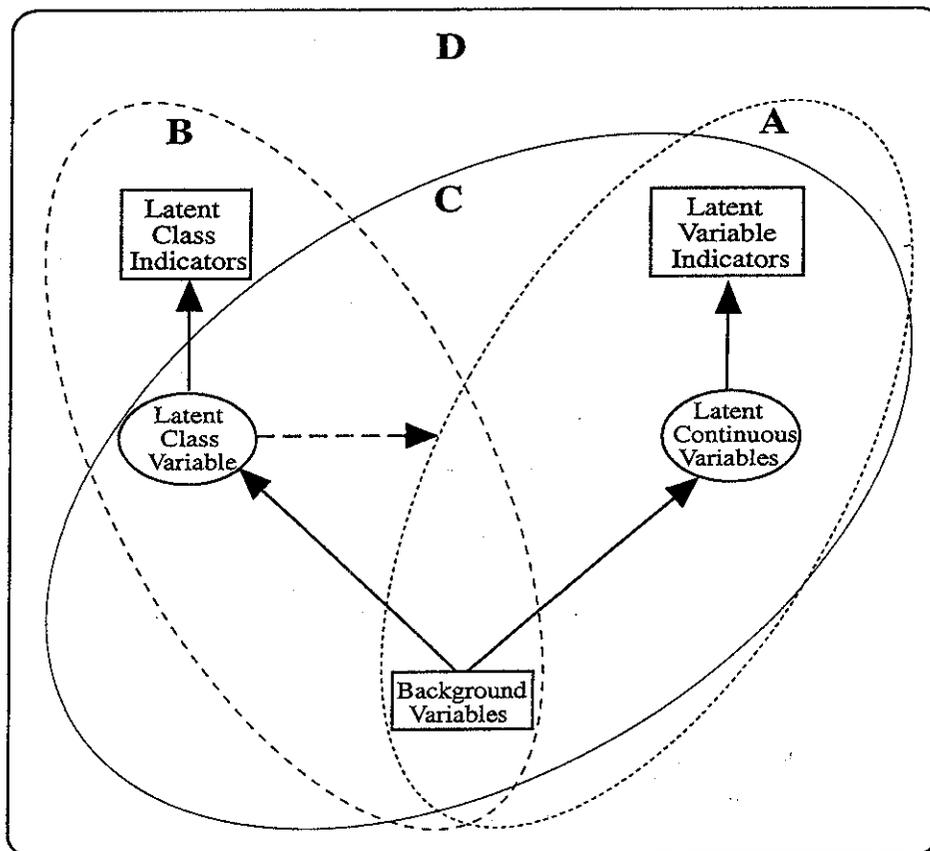


Figure 2. Longitudinal PSA curves estimated from the linear mixed-effects model for the group average (thick solid line) and for each individual in the study (thin solid lines)

Second-Generation SEM



Latent variable modeling with a combination of categorical and continuous latent variables

General Growth Mixture Modeling (GGMM)

Source:

- Muthén (1998). Second-generation structural equation modeling. In *New Methods for the Analysis of Change*.
- Muthén & Muthén (1998). *Mplus*

GGMM goes beyond conventional random coefficient growth modeling by using latent trajectory classes which

- Allow for heterogeneity with respect to:
 - Growth functions - different classes correspond to different growth shapes
 - Antecedents - different background variables have different importance for different classes
 - Consequences - class membership predicts later outcomes
- Allow for confirmatory analysis:
 - With respect to parameters - describing curve shapes
 - With respect to typical individuals - known classes
- Allow for classification of individuals:
 - Prediction of trajectory class membership
- Allow for enhanced preventive intervention analysis:
 - Different classes benefit differently and can receive different treatments

Analysis of Normative and Non-Normative Development in Heavy Drinking: Growth Curve Shapes

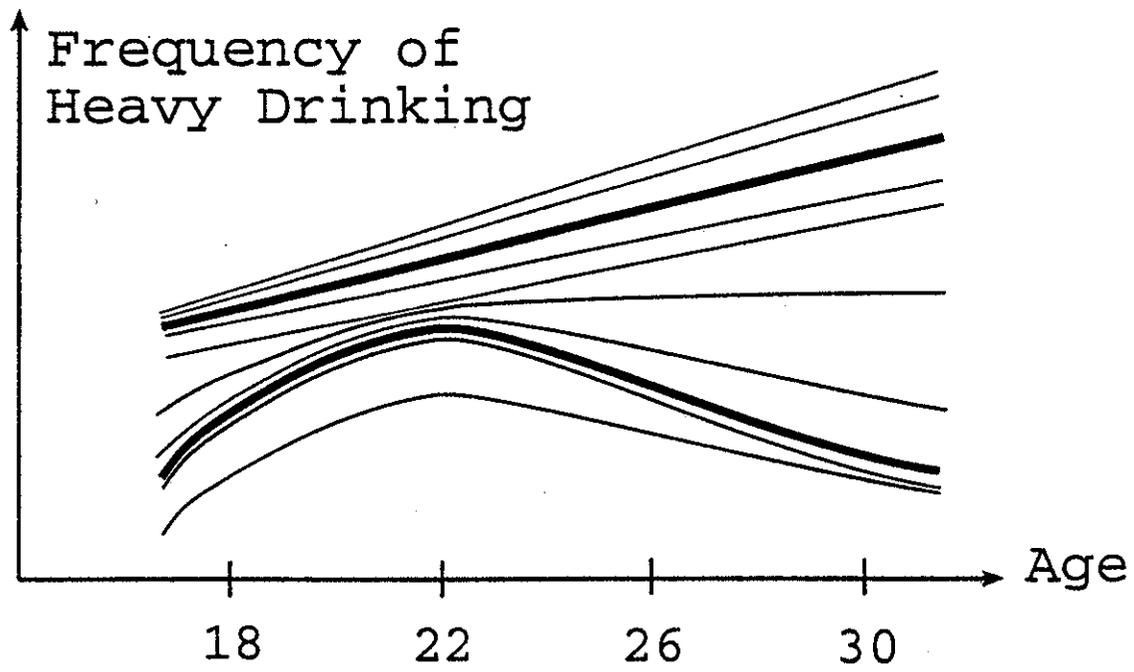
Source: Muthén & Shedden (1998). Finite mixture modeling with mixture outcomes using the EM algorithm.

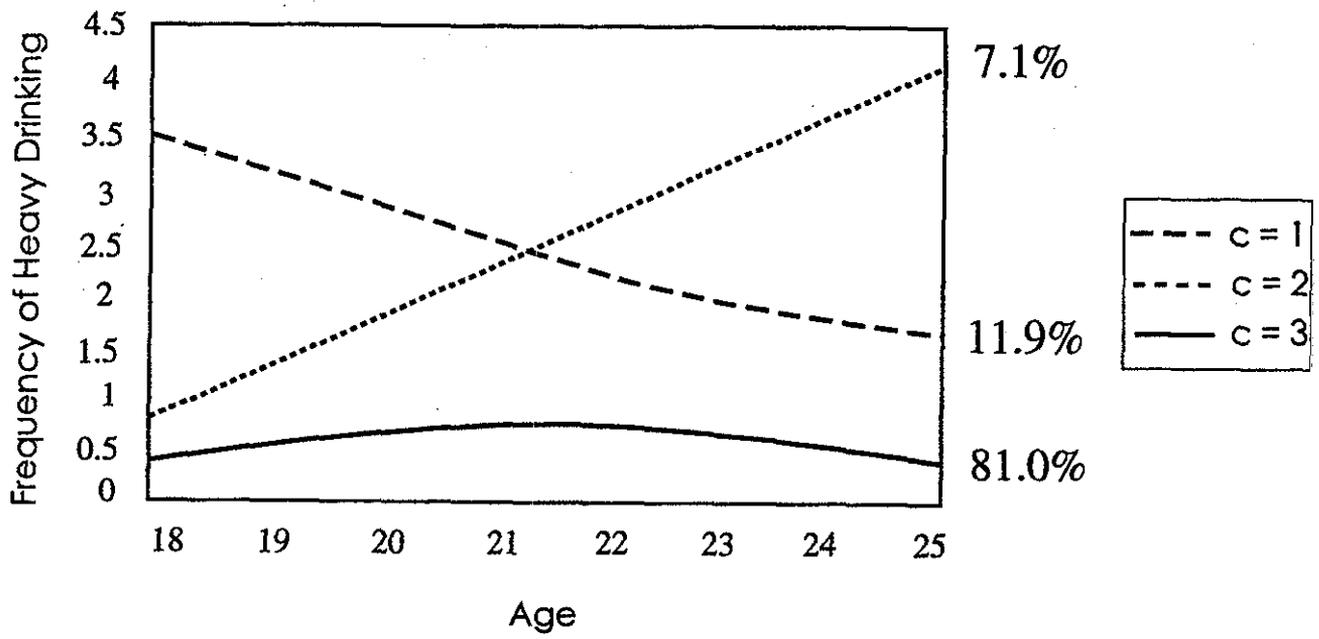
Forthcoming in *Biometrics*.

NLSY - National Longitudinal Survey of Youth

- Outcome variable: Frequency of heavy drinking during the last 30 days
- Background variables: Gender, ethnicity, family history of alcohol problems, early start, high school dropout
- This illustration: Heavy drinking at ages 18, 19, 20, 24, and 25 ($n = 935$), quadratic growth model
 - Model part 1: Predicting growth curve shapes 18 - 25
 - Model part 2: Predicting alcohol dependence at age 30 from the growth curve shapes
 - Maximum-likelihood estimation using Mplus

**Example: NLSY Heavy Drinking
Two Latent Trajectory Classes**



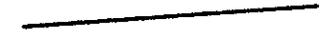
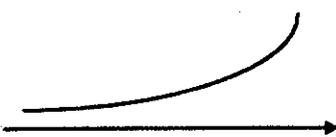
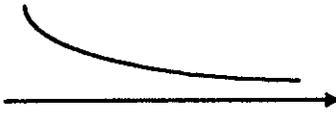


Predicting Trajectory Class Membership

Estimated Logit Coefficients:

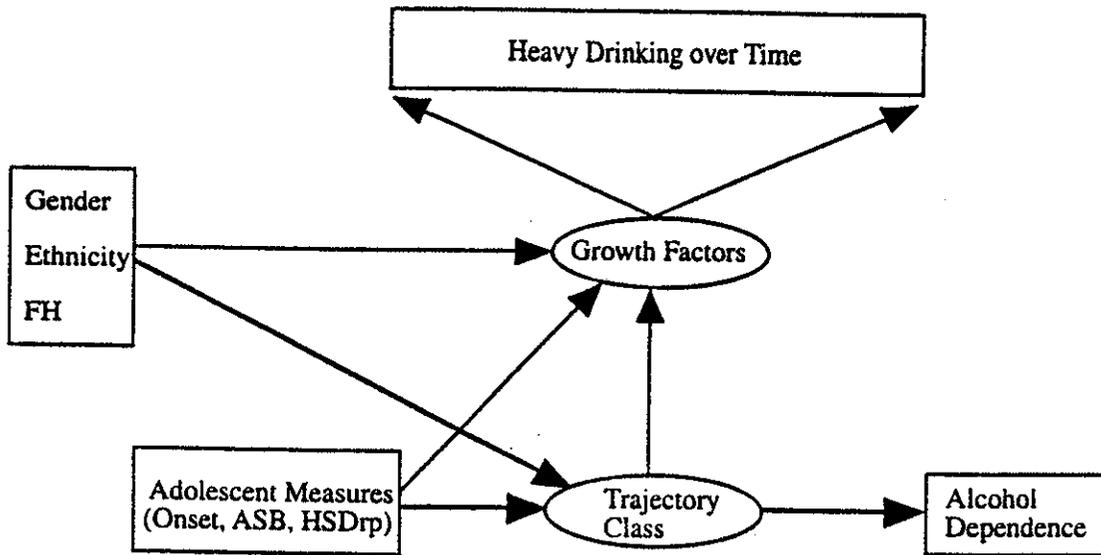
Covariate (x)	High vs Norm	Increase vs Norm
Male	1.25	1.48
Black	-1.60	-.67
Hispanic	-.22	.74
Early Onset	1.07	.62
FH123	.62	.68
Dropout	.22	.80
College	-.61	-.04

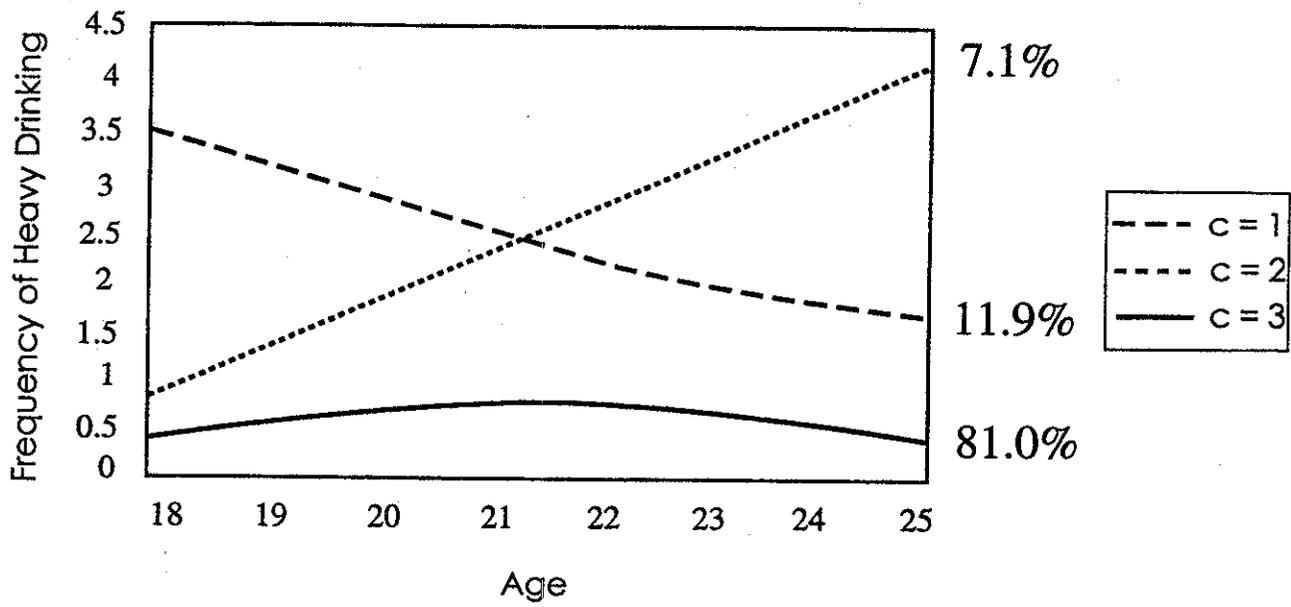
NLSY Heavy Drinking Developmental Trajectory Classes

Curve Type	Initial Status	Linear Change	Quadratic Change
	zero	zero	zero
	low	low, pos.	low, neg.
	low	high, pos.	high, neg.
	high	low, pos.*	zero
	low	high, pos.	pos.
	high	neg.	pos.

- Lower than for average curve.

NLSY: Antecedents and Consequences



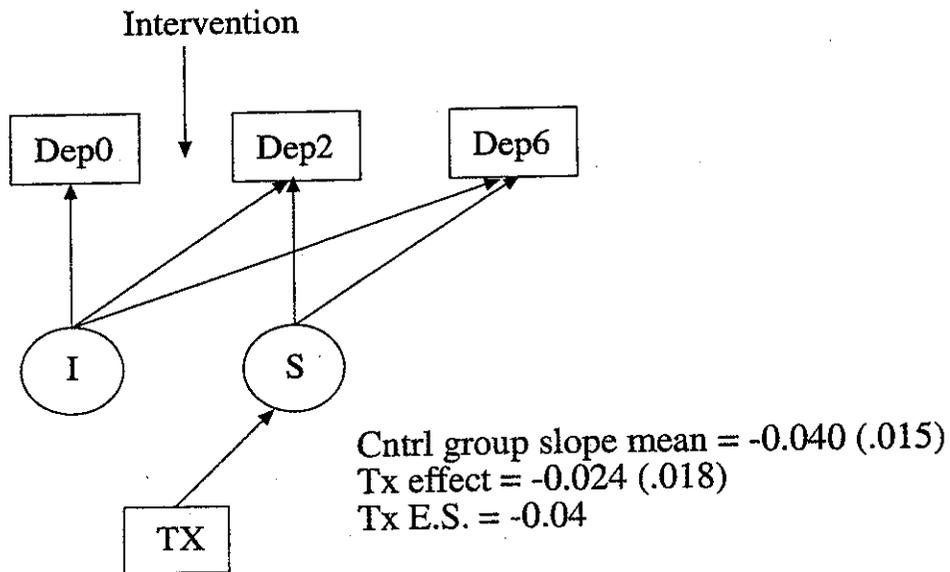


Odds Ratio

$P(\text{Dep} c=1) = 0.24$	4.90
$P(\text{Dep} c=2) = 0.36$	6.47
$P(\text{Dep} c=3) = 0.08$	1.00

Intervention Analysis with No-Shows: JOBS ITT Analysis

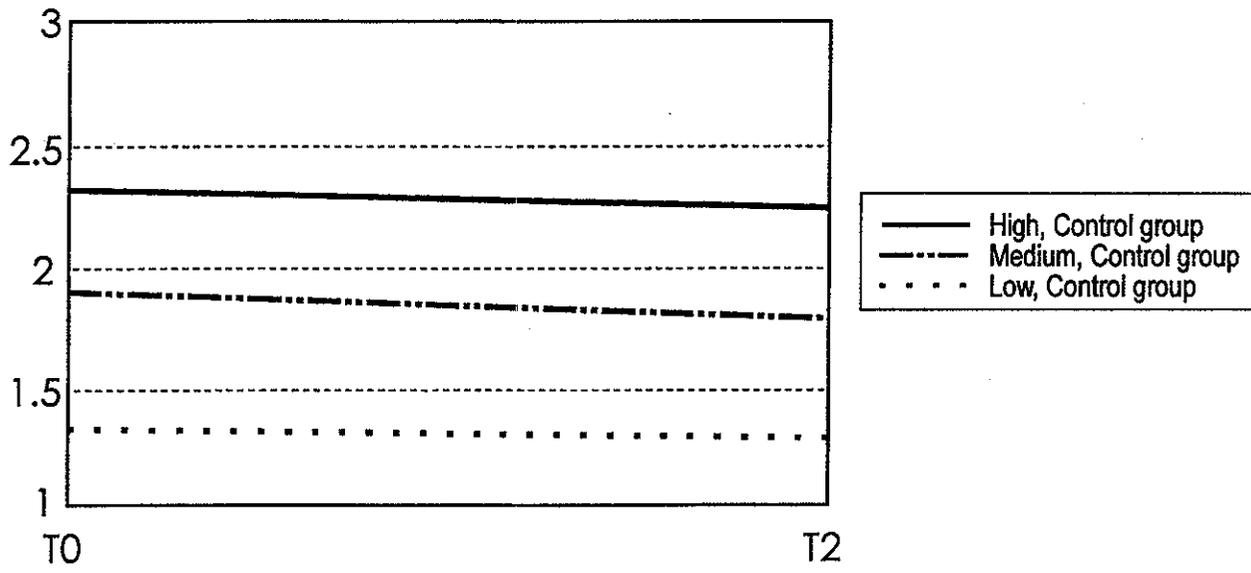
JOBS II (n = 1168): ITT Analysis



Treatment Group: Non-Compliers 308
 Compliers 488 (ratio = .61)
 Total 796 (ratio = .68)

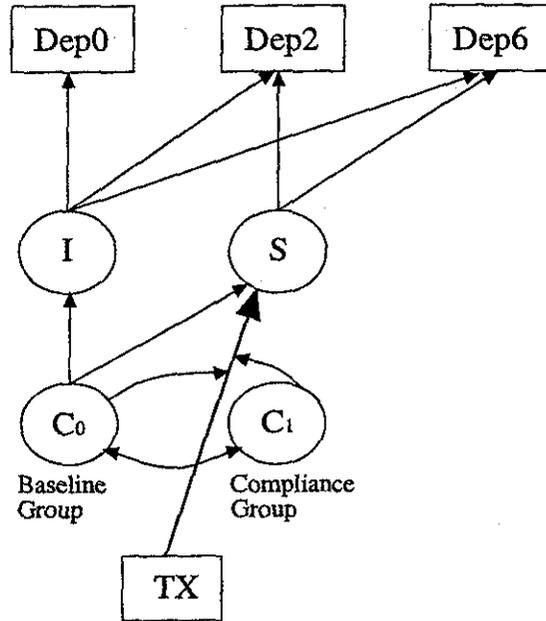
Control Group : Non-Compliers ?
 Compliers ?
 Total 372

JOBS, Controls



Intervention Analysis with No-Shows Cont'd

JOBS II : 6-Class Compliance x Baseline Mixture Analysis



Categories of People

			<u>Baseline C₀</u>			
			Low	Medium	High	
Cntrl	C ₁ : NC		a	b	c	
	C		d	e	f	
Tx	C ₁ : NC		g	h	i	g + h + i
	C		j	k	l	j + k + l

- Cell totals $g + h + i$ and $j + k + l$ known
- CACE : Comparing j with d , k with e , l with f

Jobs II: CACE Estimates for 6-Class Compliance x Baseline Mixture Model

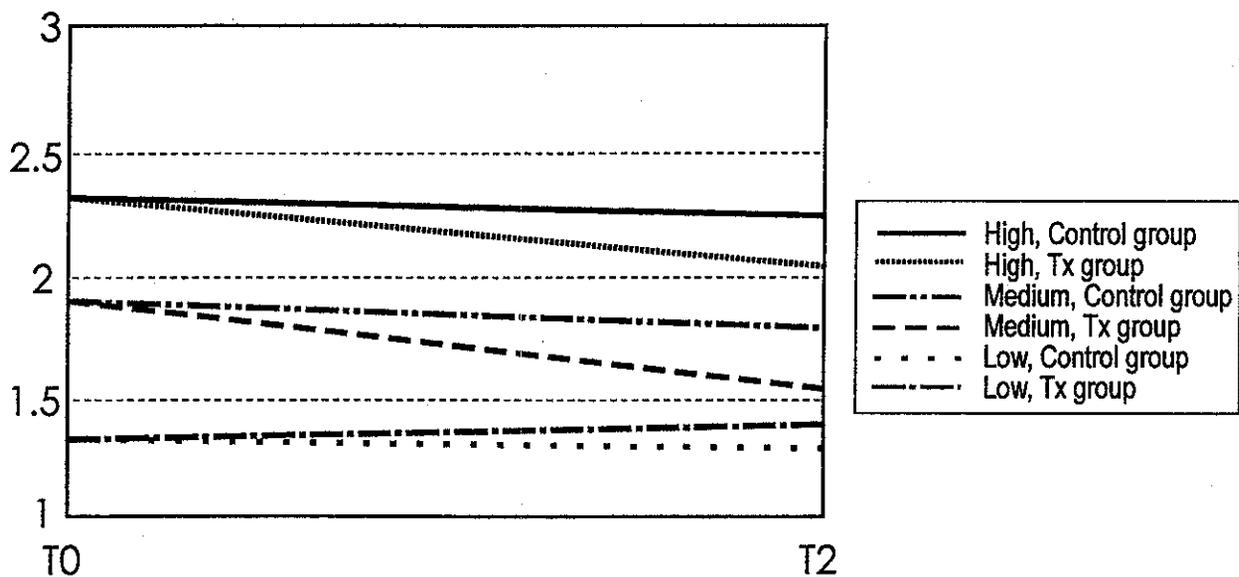
Complier Tx Effect (estimate (s.e.), E.S.):

Low baseline: .055 (.038), .16

Medium baseline: -.118 (.114), -.36

High baseline: -.103 (.024), -.32

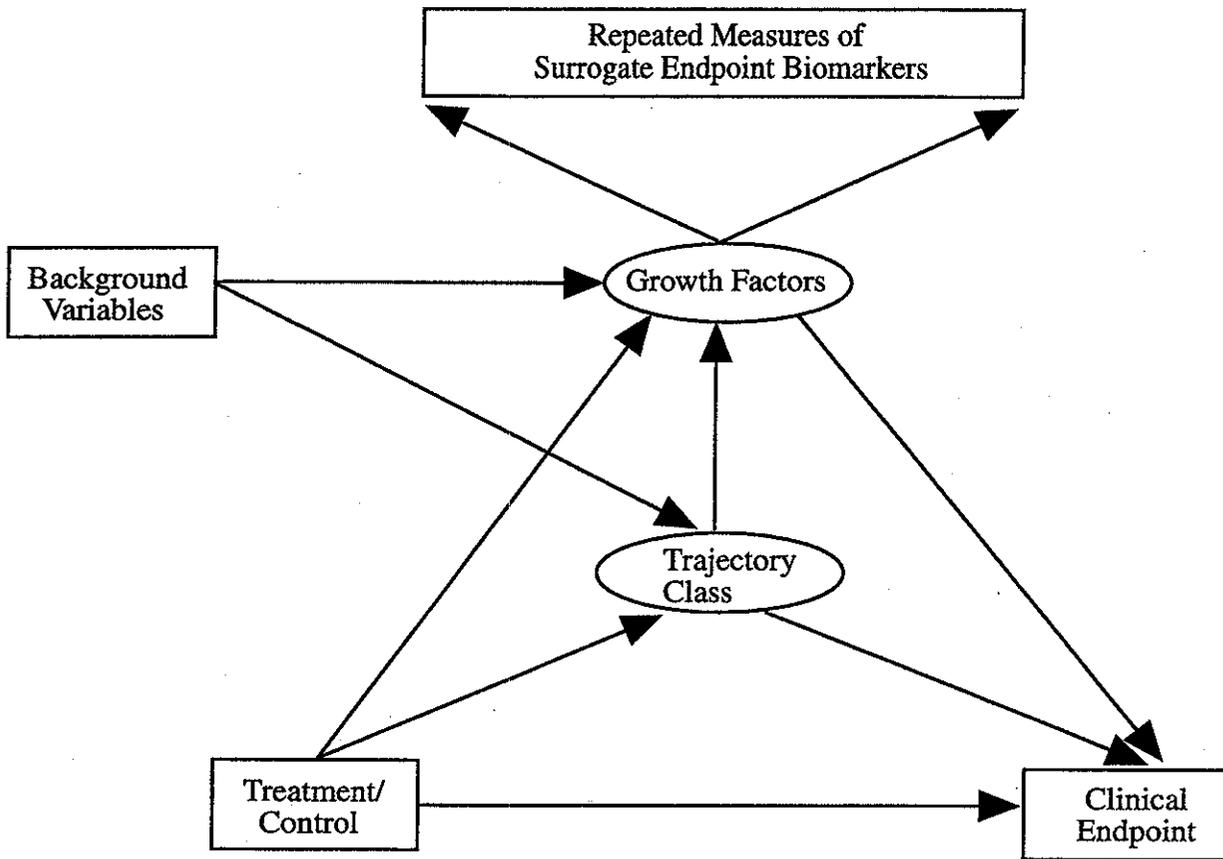
JOBS, Compliers

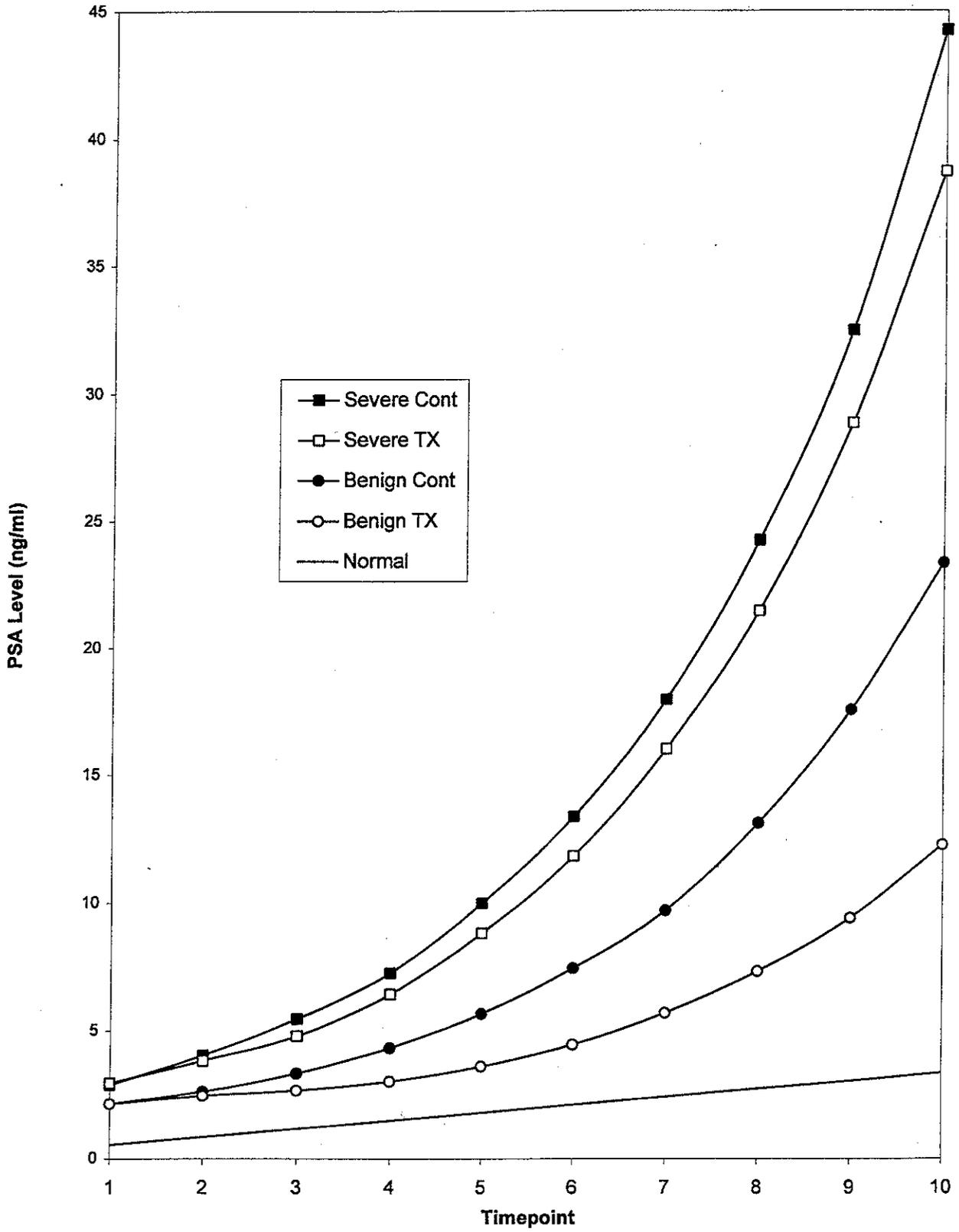


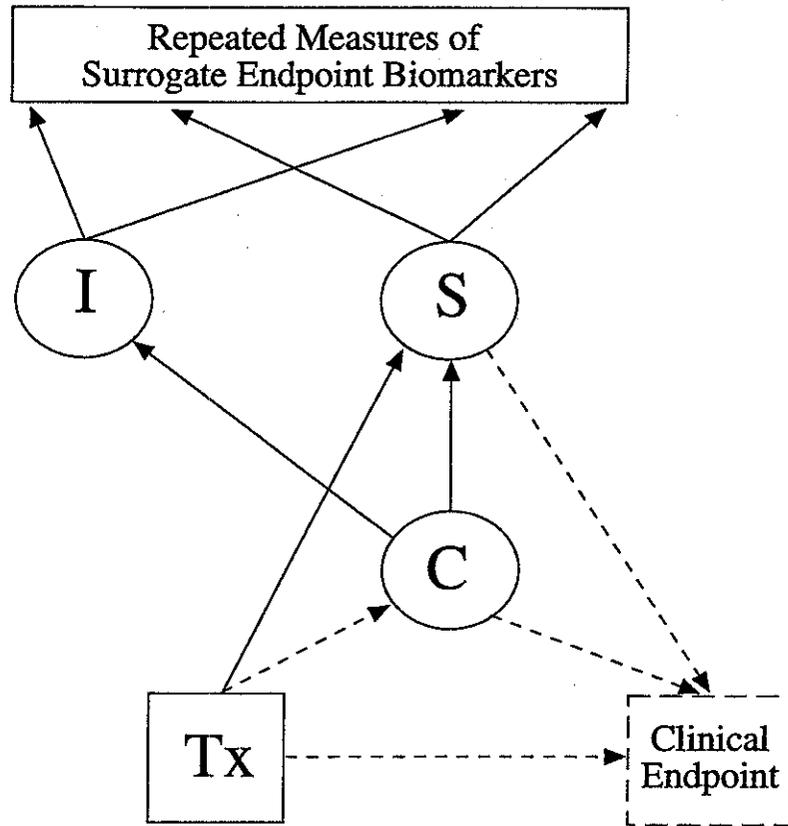
Implications for using Repeated Measures of Surrogate Endpoint Biomarkers in Clinical Trials

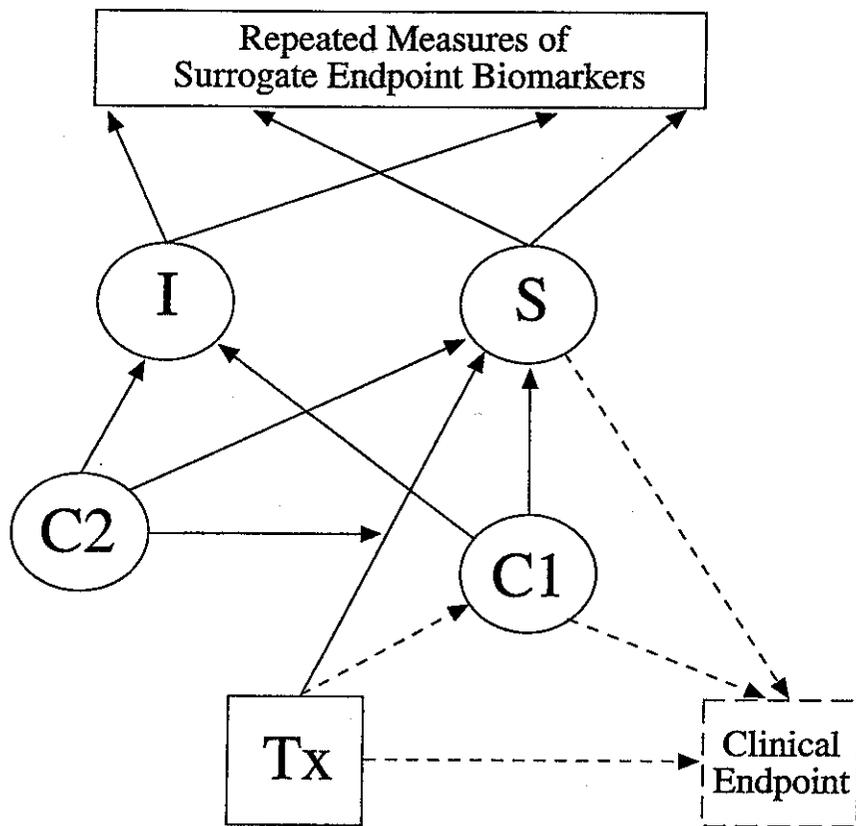
- Effort to learn maximally from surrogate markers
- Growth curve modeling of repeated measures limits measurement error problems by focusing on latent growth factors (random coefficients)
- General growth mixture modeling allows for heterogeneity in the form of latent classes of individuals with qualitatively different development
- Control group (placebo) has different growth trajectory classes
- Interventions often interact with individual characteristics (background, and/or surrogate marker baseline/growth intercept, growth rate, growth shape)
- Tx growth different from Control group growth, possibly within each class
- Tx effect estimation within class
- Non-compliance creates further classes
- Attempts can be made to absorb direct effects of Tx on clinical endpoints by including further latent variables and their measurements, adding further surrogate markers

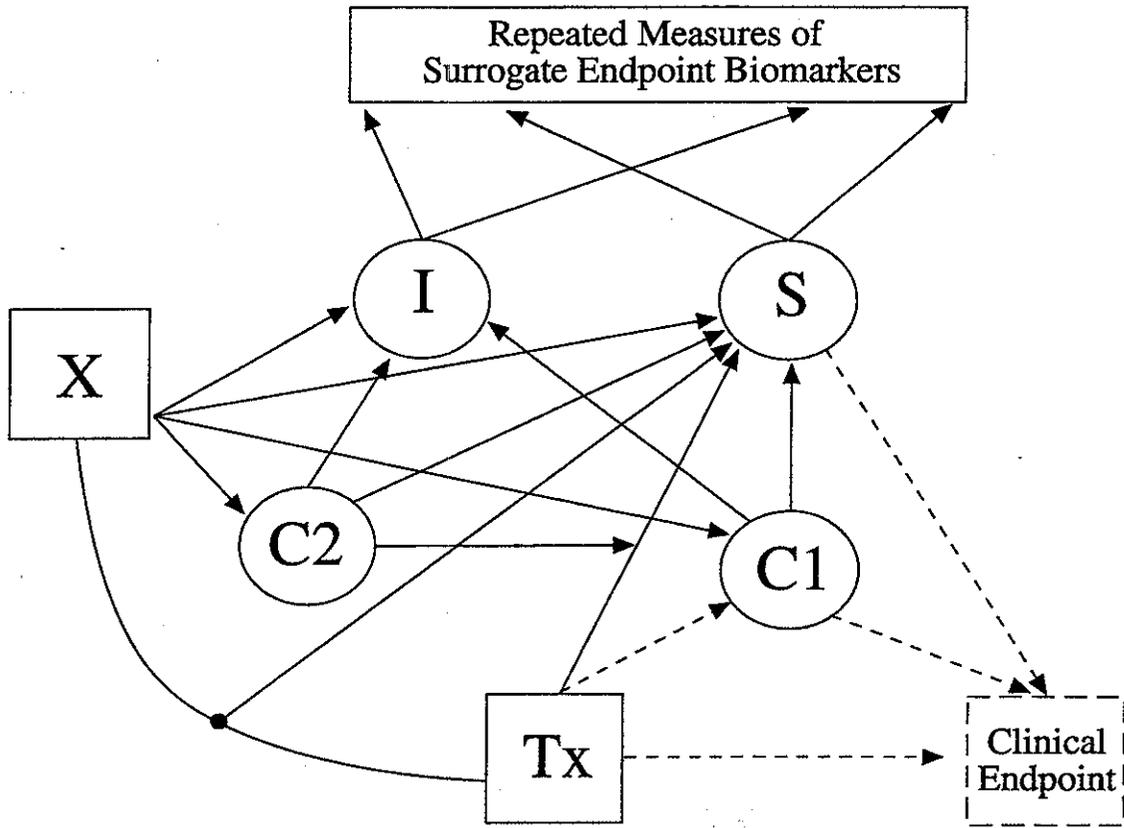
Surrogate Markers in Clinical Trials











Design Issues for using Repeated Measures of Surrogate Endpoint Biomarkers in Clinical Trials

- Sample size and power to detect Tx effects
- Number of time points
 - How soon can a study be ended?
 - Should the study go on longer for certain trajectory classes?
 - How well can individual class membership and growth factor values be estimated?
- Loss of power due to missing data
- Loss of power due to non compliance
- Increase power by
 - Pre-intervention measures of surrogate marker development
 - Pre-intervention background measures predicting growth (classes) and compliance
 - Compliance measurements
 - Using training data to limit trajectory class uncertainty