Transitional, Random Effects, and Latent Process Approaches for Analyzing Longitudinal Binary Data with Missingness: A Comparison of Approaches with Applications to an Opiate Clinical Trial

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Outline

- Motivating Example: Opiate Clinical Trial
- Four Approaches:
  1. Transitional approach, selection model.
  2. Shared random effects model
  3. Shared latent process approach
  4. Shared random transition model
- Each approach demonstrated with analysis
- Discussion

Opiate Clinical Trial

- National Institute on Drug Abuse (NIDA) conducted a trial to test the efficacy of buprenorphine in reduced the use of heroin amongst addict volunteers (Johnson et al. 1992).
- NIDA Conference in 1992.
- Design:
  - Randomize addicts into one of three groups:
    1. 40 mg Methadone (54 patients)
    2. 20 mg Methadone (55 patients)
    3. 8 mg Buprenophine (53 patients)

Opiate Clinical Trial (Continued)

- Outcome:
  - Urine tests thrice weekly on Monday, Wednesday, and Friday over a 17 week period.
  - Binary outcome assessing whether urine tests are positive for opiates at each follow-up visit.
  - Scientific focus: What is the effect of treatment on opiate-use process?
    1. Test for overall difference in process across arms
    2. Compare (1) the proportion of positive urine tests over follow-up and (2) the mean number of visits to the first occurrence of a positive test after four weeks of follow-up across treatment arms.

Features of the Data Set

- Long sequences of binary data with *Intermittent Missing* and *Dropout* (non-monotone missing data mechanism)
  - 51 scheduled follow-up visits.
  - Intermittent missing: missing for urine test.
  - Dropout-withdrawal from the study.
  - Over 50% of subjects withdrew from the study.
  - All but one patient had at least one missed visit before withdrawal or completion of the study.
  - Typical sequence: 0 0 0 1 1 2 1 1 1 2 2 9 9 9 9 9
- Potentially different opiate-use process, intermittent missing pattern, and dropout pattern by treatment group.

Features of the Data Set (Continued)

- Different nonignorable missing data mechanism in the different treatment groups.
  - It is likely that a patient will miss a visit or dropout from the study if he/she is currently using drugs.
  - Correlation between proportion of positive tests and time to dropout is -0.44 and -0.10 for the buprenorphine and methadone groups, respectively.
  - Correlation between proportion of positive tests and proportion of intermittent missing visits before dropout or completion of the study is 0.40 and 0.29 in the buprenorphine and methadone groups, respectively.

Observed Frequency of Positive Opiate Use Over Time by Treatment Group

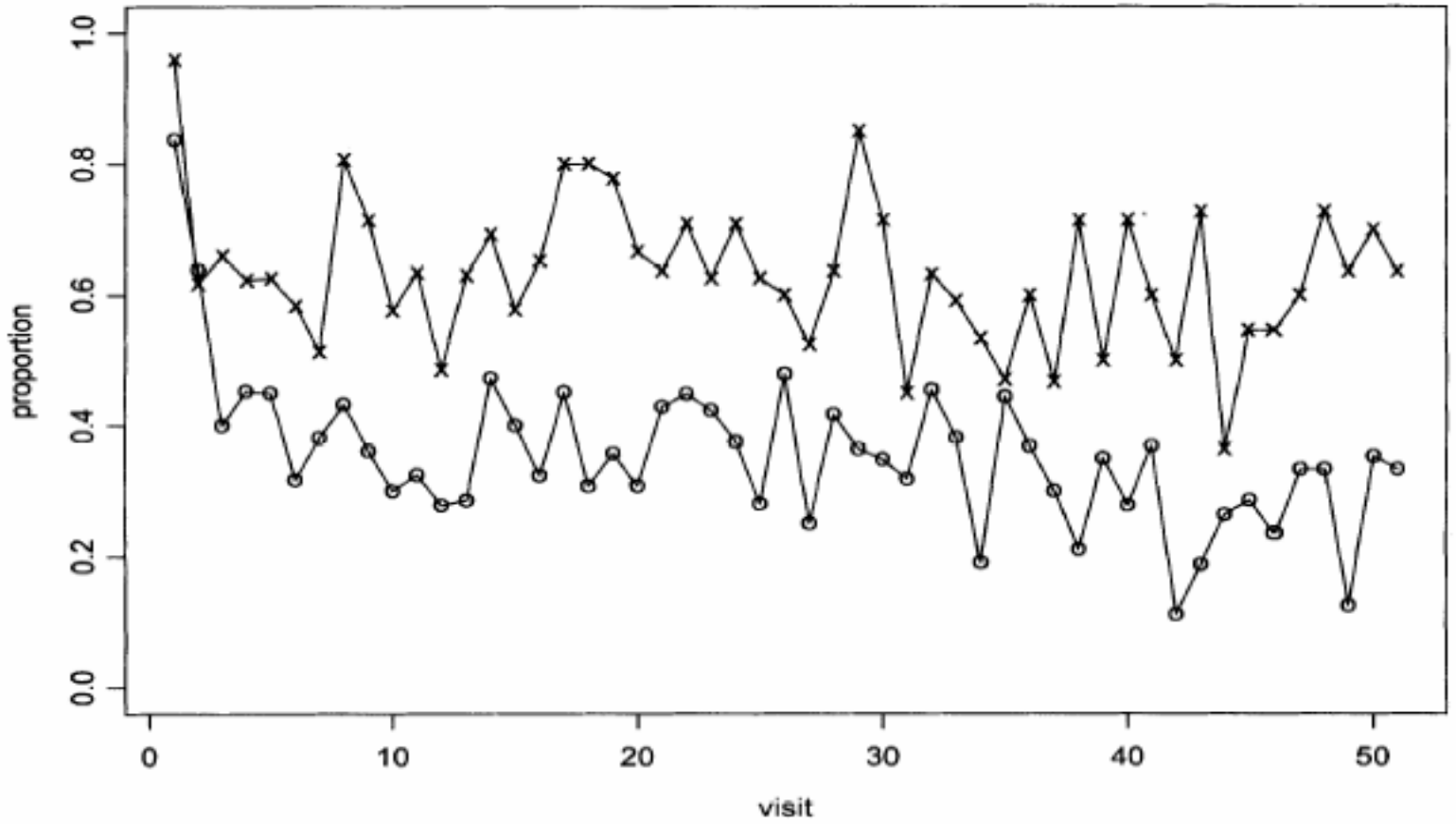
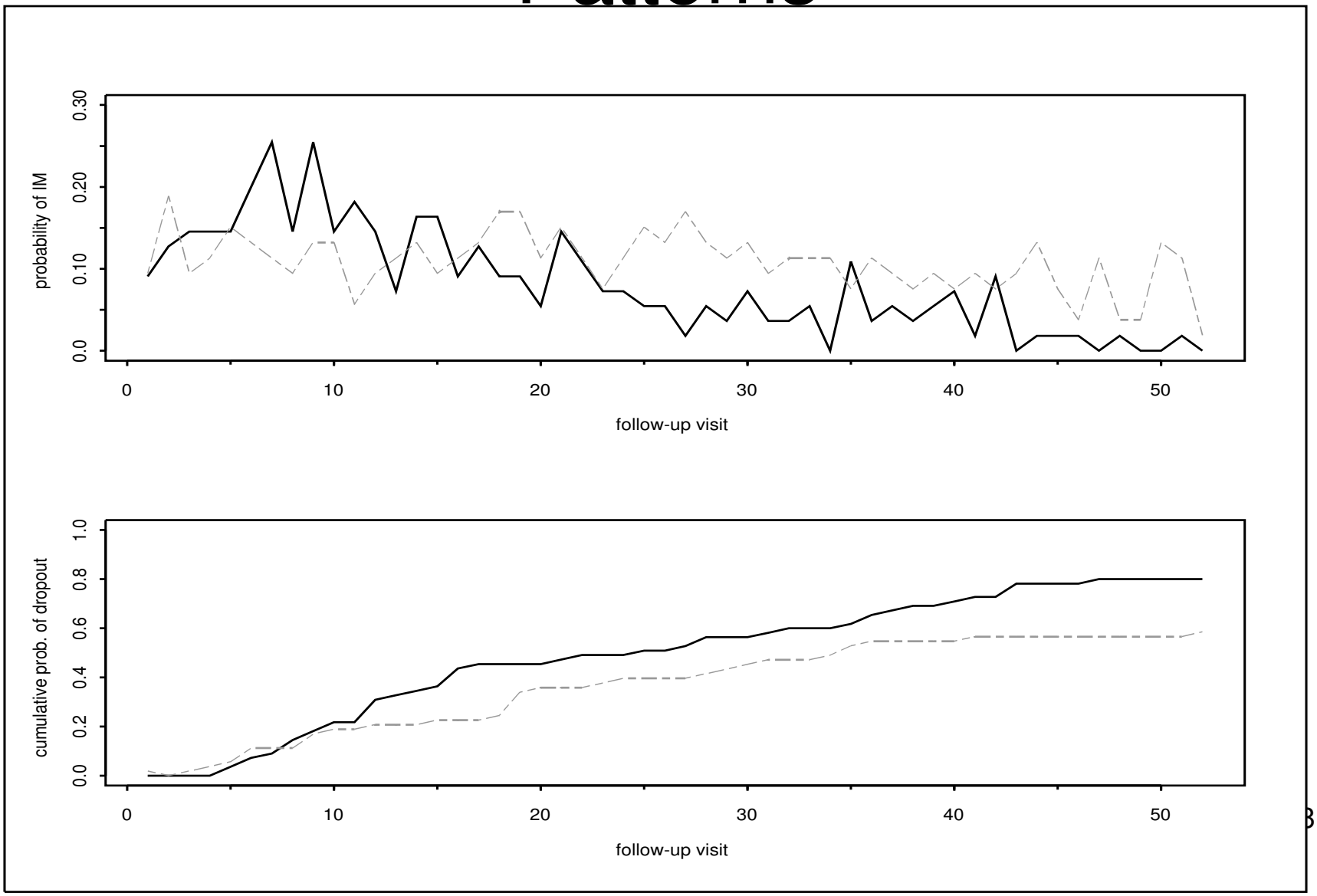


Figure 1. Observed frequency of positive opiate use over time by treatment. ×, methadone 20 mg; ∘, buprenorphine.

Intermittent Missing and Dropout Patterns



Approaches:

Y_{it} binary outcome Z_{it} missing outcome

- Transition/Selection Model:

$$\log itP(Y_{it} = 1 | Y_{i,t-1}) = X'_{it}\,\beta + \alpha Y_{i,t-1}$$

$$P(Z_{it}) = g(Y_{it})$$

- Shared Random Effects Model:

$$\log itP(Y_{it} = 1 | b_{it}) = X'_{it}\,\beta + Z'_{it}\,b_i,$$

$$P(Z_{it}) = g(\theta b_i), \qquad b_i \sim N(0,D)$$

Approaches (Continued):

- Shared Random Processes:

$$\log itP(Y_{it} = 1 \mid b_{it}) = X'_{it}\,\beta + b_{it},$$

$$P(Z_{it}) = g(\theta b_{it}), b_{it} \sim \text{AR Gaussian Process}$$

- Shared Random Transition Model:

$$\log itP(Y_{it} = 1 \mid Y_{i,t-1} = 0) = X'_{it}\,\beta_{01} + b_i$$

$$\log itP(Y_{it} = 0 \mid Y_{i,t-1} = 1) = X_{it}'\,\beta_{10} + \delta b_i$$

$$P(Z_{it}) = g(\theta b_i), \qquad b_i \sim N(0,\sigma^2)$$

Approaches (Continued):

- For Opiate Clinical Trial:
  - Model parameters themselves are not of direct interest.
  - Interest is on (i) Marginal means (μ_1) and (ii) First occurrence of a positive urine test 4 weeks after randomization (μ_2) .

Transition/Selection Model

- Transition Models:
  - Zeger and Qaqish (1988): Define H_t as the history of past q observations and present and past covariates.

$$\log itP(Y_{it} = 1 | H_t) = X_{it}'\beta + \sum_{l=1}^{Q} \theta_l f_l(H_t)$$

  - Testing for treatment effect on transition process (Q=2,q=1)

$$\log itP(Y_{it} = 1 | H_t) = \beta_0 + \beta_1 G + \theta_1 y_{i,t-1} + \theta_2 y_{i.t-1} G$$

Transition/Selection Model (Continued)

- Complete data parameterized as:

$$\log itP(Y_{it}=1 \mid H_t)=\beta_0+\beta_1 G+\theta_1 y_{i,t-1}+\theta_2 y_{i.t-1}G$$

- Missing data mechanism parameterized as

$$P(Z_{it}=m \mid Z_{i,t-1}=l, Y_{it})=\frac{\phi(l,m)}{\sum_{m=1}^{3}\phi(l,m)}$$

  - $\phi(l,l)$ is constrained to be 1
  - $\phi(2,0)=\phi(2,1)=0$
  - $\phi(l,m)=\exp(\gamma_{0lm}+\gamma_{1lm}G+\gamma_{2lm}Y_{it}+\gamma_{3lm}GY_{it})$

Transition/Selection Model (Continued)

- Let $Y_i=(Y_{i1}, Y_{i2},\ldots, Y_{in})'$ be complete binary observations and $Z_i=(Z_{i1}, Z_{i2},\ldots, Z_{in})'$ be missing data indicators

- Joint distribution for q=1:

$$P(Y_i,Z_i) = P(Y_{i1},Y_{i2},...,Y_{in},Z_{i1},Z_{i2},...,Z_{in})$$

$$= \{P(Y_{i1})\prod_{t=2}^{n} P(Y_{it} \mid Y_{i,t-1})\}\{P(Z_{i1} \mid Y_{i1})\prod_{t=2}^{n} P(Z_{it} \mid Z_{i,t-1}, Y_{it})\}$$

Transition/Selection Models (Continued)

- Estimation:
  - $L = \prod_{i=1}^{I} L(Y_i^O, Z_i),$ where $L(Y_i^o, Z_i) = \sum_{Y_i^M} L(Y_i^o, Y_i^M, Z_i)$
  - Enormous number of terms in the summation for opiate example (n=51)
  - We developed an E-M algorithm which makes estimation feasible:

$$\max_\theta \sum_{i=1}^{I} E_{Y_i^M | Y_i^o, Z_i, \theta}[\log L(Y_i^o, Y_i^M, Z_i; \theta)]$$

Transition/Selection Model (Continued)

- E-step uses a type of Forward-Backward Algorithm (Baum, et al., 1970). See Albert (2000) for details.

- Use the Bootstrap for standard errors

- Estimate proportion of positive tests (μ_1) and the mean number of visits to the first occurrence of a positive urine test four weeks after randomization (μ_2)

Transitional/Selection Model: Analysis of Opiate Trial Data

- Parameter estimates not of direct interest.
- Summary measures for buprenorphine and methadone groups:
  - Selection model:
    $\hat{\mu}_1$ =0.41 (SE=0.05) and 0.63 (0.05).
    $\hat{\mu}_2$ =3.61 (0.67) and 1.69 (0.23).
  - Ignorable model:
    $\hat{\mu}_1$ =0.34 (0.05) and 0.61 (0.06).
    $\hat{\mu}_2$ =4.48 (0.89) and 1.75 (0.31).

Shared Random Effects Model

- Response Model:

$$\log itP(Y_{it} = 1 \mid b_i) = \beta + b_i$$

- Missing Model:

$$P(Z_{it} = l \mid b_i, Z_{i,t-1} \neq 2) = \frac{\exp(\eta_l + \gamma_l b_i)}{\sum_{l=0}^{2} \exp(\eta_l + \gamma_l b_i)}$$

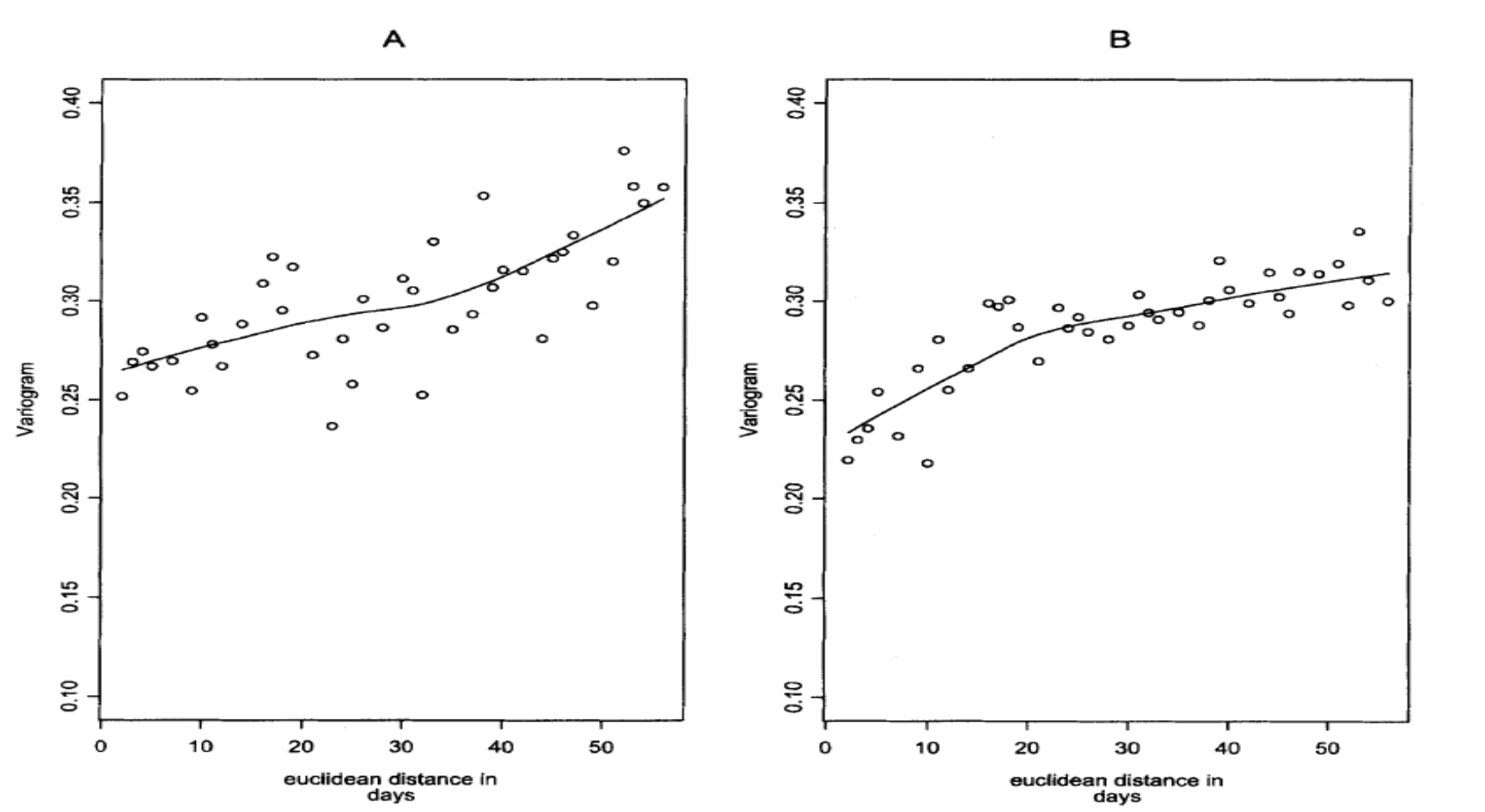
where $\eta_0 = \gamma_0 = 0$

- b_i is N(0,σ^2)

Shared Random Effects Model (Continued)

- $\mu_1 = \int \log it^{-1}(\beta + b)\phi_{\sigma^2}(b)db$
- Likelihood: $L_i = \int_{b_i} f(Y_i^o \mid b\ )g(Z_i \mid b\ )h(b\ )db$
  - Evaluate integral using Gaussian quadrature
- Estimates:
  - Nonignorable model: $\hat{\mu}_1$=0.52 (SE=0.04) and 0.73 (0.03) for buprenorphine and methadone groups.
  - Ignorable model: $\hat{\mu}_1$ =0.43 (0.06) and 0.71 (0.05).

Correlation Structure in Binary Data



Shared Latent Process Model

- Response Process:

$$\log itP(Y_{it} = 1 \mid b_{it}) = \beta + b_{it}$$

- Missing data Mechanism

$$P(Z_{it} = l \mid b_{it}, Z_{i,t-1} \neq 2) = \frac{\exp(\eta_l + \gamma_l b_{it})}{\sum_{l=0}^{2} \exp(\eta_l + \gamma_l b_{it})}$$

where

$$\eta_0 = \gamma_0 = 0$$

- Random Process: b_{it} is a Gaussian process with mean 0 and covariance structure

$$Cov(b_{it}, b_{is}) = \sigma^2 \exp(-\theta \mid t - s \mid)$$

Shared Latent Process Model (Continued)

- Generalizes shared random effects model.
- Marginal mean:

$$\mu_1 = \int \log it^{-1}(\beta + b)\phi_\sigma(b)db$$

- Intractable Likelihood

$$L_i = \int_{b_i=(b_{i1},b_{i2},\ldots,b_{in}\}} f(Y_i^o \mid b)g(Z_i \mid b)\phi_\Sigma(b)db$$

Shared Latent Process Model (Continued)

- Monte-Carlo E-M (Wei and Tanner, 1990; McCulloch, 1997):

$$\max_{\theta} \sum_{i=1}^{I} E_{b_i | Y_i^o, Z_i, \theta} [\log L(Y_i^o, Z_i, b_i; \theta)]$$

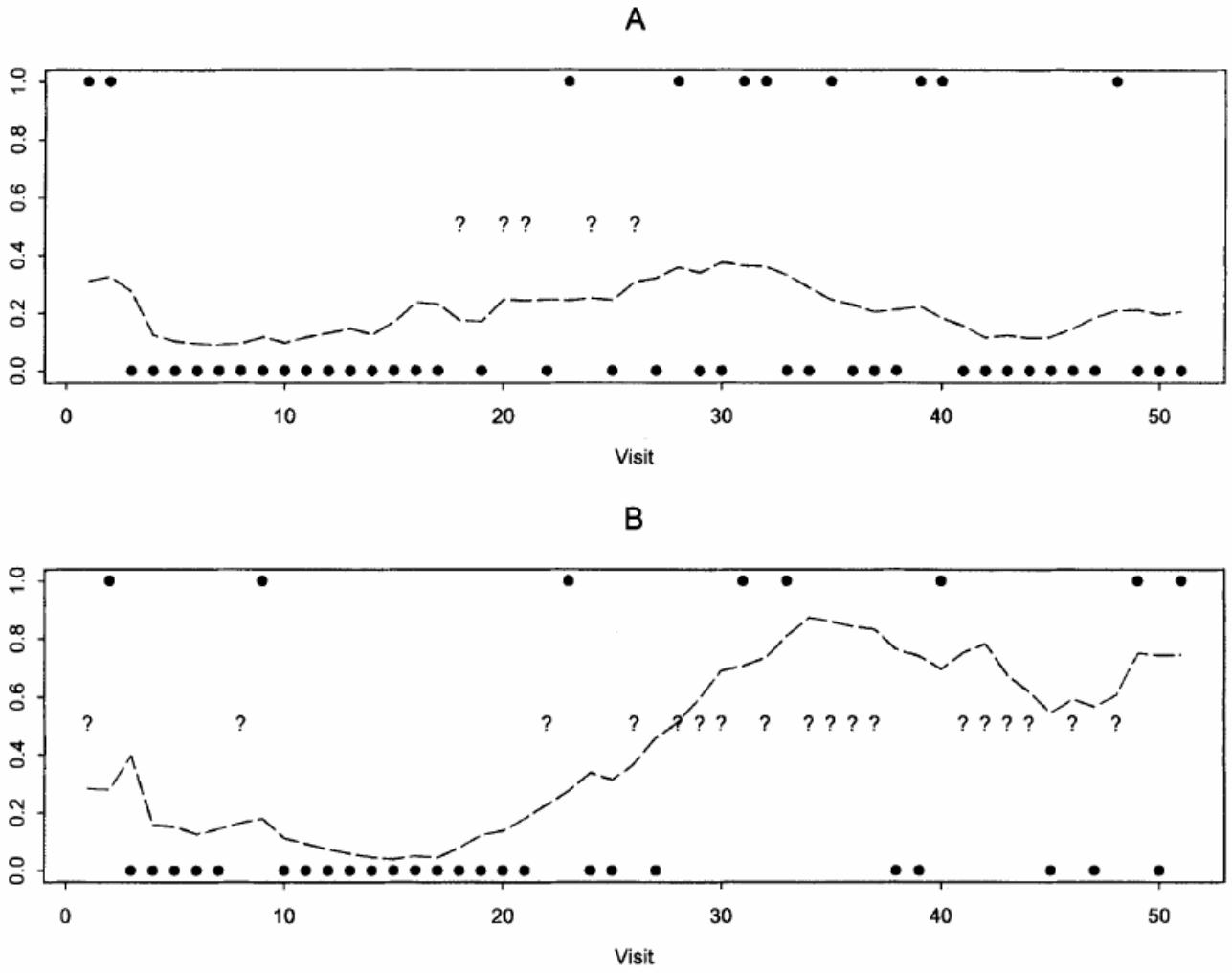
  - Generate $b_i \mid Y_i^o, Z_i$ using Metropolis algorithm.
  - Maximize $$\frac{1}{M} \sum_{i=1}^{I} \sum_{k=1}^{M} \log L(Y_i^o, Z_i, \hat{b}_i^{\,k}; \theta)$$

    where M are numb. Of MC samples.

Shared Latent Processes Approach: Analysis of Opiate Clinical Trial

	SLP		SRE	
Parm	Meth.	Brup.	Meth.	Brup.
σ	2.84	2.77	2.15	1.93
θ	0.014	0.012	--------	--------
γ_1	0.29 (0.13)	0.43 (0.09)	0.37 (0.19)	0.44 (0.19)
γ_2	0.22 (0.15)	0.48 (0.10)	0.30 (0.17)	0.58 (0.19)
μ_1	0.67 (0.04)	0.49 (0.04)	0.73 (0.03)	0.52 (0.04)

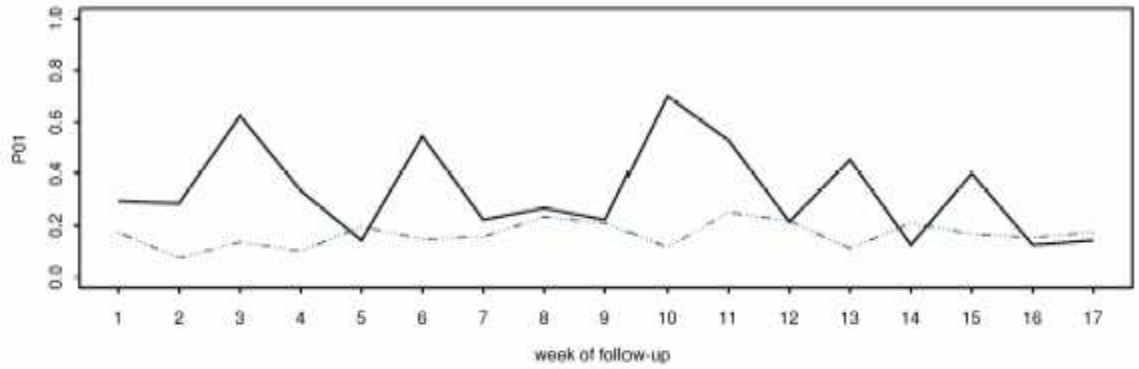
An Illustration on Two Buprenorphine Patients

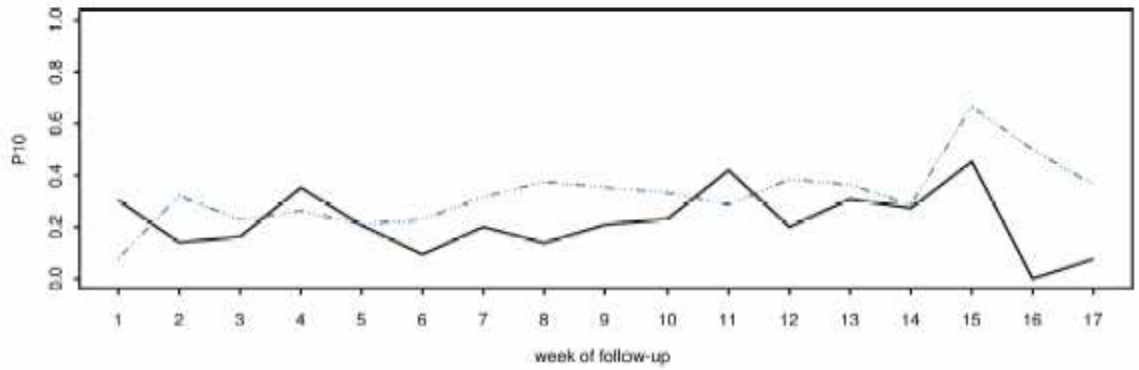


Effect of Falsely Assuming a Random Effect When Truly a Random Process

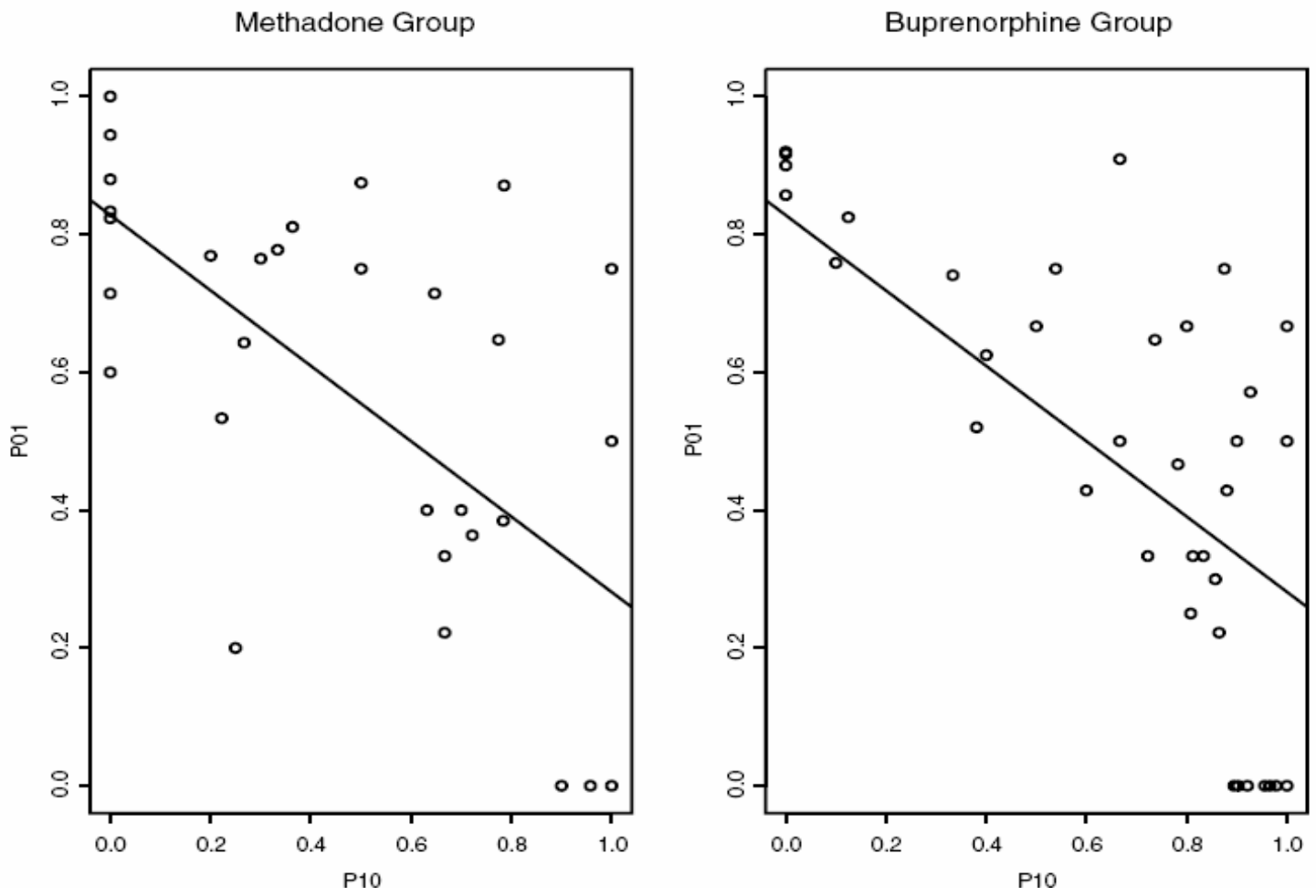
- Simulations
  - Little bias in estimating μ_1 for parameters corresponding to example (γ_1=0.3, γ_2=0.3, σ =2.25 and θ =0.02).
  - Substantial negative bias when $\gamma_1 = \gamma_2$=1.5 and θ =0.2.

Estimated Transition Probabilities by Week of Follow-up





Estimated Transition Probabilities by Treatment Group



Shared Random Effects Transition Model

- Response Process:

$$\log itP(Y_{it} = 1 \mid Y_{i,t-1} = 0) = \beta_{01} + b_i$$

$$\log itP(Y_{it} = 0 \mid Y_{i,t-1} = 1) = \beta_{10} + \delta b_i$$

- Missing Data Mechanism:

$$P(Z_{it} = l \mid b_i, Z_{i,t-1} \neq 2) = \frac{\exp(\eta_l + \gamma_l b_i)}{\sum_{l=0}^{2} \exp(\eta_l + \gamma_l b_i)}$$

where $\eta_0 = \gamma_0 = 0$ and b_i *iid* $N(0,\sigma^2)$

Shared Random Effects Transition Model (Continued)

- Denote Y_i^o as observed responses without first response

- Estimation: maximum-likelihood

$$L_i = \int_{b_i} f(Y_i^o \mid b\ ) g(Z_i \mid b\ ) h(b\ ) db$$

  - f are products of k-state transition probabilities

Shared Random Effects Transition Model (Continued)

- Summary measures:

$$\mu_1(b_i) = \frac{1}{n}\sum_{t=1}^{n}\sum_{\omega=0}^{1} p_w P_{\omega 1}^{(t-1)}(b_i)$$

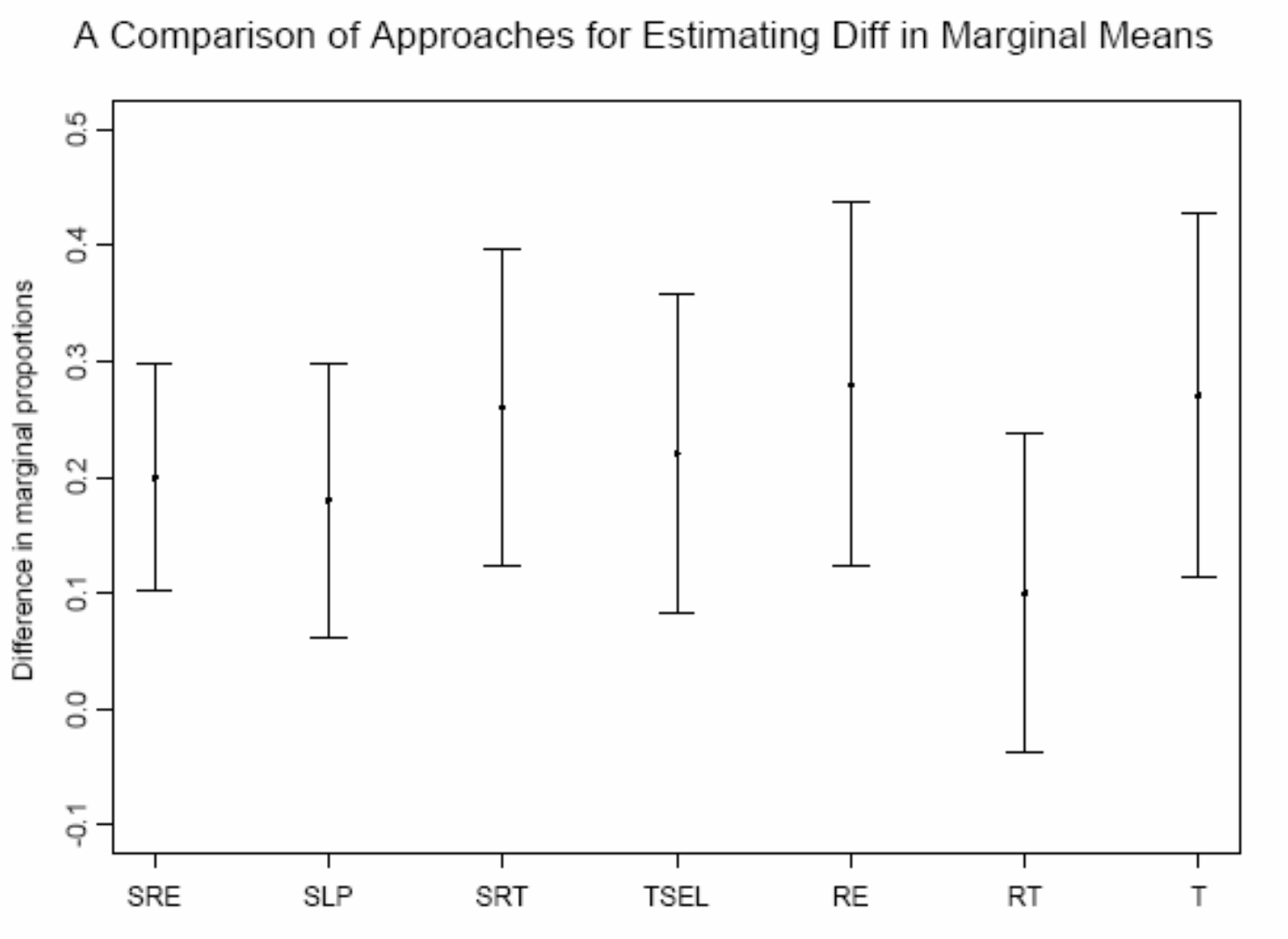
$$\mu_2(b_i) = \sum_{\omega=0}^{1} p_\omega P_{\omega 1}^{(12)}(b_i) + \sum_{\omega=0}^{1} p_\omega P_{\omega 0}^{(12)}(b_i)\{\sum_{t=2}^{\infty} tP_{00}(b_i)^{t-2}\}$$

Shared Random Effects Transition Model (Continued)

	Nonignor.		Ignorable	
Parm.	Meth.	Bupr.	Meth.	Bupr.
$med\{P_{01i}\}$	0.66 (0.07)	0.25 (0.02)	0.47 (0.04)	0.31 (0.03)
$med\{P_{11i}\}$	0.84 (0.02)	0.62 (0.03)	0.67 (0.03)	0.59 (0.03)
μ_1	0.70 (0.06)	0.46 (0.04)	0.56 (0.06)	0.46 (0.04)
μ_2	1.29 (0.18)	3.45 (1.04)	1.89 (0.32)	2.81 (0.78)

Summary

- We discuss four approaches for modeling non-ignorable missing data in the opiate clinical trial data.
- All approaches show that buprenorphine reduces opiate-use over standard methadone treatment.
- “Informal” sensitivity analysis


A Comparison of Approaches for Estimating Diff in Marginal Means
Difference in marginal proportions
-0.1
0.0
0.1
0.2
0.3
0.4
0.5
SRE
SLP
SRT
TSEL
RE
RT
T

References

1. Albert, P.S. (2000). A transitional model for longitudinal binary data subject to nonignorable missing data. *Biometrics* ***56,*** *602-608.*
2. Albert,P.S., Follmann, D.A., et al. (2002). A latent autoregressive model for longitudinal binary data subject to informative missingness. *Biometrics* **58**, 631-642.
3. Albert, P.S. and Follmann, D.A. (2003). A random effects transition model for longitudinal binary data with informative missingness. *Statistica Neerlandica* **57**, 100-111.