On the Analysis of Longitudinal Clinical Lab Data with Latent Mixture Models

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Outline

Pre-marketing analysis of safety data

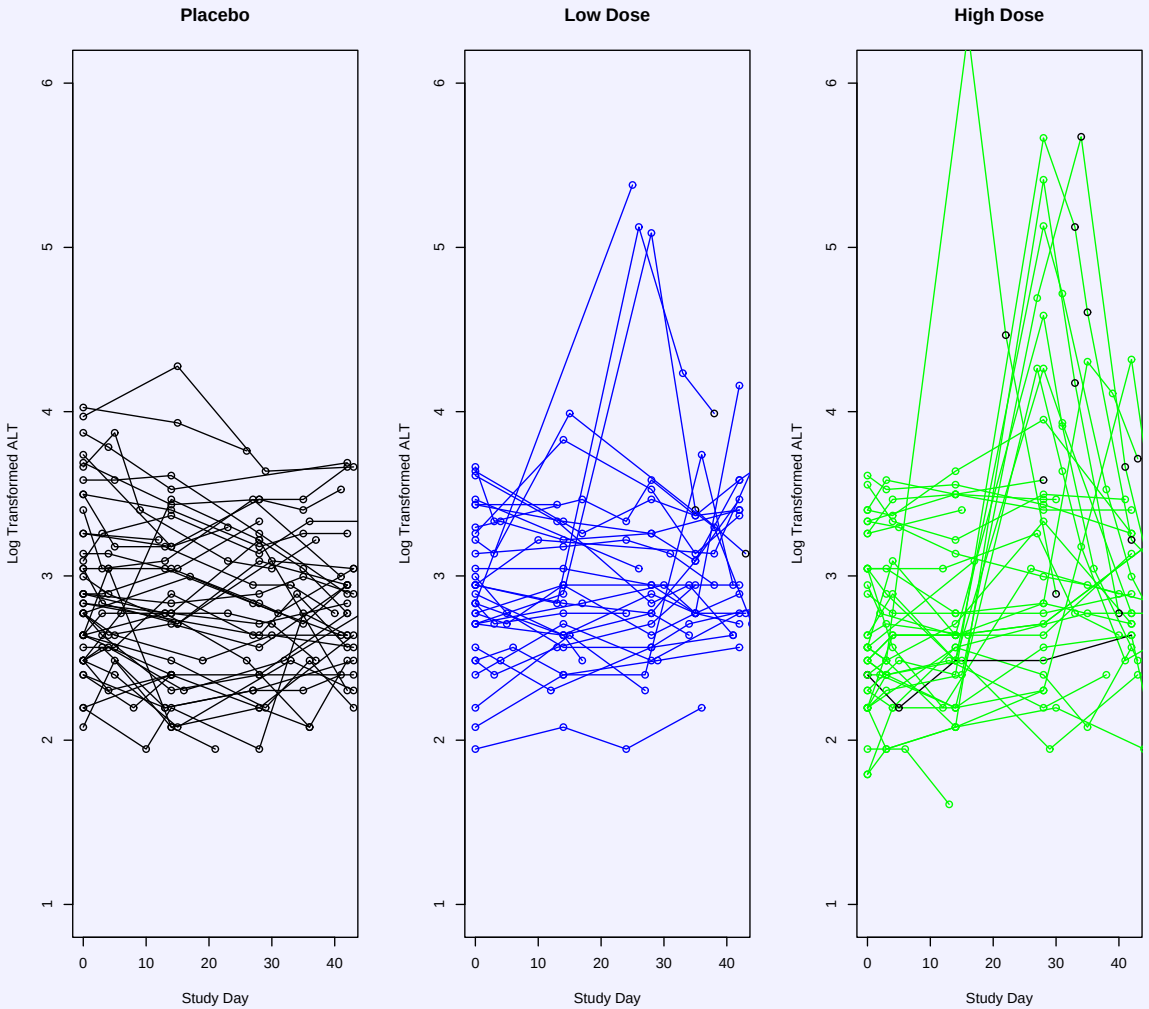
- Towards reporting to governing agencies and on label inserts, rates of adverse events (AE) over the course of followup during pre-marketing trials are used
- Often, the binary AEs are derived from continuous longitudinal clinical laboratory data
  - Liver function: alanine aminotransferase (ALT)) elevations are used to characeterize liver damage.
  - An hepatotoxic event may be defined by ALT concentrations crossing some threshold value (e.g. 3X ULN) at some time during follow-up.

- Considerations
  - Continuous data are dichotomized
    - Information loss
    - The dichotomization point (3X ULN) has no intrinsic meaning
    - Reference ranges: uncertainty / multiple labs and transformations
  - Longitudinal data are ignored.
    - Ignoring the added information by taking repeated measures on individuals.
    - Dynamic treatment effects cannot be captured (does ALT elevations at 28 days mean the same thing as ALT elevations at 7 days?)
  - Lack of power: combine multiple studies on the same product or on the same class of products
  - There is little effort to characterize the real biological impact of the products on typical subjects.

Motivating Example: Impact of drug X on liver function

	Placebo	Low Dose	High Dose
N	135	66	76
Female (%)	48	21	57
Ethnicity (%)			
White	81	85	84
Black	10	6	8
Other	9	9	8
Age (years)	50 (27, 65)	36 (24, 64)	53 (36, 66)
Weight (kilograms)	82 (60, 106)	83 (64, 105)	80 (56, 98)
Log-transformed, baseline ALT	2.8 (2.2, 3.5)	2.9 (2.4, 3.5)	2.6 (1.9, 3.4)

Motivating Example: Impact of drug X on liver function, *cont.*



A longitudinal data analysis approach

$$Y_i(t) = \mathbf{X}_i(t) \cdot \beta(t) + \epsilon_i(t)$$

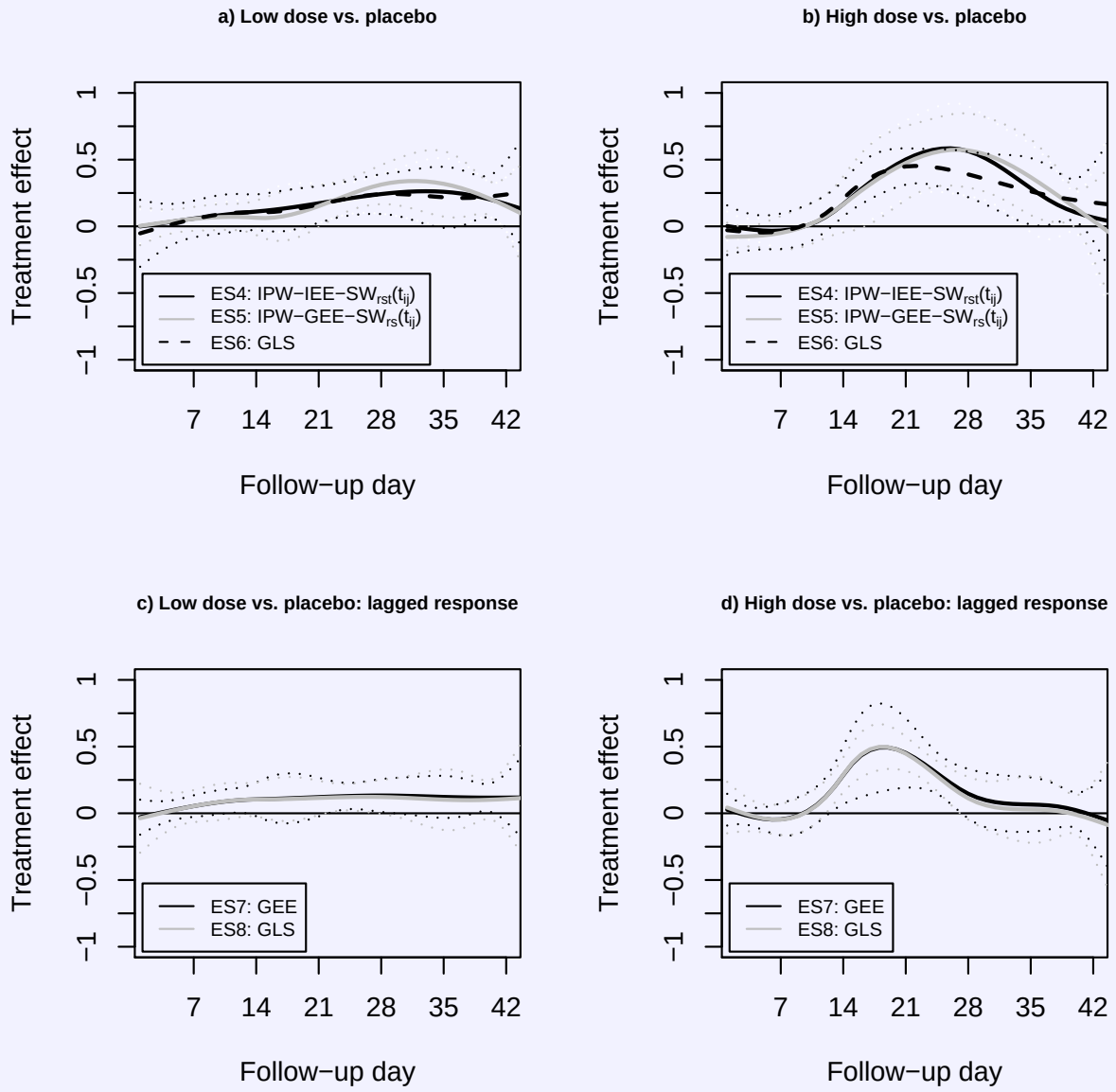
- $Y_i(t)$: response value for subject i at time t
- $\mathbf{X}_i(t)$: $p-$vector of covariates subject i at time t
- $\epsilon_i(t)$: mean-0 error process
  - Assuming a distributional form $\longrightarrow$ parametric estimation
  - Not assuming a distributional form $\longrightarrow$ semi-parametric estimation
- $\beta(t)$ parameter vector that is the target of inference
  - Flexibility in the functional form of these parameter is critical (parametrically, semi-parametrically, or non-parametrically)

Selection mechanisms

- Schildcrout JS et.al, *Statistics in Medicine (DOI: 10.1002/SIM.3071)*
- Potentially, a large number of selection mechanisms... many of which may be response history dependent

Type	Approach
Dropout	IPW-GEE
	ML
Visit rate	IPW-GEE
	ML
Tx discontinuation	IPTW-GEE
	Drop subsequent follow-up + GEE
	Drop subsequent follow-up + ML

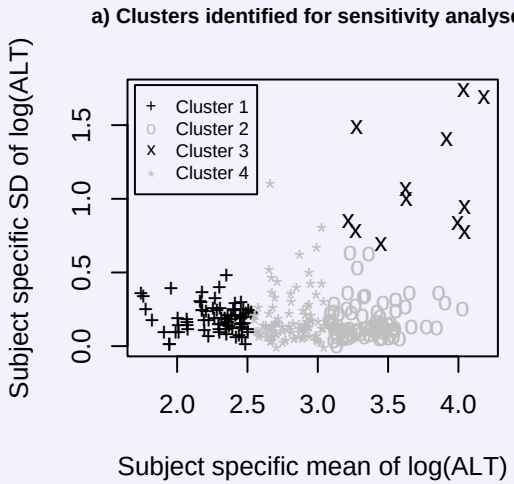
Dynamic treatment effects

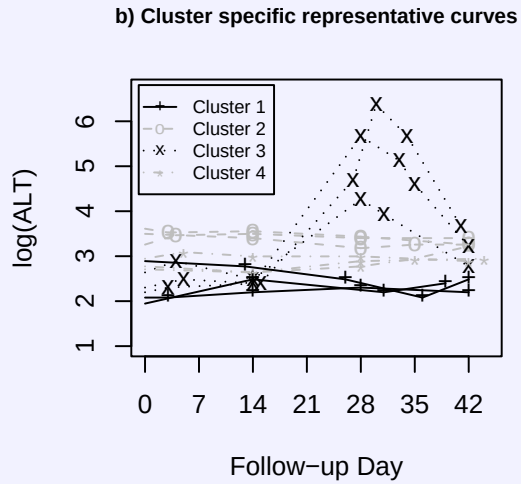


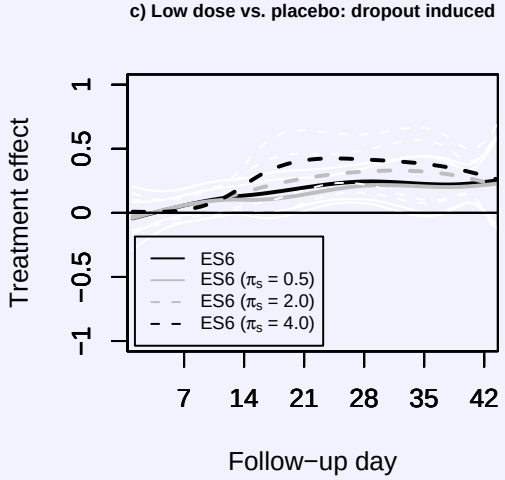
Selection mechanisms *(cont.)*

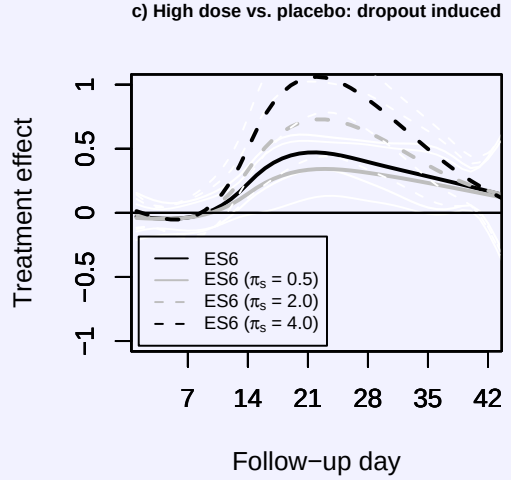
- Non-ignorable
  - Patients in clinical trials may be substantially different from those to whom we would like to generalize results
  - Exclusion criteria: counter-indicated medications, lifestyle choices
  - Post-marketing, medications are prescribed to unstudied patient populations
  - Evaluation strategies
    - Posit selection mechanisms and perform sensitivity analyses
    - Weighted estimating equations
    - Weighted resampling based approaches (e.g., tilted bootstrap)

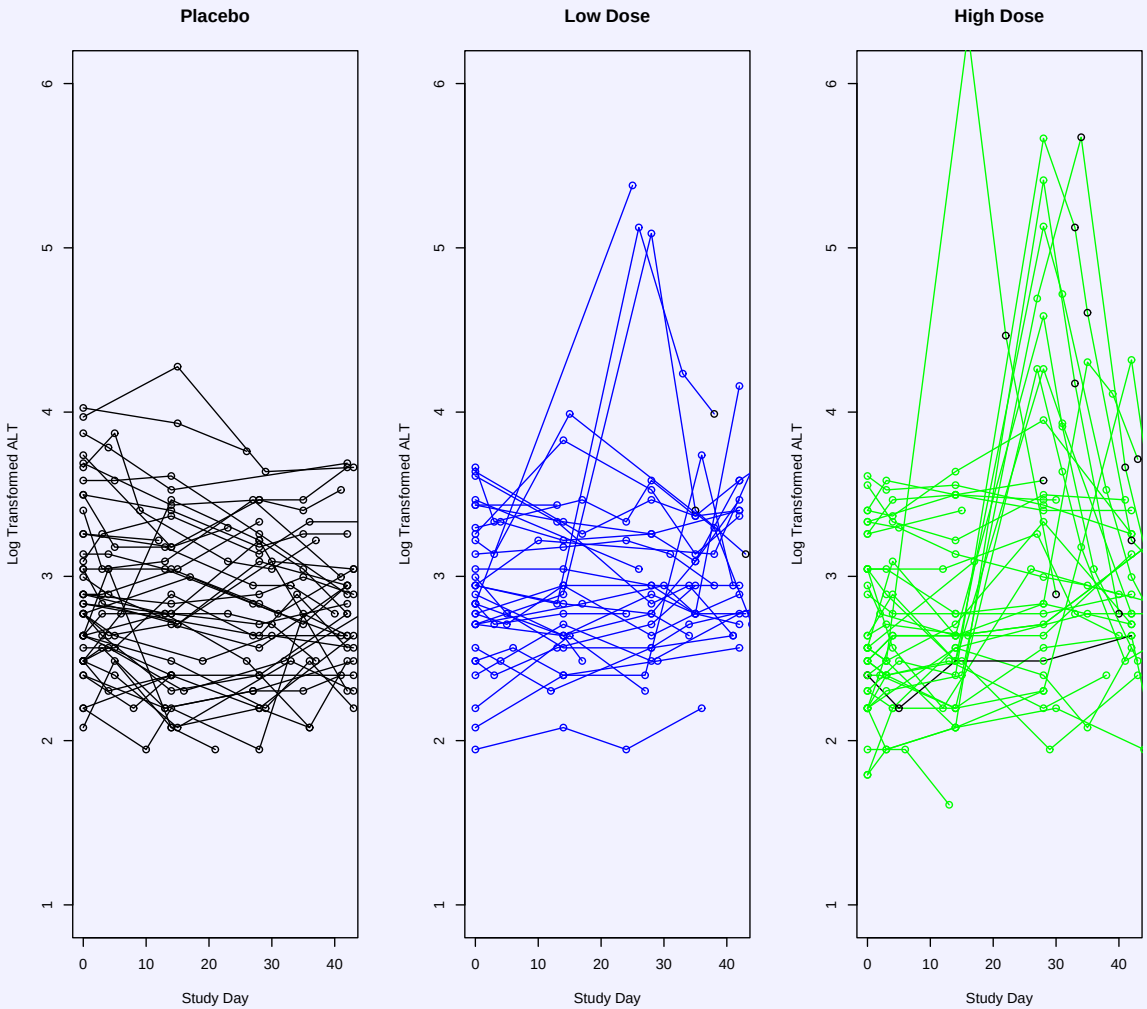
Sensitivity Analysis










Placebo
Low Dose
High Dose
Log Transformed ALT
Study Day
1
2
3
4
5
6
0
10
20
30
40

The underlying model assuming two levels of susceptibility

- Let R_i be an indicator that subject i is someone who is susceptible to the effects of treatment if given and r_i is the realized value if we knew it.

$$\begin{aligned} Y_i(t) =& (\beta_0 + \beta_1 tx_i + \beta_2 r_i + \beta_3 tx_i r_i) \\ &+ (\beta_4 + \beta_5 tx_i + \beta_6 r_i + \beta_7 tx_i r_i) \cdot f(t) + \epsilon_i(t) \\ \mu^r_{i,tx}(t) =& E(Y_i(t) \mid tx_i, r_i) \end{aligned}$$

- Treatment effect for non-susceptible subjects

$$\mu^0_{i,1}(t) - \mu^0_{i,0}(t) = \beta_1 + \beta_5 f(t)$$

- Treatment effect for susceptible subjects

$$\mu^1_{i,1}(t) - \mu^1_{i,0}(t) = (\beta_1 + \beta_3) + (\beta_5 + \beta_7) \cdot f(t)$$

The underlying model assuming two levels of susceptibility

- By randomization,

$$\pi_i \equiv p(R_i = 1) = p(R_i = 1 \mid tx_i = 1) = p(R_i = 1 \mid tx_i = 0)$$

- Marginal mean

$$\mu_{i,tx}(t) = \mu^1_{i,tx}(t)\pi_i + \mu^0_{i,tx}(t)(1 - \pi_i)$$

- Marginal treatment effect

$$\mu_{i,1}(t) - \mu_{i,0}(t) = (\mu^1_{i,1}(t) - \mu^1_{i,0}(t))\pi_1 + (\mu^0_{i,1}(t) - \mu^0_{i,0}(t))(1 - \pi_1)$$

- If it is reasonable to assume $\mu^0_{i,1}(t) = \mu^0_{i,0}(t)$,

$$\mu^1_{i,1}(t) - \mu^1_{i,0}(t) = \frac{\mu_{i,1}(t) - \mu_{i,0}(t)}{\pi_i}$$

- We may then be interested in π_i and $\mu^1_{i,1}(t) - \mu^1_{i,0}(t)$
- The challenge: R_i is unknown

Mixture models and (ML) estimation

- π_k = overall probability of membership in class k
- The mixture model density is given by,

$$g(y_i(t) \mid \mathbf{x}_i(t), \theta) = \sum_{k=1}^{K} \pi_k f(y_i(t) \mid \mathbf{x}_i(t), \theta_k)$$

where $\theta = \{\theta_1, \theta_2, \ldots, \theta_k, \pi_1, \pi_2, \ldots, \pi_k\}$

- With N subjects and n_i repeated measures for subject i, we may consider maximum likelihood estimation with the log-likelihood

$$l = \sum_{i=1}^{N} \sum_{t} log[g(y_i(t) \mid \mathbf{x}_i(t), \theta)],$$

Mixture models and (ML) estimation

- This is very similar to a missing data problem where r_i is missing for each subject, and $(\mathbf{x}_i, \mathbf{y}_i, \mathbf{r}_i)$ would be the complete data
- The EM algorithm is generally used for the maximization.
- Expectation step
  - Given the parameter estimates at the $m-1^{th}$ iteration, $\theta^{(\mathbf{m-1})}$ calculate the (*posterior*) probabilities of group membership

$$p_{ik}^{(m)} = \frac{\pi_k^{(m-1)} f(\mathbf{y}_i \mid \mathbf{x}_i, \theta_k^{(m-1)})}{\sum_{w=1}^{K} \pi_w^{(m-1)} f(\mathbf{y}_i \mid \mathbf{x}_i, \theta_w^{(m-1)})}$$

  and calculate overall class membership probabilities (prior probability at iteration $m+1$),

$$\pi_k^{(m)} = \frac{1}{N} \sum_{i=1}^{N} p_{ik}^{(m)}$$

Mixture models and (ML) estimation

- Maximization step
  - Given p_{ik}^m for all i, maximize the weighted likelihood,

$$l = \sum_{i=1}^{N} \sum_{t_{ij}} p_{ik}^{(m)} f(y_i(t) \mid \mathbf{x}_i(t), \theta_k)$$

    w.r.t. θ_k for each of the k classes.
- Notice the number of estimated parameters estimated with large K.

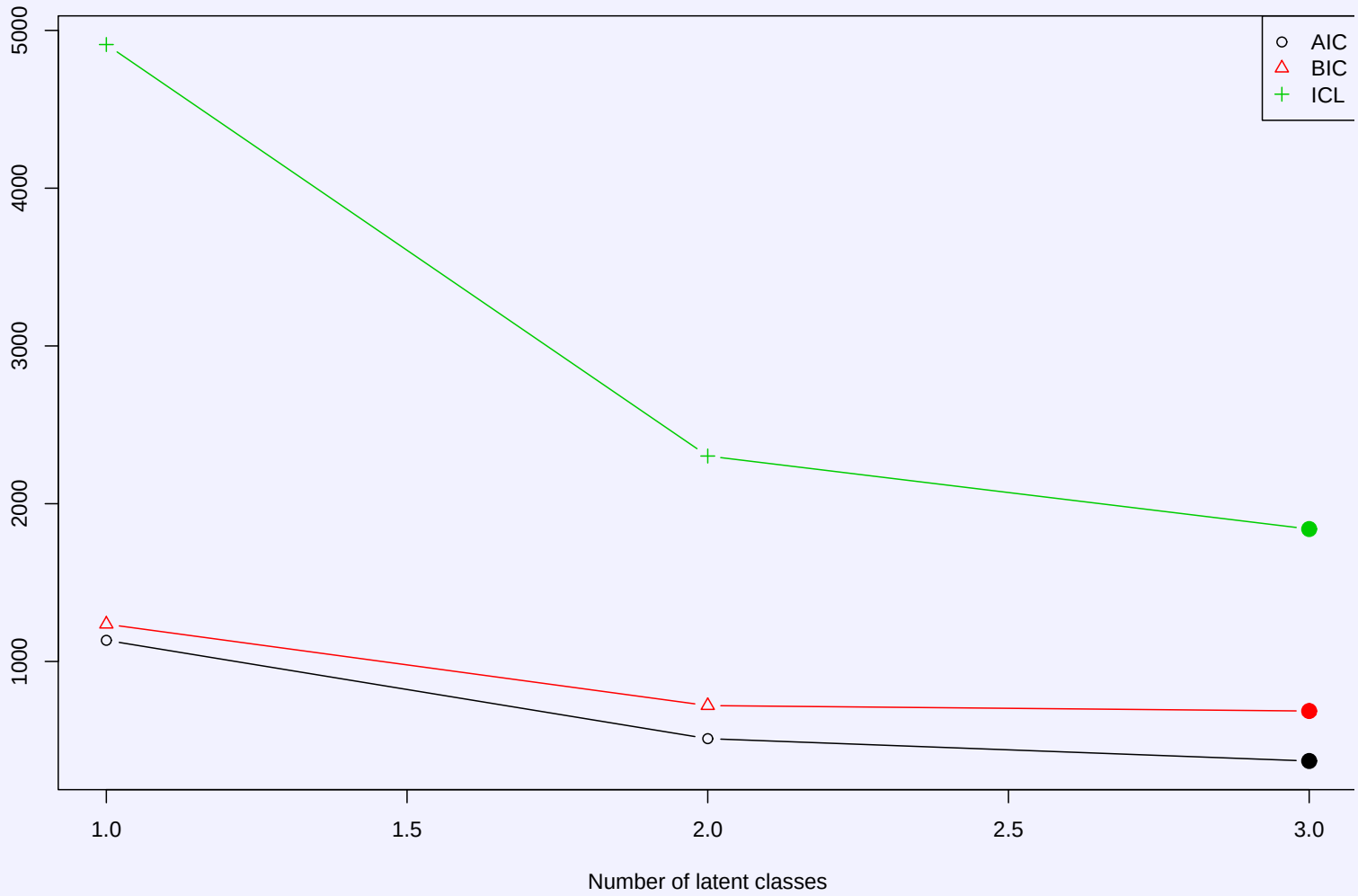
The model being used

- r_i is categorical (and not observed)

$$E(Y_i(t)) = (\beta_0 + \beta_1 tx_i + \beta_2 r_i + \beta_3 tx_i r_i) + (\beta_4 + \beta_5 tx_i + \beta_6 r_i + \beta_7 tx_i r_i) \cdot ns(t)$$

- ns : natural spline matrix with knots at days 14,28,35, and 42.
- Two factors to describe the three levels of Tx_i: $I(Tx_i = low)$ and $I(Tx_i = high)$
- The number of classes: use objective measures to determine an appropriate number of classes while acknowledging the limited sample size.

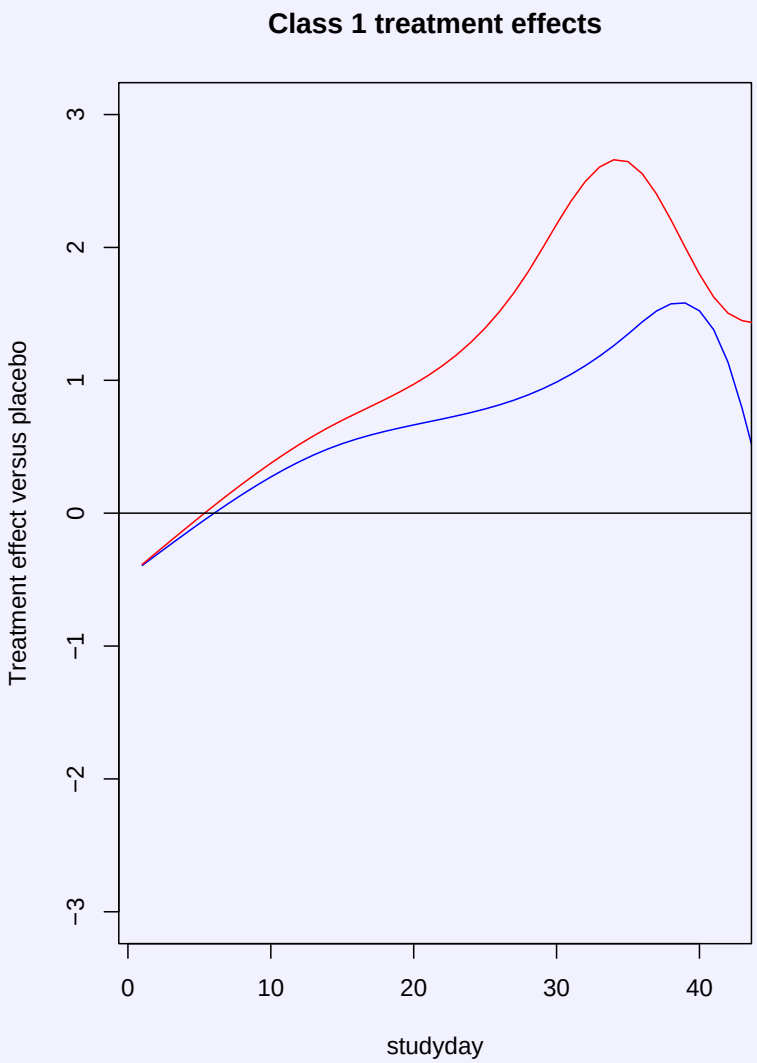
Number of Classes

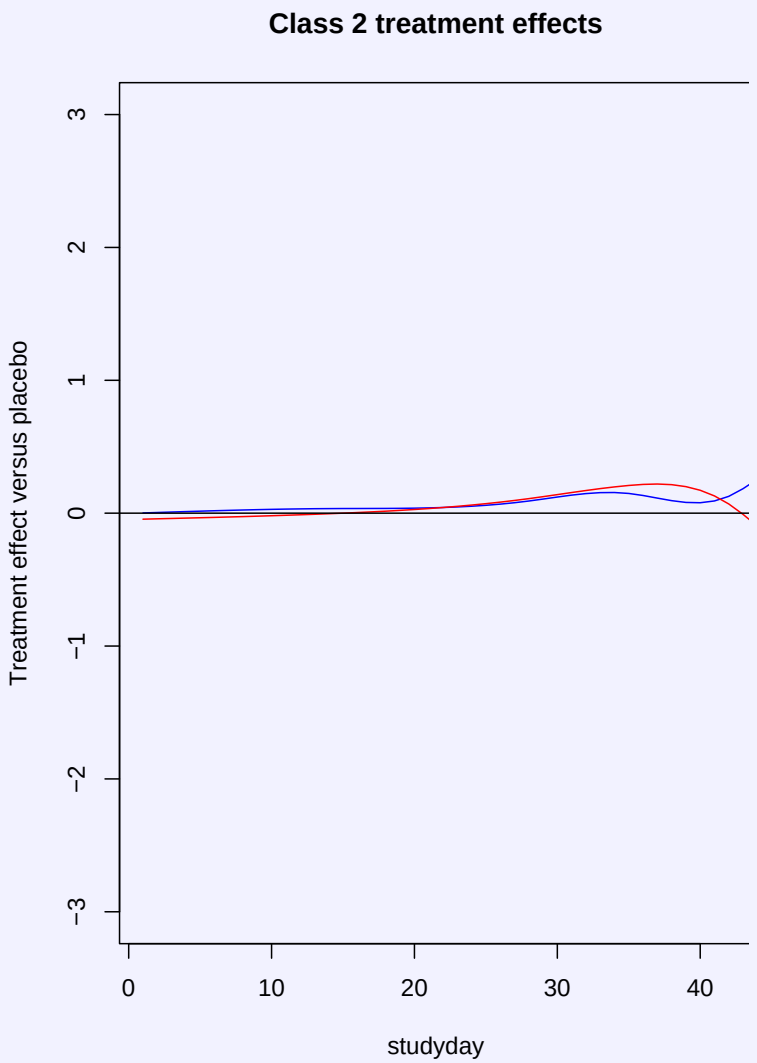


Two latent class model

- Prior class membership (π_k):
  1. 0.14
  2. 0.86

Two latent class model

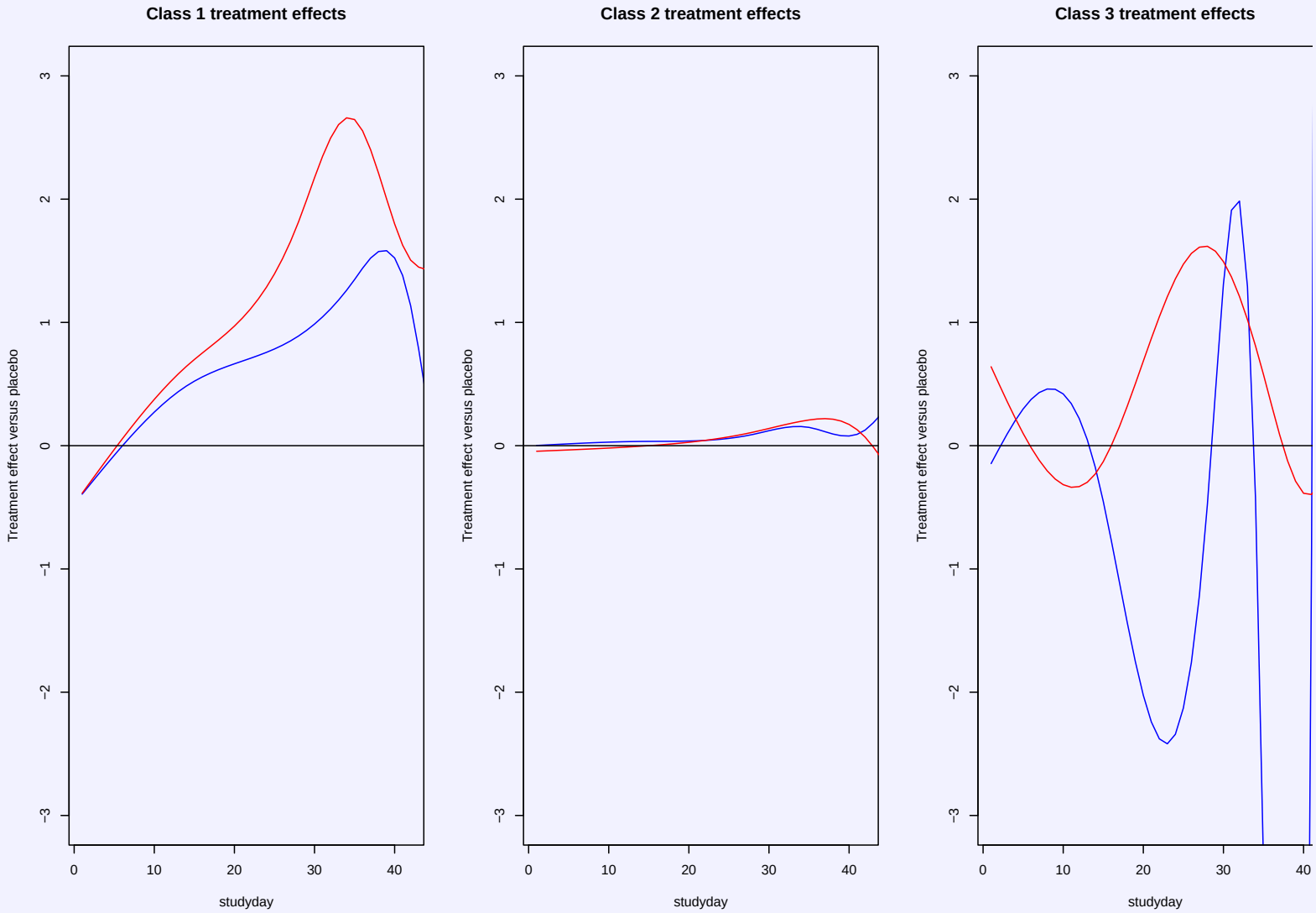




Three latent class model

- Prior class membership (π_k):
  1. 0.098
  2. 0.852
  3. 0.051

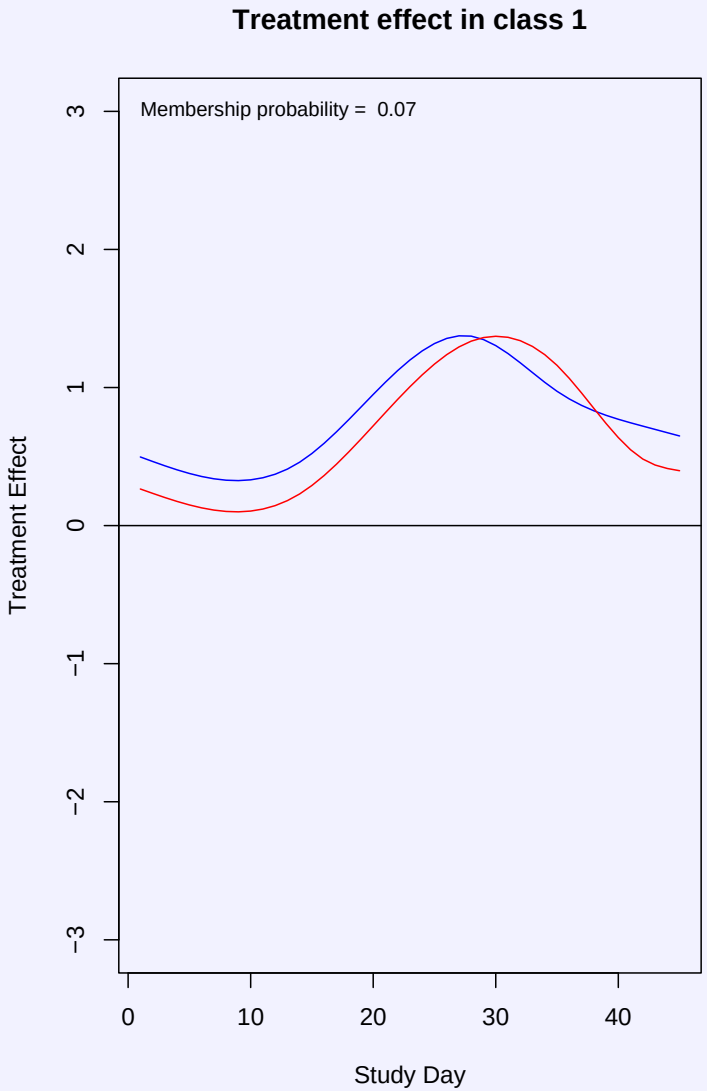
Three latent class model

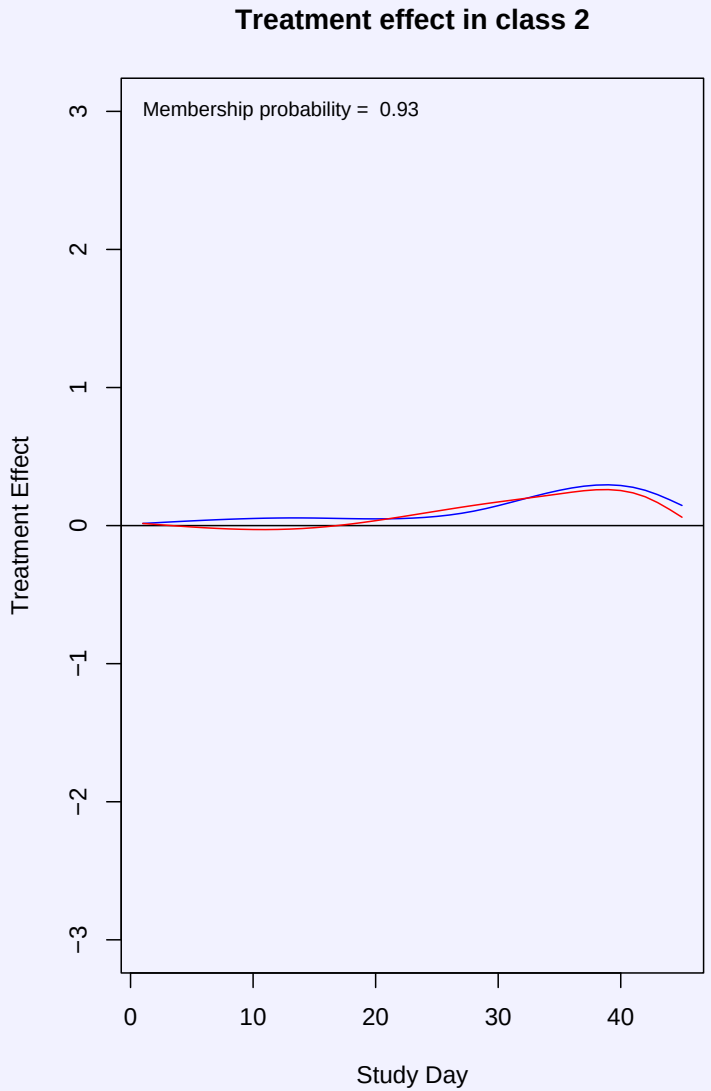


Bayesian implementation

$$
\begin{aligned}
Y_i(t) &\sim N(\mu_i(t), \tau) \\
\mu_i(t) =&(\beta_0 + \beta_1 tx_i + \beta_2 r_i + \beta_3 tx_i r_i) + \\
&(\beta_4 + \beta_5 tx_i + \beta_6 r_i + \beta_7 tx_i r_i) \cdot ns(t) \\
R_i \mid p &\sim bernoulli(p_i) \\
p_i &\sim beta(\alpha, \beta) \\
\sigma^2 &\sim U(0, 100) \\
\tau &= 1/\sigma^2 \\
\beta_j \mid \mu_j, \tau_j &\sim N(\mu_j, \tau_j) \\
\mu_j &\sim N(0, 100) \\
\sigma_j^2 &\sim U(0, 100) \\
\tau_j &= 1/\sigma_j^2
\end{aligned}
$$

Treatment Effects based on means of posteriors

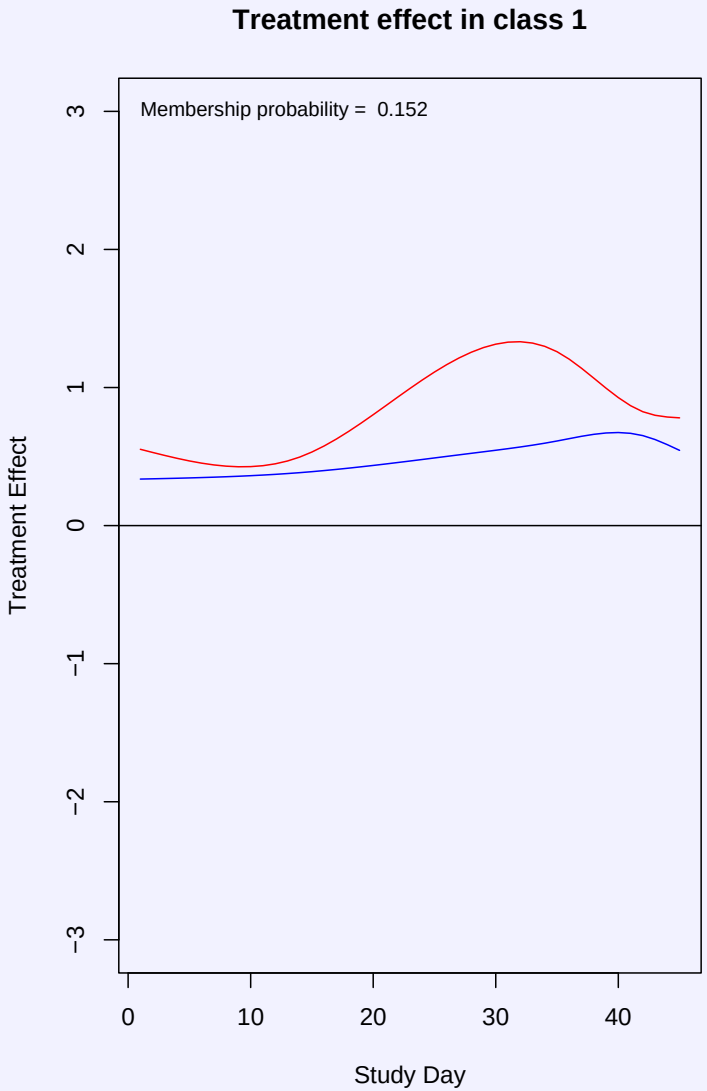


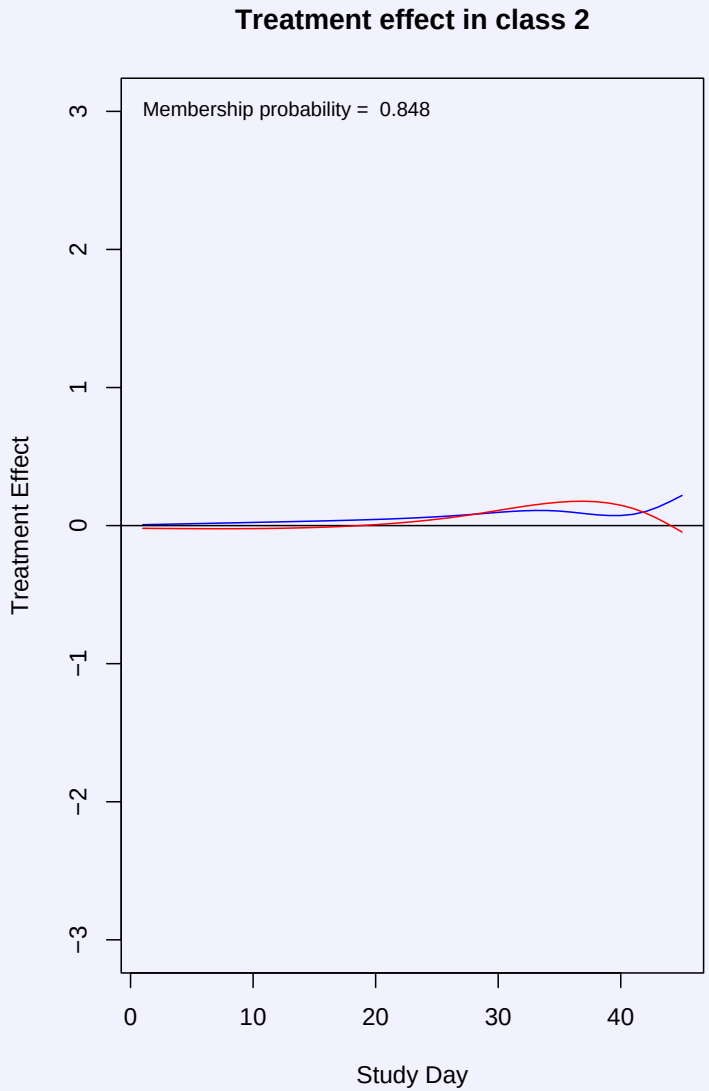


Bayesian implementation (unequal variance)

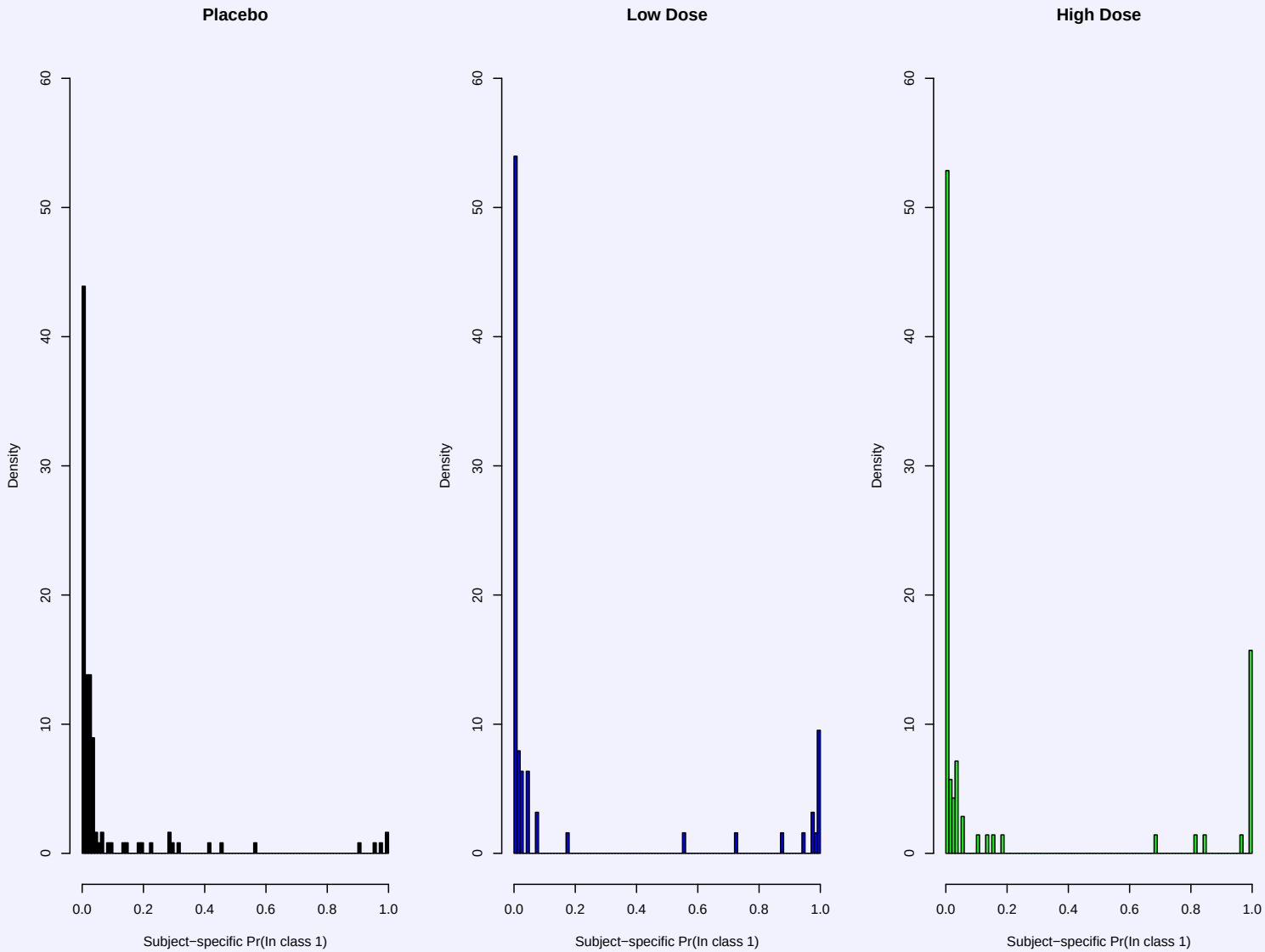
$$
\begin{aligned}
Y_{it} &\sim N(\mu_i(t), \tau_r) \\
\mu_i(t) =&(\beta_0 + \beta_1 tx_i + \beta_2 r_i + \beta_3 tx_i r_i) + \\
&(\beta_4 + \beta_5 tx_i + \beta_6 r_i + \beta_7 tx_i r_i) \cdot ns(t) \\
\sigma_r^2 \mid r &\sim U(0, 100) \\
\tau_r \mid r &= 1/\sigma_r^2 \\
R_i \mid p &\sim bernoulli(p_i) \\
p_i &\sim beta(1, 1) \\
\beta_j \mid \mu_j, \tau_j &\sim N(\mu_j, \tau_j) \\
\mu_j &\sim N(0, 100) \\
\sigma_j^2 &\sim U(0, 100) \\
\tau_j &= 1/\sigma_j^2
\end{aligned}
$$

Treatment Effects based on means of posteriors

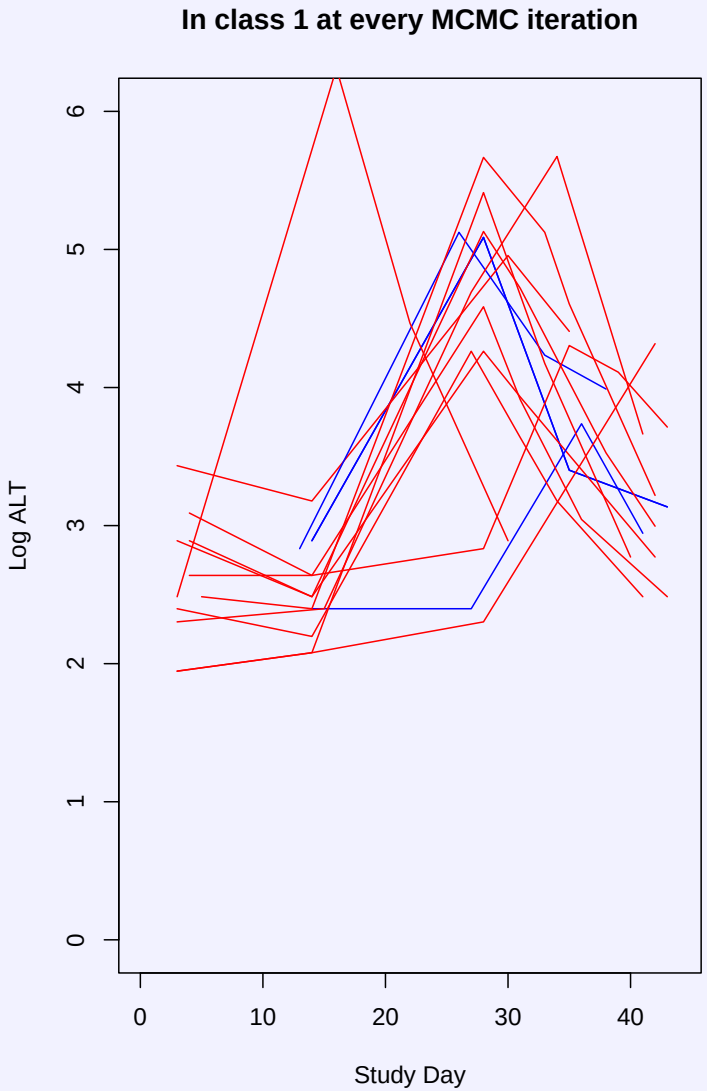


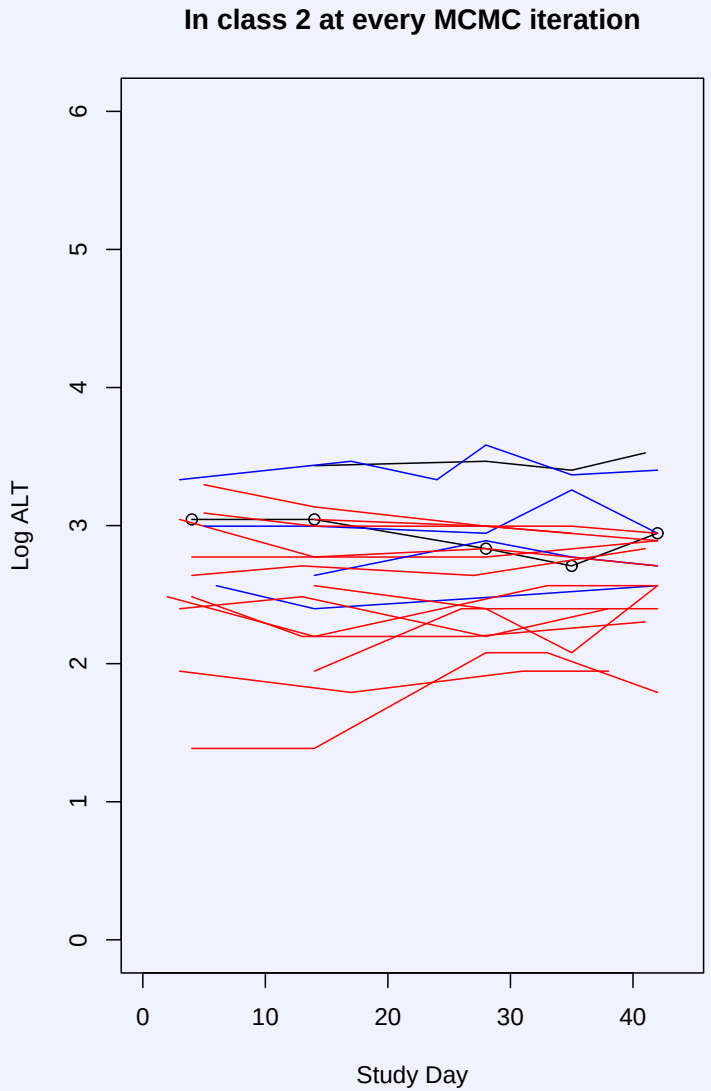


Classification Probabilities



Profiles for subjects classified with certainty





Identifiability

- Maximum Likelihood
  - Overfitting: Number of classes
    - Can be dealt with by requiring $\pi_k > 0$ and $\theta_k \neq \theta_{k'}$
  - Component relabelling
    - Compenent labels are interchangeable e.g., there are $K!$ label combinations that lead to a common maximized likelihood
    - Affects interpretation and not fitting of the EM algorithm... or we can impose restrictions
- Bayesian approach
  - Label reshuffling
    - No real way to discriminate between components of the mixture belongng to the same parametric family
    - During MCMC, labels can be permuted which can be very problematic (e.g., bimoddal posterior distributions)
    - Post-processing may be recommended

Summary

- Routinely collected laboratory data are not utilized effectively
- Longitudinal data analysis (acknowledging mechanisms of selection) improves our ability to characterize pharmaceutical safety
- Latent class regression seems to have the potential to improve this characterization in a very meaningful way.
- There are a number of challenges with it practically: primarily associated with the fact that class membership is not observed