“Precision Medicine: Subgroup Identification in Longitudinal Pharmacogenetic Studies”

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Outline

- Motivation
- Method
- Simulation Study
- Real Data Analysis
- Concluding Remarks

Alcohol Use Disorders (AUDs)

- Alcohol use disorders (AUDs) are a major public health problem that accounts for significant morbidity and mortality.
- 18 million Americans suffer from an AUD during a one-year period.
- The estimated annual expense attributable to the excessive consumption of alcohol is $185 billion
- Excessive use of alcohol is the third leading preventable cause of death in the U.S. (Mokdad et al. 2004), associated with multiple adverse health problems.
- However, only 7.1% of those with AUD received any treatment in the past year.

Treatment of AUD

- Counseling and referral to community support groups are the most prevalent forms of treatment for AUD in the U.S, e.g., twelve-step program by Alcoholics Anonymous.
- Three medications have been approved to treat AUD: disulfiram, acamprosate, and naltrexone.
- However, many patients have limited or no response to these medications (e.g., Anton et al. 2006; Chen et al. 2012), which leads to physicians' unwillingness to prescribe medications - an important barrier to the dissemination of pharmacotherapy treatments (Oliva et al. 2011; Weber 2010).
- Developing new and more effective medications to treat alcoholism remains a high priority for the National Institute on Alcohol Abuse and Alcoholism (NIAAA, Willenbring 2007).

Personalized Medicine in Alcohol Trials

- Traditionally, pharmacotherapy for treating alcohol dependence has been developed and evaluated using population data, a "one size fits all" approach that leaves little room for individualized treatment.
- However, considerable heterogeneity exists among people with alcohol addiction, suggesting a need for personalized treatment approaches based on individual features, e.g., genetic variation (Heilig et al. 2011).
- The goal of personalized medicine is "to develop new therapies and optimize prescribing by steering patients to the right drug at the right dose at the right time" (Hamburg and Collins 2010).
- Ongoing research has informed studies that match alcohol medications to patients based on genotype (Kranzler and McKay 2012).

Subgroup Identification

- Clinical question of interest in alcohol studies: how can we identify patient subgroups which are most responsive to a medication (which may fail in general population)?
- On the other hand, other medical fields (e.g., cancer) with many medications to treat a disease/symptom: what is the best medication to use for a given patient?
- However, these two questions are two sides of the same coin
- Of note, here we will NOT consider dynamic treatment regimen.

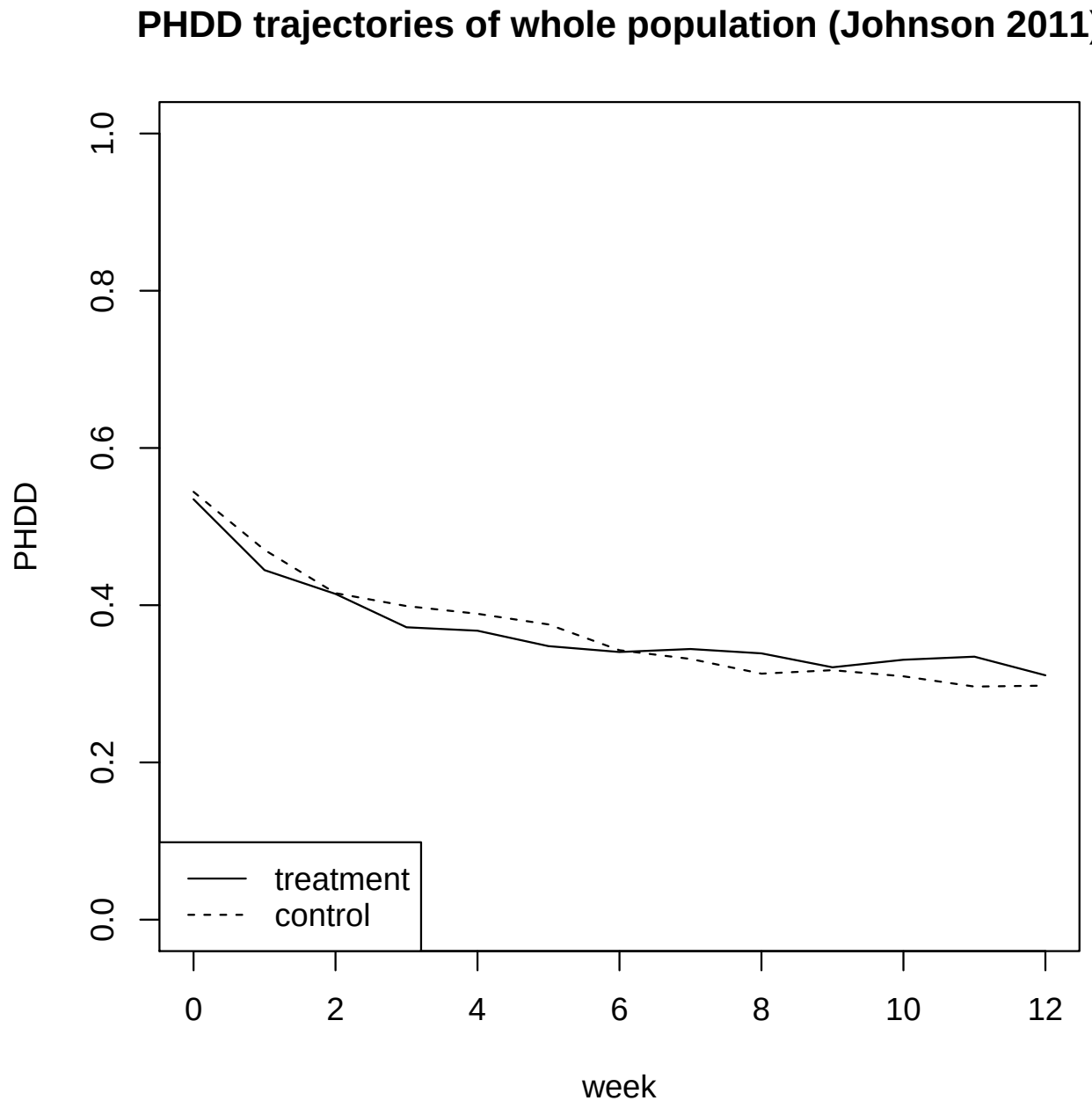
Motivating Example

- Johnson et al. (2011) conducted a 12-week double-blind controlled trial of ondansetron vs. placebo, in 283 alcohol-dependent subjects.
- Ondansetron has been used to prevent nausea and vomiting caused by cancer chemotherapy and radiation therapy
- New indication for ondansetron to treat alcohol dependence
- Individuals with both the 5'-HTTLPR LL and rs1042173 TT genotypes who received ondansetron had better drinking outcomes than all other genotypes and treatment groups combined.
- Johnson et al. (2013) also examined 19 SNPs in HTR3A and HTR3B genes, for their ability to predict ondansetron treatment outcome

Data

- Outcome: Longitudinal daily drinking levels summarized as weekly percentage of heavy drinking days (PHDD)
  - Heavy drinking is defined as $>= 5$ standard drinks (roughly 14 grams of pure alcohol) for men and $>= 4$ for women in a day
- Treatment: Ondansetron vs. Placebo
- Other Covariates
  - Time in weeks (could be nonlinear), age of onset, race, sex, age, PhD_base90 (heavy drinking percentage in past 90 days before baseline)
  - 21 genetic polymorphisms: e.g., aa, Aa, AA (non-ordered categorical)
- We are interested in finding interaction between treatment and covariates, and thus identify subgroups with enhanced treatment effect

PHDD Trajectories of Two Arms (Johnson 2011)



Ondansetron Effect

- Overall there is no ondansetron effect in the whole population
- Nonlinear drinking trajectory in both groups
- Subgroup identification: can we find some subgroups (based on covariates) which respond to ondansetron?

Literature Review of Subgroup Identification

- Model-based recursive partitioning (MoB, Zeileis et al. 2008), interaction trees (IT, Su et al. 2008, 2009), STIMA (Dusseldorp et al. 2010), SIDES (Lipkovich et al. 2011), virtual twins (VT, Foster et al. 2011), GUIDE (Loh et al. 2016)
- A tutorial has been published by Lipkovich et al. (2017): Tutorial in biostatistics: data-driven subgroup identification and analysis in clinical trials
- Hou et al. (2015) applied IT and VT methods to the Ondansetron clinical trial data, using the difference between treatment period and baseline measure as a scalar outcome

Why tree-based methods for interaction?

- Tree-based methods include interactions by construction, therefore, we do not need to specify the model structure in advance (in contrast to including all p-way interactions in a regression model)
- Tree-based methods more naturally accommodate discontinuous relationships and nonlinear interaction effects
- Graphical presentation of tree structure shows the interaction effects more intuitively

General Framework of Tree-based Methods

- At each step, greedily search among covariates for splitting
- Growing: large tree to avoid missing deeper interaction
- Pruning: model selection (Leblanc and Crowley 1993)

Splitting for Interaction Tree (IT) for Scalar Outcome

- A bisection of data is induced by a binary question on some covariate X.

$$y_i = \beta_0 + \beta_1 T_i + \beta_2 Z_i + \gamma T_i \times Z_i + \epsilon_i \tag{1}$$

  - y_i: outcome for subject i;
  - T_i: treatment;
  - $Z_i = I_{X_i \leq c}$: node for a continuous covariate X_i, where c is the cutpoint to be estimated

- Among all permissible splits, select the split such that the treatment effect differs the most between its two resultant child nodes, i.e., the greatest interaction with the treatment.
- That is, a natural measure for this interaction effect is equivalent to testing $H_0 : \gamma = 0$

Problem of interest: Interaction tree for longitudinal trajectories (IT-LT)

- Most of current studies considered cross-sectional studies, or condensed the longitudinal outcome to a scalar one
- In this talk we will consider the extension of interaction tree (IT) to the longitudinal outcome
- We are interested in finding interaction between treatment and covariates, and thus identify subgroups with enhanced treatment effect in longitudinal studies with possible nonlinear trajectories
  - How to consider the trajectories of drinking, which could be nonlinear?
  - Account for correlation among repeated measures.

Our Method: IT-LT (Longitudinal Trajectories)

- At each split: four types of curves of drinking trajectories
  - $\boldsymbol{y}_{lc}$: control group, left node
  - $\boldsymbol{y}_{lt}$: treatment group, left node
  - $\boldsymbol{y}_{rc}$: control group, right node
  - $\boldsymbol{y}_{rt}$: treatment group, right node
- Treatment effect curve = treatment curve - control curve

  $\boldsymbol{y}_{le} = \boldsymbol{y}_{lt} - \boldsymbol{y}_{lc}$, $\boldsymbol{y}_{re} = \boldsymbol{y}_{rt} - \boldsymbol{y}_{rc}$

The Mixed Effects Model with Splines

- $B_k(t)$: the *k-th* knot for the spline basis of time
- $a_i \sim N(0, \sigma_a^2)$: subject specific random effect
- $T_i = 1$ indicates treatment group
- Under H_a:

$$
\begin{aligned}
y_l(t_{ij}) &= a_i + \sum_{k=1}^{K} [\beta_k^{lc} B_k(t_{ij}) + \mathbf{I}_{T_i=1} \beta_k^{le} B_k(t_{ij})] + \epsilon_{ij}. \\
y_r(t_{ij}) &= a_i + \sum_{k=1}^{K} [\beta_k^{rc} B_k(t_{ij}) + \mathbf{I}_{T_i=1} \beta_k^{re} B_k(t_{ij})] + \epsilon_{ij}.
\end{aligned} \tag{2}
$$

- Under H_0: $\beta_k^{le} = \beta_k^{re}$ for all k
- Testing of heterogeneity of treatment effect $\iff$ testing model fit of H_0 vs. H_a

Test statistics in mixed effects based IT-LT

- Normality assumption of random effects $N(0, \sigma_a^2)$ and error terms $N(0, \sigma_e^2)$
- Repeated measures for subject i, $\mathbf{y}_i = (y_{i1}, y_{i2}, ..., y_{in_i})$ is distributed as $\mathbf{y}_i \sim (\boldsymbol{\mu}_i, \sigma_a^2 \boldsymbol{I}_{\boldsymbol{n_i}} \boldsymbol{I}_{\boldsymbol{n_i}}^{\boldsymbol{T}} + \sigma_e^2 \mathbf{I}_{n_i})$
- $\boldsymbol{\mu}_i$ is defined in Eqn. (2)
- Likelihood $\hat{L}_0$, $\hat{L}_1$ is the product of the multivariate normal densities
- Likelihood ratio test at each split is

$$\Lambda = 2 \log \frac{\hat{L}_1}{\hat{L}_0}.$$

- The degree of freedom of the LRT statistics in IT-LT depends on the number of knots.

The pruning process and control parameters

- To avoid missing important higher-order interactions, it is preferable to build a large tree at the beginning and then gradually prune the tree.
- As in Su et al. (2008) and Hou et al. (2015), we use the split-complexity pruning algorithm originally developed by LeBlanc and Crowley (1993)
- The tuning parameter in the pruning process is set to be $\lambda = log(n)$, corresponding to BIC.

Nonlinear longitudinal trajectories

- We adopt the natural cubic splines bases (i.e., setting the highest polynomial power to 3) with additional boundary constraints
- Natural cubic spline is a common choice to achieve adequate smoothness in approximation and computational convenience.
- Other spline basis function can be used, e.g., truncated power basis for simplicity (Chen et al. 2013)

Knot selection

- There are 12 repeated measures for each subject in our real data. We experimented many choices of the number of knots through simulation
- It turns out that the results are generally satisfactory and robust when a medium number of knots (e.g., K $=$ 4 to 6 knots out of 12 observations in the ondansetron trial data) are used.
- $K = 5$ is used in the Simulation and Application Studies.

Simulation settings

- Six settings, each has 100 datasets
- 250 subjects, 13 observations for each subject (12 weeks).
- Each observation has probability of 0.1 to be missing
- Randomly ($p = 0.5$) assign to treatment/control group
- $$y_{ij} = \mu_i(t_{ij}) + a_i + \epsilon_{ij}. \tag{3}$$

  where $a_i \sim N(0, 0.1)$, $\epsilon_{ij} \sim N(0, 0.2)$

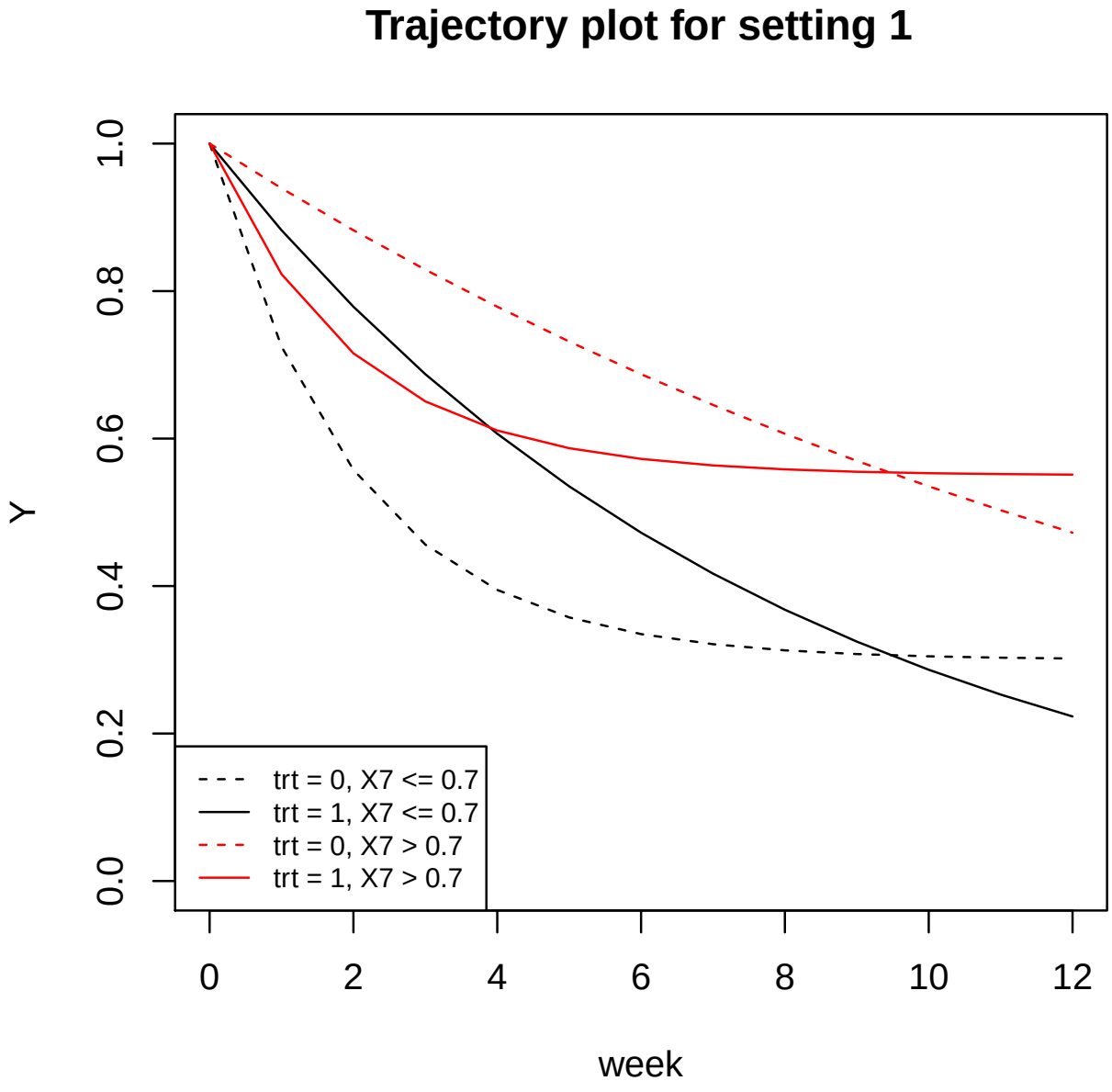
Simulation settings

- Six *Bernoulli*(0.5) covariates and four $N(0, 1)$ covariates
- In the first 4 settings, a continuous covariate, X_7, is chosen to be the true splitting variable in most settings, and 0.7 is the splitting point: $X_7 > .7$ vs. $X_7 \leq .7$.
- In Setting 5, X_7 and $X1$ are chosen to be the true splitting variables
- In Setting 6, X_7, $X1$, and $X2$ are chosen to be the true splitting variables

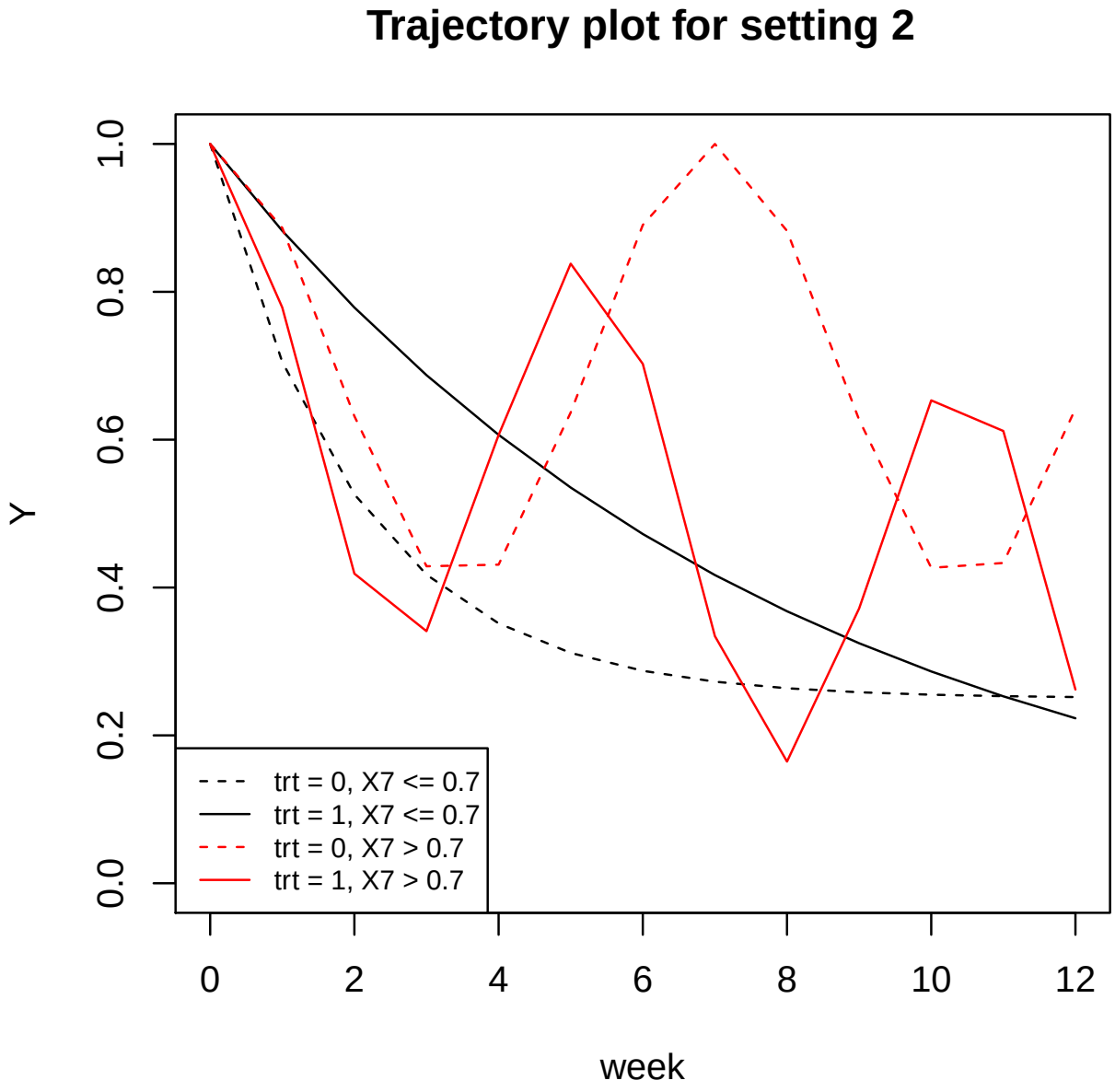
Table 1: Simulation settings in one level tree

Setting	Partition (z)	Trt	Trajectory
1	$X_7 <= 0.7$	0	$0.55 + 0.45 \times e^{-t_{ij}/2}$
		1	$e^{-t_{ij}/16}$
	$X_7 > 0.7$	0	$e^{-t_{ij}/8}$
		1	$0.3 + 0.7 \times e^{-t_{ij}/2}$
2	$X_7 <= 0.7$	0	$0.7 + 0.3 * \cos(0.9 t_{ij})$
		1	$\max(0.7 + 0.3 * \cos(1.2 t_{ij}) - 0.03 t_{ij}, 0)$
	$X_7 > 0.7$	0	$0.25 + 0.75 \times e^{-t_{ij}/2}$
		1	$e^{-t_{ij}/8}$
3	$X_7 <= 0.7$	0	$e^{-t_{ij}/8}$
		1	$0.5 + 0.5 \times e^{-t_{ij}}$
	$X_7 > 0.7$	0	$0.25 + 0.75 \times e^{-t_{ij}}$
		1	$e^{-t_{ij}/4}$
4		0	$0.3 + 0.7 \times e^{-t_{ij}/2}$
		1	$e^{-t_{ij}/8}$

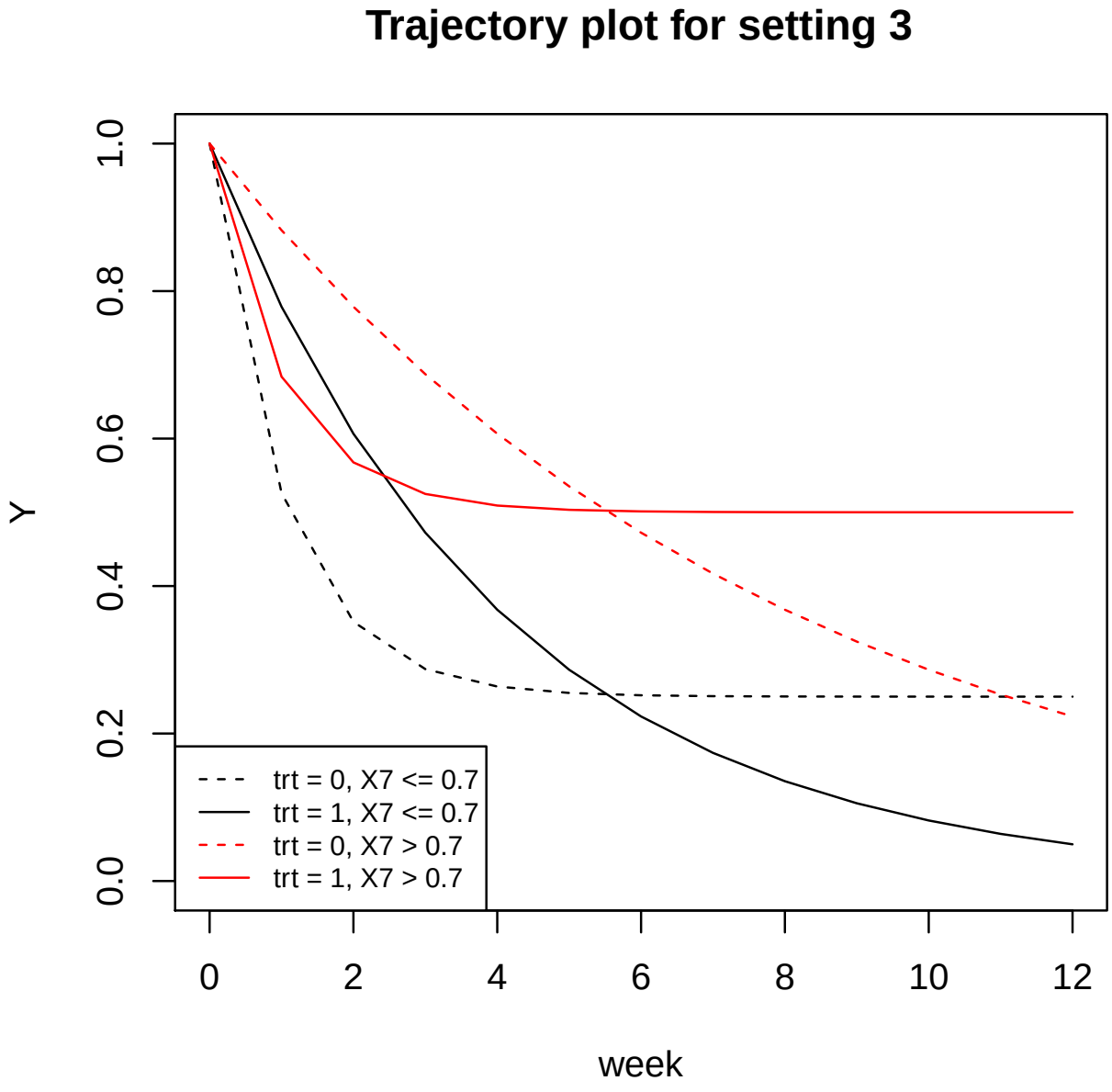
Simulation settings



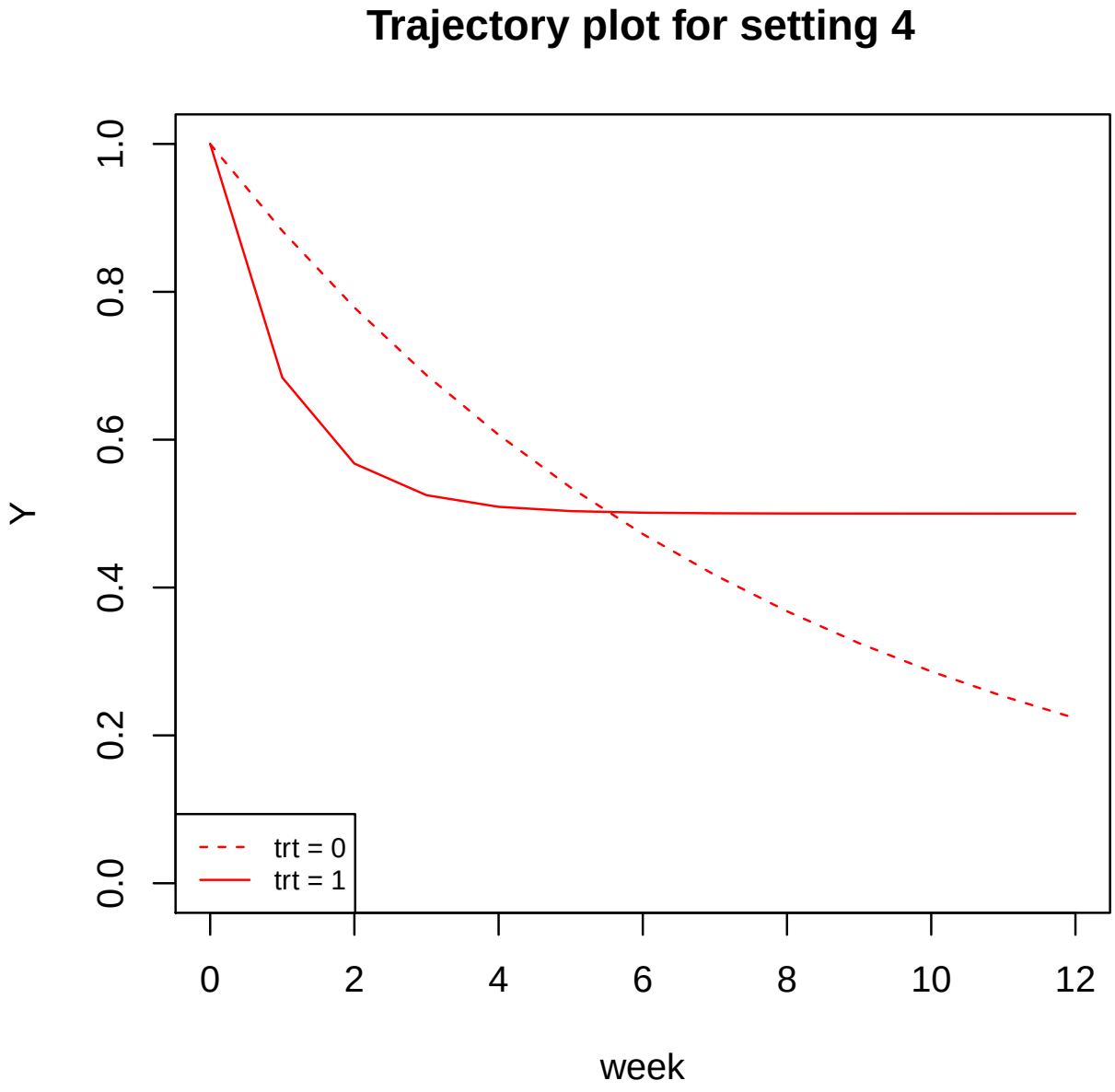
Simulation settings



Simulation settings



Simulation settings



Choice of control parameters

- The maximum depth of the tree: $d_{max} = 4$.
- The least number of samples needed for a split to be considered: $s_{split} = 30$.
- The number of cut-off points: for continuous variables, we set $N_{cut} = 20$ equally spaced cut-off points. For discrete variable, the power set (collection of all subsets) will be considered.

Comparison to IT with scalar outcome

We compare the performance of IT-LT with several scalar based interaction tree methods

- "avg" method calculates the difference between the average measure after baseline and the baseline measure as a scalar variable.
- "last-1" method simply uses the difference between the last weekly observation and the baseline measure.
- "last-4" method uses the difference between the mean of the last 4 weekly measures (last month) and the baseline measure (Falk et al. 2010)

Evaluation criteria

- $root_{rate}$: proportion of trees built
- *size*: number of non-terminal nodes
- hit_{root}: proportion of root nodes that "hit" (selecting the right variable)
- hit_{total}: proportion of all nodes that "hit" (Su et al. 2008, 2011)
- Rand index (Rand 1971): Rand index between fitted group memberships and true group memberships

Simulation results

Table 2: Performance of different methods in one level tree

Setting	method	hit_{root}	hit_{total}	$root_{rate}$	*size*	Rand index
1	IT-LT	1.00	0.98	1.00	1.02	0.98
	avg	0.98	0.80	1.00	1.42	0.91
	last1	0.76	0.67	1.00	1.34	0.78
	last4	0.50	0.38	1.00	1.84	0.66
2	IT-LT	1.00	0.98	1.00	1.02	0.98
	avg	1.00	0.87	1.00	1.22	0.95
	last1	1.00	0.89	1.00	1.14	0.93
	last4	0.58	0.44	1.00	1.86	0.67
3	IT-LT	1.00	0.98	1.00	1.02	0.98
	avg	0.44	0.31	1.00	2.16	0.63
	last1	1.00	0.90	1.00	1.18	0.95
	last4	1.00	0.95	1.00	1.14	0.96
4	IT-LT	–	–	0.00	0.00	–
	avg	–	–	0.82	3.41	–
	last-1	–	–	0.84	2.44	–
	last-4	–	–	0.76	3.40	–

Table 3: Simulation settings for two level tree

Setting	Partition (z)	Trt	Trajectory
5	$X_1 = 1, X_7 <= 0.7$	0	$0.7 + 0.3 * \cos(0.9 t_{ij})$
		1	$\max(0.7 + 0.3 * \cos(1.2 t_{ij}) - 0.03 t_{ij}, 0)$
	$X_1 = 1, X_7 > 0.7$	0	$0.25 + 0.75 \times e^{-t_{ij}/2}$
		1	$e^{-t_{ij}/8}$
	$X_1 = 0, X_7 <= 0.7$	0	$0.25 + 0.75 \times e^{-t_{ij}}$
		1	$e^{-t_{ij}/2}$
	$X_1 = 0, X_7 > 0.7$	0	$e^{-t_{ij}/8}$
		1	$0.5 + 0.5 \times e^{-t_{ij}/2}$
6	$X_7 > 0.7, X_1 = 0$	0	$0.7 + 0.3 * \cos(0.9 t_{ij})$
		1	$\max(0.7 + 0.3 * \cos(1.2 t_{ij}) - 0.03 t_{ij}, 0)$
	$X_7 > 0.7, X_1 = 1$	0	$0.25 + 0.75 \times e^{-t_{ij}/2}$
		1	$e^{-t_{ij}/8}$
	$X_7 <= 0.7, X_2 = 0$	0	$0.25 + 0.75 \times e^{-t_{ij}}$
		1	$e^{-t_{ij}/2}$
	$X_7 <= 0.7, X_2 = 1$	0	$e^{-t_{ij}/8}$
		1	$0.5 + 0.5 \times e^{-t_{ij}/2}$

Simulation results

Table 4: Performance of different methods in two level tree

Setting	method	hit_{root}	hit_{total}	$root_{rate}$	*size*	Rand index
5	IT-LT	1.00	1.00	1.00	3.14	0.98
	avg	1.00	0.82	1.00	1.24	0.72
	last1	1.00	0.99	1.00	1.86	0.83
	last4	1.00	0.97	1.00	2.36	0.86
6	IT-LT	1.00	1.00	1.00	3.26	0.95
	avg	0.96	0.90	1.00	2.52	0.78
	last1	1.00	0.97	1.00	2.22	0.84
	last4	1.00	0.99	1.00	2.18	0.85

Application to Ondansetron Data

- Johnson et al. (2011) conducted a 12-week double-blind controlled trial of ondansetron vs. placebo, in 283 alcohol-dependent subjects.
- Outcome: Longitudinal daily drinking levels summarized as weekly percentage of heavy drinking days (PHDD)
- Other Covariates
  - Time in weeks, Age of onset, race, sex, age, PhD_base90 (drinking history)
  - 21 genetic polymorphisms: coded as 0, 1, 2 (e.g., aa, Aa, AA): resulting in a total of 3^{21} genotype combinations

Application to Ondansetron Data

- Due to missingness in genotype information, only 251 subjects were included in the analysis
- Missing longitudinal observations are imputed by the last value carried forward method.
- Random intercept is included to account for heterogeneity in repeated measures

PHDD Trajectories of Two Arms (Johnson 2011)

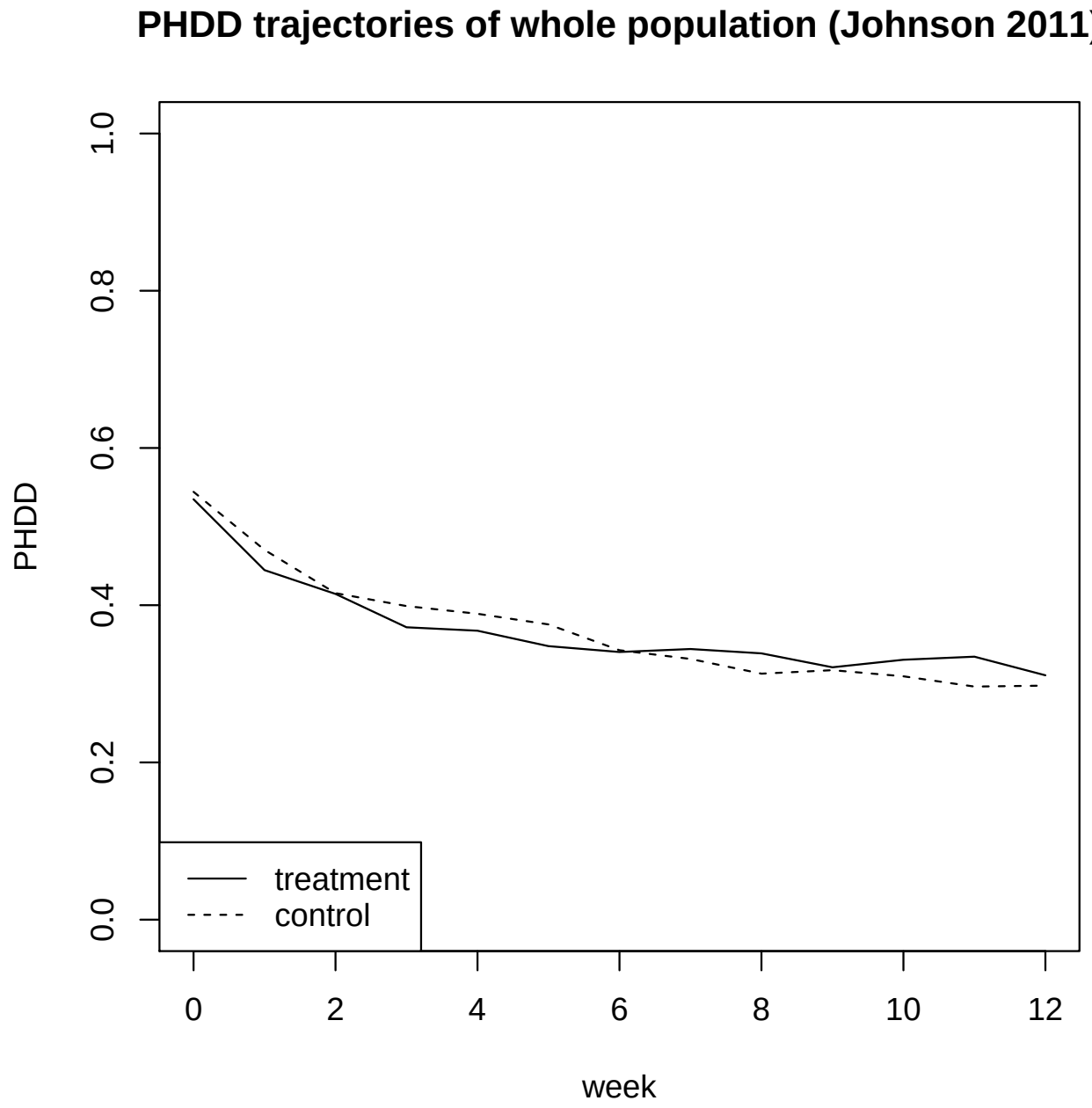
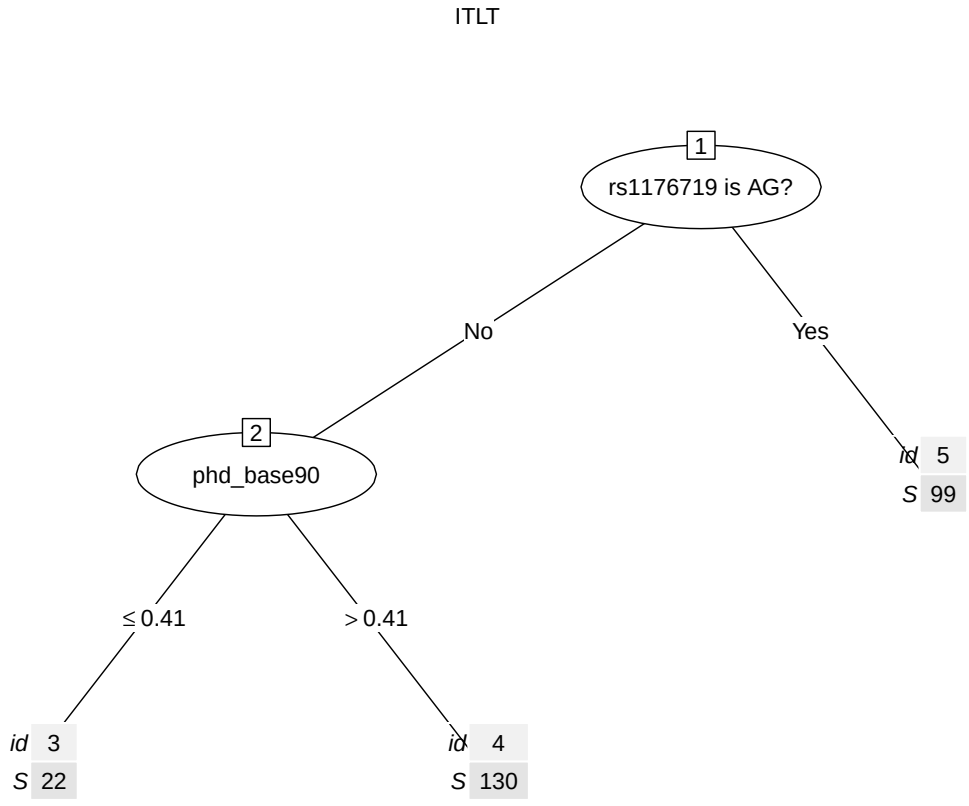
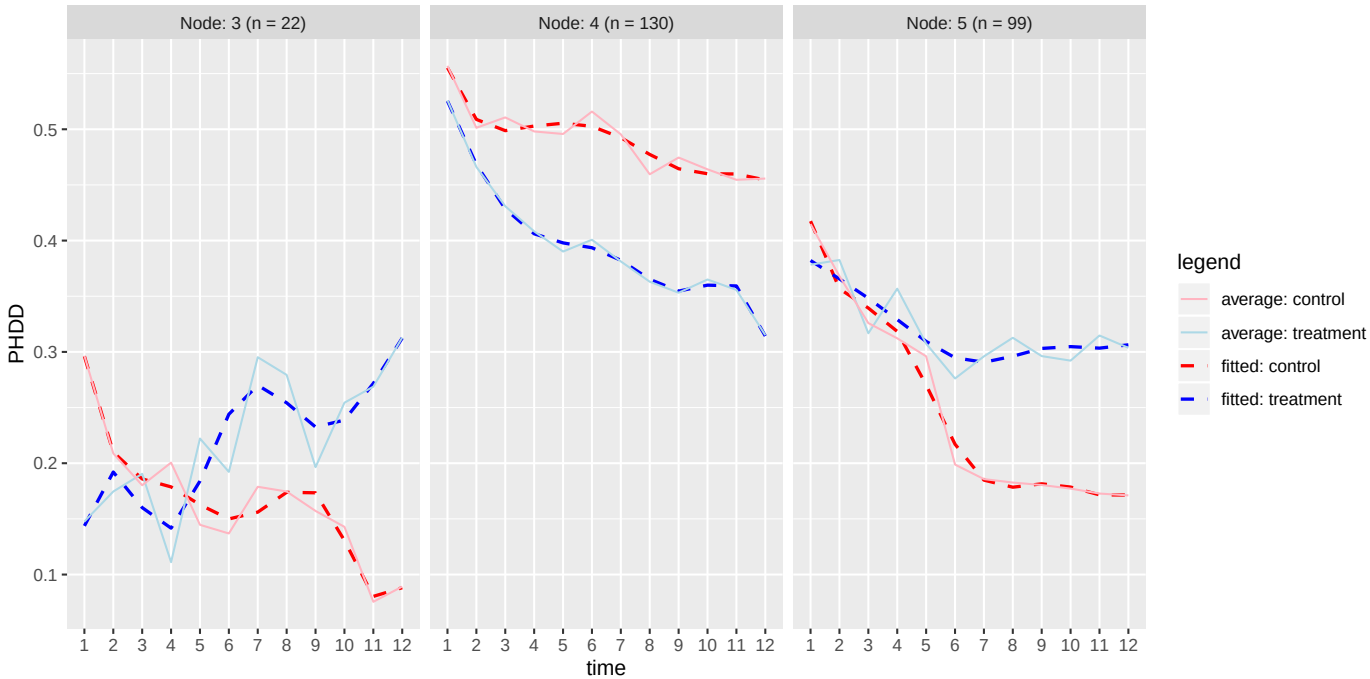


Figure 1: Tree built in the Ondansetron trial on weekly PHDD data



For each node, node id (id), node size (S) are plotted.

Figure 2: Nodes identified by IT-LT method on weekly PHDD data



Application Results

- The largest node (# 4) with 130 (52%) subjects: rs1176719 !=AG and baseline heavy drinking rate > 0.41
  - Early separation, Ondansetron is more effective
- Node 5 (99 subjects): rs1176719=AG:
  - After week 5, treatment is worse than placebo
- Node 3 (22 subjects): rs1176719 !=AG and baseline heavy drinking rate ≤ 0.41:
  - Two curves cross each other around week 5
- A remarkably strong placebo effect (compared to baseline) is observed in this study across all subgroups

Mechanisms

- rs1176719 is located in the intron 4 region (NM 000869.5) of the HTR3B gene, close to an intron-exon boundary (Hou et al. 2015).
- Heavy drinking at baseline could affect the treatment effect
- These nonlinear trajectory patterns identified by the IT-LT subgroups provide valuable insight into the heterogeneous effects of ondansetron and inform future studies.

Discussion of mixed effects model based IT-LT

- IT-LT corrects the deficiency in scalar based methods, which could be flawed when nonlinear trajectories exist
- IT-LT is based on splines, which is more flexible and correctly identifies the subgroups
- Able to accommodate sophisticated longitudinal models
- **CAUTION**: This is a POST-HOC analysis: a Phase III trial should be conducted to confirm this personalized medicine result

Future Work

- Apply to larger clinical trial data, e.g., the Ocular Hypertension Treatment Study with 1636 subjects
- GEE approach
- Take into account efficacy and safety simultaneously
- Prediction of individual treatment effects
- Extensions to longitudinal observational studies warrants future research efforts, e.g., using the facilitating score (Su et al. 2012)
- Rather than last value carried forward method to impute the missing values after dropout, more advanced methods, e.g., joint random effects model of longitudinal drinking and time to dropout could be considered in the future work to tackle the potential informative drop-out issue.

R package

- R package available: https://github.com/yishuwei2019/itlt

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Thank You!