Treatment Switching Estimation based on Principal Stratification

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Agenda

- Introduction to Bayesian latent variable Principal Stratification Model[1] for Treatment Switching
- Demonstration based on Simulations
- Conclusion and Discussion

1. Alessandra Mattei, Fabrizia Mealli, Peng Ding, “Assessing causal effects in the presence of treatment switching through principal stratification”, 2020, 2002.11989, arXiv, stat.AP
link: *[2002.11989] Assessing causal effects in the presence of treatment switching through principal stratification (arxiv.org)*

Introduction to Bayesian latent variable Principal Stratification Model for Treatment Switching

GSK

Motivation

- Clinical trials focusing on survival outcomes often allow patients in the control arm to switch to the treatment arm if their physical conditions are worse than certain tolerance levels.
- The intention-to-treat analysis ignores the information of treatment switching.
- Other existing methods[2,3,4,5] propose to reconstruct the outcome a subject would have had if he or she had not switched under strong assumptions.
- The proposed method[1] focuses on principal causal effects for patients belonging to subpopulations defined by the switching behavior under control.

1. Alessandra Mattei, Fabrizia Mealli, Peng Ding, "Assessing causal effects in the presence of treatment switching through principal stratification", 2020, 2002.11989, arXiv, stat.AP
2. Dodd, S., et al. (2019). "Adjustment for treatment changes in epilepsy trials: A comparison of causal methods for time-to-event outcomes." Stat Methods Med Res **28(3): 717-733.**
3. Latimer NR, Abrams KR. NICE DSU Technical Support Document 16: Adjusting Survival Time Estimates in the Presence of Treatment Switching [Internet]. London: National Institute for Health and Care Excellence (NICE); 2014 Jul. PMID: 27466662.
4. Robins, J. M. and A. A. Tsiatis (1991). "Correcting for non-compliance in randomized trials using rank preserving structural failure time models." Communications in Statistics - Theory and Methods **20(8): 2609-2631.**
5. Sullivan TR, Latimer NR, Gray J, Sorich MJ, Salter AB, Karnon J. Adjusting for Treatment Switching in Oncology Trials: A Systematic Review and Recommendations for Reporting. Value Health. 2020 Mar;23(3):388-396. doi: 10.1016/j.jval.2019.10.015. Epub 2020 Jan 23. PMID: 32197735.

Causal estimands

- Intention-to-treat causal effects
  - Average causal effect:

$$ACE = E[Y_i(1)] - E[Y_i(0)]$$

  - Distributional causal effect:

$$DCE(y) = P\{Y_i(1) > y\} - P\{Y_i(0) > y\}$$

- Principal causal effects
  - Principal average causal effects:

$$ACE(s) = E[Y_i(1)|S_i(0) = s] - E[Y_i(0)|S_i(0) = s]$$

  - Principal distributional causal effects:

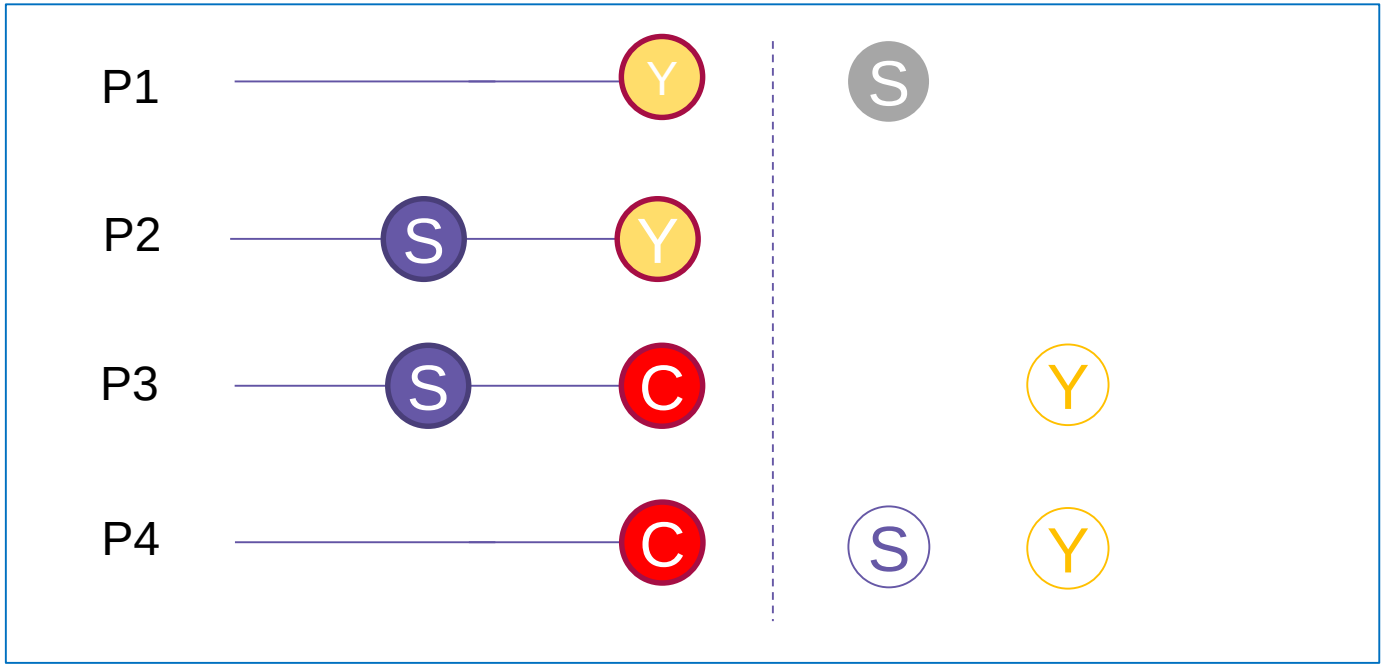
$$DCE(y|s) = P\{Y_i(1) > y|S_i(0) = s\} - P\{Y_i(0) > y|S_i(0) = s\}$$

  - Conditional principal distributional causal effects for switchers:

$$cDCE(y|s) = P\{Y_i(1) > y|Y_i(1) \geq S_i(0), S_i(0) = s\} - P\{Y_i(0) > y|Y_i(1) \geq S_i(0), S_i(0) = s\}$$

Observed Data Pattern & Principal Strata Setup for Treatment Switching

Placebo arm



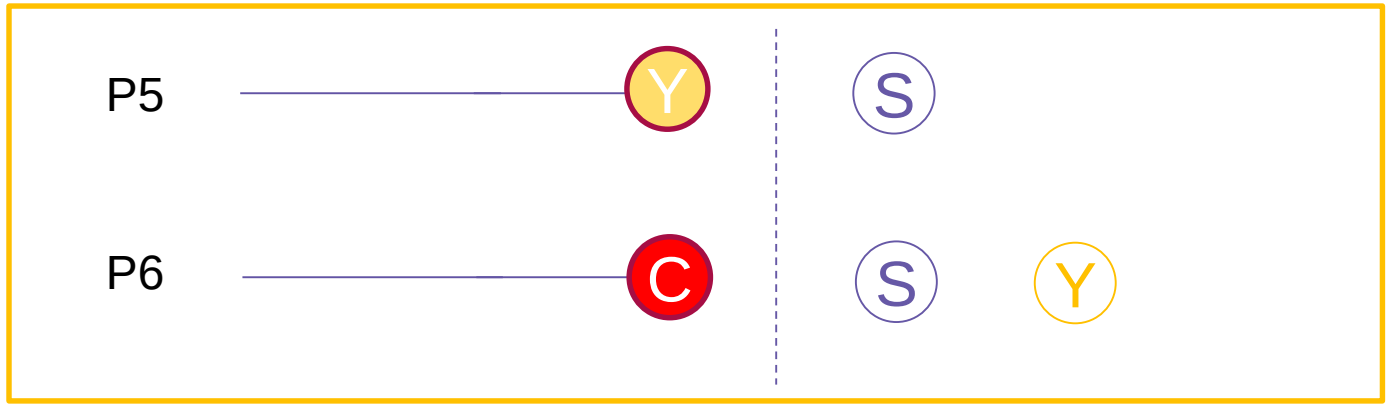
Non-switcher

Switcher

Switcher

Switcher/
Non-switcher

Treatment arm

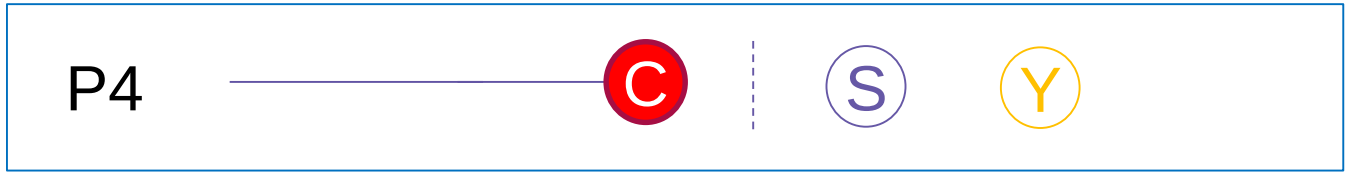


Switcher/
Non-switcher
If treated with placebo

Switcher/
Non-switcher
If treated with placebo

Assumptions on Switching Behaviour

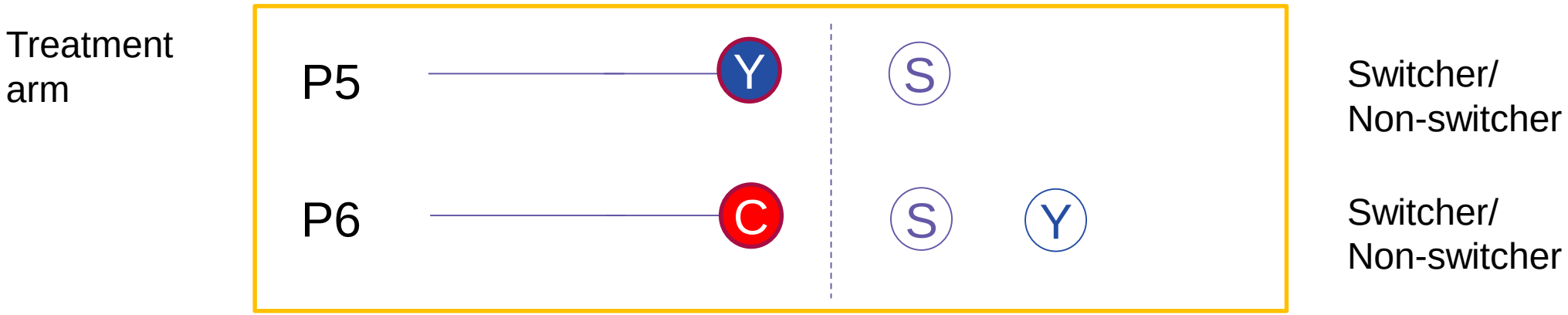
Placebo arm



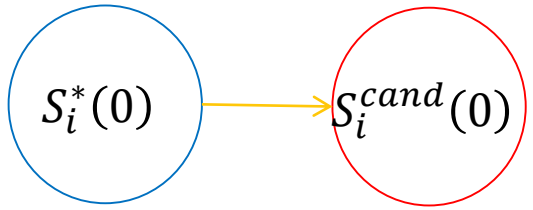
Switcher/
Non-switcher

$$\pi_{NS} = \frac{\pi G^{\bar{S}}_{Y(0)}(C_i)}{\pi G^{\bar{S}}_{Y(0)}(C_i) + (1-\pi) G_{S(0)}(C_i) \times 1}$$

Assumptions on Switching Behaviour



Metropolis-Hastings

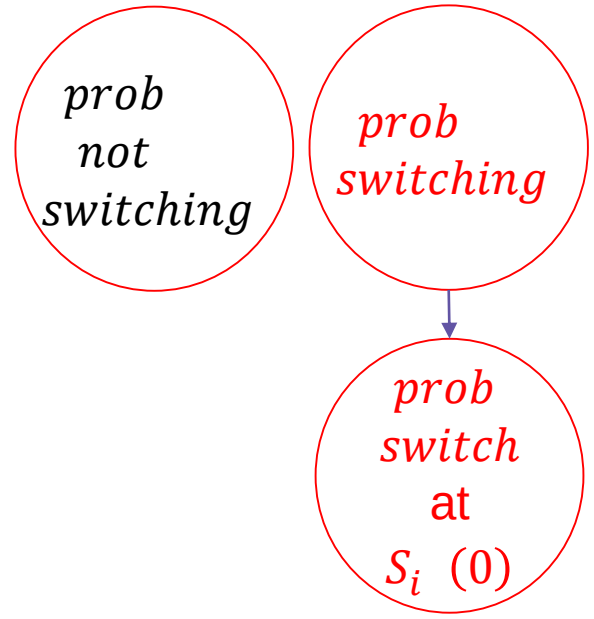


Previous draw

Candidate draw

$$Accept\ current\ draw\ with\ P = \min\left(P\left(S_i\ (0)\right), 1\right)$$

$$P\left(S_i\ (0)\right) = \frac{P\{S_i^{cand}(0)|\boldsymbol{\theta}, D_i^{obs}\}}{P\{S_i^*(0)|\boldsymbol{\theta}, D_i^{obs}\}} \times \frac{g\left(S_i^*(0)\right)}{g\left(S_i^{cand}(0)\right)}$$



Assumptions on Outcome conditioned on Switching

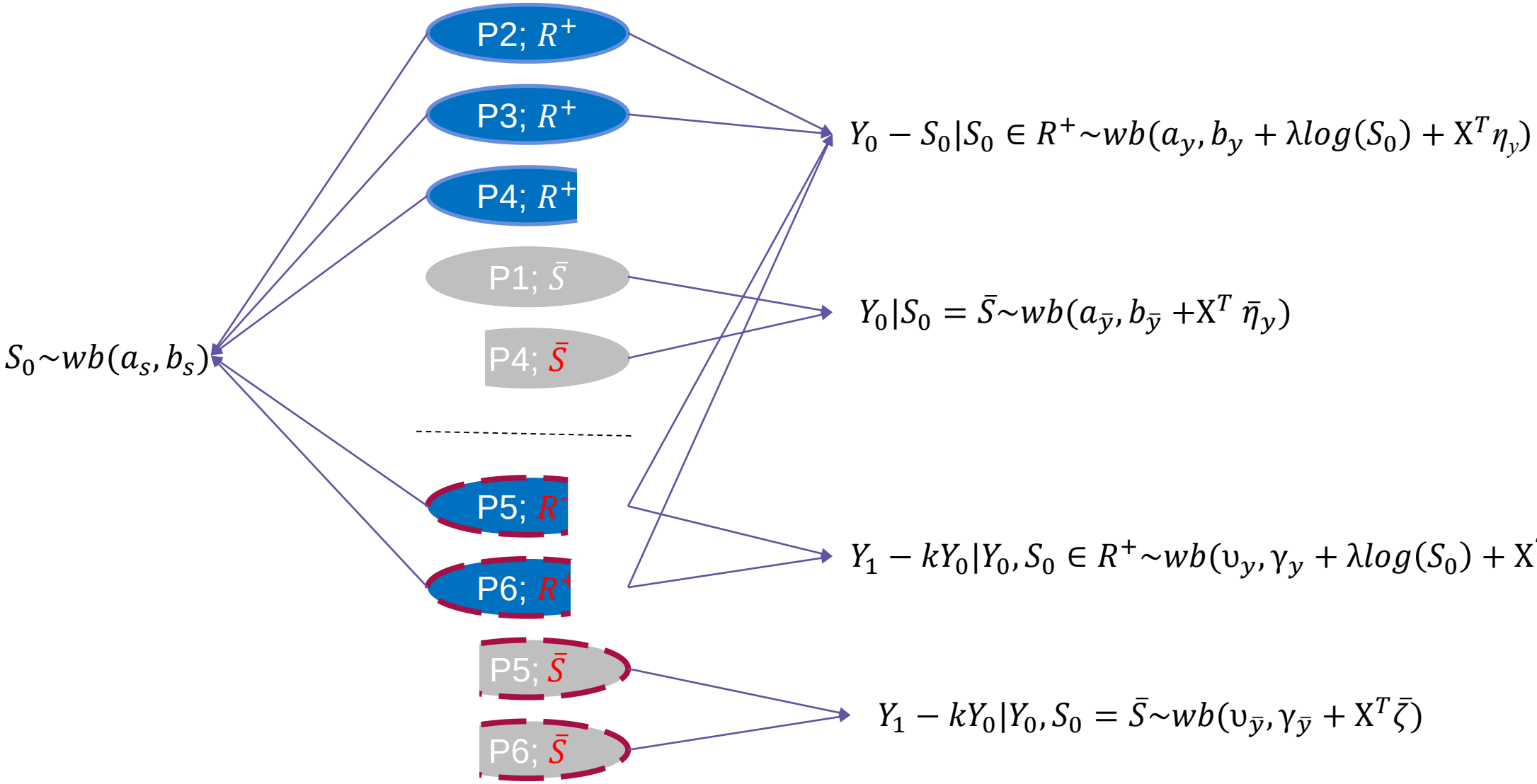
Control Arm

- $Y_i(0)|S_i(0) = \bar{S} \sim \text{Weibull}\left(\bar{\alpha}_Y, \bar{\beta}_Y + \text{X}^T \bar{\eta}_y\right)$
- $Y_i(0)|S_i(0) \in R_+ \sim S_i(0) + \text{Weibull}\left(\alpha_Y, \beta_Y + \boldsymbol{\lambda} \log\left(S_i(0)\right) + \text{X}^T \eta_y\right)$

Treatment arm

- $Y_i(1)|Y_i(0), S_i(0) = \bar{S} \sim \boldsymbol{\kappa} Y_i(0) + \text{Weibull}(\bar{\nu}_Y, \bar{\gamma}_Y + \text{X}^T \bar{\zeta})$
- $Y_i(1)|Y_i(0), S_i(0) \in R_+ \sim \boldsymbol{\kappa} Y_i(0) + \text{Weibull}\left(\nu_Y, \gamma_Y + \boldsymbol{\lambda} \log\left(S_i(0)\right) + \text{X}^T \zeta\right)$

Bayesian Latent Variable Principal Stratification Model



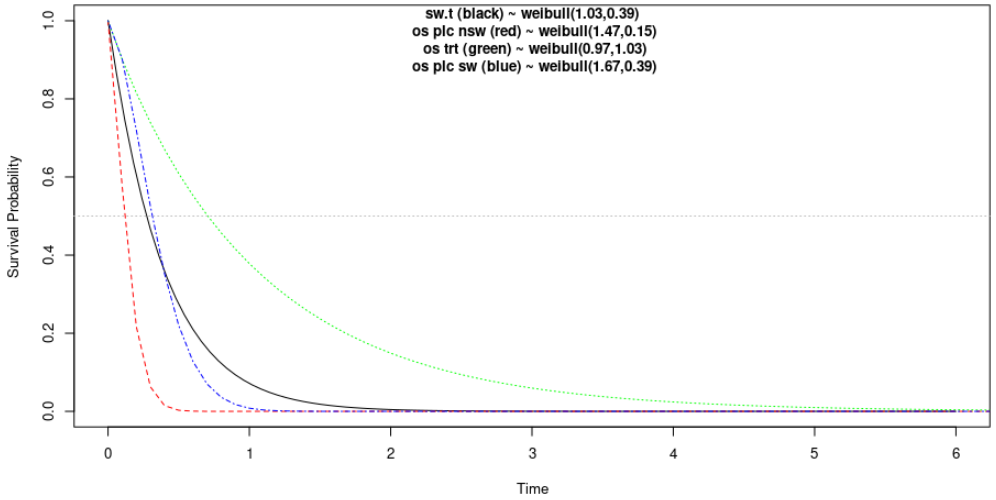
Demonstration based on Simulations

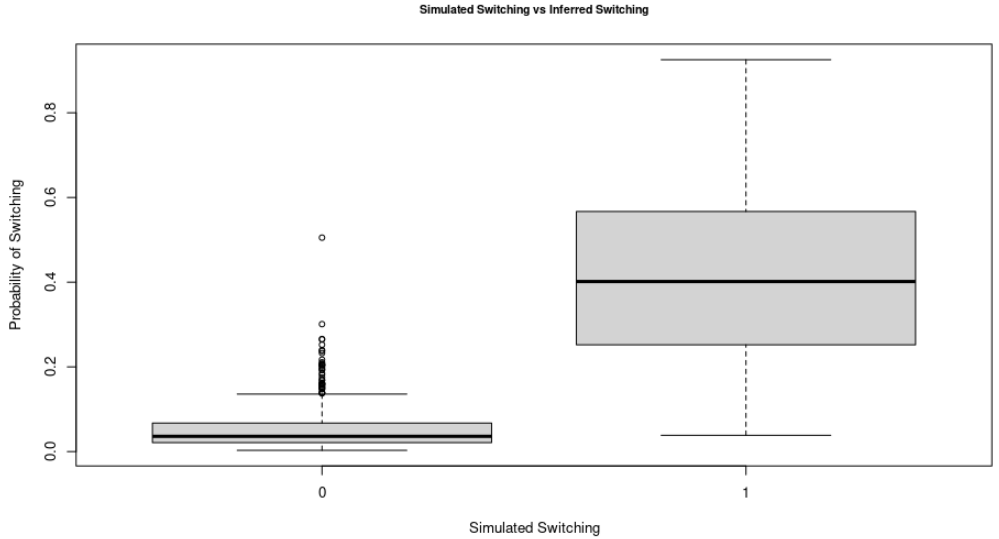
Summary of Simulation

Data Pattern	Treatment	Switching status	OS event	n(%)	Time of switching	OS
1	0	0	1	120(12%)	$cens_{t1}$	wb(1, 0.6)
2	0	1	1	50(5%)	wb(1,0.4)	c [1] × wb(1, 0.6) + (1-c) × wb(1, 1)
3	0	1	0	140(14%)	wb(1,0.4)	$cens_{t.mx}$ [5]
4	0	0	0	190(19%)	$cens_{t1}$ [2]	$cens_{t2}$ [3]
5	1	n/a	1	140(14%)	N/A	wb(1,1)
6	1	n/a	0	360(36%)	N/A	$cens_{t3}$ [4]

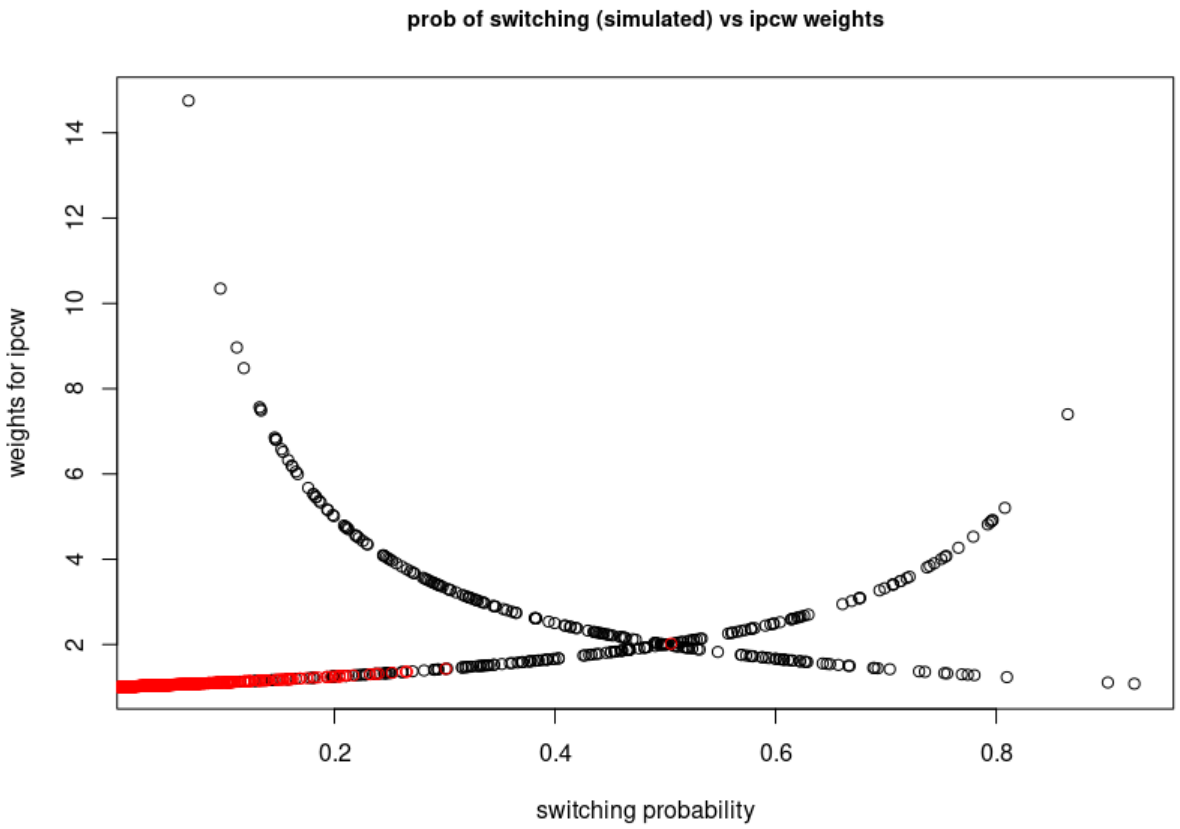
1. c is the proportion of time on plc
2. $cens_{t1}$: censoring quantile of wb(1, 0.4)
3. $cens_{t2}$: censoring quantile of wb(1, 0.6)
4. $cens_{t3}$: censoring quantile of wb(1, 1)
5. $cens_{t.mx}$: censoring quantile of c*wb(1,0.6) + censoring quantile of (1-c)*wb(1,1)

Bayesian Latent Variable Principal Stratification Model





IPCW[2,3]

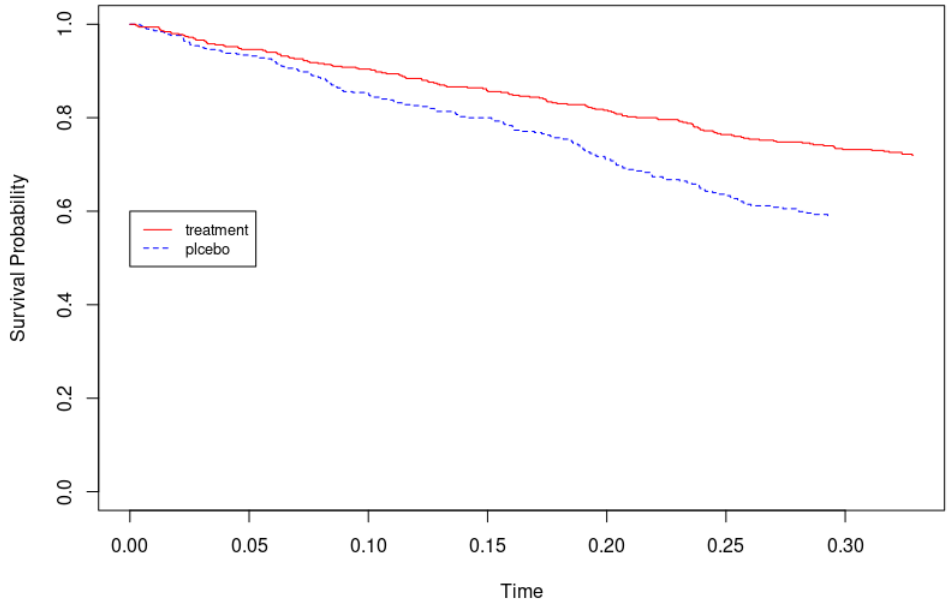


	HR	95% CIs	P-value
Naïve approach*	0.9	(0.70, 1.12)	0.395
IPCW	0.57	(0.43, 0.75)	8.71×10^{-5}
*** censored at switching**			

2. Dodd, S., et al. (2019). "Adjustment for treatment changes in epilepsy trials: A comparison of causal methods for time-to-event outcomes." Stat Methods Med Res **28(3): 717-733.**

3. Latimer NR, Abrams KR. NICE DSU Technical Support Document 16: Adjusting Survival Time Estimates in the Presence of Treatment Switching [Internet]. London: National Institute for Health and Care Excellence (NICE); 2014 Jul. PMID: 27466662.

RPSFTM[3,4]



	HR	95% CIs	P-value
RPSFTM	0.59	(0.47, 0.74)	6.05×10^{-6}

3. Latimer NR, Abrams KR. NICE DSU Technical Support Document 16: Adjusting Survival Time Estimates in the Presence of Treatment Switching [Internet]. London: National Institute for Health and Care Excellence (NICE); 2014 Jul. PMID: 27466662.
4. Robins, J. M. and A. A. Tsiatis (1991). "Correcting for non-compliance in randomized trials using rank preserving structural failure time models." Communications in Statistics - Theory and Methods **20(8): 2609-2631.**

Principal Stratification

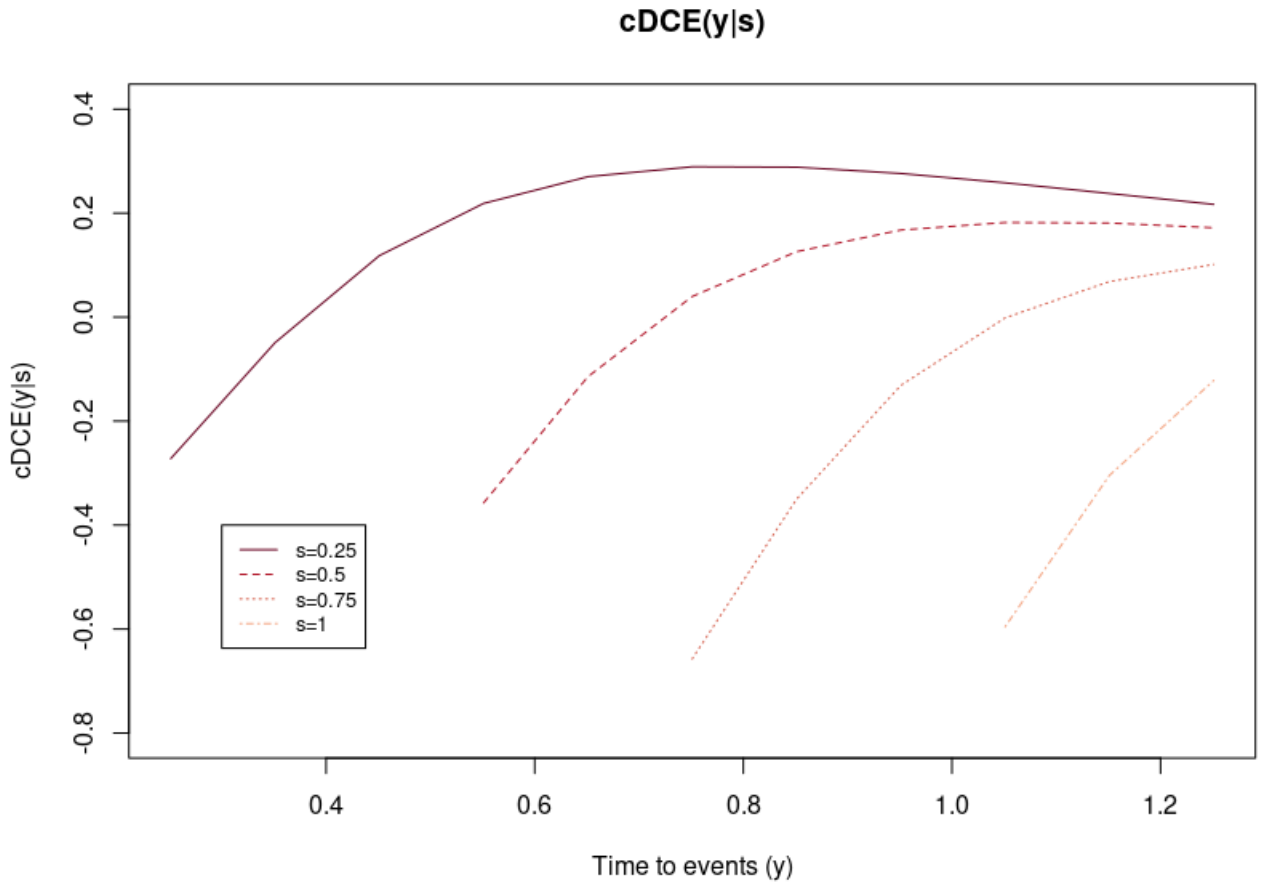
Model fitted in R 4.1.2 with R::Rcpp, R:: Armadillo

3 chains;
150,000 posterior samples each chain with thinning of 10

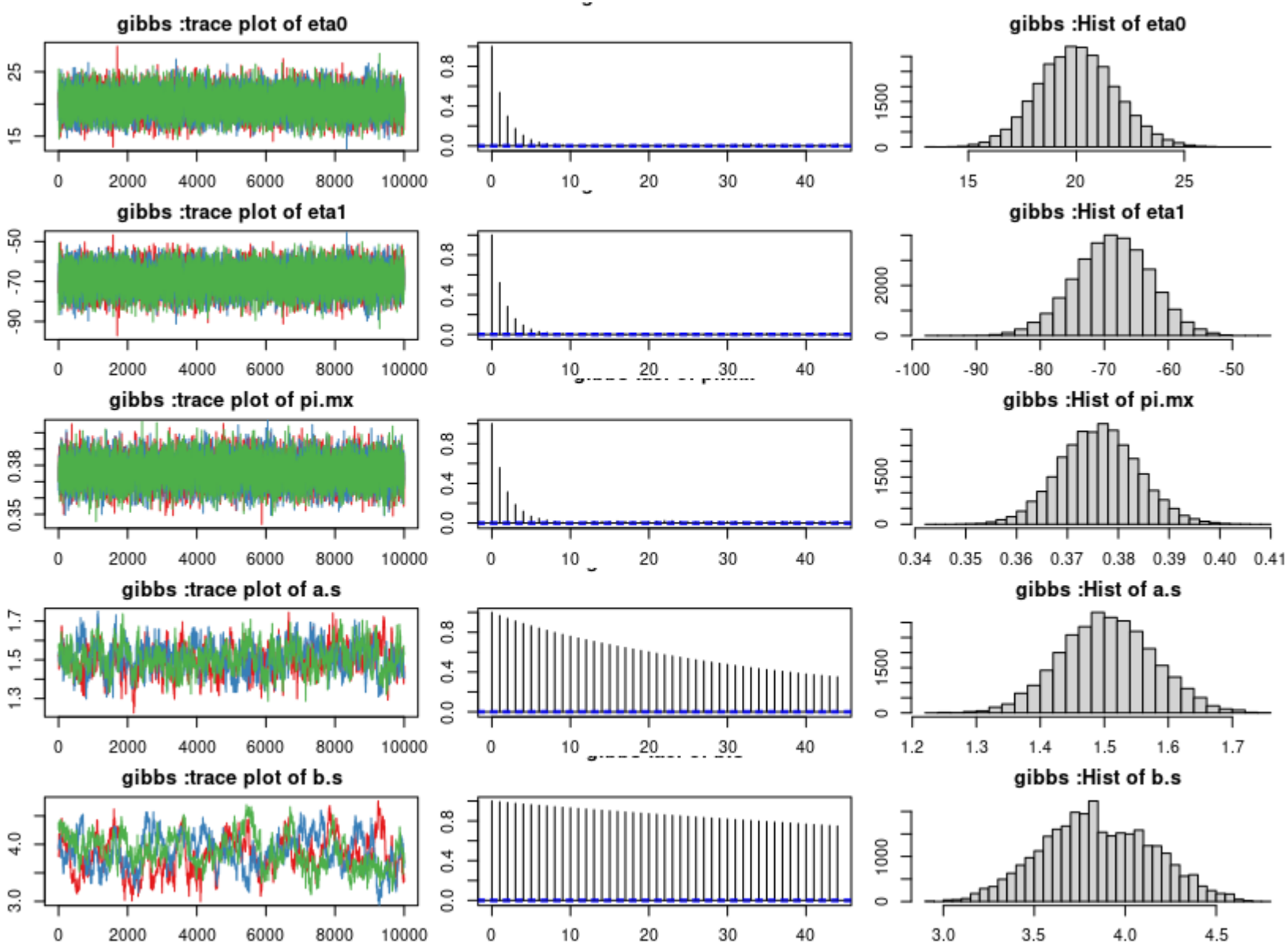
Principal Stratification

Par	mean	s.d.	Percentile					Accept Rate	Gelman R
			2.5%	25%	50%	75.00%	97.50%		
η_0	20.05	1.79	16.61	18.81	20.02	21.22	23.66	N/A	1
$\eta 1$	-68.76	5.89	-80.61	-72.71	-68.65	-64.66	-57.43	N/A	1
π	0.38	0.01	0.36	0.37	0.38	0.38	0.39	N/A	1
α_s	1.5	0.07	1.36	1.46	1.5	1.55	1.65	29.00	1
β_s	3.85	0.3	3.27	3.63	3.83	4.07	4.43	24.80	1.01
η_s	-1.91	1.32	-4.55	-2.78	-1.9	-0.96	0.61	29.90	1.03
$\bar{\alpha}_y$	1.02	0.09	0.85	0.96	1.02	1.08	1.2	30.63	1.01
$\bar{\beta}_y$	0.6	0.71	-0.74	0.08	0.6	1.12	1.92	22.33	1.08
$\bar{\eta}_y$	-0.19	1.73	-3.36	-1.43	-0.19	1.07	3.05	26.93	1.07
α_y	0.86	0.12	0.64	0.77	0.85	0.93	1.1	24.73	1
β_y	0.49	0.8	-1.11	-0.04	0.48	1.04	2.06	33.10	1.02
η_y	0.71	2.54	-4.09	-1	0.61	2.39	5.89	17.43	1.03
$\bar{\upsilon}_y$	1.02	0.07	0.89	0.98	1.02	1.07	1.16	28.40	1
$\bar{\gamma}_y$	-0.03	0.42	-0.85	-0.32	-0.03	0.25	0.81	24.93	1.04
$\bar{\zeta}$	0.29	1.08	-1.82	-0.42	0.27	1.02	2.38	30.77	1.04
υ_y	1.04	0.09	0.88	0.98	1.04	1.1	1.23	38.07	1
γ_y	0.91	0.23	0.47	0.76	0.91	1.06	1.36	34.93	1
ζ	-6.24	2.62	-11.38	-7.88	-6.14	-4.54	-1.33	19.53	1.01
λ	-0.05	0.17	-0.37	-0.16	-0.05	0.06	0.28	37.90	1.01
$ACE(\bar{S})$	0.32	0.17	**0.01**	0.21	**0.31**	0.43	**0.69**	N/A	1.01

Principal Stratification



Principal Stratification



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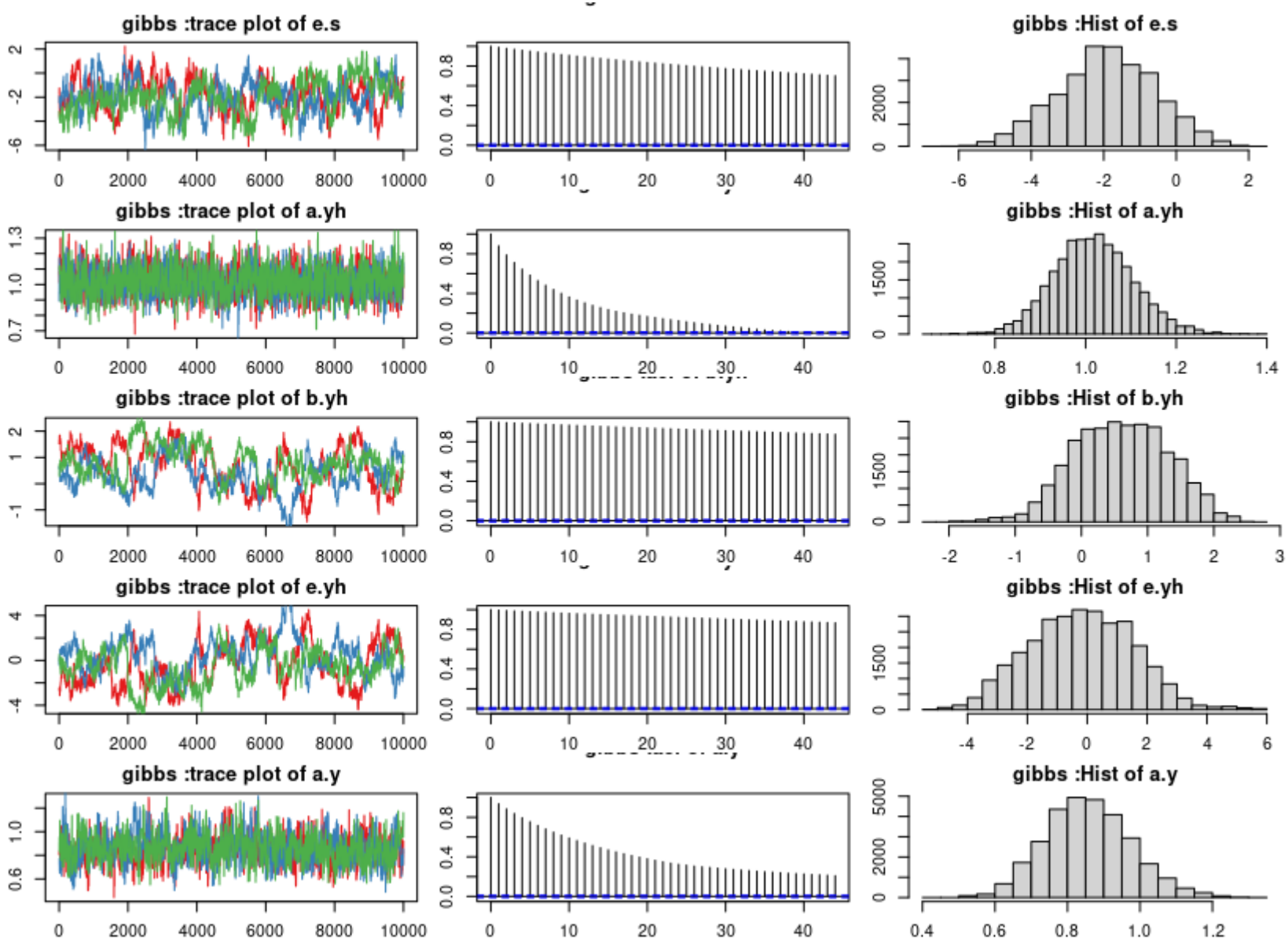

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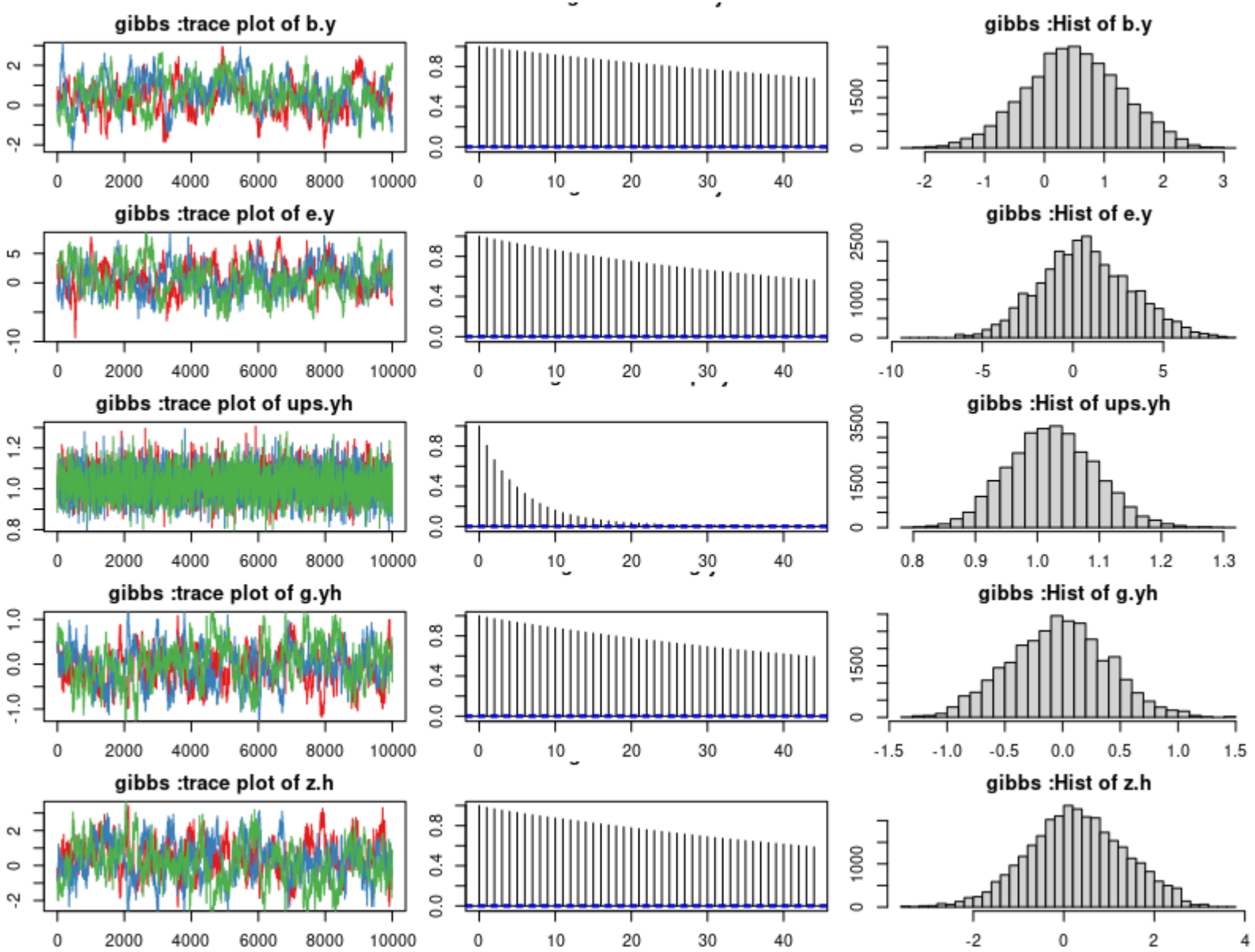

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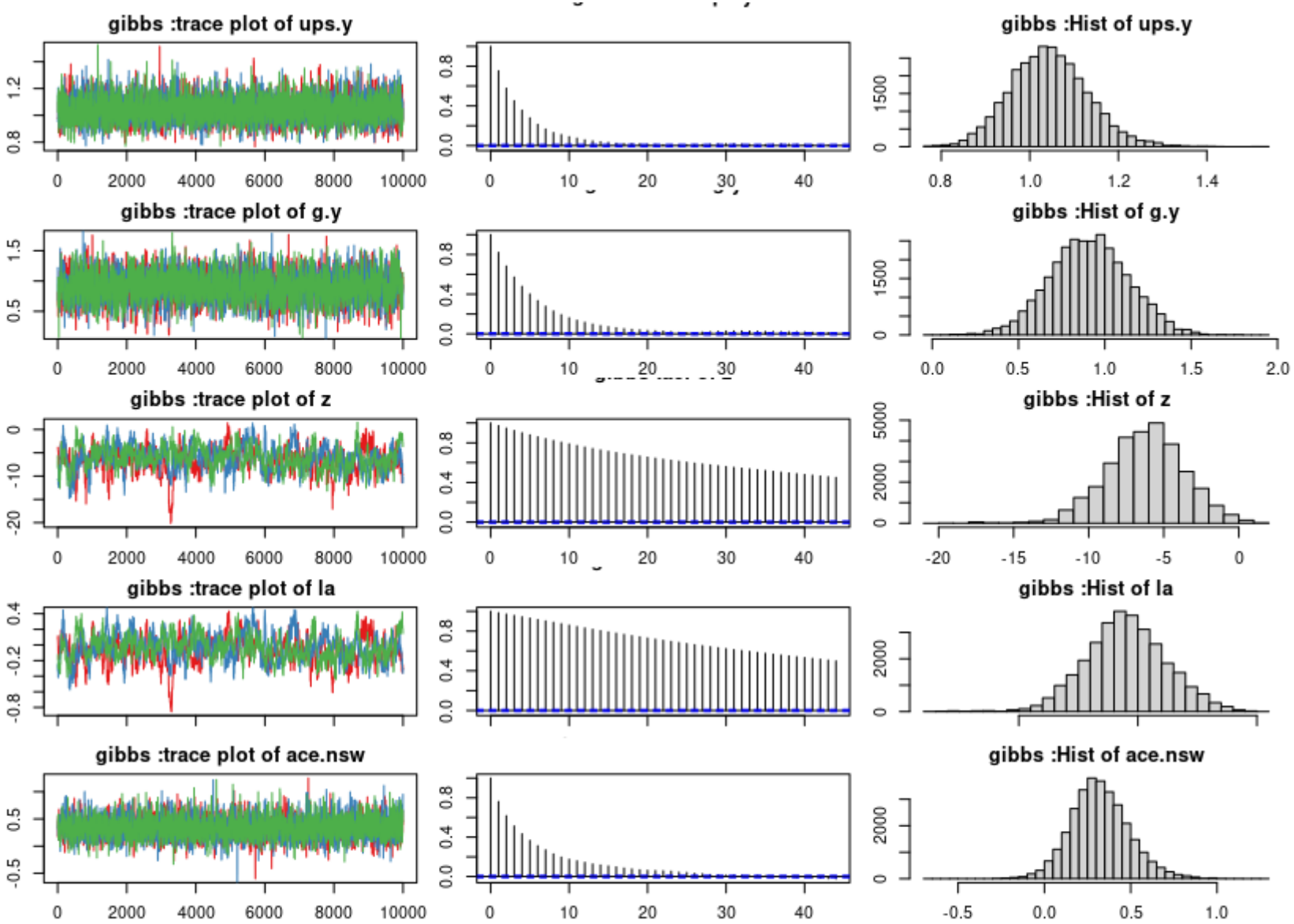

Conclusion and Discussion

Conclusions

- The proposed method targets the principal causal effects for subpopulations defined by switching status and time
- The Bayesian parametric modelling is flexible; however, the results are sensitive to the assumed relationship between potential survival outcomes within a principal stratum
- The method may be extended to handle two-way switching and informative censoring

References

1. Alessandra Mattei, Fabrizia Mealli, Peng Ding, “Assessing causal effects in the presence of treatment switching through principal stratification”, 2020, 2002.11989, arXiv, stat.AP

link: *[2002.11989] Assessing causal effects in the presence of treatment switching through principal stratification (arxiv.org)*

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Thank You!

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