A Bayesian Parametric Approach to Handle Missing Longitudinal Outcome Data in Trial-Based Health Economic Evaluations

Andrea Gabrio[1], Michael J. Daniels[2], Gianluca Baio[1]

[1]Department of Statistical Science, University College London, [2]Department of Biostatistics, University of Florida

PNS76, ISPOR Europe, 2-6 November 2019, Copenhagen, Denmark

UCL

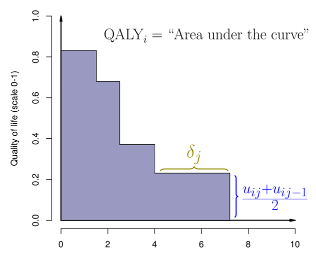
1 Standard Approach for Trial-Based Analyses

ID	Trt	Demographics: Sex	Age	...	HRQL data: u_0	u_1	...	u_J	Resource use data: c_0	c_1	...	c_J
1	1	M	23	...	0.32	0.66	...	0.44	103	241	...	80
2	1	M	21	...	0.12	0.16	...	0.38	1 204	1 808	...	877
3	2	F	19	...	0.49	0.55	...	0.88	16	12	...	22
...	...	...	...	...	...	...	...	...	...	...	...	...

Table 1: An example for the typical individual level data collected in a clinical trial.

1. Compute individual QALYs and total costs as

$$e_i = \sum_{j=1}^{J}(u_{ij}+u_{ij-1})\frac{\delta_j}{2} \quad \text{and} \quad c_i = \sum_{j=1}^{J} c_{ij},$$



2. Assume normality and model **independently** QALYs and total costs by controlling for baseline values

$$\begin{aligned} e_i &= \alpha_{e0}+\alpha_{e1}u_{0i}+\alpha_{e2}\text{Trt}_i+\varepsilon_{ei}[+\ldots], & \varepsilon_{ei} &\sim \text{Normal}(0,\sigma_e)\\ c_i &= \alpha_{c0}+\alpha_{c1}c_{0i}+\alpha_{c2}\text{Trt}_i+\varepsilon_{ci}[+\ldots], & \varepsilon_{ci} &\sim \text{Normal}(0,\sigma_c)\end{aligned}$$

3. Estimate mean differentials and use bootstrap to quantify **uncertainty**

What is wrong with this?

- Ignoring **correlation** may inflate variability in the estimates
- Non-Normal empirical distributions (**skewness** and **spikes**)
- **Partially-observed** data are typically discarded and results presented under a single missingness assumption (e.g. **MAR**) without conducting any sensitivity analysis

2 Modelling Framework

Key features:

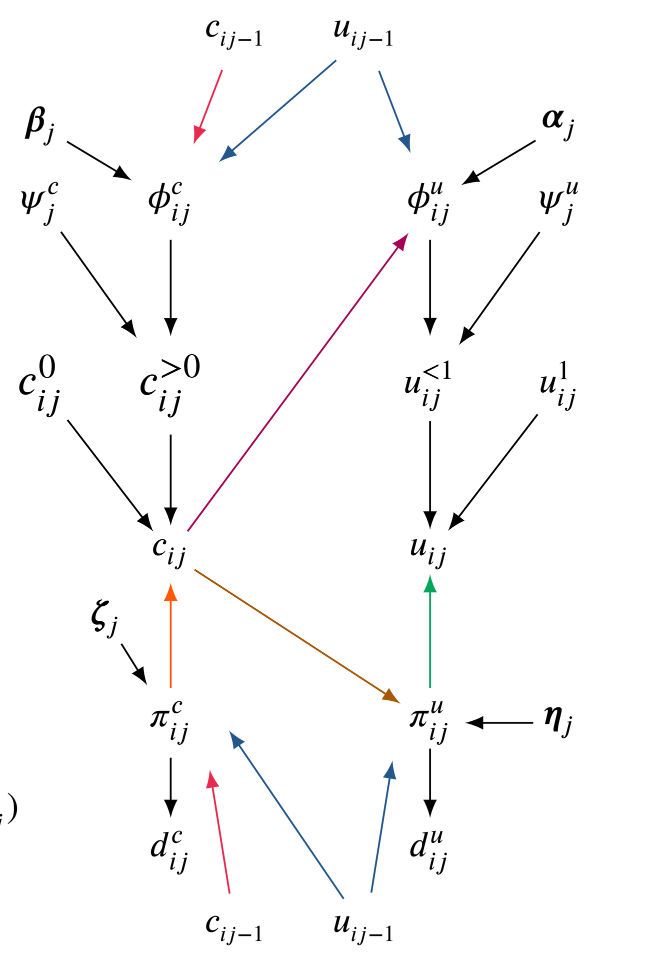
- Jointly model $\boldsymbol{y}_{ij}=(u_{ij},c_{ij})$ to make use of all available data in each missing data pattern $\boldsymbol{r}_{ij}$
- Use parametric distributions to deal with skewness (e.g. Beta and LogNormal) with an hurdle approach to handle spikes at one in the utilities and zero in the costs
- Factor the model using conditional distributions $p(c_j \mid c_{j-1},u_{j-1})$ and $p(u_j \mid u_{j-1},c_j)$

Mixture model for $c_j \mid c_{j-1},u_{j-1}$

$$c^0_{ij} := 0$$
$$c^{>0}_{ij} \sim \text{LogNormal}(\phi^c_{ij},\psi^c_j)$$
$$\log(\phi^c_{ij}) = \beta_{0j}+\beta_{1j}\log c_{ij-1} + \beta_{2j}u_{ij-1}$$
$$c_{ij} = \pi^c_{ij}c^0_{ij} + (1-\pi^c_{ij})c^{>0}_{ij}$$

Model for $d^c_j \mid c_{j-1},u_{j-1}$

$$d^c_{ij} := \mathbb{I}(c_{ij}=0) \sim \text{Bernoulli}(\pi^c_{ij})$$
$$\text{logit}(\pi^c_{ij}) = \zeta_{0j}+\zeta_{1j}\log c_{ij-1} + \zeta_{2j}u_{ij-1}$$



Mixture model for $u_j \mid c_j,u_{j-1}$

$$u^1_{ij} := 1$$
$$u^{<1}_{ij} \sim \text{Beta}\left(\phi^u_{ij}\psi^u_j,(1-\phi^u_{ij})\psi^u_j\right)$$
$$\text{logit}(\phi^u_{ij}) = \alpha_{0j}+\alpha_{1j}\log c_{ij} + \alpha_{2j}u_{ij-1}$$
$$u_{ij} = \pi^u_{ij}u^1_{ij} + (1-\pi^u_{ij})u^{<1}_{ij}$$

Model for $d^u_j \mid c_j,u_{j-1}$

$$d^u_{ij} := \mathbb{I}(u_{ij}=1) \sim \text{Bernoulli}(\pi^u_{ij})$$
$$\text{logit}(\pi^u_{ijt}) = \eta_{0j}+\eta_{1j}\log c_{ij} + \eta_{2j}u_{ij-1}$$

Figure 1: Graphical representation of the framework

Focus in **decision-making**, not inference – Bayesian approach well-suited

- **Uncertainty** about any unobserved quantities is fully propagated using MCMC
- Priors can be used to incorporate **external evidence** about missingness

2.1 Model Fitting and Sensitivity Analysis

- Conduct sensitivity analysis using a **pattern mixture model** for $p(\boldsymbol{y},\boldsymbol{r}) = p(\boldsymbol{y}\mid\boldsymbol{r})p(\boldsymbol{r})$:
  - Specify the model $p(\boldsymbol{r}) \sim \text{Multinomial}(\boldsymbol{\pi}^r)$ to estimate the probability for each pattern
  - Fit the model $p(\boldsymbol{y}\mid\boldsymbol{r})$ to the completers ($\boldsymbol{r}=\mathbf{1}$) and non-completers ($\boldsymbol{r}\neq\mathbf{1}$)
- Use **identifying restrictions** and **sensitivity parameters** to identify the population means
  - Integrate out $\mathbf{y}^{\mathbf{r}}_{mis}$ from $p(\boldsymbol{y},\boldsymbol{r})$ to estimate $\text{E}[\mathbf{y}^{\mathbf{r}}_{obs}\mid\boldsymbol{r}]$ using Monte Carlo integration
  - Use sensitivity parameters $\boldsymbol{\Delta}=(\Delta^u,\Delta^c)$ to identify $\text{E}[\mathbf{y}^{\mathbf{r}}_{mis}\mid\mathbf{y}^{\mathbf{r}}_{obs},\boldsymbol{r}] = \text{E}[\mathbf{y}^{\mathbf{r}}_{obs}\mid\boldsymbol{r}]+\boldsymbol{\Delta}$
  - Compute weighted averages over $\boldsymbol{r}$ using $\boldsymbol{\pi}^r$ to estimate $\text{E}[\boldsymbol{Y}]=\boldsymbol{\mu}_{jt}=(\mu^u_{jt},\mu^c_{jt})$ in each arm
- Assess the robustness of the results to missingness assumptions using informative priors on $\boldsymbol{\Delta}$
  - Set $\boldsymbol{\Delta}=\mathbf{0}$ as benchmark assumption ($\approx$ **MAR**)
  - Specify alternative priors on $\boldsymbol{\Delta}$ to explore plausible **MNAR** departures from the benchmark

3 Motivating Example – The PBS trial

- RCT that evaluates the cost-effectiveness of a new multicomponent intervention (PBS) relative to a control for individuals suffering from intellectual disability and challenging behaviour
- Utilities (EQ-5D) and costs (clinic records) collected at baseline, 6 and 12-months ($j=0,1,2$)

Time	Control ($t=1$): utilities	costs	Intervention ($t=2$): utilities	costs
$j=0$	127 (93%)	136 (100%)	103 (95%)	108 (100%)
$j=1$	119 (86%)	128 (94%)	102 (94%)	103 (95%)
$j=2$	125 (92%)	130 (96%)	103 (95%)	104 (96%)
$\boldsymbol{r}=\mathbf{1}$	108 (79%)		96 (89%)	

Table 2: Proportions of observed utility and cost data at each time j in the PBS trial.

4 Three alternative MNAR priors on Δ

Assumption: individuals with missing data at time j have lower utility and higher cost values compared with those with observed data at time j

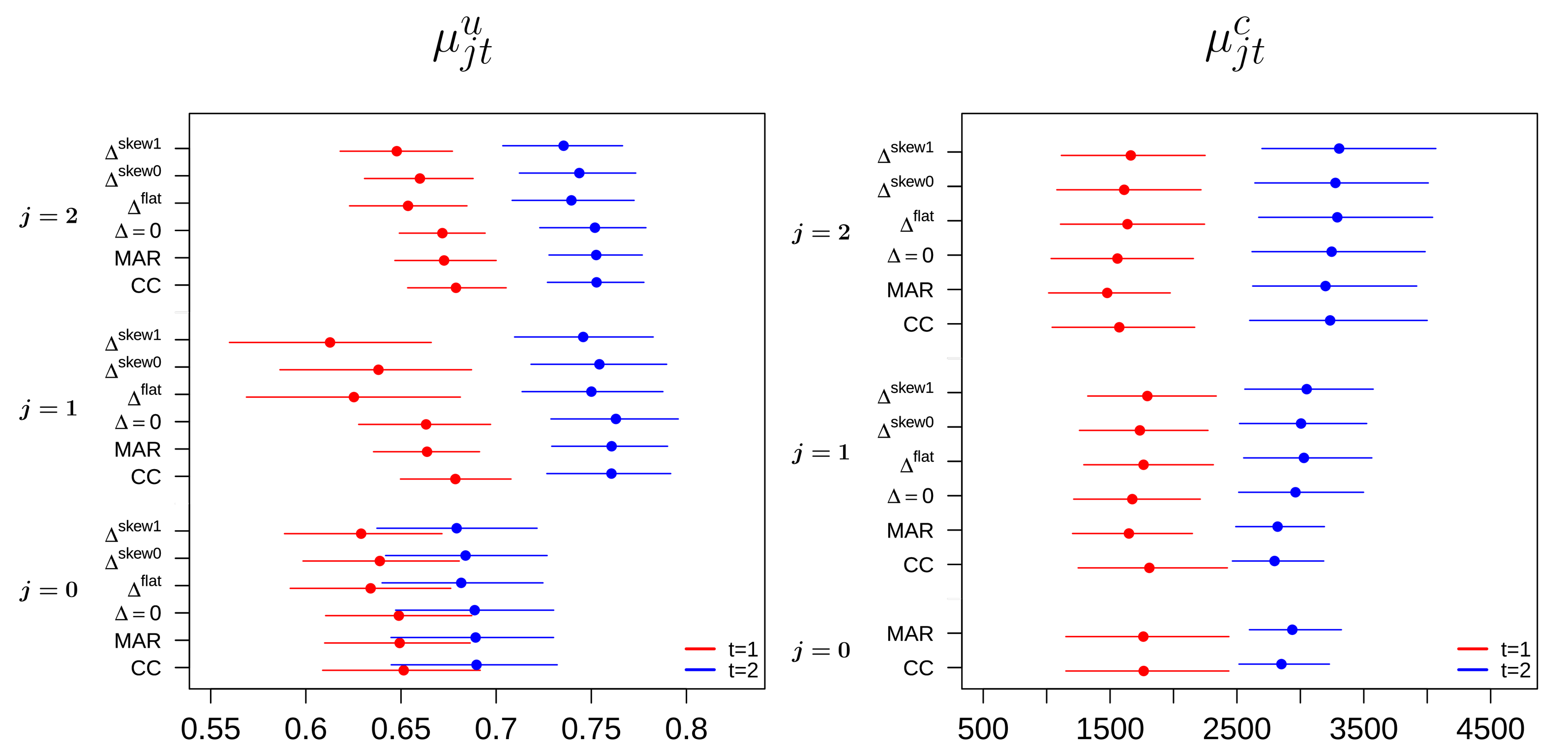
- $\boldsymbol{\Delta}^{\text{flat}}$: Flat between 0 and twice the observed standard deviation:

$$\Delta_{c_j} \sim \text{Uniform}[0,2\,\text{sd}(c_j)] \quad \text{and} \quad \Delta_{u_j} \sim \text{Uniform}[-2\,\text{sd}(u_j),0]$$

- $\boldsymbol{\Delta}^{\text{skew0}}$: Skewed towards values closer to 0, over the same range as $\boldsymbol{\Delta}^{\text{flat}}$.
- $\boldsymbol{\Delta}^{\text{skew1}}$: Skewed towards values far from 0, over the same range as $\boldsymbol{\Delta}^{\text{flat}}$.

5 Results

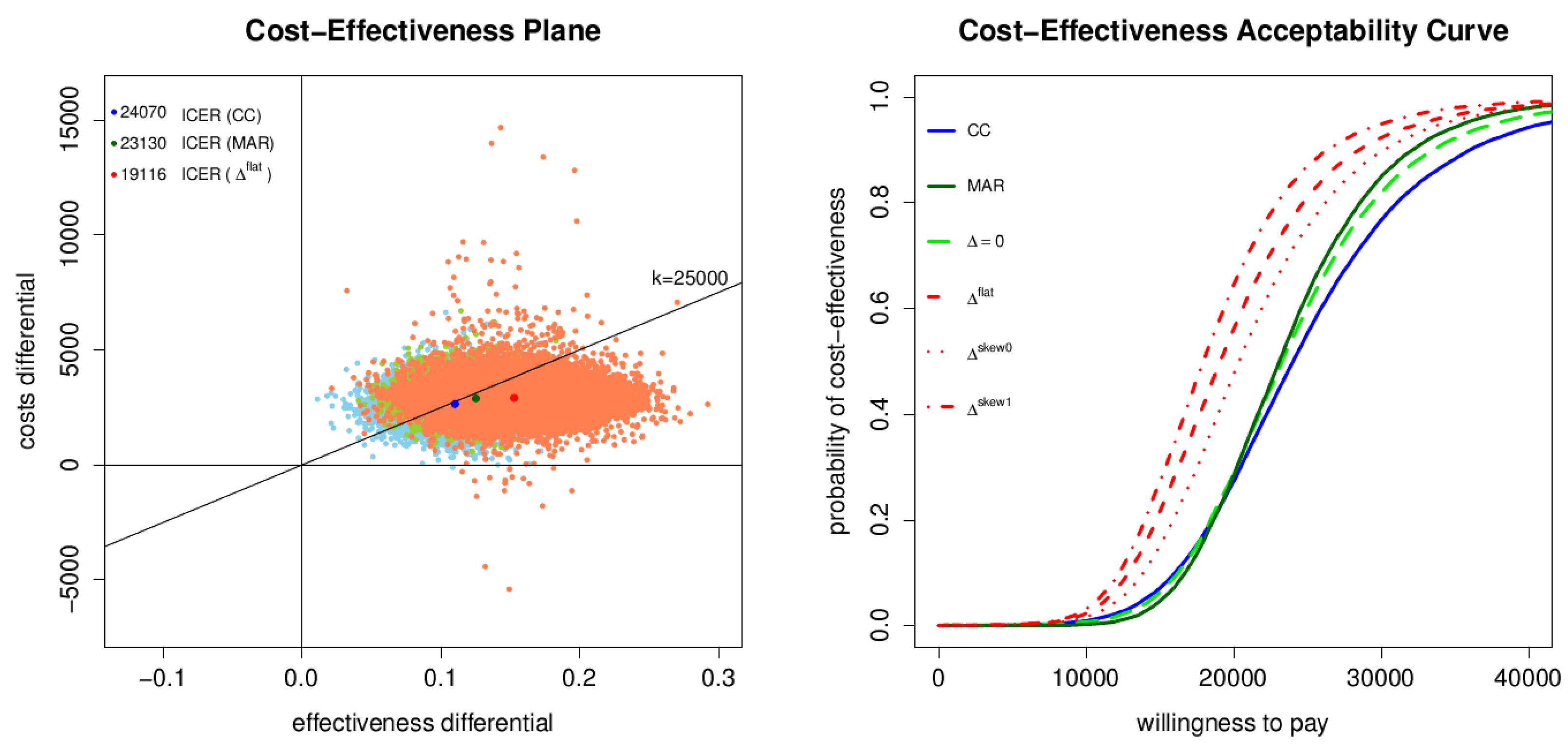
5.1 Posterior utility and cost means



(a) Utilities (b) Costs (£)

Figure 2: Posterior mean and 95% CIs for the mean utilities and costs in the PBS trial.

5.2 Economic Evaluation



(a) Cost-Effectiveness Plane) (b) Cost-Effectiveness Acceptability Curve)

Figure 3: CEP and CEAC associated with different missingness scenarios

Conclusions

- The **flexibility** of the framework can handle multiple complexities (correlation, skewness, spikes, missing data)
- **Estimation** and **imputation** are done simultaneously using all available evidence in the trial
- Informative priors can be used to incorporate external evidence to explore **MNAR departures**
- **Sensitivity analysis** to a range of plausible missingness assumptions should always be conducted

References

Bailey, J., Webster, R., Hunter, R., Griffin, M., N, F., Rait, G., Estcourt, C., Michie, S., Anderson, J., and Stephenson, J. (2016). The men's safer sex project: intervention development and feasibility randomised controlled trial of an interactive digital intervention to increase condom use in men. *Health Technology Assessment*, 20.

Daniels, M. and Hogan, J. (2008). *Missing Data in Longitudinal Studies: Strategies for Bayesian Modeling and Sensitivity Analysis*. Chapman and Hall, New York, US.

Gabrio, A., Mason, A., and Baio, G. (2019). A full Bayesian model to handle structural ones and missingness in economic evaluations from individual-level data. *Statistics in Medicine*, 38:1399–1420.

ISPOR Improving healthcare decisions