Identifying Heterogeneous Treatment Effects in Aggregated N-of-1 Trials Using Bayesian Analyses with Real Data Application

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Background

N-of-1 trials are multiple cross-over studies within a single patient, where the patient serves as their own control. Unlike traditional group-based trials that estimate average treatment effects, N-of-1 designs capture individual responses that may differ from group averages and provide personalized evidence.

We develop a Bayesian framework to estimate individual treatment effects in aggregated N-of-1 trials, using a Bayesian clustering method and comparing it with a Bayesian hierarchical approach for treatment-effect estimation and patient grouping by similar responses.

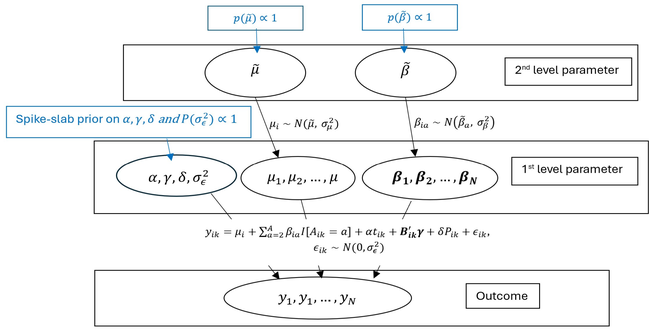
Methods

Our primary estimand is the treatment effect β_i. To avoid bias in estimating β_i, we additionally adjust for nuisance temporal and design-related effects:

$$y_{ik} = \mu_i + \beta_i A_{ik} + \alpha\, t_{ik} + \mathbf{B}_{ik}^{\top}\boldsymbol{\gamma} + \delta\, P_{ik} + \epsilon_{ik}.$$

Here, nuisance terms include a common time trend (αt_{ik}), fixed block effects ($\mathbf{B}_{ik}^{\top}\boldsymbol{\gamma}$), and a fixed period effect (δP_{ik}). We used two Bayesian approaches to estimate parameters.

1. Bayesian Hierarchical Approach:



2. Bayesian Clustering Approach:

- ζ_{β_i} is the cluster indicator for β_i. If $\zeta_{\beta_i} = i$, then β_i is unclustered (home); otherwise it clusters with another subject effect.
- Prior for ζ_{β_i}:

$$\zeta_{\beta_i} = \begin{cases} i, & \text{with probability } p, \\ j : \zeta_{\beta_j} = j,\ j \neq i, & \text{with probability } 1 - p. \end{cases}$$

- Prior for $\beta_i \mid \zeta_{\beta_i}$:

$$p(\beta_i \mid \zeta_{\beta_i}) \propto I(\zeta_{\beta_i} = i)\, p_0(\beta_i) + \sum_{\substack{j:\, \zeta_{\beta_j} = j, \\ j \neq i}} I(\zeta_{\beta_i} = j)\, \delta_{\beta_j}(\beta_i),$$

where

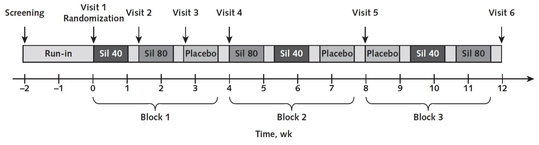
$$p_0(\beta_i) \propto 1, \qquad \beta_i \in \mathbb{R}.$$

Iteration #	Home of β_1	Home of β_2	Home of β_3	Home of β_4
1	β_1, $\zeta_{\beta_1} = 1$	β_2, $\zeta_{\beta_2} = 2$	β_3, $\zeta_{\beta_3} = 3$	β_4, $\zeta_{\beta_4} = 4$
2	β_1, β_3, $\zeta_{\beta_1} = 1$	β_2, $\zeta_{\beta_2} = 2$	$\zeta_{\beta_3} = 1$	β_4, $\zeta_{\beta_4} = 4$
3	β_1, β_3, $\zeta_{\beta_1} = 1$	$\zeta_{\beta_2} = 4$	$\zeta_{\beta_3} = 1$	β_2, β_4, $\zeta_{\beta_4} = 4$
4	$\beta_1, \beta_2, \beta_3$, $\zeta_{\beta_1} = 1$	$\zeta_{\beta_2} = 1$	$\zeta_{\beta_3} = 1$	β_4, $\zeta_{\beta_4} = 4$
5	β_1, β_3, $\zeta_{\beta_1} = 1$	β_2, $\zeta_{\beta_2} = 2$	$\zeta_{\beta_3} = 1$	β_4, $\zeta_{\beta_4} = 4$

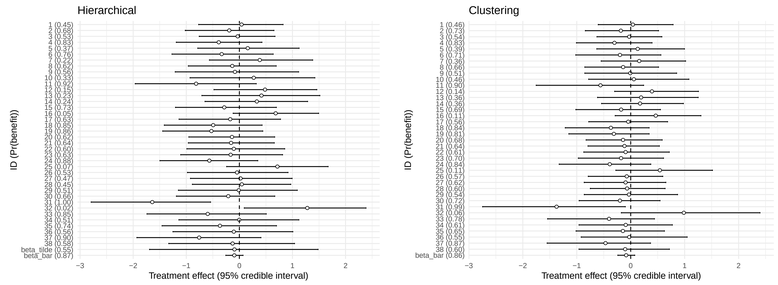
Spike-and-slab priors were used for the nuisance parameters (α, γ, and δ).

Real Data Application

Data were obtained from aggregated N-of-1 trials reported by Roustit et al. (2018) in patients with Raynaud phenomenon. The response was the daily Raynaud Condition Score (RCS), a patient-reported symptom severity measure on a 0–10 scale. Lower RCS values indicate fewer/milder symptoms (better condition), whereas higher RCS values indicate more severe symptoms (worse condition).



Within each block, the period sequence (Sil 40, Sil 80, or placebo) was randomized. Sil 40 = sildenafil, 40 mg per dose; Sil 80 = sildenafil, 80 mg per dose.

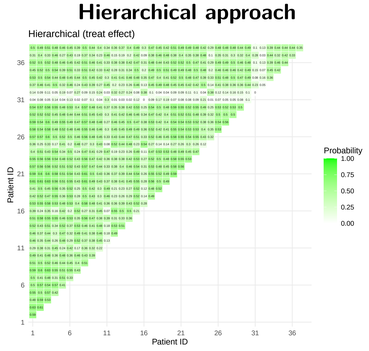


Treatment effects vary across patients. Both hierarchical and clustering analyses show opposite treatment directions for patients 31 and 32.

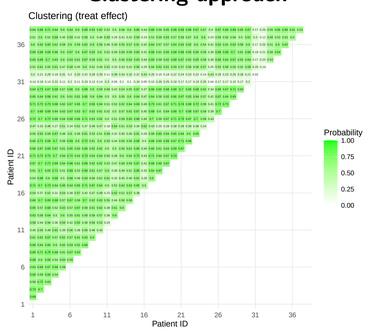
Similarity Matrices

Construction: For each patient pair (i, j), if $|\beta_i - \beta_j| \leq 0.5$, the pair is classified as similar; otherwise, not similar, in each MCMC sample. Each cell (i, j) reports $\Pr\big(|\beta_i - \beta_j| \leq 0.5 \mid \text{data}\big)$.

Hierarchical approach



Clustering approach



Clustering Patients with Clustering Approach

Table 1. Clusters from the clustering similarity matrix ($\epsilon = 0.5$, probability threshold $= 0.5$).

Group	Members	Group mean	95% credible interval
1	1,2,3,4,5,6,7,8,9,10,12,13,14,15,16,17,18,19,20,21,22,23,24,26,27,28,29,30,33,34,35,36,37,38	-0.08	(-0.98, 0.85)
2	2,3,4,5,6,7,8,9,10,11,13,14,15,17,18,19,20,21,22,23,24,26,27,28,29,30,33,34,35,36,37,38	-0.13	(-1.05, 0.75)
3	5,6,7,8,9,10,12,13,14,15,16,17,19,20,21,22,23,25,26,27,28,29,30,34,35,36,38	-0.01	(-0.85, 0.96)
4	31	-1.37	(-2.74, -0.10)
5	32	0.98	(-0.17, 2.40)

Clustering Patients with Hierarchical Approach

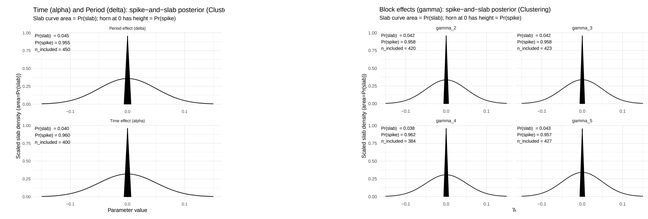
Table 2. Hierarchical clusters at $\epsilon = 0.5$ and probability threshold 0.5.

Group	Members	Group mean	95% CrI
1	1, 2, 3, 5, 7, 8, 9, 14, 15, 17, 20, 21, 22, 23, 26, 27, 28, 29, 30, 34, 36, 38	-0.04	(-1.05, 0.99)
2	2, 3, 4, 5, 6, 8, 9, 15, 17, 18, 19, 20, 21, 22, 23, 24, 26, 27, 28, 29, 30, 35, 36	-0.19	(-1.20, 0.83)
3	3, 4, 5, 6, 8, 9, 14, 15, 17, 20, 21, 22, 23, 26, 27, 28, 29, 30, 34, 36, 38	-0.09	(-1.10, 0.94)
4	4, 6, 8, 15, 17, 18, 19, 20, 21, 22, 23, 24, 26, 30, 33, 35	-0.29	(-1.30, 0.69)
5	7, 12, 14, 16	0.47	(-0.51, 1.41)
6	8, 9, 15, 17, 20, 21, 22, 23, 26, 27, 28, 29, 30, 35, 36, 38	-0.13	(-1.14, 0.89)
7	12, 14, 16, 25	0.55	(-0.44, 1.50)
8	13, 14	0.37	(-0.67, 1.42)
9	10	0.27	(-0.93, 1.42)
10	11	-0.81	(-1.96, 0.32)
11	31	-1.64	(-2.79, -0.54)
12	32	1.28	(0.09, 2.38)
13	37	-0.76	(-1.93, 0.41)

Posterior Distribution of Nuisance Parameters

Hierarchical method

Clustering method



For all nuisance parameters, the prior inclusion probability was set to 0.3 in both methods. The posterior inclusion probabilities were close to zero, indicating little evidence of nuisance effects. We examined trace plots for all parameters to assess convergence.

References

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