Don’t disregard the data for lack of a likelihood:

Bayesian synthetic likelihood for multilevel network meta-regression

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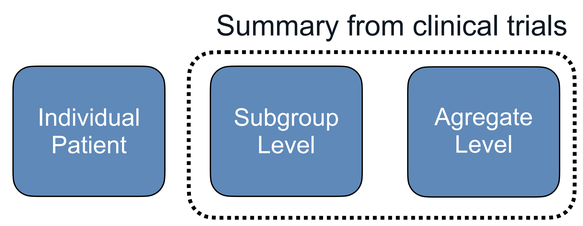
Overview



Illustrative Example

$$y_i \sim \text{normal}(\mu, \sigma^2) \qquad \text{(observed for } i = 1,\cdots,m < n\text{)}$$

$$s = \frac{1}{n}\sum_{i=1}^{n} \mathbb{I}(y_i > c) \qquad \text{(observed)}$$

Posterior inference.

$$p(\theta \mid y_{1:m}, s) \propto p(\theta)\; p(y_{1:m} \mid \theta)\; p(s \mid y_{1:m}, \theta)$$

intractable likelihood

At each MCMC iteration:

1. Simulate summary statistics for $b = 1,\cdots,B$:

$$y^{(b)}_{m+1:n} \sim \text{normal}(y_{m+1:n} \mid \theta)$$

$$\hat{s}^{(b)} = \frac{1}{n}\sum_{i=1}^{m} \mathbb{I}(y_i > c) + \sum_{i=m+1}^{n} \mathbb{I}(y^{(b)}_i > c)$$

In practice, need to reduce cost by directly simulating summary statistics for $y_{m+1:n}$:

$$x^{(b)} \sim \textit{Binomial}(m-n, p^\star)$$

2. Form synthetic likelihood:

$$\hat{p}(s \mid y_{1:m}, \theta) \approx \text{normal}\left(\text{mean}(\hat{s}^{(b)}), \text{sd}(\hat{s}^{(b)})\right). \qquad \text{(*)}$$

Challenge: stochastic target with discontinuous surface.

Implementation in Stan

① **Continuous relaxation.** Rather than sample from Binomial, sample summary statistics from approximating normal:

$$x^{(b)} \sim \text{normal}\left((n-m)p^\star, \sqrt{(n-m)p^\star(1-p^\star)}\right)$$

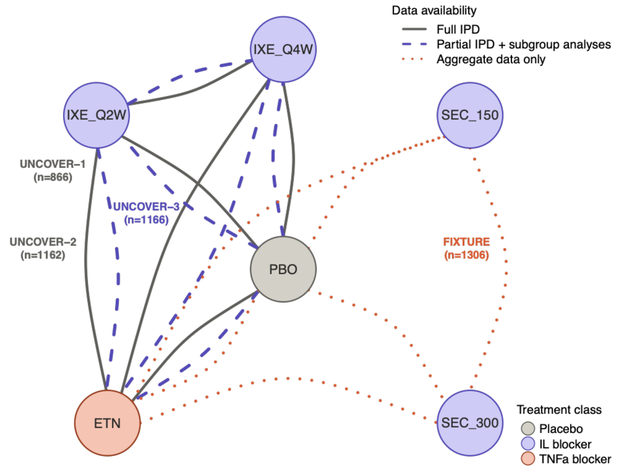
② **Common random numbers.** $w^{(b)} \sim \text{normal}(0,1)$ passed to `data`.

③ **Pareto-smooth Importance sampling (PSIS) correction [2].**
Correct error due to continuous relaxation and finite B by calculating (*) with random discrete samples and large B in `generated quantities`.

Network Meta-Regression

Network of J randomized studies with T treatments for binary outcome.

	Full IDP	Partial IDP	Agregate
Response $y_{ij} \in \{0,1\}$	✅	✅	✅
Treatment $t_{ij} \in \{1,\cdots,T\}$.	✅	✅	✅
Covariate x_{ij}	✅	❌	❌
Marginal covariate dist. π_j		✅	✅
Subgroup treatment s_j		✅	❌



Plaque Psoriasis Network

Binary response: Psoriasis Area and Severity Index response (after 12 weeks)

6 treatments: placebo, Etanercept, Ixekizumab Q2W and Q4W, Secukinumab (150mg and 300mg)

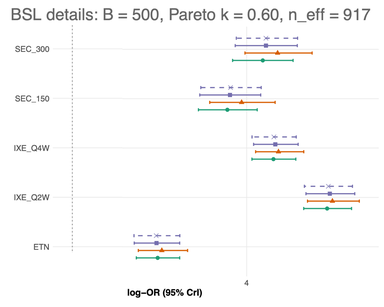
5 covariates: previous treatment, psoriatic arthritis, weight, body surface area, and duration of psoriasis

4 randomized clinical trials: uncover-1, -2, -3, and Fixture

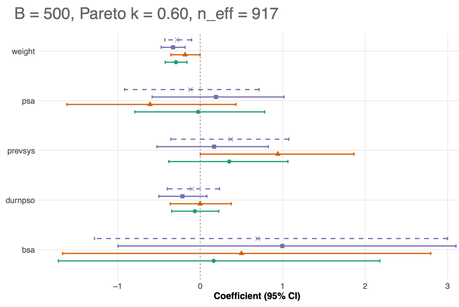
Setup. Treat uncover-3 as if individual covariates were not available (partial IDP) and compare:

- **Oracle:** full covariates data for all studies.
- **ML-NRP:** ignores uncover-3 subgroup data.
- **BLS-NRP:** incorporate uncover-3 subgroup data.

Treatment Effects vs. PBO



Effect Modification – TNFa blocker



Oracle ML–NMR BSL BSL (IS–adjusted)

BSL estimates closely track the Oracle.

- Improves on NL-NMR, especially for effect-modification.
- PSIS-adjustment yields further improvement (but $0.5 < \hat{k} < 0.7$)
- BSL fit takes ~10 hours vs. a few minutes for standard ML-NMR.

REFERENCES

Phillippo, D.M. *et al.* (2020). Multilevel network meta-regression for population-adjusted treatment comparisons. *J. R. Stat. Soc. A*, **183**(3), 1189–1210.

Vehtari, A. *et al.* (2024). Pareto smoothed importance sampling. *J. Mach. Learn. Res.*, **25**(72), 1–58.