Incorporating Published Subgroup Analyses into Multilevel Network Meta-Regression via Bayesian Synthetic Likelihood

MSR117

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BACKGROUND

- Health technology assessment (HTA) increasingly requires population-adjusted indirect treatment comparisons (PA-ITCs).
- **ML-NMR** [Phillippo et al., 2020] is the current standard: combines individual patient data (IPD) from some studies with aggregate-level data (AD) from others, adjusting for differences in effect-modifying covariates. When a study reports only AD and withholds individual-level covariate values (privacy or proprietary concerns), ML-NMR marginalizes over the covariate distribution.
- But clinical trial publications routinely report subgroup analyses (e.g., treatment effects stratified by sex, weight, disease severity) and ML-NMR has no way to use them.
- This is a real loss of efficiency: subgroup results directly describe how treatment effects vary with patient characteristics -- exactly the effect modification PA-ITC is trying to capture.

OBJECTIVE

Extend ML-NMR to incorporate published subgroup summary statistics using Bayesian Synthetic Likelihood (BSL) and implement it within a Hamiltonian Monte Carlo (HMC) framework (Stan).

METHODS

BSL is a likelihood-free inference method: it replaces an intractable likelihood with one built from simulated data. At each MCMC iteration the method:

- **Imputes** the missing individual covariates in a way consistent with the current model parameters and the observed outcomes by sampling from the model-implied conditional distribution.
- **Computes** subgroup statistics from the imputed data: the *synthetic summaries*
- **Compares** these to the published subgroup results (via a multivariate normal likelihood), pulling parameter estimates toward values that are consistent with all available evidence: IPD, AD, *and* published subgroup analyses.

Challenge	Solution
Generating synthetic summaries without breaking HMC's deterministic likelihood	**Common random numbers:** pre-draw all randomness and pass it in as fixed data
High per-iteration computational cost	**Sufficient statistic representation:** replace individual-level imputation with multinomial draws
Discrete summaries produce zero gradients and break HMC	**Continuous relaxation:** replace discrete distributions with smooth normal approximations
Bias introduced by the relaxation	**Pareto-smoothed importance sampling (PSIS)**: post-hoc correction with $\hat{k}$ diagnostic

APPLICATION

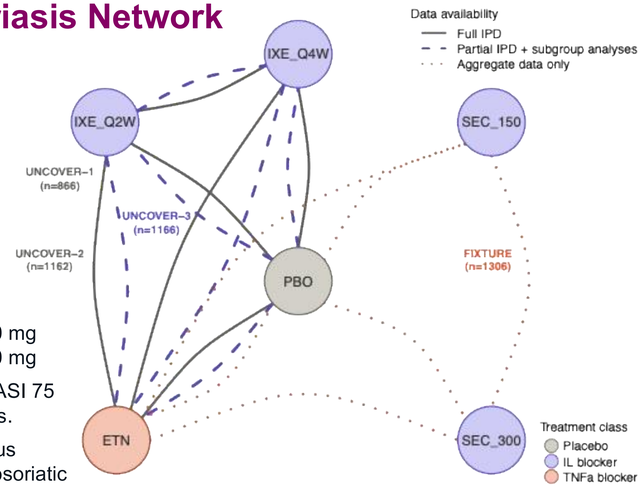
Plaque Psoriasis Network

4 RCTs:
- UNCOVER-1
- UNCOVER-2
- UNCOVER-3
- FIXTURE

6 treatments:
- Placebo
- Etanercept
- Ixekizumab Q2W
- Ixekizumab Q4W
- Secukinumab 150 mg
- Secukinumab 300 mg

Binary outcome: PASI 75 response at 12 weeks.

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

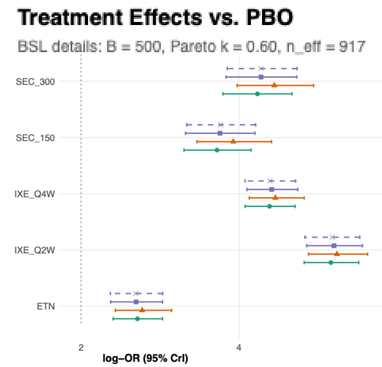


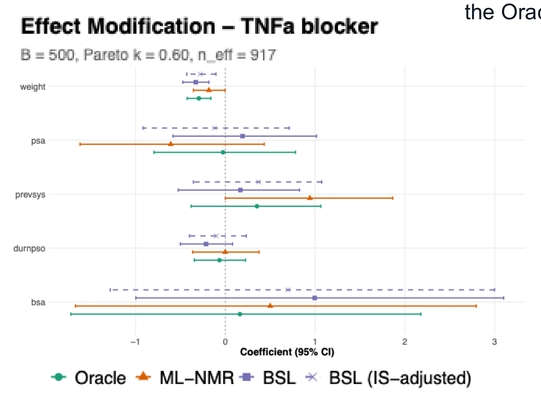
Setup

To test the BSL-ML-NMR method, we treated UNCOVER-3 as if its individual covariates were unavailable, and compared three analyses:

- **Oracle:** full IPD for all studies (best achievable)
- **Standard ML-NMR:** UNCOVER-3 covariates discarded
- **BSL-enhanced ML-NMR:** UNCOVER-3 contributes its subgroup analyses

Results





BSL-enhanced ML-NMR parameter estimates closely tracked the Oracle, generally much more closely than standard ML-NMR.

- Improvement is largest for **effect-modification.** For prior systemic therapy × TNFα blocker, standard ML-NMR suggests an effect modifier whereas Oracle and BSL-enhanced analyses show no such effect. For weight × TNFα blocker, standard ML-NMR's estimate is attenuated toward zero, while BSL-enhanced recovers the Oracle's clearly non-null effect.
- PSIS importance sampling appears to de-bias estimates and Pareto $\hat{k}$ = 0.598 indicates the continuous relaxation introduces only mild approximation error, well within acceptable bounds.
- BSL-enhanced fit takes ~10 hours vs. a few minutes for standard ML-NMR.

CONCLUSION

- Published subgroup analyses carry valuable information and ignoring them sacrifices efficiency and may be misleading with respect to effect modification.
- For HTA analyses where individual covariates can't be shared, routinely published subgroup results may substantially close the gap to a full-IPD analysis.
- BSL-enhanced methods currently only implemented for binary outcomes; time-to-event extensions remain open.
- Like all indirect comparisons, validity still depends on the assumption of no *unmeasured* effect modification. BSL improves use of *observed* effect-modifiers but it does not eliminate the need for the standard transportability assumptions.
- As the demand for PA-ITCs grows, approaches that make full use of the available evidence will become increasingly important.

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