Bayesian sparse survival analysis for detecting subgroup effects: with application to comparing first-line hypertension treatments

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Beyond Population-level Drug Effect

Current OHDSI (and most other) observational studies quantify effectiveness and safety averaged over cohorts of patients.

To generate further scientific and clinical insights, we would like to identify subgroups who benefit most from particular treatments.

Tailor treatment based on patient characteristics.

Detecting Subgroup via Feature Selection Method

Is the feature \( x_j \) relevant? i.e. does treatment effect vary as a function of \( x_j \)?

In a statistics language, identifying subgroups amounts to deciding

\[
\gamma_j = 0 \text{ or } \gamma_j \neq 0 \text{ in the model: (hazard rate) } = \sum_{j=1}^{p} (\beta_j + \gamma_j z_j) x_j,
\]

where \( z_j \in \{0, 1\} \) indicates treatment assignment.

Challenge — high-dimensional features & low incidence:
- the number of covariates \( p \sim 10,000+ \).
- the number of observed events — 100s \( \sim 1,000s \).

Bayesian Sparse Regression / Feature Selection

We look for \( \gamma_j \)'s distinguishable from 0 via Bayesian sparse regression:

Illustration of the posterior distribution of a coefficient \( \gamma_j \) under different effect sizes and levels of uncertainty in data.

Compare to alternatives, Bayesian method has the advantages of
- better separation of the significant coefficients from the rest.
- quantified uncertainty in the estimate and decision \( \gamma_j \neq 0 \).

Widely-used Lasso only provides a point estimate despite the substantial uncertainty in whether \( \gamma_j = 0 \) or \( \gamma_j \neq 0 \).

State-of-the-art Computational Techniques

Bayesian sparse regression had previously been computationally intractable at the scale of OHDSI studies. We develop a new approach based on Hamiltonian Monte Carlo (HMC) algorithm.

HMC’s performance is sensitive to its tuning parameters; to achieve the algorithm’s full potential, we rely on
- theory of prior-preconditioning by Nishimura and Suchard [1].
- Lanczos iteration from numerical linear algebra to determine the curvature (largest eigenvalue of Hessian) of the posterior log-density.

Application: ACE inhibitor & thiazide comparison

Goal: Compare effectiveness of the two most common hypertension treatment in preventing major cardiovascular events.

Data: 1,065,745 patients with 7,884 clinical covariates, among whom 5,054 events are observed (0.5% incidence rate).

Result: Bayesian sparse survival analysis identifies gender as a significant source of heterogeneity in the treatment effect.

Motivated by the above finding and pathophysiology of hypertension among women, we investigated whether the effect varies by age:

Effect of treatment by thiazide

Our result suggests that women in their peri-menopausal stage benefit most from treatment by thiazide over ACE.

Conclusion & References

Our Bayesian method identifies a statistically significant subgroup effect among 7,884 possibilities in the hypertension data. Software is under development to conduct a further study at larger scale.
