

Horseshoe prior as a fast and efficient approach for covariate selection in pharmacometric modelling

Tomás Sou¹, Brigitte Lacroix², Himanshu Naik², Akash Khandelwal², Neva Coello¹

¹Novartis Pharma AG, Basel, Switzerland, ²UCB Biopharma, Braine-l'Alleud, Belgique

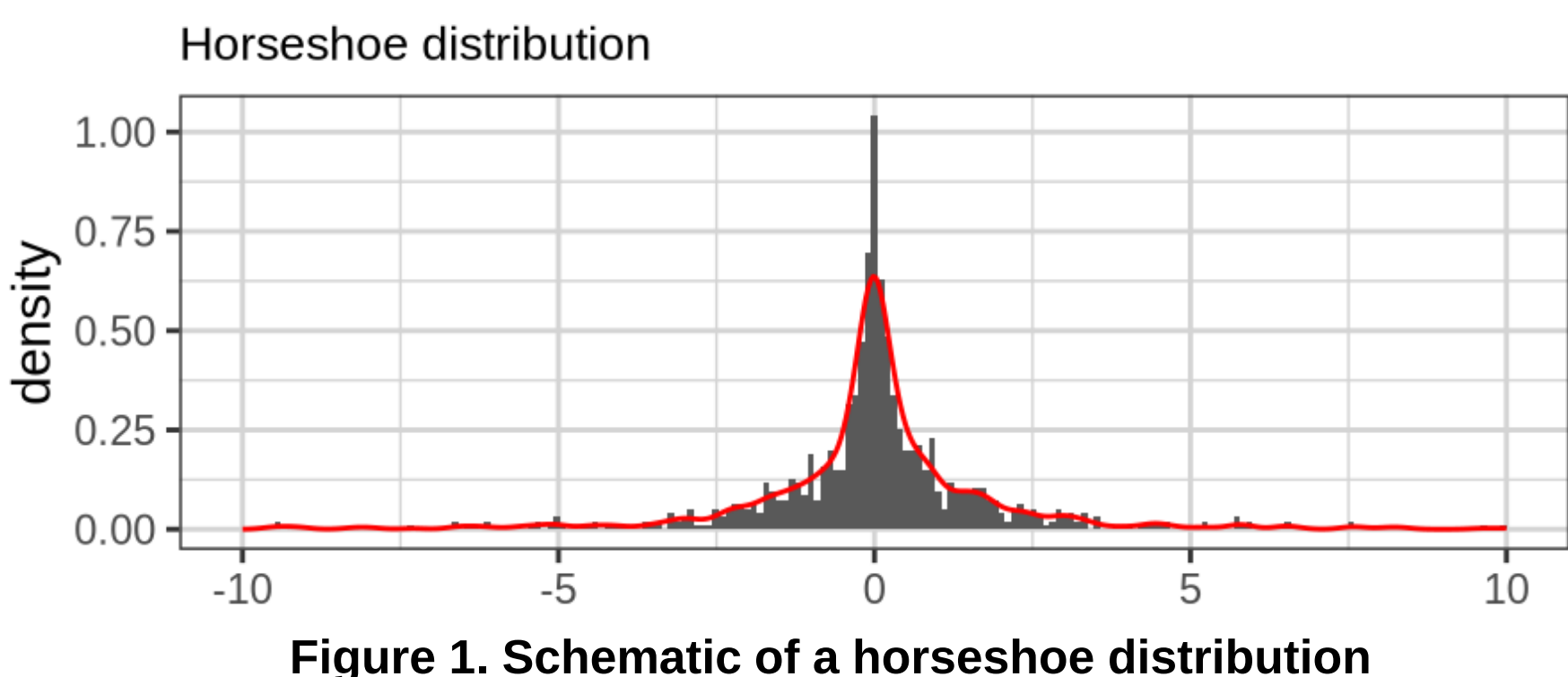
Introduction

Covariate selection – limitations of common search algorithms

- Covariate model building is a crucial step in pharmacometric analysis. The selected covariate model may be used to support individualised dosing and the design of clinical trials in drug development [1]. Following judicious covariate scoping, search algorithms may be used to facilitate covariate selection from a curated list of candidate covariates.
- Automated procedures such as Stepwise Covariate Modelling (SCM), Conditional Sampling use for Stepwise Approach (COSSAC) [2] and Stochastic Approximation for Model Building Algorithm (SAMBA) [3] are often time-consuming requiring many iterations.
- Full model approaches such as full fixed effects model (FFEM) and full random effects model (FREM) [4,5] are subject to challenges such as model instability and the need of data reconfiguration.

Horseshoe distribution – a special shrinkage prior distribution

- The horseshoe distribution is symmetric around zero with fat tails and an infinitely large spike at zero [6]. It has been proposed as a sparsity-inducing shrinkage prior for Bayesian regression. With the horseshoe prior, large coefficients face relatively little shrinkage given the heavy tails, whereas the infinitely tall spike at zero pushes small coefficients towards zero. Its properties make it ideal for sparse models that have many regression coefficients, while only a subset of them is non-zero. (Figure 1)



- This work presents the implementation of regularised horseshoe prior as an alternative approach to support fast and efficient covariate selection in pharmacometric modelling. The Bayesian approach requires minimal preparation and provides posterior distributions for uncertainty information on covariate effects to guide covariate selection.

Objective

Horseshoe prior – for covariate selection in model building

- This work aims to demonstrate the implementation of regularised horseshoe prior as a fast and efficient approach to guide covariate selection in pharmacometric modelling.

Methods

Population PK modelling

- In this work, a population pharmacokinetic (PopPK) model developed for minzasolmin, an investigational treatment for Parkinson's disease (PD), was used to evaluate covariate search algorithms. The modelling dataset included 7727 plasma concentrations from 462 subjects, including healthy volunteers (HV) and PD patients, across five clinical studies.
- Baseline covariates available from the studies included age, body weight, sex, disease status, alanine transaminase, aspartate transferase, renal function and the use of concomitant medications including CYP3A4 inhibitors, CYP3A4 inducers and acid-reducing agents.
- Initially, a base model was developed to describe the concentration-time profiles of the drug collected in HV and PD patients. Following base model development and covariate scoping, candidate covariates were evaluated for covariate model building.

Covariate selection using horseshoe prior

- For covariate selection using horseshoe prior, empirical Bayes estimates and covariate values were extracted from the base model and standardised before using them as input for the procedure.
- The regularised horseshoe prior (HSP) covariate selection procedure was implemented in R (version 4.3.1) supported by the brms package [7]. Based on the posterior distributions of the coefficients, covariates were selected if the 95% credible intervals did not include zero. The selected covariates were then included in the final covariate model.
- For comparison, automated procedures with default settings as available in the Monolix Suite 2023R1 including SAMBA, COSSAC and SCM were also performed.

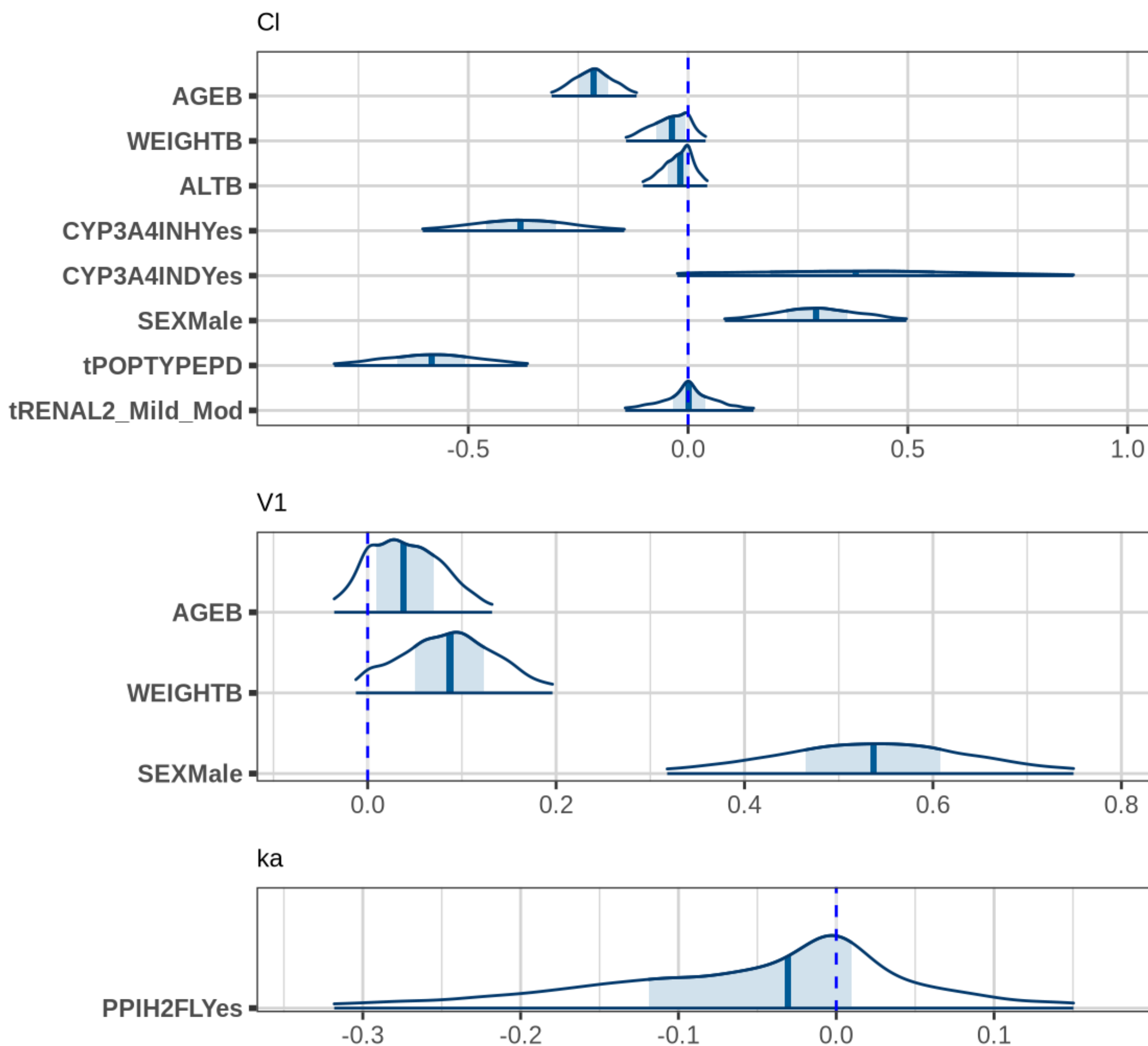
Results

Model development

- The base model selected was a two-compartment disposition model with first-order absorption and lag time before absorption.
- Following covariate scoping, candidate covariates were selected for evaluation on key model parameters of interest, including apparent clearance (Cl), apparent central volume of distribution (V1) and absorption rate constant (ka).

Fast covariate selection guided by horseshoe prior

- The HSP procedure was able to evaluate all candidate covariates on a given parameter and provide posterior distributions of their coefficients efficiently in a single run.
- The HSP results suggested AGE, CYP3A4INH, SEX and POPTYPE as significant covariates on Cl and SEX as a significant covariate on V1. No covariate was selected on ka. (Figure 2)
- The HSP selected covariates were comparable to the ones selected by SAMBA, COSSAC and SCM. However, the HSP procedure was significantly faster requiring substantially shorter runtime (<66 sec) compared to SAMBA (65x faster), COSSAC (295x faster) and SCM (1447x faster). (Table 1)



ALTb: alanine transaminase at baseline; CYP3A4IND: CYP3A4 inducer; CYP3A4INH: CYP3A4 inhibitor; POPTYPE: disease status; RENAL: renal function; PPIH2: acid-reducing agents

Figure 2. Covariate selection results from the horseshoe prior method, showing the posterior distributions of the covariate coefficients with the corresponding median and the 95% credible interval for each candidate covariate.

Table 1. Covariate selection results from HSP, SAMBA, COSSAC and SCM

Method	Runtime vs. HSP	CYP3A4IND	CYP3A4INH	SEX	AGE	POPTYPE
HSP	<66 sec	-	Cl	Cl, V1	Cl	Cl
SAMBA	65x longer	Cl	Cl	Cl, V1	Cl	Cl
COSSAC	295x longer	-	Cl	V1	-	Cl
SCM	1447x longer	-	Cl	V1	-	Cl

HSP: Horseshoe prior; CYP3A4IND: CYP3A4 inducer; CYP3A4INH: CYP3A4 inhibitor; POPTYPE: disease status

Conclusions

Horseshoe prior for covariate model building in pharmacometrics

- The horseshoe prior method was able to guide covariate model building comparable to other automated search algorithms but with a much faster runtime.
- The Bayesian approach provides posterior distributions of the covariate coefficients for uncertainty information on the covariate effects.
- The procedure can serve as an alternative approach to guide fast and efficient covariate model building in pharmacometric analysis.

References

- Sanghavi K et al. CPT Pharmacometrics Syst Pharmacol. 2024 May;13(5):710-728.
- Aryal et al. CPT Pharmacometrics Syst Pharmacol. 2021 Apr;10(4):318-329.
- Prague et al. CPT Pharmacometrics Syst Pharmacol. 2022 Feb;11(2):161-172.
- Yngman et al. CPT Pharmacometrics Syst Pharmacol. 2022 Feb;11(2):149-160.
- Jonsson et al. CPT Pharmacometrics Syst Pharmacol. 2024 Aug;13(8):1297-1308.
- Carvalho et al. PMLR 2009;5:73-80.
- <https://CRAN.R-project.org/package=brms>

Acknowledgement

The authors are grateful to Christian Bartels and Sebastian Weber for helpful discussions and Xinrui Zhang and Kamunkhuala Gausi for the initial implementation of this approach in R.