



Introduction to SaddlePoint Signature

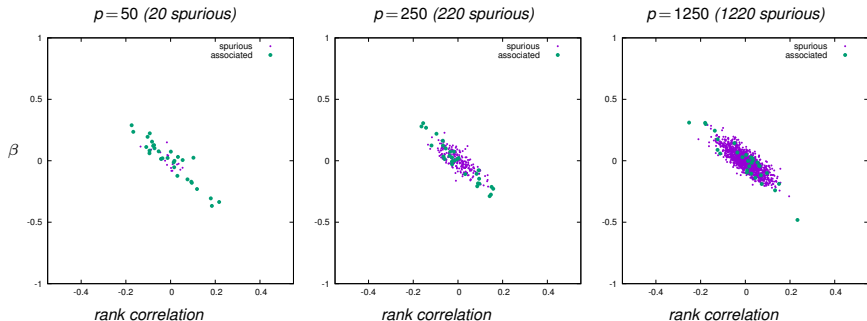
January 2019

London, UK
www.saddlepointscience.com

Survival data with many covariates and few samples

synthetic data:

$n = 150$ samples, p covariates,
30 true associations

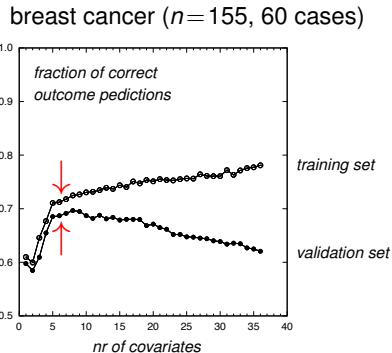
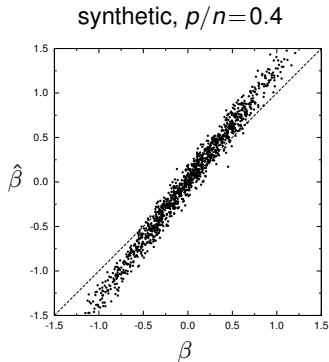


rank correlations of covariates with outcome,
univariate Cox association parameters β

Overfitting in multivariate regression

two effects

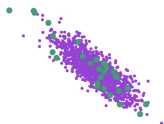
- ▶ bias, inflation of associations
- ▶ extra inference noise



Task: decontaminate multivariate regression
for overfitting effects ...

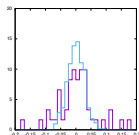
Automated pipeline

preprocessing



normalization, imputation
informative missingness
multiplexing

covariate pre-selection



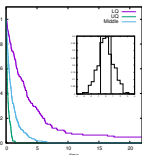
univariate regression,
correlation with outcome,
relative to randomized

main regression loop



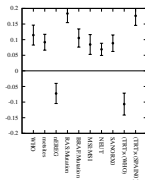
10^3 regressions for randomly selected training sets
 L_2 priors with adaptive hyperparameters
replica theory overfitting correction
compute average training and validation errors
remove least relevant covar (probabilistic criterion)
repeat until nr of covariates is zero

visualize stratification



survival curves of risk
or response score quartiles

robust signatures

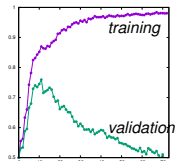


prognostic score (incl interactions)
treatment response score

multivariate risk score formula

$$\begin{aligned} S = & (0.183736) * \text{MHO} \\ & + (0.104023) * \text{metsites} \\ & + (-0.032011) * \text{nEREG} \\ & + (0.368074) * \text{RAS:Mutation} \\ & + (0.390275) * \text{BRAF:Mutation} \\ & + (0.411698) * \text{MSI:MSI} \\ & + (0.019277) * \text{NEUT} \\ & + (0.154350) * \text{SANDRX0} \\ & + (-0.197740) * (\text{TRT}) * (\text{MHO}) \\ & + (0.287004) * (\text{TRT}) * (\text{SPAIN0}) \\ & - (0.815596) \end{aligned}$$

covariate selection

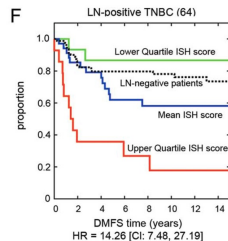
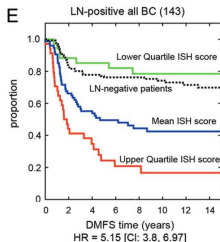


optimal covariate set
without overfitting

Some application examples

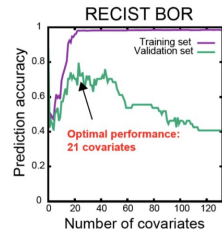
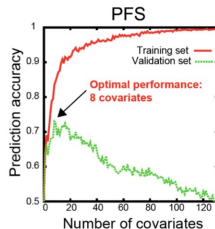
- ▶ breast cancer:
multivariate immune-stroma
histological risk score (ISH)

*Grigoriadis et al,
J Path: Clin Res 2018*



- ▶ head and neck cancer:
Exosome and immune profiling
after anti-EGFR and
platinum therapy

*Flores-Borja et al,
under review 2019*



- ▶ colorectal cancer:
re-analysis of the COIN trial (NEJM, 2011)
Barber et al, under review 2019