High-Dimensional Variable Selection for Competing Risks with Cooperative Penalized Regression

«CooPeR»

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Motivation

- Setting: High-dimensional survival data w/ competing risks
  - e.g.: Time to death from cause 1 (bladder cancer) or cause 2 (other)
- Typical approach:
  - Fit cause-specific model(s) for event(s) of interest
  - Treats other events as censored
  - → discards (potential) shared information
- **Main goal**: Fit cause-specific model for event 1 *using shared information* from event 2

Building Blocks

1. Penalized Cox regression
   - Elastic net / feature-weighted elastic net (fwelnet)
2. An iterative Algorithm
   - Adapted from multi-task algorithm by fwelnet authors
3. Assumption of shared information between causes
   - Idea: Some features predictive for event 1 will also be predictive for event 2

Foundation: Elastic Net

The elastic net objective function with some negative log-likelihood term:

$$\underset{\beta}{\operatorname{argmin}} \quad \mathrm{NLL}(\beta) + \lambda \sum_{j=1}^{p} \left(\alpha |\beta_j| + \frac{1-\alpha}{2} \beta_j^2 \right)$$

- $\lambda \in \mathbb{R}_+$ controls overall penalty
- Higher → larger penalty on all β_j, **equally**

- $\alpha \in [0, 1]$ is the mixing parameter
- $1 \Rightarrow$ only ℓ_1 penalty (LASSO)
- $0 \Rightarrow$ only ℓ_2 penalty (ridge)

Elastic Net: Flexibility?

- What if we don't want to penalize all β_j equally?
- This does **not** work:

$$\underset{\beta}{\operatorname{argmin}} \quad \mathrm{NLL}(\beta) + \sum_{j=1}^{p} \boldsymbol{\lambda_p} \left(\alpha|\beta_j| + \frac{1-\alpha}{2}\beta_j^2 \right)$$

→ Need different approach

Feature-Weighted Elastic Net (`fwelnet`)

- Motivation: Using external information
- Adjust penalization weights on individual or groups of features
- Assign weights / groups via matrix $\mathbf{Z} \in \mathbb{R}^{p \times K}$

Two Applications

1. Assign features to K groups w/ separate penalization weights
2. Adjust penalization weights within group

Feature Weighting: Groups

Example for $p = 5$ features $X_{1,2,3,4,5}$ and $K = 2$ groups

$$\mathbf{Z} = \begin{pmatrix} 1 & 0 \\ 1 & 0 \\ 0 & 1 \\ 0 & 1 \\ 0 & 1 \end{pmatrix}$$

- X_1, X_2 ➔ group 1
- X_3, X_4, X_5 ➔ group 2

Interesting when e.g. $p >> 1000$ w/ 50 clinical + 5000 gene expression features

Feature Weighting: Per Variable

Example for $p = 4$ features $X_{1,2,3,4}$:

$$\mathbf{z} = \begin{pmatrix} 0.5 \\ 1 \\ 2 \\ 0 \end{pmatrix}$$

- X_1: Less important, strong penalization
- X_2, X_3: More important → weaker penalization
- X_4: “Irrelevant” → stronger penalization

Feature-Weighting: New Objective Function

$$\underset{\beta}{\operatorname{argmin}} \quad \mathrm{NLL}(\beta) + \lambda \sum_{j=1}^{p} \color{blue}{w_j(\theta)} \left(\alpha |\beta_j| + \frac{1-\alpha}{2} \beta_j^2 \right)$$

$$\color{blue}{w_j(\theta)} = \frac{\sum_{l=1}^{p} \exp(\mathbf{z}_l^T \theta)}{p \exp(\mathbf{z}_j^T \theta)}$$

- **Penalization weight** of β_j based on corresponding value in $\mathbf{Z}$ and parameter $\theta \in \mathbb{R}^{K \times 1}$

Penalization Weights

- $w_j(\theta)$ is chosen heuristically by the authors for desirable properties
- $\mathbf{z}_j^T\theta$ acts as a *score*
  - $= 0$, reduces to original elastic net
  - Higher score $\rightarrow$ lower w_j, feature is "more important"

Feature-Weighting: Single Group

- $\mathbf{Z} \in \mathbb{R}^{p \times 1}$: No groups, just weights
- Simulation from Tay et al. (2023): $\mathbf{Z}$ set to noisy version of true $|\beta|$
- Larger $|\beta_j| \Rightarrow$ weaker penalization for $\hat{\beta}_j$
- $|\beta_j| \approx 0 \Rightarrow$ stronger penalization for $\hat{\beta}_j$

Application for Multi-Task Learning

- Authors suggest multi-task learning algorithm: $\mathbf{X}$ and targets $\mathbf{y}_1, \mathbf{y}_2$

1. Set $\beta_1^{(0)}, \beta_2^{(0)}$ to `glmnet` solution for $(\mathbf{X}, \mathbf{y}_1)$, $(\mathbf{X}, \mathbf{y}_2)$ respectively
2. For $k = 0, 1, \ldots$:
    a. $\mathbf{Z}_2 = \left|\beta_1^{(k)}\right|$. Fit `fwelnet` with $(\mathbf{X}, \mathbf{y}_2, \mathbf{Z}_2)$
        - Set $\left|\beta_2^{(k+1)}\right|$ to solution with optimal `lambda`

    b. $\mathbf{Z}_1 = \left|\beta_2^{(k+1)}\right|$. Fit `fwelnet` with $(\mathbf{X}, \mathbf{y}_1, \mathbf{Z}_1)$
        - Set $\left|\beta_1^{(k+1)}\right|$ to solution with optimal `lambda`

Transfer to Competing Risks

- Setting with two outcomes/event types: $(\mathbf{t}_1, \delta_1), (\mathbf{t}_2, \delta_2)$
- Assumption: Shared information for both causes:
  - If X_j is important for cause 1, may also be relevant for cause 2
  - $\Rightarrow$ lower its penalty in cause-specific models
- Basic idea: Adapt previous algorithm to Cox regression
- Multi-task $\simeq$ "Multi-cause"

Dubbed "Cooperative Penalized (Cox) Regression" (CooPeR)

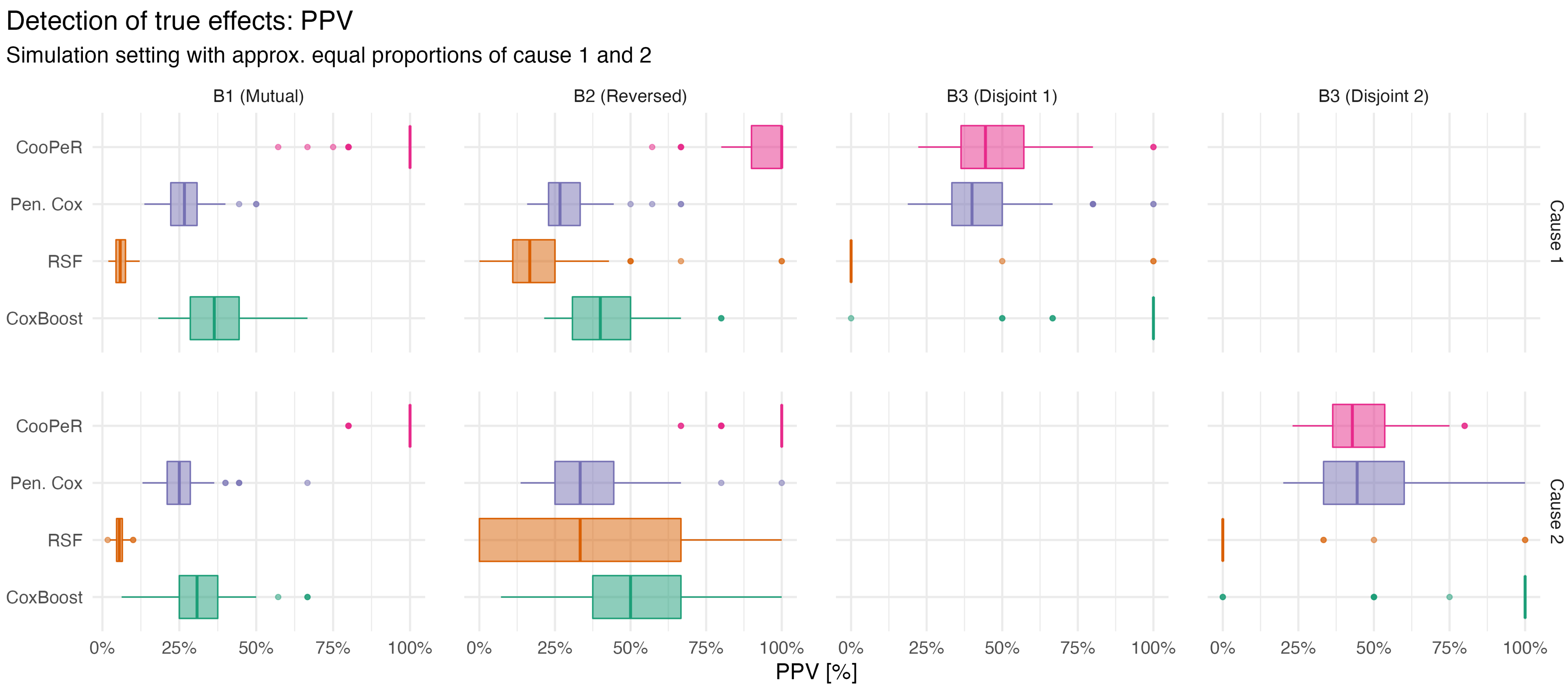
High-Dimensional Variable Selection

- Simulation setup borrowed from Binder et al. (2009)
- Context: Gene expression data with competing risk target
- n = 400, p = 5000, organized in 4 main blocks, few informative variables overall (16)
- Fit models, use $\mathbf{1}\{\hat{\beta}_j \neq 0\}$ as classification decision
- Compare CooPeR, penalized Cox (glmnet), RSF (rsfrc), CoxBoost

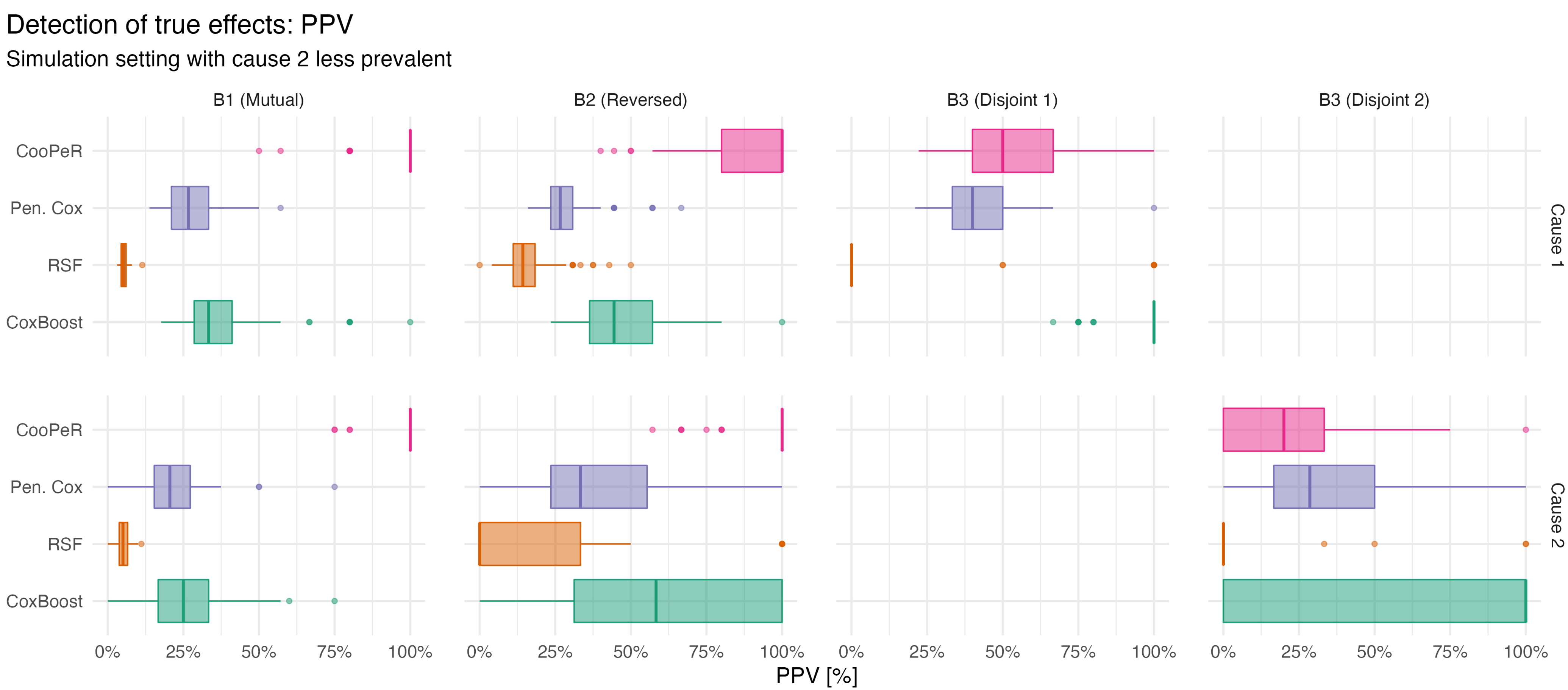
Simulation of True Effects

- Block 1 (**Mutual**): 250 variables, $\rho \approx 0.5$
  4 vars w/ *same effect* (0.5) on both causes
- Block 2 (**Reversed**): 250 variables, $\rho \approx 0.35$
  4 w/ effect of 0.5 on cause 1 and -0.5 on cause 2
- Block 3 (**Disjoint**): 500 variables, $\rho \approx 0.05$
  3.1: 4 w/ effect on *cause 1 only*
  3.2: 4 w/ effect on *cause 2 only*
- Block 4 (**Cor. Noise**): 500 variables, $\rho \approx 0.32$
- Remaining variables: Uncorrelated noise

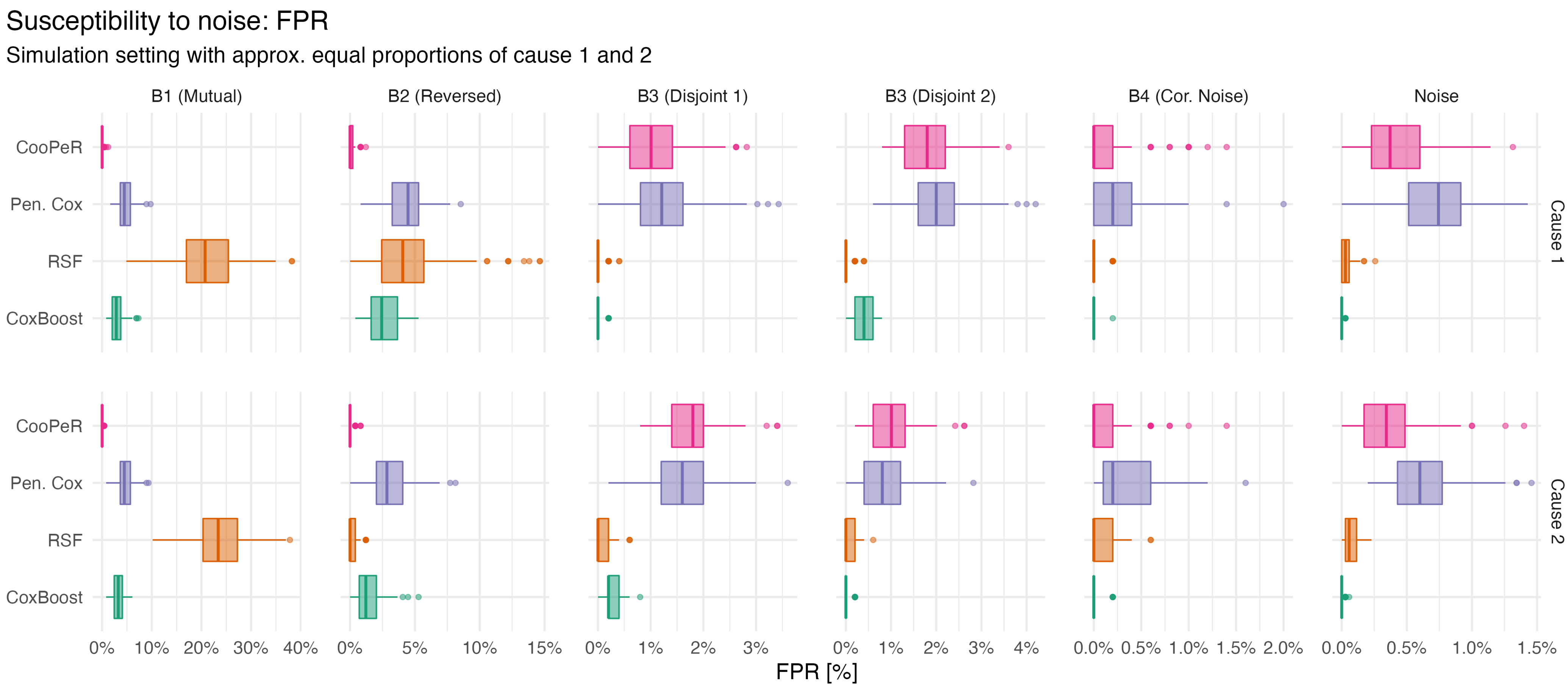
Positive Predictive Value



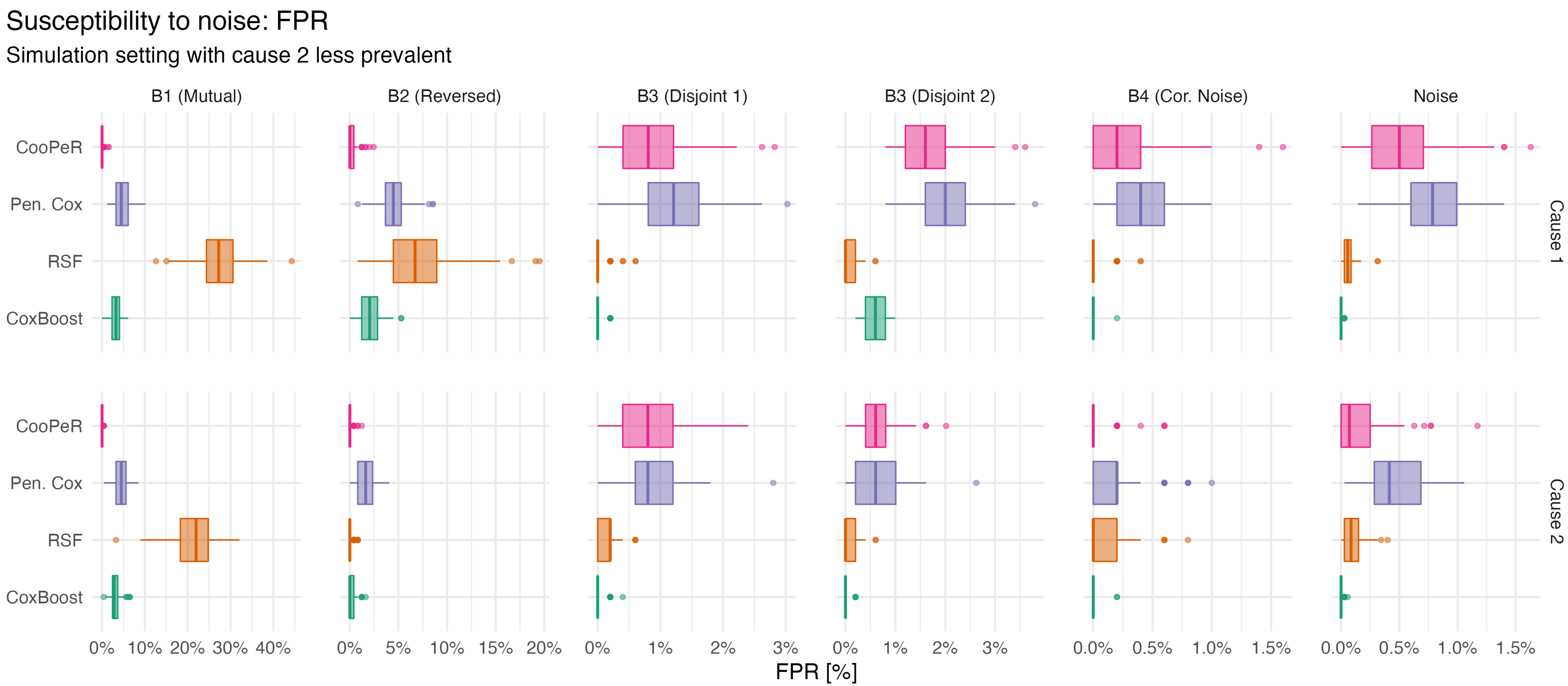
Positive Predictive Value



False Positive Rate



False Positive Rate



How about real data?

- Still WIP
- Idea:
  1. Use algorithms for variable selection
  2. Fit standard cause-specific Cox model using only selected variables
  3. Evaluate prediction performance (tBrier, tAUC)
- Tried bladder cancer data (Dyrskjøt et al. (2005)), did not go well

What’s Next

- Would be nice to have a “working” real data example (Maybe TCGA)
- Finishing the paper for journal submission
- Talk about this at CEN in September

Open questions

- What does the actual optimization problem look like?
  (Does the algorithm converge? To what?)
- What about $k > 2$ events? No trivial generalization

Thanks for listening!

References

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