Permutation test for general dependent truncation

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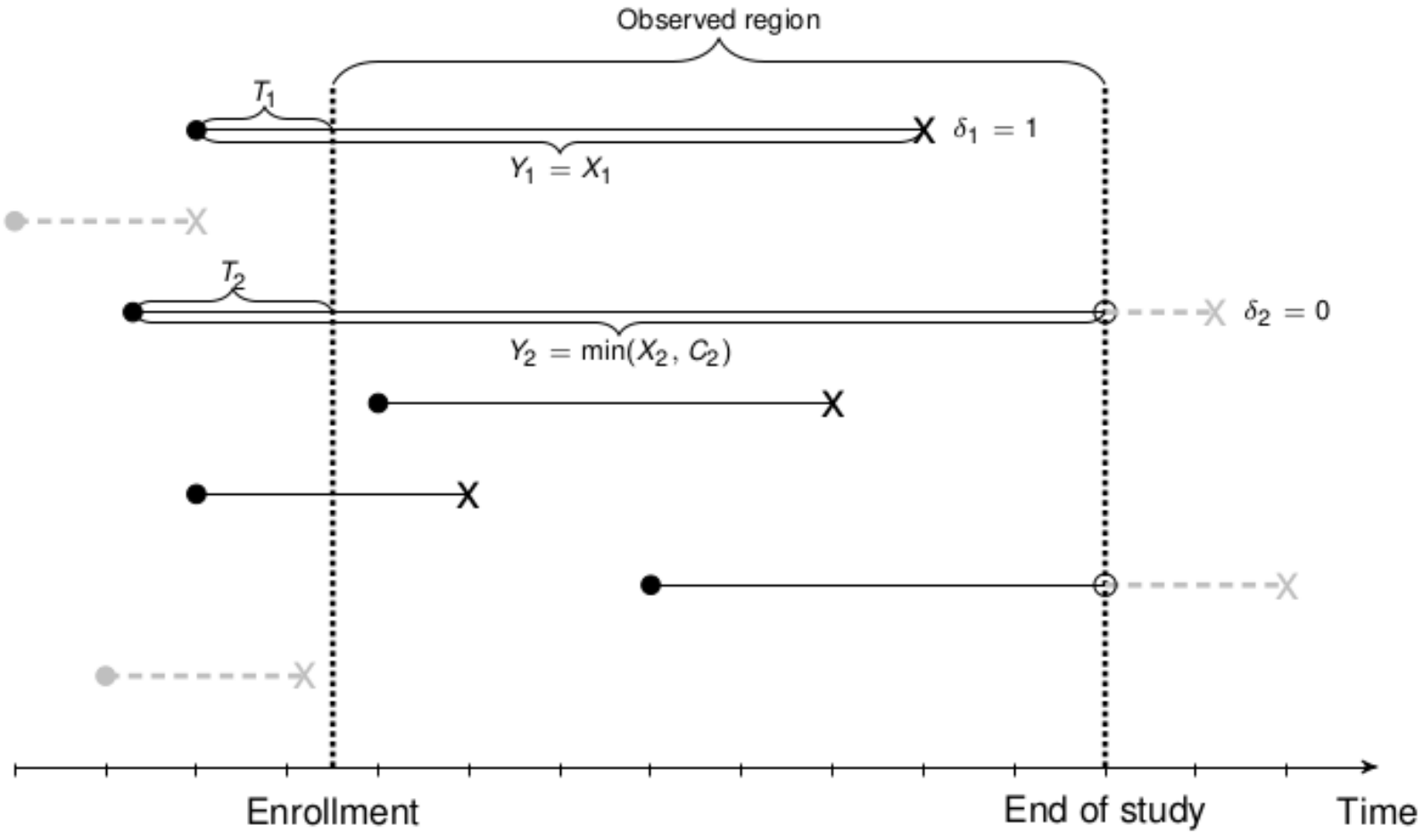
Background

Left-truncated right-censored survival data

- An example of a left-truncated right-censored survival data



Notations

- X is the failure or event time
- T is the truncation time for X
- C is the right censoring time
- Y is the observed failure time: $Y = \min(X, C)$
- δ is the censoring indicator: $\delta = 1$ if $X \leq C$ and 0 otherwise.
- The observed data are $(Y, T, \delta \mid Y \geq T)$

Statistical challenges

- No information is observed when $X \leq T$
- Independence in the observable region, i.e., quasi-independence.
- Substantial bias if falsely assumed.
- Possible dependence could be non-monotonic.

Quasi-independence

- Quasi-independence is independence in the observable region:

$$h(x, t|X > T) \propto f(x)g(t), x \geq t,$$

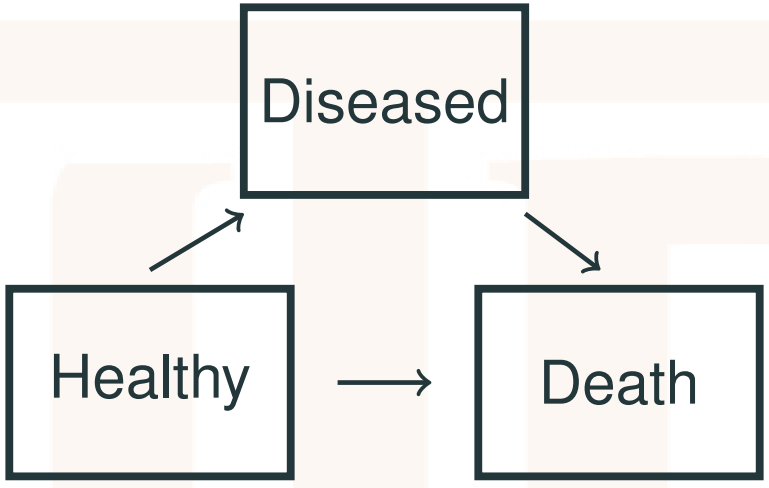
  where, $h(\cdot, \cdot)$, $f(\cdot)$, and $g(\cdot)$ are probability density* functions [Vakulenko-Lagun et al., 2018+].
- This condition can be tested, but available tests are limited.

Existing tests

- Tsai [1990]: conditional Kendall's tau (τ_c) based permutation test.
- Jones and Crowley [1992]: Cox model based tests
- Chen et al. [1996]: conditional Pearson correlation coefficient
- Martin and Betensky [2005]: general truncation via U-statistics
- Austin and Betensky [2014]: modifies τ_c via inverse probability weighting to accommodate censoring effect
- Emura and Wang [2010]: weighted log rank statistic based on Copula

Existing tests

Tests for the Markov condition in illness-death model:



- de Uña-Álvarez [2012], Rodríguez-Girondo and Uña-Álvarez [2012]:
  - local tests based on marginal estimators and Kendall's tau
  - poor performance under moderate censoring.
- Rodríguez-Girondo and Uña-Álvarez [2016]:
  - double bootstrap for maximized local Kendall's tau
  - improved but still sensitive to censoring.

Permutation test

Permutation test

- In general, permutation test consists of the following procedures:
  1. Generate a large number of permuted data under null
  2. For each permuted data, compute a test statistics
  3. Compute a *p*-value
- The knowledge of the distribution of a test statistics under null hypothesis is not required

Permutation

- Permute T and let $\{(T_i^*, X_i); i = 1, \ldots, n\}$ be the permuted data.
- We consider two permutation approaches under left truncation
  1. Conditional permutation [Tsai, 1990, Efron and Petrosian, 1992]
  2. Unconditional permutation

Conditional permutation

- The conditional permutation procedure:
  1. Initialize with $m = 1$
  2. For X_m, selects a T_m^* from $\{i : T_i \leq X_i\}$
  3. Remove T_m^* from $\{T_1, \ldots, T_n\}$ and repeat step 2. with $m = 2, \ldots, n$.

Conditional permutation approach – example

- Suppose the observed data consists of 4 observations:

$$\{(X, T) : (3, 2), (5, 1), (8, 7), (9, 6)\}$$

- Four possible legal permutations:

$$\begin{array}{llll} \{(3,\ 1) & (5,\ 2) & (8,\ 6) & (9,\ 7)\} \\ \{(3,\ 1) & (5,\ 2) & (8,\ 7) & (9,\ 6)\} \\ \{(3,\ 2) & (5,\ 1) & (8,\ 6) & (9,\ 7)\} \\ \{(3,\ 2) & (5,\ 1) & (8,\ 7) & (9,\ 6)\} \end{array}$$

Unconditional permutation

- The unconditional permutation approach:
  1. Permutes T across all subjects in the dataset
  2. Delete those with $T_i^* > X_i, i = 1, \ldots, n$

Unconditional permutation approach – example

- Suppose the observed data consists of 4 observations:

$$\{(X, T) : (3, 2), (5, 1), (8, 7), (9, 6)\}$$

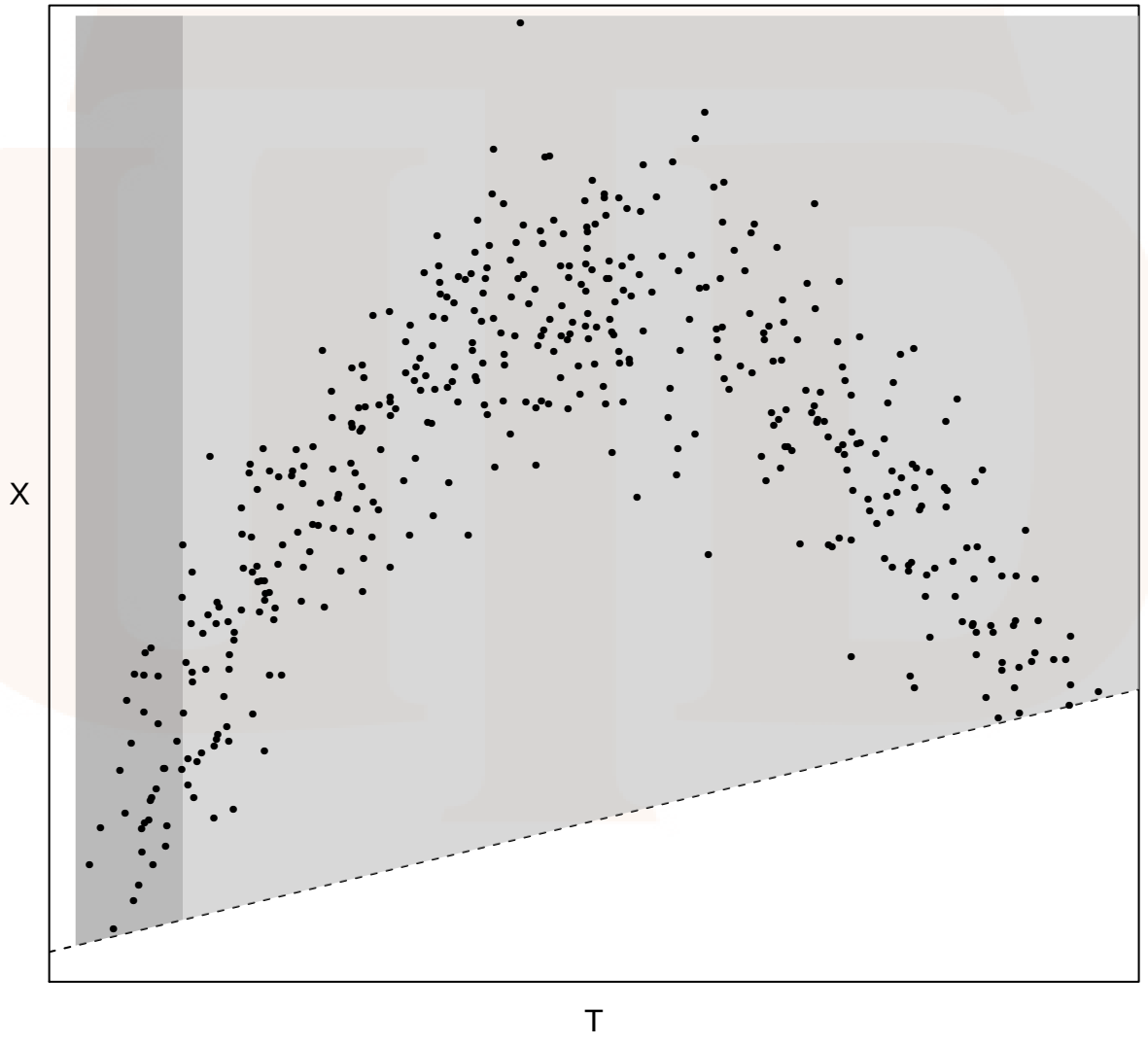
- Twenty four (4! = 24) possible legal permutations:

$$\begin{array}{llll}
\{(3,\ 1) & (5,\ 2) & (8,\ 6) & (9,\ 7)\} \\
\{(3,\ 1) & (5,\ 2) & (8,\ 7) & (9,\ 6)\} \\
\{(3,\ 1) & \cancel{(5,\ 6)} & (8,\ 2) & (9,\ 7)\} \\
\{(3,\ 1) & \cancel{(5,\ 6)} & (8,\ 7) & (9,\ 2)\}
\end{array}$$

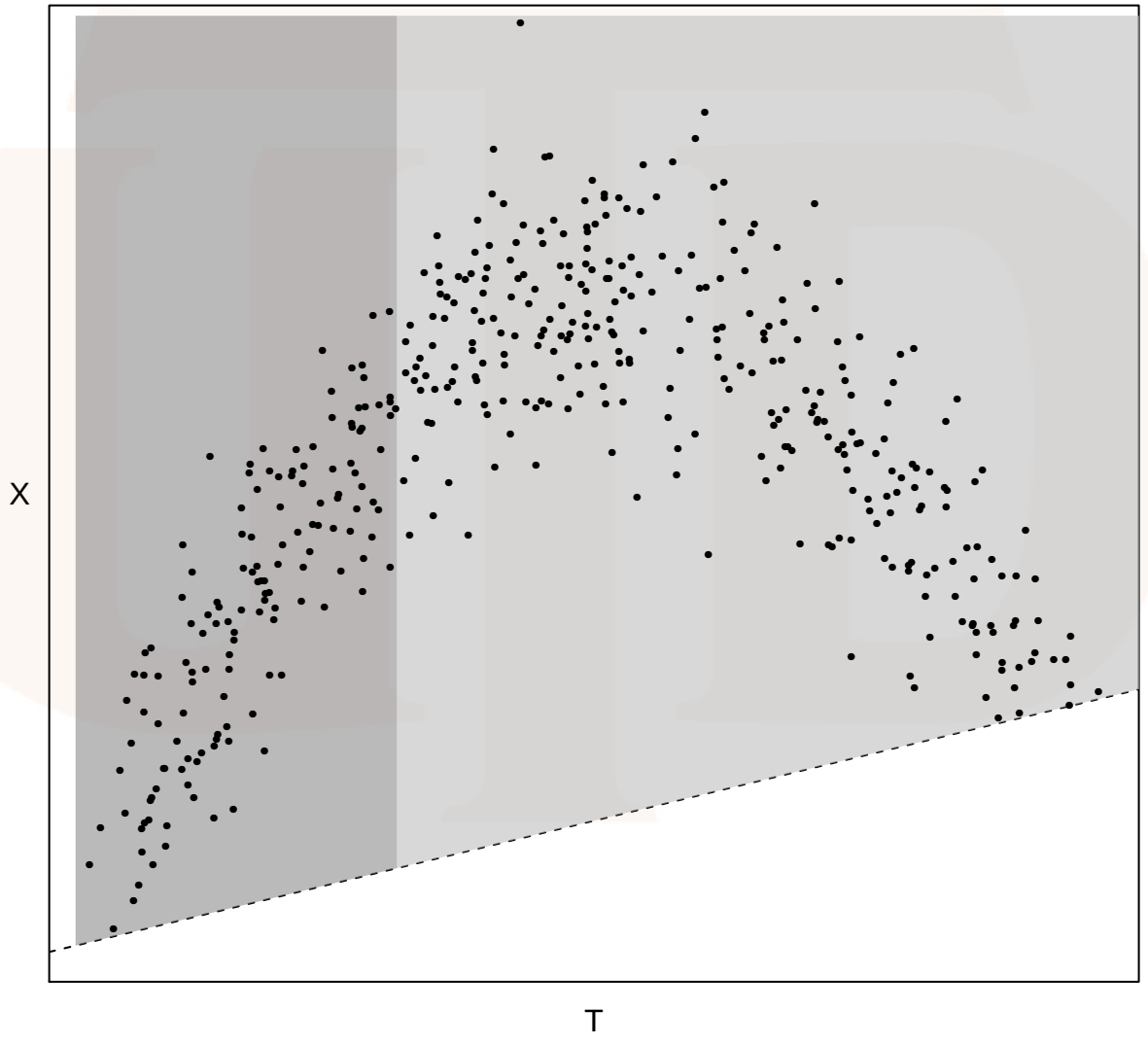
Test statistics: minimally selected p-value, minp_1

- Minimally selected p-value (minp) tests to detect non-monotone dependencies.
- We proposed to obtain minp_1 p-value from:
  1. Partition the data into two groups: $\{T < t\}$ or $\{T > t\}$
  2. Compute the log-rank p-value for the two groups
  3. Repeat 1. and 2. for $t \in \{T_1, \ldots, T_n\}$
  4. The minp_1 test statistic is the minimum of these p-values
- For every cut-point, require at least E events in the each group.

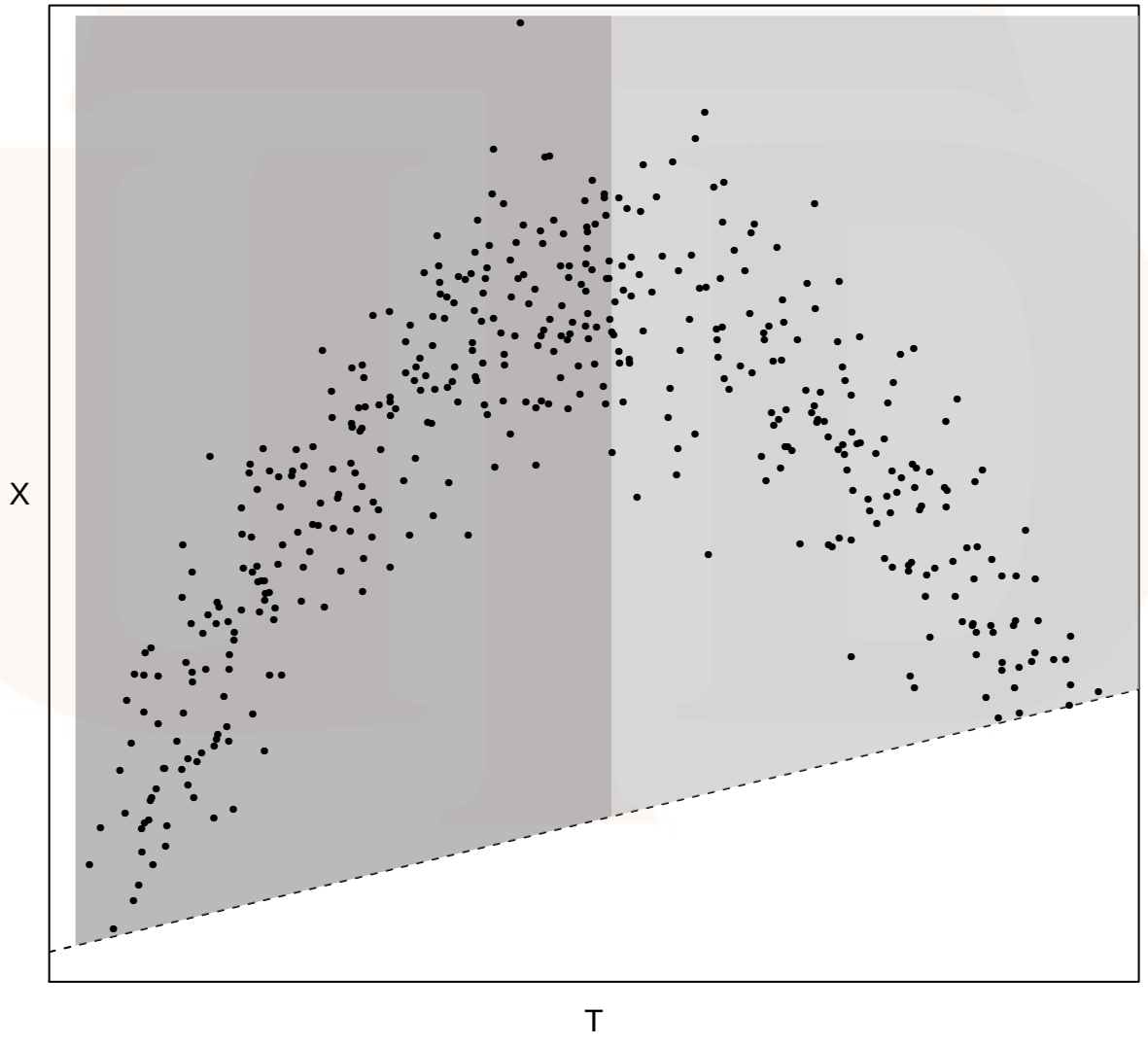
Minimally selected p-value, minp_1



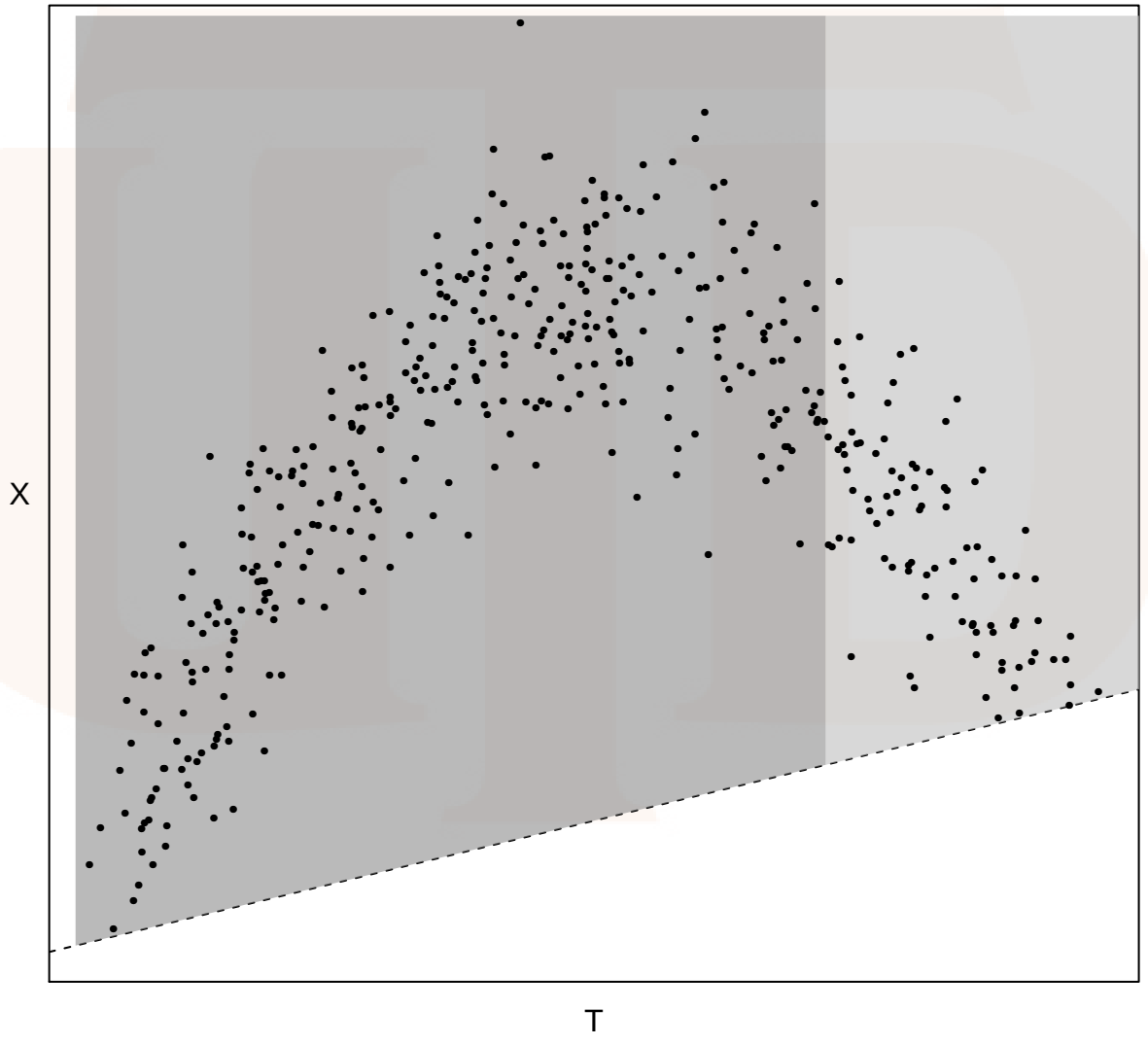
Minimally selected p-value, minp_1



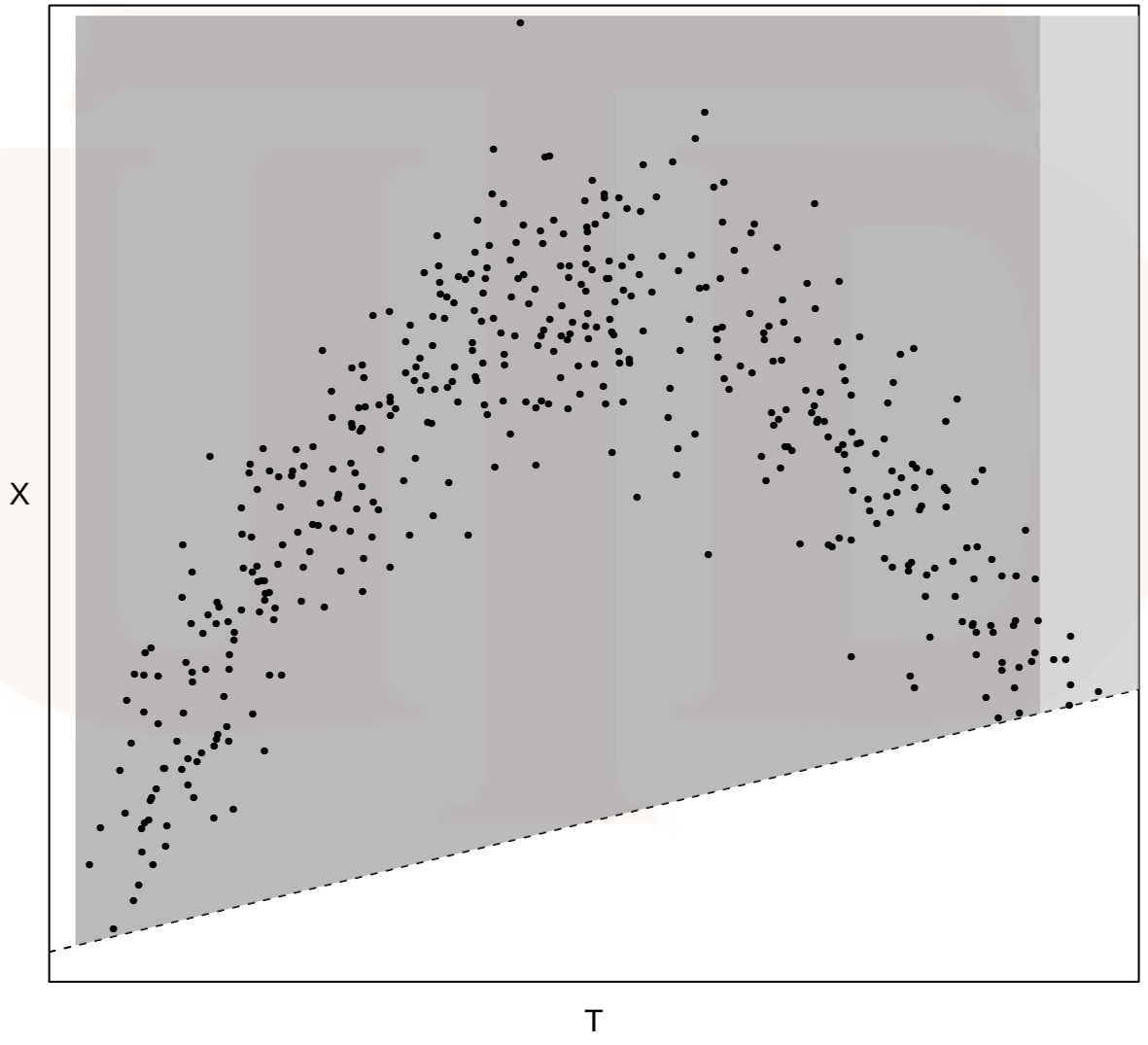
Minimally selected p-value, minp_1



Minimally selected p-value, minp_1



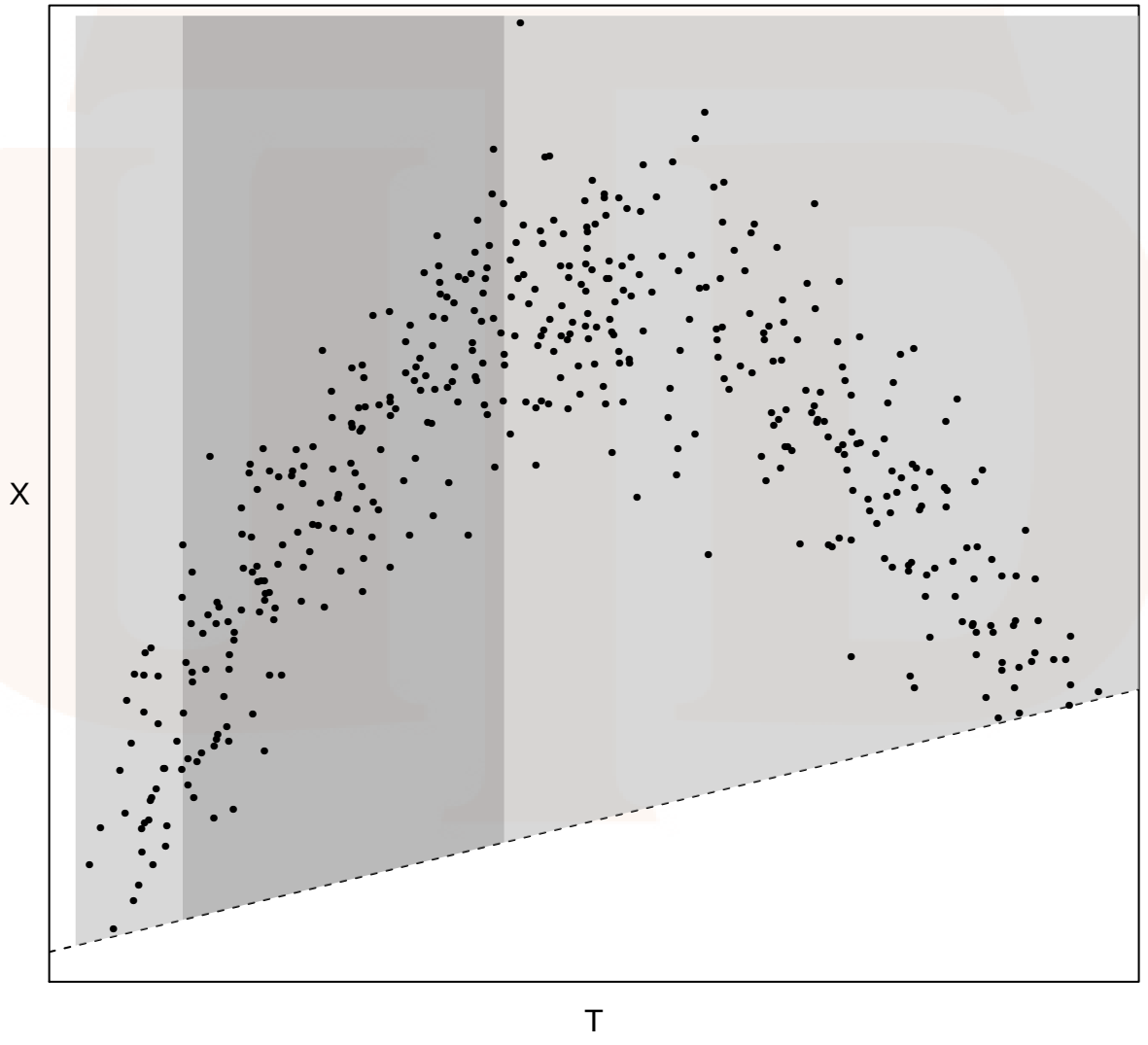
Minimally selected p-value, minp_1



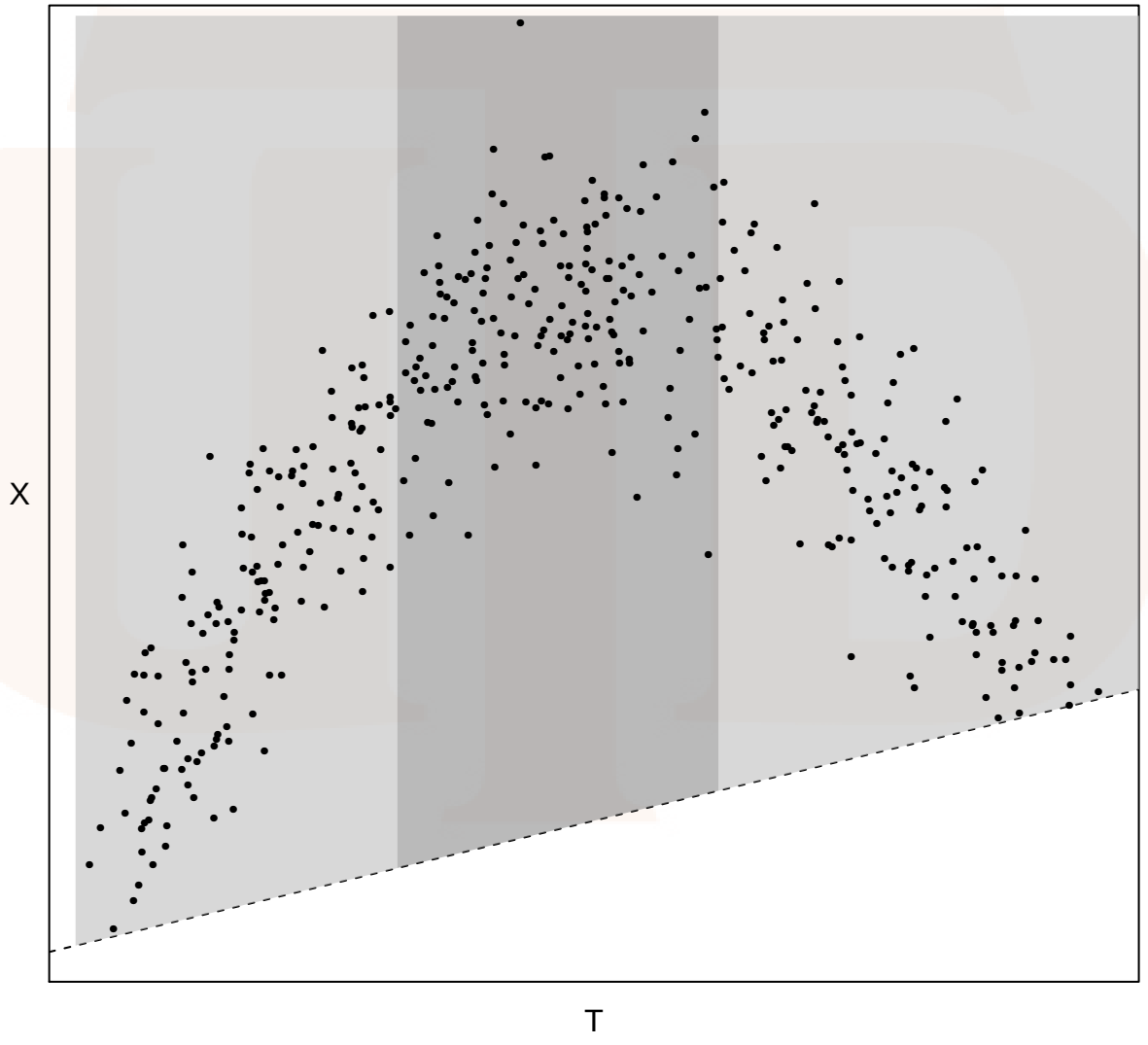
Minimally selected p-value, minp_2

- An alternative is the minp_2 test:
  1. Partition the data into two groups: $\{T \in (t-\epsilon, t+\epsilon)\}$ or $\{T \notin (t-\epsilon, t+\epsilon)\}$
  2. Compute the log-rank p-value for the two groups
  3. Repeat 1. and 2. for $t \in \{T_1, \ldots, T_n\}$
  4. The minp_2 test statistic is the minimum of these p-values
- This allows for X to be associated with moderate T differently from small or large T.
- Choose ϵ so that each group retains at least E events.

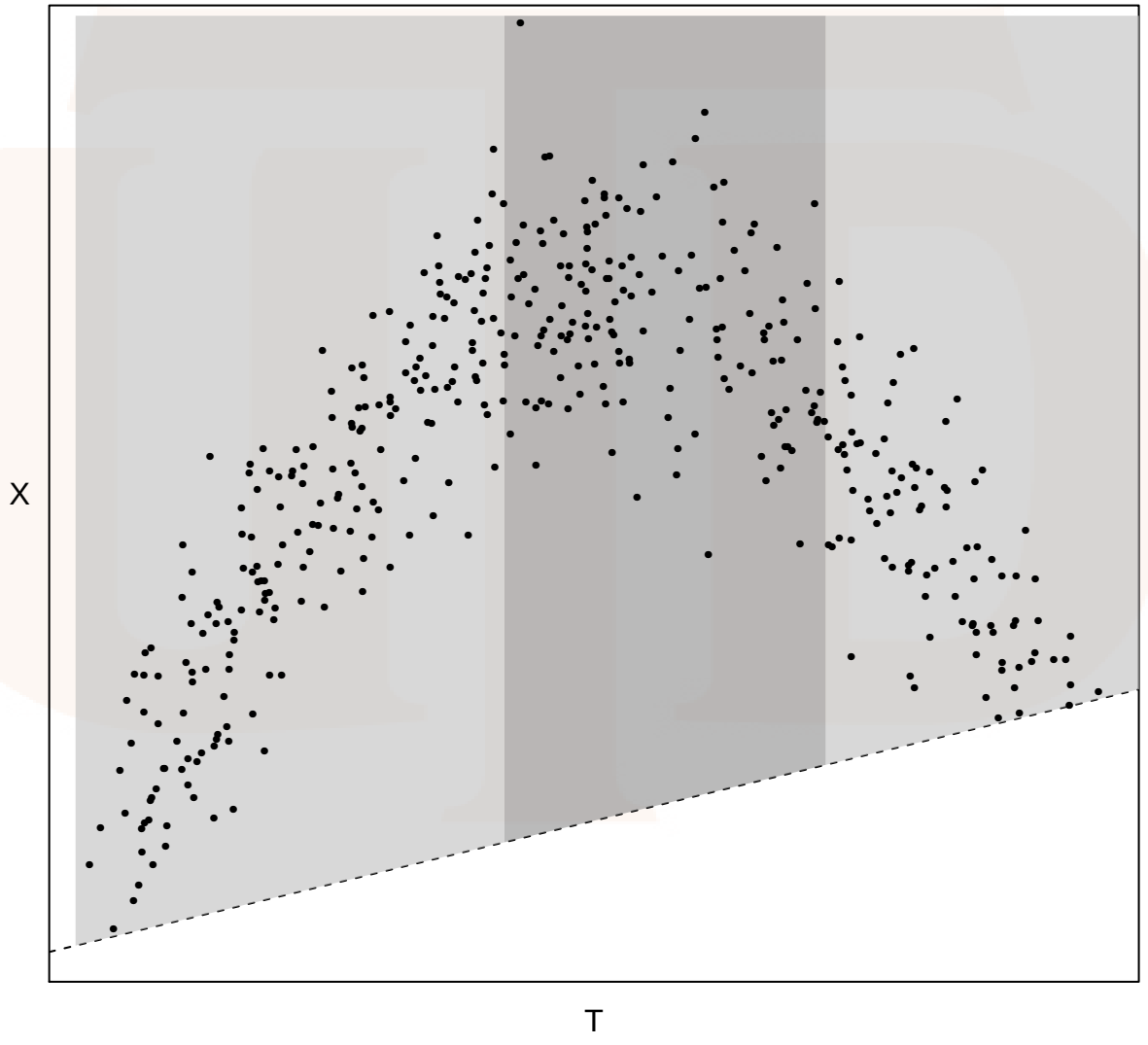
Minimally selected p-value, minp_2



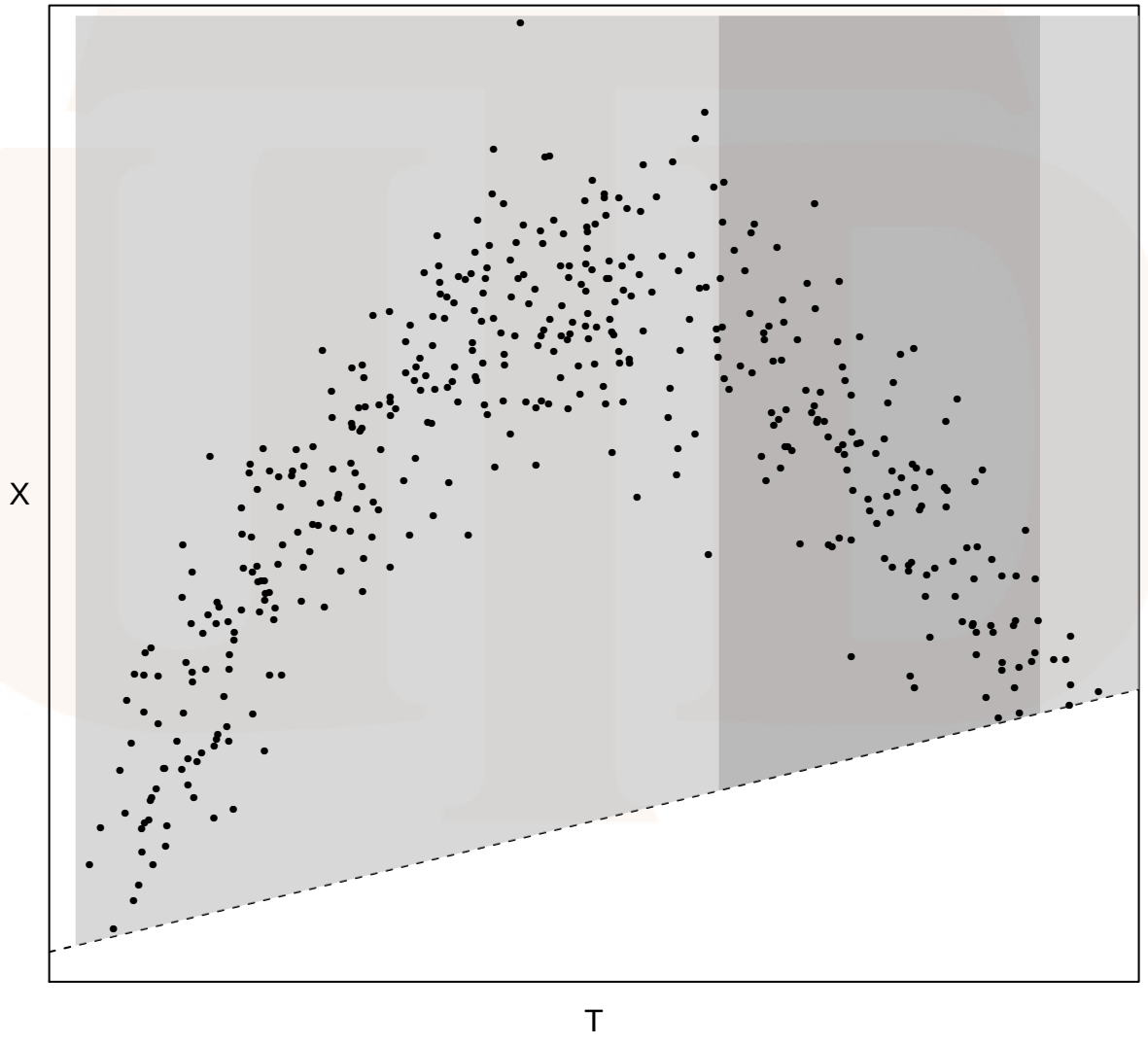
Minimally selected p-value, minp_2



Minimally selected p-value, minp_2



Minimally selected p-value, minp_2



Permutation p-values

- We approximate the p-value with

$$\frac{\sum_{i=1}^{N^*} I(|z_i^*| \geq |z_{\text{obs}}|) + 1}{N^* + 1},$$

where z_i^*'s and z_{obs} are the test statistics based on the sampled permutation and observed data, respectively.

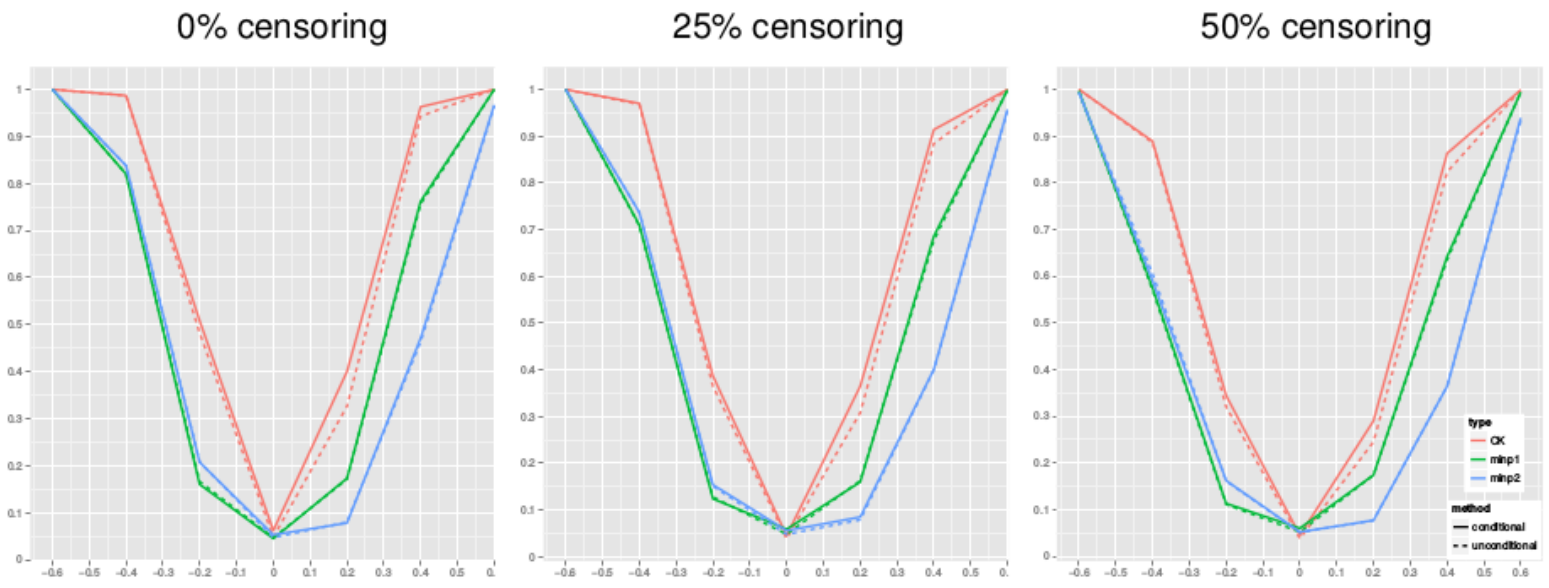
Simulation

Simulation 1: Monotone settings

- Generate (X, T) from a bivariate normal copula
  - $X \sim \text{Weibull}(3, 8.5)$
  - $T \sim \exp(0.2)$
- Nine levels of dependence
  - $\tau = 0, \pm 0.2, \pm 0.4, \pm 0.6, \pm 0.8$
- Sample size after truncation: 100 and 200.
- Censoring times follow an independent Uniform$(0, c)$
  - $0\%, 25\%$, and 50% after truncation
- 5000 permutations
- 1000 replications
- We compare the rejection proportions at a significant level of 0.05

Simulation 1: Rejection proportion

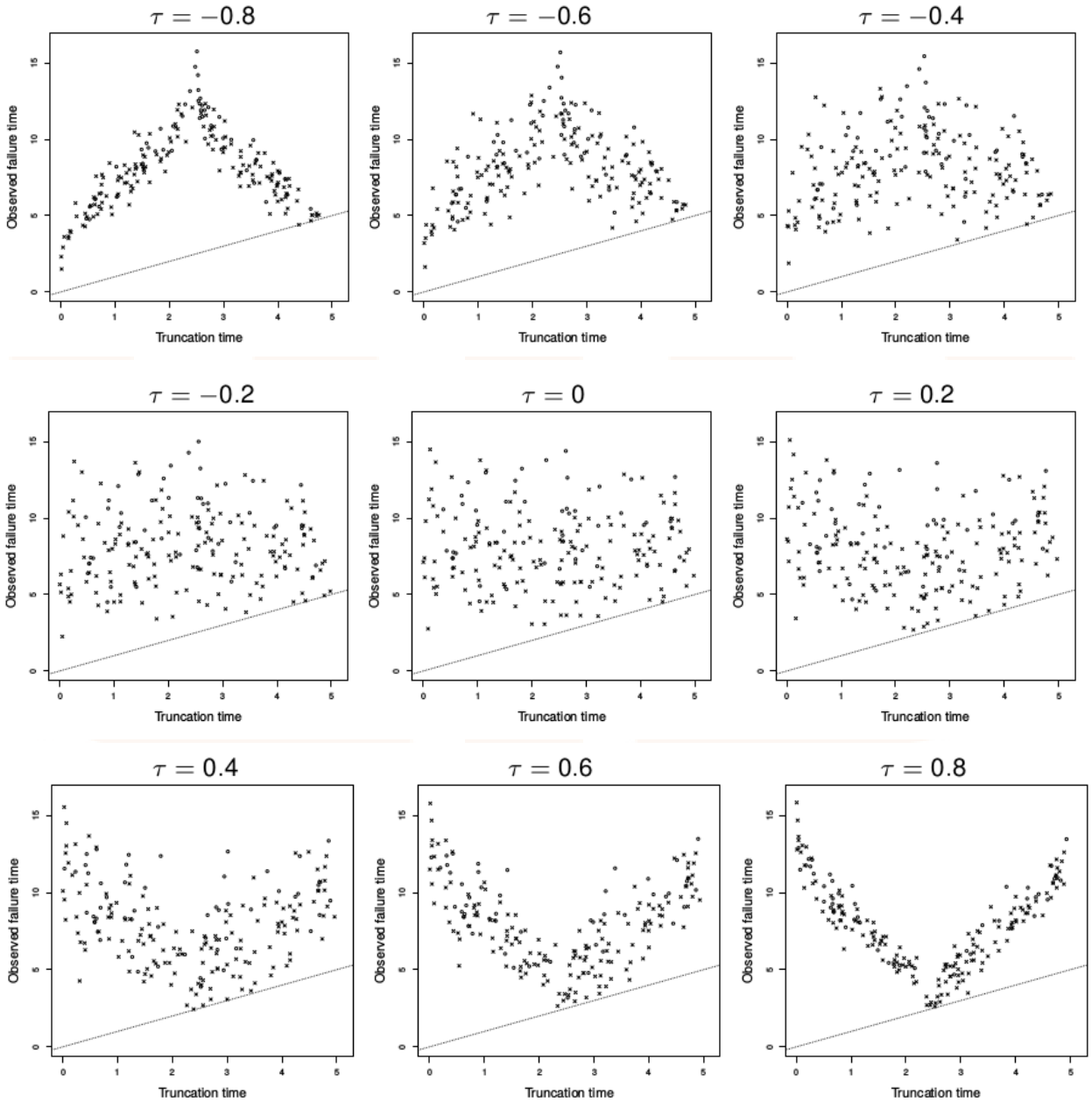
- Rejection proportion with $n = 100$:



Simulation 2: Non-monotone settings

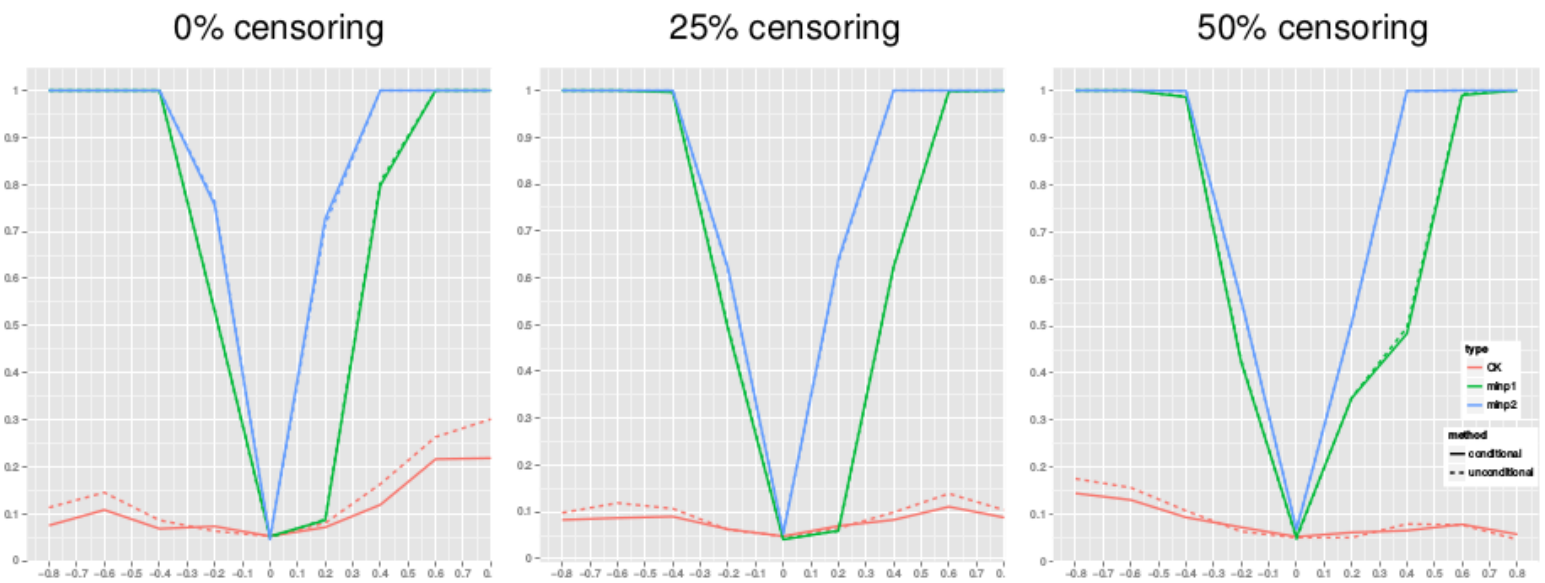
- Generate $(\mid T - 2.5 \mid, X)$ from a bivariate normal copula
  - $T \sim \text{Uniform}(0, 5)$
  - $X \sim \text{Weibull}(3, 8.5)$
- Nine dependence level
  - $0, \pm 0.2, \pm 0.4, \pm 0.6, \pm 0.8$
- Sample size after truncation: 100 and 200
- Censoring times follow an independent $\text{Uniform}(0, c)$
  - 0%, 25%, and 50% after truncation
- 5000 permutations
- 1000 replications
- We compare the rejection proportions at a significant level of 0.05.

Simulation 2: Data



Simulation 2: Rejection proportion

- Rejection proportion with $n = 100$:



Conclusion

Conclusion

- Minp tests are powerful against non-monotone dependencies.
- Minp tests are able to detect nonlinear dependence not detected by Kendall's tau in the aging study
- Unconditional permutation is a reasonable alternative
  - faster
  - useful for evaluation of statistics that fix risk set sizes
  - not strictly valid due to non-exchangeability
  - preserve type I error and have high power

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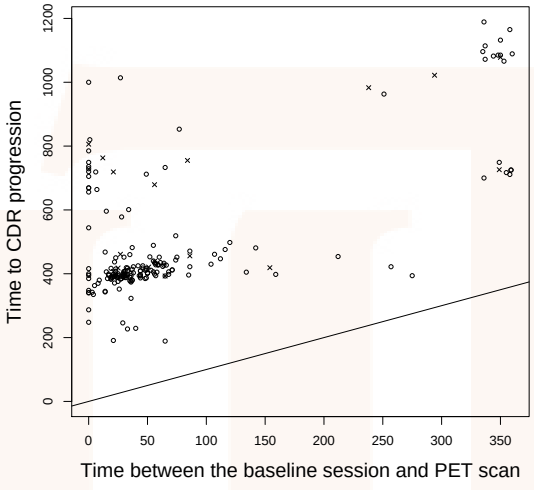
Aging study

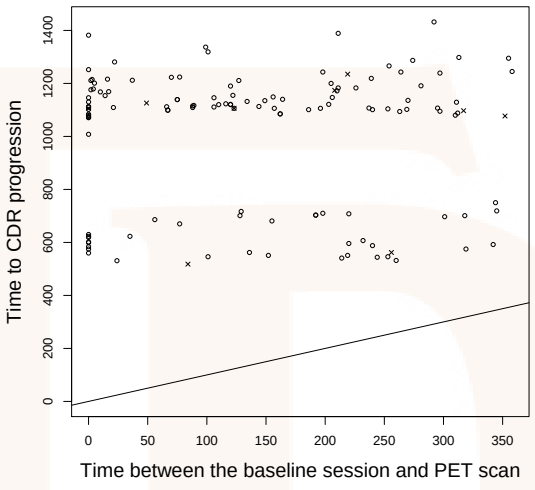
- Cognitively normal older individuals (n = 490):
  1. Alzheimer's Disease Neuroimaging Initiative (n = 198)
  2. Australian Imaging Biomarkers and Lifestyle Study of Ageing (n = 131)
  3. Harvard Aging Brain Study (n = 161)
- Participants had a Clinical Dementia Rating (CDR) 0 at enrollment
- Test for quasi-independence between time to PET scan and time to CDR progression

Aging study

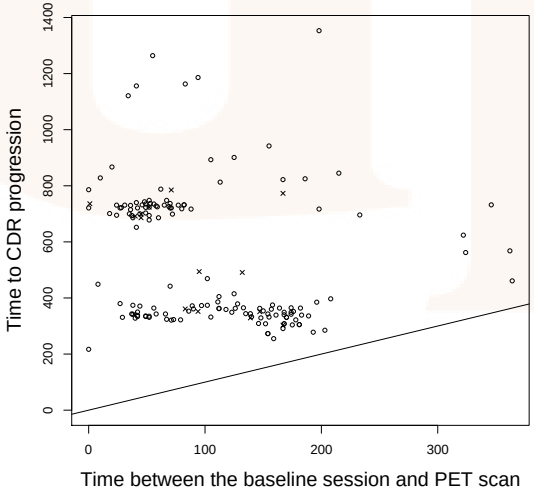
ADNI



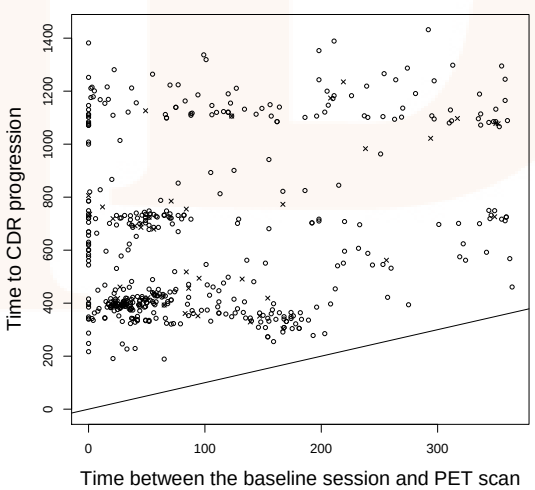
AIBL



HABS



ALL



Aging study – results ($E = 8$, 5000 permutations)

					Conditional		Unconditional	
	n	$\Delta = 1$	$\hat{\tau}_c^*$	ACK	minp_1	minp_2	minp_1	minp_2
ALL	490	41	−0.010	0.904	0.518	0.410	0.507	0.394
ADNI	198	17	0.149	0.292	0.111	0.019	0.082	0.018
HABS	161	15	−0.174	0.276	0.703	0.076	0.692	0.074
AIBL	131	9	−0.185	0.418	0.456	0.317	0.257	0.308

- no evidence of monotone dependence
- minp_2 does appear to be more powerful than minp_1
- Some evidence of nonlinear association in ADNI; possibly in HABS (marginally significant minp_2)