Surrogacy in Survival-Survival Setting

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New Assumptions/restrictions

- original document: assumptions on (conditional) copula parameters
  - difficult to interpret and justify
  - meaning of association in $T_0, T_1 | S_1$ or $S_0, T_1 | T_0, S_1$?
- new proposal: restrictions on marginal associations
  - do sensitivity analysis (as before) without any additional assumptions
  - for every sample of unidentifiable parameters
    - compute all marginal Kendall's τ's (by sampling)
    - discard replicate if these marginal τ's do not satisfy assumptions
  - **(stochastic) monotonicity:**

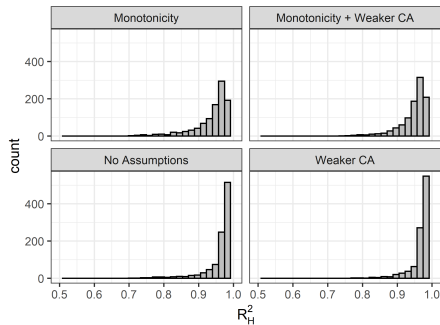 $$\min(\tau_{S_0,S_1}, \tau_{T_0,T_1}, \tau_{S_0,T_1}, \tau_{S_1,T_0}) > 0 \qquad (1)$$

  - **weaker cross-association:**

  $$\min(\tau_{S_0,T_0}, \tau_{S_1,T_1}) > \max(\tau_{S_0,T_1}, \tau_{S_1,T_0}) \qquad (2)$$

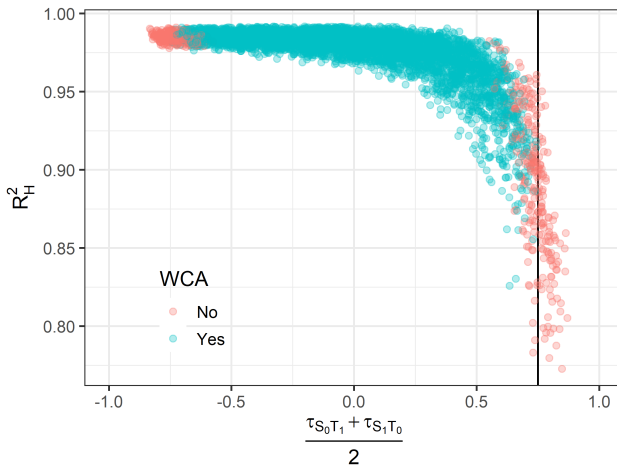# Applied to Ovarian Cancer data: Histograms
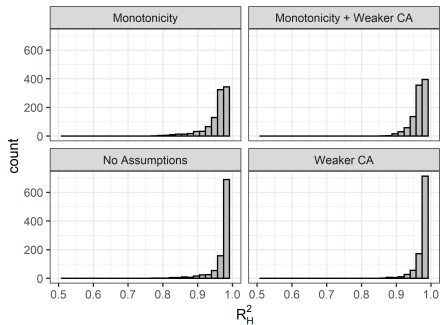
(a) With time orderings

(b) Without time orderings

Applied to Ovarian Cancer data: Alternative Representation

vertical line: $\min(\tau_{S_0, T_0}, \tau_{S_1, T_1})$

Applied to Ovarian Cancer data (Summary Statistics)

Ordering	Assumptions	Range	SD	$[p_1, p_{99}]$	median
Ordering	-	[0.773, 0.992]	0.030	[0.835, 0.991]	0.980
	M	[0.780, 0.991]	0.037	[0.815, 0.989]	0.968
	W-CA	[0.862, 0.992]	0.018	[0.899, 0.991]	0.981
	M + W-CA	[0.826, 0.991]	0.021	[0.895, 0.989]	0.971
No Ordering	-	[0.710, 0.991]	0.043	[0.771, 0.990]	0.975
	M	[0.704, 0.991]	0.052	[0.739, 0.987]	0.956
	W-CA	[0.771, 0.991]	0.029	[0.842, 0.990]	0.976
	M + W-CA	[0.742, 0.991]	0.040	[0.794, 0.987]	0.958

Remaining Issues

- Sampling unidentifiable parameters
  - **now:** by sampling corresponding Spearman's ρ from $U(0,1)$
  - **better?** use a grid for ρ and consider all combinations
- Additional assumptions
  - **now:** number of replications set equal ($n = 1000$ under different assumptions
    - more "comparable" results across different assumptions
    - BUT: counter intuitive results
    - e.g. range increases with extra assumption
  - **better?** use *all* replications that satisfy the assumptions
    - of replications decreases for additional assumptions
- Qualitatively similar results when ICA is quantified with Kendall's τ and Spearman's ρ
  - BUT: considerably weaker association
  - probably due to seemingly cured fraction $\rightarrow$ model implies some very large individual causal effects
  - Rank based metrics more appropriate?

Spearman's ρ

Ordering	Assumptions	Range	SD	$[p_1, p_{99}]$	median
Ordering	-	[0.498, 0.997]	0.063	[0.668, 0.995]	0.977
	M	[0.419, 0.997]	0.080	[0.625, 0.992]	0.951
	W-CA	[0.683, 0.997]	0.039	[0.808, 0.995]	0.979
	M + W-CA	[0.683, 0.997]	0.045	[0.769, 0.992]	0.956
No Ordering	-	[0.369, 0.996]	0.074	[0.646, 0.995]	0.973
	M	[0.486, 0.995]	0.086	[0.581, 0.988]	0.927
	W-CA	[0.677, 0.996]	0.049	[0.766, 0.994]	0.973
	M + W-CA	[0.628, 0.995]	0.062	[0.707, 0.988]	0.933

Kendall's τ

Ordering	Assumptions	Range	SD	$[p_1, p_{99}]$	median
Ordering	-	[0.342, 0.965]	0.088	[0.519, 0.953]	0.900
	M	[0.272, 0.964]	0.103	[0.473, 0.938]	0.848
	W-CA	[0.527, 0.964]	0.062	[0.654, 0.954]	0.904
	M + W-CA	[0.527, 0.964]	0.067	[0.615, 0.938]	0.857
No Ordering	-	[0.214, 0.954]	0.098	[0.491, 0.944]	0.889
	M	[0.326, 0.950]	0.109	[0.426, 0.926]	0.817
	W-CA	[0.512, 0.951]	0.071	[0.612, 0.943]	0.890
	M + W-CA	[0.468, 0.950]	0.085	[0.546, 0.924]	0.827