Cross-over studies with survival outcomes

Workshop on missing information in survival data beyond right censoring

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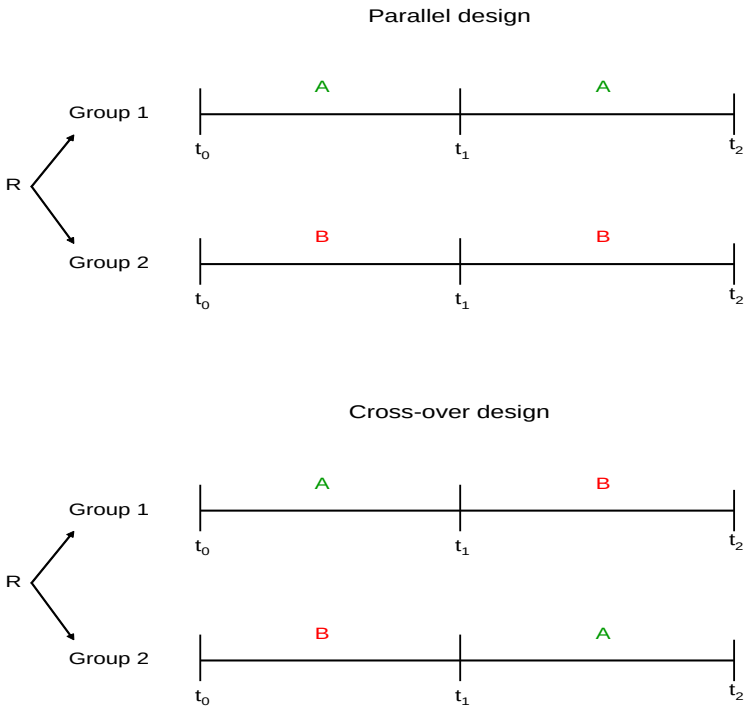
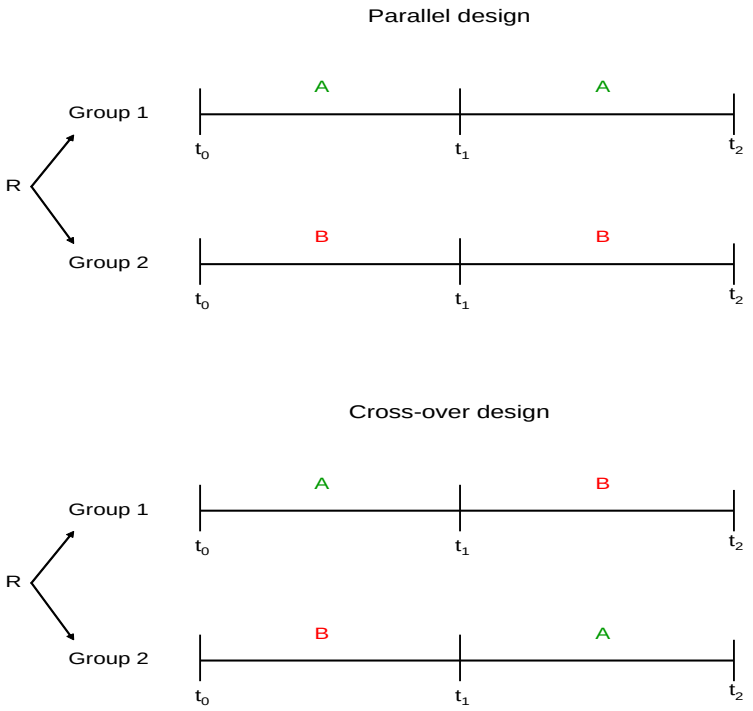
Introduction

- Research about dynamic treatment regimes with continuous outcome
  - Extend to dynamic treatment regimes with survival outcome
  - Restrict to crossover design
- In clinical trials with binary or continuous outcomes: cross-over design more efficient than parallel design because part of the inter-subject variability is eliminated.





- but rarely used with right-censored survival data e.g. Senn(2006) "... survival analysis, for which cross-over trials are unsuitable, but for re-occuring events they may be applied.".
- What is the statistical basis for this advice?
- How do things change now that we have more sophisticated analysis tools (from dynamic regimes)?
- goal: understand impact of cross-over trials for survival data

Study precision of estimated treatment effect in parallel and cross-over design in

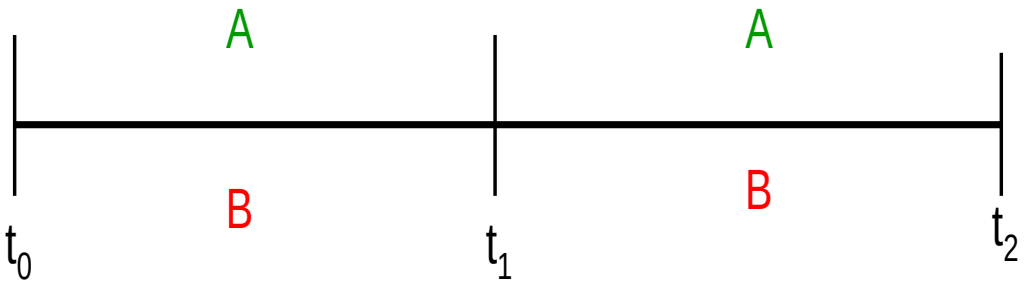
- Parametric model
  - homogeneous population
  - heterogeneous population
- Semi-parametric model: heterogeneous population
- Non-parametric estimator: heterogeneous population

Parametric model

Assumptions:

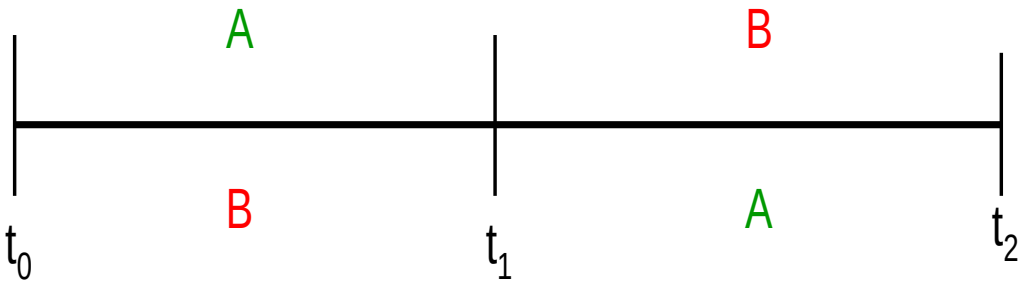
- Failure times exponentially distributed
  - $\lambda(t|R = r) = \lambda_r$
  - A constant hazard $\Rightarrow$ memory loss, renewal property
- Hazard ratio $\frac{\lambda_2}{\lambda_1} = \Delta$

MLE - Homogeneous population - Parallel design



- $\hat{\lambda}_r = \frac{\text{number of observed events in arm r}}{\text{total observation time in arm r}}$
- $\hat{\Delta} = \frac{\hat{\lambda}_2}{\hat{\lambda}_1}$
- variance-covariance matrix: minus the inverse of the information matrix

MLE - Homogeneous population - Crossover design



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- $\hat{\Delta} = \frac{\hat{\lambda}_2}{\hat{\lambda}_1}$
- variance-covariance matrix: minus the inverse of the information matrix

Homogeneous population

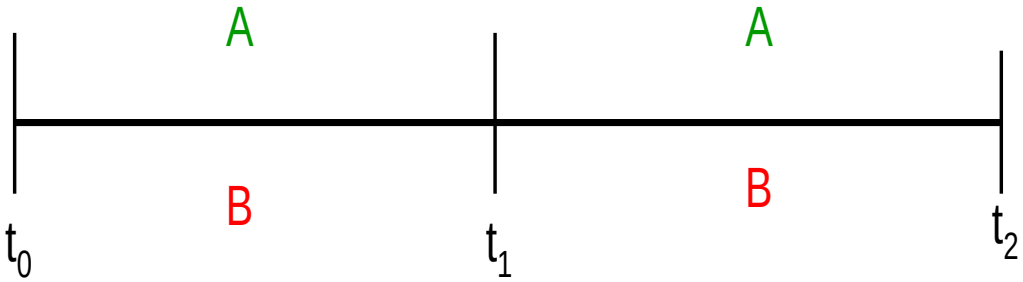
- All patients have a common constant baseline hazard $\Rightarrow$ renewal
  $\Rightarrow$ *it doesn't matter if patients are compared with themselves or with another group of patients*
  $\Rightarrow$ unlikely to benefit from cross-over design
- Only difference between cross-over and parallel design: number of patients who receive treatment A or B in the second period
  - slightly more efficient to allocate largest group to the treatment with higher risk.
    $\Rightarrow$ lower risk group (largest group) $\longrightarrow$ higher risk
    $\Rightarrow$ cross-over design slightly more efficient than parallel design
- Difference basically negligible

Simulation results - Homogeneous population

- 1000 datasets of size 2000
- real parameters: $\lambda = 0.3$, $\Delta = 1.5$, $log(\Delta) = 0.405$

	mean of estimates	mean of est. se	emp se	MSE	coverage
Parallel design					
λ	0.301	0.0098	0.0100	0.0001	0.944
Δ	1.499	0.0681	0.0680	0.0046	0.984
$log(\Delta)$	0.404	0.0454	0.0454	0.0021	0.989
Cross-over design					
λ	0.301	0.0103	0.0104	0.0001	0.949
Δ	1.496	0.0682	0.0688	0.0047	0.988
$log(\Delta)$	0.402	0.0455	0.0461	0.0021	0.990

MLE - Heterogeneous population - Parallel design



- individual hazards λ_i follow exponential distribution with mean λ
- within patient comparison may be beneficial
- $$\begin{cases} \sum_{i=1}^{n} \delta_{1,i} R_i \left(-\frac{1}{\lambda} + \frac{2}{\lambda + t_i \lambda^2} \right) + \delta_{1,i}(1-R_i) \left(-\frac{1}{\lambda} + \frac{2}{\lambda + \Delta t_i \lambda^2} \right) \\ +(1 - \delta_{1,i}) R_i \left(-\frac{1}{\lambda} + \frac{1}{\lambda + t_2 \lambda^2} \right) + (1-\delta_{1,i})(1-R_i) \left(-\frac{1}{\lambda} + \frac{1}{\lambda + \Delta t_2 \lambda^2} \right) = 0 \\ \sum_{i=1}^{n} \delta_{1,i}(1-R_i) \left(\frac{1}{\Delta} - \frac{2 t_i \lambda}{1 + \Delta t_i \lambda} \right) + (1-\delta_{1,i})(1-R_i) \left(\frac{-t_2 \lambda}{1 + \Delta t_2 \lambda} \right) = 0 \end{cases}$$
- Solve equations by Newton-Raphson with starting values λ_0 and Δ_0 from assumed homogeneous population

MLE - heterogeneous population - Cross-over design

$$
\begin{cases}
\sum_{i=1}^{n} R_i\delta_{1,i}\left(-\frac{1}{\lambda}+\frac{2}{\lambda+t_i\lambda^2}\right)+(1-R_i)\delta_{1,i}\left(-\frac{1}{\lambda}+\frac{2}{\lambda+\Delta t_i\lambda^2}\right) \\
+R_i(1-\delta_{1,i})\delta_{2,i}\left(-\frac{1}{\lambda}+\frac{2}{\lambda+t_1\lambda^2+\Delta(t_i-t_1)\lambda^2}\right) \\
+(1-R_i)(1-\delta_{1,i})\delta_{2,i}\left(-\frac{1}{\lambda}+\frac{2}{\lambda+\Delta t_1\lambda^2+(t_i-t_1)\lambda^2}\right) \\
+R_i(1-\delta_{1,i})(1-\delta_{2,i})\left(-\frac{1}{\lambda}+\frac{1}{\lambda+t_1\lambda^2+\Delta(t_2-t_1)\lambda^2}\right) \\
+(1-R_i)(1-\delta_{1,i})(1-\delta_{2,i})\left(-\frac{1}{\lambda}+\frac{1}{\lambda+\Delta t_1\lambda^2+(t_2-t_1)\lambda^2}\right)=0 \\
\sum_{i=1}^{n}(1-R_i)\delta_{1,i}\left(\frac{1}{\Delta}-\frac{2t_i\lambda}{1+\Delta t_i\lambda}\right) \\
+R_i(1-\delta_{1,i})\delta_{2,i}\left(\frac{1}{\Delta}-\frac{2(t_i-t_1)\lambda}{1+t_1\lambda+\Delta(t_i-t_1)\lambda}\right) \\
+(1-R_i)(1-\delta_{1,i})\delta_{2,i}\left(\frac{-2t_1\lambda}{1+\Delta t_1\lambda+(t_i-t_1)\lambda}\right) \\
+R_i(1-\delta_{1,i})(1-\delta_{2,i})\left(\frac{-(t_2-t_1)\lambda}{1+t_1\lambda+\Delta(t_2-t_1)\lambda}\right) \\
+(1-R_i)(1-\delta_{1,i})(1-\delta_{2,i})\left(\frac{-t_1\lambda}{1+\Delta t_1\lambda+(t_2-t_1)\lambda}\right)=0
\end{cases}
$$

Heterogeneous population

- 1000 datasets of size 2000
- real parameters: $\lambda = 0.3$, $\Delta = 1.5$, $log(\Delta) = 0.405$

	mean of estimates	mean of est. se	emp se	MSE	coverage
Parallel design					
λ	0.300	0.0165	0.0168	0.0003	0.938
Δ	1.506	0.1173	0.1189	0.0142	0.981
$log(\Delta)$	0.406	0.0782	0.0784	0.0061	0.987
Cross-over design					
λ	0.300	0.0151	0.0151	0.0002	0.946
Δ	1.502	0.0896	0.0912	0.0083	0.984
$log(\Delta)$	0.405	0.0598	0.0609	0.0037	0.986

25% lost efficiency in parallel design

Semi-parametric model - Parallel design

- True model: individual hazards λ_i follow exponential distribution with mean λ and conditional hazard ratio Δ
- $=$ first working model : $\lambda_i(t) = \lambda_0(t)\exp(\beta Z_i + b_i)$ with

$$Z_i = \begin{cases} 0 & \text{treatment A} \\ 1 & \text{treatment B} \end{cases}$$

  - $exp(\beta)$ is the *conditional* hazard ratio
- $\neq$ second working model: $\lambda_i(t) = \lambda_0(t)\exp(\beta Z_i)$
  - $exp(\beta)$ is the average of the *marginal* hazard ratios over the observed event times
  - $HR_{marg}(t) = \frac{t+\frac{1}{\lambda}}{t+\frac{1}{\lambda\Delta}}$

Semi-parametric model - Crossover design

- True model: individual hazards λ_i follow exponential distribution with mean λ and conditional hazard ratio Δ
- $=$ first working model: $\lambda_{ik}(t) = \lambda_0(t)\exp(\beta Z_{ik} + b_i) \quad k = 1, 2$
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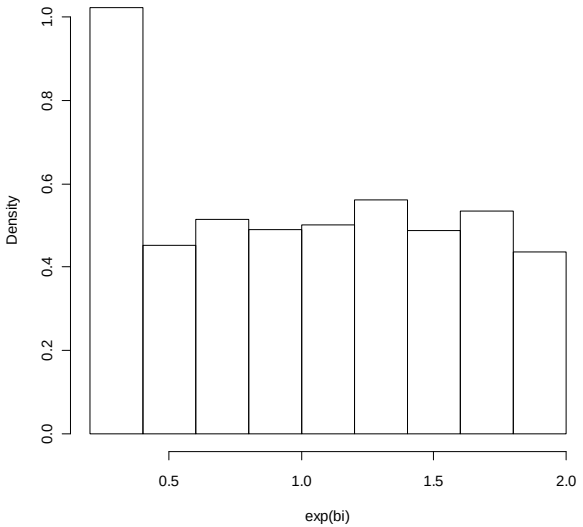
- $\neq$ second working model: $\lambda_{ik}(t) = \lambda_0(t)\exp(\beta Z_{ik}) \quad k = 1, 2$
  - $exp(\beta)$ is the average of the *marginal* hazard ratios over the observed event times
  - $HR_{marg}(t) = \begin{cases} \frac{t+\frac{1}{\lambda}}{t+\frac{1}{\lambda\Delta}} & t \leq t_1 \\ \frac{(t-t_1)+\frac{1}{\lambda}+t_1\Delta}{(t-t_1)+\frac{1}{\lambda\Delta}+\frac{t_1}{\Delta}} & t > t_1 \end{cases}$

Simulation results - heterogeneous - Semi-parametric

- 1000 datasets of size 2000
- real parameters: $\Delta = 1.5$, $log(\Delta) = 0.405$
- marginal hazard ratio in parallel design: 0.251, marginal hazard ratio in cross-over design: 0.331
- $exp(b_i)$ are gamma distributed



	Working model estimand	mean of estimates	mean of est. se	emp se	MSE	coverage
			Parallel design			
$log(\Delta)$	marginal	0.248	0.051	0.051	0.003	0.944
	conditional	0.371	0.070	0.122	0.016	0.655
			Cross-over design			
$log(\Delta)$	marginal	0.280	0.051	0.043	0.004	0.865
	conditional	0.405	0.060	0.063	0.004	0.939

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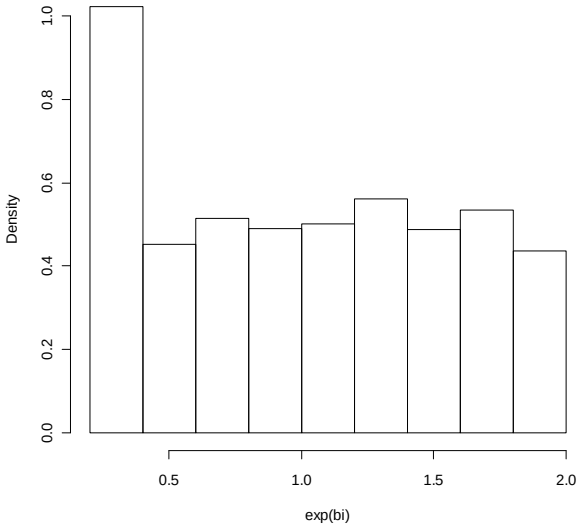

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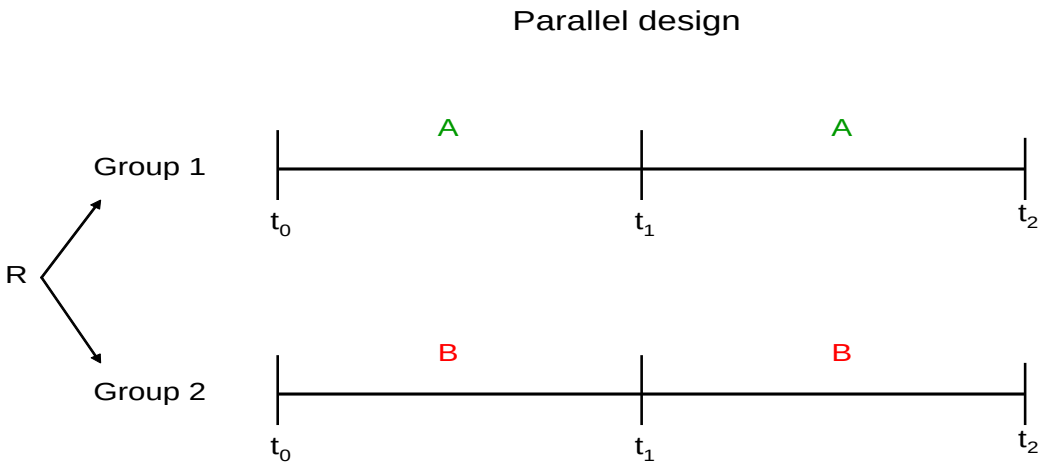
Comparison of parallel design and cross-over design

- Wish to compare efficiency of estimated survival of treatment AB between parallel and cross-over design
- Parallel design doesn't have AB arm. Can we concatenate first period of A treatment with second period of B treatment?



- Possible if no 'carry-over effect'. We compare the marginal hazard for the B treatment in the second period between patients with A in first period and patients with B in first period.

- For a group of patients with A in first period, the marginal hazard for B in the second period is

$$\lambda_B(t) = \frac{1}{t + \frac{1}{\lambda\Delta} + \frac{t_1}{\Delta}}$$

- For a group of patients with B in first period, the marginal hazard for B in the second period is

$$\lambda_B(t) = \frac{1}{t + \frac{1}{\lambda\Delta} + t_1}$$

$\Rightarrow$ carry-over effect on marginal hazard

Non-parametric estimator of survival distribution

- Wahed and Tsiatis (2004) present a estimator (LE) for the survival distribution in two-stage designs.
- For the estimator of the survival function of regime 12, we only need data from group 1·.

$$\hat{S}_{12}(t)=\frac{1}{n}\sum_{i=1}^{n}\frac{\Delta_i}{\hat{K}(U_i)}\left[\left\{(1-R_i)+\frac{R_i X_{2i}}{\pi_2}\right\}I(U_i\geq t)-R_i\left(\frac{X_{2i}-\pi_2}{\pi_2}\right)g(T_i^R,V_i,\hat{\gamma})\right]$$

with

  - $\Delta_i = I(C_i \geq T_i)$
  - $U_i = \min(T_i, C_i)$
  - $R_i = 1$ if second treatment given else $R_i = 0$
  - X_{2i} is the indicator for treatment B in the second period
  - $\pi_2 = P(X_{2i} = 1 | R_i = 1)$
  - $\hat{K}(u) = \frac{1}{n}\sum_{i=1}^{n} I(C_i \geq u)$

- In our case $X_{2i} = 1\ \forall i$ and $\pi_2 = 1$.

$$\Rightarrow \hat{S}_{12}(t) = \frac{1}{n}\sum_{i=1}^{n}\frac{\Delta_i}{\hat{K}(U_i)}I(U_i \geq t)$$

Adapted Kaplan-Meier estimator

$$\hat{S}_{12}(t) = \prod_{j:\tau_j \leq t} \left(\frac{r_{j,2} - d_{j,2}}{r_{j,2}} \right)$$

Simulation results - Non-parametric

- 100 datasets of size 100 in each arm
- failure times exponentially distributed
- we estimate $P(T > 7)$ with cross-over time $= 5$, real value=0.3156 (parallel design, group A),0.2859 (cross-over design, group AB)

	mean of estimator	emp SE	MSE	95% CI for bias
Parallel design				
KM	0.3156	0.0460	0.0021	[-0.0090,0.0090]
Cross-over design				
LE	0.2845	0.0434	0.0019	[-0.0099,0.0071]
Adapted KM	0.2850	0.0433	0.0019	[-0.0094,0.0076]

Summary

- The cross-over design is more efficient than the parallel design for the parametric model and a heterogeneous population (relative efficiency=58%).
- The cross-over design is more efficient to estimate the conditional hazard ratio in the semi-parametric model.
- One can estimate the survival function more efficiently in the cross-over design with the LE estimator than in the parallel design.
- Further work: use the non-parametric LE estimator of the survival function to estimate the hazard ratio.

References

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- Wahed A.S. and Tsiatis A.A. (2004). Optimal estimator for the survival distribution and related quantities for treatment policies in two-stage randomization designs in clinical trials. *Biometrics*, **60**: 124-133.