Multiple Imputation for Incomplete Survival Data with Missing Covariates

Toward Valid Causal Inference

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Outline

1. Multiple Imputation for Incomplete Survival Data
   - Weighted Analysis vs Imputation
   - Multiple Imputation
   - Multiple Imputation in Sub-sample Study

2. Causality of Hazard Ratio
   - Against Causal Interpretation of Hazard Ratio
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Motivation

- High-cost covariates (e.g., Blood test samples, Genomic data) are infeasible to collect for all members in the cohort.
- Commonly used sampling strategies are Nested case-control (NCC) and Case-cohort (CC) designs.

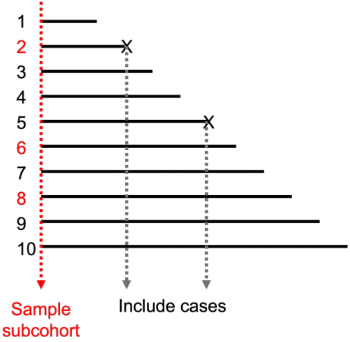
Units	Z	T	X_j
1			
$\vdots$			X_j^{obs}
n_j			
n_j+1			
$\vdots$			X_j^{mis}
N			

Table 1: Green = Observed, Red = Missing

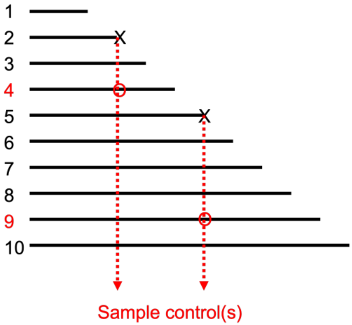
Two Sampling Designs

- In case-cohort design, a random **subcohort** is drawn at the beginning of the study and all cases outside the subcohort are included.

- In nested case-control design, controls are randomly sampled from those still at risk at each failure time.



(a) Case-cohort sampling (CC)



(b) Nested case-control sampling (NCC)

Notation

Symbol	Description
X_j^{obs}	Observed subvector of the expensive covariate $\in \mathrm{R}^{n_j}$
X_j^{mis}	Missing subvector of the expensive covariate $\in \mathrm{R}^{N-n_j}$
$X_j^{(m)}$	The mth imputed $X_j^{\mathrm{mis}} \in \mathrm{R}^{N-n_j}$
Z^i	Cheap covariates for unit $i \in \mathrm{R}^q$
T	Observed survival time
δ	Event type; failure$(=1)$ and censored$(=0)$
$\tilde{R}(t)$	Sampled risk set at time t

Weighted Partial Likelihood

- With the sub-sample data, we want to fit Cox proportional hazards model to quantify the hazard of the expensive covariate.

$$\hat{\boldsymbol{\beta}} = \arg\max_{\boldsymbol{\beta}} \prod_{i:\delta_i=1} \frac{\exp\left(\beta_{X_j} X_j^{\mathrm{obs},i} + \beta_Z Z^i\right)}{\sum_{k\in\tilde{R}(t_i)} w_k \exp\left(\beta_{X_j} X_j^{\mathrm{obs},k} + \beta_Z Z^k\right)}$$

where $w_i = \begin{cases} \delta_i + (1-\delta_i)\,\tilde{N}/\tilde{n} & \text{for CC} \\ \delta_i + (1-\delta_i)\left(1 - \prod_{k:t_k<t_i}\left(1 - \frac{m\delta_k}{n_{t_k}-1}\right)\right)^{-1} & \text{for NCC} \end{cases}$

- However, weighted partial likelihoods do not make use of cheap covariates.

Weighted Analysis vs Imputation

- Instead, we can **impute** the expensive covariate and use the full cohort.

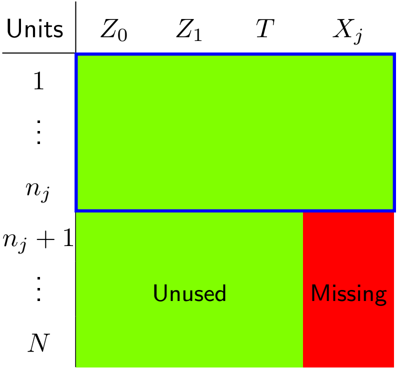


Table 2: Weighted Analysis

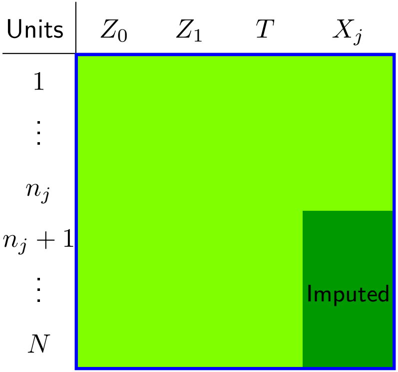


Table 3: Imputation

Multiple Imputation

1. Impute the missing value M times
2. Fit Cox PH model on each imputed data set,

$$\lambda^{(m)}(t) = \lambda_{\text{base}}(t) \exp(\hat{\beta}_{X_j}^{(m)} X_j + \hat{\beta}_{Z_1}^{(m)} Z_1)$$

3. Combine log hazard ratios, $\hat{\boldsymbol{\beta}}^{(m)}$, using Rubin's rule.

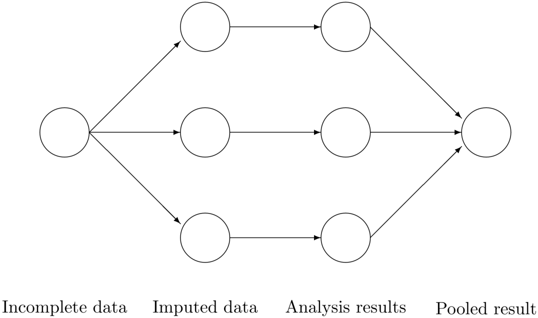


Figure 2: Main steps in multiple imputation

Multivariate Imputation by Chained Equation

- Let's look at how we obtain a single imputed data set in MICE algorithm.

Algorithm 1 MICE (Van Buuren, 2012)

Input: Incomplete cohort data with $\boldsymbol{X}^{\text{mis}}$
Output: Single imputed data set

```
for t = 1, ..., k do
    for j = 1, ..., p do
        Sample θ_j^(t) ~ π_j(θ_j | X_j^obs, X_{-j}^(t), Z, δ, T)
                       ∝ f_j(X_j^obs | X_{-j}^(t), Z, δ, T, θ_j) p_j(θ_j)
        Sample X_j^(t) ~ f_j(X_j^mis | X_{-j}^(t), Z, δ, T, θ_j^(t))
    end for
end for
```

for $t = 1, \ldots, k$ **do**
  for $j = 1, \ldots, p$ **do**
    Sample $\theta_j^{(t)} \sim \pi_j(\theta_j \mid X_j^{\text{obs}}, \boldsymbol{X}_{-j}^{(t)}, Z, \delta, T)$
    $\propto f_j(X_j^{\text{obs}} \mid \boldsymbol{X}_{-j}^{(t)}, Z, \delta, T, \theta_j)\, p_j(\theta_j)$
    Sample $X_j^{(t)} \sim f_j(X_j^{\text{mis}} \mid \boldsymbol{X}_{-j}^{(t)}, Z, \delta, T, \theta_j^{(t)})$
  end for
end for

where $\boldsymbol{X}_{-j}^{(t)} = (X_1^{(t)}, \ldots, X_{j-1}^{(t)}, X_{j+1}^{(t-1)}, \ldots, X_p^{(t-1)}) \in \mathrm{R}^{(N-n_j)\times(p-1)}$

- MICE algorithm is different from Gibbs sampler. In Gibbs sampler,

$$\theta_j^{(t)} \sim \pi_j\big(\theta_j \mid X_j^{\text{obs}}, X_j^{(t-1)}, \boldsymbol{X}_{-j}^{(t)}, Z, \delta, T\big)$$

Rubin's Rule

Rubin's Combining Rule

The combined **mean** and **variance** estimates for β:

$$\hat{\beta} := \frac{1}{M}\sum_{m=1}^{M}\hat{\beta}^{(m)}, \qquad \mathrm{var}(\hat{\beta}) := \bar{V} + \left(1 + \frac{1}{M}\right)B$$

where $\bar{V}$ and B are within and between imputation variances, respectively.

- Rubin's combining rule is based on Bayesian derivation.

$$p\big(\beta \mid X^{\mathrm{obs}}\big) = \int p\big(\beta \mid X^{\mathrm{mis}}, X^{\mathrm{obs}}\big)\, p\big(X^{\mathrm{mis}} \mid X^{\mathrm{obs}}\big)\, \mathrm{d}X^{\mathrm{mis}}$$

$$E\big(\beta \mid X^{\mathrm{obs}}\big) = E\Big[E\big(\beta \mid X^{\mathrm{mis}}, X^{\mathrm{obs}}\big) \mid X_{\mathrm{obs}}\Big]$$

$$\mathrm{Var}\big(\beta \mid X^{\mathrm{obs}}\big) = E\Big[\mathrm{Var}\big(\beta \mid X^{\mathrm{mis}}, X^{\mathrm{obs}}\big) \mid X^{\mathrm{obs}}\Big] + \mathrm{Var}\Big[E\big(\beta \mid X^{\mathrm{mis}}, X^{\mathrm{obs}}\big) \mid X^{\mathrm{obs}}\Big]$$

Rubin's Rule

- By $p\left(\beta \mid X^{\text{obs}}\right) \approx \frac{1}{M}\sum_{m=1}^{M} p\left(\beta \mid X^{(m)}, X^{\text{obs}}\right)$ where $X^{(m)} \sim p\left(X^{\text{mis}} \mid X^{\text{obs}}\right)$, we easily derive the Rubin's combining rule.

$$\begin{aligned} E\left(\beta \mid X^{\text{obs}}\right) &\approx \int \beta \frac{1}{M} \sum_{m=1}^{M} p\left(\beta \mid X^{(m)}, X^{\text{obs}}\right) \mathrm{d}\beta \\ &= \frac{1}{M} \sum_{m=1}^{M} E\left(\beta \mid X^{(m)}, X^{\text{obs}}\right) = \frac{1}{M} \sum_{m=1}^{M} \hat{\beta}^{(m)} \\ &=: \hat{\beta} \end{aligned} \tag{1}$$

$$\begin{aligned} \text{Var}\left(\beta \mid X^{\text{obs}}\right) &\approx \frac{1}{M} \sum_{m=1}^{M} V^{(m)} + \left(1 + \frac{1}{M}\right) \frac{1}{M-1} \sum_{m=1}^{M} \left(\hat{\beta}^{(m)} - \hat{\beta}\right)^2 \\ &= \bar{V} + \left(1 + \frac{1}{M}\right) B \\ &=: \text{var}(\hat{\beta}) \end{aligned} \tag{2}$$

Is Multiple Imputation Adequate in this Setting?

- For multiple imputation (MI) to be valid, we need several assumptions.
  1. **Missing at Random (MAR)** assumption
     $$\mathbb{P}(R = 1 \mid X, Z, \delta, T) = \mathbb{P}(R = 1 \mid Z, \delta, T)$$
     where R is missingness indicator and X is expensive covariate
  2. **Proper imputation** (Rubin, 1987)
  3. **Congeniality** (Meng, 1994) or **Compatibility** (Liu et al. 2014)
- Remember that the sampling designs rely on the failure indicator δ, and the failure time T.
- MAR assumption is met since the expensive covariate is missing by design!

What is Congeniality(Compatibility)?

Congeniality (Informal)

Analyst's model $P_A(\beta \mid X^{\text{com}})$ is **congenial** to imputer's model $P_I(X^{\text{mis}} \mid X^{\text{obs}})$ if:

1. $\mathrm{E}_A(\beta \mid X) = \hat{\beta}(X^{\text{com}}), \quad \mathrm{Var}_A(\beta \mid X) = \hat{V}(X^{\text{com}})$
2. $P_A(X^{\text{mis}} \mid X^{\text{obs}}) = P_I(X^{\text{mis}} \mid X^{\text{obs}})$

- A statistician can be the imputer and an epidemiologist can be the analyst.
- *Unconongeniality is generally "a rule not the exception".* (Xie & Meng, 2017)
- **Imputation model should be more general than the analysis model.**

MI Strategies for Sub-sample Study

- Keogh & White (2013) introduce two different imputation procedures.

  1. **Approximate Imputation Model**

  $$X = \theta_0 + \theta_Z^{\mathrm{T}} Z + \theta_\delta \delta + \theta_{\delta Z}^{\mathrm{T}} \delta Z + \theta_T \Lambda_{\text{base}}(T) + \theta_{ZT}^{\mathrm{T}} Z \Lambda_{\text{base}}(T) + \epsilon$$

  2. **Rejection Sampling**
     We add a rejection sampling step to the above imputation model.

- How should we construct the rejection rule?

  Target density

  $$f(X_j \mid \boldsymbol{X}_{-j}, Z, T, \delta) \propto f(T, \delta \mid X_j, \boldsymbol{X}_{-j}, Z, \beta) f(X_j \mid \boldsymbol{X}_{-j}, Z, \theta_j)$$

  Proposal density

  $$f(X_j \mid \boldsymbol{X}_{-j}, Z, \theta_j)$$

Rejection Sampling Method

- **Ratio of target density to proposal density**

$$\frac{f(T, \delta \mid X_j, \boldsymbol{X}_{-j}, Z, \beta) f(X_j \mid \boldsymbol{X}_{-j}, Z, \theta_j)}{f(X_j \mid \boldsymbol{X}_{-j}, Z, \theta)} = f(T, \delta \mid X_j, \boldsymbol{X}_{-j}, Z, \beta)$$
$$< c(T, \delta, \boldsymbol{X}_{-j}, Z, \beta)$$

- **Accept if,**

$$\begin{aligned} U &\leq \frac{f(T, \delta \mid X_j^*, \boldsymbol{X}_{-j}, Z, \beta)}{c(T, \delta, \boldsymbol{X}_{-j}, Z, \beta)} \\ &= \exp(-\Lambda_{\text{base}} e^{g(X_j^*, \boldsymbol{X}_{-j}, Z, \beta)}) \\ &= S^*(t) \end{aligned}$$

where $U \sim \text{Unif}(0, 1)$ and X_j^* is the imputed covariate.

Recent Work on MI for Sub-sample Study

- Borgan et al. (2023) proposed performing imputation only for the randomly selected **super-sample in order to reduce computational burden**.

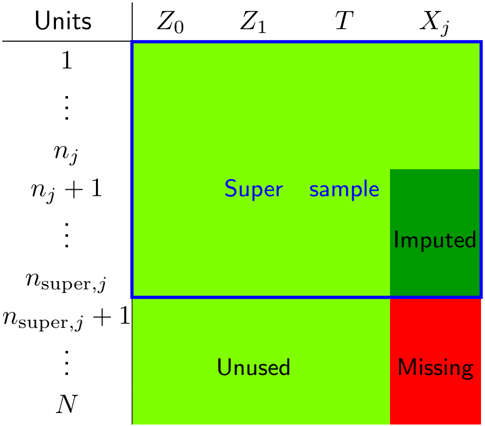


Table 4: Super-sample Weighted Analysis

Ongoing Work on MI for Sub-sample Study

- My current research extends the work of Borgan et al. (2023) by sampling units with **high influence** on both the estimator of interest($\hat{\beta}$) and the accuracy of imputation.

- Imputation Model Loss (Miao et al. 2021)

$$\mathcal{L}(\boldsymbol{X}, \boldsymbol{M}, \boldsymbol{\theta}) = \frac{1}{n} \sum_{i=1}^{n} \frac{\left(f_\theta(\boldsymbol{x}_i) - \boldsymbol{x}_i\right)^\top \operatorname{diag}(\boldsymbol{m}_i) \left(f_\theta(\boldsymbol{x}_i) - \boldsymbol{x}_i\right)}{2 \left\|\boldsymbol{m}_i\right\|_2^2}$$

- Influence Function for log hazard ratio (Reid & Crepeau, 1985)

$$\hat{\beta} - \beta = \frac{1}{N} \sum_{i=1}^{N} \mathrm{IF}_i + o_p(N^{-1/2}), \quad \operatorname{var}(\hat{\beta}) \approx \frac{1}{N^2} \sum_{i=1}^{N} \mathrm{IF}_i^2$$

- **Objective function:** $\operatorname{argmax}_{V_1, \ldots, V_{N-n}} (\sum_{i=1}^{N-n} V_i \, \mathrm{IF}_i^2 - \lambda \sum_{i=1}^{N-n} V_i)$ where V_i is a sampling indicator

Outline

Causal Interpretation of Hazard Ratio

- Why is hazard ratio (HR) difficult to causally interpret?
  1. HR may change over time.
  2. Period-specific HRs have **selection bias**.

$$\lambda_a(t) = \lim_{h \to 0} \frac{\Pr\left[t \leq T_i(a) < t + h \mid T_i(a) \geq t\right]}{h} \tag{3}$$

$$\mathrm{HR} = \frac{\lambda_1(t)}{\lambda_0(t)} = \lim_{h \to 0} \frac{\Pr\left[t \leq T_i(1) < t + h \mid {\color{red} T_i(1) \geq t}\right]}{\Pr\left[t \leq T_i(0) < t + h \mid {\color{blue} T_i(0) \geq t}\right]} \tag{4}$$

	$T(0) \geq t$	$T(0) < t$
$T(1) \geq t$	Always survivor	Protected
$T(1) < t$	Harmed	Never survivor

Table 5: Principal Strata at Time t

Marginal HR vs Conditional HR

- **Marginal HR**

$$\lambda(t) = \lambda_0(t)\exp(\beta_A A)$$

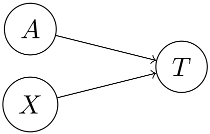
- **Conditional HR**

$$\lambda^\star(t) = \lambda_0^\star(t)\exp(\beta_A^\star A + \beta_X X)$$

- **Non-collapsibility**

$$\hat{\beta}_A \neq \hat{\beta}_A^\star$$

even if the following DAG is true:



where A is treatment and X is covariate, and T is survival time.

When does HR have causal interpretations?

Causal Proportional hazards assumption (Fay & Li, 2024)

$$\frac{\lambda_1(t)}{\lambda_0(t)} = \exp(\beta) \quad \forall t$$

- Under this assumption, the following holds,

$$\frac{\log S_1(t)}{\log S_0(t)} = \exp(\beta) \quad \forall t$$

- Hazard ratio, $\exp(\beta)$, is a **population-level causal estimand** if the proportional hazards assumption holds.

- Note that this assumption is different from the usual PH assumption,

$$\frac{\lambda(t \mid x+1)}{\lambda(t \mid x)} = \exp(\beta_x)$$

Causal Hazard Ratio

Causal HR (Martinussen et al. 2020)

$$\mathrm{HR}_{\text{causal}} = \frac{\lambda_1^*(t)}{\lambda_0^*(t)} = \lim_{h\to 0} \frac{\Pr\left[t \le T_i(1) < t+h \mid T_i(1) \ge t, T_i(0) \ge t\right]}{\Pr\left[t \le T_i(0) < t+h \mid T_i(1) \ge t, T_i(0) \ge t\right]}$$

- Causal HR is the ratio of instantaneous risk at t for always survivors.
- However, it is not nonparametrically identifiable without strong assumptions.

	$T(0) \ge t$	$T(0) < t$
$T(1) \ge t$	Always survivor	Protected
$T(1) < t$	Harmed	Never survivor

Table 6: Principal Strata at Time t

Conclusion of Hazard Ratio

- In practice, researchers should be cautious in interpreting hazard ratios causally.
- **Alternative causal estimands**:
  - Survival probability causal effect(SPCE) at time t (Mao et al. 2018):

$$\Delta^{SPCE}(t) = S_1(t) - S_0(t)$$

  - Restricted average causal effect (RACE):

$$\Delta^{RACE}(\tau) = \int_0^\tau S_1(t)dt - \int_0^\tau S_0(t)dt$$

- These can offer more robust causal interpretations, especially under non-proportional hazards.

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Thank you for your attention!