Comparison of multiple imputation methods for systematically and sporadically missing multilevel data

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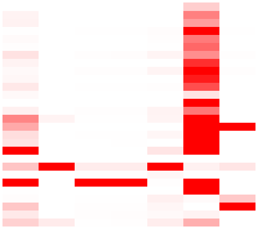
Motivation: GREAT data (Great Network, 2013)

- Risk factors associated with short-term mortality in acute heart failure
- 28 observational cohorts, 11685 patients, 2 **binary** and 8 **continuous** variables (patient characteristics and potential risk factors)
- sporadically and systematically **missing data**



Aim: explain the relationship between biomarkers (BNP, AFIB,...) and the left ventricular ejection fraction (LVEF)

$$y_{ik} = \mathbf{x}_{ik}\beta + \mathbf{z}_{ik}b_k + \varepsilon_{ik} \quad b_k \sim \mathcal{N}(0, \Psi) \qquad \varepsilon_{ik} \sim \mathcal{N}\left(0, \sigma^2\right)$$

$\hat{\beta}$ **and associated variability** $var\left(\widehat{\beta}\right)$

MI methods for multilevel data

Two standard ways to perform MI

- **Fully conditional specification** (FCS, MICE): a conditional imputation model for each variable
- **Joint modelling** (JM): a joint imputation model for all variables

Some MI methods to impute **multilevel data**

- FCS-2lnorm (van Buuren, 2010): continuous / sporadic
- **FCS-1step** (Jolani et al., 2015; Resche-Rigon et al., 2013): mixed / systematic
- **FCS-2step** (Resche-Rigon and White, 2016): mixed / systematic and sporadic
- JM-Pan (Schafer, 1997): continuous / systematic and sporadic
- **JM-jomo** (Quartagno and Carpenter, 2016): mixed / systematic and sporadic

However, only **FCS-1step**, **FCS-2step** and **JM-jomo** handle **systematically missing** values and **mixed data**

Continuous variables

Heteroscedastic mixed-effects model as **imputation model**

$$\begin{aligned} \mathbf{y}_{ik} &= \mathbf{x}_{ik}\beta + \mathbf{z}_{ik}b_k + \varepsilon_{ik} \\ b_k &\sim \mathcal{N}(0, \Psi) \\ \varepsilon_{ik} &\sim \mathcal{N}(0, \Sigma_k) \end{aligned}$$

Multiple imputation under this model

1. generating M sets of parameters $\theta_m = (\beta^m, \Psi^m, \Sigma_k^m)$
2. imputing the data according each set θ_m
   - draw $b_k^m | \mathbf{y}_k^{obs}, \theta_m$
   - draw $\mathbf{y}_{ik}^{miss} | \theta_m, b_k^m$

Specific issues

1. how to generate Σ_k without $\mathbf{y}_{ik}$? (systematic)
2. how to draw b_k^m without $\mathbf{y}_{ik}$ (systematic) or given $\mathbf{y}_{ik}$ (sporadic)?

FCS-1step (Jolani et al., 2015)

Conditional imputation models

$$y_{ik} = \mathbf{x}_{ik}\beta + \mathbf{z}_{ik} b_k + \varepsilon_{ik} \quad b_k \sim \mathcal{N}(0, \Psi) \quad \varepsilon_{ik} \sim \mathcal{N}(0, \sigma^2)$$

For each incomplete variable

1. generate $\theta_m = (\beta_m, \Psi_m, {\sigma^2}_m) \qquad 1 \leq m \leq M$
    - estimate θ and $var\left(\widehat{\theta}\right)$ by REML
    - draw θ_m from an appropriate distribution with expectation $\widehat{\theta}$, and variance $\widehat{var}\left(\widehat{\theta}\right)$
2. impute in each cluster k with systematically missing data
    - draw $b_k \sim \mathcal{N}(0, \Psi_m)$
    - impute data according to the imputation model

FCS-1step (Jolani et al., 2015)

Conditional imputation models

$$y_{ik} = \mathbf{x}_{ik}\beta + \mathbf{z}_{ik}b_k + \varepsilon_{ik} \quad b_k \sim \mathcal{N}(0, \Psi) \quad \varepsilon_{ik} \sim \mathcal{N}(0, \sigma^2)$$

For each incomplete variable

1. generate $\theta_m = (\beta_m, \Psi_m, {\sigma^2}_m) \qquad 1 \leq m \leq M$
   - estimate θ and $var\left(\widehat{\theta}\right)$ by REML
   - draw θ_m from an appropriate distribution with expectation $\widehat{\theta}$, and variance $\widehat{var}\left(\widehat{\theta}\right)$
2. impute in each cluster k with **sporadically missing data**
   - draw $b_k \sim \mathcal{N}\left(\mu_{b_k|y_k}, \Psi_{b_k|y_k}\right)$
   - impute data according to the imputation model

FCS-2step (Resche-Rigon and White, 2016)

Conditional imputation models

$$y_{ik} = \mathbf{x}_{ik}\beta_k + \varepsilon_{ik} \qquad \beta_k = \beta + b_k \qquad b_k \sim \mathcal{N}(0, \Psi) \qquad \varepsilon_{ik} \sim \mathcal{N}\left(0, \sigma_k^2\right)$$

→ **the same imputation model, with heteroscedastic assumption**

1. generate $\theta_m = \left(\beta_m, \Psi_m, \left(\sigma_1^2, \ldots, \sigma_K^2\right)_m\right)$
   - estimate θ and $var\left(\widehat{\theta}\right)$ by **a two-step estimator**:

     step a fit $y_{ik} = \mathbf{x}_{ik}\beta_k + \varepsilon_{ik}$ to each cluster

     step b combine the $\widehat{\beta}_k$ and $\widehat{\sigma}_k^2$ by multivariate meta-analysis (by REML or MM)
   - draw θ_m from an appropriate distribution with expectation $\widehat{\theta}$, and variance $\widehat{var}\left(\widehat{\theta}\right)$
2. impute in each cluster k
   - draw $b_k \sim \mathcal{N}\left(\mu_{b_k|y_k}, \Psi_{b_k|y_k}\right)$
   - impute data according to the imputation model

JM-jomo (Quartagno and Carpenter, 2016)

$$\mathbf{y_{ik}} = \mathbf{x}_{ik}\beta + \mathbf{z}_{ik} b_k + \varepsilon_{ik} \qquad b_k \sim \mathcal{N}(0, \Psi) \qquad \varepsilon_{ik} \sim \mathcal{N}(0, \Sigma_k)$$

1. Bayesian formulation to generate $\theta_m = (\beta_m, \Psi_m, \Sigma_m)_{1 \leq m \leq M}$
   - prior: $\Sigma_k^{-1} \sim W(\nu_1, \Lambda_1)$, $\Psi^{-1} \sim W(\nu_2, \Lambda_2)$, $\beta \propto 1$
   - posterior: unknown $\rightarrow$ **Gibbs sampler**

$$\begin{aligned}
\beta^{(\ell+1)} &\sim P\left(\beta | X^{obs}, X^{miss\,(\ell)}, \Sigma^{(\ell)}, b^{(\ell)}\right)\\
b_k^{(\ell+1)} &\sim P\left(b_k | X^{obs}, X^{miss\,(\ell)}, \beta^{(\ell+1)}, \Psi^{(\ell)}, \Sigma_k^{(\ell)}\right)\\
\Psi^{-1\,(\ell+1)} &\sim P\left(\Psi^{-1} | X^{obs}, X^{miss\,(\ell)}, b^{(\ell+1)}\right)\\
\Sigma_k^{-1\,(\ell+1)} &\sim P\left(\Sigma_k^{-1} | X^{obs}, X^{miss\,(\ell)}, b_k^{(\ell+1)}\right)\\
X_k^{miss\,(\ell+1)} &\sim P\left(X_k^{miss} | X^{obs}, \beta^{(\ell+1)}, \Psi^{(\ell+1)}, \Sigma^{(\ell+1)}, b_k^{(\ell+1)}\right)
\end{aligned}$$

2. Imputation (given by step 1)

Binary variables

- **FCS-1step** (Jolani et al., 2015)
    - fit a logistic model with mixed effect to all clusters

  $\rightarrow$ sporadically missing values not handled

- **FCS-2step** (Resche-Rigon and White, 2016)
    - fit a logistic model with fixed effect to each cluster
    - combine estimates using a meta-analysis

  $\rightarrow$ large clusters are required

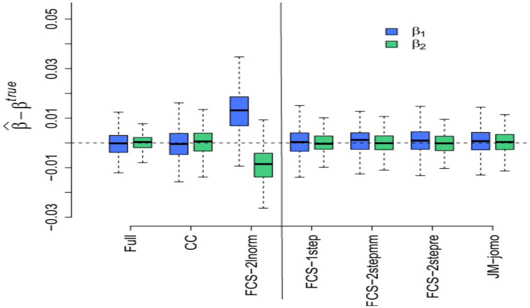
- **JM-jomo** (Quartagno and Carpenter, 2016)
    - draw latent normal variables
    - derive categories

  $\rightarrow$ more time consuming

Simulation design

- **Data generation**: 500 incomplete data sets are independently simulated ($n = 11685$, $K = 28$, $18 \leq n_k \leq 1834$)
  - $y_{ik} = \beta^0 + \beta^1 \mathbf{x}_{ik}^{(1)} + \beta^2 \mathbf{x}_{ik}^{(2)} + b_k^0 + b_k^1 \mathbf{x}_{ik}^{(1)} + \varepsilon_{ik}$
    with $\beta = (.72, .11, .03)$, $\Psi = \begin{bmatrix} .0077 & .0015 \\ .0015 & .0004 \end{bmatrix}$, $\sigma = .15$
  - $\mathbf{x}_{ik}^{(1)} : \mathcal{N}\left(\mu + \mu_k, .36\right)$
  - $\mathbf{x}_{ik}^{(2)} : logit\left(P\left(\mathbf{x}_{ik}^{(2)} = 1\right)\right) = \nu + \nu_k$
  - add missing values on $\mathbf{x}^{(1)}, \mathbf{x}^{(2)}$ varying π_{syst} and π_{spor}
- **Analysis**: β and $var\left(\widehat{\beta}\right)$ estimated by applying MI methods using $M = 5$ imputed arrays
- **Criteria**: bias, rmse, variance estimate, coverage

Results: $\pi_{syst} = .1$, $\pi_{spor} = .375$



Method	$\sqrt{\widehat{var}\left(\widehat{\beta}\right)}$		$\sqrt{var\left(\widehat{\beta}\right)}$		95% Cover		Time (min)
	β_1	β_2	β_1	β_2	β_1	β_2	
Full	0.0047	0.0029	0.0048	0.0030	93.8	94.2	
CC	0.0063	0.0052	0.0066	0.0053	90.4	93.4	
FCS-2lnorm	0.0086	0.0044	0.0086	0.0068	71.8	57.0	2.078
FCS-1step	0.0050	0.0044	0.0055	0.0043	91.6	95.4	82.722
FCS-2step-mm	0.0055	0.0047	0.0055	0.0042	94.2	95.5	0.77
FCS-2step-re	0.0056	0.0045	0.0056	0.0042	93.2	95.9	1.835
JM-jomo	0.0059	0.0053	0.0054	0.0043	95.8	96.0	6.3

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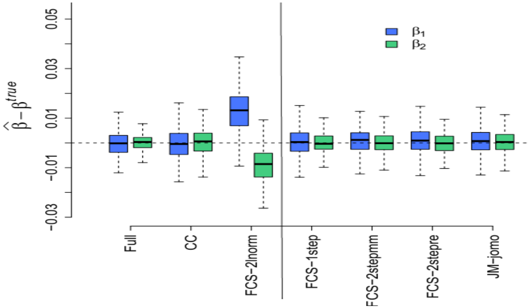

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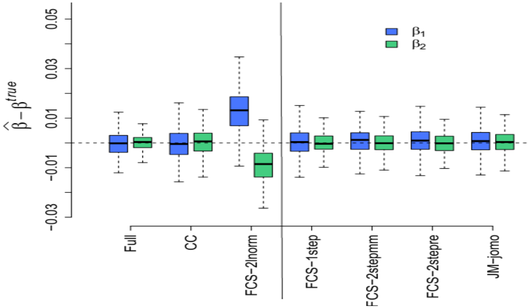

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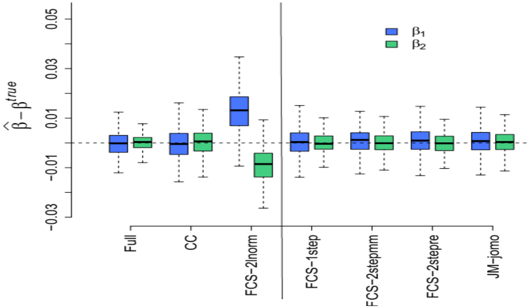

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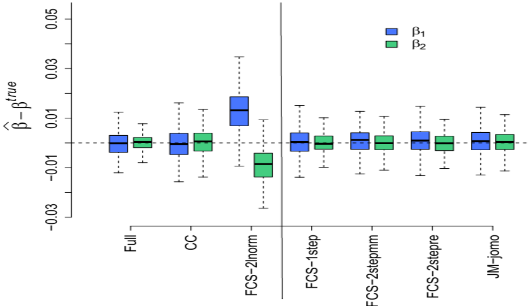

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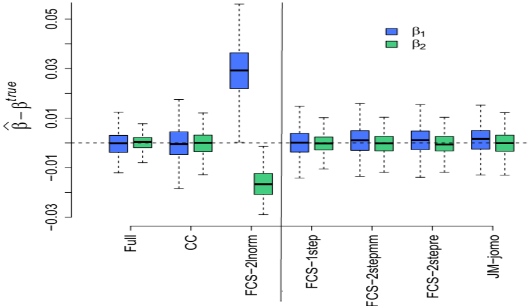
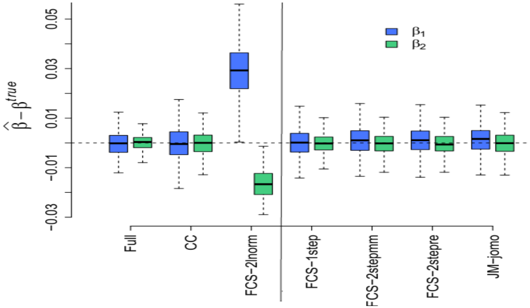
FCS-2step-re	0.0056	0.0045	0.0056	0.0042	93.2	95.9	1.835
JM-jomo	0.0059	0.0053	0.0054	0.0043	**95.8**	**96.0**	6.3

Results: $\pi_{syst} = .25, \pi_{spor} = .25$



Method	$\sqrt{\widehat{var}\left(\widehat{\beta}\right)}$		$\sqrt{var\left(\widehat{\beta}\right)}$		95% Cover		Time (min)
	β_1	β_2	β_1	β_2	β_1	β_2	
Full	0.0047	0.0029	0.0048	0.0030	93.8	94.2	
CC	0.0070	0.0053	0.0071	0.0053	92.2	94.4	
FCS-2lnorm	0.0105	0.0038	0.0106	0.0058	19.8	11.8	1.967
FCS-1step	0.0049	0.0046	0.0056	0.0043	**90.4**	96.8	63.43
FCS-2step-mm	0.0059	0.0054	0.0058	0.0044	95.0	97.0	0.538
FCS-2step-re	0.0059	0.0049	0.0058	0.0044	95.0	96.2	1.304
JM-jomo	0.0066	0.0069	0.0057	0.0050	**96.8**	**97.6**	6.739

Results: $\pi_{syst} = .25, \pi_{spor} = .25$



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FCS-1step	0.0049	0.0046	0.0056	0.0043	90.4	96.8	**63.43**
FCS-2step-mm	0.0059	0.0054	0.0058	0.0044	95.0	97.0	**0.538**
FCS-2step-re	0.0059	0.0049	0.0058	0.0044	95.0	96.2	**1.304**
JM-jomo	0.0066	0.0069	0.0057	0.0050	96.8	97.6	**6.739**

Conclusion

An overview of MI methods for multilevel mixed data

- standard methods are irrelevant
- FCS-1step, FSC-2step and JM-jomo all appear to perform well
- inference performances are quite similar
- FCS-2step is quicker to perform

Perspectives

- a larger simulation study (MAR mechanism, number of clusters, size of clusters,...)
- a precise guidance

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