EP16: Missing Values in Clinical Research: Multiple Imputation

10. Requirements for MICE to work (well)

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Joint and Conditional Distributions

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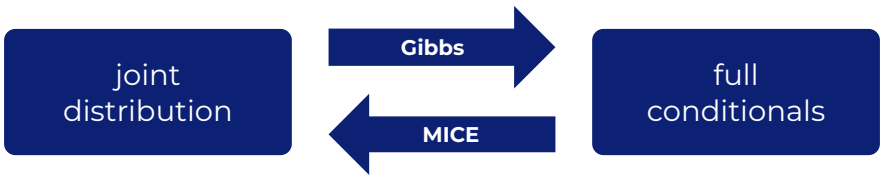
Gibbs sampling exploits the fact that a joint distribution is fully determined by its full conditional distributions.



In MICE, the full conditionals are not derived from the joint distribution: we directly specify the full conditionals and hope a joint distribution exists.

Joint and Conditional Distributions

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However, as we have seen in the examples on the previous slides, there are **settings where the direct specification** of the full conditionals/imputation models **may lead to problems**, causing biased results.

Some Conditions and Definitions

Two important definitions:

Compatibility:

A joint distribution exists, that has the full conditionals (imputation models) as its conditional distributions.

Congeniality:

The imputation model is compatible with the analysis model.

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- **All relevant variables** need to be included. (Omission might result in MNAR.)
- **The outcome needs to be included** as predictor variable (but we usually do not impute missing outcome values).
- The imputation models (and analysis model) need to be **correctly specified** (which is a requirement in any standard analysis).

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Omission, or inadequate inclusion, of the outcome may result in **MNAR** missing mechanisms. The same is the case when other relevant predictor variables are not used as predictor variables in the imputation.

Furthermore, **omission of variables** may lead to **mis-specified models**, however, models may also be mis-specified when all relevant covariates are included, but **distributional assumptions** or the specified **form of associations** are incorrect.

Alternatives to MICE

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Problem:
The joint distribution may not be of any known form:

$$\begin{array}{l} x_1 \sim N(\mu_1, \sigma_1^2) \\ x_2 \sim N(\mu_2, \sigma_2^2) \end{array} \quad \Rightarrow \quad \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} \sim N\left(\begin{bmatrix} \mu_1 \\ \mu_2 \end{bmatrix}, \begin{bmatrix} \sigma_1^2 & \sigma_{12} \\ \sigma_{12} & \sigma_2^2 \end{bmatrix} \right)$$

but $$\begin{array}{l} x_1 \sim N(\mu_1, \sigma_1^2) \\ x_2 \sim Bin(\mu_2) \end{array} \quad \Rightarrow \quad \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} \sim ???$$

Alternatives to MICE

Possible approaches:

Approach 1: **Multivariate Normal Model**
Approximate the joint distribution by a known multivariate distribution.

(usually the normal distribution; this is the approach mentioned in Section 01)

Approach 2: **Sequential Factorization**
Factorize the joint distribution into a (sequence of) conditional and a marginal distributions.

Multivariate Normal Model

Assumption:
The outcome and incomplete variables follow a **joint multivariate normal distribution**, conditional on the completely observed covariates $\mathbf{X}_c$, parameters $\boldsymbol{\theta}$ and, possibly, random effects, $\mathbf{b}$:

$$p(\mathbf{y}, \mathbf{x}_1, \ldots, \mathbf{x}_p \mid \mathbf{X}_c, \boldsymbol{\theta}, \mathbf{b}) \sim N(\boldsymbol{\mu}, \Sigma)$$

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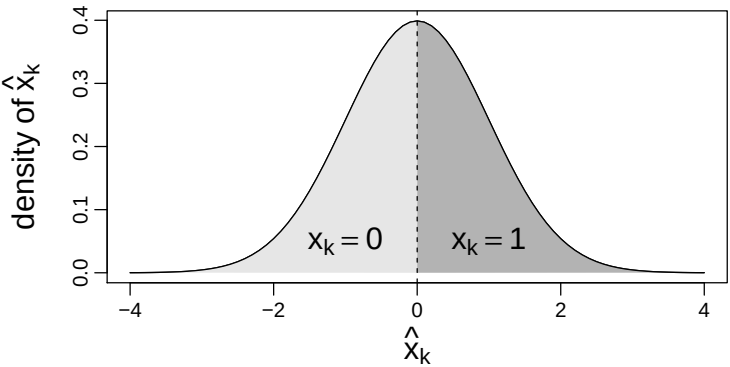
How do we get that multivariate normal distribution?

1. Assume **all** incomplete variables and the outcome are **(latent) normal**.
2. Specify linear (mixed) **models based on observed covariates**.
3. **Connect** using multivariate normal for **random effects & error terms**.

Multivariate Normal Model

1. Latent normal assumption:

e.g.: $\mathbf{x}_k$ binary $\rightarrow$ latent $\hat{\mathbf{x}}_{\boldsymbol{k}}$ is standard normal: $\begin{cases} \mathbf{x}_k = 1 & \text{if } \hat{\mathbf{x}}_{\boldsymbol{k}} \geq 0 \\ \mathbf{x}_k = 0 & \text{if } \hat{\mathbf{x}}_{\boldsymbol{k}} < 0 \end{cases}$



Multivariate Normal Model

2. Specify models:

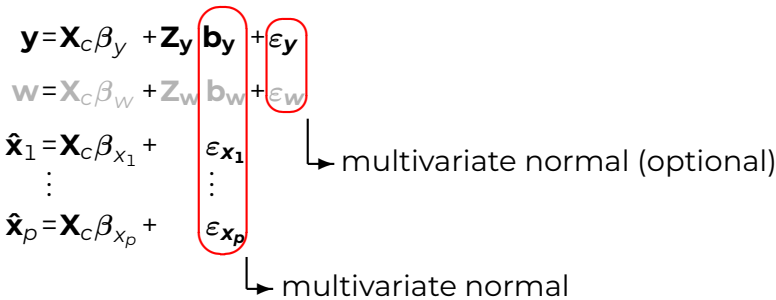
$$\mathbf{y} = \mathbf{X}_c\beta_y + \mathbf{Z_y}\,\mathbf{b_y} + \varepsilon_{\boldsymbol{y}}$$

$$\mathbf{w} = \mathbf{X}_c\beta_w + \mathbf{Z_w}\,\mathbf{b_w} + \varepsilon_{\boldsymbol{w}}$$

$$\begin{aligned} \hat{\mathbf{x}}_1 &= \mathbf{X}_c\beta_{x_1} + \varepsilon_{\boldsymbol{x_1}} \\ &\vdots \qquad\qquad \vdots \\ \hat{\mathbf{x}}_p &= \mathbf{X}_c\beta_{x_p} + \varepsilon_{\boldsymbol{x_p}} \end{aligned}$$

Multivariate Normal Model

2. Specify models / 3. Connect random effects & error terms:



Multivariate Normal Model

Advantages:

- easy to specify
- relatively easy to implement
- relatively easy to sample from
- works for longitudinal outcomes

Disadvantages:

- assumes linear associations

Imputation with **non-linear associations** or **survival data** is possible with **extensions** of the multivariate normal approach.

Sequential Factorization

The **joint distribution** of two variables y and x can be written as the product of conditional distributions:

$$p(y, x) = p(y \mid x)\, p(x)$$

(or alternatively $p(y, x) = p(x \mid y)\, p(y)$)

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This can easily be **extended for more variables**:

$$p(y, x_1, \ldots, x_p, X_c) = \underbrace{p(y \mid x_1, \ldots, x_p, X_c)}_{\text{analysis model}}\, p(x_1 \mid x_2, \ldots, x_p, X_c)\ \ldots\ p(x_p \mid X_c)$$

where $x_1, \ldots, x_p$ denote incomplete covariates and X_c contains all completely observed covariates.

Sequential Factorization

The **analysis model** is part of the specification of the joint distribution.

- ➡ The **outcome**
  - is **automatically included in the imputation** procedure
  - does not appear in any of the predictors of the imputation models:
  - ➡ **no need to approximate/summarize** complex outcomes!

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Since the joint distribution usually does not have a known form, Gibbs sampling is used to estimate parameters and sample imputed values.

Sequential Factorization

Advantages:

- **flexible:**
  - any outcome type
  - separate imputation models per variable
- can handle **non-linear associations** and interactions
- assures **congeniality and compatibility**

Disadvantages:

- specification takes requires time and consideration
- sampling may be more **computationally intensive**

Some Relevant R Packages

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For complex settings there are alternatives to **mice**:

For example the R packages **JointAI**, **smcfcs** and **jomo**.

- they use **Bayesian methodology** to impute values
- **jomo** and **smcfcs** perform **multiple imputation**;
  the imputed datasets that can then be analysed the same way data imputed by **mice** would be analysed.
- **JointAI** works **fully Bayesian**
  - performs analysis and imputation simultaneously
  - ➡ results from the analysis model of interest are obtained directly

R package smcfcs

Substantive Model Compatible Fully Conditional Specification, a hybrid approach between FCS and sequential factorization (Bartlett et al. 2015)

smcfcs (version 1.5.0) can impute incomplete covariates in

- linear regression
- logistic regression
- poisson regression
- Weibull survival models
- Cox proportional hazard models
- competing risk survival models
- nested case control studies
- case cohort studies

while ensuring compatibility between analysis model and imputation models.

For more information see the help files and the vignette.

R Package jomo

JOint MOdel imputation using the multivariate normal approach, with **extensions to assure compatibility** between analysis and imputation models. (Carpenter and Kenward 2012)

jomo (version 2.7-2) can handle

- linear regression
- generalized linear regression
- proportional odds (ordinal) probit regression
- linear mixed models
- generalized linear mixed models
- (ordinal) cumulative link mixed models
- Cox proportional hazards models.

For more info see the help file.

R Package JointAI

Joint Analysis and Imputation,
uses the **sequential factorization approach** to perform simultaneous analysis and imputation. (Erler et al. 2016, 2019)

JointAI (version 1.0.2) can analyse incomplete data using

- linear regression
- generalized linear regression
- linear mixed models
- generalized linear mixed models
- (ordinal) cumulative logit regression
- (ordinal) cumulative logit mixed models
- parametric (Weibull) survival models
- Cox proportional hazards models

while assuring compatibility between analysis model and imputation models when non-linear functions or interactions are included.

R Package JointAI

The necessary **Gibbs sampling** is performed using **JAGS** (an external program), which is free, but needs to be installed from https://sourceforge.net/projects/mcmc-jags/files/.

JointAI can be installed from CRAN or GitHub (development version containing bug fixes and other improvements)

```
install.packages("devtools")
devtools::install_github("NErler/JointAI")
```

JointAI has its own web page (https://nerler.github.io/JointAI/) with several vignettes on Visualization of Incomplete Data, a Minimal Example, details on Model Specification, etc.

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