Missing Values in Clinical Research (EP16)

Multiple Imputation

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Outline

Part I: Multiple Imputation

- How does multiple imputation work?
- How does MICE/FCS work?
  ➡ A look into the black box
- Understanding sources of uncertainty
- The 3 steps of multiple imputation

Part II: Multiple Imputation Workflow

How to perform MI with the **mice** package in R, from getting to know the data to the final results.

Practical: imputation with **mice**

Outline (cont.)

Part III: When MICE might fail

Introduction to

- settings where standard use of **mice** is problematic
- alternative imputation approaches
- alternative R packages

Practical: imputation in complex settings

Part IV: Multiple Imputation Strategies

Some tips & tricks

Part I
Multiple Imputation

Outline of Part I

- Developed by **Donald B. Rubin** in the 1970s,
- to handle missing values in **public use databases**, e.g., census data provided by the government,
- motivated by the **increase in missing values**, and
- increased **availability of computers**.

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Such data should be usable by [11]

- a **large number of analysts**, who commonly have to rely on
- standard **software that can only handle complete data**, and usually
- are **not experts in handling incomplete data**.

Rubin's thoughts: [12]

One imputed value can not be correct in general.
➡ We need to represent missing values by a **number of imputations**.

To find **sensible values** to fill in, we need some kind of **model**.

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This **distribution depends on assumptions** that have been made about the model.

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Missing data has a distribution.

This **distribution depends on assumptions** that have been made about the model.

What we want to impute is the
'predictive distribution' of the missing values given the observed values.

How to obtain that predictive distribution?

Rubin suggests to

- fit a model to the observed data ("respondents"), and to
- obtain for each "nonrespondent" the conditional distribution of the missing data (given the observed data) as if he/she was a respondent.

➡ We assume nonrespondents are just like respondents, and obtain the predictive distribution from the model of the respondents data.

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Example: survey about age, gender and height

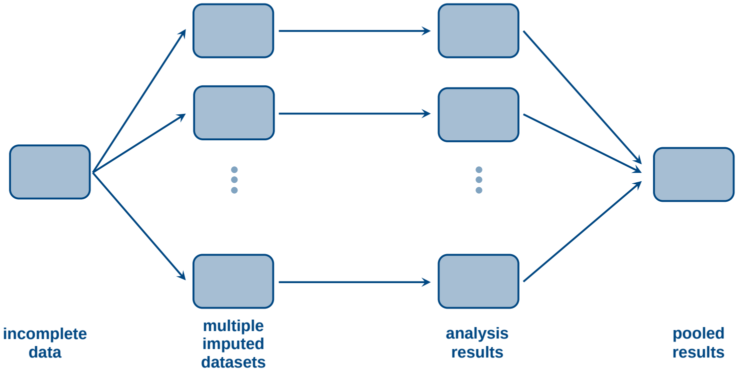
Boys aged 10 – 12 years old answered (on average) that they are 1.45m tall.
➡ We assume that boys aged 10 to 12 who did not report their height are also around 1.45m tall.

How to represent the multiple imputed values?

For each missing value, we now have multiple imputed values.

- For each set of imputed values, create a dataset
  (those datasets agree in the observed values but imputed values differ).
- Analyse each dataset, and
- take the results from each analysis.

➡ We can describe how (much) the **results vary between the imputed datasets**, and calculate summary measures.



In summary:

1. **Imputation:** impute multiple times ➡ multiple completed datasets
2. **Analysis:** analyse each of the datasets
3. **Pooling:** combine results, taking into account additional uncertainty

How can we actually get imputed values?

For now: assume only one continuous variable has missing values (**univariate missing data**)

X_1	X_2	X_3	X_4
✓	NA	✓	✓
✓	✓	✓	✓
✓	NA	✓	✓
⋮	⋮	⋮	⋮

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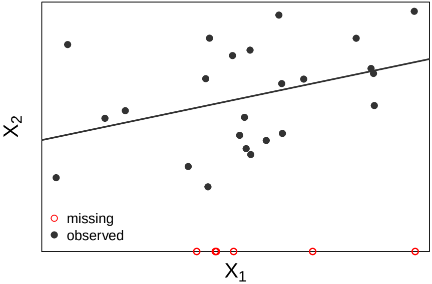
Idea: Predict values

Model:

$$x_{i2} = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i3} + \beta_3 x_{i4} + \varepsilon_i$$



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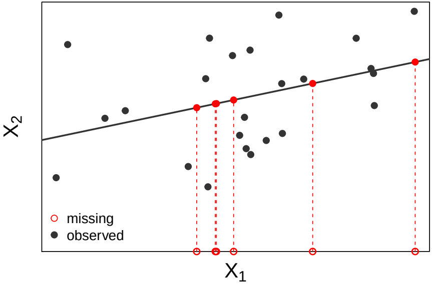
Idea: Predict values

Model:
$x_{i2} = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i3} + \beta_3 x_{i4} + \varepsilon_i$

Imputed/predicted value:
$\hat{x}_{i2} = \hat{\beta}_0 + \hat{\beta}_1 x_{i1} + \hat{\beta}_2 x_{i3} + \hat{\beta}_3 x_{i4}$



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- The predicted values do not take into account the added **uncertainty** due to the missing values.

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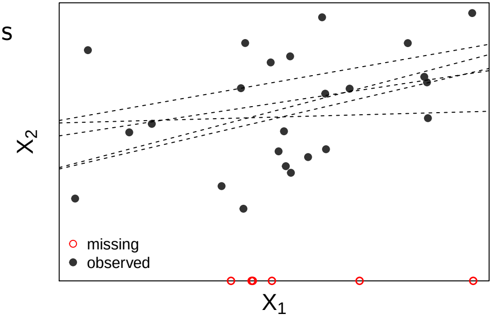
➡ We need to take into account **two sources of uncertainty**:

- The **parameters** are estimated with **uncertainty** (represented by the std. error).
- There is **random variation / prediction error** (variation of the residuals).

Taking into account uncertainty about the parameters β:
We assume that β **has a distribution**, and we can sample realizations of β from that distribution.

When plugging the different realizations of β into the predictive model, we obtain **slightly different regression lines**.



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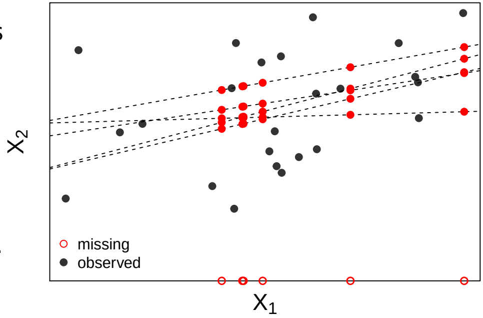
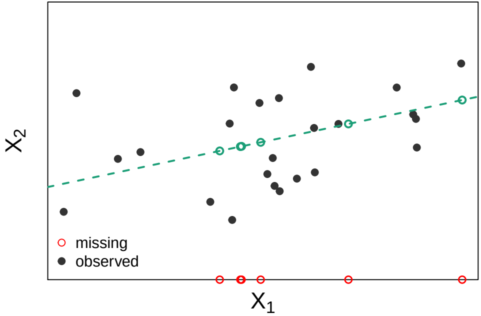
With each set of coefficients, we also get slightly **different predicted values**.



Taking into account the prediction error:
The model does not fit the data perfectly: observations are scattered around the regression lines.

We assume that the **data have a distribution**, where

- the **mean** for each value is given by the **predictive model**, and



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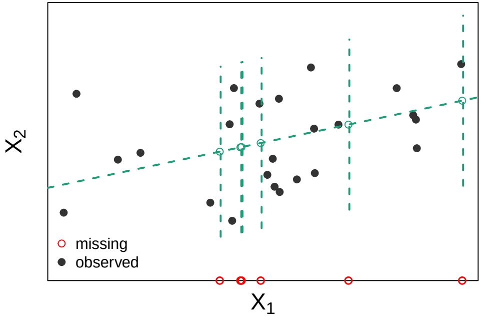

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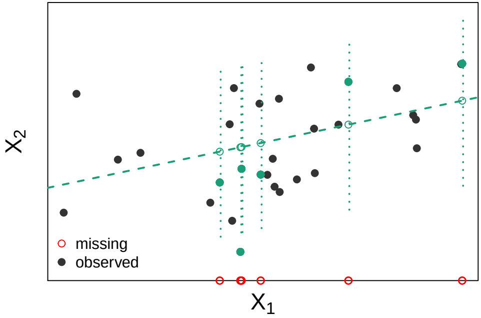

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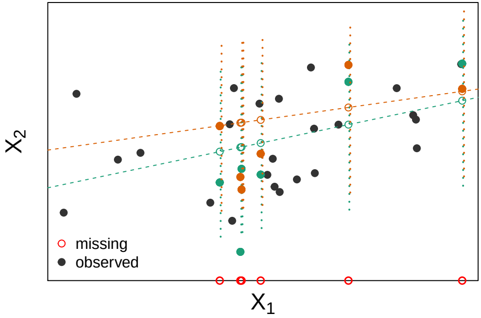

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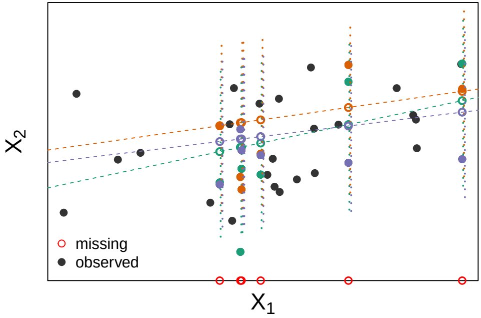

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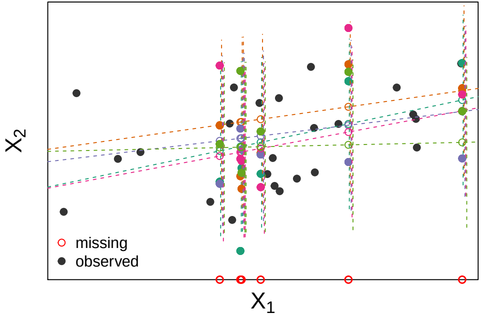

In the end, we obtain one imputed dataset for each color.

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What if we have **missing values in more than one variable**?

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In case of **monotone missing values** we can use the technique for univariate missing data in a chain:
impute x_4 given x_1
impute x_3 given x_1 and x_4
impute x_2 given x_1, x_4 and x_3

X_1	X_2	X_3	X_4
✓	NA	✓	✓
✓	NA	NA	✓
✓	NA	NA	NA
⋮	⋮	⋮	⋮

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X_1	X_2	X_3	X_4
✓	NA	✓	✓
✓	NA	NA	✓
✓	NA	NA	NA
⋮	⋮	⋮	⋮

When we have **non-monotone missing data** there is no sequence without conditioning on unobserved values.

X_1	X_2	X_3	X_4
✓	NA	✓	✓
NA	✓	NA	NA
✓	NA	✓	NA
⋮	⋮	⋮	⋮

There are **two popular approaches** for the imputation step in **multivariate non-monotone** missing data:

Fully conditional specification

- Multiple Imputation using Chained Equations (**MICE**)
- sometimes also: sequential regression
- Implemented in SPSS, R, Stata, SAS, ...
- our focus here

There are **two popular approaches** for the imputation step in **multivariate non-monotone** missing data:

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- our focus here

Joint model imputation

(more details later)

Markov Chain Monte Carlo
is a technique to **draw samples from a complex probability distribution** by creating a chain of random variables (a Markov Chain). The distribution each element in the chain is sampled from depends on the value of the previous element. When certain conditions are met, the chain eventually stabilizes and by continuing to sample elements of the chain a sample from the complex distribution of interest can be obtained.

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Gibbs sampling
is an MCMC method where a **sample from a multivariate distribution** is obtained by repeatedly drawing from each of the univariate full conditional distributions instead.

MICE (**M**ultiple **I**mputation using **C**hained **E**quations) or
FCS (multiple imputation using **F**ully **C**onditional **S**pecification)

extends univariable imputation to the setting with multivariate non-monotone missingness:

MICE/FCS

- imputes multivariate missing data on a variable-by-variable basis,
- using the technique for univariable missing data.

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- imputes multivariate missing data on a variable-by-variable basis,
- using the technique for univariable missing data.

Moreover, MICE/FCS is

- an iterative procedure, specifically
- a Markov Chain Monte Carlo (MCMC) method,
- uses the idea of the Gibbs sampler, and
- is a Gibbs sampler if the conditional distributions are compatible (we will come back to this)

Notation

- X: $n \times p$ data matrix with n rows and p variables $x_1, \ldots, x_p$
- R: $n \times p$ missing indicator matrix containing 0 (missing) or 1 (observed)

$$\begin{array}{cc} & \begin{array}{cccc} X_{-2} & X_2 & & X_{-2} \end{array} \\ \boldsymbol{X} = & \left| \begin{array}{cccc} x_{1,1} & x_{1,2} & \ldots & x_{1,p} \\ x_{2,1} & x_{2,2} & \ldots & x_{2,p} \\ \vdots & \vdots & \ddots & \vdots \\ x_{n,1} & x_{n,2} & \ldots & x_{n,p} \end{array} \right| \end{array} \qquad \boldsymbol{R} = \left| \begin{array}{cccc} R_{1,1} & R_{1,2} & \ldots & R_{1,p} \\ R_{2,1} & R_{2,2} & \ldots & R_{2,p} \\ \vdots & \vdots & \ddots & \vdots \\ R_{n,1} & R_{n,2} & \ldots & R_{n,p} \end{array} \right|$$

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$$
\begin{array}{cccccc}
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\boldsymbol{X} = & \left[\begin{array}{c} x_{1,1} \\ x_{2,1} \\ \vdots \\ x_{n,1} \end{array}\right. & \begin{array}{c} x_{1,2} \\ x_{2,2} \\ \vdots \\ x_{n,2} \end{array} & \begin{array}{c} \cdots \\ \cdots \\ \ddots \\ \cdots \end{array} & \left.\begin{array}{c} x_{1,p} \\ x_{2,p} \\ \vdots \\ x_{n,p} \end{array}\right]
\end{array}
\qquad
\boldsymbol{R} = \begin{bmatrix} R_{1,1} & R_{1,2} & \cdots & R_{1,p} \\ R_{2,1} & R_{2,2} & \cdots & R_{2,p} \\ \vdots & \vdots & \ddots & \vdots \\ R_{n,1} & R_{n,2} & \cdots & R_{n,p} \end{bmatrix}
$$

For example:

$$
\boldsymbol{X} = \begin{array}{cccc}
X_1 & X_2 & X_3 & X_4 \\
\hline
\checkmark & \text{NA} & \checkmark & \checkmark \\
\checkmark & \checkmark & \text{NA} & \text{NA} \\
\checkmark & \text{NA} & \checkmark & \text{NA}
\end{array}
\qquad \Rightarrow \boldsymbol{R} = \begin{bmatrix} 1 & 0 & 1 & 1 \\ 1 & 1 & 0 & 0 \\ 1 & 0 & 1 & 0 \end{bmatrix}
$$

Algorithm 1 MICE algorithm [17] for **one** imputed dataset

1: **for** j in $1, \dots, p$: ▷ Setup
2: Specify imputation model for variable X_j
$p(X_j^{mis} \mid X_j^{obs}, X_{-j}, R)$
3: Fill in starting imputations $\dot{X}_j^0$ by random draws from X_j^{obs}.
4: **end for**

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```
for j in 1, ..., p:                                              ▷ Setup
    Specify imputation model for variable X_j
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    Fill in starting imputations Ẋ_j^0 by random draws from X_j^obs.
end for

for t in 1, ..., T:                            ▷ loop through iterations
    for j in 1, ..., p:                         ▷ loop through variables




    end for
end for
```

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  - Specify imputation model for variable X_j $p(X_j^{mis} \mid X_j^{obs}, X_{-j}, R)$
  - Fill in starting imputations $\dot{X}_j^0$ by random draws from X_j^{obs}.
- **end for**
- **for** t in $1, \ldots, T$: ▷ loop through iterations
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  - **end for**
- **end for**

2. Imputation step
2.3. FCS/MICE

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    Fill in starting imputations $\dot{X}_j^0$ by random draws from X_j^{obs}.
end for

for t in $1, \dots, T$: ▷ loop through iterations
    for j in $1, \dots, p$: ▷ loop through variables
        Define currently complete data except X_j
        $\dot{X}_{-j}^t = \left(\dot{X}_1^t, \dots, \dot{X}_{j-1}^t, \dot{X}_{j+1}^{t-1}, \dots, \dot{X}_p^{t-1}\right)$.
    end for
end for

Algorithm 1 MICE algorithm [17] for **one** imputed dataset

```
for j in 1, ..., p:                                                        ▷ Setup
    Specify imputation model for variable X_j
    p(X_j^mis | X_j^obs, X_{-j}, R)
    Fill in starting imputations Ẋ_j^0 by random draws from X_j^obs.
end for

for t in 1, ..., T:                                     ▷ loop through iterations
    for j in 1, ..., p:                                  ▷ loop through variables
        Define currently complete data except X_j
        Ẋ_{-j}^t = (Ẋ_1^t, ..., Ẋ_{j-1}^t, Ẋ_{j+1}^{t-1}, ..., Ẋ_p^{t-1}).
        Draw parameters θ̇_j^t ~ p(θ_j^t | X_j^obs, Ẋ_{-j}^t, R).

    end for
end for
```

Where:

$p(X_j^{mis} \mid X_j^{obs}, X_{-j}, R)$

$\dot{X}_j^0$, X_j^{obs}

$\dot{X}_{-j}^t = \left(\dot{X}_1^t, \ldots, \dot{X}_{j-1}^t, \dot{X}_{j+1}^{t-1}, \ldots, \dot{X}_p^{t-1}\right).$

$\dot{\theta}_j^t \sim p(\theta_j^t \mid X_j^{obs}, \dot{X}_{-j}^t, R).$

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        Draw parameters $\dot{\theta}_j^t \sim p(\theta_j^t \mid X_j^{obs}, \dot{X}_{-j}^t, R)$.
        Draw imputations $\dot{X}_j^t \sim P(X_j^{mis} \mid \dot{X}_{-j}^t, R, \dot{\theta}_j^t)$.
    end for
end for

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    Fill in starting imputations $\dot{X}_j^0$ by random draws from X_j^{obs}.
end for

for $t = 1$: ▷ loop through iterations
    for $j = 1$: ▷ loop through variables
        Define currently complete data except X_1
        $\dot{X}_{-1}^1 = \left(\dot{X}_2^0, \dot{X}_3^0, \dot{X}_4^0\right)$.
        Draw parameters $\dot{\theta}_1^1 \sim p(\theta_1^1 \mid X_1^{obs}, \dot{X}_{-1}^1, R)$.
        Draw imputations $\dot{X}_1^1 \sim P(X_1^{mis} \mid \dot{X}_{-1}^1, R, \dot{\theta}_1^1)$.
    end for
end for

Algorithm 1 MICE algorithm [17] for **one** imputed dataset

for j in $1, \ldots, p$: ▷ Setup

  Specify imputation model for variable X_j
  $p(X_j^{mis} \mid X_j^{obs}, X_{-j}, R)$

  Fill in starting imputations $\dot{X}_j^0$ by random draws from X_j^{obs}.

end for

for $t = 1$: ▷ loop through iterations

  for $j = 2$: ▷ loop through variables

    Define currently complete data except X_2
    $\dot{X}_{-2}^1 = \left(\dot{X}_1^1, \dot{X}_3^0, \dot{X}_4^0\right)$.

    Draw parameters $\dot{\theta}_2^1 \sim p(\theta_2^1 \mid X_2^{obs}, \dot{X}_{-2}^1, R)$.

    Draw imputations $\dot{X}_2^1 \sim P(X_2^{mis} \mid \dot{X}_{-2}^1, R, \dot{\theta}_2^1)$.

  end for

end for

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  Fill in starting imputations $\dot{X}_j^0$ by random draws from X_j^{obs}.
end for

for $t = 1$: ▷ loop through iterations
  for $j = 3$: ▷ loop through variables
    Define currently complete data except X_3
    $\dot{X}_{-3}^{1} = \left(\dot{X}_1^1, \dot{X}_2^1, \dot{X}_4^0\right)$.
    Draw parameters $\dot{\theta}_3^1 \sim p(\theta_3^1 \mid X_3^{obs}, \dot{X}_{-3}^{1}, R)$.
    Draw imputations $\dot{X}_3^1 \sim P(X_3^{mis} \mid \dot{X}_{-3}^{1}, R, \dot{\theta}_3^1)$.
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end for

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end for

for $t = 1$: ▷ loop through iterations
    for $j = 4$: ▷ loop through variables
        Define currently complete data except X_4
        $\dot{X}_{-4}^1 = \left(\dot{X}_1^1, \dot{X}_2^1, \dot{X}_3^1\right)$.
        Draw parameters $\dot{\theta}_4^1 \sim p(\theta_4^1 \mid X_4^{obs}, \dot{X}_{-4}^1, R)$.
        Draw imputations $\dot{X}_4^1 \sim P(X_4^{mis} \mid \dot{X}_{-4}^1, R, \dot{\theta}_4^1)$.
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  Fill in starting imputations $\dot{X}_j^0$ by random draws from X_j^{obs}.

end for

for $t = 2$: ▷ loop through iterations

  for $j = 1$: ▷ loop through variables

    Define currently complete data except X_1 $\dot{X}_{-1}^2 = \left(\dot{X}_2^1, \dot{X}_3^1, \dot{X}_4^1\right)$.

    Draw parameters $\dot{\theta}_1^2 \sim p(\theta_1^2 \mid X_1^{obs}, \dot{X}_{-1}^2, R)$.

    Draw imputations $\dot{X}_1^2 \sim P(X_1^{mis} \mid \dot{X}_{-1}^2, R, \dot{\theta}_1^2)$.

  end for

end for

Algorithm 1 MICE algorithm [17] for **one** imputed dataset

for j in $1, \dots, p$: ▷ Setup

  Specify imputation model for variable X_j $p(X_j^{mis} \mid X_j^{obs}, X_{-j}, R)$

  Fill in starting imputations $\dot{X}_j^0$ by random draws from X_j^{obs}.

end for

for $t = 2$: ▷ loop through iterations

  for $j = 2$: ▷ loop through variables

    Define currently complete data except X_2 $\dot{X}_{-2}^{2} = \left(\dot{X}_1^2, \dot{X}_3^1, \dot{X}_4^1\right)$.

    Draw parameters $\dot{\theta}_2^2 \sim p(\theta_2^2 \mid X_2^{obs}, \dot{X}_{-2}^{2}, R)$.

    Draw imputations $\dot{X}_2^2 \sim P(X_2^{mis} \mid \dot{X}_{-2}^{2}, R, \dot{\theta}_2^2)$.

  end for

end for

The imputed values from the **last iteration**,

$$\left(\dot{X}_1^T, \ldots, \dot{X}_p^T\right),$$

are then used to replace the missing values in the original data.

One run through the algorithm ➡ one imputed dataset.

The imputed values from the **last iteration**,

$$\left(\dot{X}_1^T, \dots, \dot{X}_p^T\right),$$

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➡ To obtain m imputed datasets: **repeat** m **times**

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$$\left(\dot{X}_1^T, \ldots, \dot{X}_p^T\right),$$

are then used to replace the missing values in the original data.

One run through the algorithm ➡ one imputed dataset.

➡ To obtain m imputed datasets: **repeat m times**

We refer to the **sequence of imputations** for one missing value, from starting value to final iteration, as a **chain**. Each run through the MICE algorithm produces one chain per missing value.

Why iterations?

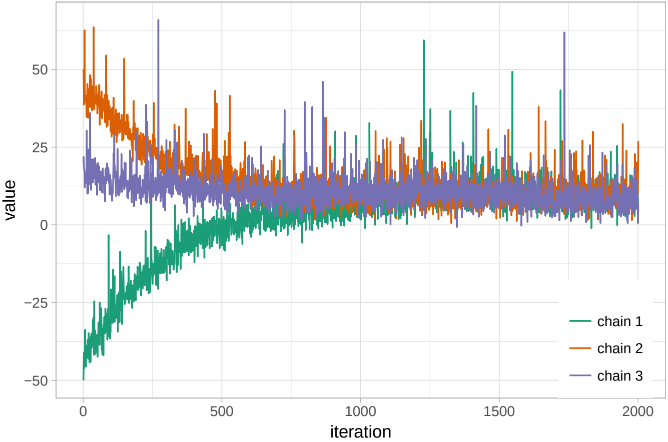
- Imputed values in one variable depend on the imputed values of the other variables (Gibbs sampling).
- If the starting values (random draws) are far from the actual distribution, imputed values from the first few iterations are not draws from the distribution of interest.

How many iterations?

Until **convergence**
= when the sampling distribution does not change any more
(Note: the imputed value will still vary between iterations.)

How to evaluate convergence?

The **traceplot** (x-axis: iteration number, y-axis: imputed value) should show a horizontal band



Each chain is the sequence of imputed values (from starting value to final imputed value) for the same missing value.

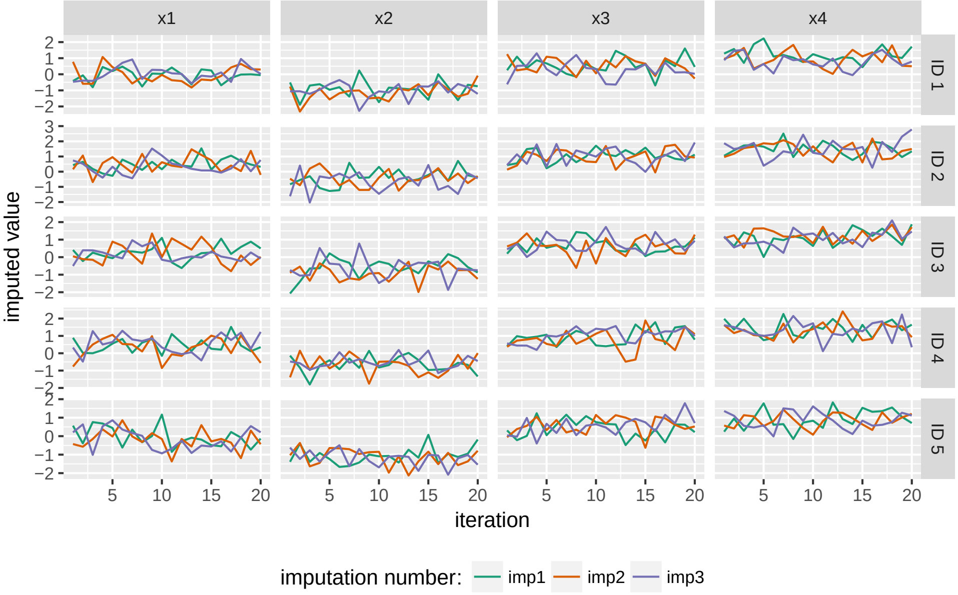
In imputation we have

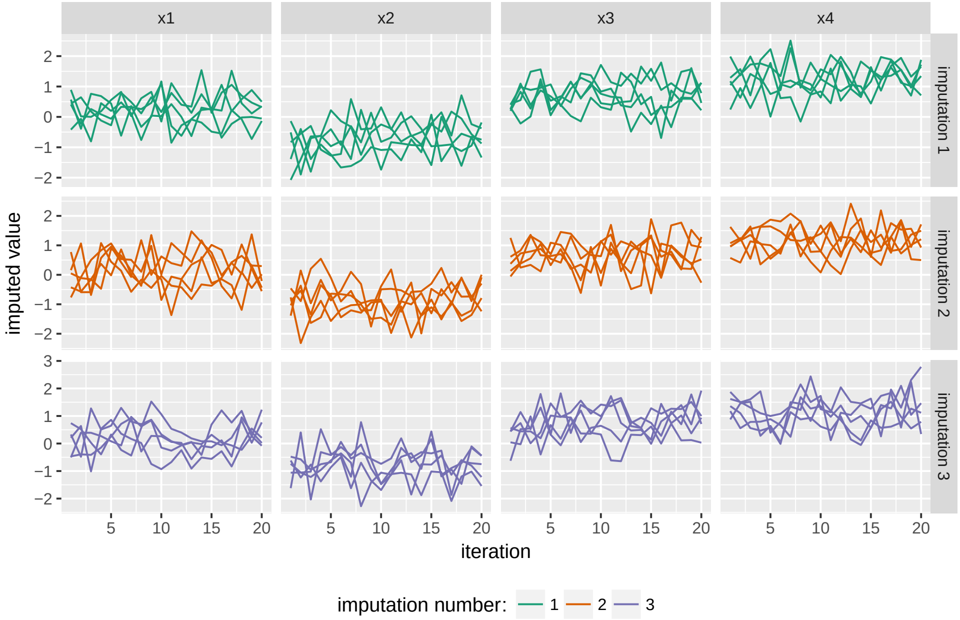
- several variables with missing values (e.g., p)
- several missing values in each of these variables
- m chains for each missing value

➡ possibly a large number of chains

To check all chains separately could be very time consuming in large datasets (and storing all iterations from all imputed values is inefficient).

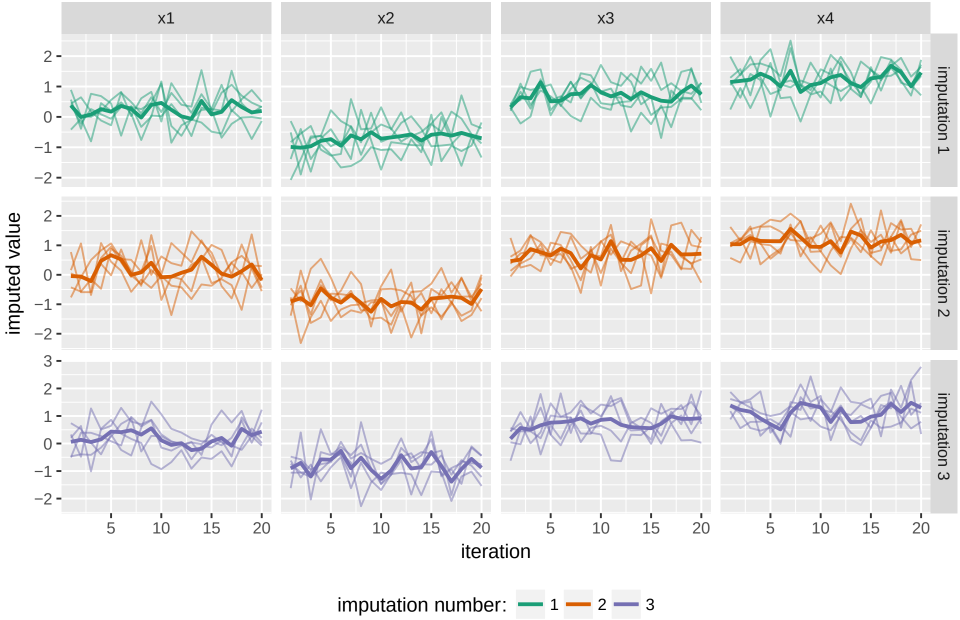
Alternative: Calculate and plot a summary (e.g., the mean) of the imputed values over all subjects, separately per chain and variable
➡ only $m \times p$ chains to check

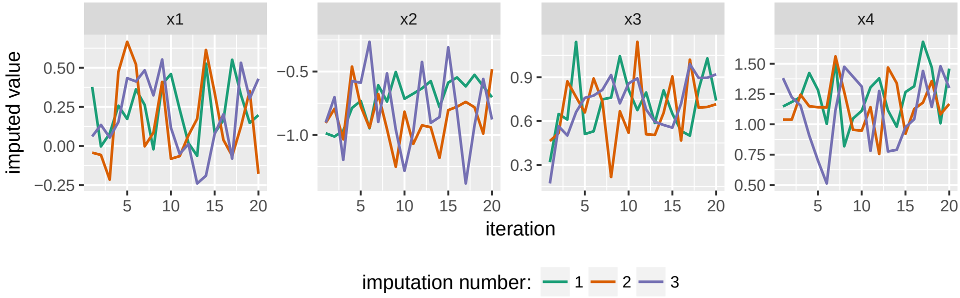

x1
x2
x3
x4
ID 1
ID 2
ID 3
ID 4
ID 5
imputed value
iteration
imputation number:
imp1
imp2
imp3


x1
x2
x3
x4
imputation 1
imputation 2
imputation 3
imputed value
iteration
5
10
15
20
imputation number: 1 2 3

2. Imputation step

2.4. Checking convergence




x1
x2
x3
x4
imputed value
0.50
0.25
0.00
−0.25
−0.5
−1.0
0.9
0.6
0.3
1.50
1.25
1.00
0.75
0.50
5
10
15
20
iteration
imputation number:
1
2
3

3. Analysis step

Multiple imputed datasets:

X_1	X_2	X_3	X_4
1.4	9.2	1.8	2.0
0.5	12.4	2.3	0.1
-0.5	10.7	2.6	-1.6
⋮	⋮	⋮	⋮

X_1	X_2	X_3	X_4
1.4	13.3	1.8	2.0
0.5	12.4	2.1	0.6
-0.5	10.2	2.6	-1.7
⋮	⋮	⋮	⋮

X_1	X_2	X_3	X_4
1.4	10.0	1.8	2.0
0.5	12.4	2.2	-1.4
-0.5	8.6	2.6	-1.0
⋮	⋮	⋮	⋮

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Analysis model of interest, e.g.,

$$x_1 = \beta_0 + \beta_1 x_2 + \beta_2 x_3 + \beta_3 x_4$$

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⋮	⋮	⋮	⋮

Analysis model of interest, e.g.,

$$x_1 = \beta_0 + \beta_1 x_2 + \beta_2 x_3 + \beta_3 x_4$$

Multiple sets of results:

	est.	se
β_0	0.35	0.21
β_1	0.14	0.02
β_2	-0.64	0.03
β_3	0.18	0.03

	est.	se
β_0	0.44	0.23
β_1	0.12	0.01
β_2	-0.61	0.03
β_3	0.22	0.03

	est.	se
β_0	0.19	0.21
β_1	0.14	0.01
β_2	-0.59	0.03
β_3	0.2	0.03

Recall from Slide 6:

We need to represent missing values by a **number of imputations**.

➡ m imputed datasets

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We need to represent missing values by a **number of imputations**.
➡ m imputed datasets

From the different imputed datasets we get **different sets of parameter estimates**, each of them with a standard error, representing the uncertainty about the estimate.

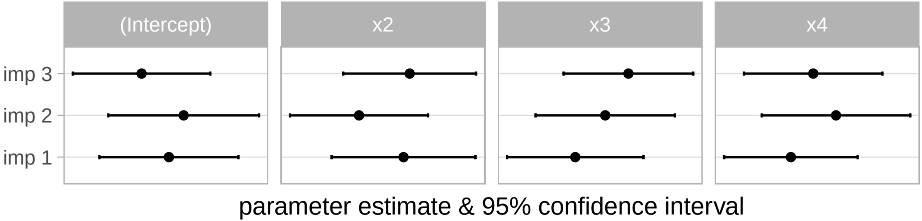
Recall from Slide 6:
We need to represent missing values by a **number of imputations**.
➡ m imputed datasets

From the different imputed datasets we get **different sets of parameter estimates**, each of them with a standard error, representing the uncertainty about the estimate.

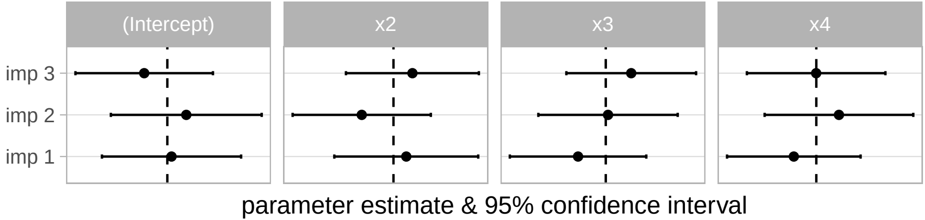
We want to **summarize** the results and describe **how (much) the results vary** between the imputed datasets.

In the results from multiply imputed data there are **two types of variation/uncertainty**:

- within imputation (represented by the confidence intervals)
- between imputation (horizontal shift between imputations)



To summarize the results, we can take the mean of the results from the separate analyses. This is the **pooled point estimate**.



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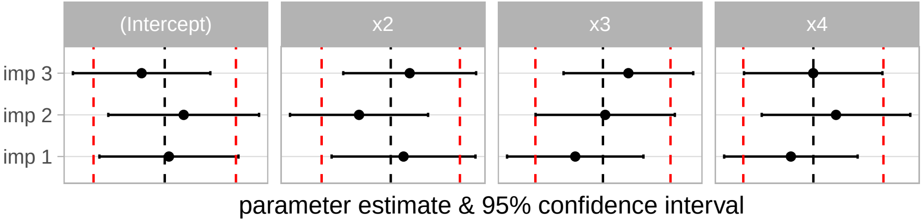

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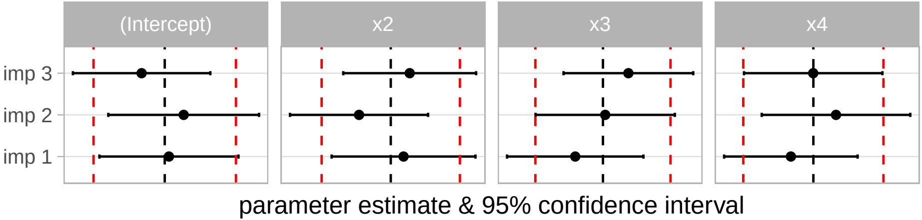


But does the same work for the std. error (or bounds of the CIs)?

The averaged CI's (marked in red) seem to underestimate the total variation (within + between).

The most commonly used method to pool results from analyses of multiply imputed data was introduced by Rubin [10], hence **Rubin's Rules**.

Notation:
m: number of imputed datasets
Q_ℓ: quantity of interest (e.g., regr. parameter β) from ℓ-th imputation
U_ℓ: variance of Q_ℓ (e.g., $var(\beta) = se(\beta)^2$)

Pooled parameter estimate:

$$\bar{Q} = \frac{1}{m}\sum_{\ell=1}^{m} \hat{Q}_\ell$$

The **variance** of the pooled parameter estimate is calculated from the **within and between imputation variance**.

Average within imputation variance:

$$\bar{U} = \frac{1}{m}\sum_{\ell=1}^{m}\bar{U}_\ell$$

Between imputation variance:

$$B = \frac{1}{m-1}\sum_{\ell=1}^{m}\left(\hat{Q}_\ell - \bar{Q}\right)^T\left(\hat{Q}_\ell - \bar{Q}\right)$$

Total variance:

$$T = \bar{U} + B + B/m$$

Confidence intervals for pooled estimates can be obtained using the **pooled standard error** $\sqrt{T}$ and a **reference t distribution** with degrees of freedom

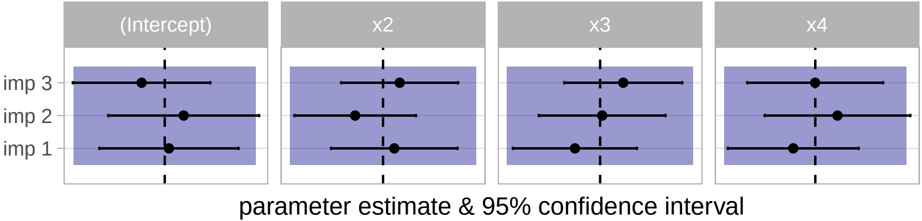
$$\nu = (m-1)\left(1 + r_m^{-1}\right)^2,$$

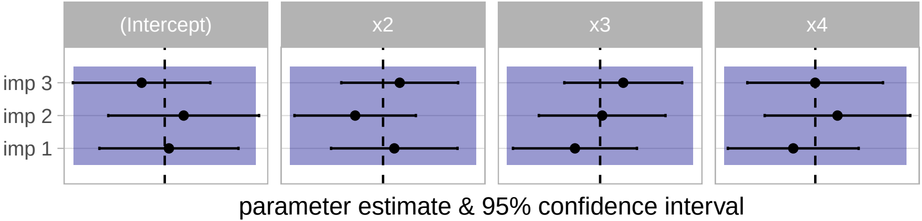
where $r_m = \frac{(B+B/m)}{\bar{U}}$ is the relative increase in variance that is due to the missing values.

The $(1-\alpha)$ **100% confidence interval** is then

$$\bar{Q} \pm t_\nu(\alpha/2)\sqrt{T},$$

where t_ν is the $\alpha/2$ quantile of the t distribution with ν degrees of freedom.


(Intercept)
x2
x3
x4
imp 3
imp 2
imp 1
parameter estimate & 95% confidence interval



The corresponding **p-value** is the probability

$$Pr\left\{F_{1,\nu} > \left(Q_0 - \bar{Q}_m\right)^2 / T\right\},$$

where $F_{1,\nu}$ is a random variable that has an F distribution with 1 and ν degrees of freedom, and Q_0 is the null hypothesis value (typically zero).

Quiz

To reiterate the content of the above sections, you can take the corresponding quiz. An interactive version can be found at

`https://emcbiostatistics.shinyapps.io/Quiz_PartI`

or you can download an html version from Canvas (Practicals/Quiz_PartI_static.html). [update links].

The imputation step consists itself of two (or three) steps:

0. Specification of the imputation model,
1. **estimation** or sampling **of the parameters**, and
2. **drawing imputed values** from the predictive distribution.

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Notation:
Let $\boldsymbol{y}$ be the incomplete covariate to be imputed, and $\boldsymbol{X}$ the design matrix of other (complete or imputed) variables.

$$\boldsymbol{y} = \begin{array}{c} \boldsymbol{y}_{obs} \left\{ \vphantom{\begin{array}{c} y_1 \\ \vdots \\ y_q \end{array}} \right. \\ \boldsymbol{y}_{mis} \left\{ \vphantom{\begin{array}{c} NA \\ \vdots \\ NA \end{array}} \right. \end{array} \begin{bmatrix} y_1 \\ \vdots \\ y_q \\ NA \\ \vdots \\ NA \end{bmatrix} \qquad \boldsymbol{X} = \begin{array}{c} \boldsymbol{X}_{obs} \left\{ \vphantom{\begin{array}{c} x \\ \vdots \\ x \end{array}} \right. \\ \boldsymbol{X}_{mis} \left\{ \vphantom{\begin{array}{c} x \\ \vdots \\ x \end{array}} \right. \end{array} \begin{bmatrix} 1 & x_{11} & \ldots & x_{1p} \\ \vdots & \vdots & \ldots & \vdots \\ 1 & x_{q1} & \ldots & x_{qp} \\ 1 & x_{q+1,1} & \ldots & x_{q+1,p} \\ \vdots & \vdots & \ldots & \vdots \\ 1 & x_{n1} & \ldots & x_{np} \end{bmatrix}$$

In the **Bayesian framework**, **everything unknown** or unobserved is considered as a **random variable**. Here, this includes for example regression coefficients $\boldsymbol{\beta}$, residual variance σ^2 and missing values $\boldsymbol{y}_{mis}$ and $\boldsymbol{X}_{mis}$.

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Random variables have a **probability distribution**. The **expectation** of that distribution quantifies where which **values** of the random variable are **most likely**, the **variance** is a measure of the **uncertainty** about the values.

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Random variables have a **probability distribution**. The **expectation** of that distribution quantifies where which **values** of the random variable are **most likely**, the **variance** is a measure of the **uncertainty** about the values.

In **Bayesian imputation**, the **information obtained from the observed data** is used to **estimate the probability distributions** for the missing values and unknown parameters, and values are **imputed by draws** from that posterior (= after having seen the data) distribution.

To determine the **expectation** of the posterior distribution of the missing values, usually a **regression model** is used, that depends on the unknown coefficients $\boldsymbol{\beta}$.

$$\mathbb{E}(\boldsymbol{y}_{mis} \mid \boldsymbol{X}, \boldsymbol{\beta}) = f(\boldsymbol{X}_{mis}\boldsymbol{\beta})$$

The posterior distribution of $\boldsymbol{\beta}$ and σ, $p(\boldsymbol{\beta}, \sigma \mid \boldsymbol{y}_{obs} \mid \boldsymbol{y}_{obs}, \boldsymbol{X}_{obs})$, is estimated from the corresponding regression model on the observed data.

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The posterior distribution of $\boldsymbol{\beta}$ and σ, $p(\boldsymbol{\beta}, \sigma \mid \boldsymbol{y}_{obs} \mid \boldsymbol{y}_{obs}, \boldsymbol{X}_{obs})$, is estimated from the corresponding regression model on the observed data.

To **impute** missing values, while **taking into account the uncertainty about $\boldsymbol{\beta}$ and σ**, the estimated posterior distributions of the missing values and parameters are multiplied

$$p(\boldsymbol{y}_{mis} \mid \boldsymbol{X}_{mis}, \boldsymbol{\beta}, \boldsymbol{\sigma})p(\boldsymbol{\beta}, \sigma \mid \boldsymbol{y}_{obs}, \boldsymbol{X}_{obs})$$

In practice, this can be implemented by first making a draw from the posterior distributions of $\boldsymbol{\beta}$ and σ, and plugging the values into the distribution of $\boldsymbol{y}_{obs}$.

Example: We assume that $\boldsymbol{y}$ given $\boldsymbol{X}$ is approximately normal.

Then $p(\boldsymbol{y}_{mis} \mid \boldsymbol{X}_{mis}, \boldsymbol{\beta}, \boldsymbol{\sigma})$ is a normal distribution and we can

- draw $\tilde{\boldsymbol{\beta}}$ from $p(\boldsymbol{\beta} \mid \boldsymbol{y}_{obs}, \boldsymbol{X}_{obs})$,
- draw $\tilde{\sigma}$ from $p(\sigma \mid \boldsymbol{y}_{obs}, \boldsymbol{X}_{obs})$,
- draw $\tilde{\boldsymbol{y}}_{mis}$ from a normal distribution with mean (= expectation) $\boldsymbol{X}\tilde{\boldsymbol{\beta}}$ and variance $\tilde{\sigma}^2$.

This is actually the approach we have seen previously on Slides 12/13 and 19.

An alternative approach is to capture the uncertainty with **bootstrap** sampling.

In empirical **Bootstrap**, (many) replications of the data are created by repeatedly drawing values from the original data.

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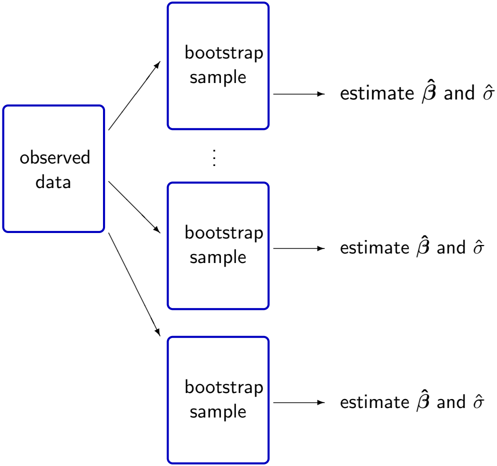

Bootstrap samples can contain some **observations multiple times** and some **observations not at all**.

The statistic of interest is then calculated on each of the bootstrap samples.

In **bootstrap multiple imputation**,

- **one bootstrap sample** of the **observed data** is created per imputation,
- the **least-squares estimates** of the parameters are calculated from

$$\boldsymbol{y}_{obs} = \boldsymbol{X}_{obs}\underset{\hat{\boldsymbol{\beta}}}{\underset{\downarrow}{\boldsymbol{\beta}}} + \underset{\hat{\sigma}}{\underset{\downarrow}{\varepsilon_{obs}}} \qquad \text{(step 1).}$$

- Imputed values are sampled from $p(\boldsymbol{y}_{mis} \mid \boldsymbol{X}_{mis}, \hat{\boldsymbol{\beta}}, \hat{\sigma})$ (step 2).

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- Imputed values are sampled from $p(\boldsymbol{y}_{mis} \mid \boldsymbol{X}_{mis}, \hat{\boldsymbol{\beta}}, \hat{\sigma})$ (step 2).

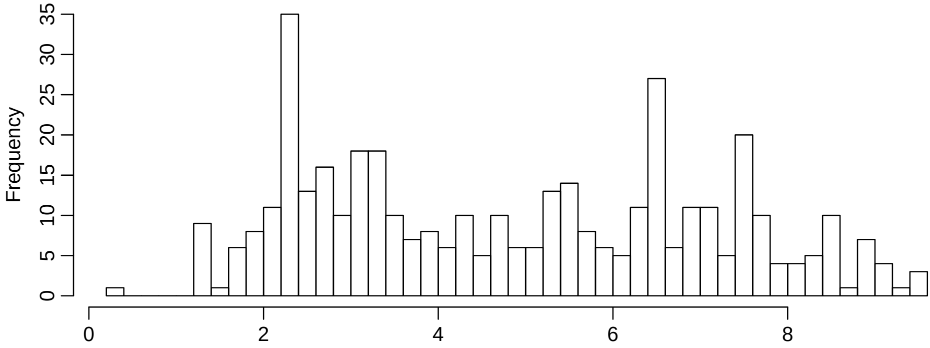
Analogous to Bayesian multiple imputation, for a normal imputation model, $p()$ is the normal distribution and

$$\tilde{\boldsymbol{y}}_{mis} = \boldsymbol{X}_{mis}\hat{\boldsymbol{\beta}} + \tilde{\varepsilon}$$

where $\tilde{\varepsilon}$ is drawn independently from $N(0, \hat{\sigma}^2)$.

Both Bayesian and bootstrap multiple imputation sample imputed values from a distribution $p()$ in step 2.

Sometimes, the empirical distribution can not be adequately approximated by a known probability distribution.



Predictive Mean Matching (PMM) was developed to provide a semi-parametric approach to imputation for settings where the normal distribution is not a good choice for the predictive distribution.[8, 9]

The idea is to **find cases in the observed data that are similar to the cases with missing values** and to fill in the missing value with the observed value from one of those cases.

To find similar cases, the predicted values of complete and incomplete cases are compared.

The steps in PMM:

1. Obtain parameter estimates for $\hat{\beta}$ and $\hat{\sigma}$ (see later)
2. Calculate the predicted values for the observed data
$$\hat{\boldsymbol{y}}_{obs} = \boldsymbol{X}_{obs}\hat{\beta}$$
3. Calculate the predicted value for the incomplete data
$$\hat{\boldsymbol{y}}_{mis} = \boldsymbol{X}_{mis}\hat{\beta}$$
4. For each missing value, find d donor candidates that fulfill a given criterium (details on the next slide).
5. Randomly select one of the donors.

Several **criteria to select donors** have been proposed:

1. The donor is the **(one) case with the smallest absolute difference** $|\hat{y}_{mis,i} - \hat{y}_{obs,j}|$, $j = 1, \ldots, q$.
2. Donor candidates are the d **cases with the smallest absolute difference** $|\hat{y}_{mis,i} - \hat{y}_{obs,j}|$, $j = 1, \ldots, q$. The donor is selected randomly from the candidates.
3. Donor candidates are those cases for which the **absolute difference is smaller than some limit** η: $|\hat{y}_{mis,i} - \hat{y}_{obs,j}| < \eta$, $j = 1, \ldots, q$. The donor is selected randomly from the candidates.
4. Select candidates like in 2. or 3., but select the donor from the candidates with probability that depends on $|\hat{y}_{mis,i} - \hat{y}_{obs,j}|$.[16]

Potential issues with donor selection

- Selection criteria 2. - 4., **require the number of candidates** d (or maximal difference η) to be specified. Common choices for d are 3, 5 or 10.

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- the **proportion of missing values is large**, or
- one/some **predictor variable(s) are strongly related to the missingness**.

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- Therefore, using $d = 1$ (selection criterion 1.) is not a good idea. On the other hand, using too many candidates can lead to bad matches.
- Schenker and Taylor [15] proposed an adaptive procedure to select d, but it is not used much in practice.

For the **sampling of the parameters** (step 1 on slide 43), different approaches have been introduced in the literature:

Type-0 point estimates $\hat{\beta}$ are used in both prediction models (least squares or maximum likelihood)

Type-I $\hat{\beta}$ to predict $\hat{y}_{obs}$; $\tilde{\beta}$ to predict $\hat{y}_{mis}$ is sampled from the posterior distribution of β (Bayesian) or bootstraped

Type-II $\tilde{\beta}$ to predict $\hat{y}_{obs}$ as well as $\hat{y}_{mis}$

Type-III different draws $\tilde{\beta}^{(1)}$ and $\tilde{\beta}^{(2)}$ to predict $\hat{y}_{obs}$ and $\hat{y}_{mis}$, respectively

The use of point estimates (Type-0 and Type-I matching) **underestimates the uncertainty** about the regression parameters.

Another point of consideration is the **choice of the set of data used to train the prediction models**.

In the version presented on slide 43, the same set of data (all cases with observed y) is used to train the model and to produce predicted values of y_{obs}.

The predictive model will likely fit the observed cases better than the missing cases, and, hence, **variation will be underestimated**.

As an alternative, the **model could be trained on the whole data** (using previously imputed values) or to use a **leave-one-out approach** on the observed data.

mice (in R):

- **PMM** via `mice.impute.pmm()`
  - specification of number of donors d (same for all variables)
  - Type-0, Type-I, Type-II matching
- **PMM** via `mice.impute.midastouch()`
  - allows leave-one-out estimation of the parameters
  - distance based donor selection
  - Type-0, Type-I, Type-II matching
- **bootstrap** linear regression via `mice.impute.norm.boot()`
- **bootstrap** logistic regression via `mice.impute.logreg.boot()`
- **Bayesian** linear regression via `mice.impute.norm()`
- ...

Summary of Part I

1. What is Multiple Imputation?

- Rubin's two ideas:
  - Missing values need to be represented by multiple imputed values.
  - A model is necessary to obain good imputations.
- Imputed values are obtained from the predictive distribution of the missing data, given the observed data.
- Multiple completed datasets are created from the muliple imputed values.
- Multiple imputation has three steps: Imputation, analysis, pooling

Summary of Part I (cont.)

2. Imputation step

- Two sources of variation need to be taken into account
  - parameter uncertainty
  - random variation
- For two main approaches to MI for imputation of non-monotone multivariate missing data
  - MICE/FCS
  - Joint model imputation
- The MICE algorithm re-uses univariate imputation models by iterating through all incomplete variables, multiple times (iterations)
- Multiple runs through the algorithm are necessary to create multiple imputed dataset
- The convergence of the chains needs to be checked.

Summary of Part I (cont.)

3. Analysis step

- Analyse each imputed dataset the way you would analyse a complete dataset

4. Pooling

- Results from analyses of multiple imputed datasets can be summarized by taking the average of the regression coefficients
- For the total variance, two sources of variation need to be considered:
    - within imputation variance
    - between imputation variance

Summary of Part I (cont.)

5. A closer look at the imputation step

- Two parametric approaches for imputation:
  - Bayesian (sample from posterior distribution of parameters)
  - Bootstrap (uses bootstrap samples of the data to estimate parameters)
- Predictive mean matching is a semi-parametric alternative
  (it matches observed and missing cases based on their predicted values).
- In PMM we need to consider
  - donor selection
  - matching type (how parameters are sampled/estimated),
  - the set of data used to calculate/estmate the parameters.
- Bayesian and bootstrap imputation take into account the variation, while many choices in PMM lead to underestimation of the variation.

Part II
Multiple Imputation Workflow

Outline of Part II

There are several packages in R that provide functions to create and plot the missing data pattern.

Examples are:
mice, **VIM**, **Amelia**, **visdat**, **naniar**, ...

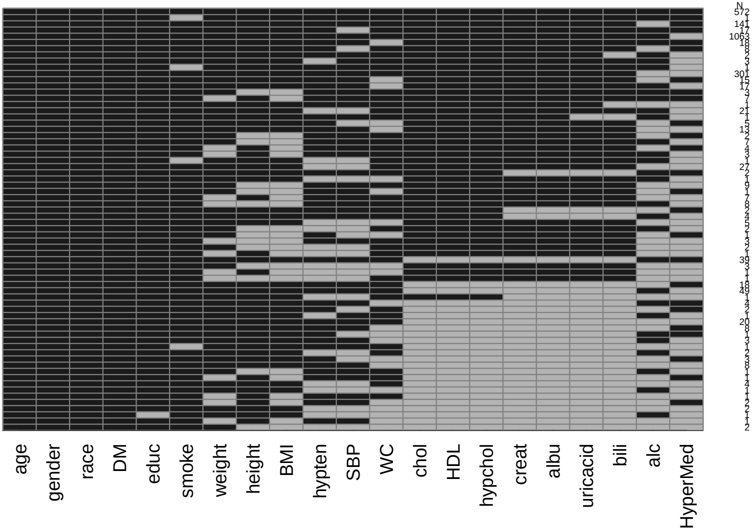
To create the plots on the following slides, we need to load the example data

```
datadir <-     # fill in path to folder containing the data
load(file.path(datadir, "NHANES.RData"))
```

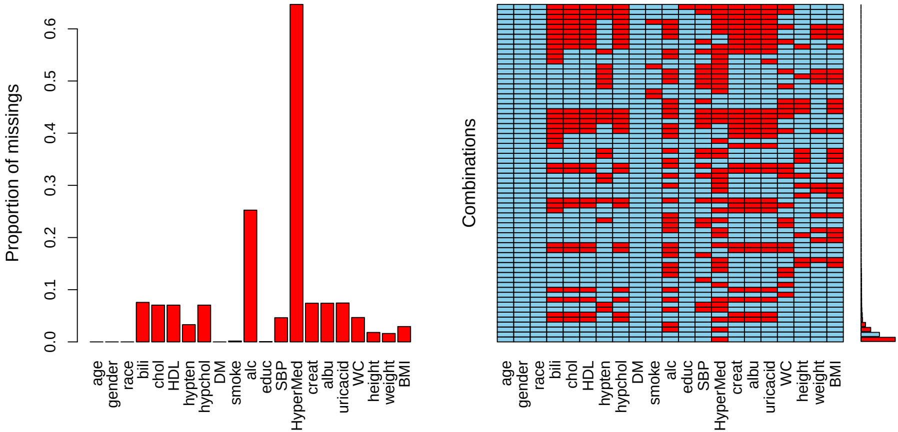
```
mdp <- mice::md.pattern(NHANES)
head(mdp[, -c(7:14)]) # omit some columns to fit it on the slide

##      age gender race DM educ smoke hypchol creat albu uricacid bili alc HyperMed
## 572    1      1    1  1    1     1       1     1    1        1    1   1        1 0
## 1      1      1    1  1    1     0       1     1    1        1    1   1        1 1
## 141    1      1    1  1    1     1       1     1    1        1    1   0        1 1
## 17     1      1    1  1    1     1       1     1    1        1    1   1        1 1
## 1063   1      1    1  1    1     1       1     1    1        1    1   1        0 1
## 18     1      1    1  1    1     1       1     1    1        1    1   1        1 1

tail(mdp[, -c(7:14)])

##      age gender race DM educ smoke hypchol creat albu uricacid bili alc HyperMed
## 2      1      1    1  1    1     1       0     0    0        0    0   0        1   11
## 2      1      1    1  1    1     1       0     0    0        0    0   0        0   12
## 1      1      1    1  1    0     1       0     0    0        0    0   1        0   12
## 1      1      1    1  1    1     1       0     0    0        0    0   0        0   12
## 2      1      1    1  1    1     1       0     0    0        0    0   0        0   14
##        0      0    0  0    1     4     175   184  184      185  188 627     1606 3975
```

6. Know your data
6.1. Missing data patterns

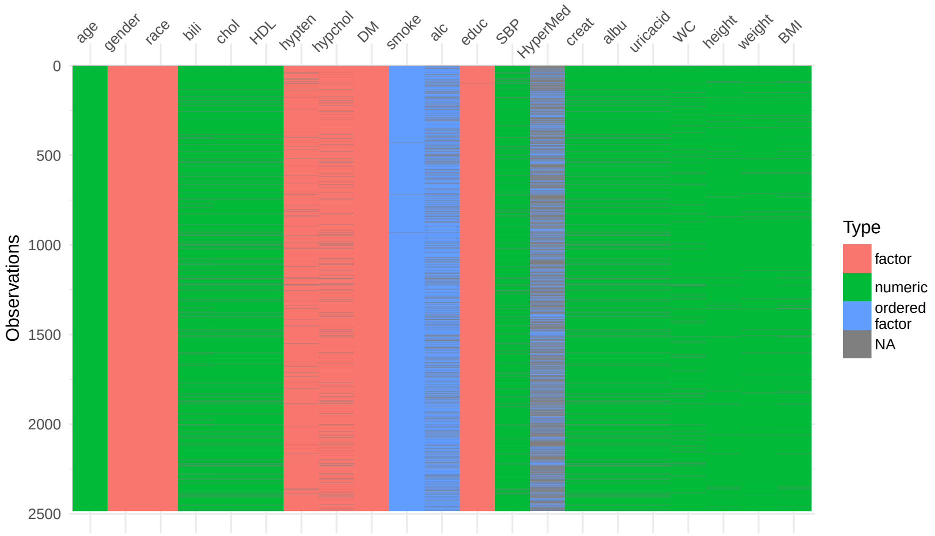
```r
par(mar = c(5, 0.5, 1, 3), mgp = c(2, 0.6, 0))
JointAI::md_pattern(NHANES, print = F, yaxis_pars = list(cex.axis = 0.5))
```



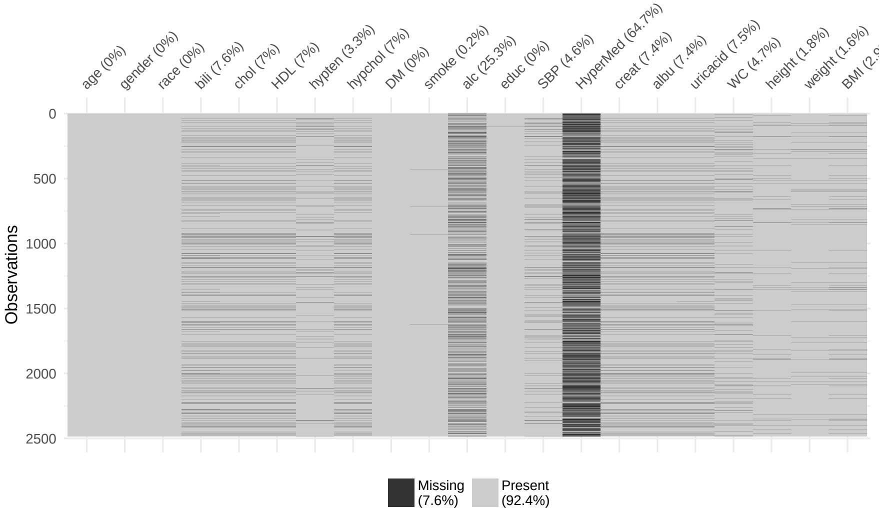
```r
par(mar = c(6, 3, 2, 1))
VIM::aggr(NHANES, prop = T, numbers = F)
```



```r
visdat::vis_dat(NHANES, sort_type = F)
```



```r
visdat::vis_miss(NHANES)
```



```r
# number and proportion of complete cases
Ncc <- cbind(
  "#" = table(complete.cases(NHANES)),
  "%" = round(100 * table(complete.cases(NHANES))/nrow(NHANES), 2)
)
rownames(Ncc) <- c("incompl.", "complete")
```

```r
# number and proportion of missing values per variable
nmis <- cbind("# NA" = sort(colSums(is.na(NHANES))),
              "% NA" = round(sort(colMeans(is.na(NHANES))) * 100, 2))
```

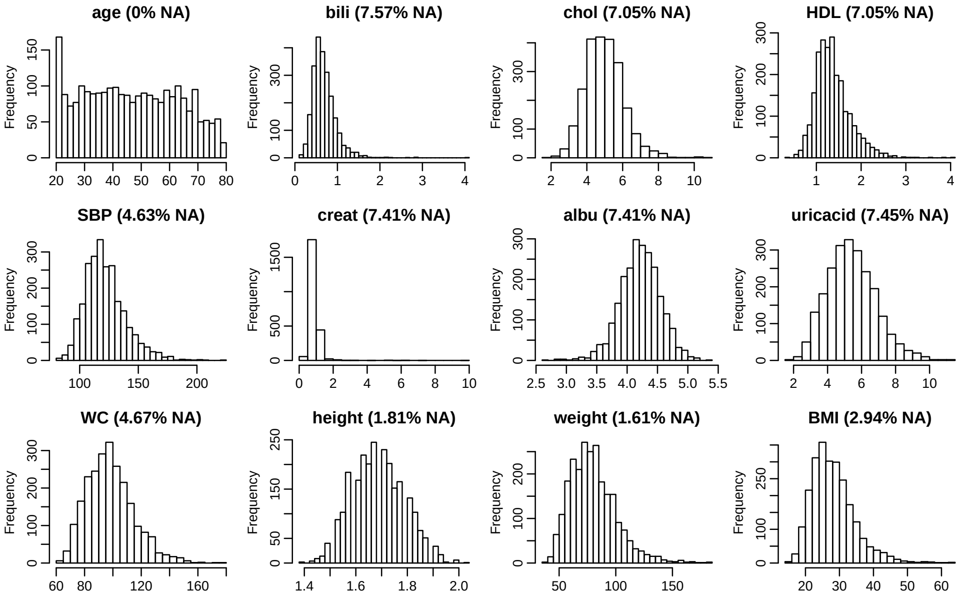
Number and proportion of (in)complete cases

```
##                #     %
## incompl. 1911 76.96
## complete  572 23.04
```

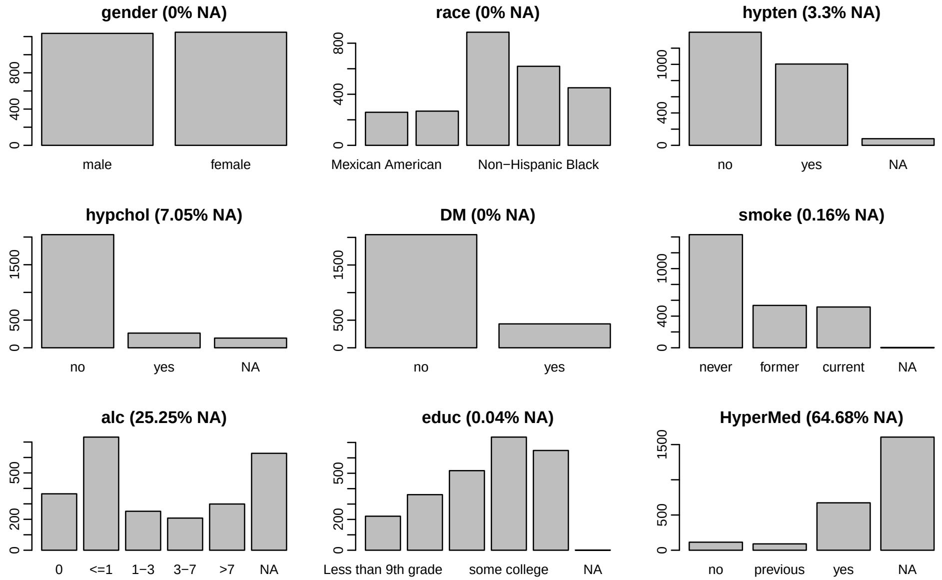
Number and proportion of missing values per variable

```
##          # NA % NA
## age         0 0.00
## gender      0 0.00
## race        0 0.00
## DM          0 0.00
## educ        1 0.04
## smoke       4 0.16
## weight     40 1.61
## height     45 1.81
## BMI        73 2.94
## hypten     82 3.30
## SBP       115 4.63
```

```
##              # NA  % NA
## WC            116  4.67
## chol          175  7.05
## HDL           175  7.05
## hypchol       175  7.05
## creat         184  7.41
## albu          184  7.41
## uricacid      185  7.45
## bili          188  7.57
## alc           627 25.25
## HyperMed     1606 64.68
```



age (0% NA)
bili (7.57% NA)
chol (7.05% NA)
HDL (7.05% NA)
SBP (4.63% NA)
creat (7.41% NA)
albu (7.41% NA)
uricacid (7.45% NA)
WC (4.67% NA)
height (1.81% NA)
weight (1.61% NA)
BMI (2.94% NA)
Frequency



gender (0% NA)
0
400
800
male
female
race (0% NA)
0
400
800
Mexican American
Non−Hispanic Black
hypten (3.3% NA)
0
400
1000
no
yes
NA
hypchol (7.05% NA)
0
500
1500
no
yes
NA
DM (0% NA)
0
500
1500
no
yes
smoke (0.16% NA)
0
400
1000
never
former
current
NA
alc (25.25% NA)
0
200
500
0
<=1
1−3
3−7
>7
NA
educ (0.04% NA)
0
200
500
Less than 9th grade
some college
NA
HyperMed (64.68% NA)
0
500
1500
no
previous
yes
NA

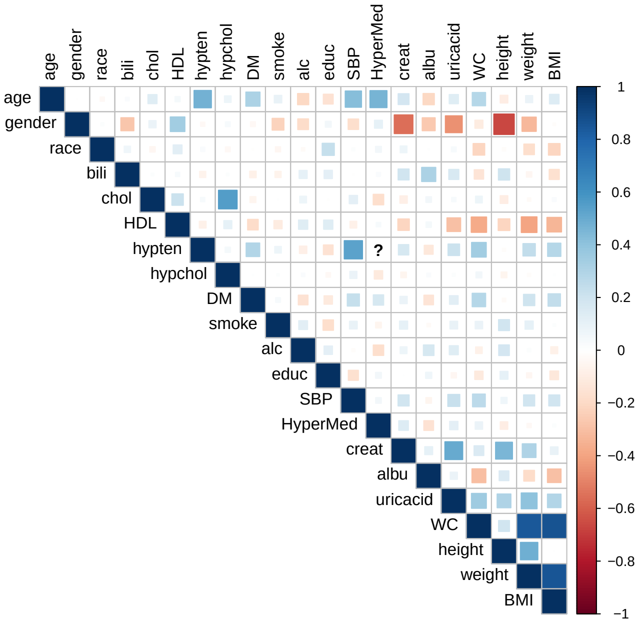
```r
# syntax for continuous variables
NHANESnum <- NHANES[, sapply(NHANES, is.numeric)]
par(mfrow = c(3, 4), mar = c(3, 3.2, 0.5, 0.5), mgp = c(2, 0.6, 0))
for (i in 1:ncol(NHANESnum)) {
  hist(NHANESnum[, i], nclass = 30, xlab = names(NHANESnum)[i], main = "")
  legend("topright", bty = "n",
         legend = paste0(round(mean(is.na(NHANESnum[, i]))*100, 2), "% NA"))
}

# syntax for factors
NHANESfac <- NHANES[, sapply(NHANES, is.factor)]
par(mfrow = c(3, 5), mar = c(3, 3.2, 2.5, 0.5), mgp = c(2, 0.6, 0))
for (i in 1:ncol(NHANESfac)) {
  tab <- table(NHANESfac[, i], exclude = NULL)
  names(tab)[is.na(names(tab))] <- "NA"
  barplot(tab, main = paste0(names(NHANESfac)[i]," (",
                             round(mean(is.na(NHANESfac[, i]))*100,
                                   2), "% NA)"))
}
```

Quick way to check for strong correlations between variables:

```
# re-code all variables as numeric and calculate spearman correlation
Corr <- cor(sapply(NHANES, as.numeric),
            use = "pairwise.complete.obs", method = "spearman")

## Warning in cor(sapply(NHANES, as.numeric), use = "pairwise.complete.obs",
: the standard deviation is zero
```

```
corrplot::corrplot(Corr, method = "square", type = "upper", tl.col = "black")
```

Note: We only use the correlation coefficient for binary variables in this visualization, not as a statistical result!



age
gender
race
bili
chol
HDL
hypten
hypchol
DM
smoke
alc
educ
SBP
HyperMed
creat
albu
uricacid
WC
height
weight
BMI
?
1
0.8
0.6
0.4
0.2
0
−0.2
−0.4
−0.6
−0.8
−1

Check out what the problem is with `hypertension` and `HyperMed`:

```
table(hypertension = NHANES$hypten,
      HyperMed = NHANES$HyperMed, exclude = NULL)
```

```
##              HyperMed
## hypertension   no previous  yes <NA>
##          no     0        0    0 1397
##          yes  114       90  673  127
##          <NA>   0        0    0   82
```

Knowing your data also means to be able to answer these questions:

- Do missing values in multiple variables always **occur together**? (e.g. blood measurements)
- Are there **structural missing values**? (e.g. pregnancy status in men)
- Are there **patterns** in the missing values? (e.g. only patients with hypertension have observations of HyperMed)
- Are values **missing by design**?
- Is the **assumption of ignorable missingness** (MAR or MCAR) justifiable?

Auxiliary variables are variables that are not part of the analysis but can help during imputation.

Good auxiliary variables

- are related to the probability of missingness in a variable, or
- are related to the incomplete variable itself,
- do not have many missing values themselves and
- are (mostly) observed when the incomplete variable of interest is missing.

The main arguments needed to impute data with `mice()` are:

- `data`: the dataset
- `m`: number of imputed datasets (default is 5)
- `maxit`: number of iterations (default is 5)
- `method`: vector of imputation methods
- `defaultMethod`: vector of default imputation methods for numerical, binary, unordered and ordered factors with > 2 levels (default is `c("pmm", "logreg", "polyreg", "polr")`)
- `predictorMatrix`: matrix specifying roles of variables

mice has implemented many **imputation methods**, the most commonly used ones are:

- `pmm`: predictive mean matching (any)
- `norm`: Bayesian linear regression (numeric)
- `logreg`: binary logistic regression (binary)
- `polr`: proportional odds model (ordered factors)
- `polyreg`: polytomous logistic regression (unordered factors)

Change the default imputation method:
To use `norm` instead of `pmm` for all continuous incomplete variables, use:

```
mice(NHANES, defaultMethod = c("norm", "logreg", "polyreg", "polr"))
```

Change imputation method for a single variable:
To change the imputation method for single variables (but also for changes in other arguments) it is convenient to do a setup run of `mice()` without iterations (`maxit = 0`) and to extract and modify the parameters from there.

Exclude variable from imputation:
When a variable that has missing values should not be imputed, the method needs to be set to `""`.

```r
library(mice)
imp0 <- mice(NHANES, maxit = 0)
meth <- imp0$method
meth

##        age    gender      race      bili      chol       HDL    hypten
##         ""        ""        ""     "pmm"     "pmm"     "pmm"  "logreg"
##    hypchol        DM     smoke       alc      educ       SBP  HyperMed
##   "logreg"        ""    "polr"    "polr" "polyreg"     "pmm"    "polr"
##      creat      albu  uricacid        WC    height    weight       BMI
##      "pmm"     "pmm"     "pmm"     "pmm"     "pmm"     "pmm"     "pmm"

meth["albu"] <- "norm"
meth["HyperMed"] <- ""
# imp <- mice(NHANES, method = meth)
```

The `predictorMatrix` is a matrix that specifies which variables are used as predictors in which imputation model.
Each row represents the model for the variable given in the rowname.

```
head(imp0$predictorMatrix)[, 1:11]

##        age gender race bili chol HDL hypten hypchol DM smoke alc
## age      0      0    0    0    0   0      0       0  0     0   0
## gender   0      0    0    0    0   0      0       0  0     0   0
## race     0      0    0    0    0   0      0       0  0     0   0
## bili     1      1    1    0    1   1      1       1  1     1   1
## chol     1      1    1    1    0   1      1       1  1     1   1
## HDL      1      1    1    1    1   0      1       1  1     1   1
```

Variables not used as predictor are (or have to be set to) zero.

By default, all variables (except the variable itself) are used as predictor.
For complete variables all entries are 0.

Important:
A variable that has missing values needs to be imputed in order to be used as predictor for other imputation models!!!

Note:
By default, **ALL** variables with missing values are imputed and **ALL** variables are used as predictor variables.
➡ Make sure to adjust the `predictorMatrix` and `method` to avoid using ID variables or other columns of the data that should not be part of the imputation.

➡ Make sure all variables are coded correctly, so that the chosen imputation models are appropriate (e.g., ordered factors).

```r
library(mice)
imp0 <- mice(NHANES, maxit = 0,
             defaultMethod = c("norm", "logreg", "polyreg", "polr"))
meth <- imp0$method
meth["educ"] <- "polr"
meth["HyperMed"] <- ""

pred <- imp0$predictorMatrix
pred[, "HyperMed"] <- 0
imp <- mice(NHANES, method = meth, predictorMatrix = pred, printFlag = F)
```

In some cases, variables are functions of other variables, e.g., $BMI = \frac{weight}{height^2}$.
If we impute `BMI` directly, its values may be inconsistent with the (imputed) values of `height` and `weight`.

```
DF1 <- complete(imp, 1) # select the first imputed dataset
round(cbind("wgt/hgt^2" = DF1$weight/DF1$height^2,
            BMI = DF1$BMI)[is.na(NHANES$BMI), ], 2)[1:5, ]

##      wgt/hgt^2   BMI
## [1,]     27.25 28.77
## [2,]     23.80 22.94
## [3,]     25.77 24.06
## [4,]     27.56 27.50
## [5,]     23.75 24.07
```

The imputed values of `BMI` are impossible given the corresponding values of `height` and `weight`.

Moreover, if some components of a variable are observed we want to use that information to reduce uncertainty.

```
table(weight_missing = is.na(NHANES$weight),
      height_missing = is.na(NHANES$height))

##                height_missing
## weight_missing FALSE TRUE
##          FALSE  2410   33
##          TRUE     28   12
```

Here we have $33 + 28 = 61$ cases in which either `height` or `weight` is observed.
We would like to impute `height` and `weight` separately and calculate `BMI` from the (imputed) values of the two variables.

If BMI is not a relevant predictor in any of the other imputation models, we could just exclude BMI from the imputation and re-calculate it afterwards.

To use BMI as predictor in the imputation, it has to be calculated in each iteration of the algorithm. In **mice** this is possible with *passive imputation*.

Instead of using a standard imputation method, we can specify a formula to calculate BMI:

```
meth["BMI"] <- "~I(weight/height^2)"      # specify formula to impute BMI
pred[c("weight", "height"), "BMI"] <- 0  # prevent feedback
```

To prevent feedback from BMI in the imputation of height and weight the predictorMatrix needs to be modified.

Since `BMI` and `weight` are highly correlated ($\rho = 0.87$) it may be beneficial not to use them simultaneously as predictors in the other imputation models. Which one to use may differ between imputation models.

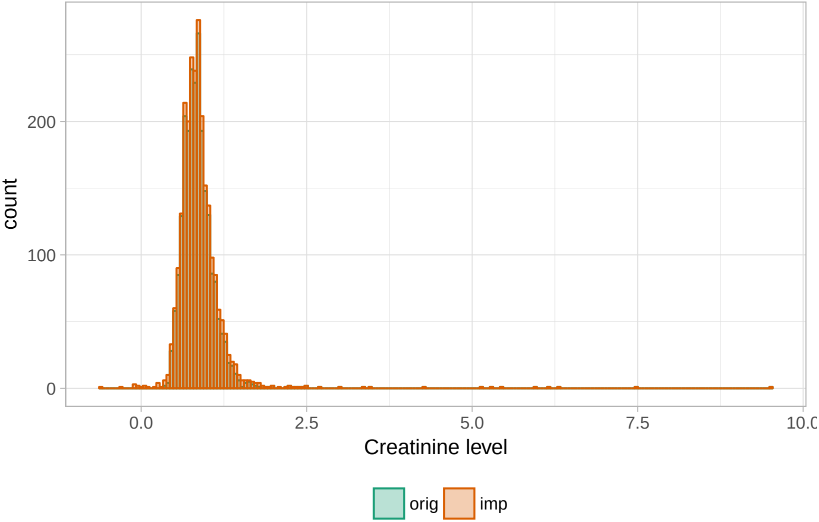
Passive imputation can also be useful in settings where imputation models include an **interaction terms** between incomplete variables (see [17, p. 133] for an example) or when a number of covariates is used to form a **sum score**. The sum score, instead of all single elements, can then be used as predictor in other imputation models.

`mice()` has an argument `post` that can be used to specify functions that modify imputed values.
Helpful functions are

- `squeeze()` to censor variables at given boundaries
- ~~`ifdo()` for conditional manipulation~~ (not yet implemented)

Example:
When inspecting the imputed values from `imp`, we find that some imputed values in `creat` are negative.

```
summary(DF1$creat) # DF1 is the first imputed dataset we extracted earlier

##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
## -0.6155  0.7000  0.8300  0.8853  0.9900  9.5100
```



count
200
100
0
0.0
2.5
5.0
7.5
10.0
Creatinine level
orig
imp

With the following syntax all imputed values of `creat` that are outside the interval `c(0, 100)` will be set to those limiting values.

```
post <- imp$post
post["creat"] <- "imp[[j]][,i] <- squeeze(imp[[j]][,i], c(0, 100))"
imp2 <- update(imp, post = post, maxit = 20, seed = 123)
```

Note:

When many observations are outside the limits it may be better to change the imputation model since the implied assumption of the current model apparently does not fit the assumption about the complete data distribution.

This post-processing allows for many more data manipulations and is not restricted to `squeeze()` and `ifdo()`. Any strings of R commands provided will be evaluated after the corresponding variable is imputed, within each iteration.

This also allows for (some) **MNAR scenarios**, for example, by multiplying or adding a constant to the imputed values or to re-impute values, depending on their current value.

When the post-processed or passively imputed values of a variable depend on other variables, the sequence in which the variables are imputed may be important to obtain consistent values.

Example:
If `BMI` is passively imputed (calculated) before the new imputations for `height` and `weight` are drawn, the resulting values of `BMI`, will match `height` and `weight` from the previous iteration, but not the iteration given in the imputed dataset.

In `mice()` the argument `visitSequence` specifies in which order the columns of the `data` are imputed. By default `mice()` imputes in the order of the columns in `data`.

```
visitSeq <- imp2$visitSequence
visitSeq

##      bili     chol      HDL   hypten  hypchol    smoke      alc     educ
##         4        5        6        7        8       10       11       12
##       SBP HyperMed    creat     albu uricacid       WC   height   weight
##        13       14       15       16       17       18       19       20
##       BMI
##        21
```

Currently, `hypten` is imputed before `SBP`, but the imputed values of `hypten` are post-processed depending on the current value of `SBP`. To get consistent values of these two variables, we need to change the `visitSequence`.

```
visitSeq <- c(visitSeq[-which(names(visitSeq) == "hypten")],
              visitSeq["hypten"])
visitSeq

##     bili     chol      HDL  hypchol    smoke      alc     educ      SBP
##        4        5        6        8       10       11       12       13
## HyperMed    creat     albu uricacid       WC   height   weight      BMI
##       14       15       16       17       18       19       20       21
##   hypten
##        7
```

The `visitSequence` may specify that a column is visited multiple times during one iteration. All incomplete variables must be visited at least once.

`visitSequence` can also be specified using one of the keywords `"roman"` (left to right), `"arabic"` (right to left), `"monotone"` (sorted in increasing amount of missingness), `"revmonotone"` (reverse of monotone) `mice()` performs some pre-processing and removes

- incomplete variables that are not imputed but are specified as predictor,
- constant variables, and
- collinear variables.

In each iteration

- linearly dependent variables are removed and
- `polr` imputation models that do not converge are replaced by `polyreg`.

Why?
To avoid problems in the imputation models.

As a **consequence**

- imputation models may differ from what the user has specified or assumes is happening, or
- variables that should be imputed are not.

➡ Know your data

➡ Make sure `method` and `predictorMatrix` are specified appropriately

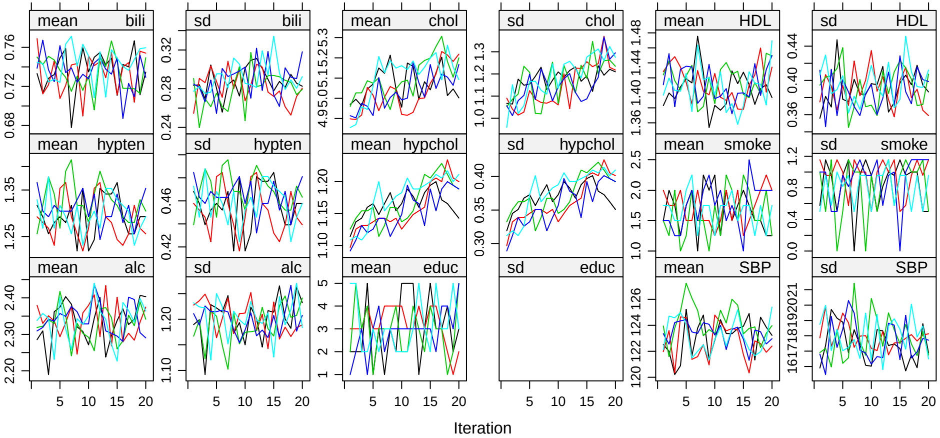
➡ Check the output and log of these automatic actions carefully

"Please realize that these choices are always needed. Imputation software needs to make default choices. These choices are intended to be useful across a wide range of applications. However, the default choices are not necessarily the best for the data at hand. There is simply no magical setting that always works, so often some tailoring is needed." [17, p. 124]

Recall from Slides 19 and 23:
mice uses an iterative algorithm and imputations from the first few iterations may not be samples from the "correct" distributions.

Traceplots can be used to visually assess convergence. In **mice** the function `plot()` produces traceplots of the mean and std. deviation (across subjects) per incomplete variable.

```r
plot(imp2, layout = c(6, 3))
```



The traceplots show that the imputations for `chol` and `hypchol` have an upward trend.

Strong trends and traces that show **correlation** between variables indicate problems of feedback. This needs to be investigated and resolved in the specification of the `predictorMatrix`.
Weak trends may be artefacts that often disappear when the imputation is performed with more iterations.

When MCMC chains have converged, the distributions of the imputed and observed values can be compared to investigate differences between observed and imputed data.

Note:
Plots usually show the marginal distributions of observed and imputed values, which do not have do be identical under MAR.

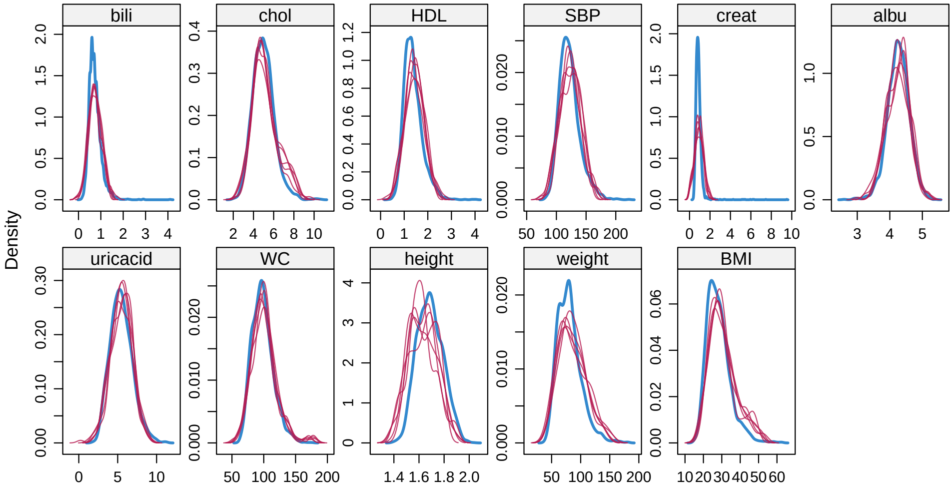
Recall: the conditional distributions (given all the other variables in the imputation model) of the imputed values are assumed to be the same as the conditional distributions of the observed data.

mice provides several functions for visual diagnosis of imputed values:

- `densityplot()` (for large datasets and variables with many NAs)
- `stripplot()` (for smaller datasets and/or variables with few NAs)
- `bwplot()`
- `xyplot()`

These functions create lattice graphics, which can be modified analogous to their parent functions from the **lattice** package.

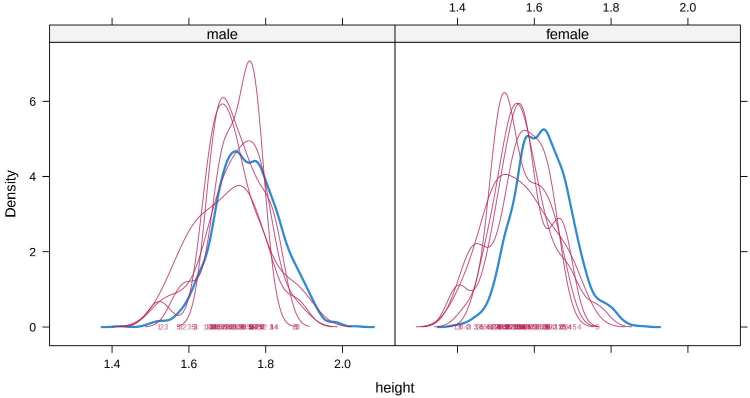
```r
densityplot(imp2)
```



The `densityplot()` shows that the distribution of imputed values of `creat` is wider than the distribution of the observed values and that imputed values of `height` are smaller than the observed values.

In some cases differences in distributions can be explained by strata in the data, however, here, `gender` does not explain the difference in observed and imputed values.

```
densityplot(imp2, ~height|gender, plot.points = T)
```



As an alternative, we might consider `race` to explain the differences

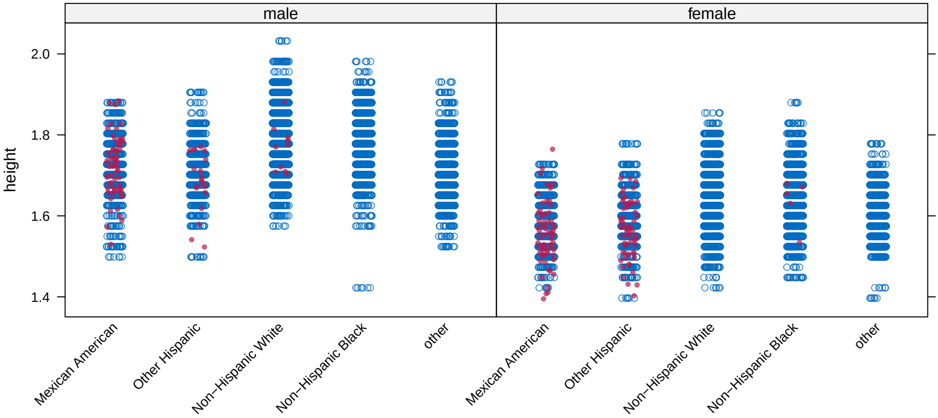
```
densityplot(imp2, ~height|race)

## Error in density.default(x = c(NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, :
need at least 2 points to select a bandwidth automatically
```

However, there are not enough missing values of `height` per categories of `race` to estimate densities.

```
with(NHANES, table(race = race, "height missing" = is.na(height)))

##                     height missing
## race                 FALSE TRUE
##   Mexican American     233   26
##   Other Hispanic       252   16
##   Non-Hispanic White   884    2
##   Non-Hispanic Black   618    1
##   other                451    0
```

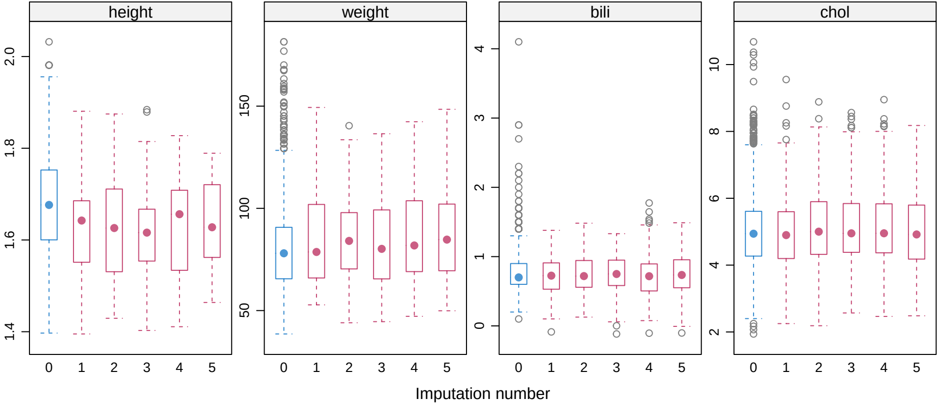
In that case, a `stripplot()` may be better suited. Here we can also split the data for `gender` and `race`.

```
stripplot(imp2, height ~ race|gender, pch = c(1, 20),
          scales = list(x = list(rot = 45)))
```



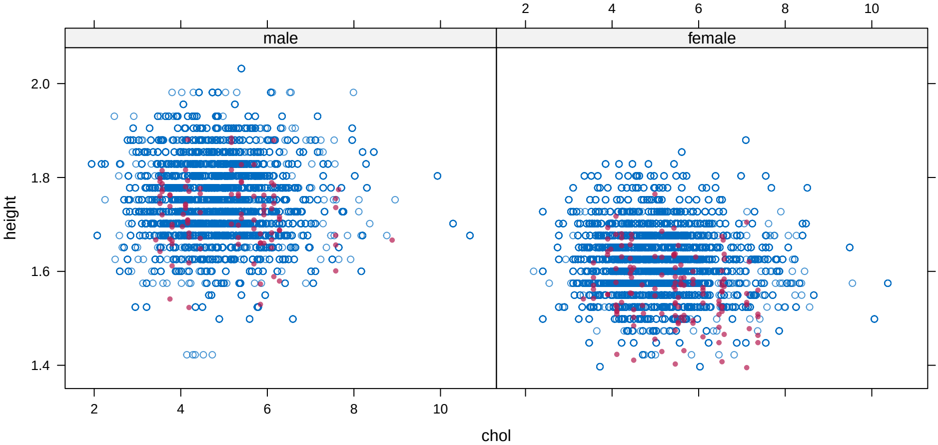
Alternatively, observed and imputed data can be represented by box-and-whisker plots:

```
bwplot(imp2, height + weight + bili + chol ~.imp)
```



The function `xyplot()` allows multivariate investigation of the imputed versus observed values.

```
xyplot(imp2, height ~ chol|gender, pch = c(1,20))
```

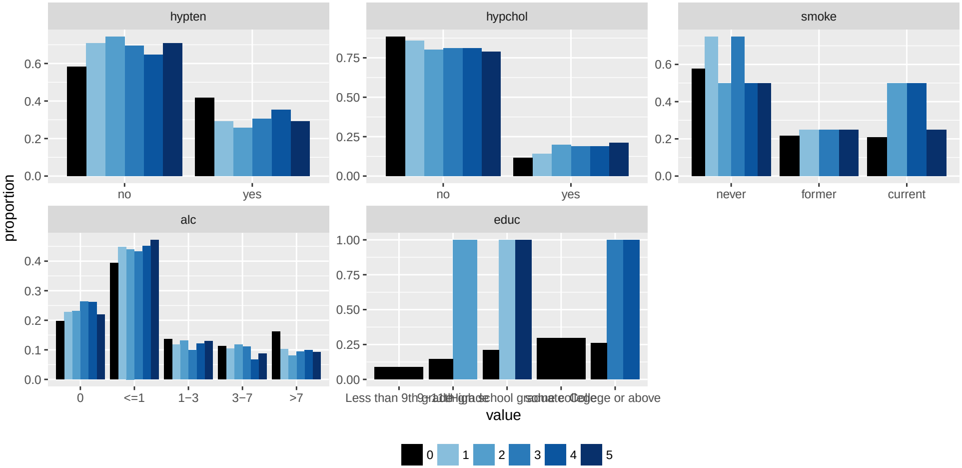


All of the above graphs displayed only continuous imputed variables. For categorical variables we can compare the proportion of values in each category.

mice does not provide a function to do this, but we can write one ourselves, as for instance the function `probplot()`, for which the syntax can be found here. The function can be loaded into R using:

```
devtools::source_gist("0d00375da460dd33839b98faeee2fdab",
                       filename = "probplot.R")
```

```r
probplot(imp2)
```

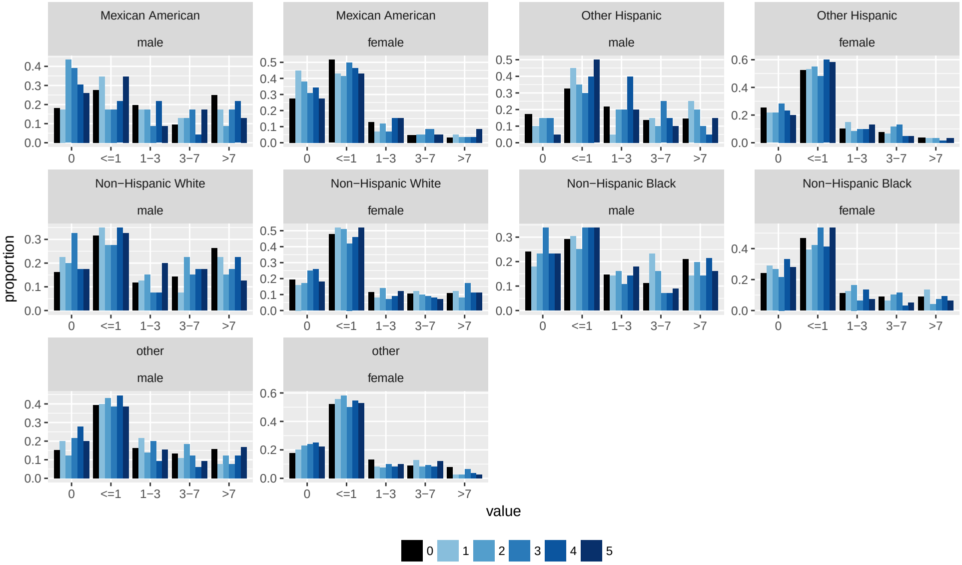


`smoke` and `educ` have very few missing values (4 and 1, respectively), so we do not need to worry about differences between observed and imputed data for those variables.

For `alc`, missing values are imputed by the lower consumption categories more often than we would expect from the observed data, `hypten` is less frequent and `hypchol` a bit more frequent, in the imputed data compared to the observed.

If we expect that `gender` and `race` might explain the differences for `hypten`, we can include those factors into the plot.

```r
probplot(imp2, formula = alc ~ race + gender)
```



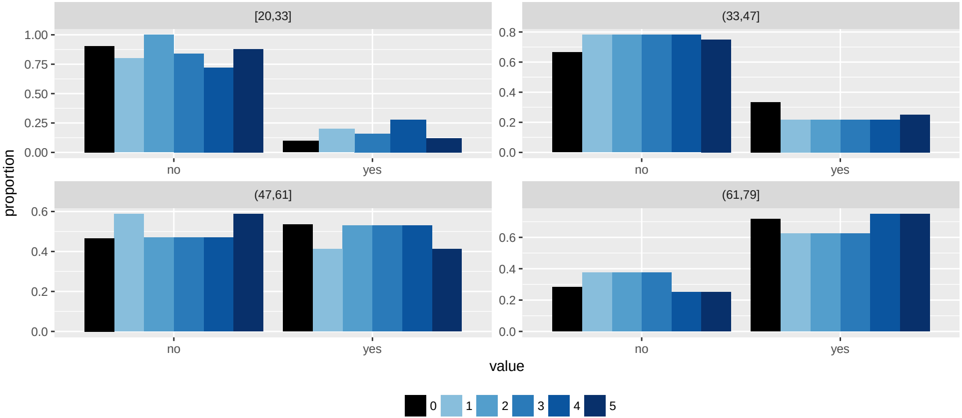
Since hypertension is more common in older individuals, we may want to investigate if `age` can explain the differences in imputed values of `hypten`.

```
round(sapply(split(NHANES[, "age"], addNA(NHANES$hypten)), summary), 1)

##           no  yes <NA>
## Min.    20.0 20.0 20.0
## 1st Qu. 28.0 47.0 30.0
## Median  38.0 59.0 38.5
## Mean    40.7 56.9 41.5
## 3rd Qu. 51.0 68.0 50.8
## Max.    79.0 79.0 78.0
```

The table shows that the `age` structure of participants with missing `hypten` is very similar to the `age` structure of participants without `hypten`.

Plotting the proportions of observed and imputed `hypten` separately per quartile of `age`:

```
probplot(imp2, formula = hypten ~ cut(age, quantile(age), include.lowest = T))
```



For the first three quartiles of `age` the distribution of the imputed values is similar to the distribution of the observed values of `hypten`.

```
with(NHANES, table(age = cut(age, quantile(age), include.lowest = T),
                   hypten, exclude = NULL))

##           hypten
## age         no yes <NA>
##   [20,33] 556  60   25
##   (33,47] 401 202   32
##   (47,61] 267 306   17
##   (61,79] 173 436    8
```

Since there are only 8 missing values for the last quartile, differences between observed and imputed values are insignificant.

The log of the automatic changes (slide 89) is returned as part of the `mids` object:

```
head(imp2$loggedEvents)

##   it im co   dep     meth out
## 1  1  1 10 smoke multinom
## 2  1  1 11   alc multinom
## 3  1  1 12  educ multinom
## 4  1  2 10 smoke multinom
## 5  1  2 11   alc multinom
## 6  1  2 12  educ multinom
```

With columns

`it`	iteration number
`im`	imputation number
`co`	column number in the data
`dep`	dependent variable
`meth`	imputation method used
`out`	names of altered or removed predictors

Once we have confirmed that our imputation was successful, we can move on to the analysis of the imputed data.
For example, we might be interested in the following logistic regression model:

```
glm(DM ~ age + gender + hypchol + BMI + smoke + alc,
    family = "binomial")
```

To fit the model on each of the imputed datasets, we do not need to extract the data from the `mids` object, but can use `with()`.

```
mod1 <- with(imp2, glm(DM ~ age + gender + hypchol + BMI + smoke + alc,
                       family = "binomial"))
```

`mod1` is an object of class `mira` and has elements

```
names(mod1)

## [1] "call"      "call1"     "nmis"      "analyses"
```

where `mod1$analyses` is a list containing the fitted model for each imputed dataset.

Pooled results can be obtained using `pool()` and its summary

```
options(width = 90)
res1 <- summary(pool(mod1))
round(res1, 3)

##                est    se       t       df Pr(>|t|)  lo 95  hi 95 nmis   fmi lambda
## (Intercept) -7.133 0.429 -16.616 2240.573    0.000 -7.975 -6.291   NA 0.013  0.012
## age          0.056 0.004  12.952 2468.059    0.000  0.048  0.065    0 0.001  0.001
## gender2     -0.422 0.128  -3.304 1749.968    0.001 -0.673 -0.172   NA 0.026  0.025
## hypchol2    -0.064 0.188  -0.342  403.591    0.732 -0.434  0.305   NA 0.095  0.090
## BMI          0.106 0.009  11.576 2265.730    0.000  0.088  0.123   73 0.012  0.011
## smoke2       0.129 0.144   0.896 2432.312    0.370 -0.153  0.411   NA 0.005  0.004
## smoke3       0.080 0.166   0.479 1953.715    0.632 -0.246  0.405   NA 0.021  0.020
## alc2        -0.277 0.150  -1.845  475.882    0.066 -0.573  0.018   NA 0.085  0.082
## alc3        -0.570 0.220  -2.585 1192.205    0.010 -1.002 -0.137   NA 0.042  0.041
## alc4        -0.466 0.246  -1.894  154.639    0.060 -0.952  0.020   NA 0.165  0.155
## alc5        -0.741 0.220  -3.375  747.163    0.001 -1.172 -0.310   NA 0.063  0.060
```

Pooling with `mice::pool()` is available only for some types of model. Generally, it should work for models for which the functions `coef()` and `vcov()` can extract the (fixed effects) coefficients and variance-covariance matrix of these coefficients.

An alternative is offered by the package **mitools** and the function `MIcombine()`.

mice currently has two functions available for evaluating model fit / model comparison

For **linear** regression models the pooled R^2 can be calculated using `pool.r.squared()`

```
mod2 <- with(imp2, lm(SBP ~ DM + age + hypten))
pool.r.squared(mod2, adjusted = TRUE)

##                est     lo 95     hi 95         fmi
## adj R^2 0.3243655 0.2940335 0.3547556 0.006885114
```

The argument `adjusted` specifies whether the adjusted R^2 or the standard R^2 is returned.

The function `pool.compare()` allows to compare **nested models** (i.e., models where one is a special case of the other, with some parameters fixed to zero) using a **Wald test**.

Example: To test if `smoke` has a relevant contribution to the model for `DM` from above we re-fit the model without `smoke` and compare the two models:

```
mod3 <- with(imp2, glm(DM ~ age + gender + hypchol + BMI + alc,
                       family = "binomial"))
# Wald test
pool.compare(mod1, mod3)$pvalue

##           [,1]
## [1,] 0.6577086
```

The package **miceadds** extends **mice**, for example with the following functionality:

Combine χ^2 or F statistics from multiply imputed data:

```
miceadds::micombine.chisquare(dk, df, display = TRUE, version = 1)
miceadds::micombine.F(values, df1, display = TRUE, version = 1)
```

These functions take vectors of statistics computed on each imputed dataset and pool them.

Calculate correlation or covariance of imputed data:

```
miceadds::micombine.cor(mi.res, variables = NULL, conf.level = 0.95,
                        method = "pearson", nested = FALSE, partial = NULL)
miceadds::micombine.cov(mi.res, variables = NULL, conf.level = 0.95,
                        nested = FALSE)
```

These functions take `mids` objects as input.

The function `complete()` allows extraction of the imputed data from a `mids` object:

```
mice::complete(x, action = 1, include = FALSE)
```

- `x`: the `mids` object
- `action`:
  - `1`, . . . , `m` (single imputed dataset)
  - `"long"`: long format (imputed data stacked vertically)
  - `"broad"`: wide format (imputed data combined horizontally; ordered by imputation)
  - `"repeated"`: (like `"broad"`, but ordered by variable)
- `include`: include the orginal data?
  (if `action` is `"long"`, `"broad"` or `"repeated"`)

The function `mids2spss()` allows the export of imputed data (`mids` objects) to SPSS.

```
mids2spss(imp2,
          filedat = "datafile.txt", # the file containing the data
          filesps = "importsyntax.sps" # syntax to convert .txt to .sav
)

## Data values written to N:/Projects/MultipleImputationCourse/Slides/datafile.txt
## Syntax file written to N:/Projects/MultipleImputationCourse/Slides/importsyntax.s
```

Data from `mids` objects can also be exported to MPLUS using `mids2mplus()`.

To increase the number of imputed datasets without re-doing the initial m imputations, a second set of imputations can be done and the two `mids` objects combined using `ibind()`.

```
# same syntax as before, but different seed
imp2b <- update(imp2, post = post, maxit = 20, seed = 456)
imp2combi <- ibind(imp2, imp2b)
imp2combi$m
```

```
## [1] 10
```

The function cbind.mids() allows to add columns to a mids object. The extra columns can either be a data.frame, matrix, vector or factor or another mids object.
For examle data columns that should be part of the imputed data for completeness, but are not needed in the imputation.

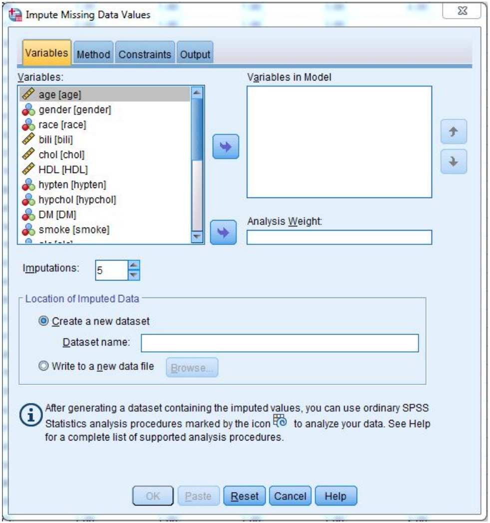
```
extravar <- rnorm(nrow(NHANES))
impextra <- mice::cbind.mids(x = imp2, extravar = extravar)
```

Note: cbind() just adds columns to the data, you need to make sure they are sorted correctly so that the rows of the new data are from the same subjects as the corresponding rows in the impute data.

A walk-through how to do multiple imputation in SPSS can be found

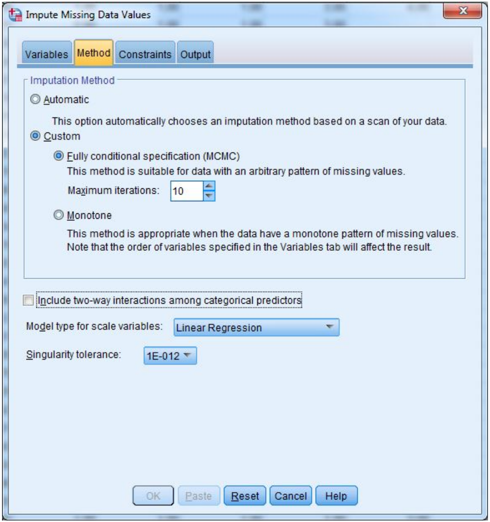
- **for older versions of SPSS**
  > Help
    > Case Studies
      > Missing Values Option
        > Multiple Imputation
          > Using Multiple Imputation to Complete and Analyze a Dataset
- **for newer versions online**
  `https://www.ibm.com/support/knowledgecenter/en/SSLVMB_24.0.0/spss/tutorials/mi_table.html`

The procedure itself is located in the menu
> Analyze
  > Multiple Imputation
    > Impute Missing Data Values



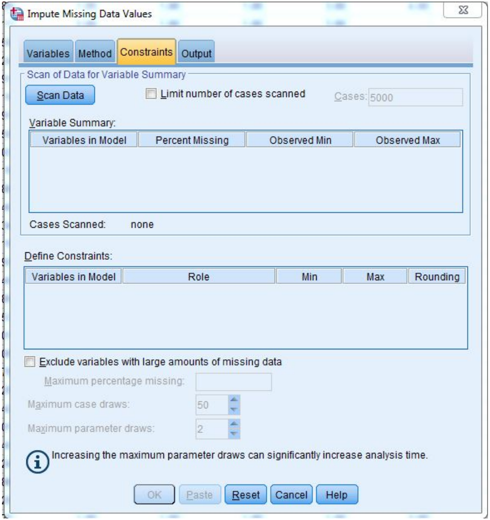
SPSS lets you

- specify number of imputations



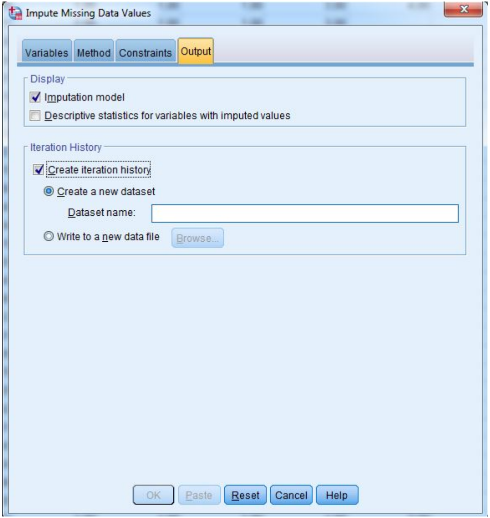
SPSS lets you

- specify number of imputations
- specify number of iterations
- include interactions
- chose between lin. regression and pmm for continuous variables



SPSS lets you

- specify number of imputations
- specify number of iterations
- include interactions
- chose between lin. regression and pmm for continuous variables
- restrict variables to certain values
- select which variables to impute
- select which variables are used as predictors



SPSS lets you

- specify number of imputations
- specify number of iterations
- include interactions
- chose between lin. regression and pmm for continuous variables
- restrict variables to certain values
- select which variables to impute
- select which variables are used as predictors
- save the iteration history

SPSS does not let you

- select between linear regression imputation and pmm **per** variable (only jointly for all variables)
- uses **only one donor** in predictive mean matching
- uses logistic regression for any categorical variable
- chose per imputation model which variables should be used as predictors
- re-calculate variables during the iterations
- ...

In SPSS the list of models that can be pooled is available in the help under

> Help
  > Missing Values Option
    > Multiple Imputation
      > Analyzing Multiple Imputation Data

`https://www.ibm.com/support/knowledgecenter/en/SSLVMB_24.0.0/spss/mva/mi_analysis.html`

Part III
When MICE might fail

Outline of Part III

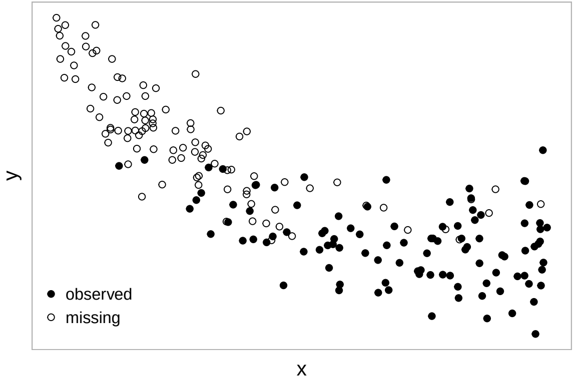
Outline of Part III (cont.)

Outline of Part III (cont.)

Consider the case where the **analysis model** (which we assume to be true) is

$$y = \beta_0 + \beta_1 x + \boldsymbol{\beta_2 x^2} + \dots,$$

i.e., y has a **quadratic relationship** with x, and x is incomplete.

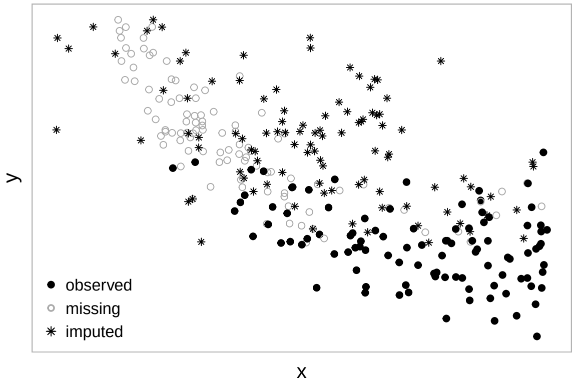


The original data show a curved pattern.

The model used to **impute** x when using MICE (naively) is

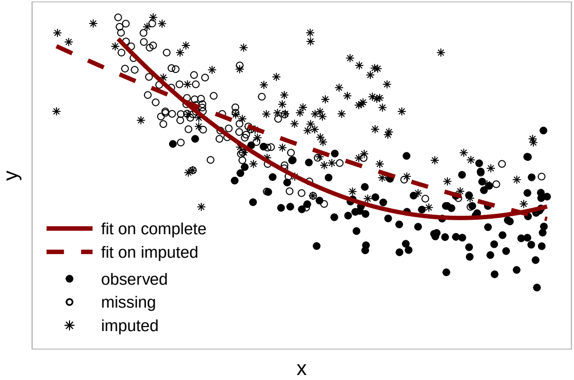
$$x = \theta_{10} + \theta_{11} y + \dots,$$

i.e., a **linear relation** between x and y is assumed.



The imputed values **distort the curved pattern** of the original data.

The model fitted on the imputed data gives **severely biased results**; the non-linear shape of the curve has almost completely disappeared.

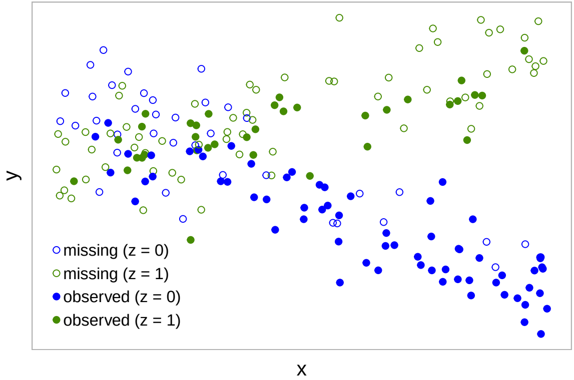


	β	95% CI
Original		
Intercept	-0.99	[-1.04, -0.95]
x	-0.61	[-0.66, -0.56]
x^2	0.52	[0.43, 0.62]
Imputed		
Intercept	-0.73	[-0.79, -0.66]
x	-0.53	[-0.62, -0.44]
x^2	0.07	[-0.07, 0.22]

Another example occurs when the analysis model (again, assumed to be true) is

$$y = \beta_0 + \beta_x x + \beta_z z + \boldsymbol{\beta_{xz} xz} + \ldots,$$

i.e., y has a **non-linear relationship** with x due to the **interaction term**.

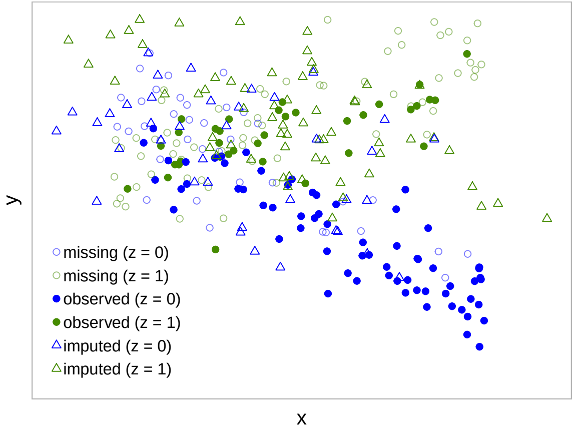


The original data shows a "<" shaped pattern.

The model used to impute x when using MICE (naively) is

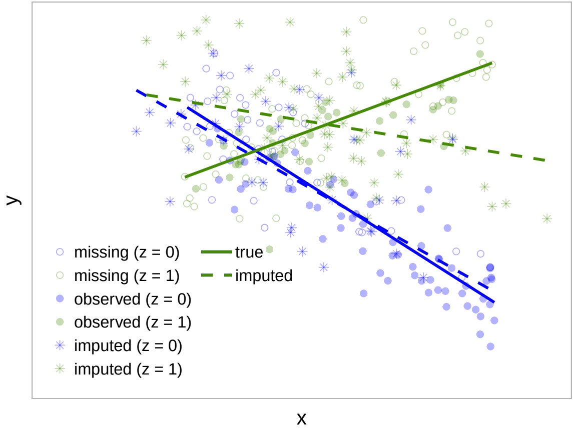
$$x = \theta_{10} + \theta_{11}y + \theta_{12}z + \ldots,$$

i.e., a linear relation between x and y is assumed.



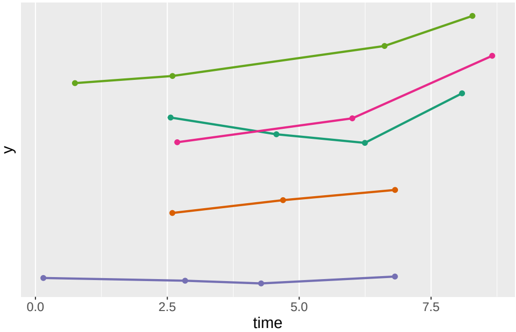
The "<" shaped pattern of the true data is **distorted by the imputed values**.

And the analysis on these naively imputed values leads to **severely biased estimates**.



	β	95% CI
Original		
Intercept	-0.96	[-1.00, -0.92]
x	-0.59	[-0.65, -0.53]
z	0.5	[0.45, 0.56]
x:z	0.94	[0.85, 1.03]
Imputed		
Intercept	-0.96	[-1.01, -0.91]
x	-0.52	[-0.61, -0.44]
z	0.46	[0.39, 0.54]
x:z	0.37	[0.24, 0.51]

Another setting where imputation with MICE is not straightforward is when the **outcome variable is longitudinal**.



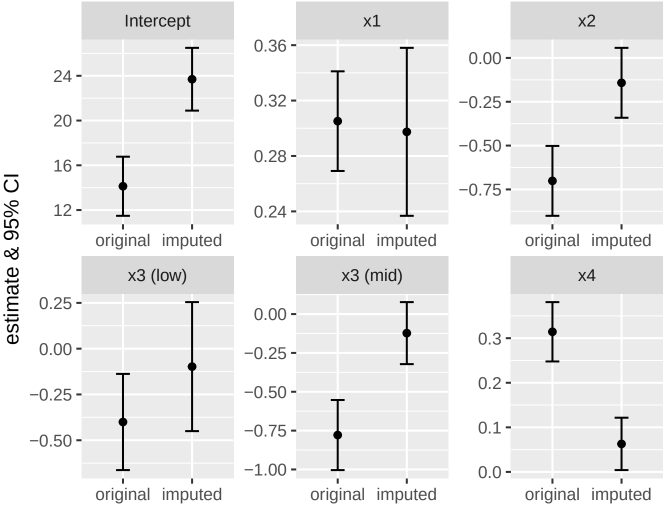
ID	y	x_1	x_2	x_3	x_4	time
5	✓	✓	NA	✓	✓	2.56
5	✓	✓	NA	✓	✓	4.57
5	✓	✓	NA	✓	✓	6.25
5	✓	✓	NA	✓	✓	8.09
6	✓	✓	NA	NA	✓	2.60
6	✓	✓	NA	NA	✓	4.69
6	✓	✓	NA	NA	✓	6.82
8	✓	✓	✓	✓	NA	2.69
8	✓	✓	✓	✓	NA	6.01
8	✓	✓	✓	✓	NA	8.66
18	✓	✓	NA	✓	✓	0.75
18	✓	✓	NA	✓	✓	2.60
18	✓	✓	NA	✓	✓	6.62
18	✓	✓	NA	✓	✓	8.28
⋮	⋮	⋮	⋮	⋮	⋮	⋮

Here, $x_1, \ldots, x_4$ are baseline covariates, i.e., not measured repeatedly.

If we use MICE in the data in this (long) format, each row would be regarded as independent, which may cause bias and **inconsistent imputations**.

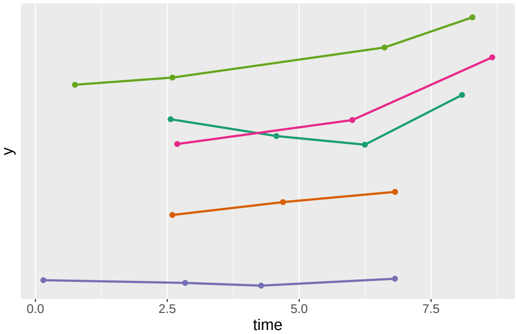
Imputed values of baseline covariates are imputed with different values, creating data that could not have been observed.

ID	y	x_1	x_2	x_3	x_4	time
5	✓	✓	boy	✓	✓	2.56
5	✓	✓	girl	✓	✓	4.57
5	✓	✓	girl	✓	✓	6.25
5	✓	✓	girl	✓	✓	8.09
6	✓	✓	girl	high	✓	2.60
6	✓	✓	boy	mid	✓	4.69
6	✓	✓	girl	high	✓	6.82
8	✓	✓	✓	✓	38.27	2.69
8	✓	✓	✓	✓	38.45	6.01
8	✓	✓	✓	✓	40.71	8.66
18	✓	✓	boy	✓	✓	0.75
18	✓	✓	boy	✓	✓	2.60
18	✓	✓	boy	✓	✓	6.62
18	✓	✓	boy	✓	✓	8.28
⋮	⋮	⋮	⋮	⋮	⋮	⋮



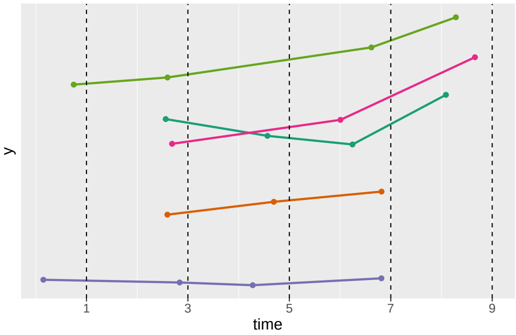
Estimates can be severely biased.

In some settings **imputation in wide format** may be possible.



ID	y	x_1	x_2	x_3	x_4	time
5	✓	✓	NA	✓	✓	2.56
5	✓	✓	NA	✓	✓	4.57
5	✓	✓	NA	✓	✓	6.25
5	✓	✓	NA	✓	✓	8.09
6	✓	✓	NA	NA	✓	2.60
6	✓	✓	NA	NA	✓	4.69
6	✓	✓	NA	NA	✓	6.82
8	✓	✓	✓	✓	NA	2.69
8	✓	✓	✓	✓	NA	6.01
8	✓	✓	✓	✓	NA	8.66
18	✓	✓	NA	✓	✓	0.75
18	✓	✓	NA	✓	✓	2.60
18	✓	✓	NA	✓	✓	6.62
18	✓	✓	NA	✓	✓	8.28
⋮	⋮	⋮	⋮	⋮	⋮	⋮

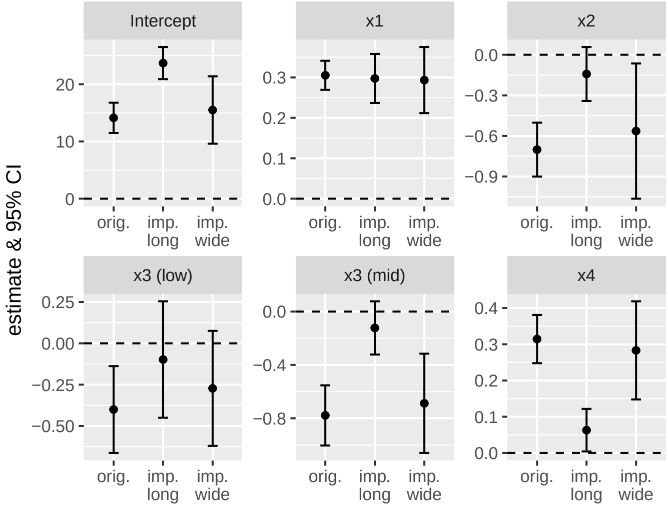
In some settings **imputation in wide format** may be possible.



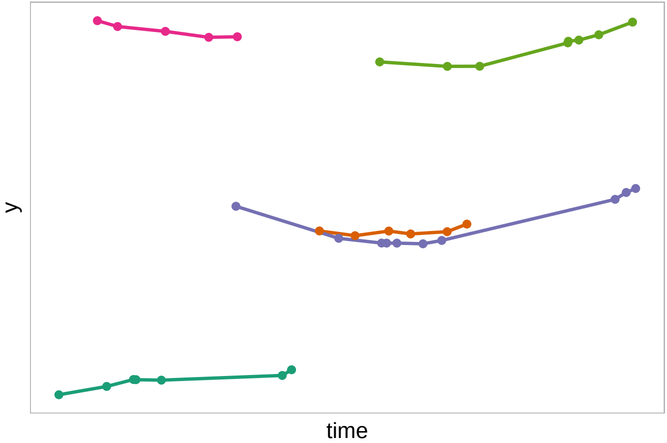
ID	y	x_1	x_2	x_3	x_4	time
5	✓	✓	NA	✓	✓	2.56
5	✓	✓	NA	✓	✓	4.57
5	✓	✓	NA	✓	✓	6.25
5	✓	✓	NA	✓	✓	8.09
6	✓	✓	NA	NA	✓	2.60
6	✓	✓	NA	NA	✓	4.69
6	✓	✓	NA	NA	✓	6.82
8	✓	✓	✓	✓	NA	2.69
8	✓	✓	✓	✓	NA	6.01
8	✓	✓	✓	✓	NA	8.66
18	✓	✓	NA	✓	✓	0.75
18	✓	✓	NA	✓	✓	2.60
18	✓	✓	NA	✓	✓	6.62
18	✓	✓	NA	✓	✓	8.28
⋮	⋮	⋮	⋮	⋮	⋮	⋮

id	y.1	y.3	y.5	y.7	y.9	time.1	time.3	time.5	time.7	time.9	...
5	NA	35.19	34.94	34.81	35.56	NA	2.56	4.57	6.25	8.09	...
6	NA	33.74	33.94	34.09	NA	NA	2.6	4.69	6.82	NA	...
8	NA	34.82	NA	35.18	36.13	NA	2.69	NA	6.01	8.66	...
18	35.71	35.82	NA	36.28	36.73	0.75	2.6	NA	6.62	8.28	...
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋱

In this **wide format data** frame, missing values in outcome and measurement times need to be imputed (to be able to use them as predictors to impute covariates), even though we would not need to impute them for the analysis (mixed model valid when outcome measurements are M(C)AR).

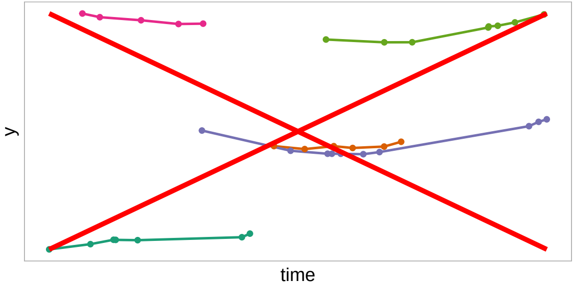


Better, but very large confidence intervals.



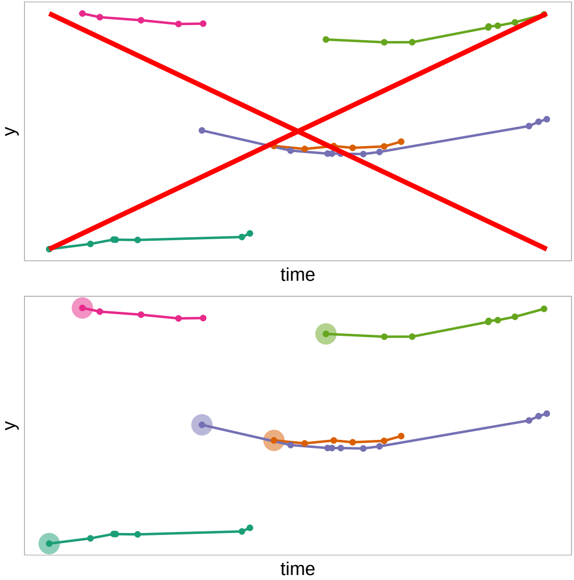
When the data is very **unbalanced**, i.e., there are no clear cut-offs in time, transformation to wide format is not possible.

(Or at least transformation to wide format leads to variables with high proportions of missing values.)



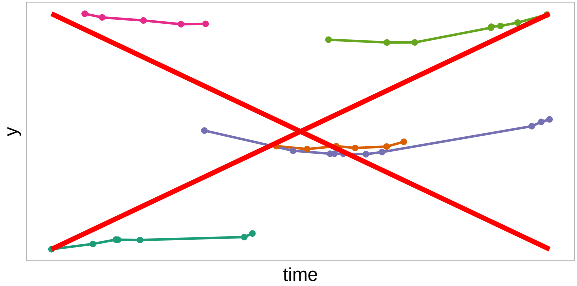
Naive approaches that are sometimes used are to

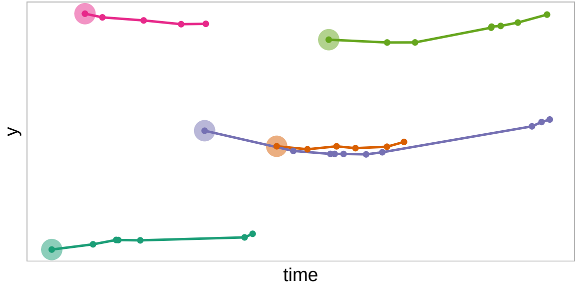
- **ignore the outcome** in the imputation



Naive approaches that are sometimes used are to

- **ignore the outcome** in the imputation, or to
- use only the **first/baseline outcome**





Naive approaches that are sometimes used are to

- **ignore the outcome** in the imputation, or to
- use only the **first/baseline outcome**

However, **important information may be lost**, resulting in invalid imputations and biased results.

In **survival analysis**, the aim is to estimate the effect of covariates on the **time until an event** of interest happens.

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In the commonly used method: **Cox proportional hazards model**

$$h(t) = h_0(t)\exp(x\beta_x + z\beta_z),$$

- $h(t)$: hazard = the instantaneous risk of an event at time t, given that the event has not occurred until time t
- $h_0(t)$: unspecified baseline hazard
- x and z: **incomplete** and **complete** covariates, respectively

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- $h_0(t)$: unspecified baseline hazard
- x and z: **incomplete** and **complete** covariates, respectively

Survival outcomes are usually represented by the **observed event time** T and the **event indicator** D ($D = 1$: event, $D = 0$: censored).

Naive use of MICE treats the columns in the data set containing T and D just like any other variable, and the resulting imputation model for X would have the form

$$p(x \mid T, D, \mathbf{z}) = \theta_0 + \theta_1 T + \theta_2 D + \theta_3 z + \ldots .$$

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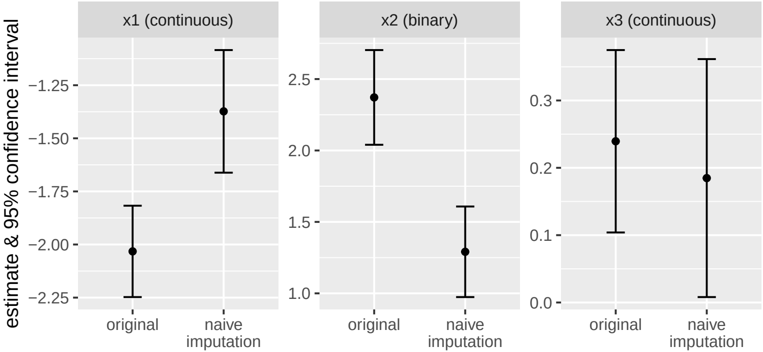
$$p(x \mid T, D, \mathbf{z}) = \theta_0 + \theta_1 T + \theta_2 D + \theta_3 z + \dots.$$

The correct conditional distribution of x given the other variables is, however,

$$\log p(x \mid T, D, z) = \log p(x \mid z) + D(\beta_x x + \beta_z z) - H_0(T) \exp(\beta_x x + \beta_z z) + const.,$$

where $H_0(T)$ is the cumulative baseline hazard.[20]

Using the naively assumed imputation model can lead to **severe bias**:



(Results from MICE imputation with two incomplete normal and one incomplete binary covariate.)

13. Requirements for MICE to work (well)
13.1. Joint and conditional distributions

Recall: The MICE algorithm is based on the idea of Gibbs sampling.

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

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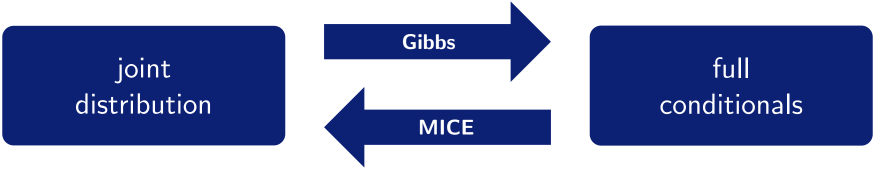

In MICE, the full conditionals are not derived from the joint distribution: we directly specify the full conditionals and hope a joint distribution exists.

The **uncertainty about whether a joint distribution exists** for the specified set of imputation models is often considered to be mainly a theoretical problem.

In practice, violations only have little impact on results in many applications.

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.

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.

Important requirements for MICE to work well include:

- Compatibility
- Congeniality
- MAR or MCAR (in the standard implementations)
- **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)

What went wrong in our previous examples?

When incomplete variables have **non-linear associations** with the outcome, or with each other, the requirement(s) of **compatibility and/or congeniality are violated**.

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.

To **avoid incompatible and uncongenial imputation models**, we need to

- specify the joint distribution
- and derive full conditionals / imputation models from this joint distribution

instead of specifying them directly.

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- specify the joint distribution
- and derive full conditionals / imputation models from this joint distribution

instead of specifying them directly.

Problem:
Especially in settings with several **variables of mixed type**, the joint distribution is usually not of any known form:

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

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

Approach 1: Multivariate Normal Model
Approximate the joint distribution by a known multivariate distribution (usually the normal distribution; this is the approach mentioned in Part I on slide 15)

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

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, $\boldsymbol{b}$:

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

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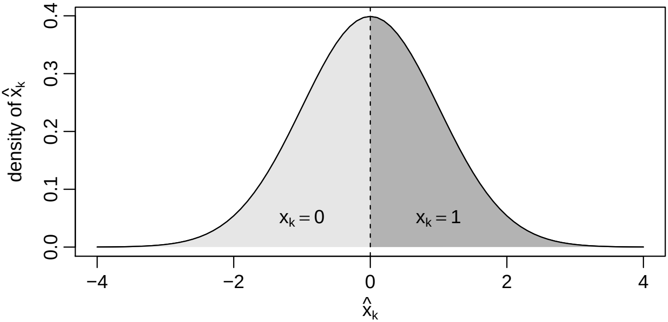
$$p(\boldsymbol{y}, \boldsymbol{x}_1, \ldots, \boldsymbol{x}_p \mid \mathbf{X}_c, \boldsymbol{\theta}, \boldsymbol{b}) \sim N(\boldsymbol{\mu}, \boldsymbol{\Sigma})$$

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**.

1. **Latent normal assumption:**

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



2. Specify models:

$$
\begin{aligned}
\boldsymbol{y} &= \boldsymbol{X}_c\beta_y + \boldsymbol{Z}_{\boldsymbol{y}}\,\boldsymbol{b}_{\boldsymbol{y}} + \varepsilon_{\boldsymbol{y}}\\
\boldsymbol{w} &= \boldsymbol{X}_c\beta_w + \boldsymbol{Z}_{\boldsymbol{w}}\,\boldsymbol{b}_{\boldsymbol{w}} + \varepsilon_{\boldsymbol{w}}\\
\hat{\boldsymbol{x}}_1 &= \boldsymbol{X}_c\beta_{x_1} + \qquad \varepsilon_{\boldsymbol{x_1}}\\
&\vdots \qquad\qquad\qquad \vdots\\
\hat{\boldsymbol{x}}_p &= \boldsymbol{X}_c\beta_{x_p} + \qquad \varepsilon_{\boldsymbol{x_p}}
\end{aligned}
$$

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

$$
\begin{aligned}
\boldsymbol{y} &= \boldsymbol{X}_c\beta_y + \boldsymbol{Z_y}\boxed{\boldsymbol{b_y}} + \boxed{\varepsilon_{\boldsymbol{y}}}\\
\boldsymbol{w} &= \boldsymbol{X}_c\beta_w + \boldsymbol{Z_w}\boldsymbol{b_w} + \varepsilon_{\boldsymbol{w}}\\
\hat{\boldsymbol{x}}_1 &= \boldsymbol{X}_c\beta_{x_1} + \varepsilon_{\boldsymbol{x_1}}\\
&\vdots\\
\hat{\boldsymbol{x}}_p &= \boldsymbol{X}_c\beta_{x_p} + \varepsilon_{\boldsymbol{x_p}}
\end{aligned}
$$

multivariate normal (optional, but suggested)

multivariate normal

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.

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

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

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

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

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

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

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.

That the analysis model is part of the specification of the joint distribution has several advantages:

- The outcome is **automatically included in the imputation** procedure.
- The outcome does not appear in any of the predictors of the imputation models:
  - **no need to approximate** complex outcomes,
  - **no need to summarize** complex outcomes.
- The parameters of interest are obtained directly
  ➡ imputation and analysis in one step
- **Non-linear associations** or interactions involving incomplete covariates are specified in the analysis model and thereby **automatically taken into account**

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

Advantages:

- flexible with regards to outcome type
- univariate conditional distributions of incomplete covariates can be chosen according to type of variable
- non-linear associations and interactions can be taken into account
- assures congeniality and compatible imputation models

Disadvantages:

- separate models need to be specified per incomplete variable: takes more time and consideration
- the joint distribution is of unknown form and sampling may be more computationally intensive

15. Imputation with non-linear functional forms

In the following we will not only consider the R package **mice**, but also three additional packages, **JointAI**, **smcfcs** and **jomo**, that provide alternatives to **mice**.

These three packages use Bayesian methodology to impute values, but once imputed datasets are obtained, standard complete data methods can be used.

jomo and **smcfcs** perform multiple imputation and create imputed datasets that can then be analysed the same way data imputed by **mice** would be analysed.

JointAI works fully Bayesian and performs the analysis and imputation simultaneously, so that the results from the analysis model of interest are obtained directly.

There is no strategy for MICE that can guarantee valid imputations when non-linear functional forms and/or interactions are involved, but some settings in **mice** may help to reduce bias in the resulting estimates.

For imputation of variables that have non-linear associations

- `pmm` often works better than `norm`,
- Just Another Variable approach can reduce bias in interactions,
- `quadratic` can help to impute variables with quadratic association.

In the **Just Another Variable (JAV)** approach the non-linear form (or interaction term) is calculated in the incomplete data, added as a column to the dataset and imputed as if it was just another variable.

`quadratic` provides imputation of covariates that have a quadratic association with the outcome, using the "polynomial combination" method.[17, pp. 139–141], [19].

This is to ensure the imputed values for x and x^2 are consistent, and to reduce bias in the subsequent analysis that uses x and x^2.

In my experience, using `quadratic` can lead to numerical problems.

To demonstrate the approaches, we use a simulated example dataset `DFnonlin`, with

- continuous outcome y
- continuous (normal) covariate x (50% missing values MCAR)
- quadratic effect of x on y
- binary covariate z (complete)
- interaction between x and z

To demonstrate the approaches, we use a simulated example dataset `DFnonlin`, with

- continuous outcome y
- continuous (normal) covariate x (50% missing values MCAR)
- quadratic effect of x on y
- binary covariate z (complete)
- interaction between x and z

In the naive approach, we leave all settings to the defaults.

```
# naive imputation, using only y, x, z
impnaive <- mice(DF_nonlin, printFlag = F)
```

We use two different JAV approaches:

JAV: calculating the quadratic and interaction term before imputation

```
# add quadratic term and interaction to data
DF2 <- DF_nonlin
DF2$xx <- DF2$x^2
DF2$xz <- DF2$x * DF2$z

# JAV imputation
impJAV <- mice(DF2, printFlag = F, maxit = 20)
```

JAV2: additionally using an interaction between z and y

```
# add interaction between y and z to data
DF3 <- DF2
DF3$yz <- DF3$y * DF3$z

# JAV imputation with additional interaction
impJAV2 <- mice(DF3, printFlag = F, maxit = 20)
```

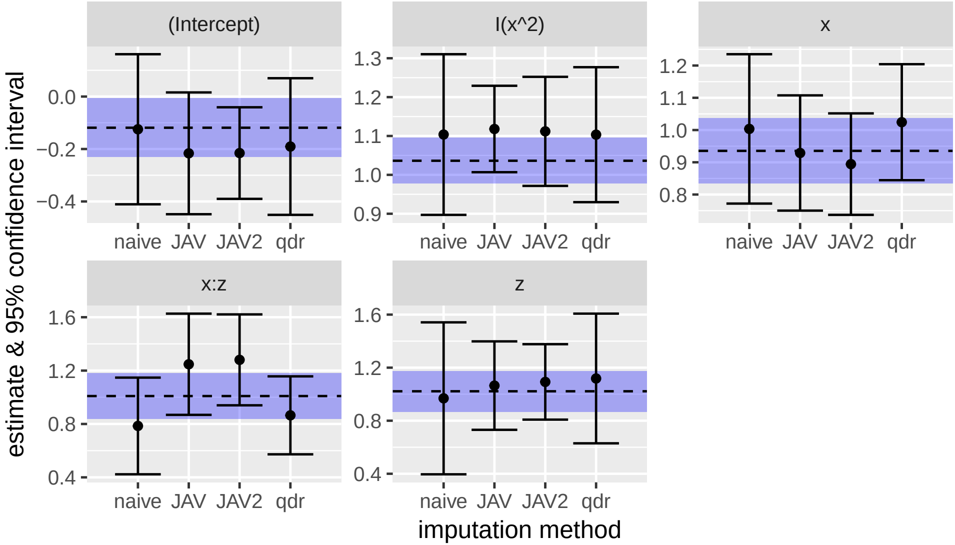
We also try using imputation method `quadratic`.

```
# adapt the imputation method for quadratic imputation
methqdr <- impJAV$meth
methqdr[c("x", "xx", "xz")] <- c("quadratic", "~I(x^2)", "~I(x*z)")

# adapt the predictor matrix
predqdr <- impJAV$pred
predqdr[, "xx"] <- 0

impqdr <- mice(DF2, meth = methqdr, pred = predqdr,
               printFlag = F, maxit = 10)
```

Note: there were warning messages about numerical issues for this approach.



For this example, **none of the approaches provided satisfying results**.

The package **JointAI** uses the **sequential factorization approach** to perform simultaneous analysis and imputation.[4, 3]

JointAI (version 0.1.0) can handle

- linear regression
- generalized linear regression
- linear mixed models

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

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

```r
install.packages("JointAI")
```

The development version (containing bug fixes and other improvements) can be installed from GitHub

```r
install.packages("devtools")
devtools::install_github(repo = "JointAI", username = "NErler")
```

A detailed explanation of the functionality is given in the help files of the package, and a vignette with an in-depth example analysis will be available soon.

The syntax we use to analyse and impute the current example using **JointAI** is similar to the specification of a standard linear model using `lm()`.

```
library(JointAI)
JointAI_nonlin <- lm_imp(y ~ x*z + I(x^2), data = DF_nonlin, n.iter = 2500)
```

Convergence of the Gibbs sampler can be checked using a traceplot.

```
traceplot(JointAI_nonlin)
```

Results (no separate analysis & pooling is necessary) can be obtained with the `summary()` function:

```
res_JointAI_nonlin <- summary(JointAI_nonlin)
```

The package **smcfcs** performs multiple imputation using *substantive model compatible fully conditional specification*, a **hybrid approach between FCS and sequential factorization**.[1]

smcfcs (version 1.3.0) can handle

- linear regression,
- logistic regression,
- poisson regression,
- Cox proportional hazard models, and
- competing risk survival models,

while ensuring compatibility between analysis model and imputation models.

For more information see the help files and the vignette.

The syntax to impute the data in the current example using the package **smcfcs** is:

```
library(smcfcs)
smcfcs_nonlin <- smcfcs(originaldata = DF_nonlin, smtype = "lm",
                        smformula = "y~x*z + I(x^2)",
                        method = c("", "norm", ""),
                        rjlimit = 3000, numit = 20)
```

The convergence of the procedure should be checked, for example with the following syntax:

```
par(mfrow = c(2,3), mar = c(2, 2, 0.5, 0.5), mgp = c(2, 0.6, 0))
for(i in 1:dim(smcfcs_nonlin$smCoefIter)[2]) {
  matplot(t(smcfcs_nonlin$smCoefIter[, i, ]), type = 'l', ylab = '')
}
```

To be able to use the convenient pooling function from the **mice** package we first need to convert the imputed data (which is a list) to a `mids` object.

This can be done with the function `datalist2mids()` from the **miceadds** package.

```
library(miceadds)
impobj_smcfcs_nonlin <- datalist2mids(smcfcs_nonlin$impDatasets)
```

The `mids` object can then be pooled and summarized as we have seen before with `mids` objects created by `mice()`.

```
models_smcfcs_nonlin <- with(impobj_smcfcs_nonlin, lm(y ~ x*z + I(x^2)))
res_smcfcs_nonlin <- summary(pool(models_smcfcs_nonlin))
```

The package **jomo** performs **joint model imputation** using the multivariate normal approach, with **extensions to assure compatibility** between analysis and imputation models.[2]

jomo (version 2.6-1) can handle

- linear regression,
- generalized linear regression,
- linear mixed models,
- generalized linear mixed models, and
- Cox proportional hazards models.

Using **jomo** we can impute the data in the current example as follows:

```
library(jomo)
jomo_nonlin <- jomo.lm(y ~ x*z + I(x^2), data = DF_nonlin)
```

To check the convergence of the model, the corresponding function with ending `.MCMCchain()` as to be used.

```
jomo_nonlinMCMC <- jomo.lm.MCMCchain(y ~ x*z + I(x^2), data = DF_nonlin)

par(mfcol = c(2, 3), mar = c(3, 2.5, 0.5, 0.5), mgp = c(2, 0.6, 0))
apply(jomo_nonlinMCMC$collectbeta[1, ,], 1, plot, type = "l",
      xlab = 'iteration', ylab = '')
for (k in 1:dim(jomo_nonlinMCMC$collectomega)[1]) {
  apply(jomo_nonlinMCMC$collectomega[k, , ], 1, plot, type = "l",
        xlab = 'iteration', ylab = '')
}

apply(jomo_nonlinMCMC$collectbetaY[1, ,], 1, plot, type = "l",
      xlab = 'iteration', ylab = '')
plot(jomo_nonlinMCMC$collectvarY, type = 'l')
```

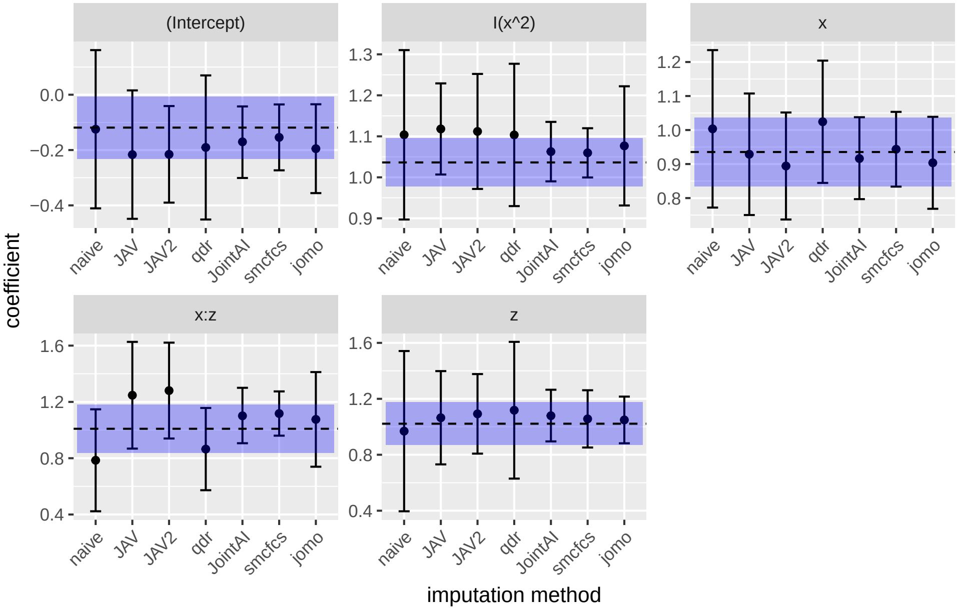
Again, we need to convert the output to a `mids` object using `datalist2mids()`. However, `jomo.lm()` returns a data frame, in which the original data and all imputed datasets are stacked onto each other.

`split()` splits the dataset by imputation number into a list of datasets, from which we need to exclude the first element (the original/incomplete data).

```
impobj_jomo_nonlin <- datalist2mids(split(jomo_nonlin,
                                          jomo_nonlin$Imputation)[-1])
```

With the resulting `mids` object, analysis of the imputed data and pooling of the results works as in the above examples.

```
models_jomo_nonlin <- with(impobj_jomo_nonlin, lm(y ~ x*z + I(x^2)))
res_jomo_nonlin <- summary(pool(models_jomo_nonlin))
```


(Intercept)
I(x^2)
x
x:z
z
coefficient
imputation method
naive
JAV
JAV2
qdr
JointAI
smcfcs
jomo

mice has functions to allow imputation of longitudinal (2-level) data.

- **Level 1:**
  repeated measurements (within subjects) or subjects (within classes)
- **Level 2:**
  time-constant/baseline covariates, between subjects effects, variables on the group level

Imputation methods for **level-1** variables:

- `2l.pan`
- `2l.norm`
- `2l.lmer`

Imputation methods for **level-2** variables:

- `2lonly.norm`
- `2lonly.pmm`
- `2lonly.mean`

`2l.pan` uses a linear two-level model with **homogeneous within group variances** using Gibbs sampling [14]. It needs the package **pan** to be installed.

`2l.pan` allows for different roles of predictor variables, that can be specified as different values in the `predictorMatrix`:

- grouping/ID variable: -2
- random effects (also included as fixed effects): 2
- fixed effects of group means: 3
- fixed effects of group means & random effects: 4

```r
# random effects of x in model for y
pred["y","x"] <- 2
# fixed effects of x and group mean of x
pred["y","x"] <- 3
# random effects of x and group mean of x
pred["y","x"] <- 4
```

`2l.norm` implements a (Bayesian) linear two-level model with **heterogenous** group variances.
In the current implementation all predictors should be specified as random effects (set to 2 in the `predictorMatrix`, because the algorithm does not handle predictors that are specified as fixed effects).

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`2l.lmer` imputes univariate systematically and sporadically missing data using a two-level normal model using `lmer()` from package **lme4** (developed in the context of individual patient meta analysis. [7, 6])

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In the current implementation all predictors should be specified as random effects (set to 2 in the `predictorMatrix`, because the algorithm does not handle predictors that are specified as fixed effects).

`2l.lmer` imputes univariate systematically and sporadically missing data using a two-level normal model using `lmer()` from package **lme4** (developed in the context of individual patient meta analysis. [7, 6])

`2lonly.norm` and `2lonly.pmm` can be used to impute level-2 variables (in combination with `2l.pan` for level-1 variables).

In all case, the group identifier ("id" variable") needs to be set to -2 in the `predictorMatrix`.

`2lonly.mean` imputes values with the mean of the observed values per class. This method should only be used to fill in values that are known to be constant per class and have some values observed in each class.

Example: In a multi-center trial the type of some medical equipment is known to be the same for all patients treated in the same hospital, but not filled in for some patients.

As an example, we will impute the second (unbalanced) longitudinal data example from above. The data contain

- $x1$ (complete)
- $x2$ (binary, 30% missing values)
- $x3$ (3 categories, 30% missing values)
- $x4$ (continuous/normal, 30% missing values)
- y (longitudinal outcome)
- *time* (time variable with quadratic effect)
- *id* (id variable)

Since there is no 2-level method for categorical data, we use `2lonly.pmm` to impute $x2$ and $x3$.

As usual, we start with the setup run of `mice()`

```
imp0 <- mice(DFexlong2, maxit = 0)
meth <- imp0$method
pred <- imp0$predictorMatrix
```

and adjust the imputation `method` and `predictorMatrix`

```
meth[c("x2", "x3")] <- "2lonly.pmm"
meth[c("x4")] <- "2lonly.norm"

pred[, "id"] <- -2  # identify id variable
pred[, "ti"] <- 0 # don't use time-point indicator
```

We can then perform the imputation.

```
imp <- mice(DFexlong2, maxit = 10, meth = meth, pred = pred, printFlag = F)
```

The imputed data can be analysed using either `lmer()` from the package **lme4**, or `lme()` from **nlme**. Here we use the former.

```
library(lme4)
models <- with(imp, lmer(y ~ x1 + x2 + x3 + x4 + time + I(time^2) +
                           (time|id)))
mice_longimp <- summary(pool(models))
```

Currently, there is only limited documentation and examples available that show how to use these functions in **mice**.
Technical details can be obtained from the methodological references given in the help files of the R functions.

A vignette on multi-level imputation with **mice** is available. It gives a more elaborate example of how to analyse such data.

Linear mixed models with incomplete covariates can also be analysed using the package **JointAI**.

The syntax is analogous the syntax used in `lme()` of the package **nlme**.

```
library(JointAI)
JointAI_long <- lme_imp(y ~ x1 + x3 + x2 + x4 + time + I(time^2),
                        random = ~time|id, data = DFexlong2,
                        n.iter = 5000)
```

Again, convergence of the Gibbs sampler should be checked using a traceplot,

```
traceplot(JointAI_long)
```

before obtaining the results:

```
res_JointAI_long <- summary(JointAI_long)
```

Contrary to the two-level imputation of **mice**, non-linear associations are appropriately handled.

In **jomo**, the functions `jomo.lmer()` and `jomo.glmer()` can be used to impute longitudinal data with normal or non-normal outcomes.

In the multi-level setting, the level of each variable needs to be specified (1: repeated measurements, 2: baseline covariates), and ordered the same way the variables occur in the data frame.

```
library(jomo)
# specify the level of each variable
lvl <- c("id" = 1, y = 1, x1 = 2, x2 = 2, x3 = 2, x4 = 2, time = 1)

jomo_long <- jomo.lmer(formula = y ~ x1 + x2 + x3 + x4 +
                         time + I(time^2) + (time|id),
                       data = DFexlong2[, names(lvl)], level = lvl)
```

Like in the example with non-linear effects, convergence of the imputation needs to be checked.

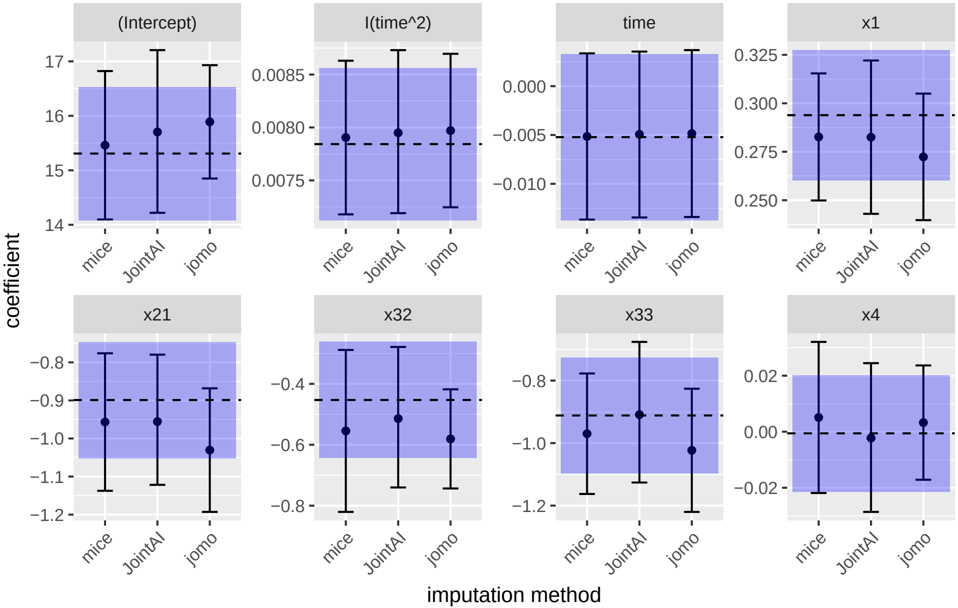
Again, the stacked dataframe returned by `jomo.lmer()` needs to be split by imputation number and the original data excluded, before fitting the model and pooling the results.

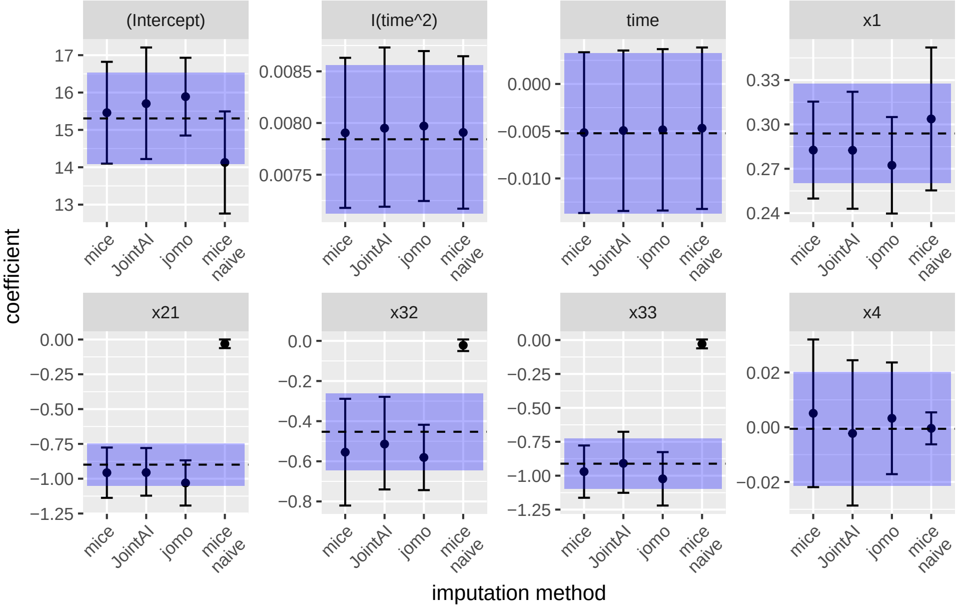
```
library(miceadds)
impobj_jomo_long <- datalist2mids(split(jomo_long,
                                        jomo_long$Imputation)[-1])
models_jomo_long <- with(impobj_jomo_long,
                         lmer(y ~ x1 + x3 + x2 + x4 + time + I(time^2) +
                                (time|clus)))

res_jomo_long <- summary(pool(models_jomo_long))
```

(Note: `jomo.lmer()` re-names the grouping variable to `clus`).

As in the examples for non-linear functional forms, congeniality of imputation models is maintained.


(Intercept)
I(time^2)
time
x1
x21
x32
x33
x4
17
16
15
14
0.0085
0.0080
0.0075
0.000
−0.005
−0.010
0.325
0.300
0.275
0.250
−0.8
−0.9
−1.0
−1.1
−1.2
−0.4
−0.6
−0.8
−0.8
−1.0
−1.2
0.02
0.00
−0.02
mice
JointAI
jomo
coefficient
imputation method


(Intercept)
I(time^2)
time
x1
x21
x32
x33
x4
17
16
15
14
13
0.0085
0.0080
0.0075
0.000
−0.005
−0.010
0.33
0.30
0.27
0.24
0.00
−0.25
−0.50
−0.75
−1.00
−1.25
0.0
−0.2
−0.4
−0.6
−0.8
0.02
0.00
−0.02
mice
JointAI
jomo
mice naive
coefficient
imputation method

On slide 145 we have seen the rather complex formula for imputation of an incomplete covariate in survival data.

White et al. [20] derived versions of this model for different settings (binary or continuous incomplete covariate X, and continuous, categorical or no complete covariate Z) and investigated how to best approximate it.

They found that when **covariate effects and cumulative incidences are rather small**, using **Z, D and $H_0(T)$**, and possibly an interaction term, as predictor variables in the imputation for X in MICE may work satisfactorily.

However, in practice $H_0(T)$ is unspecified.

Two main ideas:

- If covariate effects β_x and β_z are small, $H_0(t) \approx H(t)$, which can be approximated by the **Nelson-Aalen estimator**.
- **Estimate $H_0(T)$ in an additional step** inside the MICE procedure by fitting a Cox model on the imputed data.

Neither of these approaches takes into account uncertainty about $H_0(t)$ (but the impact is likely to be small).

Two main ideas:

- If covariate effects β_x and β_z are small, $H_0(t) \approx H(t)$, which can be approximated by the **Nelson-Aalen estimator**.
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Neither of these approaches takes into account uncertainty about $H_0(t)$ (but the impact is likely to be small).

Based on results from their simulation study, White et al. conclude that **using Z, D and the Nelson-Aalen estimator $\hat{H}(T)$** as predictors for the imputation of X worked best.

However, some **bias towards the null** should be expected when covariates have large effects.

In **mice**, `nelsonaalen()` can be used to **calculate the Nelson-Aalen estimator**, to use it as covariate in the imputation.

```
survdat$H0 <- nelsonaalen(survdat, timevar = Time, statusvar = event)
```

Then, we can prepare the imputation using the same steps as in previous examples:

```
# setup run
imp0 <- mice(survdat, maxit = 0)
meth <- imp0$method
pred <- imp0$predictorMatrix

# specify normal imputation for continuous covariates
meth[c("x1", "x3")] <- "norm"

# remove event time from predictor (high correlation with H0)
pred[, "Time"] <- 0
```

With the modified arguments `method` and `predictorMatrix` we run the imputation:

```
survimp <- mice(survdat, maxit = 10, method = meth, predictorMatrix = pred,
                printFlag = F)
```

To obtain the pooled results, we first fit the model of interest

```
cox_mice <- with(survimp, coxph(Surv(Time, event) ~ x1 + x2 + x3))
```

and pool and summarize the results.

```
res_mice_surv <- summary(pool(cox_mice))

## Warning in mice.df(m, lambda, dfcom, method):  Large sample assumed.
```

The warning message refers to the way the degrees of freedom for the formulas we saw in part I (slide 32) are calculated and can be ignored.

Using the package **smcfcs**, the same data can be imputed with the following syntax:

```
library(smcfcs)
smcfcs_surv <- smcfcs(originaldata = survdat, smtype = "coxph",
                      smformula = "Surv(Time, event) ~ x1 + x2 + x3",
                      method = c("", "", "logreg", "norm", "norm", ""),
                      numit = 20, rjlimit = 1500)
```

Convergence of the procedure should be checked, analogously to the previous example (see slide 172).

After the resulting object is converted to a `mids` object, fitting the model and pooling the results is identical to what was done with the data imputed by **mice**.

```
impobj_smcfcs_surv <- datalist2mids(smcfcs_surv$impDatasets)
models_smcfcs_surv <- with(impobj_smcfcs_surv,
                           coxph(Surv(Time, event) ~ x1 + x2 + x3))
res_smcfcs_surv <- summary(pool(models_smcfcs_surv))
```

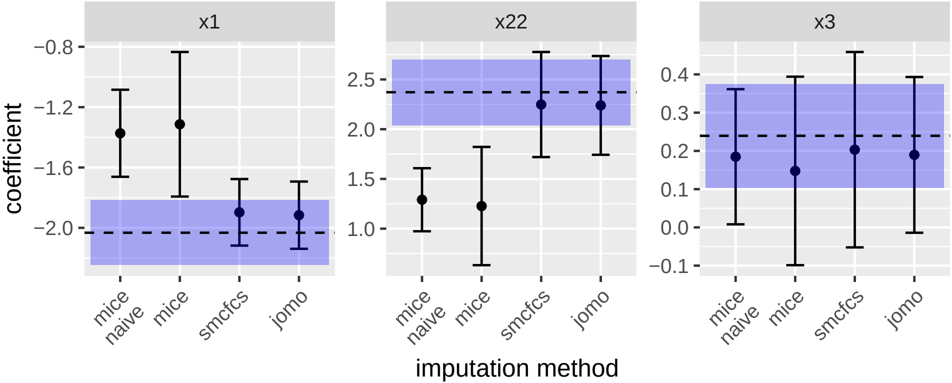
In the package **jomo**, the function `jomo.coxph()` can be used to impute our example survival data:

```
library(jomo)
jomo_surv <- jomo.coxph(formula = Surv(Time, event) ~ x1 + x2 + x3,
                        data = survdat)
```

Note that the convergence of the procedure should be checked using `jomo.coxph.MCMCchain()` (see the previous examples using **jomo**).

To analyse & pool the imputed data the steps are identical to the other examples:

```
impobj_jomo_surv <- datalist2mids(split(jomo_surv, jomo_surv$Imputation)[-1])
models_jomo_surv <- with(impobj_jomo_surv,
                         coxph(Surv(Time, event) ~ x1 + x2 + x3))
res_jomo_surv <- summary(pool(models_jomo_surv))
```



The naive mice approach, and mice using the Nelson-Aalen estimator give very biased results for the effects of $x1$ and $x2$, but performed acceptably well for $x3$.

Note that the **true effects** (log HR) of $x1$ and $x2$ are **very large** (-2 and 2.5, respectively), and represent the setting where the approximation by the Nelson-Aalen estimate is **expected to be biased**.

Summary & Conclusion of Part III

- MICE requires congenial & compatible imputation models to work well.
- When this is not the case, (naive) use of MICE can lead to biased results.
- Common settings that require special attention are
  - non-linear functional forms & interaction terms
  - longitudinal data
  - survival data
- When using the package **mice**, there are choices that can reduce bias
  - `pmm` tends to be less biased than `norm` for interactions or non-linear associations
  - JAV approach reduces bias in settings with interactions or non-linear associations
  - special 2-level imputation methods are available for longitudinal data
  - The Nelson-Aalen estimator can be used instead of the time variable for imputing survival data when effects are not too large.

Summary & Conclusion of Part III (cont.)

- Generally, problems are more severe when
  - proportions of missing values are large,
  - effect sizes are large,
  - little other covariate information is available.

  (Note that in the examples we had all of the above.)
- In settings where MICE may not provide valid imputations, alternative approaches are available and should be considered.
- R packages that provide such alternative approaches are for example:
  - JointAI (non-linear & longitudinal)
  - smcfcs (non-linear & survival)
  - jomo (non-linear, longitudinal & survival)
- These packages are very young.
  - Hence, they may still have some problems.
    ➡ Use them carefully! (and email the maintainer about problems)
  - They are under active development, so resolutions of bugs and features are frequently added.

Part IV
Multiple Imputation Strategies

Outline of Part IV

We have focussed on a few imputation methods that cover the most common types of data but there are many more methods implemented.

Imputation methods implemented in the **mice** package:

mice.impute.2l.lmer	mice.impute.logreg	mice.impute.passive
mice.impute.2l.norm	mice.impute.logreg.boot	mice.impute.pmm
mice.impute.2l.pan	mice.impute.mean	mice.impute.polr
mice.impute.2lonly.mean	mice.impute.midastouch	mice.impute.polyreg
mice.impute.2lonly.norm	mice.impute.norm	mice.impute.quadratic
mice.impute.2lonly.pmm	mice.impute.norm.boot	mice.impute.rf
mice.impute.cart	mice.impute.norm.nob	mice.impute.ri
mice.impute.lda	mice.impute.norm.predict	mice.impute.sample

Note: Just because a method is implemented does not mean you need to / should use it.

Imputation methods implemented in the **miceadds** package:

mice.impute.2l.binary	mice.impute.bygroup
mice.impute.2l.contextual.norm	mice.impute.eap
mice.impute.2l.contextual.pmm	mice.impute.grouped
mice.impute.2l.continuous	mice.impute.hotDeck
mice.impute.2l.eap	mice.impute.ml.lmer
mice.impute.2l.groupmean	mice.impute.plausible.values
mice.impute.2l.groupmean.elim	mice.impute.pls
mice.impute.2l.latentgroupmean.mcmc	mice.impute.pmm3
mice.impute.2l.latentgroupmean.ml	mice.impute.pmm4
mice.impute.2l.plausible.values	mice.impute.pmm5
mice.impute.2l.pls	mice.impute.pmm6
mice.impute.2l.pls2	mice.impute.tricube.pmm
mice.impute.2l.pmm	mice.impute.tricube.pmm2
mice.impute.2lonly.function	mice.impute.weighted.norm
mice.impute.2lonly.norm2	mice.impute.weighted.pmm
mice.impute.2lonly.pmm2	

In complex settings, variables may need to be **re-calculated** or **re-coded** after imputation:

- Use `complete()` to convert the imputed data from a `mids` object to a `data.frame`.
- Perform the necessary calculations.
- Convert the changed `data.frame` back to a `mids` object using the functions from the flow-diagram in the second practical (e.g., `as.mids()`, `datalist2mids()`, `imputationList()`, ...)

Not just in imputation: Set a **seed value** to create reproducible results.

- in R: `set.seed()`
- in `mice()`: `seed`

Early publications on multiple imputation suggested that $3-5$ imputations are sufficient and this is still a common assumption in practice.[12]

The reasoning behind using a small number of imputed datasets was that **storage of imputed data was "expensive"** (which is no longer the case) and a larger number of imputations would only have little advantage.[13]

More **recent work** from various authors [21, 17, 5] considers the efficiency of the pooled estimates, reproducibility of the results, statistical power of tests or the width of the resulting confidence intervals compared to the width of the true confidence intervals.

A **suggested rule of thumb** is that the **number of imputed datasets** should be similar to the **percentage of incomplete cases**.[21] Since this percentage depends on the size of the dataset, the **average percentage of missing values** per variable could be used as an alternative.[17]

Generally, using **more imputed datasets should be preferred**, especially in settings where the computational burden allows for it. Even though results are unlikely to change with a larger number of imputations, it can increase the efficiency and reproducibility of the results.

In imputation, generally the **advice is to include as much information as possible** in the imputation models. Using a large number of predictor variables makes the **MAR assumption more plausible** (and, hence, reduces bias due to MNAR missingness) and can **reduce uncertainty** about the missing values.

This can **work well in small or medium sized datasets** (20 – 30 separate variables, i.e. without interactions, variables derived from others, . . .) however, **in large datasets** (contain hundreds or thousands of variables) this is **not feasible**.[17]

For large datasets a possible strategy is to

- Include all **variables used in the analysis model(s)** (including the outcome!).
- Include auxiliary variables if they are **strong predictors of missingness**.
- Include auxiliary variables if they have **strong associations with the incomplete variables**.
- Use **auxiliary variables only if they do not have too many missing values** themselves (and are observed for most of the incomplete cases of the variable of interest).
- Use **auxiliary variables** only in those imputation models for which they are **relevant** (and exclude them for others using the predictor matrix).
- Calculate **summary scores** from multiple items referring to the same concept and use the summary score as predictor variable.

Multiple imputation is not a quick and easy solution for missing data. It requires care and knowledge about

- the data to be imputed (and the context of the data),
- the statistical method used for imputation, and
- the software implementation used.

Moreover

- Never accept default settings of software blindly.
- Question the plausibility of the MAR assumption. If it is doubtful, use sensitivity analysis.

Remember:

- Use as much information as possible
  - include all covariates and the outcome
  - use auxiliary information
  - use the most detailed version of variables if possible
- Avoid feedback from derived variables to their originals.
- **Imputation models must fit the data**
  (correct assumption of error distribution and functional forms and possible interactions of predictor variables).
- Think carefully how to handle variables that are derived from other variables.
- Consider the impact the visit sequence may have.
- Choose an appropriate number of imputations.
- Make sure the imputation algorithm has converged.
- Use common sense when evaluating if the imputed values are plausible.

In Part III of this course (and the second practical) we have worked with some R packages that perform imputation or provide functionality for missing data other than **mice**.

Currently, there are **222 packages** available on CRAN that **use the word "missing"** in either the titel or description of the package, **133** that **use either "impute" or "imputation"** and **47** that **use the word "incomplete"**.

Not all of these packages perform imputation or are usefull for our purposes, but even if we excluded those packages, the number of useful packages for dealing with missing data would still be to large to mention them all.

➡ **The mice package is often a good option, but certainly not the only option to perform imputation!**

In this second half of the course, we have focused on (multiple) imputation using R.

Naturally, R is not the only statistical software that can perform multiple imputation.

- **Stata, SAS and MPLUS** provide packages/functions to perform multiple imputation and pool the results.
- There are macros and additional packages available, e.g.e, **smcfcs** is implemented for **Stata** as well
- **SPSS** provides some functionality to perform MI

Finally, we should not forget that **MICE is not the only method to handle missing values**.

Besides MICE, **multiple imputation** can be performed in a **joint model approach** (as for instance implemented in the R package **jomo**).

Furthermore, **direct likelihood methods**, **fully Bayesian methods** (as implemented in **JointAI**) or **weighted estimating equations** are valid alternative approaches when data are incomplete.

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