EP16: Missing Values in Clinical Research: Multiple Imputation

2. Imputation Step

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Univariate Missing Data

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

X_1	X_2	X_3	X_4
✓	NA	✓	✓
✓	✓	✓	✓
✓	NA	✓	✓
$\vdots$	$\vdots$	$\vdots$	$\vdots$

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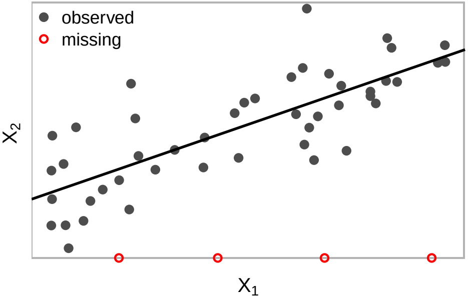
✓	NA	✓	✓
⋮	⋮	⋮	⋮

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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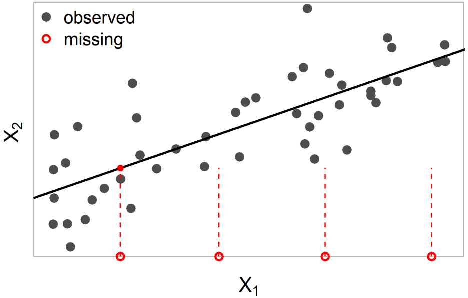
Idea: Predict values

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

Imputed/predicted value:

$\hat{x}_{i2} = \hat{\beta}_0 + \hat{\beta}_1 x_{i1} + \hat{\beta}_2 x_{i3} + \hat{\beta}_3 x_{i4}$



Univariate Missing Data

Problem:

- We can obtain **only one imputed value** per missing value (but we wanted a whole distribution).
- The predicted values do not take into account the added **uncertainty** due to the missing values.

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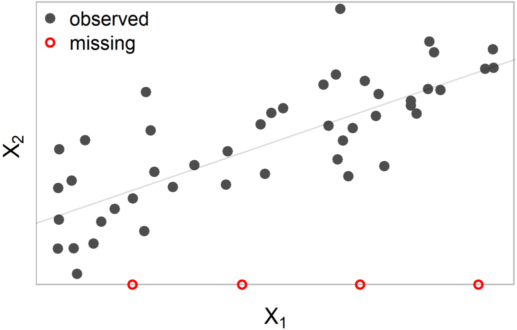
➡ We need to take into account **two sources of uncertainty**:

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

Univariate Missing Data

Taking into account uncertainty about the parameters:
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**.

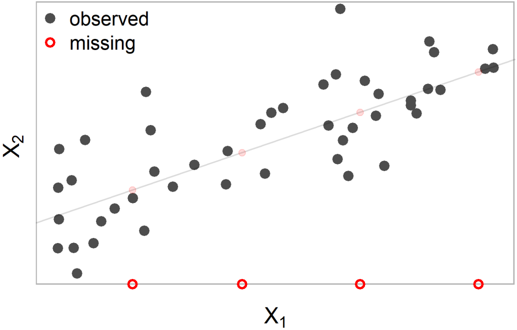


Univariate Missing Data

Taking into account uncertainty about the parameters:
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**.

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

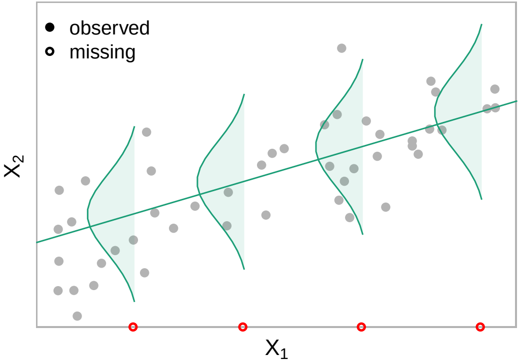


Univariate Missing Data

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
- the **variance** is determined by the variance of the residuals ε.



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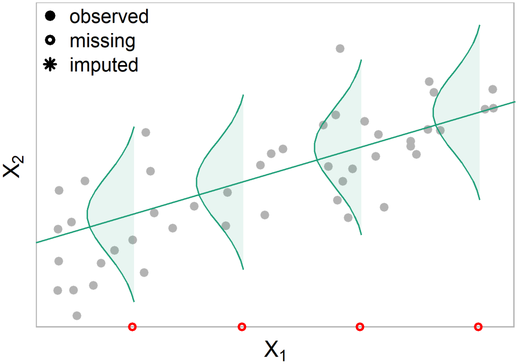
➡ sample imputed values from this distribution.



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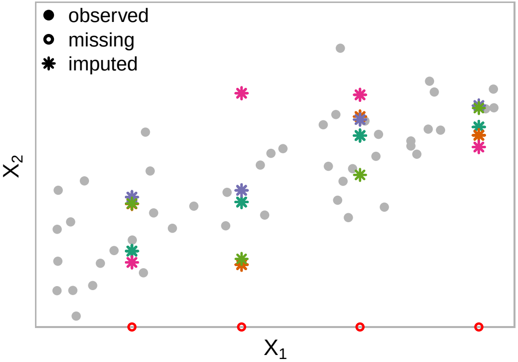

In the end, we obtain one imputed dataset for each colour.

Multivariate Missing Data

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

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

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
⋮	⋮	⋮	⋮

Multivariate Missing Data

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

Multivariate Missing Data

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

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Joint Model Imputation

(more details later)

MICE / FCS

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 univariate missing data.

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MICE / FCS

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

Moreover, MICE/FCS is

- an **iterative** procedure, specifically
- a **Markov Chain Monte Carlo (MCMC)** method,
- uses the idea of the **Gibbs sampler**

MICE / FCS: Sidenote

Markov Chain Monte Carlo

- a technique to **draw samples from a complex probability distribution**
- works via creating a chain of random variables (a Markov chain)
➡ The distribution that 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
- samples of the chain are then a sample from the complex distribution of interest

MICE / FCS: Sidenote

Gibbs sampling

- a MCMC method to obtain a **sample from a multivariate distribution**
- the multivariate distribution is split into a set of univariate full conditional distributions
- a sample from the multivariate distribution can be obtained by repeatedly drawing from each of the univariate distributions

MICE / FCS: 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)

$$\begin{array}{cc} & \begin{array}{cccc} X_{-2} & X_2 & X_{-2} & \end{array} \\ \mathbf{X} = & \begin{vmatrix} x_{1,1} & x_{1,2} & \cdots & x_{1,p} \\ x_{2,1} & x_{2,2} & \cdots & x_{2,p} \\ \vdots & \vdots & \ddots & \vdots \\ x_{n,1} & x_{n,2} & \cdots & x_{n,p} \end{vmatrix} \end{array}$$

$$\mathbf{R} = \begin{vmatrix} R_{1,1} & R_{1,2} & \cdots & R_{1,p} \\ R_{2,1} & R_{2,2} & \cdots & R_{2,p} \\ \vdots & \vdots & \ddots & \vdots \\ R_{n,1} & R_{n,2} & \cdots & R_{n,p} \end{vmatrix}$$

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\end{array}
\qquad
\mathbf{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:

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

The MICE Algorithm (Van Buuren, 2012)

```
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
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for $t$ in $1, \ldots, T$:                       ▷ loop through iterations
    for $j$ in $1, \ldots, p$:                   ▷ loop through variables



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



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

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end for
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    for $j$ in $1, \dots, p$:                             ▷ loop through variables
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        Draw parameters $\dot{\theta}_j^t \sim p(\theta_j^t \mid X_j^{obs}, \dot{X}_{-j}^t, R)$.
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    end for
end for
```

The MICE Algorithm (Van Buuren, 2012)

```
for $j$ in $1, \ldots, 4$:                                        ▷ 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 $j = 1$:                                   ▷ 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
```

The MICE Algorithm (Van Buuren, 2012)

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for $j$ in $1, \ldots, 4$:                                                    ▷ 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 $\dot{\theta}_2^1 \sim p(\theta_2^1 \mid X_2^{obs}, \dot{X}_{-2}^1, R)$.
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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 $\dot{\theta}_3^1 \sim p(\theta_3^1 \mid X_3^{obs}, \dot{X}_{-3}^1, R)$.
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for $j$ in $1, \ldots, 4$:                                          ▷ Setup
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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 $j = 4$:                                   ▷ 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 $\dot{\theta}_4^1 \sim p(\theta_4^1 \mid X_4^{obs}, \dot{X}_{-4}^1, R)$.
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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 $\dot{\theta}_1^2 \sim p(\theta_1^2 \mid X_1^{obs}, \dot{X}_{-1}^2, R)$.
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for $j$ in $1, \dots, 4$:                                                    ▷ Setup
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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 $j = 2$:                                          ▷ loop through variables
        Define currently complete data except $X_2$
        $\dot{X}^{2}_{-2} = \left(\dot{X}^2_1, \dot{X}^1_3, \dot{X}^1_4\right)$.
        Draw parameters $\dot{\theta}^2_2 \sim p(\theta^2_2 \mid X^{obs}_2, \dot{X}^2_{-2}, R)$.
        Draw imputations $\dot{X}^2_2 \sim p(X^{mis}_2 \mid \dot{X}^2_{-2}, R, \dot{\theta}^2_2)$.
    end for
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```

The MICE Algorithm

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.

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One run through the algorithm ➡ one imputed dataset.

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

Iterations & Convergence

- The **sequence of imputations** for one missing value (from starting value to final iteration) is called a **chain**.
- Each run through the MICE algorithm produces one chain per missing value.

Why iterations?

Iterations & Convergence

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- 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.

Iterations & Convergence

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

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= when the sampling distribution does not change any more
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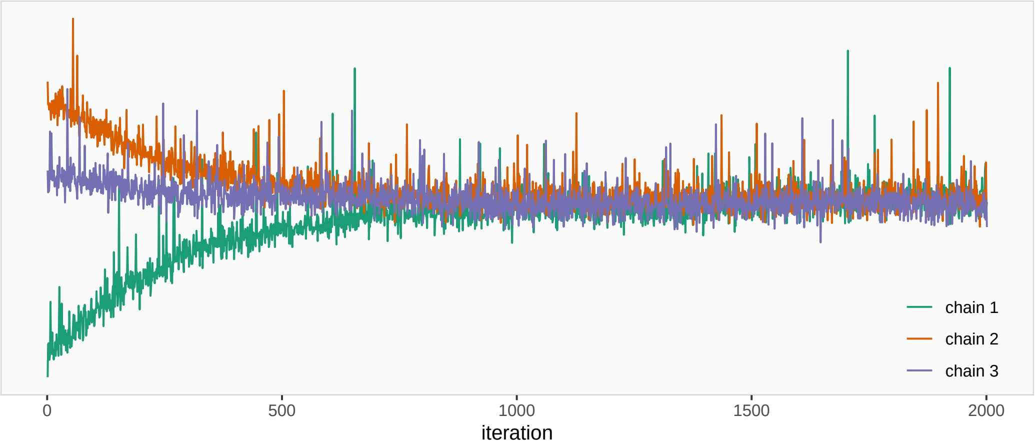
How to evaluate convergence?
The **traceplot** (x-axis: iteration number, y-axis: imputed value) should show a horizontal band

Checking Convergence



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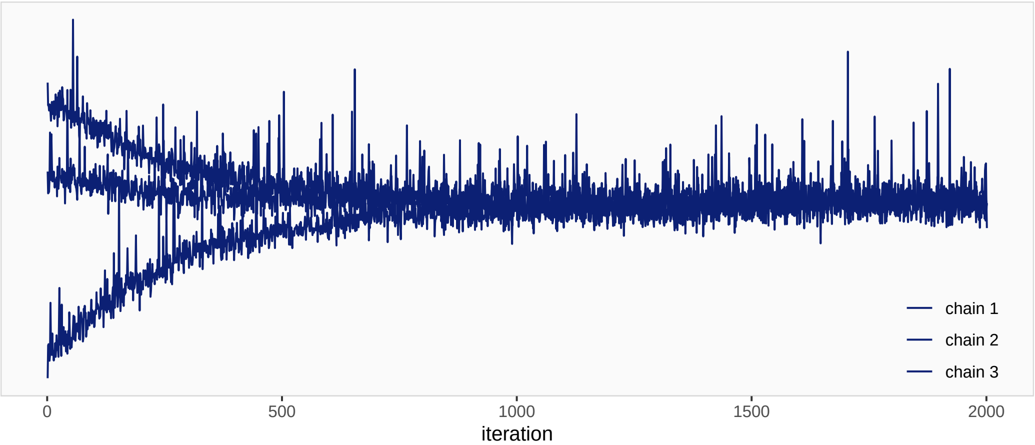
Checking Convergence



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Checking Convergence

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 MCMC chains

To check all chains separately could be very time consuming in large datasets.

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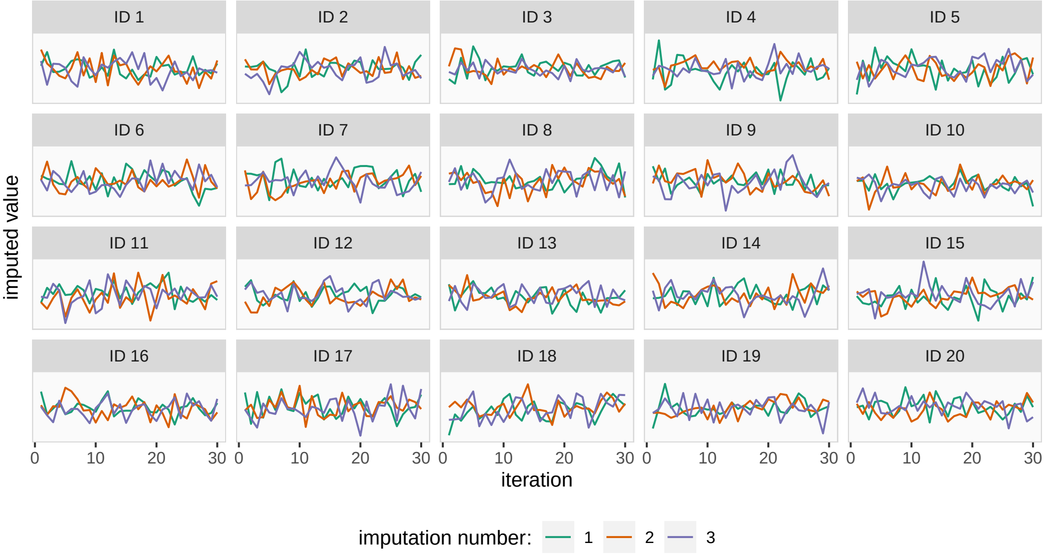
To check all chains separately could be very time consuming in large datasets.

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

Checking Convergence



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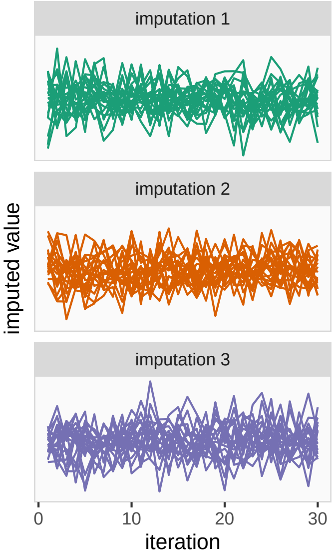

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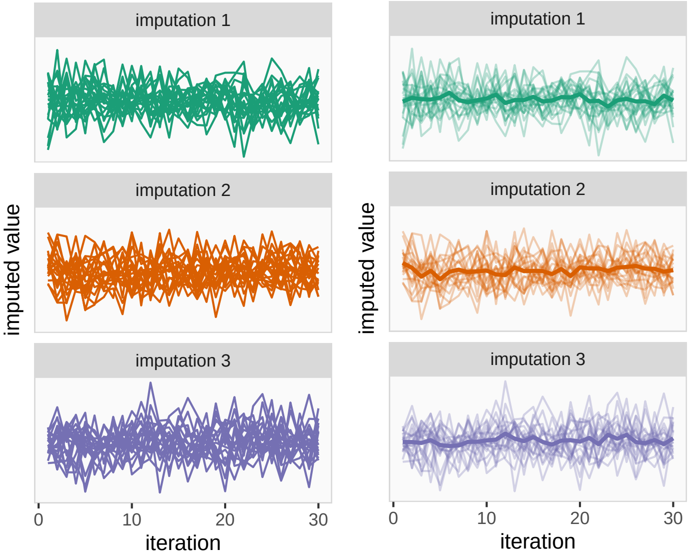
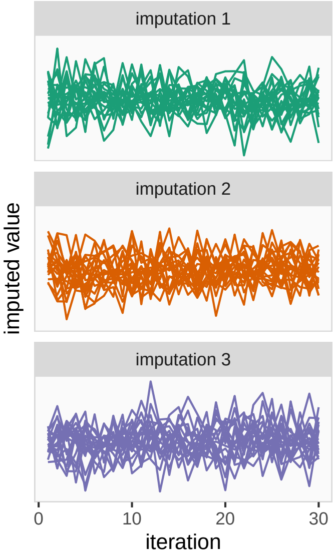
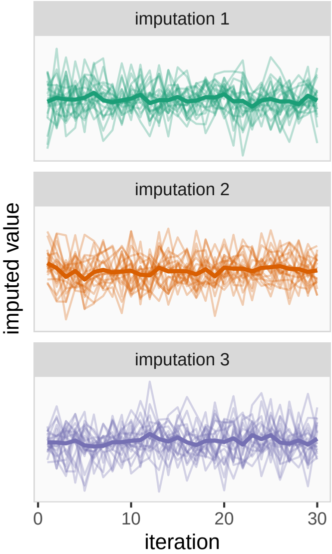
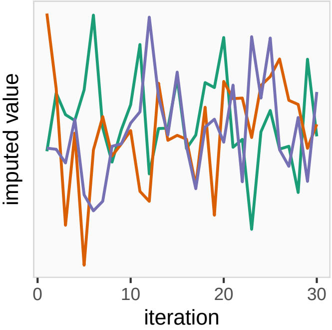


Checking Convergence







References

Van Buuren, S. (2012). *Flexible Imputation of Missing Data*. Taylor & Francis. https://stefvanbuuren.name/fimd/