Dealing with Missing Data

Challenges and Solutions

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Handling Missing Values is Easy!

Functions automatically exclude missing values:

```
## [...]
## Residual standard error:  2.305 on 69 degrees of freedom
##   (25 observations deleted due to missingness)
## Multiple R-squared:  0.09255, Adjusted R-squared:  0.02679
## F-statistic:  1.407 on 5 and 69 DF, p-value:  0.2325
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```

Imputation is super easy:

```r
library("mice")
imp <- mice(mydata)
```

However ...

Handling Missing Values Correctly is Not So Easy!

Complete case analysis is usually **biased**

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violation ➡ bias

Imputation ???

Remind me,
how did that imputation
thing work again???

Imputation

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filling in missing values with (good) guesses

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Important:

Missing values ➡ **uncertainty**
This needs to be taken into account!!!

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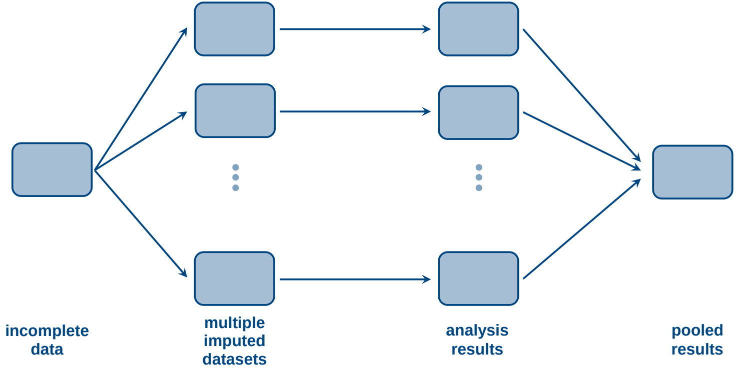
Donald Rubin (in the 1970s):
Represent each missing value with **multiple imputed values**

Multiple Imputation

Note:
Imputation is not the only approach to handle missing values.
(Also: maximum likelihood, inverse probability weighting, ...)

Multiple Imputation



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

Imputation Step

Two main approaches

Joint Model Multiple Imputation

- the "original" approach
- often using a multivariate normal distribution

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Multiple Imputation with Chained Equations (MICE)

- also: **Fully Conditional Specification** (**FCS**)
- now often considered the gold standard

Multiple Imputation with Chained Equations (MICE)

For each incomplete variable, specify a $\underbrace{\text{model using } \textbf{all other variables}}_{\text{full conditionals}}$:

x_1	x_2	x_3	x_4	$\dots$
✓	✓	NA	NA	$\dots$
NA	✓	✓	NA	$\dots$
✓	NA	NA	✓	$\dots$
$\vdots$	$\vdots$	$\vdots$	$\vdots$	

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⋮	⋮	⋮	⋮	

$$x_1 \sim x_2 + x_3 + x_4 + \dots$$
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$$\vdots$$

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$$

For example:

- linear regression
- logistic regression
- ...

Multiple Imputation with Chained Equations (MICE)

MICE is an iterative algorithm:

- start with initial guess

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- update x_2 based on new x_1 and initial values of $x_3, x_4, \dots$
- ...

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NA	✓	✓	NA	$\dots$
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- update x_1 based on initial values of $x_2, x_3, x_4, \ldots$
- update x_2 based on new x_1 and initial values of $x_3, x_4, \ldots$
- $\ldots$
- update x_1 again, based on updated $x_2, x_3, x_4, \ldots$
- $\ldots$

x_1	x_2	x_3	x_4	$\ldots$
✓	✓	NA	NA	$\ldots$
NA	✓	✓	NA	$\ldots$
✓	NA	NA	✓	$\ldots$
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MICE makes assumptions

(**Imputation**) methods make certain **assumptions**, e.g.:

- **missingness** is M(C)AR
- the incomplete variable has a certain conditional **distribution** (e.g. normal)
- all associations are **linear**
- **compatibility** and **congeniality**

Missing Data Mechanisms

Missing Completely At Random (MCAR)

Missing At Random (MAR)

Missing Not At Random (MNAR)

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Missing Completely At Random (MCAR)

$$p(R \mid X_{obs}, X_{mis}) = p(R)$$

Missingness is independent of all data.

questionnaire got lost in mail

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Missingness depends only on observed data.

overweight participants are less likely to report their chocolate consumption (and we know their weight)

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Missing Not At Random (MNAR)

$$p(R \mid X_{obs}, X_{mis}) \neq p(R \mid X_{obs})$$

Missingness depends (also) on unobserved data.

overweight participants are less likely to report their weight

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In case of MNAR:
MICE ➡ bias

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Imputation model misspecification

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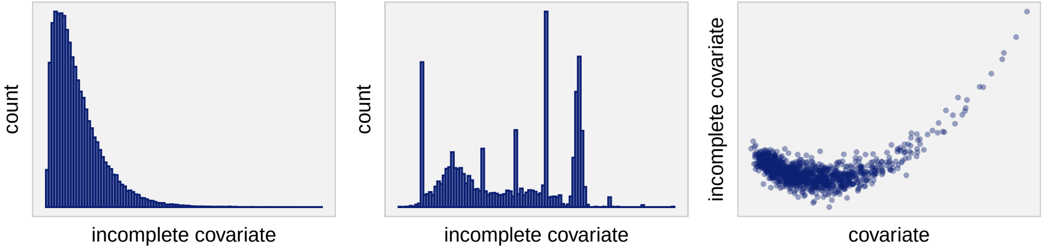
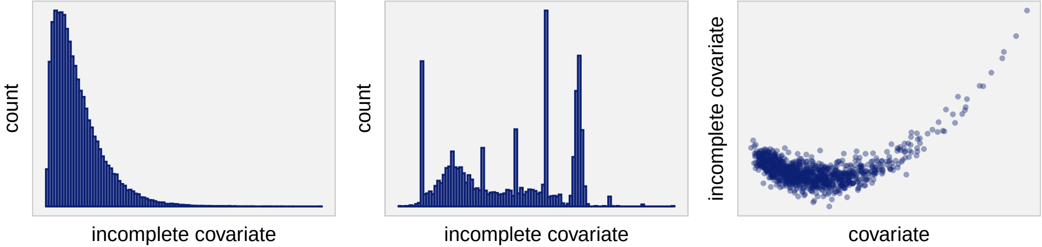


Imputation model misspecification



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- misspecification of the **association structure**

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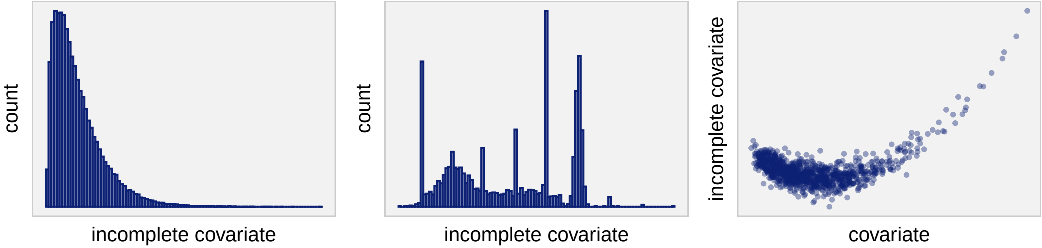

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Partial solutions:

- Predictive Mean Matching
- Passive imputation

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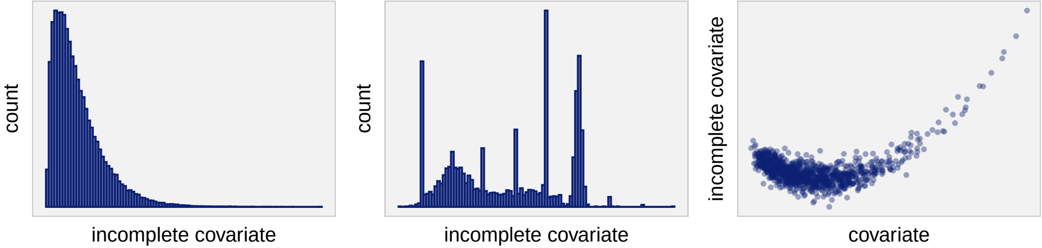

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Partial solutions:

- Predictive Mean Matching
- Passive imputation

But...

- can get tedious
- requires knowledge (about data & methods)
- users often inexperienced and/or lazy

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Model misspecification ➡ bias

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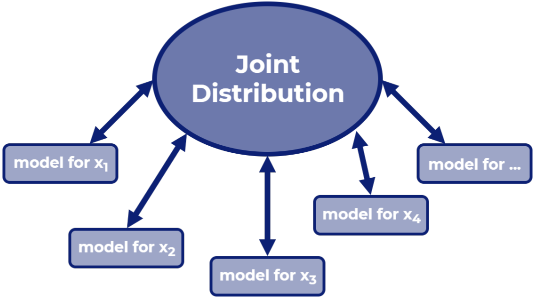
Compatibility & Congeniality

Compatibility

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



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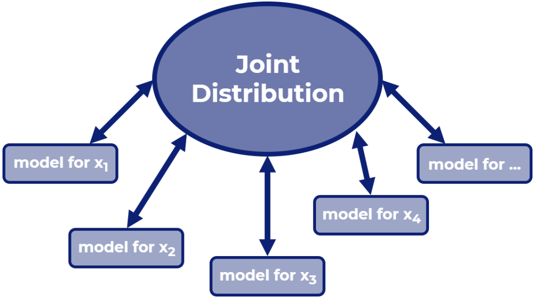
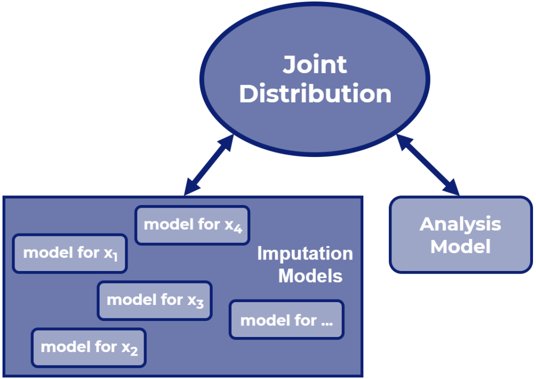


Congeniality

The imputation model is compatible with the **analysis model**.

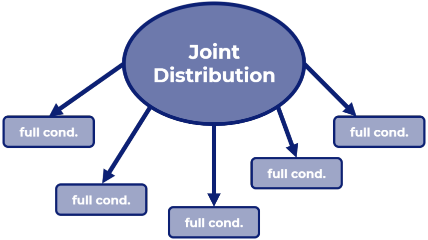


Compatibility & Congeniality in MICE

MICE is based on the idea of

Gibbs sampling

Exploits the fact that a joint distribution is fully determined by its full conditional distributions.



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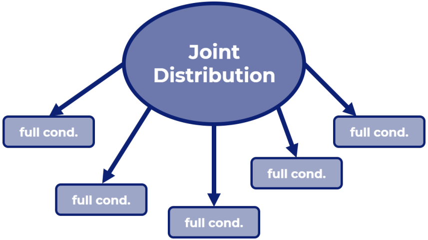
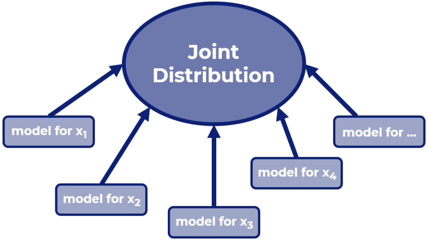


But:

In MICE

Imputation models are specified directly
➡ no guarantee that a corresponding joint distribution exists



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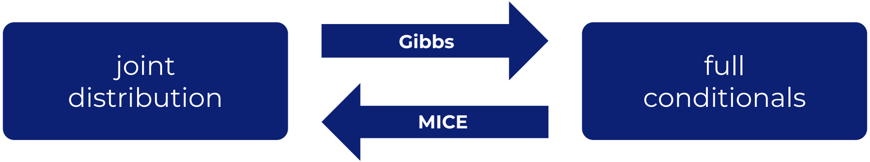

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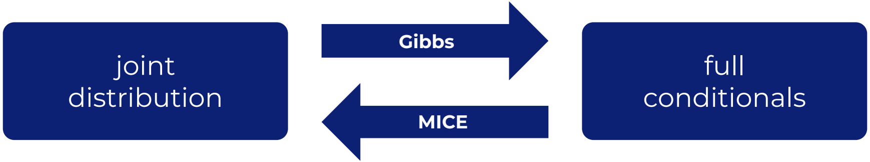


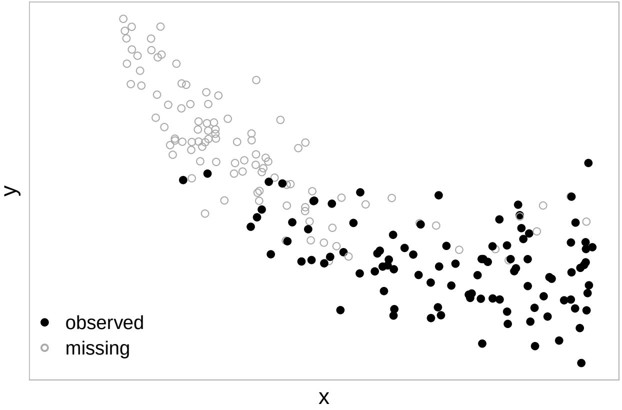
Is this a problem?

- often not
- but it can be when
  - imputation/analysis **models contradict each other**
  - **different assumptions** are made during analysis and imputation
  - the **outcome cannot easily be included** in the imputation models

Example 1: Contradicting Models

Analysis model with a **quadratic association**:

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

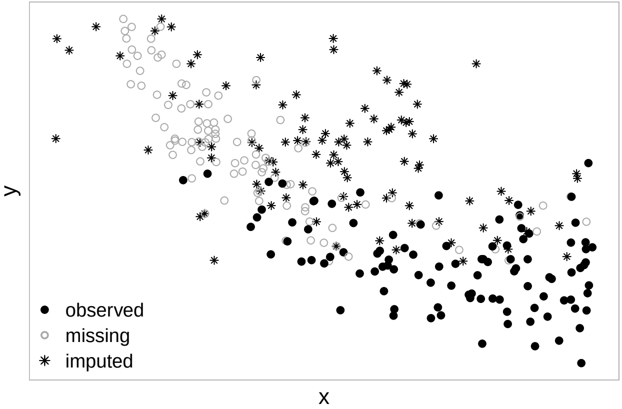


Example 1: Contradicting Models

Imputation model for x (when using MICE naively):

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

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



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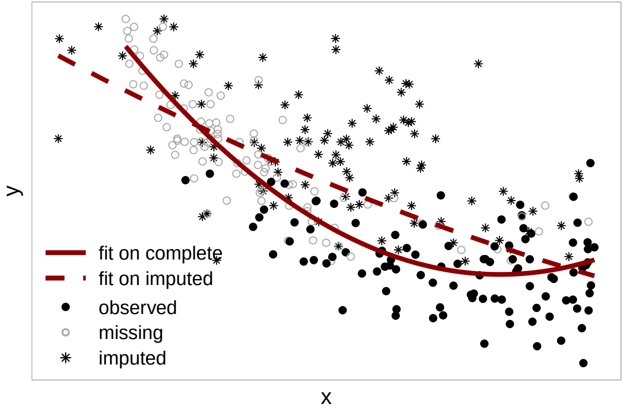
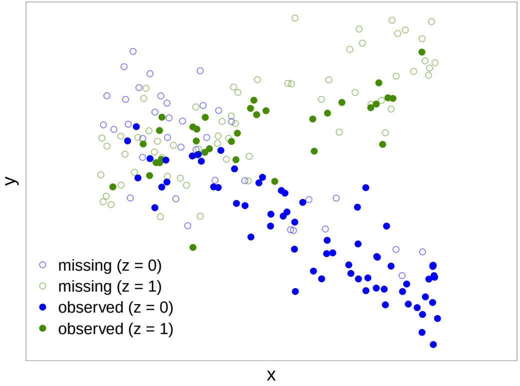


Example 2: Contradicting Models

Analysis model with **interaction term**:

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

i.e., y again has a **non-linear relationship** with x



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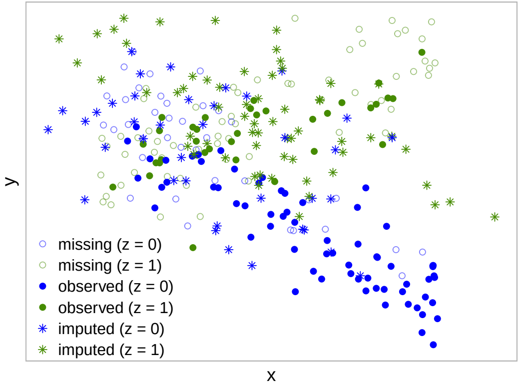
Imputation model for *x* (when using MICE naively):

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



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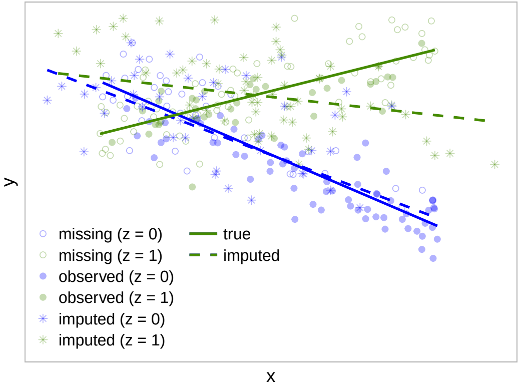
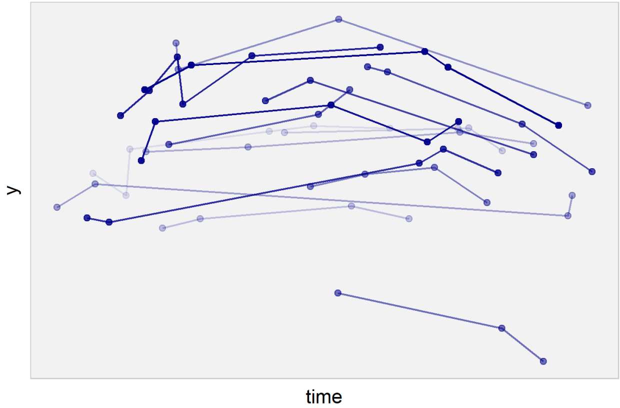


Example 3: Longitudinal / Multi-level Data



id	time	y	x
1	0.34	0.12	✓
1	0.65	-0.04	✓
1	0.68	0.30	✓
1	1.97	0.44	✓
1	2.38	0.48	✓
1	3.09	0.46	✓
2	2.11	0.43	NA
2	3.72	0.46	NA
2	3.82	0.46	NA
2	4.13	0.29	NA
⋮	⋮	⋮	⋮

Example 3: Longitudinal / Multi-level Data

Imputation in **long format**

- rows are treated as independent
- imputations in baseline covariates will vary over time

➡ **bias**

Can we use data in **wide format** (one row per subject)?

- can be very inefficient
- not always possible

id	time	y	x
1	0.34	0.12	✓
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1	0.68	0.30	✓
1	1.97	0.44	✓
1	2.38	0.48	✓
1	3.09	0.46	✓
2	2.11	0.43	NA
2	3.72	0.46	NA
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⋮	⋮	⋮	⋮

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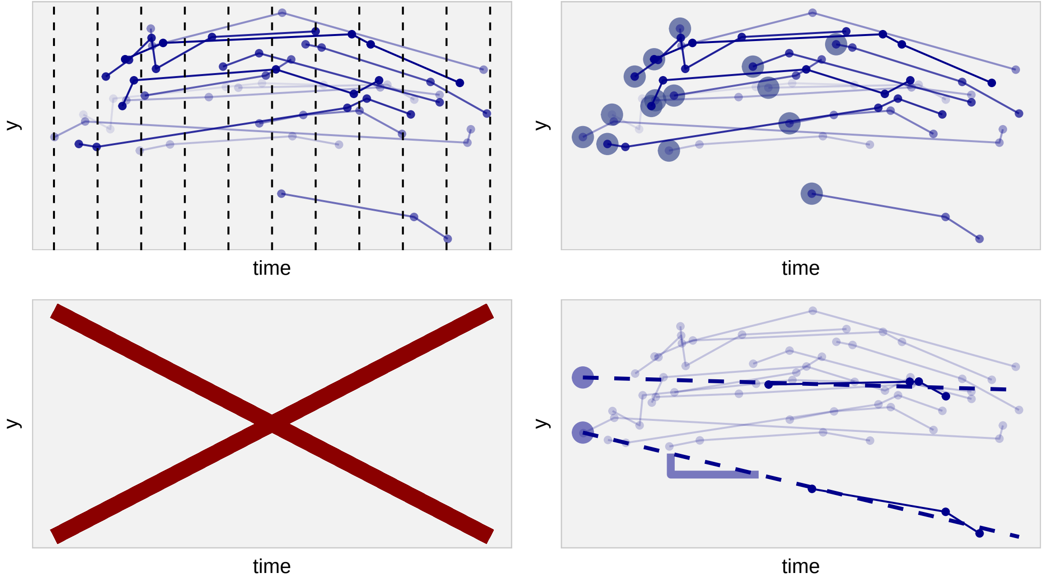


Compatibility & Congeniality in MICE

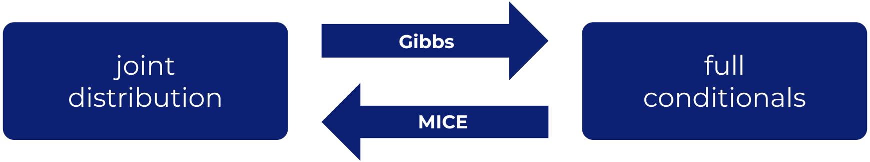
Lack of compatibility / congeniality can become a **problem for MICE** in settings with

- Non-linear associations
  - non-linear effects
  - interaction terms
  - ...
- complex outcomes
  - multi-level settings
  - time-to-event outcomes
  - ...

What can we do in these settings?

Imputation in Complex Settings

Remember, the **problem** is



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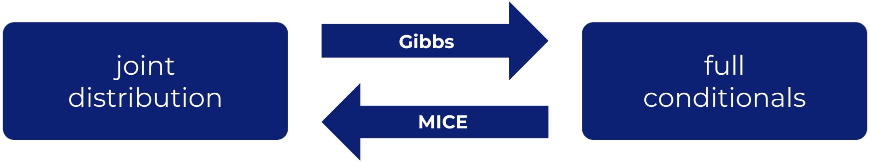

➡ **Solution:** Start with the joint distribution!

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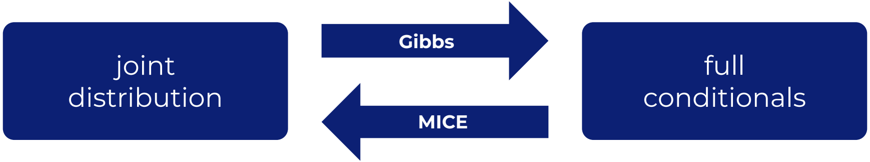

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New problem:
What is the multivariate distribution of **multiple variables** of **different types**?

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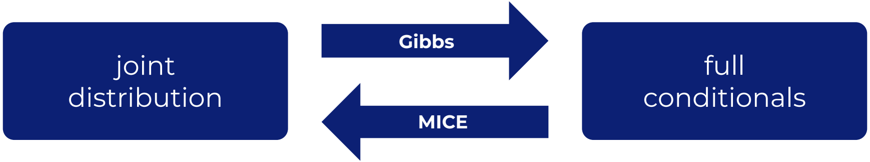

➡ **Solution:** Start with the joint distribution!

New problem:
What is the multivariate distribution of **multiple variables** of **different types**?

☹ Usually, the joint distribution is not of any known form.

Joint Model Imputation

Multivariate Normal Model

Approximate the joint distribution by a known multivariate (usually normal) distribution

- this is **Joint Model** Multiple Imputation
- ☺ assures compatibility & congeniality
- ☹ can't handle non-linear associations

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Sequential Factorization

Factorize the joint distribution into (a sequence of) conditional distributions.

- ☺ assures compatibility & congeniality
- ☺ can handle non-linear associations

Sequential Factorization

A **joint distribution** $p(y, x)$ can be written as the product of conditional distributions:

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

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

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

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

$$p(y, x_1, \ldots, x_p) = p(y \mid x_1, \ldots, x_p)\ p(x_1 \mid x_2, \ldots, x_p)\ p(x_2 \mid x_3, \ldots, x_p)\ \ldots\ p(x_p)$$

Sequential Factorization in the Bayesian Framework

Joint Distribution

$$p(y, X, \theta) = \underbrace{p(y \mid X, \theta)}_{\substack{\text{analysis}\\ \text{model}}} \quad \underbrace{p(X \mid \theta)}_{\substack{\text{imputation}\\ \text{part}}} \quad \underbrace{p(\theta)}_{\text{priors}}$$

θ contains regr. coefficients, variance parameters, ...

Sequential Factorization in the Bayesian Framework

Joint Distribution

$$p(y, X, \theta) = \underbrace{p(y \mid X, \theta)}_{\substack{\text{analysis}\\\text{model}}} \quad \underbrace{p(X \mid \theta)}_{\substack{\text{imputation}\\\text{part}}} \quad \underbrace{p(\theta)}_{\text{priors}}$$

θ contains regr. coefficients, variance parameters, ...

Imputation part

$$p(\overbrace{x_1, \ldots, x_p, X_{compl.}}^{X} \mid \theta) \quad = \quad \begin{array}{l} p(x_1 \mid X_{compl.}, \theta) \\ p(x_2 \mid X_{compl.}, x_1, \theta) \\ p(x_3 \mid X_{compl.}, x_1, x_2, \theta) \\ \ldots \end{array}$$

Sequential Factorization in the Bayesian Framework

Extension for a Multi-level Setting

$$\underbrace{p(y \mid X, b, \theta)}_{\substack{\text{analysis}\\\text{model}}}\;\underbrace{p(X \mid \theta)}_{\substack{\text{imputation}\\\text{part}}}\;\underbrace{p(b \mid \theta)}_{\substack{\text{random}\\\text{effects}}}\;\underbrace{p(\theta)}_{\text{priors}}$$

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Extension for a Time-to-Event Outcome

$$\underbrace{p(T, D \mid X, \theta)}_{\substack{\text{analysis}\\\text{model}}} \underbrace{p(X \mid \theta)}_{\substack{\text{imputation}\\\text{part}}} \underbrace{p(\theta)}_{\text{priors}}$$

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Extension for a Multivariate Outcome

$$\underbrace{p(y_1, y_2 \mid X, \theta)}_{\substack{\text{analysis}\\\text{model}}} \; \underbrace{p(X \mid \theta)}_{\substack{\text{imputation}\\\text{part}}} \; \underbrace{p(\theta)}_{\text{priors}}$$

MICE vs Sequential Factorization

Imputation in MICE

$$p(x_1 \mid y, X_{compl.}, x_2, x_3, x_4, \ldots, \theta)$$
$$p(x_2 \mid y, X_{compl.}, x_1, x_3, x_4, \ldots, \theta)$$
$$p(x_3 \mid y, X_{compl.}, x_1, x_2, x_4, \ldots, \theta)$$
$$\ldots$$

Sequential Factorization

$$p(y \mid X_{compl.}, x_1, x_2, x_3, \ldots, \theta)$$
$$p(x_1 \mid X_{compl.}, \theta)$$
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$$\ldots$$

Sequential Factorization

$$\mathbf{p}(\mathbf{y} \mid \mathbf{X_{compl.}}, \mathbf{x_1}, \mathbf{x_2}, \mathbf{x_3}, \ldots, \theta)$$
$$p(x_1 \mid X_{compl.}, \theta)$$
$$p(x_2 \mid X_{compl.}, x_1, \theta)$$
$$p(x_3 \mid X_{compl.}, x_1, x_2, \theta)$$
$$\ldots$$

No issues with

- complex outcomes, e.g.:
  - multi-level
  - survival
- non-linear effects
- congeniality
- compatibility

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Sequential Factorization

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$$\ldots$$

Analysis model part of specification

- ➡ parameters of interest directly available
- ➡ no need for pooling
- ➡ simultaneous analysis and imputation

Joint Analysis and Imputation in R

Sequential Factorization is implemented in the R package **JointAI**

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Bayesian analysis of **incomplete data** using

- (generalized) linear regression
- (generalized) linear mixed models
- ordinal (mixed) models
- parametric (Weibull) time-to-event models
- Cox proportional hazards models

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- **on CRAN:** https://CRAN.R-project.org/package=JointAI
- **webpage:** https://nerler.github.io/JointAI/
- **GitHub:** https://github.com/NErler/JointAI

Joint Analysis and Imputation in R

type	standard regression		mixed model	
	outcome	covariate	outcome	covariate
normal	✓	✓	✓	✓
lognormal	(soon)	✓	(soon)	✓
Gamma	✓	✓	✓	✓
beta	(soon)	✓	(soon)	(soon)
binomial	✓	✓	✓	✓
poisson	✓	(soon)	✓	✓
ordinal	✓	✓	✓	✓
multinomial	(soon)	✓	(soon)	(soon)

Available soon:

- Joint models (of longitudinal & time-to-event data)
- Multivariate models

JointAI: How does it work?

Requirements:

- R (https://cran.r-project.org/)
- **JAGS** (Just Another Gibbs Sampler; https://sourceforge.net/projects/mcmc-jags/files/JAGS/4.x/)

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Installation:

```
install.packages("JointAI")
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Installation:

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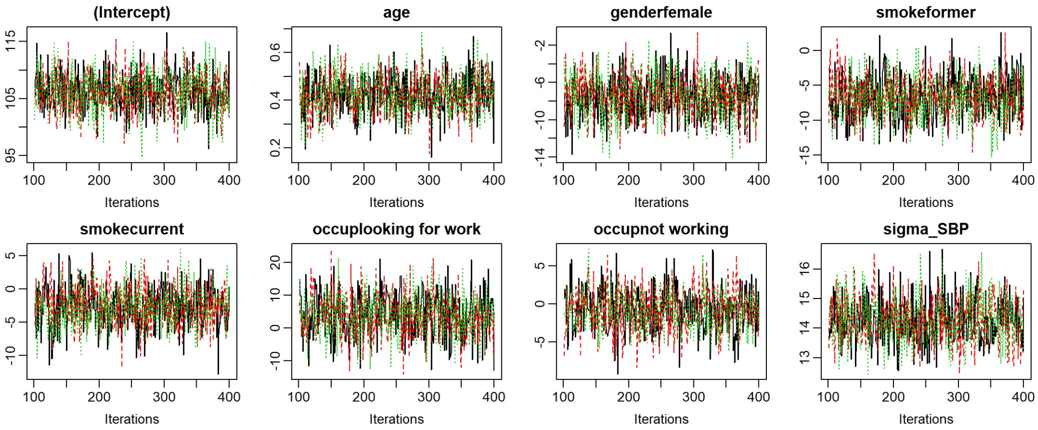
Usage:

```
library("JointAI")
res <- lm_imp(SBP ~ age + gender + smoke + occup, data = NHANES,
              n.iter = 300)
```

JointAI: How does it work?

```
traceplot(res)
```



JointAI: How does it work?

```r
summary(res)
```

```
##
##  Linear model fitted with JointAI
##
## Call:
## lm_imp(formula = SBP ~ age + gender + smoke + occup, data = NHANES,
##     n.iter = 300)
##
## Posterior summary:
##                          Mean     SD    2.5%   97.5% tail-prob. GR-crit
## (Intercept)           106.222 3.3979  99.461 112.961     0.0000    1.00
## age                     0.427 0.0798   0.278   0.583     0.0000    1.00
## genderfemale           -7.450 2.2718 -11.755  -3.072     0.0000    1.00
## smokeformer            -6.692 3.0297 -12.342  -0.885     0.0267    1.03
## smokecurrent           -2.658 3.0229  -8.450   3.313     0.3711    1.01
## occuplooking for work   3.817 6.4037  -9.487  16.087     0.5044    1.01
## occupnot working       -0.869 2.6858  -6.110   4.256     0.7511    1.02
##
## Posterior summary of residual std. deviation:
##           Mean    SD 2.5% 97.5% GR-crit
## sigma_SBP 14.3 0.753 12.8  15.8   0.999
##
##
## MCMC settings
## [...]
```

What is left to do?

(**Imputation**) methods make certain **assumptions**, e.g.:

- **missingness** is M(C)AR
- the incomplete variable has a certain conditional **distribution**
- all associations are **linear**
- **compatibility** and **congeniality**

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➡ extension to MNAR using pattern mixture model

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➡ extension to MNAR using pattern mixture model

➡ non-parametric Bayesian methods

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(**Imputation**) methods make certain **assumptions**, e.g.:

- ? **missingness** is M(C)AR ➡ extension to MNAR using pattern mixture model
- ? the incomplete variable has a certain conditional **distribution** ➡ non-parametric Bayesian methods
- ? all associations are **linear** ➡ semi-parametric methods
- ☑ **compatibility** and **congeniality**

Take-Home Message

- handling missing values **correctly: not that easy**
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  violation ➡ bias

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  - **time & patience!**

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  - simultaneous analysis & imputation
  - especially for complex settings

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  - especially for complex settings
- **There is no magical solution** that will always work in all settings.

Thank you for your attention.

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