EP16: Missing Values in Clinical Research: Multiple Imputation

11. Imputation with Non-linear Functional Forms

Nicole Erler

Department of Biostatistics, Erasmus Medical Center

n.erler@erasmusmc.nl

Erasmus MC
University Medical Center Rotterdam

Imputation with mice

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.

Imputation with mice

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 imputation with a normal model,
- the **Just Another Variable** approach can reduce bias in interactions,
- passive imputation
- `quadratic` can help to impute variables with quadratic association.

Imputation with mice

For demonstration, we use a simulated example dataset `DFnonlin`:

y continuous outcome

x continuous (normal) covariate (50% missing values MCAR)

z binary covariate (complete)

We assume a

- **quadratic effect** of x on y, and
- an **interaction** between x and z

```
head(DF_nonlin)
```

```
##            y           x z
## 1 -0.4002016 -0.42298398 1
## 2  0.7883355 -1.54987816 0
## 3  0.1900922 -0.06442932 0
## 4  0.3321608  0.27088135 0
## 5  4.6146593  1.73528367 0
## 6  0.3705739          NA 0
```

```
dim(DF_nonlin)
```

```
## [1] 200   3
```

Imputation with mice: JAV

Just Another Variable (JAV) approach:

- **pre-calculate** the non-linear form (or interaction term) in the incomplete data,
- add it as a column to the dataset, and
- impute it as if it was just another variable.

Imputation with mice: JAV

Just Another Variable (JAV) approach:

- **pre-calculate** the non-linear form (or interaction term) in the incomplete data,
- add it as a column to the dataset, and
- impute it as if it was just another variable.

```
DF2 <- DF_nonlin          # copy of the data, only for this example
DF2$xx <- DF2$x^2         # pre-calculate the quadratic term
DF2$xz <- DF2$x * DF2$z   # pre-calculate the interaction
```

```
# JAV imputation (using pmm and full predictor matrix)
impJAV <- mice(DF2, maxit = 20, printFlag = FALSE)
```

Imputation with mice: JAV

To **relax the assumption** of linear associations even more, we could introduce **additional interactions** with the outcome.

In this example, we can add an interaction between *z* and *y*:

```
DF3 <- DF2                  # make another copy of the data
DF3$yz <- DF3$y * DF3$z     # add interaction y and z
```

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

Imputation with mice: Passive Imputation

Alternative: impute all non-linear terms and interactions passively:

```
# adapt the imputation method (we re-use the vector from impJAV2 here)
meth_passive <- impJAV2$method
meth_passive[c("xx", "xz", "yz")] <- c("~I(x^2)", "~I(x*z)", "~I(y*z)")
```

Imputation with mice: Passive Imputation

Alternative: impute all non-linear terms and interactions passively:

```
# adapt the imputation method (we re-use the vector from impJAV2 here)
meth_passive <- impJAV2$method
meth_passive[c("xx", "xz", "yz")] <- c("~I(x^2)", "~I(x*z)", "~I(y*z)")
```

```
# adapt the predictor matrix (we re-use the matrix from impJAV2 here)
pred_passive <- impJAV2$predictorMatrix
pred_passive['x', 'xx'] <- 0
pred_passive[c('x', 'z'), 'xz'] <- 0
pred_passive[c('y', 'z'), 'yz'] <- 0
```

Imputation with mice: Passive Imputation

Alternative: impute all non-linear terms and interactions passively:

```
# adapt the imputation method (we re-use the vector from impJAV2 here)
meth_passive <- impJAV2$method
meth_passive[c("xx", "xz", "yz")] <- c("~I(x^2)", "~I(x*z)", "~I(y*z)")
```

```
# adapt the predictor matrix (we re-use the matrix from impJAV2 here)
pred_passive <- impJAV2$predictorMatrix
pred_passive['x', 'xx'] <- 0
pred_passive[c('x', 'z'), 'xz'] <- 0
pred_passive[c('y', 'z'), 'yz'] <- 0
```

```
imp_passive <- mice(DF3, method = meth_passive,
                    predictorMatrix = pred_passive,
                    maxit = 20, printFlag = FALSE)
```

Imputation with mice: Polynomial Combination

The imputation method `quadratic` uses the **"polynomial combination" method** to impute covariates that have a **quadratic association** with the outcome (Van Buuren 2012 pp. 139–141; Vink and van Buuren 2013).

➡ ensure the **imputed values** for x and x^2 are **consistent**

➡ **reduce bias** in the subsequent analysis that uses x and x^2

Imputation with mice: Polynomial Combination

The imputation method `quadratic` uses the **"polynomial combination" method** to impute covariates that have a **quadratic association** with the outcome (Van Buuren 2012 pp. 139–141; Vink and van Buuren 2013).

- ➡ ensure the **imputed values** for x and x^2 are **consistent**
- ➡ **reduce bias** in the subsequent analysis that uses x and x^2

```r
# adapt the imputation method (we re-use the vector from impJAV here)
methqdr <- impJAV$meth
methqdr[c("x", "xx", "xz")] <- c("quadratic", "~I(x^2)", "~I(x*z)")
```

➡ Here we use passive imputation for x^2 and the interaction.

Imputation with mice: polynomial combination

```r
# adapt the predictor matrix (we re-use the matrix from impJAV here)
predqdr <- impJAV$pred
predqdr['x', "xx"] <- 0            # prevent feedback
predqdr[c('x', 'z'), 'xz'] <- 0  # prevent feedback

impqdr <- mice(DF3, meth = methqdr, pred = predqdr,
               maxit = 20, printFlag = FALSE)
```

Imputation with mice: polynomial combination

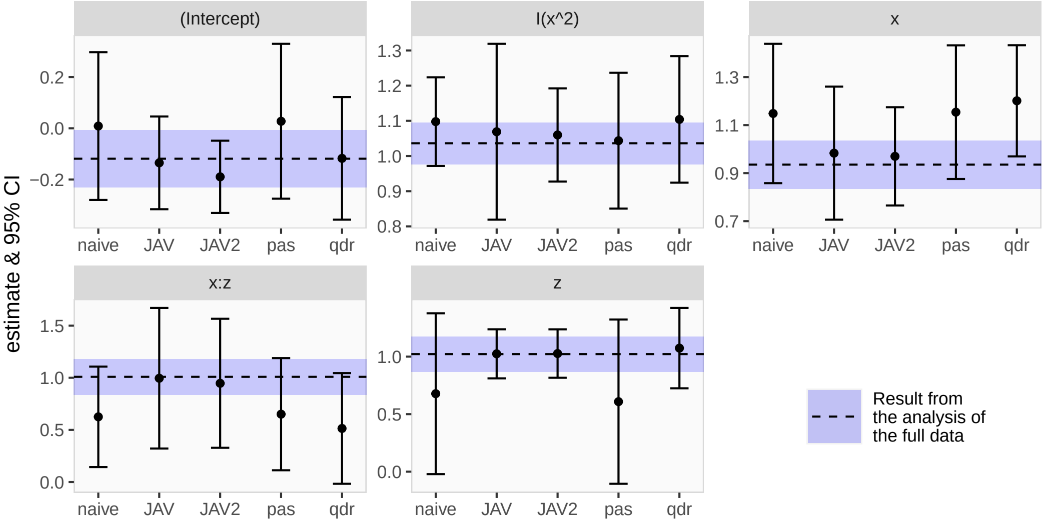
```r
# adapt the predictor matrix (we re-use the matrix from impJAV here)
predqdr <- impJAV$pred
predqdr['x', "xx"] <- 0           # prevent feedback
predqdr[c('x', 'z'), 'xz'] <- 0   # prevent feedback

impqdr <- mice(DF3, meth = methqdr, pred = predqdr,
               maxit = 20, printFlag = FALSE)
```

For comparison, we also run a naive version (using defaults):

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

Imputation with mice



Imputation with JointAI

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)
```

Imputation with JointAI

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, ncol = 3, use_ggplot = TRUE)
```

Imputation with JointAI

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)
```

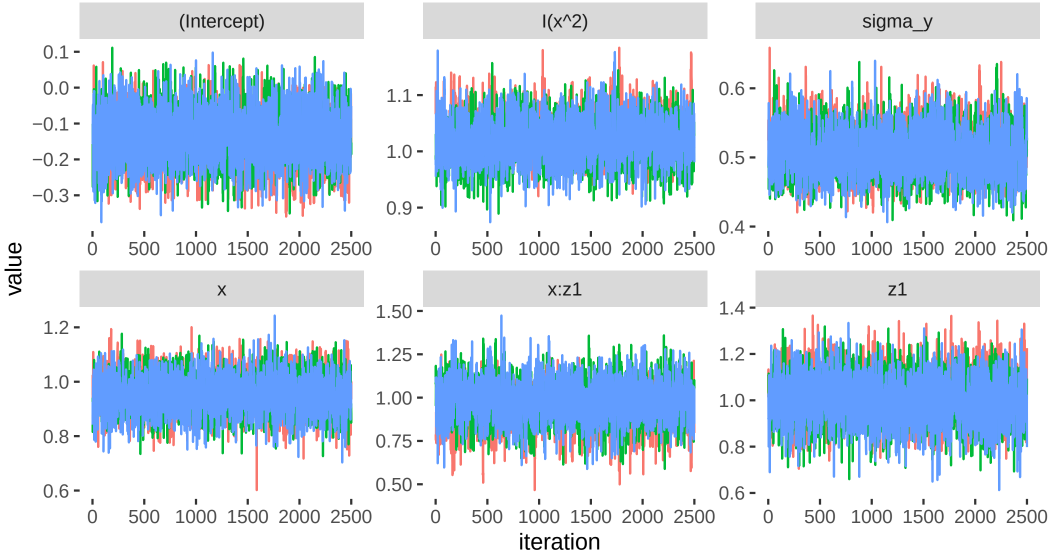
Convergence of the Gibbs sampler can be checked using a `traceplot`.

```
traceplot(JointAI_nonlin, ncol = 3, use_ggplot = TRUE)
```

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

```
summary(JointAI_nonlin)
```

Imputation with JointAI: Convergence



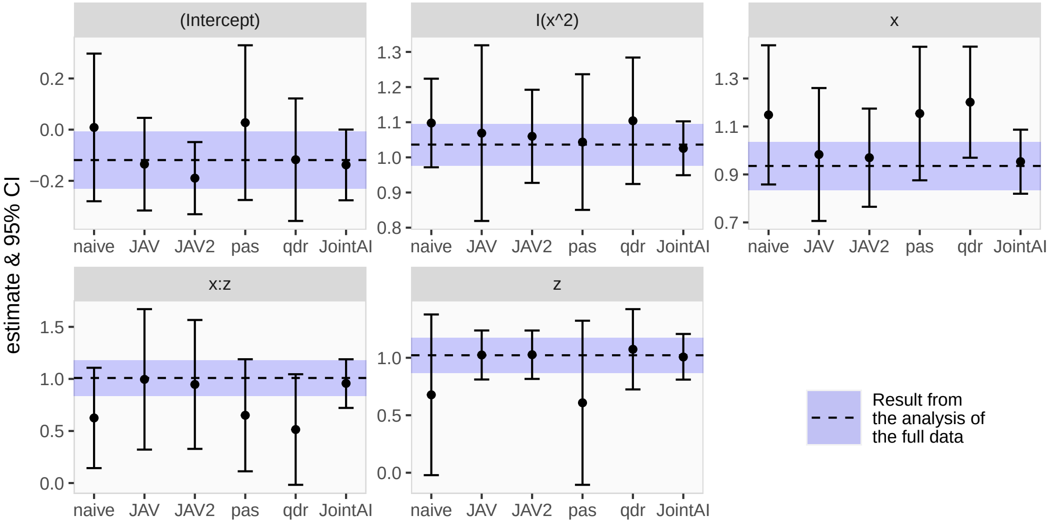
Imputation with JointAI: Model Summary

```
##
##  Linear model fitted with JointAI
##
## Call:
## lm_imp(formula = y ~ x * z + I(x^2), data = DF_nonlin, n.iter = 2500,
##     seed = 1234)
##
## Posterior summary:
##                Mean     SD   2.5%    97.5% tail-prob. GR-crit
## (Intercept) -0.138 0.0697 -0.276 0.000259     0.0512    1.09
## x            0.954 0.0683  0.820 1.086675     0.0000    1.02
## z1           1.007 0.1005  0.810 1.207309     0.0000    1.10
## I(x^2)       1.026 0.0393  0.949 1.102465     0.0000    1.32
## x:z1         0.957 0.1189  0.722 1.188642     0.0000    1.28
##
## Posterior summary of residual std. deviation:
##          Mean     SD  2.5% 97.5% GR-crit
## sigma_y 0.507 0.0334 0.447 0.576    1.01
##
##  [...]
```

Imputation with JointAI: Model Summary

```
## [...]
##
## MCMC settings:
## Iterations = 101:2600
## Sample size per chain = 2500
## Thinning interval = 1
## Number of chains = 3
##
## Number of observations: 200
```

Imputation with Non-linear Effects: Comparison



Imputation with Non-linear Effects: Comparison

Just Another Variable:

- Easy specification
- usually less bias than naive approach
- inconsistent imputed values

Imputation with Non-linear Effects: Comparison

Just Another Variable:

- Easy specification
- usually less bias than naive approach
- inconsistent imputed values

passive imputation

- easy specification
- consistent imputed values
- less flexible than JAV

Imputation with Non-linear Effects: Comparison

Just Another Variable:

- Easy specification
- usually less bias than naive approach
- inconsistent imputed values

passive imputation

- easy specification
- consistent imputed values
- less flexible than JAV

polynomial combination

- consistent imputed values
- only available for quadratic association
- often numeric instabilities (warning messages)

Imputation with Non-linear Effects: Comparison

JointAI

- theoretically valid approach (= unbiased)
- similar specification to standard models
- simultaneous analysis & imputation instead of three steps

Imputation with Non-linear Effects: Comparison

JointAI

- theoretically valid approach (= unbiased)
- similar specification to standard models
- simultaneous analysis & imputation instead of three steps

To use JointAI appropriately and to interpret the results correctly requires more knowledge about the underlying method than can be covered in this course.

Imputation with Non-linear Effects: Comparison

JointAI

- theoretically valid approach (= unbiased)
- similar specification to standard models
- simultaneous analysis & imputation instead of three steps

To use JointAI appropriately and to interpret the results correctly requires more knowledge about the underlying method than can be covered in this course.

Note:
The example used here only serves to demonstrate the different approaches. We cannot use these results to conclude which approach works better in general.

References

Van Buuren, Stef. 2012. *Flexible Imputation of Missing Data*. Chapman & Hall/Crc Interdisciplinary Statistics. Taylor & Francis. https://stefvanbuuren.name/fimd/.

Vink, Gerko, and Stef van Buuren. 2013. "Multiple Imputation of Squared Terms." *Sociological Methods & Research* 42 (4): 598–607.