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Imputation of Incomplete Multilevel Data with mice

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Abstract

This is a tutorial paper on imputing incomplete multilevel data with **mice**. Footnotes in the current version show work in progress/under construction. The last section is not part of the manuscript, but purely for reminders. We aim to submit at JSS, so there is no word count limit ("There is no page limit, nor a limit on the number of figures or tables").

Keywords: missing data, multilevel, clustering, **mice**, R.

1. Introduction

~~In many contemporary data analysis efforts, some form of hierarchical or clustered structure is recorded.~~ Contemporary decision making is driven increasingly often and sometimes even entirely dictated by data. Although data relevant for decision makers were initially collected using small and well-designed studies, there has been a growing need to address more complex questions at a wider scale. This not only requires to collect larger amounts of data, but also from more diverse settings and populations. For example, [TD: introduce IPDMA here; eg. HIV studies Johanna is referring to]. Another example is the use of large databases with information from thousands or even millions of individuals from multiple cities, regions or even countries. Finally, a third situation arises when data are collected from multicenter studies [TD: maybe refer to the schools/classes example here]. For example, students may be clustered in classes in psychometrics research, or patients may be clustered in studies

in individual patient data meta-analyses in medical research. A common characteristic in aforementioned examples is the presence of clustering. [TD: briefly explain what is clustering?] Ignoring the clustered structure of such multilevel data can be harmful to the statistical inferences and introduce bias in estimators (Hox, Moerbeek, and van de Schoot 2017). ~~Imagine a case where cross-level interactions between unit-level variables and cluster-level variables are present. The cluster to which a unit belongs may then influence the unit-level observations and vice versa for each of the units that make up the cluster.~~ These relations can and should be taken into account when developing analysis models for multilevel data for the simple reason that groups of observations share some common variance. ~~The variability due to clustering is often measured by means of the intraclass coefficient (ICC). The ICC can be seen as the percentage of variance that can be attributed to the cluster-level, where a high ICC would indicate that a lot of variability is due to the cluster structure.~~ Multilevel models typically accommodate for this variability by including a separate group mean for each cluster. In addition to random intercepts, multilevel models can also include random effects and heterogeneous residual error variances across clusters (see e.g. Gelman and Hill 2006, Hox et al. (2017) and de Jong, Moons, Eijkemans, Riley, and Debray (2021)). There are many names for models that take clustering into account. Some popular examples are 'multilevel models', 'hierarchical models', 'mixed effect models' and 'random effect models'. [TD: emphasize when/why we need to account for clustering in the analysis of clustered data. Why is the presence of clustering relevant when considering multiple imputation of missing data? e.g. distinction between systematically and sporadically missing data. But also: mechanisms of missing data (e.g. MCAR, MAR, MNAR) may differ between clusters. But also: relation between observed data may differ between clusters? When/ why should we avoid using traditional imputation methods? e.g. congeniality issues.]

1.1. Missingness in multilevel data

The process of analyzing multilevel data is further complicated when not all data entries are observed. Just as with single level data, missingness may occur at the unit level. But with multiple levels of data comes the potential for clustered missingness. Therefore, incomplete multilevel data can be categorized into two general patterns: systematic missingness and sporadic missingness (Resche-Rigon, White, Bartlett, Peters, and Thompson 2013). Systematic missingness implies that one or more variables are never observed in a certain cluster. With sporadic missingness there may be observed data for some but not all units in a cluster (Van Buuren 2018; Jolani 2018). We have visualized this difference in Figure 1, which shows an $n \times p$ set $\mathbf{X} = X_1, \ldots, X_p$, with n units distributed over N clusters, and $p = 3$ columns. Column $X1$ is completely observed, column $X2$ is systematically missing in cluster 2, and column $X3$ is sporadically missing. To analyze these incomplete data, we have to take the nature of the missingness and the cluster structure into account. For example, the sporadic missingness in $X3$ could be easily amended if this would be a cluster-level variable (and thus constant within clusters). We could then just extrapolate the true (but missing) value of $X3$ for unit 1 from unit 2, and the value for unit 4 from unit 3. If $X3$ would instead be a unit-level variable (which may vary within clusters), we could not just recover the unobserved 'truth', but would need to use some kind of missing data method or discard the incomplete units altogether (i.e., list-wise deletion/complete case analysis). Further, with the systematic missingness in $X2$, it is impossible to fit a multilevel model since we cannot estimate the intercept of cluster 2. We would have to exclude this cluster from our analyses entirely to

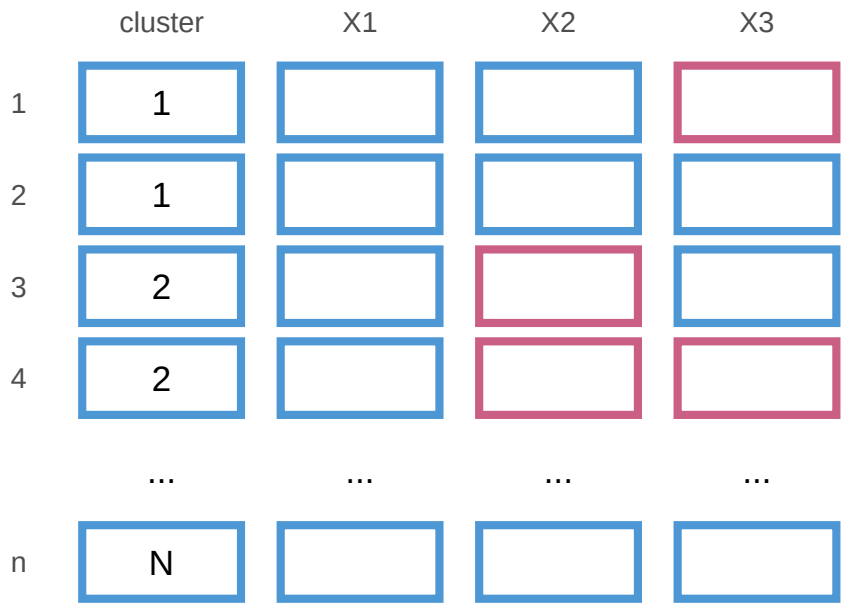


Figure 1: Missingness in multilevel data

obtain any results. Obviously, excluding observations is not a desirable workflow.

Ignoring the missingness in analyses can be extremely harmful to inferences. Complete case analysis can introduce bias in statistical inferences and lowers statistical power. Instead, the missingness should be accommodated before or within the analysis of scientific interest. Especially the former is very generic and popular. [VJ: add why multiple values are imputed.] Imputing (i.e., filling in) the missing values separates the missing data problem from the scientific problem: missing data are replaced by plausible values whereafter the completed data is analyzed as if it were completely observed. The R package **mice** has become the de-facto standard for imputation by chained equations, which iteratively solves the missingness on a variable-by-variable basis. **mice** is known to yield valid inferences under many different missing data circumstances (Van Buuren 2018). In this paper, we will discuss how to use **mice** in the context of multilevel data.

1.2. Aim of this paper

This papers serves as a tutorial for imputing incomplete multilevel data with **mice**. We provide practical guidelines and code snippets for different missing data situations, including missing not at random (MNAR) mechanisms (where the probability to be missing depends on unrecorded information, making the missingness non-ignorable, Rubin 1976; Meng 1994). For reasons of brevity, we focus on imputation by chained equations wit **mice** exclusively[1]. Other useful resources for the analysis of incomplete multilevel data include the R packages **mitml**, **miceadds**, and **mdmb**, and empirical work by Audigier, White, Jolani, Debray, Quartagno,

[1]Note that the alternative, joint modeling imputation for multilevel data or **jomo** Quartagno, Grund, and Carpenter (2019), has been implemented in **mice** as well but is outside the scope of this tutorial.

Carpenter, van Buuren, and Resche-Rigon (2018) and Grund, Lüdtke, and Robitzsch (2018). Please note that this tutorial paper assumes a basic level of knowledge on multilevel models.[2] Assumed knowledge also includes the use of the 'piping operator', `%>%`, adopted from the **magrittr** package, and the **lme4** notation for multilevel models.[3]

We illustrate how to impute incomplete multilevel data by means of three case studies:

- `popmis` from the **mice** package (simulated data on perceived popularity, $n = 2,000$ pupils across $N = 100$ schools, van Buuren and Groothuis-Oudshoorn 2021);
- `hiv` from the **GJRM** package (simulated data on HIV diagnoses, $n = 6,416$ patients across $N = 9$ regions, Radice 2021);
- `impact` from the **metamisc** package (empirical data on traumatic brain injuries, $n = 11,022$ patients across $N = 15$ studies, Debray and de Jong 2021).

For each of these datasets, we will discuss the nature of the missingness, choose one or more imputation models and evaluate the imputed data, but we will also highlight one specific aspect of the imputation workflow. With the `popmis` data, we show how (and how not) to develop an imputation model. With the `hiv` data we focus on extending the imputation model to include Heckman-type selection-inclusion methods. With the `impact` data we provide an example of multivariate missingness in real-world data. Together, this should give enough scaffolding for applied researchers who are faced with incomplete multilevel data.

REVIEW UNTIL THIS POINT SVP

---

2. How (not) to impute (Case Study I: Popularity)

In this section we'll go over the different steps involved with imputing incomplete multilevel data. The data we're using is the `popmis` dataset from the `mice` package. This is a simulated dataset with pupils ($n = 2000$) clustered within schools ($N = 100$). In this tutorial we'll use the following variables:

- `school`, school identification number (clustering variable);
- `popular`, pupil popularity (self-rating between 0 and 10; unit-level);
- `sex`, pupil sex (0=boy, 1=girl; unit-level);
- `texp`, teacher experience (in years; cluster-level).

The analysis model corresponding to this dataset is multilevel regression with random intercepts, random slopes and a cross-level interaction. The outcome variable is `popular`, which is

[2] Note to self: We're providing an overview of implementations. It's up-to the reader to decide which multilevel strategy suits their data. We won't go into detail for the different methods (and equations). This paper is just a software tutorial, so we'll keep it practical.

[3] Add environment info, seed and version number(s) somewhere!

predicted from the unit-level variable `sex` and the cluster-level variable `texp`. The regression equation[4] and `lme4` notation for this model are

$$\text{popular}_{ij} = \gamma_{00} + \gamma_{10}\ \text{sex}_{ij} + \gamma_{01}\ \text{texp}_j + \gamma_{11}\ \text{texp}_j \times \text{sex}_{ij} + u_{0j} + u_{1j}\ \text{sex}_{ij} + e_{ij}$$

```
popular ~ 1 + sex + texp + sex:texp + (1 + sex | school)
```

TODO: make a 'translation table' between model equation and lme4. Use betas instead of gamma's and mu's.

Since the data is simulated and the missingness is induced, we can compare our inferences after imputation to the true complete data. The data is created in such a way that the clustering variable `school` explains quite some variance in the outcome variable `popular`. We express this using the intraclass correlation, ICC = 0.58. We'll evaluate the ICC after each missing data strategy, and compare the estimated fixed effects:

```
                Estimate with 95% CI
1 (Intercept)  3.314 [ 2.998,  3.629]
2         sex  1.330 [ 1.069,  1.590]
3        texp  0.110 [ 0.090,  0.130]
4    sex:texp -0.034 [-0.051, -0.017]
```

Incomplete data

Load the data into the environment and select the relevant variables:

```
R> popmis <- mice::popmis[, c("school", "popular", "sex", "texp")]
```

The missingness is univariate and sporadic, which is illustrated in the missing data pattern in Figure 2. The ICC in the incomplete data is 0.56.

To develop the best imputation model for the incomplete variable `popular`, we need to know whether the missingness depends on the observed values of other variables. We'll highlight only one other variable to illustrate, but ideally one would inspect all relations. The questions we'll ask are: 'Does the missing data of pupil popularity (`popular`) depend on observed teacher popularity (`texp`)?'. This can be evaluated statistically, but visual inspection usually suffices. We'll make a histogram of `texp` separately for the pupils with known popularity and missing popularity.

In Figure 3 we see that [**update this part**] the distribution for the missing `popular` is further to the right than the distribution for observed `popular`. This would indicate a right-tailed MAR missingness. (In fact, this is exactly what happens, because the missingness in these data was created manually.) We've made it observable by examining the relations between the missingness in popular and the observed data in `texp`.

Complete case analysis (not recommended)

[4] add the 'level notation' (Bryk and Raudenbush, 1992) and/or matrix notation ('linear mixed effects model'; Laird and Ware, 1982) too?

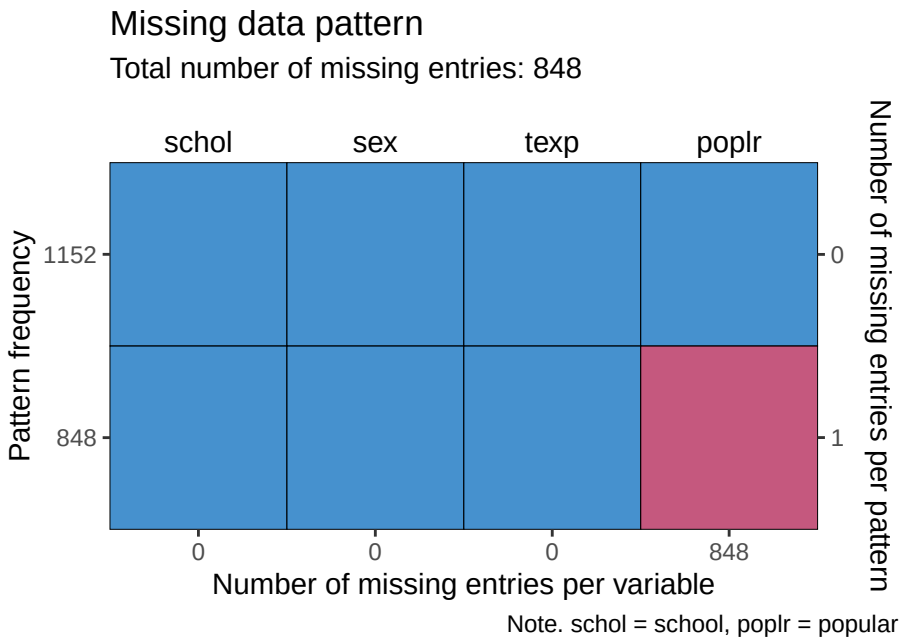


Figure 2: Missing data pattern in the popularity data

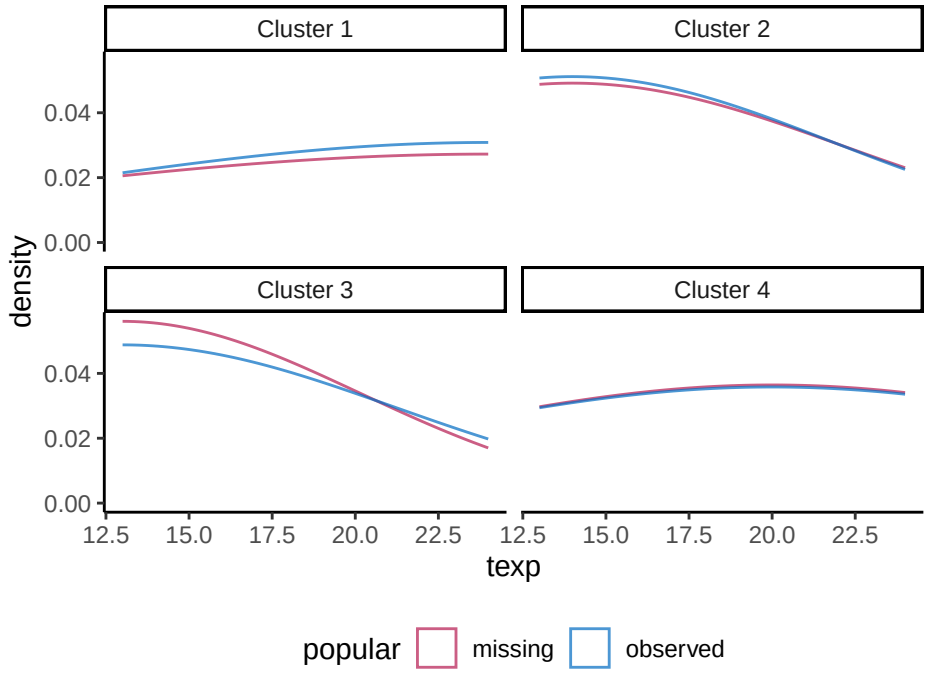


Figure 3: Conditional distributions in the popularity data

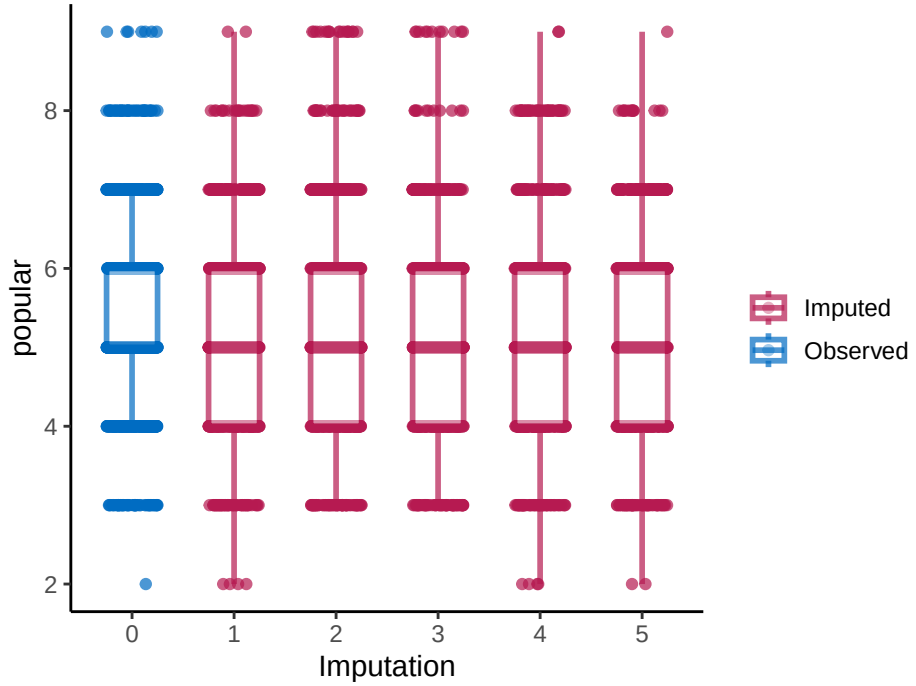
Complete case analysis ignores the observations with missingness altogether, which may even introduce bias in MCAR situations.

Imputation ignoring the cluster variable (not recommended)

The first imputation model that we'll use is likely to be invalid. In this model, we ignore the multilevel structure of the data, despite the high ICCs. And assumes exchangeability between units. This is purely to illustrate the effects of ignoring the clustering in our imputation effort.

We'll use predictive mean matching to impute the continuous variables and logistic regression to impute the binary variable `sex`. We do not use the observation identifier `pupil` or cluster identifier `school` as predictors to impute other variables.

```
R> # dry run to get imputation parameters
R> ini <- mice(popmis, maxit = 0)
R>
R> # extract predictor matrix and adjust
R> pred <- ini$pred
R> pred[, c("school")] <- 0
R>
R> # impute the data, ignoring the cluster structure
R> imp_ignored <- mice(popmis, maxit = 1, pred = pred, print = FALSE)
```



As the original ICCs show, 100% of the variance in `texp` can be attributed to the clustering variable `school`. This tells us that the multilevel structure of the data should be taken into account. If we don't, we'll end up with incorrect imputations, biasing the effect of the clusters towards zero.

We can also observe that the teacher experience increases slightly after imputation. This is due to the MNAR missingness in `texp`. Higher values for `texp` have a larger probability to be missing. This may not a problem, however, if at least one pupil in each school has teacher experience recorded, we can deductively impute the correct (i.e. true) value for every pupil in the school.

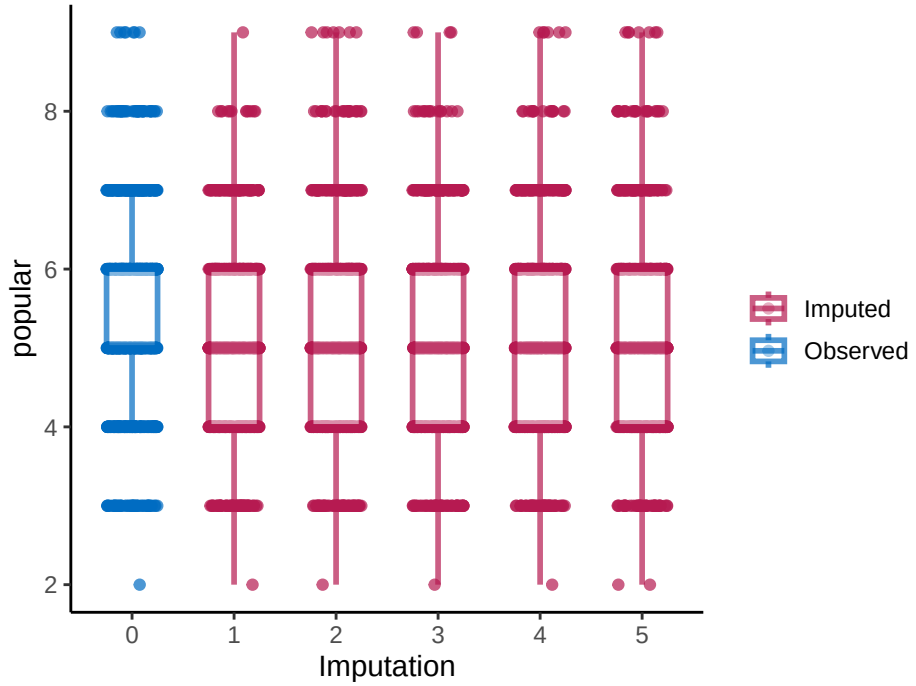
Imputation with the cluster variable as predictor (not recommended)

We'll now use `school` as a predictor to impute all other variables. This is still not recommended practice, since it only works under certain circumstances and results may be biased (Drechsler 2015; Enders, Mistler, and Keller 2016). But at least, it includes some multilevel aspect. This method is also called 'fixed cluster imputation', and uses N-1 indicator variables representing allocation of N clusters as a fixed factor in the model (Reiter, Raghunathan, and Kinney 2006; Enders et al. 2016). Colloquially, this is 'multilevel imputation for dummies'.

Add: doesn't work with syst missing (only sporadically). There's some pro's and con's. May not differ much if the number of clusters is low.

The more the random effects are of interest, the more you need ml models.

```
R> # adjust the predictor matrix
R> pred <- ini$pred
R> # pred[, "pupil"] <- 0
R>
R> # impute the data, cluster as predictor
R> imp_predictor <- mice(popmis, maxit = 1, pred = pred, print = FALSE)
```



Now, we can clearly see that the imputed values of `texp` are higher than the observed values, which is in line with right-tailed MAR.

The ICCs are way more in line with the ICCs in the incomplete data. But this is a quick and dirty way of imputing multilevel data. We should be using a multilevel model.

Imputation with random effects

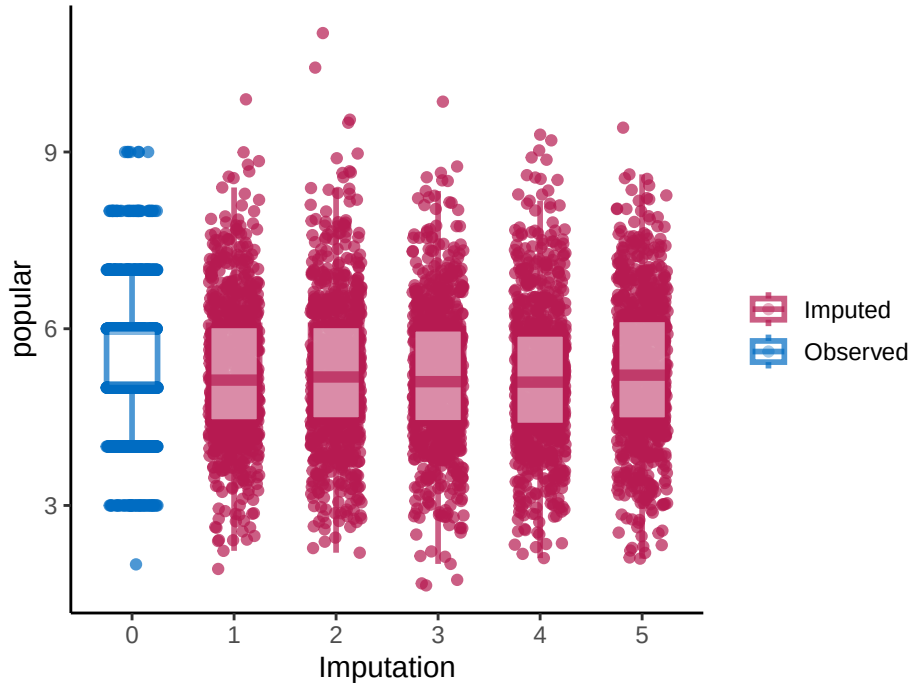
With `2l.norm` we impute the outcome with a multilevel model assuming random slopes for each variable in the imputation model and homogeneous within-cluster variance.

"Van Buuren (2011) considered the homoscedastic linear mixed model as invalid for imputing incomplete predictors, and investigated only the 2l.norm method, which allows for heterogeneous error variances" (Van Buuren 2018).

```
R> pred <- ini$pred
R> pred["popular", ] <- c(-2, 2, 2, 2)
R> #-2 for the cluster variable, 2 for random effects
R> meth <- ini$meth
R> meth <- c("", "2l.norm", "",  "")
R> # meth <- c("", "2l.pmm", "",  "")
R> imp_norm_2l <-
+   mice(
+     popmis %>% mutate(school = as.integer(school)),
+     pred = pred,
+     meth = meth,
+     maxit = 1,
+     print = FALSE
+   )
```

```
Warning: Removed 848 rows containing non-finite values (stat_boxplot).
```

```
Warning: Removed 848 rows containing missing values (geom_point).
```



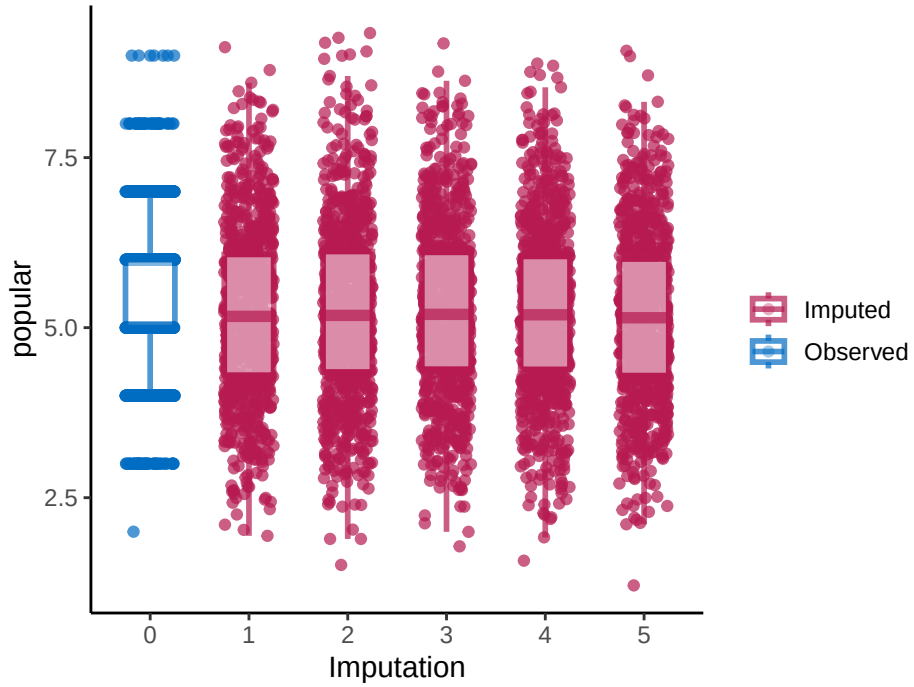
Imputation with random effects and heterogeneity

This method assumes random slopes for each variable in the imputation model. In contrast to `2l.norm` this method allows a cluster-specific residual error variance.

```
R> pred["popular", ] <- c(-2, 2, 1, 2)
R> meth <- c("", "2l.pan", "", "")
R> imp_pan_2l <-
+   mice(
+     popmis %>% mutate(school = as.integer(school)),
+     pred = pred,
+     meth = meth,
+     maxit = 1,
+     print = FALSE
+   )
```

```
Warning: Removed 848 rows containing non-finite values (stat_boxplot).
```

```
Warning: Removed 848 rows containing missing values (geom_point).
```

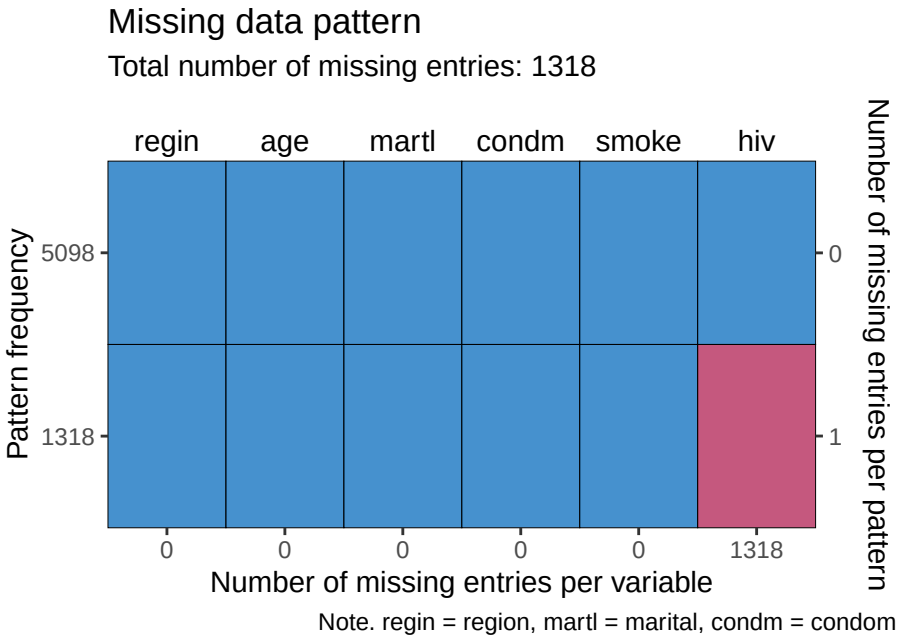


3. How to handle non-random selection (Case study II: HIV)

Data are simulated and included in the `GJRM` package. We will use the following variables:

- `region` Cluster variable,
- `hiv` HIV diagnosis (0=no, 1=yes),
- `age` Age of the patient,
- `marital` Marital status,
- `condom` Condom use during last intercourse,
- `smoke` Smoker (levels; inclusion restriction variable).

The imputation of these date is based on the toy example from IPDMA Heckman Github repo.



From the missing data pattern we see that we can set `maxit` to 1, since there is only one variable with missingness.

The inclusion restriction variable should be a predictor of the the actual value of the variable of interest, but not of missingness indicator for the variable of interest. In this case, the data were simulated to adhere to this requirement. Namely, β_{smoke} = -0.064, 95% CI [-0.256, 0.126] for the analysis model (`formula = hiv ~ .`), and β_{smoke} = -0.265, 95% CI [-0.422, -0.11] for the selection model (`formula = is.na(hiv) ~ .`). This means the assumptions for the Heckman-type selection model are met.

4. How to handle multivariate missingness (Case study III: IMPACT)

`impact` is traumatic brain injury data with patients, $n = 11022$, clustered in studies, $N = 15$. With the following 11 variables:

- `name` Name of the study,
- `type` Type of study (RCT: randomized controlled trial, OBS: observational cohort),
- `age` Age of the patient,
- `motor_score` Glasgow Coma Scale motor score,
- `pupil` Pupillary reactivity,
- `ct` Marshall Computerized Tomography classification,
- `mort` 6-month mortality (0=alive, 1=dead).

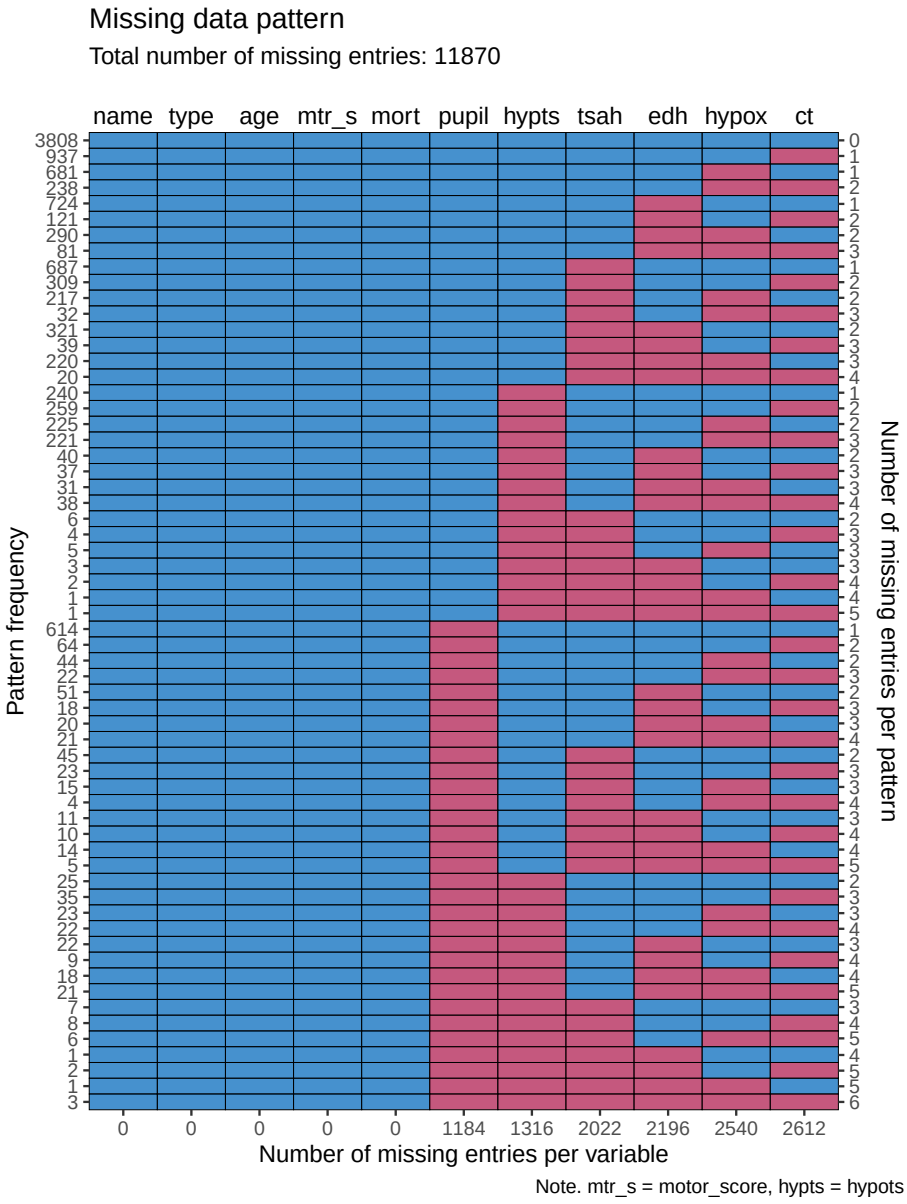
The analysis model for this dataset is a prediction model with `mort` as the outcome.[5] The

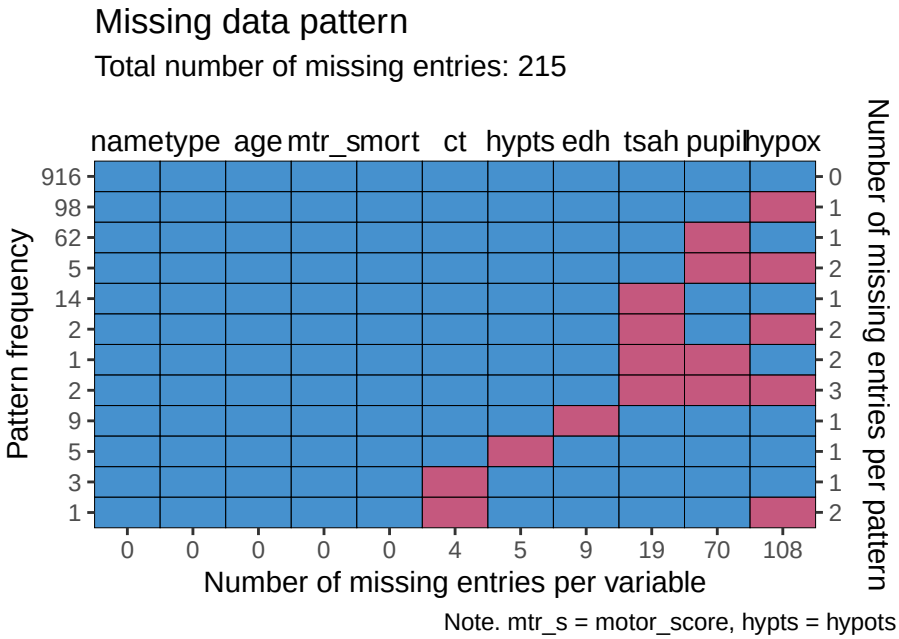
[5]Look at analysis model, maybe copy from GREAT data example e.g., adjusted prognostic effect of `ct` on unfortunate outcomes, we just want to know the adjusted odds ratio for `ct`. Add something about systematically missing data here.

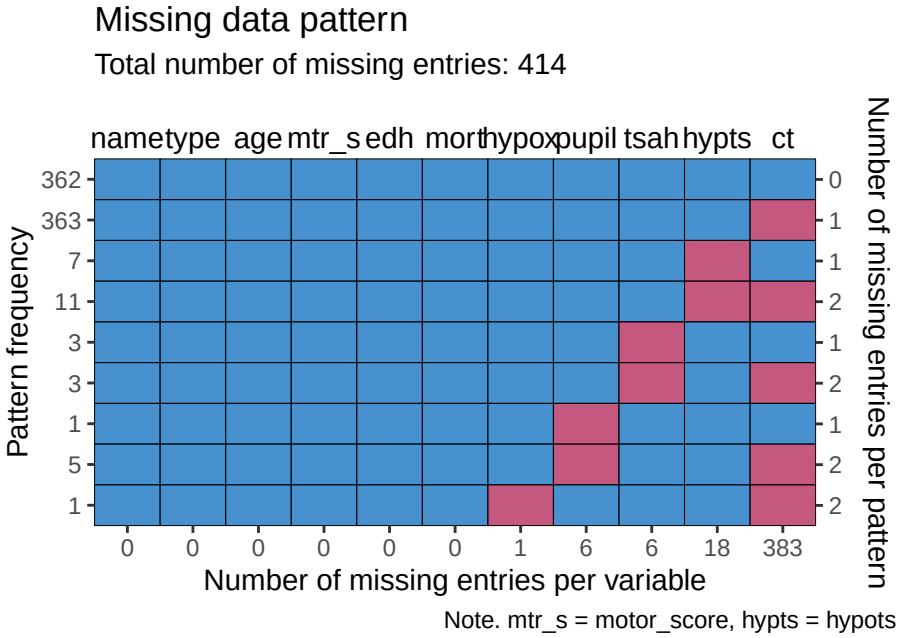
data is already imputed (Steyerberg et al, 2008), so we've induced missingness again based on the missingness in the original data.

$$\text{mort}_{ij} = \gamma_{00}+\gamma_{01}\ \text{type}_j+\gamma_{10}\ \text{age}_{ij}+\gamma_{10}\ \text{moter\_score}_{ij}+\gamma_{10}\ \text{pupil}_{ij}+\gamma_{10}\ \text{ct}_{ij}+u_{0j}+u_{1j}\ \text{age}_{ij}+u_{1j}\ \text{moter\_score}$$

```
glmer(mort ~ 1 + type + age + motor_score + pupil + ct + hypox + hypots + tsah
+ edh + (1 | name))
```








```
R> mod_cca <- glmer(mort ~ type + age + motor_score + pupil + ct + (1 | name), family = "b

Warning in checkConv(attr(opt, "derivs"), opt$par, ctrl = control$checkConv, : Model is ne
 - Rescale variables?

R> mod_cca %>% broom.mixed::tidy()
```

```
# A tibble: 9 x 7
  effect   group term            estimate std.error statistic   p.value
  <chr>    <chr> <chr>              <dbl>     <dbl>     <dbl>     <dbl>
1 fixed    <NA>  (Intercept)      -2.66     0.194      -13.7   1.11e-42
2 fixed    <NA>  typeRCT          -0.412    0.172       -2.40  1.64e- 2
3 fixed    <NA>  age                0.0298   0.00190     15.7   2.56e-55
4 fixed    <NA>  motor_score3     -0.631    0.0823      -7.66  1.82e-14
5 fixed    <NA>  motor_score4     -0.994    0.0845     -11.8   5.61e-32
6 fixed    <NA>  motor_score5/6   -1.54     0.0868     -17.7   2.88e-70
7 fixed    <NA>  pupil              0.438    0.0397      11.0   3.01e-28
8 fixed    <NA>  ct                 0.430    0.0343      12.5   5.34e-36
9 ran_pars name  sd__(Intercept)    0.257   NA           NA    NA
```

```
R> # use glm with name as dummy
R> # only random effect on ct, not the other variables
R> # make forest plot of ct variable
R> # is there heterogen in association of ct with mort?
R> # is there any random effect on that variable at all?
R> #
```

```
R> pred <- quickpred(impact_NA)
R> pred[pred == 1] <- 2
R> pred[, "name"] <- -2
R> pred["mort", ] <- 2
R> pred[, "mort"] <- 2
R> diag(pred) <- 0
R> pred[c("name", "type", "age", "motor_score", "mort"), ] <- 0
R> pred
```

```
            name type age motor_score pupil ct hypox hypots tsah edh mort
name           0    0   0           0     0  0     0      0    0   0    0
type           0    0   0           0     0  0     0      0    0   0    0
age            0    0   0           0     0  0     0      0    0   0    0
motor_score    0    0   0           0     0  0     0      0    0   0    0
pupil         -2    0   0           2     0  2     0      2    0   0    2
ct            -2    2   2           2     2  0     0      0    2   2    2
hypox         -2    2   0           2     0  0     0      2    0   0    2
hypots        -2    0   0           2     2  0     2      0    0   0    2
tsah          -2    0   2           0     0  2     0      0    0   0    2
edh           -2    0   0           0     0  2     0      0    0   0    2
mort           0    0   0           0     0  0     0      0    0   0    0
```

```
R> meth <- make.method(impact_NA)
R> meth[meth != ""] <- "2l.pmm"
```

```
R> # imp_impact <- impact_NA %>%
R> #   mutate(name = as.integer(name), motor_score = as.numeric(motor_score)) %>%
```

```
R> #   mice::mice(., m = 2, maxit = 1, method = meth, predictorMatrix = pred)
R> # look at jomo for categorical variables?
R> # semi-cont with jomo is not ideal (schafer, '97) because you need 2-step approach
R> # pmm is better (more efficient) because it will still look for donors (maybe outside c
R> # make assumptions of these methods explicit!
```

5. Discussion

- JOMO in **mice** -> on the side for now
- Additional levels of clustering
- More complex data types: timeseries and polynomial relationship in the clustering.

6. Think about

- Adding some kind of help function to mice that suggests a suitable predictor matrix to the user, given a certain analysis model.
- Adding a `multilevel_ampute()` wrapper function in mice.
- Exporting `mids` objects to other packages like `lme4` or `coxme`?
- Adding a ICC=0 dataset to show that even if there is no clustering it doesn't hurt.
- env dump in repo

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