Causal inference with missing values

Effect of tranexamic acid on mortality for head trauma patient

Julie Josse (X - INRIA XPOP) - Imke Mayer
22 January, 2019

Statistic seminar Lyon
Research activities

- Dimensionality reduction methods to visualize complex data (PCA based): multi-sources, textual, arrays, questionnaire
- Low rank estimation, selection of regularization parameters
- Missing values - matrix completion
- Causal inference
- Fields of application: bio-sciences (agronomy, sensory analysis), health data (hospital data)
- R community: book R for Stat, R foundation, taskforce, packages: FactoMineR explore continuous, categorical, multiple contingency tables (correspondence analysis), combine clustering and PC, .. MissMDA for single and multiple imputation, PCA with missing denoiseR to denoise data with low-rank estimation R-miss-tastic missing values plateform
Overview

1. Introduction

2. Causal inference
   - Inverse-propensity weighting
   - Double robust methods

3. Handling missing values
   - Single imputation with PCA
   - Supervised learning with missing values
     - Logistic regression with missing values

4. Results

5. Conclusion
Introduction
Collaborators

PhD students : G. Robin, W. Jiang, I. Mayer, N. Prost, polytechnique
Colleagues : J-P Nadal (EHESS), E. Scornet (X), G. Varoquaux (INRIA), S. Wager (Stanford), B. Naras (Stanford)
Traumabase (APHP) : T. Gauss, S. Hamada, J-D Moyer
Capgemini
**Major trauma**: any injury that endangers the life or the functional integrity of a person. Road traffic accidents, interpersonal violence, self-harm, falls, etc → hemorrhage and traumatic brain injury.

**Major source of mortality and handicap in France and worldwide**
(3rd cause of death, 1st cause for 16-45 - 2-3th cause of disability)

⇒ A public health challenge

Patient prognosis can be improved: **standardized and reproducible procedures** but **personalized** for the patient and the trauma system.

Trauma decision making: rapid and **complex decisions** under **time pressure** in a dynamic and multi-player environment (fragmentation: loss or distortion of information) with high levels of uncertainty and **stress**.

Issues: patient management exceeds time frames, diagnostic errors, decisions not reproducible, etc

⇒ Can Machine Learning, AI help?
Decision support tool for the management of severe trauma: Traumamatrix

PATIENT CENTERED PROBABILISTIC DECISION SUPPORT

REAL TIME ADAPTIVE AND LEARNING INFORMATION MANAGEMENT FOR ALL PROVIDERS

Audio-Visual Cockpit style Decision Support
Traumabase

15000 patients/ 250 variables/ 11 hospitals, from 2011 (4000 new patients/ year)

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⇒ **Predict** the Glasgow score, whether to start a blood transfusion, to administer fresh frozen plasma, etc...
⇒ (Logistic) regressions with missing categorical/continuous values
15000 patients/ 250 variables/ 11 hospitals, from 2011 (4000 new patients/ year)

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⇒ Estimate causal effect: administration of the treatment "tranexamic acid" (within the first 3 hours after the accident) on mortality (outcome) for traumatic brain injury (TBI) patients.
Causal inference for traumatic brain injury with missing values

- 3050 patients with a brain injury (a lesion visible on the CT scan)
- Treatment: tranexamic acid (binary)
- Outcome: in-ICU death (binary), causes: brain death, withdrawal of care, head injury and multiple organ failure.
- 45 **quantitative & categorical** covariates selected by experts (Delphi process). Pre-hospital (blood pressure, patients reactivity, type of accident, anamnesis, etc.) and hospital data
⇒ Causal inference

Causal inference methodology: estimate causal relationships between an intervention (acid administration) and an outcome (mortality), when the study is potentially confounded by selection bias due to the absence of randomization.

⇒ How to handle missing values?
⇒ Causal inference with missing values, analysis of the data
Causal inference
Potential outcome framework (Rubin, 1974)

**Causal effect**

Binary treatment $w \in \{0, 1\}$ on $i$-th individual with potential outcomes $Y_i(1)$ and $Y_i(0)$. Individual causal effect of the treatment:

$$\Delta_i = Y_i(1) - Y_i(0)$$
Potential outcome framework (Rubin, 1974)

**Causal effect**

Binary treatment \( w \in \{0, 1\} \) on \( i \)-th individual with potential outcomes \( Y_i(1) \) and \( Y_i(0) \). Individual causal effect of the treatment:

\[
\Delta_i = Y_i(1) - Y_i(0)
\]

- Problem: \( \Delta_i \) never observed (only observe one outcome/indiv).
  Causal inference as a missing value pb?
- **Average treatment effect (ATE)** \( \tau = \mathbb{E}[\Delta_i] = \mathbb{E}[Y_i(1) - Y_i(0)] \):
  The ATE is the difference of the average outcome had everyone gotten treated and the average outcome had nobody gotten treated.

⇒ First solution: estimate \( \tau \) with randomized controlled trials (RCT).
Average treatment effect estimation in RTCs

Assumptions:
Observe $n$ iid samples $(Y_i, W_i)$ each satisfying:

- $Y_i = Y_i(W_i)$ (SUTVA)
- $W_i \perp \{Y_i(0), Y_i(1)\}$ (random treatment assignment)

### Difference-in-means estimator

\[
\hat{\tau}_{DM} = \frac{1}{n_1} \sum_{W_1=1} Y_i - \frac{1}{n_0} \sum_{W_1=0} Y_i
\]

### Properties of $\hat{\tau}_{DM}$

$\hat{\tau}_{DM}$ is unbiased and $\sqrt{n}$-consistent. $\sqrt{n}(\hat{\tau}_{DM} - \tau) \xrightarrow{d} N(0, V_{DM})$, where $V_{DM} = \frac{\text{Var}(Y_i(0))}{P(W_i=0)} + \frac{\text{Var}(Y_i(1))}{P(W_i=1)}$. 
Average treatment effect estimation in RTCs

\[ \hat{\tau}_{DM} = \frac{1}{n_1} \sum_{W_1=1} Y_i - \frac{1}{n_0} \sum_{W_1=0} Y_i \]

Furthermore assume a linear model for the two potential outcomes:

**Linear assumptions n iid samples** \((X_i, Y_i, W_i)\)

- \(Y_i(w) = c(w) + X_i \beta(w) + \varepsilon_i(w), \ w \in \{0,1\},\)
- \(Y_i(w) = \mu(w)(X_i) + \varepsilon_i(w)\)
- \(\mathbb{E}[\varepsilon_i(w)|X_i] = 0\) and \(\text{Var}(\varepsilon_i(w)|X_i) = \sigma^2.\)

**OLS estimator**

\[ \hat{\tau}_{OLS} = \hat{c}_1 - \hat{c}_0 + \bar{X} (\hat{\beta}_1 - \hat{\beta}_0) = \frac{1}{n} \sum_i \left( (\hat{c}_1 + X_i \hat{\beta}_1) - (\hat{c}_0 - X_i \hat{\beta}_0) \right) = \frac{1}{n} \sum_i (\hat{\mu}_1 X_i - \hat{\mu}_0(X_i)) \]

**Properties of \( \hat{\tau}_{OLS} \)**

\[ \sqrt{n} (\hat{\tau}_{OLS} - \tau) \xrightarrow{n \to \infty} \mathcal{N}(0, V_{OLS}). \text{ And } V_{DM} = V_{OLS} + \|\beta(0) + \beta(1)\|_A^2. \]
Observational data. Non random assignment: confusion

Mortality rate 16% - treated 28 - not treated 13: treatment kills?

<table>
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<tr>
<th>Died</th>
<th>P(Outcome</th>
<th>Treatment)</th>
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<tbody>
<tr>
<td>Treated</td>
<td>0 1 0 1</td>
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</tr>
<tr>
<td>FALSE</td>
<td>2225 340</td>
<td>0.867 0.133</td>
</tr>
<tr>
<td>TRUE</td>
<td>436 168</td>
<td>0.722 0.278</td>
</tr>
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Strong indication for confounding factors that need to be controlled for.

Standardized mean differences between treated and control.

Treated patients are more severe with higher risk of death (graphical model)
Solutions to estimate ATE with observational data

- **Matching**: pair each treated (resp. untreated) patient with one or more similar untreated (resp. treated) patient (R package Match)
- **Inverse-propensity weighting**: to adjust for biases in the treatment assignment

- **Double robust methods** for model misspecifications: covariate balancing propensity score, augmented IPW. (Robins et al., 1994)
- **Regression adjustment**, regression-adjusted matching, etc.
Unconfoundedness and the propensity score

Assumptions

- $n$ iid samples $(X_i, Y_i, W_i)$,
- Treatment assignment is random conditionally on $X_i$:
  $\{Y_i(0), Y_i(1)\} \perp \perp W_i \mid X_i \equiv \text{unconfoundedness assumption}$.

Measure enough covariates to capture any dependence between $W_i$ and the PO

**Propensity score**

$$e(x) = P(W_i = 1 \mid X_i = x) \quad \forall x \in \mathcal{X}.$$

We will assume overlap assumption, i.e. $0 < e(x) < 1 \quad \forall x \in \mathcal{X}$.

**Key property**

$e$ is a balancing score, i.e. under unconfoundedness, it satisfies

$$\{Y_i(0), Y_i(1)\} \perp \perp W_i \mid e(X_i)$$

As a consequence, it suffices to control for $e(X)$ (rather than $X$), to remove biases associated with non-random treatment assignment.
Unconfoundedness and the propensity score

**Propensity score**

\[ e(x) = \mathbb{P}(W_i = 1 \mid X_i = x) \quad \forall x \in \mathcal{X}. \]

**Key property**

Under unconfoundedness, \( e(x) \) satisfies \( \{Y_i(0), Y_i(1)\} \perp \perp W_i \mid e(X_i). \)

**Proof**

To prove this balancing property, we note that the distribution of \( W \) is fully specified by its mean. Therefore we need to prove that :

\[
\mathbb{E}[W_i \mid \{Y_i(0), Y_i(1)\}, X_i] = \mathbb{E}[W_i \mid X_i] \Rightarrow \mathbb{E}[W_i \mid \{Y_i(0), Y_i(1)\}, e(X_i)] = \mathbb{E}[W_i \mid e(X_i)]
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Unconfoundedness and the propensity score

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a) By the law of total expectation we have :

\[ \mathbb{E}[W_i \mid e(X_i)] = \mathbb{E}[\mathbb{E}[W_i \mid X_i, e(X_i)] \mid e(X_i)] = \mathbb{E}[\mathbb{E}[W_i \mid X_i] \mid e(X_i)] = e(X_i) \]
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\]

b) And again using the law of total expectation we have the following:

\[
E[W_i \mid \{ Y_i(0), Y_i(1) \}, e(X_i)] = E[E[W_i \mid \{ Y_i(0), Y_i(1) \}, X_i, e(X_i)] \mid \{ Y_i(0), Y_i(1) \}, e(X_i)]
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= E[E[W_i \mid X_i] \mid \{ Y_i(0), Y_i(1) \}, e(X_i)] \quad \text{(unconfoundedness)}
\]

\[
= E[e(X_i) \mid \{ Y_i(0), Y_i(1) \}, e(X_i)] = e(X_i)
\]

■
Inverse-propensity weighting estimation of ATE

\[ \hat{\tau}_{IPW} = \frac{1}{n} \sum_{i=1}^{n} \left( \frac{W_i Y_i}{\hat{e}(X_i)} - \frac{(1 - W_i) Y_i}{1 - \hat{e}(X_i)} \right) \]

⇒ Balance the difference between the two groups

The quality of this estimator depends on the estimation quality of \( \hat{e}(x) \) on the postulated propensity score model. Indeed we have:

\[
\mathbb{E} \left[ \frac{WY}{e(X)} \right] = \mathbb{E} \left[ \frac{WY(1)}{e(X)} \right] = \mathbb{E} \left[ \mathbb{E} \left[ \frac{WY(1)}{e(X)} \mid Y(1), X \right] \right] \\
= \mathbb{E} \left[ \frac{Y(1)}{e(X)} \mathbb{E}[W \mid Y(1), X] \right] = \mathbb{E} \left[ \frac{Y(1)}{e(X)} \mathbb{E}[W \mid X] \right] \\
= \mathbb{E} \left[ \frac{Y(1)}{e(X)} e(X) \right] = \mathbb{E}[Y(1)].
\]

This holds if \( e(X) = \mathbb{P}(W = 1 \mid X) \), therefore if \( \hat{e}(X) \) is not the true propensity score then \( \hat{\tau}_{IPW} \) is not necessarily a (consistent) estimate of \( \tau \). Variance of the oracle estimate is bad!
Covariate balancing propensity score (CBPS)

Assume a linear-logistic model:

1. \( e(x) = P(W_i = 1 \mid X_i = x) = \frac{1}{1 + e^{-x^T \alpha}} \)
2. \( \mu_w(x) = x^T \beta_w \) (for \( w \in \{0, 1\} \)).
3. \( Y_i(w) = \mu_w(X_i) + \varepsilon_i. \)

Decompose ATE \( \hat{\tau} = \frac{1}{n} \sum_{i=1}^{n} (\hat{\gamma}(1)(X_i) W_i Y_i - \hat{\gamma}(0)(X_i)(1 - W_i) Y_i) : \)

\[
\hat{\tau} = \bar{X}(\beta(1) - \beta(0)) + [\text{term for } \varepsilon] + \left( \frac{1}{n} \sum_{i=1}^{n} \hat{\gamma}(1)(X_i) W_i X_i - \bar{X} \right) \beta(1) - \left( \frac{1}{n} \sum_{i=1}^{n} \hat{\gamma}(0)(X_i)(1 - W_i) X_i - \bar{X} \right)
\]

\[
= \bar{X}(\beta(1) - \beta(0)) + \frac{W_i(Y_i - \mu(1)(X_i))}{e(X_i)} - \frac{(1 - W_i)(Y_i - \mu(0)(X_i))}{1 - e(X_i)}
\]

What happens when models are mis-specified? Double robustness

For specific \( \hat{\gamma}(1) \) and \( \hat{\gamma}(0) \) (functions of \( \alpha \)), \( \hat{\tau} \) is the CPBS and it is doubly robust, i.e. it is consistent in either one of the following cases:

1. Outcome model is linear but propensity score \( e(x) \) is not logistic.
2. Propensity score \( e(x) \) is logistic but outcome model is not linear.
Define $\mu(w)(x) := \mathbb{E}[Y_i(w) \mid X_i = x]$ and $e(x) := \mathbb{P}(W_i = 1 \mid X_i = x)$.

### Doubly robust estimator

$\hat{\tau}_{DR} := \frac{1}{n} \sum_{i=1}^{n} \left( \hat{\mu}(1)(X_i) - \hat{\mu}(0)(X_i) + W_i \frac{Y_i - \hat{\mu}(1)(X_i)}{\hat{e}(X_i)} - (1 - W_i) \frac{Y_i - \hat{\mu}(0)(X_i)}{1 - \hat{e}(X_i)} \right)$

is consistent if either the $\hat{\mu}(w)(x)$ are consistent or $\hat{e}(x)$ is consistent.

Furthermore $\hat{\tau}_{DR}^*$ has good asymptotic variance.
Another doubly robust ATE estimator

Define \( \mu_w(x) := \mathbb{E}[Y_i(w) \mid X_i = x] \) and \( e(x) := \mathbb{P}(W_i = 1 \mid X_i = x) \).

**Doubly robust estimator**

\[
\hat{\tau}_{DR} := \frac{1}{n} \sum_{i=1}^{n} \left( \hat{\mu}(1)(X_i) - \hat{\mu}(0)(X_i) + W_i \frac{Y_i - \hat{\mu}(1)(X_i)}{\hat{e}(X_i)} - (1 - W_i) \frac{Y_i - \hat{\mu}(0)(X_i)}{1 - \hat{e}(X_i)} \right)
\]

is consistent if either the \( \hat{\mu}_w(x) \) are consistent or \( \hat{e}(x) \) is consistent. Furthermore \( \hat{\tau}_{DR^*} \) has good asymptotic variance.

**Remark 1**: Possibility to use **any (machine learning) procedure** such as random forests, deep nets, etc. to estimate \( \hat{e}(x) \) and \( \hat{\mu}_w(x) \) without harming the interpretability of the causal effect estimation.

**Remark 2**: In case of overparametrization or non-parametric estimation \( \hat{\mu}_w(x) \) and \( \hat{e}(x) \) should be learned/estimated by **cross-splitting** to avoid overfitting. Package `grf` (Wager, Tibshirani)
Semiparametric efficiency for ATE estimation

**Efficient score estimator**

Given unconfoundedness \(\{Y_i(1), Y_i(1)\} \perp W_i | X_i\) but no further parametric assumptions on \(\mu(w)(x)\) and \(e(x)\), the previously attained asymptotic variance,

\[ V^* := \text{Var}(\tau(X)) + \mathbb{E} \left[ \frac{\sigma^2(X)}{e(X)(1 - e(X))} \right], \]

is optimal and any estimator \(\tau^*\) that attains it is asymptotically equivalent to \(\hat{\tau}_{DR^*}\).

\(V^*\) is the **semiparametric efficient variance** for ATE estimation.

**Semiparametric**: we are interested in a parametric estimand, \(\tau\), which we estimate using nonparametric estimates \((\hat{\tau}_{DR} \text{ depends on nonparametric estimates } \hat{\mu}(w)(x) \text{ and } \hat{e}(x))\).
Handling missing values
Solutions to handle missing values

Litterature: Schaefer (2002); Little & Rubin (2002); Gelman & Meng (2004); Kim & Shao (2013); Carpenter & Kenward (2013); van Buuren (2015)

⇒ Modify the estimation process to deal with missing values. Maximum likelihood: EM algorithm to obtain point estimates + Supplemented EM (Meng & Rubin, 1991); Louis for their variability
Difficult to establish?
Not many implementations, even for simple models
One specific algorithm for each statistical method...

⇒ Imputation (multiple) to get a completed data set on which you can perform any statistical method (Rubin, 1976)

⇒ Mechanism - Visualisation
Dealing with missing values

⇒ Imputation to get a completed data set

Mean imputation

\[
\begin{align*}
\mu_y &= 0 \\
\sigma_y &= 1 \\
\rho &= 0.6
\end{align*}
\]

\[
\begin{array}{|c|}
\hline
\hat{\mu}_y &= 0.01 \\
\hat{\sigma}_y &= 0.5 \\
\hat{\rho} &= 0.30 \\
\hline
\end{array}
\]
Wright IJ, et al. (2004). The worldwide leaf economics spectrum. Nature, 69 000 species - LMA (leaf mass per area), LL (leaf lifespan), Amass (photosynthetic assimilation), Nmass (leaf nitrogen), Pmass (leaf phosphorus), Rmass (dark respiration rate)
Imputation methods

\[ \mu_y = 0 \quad \sigma_y = 1 \quad \rho = 0.6 \]

\[ y_i \overset{\text{impute}}{\rightarrow} \hat{y}_i \]

Stochastic regression imputation

\[ 0.01 \]

\[ 0.5 \]

\[ 0.30 \]
Imputation methods

- Impute by regression take into account the relationship: estimate $\beta$ - impute $\hat{y}_i = \hat{\beta}_0 + \hat{\beta}_1 x_i \Rightarrow$ variance underestimated and correlation overestimated.

![Mean imputation](image1.png)

![Regression imputation](image2.png)

| $\mu_y = 0$ | 0.01 |
| $\sigma_y = 1$ | 0.5 |
| $\rho = 0.6$ | 0.30 |

| 0.01 |
| 0.72 |
| 0.78 |
Imputation methods

- Impute by regression take into account the relationship: estimate $\beta$ - impute $\hat{y}_i = \hat{\beta}_0 + \hat{\beta}_1 x_i \Rightarrow$ variance underestimated and correlation overestimated.
- Impute by stochastic reg: estimate $\beta$ and $\sigma$ - impute from the predictive $y_i \sim N(x_i \hat{\beta}, \hat{\sigma}^2) \Rightarrow$ preserve distribution.

\[
\mu_y = 0 \quad 0.01 \\
\sigma_y = 1 \quad 0.5 \quad 0.72 \quad 0.99 \\
\rho = 0.6 \quad 0.30 \quad 0.78 \quad 0.59
\]
Imputation assuming a joint modeling with gaussian distribution

based on Gaussian assumption: $x_i \sim \mathcal{N}(\mu, \Sigma)$

- Bivariate with missing on $x_{i1}$ (stochastic reg): estimate $\beta$ and $\sigma$ - impute from the predictive $x_{i1} \sim \mathcal{N}(x_{i2}\hat{\beta}, \hat{\sigma}^2)$
- Extension to multivariate case: estimate $\mu$ and $\Sigma$ from an incomplete data with EM - impute by drawing from $\mathcal{N}(\hat{\mu}, \hat{\Sigma})$ equivalence conditional expectation and regression (complement Schur)

packages Amelia, mice (conditional)
PCA reconstruction

⇒ Minimizes distance between observations and their projection
⇒ Approx $X_{n \times p}$ with a low rank matrix $k < p \|A\|_2^2 = \text{tr}(AA^\top)$:

$$\arg\min_{\mu} \left\{ \|X - \mu\|_2^2 : \text{rank}(\mu) \leq k \right\}$$

SVD $X$:

$$\hat{\mu}^{\text{PCA}} = U_{n \times k} D_{k \times k} V'_{p \times k} \quad F = UD \quad \text{PC - scores}$$

$$= F_{n \times k} V'_{p \times k} \quad V \quad \text{principal axes - loadings}$$
PCA reconstruction

$X$

Minimizes distance between observations and their projection

Approx $X_{n \times p}$ with a low rank matrix $k < p \|A\|_2^2 = \text{tr}(AA^\top)$:

$\arg\min_{\mu} \left\{ \|X - \mu\|_2^2 : \text{rank} (\mu) \leq k \right\}$

$X \approx F \hat{\mu}$

$\hat{\mu}_{\text{PCA}} = U_{n \times k} D_{k \times k} V'_{p \times k}$

$F = UD$  PC - scores

$V$ principal axes - loadings
Missing values in PCA

⇒ PCA : least squares

\[
\arg\min_{\mu} \left\{ \| X_{n \times p} - \mu_{n \times p} \|_2^2 : \text{rank}(\mu) \leq k \right\}
\]

⇒ PCA with missing values : weighted least squares

\[
\arg\min_{\mu} \left\{ \| W_{n \times p} \odot (X - \mu) \|_2^2 : \text{rank}(\mu) \leq k \right\}
\]

with \( w_{ij} = 0 \) if \( x_{ij} \) is missing, \( w_{ij} = 1 \) otherwise ; \( \odot \) elementwise multiplication

Many algorithms :
Gabriel & Zamir, 1979 : weighted alternating least squares (without explicit imputation)
Kiers, 1997 : iterative PCA (with imputation)
Iterative PCA

```
x1  x2
-2.0 -2.01
-1.5 -1.48
 0.0 -0.01
 1.5  NA
 2.0  1.98
```
Iterative PCA

Initialization $\ell = 0 : X^0$ (mean imputation)
Iterative PCA

PCA on the completed data set $\rightarrow (U^\ell, \Lambda^\ell, D^\ell)$;
Iterative PCA

\[
\hat{\mu}^\ell = U^\ell D^\ell V^{\ell,\prime}
\]

Missing values imputed with the fitted matrix \( \hat{\mu}^\ell = U^\ell D^\ell V^{\ell,\prime} \).
The new imputed dataset is $\hat{X}^\ell = W \odot X + (1 - W) \odot \hat{\mu}^\ell$. 

\begin{verbatim}
x1  x2
-2.0 -2.01
-1.5 -1.48
0.0 -0.01
1.5  NA
2.0  1.98

x1  x2
-2.0 -2.01
-1.5 -1.48
0.0 -0.01
1.5  0.00
2.0  1.98

\h^{\wedge} x1 \h^{\wedge} x2
-1.98 -2.04
-1.44 -1.56
0.15 -0.18
1.00  0.57
2.27  1.67

x1  x2
-2.0 -2.01
-1.5 -1.48
0.0 -0.01
1.5  0.57
2.0  1.98
\end{verbatim}
Iterative PCA

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<td>2.0</td>
<td>1.98</td>
</tr>
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</table>

-2 -1 0 1 2 3
-2 -1 0 1 2 3

\(x_1\) vs. \(x_2\) plot with coordinates (-2, -2.01), (-1.5, -1.48), (0.0, -0.01), (1.5, 0.57), and (2.0, 1.98).
Iterative PCA

-2.0 -2.01
-1.5 -1.48
0.0 -0.01
1.5 \text{NA}
2.0 1.98

-2.00 -2.01
-1.47 -1.52
0.09 -0.11
1.20 0.90
2.18 1.78
Iterative PCA

Steps are repeated until convergence
Iterative PCA

PCA on the completed data set $\rightarrow (U^\ell, D^\ell, V^\ell)$

Missing values imputed with the fitted matrix $\hat{\mu}^\ell = U^\ell D^\ell V^{\ell\prime}$
Iterative PCA

1. initialization $\ell = 0 : X^0$ (mean imputation)

2. step $\ell$:
   (a) PCA on the completed data $\rightarrow (U^\ell, D^\ell, V^\ell)$; $k$ dim kept
   (b) $\hat{\mu}_{\text{PCA}} = \sum_{q=1}^{k} d_q u_q v_q'$

3. steps of estimation and imputation are repeated

$\Rightarrow$ Overfitting : nb param $(U_{n \times k}, V_{k \times p})$/obs values : $k$ large - NA ; noisy

**Regularized** versions. Imputation is replaced by

$$(\hat{\mu})_\lambda = \sum_{q=1}^{p} (d_q - \lambda)_+ u_q v_q'$

$$\arg\min_\mu \left\{ \| W \odot (X - \mu)\|_2^2 + \lambda \| \mu \|_* \right\}$$


$\Rightarrow$ Iterative SVD algo good to impute data (matrix completion, Netflix)

$\Rightarrow$ Model makes sense : data = rank $k$ signal + noise

$X = \mu + \varepsilon \varepsilon_{ij} \overset{iid}{\sim} \mathcal{N}(0, \sigma^2)$ with $\mu$ of low rank

(Udell & Townsend, 2017)
⇒ Imputation with FAMD for mixed data:

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```

ImputeAFDM

```
| NA  | 100    | 190   | NA      | 1 0 | 0 1  | 1 0 0  |
| 70  | 96     | 186   | 0 1 0   | 1 0 | NA   | NA 0 1 |
| NA  | 104    | 194   | 1 0 0   | 0 1 | 1 0  | NA  NA |
| 62  | 68     | 165   | 0 1 0   | 1 0 | 1 0  | 0 1 0  |
```

⇒ Multilevel imputation: hospital effect with patient nested in hospital.

(J., Husson, Robin & Balasu., 2018, Imputation of mixed data with multilevel SVD. *JCGS*)

package MissMDA.
Iterative random forests imputation

Imputation with fully conditional specification (FCS). Impute with a joint model defined implicitly through the conditional distributions (mice). Here, imputation model for each variable is a forest.

1. Initial imputation: mean imputation - random category
2. for \( t \) in 1 : \( T \) loop through iterations \( t \)
3. for \( j \) in 1 : \( p \) loop through variables \( j \)

Define currently complete data set except \( X_{-j}^t = (X_1^t, X_{j-1}^t, X_{j+1}^t, X_{p-1}^t) \), then \( X_j^t \) is obtained by
- fitting a RF \( X_j^{obs} \) on the other variables \( X_{-j}^t \)
- predicting \( X_j^{miss} \) using the trained RF on \( X_{-j}^t \)

R package missForest (Stekhoven & Buhlmann, 2011)
Random forests versus PCA

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⇒ Missing
⇒ Random forests
⇒ PCA

⇒ RF good for non linear relationship / PCA linear relation
⇒ RF computationally costly ⇒ Imputation inherits from the method
Logistic regression with missing covariates: parameter estimation, model selection and prediction. (Jiang, J., Lavielle, Gauss, Hamada, 2018)

\[ x = (x_{ij}) \text{ a } n \times p \text{ matrix of quantitative covariates} \]
\[ y = (y_i) \text{ an } n\text{-vector of binary responses } \{0, 1\} \]

**Logistic regression model**

\[
\mathbb{P}(y_i = 1|x_i; \beta) = \frac{\exp(\beta_0 + \sum_{j=1}^{p} \beta_j x_{ij})}{1 + \exp(\beta_0 + \sum_{j=1}^{p} \beta_j x_{ij})}
\]

**Covariables**

\[ x_i \sim \text{i.i.d. } \mathcal{N}_p(\mu, \Sigma) \]

**Log-likelihood** for complete-data with \( \theta = (\mu, \Sigma, \beta) \)

\[
\mathcal{L}\mathcal{L}(\theta; x, y) = \sum_{i=1}^{n} \left( \log(p(y_i|x_i; \beta)) + \log(p(x_i; \mu, \Sigma)) \right).
\]

Decomposition: \( x = (x_{\text{obs}}, x_{\text{mis}}) \)

**Observed likelihood**  
\[
\arg \max \mathcal{L}\mathcal{L}(\theta; x_{\text{obs}}, y) = \int \mathcal{L}\mathcal{L}(\theta; x, y) dx_{\text{mis}}
\]
Stochastic Approximation EM

- **E-step:** Evaluate the quantity
  \[ Q_k(\theta) = \mathbb{E}[\mathcal{L}\mathcal{L}(\theta; x, y)|x_{\text{obs}}, y; \theta_{k-1}] \]
  \[ = \int \mathcal{L}\mathcal{L}(\theta; x, y)p(x_{\text{mis}}|x_{\text{obs}}, y; \theta_{k-1})dx_{\text{mis}} \]

- **M-step:** \( \theta_k = \arg \max_\theta Q_k(\theta) \)

\( \Rightarrow \text{Unfeasible computation of expectation} \)

**MCEM** *(Wei & Tanner, 1990)*: generate samples of missing data from \( p(x_{\text{mis}}|x_{\text{obs}}, y; \theta_{k-1}) \) and replaces the expectation by an empirical mean.

\( \Rightarrow \text{Require a huge number of samples} \)

**SAEM** *(Lavielle, 2014)* almost sure convergence to MLE. *(Metropolis Hasting - Variance estimation with Louis)*.

Comparison with competitors (mice). Unbiased, good coverage.
Time: \( n = 1000, \text{MCEM: 700s - SAEM: 13s - mice 1s} \)
An integrated procedure

⇒ Model selection: \( \text{BIC}(M) = -2 \mathcal{L}(\hat{\theta}_M; x_{\text{obs}}, y) + \log(n) d(M) \)

How to estimate observed likelihood?

\[
p(y_i, x_{i,\text{obs}}; \theta) = \int p(y_i, x_{i,\text{obs}}|x_{i,\text{mis}}; \theta)p(x_{i,\text{mis}}; \theta)dx_{i,\text{mis}}
\]

Empirical mean using sample from the proposal distribution in SAEM.

⇒ Prediction on a test set (with missing entries !).

\[
\hat{y} = \arg \max_y p(y|x_{\text{obs}})
\]

\[
= \arg \max_y \int p(y|x)p(x_{\text{mis}}|x_{\text{obs}})dx_{\text{mis}}
\]

\[
= \arg \max_y \mathbb{E}_{p_{x_{\text{mis}}|x_{\text{obs}}}} p(y|x)
\]

\[
= \arg \max_y \sum_{m=1}^M p\left(y|x_{\text{obs}}, x_{\text{mis}}^{(m)}\right).
\]

⇒ R package misaem
Random forests with missing values

Erwan Scornet, Nicolas Prost, Gael Varoquaux, Stefan Wager
Confounders estimated by matrix factorization on the observed covariates (Kallus, Mao and Udell (2018)) .

**Main assumptions**

- Linear regression model $Y_i = U_i^T \alpha + \tau T_i + \varepsilon_i$.
- Covariates $X$ are noisy and incomplete proxies of true confounders $U$.
- $X$ is a noisy realization of a low rank matrix $X = UV' + \varepsilon$.
- MCAR.

**Results :**

Under appropriate assumptions on $\alpha$, $\|U\|$, the relationship between $U$ and $T$ and the estimation of $\text{col}(U)$ by $\text{col}(\hat{U})$ and assuming unconfoundedness, then the resulting ATE estimator is consistent.

In practice : perform MF on $X$, keep $U$, perform the linear regression and estimate ATE with $\hat{\tau}$.
Results
Many choices, issues in practice....

- Coding issues: recode certain not really missing values, for ex Glasgow score ($\in \{3, \ldots, 15\}$) is missing for deceased patients. Recode by a category or a constant (lower bound $\min(GCS) = 3$).
Many choices, issues in practice....

- Coding issues: recode certain not really missing values, for example, Glasgow score ($\in \{3, \ldots, 15\}$) is missing for deceased patients. Recode by a category or a constant (lower bound $\min(GCS) = 3$).

- Impute with iterative FAMD (out-of-range imputation), Random forests (computational costly), mice (invertibility pbs with many categories)?

- Which observations? All individuals (TBI and no-TBI patients)

- Which variables? All available variables or the pre-selected ones

- Impute with treatment, covariates and outcome? (Impute with $Y$?)
Many choices, issues in practice....

- Coding issues: recode certain not really missing values, for example, Glasgow score ($\in \{3, \ldots, 15\}$) is missing for deceased patients. Recode by a category or a constant (lower bound $\min(GCS) = 3$).
- Impute with iterative FAMD (out-of-range imputation), Random forests (computational costly), mice (invertibility pbs with many categories)?
- Which observations? All individuals (TBI and no-TBI patients)
- Which variables? All available variables or the pre-selected ones
- Impute with treatment, covariates and outcome? (Impute with $Y$?)

Imputation (FAMD, RF) + IPW: $\hat{\tau}_{IPW} = \frac{1}{n} \sum_{i=1}^{n} \left( \frac{W_i Y_i}{\hat{e}(X_i)} - \frac{(1-W_i) Y_i}{1-\hat{e}(X_i)} \right)$

Model treatment on covariates $e(x) = \mathbb{P}(W_i = 1 \mid X_i = x)$ weights:

GLM, GRF, GBM. Trimming (0.1% & 99.9% quantiles to threshold the weights).

SAEM (quanti) + IPW (weights glm, trimming, grf)

Imputation (FAMD, RF) + double robusts: models outcome on covariates and treatment on covariates (GLM, RF, GBM)
Results

ATE estimations (bootstrap CI) for the effect of Tranexamic acid on in-ICU mortality for TBI patients. Imputations/SAEM on all patients (TBI + no-TBI).

We compute the mortality rate in the treated group and the mortality rate in the control group (after covariate balancing). The value obtained corresponds to the difference in percentage points between mortality rates in treatment and control.
Results

**ATC** estimations (bootstrap CI) for the effect of Tranexamic acid on in-ICU mortality for TBI patients. Imputations/SAEM on all patients (TBI + no-TBI).

(y-axis: imputation . ps estimation), (x-axis: ATC estimation with bootstrap CI)

ATC: average treatment effect on the control. In this case, assuming compliance, the control group is composed of TBI patients without extracranial bleeding.
Conclusion
On-going work, perspectives

Methodology/Theory

- Different missing values mechanism. Sportisse, A., Boyer, C. and Josse, J. Low-rank estimation with missing non at random data.
- Logistic regression for mixed variables.
- Identify subgroups of patients who could benefit from treatment? Optimal Prescription Trees (Bertsimas et al., 2018).
- Heterogeneous treatment effects (Athey and Imbens, 2015) and optimal policy learning (Imai and Ratkovic, 2013).
- Multiple imputation.
- Towards more complex treatment strategies: Do certain treatment strategies, i.e. bundles of treatments (administration of noradrenaline and SSH and tranexamic acid, etc.), have an effect on 24h mortality, on 14d mortality, etc.?
- Consistency of ATE estimators with missing values.
On-going work, perspectives

Traumabase - Traumatic brain injury

- Bias of mortality (dead before receiving?)
- Unconfoundedness?
- Choice of pre- and post-treatment covariates. Depending on future application. Ideally real-time treatment decision $\rightarrow$ learning optimal treatment policies.
- Compare results to the ones from CRASH3 study (not published yet).
Do you have any questions or comments?
Results

Imputations/SAEM on all patients. PS estimated with logistic regr.

- (SAEM)

FAMD

MF (Udell)
Results

Imputations/SAEM on all patients. PS estimated with **logistic regr.**

- (SAEM)  

**FAMD**

**MF (Udell)**
Results

Imputations on all patients. PS estimated with grf.

FAMD

MF (Udell)
Imputations on all patients. PS estimated with grf.

FAMD

MF (Udell)
Results

FAMD imputation on all patients. Bootstrap CI for DR ATE estimations. \((N = 200)\).

Logistic regression  
(Generalized) random forest

**blue dotted line**: Bootstrap quantiles (2.5% and 97.5%)  
**red dotted line**: Bootstrap mean  
**black segment**: ATE estimation with \(\pm 1.96SE\).
Results

FAMD imputation on all patients. Bootstrap CI for IPW ATE estimations. ($N = 200$).

Logistic regression

Generalized random forest

**blue dotted line**: Bootstrap quantiles (2.5% and 97.5%)

**red dotted line**: Bootstrap mean

**black segment**: ATE estimation with ±1.96SE.
S. Athey, J. Tibshirani, and S. Wager. 
**Generalized random forests.**

J. Carpenter and M. Kenward. 
**Multiple Imputation and its Application.**

**Effect of fibrinogen administration on early mortality in traumatic haemorrhagic shock : a propensity score analysis.**
*Submitted*, 2018.
Stochastic approximation em for logistic regression with missing values.

J. Josse, J. Pagès, and F. Husson.
Multiple imputation in principal component analysis.

N. Kallus, X. Mao, and M. Udell.
Causal inference with noisy and missing covariats via matrix factorization.

J. K. Kim and J. Shao.
Statistical Methods for Handling Incomplete Data.
R. J. A. Little and D. B. Rubin.  
**Statistical Analysis with Missing Data.**  

D. K. Menon and A. Ercole.  
**Critical care management of traumatic brain injury.**  

**Estimation of regression coefficients when some regressors are not always observed.**  
J. L. Schafer and J. W. Graham.
**Missing data: our view of the state of the art.**

A. Sportisse, C. Boyer, and J. Josse.
**Imputation and low-rank estimation with missing non at random data.**

S. van Buuren.
**Flexible Imputation of Missing Data.**

S. Wager.
**Lecture notes in causal inference and treatment effect estimation (oit 661), 2018.**