

UNIVERSITY OF OXFORD

MSC IN STATISTICAL SCIENCE

FINAL THESIS

Missing data imputation for Haemorrhagic shock prediction

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September 2018



Abstract

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Acknowledgements

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Introduction

Main outline: Haemorrhagic shock is a condition that can be life-threatening but that has much higher survival rates if treated early. In addition, doctors tend to have a fairly bad record of detecting it. Because of this, we want to build a tool that predicts it based on measurement on trauma patients. For this we use Traumabase, a large patient-records database. Problem: lots of missing data in it. Solutions: use algorithms specifically made for missing data or impute missing data. Nice thing about imputation: once it is done, you can use any existing method -> here we only work on imputation (not so much the prediction part).

We present the data (Chapter 1), then present the state of the art in imputation (Chapter 2). Then, we derive some theory on imputation when it is performed with prediction as a goal (Chapters 3 and 4). Finally, we come back to the data to apply what we learn, in order to choose the best imputation method for this problem (Chapter 6) and present our results.

Chapter 1

Goal and data

1.1 Hemorrhagic shock: a lethal but preventable condition

1.1.1 Description

Post-traumatic bleeding is the primary cause of preventable deaths among injured patients around the world [1][13]. When a person sustains a severe injury (e.g. due to a car accident or violent assault), she may present serious internal or external bleeding. If the injury is serious enough, the natural coagulation process is not sufficient to stop the blood loss. In that case, if too much blood is lost, the patient enters a state called hemorrhagic shock (HS) where the body is no longer able to provide vital organs with enough dioxygen to sustain them [9]. At this point, even proper care may not be enough to save the patient [15].

When an individual sustains an injury, she is usually first taken in charge by first responders who evaluate the situation and the patient's state, before transporting her to a trauma centre when the patient will be treated. To prevent patients from falling into HS, procedures have been established in most hospitals to trigger a fast response to suspected haemorrhage [39]: massive transfusion (MT) protocols can be activated even before the patient enters the hospital [34]. When this happens, the hospital gets ready to transfuse the patient with large amounts of blood as soon as she arrives, and frees up the necessary personnel. This way, the time interval between the injury and the transfusion is minimal. Studies [23] [35] show that early transfusion, followed by surgical bleeding control if necessary, can greatly improve the survival odds of patients that are at risk of entering hemorrhagic shock.

This means that it is essential to activate the procedure as early as possible if a patient's condition requires it. Unfortunately, it is quite hard to evaluate whether a patient is at risk of hemorrhagic shock[39]. While external bleeding (e.g. from a knife wound) is obvious, internal bleeding (usually from blunt trauma) on the other hand is not easily diagnosed visually or using physiological parameters (heart rate, blood pressure, ...) [16]. A full-body scan or at least an ultrasound examination may be needed[38]. This results in a significant delay in the activation of the procedure.

1.1.2 Motivation for an assistance tool

As we mentioned, it is both far from obvious and very important to diagnose a risk of HS early, and doctors often fail to do so without advanced tests: a study [39] showed doctors to have quite limited performance when trying to predict a patient's risk of HS even after 10 minutes in the hospital. This highlights the difficulty of evaluating the need for the MT procedure before arrival, even when a doctor is present in the ambulance.

This combination of factors means that it makes sense to try to provide tools that would assist a doctor in detecting possible HS. To that end, a number of scoring systems have been developed to evaluate the risk of HS for a patient [37] [17] [33]: the idea is to determine a set of conditions on physiological measurements that determine a numeric score for the patient. The idea is that with well-chosen criteria, the score gives an objective assessment of a patient's condition that can supplement a doctor's expertise, or be used directly as a prediction (e.g. if the score is higher than some threshold, then the patient is at risk). However, the same study that evaluated the performance of doctors' prediction [39] showed that numeric criteria perform no better than doctors in predicting HS.

This might mean that it is simply impossible to accurately predict HS before advanced examinations are performed. However, it is also possible, that the relations between HS and physiological measurements are complex enough that a simple hand-made criterion is not enough to capture them. In that case, it would be useful to build a statistical model capable of representing this relationship and of providing hospitals with early estimates of a patient's level of risk.

This is why a team of researchers is trying to develop a tool that would leverage machine learning techniques to predict hemorrhagic shock, using a database of patient records (cf Section 1.2). Our paper is part of that effort, with a specific focus on missing data imputation.

1.2 The Traumabase data

1.2.1 The Traumabase project

1.2.2 Data overview

General information

The Traumabase contained the records of 7477 patients at the time of this work. On recommendation of the doctors we worked with, we removed patients who sustained penetrating injuries such as knife or gunshot wounds — 826 patients — (because the presence of a hemorrhage is obvious to assess in this case) and those who had a cardiac arrest before their arrival in the hospital — 396 patients — because this level of gravity is always enough to justify an emergency procedure. We also excluded patients who were redirected to the trauma centre from another hospital (as opposed to directly by the first responders) — 1102 patients — since this does not correspond to our case of study (prehospital evaluation). This leaves us with a total of 5153 patients.

In this population, 500 patients went through hemorrhagic shock and 4653 did not.

The Traumabase records dozens of variables that trace a patient's history from the moment first responders arrive to the end of the patient's stay in the hospital (i.e. death or recovery). Here we are interested in performing a prehospital evaluation, so when we perform the prediction we only consider a few measurements that correspond to those performed by the first responders.

Definition of the variables

There are 9 variables in the data that we can use for prediction.

General physical criteria These values are the sex, age and BMI (body-mass index) of the patient. They do not give any direct indication of shock, but they are necessary to control for natural differences between individuals (for instance, males naturally have a higher level of hemoglobin in their blood than females).

Basic physiological measurements These values are measured by the response team as soon as they arrive at the scene. They are:

1. Heart rate: The heart rate of the patient. Intuitively, if the patient has been losing blood, their heart should be beating faster in order to keep supplying the body with oxygen in spite of the blood loss [18]
2. Pulse pressure: The difference between the systolic (maximal) and diastolic (minimal) blood pressure during a heart beat. When the volume of blood in the body is low, this pressure may decrease [18]
3. Hemoglobin level: This is the concentration of hemoglobin (Hb) in the blood. The blood is composed, among other things, of red blood cells which contain hemoglobin that is used to carry oxygen. During blood loss, the liquid part of the blood can be regenerated faster than the red cells [18] which causes a drop in the Hb concentration. It is easily measured on location using measurement kits [30].
4. Peripheral oxygen saturation: This value ranges from 0% to 100% and represents the fraction of Hb molecules in the blood carrying dioxygen. During bleeding, if the oxygen carrying capacity is reduced (lower Hb concentration, lower blood flow due to hypotension, ...) then organs will draw more oxygen relative to the total carrying capacity and the saturation will decrease [12]. Measurement is easy and standard [40].

Glasgow coma scale (GCS) The GCS is a score assessing the conscious state of the patient [25]. It is computed from three criteria (eye movement, verbal response, motor functions) and ranges from 3 (deep coma or death) to 15 (fully awake). It gives a standardized way of reporting a patient's consciousness.

Volume expander injection To stabilise the patient and compensate major fluid loss, the emergency responder may decide to inject the patient with volume expanders [29], that is fluids specifically designed to fill some of the volume of the vascular system in order to rise blood pressure. This is a proxy for the responder's assessment of the patient's gravity, which is useful since many hard-to-quantify factors (paleness, gravity of the incident, general aspect, ...) may impact this assessment and would otherwise be unavailable to us.

This variable gives us the total volume (in mL) of expander that was injected into the patient.

Exploration

Continuous variables: The following table gives a general summary of the continuous covariates:

•	Min	Max	Mean	Median
Age	12	95	37.9	34
BMI	12	100	24.8	24.2
Heart rate	12	222	95.7	93
Pulse pressure	0	169	46.3	45
Hb level	0	19	13.9	14
O2 saturation	0	100	96.5	98
Expander	0	6250	791	500

Their distribution is illustrated in Figure 1.1. We see that all the variables seem to have a unimodal distribution (some variables such as the expander are artificially rounded by the doctors when reporting, which accounts for the apparent drops in density). Additionally, on all variables but the expander dose, the mean and median are very close together.

The age has a rather heavy tail on the right (many old patients). The O2 saturation has a very long lower tail: while almost all patients are above 90% saturation, it is much lower for a few patients.

The differences between the populations of patients with and without shock are in line with our expectations: shocked patients have in general lower Hb levels, a higher heart rate, lower pressure and lower saturation. However, we also see that no single factor gives an easy separation, and that shocked patients can have normal readings for any given measurement.

Categorical variables We have just two variables which can be seen as categorical: the sex and the GCS score. For the GCS, this is a discrete scale from 3 to 15. Its distribution is shown on figure 1.2. As before, shocked patients tend to have a lower score but many of them have a perfect score (15).

As regards the sex, there are 1177 females and 3976 males in the population.

Correlation structure Figure 1.3 shows the correlation between the values of the observations (including the patient outcome). We see that not all variables have obvious correlation, but there are some subgroups of variables that are all correlated (e.g. Glasgow, heart rate, pulse pressure and saturation; or age, BMI and Hb level).

As expected, the physical measurements (Sex, BMI, age) show no correlation with patient outcome, while all the other variables do.

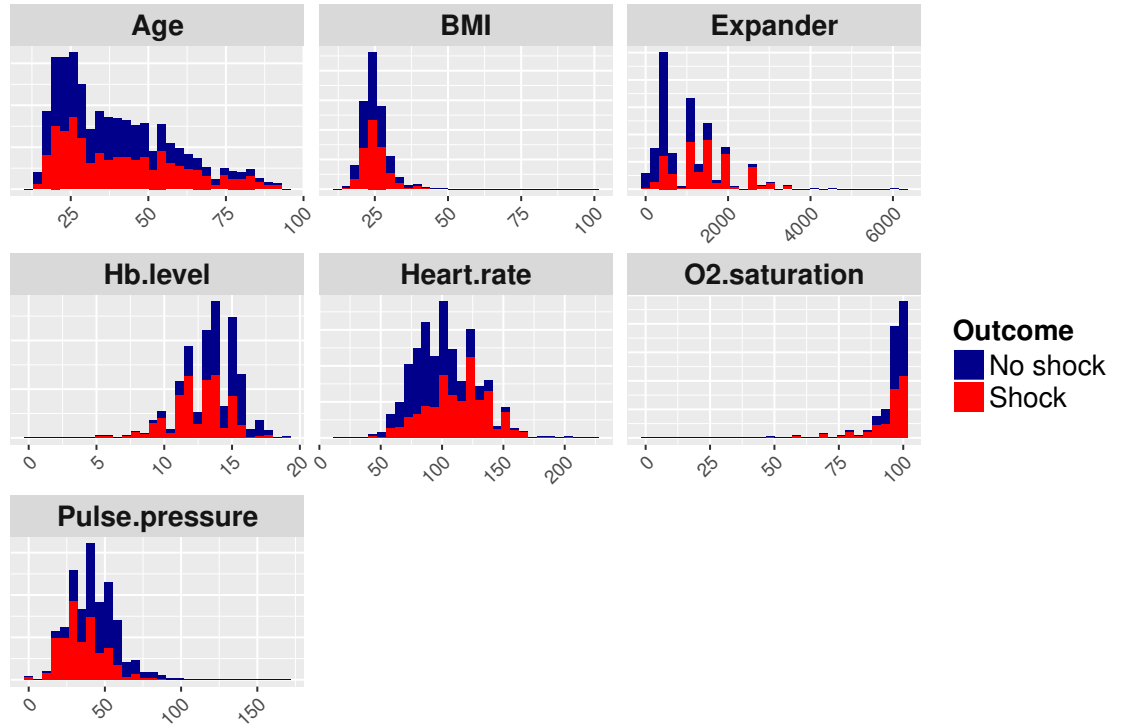


Figure 1.1: Distribution of the continuous variables depending on patient outcome

Sex	1.00	-0.07	0.10	-0.02	-0.04	0.09	0.38	-0.02	-0.03	-0.07
Age	-0.07	1.00	0.23	-0.04	-0.08	0.01	-0.19	-0.10	0.04	0.09
BMI	0.10	0.23	1.00	0.02	0.05	0.02	0.05	-0.05	0.02	0.04
Glasgow	-0.02	-0.04	0.02	1.00	-0.11	0.04	0.10	0.17	-0.22	-0.14
Heart.rate	-0.04	-0.08	0.05	-0.11	1.00	-0.12	-0.03	-0.17	0.22	0.23
Pulse.pressure	0.09	0.01	0.02	0.04	-0.12	1.00	0.11	0.08	-0.20	-0.21
Hb.level	0.38	-0.19	0.05	0.10	-0.03	0.11	1.00	0.04	-0.17	-0.24
O2.saturation	-0.02	-0.10	-0.05	0.17	-0.17	0.08	0.04	1.00	-0.16	-0.12
Expander	-0.03	0.04	0.02	-0.22	0.22	-0.20	-0.17	-0.16	1.00	0.36
Shock	-0.07	0.09	0.04	-0.14	0.23	-0.21	-0.24	-0.12	0.36	1.00

Figure 1.3: Correlation between the measurements (based on complete cases)

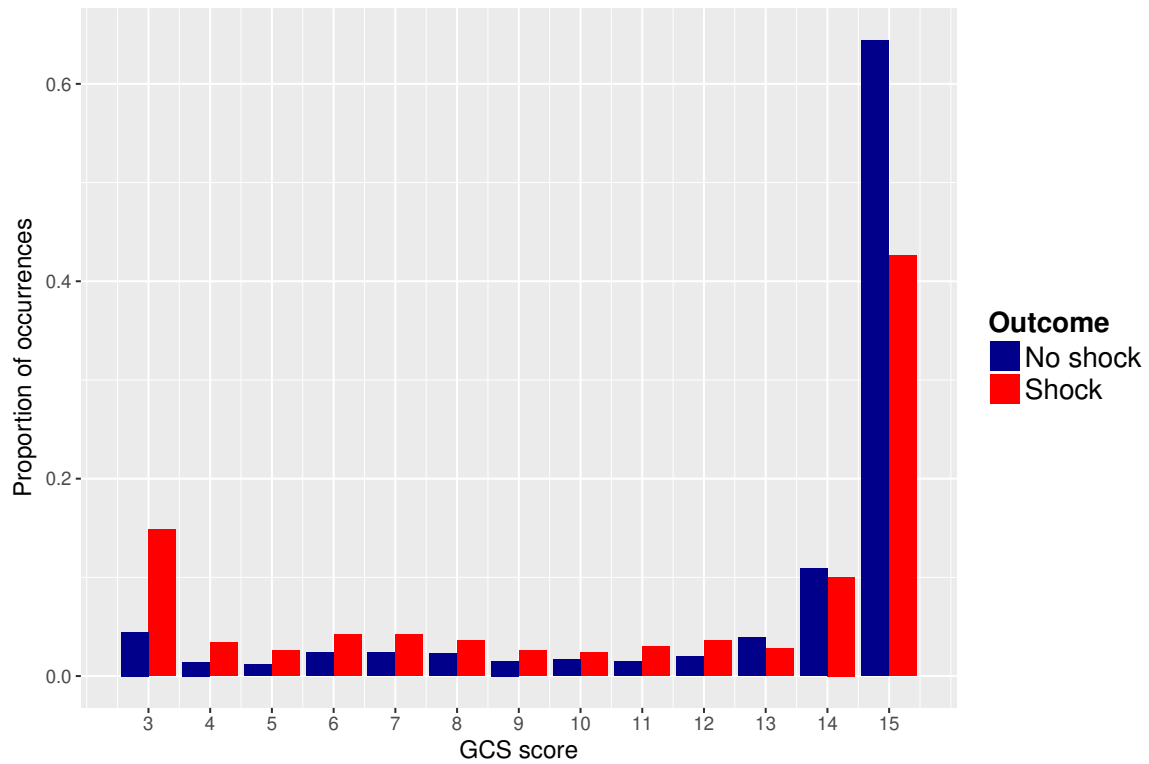


Figure 1.2: Distribution of Glasgow Coma Scale score depending on patient outcome

Missing data

An important aspect of the Traumabase is that it contains a significant amount of missing data. That is, some measurements or informations about the patients were not collected or not reported into the database, which makes them unavailable to us. In total, 5% of the observations are missing. The table below gives the amount and proportion of missing data for each variable:

•	Amount	Proportion
Sex	0	0%
Age	7	0.1%
BMI	778	15%
GCS	18	0.4%
Heart rate	110	2.1%
Pulse pressure	126	2.5%
Hb level	301	5.8%
O2 saturation	171	3.3%
Expander	795	15.4%

Figure 1.4 shows the repartition of the number of missing observations in the data. 1686 patients (33 %) have at least one missing observation.

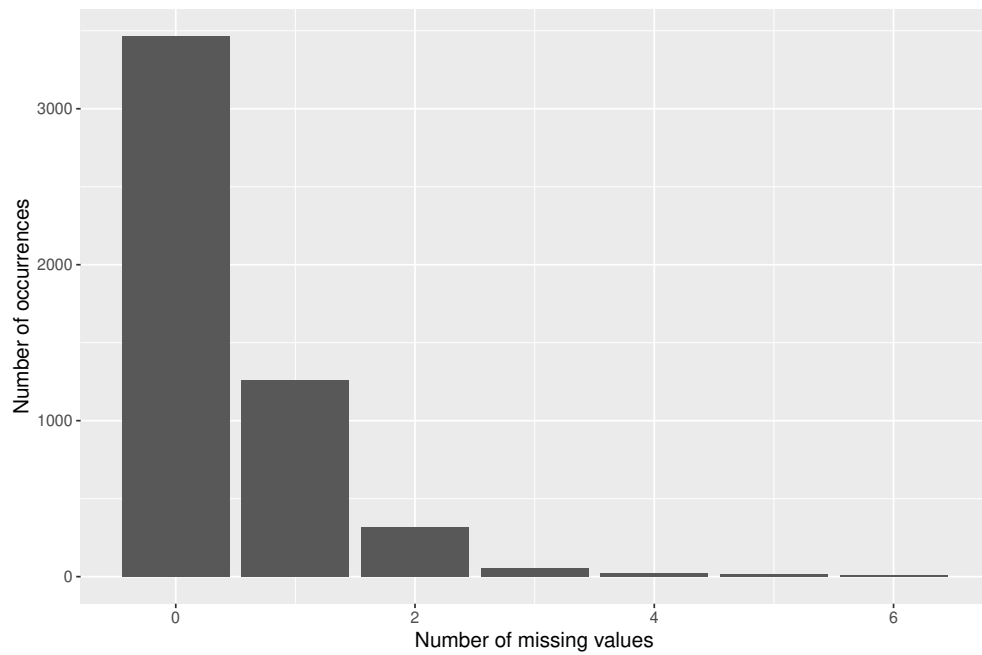


Figure 1.4: Distribution of the number of missing values

Figure 1.5 shows the correlation between the missingness of the variables. They are mostly uncorrelated, but we see that physiological measurements tend to be missing at the same time.

Age	1.00	0.03	-0.00	-0.01	-0.01	-0.01	0.02	0.03
BMI	0.03	1.00	0.00	0.06	0.07	0.04	0.09	0.13
Glasgow	-0.00	0.00	1.00	0.01	0.05	0.06	0.03	0.01
Heart.rate	-0.01	0.06	0.01	1.00	0.64	0.23	0.26	0.14
Pulse.pressure	-0.01	0.07	0.05	0.64	1.00	0.21	0.34	0.12
Hb.level	-0.01	0.04	0.06	0.23	0.21	1.00	0.11	0.06
O2.saturation	0.02	0.09	0.03	0.26	0.34	0.11	1.00	0.08
Expander	0.03	0.13	0.01	0.14	0.12	0.06	0.08	1.00

Figure 1.5: Correlation between the missingness of each variable

Lastly, the table below gives the correlation between the missingness of each variable with the patient outcome:

Age	$5.7 \cdot 10^{-3}$
BMI	$5.7 \cdot 10^{-3}$
GCS	$2.8 \cdot 10^{-3}$
Heart rate	$-7.6 \cdot 10^{-3}$
Pulse pressure	$5 \cdot 10^{-2}$
Hb level	$-4.5 \cdot 10^{-2}$
O2 saturation	0.11
Expander	$-2.6 \cdot 10^{-2}$

There is some amount of correlation between the missingness of the O2 saturation and the shock, but it is still quite low so it is hard to tell whether this has any significance.

1.3 Objective and formalization

1.3.1 Objective of this work

Given the importance of treating HS quickly, and the difficulty of detecting it — especially for first responders not specialized in major trauma and do not have access to a hospital’s equipment —, there is a strong case for trying to predict HS automatically during the prehospital phase. This would enable a hospital to have an assessment of a patient’s level of risk as soon as first responders reach them, and make preparations in advance to treat them urgently if necessary.

If one is to develop a tool that would predict hemorrhagic shock, an issue that will need to be addressed is that of missing data. Indeed, there are missing observations in the records of 33% of the patients. Although this leaves us with a rather large number of complete cases, using only those would still be a major loss of information. Even more importantly, some data may also be missing in the real world when a prediction needs to be made. In that case, there no way around handling the missing observations to output a prediction.

In this work, we will address the particular issue of missing data, and more precisely of imputation: replacing the missing values in the dataset by plausible ones. Indeed, it is possible to create a model that takes missing data into account without trying to fill in the missing values and it has been done successfully in the past [45]. However, existing missing-data implementations are fairly rare, so trying out any model means working almost from the ground up. This greatly limits our ability to compare several models.

Comparatively, once the dataset is imputed, it can be used with any existing complete-data prediction method. Additionally, it allows a separation of the tasks: the person or team performing the imputation is not necessarily the same as the one performing the subsequent analysis. Of course, this approach has drawbacks as well. In particular, once the dataset is imputed, any method used to perform a prediction with this dataset will use the observed and imputed values indiscriminately, which may lead to errors if the imputation is not correct.

In the following chapters, we investigate the possibility of performing imputation in a predictive context, and how it should be done. Below we present the formal setting of the problem we investigate.

1.3.2 The God/Imputer/Analyst/Practitioner framework

Let us recall the tasks at hand: imputing the data in the Traumabase, then applying a complete-data procedure to learn a model for the outcome. Finally, for new incoming patients, use the new measurements (possibly with missing data) to evaluate whether they are at risk of HS.

It is clear that from the point of view of the end user (the hospital or medical practitioner), the performance of this procedure should be judged by its predictive performance on new patients. This separation between historical data and new patients is central to our problem, and we investigate it further in chapters 3 and 4.

To formalize this setting, we draw inspiration from the framework proposed by Xie and Meng [53] to explore the issue of imputation. In their work, three actors come into play, God, the Imputer and the Analyst. We adapt this framework by adding a fourth actor, the Practitioner, who represents the end user who is only interested in prediction. Their interaction goes as follows:

- "God" (i.e. nature) generates some data \tilde{X} and outcome y based on a process known only to him.
- A dataset X is generated by adding missing values to \tilde{X} . X and y are transferred to an Imputer. The Imputer is tasked with filling in the missing observations. She chooses an imputation model with parameter α and computes an estimate $\hat{\alpha}$ which she uses to generate a completed dataset X_{imp} .
- The Imputer transfers X_{imp} to an Analyst, along with y . The Analyst does not know which observations were initially missing.
- The Analyst uses X_{imp} and y to learn a predictive model with parameter β . Her estimation for this parameter is $\hat{\beta}$.
- God generates a new pair of data and outcome \tilde{X}_{new}, y_{new} . Some missing data are added to \tilde{X}_{new} to generate X_{new} .
- The Practitioner receives X_{new} . She has no access to the data used for training. The Analyst and Imputer provide the Practitioner with black-box functions that allow her to perform imputation and prediction on the new data. They are derived from their model and parameter estimate; we call them $f(\cdot, \hat{\alpha}), g(\cdot, \hat{\beta})$.

- The Practitioner uses those functions to compute $X_{new}^{imp} = g(X_{new}, \hat{\alpha})$ and $\hat{y}_{new} = f(X_{new}^{imp}, \hat{\beta})$.
- \hat{y}_{new} is finally compared to y_{new} and the loss $L(y_V, \hat{y}_V)$ is computed. This gives the final performance evaluation of the process.

This process is illustrated in Figure 1.6

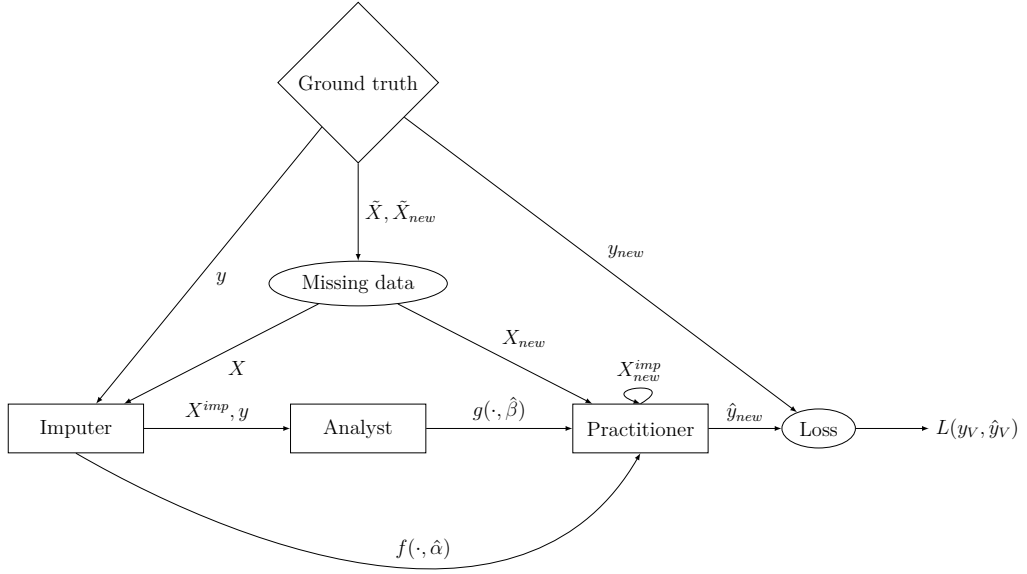


Figure 1.6: Imputation framework

The purpose of this formalization is to clarify the separation between the different phases of the inference, and show how the information is divided. Note that the separation between the Imputer and the Analyst is artificial — we choose it because we are interested in performing imputation separately — while the distinction between the Practitioner and the Analyst is imposed by the problem we are trying to solve: during an intervention, the users need a black-box tool that takes in the available data and outputs a prediction more or less instantly. Even if they had access to the training data, it would be impractical to learn a model all over again every time a new patient comes up. Additionally, the data we are using to learn the model cannot be widely shared since it contains patient records, so the Practitioner will not have access to it.

In a setting where all three roles are regrouped, the sensible way to proceed would be to define a joint model on the full data (including the

response) and use it to find the maximum likelihood estimator for the unknown outcomes. However, the segmentation of the roles makes it necessary for each agent to work with partial information. In the rest of this work, we investigate the implications of this division, both in terms of theory and of practical implementation.

In Chapter 2, we present an overview of methods used for imputation. Chapter 3 considers the practical difficulties encountered when trying to impute new data with a previously learned model. Chapter 4 explores the asymmetry that exists between missing values present in the training set and in the new data. Then, Chapter 6 goes back to the Traumabase data to explore the best way to perform imputation in this particular case and Chapter 6.2 presents our final results and compares the performance to that of doctors and criteria-based scores.

Chapter 2

Imputation

2.1 Missing data mechanisms

Data may be missing for various reasons, and this leads to various patterns of missing data: in particular, the relationship between the missingness of observations and the true values.

Given some data X , we denote by M the missingness indicator matrix: its coefficients are 1 if the corresponding value is missing in X and 0 otherwise. We call $f(M|X, \phi)$ the distribution of M given the data and some unknown parameters. The missingness patterns can be classified into three categories [32, Ch. 1]:

- *Missing completely at random (MCAR)*: The missingness of any given value is independent of the values of the data

$$f(M|X, \phi) = f(M|\phi)$$

- *Missing at random (MAR)*: The missingness depends only on the values of X that are observed and not on the missing ones

$$f(M|X, \phi) = f(M|X_{\text{obs}}, \phi)$$

An example would be a survey on revenue where we know the age of respondent, and younger people fail to declare their revenue more often.

- *Missing not at random (MNAR)*: The missingness depends on the values that are missing. In the same survey example, this would occur if richer people fail to declare their revenue more often.

In particular, Rubin showed [41] that if the data is MAR or MCAR, then any likelihood ratio (LR) computed on the observed data is equal to the correct LR, so the missingness mechanism can be ignored for inference on this type of data.

2.2 Main types of imputation

2.2.1 Joint maximum likelihood

2.2.2 Fully conditional specification (FCS)

In FCS rather than a joint model we define p conditional models π_1, \dots, π_p where π_i gives the distribution of variable i conditional on the others. We can then obtain an imputed dataset iteratively using the Multiple Imputation by Chained Equations (MICE) algorithm [43]

Algorithm 2.1 MICE Algorithm

Input: X, π_1, \dots, π_p

Output: \hat{X}

- 1: $\hat{X} \leftarrow$ plausible imputation of the missing data (e.g. mean imputation)
 - 2: **while** not converged **do**
 - 3: **for** $i = 1 \dots p$ **do**
 - 4: $X^{(i)} \leftarrow$ the i^{th} column of X
 - 5: $\hat{X}^{(-i)} \leftarrow \hat{X}$ without its i^{th} column
 - 6: $\hat{X}_{\text{miss}}^{(i)} \sim P(\hat{X}_{\text{miss}}^{(i)} | X_{\text{obs}}^{(i)}, \hat{X}^{(-i)})$
 - 7: **end for**
 - 8: **end while**
-

The interest of this approach is that it can be very flexible when the variables have very different distribution profiles.

2.2.3 Low-rank approaches

An alternative to assuming some distribution for the dataset is to find a low-rank representation of the data and use it to impute unobserved values. Such approaches [26][11][8] are generally based on Principal Component Analysis (PCA)[52], using the iterative PCA algorithm [28]:

Algorithm 2.2 Iterative PCA Algorithm

Input: X, k **Output:** \hat{X}

- 1: $\hat{X} \leftarrow$ plausible imputation of the missing data (e.g. mean imputation)
 - 2: **while** not converged **do**
 - 3: $V \leftarrow k$ first principal components of \hat{X} (complete dataset)
 - 4: $\tilde{X} \leftarrow \hat{X}$ projected on the span of V (i.e. PCA fitted values)
 - 5: $\hat{X} \leftarrow \hat{X} * (1 - M) + (\tilde{X} * M$ where M the missingness indicator
 - 6: **end while**
-

That is, the missing values are repeatedly imputed by projection on the principal components. Many methods using different univariate models exist [43][47][50].

2.2.4 Nearest-neighbors

Other methods exist to impute missing values. *Nearest-neighbor imputation*[10] consists in replacing missing values for one individual by the values observed in similar individuals. Using the observed value, a distance metric is computed with the other observations in the data, and we pick the closest one which has observations in the variable we need to impute. This value is then used for imputation.

The related *hot-deck imputation* [7] use multiple similar individuals to generate imputed values. Rather than pick a single closest value, we can pick a pool of similar individuals and draw at random between their observed values, or impute via a combination of those values.

2.3 Multiple imputation

2.3.1 Principle

One major drawback of imputation is that it hides the difference between values that were really observed and those that were initially missing. If one uses full-data analysis on an imputed dataset, the results may be overconfident, and in particular underestimate variances because the uncertainty from missing data is not taken into account.

In order to retain the advantages of imputation (using any complete-data method) while compensating for this overconfidence, Rubin [42] introduced *multiple imputation*. The idea is that rather than just one dataset, one should generate m plausible imputed values for each missing observation,

in order to account for the uncertainty of the imputation. By performing her inference on each imputed dataset, the Analyst then obtains a set of estimates rather than just one.

When the imputation is based on a distribution, one can use draws from the distribution rather than the expected mean as one would do for single imputation. In other cases, method-specific approaches have to be designed.

Once the datasets are generated, and estimates have been computed, it is possible to combine them to obtain a new estimation for the variances of our estimates[32, Ch. 5].

2.3.2 Rubin's rule for result aggregation

Let us denote $(\hat{\theta}_1, \dots, \hat{\theta}_m)$ the m estimates for a given parameter θ , and W_1, \dots, W_m the variance for θ estimated by the complete-data method (within-imputation variance). The aggregated estimate for θ is

$$\hat{\theta} = \frac{1}{m} \sum_{i=1}^m \hat{\theta}_i$$

And the aggregated within-imputation variance

$$\hat{W} = \frac{1}{m} \sum_{i=1}^m W_i$$

The between-imputation variance can be computed as the sample variance of the estimates:

$$\hat{B} = \frac{1}{m-1} \sum_{i=1}^m (\hat{\theta}_i - \hat{\theta})^2$$

Then the total variability associated to θ is then [32, Ch. 5]:

$$\hat{T} = \hat{W} + \frac{m+1}{m} \hat{B}$$

Moreover, if θ is a scalar, asymptotically we can approximate [42]

$$(\theta - \hat{\theta})\hat{T}^{-\frac{1}{2}} \sim t_\nu$$

where t_ν is a t-distribution with $\nu = (m-1)(1 + \frac{1}{m+1} \frac{\hat{W}}{\hat{B}})^2$.

Using this approximation, it is possible to compute confidence intervals for θ that take into account the uncertainty related to missing data.

Chapter 3

Methodology: imputation and the validation split

Let us now go back to the issue of imputing missing data when there is a separation between the Practitioner and the Analyst, that is, when it is necessary to impute new incoming data without having access to the historical data.

As described Chapter 2, a number of methods exist to impute missing data. However, they have been designed with parameter estimation in mind: in that case, there is just one dataset that needs to be imputed. The issue, as we show in this chapter, is that current implementations of these methods may not be suitable when we need to use the same model to impute two separate datasets.

This is not only problematic for our particular problem. As we remind in Section 3.1, it is standard practice when working on prediction to resort to CV, that is to hold out part of the data and use it to validate the model. Section 3.2 shows how this clashes with current implementation of imputation methods. In section 3.3, we investigate possible ways to address this issue and compare them empirically.

3.1 Empirical risk minimization and cross-validation

Let us start by ignoring the issue of missing data and assume that the data is complete. That is, we place ourselves in the same situation as described in 1.3.2 but there is no need for an Imputer, and the Analyst directly receives the data X .

As stated in Chapter 1, our end goal is to make good predictions in the real world by learning on historical data. Of course, by definition we do not have access to any future data right now, but we still need to choose a prediction and imputation model, and estimate how it will perform when we use it on the field.

To learn and evaluate the model, we go through two steps: Empirical risk minimization (ERM) and cross-validation (CV). We describe them below

3.1.1 Empirical risk minimization

Let us denote the X a $n \times p$ matrix of covariates and y a response vector of size n , where our goal is to predict the response y_{new} from some future data X_{new} , assuming that (X_{new}, y_{new}) follow the same distribution as X, y .

We choose a class of functions $f(\cdot, \beta), \beta \in B$. We want to choose a parameter $\hat{\beta}$ which we can use to predict $\hat{y}_{new} = f(X_{new}, \hat{\beta})$. The quality of a prediction is evaluated by some loss $L(y_{new}, \hat{y}_{new})$. Since we do not have access to X_{new} , our goal is to minimize the risk: $R(\beta) = \mathbb{E}_{X_{new}, y_{new}}(L(y_{new}, f(X_{new}, \beta)))$.

However, we do not know the true distribution of those values. This is why we resort to ERM [51]: we define the empirical risk

$$R_{\text{emp}}(\beta) = \frac{1}{n} \sum_{i=1}^n L(y_i, f(X_i, \beta))$$

that is, the average value of the loss when predicting the known y from X with β .

We then select $\hat{\beta} = \arg \min_{\beta} R_{\text{emp}}(\beta)$ as our ERM estimator for β . However, this is not enough. Once we have chosen $\hat{\beta}$, we need to have an estimate of how well this estimate will perform on new data.

This is important because this is what we will take into account if we need to compare multiple choices for f . But the empirical risk gives us no measure of how well our model generalizes, only of how closely it can fit known data. In particular, if the class f is very broad, one may find a β that exactly interpolates the values of y but does not generalize at all (an issue known as overfitting [19])

To address the issue of model selection, we need to resort to CV as described below.

3.1.2 Cross-validation

CV, consists in dividing the available data in two datasets: first we choose $n_A < n$ entries in the dataset that will be used in ERM to learn $\hat{\beta}$: this is

the training dataset X_A and response y_A . We denote $I_A = (i_1, \dots, i_{n_A})$ the set of indices chosen for the training data.

The rest of the observations are noted X_V and y_V and called the validation dataset. They are used as a substitute for X_{new}, y_{new} .

Once this is done, the Analyst performs ERM as before, using only the training data. The obtained parameter $\hat{\beta}$ can then be evaluated with the validation error:

$$R_V(\hat{\beta}) = \frac{1}{n_V} \sum_{i=1, i \notin I_A}^n L(y_i, f(X_i, \hat{\beta}))$$

It is this value that we can compare to choose the model class f . Once the Analyst has decided on a choice of f and $\hat{\beta}$ using ERM and CV, she can send $f(\cdot, \hat{\beta})$ over to the Practitioner so that she can proceed to prediction on new data using $y_{new} = f(X_{new}, \hat{\beta})$.

3.2 ERM with missing data: the problem of current methodologies

We now place ourselves in the same context as before, except some values are missing from X , both in the training and the validation data. This means that we are back to a case where there is an Imputer in addition to the Analyst.

3.2.1 Imputation seen as an ERM

Remember that the purpose of this work is to impute the data independently of the model used afterwards for prediction. This means that we cannot perform ERM exactly as before and use any function we like to go from X (which has missing data) to \hat{y} . The prediction is the composition of two steps.

Imputation step First we choose an imputation model $X^{\text{complete}} = g(X, \alpha)$ where X^{complete} is the completed dataset and α some parameter. This is similar to the previously described ERM, except we do not know the true data (while we had y to compare to \hat{y} , we do not know the true full dataset \tilde{X}). Thus, we choose $\hat{\alpha}$ to minimize some unsupervised empirical risk

$$R'_{emp}(\alpha) = L'(g(X, \alpha), \alpha)$$

Sometimes the loss L' is related to the likelihood of the completed data according to some distribution[21] (though it is not always the case [47]). Once this is done, we obtain a completed dataset \hat{X} .

Prediction step With imputation done, we can proceed as before to choose a parameter $\hat{\beta}$ that minimizes the empirical risk when using the completed data:

$$R_{\text{emp}}(\beta, \hat{X}) = \frac{1}{n} \sum_{i=1}^n L(y_i, f(\hat{X}_i, \beta))$$

Putting it all together, we can define

$$h(X, (\alpha, \beta)) = f(X^{\text{imp}}, \beta) = f(g(X, \alpha), \beta)$$

the combined model that takes the observed data as input and outputs a predicted y . Formally, the two successive steps yield:

$$\begin{aligned}\hat{\alpha} &= \arg \min_{\alpha} L'(g(X, \alpha)) \\ \hat{\beta} &= \arg \min_{\beta} R_{\text{emp}}(\beta, f(X, \hat{\alpha})) \\ \hat{y} &= h(X, (\hat{\alpha}, \hat{\beta}))\end{aligned}$$

We choose to use this notation to illustrate our point that imputation is an integral part of the ERM, not a separate, preliminary process. In particular, it means that its parameters must be subjected to CV just like those of the prediction. That is, only X_A and y_A are used to estimate $(\hat{\alpha}, \hat{\beta})$ as shown above, while X_V and y_V are held out. Then, we can compute a prediction $\hat{y}_V = h(X_V, (\hat{\beta}, \hat{\alpha}))$ and we compute $L(y_V, \hat{y}_V)$ to evaluate the choice of model.

This implies that just like β , the imputation parameter α should be estimated only on the training data and then used on the validation data. As we will see, this raises an issue with the way current imputation methods are implemented.

3.2.2 Unsuitability of current methods

Implementations of imputation methods have one thing in common: they are used through a single function which takes a dataset with missing values as an input and returns the dataset completed by the method of choice, *without giving the user any access to the imputation model itself*. [47] [27][43][21]

This is a problem because of how CV is supposed to be performed. Supposedly, one would estimate $(\hat{\alpha}_A, \hat{\beta}_A)$ through ERM, and then make a prediction on the validation set as $h(X_V, (\hat{\beta}_{X_A}, \hat{\alpha}_{X_A}))$. But here, all we have access to is a black-box function $g' : X \mapsto g(X, \hat{\alpha}_X)$ where $\hat{\alpha}_X$ is the optimised parameter for the argument X . This means that one cannot choose what parameters are used to impute the input to function g' : a new parameter will be estimated at every call of the function. But in that case, it is impossible to use the same α for the training dataset and for the validation data — or for new data.

This issue has started to arise in the machine learning community in the past few years [2][4][3], but for now no implementation exists that separates the parameter estimation and the imputation itself (except for the very basic imputation by the mean [5]). Below, we investigate the alternatives available to perform imputation with held out data.

3.3 Possible solutions

If we were to follow exactly the principles of CV, we would proceed as follows:

Algorithm 3.1 Identical imputation

Input: $X, y, I_A = i, X_i \in X_A$

Output: \hat{y}_V

1: **Parameter estimation:**

2: $\hat{\alpha}_A \leftarrow \arg \min_{\alpha} L'(g(X_A, \alpha))$

3: $\hat{X}_A \leftarrow g(X_A, \hat{\alpha}_A)$

4: $\hat{\beta}_A \leftarrow \arg \min_{\beta} R_{\text{emp}}(\beta, \hat{X}_A)$

5: **Prediction:**

6: $\hat{X}_V \leftarrow g(X_V, \hat{\alpha}_A)$ \triangleright Uses the same α as for the training set

7: $\hat{y}_V \leftarrow f(\hat{X}_V, \hat{\beta}_A)$

But this is not possible using a black-box function because we need to recover $\hat{\alpha}_A$ and reuse it with X_V .

3.3.1 Alternatives using current implementations

Motivation

As mentioned above, many implementation of imputation methods only provide a black-box function. If we are to use one of these methods to

build a tool for hemorrhagic shock, we need to be able to impute on a new incoming patient, without any access to the training data or to other new patients' data, so we have no choice but to use past estimated parameters as in identical imputation. This necessitates a new implementation of the same method.

However, before building a final model for real-world use, there is a phase of model selection that is done using CV, where we actually have access to all of the data. Reimplementing a method is a time-consuming process, so we would prefer to be able to choose the best imputation method and reimplement just this one, rather than having to remake every method we are interested in just to compare them.

This is why we explore options that can be used to impute the training and validation CV datasets, using only a black-box function. In particular, we try to see if those methods give a good idea of a method's true performance, and so would allow us to perform model selection with existing implementations.

Methods

Grouped imputation Impute all the data at once before performing the CV split:

Algorithm 3.2 Grouped imputation

Input: $X, y, I_A = i, X_i \in X_A$

Output: \hat{y}_V

1: **Imputation:**

2: $\hat{X} \leftarrow g'(X) = g(X, \hat{\alpha}_X)$

3: $(\hat{X}_A, \hat{X}_V) \leftarrow \hat{X}$ \triangleright Split the data after imputation

4: **Estimation of the prediction parameter**

5: $\hat{\beta}_A \leftarrow \arg \min_{\beta} R_{\text{emp}}(\beta, \hat{X}_A)$ \triangleright Note that $\hat{X}_A = g(X_A, \hat{\alpha}_X)$

6: **Prediction:**

7: $\hat{y}_V \leftarrow f(\hat{X}_V, \hat{\beta}_A) = f(g(X_V, \hat{\alpha}_X))$

Here, both datasets are indeed imputed with the same parameter α_X but this means that the validation data is used to choose that parameter which then serves to impute the training data. This is contrary to the principles of CV, we are 'cheating' in some way.

Separate imputation Divide the data first, then impute each dataset separately:

Algorithm 3.3 Separate imputation**Input:** $X, y, I_A = i, X_i \in X_A$ **Output:** \hat{y}_V 1: **Training parameter estimation:**2: $\hat{X}_A \leftarrow g'(X_A) = g(X_A, \hat{\alpha}_A)$ 3: $\hat{\beta}_A \leftarrow \arg \min_{\beta} R_{\text{emp}}(\beta, \hat{X}_A)$ 4: **Imputation of X_V :**5: $\hat{X}_V \leftarrow g'(X_V) = g(X_V, \hat{\alpha}_V) \quad \triangleright \text{Imputation made independently of that of } X_A$ 6: **Prediction:**7: $\hat{y}_V \leftarrow f(\hat{X}_V, \hat{\beta}_A)$

Contrarily to grouped imputation, we are not cheating. However, we are using parameter $\hat{\alpha}_V$ to impute X_V , while we learned $\hat{\beta}_A$ on \hat{X}_A which was imputed with $\hat{\alpha}_A$. That is, we are optimising $h(\cdot, (\hat{\alpha}_A, \hat{\beta}_A)$ and predicting with $h(\cdot, (\hat{\alpha}_V, \hat{\beta}_A)$.

$\hat{\alpha}_V$, $\hat{\alpha}_A$ and $\hat{\alpha}_X$ are asymptotically the same for large n — since X_A , X_V and X have the same distribution —, so all three methods should be identical for large n . But for smaller n , harmful effects may be present — overoptimistic validation due to 'cheating' for the grouped imputation, high error due to the difference in parameters for separate imputation.

Need for a new implementation

We want to understand if the alternatives proposed here are good enough to be used if Identical imputation is infeasible. To do that, we need to be able to compare these with the correct method. That means that for at least one imputation method we need to build an implementation that allows us to separate the estimation and the imputation. That way we will be able to compare its performance with the other alternatives we propose.

Moreover, in addition to this theoretical pursuit, we need this because of what we are trying to achieve with Traumabase: the end goal is to make a recommendation system that can produce a prediction for *a single new patient* arriving to the hospital, without needing to have access to the whole Traumabase data. Without access to the initial training data, this means that only a fully parametric approach can be taken in this particular case (separate imputation is impossible on just one line of data, and grouped imputation requires access to the full data).

Below, we design a very simple imputation method for those purposes.

3.3.2 Multivariate normal conditional expectation

The principle of this imputation is inspired from R package *Amelia* [21], and a large part of the code is from the *norm* package [49]. The idea is to model both X_A and X_V as normally distributed $\mathcal{N}(\mu, \Sigma)$ with unknown parameters. This will allow us to impute the missing data conditionally on the observed data.

Parameter estimation It is possible to approximate maximum-likelihood estimators for μ and σ with an iterative procedure, using the EM (expectation-maximisation) algorithm [14] [44]. The algorithm is as follows:

Algorithm 3.4 Normal parameter estimation with EM

Input: X

Output: $\hat{\mu}, \hat{\Sigma}$

- 1: $X^{(0)} \leftarrow X$ where missing values are replaced using the observed mean of X (mean imputation)
 - 2: $t \leftarrow 0$
 - 3: **while** not converged **do**
 - 4: $(\mu^{(t)}, \Sigma^{(t)}) \leftarrow$ sample mean and covariance matrix of $X^{(t)}$ *▷ i.e. maximum likelihood estimates on the completed data*
 - 5: $X^{(t+1)} \leftarrow \mathbb{E}_{X^{\text{miss}}}(X|X^{\text{obs}}; \mu^{(t)}, \Sigma^{(t)})$ *▷ Missing values are replaced by their expected value under the new parameters*
 - 6: $t \leftarrow t + 1$
 - 7: **end while**
 - 8: $\hat{\mu}, \hat{\Sigma} = \mu^{(t)}, \Sigma^{(t)}$
-

The conditional expectations are easily derived using the Schur complement [55]. For this step, we use a slightly modified version of the code from the *norm* package. In all that comes next, unless specified otherwise this imputation method is the one we use, with identical imputation.

Imputation Once we have the parameters, it is very straightforward to get an imputation of the missing data. Just as during the EM procedure, we impute using the conditional expectation of the dataset conditioned on the observed values:

$$\hat{X} = \mathbb{E}_{X^{\text{miss}}}(X|X^{\text{obs}}; \hat{\mu}, \hat{\Sigma})$$

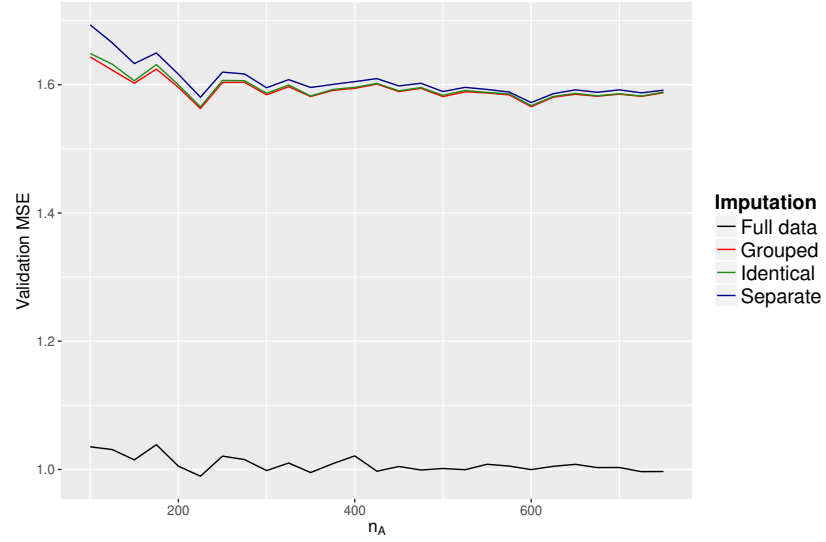
We implemented this step as well to get a complete imputation procedure divided in two functions that implement the estimation and imputation steps separately. The code is available in package

make package
and insert refer-
ence

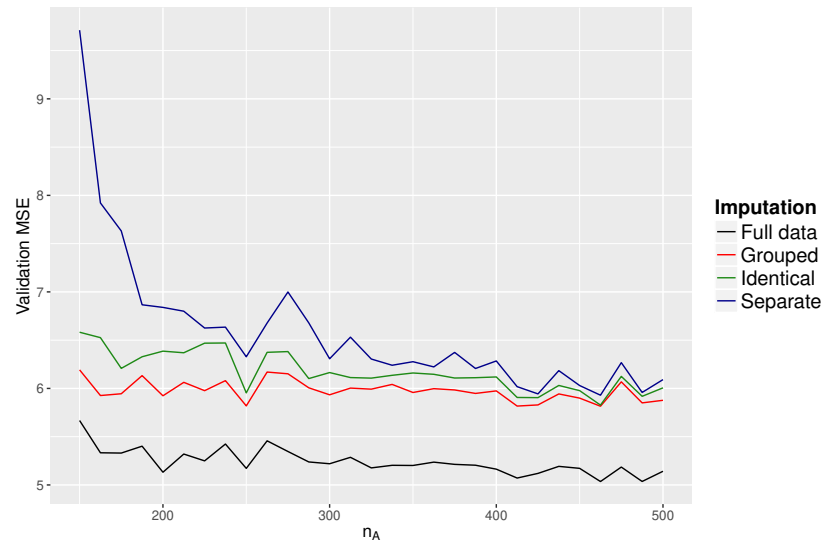
3.3.3 Comparison on simulated data

Now that we have an implementation that separates estimation and imputation, we use it to compare the three imputation procedures on simulated data (cf Appendix A, with $\rho = 0.5, p = 4, \sigma = 1$) and the abalone data (cf Appendix B) with various sample sizes and adding 30% missing data MCAR. The results are in Figure 3.1.

We see that indeed grouped imputation seems to always have lower error than identical imputation, while separate imputation has higher error. However, when n is not too small, all three are quite close together. Separate imputation seems to be further off than the other two, and sometimes has very high error. As a result, if no implementation exists for a given method to perform identical imputation, trying it out with grouped imputation would be a good first step to get an idea of how it can perform.



(a) Results for simulated data



(b) Results for abalone data

Figure 3.1: Comparison of imputation methodologies (averaged over 100 runs)

Chapter 4

Impact of missing data: the case of linear regression

In order to make good decisions for imputation, it is important to understand how it impacts prediction. To gain a better understanding of this issue, we solve a very simple case of cross-validated regression with missing data. Although quite restrictive, this situation provides some insights into the way that missing data impacts prediction performance. In particular, we want to understand what makes this situation different from one of pure parameter estimation (i.e., without a Practitioner), and the implications of missing data in a prediction context.

We show that these objectives are compatible, in the sense that if the imputer performs a good imputation while the analyst uses a good full-data procedure in some sense, then the predictive loss is asymptotically good. In addition, this exaples makes it clear that missing values in the training and validation dataset have a very different impact on the loss.

4.1 Problem set-up

We place ourselves in a linear regression setup with cross-validation (cf Chapter 3). The data is split between a training dataset X_A, y_A and validation dataset X_V, y_V . We use the multi-agent framework described in 1.3.2.

4.1.1 Notations

God's data

The response variable is a noisy linear combination of the covariates in X :

$$\tilde{X}_A = \begin{pmatrix} x_{11} & x_{12} \\ \vdots & \vdots \\ x_{n1} & x_{n2} \end{pmatrix} \quad \text{and} \quad y_A = X_A \beta + \epsilon_A \quad \text{with} \quad \epsilon_A \sim \mathcal{N}(0, \sigma^2)$$

$$\tilde{X}_V = \begin{pmatrix} x_{11}^V & x_{12}^V \\ \vdots & \vdots \\ x_{n_V 1}^V & x_{n_V 2}^V \end{pmatrix} \quad \text{and} \quad y_V = X_V \beta + \epsilon_V \quad \text{with} \quad \epsilon_V \sim \mathcal{N}(0, \sigma^2)$$

Observed data

The observed data is God's data with some missing values. Specifically, some observations are missing from the first column of each dataset. We observe the full y^A , but the covariate matrices we actually have access to are:

$$X_A = \begin{pmatrix} ? & x_{12} \\ \vdots & \vdots \\ ? & x_{k_A 2} \\ x_{(k_A+1)1} & x_{(k_A+1)2} \\ \vdots & \vdots \\ x_{n1} & x_{n2} \end{pmatrix}$$

which is sent to the Imputer, and

$$X_V = \begin{pmatrix} ? & x_{12}^V \\ \vdots & \vdots \\ ? & x_{k_V 2}^V \\ x_{(k_V+1)1}^V & x_{(k_V+1)2}^V \\ \vdots & \vdots \\ x_{n_V 1}^V & x_{n_V 2}^V \end{pmatrix}$$

which is sent to the Practitioner. That is, there are k_A and k_v missing values in the datasets (the mechanism is MCAR).

Note that the datasets have a different status. The training dataset is available to the Imputer then the Analyst at the time of analysis, it is some given historical data. The validation dataset is some future data available only to the Practitioner who will perform a black-box prediction based on

the Analyst's and the Imputer's indications. That is why when we take expectations in this chapter, we will condition only on the observed data X_A while we integrate on $X_V, \epsilon_A, \epsilon_V$ and the missing data $X_A^{\text{miss}}, X_V^{\text{miss}}$ which are all unknowns at the time of analysis.

4.1.2 Imputed data and regression

Principle

The Imputer fits an imputation model $g(\cdot, \alpha)$ and fills in X_A and instructs the Practitioner on how to impute X_V . The resulting filled-in datasets are:

$$\hat{X}_A = \begin{pmatrix} g(x_{12}, \hat{\alpha}) & x_{12} \\ \vdots & \vdots \\ g(x_{k_A 2}, \hat{\alpha}) & x_{k_A 2} \\ x_{(k_A+1)1} & x_{(k_A+1)2} \\ \vdots & \vdots \\ x_{n1} & x_{n2} \end{pmatrix} \quad \text{and} \quad \hat{X}_V = \begin{pmatrix} g(x_{12}^V, \hat{\alpha}) & x_{12}^V \\ \vdots & \vdots \\ g(x_{k_V 2}^V, \hat{\alpha}) & x_{k_V 2}^V \\ x_{(k_V+1)1}^V & x_{(k_V+1)2}^V \\ \vdots & \vdots \\ x_{n_V 1}^V & x_{n_V 2}^V \end{pmatrix}$$

Then, \hat{X}_A is sent by the Imputer to the Analyst. The Analyst only has access to \hat{X}_A and y_A . The end goal is to learn an estimator on the training set that minimizes the expected loss on the validation set:

$$L(y_V, \hat{y}_V) = (y_V - \hat{y}_V)^2$$

In line with the principles of ERM and CV (cf Chapter 3), the Analyst minimizes the equivalent quantity in the training set. Assuming a linear relationship between the covariates and response, the least-squares estimate for β is standard [46]

$$\hat{\beta}_n = (\hat{X}_A^T \hat{X}_A)^{-1} \hat{X}_A^T y_A$$

$\hat{\beta}$ is then transferred to the Practitioner who can use it to compute a prediction

$$\hat{y}_V = \hat{X}_V \hat{\beta}_n$$

which will be compared to y_V :

$$L(\hat{y}_V, y_V) = \sum_{i=1}^{n_V} (y_V^{(i)} - \hat{y}_V^{(i)})^2$$

Our end goal is to minimise this metric.

In what we described above, the actions of the Analyst and the Practitioner are completely determined. On the other hand, we have not specified

how the Imputer proceeds to the imputation. We want to investigate the effect of the choice of imputation on the expected loss:

$$R = \mathbb{E}_{\tilde{X}_V, X_A^{miss}, \epsilon_A, \epsilon_V} [(y_V^{(i)} - \hat{y}_V^{(i)})^2 | X_A]$$

Distribution hypotheses

Lastly, for this last expression to have any meaning, fix the distribution of \tilde{X} the true data.

We assume that $X \sim \pi$ where the lines of X are independent and identically distributed (i.i.d), and that π is known to the Imputer. This is unlikely in a real setting, but we explore the best-case scenario where we have all the necessary information to perform the imputation in order to isolate the error terms that are specific to the presence of missing data — as opposed to bad imputation.

4.2 Analysis

4.2.1 Expected loss

To be able to estimate the expected loss, we break it up into several components. We first denote

$$\tilde{\beta}_n = (\tilde{X}_A^T \tilde{X}_A)^{-1} \tilde{X}_A^T y_A$$

the estimated parameter we would obtain if the training data were completely observed. We consider the loss for the i^{th} line of validation data x_i^V :

$$\begin{aligned}
L_i(y_V, \hat{y}_V) &= (y_V - \hat{y}_V)^2 \\
&= (\tilde{x}_i^V \beta + \epsilon_V - \hat{x}_i^V \hat{\beta}_n)^2 \\
&= (\tilde{x}_i^V (\beta - \tilde{\beta}_n) + \tilde{x}_i^V (\tilde{\beta}_n - \hat{\beta}_n) + (\tilde{x}_i^V - \hat{x}_i^V) \hat{\beta}_n + \epsilon_V)^2 \\
&= (\tilde{x}_i^V (\beta - \tilde{\beta}_n))^2 & (1) \\
&\quad + (\tilde{x}_i^V (\tilde{\beta}_n - \hat{\beta}_n))^2 & (2) \\
&\quad + ((\tilde{x}_i^V - \hat{x}_i^V) \hat{\beta}_n)^2 & (3) \\
&\quad + 2\tilde{x}_i^V (\beta - \tilde{\beta}_n) \tilde{x}_i^V (\tilde{\beta}_n - \hat{\beta}_n) & (4) \\
&\quad + 2\tilde{x}_i^V (\beta - \tilde{\beta}_n) (\tilde{x}_i^V - \hat{x}_i^V) \hat{\beta}_n & (5) \\
&\quad + 2\tilde{x}_i^V (\tilde{\beta}_n - \hat{\beta}_n) (\tilde{x}_i^V - \hat{x}_i^V) \hat{\beta}_n & (6) \\
&\quad + \epsilon_V^2 \\
&\quad + \epsilon_V C
\end{aligned}$$

Where C is some term that will not matter (since it will not count in the expectation — ϵ_V has zero expectation and is independent of the other terms). We can see that terms (1), (2) and (4) depend only on the imputation of the training values (\hat{x}^V is absent), while term (3) depends only on the imputation of the validation data ($\hat{\beta}_n$ is absent). Terms (5) and (6) show the interaction between both imputations.

Influence of missing validation values In particular,

Proposition 4.1. *The expected validation error depends linearly with the proportion of missing data in the validation set (with a fixed amount of missing data in the training set).*

Proof. The risk we want to minimize is R_i the expectation of this loss, summed over all rows. Since the rows are i.i.d, (so the order does not count), the expected value of terms (1), (2), (4) is the same for all i . For terms (3), (5), (6) there are two possibilities: if there is no missing data in the row, these terms are zero. If a value is missing, they are nonzero but their expectation is the same for all lines with missing data.

Consequently, denoting $r_V = \frac{k_V}{n_V}$ the proportion of missing validation data, we can express the expected loss as:

$$\sum_{i=1}^{n_V} L_i = \underbrace{\mathbb{E}_{\tilde{X}_V, X_A^{miss}, \epsilon_A, \epsilon_V} [(1) + (2) + (4) | X_A]}_A + \quad (4.1)$$

$$r_V \underbrace{\mathbb{E}_{\tilde{X}_V, X_A^{miss}, \epsilon_A, \epsilon_V} [(3) + (5) + (6) | X_A]}_B + \sigma^2 \quad (4.2)$$

Thus, for X_A fixed and for a given imputation rule, the expected loss is $A + \sigma^2 + Br_V$ with A and B fixed, and the expected loss depends linearly on the proportion of missing values. \square

Consistency In linear regression without missing data, the estimation of the parameter is consistent[6], that is in our case $\hat{\beta}_n$ is a consistent estimate of β . Moreover Little [31] studied parameter estimation with missing values and showed:

Proposition 4.2. *If the missing data is MCAR and the imputed values are the expected values of the unobserved data conditioned on the observed data ($\hat{x} = \mathbb{E}[x|x_{obs}]$), then the least-square estimator $\hat{\beta}_n$ is consistent for β .*

Note that to do this means the Imputer must know the distribution of X , in order to find the expected values.

If $\hat{\beta}_n$ are consistent, then all terms but $(3) + \epsilon_V^2$ in the loss tend to 0 when $n \rightarrow \infty$. Additionally, term (3) is zero for lines without missing data, and for lines with missing data its expectation is:

$$\mathbb{E}[(\tilde{x}_i^V - \hat{x}_i^V)\hat{\beta}_n^2] = \mathbb{E}[(\hat{\beta}_n^2)^2]\mathbb{E}[(x_{i2}^V - \hat{x}_{i2}^V)^2]$$

Which is minimized by the choice of imputation $\hat{x}_{i2}^V = \mathbb{E}[x_{i2}^V]$, i.e. the same that ensures a consistent estimator for β .

4.2.2 Consequences

These results highlight the asymmetry between training and validation data. In a very simple case, it give us an intuition of the behavior of the prediction error with missing data.

We see that when the imputation is done well, consistency results ensure that in the training data, it is ultimately possible to make up for the unobserved values and have an arbitrarily good parameter estimate, if we have enough observations.

On the other hand, missingness in the validation set adds some inevitable terms to the error. This is important because although training and validation data have the same distribution by hypothesis, in some cases the missingness could be somehow different between those datasets.

For instance, in the Traumabase it is possible that missing data comes from doctors who fail to record some values in the database, although the data was available when treating the patient. In that case when real-world prediction are made, there may be less missing values than there were when we performed CV and model selection. On the contrary, maybe some values were collected late in the process and would have been unavailable for the prehospital diagnostic. Proposition 4.1 show sthat this matters a lot, and that efforts to reduce the amount of missing data at the time of real-world predictions may have a more direct effect on performance than efforts to reduce missing data in the database (e.g. by improving recording).

Lastly, presence of term (3) even for large n and consistent estimation also shows that the intrisinc variability of the covariates imposes a limit on the performance of the prediction with missing data (while otherwise the only limit would be linked to the noise ϵ in the response).

Still, we see that in this case at least, what could seem like independent goals (imputation and full-data parameter estimation) are actually compatible: if we try to minimize error term that depends only on imputation (using imputation by the conditional mean), then we are also enabling consistent parameter estimation which makes the other error terms tend to zero.

In the next chapter, we take a more empirical approach to investigate similar issues.

Chapter 5

Imputation and prediction: Empirical findings

5.1 Impact of missing data

5.1.1 Is less missing data always better?

When performing an analysis, it is intuitive that we should limit the amount of missing data as much as possible, since missing data pollutes our estimates.

In particular, if the missing data is MCAR — and so the complete cases have exactly the same distribution as those with missing data —, and we have a large enough dataset with many complete cases (as in the Traumabase), it is tempting to use only those complete cases to learn our model. Even in a context where we are training for prediction, and the real-world data will have some missing values we need to handle, it seems that we can use complete cases in the training data to learn both our prediction and imputation parameters as accurately as possible and then use those to predict the new data at best.

However, it may not be so: when imputing missing data, we do not recover the exact initial data. What if these errors change the structure of the dataset enough that a different parameter (possibly different from the one that generated the data) can yield better predictions? In that case, learning our model without any missing data may yield the true parameter but still not be optimal for prediction.

We investigated this on some simulated (cf Appendix A with $n = 4000, p = 5, rho = 0.9, \sigma = 10$) and real-world data (abalone, cf Appendix B) by adding a fixed proportion of missing values to the validation data and varying the amount of missing data in the training set:

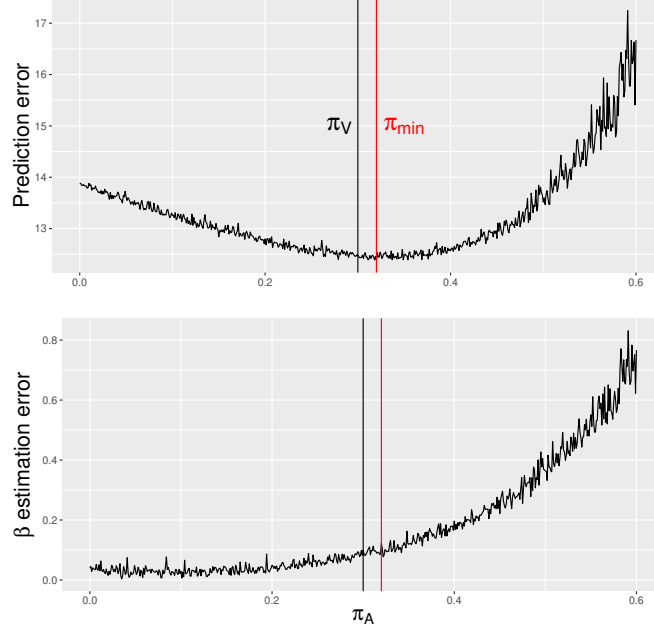
Algorithm 5.1 Impact of missing data

Input: $\pi_V, m, X_A, X_V, y_A, y_V$

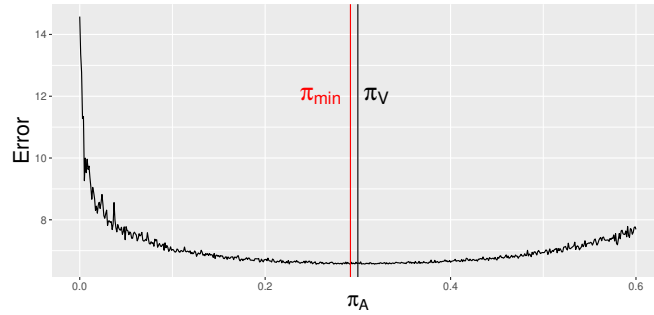
Output: L_1, \dots, L_m

- 1: **for** $\pi_A \in [0, \frac{1}{m}, \dots, \frac{m-1}{m}]$ **do**
 - 2: Add proportion π_A of MCAR missing data to X_A
 - 3: Add proportion $\pi_V A$ of MCAR missing data to X_V
 - 4: Impute \hat{X}_A and \hat{X}_V using μ_A the observed mean of X_A
 - 5: Compute $\hat{\beta}_A$ by linear regression on \hat{X}_A, y_A
 - 6: Predict $\hat{y}_V = \hat{X}_V \hat{\beta}_A$
 - 7: $L_i \leftarrow L(\hat{y}_V, y_V)$
 - 8: **end for**
-

The results are shown in Fig.5.1 (where π_{min} indicates the point where the lowest error is achieved).



(a) Prediction and parameter estimation errors for simulated data



(b) Prediction error for abalone data

Figure 5.1: Impact of missing data in the training set

What we can see here is that when the training dataset is fully observed while the validation has missing data, the prediction error is *higher* than in the same situation with missing data in the training set as well. More precisely, the best prediction is achieved when both datasets have roughly the same amount of missing data.

It is not clear how general this result is. In particular, we could obtain it *only when using mean imputation*: with more elaborate imputation methods it did not show.

In any case, this warrants caution when doing cross-validation with missing data: while reducing the amount of missing data in our records is a worthy endeavour — e.g. by deleting incomplete cases —, it is possible that it will only be useful if the real-world (or validation) data also has less missing data as a result — e.g., improving the data-collection process. Additionally, just as it is important to ensure that the distribution of the data is stable between training and application — no temporal trend in the data —, the same should be done about the missing-data pattern.

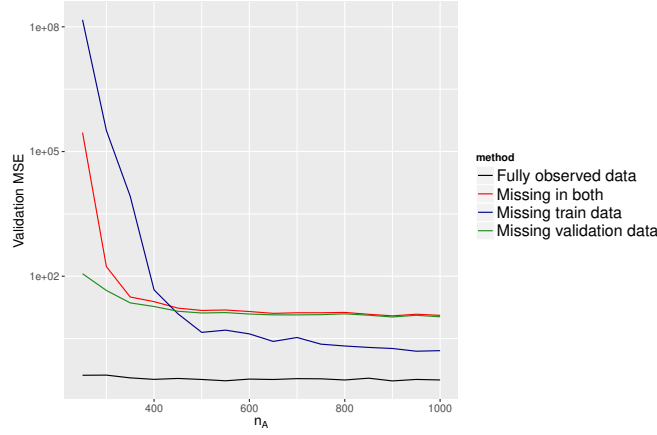
5.1.2 Asymmetry between the two datasets

We want to keep investigating an observation from the previous chapter: missing data does not have the same impact on performance when it is in the training set as when it is in the validation set, and depending on the situation one or the other may be determinant of the value of the error.

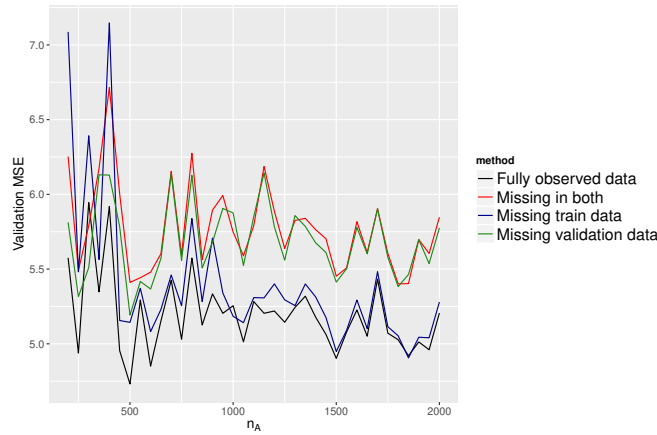
To do this we simulate data in the same fashion as above, that is with a normal X and a linearly derived response y . For various proportions π , we then perform imputation and prediction in 4 different cases:

- Proportion π of MCAR missing values in both datasets: we note the loss L_B
- Proportion π of MCAR missing values just in the validation set: we note the loss L_V
- Proportion π of MCAR missing values just in the training set: we note the loss L_A
- Fully observed data: we note the loss L_F .

Figure 5.2 shows the results of this process, for simulated (cf Appendix A with $p = 45, rho = 0.5, \sigma = 1$) and real-world data (abaone, cf Appendix B), adding 30% MCAR data. We observed that the variable that caused the most change in the relationship between each type of error was p , the number of covariates, which is why we choose to present the results for different values of p . We can see that L_B tends to follow the trend imposed by either L_A or L_V , whichever is worse: when p is small, L_B is almost equal to L_V (i.e., with few parameters to estimate the estimation of β is good so the biggest impact is from the imputation error in X_V). When p is larger, L_B starts following the trend of L_A (with many parameters to estimate, the error on β causes very large errors to appear), although L_B stays smaller than L_A , which is the same effect that we showed in 5.1.1.



(a) Results for simulated data (log scale)



(b) Results for abalone data

Figure 5.2: Impact of missing data in the train and validation set

5.2 Multiple imputation

Instead of making only one imputation, it is possible (see Chapter 2) to instead impute multiple datasets and perform the analysis on each dataset. Just like for parameter estimates, we can generate multiple predictions and use these to estimate prediction uncertainty from missing data.

5.2.1 Partial multiple imputation

In Chapter 4, we mention the fact that if the estimation is consistent, then most of the prediction uncertainty is linked to missing data in the validation dataset, and not to that in the training one. This suggests an idea that would allow predictive multiple imputation while keeping the computational cost rather low.

Given some training data X_A and validation X_V , we can impute m datasets $X_A^{(1)}, \dots, X_A^{(m)}, X_V^{(1)}, \dots, X_V^{(m)}$ which would yield estimates $\hat{\beta}_n^{(1)}, \dots, \hat{\beta}_n^{(m)}$ and then $\hat{y}_V^{(1)}, \dots, \hat{y}_V^{(m)}$. However, this implies making m separate parameter estimations. If n is large, the variance of $\hat{\beta}$ may be insignificant in the variance of \hat{y}_V compared to the direct impact of missing validation data.

This is why we can try instead to impute the training dataset only once, while imputing the validation data m times as usual, and use the same $\hat{\beta}$ to predict on each imputed validation set. This would be a major computational gain, since the most computing-intensive part of the analysis is usually parameter estimation, not prediction.

To see if this is worth considering, we perform an analysis on some very simple simulated data.

5.2.2 Prediction intervals

As in 5.1.1 we generate X normal covariates and y a noised linear combination of these, then split them for CV. We add the same amount of MCAR missing data in both datasets, then impute them multiply (both as described just above and by only imputing the training data once). We train a linear regression on X_A, y_A and predict on X_V .

This allows us to compute the between-imputation variance for each entry in \hat{y}_V , and the linear regression model gives us an estimation for the within-imputation variance of the predictions. We can then use Rubin's rule (cf Chapter 2) to compute a total variance for each prediction, and the t-distribution approximation to obtain an interval. Figure 5.3 shows average coverage rates for $p = 20, \rho = 0.5, m = 30$, 30% missing data and multiple values of n (averaging over several runs). We see that when n is very small, partial MI tends to severely underestimate variance while full MI overestimates it. When n is larger, both perform similarly and close to nominal coverage.

Note, though, that we could not reproduce those results even on simple real-world data: coverage was vastly inferior to nominal values. It is plausible that unless the model fits the data perfectly, the estimated intervals can be very misleading.

explain within-imputation variance calc

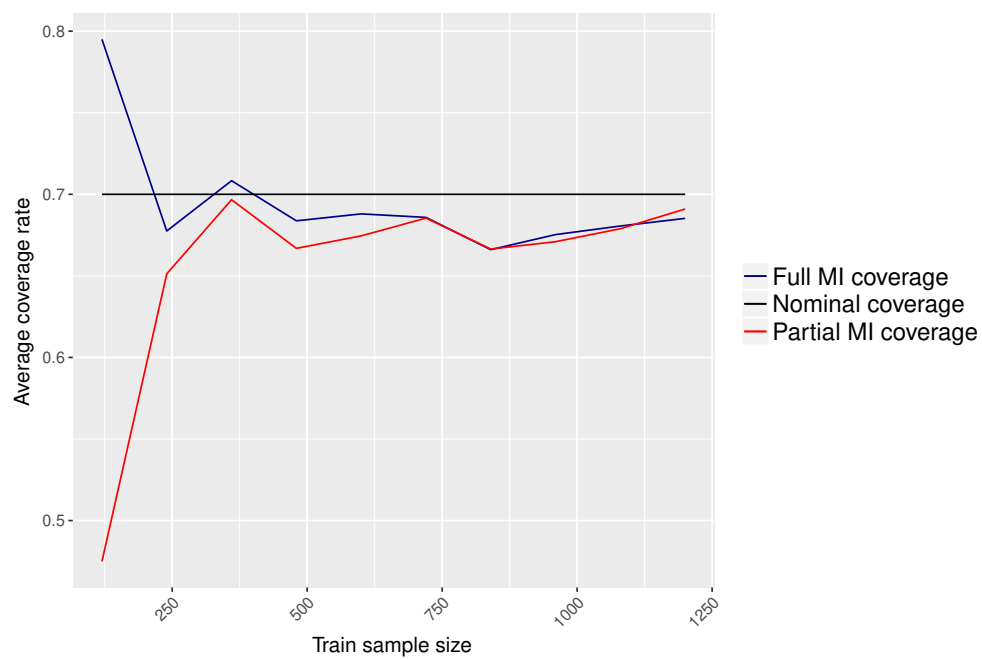


Figure 5.3: Mean coverage rate of prediction intervals

Chapter 6

Analysis: imputing the Traumabase data for prediction

We now evaluate the potential for prediction of HS using the Traumabase. For that, we perform a prediction with CV (cf Chapter 3) and compare it with other methods of HS evaluation. An advantage of imputation is that one can predict with various models: we compare predictions using logistic regression [22], Support Vector Machines (SVM) [20] and random forests [48] in predicting the probability of HS.

6.1 Methodology

6.1.1 Evaluating the prediction

The response variable in our data is binary, and we predict a probability. This, and the unbalance in the response (only 10% of positive cases) means that the choice of metric is not straightforward. A first choice we have to make is whether we choose a threshold for the prediction (predict a positive when the predicted probability is above some value), or evaluate the predicted probability as-is.

Some metrics allow us to evaluate the predicted probability directly, such as the AUC [24] or log-loss (minimized by the logistic regression). However, we want to be able to compare our results with those given by scores or the historical decisions of doctors, which are binary. We want to see if our predictions are able to separate patients with and without shocks at least as well as those references, so we need a metric that puts our predictions and those scores on an equal footing.

To that end, we choose a simple cost function that, given a binary pre-

diction, assigns some user-defined cost to false negatives and false positives. That is:

$$L(\hat{y}, y) = \frac{1}{n} \sum_{i=1}^n c_1 \mathbb{I}_{y_i=1, \hat{y}_i=0} + c_2 \mathbb{I}_{y_i=0, \hat{y}_i=1}$$

To evaluate our predicted probability, we take the best value of this loss for any choice of threshold: this gives us a measure of the separation power of those predictions.

6.1.2 Choice of imputation method

There are many methods of imputation we can choose from (cf Chapter 2). In order to compare them, we proceed to grouped imputation (as described in Chapter 3) with each of them, and then perform a prediction on each imputed dataset. The resulting validation errors are presented in figure ??.

It is striking that the difference between imputation methods is very small: even though there are differences in the mean performance, these differences are very small compared to the variation of the performance for different CV splits.

6.2 Results

We performed predictions on the traumabase data by repeatedly choosing CV splits, and then going through imputation and prediction with a logistic regression.

In order to evaluate the prediction, we compute the loss as described above (for various choices of c_1, c_2) and then compare it to that obtained with the doctors' prediction (which we know because the decision to initiate the MT procedure is stored in the Traumabase), and two scores of hemorrhage gravity that were designed with diagnosis in mind (as opposed to posterior analysis): the TASH (Trauma Associated Sever Hemorrhage)[54] and ABC (Assessment of Blood Consumption)[37] scores.

Conclusion

Appendix A

Simulated normal data

To simulate a regression dataset with normally distributed covariates, we proceed as follows.

Algorithm A.1 Data simulation

Input: $n_A, n_V, p, \rho, \sigma$

Output: X_A, X_V, y_A, y_V

- | | |
|--|---|
| 1: $\Sigma \leftarrow (1 - \rho)I_p + \rho\mathbb{1}_{p \times p}$ | \triangleright Same correlation ρ between all pairs of variables |
| 2: $X_A \sim \mathcal{N}(0, \Sigma)$ | \triangleright Of size $n_A \times p$ |
| 3: $X_V \sim \mathcal{N}(0, \Sigma)$ | \triangleright Of size $n_V \times p$ |
| 4: $\beta \leftarrow (1, \dots, 1)$ | |
| 5: $y_A \leftarrow X_A\beta + \epsilon_A$ | \triangleright Where $\epsilon_A \sim \mathcal{N}(0, \sigma^2)$ |
| 6: $y_V \leftarrow X_V\beta + \epsilon_V$ | \triangleright Where $\epsilon_V \sim \mathcal{N}(0, \sigma^2)$ |
-

That is, for both the training and validation data, we generate a normally distributed X and a response y that is a linear combination of X with normal noise.

Appendix B

Abalone data

In addition to simulated data, we want to make some tests on real-world data. The Traumabase data is not adapted for this use, because it has missing data (while we want a dataset where we know the full data, in order to add missing values ourselves and see the effects). In addition, it has a binary response which makes it harder to evaluate the prediction.

Instead we use the Abalone [36] dataset. It consists in measurements on abalone (sea snails) shells where the goal is to predict their age. It has 4177 observations, 7 numerical covariates and one categorical covariate. We keep only the numerical ones. The dataset is fully observed.

In addition, there is a strong correlation between all the pairs of variables (> 0.8).

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