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Missing data imputation for Hemorrhagic shock prediction

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Abstract

Hemorrhagic shock is a condition that can be life-threatening but that has much higher survival rates if treated early. It is also quite difficult to detect. Because of this, there is a strong case for a tool that predicts it based on prehospital measurement made on trauma patients.

The Traumabase dataset provides a large history of such measurements, and could be used to learn a model to predict hemorrhagic shock (Chapter 1). However, the presence of missing data complicates the task. In this work, we specifically explore missing data imputation, which consists in replacing missing values by credible ones in order to use complete-data methods on the dataset (Chapter 2). In a context where the final goal is prediction on new real-world patients, rather than parameter estimation, some questions arise regarding the way imputation should be implemented and used. Focusing on parametric models, we investigate methodologies that allow fast comparisons of imputation models (Chapter 3) and discuss grouped imputation, a proxy for actual cross-validation performance.

The possible presence of missing values for new patients at the time of prediction (in addition to those in the records) means that some dynamics beyond parameter estimation appear. In a simplistic linear regression setting (Chapters 4), we show that parameter estimation and imputation can be optimal simultaneously, but that even in that case some error terms are introduced by missing data and do not tend to zero for large sample sizes.

After investigating the issues linked to imputation in this context, we go back to the Traumabase and estimate its potential for hemorrhagic shock prediction (Chapter 5). We find that prediction is promising when compared with hand-made gravity scores or doctors' assessments, though SAEM, a joint optimization model, outperforms the models that use imputation.

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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][10]. When a person sustains a severe injury (e.g. due to a car accident or a 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 [6]. At this point, even proper care may not be enough to save the patient [12].

When an individual sustains an injury, they are usually taken in charge by first responders who evaluate the situation and the patient's state, before transporting them to a trauma centre when they will be treated. To prevent patients from falling into HS, procedures have been established in most hospitals to trigger a fast response to suspected hemorrhage [41]: massive transfusion (MT) protocols can be activated even before the patient enters the hospital [35]. When this happens, the hospital gets ready to transfuse the patient with large amounts of blood as soon as they arrive, and frees up the necessary personnel. This way, the time interval between the injury and the transfusion is minimal. Studies [22] [36] 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[41]. 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, ...) [14]. A full-body scan or at least an ultrasound examination may be needed[40]. 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 [41] 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 [38] [15] [34] [17]. The idea is to determine a set of conditions on physiological measurements that determine a numeric score for the patient. 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 [41] 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 does not manage 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 Medical 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 [16]
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 [16]
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 [16] which causes a drop in the Hb concentration [13]. It is easily measured on location using measurement kits [31].
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 [9]. Measurement is easy and standard [42].

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	20	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).

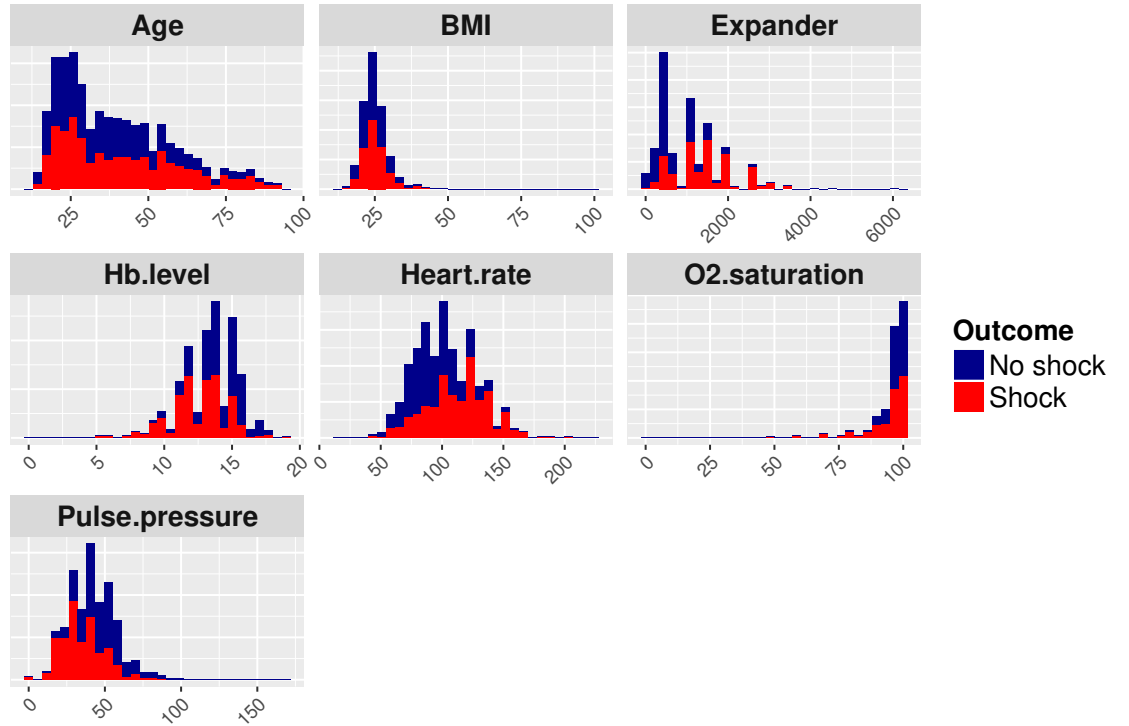


Figure 1.1: Distribution of the continuous variables depending on patient outcome

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

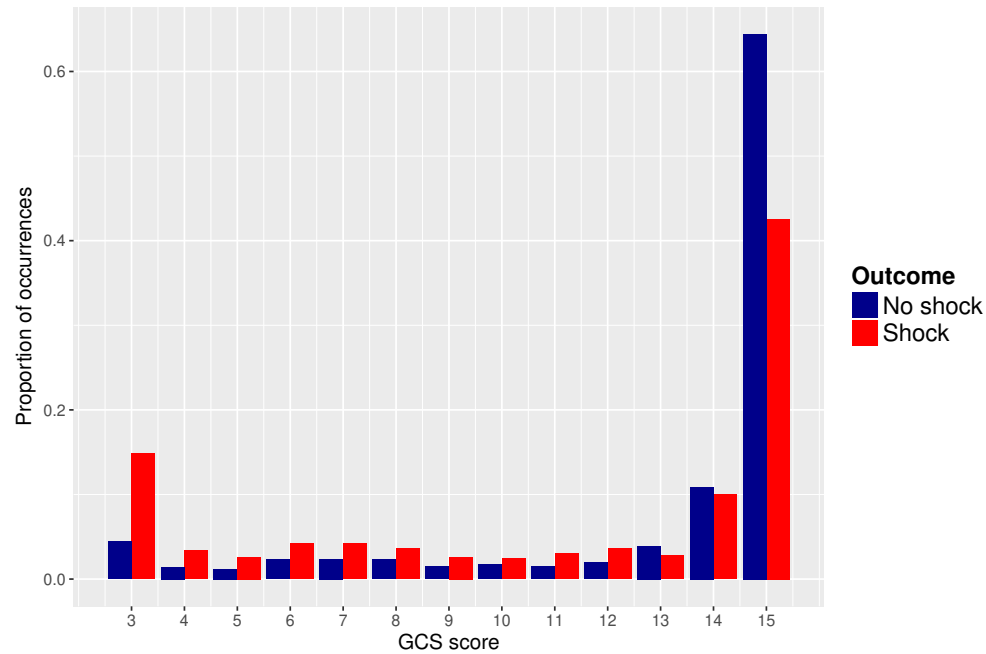


Figure 1.2: Distribution of Glasgow Coma Scale score depending on patient outcome

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)

Missing data

An important aspect of the Traumabase is that it contains a significant amount of missing data. That is, some measurements or information about the patients were not collected or not recorded in 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 1.5 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.

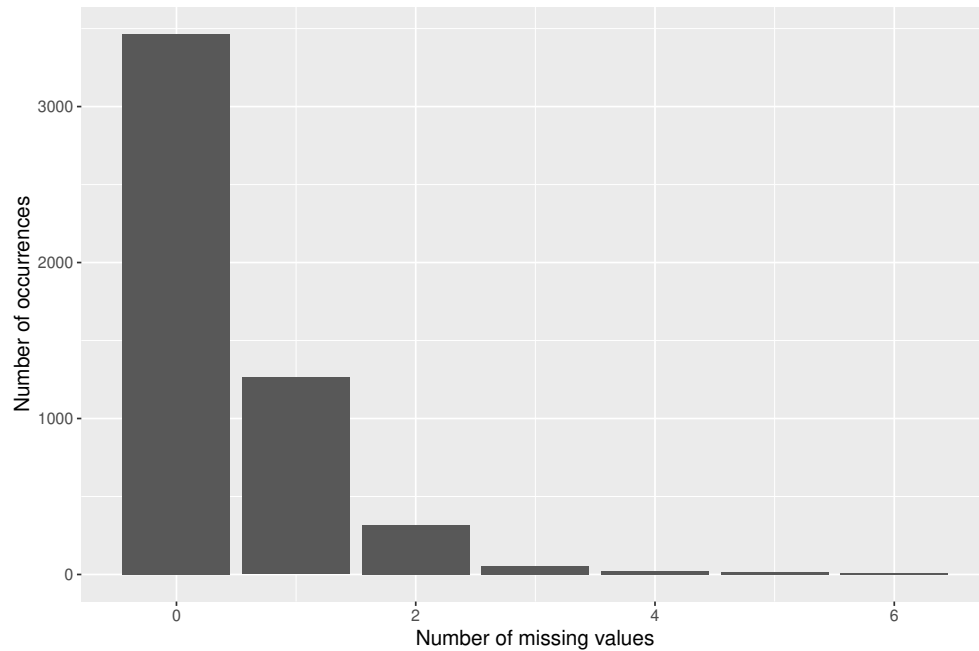


Figure 1.4: Distribution of the number of missing values per patient record

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 (excluding Sex and Shock which have no missing values)

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, many models exist that take missing data into account without trying to fill in the missing values [47]. However, generic software implementations of missing data methods are fairly rare, as such methods tend to be quite problem-specific. This means that building such a method usually requires working from the ground up: this is of course possible, but it limits one’s ability to compare many possible models before choosing a definitive implementation..

Comparatively, once the dataset is imputed, it can be used with any existing complete-data prediction method — necessarily in a sub-optimal way since the fact that data was missing is now hidden, but giving one an insight into this method’s potential. 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. As we will explain, this was a prerequisite in our context.

In the following chapters, we investigate the methodology and dynamics of imputation, performed in a context where the prediction model is not fully known, and new data also has missing values. 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 [56] 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} (y is fully observed). X and y are transferred to an Imputer. The Imputer is tasked with filling in the missing observations. She chooses an imputation model with a parameter α of her choice, 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 $L(y_{new}, \hat{y}_{new})$ is computed. This gives the final performance evaluation of the process.

This process is illustrated in Figure 1.6

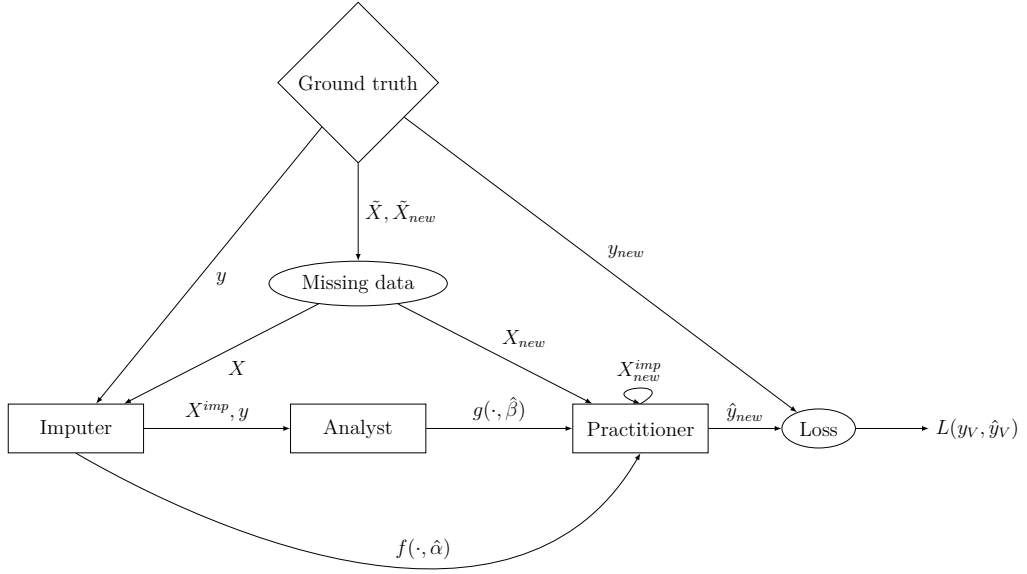


Figure 1.6: Imputation framework

The purpose of this formalization is to clarify the separation between the different phases of the inference, and show how the information is divided. 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. Indeed, 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, only to one line of new data at a time when a new patient needs a diagnostic.

On the other hand, the distinction between Imputer and Analyst is a prerequisite related to the work we were asked to perform: namely, impute the dataset so that others in the HS research group can work on it without having to handle missing data — which compromises optimal performance in favor of the breadth of the investigation.

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.

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 [33, 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 income where we know the age of respondent, and younger people fail to declare their income 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 income more often.

In particular, Rubin showed [43] that if the data is MAR or MCAR, then the likelihood factorises so that maximum-likelihood estimates can be computed by maximizing just the observed likelihood.

2.2 Main types of imputation

2.2.1 Joint maximum likelihood

The most straightforward way to impute data is to assume that the data is distributed according to some parametric joint distribution on all of the variables. In that case, once the distribution has been chosen, one needs to estimate the distribution parameters, and it is then possible to replace missing values by their expected value conditional on the observed data (or draws from this distribution for multiple imputation, see below).[30] [20] [52]

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 an iterative algorithm [45].

Algorithm 2.1 FCS 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: $\hat{X}_{\text{miss}}^{(i)} = \max_{\alpha} P(\alpha | X_{\text{obs}}^{(i)}, \hat{X}^{(-i)})$
 - 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. It can be used with a number of univariate conditional models [45][50][53].

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][8][5] are generally based on Principal Component Analysis (PCA)[55], 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.

2.2.4 Nearest-neighbors

Other methods exist to impute missing values. *Nearest-neighbor imputation*[7]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* [3] 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 [44] 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 [33, 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 [33, Ch. 5]:

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

Moreover, if θ is a scalar, when $n \rightarrow \infty$ we can approximate [44]

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

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

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.

In Section 3.1 we describe the process of cross-validation used to evaluate the performance that a model will have on new data. Section 3.2 shows how this clashes with standard implementation of imputation methods, especially when trying to compare different 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 use ERM [54]: 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 [18]).

To address the issue of model selection, we need to use 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 and I_V its complement.

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:

$$R_V(\hat{\beta}) = \frac{1}{n_V} \sum_{i \in I_V} L(y_i, f(X_i, \hat{\beta}))$$

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 $\hat{X} = g(X, \alpha)$ where \hat{X} 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 loss

$$L'(g(X, \alpha), \alpha)$$

The loss L' would usually be the negative log-likelihood of a distribution model for X . For example, we can choose to perform imputation by maximum likelihood using a normal approximation. In that case, we would have $alpha = (\mu, \Sigma)$ and [20]

$$L'(\hat{X}, \alpha) = \phi(\hat{X}; \mu, \Sigma)$$

(where ϕ is the p.d.f. of the normal distribution) with $\hat{X} = \arg \max_A \phi(A; \mu, \Sigma)$ (in this case, this corresponds the expected value of 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 (with a slight abuse of notation, we use $f(\hat{X}, \beta)$ to refer to function f applied to each line of \hat{X}):

$$h(X, (\alpha, \beta)) = f(\hat{X}, \beta) = f(g(X, \alpha), \beta)$$

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

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

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 to impute and predict the validation data. As we see below, this particular requirement clashes with standard implementations of imputation methods.

3.2.2 Implementation issues

Current standard implementations of imputation methods are usually used through a single function which takes a dataset with missing values as an input and returns a completed dataset, but not simple a way to impute a new dataset with the exact same parameters. [50] [27][45][20]

Although this is fine for most applications, in the case of CV this is problematic. To perform CV properly, 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 if all one has 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 , then 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.

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 reuse previously computed parameters: a reimplementation is unavoidable.

In some cases it is straightforward to reimplement a given method to separate the parameter estimation and the imputation. However, in other cases (e.g. iterative methods such as PCA imputation) this is a much more involved task. In particular, one may want a way to rapidly compare many imputation methods using existing software packages, before choosing one to reimplement.

This is why we are interested in alternatives that could be used to impute the data using only a black-box function, to use as a proxy of the performance of the properly reimplemented method. We want to see if there is a way to order the relative performance of various imputation methods using such a proxy, before choosing one to implement.

3.3 Possible solutions

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

Algorithm 3.1 Separate 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: $\hat{X}_V \leftarrow g(X_V, \hat{\alpha}_A) \quad \triangleright \text{Uses the same } \alpha \text{ as for the training set}$

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

We call this Separate Imputation (SI). 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

Methods

Grouped imputation (GI) A way to perform the imputation with just one function is to 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: $(\hat{X}_A, \hat{X}_V) \leftarrow \hat{X} \quad \triangleright \text{Split the data after imputation}$

4: **Estimation of the prediction parameter**

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

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 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. In that sense, the CV does not faithfully reproduce the actual real-world application where the new data would be unavailable at the time of training — and the training data unavailable at the time of prediction. As a consequence the validation error may not be

representative of real-world performance and could modify the performance order when comparing multiple methods.

Independent imputation (II) Another approach is to divide the data first, then impute each dataset independently:

Algorithm 3.3 Independent 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: $\hat{y}_V \leftarrow f(\hat{X}_V, \hat{\beta}_A)$

Here, we respect the rules of CV (the validation data is not used at all during training), but 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 $h(\cdot, (\hat{\alpha}_V, \hat{\beta}_A))$. As for GI, this could have an impact on the validation error.

$\hat{\alpha}_V, \hat{\alpha}_A$ and $\hat{\alpha}_X$ are asymptotically the same for large n — X_A, X_V and X have the same distribution since the lines of X are i.i.d —, so all three methods (Separate, Grouped and Independent) should be identical for large n . But for smaller n , harmful effects may be present — overoptimistic validation error due to 'cheating' for GI, high error due to the difference in parameters for II.

Need for a new implementation

We want to understand whether the alternatives proposed here are good enough to be used if SI is not available. To do that, we need at least one implementation where SI is available. That way we will be able to compare its performance with GI and II.

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 (it is impossible on just one line of data, and GI 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* [20], and a large part of the code is from the *norm* package [52]. The idea is to model both X_A and X_V as normally distributed $\mathcal{N}(\mu, \Sigma)$ with unknown parameters. Although this is often a rough approximation of the true distribution, it has been shown to perform well on a range of datasets [45][48]. In the Traumabase data, the variables are unimodal and have almost symmetric distributions, so we can expect a normal approximation to be reasonable.

This hypothesis allows 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 [11]. The algorithm is detailed in [46, Chapter 5.3]

For this step, we use a slightly modified version of the code from the *norm* package.

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

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

The conditional expectations are easily derived using the Schur complement [58].

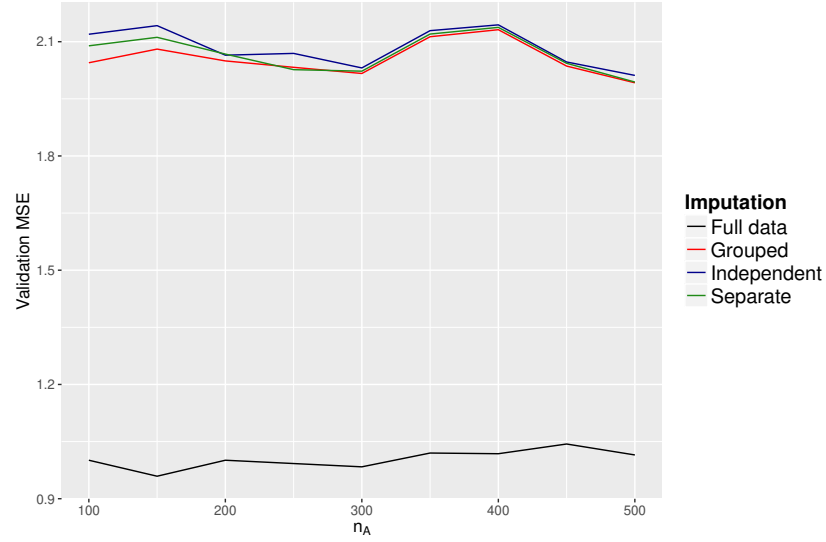
We implemented this step as well to get a complete imputation procedure divided in two functions that implement the estimation and imputation steps separately. The code is available in package SIMVN [39].

In all that comes next, unless specified otherwise this imputation method is the one we use.

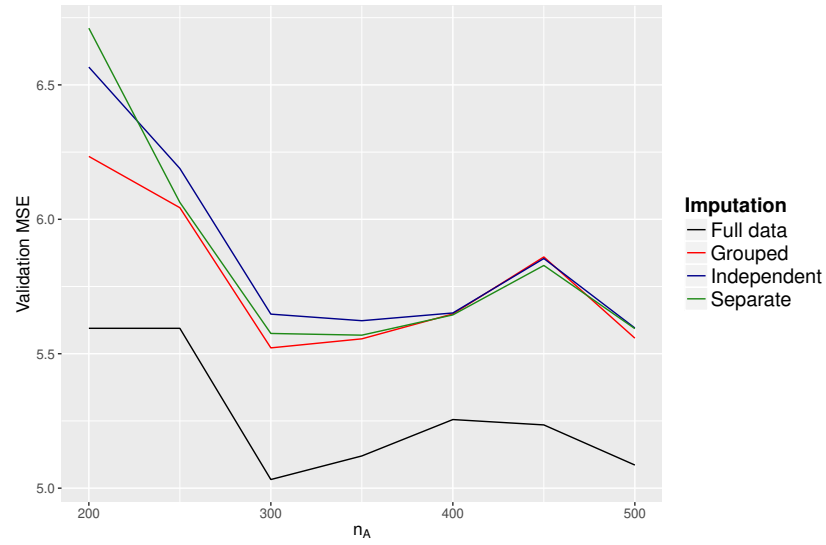
3.3.3 Comparison on simulated data

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% MCAR missing data. The results are in Figure 3.1.

We see that indeed GI seems to always have lower error than SI, while II has higher error. However, when n is not too small, the relative difference between GI and SI is small. II seems to be further off than the other two, and sometimes has high error. As a result, GI appears to be a good proxy for SI performance: it can be used as a quick check to compare the performances of a range of imputation methods, in order to choose one method to reimplement for the final SI imputation.



(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 linear 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 get an intuition of 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 first describe the setting and notation. Then (4.2) we derive some results on the behaviour of the loss. We first show that in this case there is a very simple relationship between the amount of missing data and the loss (Prop. 4.1). Then we move on to asymptotic results and show that while prediction and parameter estimation can be optimised simultaneously by choosing the right imputation (Prop. 4.2), the imputation uncertainty introduces some new error terms that do not vanish for large n (Prop. 4.3).

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 :

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

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

The true data X follows some distribution $X \sim \pi$ where the lines of X are independent and identically distributed (i.i.d). We investigate the simplest case where the Imputer knows π .

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 [49]

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

$\hat{\beta}$ 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:

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

4.2 Analysis

Now that we chosen a setting, we can study how the expected CV loss behaves in this context where we perform imputation, followed by parameter estimation and prediction.

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 terms (3), (5) and (6) are linked to the interaction between the training and validation imputations.

Influence of missing validation values Let us define $r_V = \frac{k_V}{n_V}$ the proportion of missing values in the validation dataset and $r_A = \frac{k_A}{n_A}$. The other lines are fully observed. Then for r_A fixed, the expected value error depends linearly on r_V . More precisely,

Proposition 4.1.

$$\mathbb{E}_{\tilde{X}_V, X_A^{miss}, \epsilon_A, \epsilon_V} \left[\sum_{i=1}^{n_V} L_i | X_A \right] = A + \sigma^2 + Br_V$$

for some A, B depending only on the training data.

Proof. The expected values of terms (1), (2), (4) are the same for all the lines of the validation set — in these three terms, the only variable that depends on the validation data is \tilde{x}_i^V and it has the same distribution for all lines because the lines are i.i.d. . For terms (3), (5), (6) there are two possibilities: if there is no missing data in the row, these terms are zero ($\tilde{x}_i^V = \hat{x}_i^V$). If a value is missing, they are nonzero but their expectations are the same for all lines with missing data — because the validation values are i.i.d. (and thus exchangeable) and we integrate over them in the expectation.

Consequently, we can express the expected loss as:

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

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

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[2], that is in our case $\tilde{\beta}_n$ is a consistent estimate of β . Moreover, Little [32] 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 (when the proportion r_A is fixed).*

When this holds, another result is immediate:

Proposition 4.3. *If $\tilde{\beta}_n, \hat{\beta}_n$ are consistent, then all terms but (3) + ϵ_V^2 in the loss tend to 0 when $n \rightarrow \infty$.*

This is important because it means that there is a new variance term in the error: in addition to the usual regression variance term, there is a term linked to the variance of the missing values that does not vanish asymptotically.

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 $\hat{x}_{i2}^V = \mathbb{E}[x_{i2}^V]$: this is the same choice that we need in Proposition 4.2 to ensure that the estimation is consistent. In this sense, the goal of having a good imputation does not clash with parameter estimation.

4.2.2 Consequences

Two main insights come out of this analysis:

- In this example, imputing with the conditional expectation of the missing data is the right choice both for parameter estimation (Prop. 4.2) and for prediction (to minimize term (3)): these two goals are compatible here.
- On the other hand, uncertainty on the true values in the validation dataset adds some terms to the error that do not go away asymptotically (term (3)).

In particular, there is a direct (linear here) repercussion of missing validation data as error, while error terms from missing training data can be decreased arbitrarily with larger samples sizes.

This last point is noteworthy for our purposes, 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 — such as the patient’s age — were collected late in the process and would have been unavailable for the prehospital diagnostic. Proposition 4.1 shows that this matters, and that efforts to reduce the amount of missing data at the time of real-world predictions (e.g. incentivising the practitioner to enter more measurements) may have a more direct effect on performance than efforts to reduce missing data in the database (e.g. by improving the collection of patient data a posteriori).

Chapter 5

Imputing the Traumabase data for prediction

Our final step is to see how well prediction with imputation works to predict hemorrhagic shock. For that, we proceed to cross-validation (cf Chapter 3) to get an idea of the performance we can achieve this way. We compare it to several references to see whether this is an improvement over other methods of prediction.

5.1 Methodology

5.1.1 Prediction pipeline

To evaluate our method we perform imputation and prediction on the data, by training on a training set X_A, y_A and validating on X_V, y_V . In order to get an idea of the average performance, we repeat this for multiple X_A, X_V splits. As in Chapter 3 we need to choose two things: an imputation model $g(\cdot, \alpha)$ and a complete-data prediction model $f(\cdot, \beta)$.

For the choice of function g , we have argued in Chapter 3 that we can use grouped imputation (GI) to compare different existing implementations. We perform such a comparison in 5.1.3, for a variety of possible f models: logistic regression [21], Support Vector Machine (SVM) [19] and random forest (RF) [51].

5.1.2 Evaluating the prediction

Metric 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 [23] 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 prediction, assigns some user-defined cost to false negatives and false positives. That is:

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

with $c_1 + c_2 = 1$.

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. The choice of costs is not obvious, which is why in this chapter we show the results for multiple possible values.

Benchmarks In order to have a reference performance for HS prediction, we compare the value of the loss with the loss obtained from several other predictions:

- *Doctor's prediction:* The decision to initiate a MT procedure is recorded in the Traumabase. It determines whether the doctor considered the patient to be at risk of HS.
- *ABC (Assessment of Blood Consumption)[38] score:* this gravity score is the only one that was designed with prehospital prediction in mind. It is a very simple score that only uses a few measurements. It does, though, use the FAST echography results, which is an examination usually performed when the patient arrives at the trauma centre. As such, the score is not exactly prehospital but can be computed very early once the patient is hospitalized.
- *TASH (Trauma Associated Severe Hemorrhage)[57]) score:* this score was also designed for hemorrhage detection, but at a later stage: it uses some values that are only available after laboratory tests (e.g. base excess) or radiography (presence of a fracture).

- *SAEM Logistic regression*: this a method for logistic regression without imputation of the training dataset, developed by Jiang [24] to address the specific issue of HS prediction on the Traumabase. Contrarily to the models we evaluate, it is a joint model i.e. it can be used in the case when the Analyst and Imputer are not distinct. The hypotheses on the data are the same as those that those of normal imputation followed by linear regression (same f and g models). The difference, if we take the notations from Chapter 3, is that α the imputation parameter and β the regression parameter are optimised jointly rather than one after the other.

This gives us some points of comparison for predictive performance. Both scores work based on a point system, where points are added when a certain criterion is met, and the sum of the points is used as an indicator of gravity (like the predicted probability for our models). Since there is missing data, when a criterion cannot be verified it is counted as unactivated (no points added to the gravity score).

5.1.3 Choice of imputation method

There are many methods of imputation we can choose from (cf Chapter 2) to impute missing values in. 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 Fig. 5.1 (using the previously described loss with $\frac{c_1}{c_2} = 5$).

We used the following imputation methods (c.f. Chapter 2):

- *Mean imputation*: replace missing values by the observed mean of the corresponding column
- *Normal expectation*: impute by approximating the data as multivariate normal and taking conditional expectations (c.f. Chapter 3)
- *PCA imputation*: impute through a low-rank approximation of the data
- *FCS with adapted methods*: FCS with a normal regression model for all variables except the Sex (logistic regression) and GCS (proportional odds model for ordered variables).
- *MissForest*: a FCS method that uses random forests [51] as the univariate predictor

Note that the Sex is binary and the GCS is ordered discrete, so we cannot in theory impute them with the PCA or normal imputation, as they only handle numerical data. However, the Sex has no missing data and the GCS has only a handful (0.4%) so we proceed with the imputation by treating them as numerical variables (it has been shown [4] that this can achieve satisfactory results).

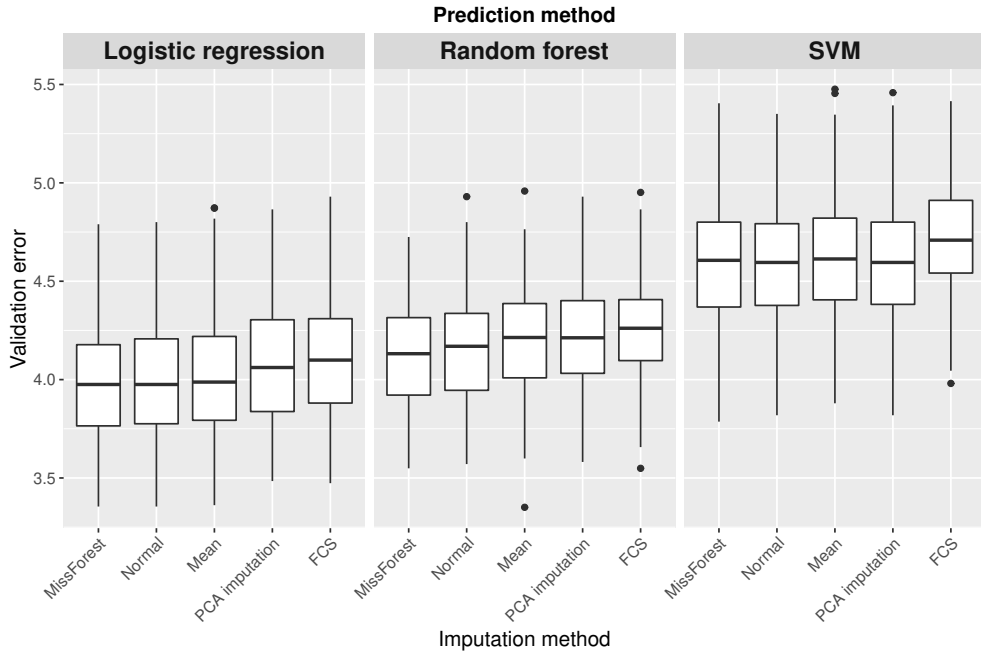


Figure 5.1: Prediction performance for multiple prediction and imputation methods

It is striking that the difference between imputation methods is very small: even though there are differences in the mean performance, these differences are minor compared to the variation of the performance for different CV splits. Even imputation by the mean, which is supposedly very inaccurate, is on par with other methods in terms of performance. We were not able to determine the reason for this: the relatively low proportion of missing data does not seem to be in cause, given that the same trend shows if we artificially add missing values.

We chose to use normal imputation. Thanks to the MIMVN implementation designed in Chapter 3, we can perform Separate Imputation on the data in order to mimic exactly the real-world situation during CV.

5.2 Results

We performed predictions on the Traumabase data as described above, for 16 different CV splits and the same choices of prediction models as before (logistic regression, RF, SVM). Figure 5.2 shows the average loss of the predictions for different values of $\frac{c_1}{c_2}$, i.e. different possible costs for false negatives.

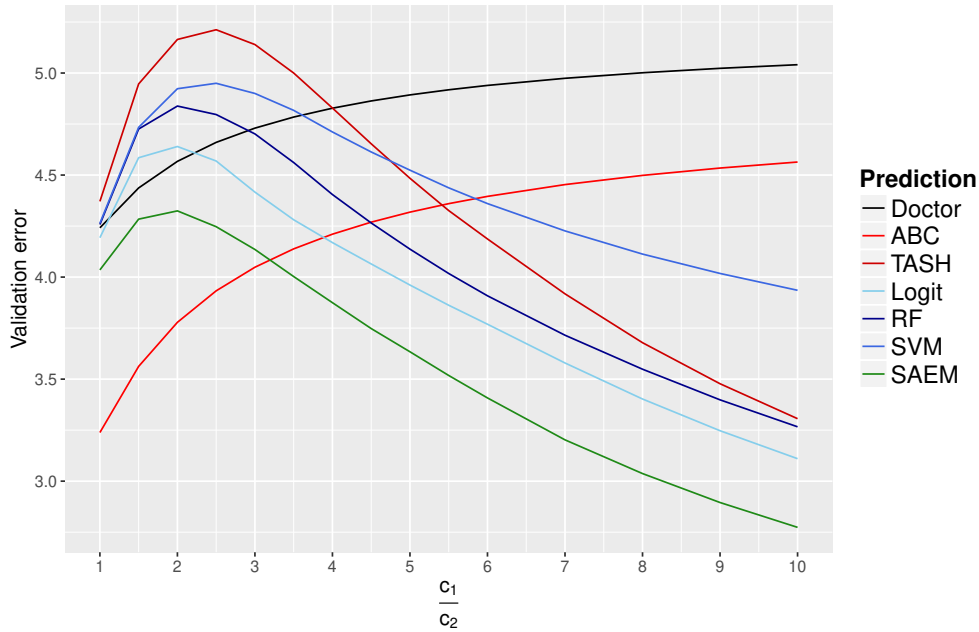


Figure 5.2: Error for each prediction depending on c_1, c_2

First note that there are two possible main trends for the loss depending on the method:

- The loss increases with c_1 : this means that the predictions are more conservative, and tend to have fewer false positives but more false negatives. This is the case of the doctors' prediction and the ABC score.
- The loss decreases when c_1 increases: this means that the prediction tends to favour overpredicting HS, so it has fewer false negatives but more false positives. This is the case of all our predictions, as well as the TASH score and SAEM prediction.

When two predictions follow the same trend, it is easy to compare them as one is above the other regardless of the choice of weights. In particular,

the ABC score seems to be better at predicting hemorrhage than doctors, even though it is extremely simple in principle.

Likewise, we see that for the descending trend, the best predictor is without a doubt the SAEM regression, followed by the logistic regression with imputation, the random forest with imputation, the TASH score and the SVM with imputation in that order.

Whether the ABC score should be preferred to other predictors depends on the choice of weights: for the SAEM prediction, the loss is lower than for ABC if $\frac{c_1}{c_2}$ is greater than approximately 3, while for the regression with imputation this happens for a ratio above 4.

What this also shows is that although imputation gives promising results, the joint SAEM model outperforms it significantly. Still, imputing is a good first step: thanks to grouped imputation and subsequent prediction, we have evaluated many methods using only out-of-the box implementations, without having to create a dedicated model. For instance, we can see that it is visibly not worth trying to implement a model for SVM with missing data. Conversely, the performance on the imputed data had been better for RF than for logistic regression, it would have given us a strong case for building a missing-data random forest as a next step. Model selection using imputed datasets allows us to single out one method that we can then choose to improve by implementing it to work without imputation.

Conclusion

In this work, we investigated the possibility to predict hemorrhagic shock in trauma patients when performing imputation on both the training data and new observations. We placed ourselves in a context when three successive agents have to handle the data: an Imputer and an Analyst who work on some historical data, and a Practitioner on the field who does not have access to the training data and must diagnose a new patient.

In order to evaluate a wide range of imputation methods, we investigated the possibility to use standard software packages to perform our task. Although in most cases this is impossible to do in full accordance with the principles of CV, we created an implementation that allows it, and used it to compare some alternatives. Grouped Imputation seemed promising as a fast to implement proxy for separate imputation.

We studied a simplified case in order to better understand the specificities of our task and the dynamics of the loss in this case. We found that two apparently separate goals played a large part in a method's performance: parameter estimation on the training data and accurate imputation of the validation data. In this very simple setting, we show that these two objectives are actually compatible: when the imputation is done using the true conditional expectation and the estimation uses a consistent full-data method on the imputed data, then the imputation error is minimal and the parameter estimation remains consistent on the imputed data.

It also appears that some error terms, introduced by missingness in the validation data, do not disappear asymptotically — and in our simplified setting, scale linearly with the proportion of missing validation error. This shows the importance of limiting the amount of missing data at the time of a real-world prediction, as one can never completely make up for the additional variance introduced by missing validation values — *in the case of imputation*. In the case of the Traumabase, this means we should focus on incentivising thorough data collection before prediction, while also investigating whether some covariates tend to have different missingness in the real setting than in the database — and try to avoid using predictor variables that have high

missingness at the time of prediction.

The final evaluation of imputation on the Traumabase data allowed us to compare multiple imputation and prediction models. While the choice of imputation model was not clear, logistic regression stood out as a better predictor than our other options. The SAEM logistic regression, which is an imputation-less version of the same regression model, gives significantly better results than prediction after imputation, which confirms the intuition that imputation involves a trade-off between ease of implementation and performance. Still, performing imputation allowed us to compare many prediction methods with minimal efforts, which had the potential to guide us in our future choices, and seemed to indicate that SAEM was a sound choice of model.

We observed that SAEM performs better than doctors in our evaluations. Comparatively, whether or not our predictions outperform the ABC score depends on an arbitrary choice of weighting between false positives and false negatives. Such a choice should be made based on a medical consensus and would need further work to establish. All in all, these results very encouraging regarding the possibility to detect hemorrhagic shock very early: using only very basic measurements available early in the prehospital phase, we were able to build models that perform similarly to predictions that are usually made much later in the process (in-hospital doctor’s assessment, ABC and TASH scores) — remember, though, that some amount of human expertise is built into our model given that the total amount of injected expander is used as a predictor, and is mostly a proxy for the first responder’s assessment of the patient’s condition.

In the future, it would be worthwhile to quantify formally the gap in predictive performance between joint optimization and imputation followed by prediction with the same hypotheses (for instance, SAEM has the same distribution hypotheses as normal imputation followed by logistic regression: it is only the choice of parameters that differs). In the investigation of HS prediction, an important next step would be to understand what characteristics of the data make it hard to beat mean imputation even though many variables are correlated.

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 [37] 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).

Bibliography

- [1] Cause-specific mortality and morbidity - World Health Organization. http://www.who.int/whosis/whostat/EN_WHS09_Table2.pdf.
- [2] TW Anderson, John B Taylor, et al. Strong consistency of least squares estimates in normal linear regression. *The Annals of Statistics*, 4(4):788–790, 1976.
- [3] Rebecca R Andridge and Roderick JA Little. A review of hot deck imputation for survey non-response. *International statistical review*, 78(1):40–64, 2010.
- [4] Coen A Bernaards, Thomas R Belin, and Joseph L Schafer. Robustness of a multivariate normal approximation for imputation of incomplete binary data. *Statistics in medicine*, 26(6):1368–1382, 2007.
- [5] Matthew Brand. Incremental singular value decomposition of uncertain data with missing values. In *European Conference on Computer Vision*, pages 707–720. Springer, 2002.
- [6] Jeremy W Cannon. Hemorrhagic shock. *New England Journal of Medicine*, 378(4):370–379, 2018.
- [7] Jiahua Chen and Jun Shao. Nearest neighbor imputation for survey data. *Journal of Official statistics*, 16(2):113, 2000.
- [8] Pei Chen and David Suter. Recovering the missing components in a large noisy low-rank matrix: Application to sfm. *IEEE transactions on pattern analysis and machine intelligence*, 26(8):1051–1063, 2004.
- [9] Stephen M Cohn, Avery B Nathens, Frederick A Moore, Peter Rhee, Juan Carlos Puyana, Ernest E Moore, and Gregory J Beilman. Tissue oxygen saturation predicts the development of organ dysfunction during traumatic shock resuscitation. *Journal of Trauma and Acute Care Surgery*, 62(1):44–55, 2007.

- [10] C Clay Cothren, Ernest E Moore, Holly B Hedegaard, and Katy Meng. Epidemiology of urban trauma deaths: a comprehensive reassessment 10 years later. *World journal of surgery*, 31(7):1507–1511, 2007.
- [11] Arthur P Dempster, Nan M Laird, and Donald B Rubin. Maximum likelihood from incomplete data via the em algorithm. *Journal of the royal statistical society. Series B (methodological)*, pages 1–38, 1977.
- [12] Richard P Dutton. Current concepts in hemorrhagic shock. *Anesthesiology clinics*, 25(1):23–34, 2007.
- [13] S Figueiredo, C Taconet, A Harrois, S Hamada, T Gauss, M Raux, and J Duranteau. How useful are hemoglobin concentration and its variations to predict significant hemorrhage in the early phase of trauma? a multicentric cohort study. *Annals of intensive care*, 8(1):76, 2018.
- [14] Matthias Frank, Uli Schmucker, Dirk Stengel, Lutz Fischer, Joern Lange, Rico Grossjohann, Axel Ekkernkamp, and Gerrit Matthes. Proper estimation of blood loss on scene of trauma: tool or tale? *Journal of Trauma and Acute Care Surgery*, 69(5):1191–1195, 2010.
- [15] Eduardo Gonzalez, Ernest E Moore, Hunter B Moore, Michael P Chapman, Theresa L Chin, Arsen Ghasabyan, Max V Wohlauser, Carlton C Barnett, Denis D Bensard, Walter L Biffl, et al. Goal-directed hemostatic resuscitation of trauma-induced coagulopathy: a pragmatic randomized clinical trial comparing a viscoelastic assay to conventional coagulation assays. *Annals of surgery*, 263(6):1051, 2016.
- [16] Guillermo Gutierrez, HDavid Reines, and Marian E Wulf-Gutierrez. Clinical review: hemorrhagic shock. *Critical care*, 8(5):373, 2004.
- [17] Sophie Rym Hamada, Anne Rosa, Tobias Gauss, Jean-Philippe Desclefs, Mathieu Raux, Anatole Harrois, Arnaud Follin, Fabrice Cook, Mathieu Boutonnet, Arie Attias, et al. Development and validation of a pre-hospital “red flag” alert for activation of intra-hospital haemorrhage control response in blunt trauma. *Critical Care*, 22(1):113, 2018.
- [18] Douglas M Hawkins. The problem of overfitting. *Journal of chemical information and computer sciences*, 44(1):1–12, 2004.
- [19] Marti A. Hearst, Susan T Dumais, Edgar Osuna, John Platt, and Bernhard Scholkopf. Support vector machines. *IEEE Intelligent Systems and their applications*, 13(4):18–28, 1998.

- [20] James Honaker, Gary King, Matthew Blackwell, et al. Amelia ii: A program for missing data. *Journal of statistical software*, 45(7):1–47, 2011.
- [21] David W Hosmer Jr, Stanley Lemeshow, and Rodney X Sturdivant. *Applied logistic regression*, volume 398. John Wiley & Sons, 2013.
- [22] David B Hoyt, Eileen M Bulger, M Margaret Knudson, John Morris, Ralph Ierardi, Harvey J Sugerman, Steven R Shackford, Jeffery Lander-casper, Robert J Winchell, and Gregory Jurkovich. Death in the operating room: an analysis of a multi-center experience. *The Journal of trauma*, 37(3):426–432, 1994.
- [23] Jin Huang and Charles X Ling. Using auc and accuracy in evaluating learning algorithms. *IEEE Transactions on knowledge and Data Engineering*, 17(3):299–310, 2005.
- [24] Wei Jiang, Julie Josse, and Marc Lavielle. Saem for logistic regression with missing data.
- [25] Cathy Jones. Glasgow coma scale, 1979.
- [26] Julie Josse and François Husson. Handling missing values in exploratory multivariate data analysis methods. *Journal de la Société Française de Statistique*, 153(2):79–99, 2012.
- [27] Julie Josse, François Husson, et al. missmda: a package for handling missing values in multivariate data analysis. *Journal of Statistical Software*, 70(1):1–31, 2016.
- [28] Henk AL Kiers. Weighted least squares fitting using ordinary least squares algorithms. *Psychometrika*, 62(2):251–266, 1997.
- [29] George C Kramer. Hypertonic resuscitation: physiologic mechanisms and recommendations for trauma care. *Journal of Trauma and Acute Care Surgery*, 54(5):S89–S99, 2003.
- [30] Jonathan Kropko, Ben Goodrich, Andrew Gelman, and Jennifer Hill. Multiple imputation for continuous and categorical data: Comparing joint multivariate normal and conditional approaches. *Political Analysis*, 22(4):497–519, 2014.
- [31] Lionel Lamhaut, Roxana Apriotesei, Xavier Combes, Marc Lejay, Pierre Carli, and Benoît Vivien. Comparison of the accuracy of noninvasive hemoglobin monitoring by spectrophotometry (sphb) and hemocue®

- with automated laboratory hemoglobin measurement. *Anesthesiology: The Journal of the American Society of Anesthesiologists*, 115(3):548–554, 2011.
- [32] Roderick JA Little. Regression with missing x’s: a review. *Journal of the American Statistical Association*, 87(420):1227–1237, 1992.
- [33] Roderick JA Little and Donald B Rubin. *Statistical analysis with missing data*, volume 333. John Wiley & Sons, 2014.
- [34] M1 Maegele, R Lefering, A Wafaisade, P Theodorou, S Wutzler, P Fischer, B Bouillon, T Paffrath, and Trauma Registry of the Deutsche Gesellschaft für Unfallchirurgie (TR-DGU). Revalidation and update of the tash-score: a scoring system to predict the probability for massive transfusion as a surrogate for life-threatening haemorrhage after severe injury. *Vox sanguinis*, 100(2):231–238, 2011.
- [35] Debra L Malone, John R Hess, and Abe Fingerhut. Massive transfusion practices around the globe and a suggestion for a common massive transfusion protocol. *Journal of Trauma and Acute Care Surgery*, 60(6):S91–S96, 2006.
- [36] Matthew Martin, John Oh, Heather Currier, Nigel Tai, Alec Beekley, Matthew Eckert, and John Holcomb. An analysis of in-hospital deaths at a modern combat support hospital. *Journal of Trauma and Acute Care Surgery*, 66(4):S51–S61, 2009.
- [37] Warwick J Nash, Tracy L Sellers, Simon R Talbot, Andrew J Cawthorn, and Wes B Ford. The population biology of abalone (haliotis species) in tasmania. i. blacklip abalone (h. rubra) from the north coast and islands of bass strait. *Sea Fisheries Division, Technical Report*, (48), 1994.
- [38] Timothy C Nunez, Igor V Voskresensky, Lesly A Dossett, Ricky Shinall, William D Dutton, and Bryan A Cotton. Early prediction of massive transfusion in trauma: simple as abc (assessment of blood consumption)? *Journal of Trauma and Acute Care Surgery*, 66(2):346–352, 2009.
- [39] Antoine Ogier. Simvn package. <https://github.com/Anogio/SIMVN>, 2018.
- [40] Phillips Perera, Thomas Mailhot, David Riley, and Diku Mandavia. The rush exam: Rapid ultrasound in shock in the evaluation of the critically ill. *Emerg Med Clin North Am*, 28(1):29–56, 2010.

- [41] Matthew J Pommerening, Michael D Goodman, John B Holcomb, Charles E Wade, Erin E Fox, Deborah J Del Junco, Karen J Brasel, Eileen M Bulger, Mitch J Cohen, Louis H Alarcon, et al. Clinical gestalt and the prediction of massive transfusion after trauma. *Injury*, 46(5):807–813, 2015.
- [42] Gerhard Rall. Use of a pulse oxymetry sensor device, June 15 1999. US Patent 5,911,690.
- [43] Donald B Rubin. Inference and missing data. *Biometrika*, 63(3):581–592, 1976.
- [44] Donald B Rubin and Nathaniel Schenker. Multiple imputation for interval estimation from simple random samples with ignorable nonresponse. *Journal of the American statistical Association*, 81(394):366–374, 1986.
- [45] Joseph L Schafer. *Analysis of incomplete multivariate data*. Chapman and Hall/CRC, 1997.
- [46] Joseph L Schafer. *Analysis of incomplete multivariate data*. Chapman and Hall/CRC, 1997.
- [47] Joseph L Schafer and John W Graham. Missing data: our view of the state of the art. *Psychological methods*, 7(2):147, 2002.
- [48] Joseph L Schafer and Maren K Olsen. Multiple imputation for multivariate missing-data problems: A data analyst’s perspective. *Multivariate behavioral research*, 33(4):545–571, 1998.
- [49] George AF Seber and Alan J Lee. *Linear regression analysis*, volume 329. John Wiley & Sons, 2012.
- [50] Daniel J Stekhoven. missforest: Nonparametric missing value imputation using random forest. *Astrophysics Source Code Library*, 2015.
- [51] Vladimir Svetnik, Andy Liaw, Christopher Tong, J Christopher Culberson, Robert P Sheridan, and Bradley P Feuston. Random forest: a classification and regression tool for compound classification and qsar modeling. *Journal of chemical information and computer sciences*, 43(6):1947–1958, 2003.
- [52] Ported to R by Alvaro A. Novo. Original by Joseph L. Schafer <jls@stat.psu.edu>. *norm: Analysis of multivariate normal datasets with missing values*, 2013. R package version 1.0-9.5.

- [53] Stef Van Buuren. Multiple imputation of discrete and continuous data by fully conditional specification. *Statistical methods in medical research*, 16(3):219–242, 2007.
- [54] Vladimir Naumovich Vapnik. An overview of statistical learning theory. *IEEE transactions on neural networks*, 10(5):988–999, 1999.
- [55] Svante Wold, Kim Esbensen, and Paul Geladi. Principal component analysis. *Chemometrics and intelligent laboratory systems*, 2(1-3):37–52, 1987.
- [56] Xianchao Xie and Xiao-Li Meng. Dissecting multiple imputation from a multi-phase inference perspective: What happens when god’s, imputer’s and analyst’s models are uncongenial. *Statist. Sinica*, 27:1485–1545, 2017.
- [57] Nedim Yücel, Rolf Lefering, Marc Maegele, Matthias Vorweg, Thorsten Tjardes, Steffen Ruchholtz, Edmund AM Neugebauer, Frank Wappler, Bertil Bouillon, Dieter Rixen, et al. Trauma associated severe hemorrhage (tash)-score: probability of mass transfusion as surrogate for life threatening hemorrhage after multiple trauma. *Journal of Trauma and Acute Care Surgery*, 60(6):1228–1237, 2006.
- [58] Fuzhen Zhang. *The Schur complement and its applications*, volume 4. Springer Science & Business Media, 2006.