Regression without regrets

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# Preface

The focus of this report is to provide guidance on conducting initial data analysis in a reproducible manner in the context of intended regression analyses.

# 1. Bacteremia study

## 1.1 Bacteremia study overview

We will exemplify our proposed systematic approach to data screening by means of a diagnostic study with the primary aim of using age, sex and 49 laboratory variables to fit a diagnostic prediction model for the bacteremia status (= presence of bacteria in the blood stream) of a blood sample. A secondary aim of the study is to describe the functional form of each predictor in the model. Between January 2006 and December 2010, patients with the clinical suspicion to suffer from bacteremia were included if blood culture analysis was requested by the responsible physician and blood was sampled for assessment of hematology and biochemistry. An analysis of this study can be found in Ratzinger et al. (2014).

The data consists of 14,691 observations from different patients and 51 potential predictors. To protect data privacy our version of this data was slightly modified compared to the original version, and this modified version was cleared by the Medical University of Vienna for public use (**DC 2019-0054**). Compared to the official results given in (Ratzinger et al. 2014), our results may differ to a negligible degree.

## 1.2 Source dataset

### 1.2.1 Where to access the data?

We refer to the **source** data as the raw data set available in this repository (**DC 2019-0054**). The data set is published on [Zenodo](https://doi.org/10.5281/zenodo.7554815) with the following doi: https://doi.org/10.5281/zenodo.7554815.

For simplicity, we have also stored the *source* data and accompanying materials such as the **data dictionary** the data-raw directory.

### 1.2.2 Data dictionary

The data dictionary provides an overview of the collected data. First, we read and display the data dictionary below providing an overview of the collected measurements.

The variable name and label are displayed alongside the measurement scale and units as well as remarks and relevant study information from\_paper.

| variable | label | scale\_of\_measurement | units | remark | from\_paper |
| --- | --- | --- | --- | --- | --- |
| ID | Patient Identification | nominal | 1-14691 | NA | NA |
| SEX | Patient sex | nominal | 1=male, 2=female | NA | Female: Male |
| AGE | Patient Age | continuous | years | Alter=German age | Albumin (G/L) 14,187 33.7 (28?39.3) 32 (26.925?36.7) ,0.0001 0.568 |
| MCV | Mean corpuscular volume | continuous | pg | NA | MCV (pg) 15,941 88.1 (84.6?91.9) 88.6 (84.8?92.5) 0.0044 0.524 |
| HGB | Haemoglobin | continuous | G/L | NA | Haemoglobin(G/L) 15,942 11.4 (9.9?13.2) 11.1 (9.5?12.6) ,0.0001 0.554 |
| HCT | Haematocrit | continuous | % | NA | Haematocrit (%) 15,941 34.4 (29.8?39.2) 33.1 (28.5?37.5) ,0.0001 0.561 |
| PLT | Blood platelets | continuous | G/L | NA | PLT (G/L) 15,940 206 (142?279.25) 180.5 (115?248) ,0.0001 0.575 |
| MCH | Mean corpuscular hemoglobin | continuous | fl | NA | MCH (fl) 15,941 29.7 (28.3?30.9) 29.8 (28.5?31.2) 0.0019 0.526 |
| MCHC | Mean corpuscular hemoglobin concentration | continuous | g/dl | NA | MCHC (g/dl) 15,941 33.5 (32.6?34.4) 33.6 (32.7?34.5) n.s. |
| RDW | Red blood cell distribution width | continuous | % | NA | RDW (%) 15,924 14.4 (13.3?15.925) 14.9 (13.7?16.6) ,0.0001 0.572 |
| MPV | Mean platelet volume | continuous | fl | NA | MPV (fl) 15,214 10.3 (9.7?11) 10.4 (9.7?11.1) n.s. |
| LYM | Lymphocytes | continuous | G/L | NA | Lymphocytes (G/L) 15,695 1.1 (0.7?1.6) 0.7 (0.4?1.1) ,0.0001 0.683 |
| MONO | Monocytes | continuous | G/L | NA | Monocytes (G/L) 15,710 0.8 (0.5?1.1) 0.6 (0.3?1) ,0.0001 0.598 |
| EOS | Eosinophils | continuous | G/L | NA | Eosinophils (G/L) 15,373 0.6 (0.1?1.8) 0.2 (0?0.8) ,0.0001 0.641 |
| BASO | Basophiles | continuous | G/L | NA | Basophiles % 15,375 0.2 (0.1?0.3) 0.1 (0.1?0.2) ,0.0001 0.606 |
| NT | Normotest | continuous | % | Measures thromboplastin time | Normotest (%) 13,339 84 (67?101) 78 (60?94) ,0.0001 0.571 |
| APTT | Activated partial thromboplastin time | continuous | sec | NA | aPTT (sec) 13,251 37.8 (34.2?42.8) 37.8 (34.2?43) n.s. |
| FIB | Fibrinogen | continuous | mg/dl | NA | Fibrinogen (mg/dl) 13,211 526 (393?667) 546 (424?701) 0.0001 0.538 |
| SODIUM | Sodium | continuous | mmol/L | Natrium=German sodium | Sodium (mmol/L) 14,542 138 (135?140) 136 (133?139) ,0.0001 0.602 |
| POTASS | Potassium | continuous | mmol/L | NA | Potassium (mmol/L) 13,774 3.95 (3.67?4.3) 3.97 (3.595?4.365) n.s. |
| CA | Calcium | continuous | mmol/L | NA | Calcium (mmol/L) 14,592 2.23 (2.09?2.35) 2.21 (2.08?2.33) 0.0001 0.533 |
| PHOS | Phosphate | continuous | mmol/L | NA | Phosphate(mmol/L) 14,664 1 (0.81?1.2) 0.95 (0.76?1.19) ,0.0001 0.537 |
| MG | Magnesium | continuous | mmol/L | NA | MG (mmol/L) 13,989 0.81 (0.73?0.89) 0.77 (0.68?0.86) ,0.0001 0.582 |
| CREA | Creatinine | continuous | mg/dl | NA | Creatinine (mg/dl) 15,813 0.99 (0.81?1.31) 1.2 (0.89?1.87) ,0.0001 0.611 |
| BUN | Blood urea nitrogen | continuous | mg/dl | NA | BUN (mg/dl) 15,800 16.2 (11.4?25.8) 22.5 (14.7?37.78) ,0.0001 0.633 |
| HS | Uric acid | continuous | mg/dl | Harns?ure=German Uric acid | Uric acid (mg/dl) 12,709 5 (3.7?6.5) 5.5 (3.9?7.6) ,0.0001 0.562 |
| GBIL | Bilirubin | continuous | mg/dl | NA | Bilirubin (mg/dl) 14,431 0.75 (0.52?1.19) 1.02 (0.66?1.73) ,0.0001 0.621 |
| TP | Total protein | continuous | G/L | NA | TP (G/L) 14,301 65.8 (56.8?73.4) 64.7 (56.4?71.5) 0.0019 0.528 |
| ALB | Albumin | continuous | G/L | NA | ALAT (U/L) 14,919 26 (16?47) 30 (18?60) ,0.0001 0.55 |
| AMY | Amylase | continuous | U/L | NA | Amylase (U/L) 11,783 50 (34?77) 44 (28?70) ,0.0001 0.565 |
| PAMY | Pancreas amylase | continuous | U/L | NA | PAMY (U/L) |
| LIP | Lipases | continuous | U/L | NA | Lipases (U/L) 11,988 23 (13?40) 22 (12?38) n.s. |
| CHE | Cholinesterase | continuous | kU/L | NA | CHE (kU/L) 13,353 4.66 (3.2?6.29) 3.94 (2.66?5.48) ,0.0001 0.591 |
| AP | Alkaline phosphatase | continuous | U/L | NA | ALP (U/L) 14,479 83 (62?120) 100 (72?164) ,0.0001 0.601 |
| ASAT | Aspartate transaminase | continuous | U/L | NA | ASAT (U/L) 14,745 31 (22?56) 37 (24?70.25) ,0.0001 0.558 |
| ALAT | Alanin transaminase | continuous | U/L | NA | Age 15,985 58 (42?69) 65 (53?74) ,0.0001 0.611 |
| GGT | Gamma-glutamyl transpeptidase | continuous | G/L | NA | GGT (G/L) 14,629 48 (25?112) 73 (35?180) ,0.0001 0.599 |
| LDH | Lactate dehydrogenase | continuous | U/L | NA | LDH (U/L) 14,150 239 (186?334) 249 (199?331.5) 0.0037 0.527 |
| CK | Creatinine kinases | continuous | U/L | NA | CK (U/L) 13,763 82 (42?190) 67 (34?142) ,0.0001 0.557 |
| GLU | Glucoses | continuous | mg/dl | NA | Glucoses (mg/dl) 11,350 113 (96?137) 121 (99?154) ,0.0001 0.559 |
| TRIG | Triclyceride | continuous | mg/dl | NA | Triglyceride (mg/dl) 10,549 115 (83?164) 118 (85?170) n.s. |
| CHOL | Cholesterol | continuous | mg/dl | NA | Cholesterol (mg/dl) 10,565 146 (114?183) 132 (105?171) ,0.0001 0.564 |
| CRP | C-reactive protein | continuous | mg/dl | NA | CRP (mg/dl) 15,820 8.39 (2.77?16.15) 11.68 (5.22?21.19) ,0.0001 0.596 |
| BASOR | Basophile ratio | continuous | % | NA | Basophiles (G/L) 15,827 0 (0?0) 0 (0?0) ,0.0001 0.47 |
| EOSR | Eosinophil ratio | continuous | % | NA | Eosinophil % 15,831 0.1 (0?0.2) 0 (0?0.1) ,0.0001 0.626 |
| LYMR | Lymphocyte ratio | continuous | % (mg/dl) | NA | Lymphocytes % (mg/dl) 15,250 11.6 (7.1?18.6) 7 (4.15?12.2) ,0.0001 0.674 |
| MONOR | Monocyte ratio | continuous | % | NA | Monocytes % 15,268 8.1 (5.8?10.7) 6.1 (3.5?8.8) ,0.0001 0.645 |
| NEU | Neutrophiles | continuous | G/L | NA | Neutrophiles (G/L) 15,181 7.3 (4.6?10.7) 8.4 (5.23?12.7) ,0.0001 0.559 |
| NEUR | Neutrophile ratio | continuous | % | NA | Neutrophiles % 15,181 77.7 (68.7?84.6) 85.8 (78.3?90.5) ,0.0001 0.696 |
| PDW | Platelet distribution width | continuous | % | NA | PDW (%) 14,776 12 (10.8?13.4) 12.1 (10.8?13.7) n.s. |
| RBC | Red blood count | continuous | T/L | NA | RBC (T/L) 15,478 3.9 (3.4?4.5) 3.7 (3.2?4.2) ,0.0001 0.567 |
| WBC | White blood count | continuous | G/L | NA | WBC (G/L) 15,477 9.58 (6.64?13.46) 10.205 (6.61?14.86) n.s. |
| BloodCulture | Blood culture result for bacteremia | nominal | no, yes | NA | NA |

### 1.2.3 Source data

We also display a short snapshot of source data set from the data-raw folder of the project directory. The snapshot provides a glimpse of the data, giving the data dictionary more context.

We do not display all observations measured as it is too wide and long to fit reasonably in to the report. However, we refer you to the [Zenodo page](https://doi.org/10.5281/zenodo.7554815) for an interactive overview of the source data.

Rows: 14,691  
Columns: 53  
$ ID <dbl> 1, 3, 5, 7, 9, 10, 11, 12, 13, 19, 21, 22, 23, 25, 26, 27~  
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$ HCT <dbl> 35.9, 34.7, 22.8, 31.1, 38.7, 46.9, 43.5, 34.8, 30.4, 30.~  
$ PLT <dbl> 307, 182, 64, 309, 183, 144, 242, 38, 88, 105, 216, 188, ~  
$ MCH <dbl> 31.5, 26.0, 31.2, 30.4, 30.2, 34.8, 33.1, 23.8, 33.6, 28.~  
$ MCHC <dbl> 31.8, 30.6, 32.4, 33.3, 35.3, 33.5, 33.4, 30.5, 35.3, 34.~  
$ RDW <dbl> 19.5, 15.0, 19.7, 13.8, 12.6, 13.9, 13.1, 16.8, 13.3, 13.~  
$ MPV <dbl> 10.8, 9.7, 11.1, 8.5, 10.0, 10.9, 10.3, NA, 10.7, 11.3, 1~  
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$ MONO <dbl> 1.7, 0.2, 1.2, 0.8, 0.4, 0.9, 1.6, 0.1, 0.2, 0.9, 0.6, 0.~  
$ EOS <dbl> 0.0, 0.1, 0.1, 0.0, 0.0, 0.1, 0.3, 0.1, 0.0, 0.3, 0.0, 0.~  
$ BASO <dbl> 0.1, 0.0, 0.1, 0.0, 0.0, 0.0, 0.0, 0.0, 0.0, 0.1, 0.1, 0.~  
$ NT <dbl> 86, 90, 58, 67, 95, 61, NA, 93, 57, 69, 108, 86, 93, 83, ~  
$ APTT <dbl> 28.8, 29.8, 36.3, 38.2, 33.1, 41.8, NA, 36.3, 33.8, 28.1,~  
$ FIB <dbl> 578, NA, 313, 487, 490, 400, NA, 413, 431, 407, 604, 476,~  
$ SODIUM <dbl> 137, 141, 147, 141, 137, 141, 139, 142, 143, 136, 131, 13~  
$ POTASS <dbl> 3.88, NA, 4.61, 4.71, NA, 4.41, 3.69, 4.67, 2.35, 3.80, 5~  
$ CA <dbl> 2.29, 2.21, 1.92, 2.05, 2.34, 2.08, NA, 2.31, 2.10, 1.92,~  
$ PHOS <dbl> 1.20, 0.58, 1.51, 2.17, 0.97, 0.99, NA, 1.16, 0.51, 0.72,~  
$ MG <dbl> 0.66, NA, 1.03, 0.83, 0.74, 0.56, NA, 0.87, 0.36, 0.53, 0~  
$ CREA <dbl> 0.65, 0.76, 1.25, 2.78, 0.65, 0.82, 1.21, 1.77, 1.00, 0.5~  
$ BUN <dbl> 5.7, 19.9, 50.6, 47.5, 8.5, 15.3, 13.0, 29.8, 15.0, 14.0,~  
$ HS <dbl> 5.3, NA, NA, 9.7, 3.0, 5.5, NA, 6.2, 4.7, 4.0, 4.0, 4.1, ~  
$ GBIL <dbl> 0.59, 0.48, 8.42, 0.35, 0.42, 2.40, 1.13, 0.45, 1.21, 2.4~  
$ TP <dbl> 67.0, 65.3, 40.5, 61.2, 78.4, 57.5, NA, 70.8, 67.4, 53.8,~  
$ ALB <dbl> 36.7, 37.4, 22.1, 33.2, 43.8, 30.1, NA, 43.6, 35.4, 24.8,~  
$ AMY <dbl> 30, NA, 146, 92, 84, 95, 117, 177, NA, 35, 79, 16, 25, 32~  
$ PAMY <dbl> 16, NA, NA, 28, 50, 57, NA, 43, NA, 35, 63, 14, 15, 20, 3~  
$ LIP <dbl> 10, NA, 89, 18, 50, 25, 73, 30, NA, 38, 52, 19, 14, 26, 5~  
$ CHE <dbl> 5.12, 5.61, 2.52, 4.10, 6.91, 6.79, NA, 7.40, NA, 2.64, 2~  
$ AP <dbl> 85, 80, 119, 94, 108, 68, 51, 153, 239, 146, 180, 64, 74,~  
$ ASAT <dbl> 22, 28, 124, 774, 35, 32, 29, 26, 91, 97, 24, 13, 25, 31,~  
$ ALAT <dbl> 14, 25, 135, 72, 22, 11, 20, 32, 57, 156, 63, 23, 27, 53,~  
$ GGT <dbl> 48, 61, 134, 23, 72, 68, 138, 96, 446, 192, 266, 19, 66, ~  
$ LDH <dbl> 284, NA, 696, 1787, NA, 263, 303, 181, 183, 277, 221, 299~  
$ CK <dbl> 23, 36, 40, 2422, 79, 75, 230, 87, 53, 87, 30, 118, 17, 1~  
$ GLU <dbl> 107, 84, 107, 105, 93, 89, 91, 96, 86, 104, 104, 102, 161~  
$ TRIG <dbl> 105, NA, NA, 134, 152, 85, NA, 129, 62, 207, 292, 221, 12~  
$ CHOL <dbl> 175, NA, NA, 141, 167, 144, NA, 156, 118, 123, 194, 151, ~  
$ CRP <dbl> 3.94, 1.42, 12.09, 3.78, 11.17, 5.89, 17.84, 1.29, 1.36, ~  
$ BASOR <dbl> 0.4132231, 0.0000000, 0.5681818, 0.0000000, 0.0000000, 0.~  
$ EOSR <dbl> 0.0000000, 0.8264463, 0.5681818, 0.0000000, 0.0000000, 1.~  
$ LYMR <dbl> 1.652893, 3.305785, 8.522727, 11.016949, 8.333333, 22.000~  
$ MONOR <dbl> 7.024793, 1.652893, 6.818182, 6.779661, 4.166667, 9.00000~  
$ NEU <dbl> 22.0, 11.4, 14.7, 9.7, 8.4, 6.8, 8.9, 1.2, NA, 3.8, 8.2, ~  
$ NEUR <dbl> 90.90909, 94.21488, 83.52273, 82.20339, 87.50000, 68.0000~  
$ PDW <dbl> 10.6, 11.4, 14.1, 8.7, 12.2, 12.9, 12.5, NA, NA, 13.2, 12~  
$ RBC <dbl> 3.7, 3.9, 2.5, 3.5, 4.4, 4.3, 4.5, 4.7, NA, 3.5, 3.3, 2.5~  
$ WBC <dbl> 24.10, 12.17, 17.45, 11.58, 9.86, 9.94, 13.06, 1.78, NA, ~  
$ BloodCulture <chr> "no", "no", "no", "no", "no", "no", "no", "no", "yes", "n~

# 2. IDA plan

This document exemplifies the pre-specified plan for initial data analysis (IDA plan) for the bacteremia study.

## 2.1 Prerequisites for the IDA plan

### 2.1.1 Analysis strategy

We assume that the aims of the study are to fit a diagnostic prediction model and to describe the functional form of each predictor. These aims are addressed by fitting a logistic regression model with bacteremia status as the dependent variable.

Based on domain expertise, the predictors are grouped by their assumed importance to predict bacteremia. Variables with known strong associations with bacteremia are age (AGE), leukocytes (WBC), blood urea neutrogen (BUN), creatinine (CREA), thrombocytes (PLT), and neutrophiles (NEU) and these predictors will be included in the model as key predictors. Predictors of medium importance are potassium (POTASS), and some acute-phase related parameters such as fibrinogen (FIB), C-reactive protein (CRP), aspartate transaminase (ASAT), alanine transaminase (ALAT), and gamma-glutamyl transpeptidase (GGT). All other predictors are of minor importance.

Continuous predictors should be modelled by allowing for flexible functional forms, where for all key predictors four degrees of freedom will be spent, and for predictors of medium and minor importance, three or two degrees of freedom should be foreseen at maximum, respectively. The decision on whether to use only key predictors, or to consider predictors also from the predictor sets of medium or minor importance depends on results of data screening, but will be made before uncovering the association of predictors with the outcome variable.

An adequate strategy to cope with missing values will also be chosen after screening the data. Candidate strategies are omission of predictors with abundant missing values, complete case analysis, single value imputation or multiple imputation with chained equations.

### 2.1.2 Data dictionary

The data dictionary of the bacteremia data set consists of columns for variable names, variable labels, scale of measurement (continuous or categorical), units, plausibility limits, and remarks:

| variable | label | scale\_of\_measurement | units | remark | from\_paper |
| --- | --- | --- | --- | --- | --- |
| ID | Patient Identification | nominal | 1-14691 | NA | NA |
| SEX | Patient sex | nominal | 1=male, 2=female | NA | Female: Male |
| AGE | Patient Age | continuous | years | Alter=German age | Albumin (G/L) 14,187 33.7 (28?39.3) 32 (26.925?36.7) ,0.0001 0.568 |
| MCV | Mean corpuscular volume | continuous | pg | NA | MCV (pg) 15,941 88.1 (84.6?91.9) 88.6 (84.8?92.5) 0.0044 0.524 |
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| HCT | Haematocrit | continuous | % | NA | Haematocrit (%) 15,941 34.4 (29.8?39.2) 33.1 (28.5?37.5) ,0.0001 0.561 |
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| PAMY | Pancreas amylase | continuous | U/L | NA | PAMY (U/L) |
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| AP | Alkaline phosphatase | continuous | U/L | NA | ALP (U/L) 14,479 83 (62?120) 100 (72?164) ,0.0001 0.601 |
| ASAT | Aspartate transaminase | continuous | U/L | NA | ASAT (U/L) 14,745 31 (22?56) 37 (24?70.25) ,0.0001 0.558 |
| ALAT | Alanin transaminase | continuous | U/L | NA | Age 15,985 58 (42?69) 65 (53?74) ,0.0001 0.611 |
| GGT | Gamma-glutamyl transpeptidase | continuous | G/L | NA | GGT (G/L) 14,629 48 (25?112) 73 (35?180) ,0.0001 0.599 |
| LDH | Lactate dehydrogenase | continuous | U/L | NA | LDH (U/L) 14,150 239 (186?334) 249 (199?331.5) 0.0037 0.527 |
| CK | Creatinine kinases | continuous | U/L | NA | CK (U/L) 13,763 82 (42?190) 67 (34?142) ,0.0001 0.557 |
| GLU | Glucoses | continuous | mg/dl | NA | Glucoses (mg/dl) 11,350 113 (96?137) 121 (99?154) ,0.0001 0.559 |
| TRIG | Triclyceride | continuous | mg/dl | NA | Triglyceride (mg/dl) 10,549 115 (83?164) 118 (85?170) n.s. |
| CHOL | Cholesterol | continuous | mg/dl | NA | Cholesterol (mg/dl) 10,565 146 (114?183) 132 (105?171) ,0.0001 0.564 |
| CRP | C-reactive protein | continuous | mg/dl | NA | CRP (mg/dl) 15,820 8.39 (2.77?16.15) 11.68 (5.22?21.19) ,0.0001 0.596 |
| BASOR | Basophile ratio | continuous | % | NA | Basophiles (G/L) 15,827 0 (0?0) 0 (0?0) ,0.0001 0.47 |
| EOSR | Eosinophil ratio | continuous | % | NA | Eosinophil % 15,831 0.1 (0?0.2) 0 (0?0.1) ,0.0001 0.626 |
| LYMR | Lymphocyte ratio | continuous | % (mg/dl) | NA | Lymphocytes % (mg/dl) 15,250 11.6 (7.1?18.6) 7 (4.15?12.2) ,0.0001 0.674 |
| MONOR | Monocyte ratio | continuous | % | NA | Monocytes % 15,268 8.1 (5.8?10.7) 6.1 (3.5?8.8) ,0.0001 0.645 |
| NEU | Neutrophiles | continuous | G/L | NA | Neutrophiles (G/L) 15,181 7.3 (4.6?10.7) 8.4 (5.23?12.7) ,0.0001 0.559 |
| NEUR | Neutrophile ratio | continuous | % | NA | Neutrophiles % 15,181 77.7 (68.7?84.6) 85.8 (78.3?90.5) ,0.0001 0.696 |
| PDW | Platelet distribution width | continuous | % | NA | PDW (%) 14,776 12 (10.8?13.4) 12.1 (10.8?13.7) n.s. |
| RBC | Red blood count | continuous | T/L | NA | RBC (T/L) 15,478 3.9 (3.4?4.5) 3.7 (3.2?4.2) ,0.0001 0.567 |
| WBC | White blood count | continuous | G/L | NA | WBC (G/L) 15,477 9.58 (6.64?13.46) 10.205 (6.61?14.86) n.s. |
| BloodCulture | Blood culture result for bacteremia | nominal | no, yes | NA | NA |

### 2.1.3 Domain expertise

The demographic variables age and sex are are chosen as the structural variables in this analysis for illustration purposes, since they are commonly considered important for describing a cohort in health studies. Key predictors and predictors of medium importance are as defined above. Laboratory analyses always bear the risk of machine failures, and hence missing values are a frequent challenge. This may differ between laboratory variables, but no a priori estimate about the expected proportion of missing values can be assumed. As most predictors measure concentrations of chemical compounds or cell counts, skewed distributions are expected. Some predictors describe related types of cells or chemical compounds, and hence some correlation between them is to be expected. For example, leukocytes consist of five different types of blood cells (BASO, EOS, NEU, LYM and MONO), and the sum of the concentration of these types approximately (but not exactly) gives the leukocyte count, which is recorded in the variable WBC. Moreover, these variables are given as absolute counts and as percentages of the sum of the five variables, which creates some correlation. Some laboratory variables differ by sex and age, but the special selection of patients for this study (suspicion of bacteremia) may distort or alter the expected correlations with sex and age.

For the purpose of stratifying IDA results by age, age will be categorized into the following three groups: [16, 50], (50, 65], (65, 101].

The predictor grouping is defined here:

## 2.2 IDA plan

### 2.2.1 M1: Prevalence of missing values

Numbers and proportions of missing values will be reported for each predictor separately (M1). Type of missingness has not been recorded.

### 2.2.2 M2: Complete cases

The number of available complete cases (outcome and predictors) will be reported when considering:

1. the outcome variable (BC)
2. outcome and structural variables (BC, AGE, SEX)
3. outcome and key predictors only (BC, AGE, WBC, BUN, CREA, PLT, NEU)
4. outcome, key predictors and predictors of medium importance (BC, AGE, WBC, BUN, CREA, PLT, NEU, POTASS, FIB, CRP, ASAT, ALAT, GGT)
5. outcome and all predictors.

### 2.2.3 M3: Patterns of missing values

Patterns of missing values will be investigated by:

1. computing a table of complete cases (for the three predictor sets described above) for strata defined by the structural variables age and sex,
2. constructing a dendrogram of missing values to explore which predictors tend to be missing together.

### 2.2.4 U1: Univariate descriptions: categorical variables

For sex and bacteremia status, the frequency and proportion of each category will be described numerically.

### 2.2.5 U2: Univariate descriptions: continuous variables

For all continuous predictors, combo plots consisting of high-resolution histograms, boxplots and dotplots will be created. Because of the expected skew distribution, combo plots will also be created for log-transformed predictors.

As numerical summaries, minimum and maximum values, main quantiles (5th, 10th, 25th, 50th, 75th, 90th, 95th), and the first four moments (mean, standard deviation, skewness, curtosis) will be reported. The number of distinct values and the five most frequent values will be given, as well as the concentration ratio (ratio of frequency of most frequent value and mean frequency of each unique value).

Graphical and parametric multivariate analyses of the predictor space such as cluster analyses or the computation of variance inflation factors are heavily influenced by the distribution of the predictors. In order to make this set of analyses more robust to highly influential points or areas of the predictor support, some predictors may need transformation (e.g. logarithmic). We will compute the correlation of the untransformed and log-transformed predictors with normal deviates. Since some predictors may have values at or close to 0, we will consider the pseudolog transformation (Johnson, 1949) which provides a smooth transition from linear (close to 0) to logarithmic (further away from 0). The transformation has a parameter which we will optimize separately for each predictor in order to achieve an optimal approximation to a normal distribution monitored via the correlation of normal deviates with the transformed predictor. For those predictors for which the pseudolog-transformation increases correlation with normal deviates by at least 0.2 units of the correlation coefficient, the pseudolog-transformed predictor will be used in multivariate IDA instead of the respective original predictor. For those predictors, histograms and boxplots will be provided on both the original and the transformed scale.

### 2.2.6 V1: Multivariate descriptions: associations of predictors with structural variables

A scatterplot of each predictor with age, with different panels for males and females will be constructed. Associated Spearman correlation coefficients will be computed.

### 2.2.7 V2: Multivariate descriptions: correlation analyses

A matrix of Spearman correlation coefficients between all pairs of predictors will be computed and described numerically as well as by means of a heatmap.

### 2.2.8 VE1: Multivariate descriptions: comparing nonparametric and parametric predictor correlation

A matrix of Pearson correlation coefficients will be computed. Predictor pairs for which Spearman and Pearson correlation coefficients differ by more than 0.1 correlation units will be depicted in scatterplots.

### 2.2.9 VE2: Variable clustering

A variable clustering analysis will be performed to evaluate which predictors are closely associated. A dendrogram groups predictors by their correlation. Scatterplots of pairs of predictors with Spearman correlation coefficients greater than 0.8 will be created.

### 2.2.10 VE3: Redundancy

Variance inflation factors will be computed between the candidate predictors. This will be done for the three possible candidate models, and using all complete cases in the respective candidate predictor sets. Redundancy will further be explored by computing parametric additive models for each predictor in the three candidate models.

# 3. Results of IDA: Missing values

## 3.1 M1: Prevalence of missing values

Number and percentage of missingness for each predictor, sorted by descending missingness proportion.

### 3.1.1 Outcome and Structural variables

| Variable | Missing (count) | Missing (%) |
| --- | --- | --- |
| BACTEREMIA | 0 | 0.00 |
| AGE | 0 | 0.00 |
| SEX | 0 | 0.00 |

### 3.1.2 Lab parameters

| Variable | Missing (count) | Missing (%) |
| --- | --- | --- |
| Pancreas amylase (U/L) | 7114 | 48.42 |
| Triclyceride (mg/dl) | 5061 | 34.45 |
| Cholesterol (mg/dl) | 5045 | 34.34 |
| Glucoses (mg/dl) | 4192 | 28.53 |
| Amylase (U/L) | 3913 | 26.64 |
| Lipases (U/L) | 3699 | 25.18 |
| Uric acid (mg/dl) | 3061 | 20.84 |
| Fibrinogen (mg/dl) | 2567 | 17.47 |
| Activated partial thromboplastin time (sec) | 2549 | 17.35 |
| Normotest (%) | 2467 | 16.79 |
| Cholinesterase (kU/L) | 2447 | 16.66 |
| Creatinine kinases (U/L) | 2080 | 14.16 |
| Potassium (mmol/L) | 2008 | 13.67 |
| Magnesium (mmol/L) | 1869 | 12.72 |
| Lactate dehydrogenase (U/L) | 1714 | 11.67 |
| Albumin (G/L) | 1676 | 11.41 |
| Total protein (G/L) | 1583 | 10.78 |
| Bilirubin (mg/dl) | 1441 | 9.81 |
| Alkaline phosphatase (U/L) | 1400 | 9.53 |
| Sodium (mmol/L) | 1282 | 8.73 |
| Calcium (mmol/L) | 1276 | 8.69 |
| Gamma-glutamyl transpeptidase (G/L) | 1262 | 8.59 |
| Phosphate (mmol/L) | 1242 | 8.45 |
| Aspartate transaminase (U/L) | 1154 | 7.86 |
| Platelet distribution width (%) | 1102 | 7.50 |
| Alanin transaminase (U/L) | 987 | 6.72 |
| Basophile ratio (%) | 732 | 4.98 |
| Eosinophil ratio (%) | 732 | 4.98 |
| Lymphocyte ratio (% (mg/dl)) | 732 | 4.98 |
| Monocyte ratio (%) | 732 | 4.98 |
| Neutrophile ratio (%) | 732 | 4.98 |
| Neutrophiles (G/L) | 728 | 4.96 |
| Mean platelet volume (fl) | 702 | 4.78 |
| White blood count (G/L) | 462 | 3.14 |
| Red blood count (T/L) | 461 | 3.14 |
| Lymphocytes (G/L) | 262 | 1.78 |
| Monocytes (G/L) | 246 | 1.67 |
| Blood urea nitrogen (mg/dl) | 172 | 1.17 |
| Creatinine (mg/dl) | 159 | 1.08 |
| C-reactive protein (mg/dl) | 155 | 1.06 |
| Basophiles (G/L) | 146 | 0.99 |
| Eosinophils (G/L) | 135 | 0.92 |
| Red blood cell distribution width (%) | 56 | 0.38 |
| Mean corpuscular volume (pg) | 42 | 0.29 |
| Haematocrit (%) | 42 | 0.29 |
| Blood platelets (G/L) | 42 | 0.29 |
| Mean corpuscular hemoglobin (fl) | 42 | 0.29 |
| Mean corpuscular hemoglobin concentration (g/dl) | 42 | 0.29 |
| Haemoglobin (G/L) | 41 | 0.28 |
| Patient Age (years) | 0 | 0.00 |

## 3.2 M2: Complete cases

Number of available complete cases (outcome and predictors):

| Set | Complete (count) | Complete (%) |
| --- | --- | --- |
| Outcome | 14691 | 100.0 |
| Outcome and structural variables | 14691 | 100.0 |
| Outcome and key predictors only | 13793 | 93.9 |
| Outcome key predictors and predictors of medium importance | 9389 | 63.9 |
| Outcome and all predictors | 3979 | 27.1 |

## 3.3 ME1: Patterns of missing values

### 3.3.1 Complete cases by strata defined by structural variables

| Set | Complete (count) | Complete (%) |
| --- | --- | --- |
| female - (50, 65] |
| All predictors | 1468 | 93.0 |
| Key predictors | 1468 | 93.0 |
| Medium importance predictors | 1075 | 68.1 |
| male - (65, 101] |
| All predictors | 2793 | 94.3 |
| Key predictors | 2793 | 94.3 |
| Medium importance predictors | 2014 | 68.0 |
| male - [16, 50] |
| All predictors | 2744 | 94.5 |
| Key predictors | 2744 | 94.5 |
| Medium importance predictors | 1993 | 68.7 |
| female - [16, 50] |
| All predictors | 2309 | 93.8 |
| Key predictors | 2309 | 93.8 |
| Medium importance predictors | 1656 | 67.3 |
| male - (50, 65] |
| All predictors | 2504 | 93.7 |
| Key predictors | 2504 | 93.7 |
| Medium importance predictors | 1862 | 69.7 |
| female - (65, 101] |
| All predictors | 1975 | 93.4 |
| Key predictors | 1975 | 93.4 |
| Medium importance predictors | 1389 | 65.7 |

### 3.3.2 Dendrogram of missingness indicators

The dendrogram depicts the results of a cluster analysis using the complete linkage method based on the percentage of discordant missing indicators. (This percentage was computed via the squared Euclidian distance of missingness indicators between predictors.) The vertical axis shows the distance between two clusters, which is given by the maximum distance between any element of the first and the second clusters. For example, if two clusters are merged at a height of 25 it means that in 25% of the observations the missingness indicators of the most discordant predictors contained in the two clusters are discordant.

The numbers in brackets are the percentages of missing observations for each predictor.

|  |
| --- |
| Clustered variables by percentage observations discordantly missing [by variable percentage missing] |

# 4. Pseudo-log transformations

## 4.1 Introduction

This supplemental section illustrates how pseudo-log transformations can be used to transform skewed distributions towards normality.

The transformation is a pseudo-logarithmic transformation mentioned by (Johnson 1949). It has the following advantages over ordinary logarithmic transformations:

* it is defined also for as
* it is a signed logarithmic transformation, and is defined also for negative values as

Of course, this comes at the cost of deviation from the logarithmic transformation in terms of interpretability.

The parameter may be used to adapt the transformation to a specific range of an empirical distribution.

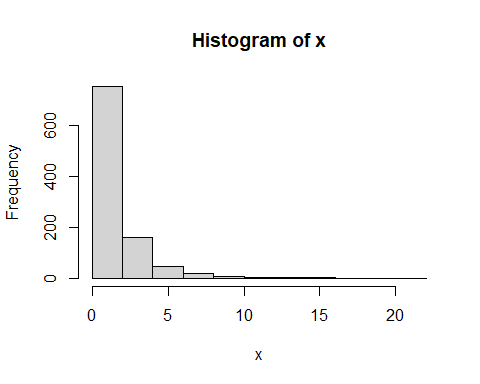
We define the pseudo-logarithmic transformation in R as:

pseudo\_log <- function(x, sigma=1, base=10) asinh(x/(2 \* sigma))/log(base)  
inv\_pseudo\_log <- function(x, sigma=1, base=10) 2 \* sigma \* sinh(x \* log(base))

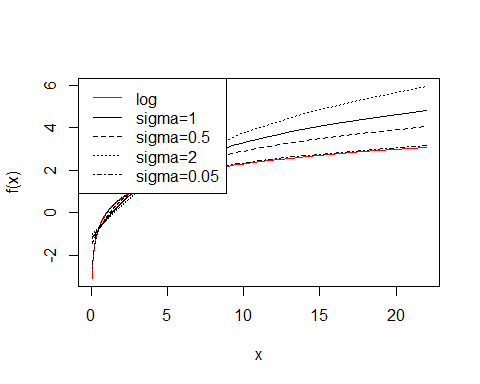
## 4.2 Impact of choice of

Next, we investigate how the parameter impacts the result of the transformation. We assume that follows a log-normal distribution, and we will show results of with different choices of . We center and scale before plotting.

p <- seq(0.001, 0.999, 0.001)  
x <- exp(qnorm(p, mean=0, sd=1))  
  
hist(x)

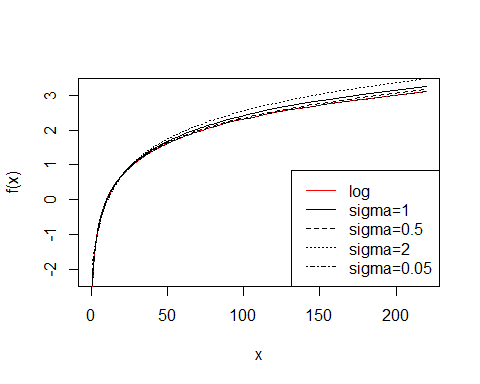


y <- cbind(log(x), scale(pseudo\_log(x, 1)), scale(pseudo\_log(x,0.5)), scale(pseudo\_log(x, 2)), scale(pseudo\_log(x, 0.05)))  
  
  
plot(x, y[,2], type="l", ylab="f(x)", ylim=range(y))  
lines(x, y[,1], col="red")  
lines(x, y[,3], type="l", lty=2)  
lines(x, y[,4], type="l", lty=3)  
lines(x, y[,5], type="l", lty=4)  
legend("topleft", lty=c(1,1,2,3,4), col=c("red","black","black","black","black"),   
 legend=c("log", "sigma=1", "sigma=0.5", "sigma=2", "sigma=0.05"))



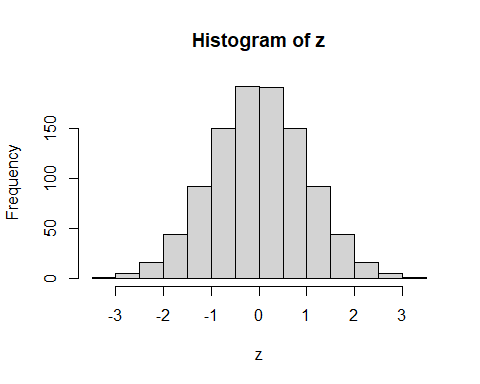
In the next code chunk, we multiply by 10 and repeat the exercise. We learn that the transformations become more similar and the choice of less relevant.

x <- x\*10  
  
y <- cbind(scale(log(x)), scale(pseudo\_log(x, 1)), scale(pseudo\_log(x,0.5)), scale(pseudo\_log(x, 2)), scale(pseudo\_log(x, 0.05)))  
  
  
plot(x, y[,2], type="l", ylab="f(x)")  
lines(x, y[,1], col="red")  
lines(x, y[,3], type="l", lty=2)  
lines(x, y[,4], type="l", lty=3)  
lines(x, y[,5], type="l", lty=4)  
legend("bottomright", lty=c(1,1,2,3,4), col=c("red","black","black","black","black"),   
 legend=c("log", "sigma=1", "sigma=0.5", "sigma=2", "sigma=0.05"))

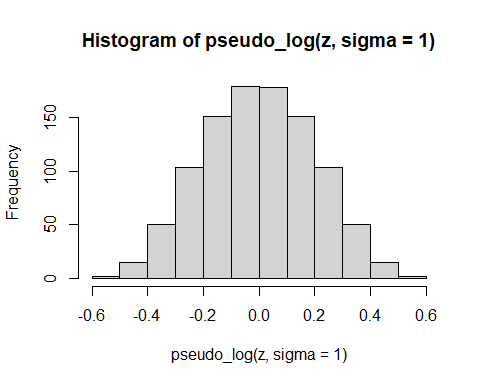


Finally, we apply the pseudo-logarithmic transformation to the original normal deviates. We learn that a higher value for the parameter makes the distribution ‘slimmer’ while a lower value makes it ‘fatter’, and it is even possible to induce bimodality with low values of sigma:

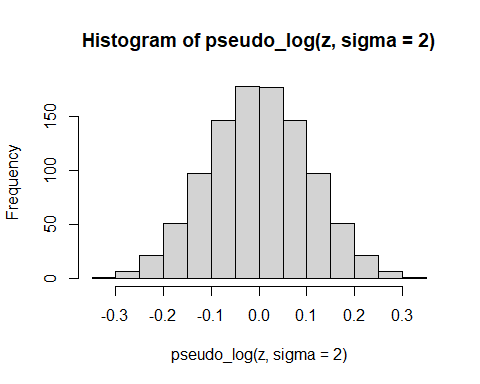
z <- qnorm(p, mean=0, sd=1)  
hist(z)



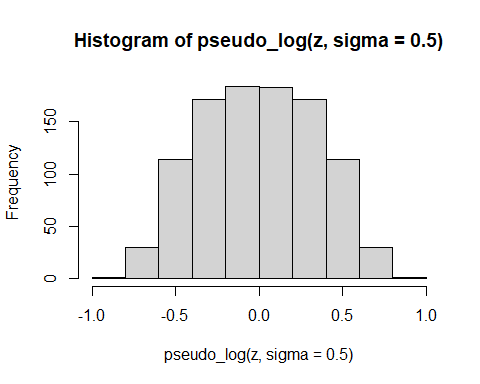
hist(pseudo\_log(z, sigma=1))



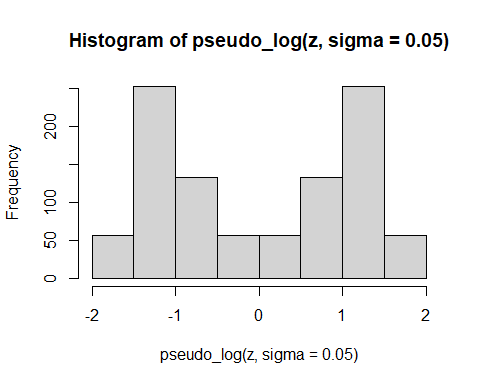
hist(pseudo\_log(z, sigma=2))



hist(pseudo\_log(z, sigma=0.5))



hist(pseudo\_log(z, sigma=0.05))



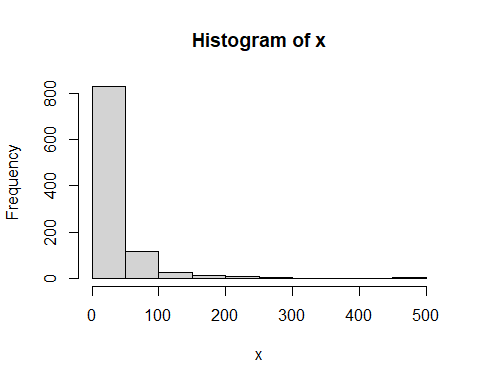
## 4.3 Finding a parameter that best achieves normality

Any test statistic for testing normality could be chosen to find a suitable value of that induces normality into the transformed values. Here we use the (Pearson) correlation coefficient to compare the empirical distribution with normal deviates.

### 4.3.1 Deviates from log normal distribution

We simulate from a shifted log normal distribution and evaluate the value of that optimizes agreement with a normal distribution:

x<-sort(exp(rnorm(1000)+3))  
  
hist(x)



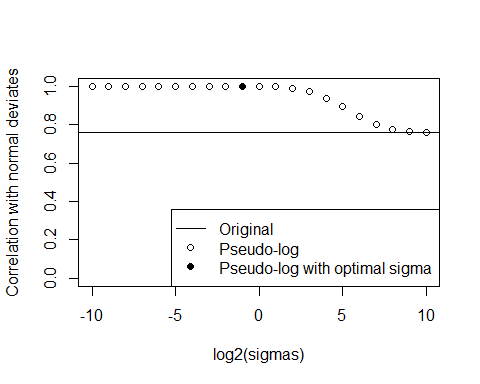
sigmas <- 2\*\*seq(-10, 10, 1)  
origcor <- cor(qnorm((1:length(x)-0.5)/length(x)), x)  
  
ncorx <- sapply(sigmas, function(X) cor(qnorm((1:length(x)-0.5)/length(x)), pseudo\_log(x,X)))  
  
cat("Optimal sigma: ")

Optimal sigma:

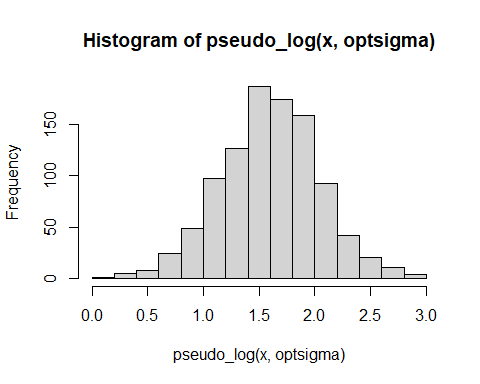
(optsigma<-sigmas[ncorx==max(ncorx)])

[1] 0.5

plot(log2(sigmas), ncorx, ylab="Correlation with normal deviates", ylim=c(0,1))  
points(log2(sigmas)[ncorx==max(ncorx)], max(ncorx), pch=19)  
abline(h=origcor)  
legend("bottomright", lty=c(1, NA,NA), pch=c(NA,1,19), legend=c("Original", "Pseudo-log", "Pseudo-log with optimal sigma"))  
box()



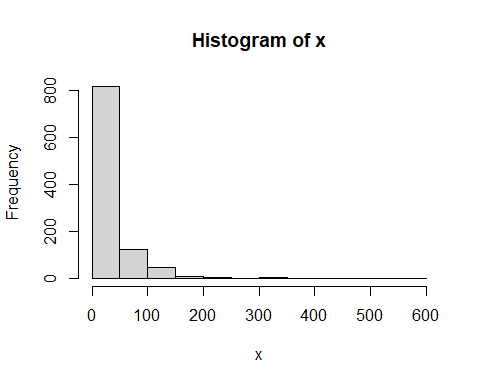
hist(pseudo\_log(x, optsigma))



### 4.3.2 Deviates from exponential distribution

Also with an exponential distribution, the pseudo-logarithm may achieve a better agreement with a normal:

x<-sort(exp(rnorm(1000)+3))  
  
hist(x)



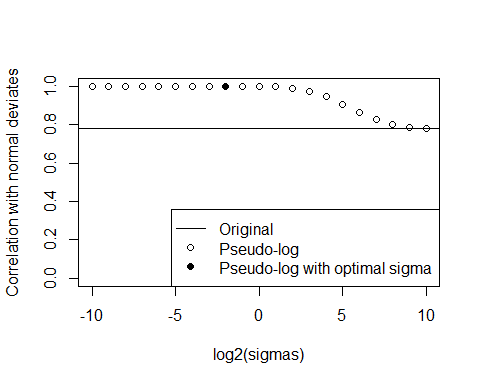
sigmas <- 2\*\*seq(-10, 10, 1)  
origcor <- cor(qnorm((1:length(x)-0.5)/length(x)), x)  
  
ncorx <- sapply(sigmas, function(X) cor(qnorm((1:length(x)-0.5)/length(x)), pseudo\_log(x,X)))  
  
cat("Optimal sigma: ")

Optimal sigma:

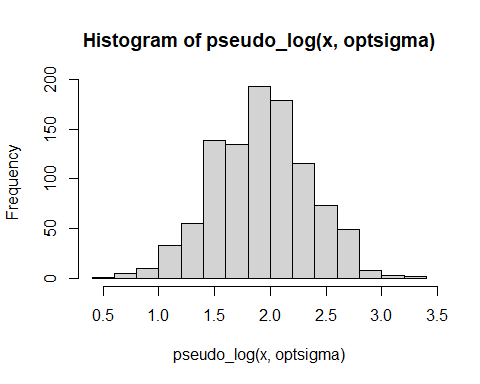
(optsigma<-sigmas[ncorx==max(ncorx)])

[1] 0.25

plot(log2(sigmas), ncorx, ylab="Correlation with normal deviates", ylim=c(0,1))  
points(log2(sigmas)[ncorx==max(ncorx)], max(ncorx), pch=19)  
abline(h=origcor)  
legend("bottomright", lty=c(1, NA,NA), pch=c(NA,1,19), legend=c("Original", "Pseudo-log", "Pseudo-log with optimal sigma"))  
box()



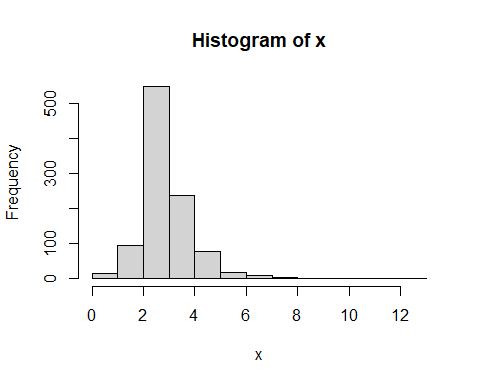
hist(pseudo\_log(x, optsigma))



### 4.3.3 Deviates from mixture distribution

Now we mix a normal, lognormal and exponential distribution:

x1 <- scale(rnorm(1000))  
x2 <- scale(rexp(1000))  
x3 <- scale(exp(rnorm(1000)))  
  
p1 <- rbinom(1000, 1, 0.33)  
p2 <- rbinom(1000, 1, 0.5)  
  
x<-p1\*x1 + (1-p1)\*(p2\*x2+(1-p2)\*x3)  
x <- x-min(x)  
x<-sort(x)  
  
hist(x)



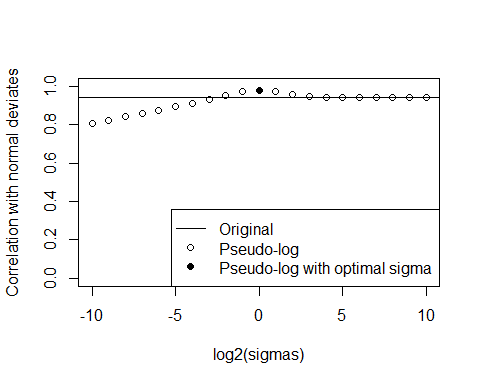
sigmas <- 2\*\*seq(-10, 10, 1)  
origcor <- cor(qnorm((1:length(x)-0.5)/length(x)), x)  
  
ncorx <- sapply(sigmas, function(X) cor(qnorm((1:length(x)-0.5)/length(x)), pseudo\_log(x,X)))  
  
cat("Optimal sigma: ")

Optimal sigma:

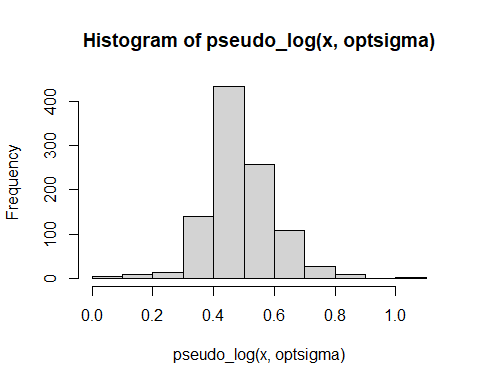
(optsigma<-sigmas[ncorx==max(ncorx)])

[1] 1

plot(log2(sigmas), ncorx, ylab="Correlation with normal deviates", ylim=c(0,1))  
points(log2(sigmas)[ncorx==max(ncorx)], max(ncorx), pch=19)  
abline(h=origcor)  
legend("bottomright", lty=c(1, NA,NA), pch=c(NA,1,19), legend=c("Original", "Pseudo-log", "Pseudo-log with optimal sigma"))  
box()



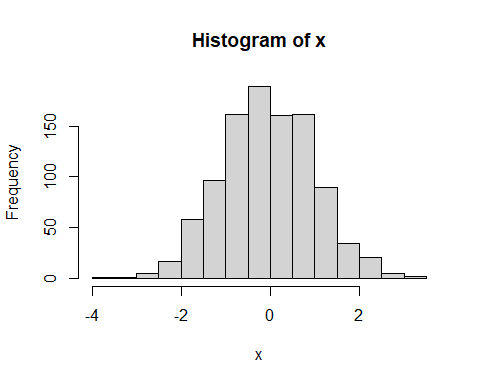
hist(pseudo\_log(x, optsigma))



### 4.3.4 Normal deviates

With simulated normal deviates, the pseudo-logarithm cannot improve the already perfect normality.

x<-sort(rnorm(1000))  
  
hist(x)



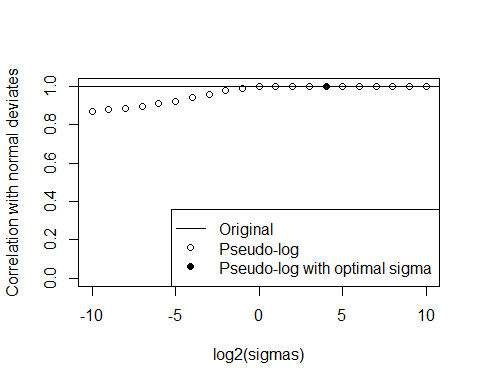
sigmas <- 2\*\*seq(-10, 10, 1)  
origcor <- cor(qnorm((1:length(x)-0.5)/length(x)), x)  
  
ncorx <- sapply(sigmas, function(X) cor(qnorm((1:length(x)-0.5)/length(x)), pseudo\_log(x,X)))  
  
cat("Optimal sigma: ")

Optimal sigma:

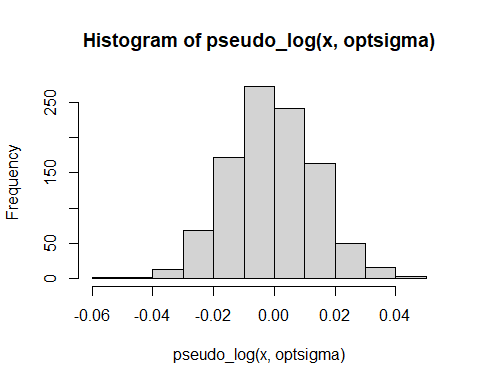
(optsigma<-sigmas[ncorx==max(ncorx)])

[1] 16

plot(log2(sigmas), ncorx, ylab="Correlation with normal deviates", ylim=c(0,1))  
points(log2(sigmas)[ncorx==max(ncorx)], max(ncorx), pch=19)  
legend("bottomright", lty=c(1, NA,NA), pch=c(NA,1,19), legend=c("Original", "Pseudo-log", "Pseudo-log with optimal sigma"))  
abline(h=origcor)  
box()



hist(pseudo\_log(x, optsigma))



Johnson, N. L. 1949. “Systems of Frequency Curves Generated by Methods of Translation.” *Biometrika* 36 (1/2): 149–76. <http://www.jstor.org/stable/2332539>.

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