# Supplementary document - The Performance of Hypotension Prediction Index May Be Overestimated Due to Selection Bias

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## Contents



## Setup

```
library(pROC)
library(tidyverse)
# install.packages("faux") # used to simulate data

# A few extra packages are used to create the simulation figure. We load these in
# the relevant section.

theme_set(theme_minimal(base_size = 12))
```

## Simulation of the selection problem

> **OBS:** This simulation does not attempt to create realistic data or to accurately preset how Hypotension Prediciton Index may have been developed.

We simulate 1000 paired observations, to show what the data selection described in the model-development paper does to the performance of a model that uses MAP as a predictor.

The specific parameters of the simulation are simply chosen to place most data in a relevant interval: between 55 and 95 mmHg. The correlation coefficient (`r = 0.6`) is chosen to give MAP a modest predictive power, similar to what is presented by Davies *et al* (http://doi.org/10.1213/ANE.0000000000004121) However, any reasonable distribution of data, and any correlation coefficient between 0 and ~0.9, will convey the intended message.

```
set.seed(12345)
correlated_map <- faux::rnorm_multi(n = 1000,
                                    mu = c(75, 75),
                                    sd = c(10, 10),
                                    r = 0.6,
                                    # "map_predictor" represents the current map value
                                    # "map_outcome" represents what map is 5 minutes from now.
                                    varnames = list("map_predictor", "map_outcome")
                                    )
```

We filter the simulated data to remove observations where the predictor MAP is below 65 mmHg. This reduces the AUC of all analyses, but the difference between the biased and unbiased selections remain clear.

We also remove a few extreme points simply to reduce white space in the plots. Again, this simulation is not intended to mimic real data!

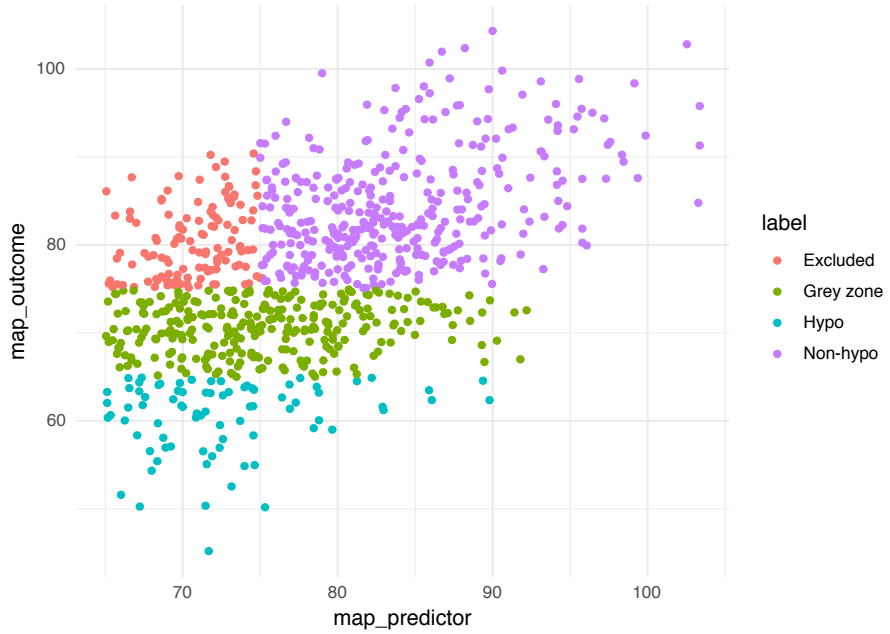
```
d <- filter(correlated_map,
        # We remove points where map is below 65 in the predictor
        map_predictor > 65,
        # Remove extreme points
        map_predictor < 105,
        map_outcome > 45,
        map_outcome < 105
        )
```

We label the relevant zones of the data. Each row is the combination of an event (hypotensive or non-hypotensive) and the sample used to predict the event (`map_predictor`).

```
d <- mutate(d,
        # If map_outcome is < than 65, this is represented as a hypotensive event
        hypo = map_outcome < 65,
        # If map_outcome is between 65 and 75, this is a greyzone event.
        grey = map_outcome >= 65 & map_outcome < 75,
        # If map_outcome and map_predictor is >= 75, this is a nonevent.
        nonhypo = map_outcome >= 75 & map_predictor >= 75
        )
```

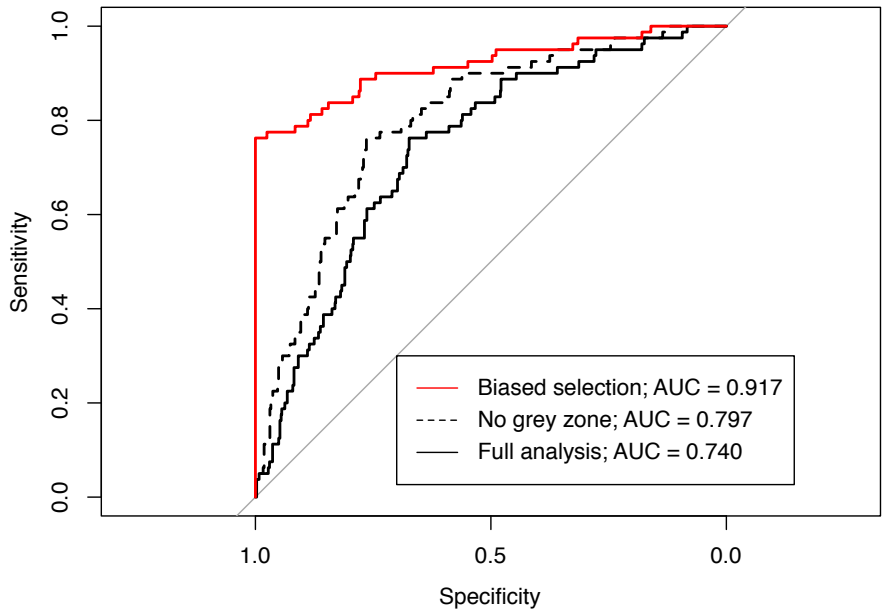
Here is a plot to show the applied labels.

```r
ggplot(d, aes(map_predictor, map_outcome, color = case_when(hypo ~ "Hypo",
                                                            grey ~ "Grey zone",
                                                            nonhypo ~ "Non-hypo",
                                                            TRUE ~ "Excluded"))) +
    geom_point() +
    labs(color = "label")
```




Now we can make the ROC analyses.

```r
# With all data
roc_analysis_full <- roc(hypo~map_predictor, data = d)
# Excluding grey zone
roc_analysis_grey <- roc(hypo~map_predictor, data = filter(d, !grey))
# Include only data that is either event or non-event per model-development definition
roc_analysis_biased <- roc(hypo~map_predictor, data = filter(d, hypo | nonhypo))

plot(roc_analysis_full)
plot(roc_analysis_grey, lty = 2, add = TRUE)
plot(roc_analysis_biased, col = "red", add = TRUE)
legend(
    x = 0.7, y = 0.3,
    legend = c(
        sprintf("Biased selection; AUC = %.3f", auc(roc_analysis_biased)),
        sprintf("No grey zone; AUC = %.3f", auc(roc_analysis_grey)),
        sprintf("Full analysis; AUC = %.3f", auc(roc_analysis_full))
    ),
    lty = c(1, 2, 1),
    col = c("red", "black", "black")
)
```



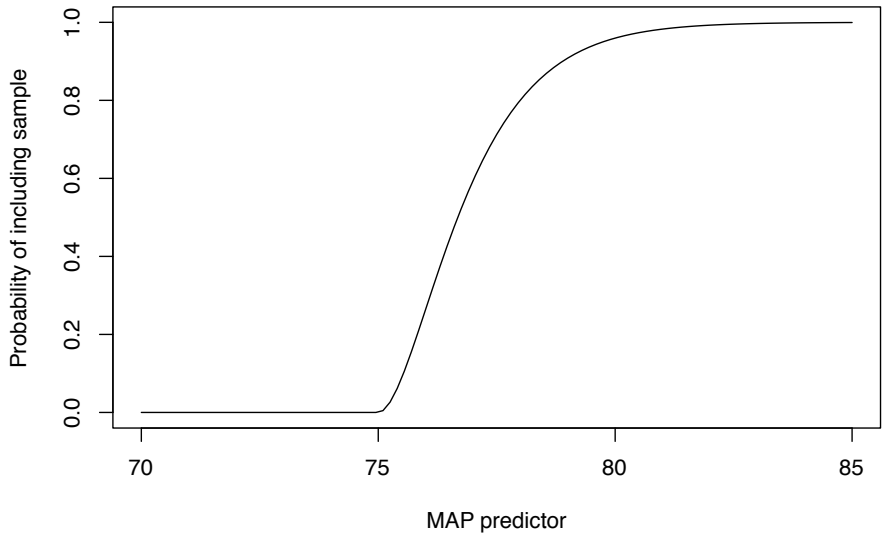

In the end of this document we paste the remaining code used the create the paper's figure 3.

## The ROC curve shape in the simulations differs slightly form those presented in the model-develop paper.

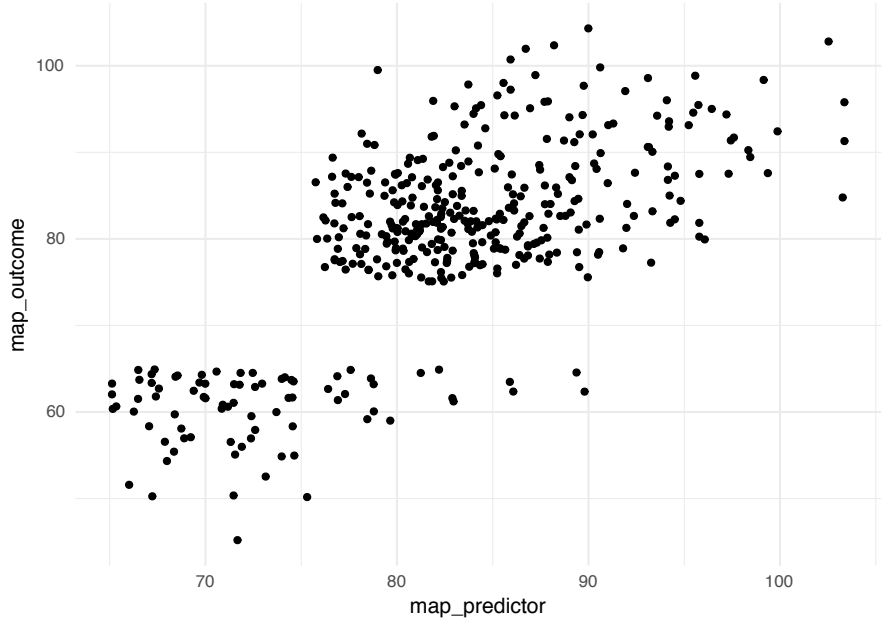
The ROC curve in the paper's fig. 2C shows a distinct decrease in specificity when the map threshold is $> 75$ mmHg. In the model-development paper, the decrease in specificity is more gradual. (fig. 1). This difference can be explained by a combination of two effects. First, in the model development, all MAP values in a 30-minute period had to be $> 75$ mmHg; due to the variation in MAP over 30 minutes, any specific measurement (here, the midpoint) is unlikely to be very close to 75 mmHg. Second, although HPI may be driven predominantly by MAP, other predictors influence HPI as well.

Here, we demonstrate the first explanation. We select non-hypotensive events based to the predictor MAP's distance from 75 mmHg. We use a gamma distribution to determine the probability that an observation should be included. (This is just one of many ways of making a simulation where non-hypotensive events with a predictor MAP close to 75 mmHg are unlikely).

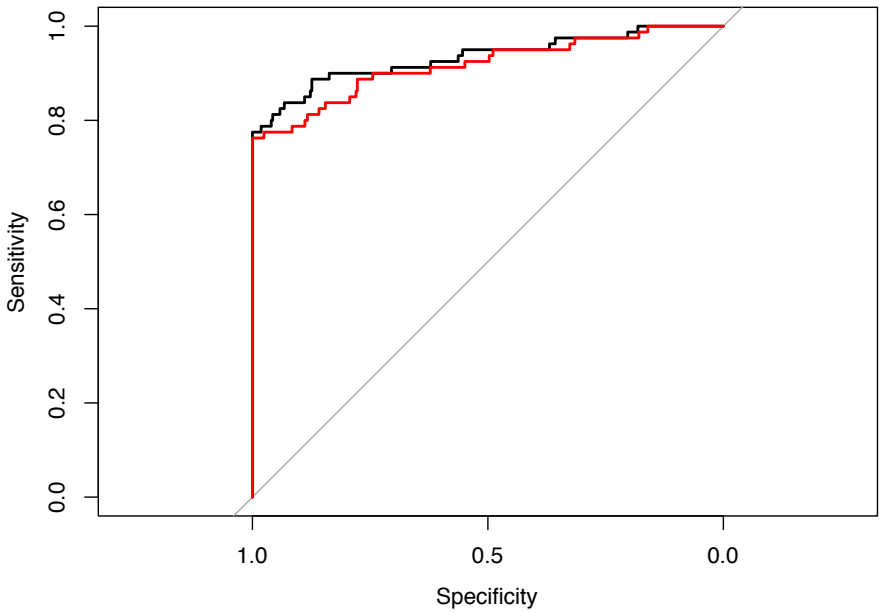
```
curve(pgamma(x-75, shape =2, rate = 1), 70, 85,
      xlab = "MAP predictor",
      ylab = "Probability of including sample")
```




```r
sampled <- rbernoulli(n=nrow(d), p = pgamma(d$map_predictor-75, shape = 2, rate = 1))

d2 <- filter(d, hypo | (nonhypo & sampled))

ggplot(d2, aes(map_predictor, map_outcome)) +
    geom_point()
```




```r
roc_d2 <- roc(hypo ~ map_predictor, data = d2)
plot(roc_d2)
plot(roc_analysis_biased, add = TRUE, col = "red")
```




## Creating a logistic regression model with only one relevant predictor

Here is a simple demonstration of how a logistic regression based prediction model could get its entire predictive ability from a single predictor, despite including multiple predictors.

In this example, we simulate a scenario, where only MAP is a relevant predictor of hypotension. The remaining variables are random noise. In reality, it is of course entirely possible that HPI is also relevantly influenced by other variables than MAP.

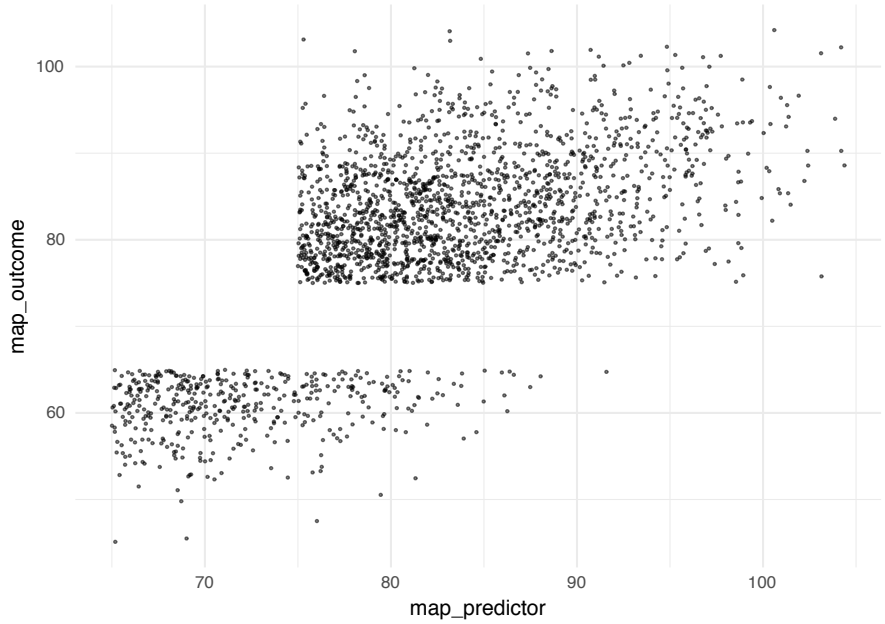
We generate data identically to presented above, only this time we generate 5000 observations.

```
library(pROC)

set.seed(1)
correlated_map_large <-
    faux::rnorm_multi(
        n = 5000,
        mu = c(75, 75),
        sd = c(10, 10),
        r = 0.6,
        varnames = list("map_predictor", "map_outcome")
    ) |>
    as_tibble() |>
    filter(map_predictor > 65,
           map_predictor < 105,
           map_outcome > 45,
           map_outcome < 105)
```

```r
d_large <- mutate(
    correlated_map_large,
    hypo = map_outcome < 65,
    grey = map_outcome >= 65 & map_outcome < 75,
    nonhypo = map_outcome >= 75 & map_predictor >= 75
)

d_model <- filter(d_large, hypo | nonhypo)

n_obs <- nrow(d_model)
```

After applying the biased data selection, we have 2209 observations.

```r
ggplot(d_model, aes(map_predictor, map_outcome)) +
    geom_point(size = 0.5, alpha = 0.5)
```




In addition to MAP, we will add 9 variables that convey no information about the risk of future hypotension. We simply draw these independently from a normal distribution. We use a standard deviation of 10, to put the random variables on the same scale as MAP.

```r
d_model <- mutate(d_model,
                  var1 = rnorm(n = n_obs, sd = 10),
                  var2 = rnorm(n = n_obs, sd = 10),
                  var3 = rnorm(n = n_obs, sd = 10),
                  var4 = rnorm(n = n_obs, sd = 10),
                  var5 = rnorm(n = n_obs, sd = 10),
                  var6 = rnorm(n = n_obs, sd = 10),
                  var7 = rnorm(n = n_obs, sd = 10),
```

```
                  var8 = rnorm(n = n_obs, sd = 10),
                  var9 = rnorm(n = n_obs, sd = 10),
                  .after = hypo)

head(d_model)
```

```
## # A tibble: 6 x 14
##   map_predictor map_outcome hypo    var1     var2    var3    var4    var5   var6
##           <dbl>       <dbl> <lgl>  <dbl>    <dbl>   <dbl>   <dbl>   <dbl>  <dbl>
## 1          76.2        62.6 TRUE   -8.04   9.57   -12.9     3.65    6.89  -12.7
## 2          75.0        60.0 TRUE  -10.6   -2.35    -2.16   -9.96    1.65   -7.57
## 3          84.0        94.5 FALSE -10.4   -0.0817  -0.483   0.951  10.6     1.68
## 4          73.2        62.1 TRUE  -11.9   11.8     19.3     9.97  -14.5   -19.2
## 5          78.9        84.3 FALSE  -5.00   0.372   -8.92  -16.2    10.9     9.23
## 6          78.8        81.5 FALSE  -5.25 -11.3    -15.3    19.4    -0.637  -3.54
## # ... with 5 more variables: var7 <dbl>, var8 <dbl>, var9 <dbl>, grey <lgl>,
## #   nonhypo <lgl>
```

We split the data into a training set and a test set (50:50).

```
set.seed(1)
sample_i <- sample(1:n_obs, size = floor(n_obs/2))
d_train <- d_model[sample_i,]
d_test <- d_model[-sample_i,]
```

We fit a logistic regression to the test set.

```
fake_hpi_model <- glm(hypo ~ map_predictor + var1 + var2 + var3 + var4 + var5 + var6 +
        var7 + var8 + var9, data = d_train, family = binomial())

gtsummary::tbl_regression(fake_hpi_model) |>
    gtsummary::as_gt() |>
    gt::as_latex()
```

| **Characteristic** | **log(OR)**[1] | **95% CI**[1] | **p-value** |
|---|---|---|---|
| map_predictor | -0.50 | -0.57, -0.43 | <0.001 |
| var1 | -0.03 | -0.05, 0.00 | 0.030 |
| var2 | 0.00 | -0.03, 0.02 | 0.8 |
| var3 | 0.01 | -0.01, 0.04 | 0.3 |
| var4 | 0.01 | -0.02, 0.03 | 0.5 |
| var5 | 0.00 | -0.02, 0.02 | 0.9 |
| var6 | -0.03 | -0.05, 0.00 | 0.023 |
| var7 | 0.01 | -0.02, 0.03 | 0.5 |
| var8 | 0.00 | -0.03, 0.02 | 0.8 |

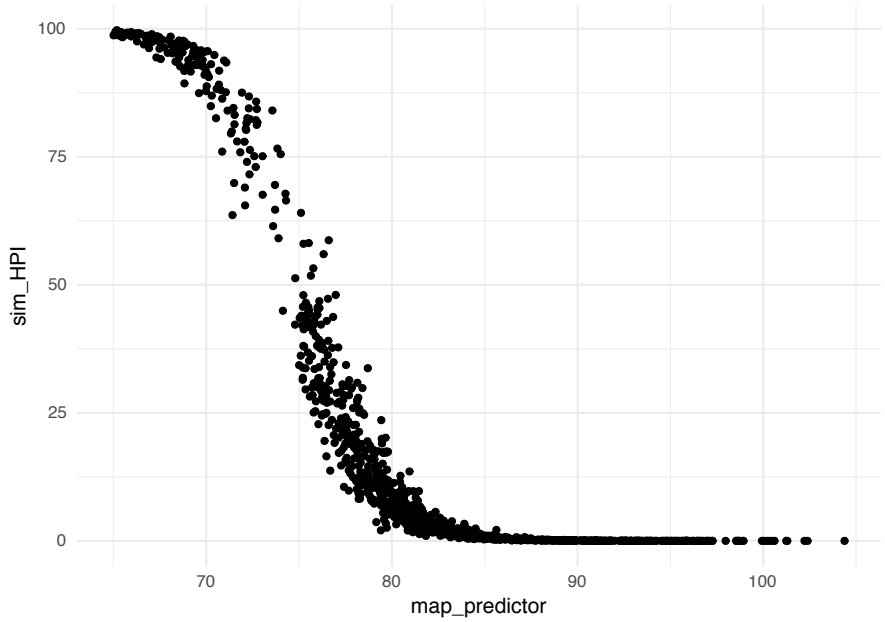
| | | | |
|---|---|---|---|
| var9 | 0.01 | -0.01, 0.03 | 0.4 |

[1]OR = Odds Ratio, CI = Confidence Interval

We can see that the model correctly identifies that only MAP is a relevant predictor of hypotension in this simulated data set.

HPI is the predictions from a logistic regression times 100. We calculate these predictions for each observation in the training set and plot it against the predictor MAP.

```
d_train$sim_HPI <- predict(fake_hpi_model, type = "response") * 100

ggplot(d_train, aes(map_predictor, sim_HPI)) +
    geom_point()
```




We use a ROC analysis to see how well this simulated HPI can discreminate future hypotension from future nonhypotension.

```
(roc_hpi_train <- roc(hypo ~ sim_HPI, data = d_train))
```

```
##
## Call:
## roc.formula(formula = hypo ~ sim_HPI, data = d_train)
##
## Data: sim_HPI in 879 controls (hypo FALSE) < 225 cases (hypo TRUE).
## Area under the curve: 0.9377
```

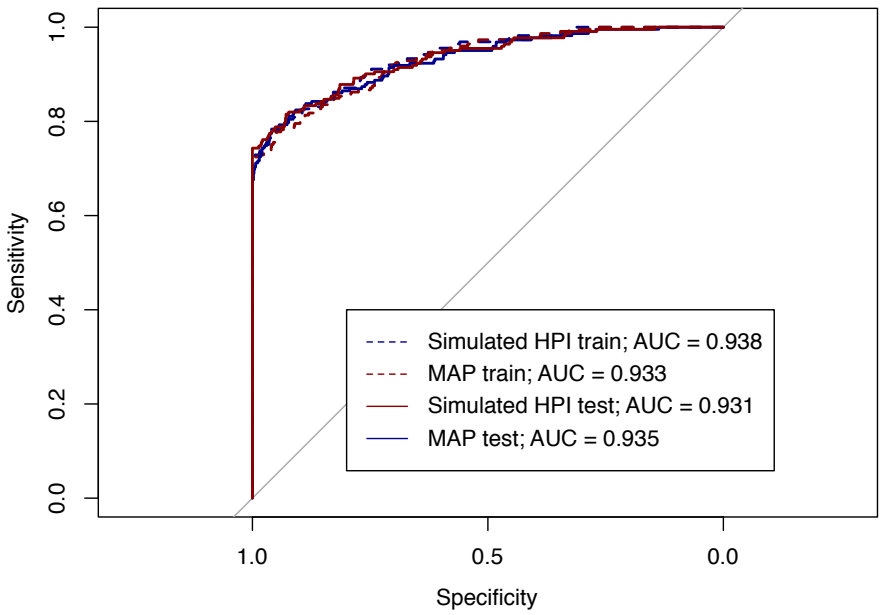
Now, we use the same fitted model to create predictions on the test set.

```r
d_test$sim_HPI <- predict(fake_hpi_model, newdata = d_test, type = "response") * 100

(roc_hpi_test <- roc(hypo ~ sim_HPI, data = d_test))
```

```
##
## Call:
## roc.formula(formula = hypo ~ sim_HPI, data = d_test)
##
## Data: sim_HPI in 883 controls (hypo FALSE) < 222 cases (hypo TRUE).
## Area under the curve: 0.9314
```

We also make the same ROC analyses for MAP directly, and plot all four ROC curves.

```r
roc_map_train <- roc(hypo ~ map_predictor, data = d_train)
roc_map_test <- roc(hypo ~ map_predictor, data = d_test)

{
    plot(roc_hpi_train, col = "darkblue", lty = 2)
    plot(roc_map_train, col = "darkred", lty = 2, add = TRUE)
    plot(roc_hpi_test, col = "darkblue", add = TRUE)
    plot(roc_map_test, col = "darkred", add = TRUE)
    legend(x = 0.8, y = 0.4,
           legend = c(sprintf("Simulated HPI train; AUC = %.3f", auc(roc_hpi_train)),
                      sprintf("MAP train; AUC = %.3f", auc(roc_map_train)),
                      sprintf("Simulated HPI test; AUC = %.3f", auc(roc_hpi_test)),
                      sprintf("MAP test; AUC = %.3f", auc(roc_map_test))),
       lty = c(2,2,1,1),
       col = c("darkblue", "darkred", "darkred", "darkblue"))
}
```



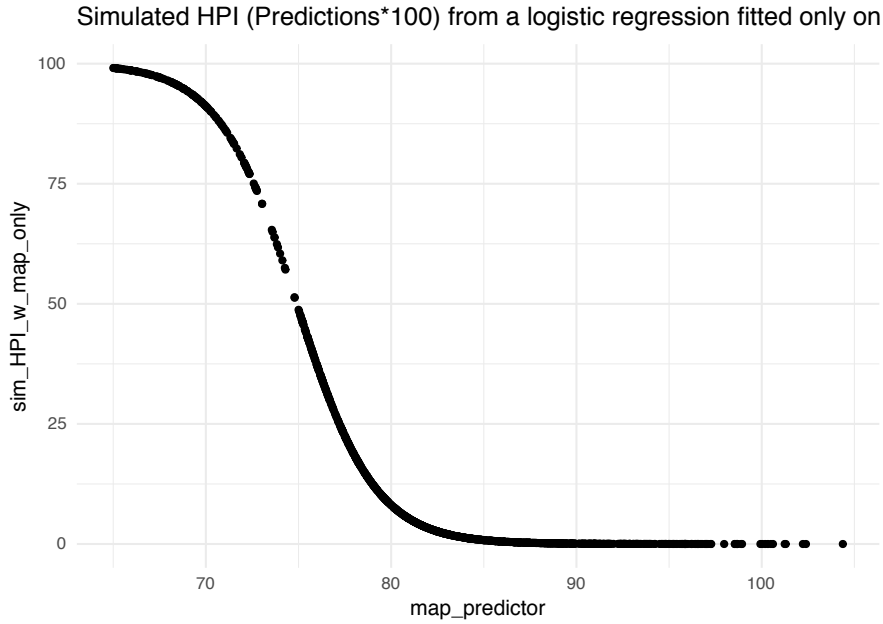
## A logistic regression with a single independent variable will return predictions ranked identically to the independent variable.

As a last example, we make a logistic regression with MAP as the only independent variable. Here, the ROC analysis will be identical to the ROC analysis using MAP directly. A ROC analysis relies only on the ranks of the predictor, and ranks are not changed by a logistic regression with one independent variable (with the exception that they can be reversed, which also does not impact the ROC analysis result). T This can also be appreciated from the logistic regression formula:

$$HPI_{map\ only} = 100 * \frac{1}{1 + e^{-(\beta_0 + \beta_1 MAP)}}$$

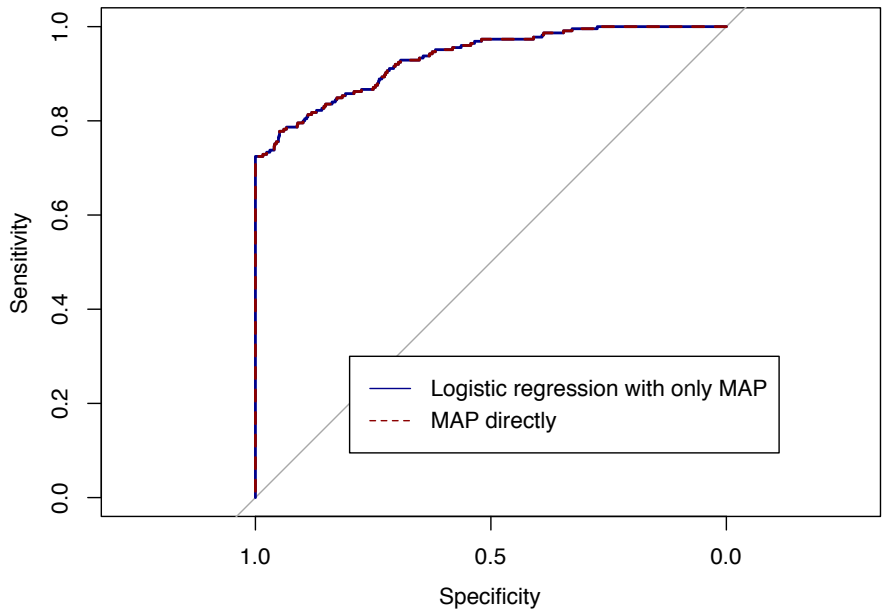
The linear part of a logistic regression $(\beta_0 + \beta_1 MAP)$ multiplies the independent variable with a constant, $\beta_1$ and adds a constant, $\beta_0$. This can reverse the ranks (if $\beta_1 < 0$) but not otherwise change them. The logisic link function also preserves the ranks (the same does multiplying by 100 to get the final HPI score).

```
map_model <- glm(hypo ~ map_predictor, data = d_train, family = binomial())

d_train <- mutate(d_train, sim_HPI_w_map_only = predict(map_model, type = "response") * 100)

ggplot(d_train, aes(map_predictor, sim_HPI_w_map_only)) +
    geom_point() +
    labs(title = "Simulated HPI (Predictions*100) from a logistic regression fitted only on MAP")
```




Here, we compare the ROC analysis from this simulated HPI based only on MAP with the ROC analysis using MAP directly.

```r
roc_map_model <- roc(hypo ~ sim_HPI_w_map_only, data = d_train)

{
    plot(roc_map_model, col = "darkblue")
    plot(roc_map_train, col = "darkred", lty = 2, add = TRUE)
    legend(
        x = 0.8,
        y = 0.3,
        legend = c("Logistic regression with only MAP",
                   "MAP directly"),
        lty = c(1, 2),
        col = c("darkblue", "darkred")
    )
}
```




## Create figure 3

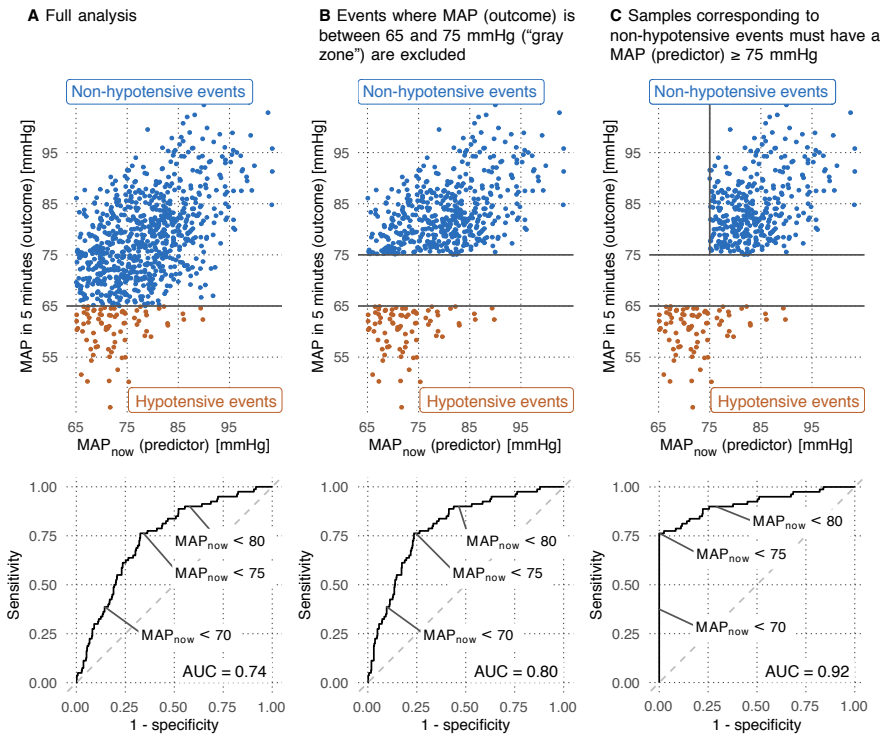
```r
library(ggrepel)
library(patchwork)

# Set plot theme
# Plot theme
# Theme for plot
theme_set(
    theme_minimal(base_size = 11) +
        theme(
            plot.title = ggtext::element_textbox_simple(
```

```
                size = 10,
                vjust = 0,
                minheight = unit(3, "lines"), width = unit(2.5, "inches")
            ),
            axis.title = element_text(size = 9.5),
            axis.text = ggplot2::element_text(size = ggplot2::rel(0.8)),
            panel.grid.major = ggplot2::element_line(
                color = "#454545",
                size = 0.3,
                linetype = "dotted"
            ),
            panel.grid.minor = ggplot2::element_blank()
        ))

plot_colors <- c("#2A6EBB", "#bb612a")

# First we extract all combinations of sensitivity, specificity and thresholds for
# all ROC analyses
roc_data_full <- as.data.frame(roc_analysis_full[c("sensitivities",
                                                   "specificities",
                                                   "thresholds")])  |>
    arrange(desc(specificities), sensitivities)

roc_data_grey <- as.data.frame(roc_analysis_grey[c("sensitivities",
                                                   "specificities",
                                                   "thresholds")]) |>
    arrange(desc(specificities), sensitivities)

roc_data_biased <- as.data.frame(roc_analysis_biased[c("sensitivities",
                                                   "specificities",
                                                   "thresholds")]) |>
    arrange(desc(specificities), sensitivities)

# We extract the rows with thresholds closest to 70, 75 and 80
# This is used for labeling the ROC curves.
roc_label_filter <- function(roc_data) {
    roc_data |>
        filter(
            row_number() == which.min(abs(thresholds - 70)) |
                row_number() == which.min(abs(thresholds - 75)) |
                row_number() == which.min(abs(thresholds - 80))
        )
}

roc_labels_full <- roc_label_filter(roc_data_full)
roc_labels_grey <- roc_label_filter(roc_data_grey)
roc_labels_biased <- roc_label_filter(roc_data_biased)
```

```r
# Make the 3 ROC panels
roc_plot_full <- ggplot(roc_data_full, aes(1-specificities, sensitivities)) +
    geom_step() +
    geom_abline(slope = 1, intercept = 0, linetype = 2, color = "grey") +
    geom_label_repel(aes(label = glue::glue("MAP[now] < {round(thresholds, 0)}")),
                     parse = TRUE,
                     size = 3.1,
                     box.padding = 0.1,
                     point.size = 0.1,
                     segment.color = "#555555",
                     position = position_nudge_repel(y = -0.2, x=0.2),
                     ylim = c(0.15, 1),
                     direction = "y",
                     label.size  = NA,
                     #vjust = 1,
                     hjust = 0,
                     family = "Helvetica",
                     data = roc_labels_full
    ) +
    annotate("label",
             x = 1, y = 0,
             label = sprintf("AUC = %.2f", auc(roc_analysis_full)),
             hjust = 1, vjust = -0,
             label.size = NA,
             family = "Helvetica",
             #label.size = NA,
             size = 3.5) +
    labs(x = "1 - specificity", y = "Sensitivity") +
    coord_equal()

roc_plot_grey <- ggplot(roc_data_grey, aes(1-specificities, sensitivities)) +
    geom_step() +
    geom_abline(slope = 1, intercept = 0, linetype = 2, color = "grey") +
    geom_label_repel(aes(label = glue::glue("MAP[now] < {round(thresholds, 0)}")),
                      parse = TRUE,
                      size = 3.1,
                      box.padding = 0.1,
                      point.size = 0.1,
                      segment.color = "#555555",
                      direction = "y",
                      position = position_nudge_repel(y = -0.2, x=0.2),
                      ylim = c(0.15, 1),
                      label.size  = NA,
                      #vjust = 1,
                      hjust = 0,
                      family = "Helvetica",
                      data = roc_labels_grey
```

```
    ) +
    annotate("label",
             x = 1, y = 0,
             label = sprintf("AUC = %.2f", auc(roc_analysis_grey)),
             hjust = 1, vjust = -0,
             label.size = NA,
              family = "Helvetica",
              #label.size = NA,
              size = 3.5) +
    labs(x = "1 - specificity", y = "Sensitivity") +
    coord_equal()

roc_plot_biased <- ggplot(roc_data_biased, aes(1-specificities, sensitivities)) +
    geom_step() +
    geom_abline(slope = 1, intercept = 0, linetype = 2, color = "grey") +
    geom_label_repel(aes(label = glue::glue("MAP[now] < {round(thresholds, 0)}")),
                     parse = TRUE,
                     size = 3.1,
                     box.padding = 0.1,
                     point.size = 0.3,
                     segment.color = "#555555",
                     position = position_nudge_repel(y = -0.1, x=0.2),
                     ylim = c(0.15, 1),
                     direction = "y",
                     label.size  = NA,
                     #vjust = 1,
                     hjust = 0,
                     family = "Helvetica",
                     data = roc_labels_biased
    ) +
    annotate("label",
             x = 1, y = 0,
             label = sprintf("AUC = %.2f", auc(roc_analysis_biased)),
             hjust = 1, vjust = -0,
             label.size = NA,
             family = "Helvetica",
             size = 3.5) +
    labs(x = "1 - specificity", y = "Sensitivity") +
    coord_equal()

# Make the 3 scatter plots
color_scale <- scale_color_manual(values = plot_colors,
                                  labels = c("Non-hypotensive events", "Hypotensive events"))

scatter_plot_full <- ggplot(d, aes(map_predictor, map_outcome, color = hypo)) +
    geom_point(size = 0.7, show.legend = FALSE) +
    geom_hline(yintercept = 65, color = "#555555") +
```

```
    scale_y_continuous(breaks = seq(55, 95, by = 10), expand = expansion(add = c(1,5))) +
    scale_x_continuous(breaks = seq(65, 95, by = 10)) +

    labs(x = "MAP<sub>now</sub> (predictor) [mmHg]", y = "MAP in 5 minutes (outcome) [mmHg]", color = "") +
    ggtitle("**A** Full analysis") +
    color_scale +
    coord_equal() +
    theme(axis.title.x = ggtext::element_markdown())

labels <- tribble(
    ~label,                  ~hypo, ~x, ~y,
    "Hypotensive events",    TRUE,  Inf, -Inf,
    "Non-hypotensive events",FALSE, -Inf, Inf
    )

event_labels <- geom_label(aes(x, y, label = label),
                     size = 3.5,
                     #label.size  = NA,
                     fill = "white",
                     vjust = "inward",
                     hjust = "inward",
                     family = "Helvetica",
                     data = labels,
                     show.legend = FALSE
    )

scatter_plot_full_w_labs <- scatter_plot_full + event_labels

scatter_plot_grey <- scatter_plot_full %+% filter(d, !grey) +
    geom_hline(yintercept = 75, color = "#555555") +
    event_labels +
    ggtitle("**B** Events where MAP (outcome) is between 65 and 75 mmHg (“gray zone”) are excluded")

scatter_plot_biased <- scatter_plot_grey %+% filter(d, hypo | nonhypo) +
    annotate("segment",
        x = 75, xend = 75,
        y = 75, yend = Inf,
        color = "#555555"
    ) +
    event_labels +
    ggtitle("**C** Samples corresponding to non-hypotensive events must have a MAP (predictor) ≥ 75 mmHg")

# Combine plots
scatter_plot_full_w_labs + scatter_plot_grey + scatter_plot_biased +
    roc_plot_full + roc_plot_grey + roc_plot_biased +
    plot_layout(ncol = 3, byrow = TRUE, guides = "collect")
```




```
ggsave("figure2_simulation.pdf", device = cairo_pdf, width = 9, height = 7)
```