Fluid responsiveness prediction

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This document contains analysis code for the receiver operator characteristic (ROC) analysis of fluid responsiveness prediction.

```
library(tidyverse)
library(pROC)
library(patchwork)
library(ggh4x)

source("plot_settings.R")

theme_set(theme_paper())
```

1 Load data

```
PPV_df <- read_csv("data/vent_setting_study-ppv.csv")
fluid_df <- read_csv("data/vent_setting_study-fluid_response.csv")

PPV_fluid <-
  left_join(
    PPV_df,
    fluid_df,
    by = "id"
  ) |>
  drop_na(PPV_gam, SV_rel_fluid_response) |>
  mutate(SV_rel_fluid_response = SV_rel_fluid_response * 100,
         SV_fluid_responder = SV_rel_fluid_response > 10)

# Check that number of complete observations is as expected.
stopifnot(nrow(PPV_fluid) == 489)
```

2 ROC analysis

```r
get_threshold_ci <- function(roc) {
  res <- ci.thresholds(roc, thresholds = "best") |>
    as.data.frame() |>
    rownames_to_column(var = "threshold")

  names(res) <- str_replace_all(names(res), c(".2.5." = "_lwr",
                                              ".50." = "_est",
                                              ".97.5." = "_upr"))

  res |>
    arrange(desc(specificity_est)) |>
    head(1) # If more than one "best", take the one with highest specificity.
}

roc_results <- PPV_fluid |>
  group_by(vent_rel_vt, vent_RR) |>
  summarise(gam_roc = list(roc(SV_fluid_responder ~ PPV_gam)),
            classic_roc = list(roc(SV_fluid_responder ~ PPV_classic)),
            n_PPV_gam = sum(!is.na(PPV_gam)),
            n_PPV_classic = sum(!is.na(PPV_classic))
            ) |>
  mutate(gam_auc = map(gam_roc, auc),
         classic_auc = map(classic_roc, auc),
         across(ends_with("auc"), .fns = ~map(.x, ci.auc, method = "delong")),
         # ci.auc returns a vector with lwr, est and upr. They are unpacked below.
         across(ends_with("auc"), .fns = list(
           "est" = ~map_dbl(.x, `[`, 2),
           "lwr" = ~map_dbl(.x, `[`, 1),
           "upr" = ~map_dbl(.x, `[`, 3)
           )),
         # Get threshold, spec, sens at maximum Youden index
         threshold_gam = map(gam_roc, get_threshold_ci),
         threshold_classic = map(classic_roc, get_threshold_ci)
         )
```

```r
# Design for faceted plot
design <- "
  A###
  BCDE
  FGHI
  J###
"

fluid_prediction_common_layers <- list(
  geom_point(size = 0.6),
  geom_abline(intercept = 10, slope = 0, color = accent_color, linetype = 2),
  scale_y_continuous(expand = expansion(add = c(5, 3)),
```

```
                      breaks = seq(-5, 20, by = 5)),
  labs(y = "ΔSV, change from baseline [%]"),
  facet_manual(vars("VT [ml kg⁻¹]" = fct_rev(factor(vent_rel_vt)),
                    "RR [min⁻¹]" = vent_RR),
               design = design, labeller = label_both,
               axes = "all", remove_labels = "none"
  ),
  theme(axis.title.x = ggtext::element_markdown(hjust = 0.1))
)

fluid_prediction_gam <- ggplot(PPV_fluid, aes(PPV_gam, SV_rel_fluid_response)) +
  geom_label(aes(label = sprintf("AUC = %.2f [%.2f; %.2f]",
                                 gam_auc_est, gam_auc_lwr, gam_auc_upr),
                 x = Inf, y = -Inf),
             size = 2.5, hjust = 1, vjust = 0,
             label.size = NA,
             data = roc_results) +
  # number of observations
  geom_label(aes(label = sprintf("n=%d", n_PPV_gam),
                 x = Inf, y = Inf),
             size = 2.5, hjust = 1, vjust = 1.5,
             label.size = NA,
             data = roc_results) +
  fluid_prediction_common_layers +
  labs(x = "PPV<sub>GAM</sub> [%]")

save_plot("fig3_fluid_prediction_gam",fluid_prediction_gam,  width = 16, height = 13)
```

```
## [1] "plots/fig3_fluid_prediction_gam.png" "plots/fig3_fluid_prediction_gam.pdf"
```

```
fluid_prediction_classic <- ggplot(PPV_fluid |> drop_na(PPV_classic),
                                   aes(PPV_classic, SV_rel_fluid_response)) +
  geom_label(aes(label = sprintf("AUC = %.2f [%.2f; %.2f]",
                                 classic_auc_est, classic_auc_lwr, classic_auc_upr),
                 x = Inf, y = -Inf),
             size = 2.5, hjust = 1, vjust = 0,
             label.size = NA,
             data = roc_results) +
  # number of observations
  geom_label(aes(label = sprintf("n=%d", n_PPV_classic),
                 x = Inf, y = Inf),
             size = 2.5, hjust = 1, vjust = 1.5,
             label.size = NA,
             data = roc_results) +
  fluid_prediction_common_layers +
  labs(x = "PPV<sub>Classic</sub> [%]")
```

```
save_plot("suppl_fluid_prediction_classic",fluid_prediction_classic,
          width = 16, height = 13)
```

```
## [1] "plots/suppl_fluid_prediction_classic.png"
## [2] "plots/suppl_fluid_prediction_classic.pdf"
```

3 Plot ROC curves

```
roc_data <- roc_results |>
  select(vent_rel_vt, vent_RR, gam_roc, classic_roc) |>
  pivot_longer(c(gam_roc, classic_roc),
               names_to = "ppv_type",
               names_pattern = "(.*)_roc",
               values_to = "roc") |>
  mutate(roc_data = map(roc, ~as.data.frame(.x[c("sensitivities",
                                                 "specificities",
                                                 "thresholds")])),
         ppv_type = str_replace(ppv_type, c("gam", "classic"), c("GAM", "Classic"))) |>
  select(ppv_type, vent_rel_vt, vent_RR, roc_data) |>
  unnest(roc_data) |>
  arrange(ppv_type, vent_rel_vt, vent_RR, desc(specificities), sensitivities)

roc_curves_plot <- ggplot(roc_data, aes(1-specificities, sensitivities,
                                        linetype = ppv_type)) +
  geom_abline(slope = 1, intercept = 0, linetype = 2, color = "grey") +
  ggtext::geom_richtext(aes(label = sprintf("AUC<sub>GAM</sub> = %.2f [%.2f; %.2f]<br>
AUC<sub>Classic</sub> = %.2f [%.2f; %.2f]",
                                            gam_auc_est, gam_auc_lwr, gam_auc_upr,
                                            classic_auc_est, classic_auc_lwr, classic_auc_upr),
                x = Inf, y = -Inf),
            size = 2.1, hjust = 1, vjust = 0,
            label.size = NA, inherit.aes = FALSE,
            data = roc_results) +
  geom_step() +
  facet_manual(vars("VT [ml kg⁻¹]" = fct_rev(factor(vent_rel_vt)), "RR [min⁻¹]" = vent_RR),
               design = design, labeller = label_both,
               axes = "all", remove_labels = "none"
  ) +
  labs(x = "1 - specificity", y = "Sensitivity",
       linetype = "PPV method") +
  coord_equal() +
  theme(axis.title.x = element_text(hjust = 0),
        legend.position = c(0.3, 0.9))

save_plot("suppl_ROC_curves", roc_curves_plot, width = 18, height = 16)
```

```
## [1] "plots/suppl_ROC_curves.png" "plots/suppl_ROC_curves.pdf"
```

4 Fluid responsiveness prediction table

```
library(gt)

fmt_est_ci <- function(est, lwr, upr) {
  sprintf("%.2f [%.2f;%.2f]", est, lwr, upr)
}

roc_table_df <- roc_results |>
  ungroup() |>
  select(-c(gam_roc, classic_roc, gam_auc, classic_auc, starts_with("n_"))) |>
  unnest_wider(c("classic" = threshold_classic, "gam" = threshold_gam), names_sep = "_") |>
  arrange(vent_RR, desc(vent_rel_vt)) |>
  pivot_longer(cols = matches("(_est|_lwr|_upr)$"), names_pattern = "(.*)_(est|lwr|upr)",
               names_to = c("variable", ".value")) |>
  mutate(label = fmt_est_ci(est, lwr, upr),.keep = "unused",
         across(ends_with("threshold"), as.numeric)) |>
  pivot_wider(names_from = variable, values_from = label) |>
  relocate(vent_rel_vt,
           vent_RR,
           gam_threshold, classic_threshold,
           gam_sensitivity, classic_sensitivity,
           gam_specificity, classic_specificity,
           gam_auc, classic_auc
           )


roc_table <- gt(roc_table_df) |>
  cols_label(
    vent_rel_vt = "Tidal volume [ml kg⁻¹]",
    vent_RR = "Respiratory rate [min⁻¹]",
    gam_auc = "AUC",
    classic_auc = "AUC",
    gam_threshold = "Optimal threshold",
    classic_threshold = "Optimal threshold",
    gam_sensitivity = "Sensitivity",
    classic_sensitivity = "Sensitivity",
    gam_specificity = "Specificity",
    classic_specificity = "Specificity"
  ) |>
  tab_spanner(
    label = "Classic PPV",
    columns = starts_with("classic")
  ) |>
```

```
  tab_spanner(
    label = "GAM PPV",
    columns = starts_with("gam")
  ) |>
  cols_align(align = "right", columns = ends_with("threshold")) |>
  fmt_percent(ends_with("threshold"), decimals = 1, scale_values = FALSE) |>
  tab_footnote("Threshold with maximum Youden index.",
               locations = cells_column_labels(ends_with("threshold"))) |>
  tab_header(md("Receiver operating characteristic analysis of fluid-responsiveness
prediction using pulse pressure variation (PPV). A positive fluid response was a >10%
increase in stroke volume from a 250 ml fluid bolus. PPV was calculated using a
classic method and derived from a generalized additive model (GAM).
Results are presented as *estimate* [95% confidence interval].")) |>
  tab_options(table.width = pct(100))

gtsave(roc_table, "tables/roc_table.html")
pagedown::chrome_print("tables/roc_table.html", wait = 0.1, options = list(scale = 0.9),
                  output = "tables/roc_table.pdf")

knitr::include_graphics("tables/roc_table.pdf")
```

Receiver operating characteristic analysis of fluid-responsiveness prediction using pulse pressure variation (PPV). A positive fluid response was a >10% increase in stroke volume from a 250 ml fluid bolus. PPV was calculated using a classic method and derived from a generalized additive model (GAM). Results are presented as *estimate* [95% confidence interval].

Tidal volume [ml kg^{-1}]	Respiratory rate [min^{-1}]	GAM PPV				Classic PPV			
		Optimal threshold[7]	Sensitivity	Specificity	AUC	Optimal threshold[7]	Sensitivity	Specificity	AUC
10	10	7.9%	0.80 [0.50;1.00]	0.65 [0.50;0.80]	0.73 [0.57;0.90]	11.4%	0.60 [0.30;0.90]	0.88 [0.78;0.97]	0.74 [0.57;0.92]
8	10	6.9%	0.70 [0.40;1.00]	0.72 [0.59;0.85]	0.68 [0.47;0.89]	8.1%	0.60 [0.30;0.90]	0.82 [0.69;0.92]	0.73 [0.55;0.91]
6	10	5.9%	0.70 [0.40;1.00]	0.74 [0.61;0.87]	0.77 [0.61;0.93]	5.8%	0.90 [0.70;1.00]	0.74 [0.58;0.87]	0.82 [0.66;0.98]
4	10	3.1%	0.80 [0.50;1.00]	0.50 [0.35;0.65]	0.67 [0.47;0.86]	4.9%	0.80 [0.50;1.00]	0.78 [0.65;0.90]	0.79 [0.62;0.96]
8	17	5.7%	0.90 [0.70;1.00]	0.62 [0.47;0.78]	0.73 [0.55;0.91]	4.9%	0.90 [0.70;1.00]	0.57 [0.42;0.72]	0.71 [0.54;0.88]
6	17	5.7%	0.70 [0.40;1.00]	0.82 [0.68;0.92]	0.74 [0.56;0.91]	4.4%	0.90 [0.70;1.00]	0.71 [0.55;0.84]	0.79 [0.62;0.96]
8	24	7.2%	0.80 [0.50;1.00]	0.80 [0.68;0.93]	0.74 [0.51;0.97]	6.7%	0.70 [0.40;1.00]	0.88 [0.75;0.95]	0.79 [0.60;0.98]
6	24	4.6%	0.70 [0.40;1.00]	0.70 [0.55;0.85]	0.70 [0.51;0.90]	4.1%	0.80 [0.50;1.00]	0.72 [0.57;0.85]	0.75 [0.59;0.91]
8	31	7.7%	0.50 [0.12;0.88]	0.94 [0.86;1.00]	0.70 [0.46;0.94]	5.0%	0.75 [0.38;1.00]	0.83 [0.69;0.94]	0.79 [0.56;1.00]
6	31	4.3%	0.70 [0.40;0.90]	0.62 [0.47;0.78]	0.65 [0.45;0.85]	3.1%	0.70 [0.40;0.90]	0.68 [0.53;0.82]	0.62 [0.40;0.84]

[7] Threshold with maximum Youden index.