Report

Signal detection of spontaneous medical device reports over time accounting for multiple comparisons

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1 Set up

1.1 Packages

```
suppressPackageStartupMessages({
  library("readr")
  library("dplyr")
  library("tidyr")
  library("forcats")
  library("lubridate") # way to handle dates better than default R way
  library("stringr")
  library("ggplot2")
  library("ggthemes")
  library("ggrepel")
  library("knitr")
  library("gsDesign")
  library("arrow")
})
```

```
Warning: package 'dplyr' was built under R version 4.2.3
```

```
col_pal <- c("darkorange", "cyan4", "purple")
```

1.2 Load data

```
sra_cum_bcpnn <-  read_parquet("out/sra_cum_bcpnn.parquet")
sra_cum_bcpnn_mc_adj <-  read_parquet("out/sra_cum_bcpnn_mc_adj.parquet")
sra_cum_maxsprt <-  read_parquet("out/sra_cum_maxsprt.parquet")


sra <-
  bind_rows(
    sra_cum_bcpnn %>% mutate(stat = "BCPNN"),
    sra_cum_bcpnn_mc_adj %>% mutate(stat = "BCPNN (MCadj)"),
    sra_cum_maxsprt %>% mutate(stat = "maxSPRT")
  ) %>%
  select(stat, everything())
```

```r
sra <-
  sra %>%
  mutate(
    test_stat = if_else(stat == "maxSPRT", maxllr, ci_lo),
    test_thresh = if_else(stat == "maxSPRT", cv, 0),
    rr_stat = if_else(stat == "maxSPRT", rre, 2 ^ est)
  )



thresholds <- sort(unique(sra[["thresh"]]))
length(thresholds)
```

```
[1] 19
```

2 Methods

2.1 Data aquisition

The data is thanks to curtis-murray at his MedicalDevicesNLP repo

- Natural language processing of the TGA spontaneous reports of medical device database (DAEN)
- Each record has an estimate of P(`topic == "pain"` | `Level`, `Doc`) using hierarchical stochastic block modelling (hSBM)
- P(`topic == "pain"` | `Level`, `Doc`) estimates for each record are roughly interpreted as the proportion of the NLP analysed free text that is considered as using/describing words related to pain

And example record and processing values:

- [to include here]

2.2 Analysis data

Signal detection of disproportionate adverse events (AEs) will often have tabulated count data accumulated over time. The data at time point t can be summarised as below:

	AE(s) $\in Y$	AE(s) $\in \bar{Y}$
Target exposure	a_t	b_t
Comparator exposure	c_t	d_t

where

- AE(s) Y is the set of AEs (or singular AE) of interest,
- AE(s) $\bar{Y}$ is the complementary set to the AEs of interest,
- *Target exposure* is the medical device(s) of interest,

- *Comparator exposure* is the medical devices to which the *Target exposure* is being compared, and
- a_t, b_t, c_t and d_t (all $\in \mathbb{Z}^+$) are the respective counts of AEs recorded up until (i.e., cumulative) time t.

In the motivating example of the pelvic mesh device, the contingency table can be written more specifically as

	Pain AEs	Not pain AEs
Pelvic mesh	a_t	b_t
Comparator exposure	c_t	d_t

where

- *AEs pain* is the count of AEs that contain "pain" themes greater or equal to some pre-specified threshold $p_t \in (0, 1)$ as estimated by the hSBM (that is, $P(\texttt{topic == "pain"}|\texttt{Level, Doc}) \geq p_t$), and
- *Comparator exposure* can be any relevant set of medical devices to compare the pelvic mesh to (e.g., hernia mesh or all other mesh devices or all other devices).

3 The signal detection statistics over time

We will consider the three signal detection statistics below:

- Proportional reporting ratio (PRR),

- Bayesian Confidence Propagation Neural Network Information Component (BCPNN IC with MCMC CIs), and
- the maxSPRT statistic

As signal detection is being undertaken repeatedly as data are being accumulated, alpha spending needs to be considered. The below table classifies the aforementioned signal detection methods by their null hypothesis as well as whether they control for the family-wise error rate (FWER)

Null hypothesis	non-FWER version	FWER version
Ratio of pain AEs to all AEs in target and comparator groups has a ratio of 1	PRR	binary, group sequential maxSPRT
Independence of pain AEs and target group (based on marginal counts)	IC	IC with α-spending scheme

We will demonstrate how the group sequential binary maxSPRT, as described in previous work, is equivalent to a FWER-controlled PRR method of signal detection.

3.1 Proportional reporting ratio (PRR)

The PRR estimate is calculated

$$\widehat{\text{PRR}}_t = \frac{\frac{a_t}{a_t+b_t}}{\frac{c_t}{c_t+d_t}}.$$

In the context of signal detection, an elevated proportional reporting ratio is of concern. Therefore the one-sided hypothesis test $H_0 : \text{PRR} \leq 1$ (proportional reporting of the target is less than the comparator) is used and is not rejected until

$$\widehat{\text{PRR}}_t \times \exp\left\{-Z^*_\alpha \sqrt{\frac{1}{a_t} + \frac{1}{a_t+b_t} + \frac{1}{c_t} + \frac{1}{c_t+d_t}}\right\} > 1$$

at the α level where Z^*_α is the $(1-\alpha)^{\text{th}}$ quantile of the standard normal distribution. The above threshold is equivalent to the lower bound of the approximate $100(1-2\alpha)\%$ confidence interval for a standard two-sided hypothesis test.

3.2 Bayesian Confidence Propagation Neural Network (BCPNN) Information Component (IC)

The Information Component (IC) statistic is an estimate of the observed-to-expected ratio of the number of target exposure AEs of interest on the $\log_2$-scale under independence between the target exposure and AEs of interest based on information theory (Bate et al., 1998)

$$\mathrm{IC}_{XY} = \log_2 \frac{P_{X,Y}(a_t + b_t, a_t + c_t)}{P_X(a_t + b_t)P_Y(a_t + c_t)}$$

where $P_X(X = x)$ denotes the marginal probability of an observed count x for the target exposure, $P_Y(Y = y)$ denotes the marginal probability of an observed count y for the AE of interest, and $P_{X,Y}(X = x, Y = y)$ denotes the joint probability.

The BCPNN IC of Noren et al. (2006) uses a Bayesian inference based *maximum a posteriori* (m.a.p.) central estimate of the IC,

$$\widehat{\mathrm{IC}}_t = \log_2 \frac{\mathrm{E}\left[\hat{p}_a\right]}{\mathrm{E}\left[\hat{p}_a + \hat{p}_b\right]\mathrm{E}\left[\hat{p}_a + \hat{p}_c\right]}$$

where p_a, p_b and p_c are the (assumed constant over time) underlying probabilities of the multinomial-distributed observed events a_t, b_t and c_t, respectively (p_d corresponding to the count d_t also included). The underlying probabilities are modelled using Dirichlet priors resulting in a Dirichlet posterior distribution. The one-sided null hypothesis of the joint probability target exposure and AEs of interest is equal or less than the marginal products ($H_0 : \mathrm{IC}_t \leq 0$) can be rejected when the α quantile of the Markov Chain Monte Carlo (MCMC) empirical distribution is greater than 0. Similarly to the rejection rule for the PRR, this threshold corresponds to the lower bound of the $100(1 - 2\alpha)\%$ equal-tailed credible region in a two-sided hypothesis test.

3.3 maxSPRT

Kulldorff et al. (2011) outlined that the relative risk (RR) at a given point-in-time for accumulated binary data (that is, "success"/"failure" events or AE of interest or not) of a target group relative to a comparator has the maximum likelihood estimate of

$$\widehat{\mathrm{RR}} = z\frac{C_n}{n - C_n}$$

where

- z is the ratio of the total AEs for the comparator to the total AEs for the target,
- C_n is the count of target exposure AEs in X,
- n is the count of all AEs in X (target and comparator exposure), and

- $n - C_n$ is therefore the count of comparator exposure AEs in X.

In the context of our data, the values z, C_n and n are the quantities $\frac{c_t+d_t}{a_t+b_t}$, a_t and $a_t + c_t$, respectively, at time t.

Therefore the RR maximum likelihood estimate at time t can be re-written

$$\begin{aligned}\widehat{\mathrm{RR}}_t &= \frac{c_t + d_t}{a_t + b_t} \times \frac{a_t}{c_t} \\ &= \frac{\frac{1}{a_t+b_t}}{\frac{1}{c_t+d_t}} \times \frac{a_t}{c_t} \\ &= \frac{\frac{a_t}{a_t+b_t}}{\frac{c_t}{c_t+d_t}}\end{aligned}$$

which is the PRR estimate at time t as before.

The (maximised) log-likelihood ratio statistic of $\widehat{\mathrm{PRR}}_t$ (equivalently, $\widehat{\mathrm{RR}}_t$) can be determined calculated as

$$\mathrm{LLR}_t = a_t \ln\left(\frac{a_t}{a_t + c_t}\right) + c_t \ln\left(\frac{c_t}{a_t + c_t}\right) - a_t \ln\left(\frac{a_t + b_t}{a_t + b_t + c_t + d_t}\right) - c_t \ln\left(\frac{c_t + d_t}{a_t + b_t + c_t + d_t}\right)$$

4 Analysis choices:

- Data structures - cumulative vs snapshot
- Threshold choose
- How many "looks"
- how to choose alpha spending
- sample size limitations for maxsprt - not an issue now can use MCMC method of `EmpiricalCalibration`

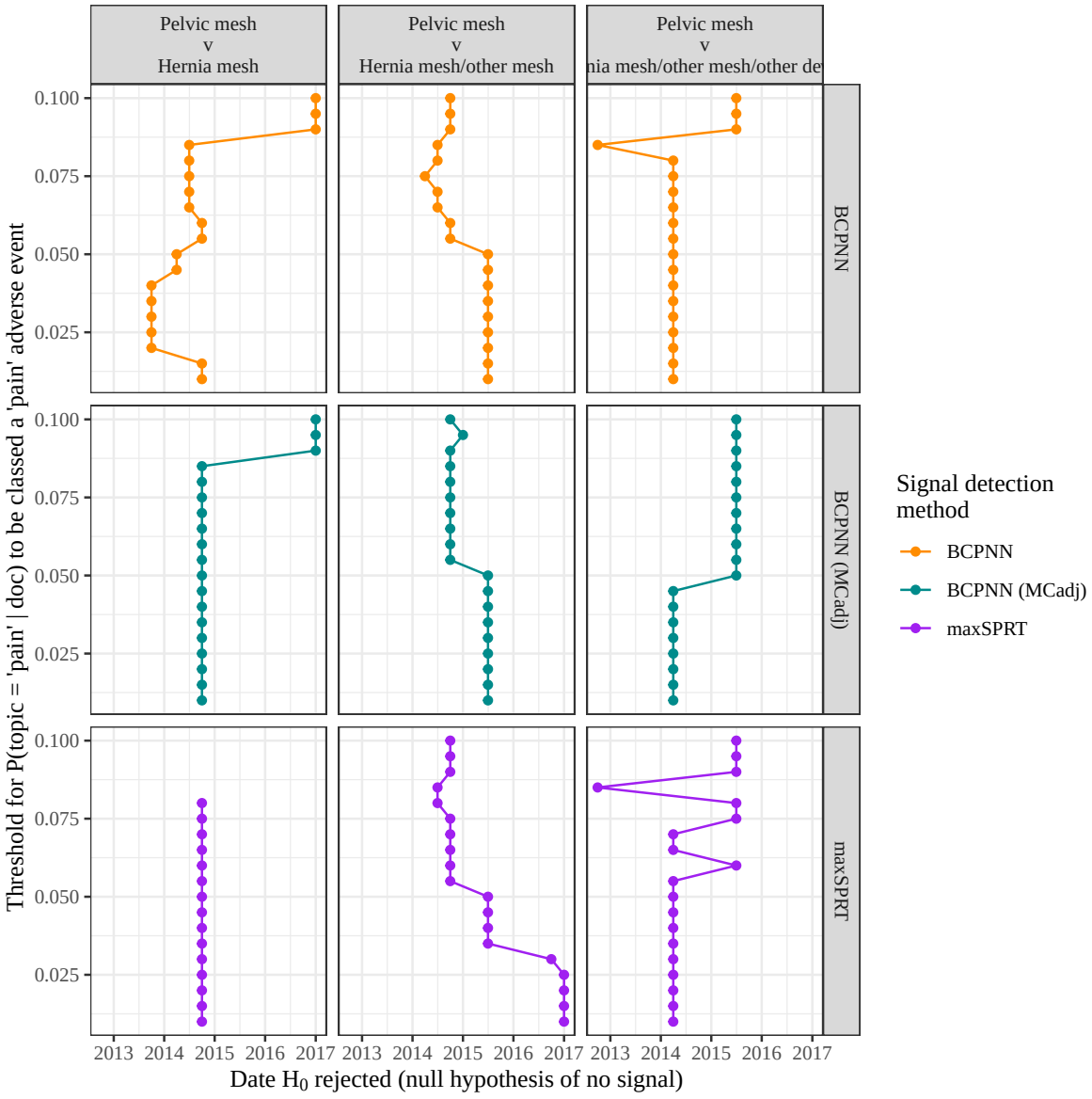
5 Plots

```
date_signif_dat <-
  sra %>%
  group_by(stat, grps, dat_type, thresh) %>%
  arrange(dte) %>%
  dplyr::filter(reach_sig) %>%
  dplyr::filter(row_number() == 1) %>%
  ungroup() %>%
  arrange(stat, grps, dat_type, thresh)


signif_plt <-
  date_signif_dat %>%
  ### only keep pelvic mesh as target vs whatever comparator
  dplyr::filter(grepl("^.*pelvic.* v ", grps)) %>%
  mutate(
    grps = gsub("\\([a-z]\\) ", "", grps),
    grps = gsub("_", " ", grps),
    grps = gsub("pelvic mesh", "Pelvic mesh", grps),
    grps = gsub("hernia mesh", "Hernia mesh", grps),
    # grps = str_to_sentence(grps),
    grps = gsub(" v ", "\nv\n", grps, fixed = TRUE),
    grps = fct_inorder(grps)
  )

levels(signif_plt$grps)
```

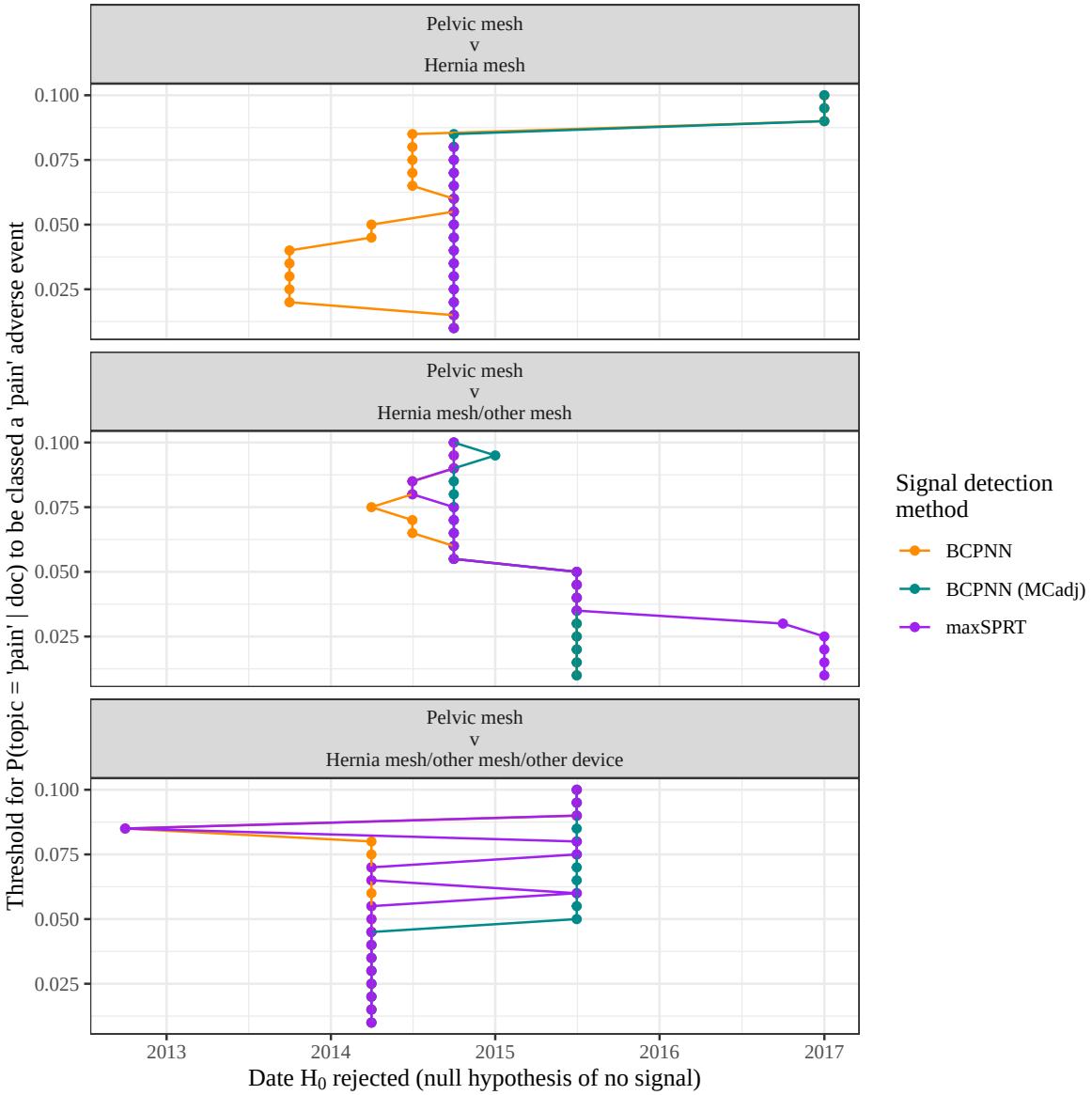
```
[1] "Pelvic mesh\nv\nHernia mesh"
[2] "Pelvic mesh\nv\nHernia mesh/other mesh"
[3] "Pelvic mesh\nv\nHernia mesh/other mesh/other device"
```

```
signif_plt %>%
  arrange(grps, thresh) %>%
  ggplot(., aes(x = dte_reach_sig, y = as.numeric(thresh), col = stat)) +
  geom_point() +
  geom_path(aes(group = stat)) +
  scale_colour_manual(values = col_pal) +
  # scale_colour_tableau(palette = "Color Blind", direction = -1) +
  facet_grid(stat ~ grps) +
```

```
  # facet_wrap( ~ grps, ncol = 1) +
  theme_bw() +
  theme(text = element_text(family = "serif")) +
  labs(
    x = expression("Date" ~ H[0] ~ "rejected (null hypothesis of no signal)"),
    y = "Threshold for P(topic = 'pain' | doc) to be classed a 'pain' adverse event",
    col = "Signal detection\nmethod"
  )
```



```r
ggsave(
  filename = "fig/time_to_signal_method_facets.png",
  dpi = 900, width = 9, height = 9
)

signif_plt %>%
  arrange(grps, thresh) %>%
  ggplot(., aes(x = dte_reach_sig, y = as.numeric(thresh), col = stat)) +
  geom_point() +
  geom_path(aes(group = stat)) +
  scale_colour_manual(values = col_pal) +
  # scale_colour_tableau(palette = "Color Blind", direction = -1) +
  # facet_grid(stat ~ grps) +
  facet_wrap( ~ grps, ncol = 1) +
  theme_bw() +
  theme(text = element_text(family = "serif")) +
  labs(
    x = expression("Date" ~ H[0] ~ "rejected (null hypothesis of no signal)"),
    y = "Threshold for P(topic = 'pain' | doc) to be classed a 'pain' adverse event",
    col = "Signal detection\nmethod"
  )
```



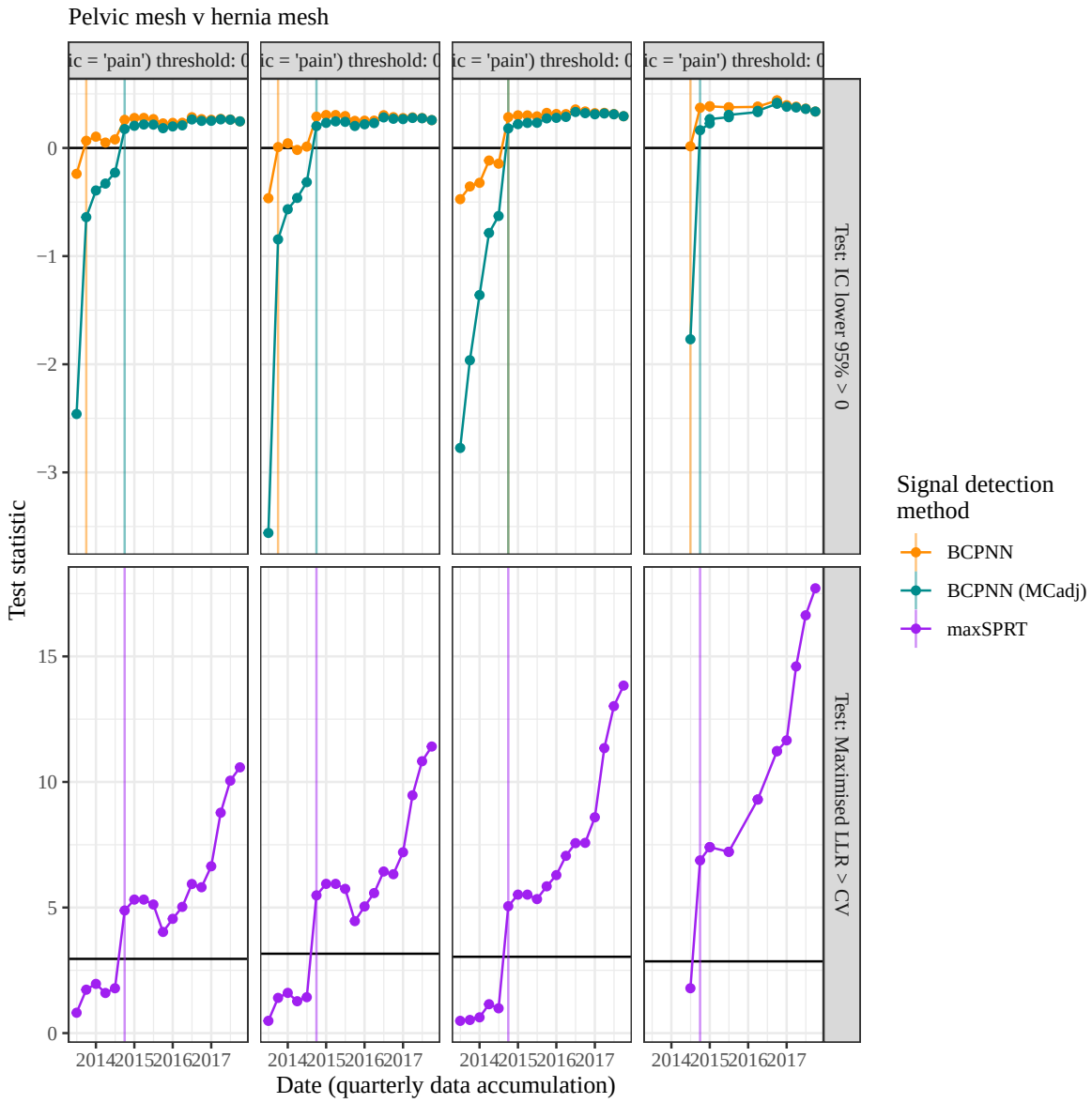

```r
ggsave(
  filename = "fig/time_to_signal_method_overlay.png",
  dpi = 900, width = 5, height = 9
)
```

```r
sra_stat_plt <-
  sra %>%
  # keep only subset of thresholds (too many colours otherwise)
  dplyr::filter(thresh %in% sprintf("%0.3f", seq(0.02, 0.08, by = 0.02))) %>%
  ### only keep pelvic mesh as target vs whatever comparator
  # dplyr::filter(grepl("^.*pelvic.* v ", grps)) %>%
  dplyr::filter(grepl("^\\(a\\)", grps)) %>%
  mutate(
    grps = gsub(" v ", "\nv\n", grps),
    grps = gsub("\\([a-z]\\) ", "", grps),
    grps = gsub("_", " ", grps),
    grps = fct_inorder(grps)
  )

thresholds <- sort(unique(sra_stat_plt[["thresh"]]))
length(thresholds)
```

```
[1] 4
```

```r
thresh_scale <- rev(hcl.colors(length(thresholds), "SunsetDark"))
# thresh_scale <- rev(hcl.colors(length(thresholds) + 1, "Inferno"))[-1]

sra_stat_plt %>%
  mutate(
    reach_sig_alpha = ifelse(reach_sig, 1, 0.8),
    `P(topic = 'pain') threshold` = thresh,
    `Test` = if_else(stat == "maxSPRT", "Maximised LLR > CV", "IC lower 95% > 0")
  ) %>%
  ggplot(
    .,
    aes(
      x = dte,
      y = test_stat,
      col = stat,
      group = interaction(stat, thresh)
      # alpha = reach_sig_alpha
    )
  ) %+%
  geom_hline(aes(yintercept = test_thresh), col = "black") %+% # null value
  geom_vline(aes(xintercept = dte_reach_sig, col = stat), alpha = 0.5) %+% # sig first rea
```

```
  geom_line() %+%
  geom_point() %+%
  # geom_ribbon(alpha = 0.05, lty = 2)  %+%
  # facet_wrap(~ grps, scales = "free_y", ncol = 1) %+%
  facet_grid(
    `Test` ~ `P(topic = 'pain') threshold`,
    scales = "free_y",
    labeller = label_both
  ) %+%
  labs(
    subtitle = "Pelvic mesh v hernia mesh",
    y = "Test statistic",
    x = "Date (quarterly data accumulation)",
    col = "Signal detection\nmethod"
  ) %+%
  # scale_y_continuous(limits = c(NA, 6)) %+%
  scale_colour_manual(values = col_pal)  %+%
  # scale_colour_tableau(palette = "Color Blind", direction = -1) +
  theme_bw() %+%
  theme(text = element_text(family = "serif"))
```

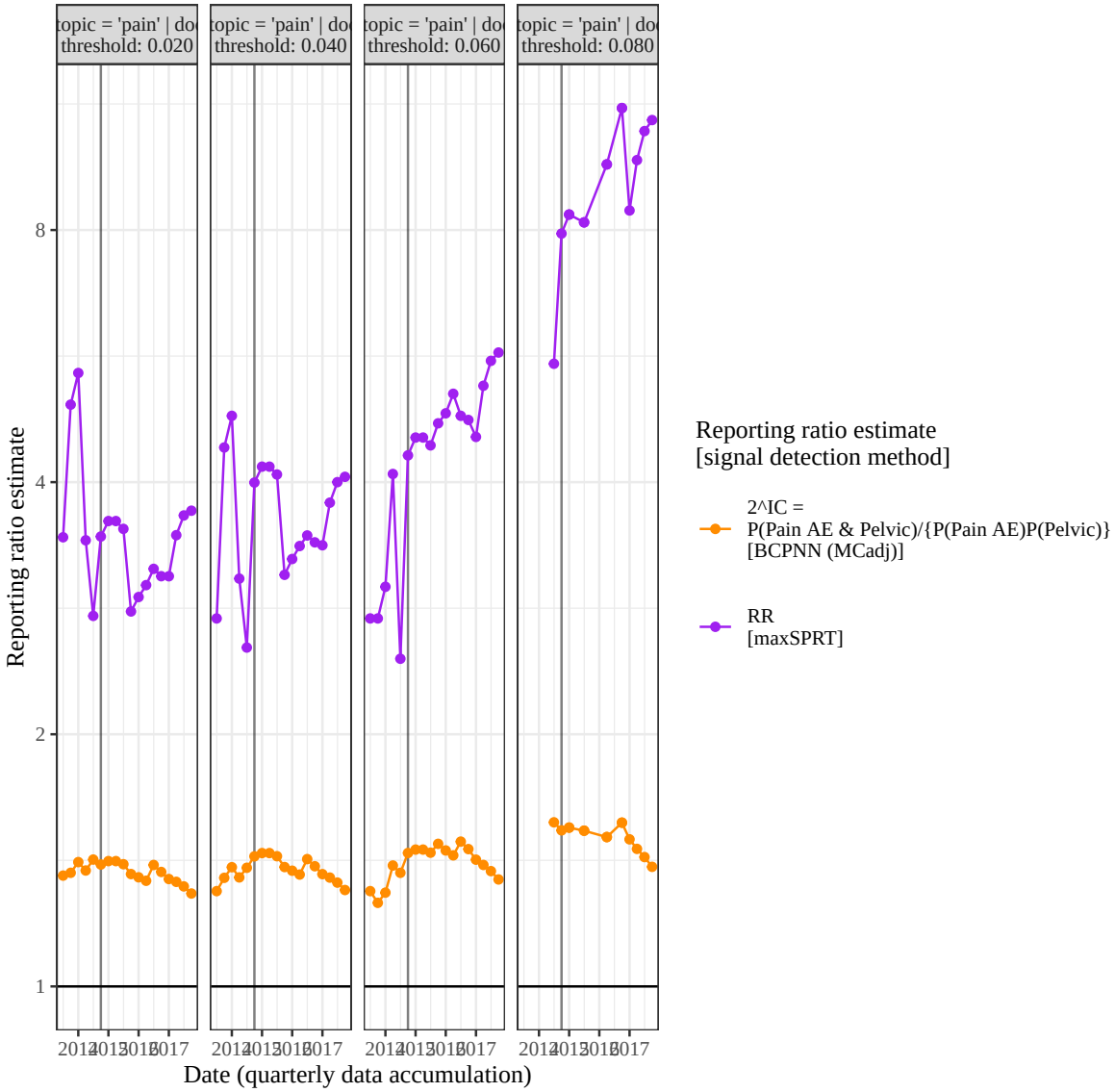



```
ggsave(
  filename = "fig/pelvic_v_hernia_sig_detect_over_time.png",
  dpi = 900, width = 10, height = 8
)

thresh_lablr <- function(string) paste0("P(topic = 'pain' | doc)\nthreshold: ", string)
```

```r
sra_stat_plt %>%
  dplyr::filter(stat != "BCPNN") %>%
  mutate(
    stat2 =
      paste0(
        ifelse(stat == "maxSPRT", "RR", "2^IC =\nP(Pain AE & Pelvic)/{P(Pain AE)P(Pelvic)}
        "\n[", stat, "]"
      ),
    reach_sig_alpha = ifelse(reach_sig, 1, 0.8),
    `P(topic = 'pain') threshold` = thresh,
    `Test` = if_else(stat == "maxSPRT", "Maximised LLR > CV", "IC lower 95% > 0"),
    `Statistic calculation method` = stat
  ) %>%
  ggplot(
    .,
    aes(
      x = dte,
      y = rr_stat,
      col = stat2,
      group = stat2
      # group = interaction(stat2, thresh)
      # alpha = reach_sig_alpha
      # ymin = ci_lo,
      # ymax = ci_hi
    )
  ) %+%
  geom_hline(aes(yintercept = 1), col = "black") %+% # null value
  geom_vline(aes(xintercept = dte_reach_sig), alpha = 0.5) %+% # sig first reached
  geom_line() %+%
  geom_point() %+%
  # geom_ribbon(alpha = 0.05)  %+%
  facet_wrap(~ thresh, nrow = 1, labeller = as_labeller(thresh_lablr)) %+%
  # facet_grid(
  #   `Statistic calculation method` ~ `P(topic = 'pain') threshold`,
  #   labeller = label_both
  # ) %+%
  labs(
    subtitle = "Pelvic mesh v hernia mesh",
    y = "Reporting ratio estimate",
    x = "Date (quarterly data accumulation)",
    col = "Reporting ratio estimate\n[signal detection method]"
```

```
) %+%
scale_y_continuous(trans = "log2") %+%
scale_colour_manual(values = col_pal[-2])  %+%
theme_bw() %+%
theme(
  text = element_text(family = "serif"),
  legend.key.height = unit(3, units = "line")
)
```

Pelvic mesh v hernia mesh



```r
ggsave(
  filename = "fig/pelvic_v_hernia_rr_est_over_time.png",
  dpi = 900, width = 12, height = 5
)
```

6 Session information

```
# Sys.info()[!(names(Sys.info()) %in% c("login", "nodename"))] %>%
#   as.data.frame(.)
format(Sys.time(), '%d %b %Y')
```

```
[1] "07 Sep 2023"
```

```
sessionInfo()
```

```
R version 4.2.2 (2022-10-31 ucrt)
Platform: x86_64-w64-mingw32/x64 (64-bit)
Running under: Windows 10 x64 (build 19045)

Matrix products: default

locale:
[1] LC_COLLATE=English_Australia.utf8  LC_CTYPE=English_Australia.utf8
[3] LC_MONETARY=English_Australia.utf8 LC_NUMERIC=C
[5] LC_TIME=English_Australia.utf8

attached base packages:
[1] stats     graphics  grDevices utils     datasets  methods   base

other attached packages:
 [1] arrow_11.0.0.2  gsDesign_3.4.0  knitr_1.42      ggrepel_0.9.3
 [5] ggthemes_4.2.4  ggplot2_3.4.1   stringr_1.5.0   lubridate_1.9.2
 [9] forcats_1.0.0   tidyr_1.3.0     dplyr_1.1.2     readr_2.1.4

loaded via a namespace (and not attached):
 [1] Rcpp_1.0.10       pillar_1.9.0      compiler_4.2.2    tools_4.2.2
 [5] bit_4.0.5         digest_0.6.31     jsonlite_1.8.4    evaluate_0.20
 [9] lifecycle_1.0.3   tibble_3.2.1      gtable_0.3.1      timechange_0.2.0
[13] pkgconfig_2.0.3   rlang_1.1.1       cli_3.6.0         rstudioapi_0.14
[17] yaml_2.3.7        xfun_0.37         fastmap_1.1.0     withr_2.5.0
[21] systemfonts_1.0.4 generics_0.1.3    vctrs_0.6.3       hms_1.1.2
[25] bit64_4.0.5       grid_4.2.2        tidyselect_1.2.0  glue_1.6.2
[29] R6_2.5.1          textshaping_0.3.6 fansi_1.0.4       rmarkdown_2.20
[33] farver_2.1.1      tzdb_0.3.0        purrr_1.0.1       magrittr_2.0.3
```

```
[37] scales_1.2.1      ellipsis_0.3.2    htmltools_0.5.4   assertthat_0.2.1
[41] xtable_1.8-4      colorspace_2.1-0  ragg_1.2.5        labeling_0.4.2
[45] utf8_1.2.3        stringi_1.7.12    munsell_0.5.0
```