Report

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

Ty Stanford et al.

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1 Set up

1.1 Packages

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

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

1.2 Load data

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


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

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]

3 The signal detection statistics over time

We will consider the three signal detection statistics below:

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

However, first let's outline the data available.

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

where

- AE(s) X is the set of AEs (or singular AE) of interest,
- AE(s) $\bar{X}$ 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 mativating example of the pelvic mesh device, the contingengy table can be written more specifically as

	AEs pain	AEs not pain
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, $P($`topic == "pain"`$|$`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).

3.2 Reporting odds ratio (ROR)

ROR with $100(1 - \alpha/2)\%$ confidence intervals

$$\hat{\text{ROR}} = \frac{\frac{a_t}{a_t + b_t}}{\frac{c_t}{c_t + d_t}}$$

3.3 BCPNN IC

BCPNN IC using the *maximum a posteriori* (m.a.p.) central estimate of the IC with MCMC simulation of the exact empirical distribution for $100(1 - \alpha/2)\%$ confidence (credible) regions of Noren (2006)

3.4 maxSPRT

The maximised log-likelihood ratio statistic

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

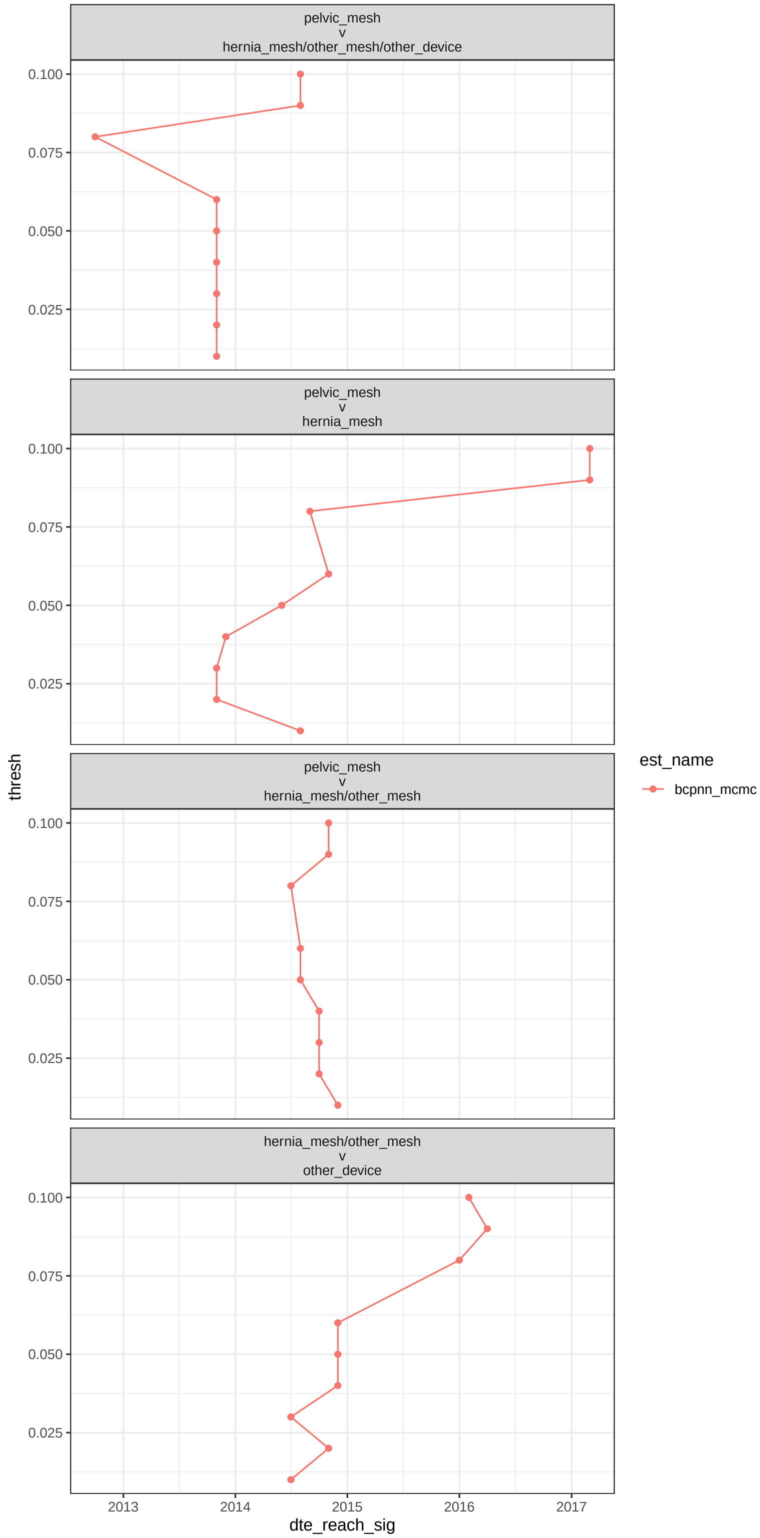
```
bcpnn_signif_plt <-
  bcpnn_signif %>%
  # keep only multiples of 0.01 (too many colours otherwise)
  dplyr::filter(abs(100 * thresh - floor(100 * thresh)) < 1e-6) %>%
  mutate(
    grps = gsub(" v ", "\nv\n", grps),
    grps = fct_inorder(grps)
  )

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

```
[1] 9
```

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

bcpnn_signif_plt %>%
  arrange(grps, thresh) %>%
  ggplot(., aes(x = dte_reach_sig, y = thresh, col = est_name)) +
  # ggplot(., aes(x = dte_reach_sig, y = est_name, col = factor(thresh))) +
  geom_point() +
  geom_path(aes(group = est_name)) +
  # scale_colour_viridis_c(option = "B", direction = -1) +
  # scale_colour_manual(values = thresh_scale) +
  facet_wrap(~ grps, ncol = 1) +
  theme_bw()
```


pelvic_mesh
v
hernia_mesh/other_mesh/other_device
pelvic_mesh
v
hernia_mesh
pelvic_mesh
v
hernia_mesh/other_mesh
hernia_mesh/other_mesh
v
other_device
0.100
0.075
0.050
0.025
thresh
2013
2014
2015
2016
2017
dte_reach_sig
est_name
bcpnn_mcmc

```r
sra_cum_bcpnn_plt <-
  sra_cum_bcpnn %>%
  # keep only multiples of 0.01 (too many colours otherwise)
  dplyr::filter(abs(100 * thresh - floor(100 * thresh)) < 1e-6) %>%
  mutate(
    grps = gsub(" v ", "\nv\n", grps),
    grps = fct_inorder(grps)
  )

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

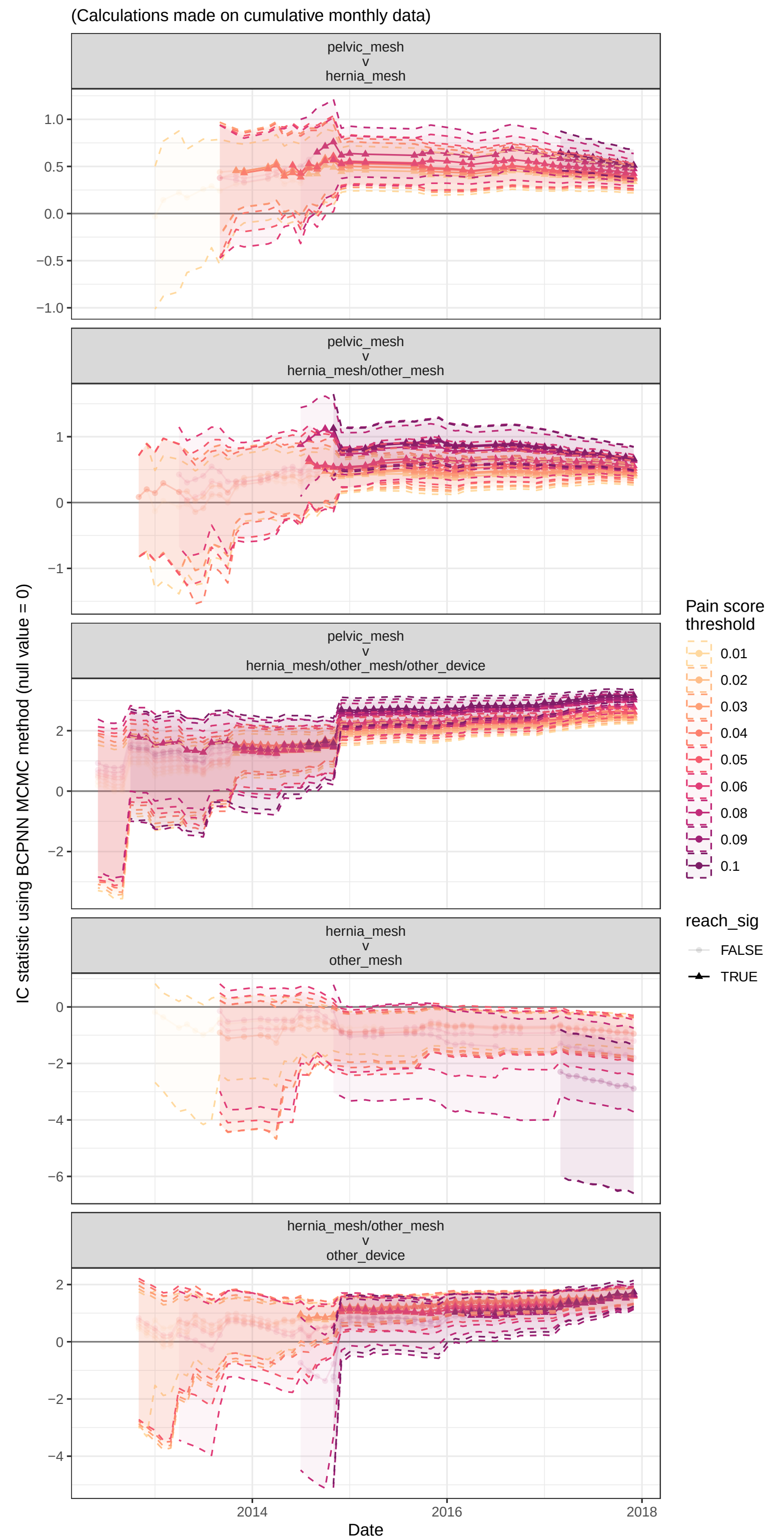
```
[1] 9
```

```r
thresh_scale <- rev(hcl.colors(length(thresholds), "SunsetDark"))


sra_cum_bcpnn_plt %>%
  ggplot(
    .,
    aes(
      dte,
      est,
      ymax = ci_hi,
      ymin = ci_lo,
      col = factor(thresh),
      fill = factor(thresh),
      group = factor(thresh),
      alpha = reach_sig,
      shape = reach_sig
    )
  ) %+%
  geom_hline(aes(yintercept = 0), col = "grey50") %+% # null value
  geom_line() %+%
  geom_point() %+%
  geom_ribbon(alpha = 0.05, lty = 2)  %+%
  facet_wrap(~ grps, scales = "free_y", ncol = 1) %+%
  labs(
    subtitle = "(Calculations made on cumulative monthly data)",
    y = "IC statistic using BCPNN MCMC method (null value = 0)",
```

```
    x = "Date",
    col = "Pain score\nthreshold",
    fill = "Pain score\nthreshold"
  ) %+%
  scale_colour_manual(values = thresh_scale, aesthetics = c("colour", "fill")) %+%
  theme_bw()
```

```
Warning: Using alpha for a discrete variable is not advised.
```



(Calculations made on cumulative monthly data)
pelvic_mesh
v
hernia_mesh
pelvic_mesh
v
hernia_mesh/other_mesh
pelvic_mesh
v
hernia_mesh/other_mesh/other_device
hernia_mesh
v
other_mesh
hernia_mesh/other_mesh
v
other_device
IC statistic using BCPNN MCMC method (null value = 0)
Date
2014
2016
2018
Pain score threshold
0.01
0.02
0.03
0.04
0.05
0.06
0.08
0.09
0.1
reach_sig
FALSE
TRUE

6 Session information

```r
format(Sys.time(), '%d %b %Y')
```

```
[1] "17 Jul 2023"
```

```r
Sys.info() %>% as.data.frame(.)
```

```
                              .
sysname                 Windows
release                  10 x64
version             build 19044
nodename        DESKTOP-R5P5N23
machine                  x86-64
login                        ty
user                         ty
effective_user               ty
```

```r
sessionInfo()
```

```
R version 4.2.2 (2022-10-31 ucrt)
Platform: x86_64-w64-mingw32/x64 (64-bit)
Running under: Windows 10 x64 (build 19044)

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] ggplot2_3.4.1   lubridate_1.9.2 forcats_1.0.0   tidyr_1.3.0
```

```
 [9] 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] generics_0.1.3   vctrs_0.6.3      hms_1.1.2        bit64_4.0.5
[25] grid_4.2.2       tidyselect_1.2.0 glue_1.6.2       R6_2.5.1
[29] fansi_1.0.4      rmarkdown_2.20   farver_2.1.1     tzdb_0.3.0
[33] purrr_1.0.1      magrittr_2.0.3   scales_1.2.1     ellipsis_0.3.2
[37] htmltools_0.5.4  assertthat_0.2.1 xtable_1.8-4     colorspace_2.1-0
[41] labeling_0.4.2   utf8_1.2.3       munsell_0.5.0
```