```
library(readr)
library(dplyr)
library(gtools)
library(ggplot2)
library(scales)

set.seed(42)

if (!dir.exists("figures")) dir.create("figures")
if (!dir.exists("results")) dir.create("results")

N <- 10^6  # Set the simulation size
```

Compare mutation proportions among myeloid neoplasms

Read neoplasm data

Read the number of times each of l codons were mutated across patients with each disease d,

$$y_d = (y_{d1}, y_{d2}, \ldots, y_{dl}).$$

```
(df <- filter(read_csv("data.csv", show_col_types=F),
              AML>0 | MDS>0 | `AML-MRC`>0))  # Disregard sites with no mutations
```

```
## # A tibble: 121 x 4
##     site   AML   MDS `AML-MRC`
##    <dbl> <dbl> <dbl>     <dbl>
##  1     4     0     1         0
##  2     9     1     0         0
##  3    11     1     0         0
##  4    23     1     0         0
##  5    39     0     0         1
##  6    46     0     1         0
##  7    47     0     1         0
##  8    48     0     1         0
##  9    54     1     0         0
## 10    72     1     0         0
## # i 111 more rows
```

```
(apply(df[,2:4], 2, sum))  # Compute the sample size of each disease
```

```
##     AML     MDS AML-MRC
##     411     286     113
```

```
(l <- nrow(df))  # The number of sites considered
```

```
## [1] 121
```

```
hotspots <- c(175, 220, 245, 248, 249, 273, 282)
```

Sample posterior proportions of mutations

We will use the counts across all diseases to set an empirical prior $\theta_d \overset{\text{iid}}{\sim} \text{Dirichlet}(\alpha)$ over the relative probabilities of mutation at each codon, where $\alpha_i = \sum_d y_{di}$.

If we assume $y_d \sim \text{Multinomial}(\sum y_d, \theta_d)$, then the posterior $\theta_d | y_d \sim \text{Dirichlet}(\alpha + y_d)$.

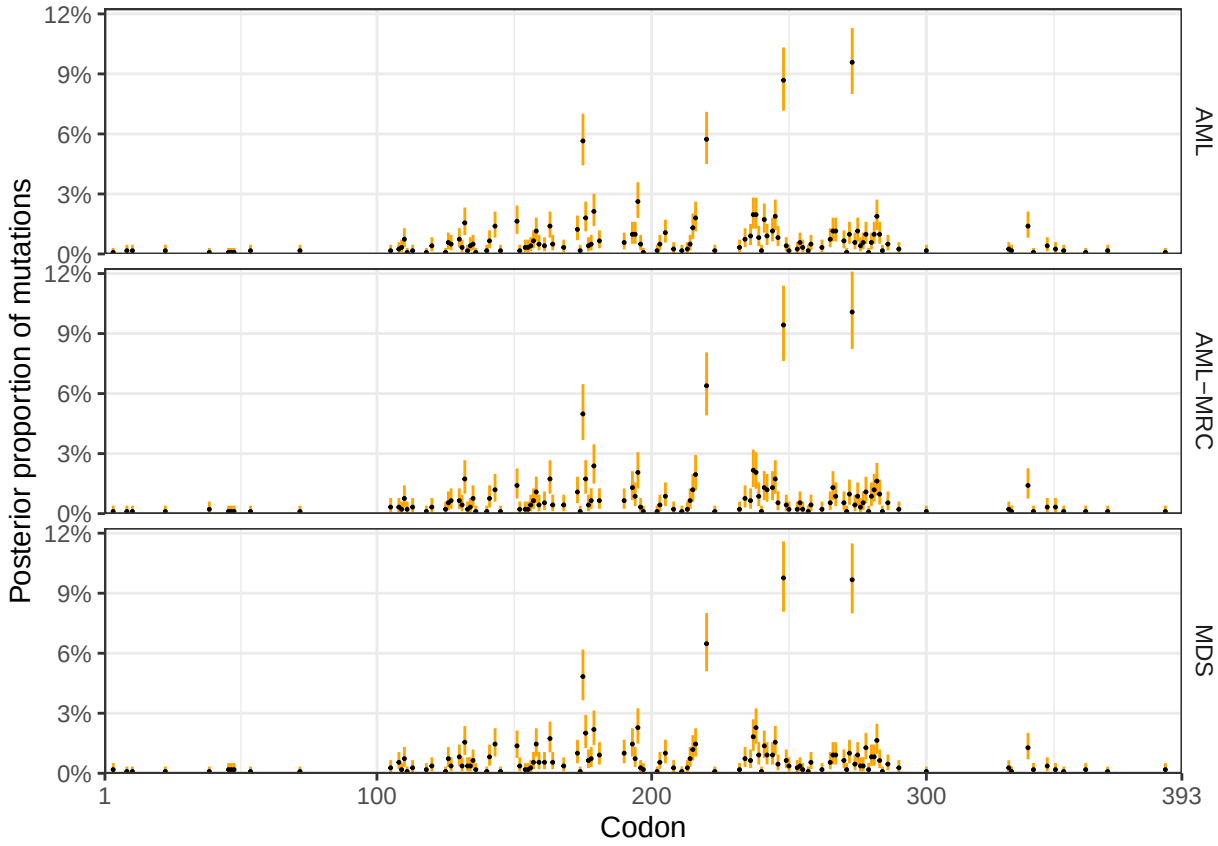
```
# Sample the posterior
prior <- apply(df[2:4], 1, sum)
posts <- list()
for (di in 2:4)
  posts[[names(df)[di]]] <- rdirichlet(N, prior + df[[di]])
```

```
# Compute posterior distribution statistics
compute_theta_stats <- function(posts) {
  thetas <- list(disease=rep(names(posts), each=l),
                 site=rep(df$site, length(posts)))
  for (d in names(posts)) {
    thetas[["mean"]] <- c(thetas[["mean"]], apply(posts[[d]], 2, mean))
    thetas[["q025"]] <- c(thetas[["q025"]], apply(posts[[d]], 2, quantile, probs=0.025))
    thetas[["q975"]] <- c(thetas[["q975"]], apply(posts[[d]], 2, quantile, probs=0.975))
  }
  as_tibble(thetas)
}

theta_df <- compute_theta_stats(posts)
write_csv(theta_df, "results/proportions_blood.csv")
```

```
# Visualize inferred mutation proportions
plot_thetas <- function(theta_df) {
  ggplot(theta_df, aes(x=site)) +
    geom_segment(aes(xend=site, y=q025, yend=q975), color="orange") +
    geom_point(aes(y=mean), size=0.2) +
    facet_grid(rows=vars(disease)) +
    scale_x_continuous(breaks=c(1,100,200,300,393), limits=c(1,393), expand=c(0,0)) +
    scale_y_continuous(labels=percent_format(),
                       limits=c(0, max(theta_df$q975)+0.0015), expand=c(0,0)) +
    xlab("Codon") +
    ylab("Posterior proportion of mutations") +
    theme_bw() +
    theme(strip.placement="outside", strip.background=element_blank(),
          panel.grid.minor.y=element_blank())
}

(theta_plot <- plot_thetas(theta_df))
```




```
ggsave("figures/proportions_blood.pdf", theta_plot,
       width=7, height=4)
```

Sample posterior differences in mutation proportions between diseases

From the posterior we can sample $(\theta_d|y_d) - (\theta_{d'}|y_{d'})$, the difference between proportions of mutations at each codon for each pair of diseases d and d'.

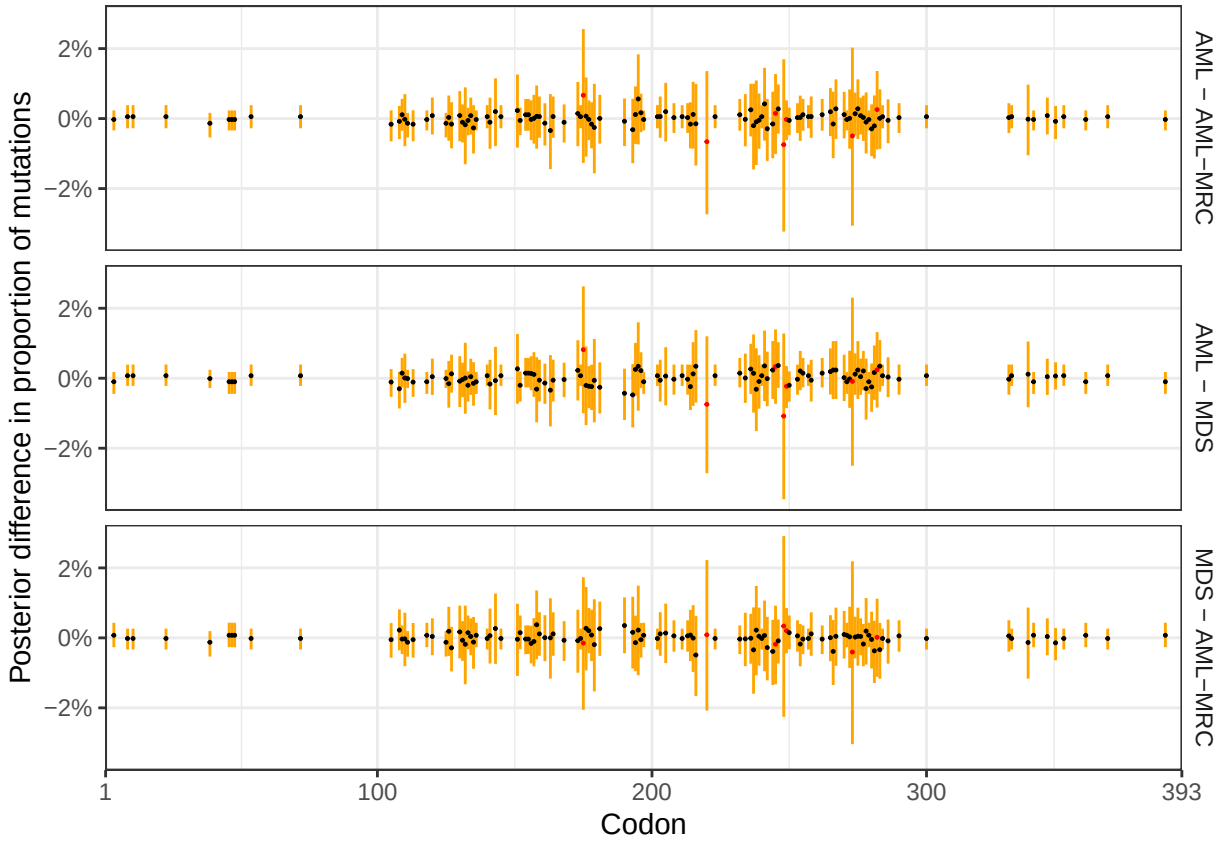
```
sample_diffs <- function(posts, combos) {
  diff_df <- c()
  for (combo in combos) {
    # Sample the posterior proportion differences between diseases
    diff <- posts[[combo[1]]] - posts[[combo[2]]]

    # Collect statistics of the differences
    diff_df <- rbind(diff_df,
                     data.frame(combo=paste(combo[1], combo[2], sep=" - "),
                                site=df$site,
                                mean=apply(diff, 2, mean),
                                q025=apply(diff, 2, quantile, probs=0.025),
                                q975=apply(diff, 2, quantile, probs=0.975)))
  }
  as_tibble(diff_df)
}
```

```
diff_df <- sample_diffs(posts,
                        list(c("AML", "MDS"), c("MDS", "AML-MRC"), c("AML", "AML-MRC")))
write_csv(diff_df, "results/differences_blood.csv")
```

```
plot_diffs <- function(diff_df) {
  ggplot(diff_df, aes(x=site)) +
    geom_segment(aes(xend=site, y=q025, yend=q975), color="orange") +
    geom_point(aes(y=mean, color=site %in% hotspots), size=0.2, show.legend=F) +
    scale_color_manual(values=c("black", "red")) +
    facet_grid(rows=vars(combo)) +
    scale_x_continuous(breaks=c(1,100,200,300,393), limits=c(1,393), expand=c(0,0)) +
    scale_y_continuous(labels=percent_format()) +
    xlab("Codon") +
    ylab("Posterior difference in proportion of mutations") +
    theme_bw() +
    theme(strip.placement="outside", strip.background=element_blank(),
          panel.grid.minor.y=element_blank())
}

(diff_plot <- plot_diffs(diff_df))
```




```
ggsave("figures/differences_blood.pdf", diff_plot,
       width=7, height=4)

# The number of positions whose 95% central credible interval excludes zero
with(diff_df, sum(0<q025 | 0>q975))
```

```
## [1] 0
```

Compare myeloid neoplasm mutation proportions with ISB-CGC

```
df <- read_csv("data.csv", show_col_types=F)
df$blood <- apply(df[2:4], 1, sum) # Pool the blood data
```

Read ISB-CGC data

> "For variants in exons, codon number at which the variant is located (1-393). If a variant spans more than one codon, (e.g. tandem variant or deletion of several bases) only the first (5') codon is entered. For variants in introns, 0 is entered." https://tp53.isb-cgc.org/help#MUT_id'

```
isb_codon_counts <- table(read_csv("TumorVariantDownload_r20.csv")$Codon_number)
isb <- c()
for (i in df$site) {
  if (as.character(i) %in% names(isb_codon_counts))
    isb <- c(isb, isb_codon_counts[[as.character(i)]])
  else
    isb <- c(isb, 0)
}
df$isb <- isb
```

```
df <- filter(df, blood>0 | isb>0)
(apply(df[,5:6], 2, sum))
```

```
## blood   isb
##   810 28851
```

```
(l <- nrow(df))
```

```
## [1] 378
```

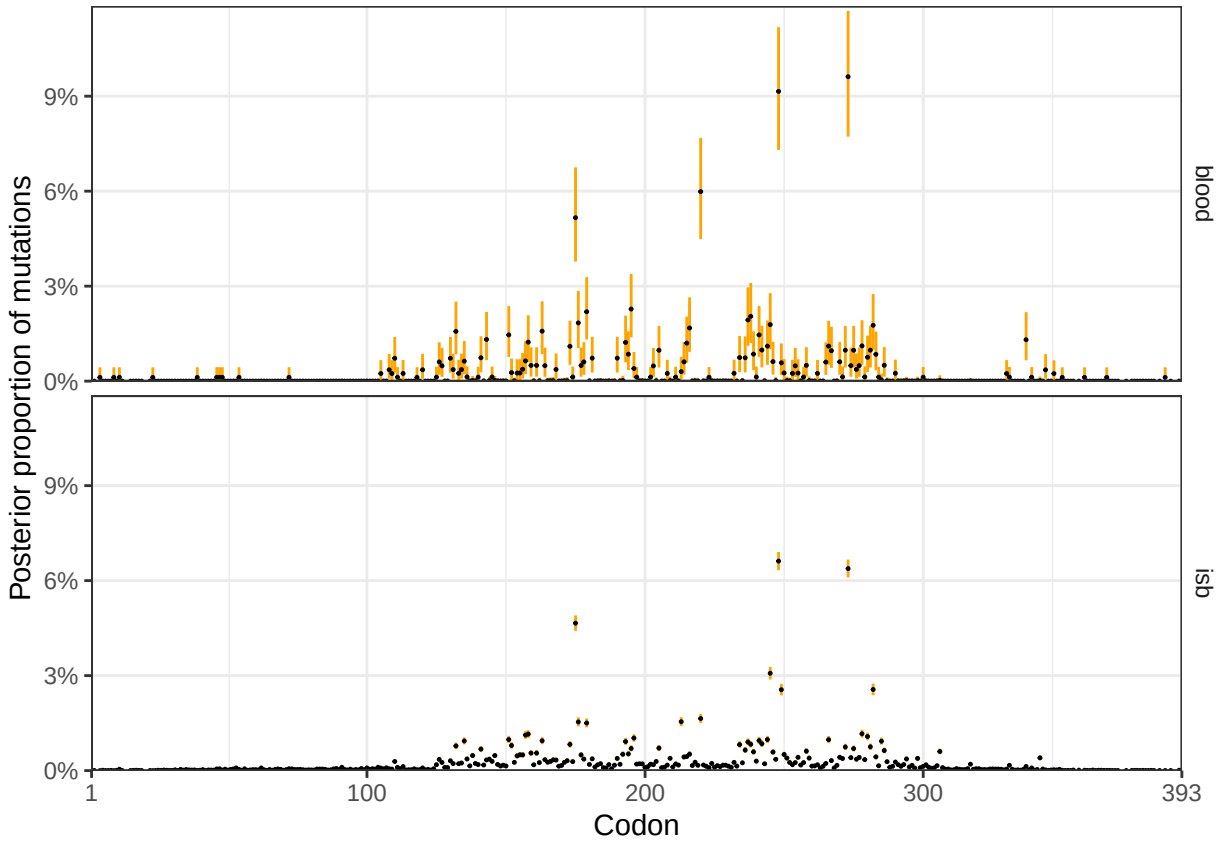
Sample posterior proportions of mutations

We will use the number of mutations at each codon observed in ISB-CGC to construct a prior θ_{blood} over the pooled myeloid neoplasm data. The prior is weighted such that $\sum \theta_{\text{blood}} = 35$. We will infer ISB-CGC proportions under a prior of $\theta_{\text{ISB}} = 0.1$.

```
posts <- list()
posts[["isb"]] <- rdirichlet(N, rep(0.1, l) + df$isb)
posts[["blood"]] <- rdirichlet(N, df$isb/sum(df$isb) * 35 + df$blood)

theta_df <- compute_theta_stats(posts)
write_csv(theta_df, "results/proportions_blood_ISB.csv")

(theta_plot <- plot_thetas(theta_df))
```

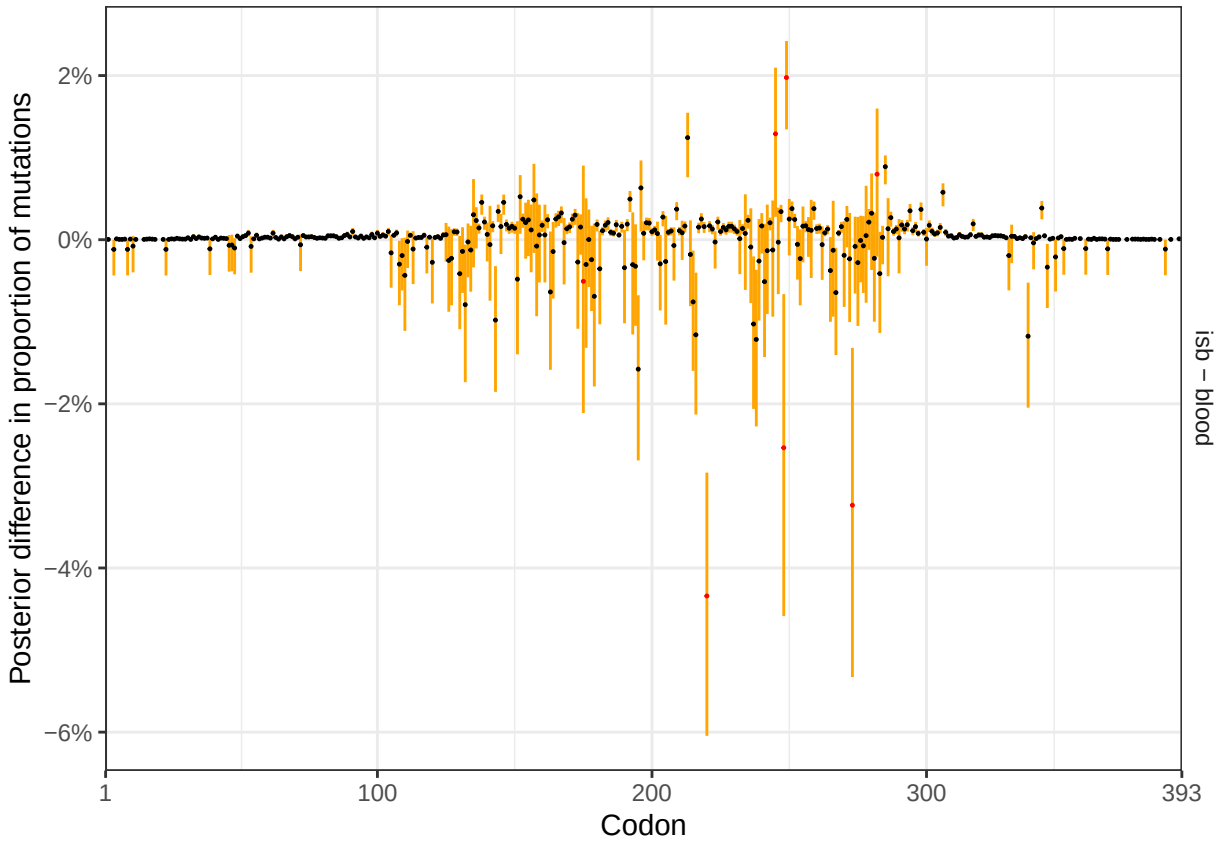



```
ggsave("figures/proportions_blood_ISB.pdf", theta_plot,
       width=7, height=4)
```

Sample posterior differences in mutation proportions

```
diff_df <- sample_diffs(posts, list(c("isb", "blood")))
write_csv(diff_df, "results/differences_blood_ISB.csv")

(diff_plot <- plot_diffs(diff_df))
```




```
ggsave("figures/differences_blood_ISB.pdf", diff_plot,
       width=7, height=4)

with(diff_df, sum(0<q025 | 0>q975))
```

```
## [1] 279
```