Fine-Gray regression and the problem of total failure probability exceeding one

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Contents

Introduction

The purpose of this document is to study the extent of the problem of the total failure probability exceeding one, when Fine-Gray models are fitted for all causes. We restrict attention here to the case of two causes of failure and a single covariate x which has has a standard normal distribution.

The problem of the total failure probability exceeding one

We start from two proportional subdistribution models, given by

$$F_1(t\,|\,x) = 1-(1-F_{10}(t))^{\gamma_1(x)}, \qquad F_2(t\,|\,x) = 1-(1-F_{20}(t))^{\gamma_2(x)},$$

where $F_{10}(t)$ and $F_{20}(t)$ are the baseline cumulative incidences of cause 1 and 2, respectively, corresponding to $x=0$, and $\gamma_1(x) = e^{\beta_1 x}$ and $\gamma_2(x) = e^{\beta_2 x}$ are the subdistribution hazard ratios for x of cause 1 and cause 2, respectively.

Fix a time point t, and define $p_1 = F_{10}(t)$ and $p_2 = F_{20}(t)$. Then the total failure probability is given by

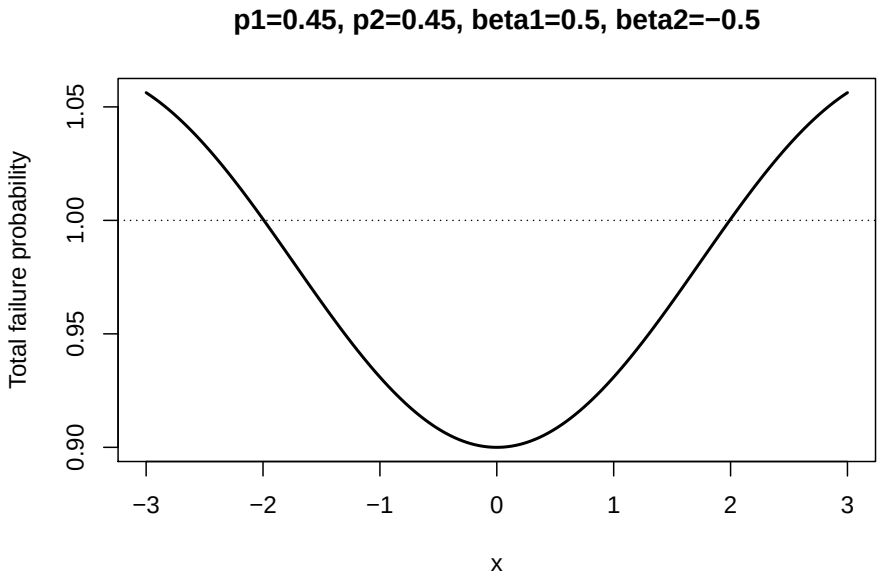
$$\text{TFP}(x) = F_1(t\,|\,x) + F_2(t\,|\,x) = 1-(1-p_1)^{\gamma_1(x)} + 1-(1-p_2)^{\gamma_2(x)}.$$

What I will do in the remainder of this document is see, for given baseline cumulative incidence values at time t, p_1 and p_2, and for given β_1 and β_2, what values of x will result in non-admissible $\text{TFP}(x) > 1$. After determining what values of x result in non-admissible $\text{TFP}(x) > 1$, we can quantify the probability that this happens (knowing X comes from a standard normal distribution). Intuition says that $\text{TFP}(x) > 1$ will happen more frequently for higher p_1 and p_2, and for larger (in absolute value) β_1 and β_2.

I will start by defining the function `TFP`, and making a plot of $\text{TFP}(x)$ against x, for $p_1 = p_2 = 0.45$, and $\beta_1 = -\beta_2 = 0.5$, reasonably close to the simulation earlier, for $t = 20$.

```
TFP <- function(x, p1, p2, beta1, beta2)
  1 - (1-p1)^(exp(beta1*x)) + 1 - (1-p2)^(exp(beta2*x))
xseq <- seq(-3, 3, by=0.01)
p1 <- 0.45; p2 <- 0.45
beta1 <- 0.5; beta2 <- -0.5
plot(xseq, TFP(xseq, p1=p1, p2=p2, beta1=beta1, beta2=beta2), type="l", lwd=2,
     xlab="x", ylab="Total failure probability")
```

```
abline(h=1, lty=3)
title(main="p1=0.45, p2=0.45, beta1=0.5, beta2=-0.5")
```



We can find the points where TFP(x) crosses 1 by applying the function `uniroot`.

```
TFPmin1 <- function(x, p1, p2, beta1, beta2)
  1 - (1-p1)^(exp(beta1*x)) + 1 - (1-p2)^(exp(beta2*x)) - 1
# Positive x
TFPplus <- uniroot(TFPmin1, c(0, 10), p1=p1, p2=p2, beta1=beta1, beta2=beta2)$root
TFPplus
```

```
## [1] 1.992583
```

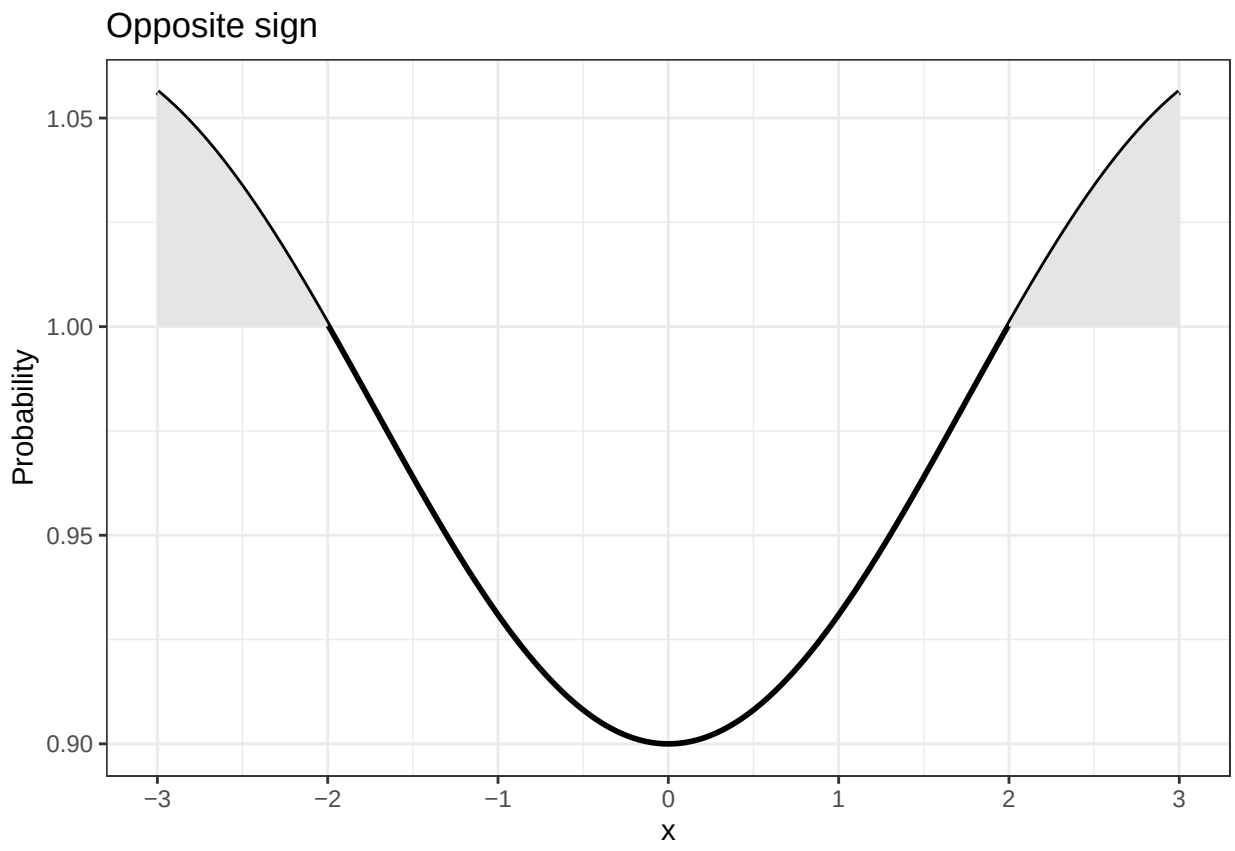
```
# Negative x
TFPmin <- uniroot(TFPmin1, c(-10, 0), p1=p1, p2=p2, beta1=beta1, beta2=beta2)$root
TFPmin
```

```
## [1] -1.992583
```

Let's go for a ggplot version of this.

```
library(ggplot2)
library(tidyverse)
tmp <- tibble(x=xseq, tfp=TFP(xseq, p1=p1, p2=p2, beta1=beta1, beta2=beta2))

ggp1 <- tmp %>%
  ggplot(aes(x = x, y = tfp)) +
  geom_line(size = 1) +
  labs(
    title = "Opposite sign",
    x = "x",
    y = "Probability"
  ) +
  scale_x_continuous(breaks = -3:3) +
```

```
  # We need two ribbons to avoid line joining them
  geom_ribbon(
    data = tmp %>% filter(tfp >= 1 & x < 0),
    aes(x = x, ymin = 1, ymax = tfp),
    fill = "grey90"
  ) +
  geom_ribbon(
    data = tmp %>% filter(tfp >= 1 & x >= 0),
    aes(x = x, ymin = 1, ymax = tfp),
    fill = "grey90"
  ) +
  theme_bw()
ggp1
```



The corresponding normal probabilities are given by

```
pnorm(TFPplus, lower.tail=FALSE)
```

```
## [1] 0.02315354
```

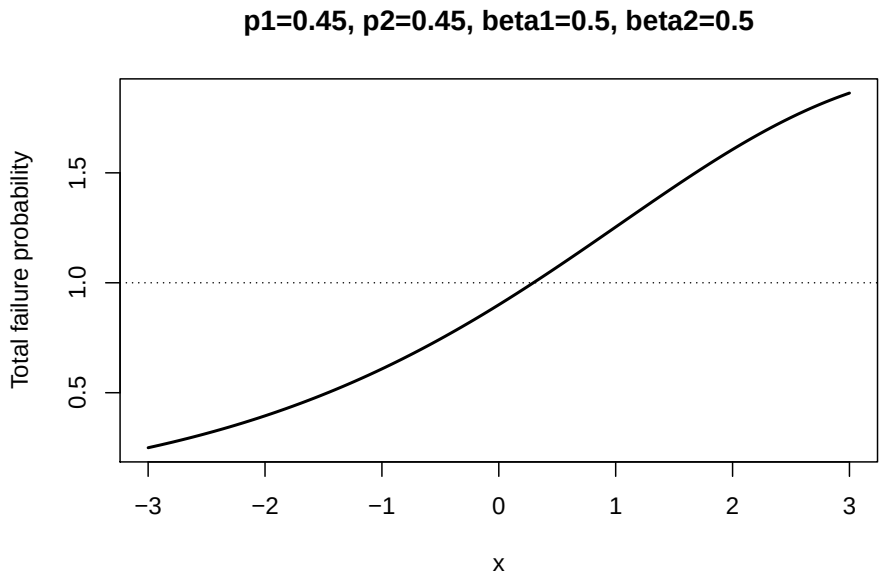
```
pnorm(TFPmin, lower.tail=TRUE)
```

```
## [1] 0.02315354
```

The sum of these probabilities, 0.0463071, is the probability of a total failure probability exceeding one, for the above values of p_1, p_2, β_1 and β_2.

Let's have a look at $\beta_1 = \beta_2 = 0.5$.

```
xseq <- seq(-3, 3, by=0.01)
p1 <- 0.45; p2 <- 0.45
beta1 <- 0.5; beta2 <- 0.5
plot(xseq, TFP(xseq, p1=p1, p2=p2, beta1=beta1, beta2=beta2), type="l", lwd=2,
     xlab="x", ylab="Total failure probability")
abline(h=1, lty=3)
title(main="p1=0.45, p2=0.45, beta1=0.5, beta2=0.5")
```




```
# Positive x
TFPplus <- uniroot(TFPmin1, c(0, 10), p1=p1, p2=p2, beta1=beta1, beta2=beta2)$root
TFPplus
```

```
## [1] 0.2958484
```

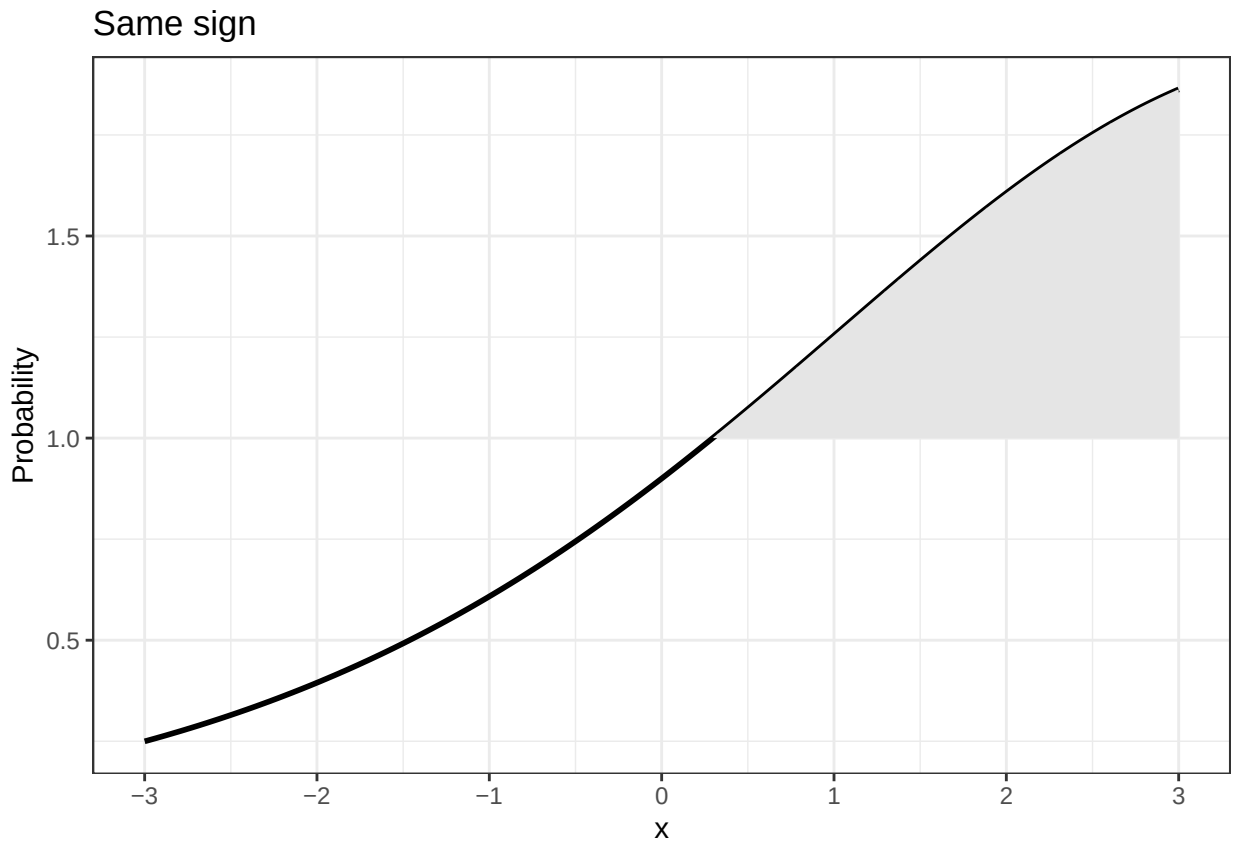
```
pnorm(TFPplus, lower.tail=FALSE)
```

```
## [1] 0.3836729
```

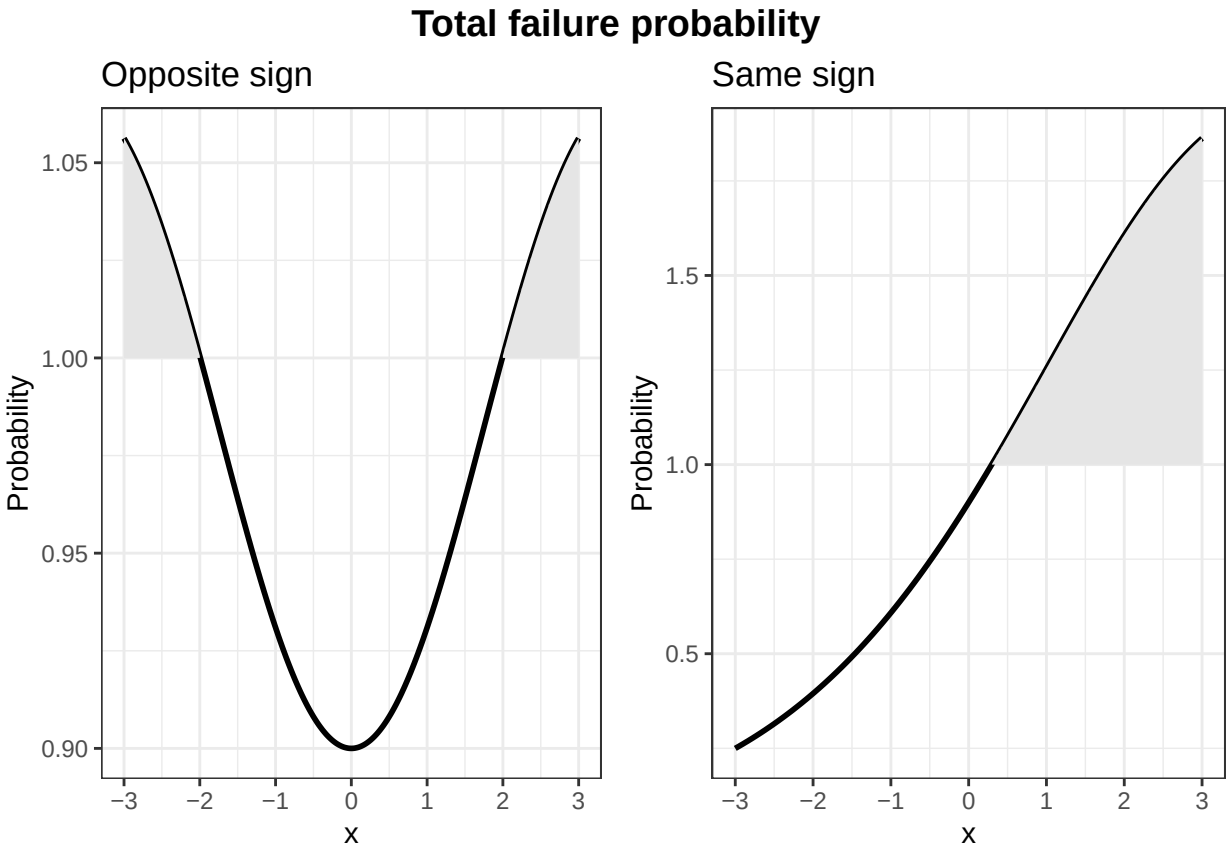
The ggplot version of this plot is now combined with the previous (opposite sign) ggplot.

```
tmp <- tibble(x=xseq, tfp=TFP(xseq, p1=p1, p2=p2, beta1=beta1, beta2=beta2))

ggp2 <- tmp %>%
  ggplot(aes(x = x, y = tfp)) +
  geom_line(size = 1) +
  labs(
    title = "Same sign",
    x = "x",
    y = "Probability"
  ) +
  scale_x_continuous(breaks = -3:3) +

  # We need two ribbons to avoid line joining them
  geom_ribbon(
    data = tmp %>% filter(tfp >= 1 & x >= 0),
```

```
    aes(x = x, ymin = 1, ymax = tfp),
    fill = "grey90"
  ) +
  theme_bw()
ggp2
```




```
library(ggpubr)
figure <- ggarrange(ggp1, ggp2, common.legend=TRUE)
annfigure <- annotate_figure(figure,
                             top = text_grob("Total failure probability", face = "bold", size = 14))
annfigure
```




```
# ggsave("TFPplots.pdf")
```

We can make all this into a function that finds the probability of a total failure probability exceeding one, for given values of p_1, p_2, β_1 and β_2.

```
pTFPexc1 <- function(p1, p2, beta1, beta2, boundary=10) {
  TFPmin1 <- function(x, p1, p2, beta1, beta2)
    1 - (1-p1)^(exp(beta1*x)) + 1 - (1-p2)^(exp(beta2*x)) - 1
  pTFPplus <- pTFPmin <- 0
  # Find root for positive x, will work unless beta1 and beta2 are both negative
  if (!(beta1<0 & beta2<0)) {
    TFPplus <- uniroot(TFPmin1, c(0, boundary), p1=p1, p2=p2, beta1=beta1, beta2=beta2)$root
    pTFPplus <- pnorm(TFPplus, lower.tail=FALSE)
  }
  # Find root for negative x, will work unless beta1 and beta2 are both positive
  if (!(beta1>0 & beta2>0)) {
    TFPmin <- uniroot(TFPmin1, c(-boundary, 0), p1=p1, p2=p2, beta1=beta1, beta2=beta2)$root
    pTFPmin <- pnorm(TFPmin, lower.tail=TRUE)
  }
  return(pTFPplus + pTFPmin)
}
pTFPexc1(p1=0.45, p2=0.45, beta1=0.5, beta2=-0.5, boundary=10)
```

```
## [1] 0.04630708
```

We can now check our intuition, which says that $\text{TFP}(x) > 1$ will happen more frequently for higher p_1 and p_2, and for larger (in absolute value) β_1 and β_2.

```
pTFPexc1(p1=0.46, p2=0.46, beta1=0.5, beta2=-0.5, boundary=10)
```

```
## [1] 0.07637164
```

```
pTFPexc1(p1=0.45, p2=0.45, beta1=0.6, beta2=-0.6, boundary=10)
```

```
## [1] 0.09681915
```

So, in a situation where Fine-Gray models have been fitted for cause 1 and cause 2, if the estimated cumulative incidences at some time point t are 0.45 for both causes, and the estimated β_1 and β_2 are equal to 0.6 and -0.6, respectively, then for 10% of the patients the model-based total failure probability (TFP) will exceed one.

If β_1 and β_2 have the same sign the probability of TFP exceeding one is a lot larger for the same p_1 and p_2.

```
pTFPexc1(p1=0.45, p2=0.45, beta1=0.5, beta2=0.5, boundary=10)
```

```
## [1] 0.3836729
```

What is perhaps less obvious is that, while keeping the total baseline cumulative incidence $p_1 + p_2$ constant, and the total effect size $|\beta_1| + |\beta_2|$ constant, the case $p_1 = p_2$ and $\beta_1 = -\beta_2$ is the most favorable in keeping the TFP below 1.

```
# Base case
pTFPexc1(p1=0.45, p2=0.45, beta1=0.5, beta2=-0.5, boundary=10)
```

```
## [1] 0.04630708
```

```
# Making p1 unequal to p2
pTFPexc1(p1=0.46, p2=0.44, beta1=0.5, beta2=-0.5, boundary=10)
```

```
## [1] 0.04656941
```

```
# Making beta1 unequal to -beta2
pTFPexc1(p1=0.45, p2=0.45, beta1=0.51, beta2=-0.49, boundary=10)
```

```
## [1] 0.04779931
```

```
# Making p1 unequal to p2 and beta1 unequal to -beta2
pTFPexc1(p1=0.46, p2=0.44, beta1=0.51, beta2=-0.49, boundary=10)
```

```
## [1] 0.04940599
```

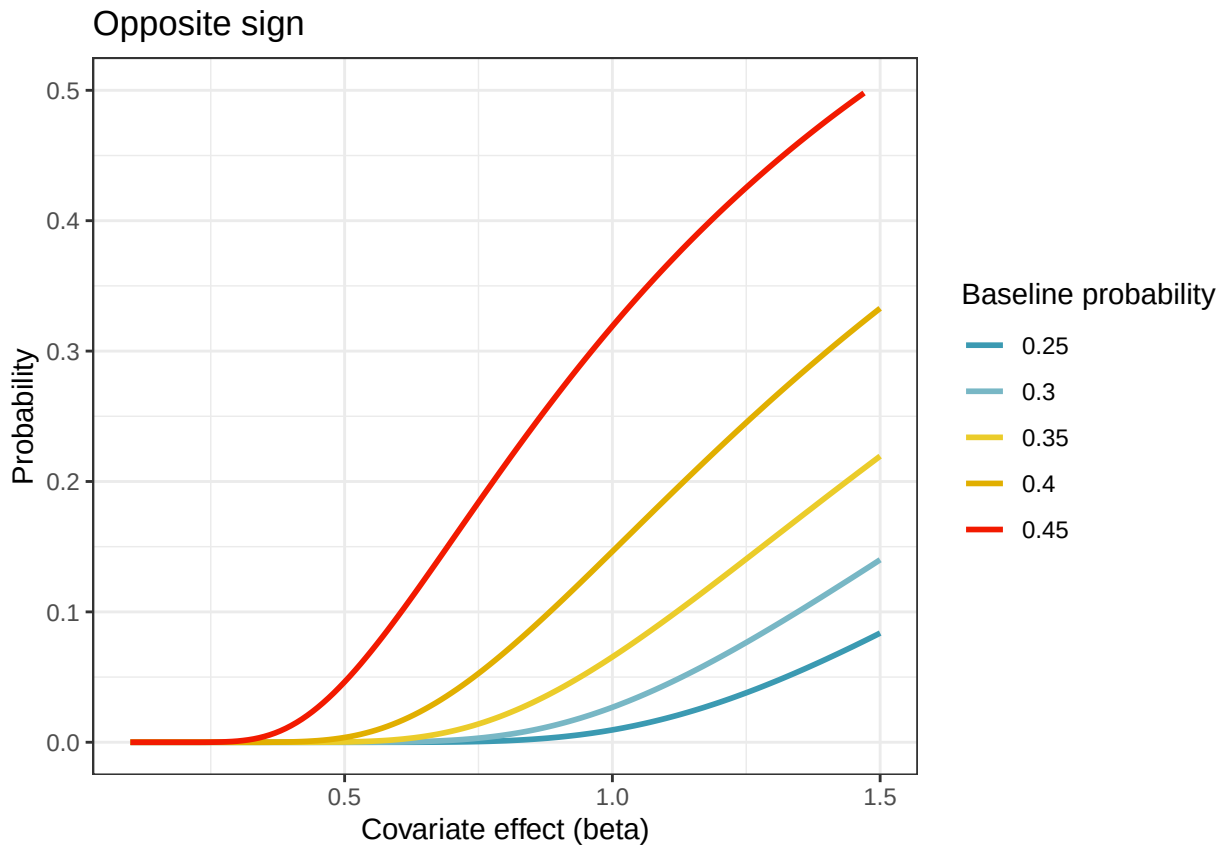
In showing that TFP exceeding one is a problem we will therefore restrict to $p_1 = p_2$ and $\beta_1 = -\beta_2$; changing to $p_1 \neq p_2$ or $\beta_1 \neq -\beta_2$ will increase the probability of TFP exceeding one, subject to the total baseline cumulative incidence $p_1 + p_2$, and the total effect size $|\beta_1| + |\beta_2|$ staying the same. That simplifies life, because we only have to keep track of two variables, $p = p_1 = p_2$ and $\beta = |\beta_1| = -|\beta_2|$.

I will now record the probabilities of TFP exceeding one for a set of baseline probabilities $p = 0.25, 0.3, \ldots, 0.45$, and a range of β values, ranging from 0.1 to 2, and make a nice plot of it.

```
pseq <- seq(0.25, 0.45, by=0.05)
betaseq <- seq(0.1, 1.5, by=0.01)
np <- length(pseq)
nbeta <- length(betaseq)
# Store results in res
res <- matrix(NA, nbeta, np)
for (i in 1:np) {
  p <- pseq[i]
  for (j in 1:nbeta) {
    beta <- betaseq[j]
```

```
    boundary <- ifelse(beta>0.3, 10, 100) # trial and error
    res[j, i] <- pTFPexc1(p1=p, p2=p, beta1=beta, beta2=-beta, boundary=boundary)
  }
}
# Prepare for plotting
library(wesanderson)
dfres <- data.frame(beta=rep(betaseq, np), p=rep(pseq, each=nbeta), prob=as.vector(res))
dfres$p <- as.factor(dfres$p)
# Plot
ggp <- ggplot(data = dfres,
              aes(x=beta, y=prob, col=p)) +
  geom_line(size=1) +
  labs(title = "Opposite sign",
       x = "Covariate effect (beta)",
       y = "Probability") +
  ylim(0, 0.5) +
  scale_x_continuous(breaks=c(0, 0.5, 1, 1.5)) +
  scale_color_manual(name="Baseline probability", values=wes_palette(n=5, name="Zissou1")) +
  theme_bw()
print(ggp)
```

```
## Warning: Removed 3 row(s) containing missing values (geom_path).
```

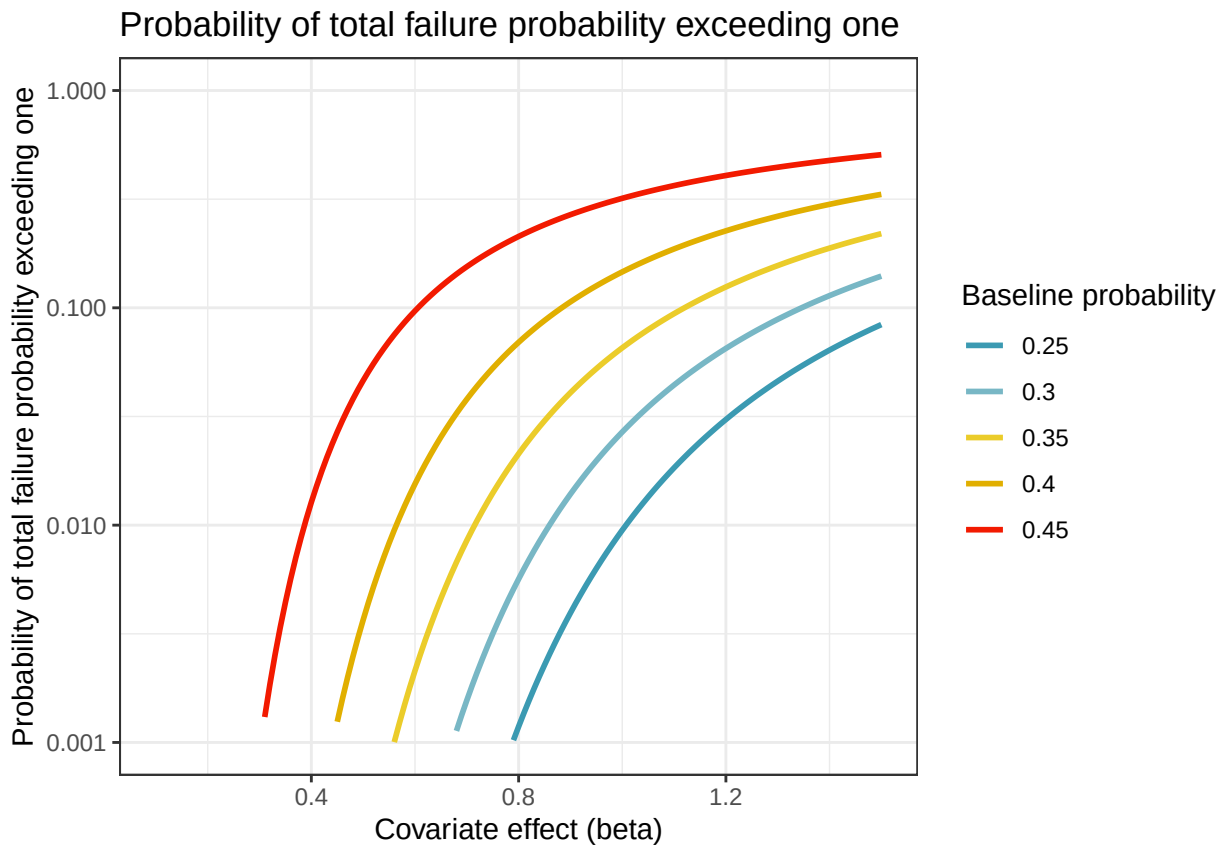



```
ggpoppsign <- ggp
```

Here is the same plot, but then with logarithmic scale on the y-axis.

```
ggp <- ggplot(data = dfres,
              aes(x=beta, y=prob, col=p)) +
  geom_line(size=1) +
  labs(title = "Probability of total failure probability exceeding one",
       x = "Covariate effect (beta)",
       y = "Probability of total failure probability exceeding one") +
  scale_color_manual(name="Baseline probability", values=wes_palette(n=5, name="Zissou1")) +
  scale_y_log10(limits=c(0.001, 1)) +
  theme_bw()
print(ggp)
```

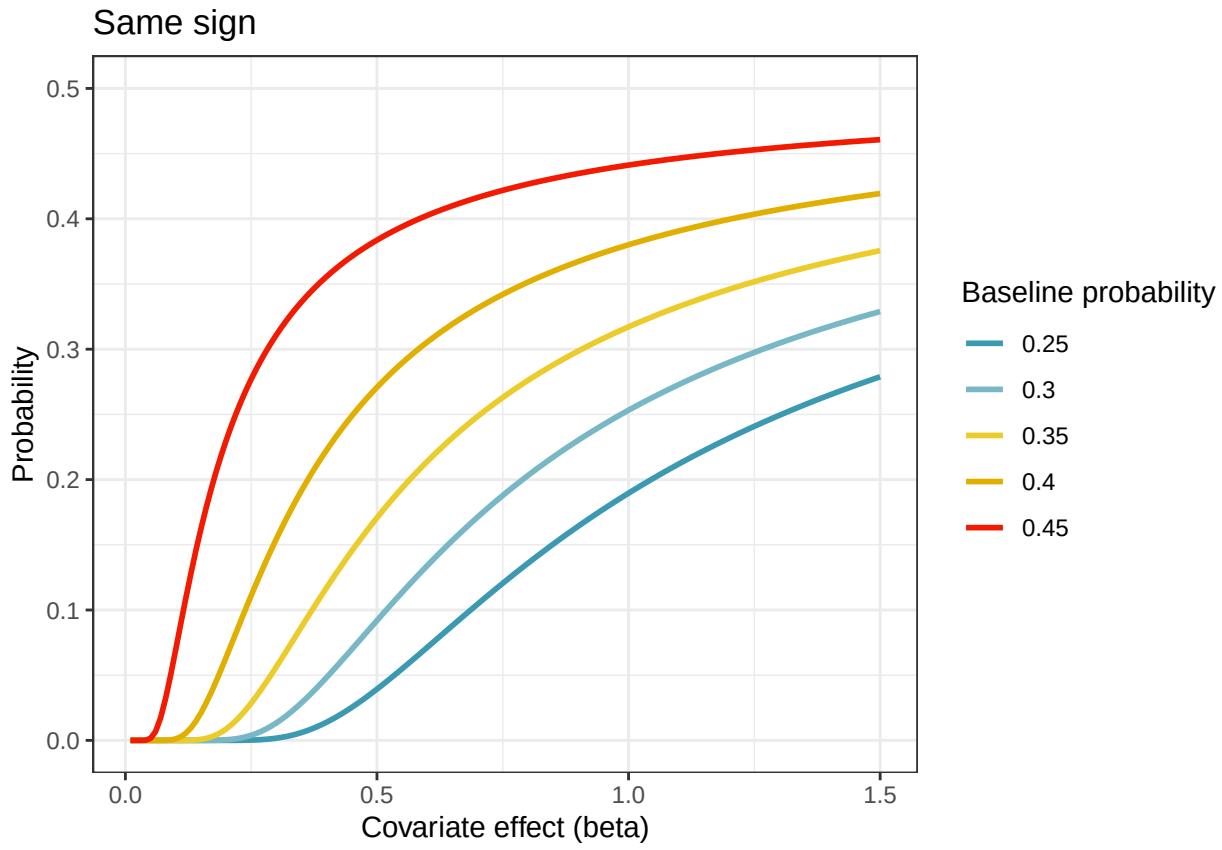
```
## Warning: Removed 229 row(s) containing missing values (geom_path).
```



It may be interesting to do the same thing, now for β_1 and β_2 having the same sign.

```
betaseq <- seq(0.01, 1.5, by=0.01)
nbeta <- length(betaseq)
res <- matrix(NA, nbeta, np)
for (i in 1:np) {
  p <- pseq[i]
  for (j in 1:nbeta) {
    beta <- betaseq[j]
    boundary <- ifelse(beta>0.3, 10, 100) # trial and error
    res[j, i] <- pTFPexc1(p1=p, p2=p, beta1=beta, beta2=beta, boundary=boundary)
  }
}
dfres <- data.frame(beta=rep(betaseq, np), p=rep(pseq, each=nbeta), prob=as.vector(res))
```

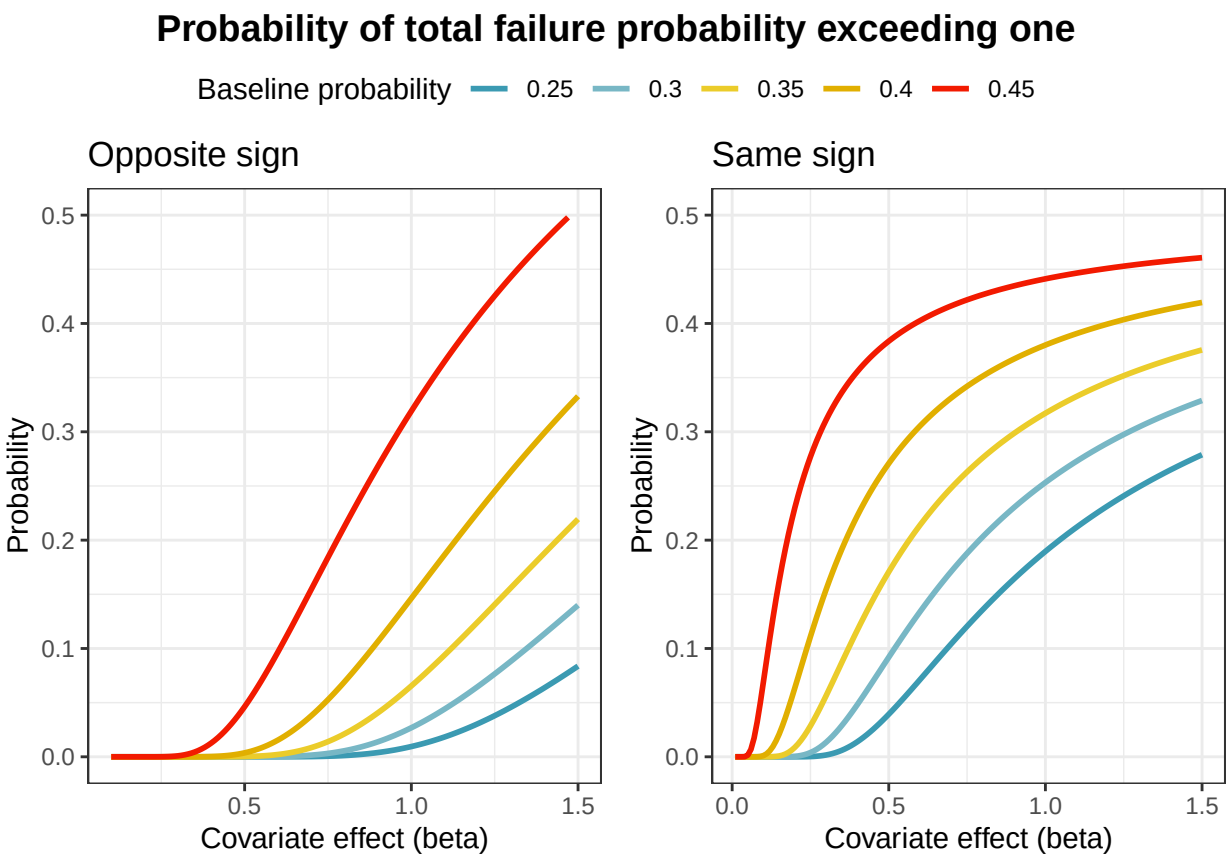
```r
dfres$p <- as.factor(dfres$p)
# Plot
ggp <- ggplot(data = dfres,
              aes(x=beta, y=prob, col=p)) +
  geom_line(size=1) +
  labs(title = "Same sign",
       x = "Covariate effect (beta)",
       y = "Probability") +
  ylim(0, 0.5) +
  scale_x_continuous(breaks=c(0, 0.5, 1, 1.5)) +
  scale_color_manual(name="Baseline probability", values=wes_palette(n=5, name="Zissou1")) +
  theme_bw()
print(ggp)
```




```r
ggpsamesign <- ggp

figure <- ggarrange(ggpoppsign, ggpsamesign, common.legend=TRUE)
```

```
## Warning: Removed 3 row(s) containing missing values (geom_path).

## Warning: Removed 3 row(s) containing missing values (geom_path).
```

```r
annfigure <- annotate_figure(figure,
                             top = text_grob("Probability of total failure probability exceeding one",
annfigure
```




```
# ggsave("TFPexc1plots.pdf")
```