Evaluation of Three Survival Models Using Simulation

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Outlines

- **Simulate survival data under 3 different distribution**
- **Fit 3 survival models under each baseline hazard function**
- **Evaluate accuracy of estimated treatment efficiency**
- **Evaluate models' robustness against misspecified baseline functions**

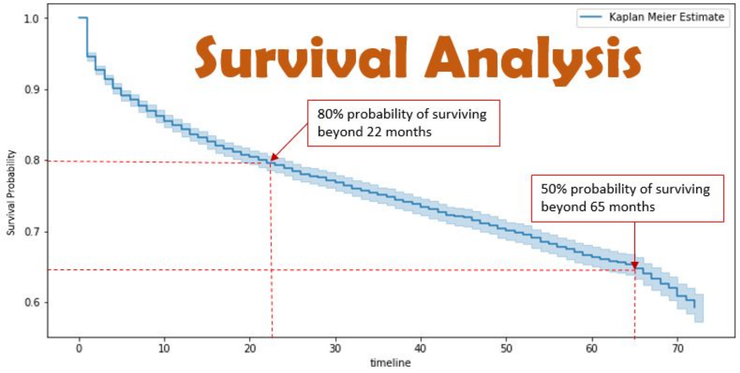
Objectives

A simulation study

Compare the accuracy and efficiency of the estimated treatment effects of three models (Exponential, Weibull, and Cox proportional-hazards models)

Evaluate their robustness against misspecified baseline hazard functions

Make practical recommendation for users to choose a suitable model



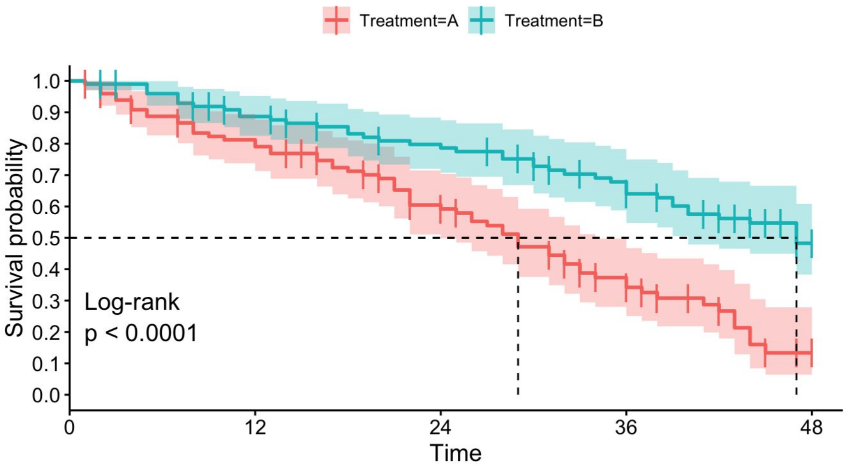
Background

- **Outcome measures**
  - Survival time
  - Outcome status

- **Hazard rate**
  - Probability of surviving beyond time t

- **Censoring**
  - loss to follow-up or termination of the experiment before the outcome state of subjects is observed

- **Models**
  - Proportional hazards models
  - Kaplan-Meier models



Statistical Methods
- Generating Survival Time

Survival Function $S(t) = \Pr(T > t) = \int_0^{\infty} f(t)dt = 1 - F(t)$

Hazard Function $h(t) = \lim_{\Delta t \to 0} \frac{\Pr(T \in (t, t+\Delta t) | T > t|)}{\Delta t} = \frac{f(t)}{S(t)} = \frac{f(t)}{1 - F(t)} = \frac{\partial}{\partial t} \ln [S(t)]$

$S(t) = e^{-H(t)}$

Hazard Ratio $h_i(t \mid X) = h_0(t) \cdot e^{X\beta}$, for i-th patient at time t

Then, $F(t) = 1 - e^{-H_0(t) \cdot e^{X\beta}} = U$ ~ Uniform(0,1)

Finally, we have $T = F^{-1}(u) = H_0^{-1}\left(-\frac{\ln(1-u)}{e^{X\beta}}\right)$, where U ~ Uniform(0,1)

Statistical Methods

- Three failure time models

Parameter/Function	Distributions		
	Exponential	**Weibull**	**Gompertz**
Parameter	$\lambda > 0$	$\lambda > 0,\ \gamma > 0$	$\lambda > 0,\ \alpha \in R$
Baseline hazard function	$h_0(t) = \lambda$	$h_0(t) = \lambda\gamma t^{\gamma-1}$	$h_0(t) = \lambda e^{\alpha t}$
Cumulative hazard function	$H_0(t) = \lambda t$	$H_0(t) = \lambda \cdot t^{\gamma}$	$H_0(t) = \frac{\lambda}{\alpha}\left(e^{\alpha t} - 1\right)$
Survival time	$T = -\frac{\ln(u)}{\lambda \cdot e^{X\beta}}$	$T = \left(-\frac{\ln(u)}{\lambda \cdot e^{X\beta}}\right)^{\frac{1}{\gamma}}$	$T = \frac{1}{\alpha} \cdot \ln\left(1 - \frac{\alpha \cdot \ln(u)}{\lambda e^{X\beta}}\right)$

Design of Simulation

```r
# Generate survival data
genn_dat <- function(n, lambda, beta, gamma, alpha, dist) {
  # Generate key for each observation
  id <- seq(1:n)
  # Predictor X (treatment = 1; control = 0)
  x <- rbinom(n, size = 1, prob = 0.5)
  ## --- Generate Survival Time T ---
  U <- runif(n)
  # Use exponential distribution
  expo <- function(U, lambda, x, beta) {
    -log(U) / (lambda * exp(x * beta))}
  # Use weibull distribution
  weibull <- function(U, lambda, x, gamma, beta) {
    (-log(U) / (lambda * exp(x * beta))) ^ (1 / gamma)}
  # Use 'Cox' distribution -- gompertz
  gompertz <- function(U, alpha, lambda, x, beta) {
    (1 / alpha) * (1 - alpha * log(U) / (lambda * exp(x * beta)))
  }
  # Select different baseline functions
  if (dist == "expo") {
    surv_t <- expo(U, lambda, x, beta)}
  else if (dist == "weibull") {
    surv_t <- weibull(U, lambda, x, gamma, beta)
  }
  else {
    surv_t <- gompertz(U, alpha, lambda, x, beta)
  }
  return(
    df = data.frame(
      id = id,
      treatment = x,
      time = surv_t
    )
  )
}
```

Step 1: Data Generation

We assumed that the predictor X follows an n times Bernoulli distribution with a probability equal to 0.5. Using Unif(0,1) as a random number generator, we can put those parameters into the inverse functions we derived before to get the survival data.

id	treatment	time
1	1	0.05360855
2	0	1.02021761
3	1	0.17072813
4	0	0.23454481
5	0	0.16339742
6	1	0.16925111

Design of Simulation

Step 2: Model Fitting

Dataset generated in each simulation above is used for fitting all three different proportional-hazards models which are the exponential, Weibull, and Cox proportional-hazards respectively to predict the treatment effects

	expo_beta	weibull_beta	cox_beta
	<dbl>	<dbl>	<dbl>
1	0.494	0.519	0.466
2	0.318	0.359	0.355
3	0.348	0.341	0.283
4	0.495	0.494	0.478
5	0.281	0.273	0.293
6	0.601	0.582	0.621

Step 3: Prediction Evaluation

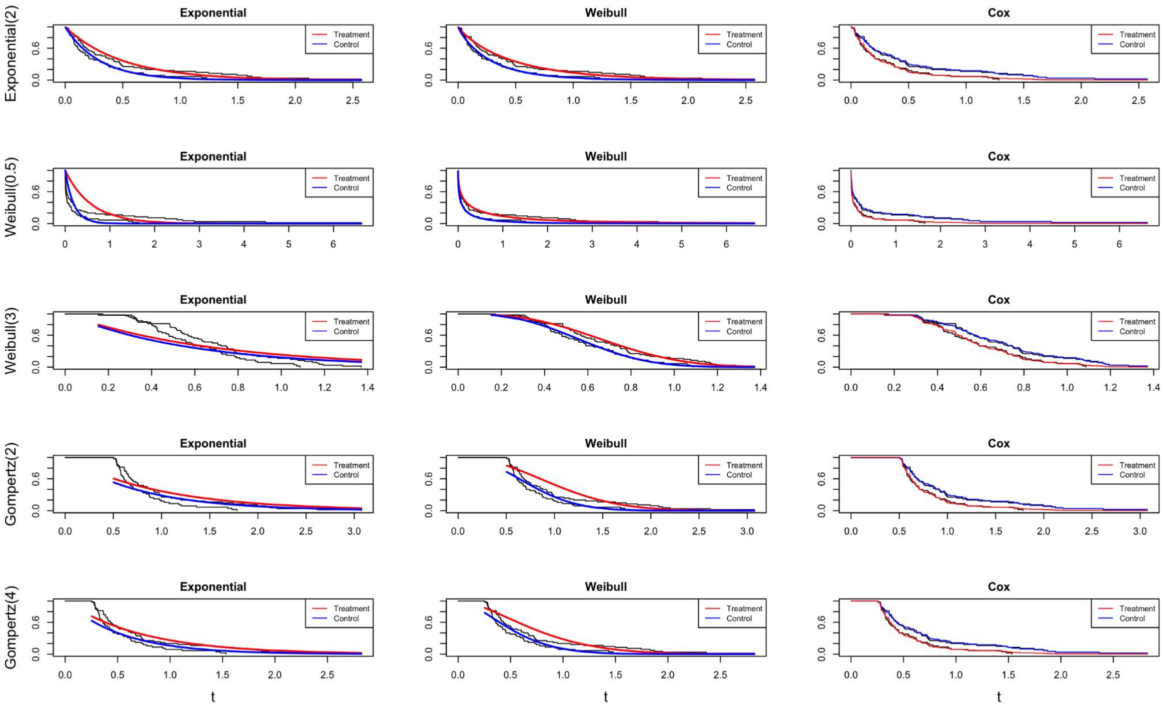
Calculate MSE, mean(SD) of the treatment effects for three different models

Results

The Goodness-of-fit model:

1. **Cox model matches all the datasets**
2. **Weibull model fits datasets generated by Exponential and Weibull well**
3. **Exponential only performs well when dataset is simulated by exponential**

Figure 1. Models curve versus Kaplan-Meier curve



Results

MSEs and Mean of β:

1. **Exponential and Weibull model perform well when their baseline function is taken for generating data**
2. **Cox model performs much more accurately regardless of the different datasets**

Table1. MSEs of β from three different models using 1000 simulations

Model	Exponential	Weibull(0.5)	Weibull(3)	Gompertz(2)	Gompertz(4)
Exponential	0.0406	0.4516	0.1153	0.0865	0.0523
Weibull	0.0448	0.0433	0.0414	0.1155	0.0895
Cox	0.0465	0.0431	0.0426	0.0458	0.0444

Table2. Mean (SD) of β from three different models using 1000 simulations

Model	Exponential	Weibull(0.5)	Weibull(3)	Gompertz(2)	Gompertz(4)
Exponential	0.501 (0.202)	0.999 (0.450)	0.168 (0.073)	0.219 (0.087)	0.306 (0.122)
Weibull	0.511 (0.212)	0.506 (0.208)	0.513 (0.203)	0.680 (0.288)	0.643 (0.263)
Cox	0.510 (0.215)	0.502 (0.208)	0.510 (0.206)	0.512 (0.214)	0.508 (0.211)

Conclusion and Discussion

Advantages and Disadvantages of the 3 models:

	Exponential	**Weibull**	**Cox**
Pros	Can estimate survival function S(t) and Hazard Ratio (HR)	Can estimate survival function S(t) and Hazard Ratio (HR)	Hazard can fluctuate with time; robust; don't need to specify the baseline hazard function
Cons	1. Not always realistic to assume a constant Hazard 2. Not robust to misspecification	Not robust to misspecification	Can not estimate the survival function S(t)

Conclusion and Discussion

- **Survival models have the best performance under their corresponding baseline**
- **We recommend Cox proportional model**
  - In general, best performance among the 3 survival models (MSE)
  - Robust against misspecified baseline hazard function
- **Limitations:**
  - We didn’t simulate right censoring
    - Unrealistic under the realistic settings
  - Only tried three baseline hazard functions

Questions?

Reference

[1] http://www.stat.columbia.edu/~madigan/W2025/notes/survival.pdf

[2] Wikipedia. “Gompertz-Makeham law of mortality”
https://en.wikipedia.org/wiki/Gompertz%E2%80%93Makeham_law_of_mortality

[3]Kalbfleisch, J.D. and Prentice, R.L. (2002). *The Statistical Analysis of Failure Time Data* (3rd ed.). Publisher: Wiley. DOI: 10.1002/9781118032985.

Thank you!