Survival Function Estimation with Recurrent Events: Case of Retinal Neural Firing

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The University of Iowa

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Introduction

Outline:

1. Introduction to Survival Analysis

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2. Survival Analysis with a Single Event

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5. Future Work

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  - Duration between administering a treatment and recovery.

Special Features of Survival Data

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  - Individuals whose survival times can not be analyzed because they have been lost to follow-up.
  - Occurance of an event due to a cause other than one of interest.

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- Let r be the number of event times amongst the individuals, so that $r \leq n$, where r does not include censored times and duplicate times are considered as one time.
- Now let $t_{(j)}$, for $j = 1, 2, 3, \ldots, r$, be the r ordered event times such that $t_{(1)} < t_{(2)} < \ldots t_{(r)}$.

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- A common way of estimating the survival function is the Kaplan-Meier estimator. (Kaplan, E.L & Meier P., 1958)

The Kaplan-Meier Estimator

- **Kaplan-Meier (Product Limit) Estimate:**

$$\widehat{S}(t) = \prod_{j=1}^{r} \left\{1 - \frac{d_j}{n_j}\right\}$$

$$\text{SE } \widehat{S}(t) \approx \widehat{S}(t) \left\{\sum_{j=1}^{r} \frac{d_j}{n_j(n_j - d_j)}\right\}^{\frac{1}{2}}$$

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- $(1-\alpha) * 100\%$ **Confidence Intervals of** $\widehat{S}(t)$**:**

$$\widehat{S}(t) \pm z_{\alpha/2} * \text{ SE } \widehat{S}(t)$$

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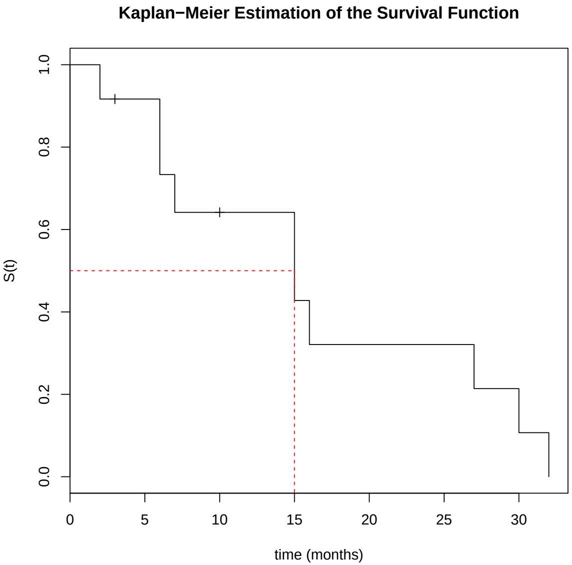
Illustrative Example of Kaplan-Meier

Example

Suppose there is a sample of 12 hemophiliacs under the age of 40 with HIV seroconversion.
Instead of using time intervals, exact times at which failures occured are used.
These times, in months, are listed below:

Patient	1	2	3	4	5	6	7	8	9	10	11	12
Months	2	3*	6	6	7	10*	15	15	16	27	30	32

NOTE: * denotes censored values.


Kaplan−Meier Estimation of the Survival Function
S(t)
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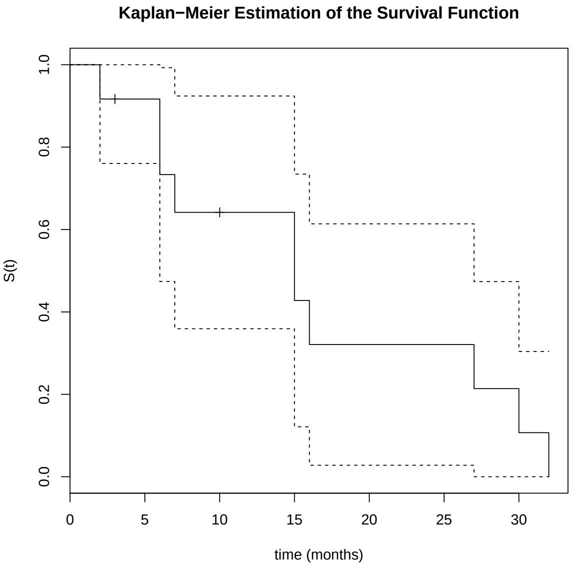
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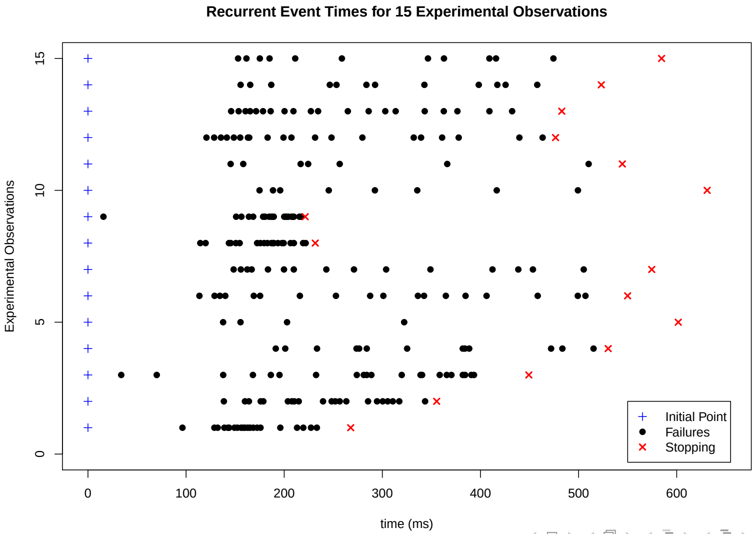
- Examples include migraines, seizures, heart attacks, strokes etc.

Time to Event Plot



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- Let T_{ij} be the time from the $(j-1)^{th}$ to the j^{th} event for subject i.
- Let the censoring time, C_i, be the time between the initial event and the end of follow-up for subject i.

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- Let m_i denote the index satisfying:

$$\sum_{j=1}^{m_i - 1} T_{ij} \leq C_i$$

and

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- Let m_i be the number of recurrent events for subject i.
m_i^* is the number of uncensored recurrent events for subject i.

$$m_i^* = \begin{cases} 1 & \text{if} \quad m_i = 1 \\ m_i - 1 & \text{if} \quad m_i \geq 2 \end{cases}$$

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- Let y_{ij} be our observed recurrence times defined by:

$$y_{ij} = \begin{cases} t_{ij} & \text{if} \quad j = 1, \ldots, m_i - 1 \\ t_{i,m_i}^{+} & \text{if} \quad j = m_i \end{cases}$$

Terminology

- Let $R^*(t)$ be the total mass of the risk set at time t be calculated as:

$$R^*(t) = \sum_{i=1}^{n} \left[\frac{a_i}{m_i^*} \sum_{j=1}^{m_i^*} I(y_{ij} \geq t) \right]$$

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  - $R^*(t)$ is the summation of the weighted average of the total number of observed uncensored recurrent times for a subject that are greater than or equal to t.

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- Let the mass evaluated at time t be:

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Wang and Chang Product-Limit Estimation (1999)

- Letting $y_1^*, y_2^*, \ldots, y_K^*$ be the ordered, and distinct uncensored times, Wang and Chang created a Kaplan-Meier type estimator:

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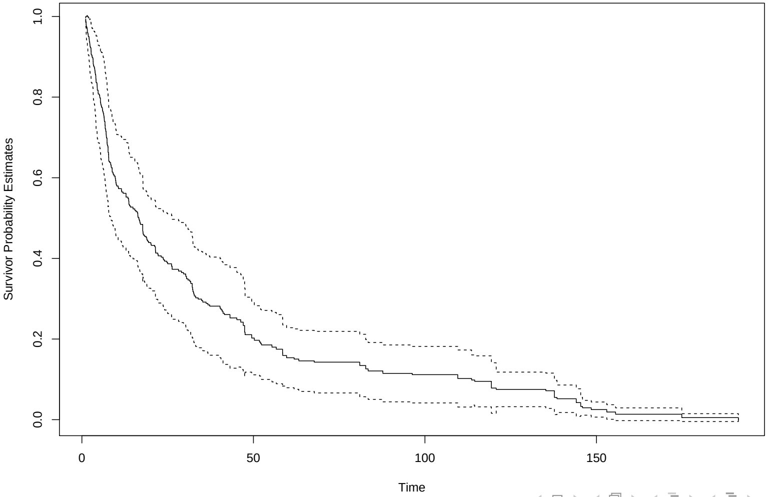
- This estimator also sets a_i equal to 1, giving every estimate equal weight.

Product-Limit Estimate



Analysis

- Using the R package **survrec**, we found the median survival time, $t_{.5}$, to be 16.6 ms.

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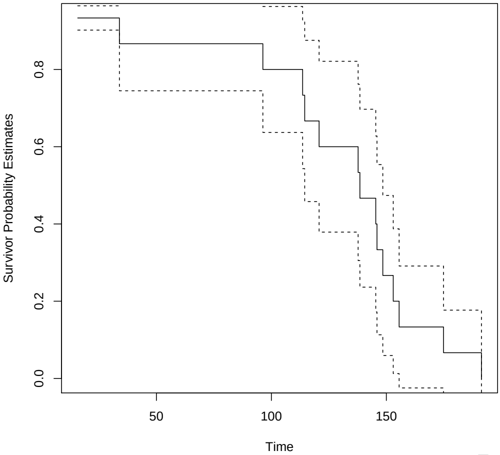
- The 95% confidence interval around the median survival time is $(0.4693057, 32.7306943)$.
  - The standard error was found through Greenwood's formula. (Greenwood M., 1926)

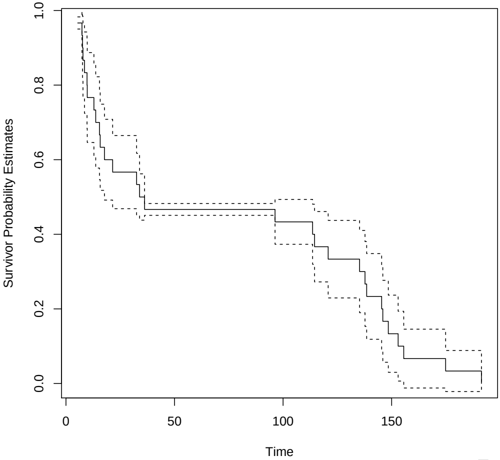
WC Plot for 2 Inter-Event Times:

Median Survival Time: 138 ms



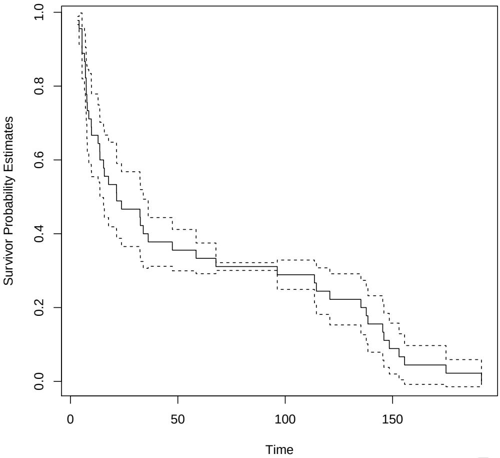
WC Plot for 3 Inter-Event Times:

Median Survival Time: 35 ms



WC Plot for 4 Inter-Event Times:

Median Survival Time: 21.5 ms



Future Work

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- More Subjects

Acknowledgements

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