

SURVIVAL ANALYSIS

BY

Lectures by
RUPERT MILLER

Notes by
GAIL GONG

Problem Solutions by
ALVARO MUÑOZ

TECHNICAL REPORT NO. 58
JULY 1980

PREPARED UNDER THE AUSPICES
OF
PUBLIC HEALTH SERVICE GRANT 2 R01 GM21215-06

DIVISION OF BIOSTATISTICS
STANFORD UNIVERSITY
STANFORD, CALIFORNIA



SURVIVAL ANALYSIS

Lectures by
RUPERT MILLER

Notes by
GAIL GONG

Problem Solutions by
ALVARO MUÑOZ

TECHNICAL REPORT NO. 58
July 1980

PREPARED UNDER THE AUSPICES
OF
PUBLIC HEALTH SERVICE GRANT 2 R01 GM21215-06

DIVISION OF BIOSTATISTICS
STANFORD UNIVERSITY
STANFORD, CALIFORNIA

PREFACE

In the Spring of 1980 the final quarter in a three-quarter graduate course on applied statistics at Stanford University was devoted to a study of the techniques used in analyzing survival data. Brad Efron suggested that it would be worthwhile writing notes for these lectures, and the contents herein represent that effort.

Bill Brown gave assistance and encouragement along the way. Jerry Halpern and Terry Therneau contributed some valuable comments. Elaine Ung read the notes very carefully and pointed out a number of misprints and inaccuracies.

Karola Decleve did a superb job of quickly but carefully typing the notes to keep up with the lectures and then making the necessary changes at the close of the quarter.

This work was partially supported by the National Institute of General Medical Sciences Research Grant GM21215.

Stanford, California
July 1980

Rupert Miller
Gail Gong
Alvaro Muñoz

TABLE OF CONTENTS

I. <u>Introduction to Survival Concepts</u>	1
Types of censoring	2
Example. African children	6
Alternative notation	6
II. <u>Parametric Models</u>	7
A. Distributions	7
1. Exponential	7
2. Gamma	8
3. Weibull	8
4. Raleigh	9
5. Log Normal	9
6. Pareto	10
7. IFR and IFRA	10
B. Estimation	11
1. Maximum likelihood	11
Newton-Raphson/Method of Scoring	12
Confidence intervals and tests	15
Example 1. Exponential	16
Delta method	19
Example 2. Weibull	20
Estimation of $S(t)$	21
2. Linear combinations of order statistics	23
Extreme value distributions	24
3. Other estimators	25
C. Regression models	27
D. Models with surviving fractions	28
1. Single sample	28
2. Regression	29
III. <u>Nonparametric Methods: One Sample</u>	29
A. Life tables	29
Reduced sample method	30
Actuarial method	32
Variance of $\hat{S}(\tau_k)$	33
Types of life tables	34
B. Product-limit (Kaplan-Meier) estimator	34
Example. AML maintenance study	36
Variance of $\hat{S}(t)$	38
1. Redistribute-to-the-right algorithm	39
2. Self-consistency	40
Self-consistency algorithm	42
3. Generalized maximum likelihood estimator	43
4. Consistency	45
5. Asymptotic normality	47

C. Hazard function estimators	49
Asymptotic normality	50
D. Robust estimators	52
1. Mean	52
2. L-estimators	54
3. M-estimators	55
4. Median	56
E. Bayes estimators	57
Empirical Bayes estimators	60
IV. <u>Nonparametric Methods: Two Samples</u>	60
Example. Hypothetical clinical trial	61
A. Gehan test	61
Mean and variance of U	64
Mantel computational form for $\text{Var}_{0,P}^*(U)$	65
Example	66
Variance under H_0	67
B. Mantel-Haenszel test	70
Single 2×2 table	70
Sequence of 2×2 tables	72
Example	73
Asymptotic normality	75
C. Tarone-Ware class of tests	76
Example	77
D. Efron test	78
V. <u>Nonparametric Methods: K Samples</u>	79
A. Generalized Gehan test (Breslow)	79
Types of tests	81
Permutational covariance matrix	83
Distribution under H_0	84
B. Generalized Mantel-Haenszel test (Tarone-Ware)	84
Types of tests	86
VI. <u>Nonparametric Methods: Regression</u>	87
A. Cox proportional hazards model	87
Conditional likelihood analysis	89
Justification of the conditional likelihood	93
Justification of asymptotic normality	97
Estimation of $S(t; \tilde{x})$	98
Discrete or grouped data	100
Time dependent covariates	103
Example 1. Stanford heart transplant data	104
Example 2. Adoption and pregnancy	105
B. Linear models	105
Accelerated time models	105
1. Linear rank tests	107
2. Least squares estimators	108
Example. Stanford heart transplant study	116

VII.	<u>Goodness of Fit</u>	122
	A. Graphical methods	122
	1. One sample	123
	2. Two to K samples	124
	Example. DNCB study	125
	3. Regression	125
	B. Tests	129
	1. One sample	129
	2. Regression	131
VIII.	<u>Miscellaneous Topics</u>	132
	A. Bivariate Kaplan-Meier estimator	132
	B. Competing risks	133
	C. Dependent censoring	135
	D. Jackknifing and bootstrapping	135
IX.	<u>Problems</u>	138
X.	<u>References</u>	159

I. Introduction to Survival Concepts

Consider the random variable $T \geq 0$, which we will think of as the lifetime or the survival time of, say, a patient or a lightbulb. We want to know how long the patient or the lightbulb will last. (We mention that although T is usually construed as time, there are situations when this is not true. For example, let T be the number of dollars that a health insurance company pays in a particular case. In some cases, a patient's illness is over and T is observed. But in other cases, a patient is still sick. The insurance company has already paid a certain amount Y but it will probably have to pay more.)

Let T have density $f(t)$ and distribution function $F(t)$. Define

$$S(t) = 1 - F(t) = P\{T > t\},$$

the survival function of T , and define

$$\lambda(t) = \frac{f(t)}{1 - F(t)},$$

the hazard rate or hazard function. (Historically in epidemiology, $\lambda(t)$ was called the force of mortality.) The hazard rate has the interpretation

$$\lambda(t)dt \approx P\{t < T < t+dt | T > t\}$$

$$= P\left\{ \begin{array}{l|l} \text{expiring in the} & \text{survived} \\ \text{interval } (t, t+dt) & \text{past time } t \end{array} \right\}.$$

Integrating $\lambda(t)$,

$$\int_0^t \lambda(u) du = \int_0^t \frac{f(u)}{1-F(u)} du = -\log(1-F(u)) \Big|_0^t ,$$

$$= -\log(1-F(t)) = -\log S(t) ,$$

which leads to the important expression

$$S(t) = e^{-\int_0^t \lambda(u) du} .$$

Notice that $F(+\infty) = 1$ (i.e., $S(+\infty) = 0$) iff $\int_0^\infty \lambda(u) du = \infty$.

Note that the above concepts can be extended to the case when T does not have a density, that is, when the d.f. F has jumps. Our convention will be to assume continuity, but to modify concepts and formulas to include jumps in the d.f. when it is important to do so.

Reference:

Leavitt and Olshen, unpublished report (1974), give the insurance example.

Types of Censoring:

Everything we have talked about so far can be found in any basic statistics course. What distinguishes survival analysis from other fields of statistics is censoring. Vaguely speaking, a censored observation contains only partial information about the random variable of interest. We will talk about three types of censoring.

Let T_1, T_2, \dots, T_n be iid each with d.f. F .

a) Type I censoring

Let t_c be some (preassigned) fixed number which we call the fixed censoring time. Instead of observing T_1, \dots, T_n (the random variables of interest) we can only observe Y_1, \dots, Y_n where

$$Y_i = \begin{cases} T_i & \text{if } T_i < t_c, \\ t_c & \text{if } t_c \leq T_i. \end{cases}$$

Notice that the distribution function of Y has positive mass $P\{T > t_c\} > 0$ at $y = t_c$.

b) Type II censoring

Let $r < n$ be fixed, and let $T_{(1)} < T_{(2)} < \dots < T_{(n)}$ be the order statistics of T_1, T_2, \dots, T_n . Observation ceases after the r th failure so we can observe $T_{(1)}, \dots, T_{(r)}$. The full ordered observed sample is

$$\begin{aligned} Y_{(1)} &= T_{(1)} \\ &\vdots \\ Y_{(r)} &= T_{(r)} \\ Y_{(r+1)} &= T_{(r)} \\ &\vdots \\ Y_{(n)} &= T_{(r)}. \end{aligned}$$

Both Type I and Type II censoring arise in engineering applications. In such situations, there is a batch of transistors or tubes; we put them all on test at $t = 0$, and record their times to failure. Some transistors may take a long time to burn out, and we will not want to wait that long to end the experiment. Therefore, we might stop the experiment at a prespecified time t_c , in which case we have Type I censoring, or we might not know beforehand what value of the fixed censoring time is good so we decide to wait until a prespecified fraction r/n of the transistors has burned out, in which case we have Type II censoring.

c) Random censoring

Let C_1, C_2, \dots, C_n be iid each with d.f. G . C_i is the censoring time associated with T_i . We can only observe $(Y_1, \delta_1), \dots, (Y_n, \delta_n)$ where

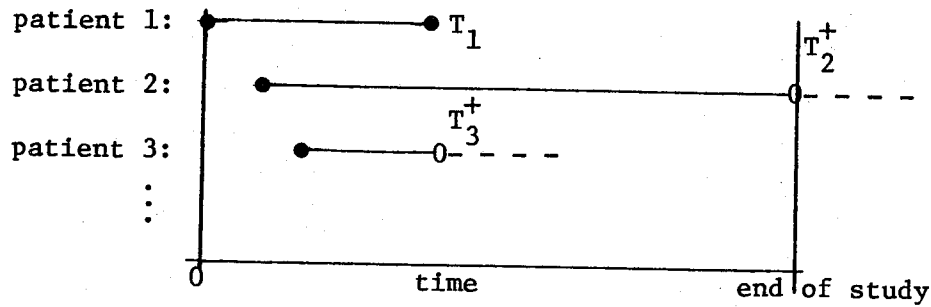
$$Y_i = \min(T_i, C_i) = T_i \wedge C_i,$$
$$\delta_i = I(T_i < C_i) = \begin{cases} 1 & \text{if } T_i \text{ is not censored,} \\ 0 & \text{if } T_i \text{ is censored.} \end{cases}$$

Notice that Y_1, \dots, Y_n are iid with some d.f. H . Also $\delta_1, \dots, \delta_n$ contains the censoring information. (In Type I and Type II censoring we also were able to observe which items were censored, but since it was easy to see which ones these were, we didn't need to define the δ_i 's explicitly.)

Random censoring arises in medical applications with animal studies or clinical trials. In a clinical trial, patients may enter the study at different times; then each is treated with one of several possible therapies. We want to observe their lifetimes, but censoring occurs in one of the following forms:

- (1) Loss to follow up. The patient may decide to move elsewhere; we never see him again.
- (2) Drop out. The therapy may have such bad side effects that it is necessary to discontinue the treatment. Or the patient may still be in contact (he hasn't moved) but he refuses to continue the treatment.
- (3) Termination of the study.

The following picture illustrates a possible trial:



Here, patient 1 entered the study at $t = 0$ and died at T_1 to give an uncensored observation; patient 2 entered the study and by the end of the study he was still alive resulting in a censored observation T_2^+ ; and patient 3 entered the study and was lost to follow up before the end of study to give another censored observation T_3^+ .

With random censoring we will make the following crucial assumption.

Assumption: T_i and C_i are independent.

Without this assumption few results are available. It seems justified with random entries to the study and randomly occurring losses to follow up. However, if the reason for dropping out is related to the course of the therapy, there may well be dependence between T_i and C_i .

d) Other types of censoring

There are other types of censoring which appear in the literature. The previous types of censoring fall under the heading of right censoring: if the random variable of interest is too large, we do not get to observe it completely. There is also left censoring. For example, in random left censoring, we can only observe $(Y_1, \epsilon_1), \dots, (Y_n, \epsilon_n)$ where

$$Y_i = \max(T_i, C_i) = T_i \vee C_i ,$$

$$\epsilon_i = I(C_i < T_i) .$$

Example. African Children

Here both right and left censoring are present. A Stanford psychiatrist wanted to know the age at which a certain group of African children learned to perform a particular task. When he arrived in the village, there were some children who already knew how to perform the task so these children contributed left-censored observations. Some children learned the task while he was present and their ages could be recorded. When he left, there remained some children who had not yet learned the task, thereby contributing to right-censored observations.

References:

Leiderman, et al., Nature (1973).

Turnbull, JASA (1974).

Both right and left censoring are special cases of interval censoring in which we may only get to see that the random variable of interest falls in an interval. If T_i is random right censored, we get to observe that T_i falls in the interval $[C_i, \infty)$, and if T_i is random left censored, we get to observe that T_i falls in the interval $(-\infty, C_i]$. There are examples of more general interval censoring.

In contrast to interval censoring there is truncation in which if the random variable of interest falls outside some interval, even its existence is unobserved. For example, suppose we want to get the distribution and expected size of a certain organelle in the cell. Because of limitations on the measuring equipment, if an organelle is below a certain size, it cannot be detected.

Alternative notation:

We have adopted the notation that T_i is the survival time, C_i is the censoring time, and the observed random variables are $Y_i = T_i \wedge C_i$ and $\delta_i = I(T_i < C_i)$. There are other notations in the literature.

(i) $X_i \sim F$ is the survival time,

$Y_i \sim G$ is the censoring time,

$Z_i = X_i \wedge Y_i \sim H$ and $\delta_i = I(X_i < Y_i)$ are the observed r.v.'s.

This is an appealing notation because it is easy to keep track of the r.v.'s and the d.f.'s. But we will be studying regression later, using X as the independent variable.

(ii) $X_i^0 \sim F^0$ is the survival time,

$Y_i \sim G$ is the censoring time,

$Z_i = X_i^0 \wedge Y_i$ and $\delta_i = I(X_i^0 < Y_i)$ are the observed r.v.'s.

In reporting actual numbers, the convention is to write T_i for a non-censored observation and T_i^+ for a censored observation. Therefore, our data might consist of

5, 11+, 6.5, 14+

where the times 5 and 6.5 are not censored and 11 and 14 are censored.

II. Parametric Models

A. Distributions

1. Exponential

The exponential model assumes constant risk:

$$\lambda(t) \equiv \lambda > 0 .$$

Therefore,

$$\int_0^t \lambda(u) du = \lambda t ,$$

$$S(t) = e^{-\int_0^t \lambda(u) du} = e^{-\lambda t} ,$$

$$f(t) = -\frac{d}{dt} S(t) = \lambda e^{-\lambda t} ,$$

$$E(T) = \frac{1}{\lambda} , \text{ and}$$

$$\text{Var}(T) = \frac{1}{\lambda^2} .$$

2. Gamma

The gamma model is a generalization of the exponential model:

$$f(t) = \frac{\lambda^\alpha}{\Gamma(\alpha)} t^{\alpha-1} e^{-\lambda t}, \quad \alpha > 0, \lambda > 0.$$

Then,

$$E(T) = \frac{\alpha}{\lambda} \quad \text{and}$$

$$\text{Var}(T) = \frac{\alpha}{\lambda^2}.$$

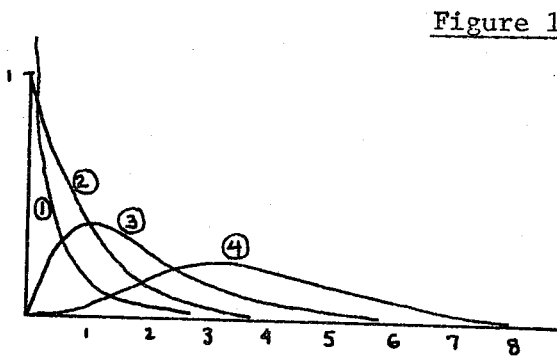


Figure 1

The gamma density for
 $\lambda = 1$ and

① $\alpha = \frac{1}{2},$

② $\alpha = 1,$

③ $\alpha = 2,$

④ $\alpha = 3.$

Unfortunately the gamma model does not have closed form expressions for $S(t)$ and $\lambda(t)$.

$$S(t) = 1 - \int_0^t f(u) du = 1 - \left(\frac{\text{incomplete gamma function}}{\text{complete gamma function}} \right).$$

3. Weibull

The Weibull model is another generalization of the exponential model:

$$S(t) = e^{-(\lambda t)^\alpha}, \quad \alpha > 0, \lambda > 0.$$

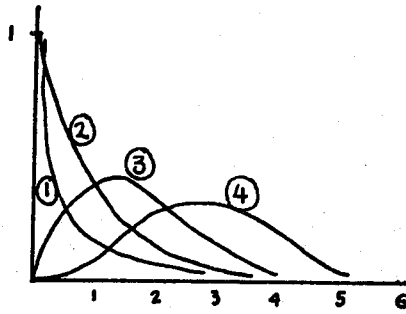
Then,

$$\int_0^t \lambda(u) du = (\lambda t)^\alpha,$$

$$\lambda(t) = \alpha \lambda (\lambda t)^{\alpha-1}, \quad \text{and}$$

$$f(t) = \lambda(t) S(t) = \alpha \lambda (\lambda t)^{\alpha-1} e^{-(\lambda t)^\alpha}.$$

Figure 2



The Weibull density for

① $\lambda = 1, \alpha = \frac{1}{2},$

② $\lambda = 1, \alpha = 1,$

③ $\lambda = .5, \alpha = 2,$

④ $\lambda = .3, \alpha = 3.$

For the Weibull model, $E(T)$ and $\text{Var}(T)$ have no nice closed form expression, but the forms of $\lambda(t)$ and $S(t)$ make the Weibull model a useful one in survival analysis.

4. Rayleigh

$$\lambda(t) = \lambda_0 + \lambda_1 t,$$

$$\int_0^t \lambda(u) du = \lambda_0 t + \frac{1}{2} \lambda_1 t^2,$$

$$S(t) = e^{-\lambda_0 t - \frac{1}{2} \lambda_1 t^2}, \text{ and}$$

$$f(t) = (\lambda_0 + \lambda_1 t) e^{-\lambda_0 t - \frac{1}{2} \lambda_1 t^2}.$$

The moments have no closed form expressions. The linear risk can be generalized to polynomials:

$$\lambda(t) = \sum_{i=1}^p \lambda_i t^i.$$

5. Log Normal

Assume

$$\log T_i \sim N(\mu, \sigma^2).$$

Then $\lambda(t)$ and $S(t)$ have no closed form representations.

$$S(t) = 1 - P\{T < t\} = 1 - P\{\log T < \log t\} ,$$

$$= 1 - P\left\{\frac{\log T - \mu}{\sigma} < \frac{\log t - \mu}{\sigma}\right\} = 1 - \Phi\left(\frac{\log t - \mu}{\sigma}\right) .$$

The log normal distribution may be convenient for use with uncensored data. A log transformation converts the data into the standard linear model setup.

6. Pareto

Assume

$$S(t) = \left(\frac{a}{t}\right)^\alpha I_{[a, \infty)}(t) , \quad \alpha > 0, a > 0 .$$

Then,

$$f(t) = \frac{\alpha a^\alpha}{t^{\alpha+1}} I_{[a, \infty)}(t) \quad \text{and}$$

$$\lambda(t) = \frac{\alpha}{t} I_{[a, \infty)}(t) .$$

The moments are easily calculated, but they may be infinite.

7. IFR and IFRA

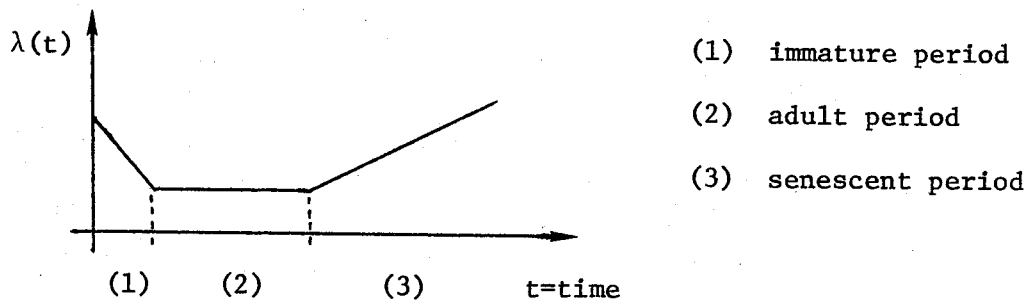
f or F has an increasing failure rate (we say f or F is IFR) if $\lambda(t)$ is increasing; f or F has an increasing failure rate average (we say f or F is IFRA) if

$$\frac{1}{t} \int_0^t \lambda(u) du$$

is increasing. Analogous definitions can be made for DFR and DFRA.

constant FR	IFR	DFR
exponential	Weibull ($\alpha > 1$)	Weibull ($\alpha < 1$)
	Gamma ($\alpha > 1$)	Gamma ($\alpha < 1$)
	Rayleigh ($\lambda_1 > 0$)	Rayleigh ($\lambda_1 < 0$)
		Pareto ($t > a$)

The concepts of IRF and IFRA distributions are useful in engineering applications, particularly in the study of systems of components. In biostatistics they are not usually helpful. For example, in epidemiological studies the risk for long-term survival usually has a bathtub shape with time divided into three periods:



Reference:

Barlow and Proschan, Statistical Theory of Reliability and Life Testing (1975).

B. Estimation

1. Maximum likelihood

We assume the random censoring model. (Note that this includes Type I censoring by simply setting $C_i \equiv t_C$. Also, the likelihoods for Type II censoring are similar to the ones for Type I censoring except for the multiplication of some constants to take account of the ordering.)

The pair (y_i, δ_i) has likelihood

$$L(y_i, \delta_i) = \begin{cases} f(y_i) & \text{if } \delta_i = 1 \text{ (uncensored),} \\ S(y_i) & \text{if } \delta_i = 0 \text{ (censored),} \end{cases}$$

$$= f(y_i)^{\delta_i} S(y_i)^{1-\delta_i},$$

and the likelihood of the full sample is

$$L = L(y_1, \dots, y_n; \delta_1, \dots, \delta_n) = \prod_{i=1}^n L(y_i, \delta_i) = \left(\prod_u f(y_i) \right) \left(\prod_c S(y_i) \right)$$

where $\prod_u (\prod_c)$ denotes a product over the uncensored (censored) observations. Actually, the complete likelihoods under random censoring are

$$L(y_i, \delta_i) = \begin{cases} f(y_i)[1-G(y_i)] & \text{if } \delta_i = 1, \\ g(y_i) S(y_i) & \text{if } \delta_i = 0, \end{cases}$$

$$L = \left(\prod_u f(y_i) \right) \left(\prod_c S(y_i) \right) \left(\prod_c g(y_i) \right) \left(\prod_u [1-G(y_i)] \right),$$

but under the assumption that the censoring time has no connection to the survival time, the last two products $\prod_c g(y_i)$ and $\prod_u [1-G(y_i)]$ do not involve the unknown lifetime parameters, so these two products can be treated like constants when maximizing L .

Let $\tilde{\theta} = (\theta_1, \dots, \theta_p)'$ be the vector of parameters. Finding $\max_{\tilde{\theta}} L(\tilde{\theta})$ is equivalent to finding the solution $\hat{\tilde{\theta}}$ to the likelihood equations

$$\begin{aligned} 0 &= \frac{\partial}{\partial \theta_j} \log L(\tilde{\theta}) = \sum_{i=1}^n \frac{\partial}{\partial \theta_j} \log L_{\tilde{\theta}}(y_i, \delta_i), \\ &= \sum_u \frac{\partial}{\partial \theta_j} \log f_{\tilde{\theta}}(y_i) + \sum_c \frac{\partial}{\partial \theta_j} \log S_{\tilde{\theta}}(y_i), \quad j = 1, \dots, p. \end{aligned}$$

Typically, calculation on a computer using iterative methods is required.

Newton-Raphson/Method of Scoring:

Denote $L_{i\tilde{\theta}}(\theta) = L_{\tilde{\theta}}(y_i, \delta_i)$, $i = 1, \dots, n$, and define

$$\frac{\partial}{\partial \tilde{\theta}} \log L(\tilde{\theta}) = \left(\frac{\partial}{\partial \theta_1} \log L(\tilde{\theta}), \dots, \frac{\partial}{\partial \theta_p} \log L(\tilde{\theta}) \right)',$$

$$\frac{\partial^2}{\partial \tilde{\theta}^2} \log L(\tilde{\theta}) = \begin{bmatrix} \frac{\partial^2}{\partial \theta_1 \partial \theta_1} \log L(\tilde{\theta}) & \dots & \frac{\partial^2}{\partial \theta_1 \partial \theta_p} \log L(\tilde{\theta}) \\ \vdots & & \vdots \\ \frac{\partial^2}{\partial \theta_p \partial \theta_1} \log L(\tilde{\theta}) & \dots & \frac{\partial^2}{\partial \theta_p \partial \theta_p} \log L(\tilde{\theta}) \end{bmatrix}.$$

Then the likelihood equations are

$$0 = \sum_i \frac{\partial}{\partial \theta_j} \log L_i(\tilde{\theta}), \quad j = 1, \dots, p,$$

or

$$0 = \frac{\partial}{\partial \tilde{\theta}} \log L(\tilde{\theta}).$$

Assume $\hat{\tilde{\theta}}^0 = (\hat{\theta}_1^0, \dots, \hat{\theta}_p^0)'$ is an initial guess at the solution. Expand about $\hat{\tilde{\theta}}^0$:

$$0 = \sum_i \frac{\partial}{\partial \theta_j} \log L_i(\hat{\tilde{\theta}}) = \sum_i \frac{\partial}{\partial \theta_j} \log L_i(\hat{\tilde{\theta}}^0) + \sum_k (\hat{\theta}_k - \hat{\theta}_k^0) \sum_i \frac{\partial^2}{\partial \theta_k \partial \theta_j} \log L_i(\hat{\tilde{\theta}}^0) + \dots,$$

$$j = 1, \dots, p,$$

or

$$0 = \frac{\partial}{\partial \tilde{\theta}} \log L(\hat{\tilde{\theta}}) = \frac{\partial}{\partial \tilde{\theta}} \log L(\hat{\tilde{\theta}}^0) + \frac{\partial^2}{\partial \tilde{\theta}^2} \log L(\hat{\tilde{\theta}}^0) (\hat{\tilde{\theta}} - \hat{\tilde{\theta}}^0) + \dots$$

Let $\hat{\tilde{\theta}}^1$ be the solution ignoring second order and higher terms:

$$\hat{\tilde{\theta}}^1 = \hat{\tilde{\theta}}^0 + \left(- \frac{\partial^2}{\partial \tilde{\theta}^2} \log L(\hat{\tilde{\theta}}^0) \right)^{-1} \frac{\partial}{\partial \tilde{\theta}} \log L(\hat{\tilde{\theta}}^0). \quad (1)$$

The vector $\frac{\partial}{\partial \theta} \log L(\hat{\theta}^0)$ is called the score vector at $\hat{\theta}^0$, and the matrix

$$i(\hat{\theta}^0) = - \frac{\partial^2}{\partial \theta^2} \log L(\hat{\theta}^0)$$

is called the sample information matrix at $\hat{\theta}^0$. Notice that

$$E(i(\theta)) = \left(-E \frac{\partial^2}{\partial \theta_k \partial \theta_j} \log L(\theta) \right) = I(\theta),$$

which is the Fisher information. We point out that $I(\theta)$ is the Fisher information of the entire sample:

$$I(\theta) = \sum_{i=1}^n I_i(\theta) = n I_1(\theta),$$

where $I_i(\theta)$ is the Fisher information of the i th observation.

The iteration scheme using (1) is called the Newton-Raphson method.

Replacing the sample information in (1) by the Fisher information gives

$$\hat{\theta}^1 = \hat{\theta}^0 + I^{-1}(\hat{\theta}^0) \frac{\partial}{\partial \theta} \log L(\hat{\theta}^0), \quad (2)$$

and the iteration scheme using (2) is called the Method of Scoring. While (2) might produce improved convergence in some instances, it may not be possible, particularly if censoring is present, to figure out $I(\theta)$ for use in (2).

References:

Gross and Clark, Survival Distributions (1975), Ch. 6.

Rao, Linear Statistical Inference (1965), 302-309.

Kalbfleisch and Prentice, The Statistical Analysis of Failure Time Data (1980), Sec. 3.7.

Confidence intervals and tests:

For random and Type I censoring, under smoothness conditions,

$$\hat{\theta} \underset{\sim}{\overset{a}{\sim}} N(\theta, \underset{\sim}{I}^{-1}(\theta)) .$$

Usually for Type II censoring, this result also holds, but the proofs are different. (The notation " $\underset{\sim}{a}$ " denotes "is asymptotically distributed as".)

For testing $H_0 : \theta = \theta^0$ or constructing confidence intervals, we have three procedures.

(i) Wald:

$$(\hat{\theta} - \theta^0)' \underset{\sim}{I}(\theta^0) (\hat{\theta} - \theta^0) \underset{\sim}{\overset{a}{\sim}} \chi_p^2 \text{ under } H_0 .$$

We can alternatively substitute $\underset{\sim}{I}(\hat{\theta})$ for $\underset{\sim}{I}(\theta^0)$.

(ii) Neyman-Pearson/Wilks likelihood ratio:

$$-2 \log \frac{L(\theta^0)}{L(\hat{\theta})} \underset{\sim}{\overset{a}{\sim}} \chi_p^2 \text{ under } H_0 .$$

(iii) Rao:

$$\frac{\partial}{\partial \theta} \log L(\theta^0)' \underset{\sim}{I}^{-1}(\theta^0) \frac{\partial}{\partial \theta} \log L(\theta^0) \underset{\sim}{\overset{a}{\sim}} \chi_p^2 \text{ under } H_0 .$$

Notice that Rao's method does not use the mle, so no iterative calculation is necessary. However, in addition to tests, we usually want estimates and confidence intervals, so we would need to calculate $\hat{\theta}$ anyway. Once we have $\hat{\theta}$ and $\underset{\sim}{I}(\theta^0)$, the Wald method is easy.

Under censoring we may need to replace $\underset{\sim}{I}(\theta)$ with $\underset{\sim}{i}(\theta)$ because calculation of $\underset{\sim}{I}(\theta)$ is usually difficult. Also, Efron and Hinkley suggest that using $\underset{\sim}{i}(\theta)$ is better than using $\underset{\sim}{I}(\theta)$ for confidence intervals even if $\underset{\sim}{I}(\theta)$ can be calculated. There is not universal agreement on this, however.

References:

Efron and Hinkley, Biometrika (1978).

Rao, Linear Statistical Inference (1965), 349-350.

Example 1. Exponential

Under random censoring, let

n_u = # of uncensored observations.

Then,

$$L = \lambda^{n_u} \exp \left\{ -\lambda \sum_u t_i - \lambda \sum_c c_i \right\} = \lambda^{n_u} \exp \left\{ -\lambda \sum_{i=1}^n y_i \right\},$$

$$\log L = n_u \log \lambda - \lambda \sum_{i=1}^n y_i,$$

$$\frac{\partial}{\partial \lambda} \log L = \frac{n_u}{\lambda} - \sum_{i=1}^n y_i,$$

$$\hat{\lambda} = \frac{n_u}{\sum_{i=1}^n y_i},$$

$$\frac{\partial^2}{\partial \lambda^2} \log L = \frac{-n_u}{\lambda^2},$$

$$i(\lambda) = \frac{n_u}{\lambda^2}.$$

We remark that $\hat{\lambda} = n_u / \sum_{i=1}^n y_i$ is also the mle under Type I and Type II censoring as well as random censoring.

To construct confidence intervals and perform tests, we need the distribution of $\hat{\lambda}$.

a) If no censoring is present,

$$\hat{\lambda} = \frac{n}{\sum_{i=1}^n T_i} = \frac{1}{\bar{T}},$$

where T_1, \dots, T_n are iid each with the exponential distribution

$$f_{T_1}(t) = \lambda e^{-\lambda t}.$$

Consequently, $S = \sum_{i=1}^n T_i$ has the gamma density

$$f_S(t) = \frac{\lambda^n}{\Gamma(n)} t^{n-1} e^{-\lambda t},$$

so $2\lambda \sum_{i=1}^n T_i \sim \chi_{2n}^2$, or equivalently,

$$\frac{2n\lambda}{\hat{\lambda}} \sim \chi_{2n}^2.$$

Therefore, $2n \lambda / \hat{\lambda}$ is a pivotal statistic and can be used for test and confidence interval construction.

b) For Type II censoring, we can rewrite

$$\begin{aligned} \sum_{i=1}^n Y_i &= T_{(1)} + T_{(2)} + \dots + T_{(r)} + (n-r) T_{(r)} \\ &= n T_{(1)} + (n-1)[T_{(2)} - T_{(1)}] + \dots + (n-r+1)[T_{(r)} - T_{(r-1)}]. \end{aligned}$$

Using the results about Poisson processes and exponential waiting times,

$$T_{(1)} = \{\text{min of } n \text{ iid exponential}(\lambda) \text{ r.v.'s}\} \sim n \lambda e^{-n\lambda t},$$

$$n T_{(1)} \sim \lambda e^{-\lambda t},$$

$$T_{(2)} - T_{(1)} = \{\text{min of } n-1 \text{ exponential}(\lambda) \text{ r.v.'s}\} \sim (n-1)\lambda e^{-(n-1)\lambda t},$$

$$(n-1)[T_{(2)} - T_{(1)}] \sim \lambda e^{-\lambda t}, \text{ etc.,}$$

and $n T_{(1)}, (n-1)[T_{(2)} - T_{(1)}], \dots, (n-r+1)[T_{(r)} - T_{(r-1)}]$ are independent, so

$$2\lambda \sum_{i=1}^n Y_i \sim \chi_{2r}^2.$$

Thus, $2r\lambda/\hat{\lambda}$ can be used in conjunction with a χ^2 distribution, where the d.f. are twice the number of uncensored order statistics, to construct confidence intervals and tests.

c) If random or Type I censoring is present, we have no recourse but to use the asymptotic theory. From above (p.16),

$$\hat{\lambda} = \frac{n_u}{\sum_{i=1}^n y_i},$$

$$\frac{\partial^2}{\partial \lambda^2} \log L = \frac{-n_u}{\lambda^2},$$

so,

$$\frac{\hat{\lambda} - \lambda}{\sqrt{\frac{\lambda^2}{n_u}}} \stackrel{a}{\sim} N(0,1),$$

where n_u may be replaced by $E(n_u)$ if the latter is available.

The normality approximation can be improved by transforming the estimate.

By the delta method (to be discussed next), since

$$\hat{\lambda} \stackrel{a}{\sim} N\left(\lambda, \frac{\lambda^2}{n_u}\right),$$

then

$$\log \hat{\lambda} \stackrel{a}{\sim} N\left(\log \lambda, \frac{1}{n_u}\right).$$

Notice that $1/n_u$, the asymptotic variance of $\log \hat{\lambda}$, does not depend on the unknown parameter λ . It is an empirical fact that transforming an estimate to remove the dependence of the variance on the unknown parameter tends to improve the convergence to normality by reducing the skewness.

Delta Method:

Suppose the random variable Y has mean μ and variance σ^2 (denoted by " $Y \sim (\mu, \sigma^2)$ ") and suppose we want the distribution of some function $g(Y)$. Expand $g(Y)$ about μ

$$g(Y) = g(\mu) + (Y-\mu) g'(\mu) + \dots$$

and ignore higher order terms to get

$$g(Y) \approx (g(\mu), \sigma^2 (g'(\mu))^2)$$

(where " \approx " denotes "is approximately distributed as"). If furthermore $Y \stackrel{a}{\sim} N(\mu, \sigma^2)$, then

$$g(Y) \stackrel{a}{\sim} N(g(\mu), \sigma^2 (g'(\mu))^2) .$$

The delta method also has a multivariate version. Suppose

$$\begin{bmatrix} X \\ Y \end{bmatrix} \sim \left(\begin{bmatrix} \mu_x \\ \mu_y \end{bmatrix}, \begin{bmatrix} \sigma_x^2 & \sigma_{xy} \\ \sigma_{xy} & \sigma_y^2 \end{bmatrix} \right) ,$$

and suppose we want the distribution of $g(X, Y)$. Then

$$g(X, Y) = g(\mu_x, \mu_y) + (X-\mu_x) \frac{\partial}{\partial x} g(\mu_x, \mu_y) + (Y-\mu_y) \frac{\partial}{\partial y} g(\mu_x, \mu_y) + \dots ,$$

so

$$g(X, Y) \approx \left(g(\mu_x, \mu_y), \sigma_x^2 \left(\frac{\partial}{\partial x} g \right)^2 + 2 \sigma_{xy} \frac{\partial}{\partial x} g \frac{\partial}{\partial y} g + \sigma_y^2 \left(\frac{\partial}{\partial y} g \right)^2 \right) .$$

If furthermore, $\begin{bmatrix} X \\ Y \end{bmatrix} \stackrel{a}{\sim} N$, then $g(X, Y) \stackrel{a}{\sim} N$.

The delta method is very useful. For example, we could use it to get an approximate value for $\text{Var}(\bar{X}/\bar{Y})$ or $\text{Var}(\bar{X}\bar{Y})$.

Example 2. Weibull

Reparametrize with $\gamma = \lambda^\alpha$ so that taking derivatives is easier:

$$S(t) = e^{-(\lambda t)^\alpha} = e^{-\gamma t^\alpha},$$

$$f(t) = \gamma \alpha t^{\alpha-1} e^{-\gamma t^\alpha}.$$

Then,

$$\begin{aligned} L &= (\gamma \alpha)^{n_u} \left(\prod_u t_i^{\alpha-1} \right) \exp \left\{ -\gamma \sum_u t_i^\alpha \right\} \exp \left\{ -\gamma \sum_c c_i^\alpha \right\}, \\ &= (\gamma \alpha)^{n_u} \left(\prod_u t_i^{\alpha-1} \right) \exp \left\{ -\gamma \sum_{i=1}^n y_i^\alpha \right\}, \end{aligned}$$

$$\log L = n_u \log \gamma + n_u \log \alpha + (\alpha-1) \sum_u \log t_i - \gamma \sum_{i=1}^n y_i^\alpha,$$

$$\frac{\partial}{\partial \gamma} \log L = \frac{n_u}{\gamma} - \sum_{i=1}^n y_i^\alpha,$$

$$\frac{\partial}{\partial \alpha} \log L = \frac{n_u}{\alpha} + \sum_u \log t_i - \gamma \sum_{i=1}^n y_i^\alpha \log y_i.$$

Therefore, the mle $(\hat{\alpha}, \hat{\gamma})$ satisfies

$$\begin{aligned} \hat{\gamma} &= \frac{n_u}{\sum_{i=1}^n y_i^{\hat{\alpha}}}, \\ 0 &= \frac{n_u}{\hat{\alpha}} + \sum_u \log t_i - \hat{\gamma} \sum_{i=1}^n y_i^{\hat{\alpha}} \log y_i. \end{aligned}$$

These equations must be solved iteratively. The Newton-Raphson method requires the sample information matrix

$$-\frac{\partial^2}{\partial \theta^2} \log L = - \begin{bmatrix} \frac{\partial^2}{\partial \gamma^2} \log L & \frac{\partial^2}{\partial \gamma \partial \alpha} \log L \\ \frac{\partial^2}{\partial \alpha^2} \log L \end{bmatrix},$$

which is calculated in the Problems section. Also, the Newton-Raphson method requires starting values $\hat{\gamma}_0, \hat{\alpha}_0$. To get reasonable starting values, observe that

$$S(t) = e^{-\gamma t^\alpha}$$

$$\log S(t) = -\gamma t^\alpha$$

$$\log(-\log S(t)) = \log \gamma + \alpha \log t,$$

so if we had estimates $\hat{S}(t_i)$, we could regress $\log(-\log \hat{S}(t_i))$ against $\log t_i$, and then let the regression coefficient be $\hat{\alpha}_0$ and the constant be $\log \hat{\gamma}_0$. Possible choices of $\hat{S}(t)$ are the Kaplan-Meier estimate, which we will discuss later, or the empirical distribution function, which ignores censoring.

Estimation of $S(t)$:

One of the goals of survival analysis is the estimation of the survival function

$$S(t) = \exp \left\{ - \int_0^t \lambda(u) du \right\}.$$

For example, one of the yardsticks of a cancer therapy is the probability of surviving at least five years. In the engineering literature the survival function is called the reliability function (usually denoted $R(t)$), and a possible concern is the reliability of a component after 1000 hours.

Once we have the mle, estimation of the survival function is easy under the exponential or Weibull model.

$$\text{Exponential: } \hat{S}(t) = e^{-\hat{\lambda}t},$$

$$\text{Weibull: } \hat{S}(t) = e^{-(\hat{\lambda}t)^{\hat{\alpha}}} = e^{-\hat{\gamma}t^{\hat{\alpha}}}.$$

Also, for any fixed t , $\hat{S}(t)$ is a function of $\hat{\lambda}$ or $(\hat{\gamma}, \hat{\alpha})$, so we can get an approximate distribution of $\hat{S}(t)$ by using the delta method. Alternatively, we can take a log log transformation which usually improves the convergence to normality.

Exponential:

$$S(t) = e^{-\lambda t},$$

$$\log(-\log S(t)) = \log \lambda + \log t,$$

$$\log(-\log \hat{S}(t)) = \log \hat{\lambda} + \log t,$$

$$\hat{\text{Var}}(\log(-\log \hat{S}(t))) \cong \frac{1}{n_u}.$$

Weibull:

$$S(t) = e^{-\gamma t^{\alpha}},$$

$$\log(-\log S(t)) = \log \gamma + \alpha \log t,$$

$$\log(-\log \hat{S}(t)) = \log \hat{\gamma} + \hat{\alpha} \log t,$$

$$\hat{\text{Var}}(\log(-\log \hat{S}(t))) \cong \frac{\text{Var}(\hat{\gamma})}{\hat{\gamma}^2} + 2 \text{Cov}(\hat{\gamma}, \hat{\alpha}) \frac{\log t}{\hat{\gamma}} + \text{Var}(\hat{\alpha}) (\log t)^2.$$

2. Linear combinations of order statistics

We will consider only the Weibull distribution, but the ideas which are illustrated here can be generalized.

First, by reparametrizing and transforming, we can change the problem of estimating λ and α in the Weibull distribution to estimating location and scale parameters. Rewrite

$$\begin{aligned} P\{Y > t\} &= e^{-(\lambda t)^\alpha}, \\ &= \exp\{-\exp(\alpha(\log \lambda + \log t))\}, \\ &= \exp\{-\exp(\frac{\log t - \mu}{\sigma})\}, \end{aligned}$$

where $\mu = -\log \lambda$ and $\sigma = 1/\alpha$. Then

$$\begin{aligned} P\{\log Y > t\} &= P\{Y > e^t\}, \\ &= \exp\{-\exp(\frac{t - \mu}{\sigma})\}. \end{aligned} \tag{3}$$

From this we see that μ and σ are the location and scale parameters of the random variable $\log Y$. This is a useful observation since there is considerable statistical theory for estimating location and scale parameters.

Suppose we want to estimate the survival of some fixed time t_0 .

$$S(t_0) = P\{Y > t_0\} = \exp\{-\exp(\frac{\log t_0 - \mu}{\sigma})\}.$$

Define $Y^0 = Y/t_0$ and $\mu_0 = \mu - \log t_0$. Then

$$S(t_0) = P\{\log Y^0 > 0\} = \exp\{-\exp(\frac{-\mu_0}{\sigma})\}$$

and μ_0 and σ are the location and scale parameters for $\log Y^0$.

If we can construct a confidence interval for their ratio $\frac{\mu_0}{\sigma}$, then by taking exponentials twice we would have a confidence interval for $S(t_0)$.

Johns and Lieberman use linear combination of order statistics:

$$\hat{\mu} = \sum_{i=1}^n a_i \log Y_{(i)}^0 ,$$

$$\hat{\sigma} = \sum_{i=1}^n b_i \log Y_{(i)}^0 ,$$

where $\sum_{i=1}^n a_i = 1$ and $\sum_{i=1}^n b_i = 0$ and $a_1, \dots, a_n, b_1, \dots, b_n$ are chosen to satisfy an asymptotic optimality criteria. This method is particularly well suited for Type II censoring where

$$a_{r+1} = \dots = a_n = 0 ,$$

$$b_{r+1} = \dots = b_n = 0 ,$$

so that the estimates are based only on the uncensored observations.

Reference:

Johns and Lieberman, Technometrics (1966).

Extreme value distributions:

The function

$$G_1(x) = \exp\{-\exp(-x)\}, -\infty < x < +\infty ,$$

is one of the three possible limiting extreme value distributions. A limiting extreme value distribution is a distribution G for which there exists a d.f. F such that if X_1, \dots, X_n are iid each with distribution F , then $\max\{X_1, \dots, X_n\}$, properly normalized, converges in

distribution to G . Another limiting extreme value distribution is

$$G_2(x) = \begin{cases} \exp\{-(-x)^\alpha\} & , \quad x < 0 , \\ 1 & , \quad x > 0 . \end{cases}$$

The upper tail of the Weibull distribution is the same as the lower tail of G_2 , properly scaled, and the upper tail of the distribution of the log of a Weibull random variable (3) is the same as the lower tail of G_1 . The d.f. G_2 arises as a normalized limit of

$$\max\{X_1, \dots, X_n\} - x_0 ,$$

where x_0 is an upper truncation point for F (i.e., $F(x_0) = 1$, $F(x_0-) < 1$) . Since

$$-\max\{X_1 - x_0, \dots, X_n - x_0\} = \min\{x_0 - X_1, \dots, x_0 - X_n\} ,$$

a Weibull random variable can be interpreted as the minimum (i.e., first failure) of a large number of potential failure times. The system fails with the occurrence of the first component failure.

3. Other estimators

The estimators in this section assume the exponential model with no censoring.

a) Bias-corrected estimators

The method here is more important than the results. Suppose we estimate the survival with

$$\hat{S}(t) = e^{-\hat{\lambda}t} = e^{-t/\bar{T}} ,$$

where $\bar{T} = (1/n) \sum_{i=1}^n T_i$. Then

$$E(\hat{S}(t)) \neq e^{-\lambda t},$$

so $\hat{S}(t)$ is a biased estimate. We can remove some of the bias by the delta method. If we denote $\theta = E(T)$,

$$\begin{aligned} e^{-t/\bar{T}} &= e^{-t/\theta} + (\bar{T}-\theta) \frac{t}{\theta^2} e^{-t/\theta} \\ &\quad + \frac{1}{2} (\bar{T}-\theta)^2 \left[\left(\frac{t}{\theta^2} \right)^2 - \frac{2t}{\theta^3} \right] e^{-t/\theta} + \dots, \\ E(e^{-t/\bar{T}}) &= e^{-t/\theta} + 0 + \frac{1}{2} \frac{\theta^2}{n} \left[\left(\frac{t}{\theta^2} \right)^2 - \frac{2t}{\theta^3} \right] e^{-t/\theta} + \dots, \\ &= \left[1 + \frac{1}{2n} \left(\frac{t^2}{\theta^2} - \frac{2t}{\theta} \right) \right] e^{-t/\theta} + \dots. \end{aligned}$$

Therefore,

$$\tilde{S}(t) = \frac{e^{-\hat{\lambda}t}}{1 + \frac{1}{2n}(t^2 \hat{\lambda}^2 - 2t \hat{\lambda})}$$

should be a less biased estimate of $S(t)$ than $\hat{S}(t)$. Also it usually turns out that $\tilde{S}(t)$ has smaller mean square error than $\hat{S}(t)$.

The jackknife estimate, which we will discuss later, produces the same sort of bias correction.

b) Uniformly minimum variance unbiased estimators

To get an UMVU estimate of $S(t)$, use the unbiased estimate

$$U = I(T_1 > t)$$

and the sufficient statistic

$$S = \sum_{i=1}^n T_i.$$

By the Rao-Blackwell theorem the UMVU estimate is $E(U|S)$, which in this case is

$$\tilde{S}(t) = E\{U|S = s\} = (1 - \frac{t}{s})^{n-1} I(t < s) .$$

c) Bayesian estimates

We only mention that Bayes estimates can be derived using gamma priors.

References:

Basu, Technometrics (1964), derives UMVUE's.

Zacks and Even, JASA (1966), compares MSE's.

Gaver and Hoel, Technometrics (1970), look at estimators in the framework of sampling from a Poisson process.

C. Regression models

In medical applications the survival time may depend on the dose of medication or radiation, and in engineering applications the lifetime of a tube may depend on the temperature or other stress conditions.

Let Y denote the dependent variable and x denote the independent variable. Feigl and Zelen propose two models.

(i) The linear model

$$E(T) = \alpha + \beta x .$$

To get estimates, use maximum likelihood. The drawback with this model is the possibility of obtaining a negative estimate of $E(T)$ when $\hat{\beta}$ is negative.

(ii) The log-linear model

$$E(T) = \alpha e^{\beta x} ,$$

$$\log E(T) = \log \alpha + \beta x .$$

Again, use maximum likelihood. This model is the precursor to the Cox proportional hazards model.

References:

Feigl and Zelen, Biometrics (1965), discuss the uncensored case for both the linear and log-linear models.

Zippin and Armitage, Biometrics (1966), discuss the censored case for the linear model.

Mantel and Myers, JASA (1971), discuss the censored case for the multiple linear model.

Glasser, JASA (1967), discusses the censored case for the log-linear model.

Zippin and Lamborn, Stanford University Technical Report No. 20 (1969), discuss the censored case for the log-linear model and goodness of fit tests.

D. Models with surviving fractions

1. Single sample

Let

$$p = P\{\text{death}\} \quad \text{and} \quad 1-p = P\{\text{survival}\} ,$$

where the latter probability is called the surviving fraction. Assume

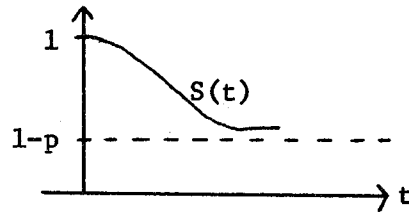
$$P\{T \leq t | \text{death}\} = 1 - e^{-\lambda t} .$$

Then the likelihood is

$$L(y, \delta) = \begin{cases} p\lambda e^{-\lambda y} & \text{if } \delta = 1 \text{ (uncensored) ,} \\ (1-p) + pe^{-\lambda y} & \text{if } \delta = 0 \text{ (censored) .} \end{cases}$$

To get estimates, use maximum likelihood.

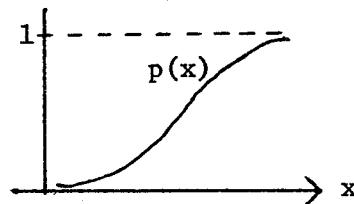
Models with surviving fractions are sometimes used for short-term experiments where one does not hypothesize that the survival function $S(t)$ necessarily approaches zero. Instead, $S(t)$ may have the form:



2. Regression

Assume

$$p(x) \equiv P\{\text{death}|x\} = \frac{e^{\alpha+\beta x}}{1+e^{\alpha+\beta x}} .$$



This is the logistic function. Also, let

$$P\{T \leq t | \text{death}\} = 1 - e^{-\lambda t} .$$

The likelihood is

$$L(y, \delta, x) = \begin{cases} p(x) \lambda e^{-\lambda y} & \text{if } \delta = 1 \text{ (uncensored) ,} \\ 1 - p(x) + p(x) e^{-\lambda y} & \text{if } \delta = 0 \text{ (censored) .} \end{cases}$$

To get estimates, use maximum likelihood.

Reference:

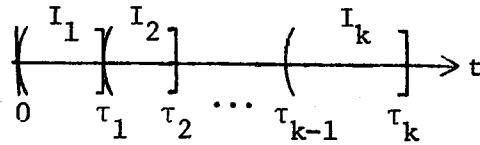
Farewell, Biometrika (1977).

III. Nonparametric Methods: One Sample

A. Life tables

The classical method of estimating $S(t)$ in epidemiology and actuarial science is the actuarial method discussed below. It depends on the life table.

Let time be partitioned into a fixed sequence of intervals I_1, \dots, I_k . These intervals are almost always, but not necessarily, of equal lengths, and for human populations the length of each interval is usually one year.



For a life table let

n_i = # alive at the beginning of I_i ,

d_i = # died during I_i ,

ℓ_i = # lost to follow-up during I_i ,

w_i = # withdrew during I_i ,

p_i = $P\{\text{surviving through } I_i | \text{alive at beginning of } I_i\}$,

$q_i = 1 - p_i$.

Table 1 is an example of a life table. I_1, I_2, \dots, I_5 each has length one year. Column (2) contains n_i , (3) contains d_i , (4) contains ℓ_i , and (5) contains w_i . We want to estimate $S(5 \text{ years})$.

Reduced sample method:

To estimate $S(\tau_k)$, use only those subjects who are at risk during $(0, \tau_k]$, the entire interval of interest. Let

$$n = n_1 - \sum_{i=1}^k \ell_i - \sum_{i=1}^k w_i,$$

$$d = \sum_{i=1}^k d_i,$$

$$\hat{S}(\tau_k) = 1 - \frac{d}{n}.$$

For the example of Table 1,

Table 1. Computation of the 5-Year Survival Rate

YEARS AFTER DIAGNOSIS (1)	ALIVE AT BEGIN- NING OF INTERVAL (2)	DIED DURING IN- TERVAL (3)	LOST TO FOLLOW- UP DUR- ING IN- TERVAL (4)	WITH- DRAWN ALIVE DURING INTERVAL (5)	EFFECTIVE NUMBER EXPOSED TO THE RISK OF DYING $(2) - \frac{1}{2}[(4)+(5)]$ (6)	PROPORTION DYING (3)/(6) (7)	PROPORTION SURVIVING 1-(7) (8)	CUMULATIVE PROPORTION SURVIVING FROM DIAG- NOSIS THROUGH END OF INTERVAL $\Pi_1^k(8)_i$ (9)
0-1	126	47	4	15	116.5	0.40	0.60	0.60
1-2	60	5	6	11	51.5	0.10	0.90	0.54
2-3	38	2	—	15	30.5	0.07	0.93	0.50
3-4	21	2	2	7	16.5	0.12	0.88	0.44
4-5	10	—	—	6	7.0	0.00	1.00	0.44

Reference: Cutler and Ederer, J. Chronic Diseases (1958)

$$n = 126 - 12 - 54 = 60 ,$$

$$d = 56 ,$$

$$\hat{S}(5 \text{ years}) = 1 - \frac{56}{60} = 0.078 .$$

The drawback with the reduced sample method is that it ignores the information that is contained in ℓ_i and w_i . It is a biased (downward) estimate of $S(t)$.

Actuarial method:

We can break up the survival probability $S(\tau_k)$ into a product of probabilities:

$$\begin{aligned} S(\tau_k) &= P\{T > \tau_k\} , \\ &= P\{T > \tau_1\} P\{T > \tau_2 | T > \tau_1\} \dots P\{T > \tau_k | T > \tau_{k-1}\} , \\ &= p_1 \cdot p_2 \dots p_k , \end{aligned}$$

where

$$p_i = P\{T > \tau_i | T > \tau_{i-1}\} .$$

The actuarial method gives an estimate for each p_i separately and then multiplies the estimates together to estimate $S(\tau_k)$.

For an estimate of p_i , we could use $1 - d_i/n_i$, if there were no losses or withdrawals in I_i . However, with ℓ_i and w_i nonzero, we assume that, on the average, those individuals who became lost or withdrawn during I_i were at risk for half the interval. Therefore, define the effective sample size

$$n'_i = n_i - \frac{1}{2}(\ell_i + w_i) ,$$

and

$$\hat{q}_i = \frac{d_i}{n'_i} ,$$

$$\hat{p}_i = 1 - \hat{q}_i .$$

The actuarial estimate is

$$\hat{S}(\tau_k) = \prod_{i=1}^k \hat{p}_i .$$

For the example of Table 1, column (6) contains n'_i , (7) contains \hat{q}_i , (8) contains \hat{p}_i , and in column (9) we see

$$\hat{S}(5 \text{ years}) = 0.44 .$$

There has been work on trying to find an improved substitute for the effective sample size, but if a finer estimate of $S(t)$ is required, the product-limit estimator of Kaplan and Meier is the approach to take.

Variance of $\hat{S}(\tau_k)$:

To estimate the variance of $\hat{S}(\tau_k)$, consider

$$\log \hat{S}(\tau_k) = \sum_{i=1}^k \log \hat{p}_i .$$

Assuming $n'_i \hat{p}_i \approx \text{Binomial}(n'_i, p_i)$, the delta method implies

$$\text{Var}(\log \hat{p}_i) \approx \text{Var}(\hat{p}_i) \left(\frac{d}{d p_i} (\log p_i) \right)^2 = \frac{p_i q_i}{n'_i} \cdot \frac{1}{p_i^2} = \frac{q_i}{n'_i p_i} ,$$

and assuming $\log \hat{p}_1, \dots, \log \hat{p}_k$ are independent,

$$\text{Var}(\log \hat{S}(\tau_k)) = \sum_{i=1}^k \frac{q_i}{n'_i p_i} ,$$

$$\hat{\text{Var}}(\log \hat{S}(\tau_k)) = \sum_{i=1}^k \frac{\hat{q}_i}{n'_i \hat{p}_i} = \sum_{i=1}^k \frac{d_i}{n'_i (n'_i - d_i)} .$$

Now using the delta method again,

$$\hat{\text{Var}}(\hat{S}(\tau_k)) = \hat{S}^2(\tau_k) \sum_{i=1}^k \frac{d_i}{n'_i (n'_i - d_i)} ,$$

which is called Greenwood's formula.

Types of life tables:

Table 1 is an example of a cohort life table. A cohort is a group of people who are followed throughout the course of the study. The people at risk at the beginning of the interval I_i are those people who survived (not dead, lost, or withdrawn) the previous interval I_{i-1} . Another type of life table is the current life table.

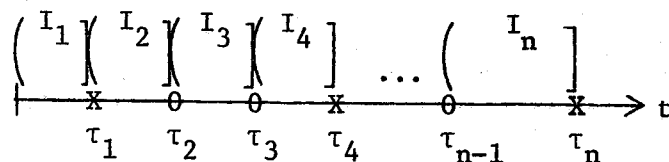
In a current life table a group of people with age τ_{i-1} are considered to be at risk at the beginning of the interval $I_i = (\tau_{i-1}, \tau_i]$, and this group of people is completely different from those at risk in the previous interval I_{i-1} . Typically, different age groups in the population are followed at the same time.

References:

- Berkson and Gage, Proceedings of Staff Meetings of the Mayo Clinic (1950).
Cutler and Ederer, J. Chronic Diseases (1958).
Elveback, JASA (1958).
Chiang, Stochastic Processes in Biostatistics (1968), Chapter 9.
Breslow and Crowley, Ann. Stat. (1974).

B. Product-limit (Kaplan-Meier) estimator

The product-limit (PL) estimator is similar to the actuarial estimator except the lengths of the intervals I_i are variable. In fact, let τ_i , the right endpoint of I_i , be the i th ordered censored or uncensored observation.



0 = censored

X = uncensored

Recall that we observe the pairs $(Y_1, \delta_1), \dots, (Y_n, \delta_n)$. For now, assume no ties. Let $Y_{(1)} < Y_{(2)} < \dots < Y_{(n)}$ be the order statistics of Y_1, Y_2, \dots, Y_n , and with an abuse of notation, define $\delta_{(i)}$ to be the value of δ associated with $Y_{(i)}$, i.e., $\delta_{(i)} = \delta_j$ when $Y_{(i)} = Y_j$. Note that $\delta_{(1)}, \dots, \delta_{(n)}$ are not ordered. Let $R(t)$ denote the risk set at time t , which is the set of subjects still alive at time t^- , and let

$$n_i = \# \text{ in } R(Y_{(i)}) = \# \text{ alive at time } Y_{(i)}^-,$$

$$d_i = \# \text{ died at time } Y_{(i)},$$

$$p_i = P\{\text{surviving through } I_i | \text{alive at beginning of } I_i\} = P\{T > \tau_i | T > \tau_{i-1}\},$$

$$q_i = 1 - p_i.$$

From the estimates

$$\hat{q}_i = \frac{d_i}{n_i},$$

$$\hat{p}_i = 1 - \hat{q}_i = \begin{cases} 1 - \frac{1}{n_i} & \text{if } \delta_{(i)} = 1 \text{ (uncensored)}, \\ 1 & \text{if } \delta_{(i)} = 0 \text{ (censored)}, \end{cases}$$

the PL estimate when no ties are present is

$$\begin{aligned} \hat{S}(t) &= \prod_{y_{(i)} \leq t} \hat{p}_i = \prod_{u: y_{(i)} \leq t} \left(1 - \frac{1}{n_i}\right) \\ &= \prod_{y_{(i)} \leq t} \left(1 - \frac{1}{n_i}\right)^{\delta_{(i)}} = \prod_{y_{(i)} \leq t} \left(1 - \frac{1}{n-i+1}\right)^{\delta_{(i)}} \\ &= \prod_{y_{(i)} \leq t} \left(\frac{n-i}{n-i+1}\right)^{\delta_{(i)}}. \end{aligned}$$

Reference:

Kaplan and Meier, JASA (1958).

Notes:

(i) For tied uncensored observations, suppose just before time t , there are m individuals alive, and at time t , d deaths occur. Split the time of the d deaths infinitesimally so that the factor for the d deaths in the product-limit estimator is

$$(1 - \frac{1}{m})(1 - \frac{1}{m-1}) \dots (1 - \frac{1}{m-d+1}) = (\frac{m-1}{m})(\frac{m-2}{m-1}) \dots (\frac{m-d}{m-d+1}) = \frac{m-d}{m} = 1 - \frac{d}{m}.$$

(ii) If censored and uncensored observations are tied, consider the uncensored observations to arrive just before the censored observations.

(iii) If the last (ordered) observation $y_{(n)}$ is censored, then for $\hat{S}(t)$ as defined above

$$\lim_{t \rightarrow \infty} \hat{S}(t) > 0.$$

Sometimes it is preferable to redefine $\hat{S}(t) = 0$ for $t \geq y_{(n)}$ or to think of it as being undefined for $t \geq y_{(n)}$ if $\delta_{(n)} = 0$.

From Notes (i) and (ii), by letting

$$y'_{(1)} < y'_{(2)} < \dots < y'_{(r)}$$

denote the distinct survival times and

$$\delta'_{(j)} = \begin{cases} 1 & \text{if the observations at time } y'_{(j)} \text{ are uncensored,} \\ 0 & \text{if censored,} \end{cases}$$

$$n_j = \# \text{ in } \mathcal{R}(y'_{(j)}),$$

$$d_j = \# \text{ died at time } y'_{(j)},$$

the PL estimate allowing for ties is

$$\hat{S}(t) = \prod_{u: y'_{(j)} \leq t} \left(1 - \frac{d_j}{n_j}\right) = \prod_{y'_{(j)} \leq t} \left(1 - \frac{d_j}{n_j}\right)^{\delta'_{(j)}}.$$

Example. AML Maintenance Study

A clinical trial to evaluate the efficacy of maintenance chemotherapy for acute myelogenous leukemia (AML) was conducted by Embury

et al. at Stanford University. After reaching a state of remission through treatment by chemotherapy, the patients who entered the study were randomized into two groups. The first group received maintenance chemotherapy; the second or control group did not. The objective of the trial was to see if maintenance chemotherapy prolonged the time until relapse, i.e., increased the length of remission.

For a preliminary analysis during the course of the trial the data (on 10/74) were as follows:

Length of complete remission (in weeks)

Maintained group:

9, 13, 13+, 18, 23, 28+, 31, 34, 45+, 48, 161+ .

Non-maintained group:

5, 5, 8, 8, 12, 16+, 23, 27, 30, 33, 43, 45 .

The Kaplan-Meier product-limit estimator for the maintained group is computed as follows:

$$\hat{S}(0) = 1$$

$$\hat{S}(9) = \hat{S}(0) \times \frac{10}{11} = .91$$

$$\hat{S}(13) = \hat{S}(9) \times \frac{9}{10} = .82$$

$$\hat{S}(18) = \hat{S}(13) \times \frac{7}{8} = .72$$

$$\hat{S}(23) = \hat{S}(18) \times \frac{6}{7} = .61$$

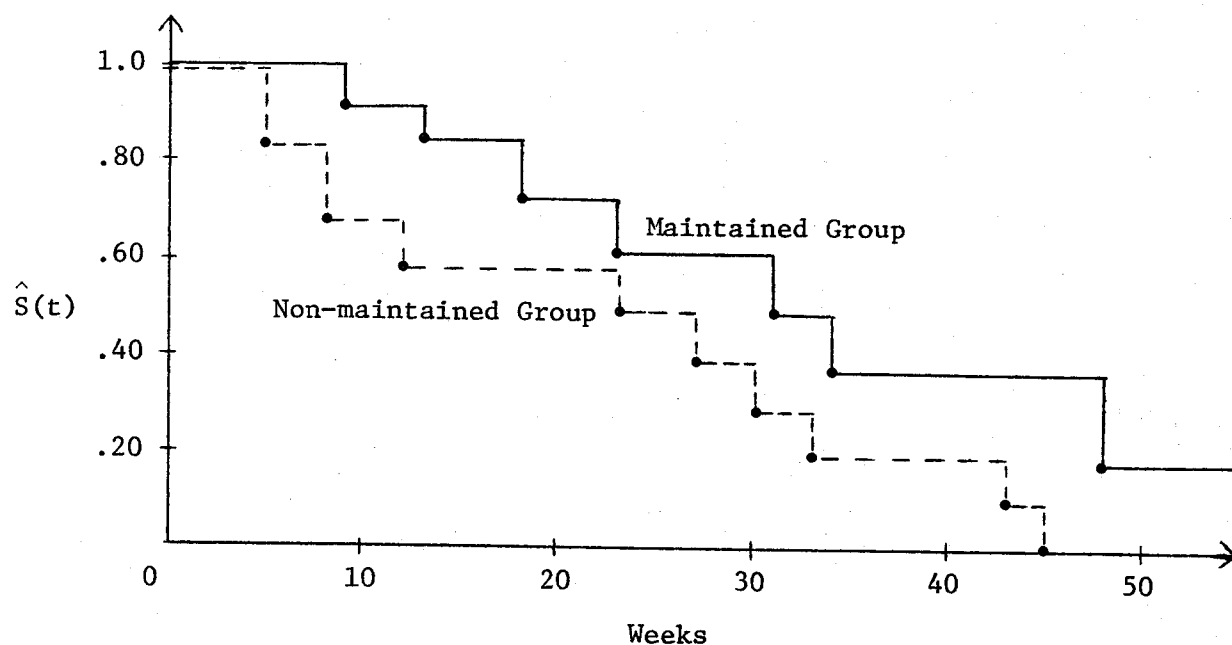
$$\hat{S}(31) = \hat{S}(23) \times \frac{4}{5} = .49$$

$$\hat{S}(34) = \hat{S}(31) \times \frac{3}{4} = .37$$

$$\hat{S}(48) = \hat{S}(34) \times \frac{1}{2} = .18$$

Figure 3 exhibits the PL estimators for the maintained and non-maintained groups.

Figure 3



Reference:

Embury et al., Western J. Medicine (1977).

Variance of $\hat{S}(t)$:

Using the same arguments as for the variance of the actuarial estimate, we can get in the case of no ties

$$\begin{aligned} \hat{\text{Var}}(\hat{S}(t)) &= \hat{S}^2(t) \sum_{y_{(i)} \leq t} \frac{\hat{q}_i}{n_i \hat{p}_i}, \\ &= \hat{S}^2(t) \sum_{y_{(i)} \leq t} \frac{\delta_{(i)}}{(n-i)(n-i+1)}. \end{aligned}$$

With ties present

$$\hat{\text{Var}}(\hat{S}(t)) = \hat{S}^2(t) \sum_{y'_{(j)} \leq t} \frac{\delta'_{(j)} d_j}{n_j (n_j - d_j)}.$$

These formulas are referred to as Greenwood's formula as well.

The justification for these formulas is not as clear as in the case of life tables because the number of terms in the product is random and there is more dependence between the terms. However, they can be justified as approximations to the asymptotic variance of $\hat{S}(t)$ to be given later.

Thomas and Grunkemeier study three different methods of confidence interval construction. One uses the approximate variance $\text{Var}(\hat{S}(t))$. Also, see the comments on page 100.

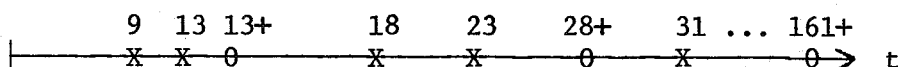
Reference:

Thomas and Grunkemeier, JASA (1975).

Properties of the PL estimator

1. Redistribute-to-the-right algorithm

Efron introduced another method of computing the PL estimator. We illustrate with the leukemia (AML) example (p. 36). Plot the (n=11) survival times:



The ordinary estimate of $S(t)$ assuming no censoring puts mass $1/11$ at each observed time. Consider the first censored time $13+$. Since a death did not occur at $13+$ but somewhere to the right of it, it seems reasonable to redistribute $1/11$, the mass at $13+$, equally among all observed times to the right of $13+$. Therefore, add $(\frac{1}{8})(\frac{1}{11})$ to the mass at $18, 23, 28+, \dots$. Now consider the next censored time $28+$; redistribute $\frac{1}{11} + (\frac{1}{8})(\frac{1}{11})$, the mass at $28+$, among all observed times to the right of $28+$. Treating the other censored times similarly results in the PL estimator.

$y_{(i)}$	mass at start	mass after first redistribution	mass after second redistribution	mass after third redistribution	$\hat{S}(y_{(i)})$
9	1/11=.09	.09	.09	.09	.91
13	.09	.09	.09	.09	.82
13+	.09	0	0	0	
18		.09+(1/8)(.09)=.10	.10	.10	.72
23	:	.10	.10	.10	.61
28+		.10	0	0	
31			.10+(1/5)(.10)=.12	.12	.49
34		:	.12	.12	.37
45+			.12	0	
48				.12+(1/2)(.12)=.18	.18
161+			:	.18	

The difference between the last column and one minus the cumulative sum of the penultimate column is due to rounding.

Reference:

Efron, Proc. Fifth Berkeley Symp. IV (1967), pp. 831-853.

2. Self-consistency

For simplicity, we will assume no ties. An estimator $\hat{SC}(t)$ is self-consistent if

$$\begin{aligned} \hat{SC}(t) = \frac{1}{n} \left[\sum_{i=1}^n 1 \cdot I(y_{(i)} > t) + \sum_{i=1}^n 0 \cdot I(y_{(i)} \leq t, \delta_{(i)} = 1) \right. \\ \left. + \sum_{i=1}^n \frac{\hat{SC}(t)}{\hat{SC}(y_{(i)})} I(y_{(i)} \leq t, \delta_{(i)} = 0) \right], \end{aligned} \quad (4)$$

where $\hat{SC}(t)/\hat{SC}(y_{(i)})$ estimates the conditional probability of surviving beyond t given alive at $y_{(i)}$. Notice that (4) is equivalent to

$$\hat{SC}(t) = \frac{1}{n} \left[N_y(t) + \sum_{y_{(i)} \leq t} (1 - \delta_{(i)}) \frac{\hat{SC}(t)}{\hat{SC}(y_{(i)})} \right], \quad (5)$$

where

$$N_y(t) = \# (y_i > t) .$$

The PL estimator is the unique self-consistent estimator for
 $t < y_{(n)}$. The proof proceeds as follows.

From (5), a self-consistent estimator satisfies

$$\begin{aligned} \hat{SC}(t) &= \frac{N_y(t)}{n - \sum_{y_{(i)} \leq t} \left(\frac{1 - \delta_{(i)}}{\hat{SC}(y_{(i)})} \right)}, \\ &= \begin{cases} 1 & \text{if } t < y_{(1)} , \\ \frac{N_y(t)}{n - \sum_{i=1}^k \left(\frac{1 - \delta_{(i)}}{\hat{SC}(y_{(i)})} \right)} & \text{if } y_{(k)} \leq t < y_{(k+1)}, \quad k = 1, 2, \dots, n-1. \end{cases} \quad (6) \end{aligned}$$

We want to show that if $\hat{SC}(t)$ satisfies (6), then $\hat{SC}(t)$ coincides with the PL estimator $\hat{S}(t)$. First notice that

$$\hat{S}(t) = 1 = \hat{SC}(t) \quad \text{if } t < y_{(1)} .$$

Also, $\hat{S}(t)$ and $\hat{SC}(t)$ are constant on $[y_{(k)}, y_{(k+1)})$ for $k=1, \dots, n-1$. Therefore, we need only show that the jump at $y_{(k)}$ of $\hat{SC}(t)$ is the same as the jump of $\hat{S}(t)$.

(i) If $\delta_{(k)} = 0$, (6) implies

$$N_y(y_{(k)}^-) - 1 = N_y(y_{(k)}) ,$$

$$\begin{aligned} &= \hat{SC}(y_{(k)}) \left[n - \sum_{i=1}^k \left(\frac{1-\delta_{(i)}}{\hat{SC}(y_{(i)})} \right) \right] , \\ &= \hat{SC}(y_{(k)}) \left[n - \sum_{i=1}^{k-1} \left(\frac{1-\delta_{(i)}}{\hat{SC}(y_{(i)})} \right) \right] - 1 , \\ &= \hat{SC}(y_{(k)}) \left[\frac{N_y(y_{(k)}^-)}{\hat{SC}(y_{(k)}^-)} \right] - 1 , \end{aligned}$$

which implies

$$\hat{SC}(y_{(k)}) = \hat{SC}(y_{(k)}^-) .$$

Thus, $\hat{SC}(t)$ has no jump at $y_{(k)}$ when $\delta_{(k)} = 0$, and therefore agrees with $\hat{S}(t)$ at $t = y_{(k)}$.

(ii) If $\delta_{(k)} = 1$, (6) implies

$$\begin{aligned} \hat{SC}(y_{(k)}) &= \frac{N_y(y_{(k)})}{n - \sum_{i=1}^k \left(\frac{1-\delta_{(i)}}{\hat{SC}(y_{(i)})} \right)} , \\ &= \frac{N_y(y_{(k)})}{N_y(y_{(k)}^-)} \frac{N_y(y_{(k)}^-)}{n - \sum_{i=1}^{k-1} \left(\frac{1-\delta_{(i)}}{\hat{SC}(y_{(i)})} \right)} , \\ &= \frac{n-k}{n-k+1} \hat{SC}(y_{(k)}^-) , \end{aligned}$$

so $\hat{SC}(t)$ has a jump at $y_{(k)}$ if $\delta_{(k)} = 1$ with $\hat{SC}(y_{(k)})/\hat{SC}(y_{(k)}^-) = (n-k)/(n-k+1)$, again agreeing with $\hat{S}(t)$ at $t = y_{(k)}$.

Self-consistency algorithm:

Consider the naive estimator

$$\hat{S}^0(t) = \frac{N_y(t)}{n} .$$

This estimator can be improved by iteration using

$$\hat{S}^{(j+1)}(t) = \frac{1}{n} \left[N_y(t) + \sum_{y_{(i)} \leq t} (1 - \delta_{(i)}) \frac{\hat{S}^{(j)}(t)}{\hat{S}^{(j)}(y_{(i)})} \right].$$

In fact, $\hat{S}^{(j)}(t)$ converges monotonically in a finite number of steps to the PL estimator. This computational algorithm can be useful in more general censoring problems.

References:

Efron, Proc. Fifth Berkeley Symp. IV (1967).

Turnbull, JASA (1974).

_____, JRSS B (1976).

3. Generalized maximum likelihood estimator

In the usual setup, we assume that our observation \tilde{X} has a probability measure P_θ which satisfies

$$dP_\theta(\tilde{x}) = f_\theta(\tilde{x}) d\mu(\tilde{x}),$$

where $\mu(\tilde{x})$ is a dominating measure for the class $\{P_\theta\}$. Getting the maximum likelihood estimator of θ involves maximizing the likelihood

$$L(\theta) = f_\theta(\tilde{x}).$$

In our case, we assume that our observation has a probability measure P_F that depends on the unknown distribution function F . The class $\{P_F\}$ has no dominating measure so we need a more general definition of maximum likelihood.

Kiefer and Wolfowitz suggest the following definition. Let $\rho = \{P\}$ be a class of probability measures. For the elements P_1 and P_2 in ρ , define

$$f(\tilde{x}; P_1, P_2) = \frac{dP_1(\tilde{x})}{d(P_1 + P_2)},$$

the Radon-Nikodym derivative of P_1 with respect to $P_1 + P_2$. Define the probability measure \hat{P} to be a generalized maximum likelihood estimator (GMLE) if

$$f(\underline{x}; \hat{P}, P) \geq f(\underline{x}; P, \hat{P}) . \quad (7)$$

for any element $P \in \mathcal{P}$.

This definition of the GMLE includes the definition of the usual MLE.

The Kaplan-Meier PL estimator gives the GMLE of F . The proof proceeds as follows. For convenience assume no ties.

If a probability measure \hat{P} gives positive probability to \underline{x} , then $f(\underline{x}; P, \hat{P}) = 0$ unless P also gives positive probability to \underline{x} . Thus, to check (7) for $P \in \mathcal{P}$ it is sufficient to check it for those P with $P\{\underline{x}\} > 0$ and in this case (7) reduces to

$$\hat{P}\{\underline{x}\} \geq P\{\underline{x}\} . \quad (8)$$

Since \hat{S} puts positive mass on the point $\underline{x} = ((y_1, \delta_1), \dots, (y_n, \delta_n))$, we need only consider probability measures P which put positive mass on this point and show that \hat{S} maximizes $P\{((y_1, \delta_1), \dots, (y_n, \delta_n))\}$. For any such P ,

$$\begin{aligned} L &= P\{((y_1, \delta_1), \dots, (y_n, \delta_n))\} , \\ &= \prod_{i=1}^n P\{T = y_i\}^{\delta_i} P\{T \geq y_i\}^{1-\delta_i} , \\ &= \prod_{i=1}^n p_i^{\delta_{(i)}} \left[\sum_{j=i}^n (p_j + r_j) \right]^{1-\delta_{(i)}} , \end{aligned}$$

where

$$p_i = P\{T = y_{(i)}\} \quad \text{and} \quad r_i = P\{y_{(i)} < T < y_{(i+1)}\} .$$

By letting any mass between $y_{(i)}$ and $y_{(i+1)}$ tend to the left to $y_{(i)}$ for $i = 1, \dots, n$, the terms $\sum_{j=i}^n (p_j + r_j)$ remain constant but the p_i are increased in the limit. Therefore,

$$\sup_{r_i \rightarrow 0} L = \prod_{i=1}^n p_i^{\delta_{(i)}} \left[\sum_{j=i}^n p_j \right]^{1-\delta_{(i)}} . \quad (9)$$

From Problem (8) (pp. 142-3), we see that (9) is maximized by

$$\hat{p}_i = \prod_{j=1}^{i-1} \left(1 - \frac{\delta(j)}{n-j+1} \right) \frac{\delta(i)}{n-i+1} .$$

This corresponds to \hat{S} . The argument for ties is identical.

References:

Kaplan and Meier, JASA (1958).

Johansen, Scand. J. Stat. (1978).

Kiefer and Wolfowitz, Ann. Math. Stat. (1956).

4. Consistency

Recall

$$S(t) = S_T(t) = P\{T > t\} = 1 - F(t) ,$$

and define S^* by

$$\begin{aligned} S^*(t) &= S_Y(t) = P\{Y > t\} = 1 - H(t) , \\ &= [1 - F(t)][1 - G(t)] . \end{aligned}$$

Define the subsurvival functions

$$S_u^*(t) = P\{Y > t, \delta=1\} = \int_t^\infty [1 - G(u)] dF(u) ,$$

$$S_c^*(t) = P\{Y > t, \delta=0\} = \int_t^\infty [1 - F(u)] dG(u) .$$

Then,

$$S^*(t) = S_u^*(t) + S_c^*(t) .$$

We will show that $S(t)$ can be expressed as a function of $S_u^*(t)$ and $S_c^*(t)$.

(i) Suppose $S_u^*(t)$ is continuous.

$$\begin{aligned} \int_0^t \frac{dS_u^*(u)}{S_u^*(u) + S_c^*(u)} &= \int_0^t \frac{-[1 - G(u)] dF(u)}{[1 - F(u)][1 - G(u)]} \\ &= \int_0^t \frac{-dF(u)}{1 - F(u)} = \log[1 - F(u)] \Big|_0^t = \log S(t) . \end{aligned}$$

Therefore,

$$S(t) = \exp \left[\int_0^t \frac{dS_u^*(u)}{S_u^*(u) + S_c^*(u)} \right].$$

(ii) Suppose S_u^* has a jump at t , but S_c^* is continuous at t .

$$\begin{aligned} \log \frac{S_u^*(t+) + S_c^*(t+)}{S_u^*(t-) + S_c^*(t-)} &= \log \frac{[1-F(t+)][1-G(t+)]}{[1-F(t-)][1-G(t-)]}, \\ &= \log \frac{[1-F(t+)]}{[1-F(t-)]} = \log \frac{S(t+)}{S(t-)}. \end{aligned}$$

(The second equality follows from the fact that S_c^* is continuous at t so $G(t+) = G(t-)$.) Therefore,

$$S(t+) = S(t-) \exp \left\{ \log \frac{S_u^*(t+) + S_c^*(t+)}{S_u^*(t-) + S_c^*(t-)} \right\}.$$

If the underlying distributions F and G have no common jumps, then from (i) and (ii)

$$S(t) = \exp \left\{ \int_0^t \frac{dS_u^*(u)}{S_u^*(u) + S_c^*(u)} + d \sum_{u \leq t} \log \frac{S_u^*(u+) + S_c^*(u+)}{S_u^*(u-) + S_c^*(u-)} \right\}, \quad (10)$$

where \int denotes integration over the continuity intervals of S_u^* and $d \sum$ denotes summation over the discrete jumps of S_u^* . Expression (10), called Peterson's representation, shows that $S(t)$ can be represented as a function of S_u^* , S_c^* and t , i.e.,

$$S(t) = \Psi(S_u^*, S_c^*; t).$$

Peterson's representation gives us a proof that the PL estimator $\hat{S}(t)$ is consistent. The proof proceeds as follows.

Define the empirical subsurvival functions

$$\hat{S}_u^*(t) = \frac{1}{n} \sum_{i=1}^n I(y_i > t, \delta_i = 1) ,$$

$$\hat{S}_c^*(t) = \frac{1}{n} \sum_{i=1}^n I(y_i > t, \delta_i = 0) .$$

It can be seen that the PL estimator is

$$\hat{S}(t) = \Psi(\hat{S}_u^*, \hat{S}_c^*; t) ,$$

provided any ties between uncensored and censored observations are interpreted as uncensored observations preceding censored. Notice that since \hat{S}_u^* is discrete, $\Psi(\hat{S}_u^*, \hat{S}_c^*; t)$ involves only the summation over the discrete jumps of \hat{S}_u^* .

By the Glivenko-Cantelli theorem,

$$\hat{S}_u^*(t) \xrightarrow{\text{a.s.}} S_u^*(t) ,$$

$$\hat{S}_c^*(t) \xrightarrow{\text{a.s.}} S_c^*(t) , \text{ uniformly in } t .$$

Also, Ψ is a continuous function of S_u^*, S_c^* in the sup norm. That is, if

$$\|S_u^* - S_u^{**}\| = \sup_t |S_u^*(t) - S_u^{**}(t)| \rightarrow 0 , \text{ and}$$

$$\|S_c^* - S_c^{**}\| \rightarrow 0 ,$$

then

$$\Psi(S_u^*, S_c^*; t) \rightarrow \Psi(S_u^{**}, S_c^{**}, t) .$$

Therefore,

$$\hat{S}(t) = \Psi(\hat{S}_u^*, \hat{S}_c^*; t) \xrightarrow{\text{a.s.}} \Psi(S_u^*, S_c^*; t) = S(t) .$$

Reference:

Peterson, JASA (1977).

5. Asymptotic normality

We will show later that if F and G are continuous on $[0, T]$ and $F(T) < 1$, then

$$Z_n(t) = \sqrt{n} [\hat{S}(t) - S(t)] \xrightarrow{W} Z(t) \text{ as } n \rightarrow \infty ,$$

where $Z(t)$ is a Gaussian process with moments

$$E(Z(t)) = 0 ,$$

$$\begin{aligned} \text{Cov}(Z(t_1), Z(t_2)) &= S(t_1) S(t_2) \int_0^{t_1 \wedge t_2} \frac{dF_u(u)}{[1-H(u)]^2} , \\ &= S(t_1) S(t_2) \int_0^{t_1 \wedge t_2} \frac{dF(u)}{[1-F(u)][1-H(u)]} , \end{aligned}$$

where

$$F_u(t) = P\{T \leq t, \delta=1\} = \int_0^t [1-G(u)] dF(u) ,$$

$$1-H(u) = [1-F(u)][1-G(u)] .$$

The proof involves hazard functions which are to be discussed in the next section.

We remark that $Z_n(t)$ converges weakly (\xrightarrow{W}) to the Gaussian process $Z(t)$ means that for any t_1, \dots, t_k , $Z_n(t_1), \dots, Z_n(t_k)$ has an asymptotic multivariate normal distribution and the sequence of probability measures for Z_n is tight so that $f(Z_n)$ converges in distribution to $f(Z)$ for any function f continuous in the sup norm.

As a particular case of the above result,

$$\hat{S}(t) \stackrel{a}{\sim} N\left(S(t), \frac{S^2(t)}{n} \int_0^t \frac{dF_u(u)}{[1-H(u)]^2}\right) .$$

We can obtain an approximation for the asymptotic variance of $\hat{S}(t)$. Because $F_u(t) = P\{T \leq t, \delta=1\}$ and $H(t) = P\{Y \leq t\}$, let (assuming no ties)

$$d\hat{F}_u(y_{(i)}) = \frac{\delta_{(i)}}{n} ,$$

$$1-\hat{H}(y_{(i)}) = 1 - \frac{i}{n} = \frac{n-i}{n} ,$$

$$1-\hat{H}(y_{(i)}^-) = 1 - \frac{i-1}{n} = \frac{n-i+1}{n} .$$

Replacement of $(1-H(u))^2$ by $(1-H(u))(1-H(u-))$ in the asymptotic variance and substitution of the above estimates gives

$$\begin{aligned} \widehat{AVar}(\hat{S}(t)) &= \frac{\hat{S}^2(t)}{n} \sum_{y_{(i)} \leq t} \frac{\delta_{(i)}/n}{\left(\frac{n-i}{n}\right)\left(\frac{n-i+1}{n}\right)}, \\ &= \hat{S}^2(t) \sum_{y_{(i)} \leq t} \frac{\delta_{(i)}}{(n-i)(n-i+1)}, \end{aligned}$$

which is precisely Greenwood's formula.

References:

Breslow and Crowley, Ann. Stat. (1974).

Billingsley, Convergence of Probability Measures (1968), for weak convergence.

C. Hazard function estimators

Recall that the hazard function is

$$\lambda(t) = \frac{f(t)}{1-F(t)}.$$

Estimating $\lambda(t)$ is essentially equivalent to the difficult problem of estimating a density. An easier problem is estimating the cumulative hazard function:

$$\Lambda(t) = \int_0^t \lambda(u) du.$$

The functions Λ and S are related by

$$S(t) = e^{-\Lambda(t)}.$$

For the sake of simpler notation, assume no ties. Nelson estimates $\Lambda(t)$ by

$$\hat{\Lambda}(t) = \hat{\Lambda}_2(t) = \sum_{y_{(i)} \leq t} \frac{\delta_{(i)}}{n-i+1},$$

and Peterson proposes

$$\hat{\Lambda}_1(t) = \sum_{y_{(i)} \leq t} -\log\left(1 - \frac{\delta_{(i)}}{n-i+1}\right).$$

The two estimators are very close because for small x , $\log(1-x) \cong -x$.

Peterson's estimator corresponds to the PL estimator of the survival function

$$\hat{S}_1(t) = e^{-\hat{\Lambda}_1(t)} = \prod_{y_{(i)} \leq t} \left(1 - \frac{\delta_{(i)}}{n-i+1}\right) = \hat{S}(t),$$

while Nelson's estimate corresponds to a different estimator of the survival function

$$\hat{S}_2(t) = e^{-\hat{\Lambda}_2(t)}.$$

Fleming and Harrington recommend $\hat{S}_2(t)$ as an alternative estimator for the survival function and have shown it to have slightly smaller mean square error in some situations.

References:

Nelson, J. Quality Tech. (1969).

———, Technometrics (1972).

Peterson, JASA (1977).

Fleming and Harrington, unpublished manuscript (1979).

Asymptotic normality:

From standard results on (sub)distribution functions,

$$\sqrt{n}[\hat{F}_u(t) - F_u(t)] \xrightarrow{W} Z_{F_u}(t),$$

$$\sqrt{n}[\hat{H}(t) - H(t)] \xrightarrow{W} Z_H(t),$$

where Z_{F_u} and Z_H are Gaussian processes.

We expand $\hat{\Lambda}(t)$:

$$\begin{aligned} \hat{\Lambda}(t) &= \int_0^t \frac{d\hat{F}_u(u)}{1-\hat{H}(u-)}, \\ &= \int_0^t \left[\frac{1}{1-H} + \frac{\hat{H}-H}{(1-H)^2} + \dots \right] \left[dF_u + d(\hat{F}_u - F_u) \right], \end{aligned}$$

$$\begin{aligned}
&= \int_0^t \frac{dF_u}{1-H} + \int_0^t \frac{\hat{H}-H}{(1-H)^2} dF_u + \int_0^t \frac{d(\hat{F}_u - F_u)}{1-H} + \dots, \\
&= \Lambda(t) + \int_0^t \frac{\hat{H}-H}{(1-H)^2} dF_u + \frac{(\hat{F}_u - F_u)(t)}{1-H(t)} - \int_0^t \frac{\hat{F}_u - F_u}{(1-H)^2} dH + \dots.
\end{aligned}$$

The last equality follows from integration by parts of the last integral.

Transposing and multiplying by \sqrt{n} ,

$$\begin{aligned}
\sqrt{n}[\hat{\Lambda}(t) - \Lambda(t)] &= \int_0^t \frac{\sqrt{n}(\hat{H}-H)}{(1-H)^2} dF_u + \frac{\sqrt{n}(\hat{F}_u - F_u)(t)}{1-H(t)} - \int_0^t \frac{\sqrt{n}(\hat{F}_u - F_u)}{(1-H)^2} dH + \dots, \\
&\stackrel{W}{\rightarrow} \int_0^t \frac{Z_H}{(1-H)^2} dF_u + \frac{Z_{F_u}(t)}{1-H(t)} - \int_0^t \frac{Z_{F_u}}{(1-H)^2} dH = Z_{\Lambda}(t).
\end{aligned}$$

The limit $Z_{\Lambda}(t)$, being a weighted average of Gaussian processes, is itself a Gaussian process with

$$E(Z_{\Lambda}(t)) = 0,$$

$$\text{Cov}(Z_{\Lambda}(t_1), Z_{\Lambda}(t_2)) = \int_0^{t_1 \wedge t_2} \frac{dF_u}{(1-H)^2}.$$

For details, see Breslow and Crowley.

Using this result together with the approximation

$$\hat{S}(t) \approx e^{-\hat{\Lambda}(t)},$$

we derive the asymptotic distribution of $\hat{S}(t)$:

$$e^{-\hat{\Lambda}(t)} = e^{-\Lambda(t)} - [\hat{\Lambda}(t) - \Lambda(t)]e^{-\Lambda(t)} + \dots,$$

$$\hat{S}(t) \approx S(t) - [\hat{\Lambda}(t) - \Lambda(t)]S(t) + \dots,$$

$$\sqrt{n}[\hat{S}(t) - S(t)] \approx -\sqrt{n}[\hat{\Lambda}(t) - \Lambda(t)]S(t) + \dots,$$

$$\stackrel{W}{\rightarrow} Z(t),$$

where $Z(t)$ is a Gaussian process with

$$E(Z(t)) = 0 ,$$

$$\text{Cov}(Z(t_1), Z(t_2)) = S(t_1) S(t_2) \int_0^{t_1 \wedge t_2} \frac{dF_u}{(1-H)^2} .$$

References:

Breslow and Crowley, Ann. Stat. (1974).

Aalen, Scand. J. Stat. (1976).

———, Ann. Stat. (1978).

D. Robust estimators

In estimation problems the parameter of interest can frequently be expressed as a functional

$$\theta = T(F)$$

of the underlying d.f. F .

With no censoring present, the usual estimator is

$$\hat{\theta} = T(F_n) ,$$

where F_n is the empirical d.f.

With censoring present, a reasonable estimator is

$$\hat{\theta} = T(\hat{F}) ,$$

where $\hat{F} = 1 - \hat{S}$ and \hat{S} is the PL estimator.

1. Mean

$$\theta = T(F) = \int_0^\infty x dF(x) = \int_0^\infty [1-F(x)] dx = \int_0^\infty S(t) dt .$$

Without censoring,

$$\hat{\theta} = T(F_n) = \int_0^\infty x dF_n(x) = \bar{x} = \int_0^\infty [1-F_n(x)] dx .$$

With censoring,

$$\hat{\theta} = T(\hat{F}) = \int_0^{\infty} x d\hat{F}(x) = \int_0^{\infty} \hat{S}(t) dt .$$

$$AVar(\hat{\theta}) = \frac{1}{n} \int_0^{\infty} \frac{1}{[1-H(s)]^2} \left\{ \int_s^{\infty} S(u) du \right\}^2 dF_u(s) .$$

With no ties present,

$$\hat{AVar}(\hat{\theta}) = \sum_{i=1}^n \left\{ \int_{y_{(i)}}^{\infty} \hat{S}(u) du \right\}^2 \frac{\delta_{(i)}}{(n-i)(n-i+1)} .$$

Immediately, we have a difficulty. If $y_{(n)}$ is censored, then $\hat{S}(t)$ does not approach zero as $t \rightarrow \infty$, so the integrals are infinite.

We discuss three possible solutions.

(i) Redefinition of last observation.

Change $\delta_{(n)} = 0$ to $\delta_{(n)} = 1$. We illustrate with the maintained AML data of Embury et al. (p. 37).

$$\begin{aligned} \hat{\theta} &= 9 \times .091 + 13 \times .091 + 18 \times .102 \\ &\quad + 23 \times .102 + 31 \times .123 + 34 \times .123 \\ &\quad + 48 \times .184 + (161 \times .184) , \\ &= 23.011 + (29.624) , \\ &= 52.635 . \end{aligned}$$

The tail, and in particular the last observation, has heavy weight. This is due both to the PL estimator putting increased weights on the last observations and to the skewness of the distribution.

(ii) Restricted mean (Meier and Sander).

For fixed s_0 define a mean over $(0, s_0]$ and estimate it by

$$\hat{\theta} = \int_0^{s_0} \hat{S}(t) dt .$$

(iii) Variable upper limit (Susarla and Van Ryzin).

Estimate

$$\theta = \int_0^{\infty} S(t) dt$$

with

$$\hat{\theta} = \int_0^{s_n} \hat{S}(t) dt ,$$

where $\{s_n\}$ is a sequence of numbers converging monotonically to ∞ . Unfortunately, the proper choice of s_n depends on F , G and there exist no good guidelines for use in practice as yet.

References:

Kaplan and Meier, JASA (1958).

Meier, Perspectives in Prob. and Stat. (1975).

Sander, Stanford Univ. Tech. Report No. 8 (1975).

Susarla and Van Ryzin, Ann. Stat. (1980).

2. L-estimators

A basic assumption when using L-estimators is that the underlying distribution F is symmetric about θ . Typically survival times do not have a symmetric distribution because they are positive. However, before estimating we can symmetrize the data by applying a transformation, as for example, by taking logarithms.

An L-estimator is of the form

$$\hat{\theta} = \int_{-\infty}^{\infty} xJ(\hat{F}(x))d\hat{F}(x) ,$$

where J , defined on $[0,1]$, is symmetric about $1/2$ and satisfies $\int_0^1 J(u)du = 1$. An important L-estimator is the trimmed mean with

$$J(u) = \frac{1}{1-2\alpha} I_{[\alpha, 1-\alpha]}(u) .$$

With censored data the asymptotic variance of an L-estimator is

$$AVar(\hat{\theta}) = \frac{1}{n} \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} S(t) J(S(t)) S(u) J(S(u)) \left\{ \int_{-\infty}^{t \wedge u} \frac{dF_u(s)}{[1-H(s)]^2} \right\} dt du .$$

References:

Sander, Stanford Univ. Tech. Report No. 8 (1975).

Reid, Stanford Univ. Tech. Report No. 46 (1979) or Ann. Stat. (1981).

3. M-estimators

Again, a basic assumption is that F is symmetric, so transform the data first. An M-estimator $\hat{\theta}$ is the solution to

$$\int_{-\infty}^{\infty} \psi(x-\hat{\theta}) d\hat{F}(x) = 0 .$$

The function $\psi(x-\theta)$ generalizes $f'(x-\theta)/f(x-\theta)$ so M-estimators generalize maximum likelihood estimators. The Tukey biweight estimator corresponds to

$$\psi(x) = \begin{cases} x(1-x^2)^2 & \text{if } |x| \leq 1 , \\ 0 & \text{if } |x| > 1 . \end{cases}$$

In actual applications the data would need to be scaled by an appropriate scale estimator.

With censored data the asymptotic variance of an M-estimator is

$$AVar(\hat{\theta}) = \frac{1}{n} \int_{-\infty}^{\infty} \frac{1}{[1-H(s)]^2} \left\{ \int_{-\infty}^{\infty} \frac{1}{S E \psi'} S(t) \psi'(t-\theta) dt \right\}^2 dF_u(s) ,$$

where

$$E\psi' = \int_{-\infty}^{\infty} \psi'(t-\theta) dF(t) .$$

Reference:

Reid, Stanford Univ. Tech. Report No. 46 (1979).

At this point in time L- and M-estimators with censored data are experimental. Their virtues and defects have not been established. However, the median estimator is frequently used.

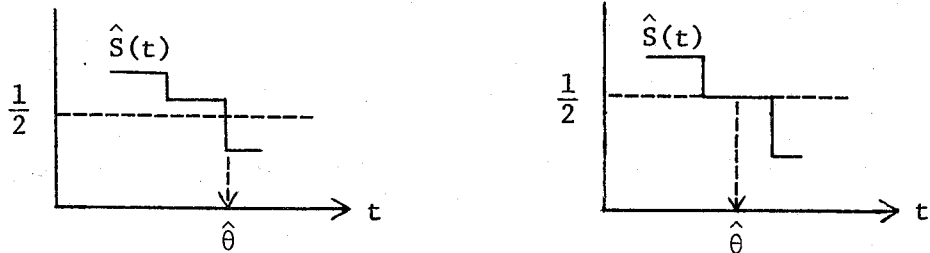
4. Median

$$\theta = S^{-1}\left(\frac{1}{2}\right) .$$

A reasonable estimator for θ is

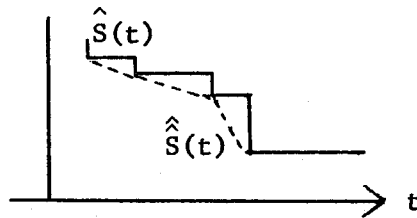
$$\hat{\theta} = \hat{S}^{-1}\left(\frac{1}{2}\right) .$$

If $\hat{S}^{-1}\left(\frac{1}{2}\right)$ does not have a unique solution, then define $\hat{\theta}$ to be the midpoint of the interval consisting of the solutions.



Empirical evidence suggests that this straightforward estimator tends to be too large. The PL estimator gives increasing jump sizes with increasing t , and due to censored observations dropping out, the gaps between uncensored observations tend to increase with t . Therefore, $\hat{\theta}$ tends to be too large.

A possible way to alleviate this problem is to define $\hat{\hat{S}}(t)$, a linear smooth of $\hat{S}(t)$, and $\hat{\hat{\theta}} = \hat{\hat{S}}^{-1}\left(\frac{1}{2}\right)$.



For example, in the maintained AML data of Embury et al. (p. 37),

$$\hat{S}(23) = .614 ,$$

$$\hat{S}(31) = .491 ,$$

$$\hat{\theta} = 31 - \frac{(8)(.009)}{(.123)} = 30.415 .$$

We need the variance of $\hat{\theta}$. The asymptotic variance is

$$\text{AVar } \hat{\theta} = \frac{\text{AVar } \hat{S}(\theta)}{f^2(\theta)} .$$

$\text{AVar } \hat{S}(\theta)$ can be estimated using Greenwood's formula, but f is an unknown density and is difficult to estimate.

References:

Sander, Stanford Univ. Tech. Report No. 5 (1975), discusses the asymptotic variance.

Reid, Stanford Univ. Tech. Report No. 46 (1979) or Ann. Stat. (1981), discusses the asymptotic variance.

Földes, Rejto, and Winter, unpublished manuscript (1978), discuss density estimation using censored data.

Reid and Iyengar, unpublished notes (1979), consider estimates of the variance.

Efron, Stanford Univ. Tech. Report No. 53 (1980), uses the bootstrap to measure the variability of $\hat{\theta}$.

E. Bayes estimators

Assume no ties. Denoting $N_y(t) = \#(y_i > t)$,

$$\begin{aligned}
\hat{S}(t) &= \prod_{y(i) \leq t} \left[\frac{n-i}{n-i+1} \right]^{\delta(i)}, \\
&= \prod_{y(i) \leq t} \left[\frac{n-i+1}{n-i} \right]^{-\delta(i)} \frac{1}{n} \left\{ \frac{n}{n-1} \cdot \frac{n-1}{n-2} \cdot \dots \cdot \frac{N_y(t)+1}{N_y(t)} \right\} \frac{N_y(t)}{1}, \\
&= \frac{N_y(t)}{n} \prod_{y(i) \leq t} \left[\frac{n-i+1}{n-i} \right]^{1-\delta(i)}.
\end{aligned}$$

Susarla and Van Ryzin show that the Bayes estimator of $S(t)$ has a similar form:

$$\hat{S}_\alpha(t) = \frac{\alpha(t, \infty) + N_y(t)}{\alpha(0, \infty) + n} \prod_{y(i) \leq t} \left[\frac{\alpha[y(i), \infty] + (n-i+1)}{\alpha[y(i), \infty] + (n-i)} \right]^{1-\delta(i)}.$$

The estimator $\hat{S}_\alpha(t)$ is the Bayes estimator under the loss function

$$L(\hat{\delta}, S) = \int_0^\infty [\hat{\delta}(t) - S(t)]^2 dw(t),$$

where w is any nonnegative nondecreasing function, and with a Dirichlet process prior P_α with parameter α on the family $\{P\}$ of all possible distributions. The parameter α is a finite nonnegative measure on $(0, \infty)$.

We say that the random probability measure P has a Dirichlet process prior with parameter α if for any measurable partition B_1, \dots, B_k of $(0, \infty)$,

$$(P(B_1), \dots, P(B_k)) \sim \text{Dirichlet}(\alpha(B_1), \dots, \alpha(B_k)).$$

Recall that the Dirichlet($\alpha_1, \dots, \alpha_k$) distribution has density

$$f(x_1, \dots, x_k) \propto x_1^{\alpha_1-1} x_2^{\alpha_2-1} \dots x_k^{\alpha_k-1} I(x_i \geq 0, x_1 + \dots + x_k = 1).$$

Notice that for $k = 2$, the Dirichlet distribution is just the beta distribution.

Under a parametric model, we assume our observation X has distribution P_θ where θ is picked by nature according to some prior distribution. In the nonparametric situation, we observe T with distribution P where P is picked by nature according to the distribution P_α . In other words, our survival time T is obtained by P_α generating P and P generating T . It can be shown that

$$\Pr\{T \in A\} = \frac{\alpha(A)}{\alpha(0, \infty)}. \quad (10)$$

The equation (10) gives an interpretation to the parameter α . The ratio $\alpha(A)/\alpha(0, \infty)$ is our prior guess on the probability of the set A . For example, if we believe T has exponential distribution with mean $1/\lambda_0$, then

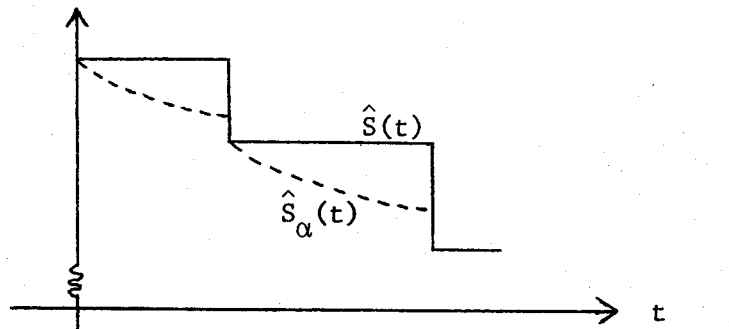
$$\frac{\alpha(t, \infty)}{\alpha(0, \infty)} = e^{-\lambda_0 t}.$$

Also, the total mass $\alpha(0, \infty)$ represents the strength of our prior belief. For example, $\alpha(0, \infty) = 10$ says our prior belief is worth 10 observations.

Return to the case where

$$\frac{\alpha(t, \infty)}{\alpha(0, \infty)} = e^{-\lambda_0 t}.$$

Then $\hat{S}_\alpha(t)$ compares with $\hat{S}(t)$ in the following way:



Rai, Susarla, and Van Ryzin show that in many cases, \hat{S}_α gives a smaller mean square error than \hat{S} , even when the prior is incorrect.

In case of ties, the Bayes estimate is

$$\hat{S}_\alpha(t) = \frac{\alpha(t, \infty) + N_y(t)}{\alpha(0, \infty) + n} \prod_{y'_{(j)} \leq t} \left[\frac{\alpha[y'_{(j)}, \infty) + N_y(y'_{(j)})}{\alpha[y'_{(j)}, \infty) + N_y(y'_{(j)})} \right]^{1-\delta'_{(j)}}.$$

References:

- Ferguson, Ann. Stat. (1973), discusses the Dirichlet process prior.
- Susarla and Van Ryzin, JASA (1976), derive the Bayes estimate in the censored case.
- Susarla and Van Ryzin, Ann. Stat. (1978b), study the asymptotic behavior of Bayes estimates.
- Rai, Susarla, and Van Ryzin, Rand Corp. Paper No. P-6357 (1979), look at mean square errors.
- Ferguson and Phadia, Ann. Stat. (1979), examine more general prior distributions.

Empirical Bayes estimators:

Instead of using a prior guess α , we could use the sample to estimate α .

References:

- Susarla and Van Ryzin, Ann. Stat. (1978a).
- Phadia, Ann. Stat. (1980).

IV. Nonparametric Methods: Two Samples

We need more notation. For the first sample, let T_1, T_2, \dots, T_m be iid each with d.f. F_1 , and C_1, C_2, \dots, C_m be iid each with d.f. G_1 . C_i is the censoring time associated with T_i . We can observe $(X_1, \delta_1), \dots, (X_m, \delta_m)$ where

$$X_i = T_i \wedge C_i, \quad \delta_i = I(T_i < C_i).$$

For the second sample, let U_1, U_2, \dots, U_n be iid each with d.f. F_2 ,

and D_1, D_2, \dots, D_n be iid each with d.f. G_2 . D_j is the censoring time associated with U_j , and we observe $(Y_1, \epsilon_1), \dots, (Y_n, \epsilon_n)$ where

$$Y_j = U_j \wedge D_j, \quad \epsilon_j = I(U_j < D_j).$$

The usual two sample problem is to test

$$H_0: F_1 = F_2.$$

Example. Hypothetical Clinical Trial

In the hypothetical clinical trial constructed by Byron Wm. Brown, Jr. in Figures 4a,b (on the next page), let the treatment A patients be the X observations and the treatment B patients be the Y observations.

Rx A: 3, 5, 7, 9+, 18

Rx B: 12, 19, 20, 20+, 33+

A. Gehan test

Gehan's test is an extension of the Wilcoxon test. Let the observations from the two samples be

$$X_1, \dots, X_m; Y_1, \dots, Y_n.$$

Order the combined sample and define

$$Z_{(1)} < Z_{(2)} \dots < Z_{(m+n)},$$

$$R_{1i} = \text{rank of } X_i,$$

$$R_1 = \sum_{i=1}^m R_{1i}.$$

Reject H_0 if R_1 is too small or too large. Use small sample tables or the large sample approximation

$$\frac{R_1 - E_0(R_1)}{\sqrt{\text{Var}_0(R_1)}} = \frac{R_1 - \frac{m(m+n+1)}{2}}{\sqrt{\frac{mn(m+n+1)}{12}}} \stackrel{a}{\sim} N(0,1),$$

Figure 4a

SURVIVAL TIMES FOR 10 CANCER PATIENTS RANDOMLY ASSIGNED TO TREATMENTS A AND B (HYPOTHETICAL DATA)

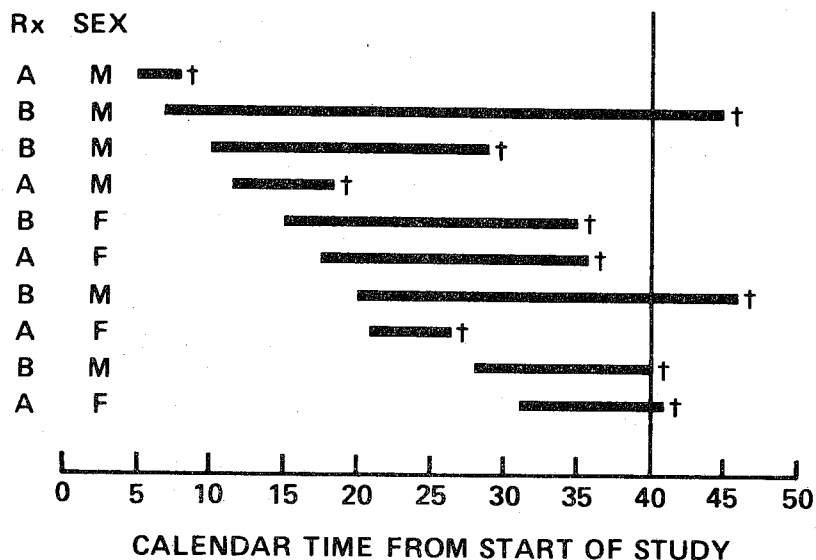
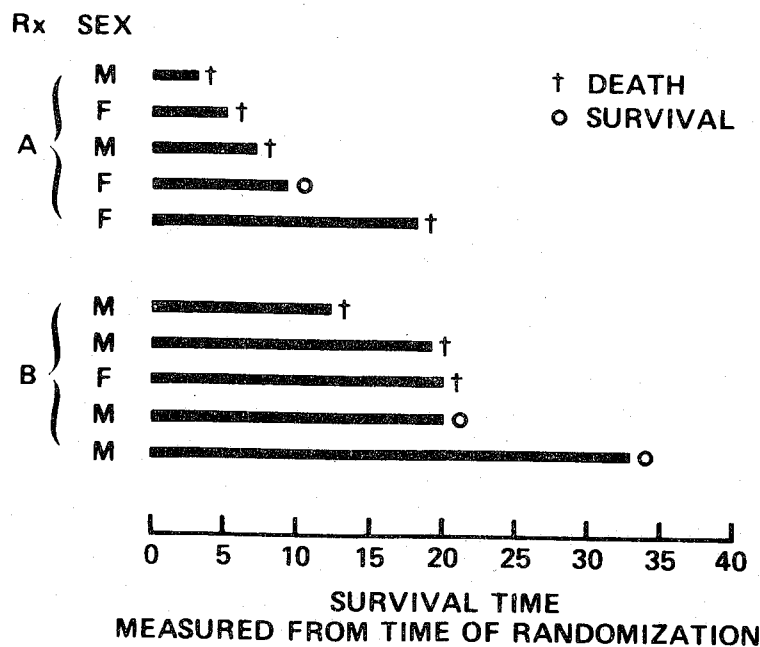


Figure 4b

SURVIVAL TIMES FROM TIME OF RANDOMIZATION FOR 10 CANCER PATIENTS – ASSUMING TERMINATION OF STUDY AT T = 40



where $E_0(R_1)$ and $\text{Var}_0(R_1)$ are the moments calculated under the null hypothesis.

The Mann-Whitney form of the Wilcoxon test will be useful. Define

$$U(X_i, Y_j) = U_{ij} = \begin{cases} +1 & \text{if } X_i > Y_j, \\ 0 & \text{if } X_i = Y_j, \\ -1 & \text{if } X_i < Y_j, \end{cases}$$

$$U = \sum_{i=1}^m \sum_{j=1}^n U_{ij}.$$

It can be shown that

$$R_1 = \frac{m(m+n+1)}{2} + \frac{1}{2} U.$$

To see this notice that if we have the total separation

$x_{(1)} < \dots < x_{(m)} < y_{(1)} < \dots < y_{(n)}$, then $R_1 = \frac{m(m+1)}{2}$. For every interchange of a contiguous x-y pair, R_1 is increased by 1, and the number of such interchanges is $\sum_i \sum_j \frac{1}{2}(U_{ij} + 1)$. Therefore,

$$\begin{aligned} R_1 &= \frac{m(m+1)}{2} + \sum_i \sum_j \frac{1}{2}(U_{ij} + 1), \\ &= \frac{m(m+1)}{2} + \frac{mn}{2} + \frac{1}{2} U, \\ &= \frac{m(m+n+1)}{2} + \frac{1}{2} U. \end{aligned}$$

The Mann-Whitney test rejects H_0 if U or $|U|$ is too large. Use small sample tables or the large sample approximation

$$\frac{U - E_0(U)}{\sqrt{\text{Var}_0(U)}} = \frac{U}{\sqrt{\frac{mn(m+n+1)}{3}}} \stackrel{a}{\sim} N(0,1).$$

For censored data, Gehan defines

$$U_{ij} = \begin{cases} 1 & \text{if we know } t_i > u_j, \text{ i.e.,} \\ & (x_i > y_j, \varepsilon_j = 1) \text{ or } (x_i = y_j, \delta_i = 0, \varepsilon_j = 1), \\ 0 & \text{otherwise,} \\ -1 & \text{if we know } t_i < u_j, \text{ i.e.,} \\ & (x_i < y_j, \delta_i = 1) \text{ or } (x_i = y_j, \delta_i = 1, \varepsilon_j = 0), \end{cases}$$

$$U = \sum_{i=1}^m \sum_{j=1}^n U_{ij}.$$

Reject H_0 if U or $|U|$ is large. The statistic U is asymptotically normally distributed by the theory of two-sample U-statistics, but to calculate the critical values we need to know the moments of U .

Mean and variance of U :

With no censoring, the mean and variance can be calculated using permutation theory. Under H_0 , consider sampling m balls without replacement from an urn containing $m+n$ balls labeled Z_1, \dots, Z_{m+n} . Think of the labels on the m sampled balls as the values of X_1, \dots, X_m , and the labels on the n unsampled balls as the values of Y_1, \dots, Y_n . Let $E_{0,P}(U)$ and $\text{Var}_{0,P}(U)$ be the moments under this permutation model. Then,

$$E_{0,P}(U) = 0 = E_0(U),$$

$$\text{Var}_{0,P}(U) = \frac{mn(m+n+1)}{3} = \text{Var}_0(U).$$

With censoring, Gehan also uses permutation theory but under the more restrictive null hypothesis

$$H_0^*: F_1 = F_2 \text{ and } G_1 = G_2.$$

Let the combined sample be denoted by

$$(Z_1, \zeta_1), \dots, (Z_{m+n}, \zeta_{m+n}) .$$

Consider sampling m balls without replacement from an urn containing $m+n$ balls labeled $(Z_1, \zeta_1), \dots, (Z_{m+n}, \zeta_{m+n})$. Think of the labels on the m sampled balls as $(X_1, \delta_1), \dots, (X_m, \delta_m)$ and the labels on the n unsampled balls as $(Y_1, \varepsilon_1), \dots, (Y_n, \varepsilon_n)$. Then,

$$E_{0,P}^*(U) = 0 ,$$

$$\text{Var}_{0,P}^*(U) = (4.3) \text{ on p. 206 of Gehan (1965).}$$

The latter is a complicated expression which we will not record here because Mantel's computational form for $\text{Var}_{0,P}^*(U)$ is easier to work with.

Mantel computational form for $\text{Var}_{0,P}^*(U)$:

$$U_{k\ell} = U((Z_k, \zeta_k), (Z_\ell, \zeta_\ell)) = \begin{cases} +1 & \text{if } (Z_k > Z_\ell, \zeta_\ell = 1) \\ & \text{or } (Z_k = Z_\ell, \zeta_k = 0, \zeta_\ell = 1) , \\ 0 & \text{otherwise ,} \\ -1 & \text{if } (Z_k < Z_\ell, \zeta_k = 1) \\ & \text{or } (Z_k = Z_\ell, \zeta_k = 1, \zeta_\ell = 0) , \end{cases}$$

$$U_k^* = \sum_{\substack{\ell=1 \\ \ell \neq k}}^{m+n} U_{k\ell} ,$$

$$U = \sum_{k=1}^{m+n} U_k^* I(k \in I_1) ,$$

where I_1 is the set of integers comprising sample 1. Notice that U is equal to Gehan's statistic because $U_{k_1 k_2} = -U_{k_2 k_1}$ so if $k_1, k_2 \in I_1$, they cancel each other out in the sum.

To calculate the permutation distribution of U , suppose we are given U_1^*, \dots, U_{m+n}^* . Under H_0^* , we sample m of these U_k^* without replacement and form U , the sum of these m values. Using results on sampling from finite populations,

$$\begin{aligned} \text{Var}_{0,P}^*(U) &= m \left(\frac{1}{m+n-1} \sum_{i=1}^{m+n} (U_i^*)^2 \right) \left(1 - \frac{m}{m+n} \right) \\ &= \frac{mn}{(m+n)(m+n-1)} \sum_{i=1}^{m+n} (U_i^*)^2 . \end{aligned}$$

Example:

For Brown's hypothetical clinical trial

Z	Rx	# < Z	# > Z	U^*
3	A	0	9	-9
5	A	1	8	-7
7	A	2	7	-5
9+	A	3	0	3
12	B	3	5	-2
18	A	4	4	0
19	B	5	3	+2
20	B	6	2	+4
20+	B	7	0	+7
33+	B	7	0	+7

$$U = -9-7-5+3+0 = -18 ,$$

$$E_{0,P}^*(U) = 0 ,$$

$$\text{Var}_{0,P}^*(U) = \frac{(5)(5)(286)}{(10)(9)} = 79.44 .$$

Under H_0^* ,

$$\frac{U}{\sqrt{\text{Var}_{0,P}^*(U)}} = \frac{-18}{8.91} = -2.02 \stackrel{a}{\sim} N(0,1),$$

so $P = .022$ is the one-tailed P -value.

References:

Gehan, Biometrika (1965).

Mantel, Biometrics (1967).

Variance under H_0 :

The above results on the variance were derived under the assumption $H_0^*: F_1 = F_2, G_1 = G_2$. What is the permutational variance under $H_0: F_1 = F_2$ with the censoring patterns held fixed? Suppose

$$V_1, \dots, V_{m+n}$$

is the combined sample of $T_1, \dots, T_m, U_1, \dots, U_n$. Under H_0 we sample from the V_k without replacement and put them in the slots

$$(_, C_1), \dots, (_, C_m); (_, D_1), \dots, (_, D_n).$$

From here, we want to form

$$(X_1, \delta_1), \dots, (X_m, \delta_m); (Y_1, \epsilon_1), \dots, (Y_n, \epsilon_n).$$

but unfortunately, because not all the T_i, C_i, U_j, D_j are observable, not all the $(X_i, \delta_i), (Y_j, \epsilon_j)$ can be constructed.

Hyde compares $E_0(\text{Var}_{0,P}^*(U))$ with $\text{Var}_0(U)$.

$$\text{Var}_0(U) = E_0(U^2),$$

$$= E \left\{ \left(\sum_{i=1}^m \sum_{j=1}^n U_{ij} \right)^2 \right\},$$

$$= mn E_0(U_{ij}^2) + mn(n-1) E_0(U_{ij} U_{ij'})$$

$$+ m(m-1)n E_0(U_{ij} U_{i'j'}) + m(m-1)n(n-1) E_0(U_{ij} U_{i'j'}),$$

$$E_0(\text{Var}_{0,P}^*(U)) = \text{sum of similar terms.}$$

Letting $m, n \rightarrow \infty$ such that $m/(m+n) \rightarrow \lambda$, where $0 < \lambda < 1$,

$$\begin{aligned}
 R^2 &= \lim_{m, n \rightarrow \infty} \frac{\text{Var}_{0,P}^*(U)}{\text{Var}_0(U)}, \\
 &= \lim_{m, n \rightarrow \infty} \frac{E_0(\text{Var}_{0,P}^*(U))}{\text{Var}_0(U)}, \tag{11} \\
 &= 3\lambda(1-\lambda) + \frac{\lambda^3 P\{C_1 \wedge C_2 \wedge C_3 > T_1 \wedge T_2 \wedge T_3\} + (1-\lambda)^3 P\{D_1 \wedge D_2 \wedge D_3 > T_1 \wedge T_2 \wedge T_3\}}{\lambda P\{C_1 \wedge C_2 \wedge D_1 > T_1 \wedge T_2 \wedge T_3\} + (1-\lambda) P\{C_1 \wedge D_1 \wedge D_2 > T_1 \wedge T_2 \wedge T_3\}}.
 \end{aligned}$$

From (11) we see that $R^2 > 3\lambda(1-\lambda)$. If $\lambda = 1/2$, then $R^2 > 3/4$, so $R > .87$. Thus, if the sample sizes are equal, $\text{SD}_{0,P}^*(U)$ cannot be very much smaller than $\text{SD}_0(U)$, no matter what the censoring patterns are.

Suppose the censoring distributions are Lehmann alternatives, i.e.,

$$(1-G_1)^{r_1} = 1-F,$$

$$(1-G_2)^{r_2} = 1-F,$$

where r_1 and r_2 are related to

$$p_1 = P\{C_1 < T_1\} = P\{\text{Obs. being censored in Pop. 1}\},$$

$$p_2 = P\{D_1 < U_1\} = P\{\text{Obs. being censored in Pop. 2}\},$$

through

$$p_1 = \frac{1}{r_1+1}, \quad p_2 = \frac{1}{r_2+1}.$$

In Table 2, Hyde reports R for $\lambda = .5$ under Lehmann alternatives for varying levels of censoring probabilities p_1 and p_2 . The table has been partitioned to identify cases in which $|R-1| < .05$. Table 3 is analogous to Table 2 with $\lambda = .2$.

We see from Table 2 that for equal sample sizes, the Gehan test (which assumes equal censoring patterns) uses an approximately correct standard

P_2	P_1									
	0.00	0.10	0.20	0.30	0.40	0.50	0.60	0.70	0.80	
0.00	1.00	1.00	1.00	1.00	1.01	1.01	1.02	1.04	1.09	1.20
0.10	1.00	1.00	1.00	1.00	1.00	1.01	1.02	1.04	1.07	1.18
0.20	1.00	1.00	1.00	1.00	1.00	1.01	1.01	1.03	1.06	1.16
0.30	1.00	1.00	1.00	1.00	1.00	1.00	1.01	1.02	1.05	1.13
0.40	1.01	1.00	1.00	1.00	1.00	1.00	1.00	1.01	1.04	1.11
0.50	1.01	1.01	1.01	1.00	1.00	1.00	1.00	1.01	1.02	1.09
0.60	1.02	1.02	1.01	1.01	1.00	1.00	1.00	1.00	1.01	1.06
0.70	1.04	1.04	1.03	1.02	1.01	1.01	1.00	1.00	1.00	1.04
0.80	1.09	1.07	1.06	1.05	1.04	1.02	1.01	1.00	1.00	1.01
0.90	1.20	1.18	1.16	1.13	1.11	1.09	1.06	1.04	1.01	1.00

Table 2

Values of R when censoring distributions are
Lehmann alternatives and $\lambda = .5$

P_2	P_1									
	0.00	0.10	0.20	0.30	0.40	0.50	0.60	0.70	0.80	0.90
0.00	1.00	1.01	1.02	1.04	1.06	1.09	1.14	1.21	1.33	1.65
0.10	0.99	1.00	1.01	1.03	1.05	1.08	1.12	1.18	1.29	1.59
0.20	0.98	0.99	1.00	1.01	1.03	1.06	1.09	1.15	1.26	1.53
0.30	0.97	0.98	0.99	1.00	1.02	1.04	1.07	1.12	1.22	1.47
0.40	0.96	0.97	0.97	0.99	1.00	1.02	1.05	1.09	1.18	1.40
0.50	0.95	0.95	0.96	0.97	0.98	1.00	1.02	1.06	1.14	1.33
0.60	0.94	0.94	0.95	0.96	0.97	0.98	1.00	1.03	1.09	1.26
0.70	0.93	0.93	0.93	0.94	0.95	0.96	0.97	1.00	1.05	1.18
0.80	0.92	0.92	0.92	0.93	0.93	0.94	0.95	0.97	1.00	1.09
0.90	0.92	0.92	0.92	0.92	0.92	0.92	0.92	0.93	0.95	1.00

Table 3

Values of R when censoring distributions are
Lehmann alternatives and $\lambda = .2$

deviation even when the censoring probabilities differ appreciably. Moreover, even when one sample size is four times the other (Table 3), Gehan's test is using a nearly correct standard deviation for a wide range of censoring probabilities.

References:

Hyde, Stanford Univ. Tech. Report No. 30 (1977).

Gilbert, Univ. Chicago thesis (1962), was the first to calculate $\text{Var}_0(U)$.

B. Mantel-Haenszel test

Single 2×2 Table:

Suppose we have two populations, and an individual in either population can have one of two characteristics. For example, Population 1 might be cancer patients under a certain treatment and Population 2 cancer patients under a different treatment. The patients in either group may either die within a year or survive beyond a year. The data may be summarized in a 2×2 table.

	Dead	Alive	
Pop. 1	a	b	n_1
Pop. 2	c	d	n_2
	m_1	m_2	n

Denote

$$p_1 = P\{\text{Dead}|\text{Pop. 1}\} \text{ and } p_2 = P\{\text{Dead}|\text{Pop. 2}\}.$$

To test

$$H_0 : p_1 = p_2,$$

use the statistic

$$\chi^2 = \left[\frac{\hat{p}_1 - \hat{p}_2}{\sqrt{\hat{p}(1-\hat{p})\left(\frac{1}{n_1} + \frac{1}{n_2}\right)}} \right]^2 = \frac{n(ad-bc)^2}{n_1 n_2 m_1 m_2},$$

where

$$\hat{p}_1 = \frac{a}{n_1}, \quad \hat{p}_2 = \frac{c}{n_2}, \quad \hat{p} = \frac{m_1}{n},$$

or, including the continuity correction,

$$\chi_c^2 = \frac{n(|ad-bc| - \frac{n}{2})^2}{n_1 n_2 m_1 m_2}.$$

χ^2 is approximately distributed as χ_1^2 . This is an approximation to the exact discrete conditional distribution under H_0 . Given n_1, n_2, m_1, m_2 fixed, the random variable A , which is the entry in the 1-1 cell of the 2×2 table, has a hypergeometric distribution

$$P\{A=a\} = \frac{\binom{n_1}{a} \binom{n_2}{m_1-a}}{\binom{n}{m_1}}.$$

The first two moments of the hypergeometric distribution are

$$E_0(A) = \frac{n_1 m_1}{n},$$

$$\text{Var}_0(A) = \frac{n_1 n_2 m_1 m_2}{n^2 (n-1)}.$$

Consequently,

$$ad-bc = n(a - E_0(A)),$$

$$n_1 n_2 m_1 m_2 = n^2 (n-1) \text{Var}_0(A),$$

$$\chi^2 = \frac{n(ad-bc)^2}{n_1 n_2 m_1 m_2} = \frac{n}{n-1} \left[\frac{a - E_0(A)}{\sqrt{\text{Var}_0(A)}} \right]^2.$$

Sequence of 2×2 Tables:

Now suppose we have a sequence of 2×2 tables. For example, we might have k hospitals; at each hospital, patients receive either treatment 1 or treatment 2 and their responses are observed.

	D	A		D	A	
Treatment 1	a_1		n_{11}	...	a_k	n_{k1}
Treatment 2			n_{12}			n_{k2}
	m_{11}	m_{12}	n_1		m_{k1}	m_{k2}
	Hospital 1				Hospital k	

Because there may be differences among hospitals, we do not want to combine all k tables into a single 2×2 table. We want to test

$$H_0 : p_{11} = p_{12}, \dots, p_{k1} = p_{k2},$$

where

$$p_{i1} = P\{\text{Dead} | \text{Treatment 1, Hospital } i\},$$

$$p_{i2} = P\{\text{Dead} | \text{Treatment 2, Hospital } i\}.$$

Use the Mantel-Haenszel statistic

$$MH = \frac{\sum_{i=1}^k (a_i - E_0(A_i))}{\sqrt{\sum_{i=1}^k \text{Var}_0(A_i)}}.$$

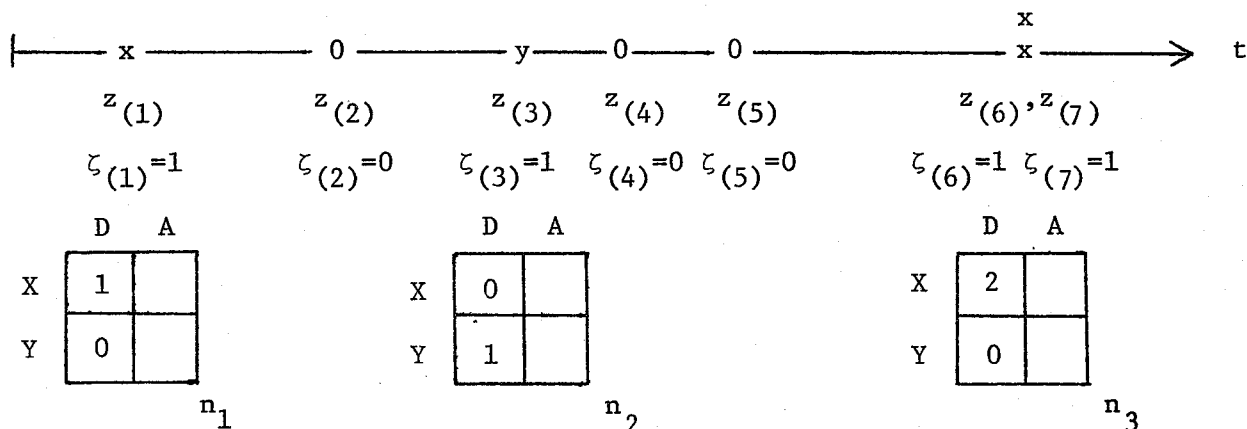
Including the continuity correction, the Mantel-Haenszel statistic is

$$MH_c = \frac{\left| \sum_{i=1}^k (a_i - E_0(A_i)) \right| - \frac{1}{2}}{\sqrt{\sum_{i=1}^k \text{Var}_0(A_i)}}.$$

Lininger et al. show that including the continuity correction is very conservative.

If the tables are independent, then $MH \stackrel{a}{\sim} N(0,1)$ either when k is fixed and $n_1 \rightarrow \infty$ or when $k \rightarrow \infty$ and the tables are also identically distributed.

In survival analysis the MH statistic is applied as follows. Recall that $(Z_{(1)}, \zeta_{(1)}), \dots, (Z_{(m+n)}, \zeta_{(m+n)})$ is the combined ordered sample. Construct a 2×2 table for each uncensored time point.



Compute the MH statistic for this sequence of tables to test $H_0: F_1 = F_2$.

The tables here are not independent because, for example, $R(z_{(1)})$ and $R(z_{(3)})$ almost coincide. But asymptotic normality still holds, as we will argue below. Varying censoring patterns have no effect on the MH statistic.

Example:

The computations for the MH statistic in Brown's hypothetical clinical trial are given in Table 4. The column labeled z contains the uncensored ordered observations. The next four columns labeled n, m_1, n_1 , a construct the 2×2 tables. The next column is $E_0(A) = n_1 m_1 / n$. The

product of the last two columns, labeled $m_1(n-m_1)/(n-1)$ and $(n_1/n)(1-n_1/n)$, is $\text{Var}_0(A)$; it is convenient to break up the calculation of $\text{Var}_0(A)$ in this way because $m_1(n-m_1)/(n-1)$ is usually equal to 1 and $(n_1/n)(1-n_1/n)$ is the product of the proportions in the two samples.

z	n	m_1	n_1	a	$E_0(A)$	$a-E_0(A)$	$\frac{m_1(n-m_1)}{n-1}$	$\frac{n_1}{n}(1-\frac{n_1}{n})$
3	10	1	5	1	.50	.50	1	.2500
5	9	1	4	1	.44	.56	1	.2469
7	8	1	3	1	.38	.62	1	.2344
12	6	1	1	0	.17	-.17	1	.1389
18	5	1	1	1	.20	.80	1	.1600
19	4	1	0	0	0	0	1	0
20	3	1	0	0	0	0	1	0

Table 4. Computations for the Mantel-Haenszel statistic in Brown's hypothetical clinical trial.

$$\begin{aligned}
 \text{MH} &= \frac{\text{sum of } a-E_0(A) \text{ column}}{\sqrt{\text{sum of } \left(\frac{m_1(n-m_1)}{n-1} \text{ col.} \times \frac{n_1}{n}(1-\frac{n_1}{n}) \text{ col.} \right)}} , \\
 &= \frac{2.31}{1.02} = 2.26 .
 \end{aligned}$$

$$P = .012 \text{ (one-tailed) .}$$

$$\begin{aligned}
 \text{MH}_c &= \frac{2.31-0.50}{1.02} , \\
 &= \frac{1.81}{1.02} = 1.77 .
 \end{aligned}$$

$$P = .038 \text{ (one-tailed) .}$$

Asymptotic normality:

To show asymptotic normality, we adapt Crowley's representation to our case. Assume no ties.

Denote

$$N = m+n ,$$

$$\hat{H}(t) = \frac{1}{N} \sum_{i=1}^N I(Z_i \leq t) ,$$

$$\hat{H}_1(t) = \frac{1}{m} \sum_{i=1}^m I(X_i \leq t) ,$$

$$\hat{H}_u(t) = \frac{1}{N} \sum_{i=1}^N I(Z_i \leq t, \zeta_i = 1) ,$$

$$\hat{H}_{1u}(t) = \frac{1}{m} \sum_{i=1}^m I(X_i \leq t, \delta_i = 1) .$$

Then the numerator of MH is

$$\sum_{i=1}^k (a_i - E(A_i)) = m \left\{ \int_0^\infty d \hat{H}_{1u}(s) - \int_0^\infty \frac{1 - \hat{H}_1(s-)}{1 - \hat{H}(s-)} d \hat{H}_u(s) \right\} .$$

To see this, recall that $E(A_i) = m_{i1}n_{i1}/n_i$ where a_i, m_{i1}, n_{i1}, n_i are gotten from the 2×2 table corresponding to the i th uncensored observation:

		D	A	
X	a_i			n_{i1}
Y				
		m_{i1}		n_i

Because we have assumed no ties, $m_{i1} = 1$. Letting s_i denote the time of the i th uncensored observation,

$$\begin{aligned}
n_{i1} &= \#(X\text{'s remaining at time } s_i-) , \\
&= m(1 - \hat{H}_1(s_i-)) , \\
n_i &= \#(Z\text{'s remaining at time } s_i-) , \\
&= N(1 - \hat{H}(s_i-)) .
\end{aligned}$$

Now that we have the numerator of MH expressed in terms of empirical (sub)distribution functions, we may apply arguments similar to those used in showing the asymptotic normality of the PL estimator.

References:

- Mantel and Haenszel, J. Natl. Cancer Inst. (1959).
Crowley, JASA (1974).
Lininger et al., Biometrika (1979).

C. Tarone-Ware class of tests

After constructing a 2×2 table for each uncensored observation, Tarone and Ware suggest weighting each table, forming

$$\sum_{i=1}^k w_i [a_i - E(A_i)] = \sum_{i=1}^k w_i \left[a_i - \frac{m_{i1} n_{i1}}{n_i} \right] . \quad (12)$$

For the variance, use

$$\sum_{i=1}^k w_i^2 \text{Var}(A_i) = \sum_{i=1}^k w_i^2 \left[\frac{m_{i1}(n_i - m_{i1})}{n_i - 1} \right] \left[\left(\frac{n_{i1}}{n_i} \right) \left(1 - \frac{n_{i1}}{n_i} \right) \right] . \quad (13)$$

There are three important special cases:

- (1) $w_i \equiv 1$ gives the MH statistic.
- (2) $w_i = n_i$ gives the Gehan statistic.
- (3) $w_i = \sqrt{n_i}$ is suggested by Tarone and Ware.

Notes:

(i) Which test should we use? The Gehan statistic puts more weight on the beginning observations, while the MH statistic puts equal weight on each observation. Tarone and Ware's suggestion is intermediate between the two, and they claim that the weights $w_i = \sqrt{n_i}$ have high efficiency over a range of alternatives.

(ii) Although (12) is identical to the Gehan statistic U , $\hat{\text{Var}}_{\text{TW}}(U)$, given by (13), is not the same as $\text{Var}_{0,P}^*(U)$. Asymptotically, $\hat{\text{Var}}_{\text{TW}}(U)$ is equivalent to the variance of U under H_0 while $\text{Var}_{0,P}^*(U)$ is the variance under H_0^* .

Example:

Referring to Table 4 (on p. 74) where we calculate the MH statistic for Brown's clinical trial,

$$\begin{aligned}\sum_{i=1}^k n_i (a_i - E(A_i)) &= (10)(.50) + (9)(.56) + (8)(.62) \\ &\quad + (6)(-.17) + 5(.80) \\ &= 17.98 ,\end{aligned}$$

which is what we got for Gehan's statistic U except for sign and roundoff.

Also,

$$\begin{aligned}\hat{\text{Var}}_{\text{TW}}(U) &= \sum n_i^2 \left[\frac{m_{i1}(n_i - m_{i1})}{n_i - 1} \right] \left[\left(\frac{n_{i1}}{n_i} \right) \left(1 - \frac{n_{i1}}{n_i} \right) \right] \\ &= (10^2)(.25) + (9^2)(.2469) + (8^2)(.2344) + (6^2)(.1389) + (5^2)(.16) , \\ &= 69 ,\end{aligned}$$

$$\text{Var}_{0,P}^*(U) = 79.44 ,$$

which give

$$\sqrt{\hat{\text{Var}}_{\text{TW}}(U)} = 8.31 \quad \text{and} \quad \sqrt{\text{Var}_{0,P}^*(U)} = 8.91 .$$

Reference:

Tarone and Ware, Biometrika (1977).

D. Efron test

Recall that in the construction of Gehan's test, we defined the score function

$$U_{ij} = \begin{cases} 1 & \text{if we know } t_i > u_j , \\ 0 & \text{otherwise,} \\ -1 & \text{if we know } t_i < u_j . \end{cases}$$

Suppose we have the situation



The Gehan test assigns a score $U_{ij} = 0$ for this pair regardless of how much larger x_i is compared to y_j . Efron suggests using the score

$$U_{ij} = \hat{P}\{T_i > U_j \mid (x_i, \delta_i), (y_j, \epsilon_j)\} .$$

For the picture above,

$$\begin{aligned} U_{ij} &= \hat{P}\{U_j < x_i \mid U_j > y_j\} , \\ &= \frac{\hat{F}_2(x_i) - \hat{F}_2(y_j)}{1 - \hat{F}_2(y_j)} , \end{aligned}$$

where \hat{F}_2 is the Kaplan-Meier PL estimator for Population 2.

Use of these scores along with 1 and 0 instead of 1 and -1 leads to the statistic

$$\int_0^{\infty} [1 - \hat{F}_1(u)] d\hat{F}_2(u) = \hat{P}\{T_1 > U_j\} . \quad (14)$$

The estimator $\hat{P}\{T_1 > U_j\}$ is the GMLE of $P\{T_1 > U_j\}$, which is the parameter the Wilcoxon statistic is estimating in the uncensored case, i.e.,

$$\frac{1}{mn} U \xrightarrow{\text{a.s.}} P\{X > Y\}$$

in the uncensored case with $U_{ij} = 0, 1/2,$ or 1 .

The estimator (14) is somewhat unstable in the tails, which has prevented its widespread use.

Reference:

Efron, Proc. Fifth Berkeley Symp. IV (1967).

V. Nonparametric Methods: K Samples

For the i th sample ($i = 1, \dots, K$), let T_{i1}, \dots, T_{in_i} be iid each with d.f. F_i , and C_{i1}, \dots, C_{in_i} be iid each with d.f. G_i . C_{ij} is the censoring time associated with T_{ij} . We can observe $(X_{i1}, \delta_{i1}), \dots, (X_{in_i}, \delta_{in_i})$ where

$$X_{ij} = T_{ij} \wedge C_{ij}, \quad \delta_{ij} = I(T_{ij} < C_{ij}) .$$

We are interested in the hypothesis

$$H_0 : F_1 = \dots = F_K .$$

A. Generalized Gehan test (Breslow)

Using the score function that we defined on p. 65, let

$$W_i = \sum_{j=1}^{n_i} \sum_{\substack{i'=1 \\ \neq i}}^K \sum_{j'=1}^{n_{i'}} U((X_{ij}, \delta_{ij}), (X_{i'j'}, \delta_{i'j'})) ,$$

$$\tilde{W} = (W_1, \dots, W_K)' .$$

Breslow obtains the asymptotic covariance matrix of W under the more restrictive hypothesis

$$H_0^* : F_1 = \dots = F_K; \quad G_1 = \dots = G_K .$$

Denote

$$N = \sum_{i=1}^K n_i .$$

Assuming $n_i/N \rightarrow \lambda_i$ as $N \rightarrow \infty$, $i = 1, \dots, K$,

$$W \stackrel{a}{\sim} N(\mu_0^*, N^3 \Sigma_0^*) ,$$

where

$$\mu_0^* = 0 ,$$

$$\Sigma_0^* = \left(\int_0^\infty [1-H(u)]^2 dH_u(u) \right) \begin{bmatrix} \lambda_1(1-\lambda_1) & & & \\ & \ddots & & \\ & & -\lambda_i\lambda_j & \\ & -\lambda_i\lambda_j & & \\ & & & \ddots & \\ & & & & \lambda_K(1-\lambda_K) \end{bmatrix} ,$$

and

$$H_i(t) = P\{X_{i1} \leq t\} ,$$

$$H_{iu}(t) = P\{X_{i1} \leq t, \delta_{i1} = 1\} ,$$

$$H(t) = \lambda_1 H_1(t) + \dots + \lambda_K H_K(t) ,$$

$$H_u(t) = \lambda_1 H_{1u}(t) + \dots + \lambda_K H_{Ku}(t) .$$

Since the asymptotic covariance matrix depends on unknown parameters, substitute

$$\hat{\lambda}_i = \frac{n_i}{N} ,$$

$$\hat{H}(t) = \frac{1}{N} \sum_{i=1}^K \sum_{j=1}^{n_i} I(X_{ij} \leq t) ,$$

$$\hat{H}_u(t) = \frac{1}{N} \sum_{i=1}^K \sum_{j=1}^{n_i} I(X_{ij} \leq t, \delta_{ij} = 1) .$$

Reference:

Breslow, Biometrika (1970).

Types of Tests:

(i) Omnibus χ^2 test

Use

$$\frac{1}{N^3 \int_0^\infty (1-\hat{H})^2 d\hat{H}_u} \sum_{i=1}^K \frac{W_i^2}{\hat{\lambda}_i} \sim \chi_{K-1}^2 .$$

This statistic is equivalent to $\tilde{W}' (\tilde{\Sigma}_0^*)^{-1} \tilde{W}$ where $(\tilde{\Sigma}_0^*)^{-1}$ is the generalized inverse of $\tilde{\Sigma}_0^*$.

With no censoring, this statistic is asymptotically equivalent to the Kruskal-Wallis statistic. Recall that if R_{ij} is the rank of X_{ij} among all N observations, and

$$R_i = \sum_{j=1}^{n_i} R_{ij} ,$$

$$\bar{R}_i = \frac{1}{n_i} R_i ,$$

$$\bar{R}_\cdot = \frac{1}{N} \sum_{i=1}^K R_i ,$$

then the Kruskal-Wallis statistic is

$$\frac{12}{N(N+1)} \sum_{i=1}^K n_i (\bar{R}_i - \bar{R}_\cdot)^2 = \left(\frac{12}{N(N+1)} \sum_{i=1}^K \frac{R_i^2}{n_i} \right) - 3N(N+1) ,$$

which has asymptotic distribution χ_{K-1}^2 under H_0 .

(ii) Test for trend

Suppose we know that if the populations are not all equal, then they are ordered. For example, the populations may correspond to increasing doses of a drug

$$d_1 < \dots < d_K ,$$

where d_i is the dose given to members in Population i . In other situations it may be known a priori that the populations should change monotonically if they differ, but there is no numerical covariate.

When a quantitative measure like dose is available, define

$$\underline{\ell} = (d_1, \dots, d_K)' .$$

If a quantitative variable is not available, then define

$$\underline{\ell} = (-(K-1), \dots, -3, -1, +1, +3, \dots, +(K-1))' \quad \text{if } K \text{ is even,}$$

$$\underline{\ell} = (-\frac{(K-1)}{2}, \dots, -1, 0, +1, \dots, +\frac{(K-1)}{2})' \quad \text{if } K \text{ is odd.}$$

Abelson and Tukey suggest the linear-2 or the linear-2-4 contrasts which we illustrate respectively for K even:

$$\underline{\ell} = (-2(K-1), -(K-3), -(K-5), \dots, +(K-5), +(K-3), +2(K-1))' ,$$

$$\underline{\ell} = (-4(K-1), -2(K-3), -(K-5), \dots, +(K-5), +2(K-3), +4(K-1))' .$$

Renormalize \underline{W} by defining

$$\bar{W}_i = \frac{W_i}{n_i(N-n_i)} ,$$

$$\bar{\underline{W}} = (\bar{W}_1, \dots, \bar{W}_K)' ,$$

and let \underline{c} be such that

$$\underline{\ell}' \bar{\underline{W}} = \underline{c}' \underline{W} .$$

Then,

$$\frac{\underline{c}' \bar{\underline{W}}}{\sqrt{N^3 \underline{c}' \sum_{i=0}^* \underline{c}}} \stackrel{a}{\sim} N(0,1) ,$$

and this statistic can be used to test

$$H_0 : F_1 = \dots = F_K \quad \text{against} \quad H_1 : F_1 < \dots < F_K .$$

When a quantitative measure is available, there are other regression techniques which can be used. These are discussed in Section VI.

Reference:

Abelson and Tukey, Ann. Math. Stat. (1963).

Permutational covariance matrix:

Define

$$W_{ij}^* = \sum_{i'=1}^K \sum_{\substack{j'=1 \\ (i',j') \neq (i,j)}}^{n_{i'}} U((X_{ij}, \delta_{ij}), (X_{i'j'}, \delta_{i'j'})) ,$$

and rename

$$W_{11}^*, \dots, W_{1n_1}^*, \dots, W_{K1}^*, \dots, W_{Kn_K}^*$$

to

$$W_1^*, \dots, W_N^* .$$

To calculate the permutation distribution of \tilde{W} , suppose we are given W_1^*, \dots, W_N^* . Under H_0^* we sample these W_i^* without replacement, letting W_1 be the sum of the first n_1 sampled, W_2 be the sum of the next n_2 sampled, and so on.

The covariance matrix of $\tilde{W} = (W_1, \dots, W_K)'$ under this sampling scheme is

$$\tilde{\Sigma}_{0,P}^* = \frac{1}{N} \left(\frac{\sum_{i=1}^K \sum_{j=1}^{n_i} (W_{ij}^*)^2}{N-1} \right) \begin{bmatrix} n_1(N-n_1) & & & \\ & \ddots & & \\ & & -n_i n_j & \\ & & & \ddots \\ -n_i n_j & & & & n_K(N-n_K) \end{bmatrix} .$$

The matrix $\tilde{\Sigma}_{0,P}^*$ can be used in place of $N^3 \hat{\Sigma}_0^*$, although the two are asymptotically equivalent.

Reference:

Marcuson and Nordbrock, Biometrical Journal (1980 or 1981)

Distribution under H_0 :

Under the hypothesis of interest

$$H_0 : F_1 = \dots = F_K ,$$

Breslow shows

$$\tilde{W} \stackrel{a}{\sim} N(\tilde{\mu}_0, N^3 \tilde{\Sigma}_0) ,$$

where the elements of $\tilde{\Sigma}_0$ are

$$\sigma_{ij}^0 = -\lambda_i \lambda_j \int_0^\infty (1-H_i)(1-H_j) dH_u \quad \text{if } i \neq j ,$$

$$\sigma_{ii}^0 = \lambda_i \int_0^\infty [(1-H)(1-H_i) - \lambda_i (1-H_i)^2] dH_u .$$

To estimate this covariance matrix, it is easier to use the Mantel-Haenszel statistic (given next) than to substitute estimates for H, H_i, H_u .

Reference:

Breslow, Biometrika (1970).

B. Generalized Mantel-Haenszel test (Tarone and Ware)

Let the ordered combined sample be denoted by

$$(Z_{(1)}, \zeta_{(1)}), \dots, (Z_{(N)}, \zeta_{(N)}) ,$$

and let

$$\mathcal{R}_{(i)} = \mathcal{R}(Z_{(i)}^-) .$$

For each uncensored time point, construct a $2 \times K$ table; i.e., if

$(Z_{u(i)}, 1)$ is the i th uncensored observation, form

		Population				
		1	2	...	K	
Dead		$a_{i1}=0$	$a_{i2}=1$...	$a_{iK}=0$	m_{i1}
Alive				...		m_{i2}
		n_{i1}	n_{i2}	...	n_{iK}	$N_i = \sum_{j=1}^K n_{ij}$

Notice that for $K=2$, the tables are the transpose of the previous 2×2 tables on page 72.

Under $H_0 : F_1 = \dots = F_K$,

$$E_0(A_{\sim i}) = (E_0(A_{i1}), \dots, E_0(A_{iK}))',$$

$$= \left(\frac{m_{i1} n_{i1}}{N_i}, \dots, \frac{m_{i1} n_{iK}}{N_i} \right)',$$

$$\Sigma_0(A_{\sim i}) = \frac{m_{i1} m_{i2}}{N_i - 1} \begin{bmatrix} \frac{n_{i1}}{N_i} \left(1 - \frac{n_{i1}}{N_i} \right) & & - \frac{n_{ik}}{N_i} \frac{n_{i1}}{N_i} \\ & \ddots & \\ - \frac{n_{ik}}{N_i} \frac{n_{i1}}{N_i} & & \frac{n_{iK}}{N_i} \left(1 - \frac{n_{iK}}{N_i} \right) \end{bmatrix}.$$

Define

$$a - E_0(A) = \sum_i w_i (a_i - E_0(A_i)),$$

$$\Sigma_0 = \sum_i w_i^2 \Sigma_0(A_{\sim i}),$$

where the w_i are weights. There are three special cases:

- (1) $w_i \equiv 1$. This gives the generalized Mantel-Haenszel test.
- (2) $w_i = N_i$. This gives the generalized Gehan test.

In Section A, we obtained the asymptotic covariance matrix of the generalized Gehan statistic under the more restrictive hypothesis H_0^* . The asymptotic covariance matrix under H_0 is Σ_0 , and the formula given here is computationally easier than Breslow's approach.

- (3) $w_i = \sqrt{N_i}$. Tarone and Ware claim this gives high efficiency over a range of alternatives.

Reference:

Tarone and Ware, Biometrika (1977).

Types of Tests:

(i) Omnibus χ^2 test

Since Σ_0 is singular, delete one population, say the first. Define $a_{-1} = E_0(A_{-1})$ and $\Sigma_{0,-1}$ to be $a - E_0(A)$ and Σ_0 respectively with the first population deleted. Then

$$W = (a_{-1} - E_0(A_{-1}))' \Sigma_{0,-1}^{-1} (a_{-1} - E_0(A_{-1})) \sim \chi_{K-1}^2$$

under H_0 . The value of W will be the same no matter which population is deleted.

For the generalized Mantel-Haenszel test ($w_i \equiv 1$) , we have the approximate test

$$\sum \frac{(O-E)^2}{E} = \sum_{k=1}^K \frac{(a_k - E_0(A_k))^2}{E_0(A_k)} \approx \chi_{K-1}^2 ,$$

where

$$a_k = \sum_i a_{ik} ,$$

$$E_0(A_k) = \sum_i E_0(A_{ik}) = \sum_i \frac{m_i n_{ik}}{N_i} .$$

Although this test is somewhat conservative since $\sum (O-E)^2/E \leq W$, it is simpler to use because no matrix inversion is involved.

References:

Peto and Pike, Biometrics (1973).

Peto et al., British J. Cancer (1976, 1977).

(ii) Test for trend

Suppose

$$H_1 : F_1 < \dots < F_K .$$

For the choices of $\tilde{\ell}$ in Section A, use the statistic

$$\tilde{\ell}'(\tilde{a} - E_0(\tilde{A})) ,$$

which asymptotically has a normal distribution.

Reference:

Tarone, Biometrika (1975).

VI. Nonparametric Methods: Regression

A. Cox proportional hazards model

Let T_1, \dots, T_n ; C_1, \dots, C_n be independent r.v.'s. C_i is the censoring time associated with the survival time T_i . We observe $(Y_1, \delta_1), \dots, (Y_n, \delta_n)$ where

$$Y_i = T_i \wedge C_i , \quad \delta_i = I(T_i < C_i) .$$

Also available are $\tilde{x}_1, \dots, \tilde{x}_n$, where

$$\tilde{x}_i = (x_{i1}, \dots, x_{ip})'$$

is the vector of independent variables or covariates associated with the dependent variable T_i .

Recall that the hazard function is

$$\lambda(t; \tilde{x}) = \frac{f(t; \tilde{x})}{1 - F(t; \tilde{x})},$$

where we have included the dependence of the distribution of T upon the covariates in \tilde{x} . The proportional hazards model assumes

$$\lambda(t; \tilde{x}) = e^{\tilde{\beta}'\tilde{x}} \lambda_0(t),$$

where $\tilde{\beta} = (\beta_1, \dots, \beta_p)'$ is the vector of regression coefficients. The hazard rate is the product of a scalar and the function $\lambda_0(t)$, where the scalar depends on the regression coefficients and the covariates. The theory could work if $e^{\tilde{\beta}'\tilde{x}}$ were replaced by any sensible $h(\tilde{\beta}'\tilde{x})$ where h is positive. Both the regression coefficients $\tilde{\beta}$ and the underlying hazard function $\lambda_0(t)$ are unknown.

We say that a family of distribution functions is a family of Lehmann alternatives if there exists a d.f. F_0 such that for any F in the family

$$1-F = (1-F_0)^\gamma$$

for some real γ , or in terms of survival functions

$$S = S_0^\gamma.$$

The proportional hazards model implies that the d.f.'s form a family of Lehmann alternatives:

$$\begin{aligned}
S(t; \tilde{x}) &= \exp\left\{-\int_0^t \lambda(u; \tilde{x}) du\right\} , \\
&= \exp\left\{-e^{\beta' \tilde{x}} \int_0^t \lambda_0(u) du\right\} , \\
&= \exp\left\{-\int_0^t \lambda_0(u) du\right\} e^{\beta' \tilde{x}} , \\
&= S_0(t) e^{\beta' \tilde{x}} ,
\end{aligned}$$

where

$$S_0(t) = \exp\left\{-\int_0^t \lambda_0(u) du\right\} .$$

Consider the special case in which $p = 1$.

$$x_i = \begin{cases} 1 & \text{if the } i\text{th observation is from Population 1 ,} \\ 0 & \text{if the } i\text{th observation is from Population 2 .} \end{cases}$$

Then

$$e^{\beta x_i} = \begin{cases} e^{\beta} & \text{if } i \text{ is from Population 1 ,} \\ 1 & \text{if } i \text{ is from Population 2 ,} \end{cases}$$

and consequently the survival functions for Population 1 and Population 2 are related by

$$S_1(t) = S_2^Y(t) .$$

Conditional Likelihood Analysis:

Cox writes:

"Suppose then that $\lambda_0(t)$ is arbitrary. No information can be contributed about β by time intervals in which no failures occur because the component $\lambda_0(t)$ might conceivably be identically zero

in such intervals. We therefore argue conditionally on the set of instants at which failures occur; in discrete time we shall condition also on the observed multiplicities. Once we require a method of analysis holding for all $\lambda_0(t)$, consideration of this conditional distribution seems inevitable".

Assume there are no ties; ties will be treated later. Order the observed times

$$y_{(1)} < y_{(2)} < \dots < y_{(n)} ,$$

and let $\delta_{(i)}$ be the censoring indicator and $\tilde{x}_{(i)}$ be the covariate associated with $y_{(i)}$. Also denote $R_{(i)} = R(y_{(i)}^-)$. For each uncensored time $y_{(i)}$,

$$P\{\text{a death in } [y_{(i)}, y_{(i)} + \Delta y) | R_{(i)}\} \approx \sum_{j \in R_{(i)}} e^{\tilde{\beta}' \tilde{x}_{(j)}} \lambda_0(y_{(i)}) \Delta y ,$$

$$P\{\text{death of } (i) \text{ at time } y_{(i)} | \text{one death in } R_{(i)} \text{ at time } y_{(i)}\} = \frac{e^{\tilde{\beta}' \tilde{x}_{(i)}}}{\sum_{j \in R_{(i)}} e^{\tilde{\beta}' \tilde{x}_{(j)}}} .$$

Taking the product of these conditional probabilities gives a (so-called) conditional likelihood:

$$L_c(\tilde{\beta}) = \prod_u \frac{e^{\tilde{\beta}' \tilde{x}_{(i)}}}{\sum_{j \in R_{(i)}} e^{\tilde{\beta}' \tilde{x}_{(j)}}} .$$

Cox suggests that we treat his conditional likelihood as an ordinary likelihood. In particular, to find the maximum likelihood estimate, use the score vector and the sample information matrix:

$$\frac{\partial}{\partial \beta} \log L_c(\beta) = \left(\frac{\partial}{\partial \beta_1} \log L_c(\beta), \dots, \frac{\partial}{\partial \beta_p} \log L_c(\beta) \right)',$$

$$i(\beta) = - \frac{\partial^2}{\partial \beta^2} \log L_c(\beta) = - \begin{bmatrix} \frac{\partial^2}{\partial \beta_1 \partial \beta_1} \log L_c(\beta) & \dots & \frac{\partial^2}{\partial \beta_1 \partial \beta_p} \log L_c(\beta) \\ \vdots & & \vdots \\ \frac{\partial^2}{\partial \beta_p \partial \beta_1} \log L_c(\beta) & \dots & \frac{\partial^2}{\partial \beta_p \partial \beta_p} \log L_c(\beta) \end{bmatrix}.$$

We want to solve the equations

$$\frac{\partial}{\partial \beta} \log L_c(\beta) = 0,$$

which usually requires iterative methods. Therefore, if $\hat{\beta}^0$ is an initial guess, let

$$\hat{\beta}^1 = \hat{\beta}^0 + i^{-1}(\hat{\beta}^0) \frac{\partial}{\partial \beta} \log L_c(\hat{\beta}^0).$$

If $\hat{\beta}$ is the solution, Cox asserts

$$\hat{\beta} \approx N(\beta, i^{-1}(\beta)).$$

Taking derivatives of

$$\log L_c(\beta) = \sum_u \left\{ \beta' x_{(i)} - \log \left(\sum_{j \in \mathcal{R}(i)} e^{\beta' x_j} \right) \right\},$$

we obtain formulas for the score vector and information matrix:

$$\frac{\partial}{\partial \beta_k} \log L_c(\beta) = \sum_u \left\{ x_{(i)k} - \frac{\sum_{j \in \mathcal{R}(i)} x_{jk} e^{\beta' x_j}}{\sum_{j \in \mathcal{R}(i)} e^{\beta' x_j}} \right\},$$

$$i_{kl}(\beta) = - \frac{\partial^2}{\partial \beta_k \partial \beta_l} \log L_c(\beta)$$

$$= \sum_u \left\{ \frac{\sum_{j \in \mathcal{R}(i)} x_{jk} x_{jl} e^{\beta' x_j}}{\sum_{j \in \mathcal{R}(i)} e^{\beta' x_j}} - \frac{\sum_{j \in \mathcal{R}(i)} x_{jk} e^{\beta' x_j}}{\sum_{j \in \mathcal{R}(i)} e^{\beta' x_j}} \cdot \frac{\sum_{j \in \mathcal{R}(i)} x_{jl} e^{\beta' x_j}}{\sum_{j \in \mathcal{R}(i)} e^{\beta' x_j}} \right\}.$$

For testing $H_0: \beta = 0$, Cox uses the Rao-type statistic

$$\left(\frac{\partial}{\partial \beta} \log L_c(0) \right)' i^{-1}(0) \left(\frac{\partial}{\partial \beta} \log L_c(0) \right),$$

which is asymptotically χ_p^2 under H_0 . The score vector and information matrix have simpler forms at $\beta = 0$:

$$\frac{\partial}{\partial \beta_k} \log L_c(0) = \sum_u \{x_{(i)k} - \bar{x}_{(i)k}\},$$

$$i_{kl}(0) = \sum_u \left\{ \frac{1}{n_i} \sum_{j \in \mathcal{R}(i)} x_{jk} x_{jl} - \bar{x}_{(i)k} \bar{x}_{(i)l} \right\},$$

$$= \sum_u \left\{ \frac{1}{n_i} \sum_{j \in \mathcal{R}(i)} (x_{jk} - \bar{x}_{(i)k})(x_{jl} - \bar{x}_{(i)l}) \right\},$$

where

$$\bar{x}_{(i)} = \frac{\sum_{j \in \mathcal{R}(i)} x_j}{n_i}, \quad n_i = \# \text{ in } \mathcal{R}(i).$$

The sample information matrix is simply a sum of the covariate covariance matrices for the risk sets of the uncensored observations.

Consider the special case $p = 1$ and

$$x_i = \begin{cases} 1 & \text{if } i \text{ is in sample 1 ,} \\ 0 & \text{if } i \text{ is in sample 2 .} \end{cases}$$

Then using the notation for the Mantel-Haenszel test,

$$\frac{\partial}{\partial \beta} \log L_c(0) = \sum_u \{x_{(i)} - \bar{x}_{(i)}\} = \sum_u \left(a_i - \frac{n_{i1}}{n_i} \right) ,$$

$$i(0) = \sum_u \left\{ \frac{1}{n_i} \sum_{j \in R(i)} x_j^2 - \bar{x}_{(i)}^2 \right\} = \sum_u \frac{n_{i1}}{n_i} \left(1 - \frac{n_{i1}}{n_i} \right) .$$

Therefore, in the case of no ties, Cox's test is exactly equal to the Mantel-Haenszel test.

References:

Cox, JRSS B (1972).

Prentice and Kalbfleisch, Biometrics (1979), has a nice survey of the Cox procedure.

Kalbfleisch and Prentice, The Statistical Analysis of Failure Time Data (1980), is an excellent new text on the Cox approach to survival analysis.

Justification of the conditional likelihood:

a) Marginal likelihood for ranks

Make the crucial assumption of no ties.

Suppose the data are uncensored. Let Y_1, \dots, Y_n be independent and Y_i have d.f. F_i with density f_i . Denote

$$\underline{Y} = (Y_1, \dots, Y_n) ,$$

$$\underline{R} = (R_1, \dots, R_n) ,$$

where

$$R_i = \text{rank of } Y_i .$$

Then the probability for the rank vector \tilde{r} is

$$p(\tilde{r}) = \int \dots \int_{u_1 < \dots < u_n} \prod_{i=1}^n f_{(i)}(u_i) du_1 \dots du_n ,$$

where $f_{(i)}$ is the density corresponding to $y_{(i)}$. For example, if $n = 3$ and $\tilde{r} = (3, 1, 2)$,

$$\begin{aligned} p(\tilde{r}) &= P\{R_1=3, R_2=1, R_3=2\} , \\ &= \int \int \int_{u_1 < u_2 < u_3} f_2(u_1) f_3(u_2) f_1(u_3) du_1 du_2 du_3 . \end{aligned}$$

Kalbfleisch and Prentice show that when

$$F_i(t) = 1 - \exp \left\{ -e^{\tilde{\beta}' \tilde{x}_i} \int_0^t \lambda_0(u) du \right\} ,$$

then

$$p(\tilde{r}) = \prod_{i=1}^n \frac{e^{\tilde{\beta}' \tilde{x}_i}}{\sum_{j \in \mathcal{R}_{(i)}} e^{\tilde{\beta}' \tilde{x}_j}} .$$

Now allow censoring. Use the usual notation $(Y_1, \delta_1), \dots, (Y_n, \delta_n)$, and let Y_i have d.f. F_i and density f_i . Define the rank vector

$$\tilde{R}^{u/c} = (R_1^{u/c}, \dots, R_n^{u/c}) ,$$

where

$$R_i^{u/c} = \begin{cases} \text{rank of } Y_i \text{ among uncensored observations} & \text{if } \delta_i=1 , \\ \text{rank of the preceding uncensored observation} & \text{if } \delta_i=0 , \end{cases}$$

and the indicator vector

$$\tilde{\delta} = (\delta_1, \dots, \delta_n) .$$

Then the probability of $(\tilde{r}^{u/c}, \tilde{\delta})$ is

$$p(\tilde{r}^{u/c}, \tilde{\delta}) = \int \dots \int_{u_1 < \dots < u_{n_u}} \prod_{i=1}^{n_u} \left\{ f_{u(i)}(u_i) \prod_{j \in C_{i,i+1}} [1 - F_j(u_i)] \right\} du_1 \dots du_{n_u} ,$$

where $f_{u(i)}$ is the density corresponding to the i th ordered uncensored observation, $C_{i,i+1}$ is the set of indices corresponding to the censored observations between the i th and $(i+1)$ -th ordered uncensored observations, and n_u is the total number of uncensored observations.

For example, for $\tilde{r} = (2,1,1)$ and $\tilde{\delta} = (1,1,0)$ corresponding to the picture

$$\begin{array}{ccc} \text{X} & \text{O} & \text{X} \\ \text{Y}_2 & \text{Y}_3 & \text{Y}_1 \end{array} ,$$

the rank probability is

$$p((2,1,1), (1,1,0)) = \int \int_{u_1 < u_2} f_2(u_1) [1 - F_3(u_1)] f_1(u_2) du_1 du_2 .$$

Kalbfleisch and Prentice show that if

$$F_i(t) = 1 - \exp \left\{ -e^{\tilde{\beta}' \tilde{x}_i} \int_0^t \lambda_0(u) du \right\} ,$$

then

$$p(\tilde{r}^{u/c}, \tilde{\delta}) = \prod_u \frac{e^{\tilde{\beta}' \tilde{x}_{(i)}}}{\sum_{j \in R(i)} e^{\tilde{\beta}' \tilde{x}_j}} = L_c .$$

Reference:

Kalbfleisch and Prentice, Biometrika (1973).

b) Partial likelihood

Consider the sequence of pairs of random quantities

$$(X_1, S_1; X_2, S_2; \dots; X_m, S_m) .$$

In regression with censored data let $y_{u(i)}$ denote the i th ordered uncensored observation. Think of X_i as containing all the censoring information in $[y_{u(i-1)}, y_{u(i)})$ together with the information that a failure occurs at time $y_{u(i)}$, and think of S_i as containing the information that the particular individual with covariate $x_{u(i)}$ failed at time $y_{u(i)}$.

The marginal likelihood of S_1, \dots, S_m is

$$p(S_1, \dots, S_m | \beta) = \prod_{i=1}^m p(S_i | S_1, \dots, S_{i-1}; \beta) ,$$

and the conditional likelihood of S_1, \dots, S_m given X_1, \dots, X_m is

$$p(S_1, \dots, S_m | X_1, \dots, X_m; \beta) = \prod_{i=1}^m p(S_i | S_1, \dots, S_{i-1}; X_1, \dots, X_m; \beta) .$$

The full likelihood is

$$\begin{aligned} p(X_1, \dots, X_m; S_1, \dots, S_m | \beta) \\ &= \prod_{i=1}^m p(X_i, S_i | X_1, \dots, X_{i-1}; S_1, \dots, S_{i-1}; \beta) \\ &= \prod_{i=1}^m p(X_i | X_1, \dots, X_{i-1}; S_1, \dots, S_{i-1}; \beta) \prod_{i=1}^m p(S_i | X_1, \dots, X_{i-1}, X_i; S_1, \dots, S_{i-1}; \beta) \end{aligned}$$

Cox calls the second product, i.e.,

$$\prod_{i=1}^m p(S_i | X_1, \dots, X_{i-1}, X_i; S_1, \dots, S_{i-1}; \beta),$$

the partial likelihood.

In regression with censored data the partial likelihood coincides with L_c , which we have called a conditional likelihood. A comparison of the definitions of partial likelihood and conditional likelihood shows that the partial likelihood is not a true conditional likelihood, nor is it a marginal likelihood. Although technically incorrect, we will continue to call L_c the conditional likelihood.

Cox claims that the partial likelihood contains most of the information about β for regression with censored data, and that we can ignore the first product, i.e.,

$$\prod_{i=1}^m p(X_i | X_1, \dots, X_{i-1}; S_1, \dots, S_{i-1}; \beta),$$

without losing much. Efron and Oakes have compared the Fisher information in the partial likelihood to the Fisher information in the full likelihood for a variety of models. Usually the information in L_c is very high with efficiency $\geq 90\%$, and in rare cases, L_c even carries as much information as the full likelihood.

References:

Cox, Biometrika (1975).

Efron, JASA (1977).

Oakes, Biometrika (1977).

Justification of asymptotic normality:

In his 1972 paper Cox asserts that $\hat{\beta}$, the solution to

$$\frac{\partial}{\partial \beta} \log L_c(\beta) = 0,$$

is asymptotically normally distributed. In his 1975 paper Cox gives a heuristic argument which is similar to the standard maximum likelihood argument.

Tsiatis gives a proof of the asymptotic normality of $\hat{\beta}$ using integral representations and stochastic processes which is similar to the proof given by Breslow and Crowley of the asymptotic normality of the PL estimator and the proof given by Crowley for the Mantel-Haenszel statistic.

Bailey gives an argument using Hajek projections.

References:

Cox, Biometrika (1975).

Tsiatis, Ann. Stat. (1981).

Bailey, Univ. of Chicago thesis (1979).

Estimation of $S(t; \tilde{x})$:

Under the Cox proportional hazards model,

$$\begin{aligned} S(t; \tilde{x}) &= \exp \left\{ -e^{\tilde{\beta}' \tilde{x}} \int_0^t \lambda_0(u) du \right\}, \\ &= \exp \left\{ -e^{\tilde{\beta}' \tilde{x}} \Lambda_0(t) \right\}, \\ &= S_0(t) e^{\tilde{\beta}' \tilde{x}}, \end{aligned}$$

where

$$S_0(t) = e^{-\Lambda_0(t)}.$$

To estimate $S(t; \tilde{x})$, we substitute $\hat{\beta}$ for $\tilde{\beta}$, but how do we estimate $\Lambda_0(t)$ or $S_0(t)$?

Breslow assumes $\lambda_0(t)$ is constant between uncensored observations:

$$\hat{\lambda}_{0,B}(t) = \frac{1}{(y_{u(i)} - y_{u(i-1)}) \sum_{j \in \mathcal{R}_{u(i)}} e^{\hat{\beta}' x_j}} \text{ if } y_{u(i-1)} < t < y_{u(i)} .$$

However, he estimates $S_0(t)$ by

$$\hat{S}_{0,B}(t) = \prod_{y_{(i)} \leq t} \left(1 - \frac{\delta_{(i)}}{\sum_{j \in \mathcal{R}_{(i)}} e^{\hat{\beta}' x_j}} \right) .$$

Notice that $\hat{\Lambda}_{0,B}(t) = \int_0^t \hat{\lambda}_{0,B}(u) du$ and $\hat{S}_{0,B}(t)$ are inconsistent in the sense that

$$\hat{S}_{0,B}(t) \neq e^{-\hat{\Lambda}_{0,B}(t)}$$

even for $t = y_{(i)}$. Moreover, $\hat{S}_{0,B}(t)$ can take negative values.

Tsiatis uses

$$\hat{S}_{0,T}(t) = e^{-\hat{\Lambda}_{0,T}(t)} ,$$

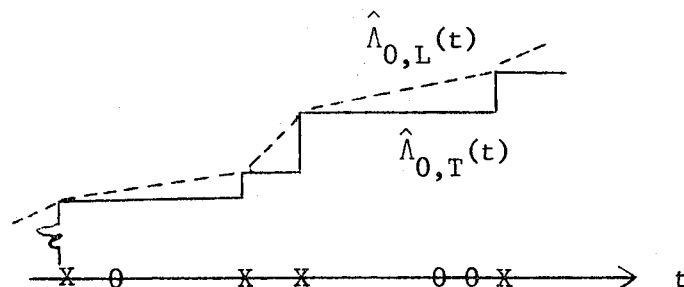
where

$$\hat{\Lambda}_{0,T}(t) = \sum_{y_{(i)} \leq t} \frac{\delta_{(i)}}{\sum_{j \in \mathcal{R}_{(i)}} e^{\hat{\beta}' x_j}} ,$$

but $\hat{S}_{0,T}$ does not simplify to the PL estimator when $\hat{\beta} = 0$. Notice that $\hat{\Lambda}_0(t)$ is a step function.

Link uses a linear smooth of $\hat{\Lambda}_{0,T}(t)$, which is the integral of the Breslow estimate of $\lambda_0(t)$, and, like Tsiatis, defines

$$\hat{S}_{0,L}(t) = e^{-\hat{\Lambda}_{0,L}(t)} .$$



Both Tsiatis and Link calculate $\text{Var}(\hat{S}_0(t))$, Tsiatis using a likelihood model and Link using the delta method. Link also uses Monte Carlo methods to study the confidence intervals associated with

$$\hat{S}_{0,L}(t), \log \hat{S}_{0,L}(t), \text{ and } \text{logit } \hat{S}_{0,L}(t) = \log \frac{\hat{S}_{0,L}(t)}{1 - \hat{S}_{0,L}(t)},$$

and finds that the coverage probabilities with $\hat{S}_{0,L}(t)$ tend to be too low, those with $\text{logit } \hat{S}_{0,L}(t)$ too high, and those with $\log \hat{S}_{0,L}(t)$ approximately correct. These results concerning the confidence interval coverages hold also for the PL estimator.

Alternative estimators of $S(t;x)$, which are computationally more complicated, have been proposed by Cox, Efron, and Kalbfleisch-Prentice (loc. cit.).

References:

Breslow, JRSS B (1972), in Discussion on Cox's paper.

———, Biometrics (1974).

Tsiatis, Univ. Wisconsin Tech. Report No. 524 (1978).

———, Ann. Stat. (1981).

Link, Stanford Univ. Tech. Report No. 45 (1979).

Discrete or grouped data:

Denote the ordered distinct survival times by

$$y'_{(1)} < \dots < y'_{(r)},$$

and let

$\mathcal{R}_{(i)}$ = risk set at time $y'_{(i)}-$,

$\mathcal{D}_{(i)}$ = death set at time $y'_{(i)}$, i.e., the set of individuals who die at time $y'_{(i)}$,

$$d_i = \#(\mathcal{D}_{(i)}) .$$

Cox suggests using

$$L_c = \prod_{i=1}^r P\{\mathcal{D}_{(i)} | \mathcal{R}_{(i)}, d_i\} ,$$

with

$$P\{\mathcal{D}_{(i)} | \mathcal{R}_{(i)}, d_i\} = \frac{\exp \left\{ \sum_{j \in \mathcal{D}_{(i)}} \beta' \tilde{x}_j \right\}}{\sum_{\mathcal{D}_{(i)}^*} \exp \left\{ \sum_{j \in \mathcal{D}_{(i)}^*} \beta' \tilde{x}_j \right\}} ,$$

where the summation in the denominator is over all subsets $\mathcal{D}_{(i)}^* \subset \mathcal{R}_{(i)}$

such that $\#(\mathcal{D}_{(i)}^*) = d_i$. For $i = 1, \dots, r$, there are

$\binom{n_i}{d_i}$ subsets to consider so for even modest-sized data sets, this approach

is not computationally feasible.

An alternative likelihood, proposed by Peto, Breslow, and Kalbfleisch-Prentice, is

$$L_c = \prod_{i=1}^r \frac{e^{\sum_{j \in \mathcal{D}_{(i)}} \beta' \tilde{x}_j}}{\left(\sum_{j \in \mathcal{R}_{(i)}} e^{\beta' \tilde{x}_j} \right)^{d_i}} ,$$

which seems to work reasonably well when the number of ties is not excessive.

Neither of these likelihoods strictly adheres to a Lehmann alternative model or a proportional hazards model, but the next proposal by Prentice and Gloeckler does.

Prentice and Gloeckler assume that the time axis is partitioned by

$$0=a_0 < a_1 < \dots < a_{r-1} < a_r=\infty ,$$

and

$$A_j = [a_{j-1}, a_j) .$$

If a survival time falls in the interval A_j , then record time j . Denote

$$\alpha_j = \exp - \int_{a_{j-1}}^{a_j} \lambda_0(t) dt ,$$

which is the conditional probability of an individual with covariate $\tilde{x}=0$ surviving A_j , given that he has survived A_{j-1} . Then the probability of the i th observation surviving to the beginning of A_j is

$$\prod_{k=1}^{j-1} \alpha_k^{e^{\beta' \tilde{x}_i}} ,$$

and

$$P\{Y_i=j, \delta_i\} = \left(\prod_{k=1}^{j-1} \alpha_k^{e^{\beta' \tilde{x}_i}} \right) \left(1 - \alpha_j^{e^{\beta' \tilde{x}_i}} \right)^{\delta_i} .$$

The full likelihood is

$$L = \prod_{i=1}^n P\{Y_i=j, \delta_i\} ,$$

which is a function of the unknown parameters $\beta, \alpha_1, \dots, \alpha_r$.

To estimate these parameters use maximum likelihood. Notice that the α_j 's are restricted by

$$0 < \alpha_j < 1, \quad j = 1, \dots, r, \quad \text{and} \quad \sum_{j=1}^r \alpha_j = 1.$$

Eliminate α_r and let

$$\gamma_j = \log(-\log \alpha_j), \quad j = 1, \dots, r-1,$$

so that

$$-\infty < \gamma_j < +\infty, \quad j = 1, \dots, r-1.$$

Maximizing with respect to $\gamma_1, \dots, \gamma_{r-1}$ is simpler than maximizing with respect to $\alpha_1, \dots, \alpha_r$ because there is no need to worry about the boundaries. Also, Newton-Raphson convergence is faster.

References:

Cox, JRSS B (1972).

Peto, JRSS B (1972), and

Kalbfleisch and Prentice, JRSS B (1972), in Discussion on
Cox's paper.

Breslow, Biometrics (1974).

Prentice and Gloeckler, Biometrics (1978).

Time dependent covariates:

We generalize to the situation in which the covariate is allowed to vary with time. Therefore, together with

$$Y_i = T_i \wedge C_i, \quad \delta_i = I(T_i < C_i),$$

we observe $x_i(t)$. The proportional hazards model assumes the hazard

function of the i th observation to be

$$\lambda_i(t) = e^{\beta' \tilde{x}_i(t)} \lambda_0(t) ,$$

so that

$$P\{\text{death of } (i) \text{ at time } y_{(i)} \mid \text{one death in } \mathcal{R}_{(i)} \text{ at time } y_{(i)}\} = \frac{e^{\beta' \tilde{x}_{(i)}(y_{(i)})}}{\sum_{j \in \mathcal{R}_{(i)}} e^{\beta' \tilde{x}_j(y_{(i)})}} ,$$

and the conditional likelihood becomes

$$L_c = \prod_u \frac{e^{\beta' \tilde{x}_{(i)}(y_{(i)})}}{\sum_{j \in \mathcal{R}_{(i)}} e^{\beta' \tilde{x}_j(y_{(i)})}} .$$

In the time varying case, no proof exists for the asymptotic normality of $\hat{\beta}$. Also, for moderate to large data sets the computations become unfeasible.

Example 1. Stanford Heart Transplant Data

Do heart transplant patients survive longer than heart-disease patients who do not receive heart transplants? Typically, a patient enters the study and receives a transplant when a donor heart becomes available. Upon transplantation, we say that the patient has migrated from the no-transplant population to the transplant population, and the covariate that indicates transplant changes from 0 to 1. Other covariates measured include age, waiting time to transplantation, calendar time from beginning of study, and a mismatch score which measures the degree of dissimilarity between donor and recipient tissues.

Reference:

Crowley and Hu, JASA (1977).

Turnbull, Brown, and Hu, JASA (1974).

Example 2. Adoption and Pregnancy

Are couples with an infertility problem who have adopted a child more likely to conceive than couples who have not adopted? Here, couples may migrate from the childless population to the adopted population. Censoring occurs when a couple stops trying for a pregnancy.

Reference:

Lamb and Leurgans, Amer. J. Obstet. Gyn. (1979).

Leurgans, Stanford Univ. Tech. Report No. 57 (1980).

B. Linear models

The standard linear model is

$$T_i = \alpha + \beta x_i + e_i ,$$

$$\text{or } T_i = \beta' \tilde{x}_i + e_i , \quad i = 1, \dots, n ,$$

where e_1, \dots, e_n are iid with common distribution F . Let C_1, \dots, C_n be independent; C_i is the censoring time associated with T_i . We observe

$$Y_i = T_i \wedge C_i , \quad \delta_i = I(T_i < C_i) .$$

Accelerated time models:

Linear models are connected to hazard models through accelerated time models. Suppose Z_0 is a survival time with hazard rate

$$\lambda_0(z) = \frac{f_0(z)}{1-F_0(z)} ,$$

and assume that the survival time of an individual with covariate \tilde{x} has the same distribution as

$$Z_{\tilde{x}} = e^{\tilde{\beta}' \tilde{x}} Z_0 .$$

Notice that if $\beta'x < 0$, then Z_x is shorter than Z_0 and we say that the covariate accelerates the time to failure. The hazard rate of Z_x is

$$\begin{aligned}\lambda_x(z) &= \frac{f_x(z)}{1-F_x(z)}, \\ &= \frac{f_0(e^{-\beta'x}z)e^{-\beta'x}}{1-F_0(e^{-\beta'x}z)} , \\ &= \lambda_0(e^{-\beta'x}z)e^{-\beta'x} .\end{aligned}$$

Define

$$T_x = \log Z_x .$$

Then

$$\begin{aligned}E(T_x) &= \beta'x + E(\log Z_0) , \\ &= \beta'x + \alpha ,\end{aligned}$$

so the accelerated time model coincides with a log-linear model:

$$\begin{aligned}T_x &= \beta'x + \alpha + e , \text{ where} \\ e &= \log Z_0 - E(\log Z_0) .\end{aligned}$$

In applying linear model methods to survival data it is frequently necessary to transform the data by a logarithmic transformation in order to symmetrize it so the accelerated time model is very relevant in this regard.

References:

- Prentice and Kalbfleisch, Biometrics (1979), and
Kalbfleisch and Prentice, The Statistical Analysis of Failure
Time Data (1980), both discuss the accelerated time model.

1. Linear rank tests

With no censoring present, the locally most powerful rank statistic for $H_0: \beta = 0$ against $H_1: \beta \neq 0$ is

$$\left. \frac{d}{d\beta} \log p(\tilde{r}) \right|_{\beta=0},$$

where $p(\tilde{r})$ is the probability of the rank vector \tilde{r} . Similarly, when censoring is present, use the statistic

$$\left. \frac{d}{d\beta} \log p(\tilde{r}^{u/c}, \tilde{\delta}) \right|_{\beta=0},$$

where from page 95,

$$p(\tilde{r}^{u/c}, \tilde{\delta}) = \int \dots \int_{u_1 < \dots < u_{n_u}} \prod_{i=1}^{n_u} \left\{ f_{u(i)}(u_i) \prod_{j \in C_{i,i+1}} [1 - F_j(u_i)] \right\} du_1 \dots du_{n_u},$$

$$f_i(u) = f(u - \beta x_i).$$

It can be shown that

$$\left. \frac{d}{d\beta} \log p(\tilde{r}^{u/c}, \tilde{\delta}) \right|_{\beta=0} = \sum_{i=1}^{n_u} \left\{ x_{u(i)} c_i + \left(\sum_{j \in C_{i,i+1}} x_j \right) c_i \right\},$$

where

$$c_i = \left(\prod_{j=1}^{n_u} n_{u(j)} \right) \int \dots \int_{u_1 < \dots < u_{n_u}} \left\{ - \frac{d}{du_i} \log f(u_i) \right\} \prod_{j=1}^{n_u} \left\{ f(u_j) [1 - F(u_j)]^{m_{u(j)}} \right\} du_1 \dots du_{n_u},$$

$$c_i = \left(\prod_{j=1}^{n_u} n_{u(j)} \right) \int \dots \int_{u_1 < \dots < u_{n_u}} \left\{ - \frac{d}{du_i} \log [1 - F(u_i)] \right\} \prod_{j=1}^{n_u} \left\{ f(u_j) [1 - F(u_j)]^{m_{u(j)}} \right\} du_1 \dots du_{n_u},$$

$$m_{u(j)} = \#C_{j,j+1}.$$

Letting the error distribution be the extreme value distribution

$$1-F(t) = e^{-e^t}, \quad f(t) = e^{t-e^t},$$

(see pp. 24-25), then

$$c_i = \sum_{j=1}^i \frac{1}{n_u(j)} - 1,$$

$$C_i = \sum_{j=1}^i \frac{1}{n_u(j)},$$

so the locally most powerful rank statistic in this case becomes

$$-\sum_u \{x_{(i)} - \bar{x}_{(i)}\},$$

which is the numerator of the Cox statistic for testing $H_0: \beta = 0$

(see p. 92). Peto and Peto named this the log rank test.

References:

- Prentice, Biometrika (1978), gives a derivation of the linear rank test statistic and calculates its variance.
- Kalbfleisch and Prentice, The Statistical Analysis of Failure Time Data (1980), Ch. 6.
- Peto and Peto, JRSS A (1972), introduce linear rank tests and coin the term "log rank test".
- Morton, Biometrika (1978), discusses permutation theory for linear rank tests.
- Latta, Biometrika (1977), establishes a connection between linear rank tests and Efron's test.

2. Least squares estimators

We assume here for simplicity

$$E(T_i) = \alpha + \beta x_i.$$

The estimators can be generalized to handle more than one covariate.

a) Miller estimators

With no censoring present, the estimates $\hat{\alpha}$ and $\hat{\beta}$ minimize

$$\sum_{i=1}^n (y_i - \alpha - \beta x_i)^2 = n \int_{-\infty}^{\infty} z^2 dF_n(z) ,$$

where F_n is the empirical d.f. of z_1, \dots, z_n and

$$z_i = y_i - \alpha - \beta x_i .$$

With censoring present, the proposal is to minimize

$$n \int_{-\infty}^{\infty} z^2 d\hat{F}(z) = \sum_{i=1}^n \hat{w}_i(\beta) (y_i - \alpha - \beta x_i)^2 ,$$

where \hat{F} is the PL estimator based on $(z_1, \delta_1), \dots, (z_n, \delta_n)$, and the weights $\hat{w}_1(\beta), \dots, \hat{w}_n(\beta)$ are the jumps of the PL estimator.

Notice that if $\delta_i = 0$ corresponding to a censored observation, $\hat{w}_i(\beta) = 0$, so at first glance the weighted sum of squares does not depend on the censored observations. However, the PL estimator, and therefore each weight, does depend on the censored observations.

If $\delta_{(n)} = 0$ so that the last ordered observation is censored, change it to be uncensored. Then, $\sum_{i=1}^n \hat{w}_i(\beta) = 1$.

We have written the weights as functions of β only. Since adding a constant α to each T_i results only in a shift of the PL estimator, the jumps of the PL estimator, and therefore the weights, do not depend on α .

To calculate $\hat{\alpha}, \hat{\beta}$, we differentiate with respect to α to obtain

$$\hat{\alpha} = \sum_{i=1}^n \hat{w}_i(\beta) y_i - \beta \sum_{i=1}^n \hat{w}_i(\beta) x_i .$$

Substituting this expression into the weighted sum of squares results in a function of β alone:

$$f(\beta) = \sum \hat{w}_i(\beta) (y_i - \hat{\alpha} - \beta x_i)^2,$$

which can be minimized by a search procedure.

Since the function $f(\beta)$ is not continuous, the search for the minimum can be tedious, especially in higher dimensions. As an alternative procedure Miller suggests the following modified approach. Define the initial estimate

$$\hat{\beta}^0 = \frac{\sum_u y_i (x_i - \bar{x}_u)}{\sum_u (x_i - \bar{x}_u)^2},$$

which is the slope of the least-squares line through the uncensored observations. With this guess $\hat{\beta}^0$, form

$$\hat{z}_i^0 = y_i - \hat{\beta}^0 x_i, \quad i = 1, \dots, n.$$

Let \hat{F}^0 be the PL estimator based on $(\hat{z}_1^0, \delta_1), \dots, (\hat{z}_n^0, \delta_n)$, and let $\hat{w}_1(\hat{\beta}^0), \dots, \hat{w}_n(\hat{\beta}^0)$ be the jumps of \hat{F}^0 . Now define the new estimate

$$\hat{\beta}^1 = \frac{\sum_u \hat{w}_i^*(\hat{\beta}^0) y_i (x_i - \bar{x}_u^*)}{\sum_u \hat{w}_i^*(\hat{\beta}^0) (x_i - \bar{x}_u^*)^2},$$

where

$$\hat{w}_i^*(\hat{\beta}^0) = \frac{\hat{w}_i(\hat{\beta}^0)}{\sum_u \hat{w}_i(\hat{\beta}^0)},$$

$$\bar{x}_u^* = \sum_u \hat{w}_i^*(\hat{\beta}^0) x_i.$$

Using the renormalized weights $\hat{w}_i^*(\hat{\beta}^0)$ allows us to ignore whether the last ordered \hat{z}_i^0 is censored or not. Only the uncensored observations appear in the summation. The usual procedure of redefining the last ordered \hat{z}_i^0 to be uncensored if it is censored gives less stable results in iteratively estimating β , but it should still be used in estimating α .

We iterate the above procedure and hope for convergence. However, the sequence of estimates of β may become trapped in a loop where they oscillate between two values, in which case we take the average of the two values.

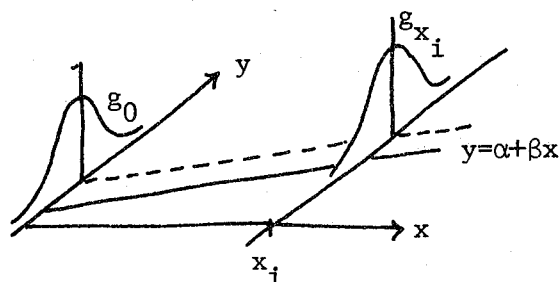
Assuming that the variability due to the weights $\hat{w}_i^*(\hat{\beta})$ is negligible,

$$\text{Var}(\hat{\beta}) \approx \frac{\sum_u \hat{w}_i^*(\hat{\beta}) (y_i - \hat{\alpha} - \hat{\beta}x_i)^2}{\sum_u \hat{w}_i^*(\hat{\beta}) (x_i - \bar{x}_u^*)^2}.$$

The derivation of this variance estimate, as well as the proof of the consistency of the estimates $\hat{\alpha}$ and $\hat{\beta}$, depends on the assumption that the censoring distribution of the i th observation is

$$G_{x_i}(c) = G_0(c - \beta x_i),$$

for some distribution function G_0 . If G_0 has density g_0 as pictured below, then G_{x_i} has density g_{x_i} , which is g_0 translated by βx_i :



Reference:

Miller, Biometrika (1976).

b) Buckley-James estimator

Our model assumes

$$E(T_i) = \alpha + \beta x_i .$$

Unfortunately, we cannot observe T_i , but only Y_i , and

$$E(Y_i) \neq \alpha + \beta x_i .$$

Buckley and James define the pseudo random variables

$$Y_i^* = Y_i \delta_i + E(T_i | T_i > Y_i) (1 - \delta_i) ,$$

and calculate

$$\begin{aligned} E(Y_i^*) &= \int_0^\infty u(1-G_i(u))dF_i(u) + \int_0^\infty \left[\int_u^\infty \frac{s dF_i(s)}{1-F_i(u)} \right] (1-F_i(u))dG_i(u) , \\ &= \int_0^\infty u(1-G_i(u))dF_i(u) + \int_0^\infty \left[\int_0^s dG_i(u) \right] s dF_i(s) , \\ &= \int_0^\infty u(1-G_i(u))dF_i(u) + \int_0^\infty G_i(s)s dF_i(s) , \\ &= \int_0^\infty u dF_i(u) , \\ &= E(T_i) , \\ &= \alpha + \beta x_i . \end{aligned}$$

Therefore, if we could observe y_1^*, \dots, y_n^* , it would be reasonable to use

$$\hat{\alpha} = \bar{y}^* - \hat{\beta}\bar{x} \quad \text{and} \quad \hat{\beta} = \frac{\sum_{i=1}^n y_i^* (x_i - \bar{x})}{\sum_{i=1}^n (x_i - \bar{x})^2} . \quad (15)$$

Since we cannot observe all of y_1^*, \dots, y_n^* , we substitute estimates for those we cannot observe. If $\delta_i = 0$, define

$$\hat{E}(T_i | T_i > y_i) = \hat{\beta}x_i + \frac{\sum_{\hat{z}_k > \hat{z}_i} \hat{w}_k(\hat{\beta}) \hat{z}_k}{1 - \hat{F}(\hat{z}_i)} , \quad (16)$$

where $\hat{z}_i = y_i - \hat{\beta}x_i$, \hat{F} is the PL estimator based on $(\hat{z}_1, \delta_1), \dots, (\hat{z}_n, \delta_n)$, and $\hat{w}_1(\hat{\beta}), \dots, \hat{w}_n(\hat{\beta})$ are the jumps of \hat{F} . Then define

$$\hat{y}_i^* = y_i \delta_i + \left[\hat{\beta}x_i + \frac{\sum_{\hat{z}_k > \hat{z}_i} \hat{w}_k(\hat{\beta}) \hat{z}_k}{1 - \hat{F}(\hat{z}_i)} \right] (1 - \delta_i) . \quad (17)$$

Since equations (15) give $\hat{\beta}$ as a function of y_i^* and equation (17) gives y_i^* as a function of $\hat{\beta}$, we need to iterate. As with the Miller estimate, the sequence of estimates of β may eventually oscillate between two values, and again we take the solution to be the average.

Buckley and James claim that if the estimates of β oscillate, then the difference between their two values is smaller than that for the Miller estimate. Furthermore, the validity of their method does not depend on assumptions on the censoring distributions G_i .

Buckley and James give the variance estimate

$$\widehat{\text{Var}}(\hat{\beta}) = \frac{\hat{\sigma}_u^2}{\sum_u (x_i - \bar{x}_u)^2}, \quad \text{where}$$

$$\hat{\sigma}_u^2 = \frac{1}{n_u - 2} \sum_u (y_i - \bar{y}_u - \hat{\beta}(x_i - \bar{x}_u))^2,$$

but they do not give a mathematical justification.

Reference:

Buckley and James, Biometrika (1979).

Notes:

(i) The Buckley-James method is a nonparametric extension of a normal theory technique due to Schmee and Hahn.

Define

$$W_i = \frac{T_i - \alpha - \beta x_i}{\sigma}.$$

If F is normal with variance σ^2 , then

$$\begin{aligned} E(T_i | T_i > y_i) &= E\left(\sigma W_i + \alpha + \beta x_i \mid W_i > \frac{y_i - \alpha - \beta x_i}{\sigma}\right), \\ &= \alpha + \beta x_i + \frac{\sigma \int_{(y_i - \alpha - \beta x_i)/\sigma}^{\infty} w \phi(w) dw}{1 - \Phi\left(\frac{y_i - \alpha - \beta x_i}{\sigma}\right)}, \\ &= \alpha + \beta x_i + \frac{\sigma \phi\left(\frac{y_i - \alpha - \beta x_i}{\sigma}\right)}{1 - \Phi\left(\frac{y_i - \alpha - \beta x_i}{\sigma}\right)}, \end{aligned}$$

where ϕ and Φ are the standard normal density and d.f. respectively.

Schmee and Hahn use the estimate

$$\hat{E}(T_i | T_i > y_i) = \hat{\alpha} + \hat{\beta}x_i + \frac{\hat{\sigma} \phi\left(\frac{y_i - \hat{\alpha} - \hat{\beta}x_i}{\hat{\sigma}}\right)}{1 - \Phi\left(\frac{y_i - \hat{\alpha} - \hat{\beta}x_i}{\hat{\sigma}}\right)}$$

in place of (16).

Reference:

Schmee and Hahn, Technometrics (1979).

(ii) Both the parametric and nonparametric methods are analogous to the EM algorithm in maximum likelihood theory.

Reference:

Dempster, Laird, and Rubin, JRSS B (1977).

c) Koul-Susarla-Van Ryzin estimator

If we define

$$Y_i^* = \frac{\delta_i Y_i}{1 - G(Y_i)},$$

then

$$\begin{aligned} E(Y_i^*) &= \int_0^\infty \frac{u}{1 - G(u)} (1 - G(u)) dF_i(u), \\ &= \int_0^\infty u dF_i(u), \\ &= E(T_i), \\ &= \alpha + \beta x_i. \end{aligned}$$

Therefore, if we could observe y_1^*, \dots, y_n^* , we could estimate α and β by (15) in the usual way. Unfortunately, we cannot observe all of y_1^*, \dots, y_n^* , but we can substitute estimates by

replacing G with a PL estimator where the roles of the survival and censoring random variables are reversed. Alternatively, Koul, Susarla, and Van Ryzin propose to use a Bayesian estimator of G .

The big advantage with this method is that no iteration is required. Also, it is based on the assumption of a common censoring distribution rather than shifted censoring distributions as for the Miller estimator. However, the \hat{y}_i^* are somewhat peculiar in that they are either zero or inflated values of the y_i . The behavior of these estimators have not been evaluated at this point.

Reference:

Koul, Susarla, and Van Ryzin, unpublished manuscript (1979).

Example. Stanford Heart Transplant Study

We compare the procedures of Cox, Miller, and Buckley-James when applied to the Stanford heart transplant data displayed in Table 5. In the first regression (Figure 5) the dependent variable is \log_{10} survival time, where the survival time is the time until death due to rejection, and the covariate is the mismatch score. In the second regression (Figure 6) the dependent variable is \log_{10} survival time, where the survival time here is the time until death regardless of whether due to the rejection of the donor heart or other cases, and the covariate is age. In the one case where the survival time is recorded as zero this is changed to a one for taking logs. The comparisons of the three procedures are presented in Tables 6 and 7.

Table 5. Stanford heart transplant data.

Patient No.	Survival Time	Dead=1 Alive=0	Reject=1 Nonrej.=0	Mismatch T5 Score	Age at Tx
3	15	1	0	1.11	54.3
4	3	1	0	1.66	40.4
7	624	1	1	1.32	51.0
10	46	1	1	0.61	42.5
11	127	1	0	0.36	48.0
13	64	1	1	1.89	54.6
14	1350	1	1	0.87	54.1
16	280	1	1	1.12	49.5
18	23	1	0	2.05	56.9
20	10	1	1	2.76	55.3
21	1024	1	1	1.13	43.4
22	39	1	1	1.38	42.8
23	730	1	1	0.96	58.4
24	136	1	1	1.62	52.0
25	1775	0	0	1.06	33.3
28	1	1	0	0.47	54.2
30	836	1	1	1.58	45.0
32	60	1	1	0.69	64.5
33	1536	0	0	0.91	49.0
34	1549	0	0	0.38	40.6
36	54	1	1	2.09	49.0
37	47	1	1	0.87	61.5
38	0	1	0	0.87	41.5
39	51	1			50.5
40	1367	0	0	0.75	48.6
41	1264	0	0	0.98	45.5
45	44	1	0	0.0	36.2
46	994	1	1	0.81	48.6
47	51	1	1	1.38	47.2
49	1106	0	0	1.35	36.8
50	897	1			46.1
51	253	1	1	1.08	48.8
53	147	1			47.5
55	51	1	1	1.51	52.5
56	875	0	0	0.98	38.9
58	322	1	1	1.82	48.1
59	838	0	0	0.19	41.6
60	65	1	1	0.66	49.1
63	815	0	0	1.93	32.7
64	551	1	0	0.12	48.9
65	66	1	1	1.12	51.3
67	228	1	0	1.02	19.7
68	65	1	1	1.68	45.2
69	660	0	0	1.20	48.0
70	25	1	1	1.68	53.0
71	589	0	0	0.97	47.5
72	592	0	0	1.46	26.7
73	63	1	1	2.16	56.4
74	12	1	0	0.61	29.2

Table 5. Stanford heart transplant data (continued).

Patient No.	Survival Time	Dead=1 Alive=0	Reject=1 Nonrej.=0	Mismatch T5 Score	Age at Tx
76	499	0	0	1.70	52.2
78	305	0	0	0.81	49.3
79	29	1	1	1.08	54.0
80	456	0	0	1.41	46.5
81	439	0	0	1.94	52.9
83	48	1	0	3.05	53.4
84	297	1	1	0.60	42.8
86	389	0	0	1.44	48.9
87	50	1	1	2.25	46.4
88	339	0	0	0.68	54.4
89	68	1	1	1.33	51.4
90	26	1	0	0.82	52.5
92	30	0	0	0.16	45.8
93	237	0	0	0.33	47.8
94	161	1	1	1.20	43.8
95	14	1			40.3
96	167	0	0	0.46	26.7
97	110	0	0	1.78	23.7
98	13	0	0	0.77	28.9
100	1	0	0	0.67	35.2

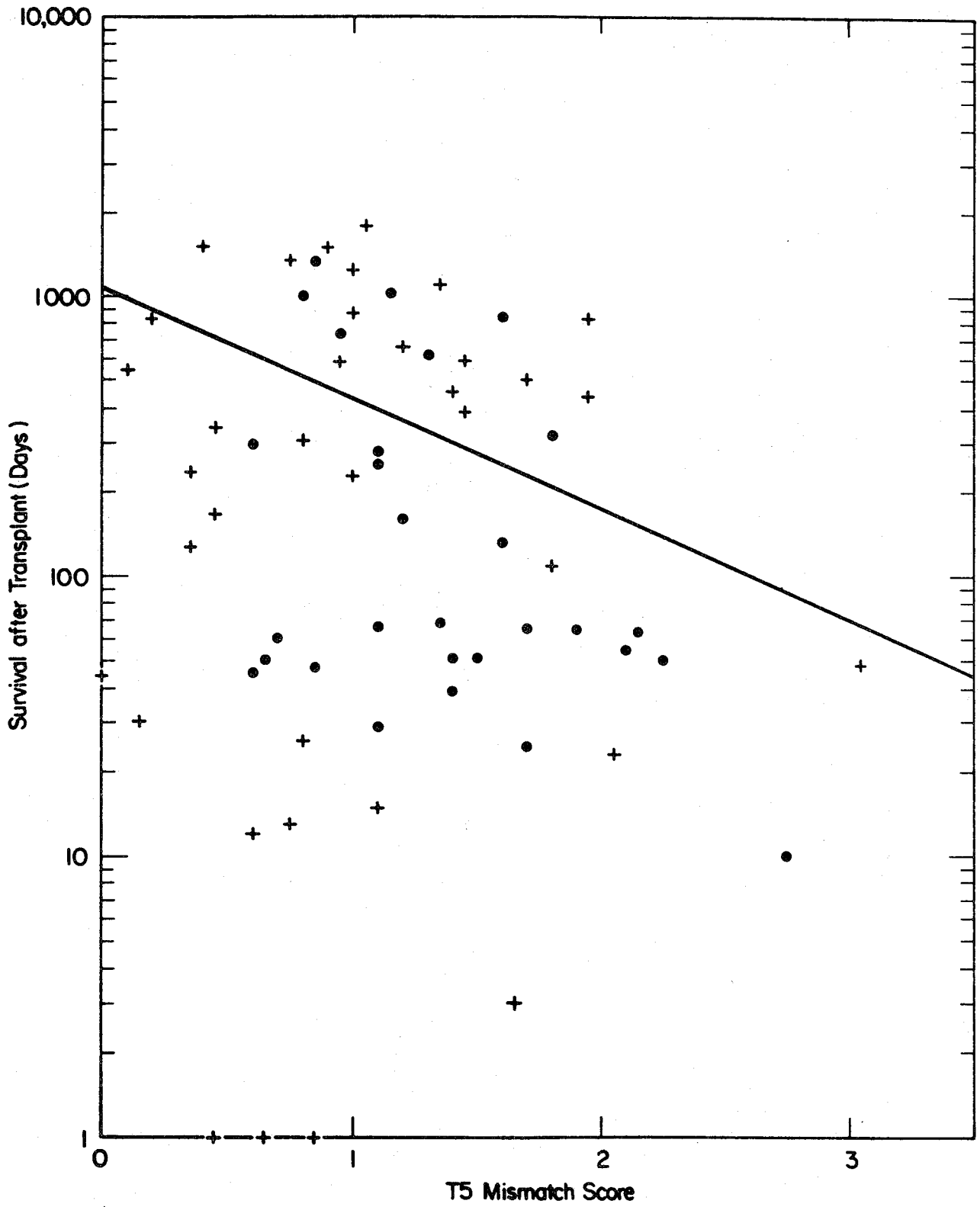


Figure 5. T5 Mismatch Score vs. Survival. + = alive or nonrejection death, • = rejection death; — Kaplan-Meier least squares line.

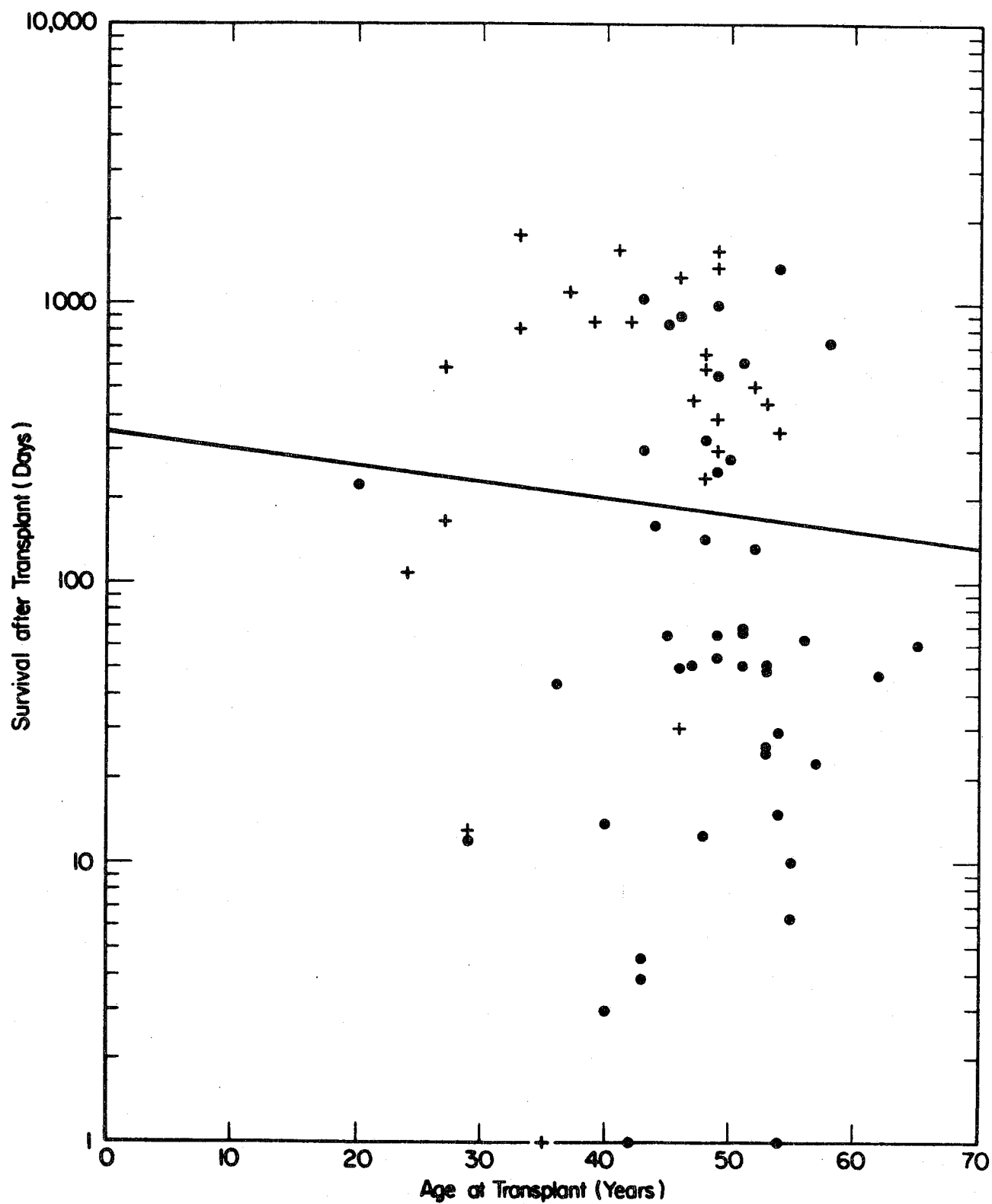


Figure 6. Age vs. Survival. + = alive, • = dead; — Kaplan-Meier least squares line.

	$\hat{\alpha}$	$\hat{\beta}$	SD($\hat{\beta}$)
Cox		1.076	.368
Miller	3.036	-.394	
Miller modified	3.120	-.452	.236
	3.145	-.471	.234
Buckley-James			

Table 6. Regression of \log_{10} survival time until rejection on mismatch score.

	$\hat{\alpha}$	$\hat{\beta}$	SD($\hat{\beta}$)
Cox		.0575	.0233
Miller	2.537	-.0058	
Miller modified	2.111	.0036	.0166
	2.171	.0024	.0163
Buckley-James	3.582	-.0278	.0149

Table 7. Regression of \log_{10} survival time on age.

The three procedures give conflicting results for the regression on age. The Cox method indicates there is a highly significant age effect. The Miller method says there is no effect due to age, and the Buckley-James approach gives borderline significance to age. The Miller estimators may be thrown off by the censoring pattern in this case.

Since there is also disagreement about the degree of significance for the mismatch score effect, further work should be done to see which model (accelerated time or proportional hazards) is more appropriate for these data.

VII. Goodness of Fit

A. Graphical methods

The human eye can distinguish well between a straight line and a curved line so the following basic principle should guide the method of plotting.

Basic Principle: Select the scales of the coordinate axes so that if the model holds, a plot of the data resembles a straight line, and if the model fails, a plot resembles a curved line.

There are two types of plots one can make, namely, survival plots and hazard plots. The two are closely related, and in each case the choice is one of convenience.

(i) Survival plots

Plot either

$$\hat{S}(y_{u(i)}) \text{ against } y_{u(i)} ,$$

or

$$\hat{S}(t) \text{ against } t .$$

This is a special case of Q-Q plots or probability plots.

Reference:

Wilk and Gnanadesikan, Biometrika (1968).

(ii) Hazard plots

Plot either

$$\hat{\Lambda}(y_{u(i)}) \text{ against } y_{u(i)} ,$$

or

$$\hat{\Lambda}(t) \text{ against } t ,$$

using (see pp. 49-50) either the Nelson formula

$$\hat{\Lambda}_2(t) = \sum_{y_{(i)} \leq t} \frac{\delta_{(i)}}{n-i+1} ,$$

or

$$\hat{\Lambda}_1(t) = -\log \hat{S}(t) .$$

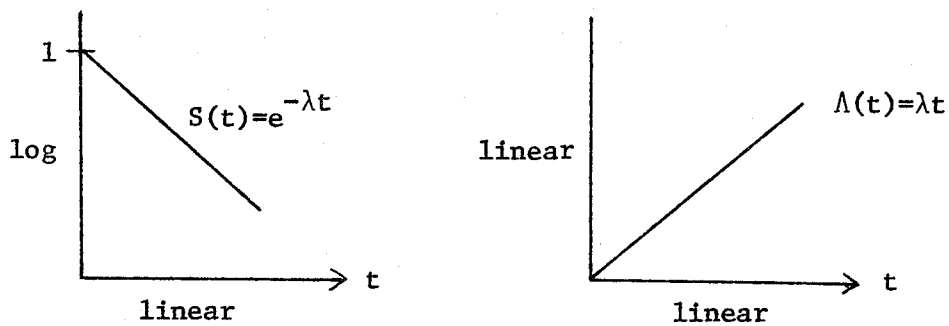
Reference:

Nelson, J. Quality Tech. (1969).

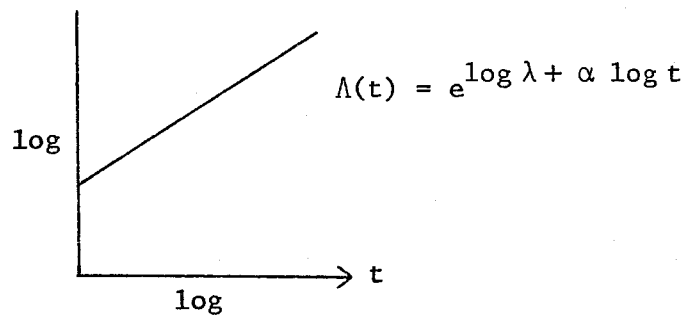
_____, Technometrics (1972).

1. One sample

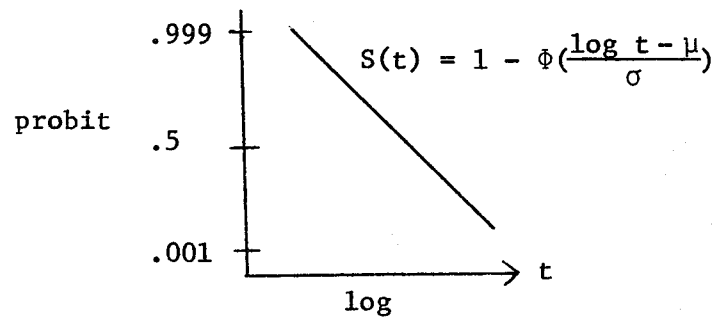
a) Exponential



b) Weibull



c) Log normal



d) Gamma and others

Without the use of special graph paper, compute and plot quantiles based on parametric assumptions against quantiles based on the PL estimator.

Reference:

Wilk, Gnanadesikan, and Huyett, Technometrics (1962),
for the gamma distribution without censoring.

2. Two to K samples

For parametric models, repeat a) through d) on each sample.

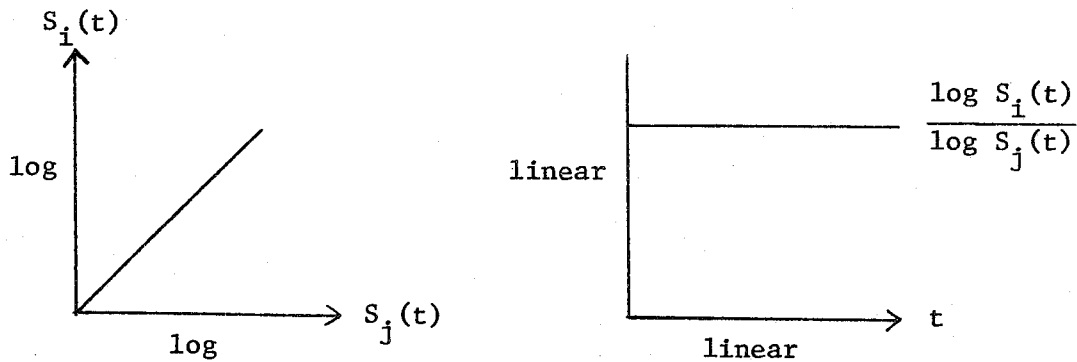
Suppose we want to check the validity of the Cox proportional hazards model. Under the model,

$$S_i(t) = S_j(t)^{\gamma_{ij}},$$

for some γ_{ij} , so

$$\log S_i(t) = \gamma_{ij} \log S_j(t), \text{ or}$$

$$\frac{\log S_i(t)}{\log S_j(t)} = \gamma_{ij}.$$



Compute individual PL estimates $\hat{S}_1(t), \dots, \hat{S}_K(t)$, and form either of the above graphs.

Example. DNCB Study

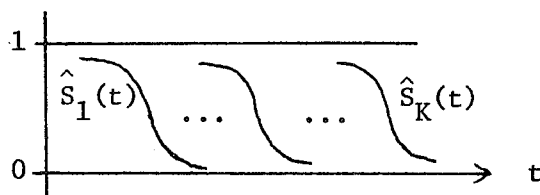
Hodgkin's disease patients were sensitized and then continually exposed to the chemical dinitrochlorobenzene (DNCB). The (+) population consists of those who react positively to exposure to DNCB while the (-) population consists of those who do not react; patients can migrate between populations. Survival time was taken to be time to relapse.

Do the patients in the (+) population survive longer than those in the (-) population? The Cox proportional hazards model was used. The plot of $\log \hat{S}^{(+)}(t) / \log \hat{S}^{(-)}(t)$ in Figure 7 shows us that except for times t close to zero, the ratio of the logs is reasonably constant, substantiating the validity of the model.

Reference:

Gong, Stanford Univ. Tech. Report No. 57 (1980).

To check the linear model, calculate the PL estimate for each of the K samples separately, and plot them, checking for shifts by translation.



3. Regression

Suppose we want to check the proportional hazards model. In the case x is one-dimensional, we might partition the x -axis into K intervals, compute a separate PL estimator for each interval, and apply K -sample procedures. If x is multidimensional, we might try to partition the x -space into K regions. However, grouping the data requires

that the number of observations be large and the required number of observations grows rapidly with the dimensionality of \tilde{x} .

As an alternative to grouping, define

$$\Lambda_{\tilde{x}_i}(T_i) = e^{\tilde{\beta}'\tilde{x}_i} \int_0^{T_i} \lambda_0(u) du .$$

Then, under the proportional hazards model,

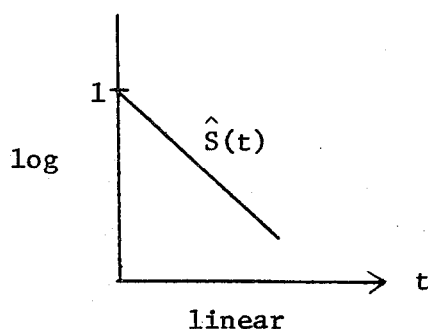
$$\begin{aligned} P\{\Lambda_{\tilde{x}_i}(T_i) > t\} &= P\{T_i > \Lambda_{\tilde{x}_i}^{-1}(t)\} , \\ &= \exp\{-\Lambda_{\tilde{x}_i}(\Lambda_{\tilde{x}_i}^{-1}(t))\}, \\ &= e^{-t} , \end{aligned}$$

showing that $\Lambda_{\tilde{x}_i}(T_i)$ is a unit exponential random variable.

Therefore, $(\Lambda_{\tilde{x}_1}(Y_1), \delta_1), \dots, (\Lambda_{\tilde{x}_n}(Y_n), \delta_n)$ is a sample from a unit exponential distribution with censoring. Because $\Lambda_{\tilde{x}_i}(Y_i)$ depends on unknown parameters $\tilde{\beta}$ and $\lambda_0(t)$, substitute estimates; define

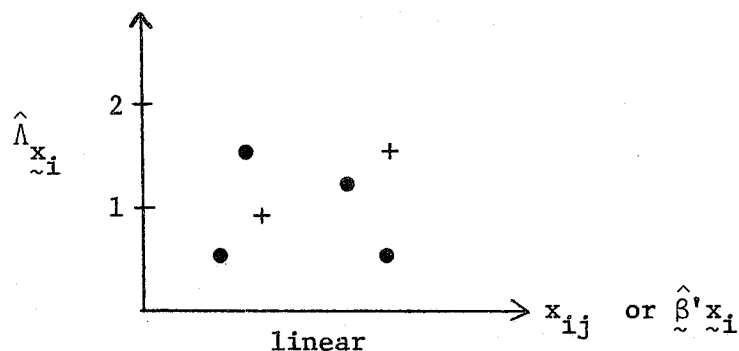
$$\hat{\Lambda}_i = \hat{\Lambda}_{\tilde{x}_i}(Y_i) = e^{\hat{\tilde{\beta}}'\tilde{x}_i} \int_0^{Y_i} \hat{\lambda}_0(u) du .$$

Let \hat{S} be the PL estimator based on $(\hat{\Lambda}_1, \delta_1), \dots, (\hat{\Lambda}_n, \delta_n)$. Under the proportional hazards model, $\log \hat{S}(t)$ should be approximately a linear function of t .



If the plot of $\log \hat{S}(t)$ against t is not linear, it may be difficult to guess what alternative model might be appropriate.

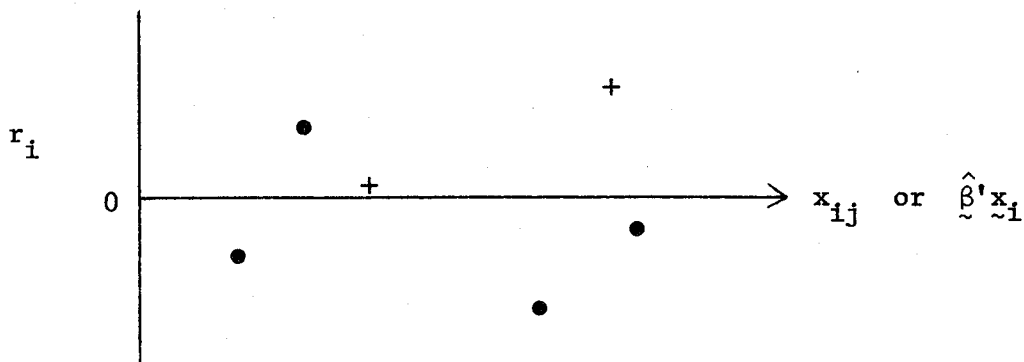
Under the proportional hazards model, $(\hat{\Lambda}_1, \delta_1), \dots, (\hat{\Lambda}_n, \delta_n)$ are censored observations of approximately iid random variables, so plotting $\hat{\Lambda}_i(t)$ against a particular covariate x_{ij} or against $\hat{\beta}'_{\sim i} x_{\sim i}$ should not reveal any systematic patterns. The estimates $\hat{\Lambda}_1, \dots, \hat{\Lambda}_n$ are called generalized residuals in the sense of Cox and Snell.



References:

- Cox and Snell, JRSS B (1968), discuss generalized residuals.
- Crowley and Hu, JASA (1977), plot generalized residuals for the Stanford heart transplant data.
- Kay, Appl. Stat. (JRSS C) (1977), discusses plotting generalized residuals.

To check the linear model, if the number of observations is large, partition the x -region into K subregions, and apply K -sample procedures. Alternatively, plot the residuals $r_i = y_i - \hat{\beta}'_{\sim i} x_{\sim i}$ against a particular covariate x_{ij} or against $\hat{\beta}'_{\sim i} x_{\sim i}$.



For both the proportional hazards and linear models the sensitivity of the residual plot to detecting the correct model effect of a particular covariate x_{ij} may be enhanced by computing the residuals without that covariate in the model.

B. Tests

1. One sample

We want to test

$$H_0 : F = F_0, \quad F_0 \text{ specified.}$$

(i) Generalized Kolmogorov (-Smirnov) test

Accept H_0 whenever

$$\sqrt{n} |\hat{F}(t) - F_0(t)| \leq \hat{C}_n(t) \quad \text{for all } t \geq 0,$$

where $\hat{F}(t)$ is the PL estimator and $\hat{C}_n(t)$ can be computed from tables. This test can be used to construct simultaneous confidence bands for $F_0(t)$:

$$P \left\{ \hat{F}(t) - \frac{\hat{C}_n(t)}{\sqrt{n}} \leq F_0(t) \leq \hat{F}(t) + \frac{\hat{C}_n(t)}{\sqrt{n}}, \quad \forall t \geq 0 \right\} = 1 - \alpha.$$

References:

Gillespie and Fisher, Ann. Stat. (1979), and
Hall and Wellner, Biometrika (1980), consider the PL
estimator and random censoring.
Barr and Davidson, Technometrics (1973), and
Koziol and Byar, Technometrics (1975), and
Dufour and Maag, Technometrics (1978), consider Type I
and Type II censoring.

(ii) Generalized Cramér-von Mises test

After performing a probability integral transformation so that
 $F_0(t) = t$, the uniform d.f., the generalized Cramér-von Mises test
uses the statistic

$$n \int_0^1 (\hat{F}(t) - t)^2 dt ,$$

where \hat{F} is the PL estimator.

References:

Koziol and Green, Biometrika (1976), consider the PL
estimator and random censoring.
Pettit and Stephens, Biometrika (1976), consider Type I
and Type II censoring. Pettit specializes to the
normal and exponential distributions in
Pettit, Biometrika (1976), and
_____, Biometrika (1977), respectively.

(iii) Mantel-Haenszel type test

Reference:

Hyde, Biometrika (1977).

(iv) Limit of Efron's test

Reference:

Hollander and Proschan, Biometrics (1979).

(v) Parametric families

Suppose we want to test

$$H_0 : F = F_\theta, \quad \theta \in \Theta.$$

The usual approach computes an estimate $\hat{\theta}$ and checks if \hat{F} is sufficiently close to $F_{\hat{\theta}}$.

Reference:

Mihalko and Moore, Ann. Stat. (1980), consider χ^2 -tests for Type II censoring with estimates which are asymptotically equivalent to linear combinations of order statistics.

If $\Theta_0 \subset \Theta$, and we want to test

$$H_0 : \theta \in \Theta_0,$$

then a likelihood ratio test is appropriate.

Reference:

Turnbull and Weiss, Biometrics (1978), consider likelihood ratio tests for discrete or grouped data.

2. Regression

(i) Parametric families

Imbed the model in a larger model (e.g., a model which includes quadratic or cubic effects or interactions) and test to see if the smaller model holds. In effect, we are testing $H_0 : \theta \in \Theta_0 \subset \Theta$.

(ii) χ^2 -tests

References:

Schoenfeld, Biometrika (1980), considers proportional hazards models with regions in the time \times covariate space.

Lamborn, Stanford Univ. Tech. Report No. 21 (1969), looks at χ^2 -tests for exponential regression.

VIII. Miscellaneous Topics

A. Bivariate Kaplan-Meier estimator

Let $\tilde{T}_i = (T_{i1}, T_{i2})$ be a pair of failure times. For example, they might be the times to failure of the left and right kidneys, or the times of cancer detection in the left and right breasts. Either or both times to failure may not be observable due to a one-dimensional random censoring variable C_i .

The observable quantities are

$$\tilde{Y}_i = (Y_{i1}, Y_{i2}) = (T_{i1} \wedge C_i, T_{i2} \wedge C_i)$$

and the indicator vector

$$\tilde{\delta} = (\delta_{i1}, \delta_{i2}) = (I(T_{i1} < C_i), I(T_{i2} < C_i)) .$$

Munoz has shown how to compute the two-dimensional generalization of the Kaplan-Meier estimator through the self-consistency and redistribute-to-the-right algorithms. In addition, he has established that this estimator is the generalized maximum likelihood estimator and that it is a consistent estimator of the bivariate d.f. $F(t_1, t_2) = P\{T_{i1} \leq t_1, T_{i2} \leq t_2\}$.

Campbell considers the model with bivariate censoring times and treats the grouped data situation. Also, Korwar treats bivariate grouped data with both left and right censoring.

References:

Muñoz, Stanford Univ. Tech. Report No. 60 (1980), defines the two-dimensional KM estimator through algorithms and proves it is the GMLE.

_____, Stanford Univ. Tech. Report No. 61 (1980), proves consistency of the two-dimensional estimator.

Campbell, Purdue Univ. Mimeoseries #79-25 (1979), and

Korwar, unpublished manuscript (1980), treat bivariate grouped data with censoring.

B. Competing risks

Let $\tilde{T}_i = (T_{i1}, \dots, T_{ip})$ be a p-dimensional vector of failure times. Each coordinate is the time to failure from a specific cause like, for example, heart failure, cancer, kidney failure, etc. The subject is observable only up to the time of the first failure. The failure times for all the other causes are censored by the failure of the system at the first failure time. The observable quantities are

$$T_i = \min\{T_{i1}, \dots, T_{ip}\}$$

and

$$\tilde{\delta}_i = (\delta_{i1}, \dots, \delta_{ip}) = (I(T_{i1} < T_i), \dots, I(T_{ip} < T_i)) .$$

The indicator vector $\tilde{\delta}$ denotes the specific cause of the failure.

The probability

$$P\{T_{ij} \leq t, \delta_{ij}=1\}$$

is called the crude probability of dying from the cause j by time t.

It is directly estimated by the observed proportion

$$\frac{1}{n} \sum_{i=1}^n I(T_{i-} \leq t, \delta_{ij}=1) .$$

The net probability is

$$P\{T_{ij-} \leq t\} ,$$

and if the causes are independent, this can be consistently estimated by the PL method where all failure times other than from cause j are considered to be censoring times. Partial crude probabilities consider the probability of dying by time t from one of a subset of possible causes.

A fundamental result in the theory of competing risks is that on the basis of the sample $T_i, \delta_i, i = 1, \dots, n$, it is impossible to tell whether

$$P\{T_{i1-} \leq t_1, \dots, T_{ip-} \leq t_p\} = \prod_{j=1}^p P\{T_{ij-} \leq t_j\}$$

or whether the failure times T_{i1}, \dots, T_{ip} are dependent. Different proofs of this result with varying conditions and degrees of rigor have appeared over the years. See the papers by Berman, Altshuler, Tsiatis, Peterson, and Langberg-Proschan-Quinzi.

References:

- Chiang, Intro. to Stochastic Processes in Biostatistics (1968), discusses the relationships between crude, net, and partial crude probabilities in Ch. 11.
- Moeschberger and David, Biometrics (1971), consider parametric likelihood methods.
- Gail, Biometrics (1975), is a review article.
- Prentice, et al., Biometrics (1978), review competing risks from the hazard rate point of view.

Berman, Ann. Math. Stat. (1963),
 Altshuler, Mathematical Biosciences (1970),
 Tsiatis, Proc. Natl. Acad. Sci. (1975),
 Peterson, Stanford Univ. Tech. Report No. 13 (1975),
 _____, Proc. Natl. Acad. Sci. (1976), and
 Langberg, Proschan, and Quinzi, Ann. Stat. (1981), examine the
 identifiability question.

C. Dependent censoring

Not much work has been done in the case where there is dependence between the failure times and the censoring times. Some of the work on dependent competing risks is relevant in this regard. Papers by Lagakos and Williams give some general discussion and results.

References:

Williams and Lagakos, Biometrika (1977).
 Lagakos and Williams, Biometrika (1978).
 Lagakos, Biometrics (1979).

D. Jackknifing and bootstrapping

Suppose that the parameter θ is a functional $T(F)$ of the d.f. F . In many instances θ is estimated by substituting the sample d.f. F_n for F in T , i.e., $\hat{\theta} = T(F_n)$. For a sample Y_1, \dots, Y_n , iid according to F , the jackknifed estimate $\tilde{\theta}$ of θ is defined as follows:

$$\tilde{\theta}_i = n\hat{\theta} - (n-1)\hat{\theta}_{-i}, \quad i = 1, \dots, n,$$

$$\tilde{\theta} = \frac{1}{n} \sum_{i=1}^n \tilde{\theta}_i = n\hat{\theta} - \frac{(n-1)}{n} \sum_{i=1}^n \hat{\theta}_{-i},$$

where $\hat{\theta}_{-i} = T(F_{n-1,-i})$ is the estimate of θ with the i th observation Y_i deleted from the sample.

When no censoring is present, it has been established that for sufficiently smooth T

$$\frac{\tilde{\theta} - \theta}{\sqrt{\frac{1}{n(n-1)} \sum_1^n (\tilde{\theta}_i - \tilde{\theta})^2}} \stackrel{a}{\sim} N(0,1) . \quad (18)$$

For confirmation of (18) in a variety of circumstances see Miller's 1974 review paper. Miller has also shown that (18) holds for randomly censored data with $\hat{\theta} = T(\hat{F})$ where \hat{F} is the PL estimator.

The smoothness in T necessary for (18) to hold is connected with the smoothness of the influence function

$$IC(y; F) = \lim_{\epsilon \rightarrow 0} \frac{T((1-\epsilon)F + \epsilon \delta_y) - T(F)}{\epsilon} ,$$

where δ_y is the d.f. which puts mass one at y . For uncensored data the jackknife and influence function are related by

$$(n-1)(\hat{\theta} - \hat{\theta}_{-i}) = \left. \frac{T((1-\epsilon)F + \epsilon \delta_y) - T(F)}{\epsilon} \right|_{\epsilon = -1/(n-1), F=F_n, y=y_i} .$$

For censored data Reid has worked out the influence functions (i.e., partial derivatives with respect to F_u and F_c) for a function of the PL estimator.

Efron's bootstrapping is accomplished in the following manner. Let Y_1^*, \dots, Y_n^* be a sample with replacement from y_1, \dots, y_n when no censoring is present, and with censoring let $(Y_1^*, \delta_1^*), \dots, (Y_n^*, \delta_n^*)$ be a sample with replacement from $(y_1, \delta_1), \dots, (y_n, \delta_n)$. Then F_n^* or F^* are the bootstrap sample distribution function or PL estimator, respectively, and $\hat{\theta}^* = T(F_n^*)$ or $T(F^*)$. This sampling procedure is repeated N times to

produce $\hat{\theta}_1^*, \dots, \hat{\theta}_N^*$. The empirical distribution of $\hat{\theta}_1^*, \dots, \hat{\theta}_N^*$ is used to approximate the distribution of $\hat{\theta}$. More specifically, with pivotal quantities the empirical distribution of $\hat{\theta}^* - \hat{\theta}$ is used as an approximation to the distribution of $\hat{\theta} - \theta$.

References:

Miller, Biometrika (1974), reviews the jackknife for uncensored data problems.

_____, Stanford Univ. Tech. Report No. 14 (1975), establishes the validity of jackknifing the PL estimator.

Reid, Stanford Univ. Tech. Report No. 46 (1979) or Ann. Stat. (1981), derives the influence functions for the PL estimator.

Efron, Ann. Stat. (1979), introduces bootstrapping for uncensored data problems.

_____, Stanford Univ. Tech. Report No. 53 (1980), studies bootstrapping censored data in general and the median in particular.

IX. Problems

- ①. Prove that the gamma distribution has IFR for $\alpha > 1$ and DFR for $\alpha < 1$.

Answer:

$$\begin{aligned} \frac{1}{\lambda(t)} &= \frac{\int_t^{\infty} x^{\alpha-1} e^{-\lambda x} dx}{t^{\alpha-1} e^{-\lambda t}}, \\ &= \int_t^{\infty} \left(\frac{x}{t}\right)^{\alpha-1} e^{-\lambda(x-t)} dx, \\ &= \int_0^{\infty} \left(1 + \frac{u}{t}\right)^{\alpha-1} e^{-\lambda u} du. \quad (\text{change of variable: } u=x-t). \end{aligned}$$

If $\alpha > 1$,

$\left(1 + \frac{u}{t}\right)^{\alpha-1}$ is decreasing in t ,

so $\lambda(t)$ is increasing. For $\alpha < 1$ the integrand is increasing in t so $\lambda(t)$ is decreasing.

- ②. Derive the Fisher information for one observation from an exponential distribution with Type I censoring.

Answer:

Let t_c be the fixed censoring time. The log of the likelihood is

$$\delta \log \lambda - \delta \lambda y - (1-\delta)\lambda t_c.$$

Differentiating twice with respect to λ one gets

$$-\frac{\delta}{\lambda^2},$$

so the Fisher information is

$$I(\lambda) = \frac{1}{\lambda^2} E(\delta) = \frac{1}{\lambda^2} P\{T \leq t_c\} = \frac{1}{\lambda^2} (1 - e^{-\lambda t_c}).$$

- ③. Derive the sample information matrix for the Weibull distribution under random censoring.

Answer:

From page 20,

$$\frac{\partial}{\partial \gamma} \log L = \frac{n_u}{\gamma} - \sum_{i=1}^n y_i^\alpha ,$$

$$\frac{\partial}{\partial \alpha} \log L = \frac{n_u}{\alpha} + \sum_u \log t_i - \gamma \sum_{i=1}^n y_i^\alpha \log y_i .$$

The sample information matrix at (γ, α) is given by

$$- \begin{bmatrix} \frac{\partial^2}{\partial \gamma^2} \log L & \frac{\partial^2}{\partial \gamma \partial \alpha} \log L \\ \frac{\partial^2}{\partial \alpha^2} \log L \end{bmatrix} = \begin{bmatrix} \frac{1}{\gamma^2} n_u & \sum_{i=1}^n y_i^\alpha (\log y_i) \\ \sum_{i=1}^n y_i^\alpha (\log y_i)^2 & \frac{1}{\alpha^2} n_u + \gamma \sum_{i=1}^n y_i^\alpha (\log y_i)^2 \end{bmatrix} .$$

- ④. From February 1972 to February 1975, 29 severe viral hepatitis patients satisfied the admission criteria for a 16 week study of the effects of steroid therapy at the Stanford, VA, and Santa Clara Valley Hospitals and were randomized into either the steroid or control group. The survival times (in weeks) of the 14 patients in the steroid group were

1, 1, 1, 1+, 4+, 5, 7, 8, 10, 10+, 12+, 16+, 16+, 16+ .

Assume an exponential distribution $S(t) = \exp(-\lambda t)$.

- Estimate λ by maximum likelihood and construct an approximate 95% confidence interval.
- Estimate $S(16)$ and construct an approximate 95% confidence interval.
- Estimate the median survival time and construct an approximate 95% confidence interval.

Reference:

Gregory et al., New England Journal of Medicine (1976).

Answer:

(a) From page 16,

$$\hat{\lambda} = \frac{n_u}{\sum_{i=1}^n y_i} = \frac{7}{108} = .065 .$$

From page 19,

$$\log \hat{\lambda} \overset{a}{\sim} N(\log \lambda, \frac{1}{n_u}) .$$

Then a 95% C.I. is given by

$$(\hat{\lambda} \exp(-Z_{.025}/\sqrt{n_u}), \hat{\lambda} \exp(Z_{.025}/\sqrt{n_u})) = (.031, .136) .$$

$$(b) \hat{S}(16) = \exp(-\hat{\lambda} \times 16) = .355 .$$

A 95% C.I. is given by

$$(e^{-.136 \times 16}, e^{-.031 \times 16}) = (.113, .609) .$$

$$(c) \hat{t}_{med} = (\log 2)/\hat{\lambda} = 10.69 .$$

A 95% C.I. is given by

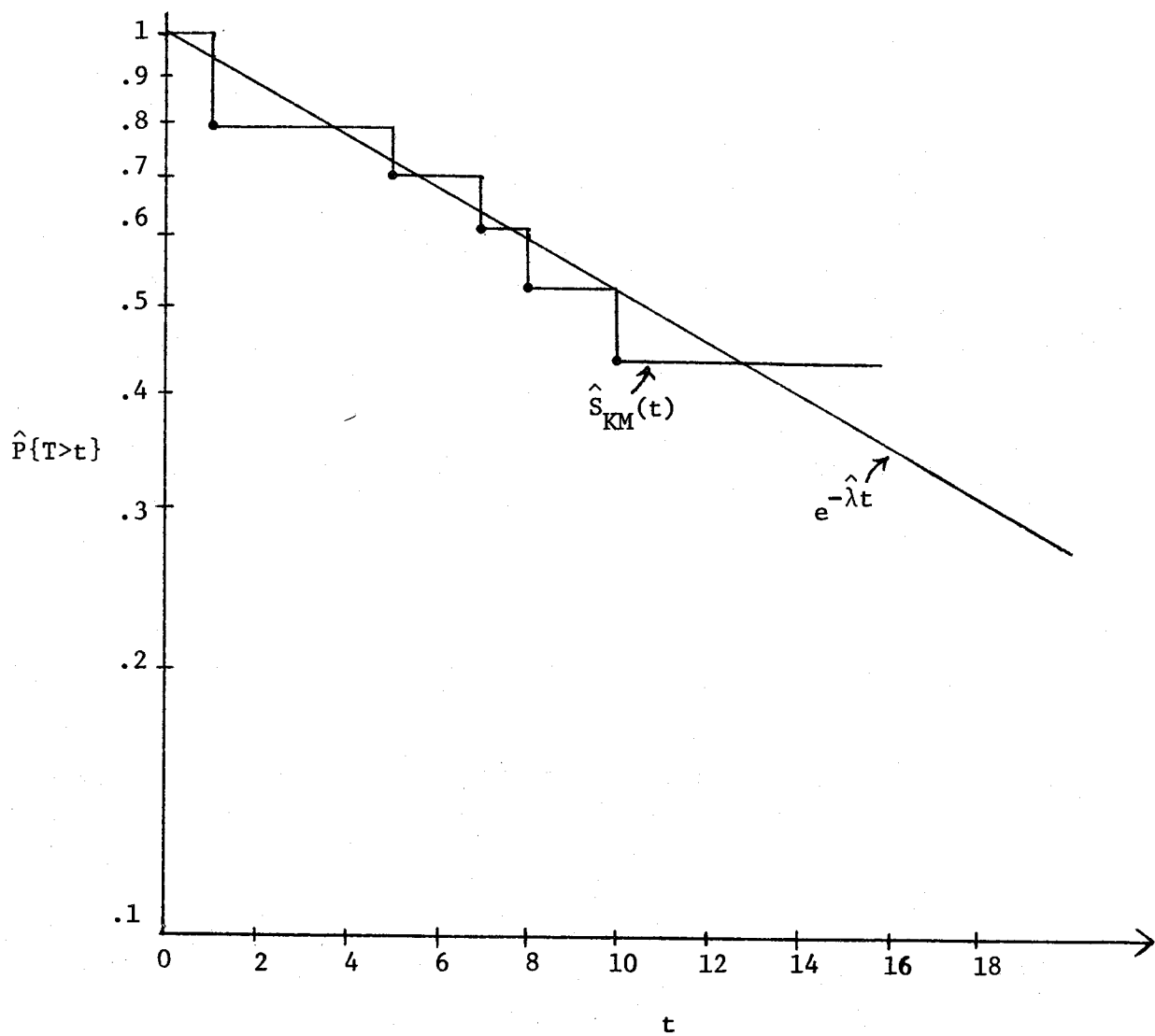
$$((\log 2)/.136, (\log 2)/.031) = (5.097, 22.36) .$$

- ⑤ For the severe viral hepatitis data compute the Kaplan-Meier product-limit estimate of the survival function. Graph it and the survival function estimated under the exponential assumption on the same log × linear graph paper. Do you think the assumption of an exponential distribution over the 16 week interval is justified?

Answer:

$$\hat{S}(t) = \begin{cases} 1 & 0 \leq t < 1 \\ 11/14 = .786 & 1 \leq t < 5 \\ 11 \times 8 / 14 \times 9 = .7 & 5 \leq t < 7 \\ 11 \times 7 / 14 \times 9 = .61 & 7 \leq t < 8 \\ 11 \times 6 / 14 \times 9 = .524 & 8 \leq t < 10 \\ 11 \times 5 / 14 \times 9 = .436 & 10 \leq t < 16 \end{cases} \quad \text{for}$$

The graphs follow.



"Democratic" goodness of fit results: out of 21 student papers, 15 were in favor of the exponential, 5 were not, and 1 did not answer.

- ⑥ For the life table from Cutler and Ederer (Table 1, p. 31) compute the approximate standard error of $\hat{S}(5)$.

Answer:

Using Greenwood's formula

$$\begin{aligned}\widehat{\text{Var}}(\hat{S}(5)) &\approx (.44)^2 \left[\frac{47}{116.5(116.5-47)} + \frac{5}{51.5(51.5-5)} \right. \\ &\quad \left. + \frac{2}{30.5(30.5-2)} + \frac{2}{16.5(16.5-2)} + \frac{0}{7(7-0)} \right], \\ &= .003608 ,\end{aligned}$$

so

$$\widehat{\text{SE}}(\hat{S}(5)) \approx .06 .$$

- ⑦ For the Embury et al. length of remission AML data (Example, p. 37) compute the approximate standard error of $\hat{S}(24)$ in the maintained group.

Answer:

Using Greenwood's formula

$$\begin{aligned}\widehat{\text{Var}}(\hat{S}(24)) &= \left(\frac{6 \times 9}{11 \times 8}\right)^2 \left(\frac{1}{10 \times 11} + \frac{1}{9 \times 10} + \frac{1}{7 \times 8} + \frac{1}{6 \times 7}\right) , \\ &= .02329 ,\end{aligned}$$

so

$$\widehat{\text{SE}}(\hat{S}(24)) = .1526 .$$

- ⑧ Show that in the proof that the PL estimator is the GMLE, the maximum of

$$\prod_{i=1}^n p_i^{\delta(i)} \left(\sum_{j=i}^n p_j \right)^{1-\delta(i)}$$

is attained for

$$p_i = \frac{\delta(i)}{n-i+1} \prod_{j=1}^{i-1} \left(1 - \frac{\delta(j)}{n-j+1}\right) .$$

Answer:

Let

$$\lambda_i = \frac{p_i}{\sum_{j=i}^n p_j} , \quad i = 1, \dots, n .$$

Then, since $1 - \lambda_i = \sum_{j=i+1}^n p_j / \sum_{j=i}^n p_j$ and $\sum_{j=1}^n p_j = 1$, we have

$$\sum_{j=i}^n p_j = \prod_{j=1}^{i-1} (1 - \lambda_j) ,$$

and since $\lambda_n = 1$, we get

$$\begin{aligned} \prod_{i=1}^n p_i^{\delta(i)} \left(\sum_{j=i}^n p_j \right)^{1-\delta(i)} &= \prod_{i=1}^n \lambda_i^{\delta(i)} \prod_{j=1}^{i-1} (1 - \lambda_j) , \\ &= \prod_{i=1}^{n-1} \lambda_i^{\delta(i)} (1 - \lambda_i)^{n-i} . \end{aligned}$$

It is well known from binomial sampling theory that each product is maximized by

$$\hat{\lambda}_i = \frac{\delta(i)}{n-i+\delta(i)} = \frac{\delta(i)}{n-i+1} .$$

Hence,

$$\hat{p}_i = \hat{\lambda}_i \left(\sum_{j=i}^n \hat{p}_j \right) = \hat{\lambda}_i \prod_{j=1}^{i-1} (1 - \hat{\lambda}_j) = \frac{\delta(i)}{n-i+1} \prod_{j=1}^{i-1} \left(1 - \frac{\delta(j)}{n-j+1}\right) .$$

9. Prove that the redistribute-to-the-right algorithm gives the Kaplan-Meier product-limit estimator. Assume no ties.

Answer:

There are two principal ways of proving this result.

(1) With the redistribute-to-the-right algorithm, all points $y_{(i)}$, censored or uncensored, initially have equal mass $1/n$. The algorithm moves from left to right through the order statistics. When it reaches $y_{(i)}^-$, all the remaining points $y_{(i)}, y_{(i+1)}, \dots, y_{(n)}$ have equal mass on them due to the way the algorithm operates. Suppose the total remaining mass is $\tilde{S}(y_{(i)}^-)$. By the equality of the masses $y_{(i)}$ has $\tilde{S}(y_{(i)}^-)/(n-i+1)$ assigned to it, which it will keep if it is uncensored. If it is censored, this mass is distributed to the right.

Since the PL estimator \hat{S} starts at 1 as does \tilde{S} and has jumps of sizes $\hat{S}(y_{(i)}^-)/(n-i+1)$ at the uncensored observations and zero at the censored observations, the two estimators are identical.

(2) For the Kaplan-Meier estimator

$$\begin{aligned}
 \hat{\Delta}_{(i)} &= \hat{S}(y_{(i)}^-) - \hat{S}(y_{(i)}) , \\
 &= \prod_{j=1}^{i-1} \left(\frac{n-j}{n-j+1} \right)^{\delta(j)} - \prod_{j=1}^i \left(\frac{n-j}{n-j+1} \right)^{\delta(j)} , \\
 &= \prod_{j=1}^{i-1} \left(\frac{n-j}{n-j+1} \right)^{\delta(j)} \frac{\delta(i)}{n-i+1} , \\
 &= \prod_{j=1}^{i-1} \left(\frac{n-j+1}{n-j} \right)^{-\delta(j)} \times \frac{1}{n} \times \frac{n}{n-1} \times \dots \times \frac{n-i+2}{1} \times \frac{\delta(i)}{n-i+1} , \\
 &= \frac{\delta(i)}{n} \prod_{j=1}^{i-1} \left(\frac{n-j+1}{n-j} \right)^{1-\delta(j)} .
 \end{aligned}$$

Let $j_1 < j_2 < \dots < j_i$ be the indices of the censored observations which precede $y_{(i)}$. For the redistribute-to-the-right algorithm the mass assigned to $y_{(i)}$ if $\delta_{(i)} = 1$ is

$$\begin{aligned}\tilde{\Delta}_{(i)} &= \frac{1}{n} \left(1 + \frac{1}{n-j_1}\right) \left(1 + \frac{1}{n-j_2}\right) \dots \left(1 + \frac{1}{n-j_i}\right), \\ &= \frac{1}{n} \prod_{j=1}^{i-1} \left(\frac{n-j+1}{n-j}\right)^{1-\delta_{(j)}},\end{aligned}$$

and if $\delta_{(i)} = 0$, $\tilde{\Delta}_{(i)} = 0$. This is identical to $\hat{\Delta}_{(i)}$ above, so the redistribute-to-the-right algorithm gives the PL estimator.

(10) Given that for the PL estimator $\hat{S}(t)$

$$\text{ACov}(\hat{S}(t_1), \hat{S}(t_2)) = \frac{S(t_1) S(t_2)}{n} \int_0^{t_1 \wedge t_2} \frac{dF_u(s)}{(1-H(s))^2},$$

show that for $\hat{\mu} = \int_0^\infty \hat{S}(t) dt$

$$\text{AVar}(\hat{\mu}) = \frac{1}{n} \int_0^\infty \frac{1}{(1-H(s))^2} \left(\int_s^\infty S(t) dt \right)^2 dF_u(s).$$

Answer:

$$\begin{aligned}\text{Var}(\hat{\mu}) &= E(\hat{\mu}^2) - (E(\hat{\mu}))^2, \\ &= E\left(\int_0^\infty \int_0^\infty \hat{S}(t_1) \hat{S}(t_2) dt_1 dt_2\right) - \left(E\left(\int_0^\infty \hat{S}(t) dt\right)\right)^2, \\ &= \int_0^\infty \int_0^\infty \text{Cov}(\hat{S}(t_1), \hat{S}(t_2)) dt_1 dt_2,\end{aligned}$$

so

$$\text{AVar}(\hat{\mu}) = \frac{1}{n} \int_0^\infty \int_0^\infty S(t_1) S(t_2) \int_0^{t_1 \wedge t_2} \frac{dF_u(s)}{(1-H(s))^2} dt_1 dt_2.$$

By interchanging integrals (applying Fubini's theorem)

$$\begin{aligned} \text{AVar}(\hat{\mu}) &= \frac{1}{n} \int_0^\infty \frac{1}{(1-H(s))^2} \int_s^\infty S(t_1) dt_1 \int_s^\infty S(t_2) dt_2 dF_u(s) , \\ &= \frac{1}{n} \int_0^\infty \frac{1}{(1-H(s))^2} \left(\int_s^\infty S(t) dt \right)^2 dF_u(s) . \end{aligned}$$

- (11) For the Embury et al. AML data in the non-maintained group (p.37), i.e.,
5, 5, 8, 8, 12, 16+, 23, 27, 30, 33, 43, 45 weeks,
compute (a) $\hat{\mu}$ and (b) $\hat{\text{Var}}(\hat{\mu})$.

Answer:

- (a) The Kaplan-Meier estimator $\hat{S}(t)$ is given by

t	[0,5)	[5,8)	[8,12)	[12,23)	[23,27)	[27,30)	[30,33)	[33,43)	[43,45)	[45,∞)
$\hat{S}(t)$	1	$\frac{10}{12}$	$\frac{8}{12}$	$\frac{7}{12}$	$\frac{7 \times 5}{12 \times 6}$	$\frac{7 \times 4}{12 \times 6}$	$\frac{7 \times 3}{12 \times 6}$	$\frac{7 \times 2}{12 \times 6}$	$\frac{7 \times 1}{12 \times 6}$	0

so

$$\begin{aligned} \hat{\mu} &= \int_0^\infty \hat{S}(t) dt , \\ &= 1 \times 5 + \frac{10}{12} \times 3 + \frac{8}{12} \times 4 + \frac{7}{12} \times 11 + \frac{7 \times 5}{12 \times 6} \times 4 + \\ &\quad + \frac{7 \times 4}{12 \times 6} \times 3 + \frac{7 \times 3}{12 \times 6} \times 3 + \frac{7 \times 2}{12 \times 6} \times 10 + \frac{7 \times 1}{12 \times 6} \times 2 , \\ &= 22.71 . \end{aligned}$$

$$\begin{aligned}
(b) \quad \hat{\text{Var}}(\hat{\mu}) &= \sum_u \left(\int_{y(i)}^{\infty} \hat{S}(t) dt \right)^2 \frac{d_i}{n_i(n_i - d_i)} , \\
&= (17.71)^2 \frac{2}{12 \times 10} + (15.21)^2 \frac{2}{10 \times 8} + (12.54)^2 \frac{1}{8 \times 7} \\
&\quad + (6.125)^2 \frac{1}{6 \times 5} + (4.18)^2 \frac{1}{5 \times 4} + (3.01)^2 \frac{1}{4 \times 3} \\
&\quad + (2.14)^2 \frac{1}{3 \times 2} + (.19)^2 \frac{1}{2 \times 1} , \\
&= 17.47 .
\end{aligned}$$

(12) For the Gregory et al. severe viral hepatitis data the steroid (I) and control (II) groups survival times (in weeks) are

I: 1, 1, 1, 1+, 4+, 5, 7, 8, 10, 10+, 12+, 16+, 16+, 16+ ,

II: 1+, 2+, 3, 3, 3+, 5+, 5+, 16+(8) ,

with $m = 14$, $n = 15$. Compute

- (a) the Gehan statistic,
- (b) its permutation variance, and
- (c) the normalized statistic and P-value.

Reference:

Gregory et al., New England Journal of Medicine (1976).

Answer:

The table in which the U^* scores are computed is

Z	Group	#<Z	#>Z	U*
1(3)	I	0	26	-26(3)
1+	I	3	0	3
1+	II	3	0	3
2+	II	3	0	3
3(2)	II	3	21	-18(2)
3+	II	5	0	5
4+	I	5	0	5
5	I	5	18	-13
5+(2)	II	6	0	6(2)
7	I	6	15	-9
8	I	7	14	-7
10	I	8	13	-5
10+	I	9	0	9
12+	I	9	0	9
16+(3)	I	9	0	9(3)
16+(8)	II	9	0	9(8)

(a) The Gehan statistic is

$$\sum_{II} U^* = 59 .$$

(b) Its permutation variance is

$$\frac{14 \times 15}{29 \times 28} \sum_{I, II} (U^*)^2 = 1086.72 .$$

(c) The normalized statistic is

$$\frac{59}{\sqrt{1086.72}} = 1.79 ,$$

which corresponds to a one-sided P-value of .0375.

- ⑬ For the Gregory et al. severe viral hepatitis data (p. 147) compute
- (a) the Mantel-Haenszel statistic and its associated P-value, and
- (b) the Tarone-Ware version of the Gehan statistic and its associated P-value.

Answer:

As on page 74,

z	n	m ₁	n ₁	a	E ₀ (A)	a-E ₀ (A)	n(a-E ₀ (A))	$\frac{m_1(n-m_1)}{n-1}$	$\frac{n_1}{n}(1-\frac{n_1}{n})$	n ₁ (n-n ₁)
1	29	3	14	3	1.448	1.552	45	2.786	.2497	210
3	23	2	10	0	.869	-.869	-20	1.909	.2457	130
5	19	1	9	1	.474	.526	10	1	.2493	90
7	16	1	8	1	.500	.500	8	1	.2500	64
8	15	1	7	1	.467	.533	8	1	.2489	56
10	14	1	6	1	.428	.572	8	1	.2449	48

(a)

$$\begin{aligned}
 \text{MH} &= \frac{\text{sum of } a-E_0(A) \text{ column}}{\sqrt{\text{sum of } \left(\frac{m_1(n-m_1)}{n-1} \text{ column times } \frac{n_1}{n} \left(1 - \frac{n_1}{n} \right) \text{ column} \right)}} , \\
 &= \frac{2.814}{\sqrt{2.1578}} = 1.916 ,
 \end{aligned}$$

so the one-sided P-value = .027 .

(b) Let U_{TW} denote the Tarone-Ware version of the Gehan statistic.

$$\begin{aligned}
 U_{TW} &= \frac{\text{sum of } n(a-E_0(A)) \text{ column}}{\sqrt{\text{sum of } \left(\frac{m_1(n-m_1)}{n-1} \text{ column times } n_1(n-n_1) \text{ column} \right)}} , \\
 &= \frac{59}{\sqrt{1091.23}} = 1.786 ,
 \end{aligned}$$

so the one-sided P-value = .037 .

14. As a prototype problem, consider the following five points from the Stanford heart transplant data:

<u>Mismatch Score (X)</u>	<u>Survival Time (Y)</u>
2.09	54
.36	127+
.60	297
1.44	389+
.91	1536+

- (a) Test the hypothesis $H_0: \beta = 1$ in the proportional hazards model by calculating the P-value associated with the Cox statistic

$$\frac{\left(\frac{\partial}{\partial \beta} \log L_c(1) \right)^2}{-\frac{\partial^2}{\partial \beta^2} \log L_c(1)} .$$

- (b) Compute the Tsiatis/Link estimate of $S(t; x)$ for $x = 1.5$ and $0 \leq t \leq 297$ using $\beta = 1$.

Answer:

- (a) Let

$i: \quad 1 \quad 2 \quad 3 \quad 4 \quad 5$

$x_i: 2.09 \quad .36 \quad .60 \quad 1.44 \quad .91 .$

From the expression at the bottom of page 91

$$\begin{aligned} \frac{\partial}{\partial \beta} \log L_c(1) &= x_1 + x_3 - \frac{\sum_{j=1}^5 x_j e^{x_j}}{\sum_{j=1}^5 e^{x_j}} - \frac{\sum_{j=3}^5 x_j e^{x_j}}{\sum_{j=3}^5 e^{x_j}} , \\ &= .0965 . \end{aligned}$$

From page 92

$$-\frac{\partial^2}{\partial \beta^2} \log L_c(1) = \frac{\sum_{j=1}^5 x_j^2 e^{x_j}}{\sum_{j=1}^5 e^{x_j}} - \left(\frac{\sum_{j=1}^5 x_j e^{x_j}}{\sum_{j=1}^5 e^{x_j}} \right)^2 + \frac{\sum_{j=3}^5 x_j^2 e^{x_j}}{\sum_{j=3}^5 e^{x_j}} - \left(\frac{\sum_{j=3}^5 x_j e^{x_j}}{\sum_{j=3}^5 e^{x_j}} \right)^2,$$

$$= .5110 .$$

Thus,

$$\frac{\left(\frac{\partial}{\partial \beta} \log L_c(1) \right)^2}{-\frac{\partial^2}{\partial \beta^2} \log L_c(1)} = .018$$

and, since $\chi_1^2(.9) = .0158$, the P-value is approximately .9.

(b) The Tsiatis estimate (see page 99) is

$$\hat{\Lambda}_{0,T}(t) = \begin{cases} 1 & \text{for } 0 \leq t < 54 , \\ \frac{1}{\sum_{j=1}^5 e^{x_j}} = .0554 & \text{for } 54 \leq t < 297 , \\ \frac{1}{\sum_{j=1}^5 e^{x_j}} + \frac{1}{\sum_{j=3}^5 e^{x_j}} = .1727 & \text{for } 297 = t , \end{cases}$$

so

$$\hat{S}_T(t; 1.5) = e^{-\hat{\Lambda}_{0,T}(t)e^{1.5}} = \begin{cases} 1 & \text{for } 0 \leq t < 54 , \\ .78 & \text{for } 54 \leq t < 297 , \\ .46 & \text{for } t = 297 . \end{cases}$$

The Link estimate (see pages 99 and 100) is

$$\hat{\Lambda}_{0,L}(t) = \begin{cases} \frac{.0554}{54} t & \text{for } 0 \leq t < 54, \\ \frac{.1727 - .0554}{297 - 54} (t - 54) + .0554 & \text{for } 54 \leq t \leq 297, \end{cases}$$

so

$$\hat{S}_L(t; 1.5) = e^{-\hat{\Lambda}_{0,L}(t)e^{1.5}} = \begin{cases} e^{-.0046t} & \text{for } 0 \leq t < 54, \\ .877 e^{-.0022t} & \text{for } 54 \leq t \leq 297. \end{cases}$$

(15) For the Embury et al. AML data

Maintained Group

9, 13, 13+, 18, 23, 28+, 31, 34, 45+, 48, 161+

Non-Maintained Group

5, 5, 8, 8, 12, 16+, 23, 27, 30, 33, 43, 45

compare the two groups by

- (a) the Gehan statistic and the Mantel permutation variance,
- (b) the Mantel-Haenszel statistic, and
- (c) the Tarone-Ware version of the Gehan statistic.

In each case obtain the normalized statistic and its associated two-sided P-value.

Answer:

(a) For the computation of the scores needed to perform the Gehan statistic the following table is useful.

Z	Group	# < Z	# > Z	U*
5(2)	NM	0	21	-21(2)
8(2)	NM	2	19	-17(2)
9	M	4	18	-14
12	NM	5	17	-12
13	M	6	16	-10
13+	M	7	0	7
16+	NM	7	0	7
18	M	7	13	-6
23	M	8	11	-3
23	NM	8	11	-3
27	NM	10	10	0
28+	M	11	0	11
30	NM	11	8	3
31	M	12	7	5
33	NM	13	6	7
34	M	14	5	9
43	NM	15	4	11
45	NM	16	3	13
45+	M	17	0	17
48	M	17	1	16
161+	M	18	0	18

The Gehan statistic is

$$\sum_{NM} U^* = -50 ,$$

and the Mantel permutation variance is

$$\frac{11 \times 12}{23 \times 22} \sum_{M, NM} (U^*)^2 = 912 ,$$

so the normalized statistic is

$$\frac{-50}{\sqrt{912}} = -1.656 ,$$

which corresponds to a two-sided P-value of .098.

(b) and (c) As in problem (13):

z	n	m ₁	n ₁	a	E ₀ (A)	a-E ₀ (A)	n(a-E ₀ (A))	$\frac{m_1(n-m_1)}{n-1}$	$\frac{n_1}{n}(1-\frac{n_1}{n})$	n ₁ (n-n ₁)
5	23	2	11	0	.9565	-.9565	-22	1.909	.2495	132
8	21	2	11	0	1.048	-1.048	-22	1.9	.2494	110
9	19	1	11	1	.579	.42	8	1	.2437	88
12	18	1	10	0	.555	-.555	-10	1	.2469	80
13	17	1	10	1	.588	.412	7	1	.2422	70
18	14	1	8	1	.571	.428	6	1	.2449	48
23	13	2	7	1	1.077	-.077	-1	1.83	.2485	42
27	11	1	6	0	.545	-.545	-6	1	.2479	30
30	9	1	5	0	.555	-.555	-5	1	.2469	20
31	8	1	5	1	.625	.375	3	1	.2344	15
33	7	1	4	0	.571	-.571	-4	1	.2449	12
34	6	1	4	1	.667	.333	2	1	.2222	8
43	5	1	3	0	.6	-.6	-3	1	.2400	6
45	4	1	3	0	.75	-.75	-3	1	.1875	3
48	2	1	2	1	1.0	0	0	1	0	0

The Mantel-Haenszel normalized statistic is (see Answer to problem (13))

$$\frac{-3.69}{\sqrt{4.0072}} = -1.84 ,$$

so the two-sided P-value = .066.

The Tarone-Ware version of the Gehan statistic is (see Answer to problem (13))

$$\frac{-50}{\sqrt{917.97}} = -1.65 ,$$

so the two-sided P-value = .099.

(16) Prove that the numerator in the Tarone-Ware version of the Gehan statistic (i.e., $\sum n_i(a_i - E_0(A_i))$) equals the numerator of the Gehan statistic

as defined by Gehan (i.e., $U = \sum \sum U_{ij}$), except possible for a factor of -1. Allow for ties.

Answer:

From page 65

$$U = \sum_{k=1}^{m+n} U_k^* I(k \in I_1) ,$$

where

$$U_k^* = \sum_{\substack{\ell=1 \\ \ell \neq k}}^{m+n} U_{k\ell} ,$$

so if the observation with label k in sample 1 is uncensored, then U_k^* is equal to the number of uncensored observations before it minus the number of observations after it.

$$\begin{aligned} U_k^* &= \sum_{j=1}^{k-1} m_{j1} - (n_k - m_{k1}) , \\ &= \sum_{j=1}^k m_{j1} - n_k \quad (\text{see page 72 for notation}). \end{aligned}$$

On the other hand, if the observation k is censored, then U_k^* is the number of uncensored observations before it.

$$U_k^* = \sum_{j=1}^k m_{j1} .$$

Therefore,

$$U = \sum_c \sum_{k=1}^{m+n} \sum_{j=1}^k m_{j1} I(k \in I_1) + \sum_u \sum_{k=1}^{m+n} \left(\sum_{j=1}^k m_{j1} - n_k \right) I(k \in I_1) ,$$

where c and u mean the sums are performed over censored and uncensored observations, respectively.

Thus,

$$\begin{aligned}
U &= \sum_{k=1}^{m+n} \sum_{j=1}^k m_{j1} I(k \in I_1) - \sum_{k=1}^{m+n} n_k I(k \in I_1, \delta_k = 1) , \\
&= \sum_{j=1}^{m+n} m_{j1} \sum_{k=j}^{m+n} I(k \in I_1) - \sum_{k=1}^{m+n} n_k a_k , \\
&= \sum_{j=1}^{m+n} (m_{j1} n_{j1} - n_j a_j) , \\
&= \sum_u (m_{j1} n_{j1} - n_j a_j) , \\
&= - \sum_u n_j (a_j - E_0(A_j)) ,
\end{aligned}$$

where the next to the last equality follows from the fact that m_j (hence a_j), which is the number of uncensored observations at z_j , is zero if z_j is a censored observation. (Recall the convention that ties between censored and uncensored observations are broken by considering the censored observations to be larger.)

- (17) Show that Mantel's permutation variance for the Gehan statistic, divided by $N^3 = (m+n)^3$, i.e.,

$$\frac{1}{N^3} \times \frac{mn}{(m+n)(m+n-1)} \sum_{i=1}^{m+n} (U_i^*)^2 ,$$

converges to

$$\lambda(1-\lambda) \int_0^\infty (1-H(t))^2 dH_u(t)$$

as $N \rightarrow \infty$, $m/N \rightarrow \lambda$ under the null hypothesis $H_0^*: F_1 = F_2; G_1 = G_2$, where

$$H(t) = P\{Z \leq t\} = \int_0^t (1-G(u))dF(u) + \int_0^t (1-F(u))dG(u) ,$$

$$H_u(t) = P\{Z \leq t, \zeta=1\} = \int_0^t (1-G(u))dF(u) ,$$

and F and G are continuous.

Answer:

Let

$$\hat{H}(t) = \frac{1}{N} \sum_{i=1}^N I(Z_{i-} \leq t) ,$$

$$\hat{H}_u(t) = \frac{1}{N} \sum_{i=1}^N I(Z_{i-} \leq t, \zeta_i=1) .$$

Then,

$$U_i^* = \begin{cases} \#(\text{uncensored obs.} < Z_i) - \#(\text{obs.} > Z_i) & \text{if } \zeta_i = 1 , \\ \#(\text{uncensored obs.} < Z_i) & \text{if } \zeta_i = 0 , \end{cases}$$

$$= \begin{cases} N \hat{H}_u(Z_{i-}) - N(1-\hat{H}(Z_i)) & \text{if } \zeta_i = 1 , \\ N \hat{H}_u(Z_{i-}) & \text{if } \zeta_i = 0 , \end{cases}$$

$$= N[\hat{H}_u(Z_{i-}) - \zeta_i(1-\hat{H}(Z_i))] .$$

Consequently,

$$\begin{aligned} \frac{1}{N^3} \sum_{i=1}^N (U_i^*)^2 &= \frac{1}{N^3} \sum_{i=1}^N N^2 [\hat{H}_u(Z_{i-}) - \zeta_i(1-\hat{H}(Z_i))]^2 , \\ &= \frac{1}{N} \sum_{i=1}^N \hat{H}_u^2(Z_{i-}) - \frac{2}{N} \sum_{i=1}^N \zeta_i \hat{H}_u(Z_{i-})(1-\hat{H}(Z_i)) \\ &\quad + \frac{1}{N} \sum_{i=1}^N \zeta_i (1-\hat{H}(Z_i))^2 , \end{aligned}$$

$$\begin{aligned}
&= \int_0^\infty \hat{H}_u^2(t-) d\hat{H}(t) - 2 \int_0^\infty \hat{H}_u(t-) (1-\hat{H}(t)) d\hat{H}_u(t) \\
&\quad + \int_0^\infty (1-\hat{H}(t))^2 d\hat{H}_u(t) .
\end{aligned}$$

Since $\hat{H}(t) \rightarrow H(t)$ and $\hat{H}_u(t) \rightarrow H_u(t)$ uniformly in t as $N \rightarrow \infty$, a.s., by the Glivenko-Cantelli theorem, it follows that as $N \rightarrow \infty$

$$\begin{aligned}
\frac{1}{N^3} \sum_{i=1}^N (U_i^*)^2 &\xrightarrow{\text{a.s.}} \int_0^\infty H_u^2(t) dH(t) - 2 \int_0^\infty H_u(t) (1-H(t)) dH_u(t) \\
&\quad + \int_0^\infty (1-H(t))^2 dH_u(t) .
\end{aligned}$$

Integration by parts gives

$$\begin{aligned}
2 \int_0^\infty H_u(t) (1-H(t)) dH_u(t) &= H_u^2(t) (1-H(t)) \Big|_0^\infty + \int_0^\infty H_u^2(t) dH(t) , \\
&= \int_0^\infty H_u^2(t) dH(t) ,
\end{aligned}$$

so the first two terms in the above limiting expression cancel. This, together with

$$\frac{mn}{(m+n)(m+n-1)} \rightarrow \lambda(1-\lambda) ,$$

establishes the result.

REFERENCES

The numbers in brackets after the references are the numbers of the pages on which the references are cited.

- Aalen, O. (1976). Nonparametric inference in connection with multiple decrement models. Scandinavian Journal of Statistics 3, 15-27. [52]
- (1978). Nonparametric inference for a family of counting processes. Annals of Statistics 6, 701-726. [52]
- Abelson, R. P. and Tukey, J. W. (1963). Efficient utilization of non-numerical information in quantitative analysis: General theory and the case of simple order. Annals of Mathematical Statistics 34, 1347-1369. [83]
- Altshuler, B. (1970). Theory for the measurement of competing risks in animal experiments. Mathematical Biosciences 6, 1-11. [135]
- Bailey, K. R. (1979). The general maximum likelihood approach to the Cox regression model. Ph.D. dissertation, University of Chicago, Chicago, Illinois. [98]
- Barlow, R. E. and Proschan, F. (1975). Statistical Theory of Reliability and Life Testing. Holt, Rinehart, and Winston, New York. [11]
- Barr, D. R. and Davidson, T. (1973). A Kolmogorov-Smirnov test for censored samples. Technometrics 15, 739-757. [130]
- Basu, A. P. (1964). Estimates of reliability for some distributions useful in life testing. Technometrics 6, 215-219. [27]
- Berkson, J. and Gage, R. P. (1950). Calculation of survival rates for cancer. Proceedings of the Staff Meetings of the Mayo Clinic 25, 270-286. [34]
- Berman, S. M. (1963). Note on extreme values, competing risks and semi-Markov processes. Annals of Mathematical Statistics 34, 1104-1106. [135]
- Billingsley, P. (1968). Convergence of Probability Measures. Wiley, New York. [49]
- Breslow, N. (1970). A generalized Kruskal-Wallis test for comparing K samples subject to unequal patterns of censorship. Biometrika 57, 579-594. [81,84]
- (1972). Discussion on Professor Cox's paper. Journal of the Royal Statistical Society, Series B 34, 216-217. [100]

- _____. (1974). Covariance analysis of censored survival data. Biometrics 30, 89-99. [100,103]
- _____. and Crowley, J. (1974). A large sample study of the life table and product limit estimates under random censorship. Annals of Statistics 2, 437-453. [34,49,52]
- Buckley, J. and James, I. (1979). Linear regression with censored data. Biometrika 66, 429-436. [114]
- Campbell, G. (1979). Nonparametric bivariate estimation with randomly censored data. Mimeoseries #79-25, Department of Statistics, Purdue University, West Lafayette, Indiana. [133]
- Chiang, C. L. (1968). Introduction to Stochastic Processes in Biostatistics. Wiley, New York. [34,134]
- Cox, D. R. (1972). Regression models and life-tables. Journal of the Royal Statistical Society, Series B 34, 187-202. [93,103]
- _____. (1975). Partial likelihood. Biometrika 62, 269-276. [97,98]
- _____. and Snell, E. J. (1968). A general definition of residuals. Journal of the Royal Statistical Society, Series B 30, 248-275. [128]
- Crowley, J. (1974). Asymptotic normality of a new nonparametric statistic for use in organ transplant studies. Journal of the American Statistical Association 69, 1006-1011. [76]
- _____. and Hu, M. (1977). Covariance analysis of heart transplant survival data. Journal of the American Statistical Association 72, 27-36. [104,128]
- Cutler, S. J. and Ederer, F. (1958). Maximum utilization of the life table method in analyzing survival. Journal of Chronic Diseases 8, 699-712. [31,34]
- Dempster, A. P., Laird, N. M. and Rubin, D. B. (1977). Maximum likelihood from incomplete data via the EM algorithm. Journal of the Royal Statistical Society, Series B 39, 1-22. [115]
- Dufour, R. and Maag, U. R. (1978). Distribution results for modified Kolmogorov-Smirnov statistics for truncated or censored samples. Technometrics 20, 29-32. [130]
- Efron, B. (1967). The two sample problem with censored data. Proceedings of the Fifth Berkeley Symposium on Mathematical Statistics and Probability, Vol. IV. University of California Press, Berkeley, California. 831-853. [40,43,79]
- _____. (1977). The efficiency of Cox's likelihood function for censored data. Journal of the American Statistical Association 72, 557-565. [97]

- _____. (1979). Bootstrap methods: Another look at the jackknife. Annals of Statistics 7, 1-26. [137]
- _____. (1980). Censored data and the bootstrap. Technical Report No. 53 (R01 GM21215), Division of Biostatistics, Stanford University, Stanford, California. [57,137]
- _____. and Hinkley, D. V. (1978). Assessing the accuracy of the maximum likelihood estimator: Observed versus expected Fisher information. Biometrika 65, 457-487. [16]
- Elveback, L. (1958). Estimation of survivorship in chronic disease: The "actuarial" method. Journal of the American Statistical Association 53, 420-440. [34]
- Embury, S. H., Elias, L., Heller, P. H., Hood, C. E., Greenberg, P. L. and Schrier, S. L. (1977). Remission maintenance therapy in acute myelogenous leukemia. Western Journal of Medicine 126, 267-272. [38]
- Farewell, V. T. (1977). A model for a binary variable with time-censored observations. Biometrika 64, 43-46. [29]
- Feigl, P. and Zelen, M. (1965). Estimation of exponential survival probabilities with concomitant information. Biometrics 21, 826-838. [28]
- Ferguson, T. S. (1973). A Bayesian analysis of some nonparametric problems. Annals of Statistics 1, 209-230. [60]
- _____. and Phadia, E. G. (1979). Bayesian nonparametric estimation based on censored data. Annals of Statistics 7, 163-186. [60]
- Fleming, T. R. and Harrington, D. P. (1979). Nonparametric estimation of the survival distribution in censored data. Unpublished manuscript. [50]
- Földes, A., Rejtő, L. and Winter, B. B. (1978). Strong consistency properties of nonparametric estimators for randomly censored data. Part II: Estimation of density and failure rate. Unpublished manuscript. [57]
- Gail, M. (1975). A review and critique of some models used in competing risk analysis. Biometrics 31, 209-222. [134]
- Gaver, D. P., Jr. and Hoel, D. G. (1970). Comparison of certain small-sample Poisson probability estimates. Technometrics 12, 835-850. [27]
- Gehan, E. A. (1965). A generalized Wilcoxon test for comparing arbitrarily singly-censored samples. Biometrika 52, 203-223. [67]
- Gilbert, J. P. (1962). Random censorship. Ph.D. dissertation, University of Chicago, Chicago, Illinois. [70]

- Gillespie, M. J. and Fisher, L. (1979). Confidence bands for the Kaplan-Meier survival curve estimate. Annals of Statistics 7, 920-924. [130]
- Glasser, M. (1967). Exponential survival with covariance. Journal of the American Statistical Association 62, 561-568. [28]
- Gong, G. (1980). Do Hodgkin's disease patients with DNCB sensitivity survive longer? Biostatistics Casebook, Vol. III, Technical Report No. 57 (R01 GM21215), Division of Biostatistics, Stanford University, Stanford, California. [125]
- Gregory, P. B., Knauer, C. M., Kempson, R. L. and Miller, R. (1976). Steroid therapy in severe viral hepatitis. New England Journal of Medicine 294, 687-690. [140]
- Gross, A. J. and Clark, V. A. (1975). Survival Distributions: Reliability Applications in the Biomedical Sciences. Wiley, New York. [14]
- Hall, W. J. and Wellner, J. A. (1980). Confidence bands for a survival curve from censored data. Biometrika 67, 133-143. [130]
- Hollander, M. and Proschan, F. (1979). Testing to determine the underlying distribution using randomly censored data. Biometrics 35, 393-401. [131]
- Hyde, J. (1977). Testing survival under right censoring and left truncation. Biometrika 64, 225-230. [130]
- _____. (1977). Life testing with incomplete observations. Technical Report No. 30 (R01 GM21215), Division of Biostatistics, Stanford University, Stanford, California. [70]
- Johansen, S. (1978). The product limit estimator as maximum likelihood estimator. Scandinavian Journal of Statistics 5, 195-199. [45]
- Johns, M. V., Jr. and Lieberman, G. J. (1966). An exact asymptotically efficient confidence bound for reliability in the case of the Weibull distribution. Technometrics 8, 135-175. [24]
- Kalbfleisch, J. and Prentice, R. L. (1972). Discussion on Professor Cox's paper. Journal of the Royal Statistical Society, Series B 34, 215-216. [103]
- _____ and _____ (1973). Marginal likelihoods based on Cox's regression and life model. Biometrika 60, 267-278. [96]
- _____ and _____ (1980). The Statistical Analysis of Failure Time Data. Wiley, New York. [14,93,106,108]
- Kaplan, E. L. and Meier, P. (1958). Nonparametric estimation from incomplete observations. Journal of the American Statistical Association 53, 457-481. [35,45,54]

- Kay, R. (1977). Proportional hazard regression models and the analysis of censored survival data. Applied Statistics (Journal of the Royal Statistical Society, Series C) 26, 227-237. [128]
- Kiefer, J. and Wolfowitz, J. (1956). Consistency of the maximum likelihood estimator in the presence of infinitely many incidental parameters. Annals of Mathematical Statistics 27, 887-906. [45]
- Korwar, R. M. (1980). Nonparametric estimation of a bivariate survivorship function with doubly censored data. Unpublished manuscript. [133]
- Koul, H., Susarla, V. and Van Ryzin, J. (1979). Regression analysis with randomly right censored data. Unpublished manuscript. [116]
- Koziol, J. A. and Byar, D. P. (1975). Percentage points of the asymptotic distributions of one and two sample K-S statistics for truncated or censored data. Technometrics 17, 507-510. [130]
- _____ and Green, S. B. (1976). A Cramér-von Mises statistic for randomly censored data. Biometrika 63, 465-474. [130]
- Lagakos, S. W. (1979). General right censoring and its impact on the analysis of survival data. Biometrics 35, 139-156. [135]
- _____ and Williams, J. S. (1978). Models for censored survival analysis: A cone class of variable-sum models. Biometrika 65, 181-189. [135]
- Lamb, E. J. and Leurgans, S. (1979). Does adoption affect subsequent fertility? American Journal of Obstetrics and Gynecology 134, 138-144. [105]
- Lamborn, K. (1969). On chi-squared goodness of fit tests for sampling from more than one population with possibly censored data. Technical Report No. 21 (T01 GM00025), Department of Statistics, Stanford University, Stanford, California. [132]
- Langberg, N. A., Proschan, F. and Quinzi, A. J. (1981). Estimating dependent life lengths, with applications to the theory of competing risks. Annals of Statistics. [135]
- Latta, R. B. (1977). Generalized Wilcoxon statistics for the two-sample problem with censored data. Biometrika 64, 633-635. [108]
- Leavitt, S. S. and Olshen, R. A. (1974). The insurance claims adjuster as patients' advocate: Quantitative impact. Report for Insurance Technology Company, Berkeley, California. [2]
- Leiderman, P. H., Babu, D., Kagia, J., Kraemer, H. C. and Leiderman, G. F. (1973). African infant precocity and some social influences during the first year. Nature 242, 247-249. [6]

- Leurgans, S. (1980). Does adoption affect fertility? A proportional hazards model. Biostatistics Casebook, Vol. III, Technical Report No. 57 (R01 GM21215), Division of Biostatistics, Stanford University, Stanford, California. [105]
- Lininger, L., Gail, M. H., Green, S. B. and Byar, D. P. (1979). Comparison of four tests for equality of survival curves in the presence of stratification and censoring. Biometrika 66, 419-428. [76]
- Link, C. L. (1979). Confidence intervals for the survival function using Cox's proportional hazard model with covariates. Technical Report No. 45 (R01 GM21215), Division of Biostatistics, Stanford University, Stanford, California. [100]
- Mantel, N. (1967). Ranking procedures for arbitrarily restricted observation. Biometrics 23, 65-78. [67]
- _____ and Haenszel, W. (1959). Statistical aspects of the analysis of data from retrospective studies of disease. Journal of the National Cancer Institute 22, 719-748. [76]
- _____ and Myers, M. (1971). Problems of convergence of maximum likelihood iterative procedures in multiparameter situations. Journal of the American Statistical Association 66, 484-491. [28]
- Marcuson, R. and Nordbrock, E. (1980 or 1981). A K-sample generalization of the Gehan-Gilbert procedure for the analysis of arbitrarily censored survival data. Biometrical Journal (Biometrische Zeitschrift) [84]
- Meier, P. (1975). Estimation of a distribution function from incomplete observations. Perspectives in Probability and Statistics. Papers in Honour of M. S. Bartlett (Ed. J. Gani). Academic Press, New York. 67-82. [54]
- Mihalko, D. P. and Moore, D. S. (1980). Chi-square tests of fit for Type II censored data. Annals of Statistics 8, . [131]
- Miller, R. G. (1974). The jackknife - a review. Biometrika 61, 1-15. [137]
- _____ (1975). Jackknifing censored data. Technical Report No. 14 (R01 GM21215), Division of Biostatistics, Stanford University, Stanford, California. [137]
- _____ (1976). Least squares regression with censored data. Biometrika 63, 449-464. [112]
- Moeschberger, M. L. and David, H. A. (1971). Life tests under competing causes of failure and the theory of competing risks. Biometrics 27, 909-923. [134]
- Morton, R. (1978). Regression analysis of life tables and related non-parametric tests. Biometrika 65, 329-333. [108]

- Muñoz, A. (1980). Nonparametric estimation from censored bivariate observations. Technical Report No. 60 (R01 GM21215), Division of Biostatistics, Stanford University, Stanford, California. [133]
- Muñoz, A. (1980). Consistency of the self-consistent estimator of the distribution function from censored observations. Technical Report No. 61 (R01 GM21215), Division of Biostatistics, Stanford University, Stanford, California. [133]
- Nelson, W. (1969). Hazard plotting for incomplete failure data. Journal of Quality Technology 1, 27-52. [50,123]
- _____. (1972). Theory and applications of hazard plotting for censored failure data. Technometrics 14, 945-966. [50,123]
- Oakes, D. (1977). The asymptotic information in censored survival data. Biometrika 64, 441-448. [97]
- Peterson, A. V., Jr. (1975). Nonparametric estimation in the competing risks problem. Technical Report No. 13 (R01 GM21215), Division of Biostatistics, Stanford University, Stanford, California. [135]
- _____. (1976). Bounds for a joint distribution function with fixed sub-distribution functions: Application to competing risks. Proceedings of the National Academy of Sciences 73, 11-13. [135]
- _____. (1977). Expressing the Kaplan-Meier estimator as a function of empirical subsurvival functions. Journal of the American Statistical Association 72, 854-858. [47,50]
- Peto, R. (1972). Discussion on Professor Cox's paper. Journal of the Royal Statistical Society, Series B 34, 205-207. [103]
- _____. and Peto, J. (1972). Asymptotically efficient rank invariant test procedures. Journal of the Royal Statistical Society, Series A 135, 185-198. [108]
- _____. and Pike, M. C. (1973). Conservation of the approximation $\Sigma(O-E)^2/E$ in the logrank test for survival data or tumor incidence data. Biometrics 29, 579-584. [87]
- _____. , _____, Armitage, P., Breslow, N. E., Cox, D. R., Howard, S. V., Mantel, N., McPherson, K., Peto, J. and Smith, P. G. (1976). Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. British Journal of Cancer 34, 585-612. [87]
- _____. , _____, _____, _____, _____, _____, _____ and _____ (1977). Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. British Journal of Cancer 35, 1-39. [87]

- Pettit, A. N. (1976). Cramér-von Mises statistics for testing normality with censored samples. Biometrika 63, 475-481. [130]
- ____ (1977). Tests for the exponential distribution with censored data using Cramér-von Mises statistics. Biometrika 64, 629-632. [130]
- ____ and Stephens, M. A. (1976). Modified Cramér-von Mises statistics for censored data. Biometrika 63, 291-298. [130]
- Phadia, E. G. (1980). A note on empirical Bayes estimation of a distribution function based on censored data. Annals of Statistics 8, 226-229. [60]
- Prentice, R. L. (1978). Linear rank tests with right censored data. Biometrika 65, 167-179. [108]
- ____ and Gloeckler, L. A. (1978). Regression analysis of grouped survival data with application to breast cancer data. Biometrics 34, 57-67. [103]
- ____ and Kalbfleisch, J. D. (1979). Hazard rate models with covariates. Biometrics 35, 25-39. [93,106]
- ____, _____, Peterson, A. V., Jr., Flournoy, N., Farewell, V. T. and Breslow, N. E. (1978). The analysis of failure times in the presence of competing risks. Biometrics 34, 541-554. [134]
- Rai, K., Susarla, V. and Van Ryzin, J. (1979). Shrinkage estimation in nonparametric Bayesian survival analysis. Paper No. P-6357, Rand Corporation, Santa Monica, California. [60]
- Rao, C. R. (1965). Linear Statistical Inference. Wiley, New York. [14,16]
- Reid, N. M. (1979). Influence functions for censored data. Technical Report No. 46 (R01 GM21215), Division of Biostatistics, Stanford University, Stanford, California. To appear in Annals of Statistics (1981). [55,56,57,137]
- ____ and Iyengar, S. (1979). Estimating the variance of the median. Unpublished notes. [57]
- Sander, J. M. (1975). The weak convergence of quantiles of the product-limit estimator. Technical Report No. 5 (R01 GM21215), Division of Biostatistics, Stanford University, Stanford, California. [57]
- ____ (1975). Asymptotic normality of linear combinations of functions of order statistics with censored data. Technical Report No. 8 (R01 GM21215), Division of Biostatistics, Stanford University, Stanford, California. [54,55]
- Schmee, J. and Hahn, G. J. (1979). A simple method for regression analysis with censored data. Technometrics 21, 417-432. [115]

- Schoenfeld, D. (1980). Chi-squared goodness-of-fit tests for the proportional hazards regression model. Biometrika 67, 145-153. [132]
- Susarla, V. and Van Ryzin, J. (1976). Nonparametric Bayesian estimation of survival curves from incomplete observations. Journal of the American Statistical Association 71, 897-902. [60]
- _____ and _____ (1978a). Empirical Bayes estimation of a distribution (survival) function from right censored observations. Annals of Statistics 6, 740-754. [60]
- _____ and _____ (1978b). Large sample theory for a Bayesian nonparametric survival curve estimator based on censored samples. Annals of Statistics 6, 755-768. [60]
- _____ and _____ (1980). Large sample theory for an estimator of the mean survival time from censored samples. Annals of Statistics 8, [54]
- Tarone, R. E. (1975). Tests for trend in life table analysis. Biometrika 62, 679-682. [87]
- _____ and Ware, J. (1977). On distribution-free tests for equality of survival distributions. Biometrika 64, 156-160. [78,86]
- Thomas, D. R. and Grunkemeier, G. L. (1975). Confidence interval estimation of survival probabilities for censored data. Journal of the American Statistical Association 70, 865-871. [39]
- Tsiatis, A. (1975). A nonidentifiability aspect of the problem of competing risks. Proceedings of the National Academy of Sciences 72, 20-22. [135]
- _____ (1978). A heuristic estimate of the asymptotic variance of the survival probability in Cox's regression model. Technical Report No. 524, Department of Statistics, University of Wisconsin, Madison, Wisconsin. [100]
- _____ (1981). A large sample study of Cox's regression model. Annals of Statistics. [98,100]
- Turnbull, B. W. (1974). Nonparametric estimation of a survivorship function with doubly censored data. Journal of the American Statistical Association 69, 169-173. [6,43]
- _____ (1976). The empirical distribution function with arbitrarily grouped, censored and truncated data. Journal of the Royal Statistical Society, Series B 38, 290-295. [43]
- _____, Brown, B. W., Jr. and Hu, M. (1974). Survivorship analysis of heart transplant data. Journal of the American Statistical Association 69, 74-80. [104]
- _____ and Weiss, L. (1978). A likelihood ratio statistic for testing goodness of fit with randomly censored data. Biometrics 34, 367-375. [131]

- Wilk, M. B. and Gnanadesikan, R. (1968). Probability plotting methods for the analysis of data. Biometrika 55, 1-17. [122]
- _____, _____ and Huyett, M. J. (1962). Probability plots for the gamma distribution. Technometrics 4, 1-20. [124]
- Williams, J. S. and Lagakos, S. W. (1977). Models for censored survival analysis: Constant-sum and variable-sum models. Biometrika 64, 215-224. [135]
- Zacks, S. and Even, M. (1966). The efficiencies in small samples of the maximum likelihood and best unbiased estimators of reliability functions. Journal of the American Statistical Association 61, 1033-1051. [27]
- Zipf, C. and Armitage, P. (1966). Use of concomitant variables and incomplete survival information in the estimation of an exponential survival parameter. Biometrics 22, 665-672. [28]
- _____, and Lamborn, K. (1969). Concomitant variables and censored survival data in estimation of an exponential survival parameter, Part II. Technical Report No. 20 (T01 GM00025), Department of Statistics, Stanford University, Stanford, California. [28]