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Analysis of survival data

Jaarlijks organiseert het Centrum voor Wiskunde en Informatica (CWI) onder auspicien van de Nederlandse Vereniging van Wiskundeleraren een vakantiecursus voor wiskundeleraren en andere belangstellenden. Bij deze gelegenheid verschijnt steeds een syllabus met teksten bij de voordrachten. Die syllabi zijn ook afzonderlijk bij het CWI verkrijgbaar. Het NAW heeft een serie gestart waarin geselecteerde teksten uit recente syllabi worden geplaatst. Het tweede artikel is afkomstig uit de syllabus bij de Vakantiecursus 2002, die als thema had: 'Wiskunde en Gezondheid'. Het onderwerp is het schatten van de tijdsduur die nodig is voor het plaatsvinden van een gebeurtenis. Svetlana Borovkova is wetenschappelijk onderzoeker bij de sectie Control, Risk, Optimization, Systems and Stochastics van de faculteit Informatietechnologie en Systemen van de Technische Universiteit Delft.

In many biomedical applications the primary endpoint of interest is the time it takes for a certain event to occur ('time to event'). Examples are the time it takes for an organism to die, the time it takes for a patient to respond to a therapy, or the time from response until disease relapse. We may be interested in characterizing the distribution of 'time to event' for a given population as well as comparing this 'time to event' among different groups (e.g., treatment vs. control), or modelling the relationship of 'time to event' to other covariates (prognostic factors or predictors). Typically, in biomedical applications the data are collected over a finite period of time and consequently the 'time to event' may not be observed for all the individuals in our study population (sample). This results in what is called *censored data*. It is also common that the amount of follow-up for the individuals in a sample vary from subject to subject. The combination of censoring and differential follow-up creates some unusual difficulties in the analysis of such data that cannot be handled properly by the standard statistical methods. Because of this, a new research area in statistics has emerged which is called *Survival Analysis* or *Censored Survival Analysis*.

To study it, we must introduce some notation and concepts for describing the distribution of 'time to event' for a population of individuals. Let the random variable T denote the time to the event of our interest. Of course, T is a positive random variable which has to be unambiguously defined; that is, we must be very specific about the start and end with the length of the time period in-between corresponding to T.

Some examples:

- Survival time (in general): measured from *birth to death* for an individual.
- Survival time of a treatment for a population with certain disease: measured from the time of *treatment initiation until death*.

– Survival time due to heart disease (the event is death from heart disease): measured from *birth* (or other time point such as treatment initiation for heart disease patients) *to death caused by heart disease*. (This may be a bit tricky if individuals die from other causes. In this case the survival time of interest is censored.)

The time of interest may be the time to something 'good' happening. For example, we may be interested in how long it takes to eradicate an infection after treatment with antibiotics, or how long it takes for a woman to get pregnant from the moment of 'start trying'.

Describing the distribution of time to an event

In routine data analysis, we may first present some summary statistics such as mean, standard error for the mean, etc. In analyzing survival data, however, because of possible censoring, the summary statistics may not have the desired statistical properties, such as unbiasedness. For example, the sample mean is no longer an unbiased estimator of the population mean (of survival time). So we need to use other methods to present our data. One way is to estimate the underlying true distribution. When this distribution is estimated, we can then estimate other quantities of interest such as mean, median, et cetera.

The distribution of the random variable T can be described in a number of equivalent ways. There is of course the usual (cumulative) distribution function

$$F(t) = P[T \leq t], \;\; t \geq 0,$$

which is right continuous, i.e., $\lim_{u \longrightarrow t+} F(u) = F(t)$. When T is a survival time, $F(t)$ is the probability that a randomly selected subject from the population will die before time t. If T is a continuous random variable, then it has a density function $f(t)$, which is related to $F(t)$ through following equations

$$f(t) = \frac{dF(t)}{dt}, \;\; F(t) = \int_0^{\infty} f(u)du.$$

In biomedical applications, it is often common to use the survival function

$$S(t) = P[T \geq t] = 1 - F(t^-),$$

where $F(t^-) = \lim_{u \longrightarrow t^-} F(u)$. When T is a survival time, $S(t)$ is the probability that a randomly selected individual will survive to time t or beyond. (So $S(t)$ has the name of *survival function*.) Some authors use the following definition of a survival function $S(t) = P[T > t] = 1 - F(t)$. This definition will be identical to the above one if T is a continuous random variable, which is the case we will focus on in this article.

The survival function $S(t)$ is a non-increasing function over time taking on the value 1 at $t = 0$, i.e., $S(0) = 1$. For a proper random variable T, $S(\infty) = 0$. However, we will also allow the possibility that $S(\infty) > 0$. This corresponds to a situation where there is a positive probability of not 'dying'. For example, if the event of interest is the time from response until disease relapse and the disease has a cure for some proportion of individuals in the population, then we have $S(\infty) > 0$.

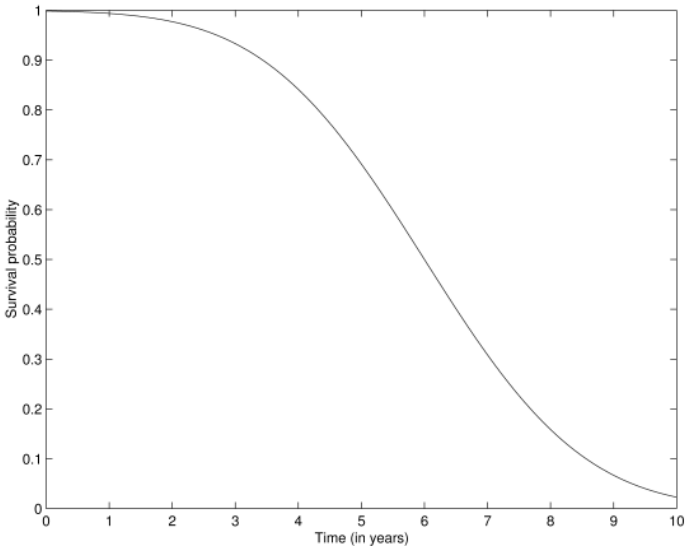

Figure 1 The survival function for a hypothetical population.

If T is a continuous random variable, we have

$$S(t) = \int_t^{\infty} f(u)du, \;\; f(t) = -\frac{dS(t)}{dt}.$$

For example, in the hypothetical population shown in Figure 1, we have a population where 70% will survive approximately five years and the median survival time is approximately six years (i.e., 50% of the population will survive at least 6 years).

We say that the survival distribution for group 1 is stochastically larger than the survival distribution for group 2 if $S_1(t) \geq S_2(t)$ for all $t \geq 0$, where $S_i(t)$ is the survival function for group i. If T_i is the corresponding survival time for group i, we also say that T_1 is stochastically larger than T_2. Note that T_1 being stochastically larger than T_2 does NOT necessarily imply that $T_1 \geq T_2$. But at any time point a greater proportion of group 1 will survive as compared to group 2.

Hazard rate

The hazard rate is a useful way of describing the distribution of 'time to event' because it has a natural interpretation that relates to the aging of a population. We motivate the definition of hazard rate by first defining the mortality rate, which is a discrete version of the hazard rate.

The *mortality rate* at time t, where t is generally taken to be an integer in terms of some unit of time (e.g., years, months, days, et cetera), is the proportion of the population who fail (die) between times t and $t + 1$ among individuals alive at time t, i.e.,

$$m(t) = P[t \leq T < t + 1 | T \geq t].$$

The hazard rate $\lambda(t)$ is the limit of the mortality rate if the interval of time is taken to be small (rather than one unit). The hazard rate is the instantaneous rate of failure at time t given that an individual is alive at time t. Specifically, $\lambda(t)$ is defined by the following equation

$$\lambda(t) = \lim_{h \longrightarrow 0} \frac{P[t \leq T < t + h | T \geq t]}{h}.$$

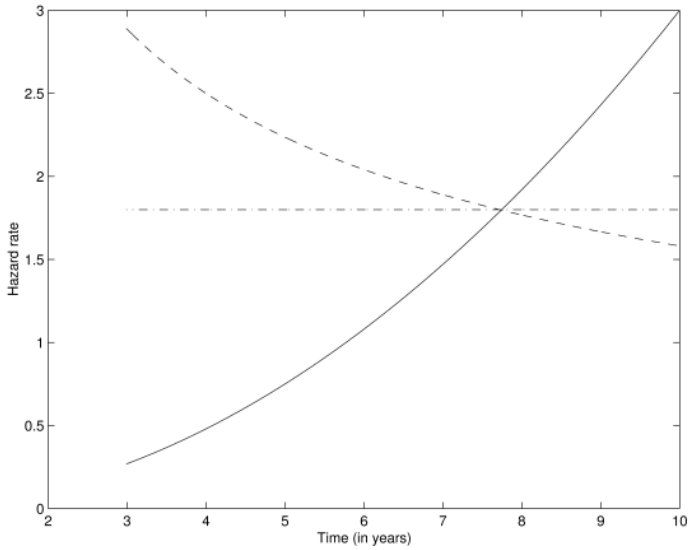

Figure 2 Three hazard patterns.

This can be expressed as

$$\lambda(t) = \frac{\lim_{h\to 0} \frac{P[t\le T<t+h]}{h}}{P[T \ge t]} = \frac{f(t)}{S(t)} = -\frac{S'(t)}{S(t)} = -\frac{d\log(S(t))}{dt}.$$

From this, we can integrate both sides to get

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

where (t) is referred to as the *cumulative hazard function*. Here we used the fact that $S(0) = 1$. Hence,

$$S(t) = \exp(-(t)) = \exp(-\int_o^t \lambda(u)du).$$

We like to remark that there is a one-to-one relationship between the hazard rate $\lambda(t),\ t \ge 0$ and the survival function $S(t)$, given by the formulas above. Notice that the hazard rate is not a probability, it is a probability rate. Therefore it is possible that a hazard rate can exceed one in the same fashion as a density function $f(t)$ may exceed one.

If we have a constant hazard, i.e., $\lambda(t) = \lambda$ for all $t \ge 0$, then $S(t) = e^{-\lambda t}$. This distribution is the exponential distribution with hazard equal to λ.

Another class of distributions widely used in survival analysis is the *Weibull model*, where the survival function is given by

$$S(t) = \exp(-\lambda t^a),\ \ a, \lambda > 0.$$

The Weibull model has hazard function

$$\lambda(t) = a\lambda t^{a-1}.$$

This model allows for constant hazard ($a = 1$), increasing hazard ($a > 1$) and decreasing hazard ($a < 1$). The corresponding hazard patterns are shown in Figure 2.

Censoring

As we already said above, *censored data* are those observations whose times to event we do not get to observe completely. In biomedical applications, especially in clinical trials, two important issues arise when studying 'time to event' data (we will assume the event to be death, but it can be any event of interest):

- Some individuals are still alive at the end of the study or analysis so the event of interest, namely death, has not occurred. In this case we only know that 'time to event' is greater than a certain value, namely the time from entry to the end of study. Therefore we have *right censored data*.
- Length of follow-up varies due to staggered entry. So we cannot observe the event for those individuals with insufficient follow-up time.

In addition to censoring because of insufficient follow-up (i.e., end of study censoring due to staggered entry), other reasons for censoring include:

- loss to follow-up: patients stop coming to clinic or move away.
- deaths from other causes: competing risks.

Censoring from these types of causes may be inherently different from censoring due to staggered entry.

There is an important assumption in Survival Analysis that individuals who are censored are at the same risk of subsequent failure as those who are still alive and uncensored. The risk set at any time point (the individuals still alive and uncensored) should be representative of the entire population alive at the same time. Statistically, this assumption is equivalent to the one that the censoring process is independent of the survival time. If censoring only occurs because of staggered entry, then the assumption of independent censoring seems plausible. However, when censoring results from loss to follow-up or death from a competing risk, then this assumption is more suspect. If at all possible, censoring from these later situations should be kept to a minimum.

Other types of censoring are:

- Left censoring, where for some individuals the time of *entry* into the 'control group' it is not known. For example, if the 'time to event' is the time from contraction of HIV until death of AIDS, then we have a typical left-censoring situation, since the time of contracting HIV is unknown in many cases.
- Interval censoring, where neither the time of entry nor the event time are known for some individuals in the study.

Statistical Inference for Survival Data

Survival analysis methods are tailored to work well with the specific characteristics of the data and the specific objectives that arise in survival studies. Often, survival data are distinguished from other types of data because they are censored. Censored data prevent the use of standard methods of statistical summarization and inference. In particular, right censored data are reported as lower bounds for the actual unobserved event times. Survival times frequently have a distribution in the population that is very different from a Gaussian (Normal) distribution. Many standard approximate statistical methods are not accurate for such data. It may happen that we are interested in the whole distribution of survival times. Many standard statistical methods are instead oriented towards inference for the mean survival time and its standard deviation. The extremes of the distribution of times to event (extreme

quantiles) are often of interest in survival analysis. For example, many people hope that they will live to the 95th percentile, rather than the 50th percentile. The rate of occurrence of events per unit time (i.e., hazard or mortality rate) is often of interest in survival analysis.

Estimation of the survival function

If we have a dataset where no censored observations are present, estimation of the survival function is straightforward and similar to the estimation of the distribution function. Namely, we can use the *empirical survival function*:

$$\hat{S}(t) = \frac{\text{number of individuals still alive at time } t}{\text{total number of individuals in the study}}.$$

This is a *nonparametric estimate* of the survival function (i.e., in obtaining it we did not assume any parametric form of the distribution of 'time to event' T).

Alternatively, one can assume that the data come from e.g., Exponential or Weibull distributions. Then estimation of the survival function boils down to estimating the unknown parameters of these distributions. (This is the so-called *parametric approach*). The parameters can be estimated by e.g., the method of maximum likelihood.

In practice it is difficult to make reasonable parametric assumptions about the distribution of the survival time. Hence, we shall not go into details of the parametric approach here and shall concentrate on the nonparametric approach.

Censoring and differential follow-up create certain difficulties in the above nonparametric approach as is illustrated by the following example taken from a clinical trial of 148 patients treated after they had a myocardial infarction (MI). The data have been grouped into one year intervals and all time is measured in terms of patient time (table 1).

The question is to estimate the 5 year survival probability, i.e., $S(5) = P[T \geq 5]$.

Year since entry into study	Number alive and under observation at beginning of interval	Number dying during interval	Number censored or withdrawn
$[0,1)$	146	27	3
$[1,2)$	116	18	10
$[2,3)$	88	21	10
$[3,4)$	57	9	3
$[4,5)$	45	1	3
$[5,6)$	41	2	11
$[6,7)$	28	3	5
$[7,8)$	20	1	8
$[8,9)$	11	2	1
$[9,10)$	8	2	6

Table 1 Data from a clinical trial on myocardial infarction (MI)

duration $[t_{i-1}, t_i)$	$n(x)$	$d(x)$	$w(x)$	$\hat{m}(x)$	$1-\hat{m}(x)$	$\hat{S}_R(t_i)$
$[0,1)$	146	27	3	0.185	0.815	0.815
$[1,2)$	116	18	10	0.155	0.845	0.689
$[2,3)$	88	21	10	0.239	0.761	0.524
$[3,4)$	57	9	3	0.158	0.842	0.441
$[4,5)$	45	1	3	0.022	0.972	0.432

Table 2 Life-table estimate of S(5) assuming censoring occurred at the end of interval. The estimated mortality rate $m(x)$ equals $\frac{d(x)}{n(x)}$.

duration $[t_{i-1}, t_i)$	$n(x)$	$d(x)$	$w(x)$	$\hat{m}(x)$	$1-\hat{m}(x)$	$\hat{S}_L(t_i)$
$[0,1)$	146	27	3	0.189	0.811	0.811
$[1,2)$	116	18	10	0.170	0.830	0.673
$[2,3)$	88	21	10	0.269	0.731	0.492
$[3,4)$	57	9	3	0.167	0.833	0.410
$[4,5)$	45	1	3	0.024	0.976	0.400

Table 3 Life-table estimate of S(5) assuming censoring occurred at the beginning of interval. The estimated mortality rate $m(x)$ equals $\frac{d(x)}{n(x)-w(x)}$.

Two naive and incorrect answers are

$$\hat{F}(5) = P[T \leq 5] = \frac{\text{76 deaths in 5 years}}{\text{146 individuals}} = 52.1\%,$$
$$\hat{S}(5) = 1 - \hat{F}(5) = 47.9\%$$

and

$$\hat{F}(5) = P[T \leq 5] = \frac{\text{76 deaths in 5 years}}{\text{146-29 (withdrawn in 5 years)}} = 65\%,$$
$$\hat{S}(5) = 35\%.$$

The first estimate would be correct if all censoring occurred after 5 years. Of course, this was not the case, leading to overly optimistic estimate (i.e., we overestimated $S(5)$). The second estimate would be correct if all individuals censored in the 5 years were censored immediately upon entering the study. This was not the case either, leading to overly pessimistic estimate (i.e., we underestimated $S(5)$).

Our clinical colleagues have suggested eliminating all individuals who are censored and use the remaining 'complete' data. This would lead to the following estimate:

$$\hat{F}(5) = P[T \leq 5] = \frac{\text{76 deaths in 5 years}}{\text{146 -46 (censored)}} = 88.4\%, \quad \hat{S}(5) = 11.6\%.$$

This is even more pessimistic than the estimate given by (2).

Life-table or actuarial method

More appropriate method is the so-called *life-table or actuarial method*.

First note that $S(5)$ can be expressed as $S(5) = q_1 \times q_2 \times q_3 \times q_4 \times q_5$, where $q_i = 1 - P[i-1 \leq T < i | T \geq i-1]$, $i = 1, \ldots, 5$. So we just need to estimate q_i in order to estimate $S(5)$. Note that $1 - q_i$ is the mortality rate $m(x)$ at year $x = i - 1$ by our definition.

duration $[t_{i-1}, t_i)$	$n(x)$	$d(x)$	$w(x)$	$\hat{m}(x)$	$1-\hat{m}(x)$	$\hat{S}(t_i)$
$[0,1)$	146	27	3	0.187	0.813	0.813
$[1,2)$	116	18	10	0.162	0.838	0.681
$[2,3)$	88	21	10	0.253	0.747	0.509
$[3,4)$	57	9	3	0.162	0.838	0.426
$[4,5)$	45	1	3	0.023	0.977	0.417

Table 4 Life-table estimate of S(5) assuming censoring occurred during the interval. The estimated mortality rate $m(x)$ equals $\frac{d(x)}{n(x)-(w(x)/2)}$.

$[t_{i-1}, t_i)$	$n(x)$	$d(x)$	$\hat{m}(x)$	$1-\hat{m}(x)$	$\hat{S}(t_i)$	S.E.
0	10	0	0	1.0	1.0	
$[0,3)$	9	1	1/9	$8/9 \approx 0.89$	0.89	0.10
$[3,5)$	7	2	2/7	$5/7 \approx 0.71$	0.63	0.15
$[5,7)$	4	2	2/4	2/4 = 0.5	0.32	0.13

Table 5 Kaplan-Meier estimate computations. The estimated mortality rate $m(x)$ equals $\frac{d(x)}{n(x)}$.

From the estimates $\hat{m}(x)$ of the mortality rates we get the estimate for the survival function as $\hat{S}(t_i) = \prod_{x \le t_i}(1-\hat{m}(x))$.

Above we denoted the number of subjects still under observation at time x as $n(x)$. The number of subjects with an event (death) at this time is $d(x)$ and the number of censored observations is denoted as $w(x)$.

Case 1: Let us first assume that anyone censored in an interval of time is censored at the end of that interval. Then the life table estimate would be computed as shown in table 2. So the 5 year survival probability estimate is 0.432. (In this case, the estimator $\hat{S}_R(5)$ is unbiased to $S(5)$.)

Case 2: Let us assume that anyone censored in an interval of time is censored right at the beginning of that interval. Then the life table estimate would be computed as shown in table 3. Here the 5 year survival probability estimate is 0.400. (In this case, the estimator $\hat{S}_L(5)$ is also unbiased to $S(5)$.)

The naive estimates range from 35% to 47.9% for the five year survival probability, while the 'complete case' (i.e., eliminating anyone censored) estimator giving an estimate of 11.6%. The life-table estimate ranges from 40% to 43.2% depending on whether we assume censoring occurred at the left (i.e., the beginning) or right (i.e., the end) of each interval.

More than likely censoring occurs during the interval. A compromise is to use the modification in table 4. The 5 year survival probability estimate is now 0.417, which is between the two estimates above. The quantity $n(x) - w(x)/2$ is often referred to as the *effective sample size*.

The Kaplan-Meier estimator

The *Kaplan-Meier* or *product limit estimator* is the limit of the life-table estimator when intervals are taken so small that only at most one observation occurs within an interval. Kaplan and Meier demonstrated in a paper in JASA (1958) that this estimator is the *maximum likelihood estimate*.

Let $d(x)$ denote the number of deaths at time x. Generally $d(x)$ is either zero or one, but we allow the possibility of tied survival times in which case $d(x)$ may be greater than one. Let $n(x)$ denote the number of individuals at risk just prior to time x, i.e., the number of individuals in the sample who neither died nor were censored prior to time x. Then the Kaplan-Meier estimate can be expressed as

$$KM(t) = \prod_{x \le t}(1 - \frac{d(x)}{n(x)}).$$

Note that in the notation above, the product changes only at times x where $d(x) \ge 1$, i.e., only at times where we observed deaths or, in general, events.

We illustrate the computation of the Kaplan-Meier estimator here on a simple example. Let us have the dataset of 10 individuals observed during 8 years; 5 of them died during the study and 5 were censored.

The calculations for the Kaplan-Meier survival function estimate correspond to the following steps.

The first step is to list all of the observed times, both censored and uncensored, from smallest to largest. If there are censored times equal to complete times, list the complete times first. Distinguish the censored and uncensored observations in some way.

The ordered data of our example are listed below.

$$1+;\ 3;\ 4+;\ 5;\ 5;\ 6+;\ 7;\ 7;\ 7+;\ 8+$$

Censored observations are denoted with a plus sign.

Next, we form a table similar to those in the actuarial table method (table 5). Each distinct uncensored time in the ordered list forms one row in the table. The first line serves to start the computations with all subjects under observation at time 0.

No subject was observed to die before 3 years. Although one subject was censored at year 1, we estimate that the probability of survival equals 1.0 up until 3 years. If T is the time to death for a random subject, we estimate that $\hat{S}(t) = \hat{P}[T > t] = 1$ for $0 < t < 3$. Note that there is no reason to believe that the subject lost to follow-up at 1 year died before 3 years.

Of the nine subjects still being observed at 3 years, one died at that time. Thus,

$$\hat{P}[T = 3 | T \ge 3] = 1/9.$$

The natural estimate for being alive past year 3 is $\hat{P}[T > 3] = 8/9$. The estimated death probability at each time is based on those subjects who are still being followed in the study at that time. Note that we are not assuming that the person lost to follow-up at year 1 did not die, which would have led to an estimate of 9/10 for the fraction alive after 3 years. Instead, we also give that person a 1/9 chance of dying at year 3. Conceptually, of the original 10 subjects, the expected number of people that die at year 3 is thus hypothesized to be $1 + 1/9$ (one observed and 1/9 hypothesized for the censored subject). The resulting hypothetical estimate for the probability of dying at year 3 would thus be $(1 + 1/9)/10 = 1/9$. This method assigns the same death probabilities to subjects who were previously censored as we observe among those who remain in the study.

No more deaths were observed between years 3 and 5, so the

natural estimate for $P[T > t]$ is $8/9$ for $3 < t < 5$.

Of the 7 subjects still alive and under observation just before year 5, two died at year 5. Among those still alive just before year 5, the natural estimate for dying at year 5 is $2/7$. That is, $\hat{P}[T = 5|T \geq 5] = 2/7$. Among those still alive at the beginning of year 5, the natural estimate for survival during that year is $5/7$. That is, $\hat{P}[T > 5|T \geq 5] = 5/7$. The cumulative probability of surviving through year 5 is equal to the probability of surviving until the beginning of year 5 multiplied by the probability of surviving through year 5 for subjects who survive until year 5. The product is $8/9 \times 5/7 = 40/63$. That is,

$$\hat{P}[T > 5] = \hat{P}[T \geq 5] \times \hat{P}[T > 5|T \geq 5].$$

Note that this multiplication of probabilities is the essential feature of the actuarial and Kaplan-Meier approaches. The conditional probability is estimated on the basis of subjects who are still being followed and who have not yet died.

The standard error (S.E.) of the Kaplan-Meier estimator for survival curve can be approximated using the Peto equation $S.E. = \hat{S}(t)\sqrt{(1 - \hat{S}(t))/n}$. We like to point out that the so-called *Greenwood's formula* yields a more accurate estimate of the standard error than does the formula presented above.

Note that if the subject with the longest follow-up has an event (i.e., has died and has not been censored), then the Kaplan-Meier survival curve drops to 0 at the time of that event. If the subject with the longest follow-up is censored, then the Kaplan-Meier estimate is undefined after that time.

Advanced statistical packages, such as Splus or SPSS, have procedures for computing the Kaplan-Meier estimator of the survival curve, together with the confidence intervals. Other quantities, such as the hazard and cumulative hazard functions, are usually estimated via formulas that relate them to the survival function, given above. Other relevant information, such as mean survival time, can also easily be extracted from the estimated survival curve (see figure 3).

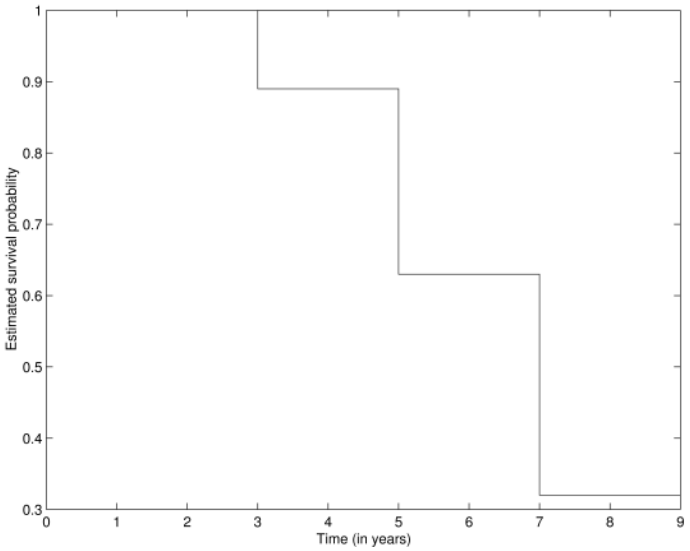

Figure 3 The estimated survival curve is a step function, i.e., it is plotted as a series of horizontal lines based on the computed values of the Kaplan-Meier estimator.

Further issues

Here we presented a clever and powerful nonparametric method for estimating the survival function from a dataset possibly containing censored observations: the Kaplan-Meier estimator. Of course, the subject of survival analysis is a lot more broad and complex and addresses a variety of other issues. For example, given two groups of individuals (e.g., males and females, smokers and non-smokers or people treated with different drugs), one can test whether one group has better chances of survival than the other group. A number of tests, such as the *log-rank test* (based on, e.g., the Kaplan-Meier estimator), were developed to give a statistically significant answer to this question.

Another very important issue is modelling the dependence of the hazard rate or survival function on external factors, such as blood pressure, dosage of a certain drug or sex or age of an individual. A celebrated method, called *Cox' proportional hazard model*, addresses this issue. This very general method was introduced in 1972 by Sir David Cox, a professor of statistics in Oxford, and since then has enjoyed wide recognition and was applied in thousands of studies and clinical trials. In fact, the original paper Cox published in the Journal of the Royal Statistical Society[2], where he introduced and studied this method, remains until today the most cited mathematical paper in the world.

For those who are interested in knowing more about survival analysis, there are plenty of books and monographs available. A good introduction into survival analysis is the book by Miller[4]. A good treatment of statistical methods of survival analysis can be found in the book by Kalbfleisch and Prentice[3]. Mathematically more advanced is the book by Andersen et al[1]. The study of this book requires sound knowledge of counting processes and of martingale theory.

References

1 Andersen, P.K., Borgan, O. Gill, R.D., Keiding, N. (1992). it Statistical Models Based on Counting Processes. Springer-Verlag.

2 Cox, D.R. (1972). Regression Models and Life-Tables. *J. Royal Stat. Soc.*, No. 2, pp. 187–220.

3 Kalbfleisch, J.D., Prentice, R.L. (1980). *The Statistical Analysis of Failure Data*. Wiley.

4 Miller, R.G. (1998). *Survival Analysis*. John Wiley & Sons, Inc.