Austral. J. Statist., 18 (3), 1976, 101–114

STATISTICAL SOCIETY OF AUSTRALIA

THE KNIBBS LECTURE FOR 1976

(July 27th, 1976)

THE THEORY OF COMPETING RISKS[1]

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Summary

The theory of competing risks is motivated, certain aspects are reviewed critically, and some extensions are indicated. A unified formulation of the theory is given covering dependent as well as independent risks. The relations between various functions useful in the theory are made explicit. In a historical note a valuable early result is put into modern notation. The currently controversial subject of identifiability when risks are dependent is discussed and it is indicated under what conditions some of the difficulties raised can be overcome. Consequences of assuming proportional hazard rates are set out. New conditions are provided under which this assumption holds and it is shown how the assumption may be tested. Some concluding remarks deal with limitations of the theory and point out areas needing further work.

1. Introduction

Suppose that, for the individuals in a particular population, possible causes of death are grouped into k classes ($k \geq 2$). Each member of the population may then be regarded as subject to k risks competing for his life. Assessing the importance of these risks over a period of time has long been a concern of demographers, vital statisticians, and actuaries, the last preferring the term *multiple decrements* where we shall speak of *competing risks*. A major aim is to gauge the effect of the elimination of one or more of the risks on the mortality structure of a population. If total elimination of a risk does not apply, we will want to be able to predict the effect of a mere change in the risk. Such a change could be brought about by a new treatment for one of the causes of death and might even be in an adverse direction due to e.g. pollution of the environment.

The situations described so far are non-experimental and refer to some large population of interest rather than to a sample from such a population. In this paper we shall be concerned primarily with experiments or observational studies in which the complications of competing risks arise. An important example is the assessment of a

[1] Work supported by the U.S. Army Research Office.

new treatment for a particular form of cancer where inferences must often be made on the basis of a limited number of cases. The experiment here consists of an operation or other treatment followed by a period of observation. This form of life testing has come to be known as *survival analysis* when human subjects are involved. If a patient dies during the course of the study, the cause of death and time to death are noted. For the survivors at the end of the experiment (and others lost to the study for extraneous reasons) the lengths of time in the experiment are recorded; technically these values are said to be *censored* since observation was stopped prior to death. Such censoring, of frequent occurrence in practice, may be regarded effectively as a competing risk, for censoring at a certain time x prevents an individual from dying from a particular cause during the experiment just as surely as does death at time x from some other cause. Thus, in particular, competing risk analysis is applicable to data in which there are no competing risks in the ordinary sense, but only a single risk with censoring. More generally, whether there is censoring or not, one may collapse all risks but the primary one into a class of ' other risks ' (the case $k=2$) or, for a more detailed analysis retain the various observed causes of death as well as censoring and loss.

There are also many applications in the physical sciences corresponding to multiple causes of failure of items undergoing a life test. The situation of k competing risks or causes of failure is in fact equivalent to that of a system of k components arranged in series, failure of one or more components leading to failure of the system. The theory of competing risks helps here in answering questions such as: If a certain component is improved what will be the effect on the performance of other parts of the system? How can we estimate the ' true ' failure rate due to a particular cause of interest in the complicating presence of other causes of failure? These questions are clearly only rewordings of earlier questions just as failure is a rewording of death. We shall move freely from one set of terms more natural in the health field to another set more familiar in a reliability context. That it is possible to do so emphasizes the unity of the theory.

As our discussion indicates it is useful to distinguish between the *crude probability* of death which refers to death from a specific cause in the presence of all other risks and the *net probability* which is the hypothetical probability of death if a specific risk is the only risk present. The probability of death from a specific cause in the presence of all risks remaining after the elimination of one or more risks is called the *partial crude probability*. These three kinds of probabilities will be made more precise in the basic mathematical formulation of the next section. First, however, we note the following important points:

(a) The distinctive feature of data admitting a competing risk analysis is that, for each individual, both cause of death and time to death must be available. The time to death must be known exactly or at least within an interval. There may possibly be more than one cause responsible for death.

(b) Our earlier statement that censoring may be regarded as a competing risk supposes that the censoring acts on individuals according to some probability distribution. Such *random censoring*

may be contrasted with the more familiar situation where censoring occurs at one or more fixed points. Even under these circumstances point estimates may still be obtained by treating the censoring as if it were a competing risk; the properties of the estimates will, however, depend on the fixed point(s) of censoring.

(c) An assumption commonly made in the theory of competing risks is that the risks act independently. As we shall see, this is a simplifying rather than an essential assumption. Likewise censoring is usually assumed to operate independently of other risks, clearly not always with justification.

2. Basic Formulation

We take the lifetimes Y_l $(l=1, \ldots, k)$ of the components in a series system to have an absolutely continuous joint distribution with p.d.f. $p(y_1, \ldots, y_k)$. The Y_l, usually assumed to be non-negative, are actually theoretical lifetimes since only the smallest, say Z, representing the life of the system, is in fact observed. As is well known, we then have, for any x,

$$\Pr\{Z>x\}=\Pr\{Y_1>x, \ldots, Y_k>x\}. \tag{1}$$

The left hand side may be termed the *survival* (or *survivor*) function of the system and denoted by $\overline{F}_Z(x)$. However, in contrast to the situation usually considered in reliability problems, we shall assume that not only Z but also the component responsible for failure is known. If this is the i-th component $(i=1, \ldots, k)$ we represent its lifetime by X_i, i.e.

$$X_i=Y_i|Y_i=Z.$$

Let π_i be the probability that failure is due to the i-th component:

$$\pi_i=\Pr\{Y_i=Z\}. \tag{2}$$

Then the p.d.f. $f_i(x)$ of X_i is given (Moeschberger and David, 1971) by

$$f_i(x)=\frac{1}{\pi_i}\int_x^\infty \cdots \int_x^\infty p(y_1, \ldots, y_{i-1}, x, y_{i+1}, \ldots, y_k) \prod_{\substack{l=1 \\ l\neq i}}^{k} dy_l. \tag{3}$$

We see that the p.d.f. $f_Z(x)$ of Z may be expressed as

$$f_Z(x)=\sum_{l=1}^{k} \pi_l f_l(x). \tag{4}$$

Now let $g_i(x)\,dx$ $(i=1, \ldots, k)$ denote the probability that, due to the i-th component, the system fails in the interval $(x, x+dx)$, given survival to time x. Then $g_i(x)$ and $f_i(x)$ are clearly related by (Gail, 1975)

$$\overline{F}_Z(x)\, g_i(x)=\pi_i f_i(x). \tag{5}$$

Note that $f_i(x)$ and $g_i(x)$ are from their definitions directly observable quantities, unlike $p_i(x)$, the p.d.f. of Y_i.

If the Y_l are independent, eqs. (1), (3), and (5) simplify respectively to

$$\overline{F}_Z(x)=\prod_{l=1}^{k} \overline{F}_l(x), \tag{1'}$$

$$(3') \qquad f_i(x) = \pi_i^{-1}\, p_i(x) \prod_{\substack{l=1 \\ l \neq 1}}^{k} \overline{P}_l(x),$$

and

$$(5') \qquad g_i(x) = p_i(x)/\overline{P}_i(x),$$

where $\overline{P}_i(x) = \Pr\{Y_i > x\}$, $i = 1, \ldots, k$. The RHS of (5') is the *hazard rate* of Y_i, commonly denoted by $r_i(x)$. Integration of (5') gives

$$(6) \qquad \overline{P}_i(x) = \exp\left[-\int_0^x r_i(t)\, dt\right]$$

which expresses the distribution of the unobservable Y_i in terms of an observable function.

The net, crude, and partial crude probabilities mentioned earlier may now all be expressed in terms of the $r_i(x)$, $r_Z(x)$, and $g_i(x)$ functions (cf. Chiang, 1968). For a time interval (a, b) we have

$$\int_a^b r_i(x)\, dx = -ln\, [\overline{P}_i(b)/\overline{P}_i(a)],$$

or

$$\exp\left[-\int_a^b r_i(x)\, dx\right] = \overline{P}_i(b)/\overline{P}_i(a)$$
$$= \text{Probability of surviving } C_i \text{ in } (a, b) \text{ after surviving } C_i \text{ to } a$$
$$= 1 - q_i(a, b),$$

where $q_i(a, b)$ is the net probability of death from C_i in (a, b). Thus

$$q_i(a, b) = 1 - \exp\left[-\int_a^b r_i(x)\, dx\right].$$

Also since

$$\exp\left[-\int_a^x r_Z(t)\, dt\right] = \text{Probability of surviving all risks in } (a, x), \text{ having survived to } a,$$

we see that the crude probability, $Q_i(a, b)$, of death for C_i in (a, b) is obtained by multiplying this expression by $g_i(x)$ and integrating. Thus

$$(7) \qquad Q_i(a, b) = \int_a^b g_i(x) \exp\left[-\int_a^x r_Z(t)\, dt\right] dx.$$

The corresponding partial crude probability with C_j eliminated is formally given by

$$(8) \qquad Q_{i \cdot j}(a, b) = \int_a^b g_i^{(-j)}(x) \exp\left[-\int_a^x r_Z^{(-j)}(t)\, dt\right] dx,$$

where $g_i^{(-j)}(x)\, dx$ and $r_Z^{(-j)}(t)$ are respectively the probability of failure in $(x, x+dx)$ from C_i and the hazard rate after elimination of C_j. Note that the probabilities q_i, Q_i, and $Q_{i \cdot j}$ are all conditional on survival to time a. In fact, (7) can equally well be written

$$(7') \qquad Q_i(a, b) = \frac{1}{\overline{F}_Z(a)} \int_a^b g_i(x)\, \overline{F}_Z(x)\, dx.$$

When the risks are independent we have $g_i^{(-j)}(x)=g_i(x)=r_i(x)$ and $r_Z^{(-j)}(t)=r_Z(t)-r_j(t)$, so that (8) reduces to

$$(8') \qquad Q_{i\cdot j}(a,b)=\int_a^b r_i(x)\exp\{-\int_a^x [r_Z(t)-r_j(t)]\,dt\}\,dx.$$

In this section and for the remainder of this paper it is assumed that there is always a single cause of death. However, multiple causes of death can also be represented by a series system provided the probability of simultaneous failure of two or more components is allowed to be positive (David, 1974 ; Lee and Thompson, 1974).

3. Historical Note

The beginnings of a theory of competing risks can be traced to a memoir read in 1760 by Daniel Bernoulli before the French Academy of Sciences. Trained in medicine as well as mathematics, Bernoulli arrived at a mathematical solution, under certain assumptions, to the following question of great interest at the time : If in a given population smallpox could be eradicated, what would be the effect on the population mortality at different ages ? Using Halley's Breslau life table of 1693 Bernoulli actually constructed a hypothetical life table corresponding to the elimination of smallpox. A key assumption was, as he recognized, that individuals saved from smallpox were subject to other causes of death in exactly the same manner as the rest of the population. This independence assumption would not hold if smallpox tended to sweep away only the weakest members of the population, a supposition Bernoulli finds reason to dismiss on the grounds that the virulence of the attack is the important element, not the state of health of the individual attacked.

Karn (1931) provides an interesting account, which allows us to be brief here, of the mathematical contributions to the above problem by Bernoulli, D'Alembert, and later writers. She includes applications of the early methods to 20th century data. Surprisingly, however, Karn does not refer to Todhunter's 1865 *History* which has several relevant entries and she does not seem to have been aware of the work of Makeham (1874).

Bernoulli assumed that in a year smallpox attacks one out of every n who have not had the disease and that one out of m attacked dies. Although he spent considerable efforts in justifying these assumptions and in estimating m and n on the basis of available data, the assumptions are unnecessarily restrictive. His severest critic D'Alembert was unduly harsh and frequently in the wrong but he did provide a modification of Bernoulli's approach which has the required flexibility. With smallpox as the first cause of death and all other causes lumped together as the second cause D'Alembert (1761) arrived at the following expression (in our notation) for the probability, $\overline{P}_2(x)$, that an individual will have lifetime exceeding x in the absence of smallpox :

$$(9) \qquad \overline{P}_2(x)=\overline{F}_Z(x)\exp\,[\int_0^x r_1(t)\,dt].$$

From (6) we see that (9) is simply $\overline{P}_2(x)=\overline{F}_Z(x)/\overline{P}_1(x)$. Karn has in effect used (9) directly on large-sample data.

4. Dependent Risks and Questions of Identifiability

From (3) it follows that the distribution of X_i $(i=1, \ldots, k)$ is completely determined by the joint distribution of the Y_l $(l=1, \ldots, k)$. Note that π_i is itself determined by this joint distribution through (2). The reverse does not necessarily hold : The $2k$ observables π_l and X_l (or equivalently, the π_l together with the distributions of the X_l) do not necessarily determine the joint distributions of the Y_l. Of course, they do so if the risks are independent, as is seen from (6). If the Y_l are not independent it can be shown (cf. Cox, 1959 ; Tsiatis, 1975) that independent random variables Y_i^* can be defined such that $f_i(x)$ in (3) can be expressed as

$$f_i(x)=\pi_i^{-1}\, p_i^*(x) \prod_{\substack{l=1 \\ l\neq i}}^{k} \bar{P}_l^*(x),$$

where $p_i^*(x)$, $\bar{P}_i^*(x)$ refer to Y_i^*. In other words, the dependent risk model with p.d.f. $p(y_1, \ldots, y_k)$ is indistinguishable from the independent risk model with p.d.f. $p_1^*(y_1) \ldots p_k^*(y_k)$.

Clearly, the possibility of explaining any set of competing risk data (for the case when the Y_l have a joint density function) by *some* independent risk model is interesting and a little disturbing. But the result must not be overinterpreted. If a specific functional form is assumed for $p(y_1, \ldots, y_k)$, there will be no difficulty, in general, in identifying the model fully, since the unknown parameters can be estimated from the likelihood function corresponding to a given set of data. The independence assumption can, in fact, be tested from e.g. the ratio of the likelihood functions under independence and under dependence. Identifiability of the joint p.d.f. has been specifically established by Nádas (1971) when Y_1 and Y_2 are bivariate normal.

5. Proportional Hazard Rates

The hazard rate of a series system is

$$r_Z(x)=f_Z(x)/\bar{F}_Z(x) \tag{10}$$

which from (4) and (5) (or directly) can be expressed as the sum of what may be termed the component hazard rates :

$$r_Z(x)=\sum_{l=1}^{k} g_l(x). \tag{11}$$

The component hazard rates may be said to be *proportional* if there exist constants K_i, such that

$$g_i(x)=K_i r_Z(x) \qquad i=1, \ldots, k. \tag{12}$$

This means that the ratio $g_i(x)/r_Z(x)$ depends only on i and not on x. The consequences of the proportionality assumption (12) have been widely studied in the case of independent risks when $g_i(x)=r_i(x)$ beginning with Cox (1959). As has been pointed out by Elandt-Johnson (1975) many of the properties proved under independence continue to hold when only (12) is true. We now list and establish the main results.

(a) *With π_i as defined in* (2)

$$K_i = \pi_i \qquad i = 1, \ldots, k.$$

Proof.
$$\pi_i = \int_0^\infty \overline{F}_Z(x)\, g_i(x)\, dx$$
$$= K_i \int_0^\infty \overline{F}_Z(x)\, r_Z(x)\, dx$$
$$= K_i \int_0^\infty f_Z(x)\, dx \qquad \text{by (10)}$$
$$= K_i.$$

(b) *If failure occurs in any interval (a, b) the probability of its being due to the i-th cause C_i is π_i, irrespective of the interval.*

Proof. Pr {failure from C_i| failure in (a, b)} =

$$\frac{\int_a^b \overline{F}_Z(x)\, g_i(x)\, dx}{\int_a^b f_Z(x)\, dx} = \pi_i.$$

(c) *The p.d.f. of X_i, given by* (3), *does not depend on i and is the same as the p.d.f. of Z.*

Proof. By (5) the p.d.f. of X_i may be written as

$$f_i(x) = \pi_i^{-1}\, g_i(x)\, \overline{F}_Z(x)$$
$$= r_Z(x)\, \overline{F}_Z(x) = f_Z(x).$$

(d) *If the theoretical lifetimes Y_l $(l = 1, \ldots, k)$ are independent, then the distribution of Y_i may be obtained from that of Z by*

$$\overline{P}_i(x) = [\overline{F}_Z(x)]^{\pi_i} \qquad i = 1, \ldots, k. \tag{13}$$

Proof. Integration of $g_i(x) = \pi_i\, r_Z(x)$ gives

$$\int_0^x g_i(t)\, dt = -\pi_i \ln \overline{F}_Z(x)$$

or

$$\exp\left[-\int_0^x g_i(t)\, dt\right] = [\overline{F}_Z(x)]^{\pi_i} \qquad i = 1, \ldots, k. \tag{14}$$

By (6) this reduces to (13) when the Y_l are independent.

A converse is immediate on reversing the steps of the proof: *If* (13) *holds then the hazard rates are proportional.*

Converses of (b) and (c) are also readily established. Corresponding to (c) we have:

If the p.d.f. of X_i does not depend on i $(i = 1, \ldots, k)$, then the Y_l $(l = 1, \ldots, k)$ have proportional hazard rates.

Proof. From $f_1(x)=\ldots=f_k(x)$ it follows by (4) that $f_i(x)=f_Z(x)$, $i=1,\ldots,k$, and hence that

$$\pi_i^{-1}\, g_i(x)\, \overline{F}_Z(x)=f_Z(x),$$

i.e.
$$g_i(x)=\pi_i\, r_Z(x) \qquad i=1,\ldots,k.$$

Thus without knowing the distribution of the Y_l we can test the null hypothesis of proportional hazard rates by a nonparametric test, e.g. Kruskal-Wallis, of whether the X's come from a common parent.

Assumption (12) is satisfied if, for example, the Y_l are independent Weibull variates with a *common* shape parameter, i.e., if for $i=1,\ldots,k$

$$p_i(x)=c\,\lambda_i\, x^{c-1} \exp\,(-\lambda_i\, x^c) \qquad x\geq 0,\ \lambda_i>0,\ c>0.$$

A simple example of proportional hazard rates for dependent risks occurs when the Y_l are exchangeable variates. We now prove the following result:

If the r.v.'s Y_l ($l=1,\ldots,k$) lead to proportional hazard rates with proportionality constants π_l, then so do the r.v.'s $Y_l^*=h(Y_l)$, where h is a monotone increasing transformation not depending on l.

Proof. Clearly, for $i=1,\ldots,k$,

$$\Pr\{Y_i^*=\min_{l=1,\ldots,k} Y_l^*\}=\Pr\{Y_i=\min Y_l\}=\pi_i.$$

Also X_i is transformed into $X_i^*=h(X_i)$. Since by (c) $f_i(x)$ does not depend on i, the p.d.f. $f_i^*(x)$ of X_i^* also cannot depend on i. The stated result follows by the converse of (c).

6. Concluding Remarks

At the end of Section 3 we indicated under what conditions dependent risk models, expressible by a joint p.d.f. of the theoretical lifetimes, remain identifiable. More work is needed to help one arrive at and test suitable models (e.g. Fisher and Kanarek, 1974). An important special case is that of survival analysis studies with just two risks, one of which is loss from the study.

It should also be noted that the independence assumption is not quite as restrictive as it may appear. Independence of the risks can often be achieved approximately by judicious grouping of perhaps a large number of distinguishable risks into k categories, within which there are similar and hence possibly dependent risks but between which there is hopefully little or no dependence. For example, Keyfitz *et al.* (1972) distinguish four causes of death: neoplasms, cardiovascular disease, accidents and violence, and all other causes. Clearly such collapsing of information is not always desirable, even if successful in creating approximately independent risk categories. Of course, one can be seriously misled, as Neyman (1975) points out forcefully, if independence of risks is assumed incorrectly. Nor must too heavy a burden be placed on the method of competing risks. It is clearly designed to deal only with relatively simple (but important) series systems which either work or have failed.

Some generalizations are possible, however. The system of interest, although still two-state, may be more complex than a series system. Simple examples such as the two-component parallel system of eyes, ears, kidneys, or lungs have already been studied (e.g., Freund, 1961). More generally it is likely that fault tree analysis (e.g., Barlow and Proschan, 1975) can be usefully combined with competing risk considerations.

In this paper only a few aspects of the theory of competing risks have been touched on. A more complete coverage will be attempted in a forthcoming short monograph (David and Moeschberger, 1977).

Addendum. I am grateful to Dr. Joseph Gani for drawing my attention to the following 72-page special publication :

Bradley, L. (1971). *Smallpox Inoculation—An Eighteenth Century Mathematical Controversy.* Adult Education Department, University of Nottingham.

This provides an English translation of Bernoulli's paper and of part of D'Alembert's. Some interesting historical remarks are also included but Bradley appears unaware of 20th century statistical references to the smallpox controversy.

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INVITED DISCUSSION OF THE PAPER BY PROFESSOR DAVID

Dr. J. S. Maritz (*CSIRO Division of Mathematics and Statistics, Melbourne*) : My own contact with the subject of Professor David's talk has been through its overlap with the analysis of survival data, especially in studies of cancer survival. Professor David's paper has introduced me to several ideas which I had not previously considered, and has made me realize that I may have taken a rather narrow view of survival analysis.

In survival analysis it has seemed reasonable to me to compound all the censoring agencies and thus to deal with two random variables, X, the survival time and $S=\min(Y_1,Y_2 \ldots)$, the censoring time. One of Professor David's references (Gail [1975]) points out that the "actuarial method" is widely used in these circumstances. The "product limit method" of Kaplan and Meier (J.A.S.A. [1958]) may be regarded as a refinement of the actuarial method and produces a maximum likelihood estimate of the survivorship function. It depends, as I understand it, on X and S being independent. On the other hand, the actuarial method does not appear to depend explicitly on such independence and is a step by step, that is, grouped, reconstruction of an approximation to the complement of the cdf of X ; for certain X and S distributions, and X and S independent this reconstruction is exact. Now, it seems to me that a general study of the goodness of this approximation may be worthwhile, and I wonder whether Professor David knows of such studies.

Professor David has dealt mainly with estimation. In survival studies one may be concerned with the comparison of two or more survivorship curves ; they would typically correspond to different treatments. An hypothesis testing approach, which I do not necessarily wish to espouse, can, in this kind of situation, be simpler than an estimation approach, especially if one uses test procedures that rely on permutation arguments. The only assumption that has to be made to test a null hypothesis of no differential treatment effect would seem to be that the censoring agencies act in the same way on the different patient groups.

It is a great pleasure to propose a vote of thanks to Professor David for a fascinating review of an interesting, and obviously important, topic.