COMPETING RISKS AND CONDITIONAL PROBABILITIES

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SUMMARY

This paper is in response to an article by Kimball [1969] on evaluation of the partial crude probabilities in the theory of competing risks. Contrary to Kimball's conclusions, it is shown that the general model of competing risks under the proportionality assumption satisfies the criteria of internal consistency and reasonableness in describing survival and death processes, and that the conditional probability suggested as a substitute for the partial crude probability violates these criteria.

1. INTRODUCTION

In a recent article in *Biometrics*, Kimball [1969] discussed extensively the partial crude probability of death in the theory of competing risks and compared it with a conditional probability. He labelled the two probabilities Model I and Model II, respectively, and made his appraisal of the two models according to three criteria: (1) internal consistency, (2) simplicity, and (3) reasonableness. I have followed Professor Kimball's criteria and used his numerical example to evaluate the two models but arrived at quite different conclusions.

2. THE TWO MODELS

In order to appreciate the argument in Kimball's article and the discussion presented below, a brief description of the two models is desirable. Detailed discussions on competing risks may be found in Chiang [1961] and [1968].

Model I. Suppose that r risks of death, denoted by $R_1, \cdots, R_r$, are acting simultaneously on an individual. For each risk, R_i, there is a mortality intensity function $\mu(t; i)$ (also known as force of mortality, hazard function, failure rate). If these risks are assumed to act independently, then it can be shown that the sum

$$\mu(t; 1) + \cdots + \mu(t; r) = \mu(t) \tag{1}$$

is the total mortality intensity function. For an individual alive at age x, we have $p_x(q_x)$ the probability of surviving (dying in) the interval $(x, x + 1)$, with $p_x + q_x = 1$. When a mortality study concerns a specific cause of death, there are three types of probabilities for an individual alive at x:

(1) *the crude probability,* $Q_i(x, x + 1)$ (or Q_{xi} for simplicity), that he will die in the interval $(x, x + 1)$ from cause R_i in the presence of all other risks;
(2) *the net probability,* $q_i(x, x + 1)$ (or q_{xi}), that he will die in $(x, x + 1)$

if R_i is the only operating risk; or conversely, the net probability, $q_{.i}(x, x+1)$ (or $q_{x.i}$), of his dying in $(x, x+1)$ if R_i is eliminated as a risk of death; and (3) *the partial crude probability,* $Q_{i.1}(x, x+1)$ (or $Q_{xi.1}$), that he will die in interval $(x, x+1)$ from R_i if R_1 is eliminated as a risk of death. Each of these probabilities serves a definite purpose in a cause-specific mortality analysis, and can be expressed in terms of the intensity functions. Thus

$$p_x = \exp\left[-\int_x^{x+1} \mu(t)\,dt\right], \qquad q_x = 1 - \exp\left[-\int_x^{x+1} \mu(t)\,dt\right], \tag{2}$$

$$Q_{xi} = \int_x^{x+1} \left\{\exp\left[-\int_x^t \mu(\tau)\,d\tau\right]\right\}\mu(t; i)\,dt \quad \text{for} \quad i = 1, \cdots, r, \tag{3}$$

with $Q_{x1} + \cdots + Q_{xr} = q_x$, and

$$\begin{aligned} q_{xi} &= 1 - \exp\left[-\int_x^{x+1} \mu(t; i)\,dt\right], \\ q_{x.i} &= 1 - \exp\left\{-\int_x^{x+1} [\mu(t) - \mu(t, i)]\,dt\right\}, \end{aligned} \tag{4}$$

$$Q_{xi.1} = \int_x^{x+1} \left[\exp\left\{-\int_x^t [\mu(\tau) - \mu(\tau; 1)]\,d\tau\right\}\right]\mu(t; i)\,dt \qquad \text{for} \quad i = 2, \cdots, r. \tag{5}$$

Consider, for example, the partial crude probability $Q_{xi.1}$. In order for an individual alive at x to die in the interval $(x, x+1)$ from risk R_i when R_1 is eliminated, he must (i) survive to a point t with the probability $\exp\{-\int_x^t [\mu(\tau) - \mu(\tau; 1)]\,d\tau\}$ and (ii) die from R_i in interval $(t, t+dt)$ with the probability $\mu(t; i)\,dt$; or, taking the two events together,

$$\left[\exp\left\{-\int_x^t [\mu(\tau) - \mu(\tau; 1)]\,d\tau\right\}\right]\mu(t; i)\,dt \quad \text{for} \quad x < t \le x + 1. \tag{6}$$

Integrating (6) over all possible values of t, for $x < t \le x + 1$, yields (5). The other formulae can be derived in a similar way. Thus the probabilities in (2), (3), (4), and (5) are mathematical representations of the corresponding process taking place continuously over a time interval in question. If for each risk R_i and within the time interval $(x, x+1)$ the ratio

$$\mu(t; i)/\mu(t) = c_{xi} \qquad \text{for } x < t \le x + 1, \qquad i = 1, \cdots, r, \tag{7}$$

is assumed independent of time t, but is a function of the interval $(x, x+1)$ and risk R_i, then the partial crude probability is given by

$$Q_{xi.1} = \frac{Q_{xi}}{q_x - Q_{x1}}\,[1 - p_x^{(q_x - Q_{x1})/q_x}], \tag{8}$$

or, in terms of the intensity functions,

$$Q_{xi.1} = \frac{\mu(t; i)}{\mu(t) - \mu(t; 1)}\left[1 - \exp\left\{-\int_x^{x+1} [\mu(t) - \mu(t; 1)]\,dt\right\}\right]. \tag{9}$$

The assumption in (7) is also known as the 'proportionality assumption.'

When the intensity functions are constant in the interval $(x, x + 1)$, with $\mu(t) = \mu(x)$ and $\mu(t; i) = \mu(x; i)$, for $x < t \leq x + 1$, the probability $Q_{xi.1}$ has the expression:

$$Q_{xi.1} = \frac{\mu(x; i)}{\mu(x) - \mu(x; 1)} [1 - e^{-[\mu(x) - \mu(x; 1)]}]. \tag{10}$$

Model II. The approach in Model II is quite different. Here one is concerned only with the probability of dying in an interval q_x (denoted by S in Kimball's original notation) and the probability of dying from a particular cause Q_{xi} (p_i in the original notation). The main feature of Model II is the conditional probability that an individual alive at x will die from R_i in $(x, x + 1)$ given that he does not die from R_1, or

$$(p_i') = Q_{xi}/(1 - Q_{x1}). \tag{11}$$

We shall now discuss the two models in terms of the criteria in Kimball's paper.

3. INTERNAL CONSISTENCY

After having examined 'Model I in terms of the criteria of desirability set forth' in his article, Kimball stated that 'It is certainly internally consistent.' This may be demonstrated as follows: Consider an individual alive at time $x = 0$ and the probability of his dying from risk R_i in the time interval (0, 2). Since the interval (0, 2) may be decomposed into two adjoining intervals (0, 1) and (1, 2), we have the equation

$$Q_i(0, 2) = Q_i(0, 1) + p(0, 1)Q_i(1, 2) \tag{12}$$

for the crude probability, where (0, 1), (0, 2), and (1, 2) indicate the intervals in question and $p(0, 1)$ is the probability of surviving the interval (0, 1). When risk R_1 is eliminated, the corresponding equations are

$$q_{.1}(0, 2) = q_{.1}(0, 1) + [1 - q_{.1}(0, 1)]q_{.1}(1, 2) \tag{13}$$

for the net probability, and

$$Q_{i.1}(0, 2) = Q_{i.1}(0, 1) + [1 - q_{.1}(0, 1)]Q_{i.1}(1, 2) \tag{14}$$

for the partial crude probability. The quantity $[1 - q_{.1}(0, 1)]$ is the net probability of surviving the interval (0, 1) when R_1 is eliminated. To verify (14), we substitute formula (5) for the partial crude probabilities and (4) for the net probability $q_{.1}(0, 1)$ in (14) and simplify the resulting expression to find

$$\begin{aligned}\int_0^2 \left[\exp\left\{-\int_0^t [\mu(\tau) - \mu(\tau; 1)]\, d\tau\right\}\right]\mu(t; i)\, dt \\ = \int_0^1 \left[\exp\left\{-\int_0^t [\mu(\tau) - \mu(\tau; 1)]\, d\tau\right\}\right]\mu(t; i)\, dt \\ + \int_1^2 \left[\exp\left\{-\int_0^t [\mu(\tau) - \mu(\tau; 1)]\, d\tau\right\}\right]\mu(t; i)\, dt.\end{aligned} \tag{15}$$

The two terms on the right-hand side of (15) have the same integrand and can be combined to give the expression on the left-hand side, proving (14). Equations (12) and (13) can be verified similarly. Therefore, Model I meets the criterion of internal consistency.

A similar statement, however, cannot be made for Model II. The conditional probability (p_i') violates this criterion. For this conditional probability, the equation corresponding to (12) is

$$\frac{Q_i(0, 2)}{1 - Q_1(0, 2)} = \frac{Q_i(0, 1)}{1 - Q_1(0, 1)} + \frac{p(0, 1)}{1 - Q_1(0, 1)} \frac{Q_i(1, 2)}{1 - Q_1(1, 2)}. \tag{16}$$

The numbers inside ( ) again indicate the time intervals involved. Equation (16) is not true in general. Take, for example, the case where $Q_i(0, 1) = Q_i(1, 2) = Q$ for $i = 1, \cdots, r$, so that $p(0, 1) = p = 1 - rQ$. the right-hand side of (16) becomes

$$\frac{Q}{1 - Q} + \frac{pQ}{(1 - Q)^2} = \frac{Q(1 - Q) + pQ}{(1 - Q)^2},$$

while the left-hand side of (16), after the substitution of (12), becomes

$$\frac{Q + pQ}{1 - Q - pQ} = \frac{Q(1 - Q) + pQ}{(1 - Q)^2} + \frac{Q^2p^2}{(1 - Q)^2(1 - Q - pQ)} > \frac{Q(1 - Q) + pQ}{(1 - Q)^2}. \tag{17}$$

Therefore Model II does not meet the criterion of internal consistency set forth in this section. See also Pike [1970]

4. SIMPLICITY

Kimball was correct in saying that the conditional probability (p_i') in Model II is simpler to compute than the partial crude probability $Q_{xi.1}$ in Model I, but neither is $Q_{xi.1}$ too complex. The important point, however, is that conceptually they are different probabilities, and one cannot be substituted for the other. Further, the simplicity of Model II seems to have been achieved with an unusual approach. In introducing the conditional probability (p_i') in place of the partial crude probability $Q_{xi.1}$, one seems to have collapsed the time interval to a single point and simply ignored the fact that survival or death of an individual in a time interval is the outcome of a continuous process. Instead of observing an individual continuously over the interval, one is in effect drawing a ball from an urn *once* to decide if the individual dies from a specific cause or survives the interval. This approach is not realistic. Of course, we could reintroduce the concept of continuous process in Model II to make the probabilities more meaningful analytically, but then we would probably find ourselves back in Model I. In this connection, Kimball was also critical about the assumption of constant forces of mortality made over a time interval, and implied that this assumption was not made in Model II. But after we have collapsed an entire time interval to a single point in Model II, there is no room for such an assumption. Certainly, using a single point to describe a continuous process is a much more bold undertaking than making an assumption of constant forces of mortality over the interval.

5. REASONABLENESS

In his investigation of 'reasonableness' of Model I, Kimball used the partial crude probability $Q_{xi.1}$ for illustration. According to Kimball, a model should be reconcilable 'with the fact that when only two diseases are present *ab initio*, the crude probability of death from R_3 decreases as μ_2 increases given μ_3 constant.' This criterion is quite reasonable. When his numerical results showed the opposite, Kimball 'was led to suspect the proportionality assumption' in (7). Further, when '$Q_{x2.1}$ and $Q_{x3.1}$ vary directly, not inversely, when R_1 is eliminated' in his example, Kimball again attributed the anomaly to the proportionality assumption. Actually, the contradictory results were not due to the proportionality assumption but rather because of differences between the crude probabilities Q_{xi} and the intensity functions $\mu(x; i)$. In the following paragraphs we shall show (a) that Model I satisfies his criterion of 'reasonableness' quoted above; (b) that his numerical example in fact supports the proportionality assumption in (7); and (c) the source of discrepancy between Kimball's conclusions and the present findings.

(a) Let us recall the formula for the partial crude probability:

$$Q_{x3.1} = \frac{\mu(x; 3)}{\mu(x) - \mu(x; 1)} [1 - e^{-[\mu(x) - \mu(x;1)]}]. \tag{10}$$

In the case of $r = 3$ risks of death, $\mu(x) - \mu(x; 1) = \mu(x; 2) + \mu(x; 3)$ and (10) may be rewritten as

$$Q_{x3.1} = \frac{\mu(x; 3)}{\mu(x; 2) + \mu(x; 3)} [1 - e^{-[\mu(x;2) + \mu(x;3)]}]. \tag{10a}$$

According to Kimball's criterion, the right-hand side of (10a) should decrease monotonically as $\mu(x; 2)$ increases for every fixed value of $\mu(x; 3)$. This can be proven as follows. Let $\mu = \mu(x; 2) + \mu(x; 3)$ and

$$f(\mu) = \mu^{-1}(1 - e^{-\mu}).$$

We need to prove that $f(\mu)$ is a monotonically decreasing function of μ, or the derivative $f'(\mu)$ is negative, for $0 < \mu < \infty$. Easy computations give the derivative

$$f'(\mu) = -\frac{e^{-\mu}}{\mu^2} (e^{\mu} - 1 - \mu) < 0 \quad \text{for} \quad 0 < \mu < \infty, \tag{18}$$

since $e^{-\mu}$, and μ^2 and $(e^{\mu} - 1 - \mu)$ are all positive, whatever may be the positive value μ. Therefore Model I under the proportionality assumption actually complies with Kimball's criterion.

TABLE 1

COMPUTATION OF THE PARTIAL CRUDE PROBABILITIES $Q_{x2.1}$ AND $Q_{x3.1}$ FROM MORTALITY INTENSITY FUNCTIONS $\mu(x; i)$

Mortality intensity functions			Partial crude probabilities*	
$\mu(x;1)$	$\mu(x;2)$	$\mu(x;3)$	$Q_{x2.1}$	$Q_{x3.1}$
(1)	(2)	(3)	(4)	(5)
.01	.01	.30	.0086	.2580
.01	.05	.30	.0422	.2531
.01	.10	.30	.0824	.2473
.01	.25	.30	.1923	.2308
.01	.50	.30	.3442	.2065
.05	.01	.30	.0086	.2580
.05	.05	.30	.0422	.2531
.05	.10	.30	.0824	.2473
.05	.25	.30	.1923	.2308
.05	.50	.30	.3442	.2065
.10	.01	.30	.0086	.2580
.10	.05	.30	.0422	.2531
.10	.10	.30	.0824	.2473
.10	.25	.30	.1923	.2308
.10	.50	.30	.3442	.2065

* Computed from equation (10).

The relationship between the partial crude probabilities $Q_{x2.1}$ and $Q_{x3.1}$ may be derived from (10a), namely

$$Q_{x2.1}/Q_{x3.1} = \mu(x; 2)/\mu(x; 3). \tag{19}$$

Thus formula (19) also is consistent with Kimball's keen observation that $Q_{x2.1}$ and $Q_{x3.1}$ should vary inversely.

(b) Numerical verification of the above theoretical results is given in Table 1. In columns (1), (2), and (3) are values of the mortality intensity functions $\mu(x; 1)$, $\mu(x; 2)$, and $\mu(x; 3)$, with $\mu(x; 3) = 0.30$ being constant in all the 15 cases. For these values of the intensity functions, the corresponding partial crude probabilities have been computed from formula (10). Column (5) shows that the partial crude probability $Q_{x3.1}$ of dying from risk R_3 'decreases as $\mu(x; 2)$ increases given $\mu(x; 3)$ constant,' again consistent with Kimball's criterion. Furthermore, $Q_{x2.1}$ and $Q_{x3.1}$ in columns (4) and (5) *do* vary inversely, as prescribed by Kimball.

(c) The remaining question is how did Kimball use the same numerical example but arrive at contradictory conclusions. The answer is that Kimball's conclusion concerning the intensity functions $\mu(x; i)$ was based on the variation of the crude probabilities Q_{xi} rather than $\mu(x; i)$. In the case of constant intensity functions assumed in the example, the probabilities Q_{xi} and the intensity functions $\mu(x; i)$ have the following relationships

$$Q_{xi} = \frac{\mu(x; i)}{\mu(x)} [1 - e^{-\mu(x)}] \quad \text{and} \quad \mu(x; i) = -\frac{Q_{xi}}{q_x} \ln (1 - q_x), \tag{20}$$

where ln stands for the natural logarithm. When several sets of values are considered, the form of variation of Q_{xi} may be quite different from the form of variation of $\mu(x; i)$. To be specific, let us take the first five cases in Kimball's example with $Q_{x2} = .01, .05, .10, .25$, and $.50$, respectively. Table 2 shows that although $Q_{x1} = .01$ and $Q_{x3} = .30$ are constant in all 5 cases, the corresponding intensity functions $\mu(x; 1)$ and $\mu(x; 3)$ are *not* constant but rather they increase with the increasing values of Q_{x2}. Generally, when Q_{xi} are kept constant, for $i \neq 2; i = 1, 3, \cdots, r$, the corresponding intensity function $\mu(x; i)$ increases with increasing values of Q_{x2}, or with increasing values of q_x (since $q_x = Q_{x1} + \cdots + Q_{xr}$). In other words, the function

$$h(q_x) = -q_x^{-1} \ln (1 - q_x) \tag{21}$$

in the second equation of (20) is a monotonically increasing function of q_x. Taking the derivative of $h(q_x)$ with respect to q_x yields

$$h'(q_x) = \frac{1}{q_x^2} \left[\ln (1 - q_x) + \frac{q_x}{1 - q_x} \right] = \sum_{n=2}^{\infty} \frac{n - 1}{n} q_x^{n-2}, \tag{22}$$

since q_x lies in the interval $0 \leq q_x \leq 1$. The last expression in (22) is always positive for positive values of q_x. Hence the function $h(q_x)$ increases with q_x, and $\mu(x; i)$ increases with Q_{x2}, as required to be shown.

Kimball used Q_{xi} and formula (8) to compute the partial crude probability $Q_{x3.1}$ and observed 'an *increase* in the probability of death from R_3 (i.e. $Q_{x3.1}$) as the probability of death from cause R_2 is increased.' Based on this observation he arrived at his conclusions regarding Model I under proportionality assumption. As we can see from Table 2 now that the increasing values of the partial crude probability $Q_{x3.1}$ are associated with the increasing values of $\mu(x; 3)$, this is not a surprising phenomenon.

It may be interesting to note in Kimball's computations (reproduced in columns (7) and (8), Table 2) that the conditional probability (p_3') in Model II *does not* decrease (but remains constant) as Q_{x2} increases given Q_{x3} constant; and neither do (p_2') and (p_3') vary inversely. Thus Model II seems to have violated the criterion of 'reasonableness.'

It should be emphasized that this paper is not intended to be critical of Kimball's fine work. Certainly the discussion in this section does not imply in any way that Kimball was unaware of the difference between the probabilities Q_{xi} and the intensity function $\mu(x; i)$. Kimball was more concerned with the biological application than mathematical properties of the models in his paper. In using the probability rather than the intensity function in his evaluation of the two models, Kimball in effect sacrificed his statistical perfection for practical application. Such an attitude is quite plausible, and we all have to have it at times. Unfortunately, in this case, unexpected contradictory results have crept in.

TABLE 2

COMPUTATION OF THE PARTIAL CRUDE PROBABILITIES $Q_{x2.1}$ AND $Q_{x3.1}$ AND CONDITIONAL PROBABILITIES (p_2') AND (p_3')

Crude probabilities			Mortality intensity functions*			Conditional probabilities		Partial crude Probabilities**	
Q_{x1}	Q_{x2}	Q_{x3}	$\mu(x;1)$	$\mu(x;2)$	$\mu(x;3)$	(p_2')	(p_3')	$Q_{x2.1}$	$Q_{x3.1}$
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
.01	.01	.30	.0121	.0121	.3615	.0101	.3030	.0101	.3016
.01	.05	.30	.0124	.0620	.3719	.0505	.3030	.0503	.3017
.01	.10	.30	.0129	.1287	.3860	.1010	.3030	.1006	.3018
.01	.25	.30	.0147	.3665	.4398	.2525	.3030	.2516	.3019
.01	.50	.30	.0205	1.0251	.6151	.5050	.3030	.5038	.3022
.05	.01	.30	.0620	.0124	.3719	.0105	.3158	.0103	.3088
.05	.05	.30	.0638	.0638	.3831	.0526	.3158	.0515	.3089
.05	.10	.30	.0664	.1328	.3985	.1053	.3158	.1030	.3092
.05	.25	.30	.0764	.3818	.4582	.2632	.3158	.2583	.3100
.05	.50	.30	.1116	1.1159	.6696	.5265	.3158	.5202	.3121
.10	.01	.30	.1287	.0129	.3860	.0111	.3333	.0106	.3183
.10	.05	.30	.1328	.0664	.3985	.0556	.3333	.0531	.3187
.10	.10	.30	.1386	.1386	.4159	.1111	.3333	.1064	.3192
.10	.25	.30	.1615	.4038	.4845	.2778	.3333	.2676	.3211
.10	.50	.30	.2558	1.2792	.7675	.5555	.3333	.5442	.3266

* Computed from the second equation in (20).

** May be computed from either Q_{xi} using equation (8) or $\mu(x;i)$ using (10).

6. INDEPENDENCE OF RISKS

Kimball has also pointed out in his paper, as many other authors have done in the past, the independence assumption regarding the risks $R_1, \cdots, R_r$ made in Model I as shown in equation (1). Under this assumption, the risks act independently from one another on every individual exposed to these risks. Actually this is much stronger an assumption than necessary for the formulation of competing risks. It was made more for the simplicity of formulae than anything else. To clarify this, let us suppose that the independence assumption is not true and that there is an 'interaction' between two risks, say R_1 (tuberculosis) and R_3 (pneumonia). How to evaluate the crude probability of dying from pneumonia if tuberculosis is removed as a cause of death in this situation? The problem can be resolved by creating another risk, say R_2 (pneumonia and tuberculosis). When tuberculosis is removed as a cause of death, the partial crude probability of dying in interval $(x, x + 1)$ from pneumonia is $Q_{x3.12}$ rather than $Q_{x3.1}$. The probability $Q_{x3.12}$ can be computed from the probabilities p_x, q_x and the crude probabilities Q_{xi}. Of course, one can visualize other situations for which more complex solutions will be necessary. Incidentally, the independence assumption is also implied in the multinomial distribution in Model II; without this assumption, we will have difficulties in justifying that Q_{xi} are multinomial probabilities.

To be quite frank, the entire idea of limiting our attention to death is not realistic. We must recognize the fact that the death of an individual is usually preceded by an illness (condition, disorder). It is not realistic to speak of a person's chance of dying from tuberculosis when he is not even affected with the disease. Also competition of risks of death depends on the health condition of an individual: a person affected with a disease (say, cardiovascular-renal (CVR) diseases) probably has a probability of dying of a second disease different from a person who is not affected with CVR. Therefore, a mortality study is incomplete unless illness is taken into consideration. Illness and death are distinct and different types of events. Illnesses are potentially concurrent, repetitive, and reversible, whereas death is an irreversible or absorbing state. The study of illness adds a new dimension and a new complexity to the general problem of mortality, but it makes the underlying assumption regarding mortality intensity functions more realistic and more reasonable. A detailed exploration of the illness processes is beyond the domain of the present note. The reader may refer to Fix and Neyman [1951] for early work and to Chiang ([1968] chapters 4 & 5) for a discussion on the illness process.

RISQUES COMPETITIFS ET PROBABILITES CONDITIONNELLES

RESUME

Cet article est écrit en réponse à un article de Kimball [1969] sur l'évaluation des probabilités brutes partielles dans la théorie des risques compétitifs. Contrairement aux conclusions de Kimball on montre que le modèle général de risques compétitifs, sous

l'hypothèse de proportionnalité, satisfait les critères de consistance interne et est un modèle raisonnable pour décrire les processus de survie et de mort, et que les probabilités conditionnelles suggérées comme substituts des probabilités brutes partielles n'obéissent pas à ces critères.

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Received December 1969, *Revised July* 1970