ON COMPARING SURVIVAL TIMES

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1. Introduction

Let us consider two positive random variables, say $\tau > 0$ and $\tau^* > 0$, representing respectively length of life of individuals, as measured from some suitable starting point $t = 0$, in two hypothetical populations, one characterized by some given set of conditions, say C, the other by a different set of conditions, C^*. We assume that each of the populations is homogeneous so that their members have the same, though unknown, probability of surviving to future times. Let us call

$$P_t = P\{\tau > t\}, \tag{1}$$

the survivorship function under C and

$$P_t^* = P\{\tau^* > t\}, \tag{2}$$

the survivorship function under C^*.

For example, τ may represent the length of life in a population of children afflicted with nephrosis at approximately the same age who did not receive adrenocortical hormones and τ^* the length of life of similar children who however have been subjected to adrenocortical hormone therapy. Or τ may represent the length of life of tumors implanted in mice when subject to a certain schedule of irradiation, and τ^* represents the regression time of such tumors when the radiotherapy is supplemented by the administration of some antimetabolite.

Our purpose in replacing the set of circumstances C by C^* in both of these examples is to influence the length of life in the population. In the first example, we would like to increase it; in the second, to decrease it. By what criteria should we judge the change, that is, how should the distributions of survival times P_t and P_t^* be compared?

In some branches of medical investigations, notably cancer research, a tradition has been developed by which a fixed value of t is selected, say t_0 and a method of management C^* is judged superior to C if the observations seem to indicate that $P_{t_0}^*$ is larger than P_{t_0}. There is by now a large statistical literature (see, for example, [1] to [17]), supplying methods of estimating and comparing the survivorship functions at a preselected point, to suit different degrees of a priori

[1] Work started under University of California Grant RG-3666, U.S. Public Health Service, and completed with partial support of the School of Aviation Medicine, Brooks Air Force Base, Texas, Contract AF 41(657)-214.

[2] Work partially supported by the School of Aviation Medicine, Brooks Air Force Base, Texas, Contract AF 41(657)-214.

knowledge about the functions on the one hand and different types of available observations on the other.

The judicious choice of the single point t_0, however, often presents a difficult if not insurmountable problem. It is clearly much less arbitrary to compare the survivorship functions simultaneously at several different time points, especially since the investigator can usually choose a set of points, say $t = 1, \cdots, T$ in such a way that observations taken at these points provide him with an adequate picture of the entire course of the curves. Let us suppose that this is indeed the case. Then, in analogy to the multiple comparisons of Scheffé in the analysis of variance [18], one would like to obtain joint confidence intervals for all true differences $P_t - P_t^*$, with $t = 1, \cdots, T$. In this paper we present an asymptotic solution to this problem. The confidence intervals obtained are such that as the number of observations is indefinitely increased, their joint confidence coefficient is in the limit at least $1 - \alpha$, where $\alpha > 0$ has been selected in advance. In extending Scheffé's method to our case we shall make use of some recent results of Gold [19] concerning the theory of discrete, finite Markov chains.

2. The simplest case

Let us assume that at $t = 0$, the time from which survival is measured, we have available a random sample of $N = M + M^*$ individuals drawn from a homogeneous population and randomly allocated to conditions C and C^*. Let M be the number of individuals under C and M^* under C^*. The simplest version of our problem arises if at each time point $t = 1, \cdots, T$ we are in a position to establish for each individual whether he is dead or alive. Then we can classify the individuals into $T + 1$ exclusive classes, by putting an individual into class R_{T+1} if he survives beyond T and into class R_j if he is alive at $t = j - 1$ but dead at $t = j$, for $j = 1, \cdots, T$. Let $P(R_j)$ be the probability of R_j for an individual under C and $P^*(R_j)$ under C^*, for $j = 1, \cdots, T + 1$. Clearly

$$(3) \qquad P_t = \sum_{j=t+1}^{T+1} P(R_j), \qquad P_t^* = \sum_{j=t+1}^{T+1} P^*(R_j),$$

so the differences $P_t - P_t^*$ are linear functions of two sets of multinomial class probabilities. To obtain confidence intervals for them, we need the following result, proved in [19], concerning multinomial trials.

Let us consider s independent sequences of multinomial trials, the ith sequence having class probabilities $P_{ij} > 0$, for $j = 1, \cdots, \nu_i$; $i = 1, \cdots, s$, such that $\sum_j P_{ij} = 1$. Let the number of trials in the ith sequence be M_i, let the number of outcomes in class j of the ith sequence be n_{ij} and put the relative frequencies

$$(4) \qquad \frac{n_{ij}}{M_i} = \hat{p}_{ij}; \qquad i = 1, \cdots, s; \quad j = 1, \cdots, \nu_i.$$

Let $N = \sum_{i=1}^{s} M_i$ increase indefinitely in such a way that the proportions M_i/N approach some constants, at least in probability.

THEOREM 1. *For any system of real numbers*

$$\{b_{ij}, j = 1, \cdots, \nu_i; i = 1, \cdots, s\}, \tag{5}$$

let

$$L = \sum_{i,j} b_{ij}P_{ij}, \qquad \hat{L} = \sum_{i,j} b_{ij}\hat{P}_{ij}. \tag{6}$$

Further, denote by $\sigma_{\hat{L}}^2$ *the variance of* $\hat{L}$ *and by* $\hat{\sigma}_{\hat{L}}$ *the value of* $\sigma_{\hat{L}}$ *at* $P_{ij} = \hat{P}_{ij}$. *Then as* $N \to \infty$ *in the manner described above,*

$$\lim_{N\to\infty} P\left\{\frac{|\hat{L} - L|}{\hat{\sigma}_{\hat{L}}} \leqq K \text{ for all } L \text{ simultaneously}\right\} \geqq 1 - \alpha, \tag{7}$$

where K *is the positive square root of the* $(1 - \alpha)$*th percentile of the* χ^2*-distribution with* $\sum_{i=1}^{s} (\nu_i - 1)$ *degrees of freedom.*

This theorem can be directly applied to our problem in the simple experimental setup described, with $s = 2$, $P_{1j} = P(R_j)$, $P_{2j} = P^*(R_j)$, $M_1 = M$, $M_2 = M^*$, $n_{1j} = n_j$ = number of individuals observed to die between $t = j - 1$ and $t = j$ under C, and $n_{2j} = n_j^*$ = number of individuals observed to die between $t = j - 1$ and $t = j$ under C^*,

$$\hat{P}(R_j) = \frac{n_j}{M}, \qquad \hat{P}^*(R_j) = \frac{n_j^*}{M^*}. \tag{8}$$

The particular linear functions we wish to estimate, namely $P_t - P_t^*$, for $t = 1, \cdots, T$, are of the form

$$P_t - P_t^* = \sum_{j=t+1}^{T+1} (P_{1j} - P_{2j}), \tag{9}$$

with

$$\hat{P}_t - \hat{P}_t^* = \sum_{j=t+1}^{T+1} (\hat{P}_{1j} - \hat{P}_{2j}) \tag{10}$$

and

$$\hat{\sigma}^2_{\hat{P}t-\hat{P}_t^*} = \frac{1}{M}\sum_{j=t+1}^{T+1} \frac{n_j}{M}\left(1 - \sum_{j=t+1}^{T+1} \frac{n_j}{M}\right) + \frac{1}{M^*}\sum_{j=t+1}^{T+1} \frac{n_j^*}{M^*}\left(1 - \sum_{j=t+1}^{T+1} \frac{n_j^*}{M^*}\right). \tag{11}$$

Thus, in the limit as the number of observations increases indefinitely, the values of the functions $P_t - P_t^*$ simultaneously satisfy the inequalities

$$(\hat{P}_t - \hat{P}_t^*) - K\hat{\sigma}_{\hat{P}t-\hat{P}_t^*} \leqq P_t - P_t^* \leqq (\hat{P}_t - \hat{P}_t^*) + K\hat{\sigma}_{\hat{P}t-\hat{P}_t^*}, \qquad t = 1, \cdots, T, \tag{12}$$

with probability at least $1 - \alpha$. Here K is the positive square root of the upper $(1 - \alpha)$th percentage point of the χ^2 distribution with $2T$ degrees of freedom.

3. A Markov chain model

While observations of the kind described may sometimes be available, for example, in studies on laboratory animals or institutionalized populations, this is not generally the case. Let us suppose for example that we are dealing with a clinical study in which the subjects of the investigation may enter or leave observation at times of their own choice. Among the $M + M^*$ individuals under observation at time 0, there may be at each subsequent observation time t some whose whereabouts have become unknown during the period $t - 1$ to t and about whom it is impossible to establish whether they are dead or alive at t. These people are usually called "lost." Under these circumstances, it has been proposed by Neyman [8], [10] and others [11], [15] that one consider the observations as sample functions from a chain, say $\{\zeta_t, t = 1, \cdots, T\}$ with states 0, 1, 2, 0*, 1*, 2*, by putting for an individual from C,

$\zeta_t = 0$, if he is alive and present at t,
$\zeta_t = 1$, if he is dead and present at t,
$\zeta_t = 2$, if he is lost at t;

and for an individual from C^*,

$\zeta_t = 0^*$, if he is alive and present at t,
$\zeta_t = 1^*$, if he is dead and present at t,
$\zeta_t = 2^*$, if he is lost at t.

Denote by $p_{ijt} = P\{\zeta_t = i | \zeta_{t-1} = j\}$ the probability that an individual is in state i at time t, given that he was in state j at time $t - 1$, for $i, j = 0, 0^*, 1, 1^*, 2, 2^*$; $t = 1, \cdots, T$. We shall assume that once an individual is lost, he is lost forever, so that the set of transitions for which $0 < p_{ijt} < 1$, for $t = 1, \cdots, T$, is given by $\{00, 01, 02, 0^*0^*, 0^*1^*, 0^*2^*\}$. It is easy to see that if the parent populations are homogeneous then $\{\zeta_t\}$ is a Markov chain.

It is important to note, as emphasized in [8], [15] that the probabilities of being present and alive at t, which are simple functions of the p_{ijt}, are not identical with the probabilities P_t and P_t^* of surviving to time t. Thus, if one hopes to draw inferences about P_t and P_t^* from observations on $\{\zeta_t\}$, one must postulate some functional relationship between P_t and P_t^* on the one hand and the p_{ijt} on the other. Several such relationships have been suggested (see [20], [4], [8], [11], [15]), reducing our problem of simultaneously estimating $(P_t - P_t^*)$, where $t = 1, \cdots, T$, to that of the joint estimation of some specified functions of the transition probabilities in a Markov chain. This problem may also arise in other experimental situations, for example when not only survivorship but also specific causes of death are of interest, or in industrial life testing. Our solution is based on some results from the theory of Markov chains which are discussed in the next section.

4. Some results concerning Markov chains

Let $\{\xi_t, t = 0, 1, \cdots, T\}$ be a Markov chain with state space $S = \{1, \cdots, m\}$ and let p_{ijt} be the conditional probability that $\xi_t = j$, given that $\xi_{t-1} = i$,

$$0 \leqq p_{ijt} \leqq 1, \qquad \sum_j p_{ijt} = 1, \qquad i, j \in S; \quad t = 1, \cdots, T. \tag{13}$$

Let (i, j, t) denote a triple of indices, $i, j \in S$, $t = 1, \cdots, T$, and let

$$I = \{(i, j, t): 0 < p_{ijt} < 1\}. \tag{14}$$

Let p denote the vector of transition probabilities

$$p = \{p_{ijt}, (i, j, t) \in I\}. \tag{15}$$

For each fixed i, t eliminate one of the p_{ijt} through the relation $\sum_j p_{ijt} = 1$ and denote by f the number of remaining components of p.

Consider N independent sample functions of $\{\xi_t\}$, to be called "individuals." For any t, let $n_i(t)$ be the number of individuals in state i at t, let n_{ijt} be the number of individuals entering state j at time t among those having been in state i at $t - 1$, and let

$$\hat{p}_{ijt} = \frac{n_{ijt}}{n_i(t-1)} \tag{16}$$

for $n_i(t-1) \neq 0$, and $(i, j, t) \in I$. Let $\hat{p}$ denote the vector p when its components have been replaced by $\hat{p}_{ijt}$.

We shall be concerned with the asymptotic behavior of the chain when N is infinitely increased but the proportions of individuals occupying the various states at time 0, that is, $n_i(0)/N$, with $i = 1, \cdots, m$, either remain constant or tend, at least in probability, to a set of constants independent of N.

Under these conditions, the limiting behavior of the chain simulates that of independent sequences of multinomial trials in some important respects. In particular, the following facts are implied by the results of Neyman [21] and of Anderson and Goodman [22]:

(a) The joint distribution of the variables $[En_i(t-1)]^{1/2}(\hat{p}_{ijt} - p_{ijt})$, $(i, j, t) \in I$, tends to the f-dimensional normal distribution with 0 means and covariance matrix $||\sigma_{ijt,i'j't'}||$, where

$$\sigma_{ijt,ijt} = p_{ijt}(1 - p_{ijt}), \qquad \sigma_{ijt,ikt} = -p_{ijt}p_{ikt}, \qquad j \neq k, \tag{17}$$

and

$$\sigma_{ijt,i'j't'} = 0, \qquad i' \neq i \quad \text{and/or} \quad t' \neq t. \tag{18}$$

(b) The random variable

$$\sum_I n_i(t-1) \frac{(\hat{p}_{ijt} - p_{ijt})^2}{\hat{p}_{ijt}} = \chi^2(N) \tag{19}$$

is asymptotically distributed as χ^2 with f degrees of freedom.

(c) If $F(p)$ is any function of p possessing continuous partial derivatives at least up to the second order, and if R is the remainder after linear terms of the Taylor expansion of $F(p)$ about $\hat{p}$, then $p \lim \sqrt{N}\, R = 0$.

(d) The distribution of the variable $\sqrt{N}[F(\hat{p}) - F(p)]$ tends to a normal distribution with zero mean and variance

$$\sigma_{\hat{p}}^2 = \sum_{i,t} \left[E \frac{n_i(t-1)}{N}\right]^{-1} \left[\sum_j \left(\frac{\partial F}{\partial p_{ijt}}\right)^2 p_{ijt} - \left(\sum_k \frac{\partial F}{\partial p_{ikt}} p_{ikt}\right)^2\right], \tag{20}$$

which is independent of N and where $(i, j, t) \in I$ and $(i, k, t) \in I$.

It has also been shown [19] that theorem 1 can be extended to Markov chains.

THEOREM 2. *For any system of real numbers* $\{b_{ijt}, (i, j, t) \in I\}$ *let*

$$L = \sum_I b_{ijt}p_{ijt}, \qquad \hat{L} = \sum_I b_{ijt}\hat{p}_{ijt}. \tag{21}$$

Denote by σ_L^2 *the variance of the limiting distribution of* $\sqrt{N}(\hat{L} - L)$ *and let* D_L *be the value of* $\sigma_{\hat{L}}$ *when* p *is replaced by* $\hat{p}$. *Then as* $N \to \infty$ *in the manner described above,*

$$\lim_{N\to\infty} P\left\{\frac{\sqrt{N}|\hat{L} - L|}{D_L} < K \text{ for all } L \text{ simultaneously}\right\} \geqq 1 - \alpha, \tag{22}$$

where $0 < \alpha < 1$ *is arbitrarily selected and* K *is the positive square root of the* $(1 - \alpha)$th *percentile of the* χ^2 *distribution with* f *degrees of freedom.*

REMARK. Let $\epsilon > 0$ be given and let N be so large that

$$P\left\{\frac{\sqrt{N}|\hat{L} - L|}{D_L} < K, \text{ for all } L\right\} > 1 - \alpha - \epsilon. \tag{23}$$

Then, if $\{\beta_{ijt}, (i, j, t) \in I\}$ is any set of functions of the observation vector $\hat{p}$, the linear functions $L = \sum_I \beta_{ijt}p_{ijt}$ are certainly included among all possible L referred to in the inequality, with

$$\hat{L} = \sum_I \beta_{ijt}\hat{p}_{ijt} \tag{24}$$

and

$$D_L^2 = \sum_{i,t} \frac{N}{n_i(t-1)} \left[\sum_j \beta_{ijt}^2\hat{p}_{ijt} - \left(\sum_k \beta_{ikt}\hat{p}_{ikt}\right)^2\right]. \tag{25}$$

We now extend theorem 2 to permit us to deal with a wider class of functions.

THEOREM 3. *For any finite collection of functions of the transition probabilities,* $F_v(p)$, $v = 1, \cdots, h$, *which possess continuous partial derivatives at least up to the second order, let* $\hat{F}_v = F_v(\hat{p})$, *let* $\sigma_{\hat{F}_v}^2$ *be the variance of the asymptotic distribution of* $\sqrt{N}(\hat{F}_v - F_v)$ *and let* D_v *be the value of* $\sigma_{\hat{F}_v}$ *when* p *is replaced by* $\hat{p}$. *Then under the limiting conditions described,*

$$\lim_{N\to\infty} P\left\{\frac{\sqrt{N}|\hat{F}_v - F_v|}{D_v} < K, \qquad v = 1, \cdots, h\right\} \geqq 1 - \alpha, \tag{26}$$

where $0 < \alpha < 1$ *is arbitrarily selected and* K *is the positive square root of the* $(1 - \alpha)$th *percentile of the* χ^2 *distribution with* f *degrees of freedom.*

PROOF. Expanding $F_v(p)$ in a Taylor series about $\hat{p}$,

$$F_v(p) = F_v(\hat{p}) + \sum_I \left.\frac{\partial F_v(p)}{\partial p_{ijt}}\right|_{p=\hat{p}} (p_{ijt} - \hat{p}_{ijt}) + R_v = L_v + R_v, \tag{27}$$

where $L_v = L_v(p)$ is a linear combination of the components of p with coefficients depending on the observations and such that $L_v(\hat{p}) = \hat{L}_v = \hat{F}_v$, and where $p \lim \sqrt{N}\, R_v = 0$ by (c).

Calculating D_{L_v} from (25), we see that

$$D_{L_v} = D_v. \tag{28}$$

It follows that

$$p \lim D_{L_v} = p \lim D_v = \sigma_{\hat{F}_v}, \tag{29}$$

by a theorem of Slutsky [23], and that

$$p \lim_{N \to \infty} \frac{\sqrt{N}|R_v|}{D_{L_v}} = 0, \qquad v = 1, \cdots, h. \tag{30}$$

Now, given any $\epsilon > 0$,

$$\begin{aligned} P\left\{\frac{\sqrt{N}|\hat{F}_v - F_v|}{D_v} < K, \quad v = 1, \cdots, h\right\} \\ \geqq P\left\{\frac{\sqrt{N}|\hat{L}_v - L_v|}{D_v} + \frac{\sqrt{N}|R_v|}{D_v} < K, \quad v = 1, \cdots, h\right\} \\ > P\left\{\frac{\sqrt{N}|\hat{L}_v - L_v|}{D_v} < K - \epsilon, \quad \frac{\sqrt{N}|R_v|}{D_v} < \epsilon, \quad v = 1, \cdots, h\right\}. \end{aligned} \tag{31}$$

By the remark following theorem 2 and by (28), for any arbitrary $\eta > 0$ and $N > N_\eta$,

$$\begin{aligned} P\left\{\frac{\sqrt{N}|\hat{L}_v - L_v|}{D_v} < K - \epsilon, \quad v = 1, \cdots, h\right\} \\ \geqq P\{\chi^2(N) < K - \epsilon\} > 1 - \alpha - \delta(\epsilon) - \eta, \end{aligned} \tag{32}$$

where $\delta(\epsilon) \to 0$ as $\epsilon \to 0$. On the other hand, for any $N > N_{(\epsilon, h)}$,

$$P\left\{\frac{\sqrt{N}|R_v|}{D_v} < \epsilon, \quad v = 1, \cdots, h\right\} > 1 - \epsilon, \tag{33}$$

by (30). Finally, for $N > \max [N_\eta, N_{(\epsilon, h)}]$ we have

$$P\left\{\frac{\sqrt{N}|\hat{F}_v - F_v|}{D_v} < K, \quad v = 1, \cdots, h\right\} > 1 - \alpha - \delta(\epsilon) - \epsilon - \eta, \tag{34}$$

which establishes the theorem.

A similar extension of theorem 1 can be obtained by the same argument.

5. Joint estimation of survival rates in a clinical follow-up

We shall illustrate the applicability of theorem 3 to our problem in the case of a clinical follow-up as described by the Markov chain $\{\zeta_t\}$ of section 3, assuming that the functional relationship between the survivorship functions and the transition probabilities of the chain is given by the so-called "actuarial" model or "half-rule." We choose this model because it is very widely used (see, for example [4]), leaving aside entirely questions of its justification. Following the notation conventional in this model, we put for $t = 0, 1, \cdots, T - 1$, for an individual in C,

$\delta_t = p_{0,1,t+1}$ = conditional probability of dying under observation by $t + 1$, given alive and present at t;

$\omega_t = p_{0,2,t+1}$ = conditional probability of being lost to observation at $t+1$, given alive and present at t;

$1 - \delta_t - \omega_t = p_{0,0,t+1}$ = conditional probability of being alive and present at $t+1$, given alive and present at t; and for an individual in C^*, the symbols δ_t^*, ω_t^*, and $1 - \delta_t^* - \omega_t^*$ are analogously defined. Let

$$q_t = 1 - \frac{P_{t+1}}{P_t}, \qquad q_t^* = 1 - \frac{P_{t+1}^*}{P_t^*}, \qquad t = 0, 1, \cdots, T-1, \tag{35}$$

be the conditional probabilities of dying by $t+1$, given that the individual was alive at t, for the members of C and C^* respectively. With this notation, the actuarial formulas state that

$$q_t = \frac{\delta_t}{1 - \omega_t/2}, \qquad q_t^* = \frac{\delta_t^*}{1 - \omega_t^*/2}, \qquad t = 0, 1, \cdots, T-1, \tag{36}$$

and

$$P_v - P_v^* = \prod_{t=0}^{v-1} (1 - q_t) - \prod_{t=0}^{v-1} (1 - q_t^*), \qquad v = 1, \cdots, T. \tag{37}$$

Let $F_v = P_v - P_v^*$, for $v = 1, \cdots, T$. By theorem 3, in the limit as $N \to \infty$, the probability is at least $1 - \alpha$ that the functions $(P_v - P_v^*)$ simultaneously satisfy the inequalities

$$(\hat{P}_v - \hat{P}_v^*) - KS_v \leqq P_v - P_v^* \leqq (\hat{P}_v - \hat{P}_v^*) + KS_v, \tag{38}$$

where K is the positive square root of the $(1 - \alpha)$th percentile of the χ^2 distribution with $4T$ degrees of freedom and S_v is defined by

$$\begin{aligned} S_v^2 = \sum_{t=0}^{v-1} \frac{1}{n_0(t)} & \left\{\hat{\delta}_t(1 - \hat{\delta}_t)\left(\frac{\partial F_v}{\partial \delta_t}\bigg|_{\hat{p}}\right)^2 + \hat{\omega}_t(1 - \hat{\omega}_t)\left(\frac{\partial F_v}{\partial \omega_t}\bigg|_{\hat{p}}\right)^2 - 2\hat{\delta}_t\hat{\omega}_t \frac{\partial F_v}{\partial \delta_t}\bigg|_{\hat{p}} \frac{\partial F_v}{\partial \omega_t}\bigg|_{\hat{p}}\right\} \\ + \sum_{t=0}^{v-1} \frac{1}{n_0^*(t)} & \left\{\hat{\delta}_t^*(1 - \hat{\delta}_t^*)\left(\frac{\partial F_v}{\partial \delta_t^*}\bigg|_{\hat{p}}\right)^2 + \hat{\omega}_t^*(1 - \hat{\omega}_t^*)\left(\frac{\partial F_v}{\partial \omega_t^*}\bigg|_{\hat{p}}\right)^2 - 2\hat{\delta}_t^*\hat{\omega}_t^* \frac{\partial F_v}{\partial \delta_t^*}\bigg|_{\hat{p}} \frac{\partial F_v}{\partial \omega_t}\bigg|_{\hat{p}}\right\}. \end{aligned} \tag{39}$$

The values of the derivatives are

$$\frac{\partial F_v}{\partial \delta_t}\bigg|_{\hat{p}} = \frac{-\hat{P}_v}{1 - \frac{\hat{\omega}_t}{2} - \hat{\delta}_t} \tag{40}$$

$$\frac{\partial F_v}{\partial \omega_t}\bigg|_{\hat{p}} = \frac{\hat{\delta}_t\hat{P}_v}{2\left(1 - \frac{\hat{\omega}_t}{2}\right)\left(1 - \frac{\hat{\omega}_t}{2} - \hat{\delta}_t\right)}, \tag{41}$$

$$\frac{\partial F_v}{\partial \delta_t^*}\bigg|_{\hat{p}} = \frac{\hat{P}_v^*}{1 - \frac{\hat{\omega}_t^*}{2} - \hat{\delta}_t^*}, \tag{42}$$

(43)
$$\left.\frac{\partial F_v}{\partial \omega_t^*}\right|_{\hat{p}} = \frac{-\hat{\delta}_t^* \hat{P}_v^*}{2\left(1 - \frac{\hat{\omega}_t^*}{2}\right)\left(1 - \frac{\hat{\omega}_t^*}{2} - \hat{\delta}_t^*\right)}.$$

Here $t = 0, 1, \cdots, v - 1; v = 1, \cdots, T$, and

(44)
$$\hat{\delta}_t = \frac{d_t}{n_0(t)}, \quad \hat{\delta}_t^* = \frac{d_t^*}{n_0^*(t)},$$
$$\hat{\omega}_t = \frac{w_t}{n_0(t)}, \quad \hat{\omega}_t^* = \frac{w_t^*}{n_0^*(t)},$$

with

d_t = number of individuals dead and present at $t + 1$ among those alive and present at t under conditions C;

w_t = number of individuals lost by $t + 1$ among those present and alive at t under conditions C; and d_t^* and w_t^* are correspondingly defined for individuals under C^*.

REFERENCES

[1] M. Greenwood, *The Natural Duration of Cancer*, Reports on Public Health and Medical Subjects, No. 33, London, His Majesty's Stationery Office, 1926.

[2] J. O. Irwin, "Recent advances in mathematical statistics," *J. Roy. Statist. Soc., Ser. A*, Vol. 98 (1935), pp. 83–127.

[3] J. W. Boag, "Maximum likelihood estimates of the proportion of patients cured by cancer therapy," *J. Roy. Statist. Soc., Ser. B*, Vol. 11 (1949), pp. 15–44.

[4] J. Berkson and R. P. Gage, "Specific methods of calculating survival rates of patients with cancer," *Treatment of Cancer and Allied Diseases*, New York, Hoeber, 1958, pp. 578–590.

[5] J. Berkson, "Estimate of the interval rate for actuarial calculation," *Ann. Math. Statist.*, Vol. 24 (1953), p. 144. (Abstract.)

[6] P. M. Densen, "Long-time follow-up in morbidity studies: the definition of the group to be followed," *Human Biology*, Vol. 22 (1950), pp. 233–237.

[7] H. F. Dorn, "Methods of analysis for follow-up studies," *Human Biology*, Vol. 22 (1950), pp. 238–248.

[8] J. Neyman, *First Course in Probability and Statistics*, New York, Holt, 1950.

[9] T. E. Harris, P. Meier, and J. Tukey, "Timing of the distribution of events between observations: a contribution to the theory of follow-up studies," *Human Biology*, Vol. 22 (1950), pp. 249–270.

[10] E. Fix and J. Neyman, "A simple stochastic model of recovery, relapse, death and loss of patients," *Human Biology*, Vol. 23 (1951), pp. 205–241.

[11] A. S. Littell, "Estimation of the T-year survival rate from follow-up studies over a limited period of time," *Human Biology*, Vol. 24 (1952), pp. 87–116.

[12] E. B. Bosworth and D. W. Alling, "The after-history of pulmonary tuberculosis. I. Methods of evaluation," *Amer. Rev. Tuberculosis*, Vol. 69 (1954), pp. 37–49.

[13] H. L. Seal, "The estimation of mortality and other decremental probabilities," *Skand. Aktuarietidskr.*, Vol. 37 (1954), pp. 137–162.

[14] P. Meier, "Non-parametric estimation of survivorship," *J. Amer. Statist. Assoc.*, Vol. 50 (1955), p. 589. (Summary.)

[15] L. Elveback, "Actuarial estimation of survivorship in chronic disease," *J. Amer. Statist. Assoc.*, Vol. 53 (1958), pp. 420–440.

[16] E. L. KAPLAN and P. MEIER, "Non-parametric estimation from incomplete observations," *J. Amer. Statist. Assoc.*, Vol. 53 (1958), pp. 457–481.

[17] P. ARMITAGE, "On the comparison of survival curves," *J. Roy. Statist. Soc., Ser. A*, Vol. 122 (1959), pp. 279–292.

[18] H. SCHEFFÉ, *The Analysis of Variance*, New York, Wiley, 1959.

[19] R. Z. GOLD, "Inference about non-stationary Markov chains," unpublished Ph.D. thesis, Columbia University, 1960.

[20] J. H. LAMBERT, *Beytrage zum Gerbrauche der Mathematik und deren Anwendungen*, Vol. 3, Berlin, 1776.

[21] J. NEYMAN, "Contribution to the theory of the χ^2-test," *Proceedings of the Berkeley Symposium on Mathematical Statistics and Probability*, Berkeley and Los Angeles, University of California Press, 1949, pp. 239–274.

[22] T. W. ANDERSON and L. GOODMAN, "Statistical inference about Markov chains," *Ann. Math. Statist.*, Vol. 28 (1957), pp. 89–110.

[23] H. CRAMÉR, *Mathematical Methods of Statistics*, Princeton, Princeton University Press, 1946.