Nonidentifiability of Lethality in the Survival Experiment with Serial Sacrifice

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Received 16 June 1981; revised 1 April 1982

ABSTRACT

This paper refers to the methodology of the survival experiment with serial sacrifice. In a finite-state, continuous-time model of this experiment, transitions between "illness states" are nonidentifiable. Turnbull and Mitchell proposed a methodology based on the "approximating assumption" A1 that changes in illness state can only occur at discrete times. This assumption identified lethality, i.e. the conditional probability of death in an interval of time, given that the experimental animal is alive in a specified illness state at the beginning of this interval. However, the TM-BT method of evaluating lethalities can lead to conclusions deviating substantially from reality when an animal has a high enough probability of contracting an illness and dying in an interval of time.

1. INTRODUCTION

The survival experiment with serial sacrifice was designed to investigate the effect of a treatment, such as radiation or chemical exposure, on animals in terms of the time course of pathological states [10]. Typically two groups, control and treated, are maintained under similar laboratory conditions and observed daily. Animals die naturally or are withdrawn, i.e., sacrificed or killed accidentally, and are examined at death (autopsied) according to a presumably fixed protocol [2]. The data are age at death, mode of death, and illness state, i.e. presence or absence of a finite number of elementary pathological states.

Analysis of the survival experiment with serial sacrifice requires assumptions to reduce the dimensionality of a statistical model. Peter Clifford [1] shows that, within the context of a Markov illness-death model, transition intensities between illness states and to death are nonidentifiable. Thus in a more general model in which transitions may depend arbitrarily on past events, they remain nonidentifiable. Toby J. Mitchell and Bruce W. Turnbull [4, 9] introduce the "approximating assumption" A1, stated in Section 2

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below, forcing all live transitions to occur only at endpoints of age intervals. Lagakos and Mosteller [3], in a similar vein, suggest that the interval between withdrawals should be short enough that an animal without a tumor is not likely to develop one and die during the interval.

The subject of this paper is lethality, i.e. the conditional probability of death in an age interval, given that the experimental animal is alive in a specified illness state at the beginning of this interval. Jerzy Neyman [6] suggested that the serial-sacrifice methodology does not provide sufficient data to answer the question: how frequently do animals, for instance mice, suffering from leukemia at age 400 days die before 450 days; that is, how lethal is leukemia to 400-day-old mice? During a 50-day interval, as in the example of TM-BT [4], an animal may contract an illness, have complications, and recover or die [5]. Thus assumption A1, which identifies lethality, is unrealistic for this experiment.

My own purpose is to show that lethality is nonidentifiable in the survival experiment with serial sacrifice under a model which weakens A1. I demonstrate with numerical examples that the methodology of Mitchell and Turnbull [4] may yield misleading results in some realistic situations in which their assumption does not hold.

2. MODEL AND IDENTIFIABILITY

This section presents a model of illness and death which has a Markov chain imbedded at age epochs $t_1,\ldots,t_{M+1}$. The process during an interval between epochs may depend arbitrarily on earlier events in that interval, and hence may be non-Markovian. This model generalizes those of Clifford [1] and Mitchell and Turnbull [4]. I define lethality and other model parameters and show that lethality is nonidentifiable.

Let age and time be synonymous. Partition age into M intervals by $t_1,\ldots,t_{M+1}$. Let illness states $k=0,1,\ldots,K-1$ represent the $K=2^I$ combinations of I elementary pathological states. I assume

A0 Changes in illness state and death transitions during an interval $(t_m, t_{m+1}]$ depend on the past, i.e. $(t_1, t_m]$, only through the illness state (k) and the last age epoch t_m.

A1′
(i) Changes in illness state can occur at any age.
(ii) Withdrawals are made only at $t_1{}^+, t_2{}^+,\ldots,t_M{}^+$.

A0 is implicit in the TM-BT methodology, while A1′ is weaker than the assumption [4]

A1 (i) Illness-state changes are made only at $t_1, t_2, \ldots, t_M$.
(ii) Withdrawals can occur only at $t_{1^+}, t_{2^+}, \ldots, t_{M^+}$, i.e., immediately after the illness state changes.

Now focus upon one group (treated or control) and one age interval $(t_m, t_{m+1}]$. I reparametrize and follow TM-BT [4] in defining *prevalence* p_k, *lethality* q_k, and *mortality* r_k, $k = 0, \ldots K-1$, as

$$p_k = \Pr\{\text{in state } k | \text{alive at } t_{m^+}\},$$
$$q_k = \Pr\{\text{die in } (t_m, t_{m+1}] | \text{alive at } t_{m^+} \text{ in state } k\},$$
$$r_k = \Pr\{\text{die in } (t_m, t_{m+1}] \text{ in state } k | \text{alive at } t_{m^+}\}.$$

One sees that

$$p_k q_k = \Pr\{\text{die in } (t_m, t_{m+1}], \quad \text{in state } k \text{ at } t_{m^+} | \text{alive at } t_{m^+}\},$$

and hence $p_k q_k = r_k$ under A1, but not in general.

The data consist of "natural" deaths (d_k) and withdrawals (w_k) for the ith treatment group during the mth age interval in illness state k. Survivors (s) cannot be categorized by illness state.

With arbitrarily large sample sizes, one can determine the survival probability and the mortalities r_k from deaths and survivors, and prevalence p_k from withdrawals. The log-likelihood, under A1′, for the response variables (d, w, s) is

$$s \log(1-r) + \sum_k [d_k \log r_k + w_k \log p_k]$$

up to an additive constant, with $r = \Sigma_k r_k$. Now focusing upon the case $k = 2$, one sees that

$$r = r_0 + r_1 = p_0 q_0 + p_1 q_1.$$

Thus although r_k and p_k are identifiable, q_k is not in general under A1′. One needs to know the transition probabilities

$$Q_{kj} = \Pr\{\text{die in } (t_m, t_{m+1}] \text{ in state } j | \text{alive at } t_{m^+} \text{ in state } k\},$$

$k, j = 0, 1$. These imply the following relations:

$$r_0 = p_0 q_0 + p_1 Q_{10} - p_0 Q_{01},$$
$$r_1 = p_1 q_1 + p_0 Q_{01} - p_1 Q_{10}.$$

Clifford [1] showed in a Markov illness-death model that live transition probabilities are nonidentifiable. In a similar manner one sees that Q_{kj} and q_k are not identifiable under the model specified by A0 and A1′. Thus in this model the lethalities are nonidentifiable.

3. EXAMPLE

This example uses data and estimates from Table 2 in BT-TM [9] for the 400-day-old mice during the succeeding 50-day interval. For the purpose of discussion, I assume the true p_k and q_k coincide with their estimates and ignore questions of estimation. Table 1 presents the model parameters collapsed to presence/absence of endocrine tumors, using the relation $r = pq$ under assumption A1. Note that lethality is highest in the treated group with endocrine tumors ($q = 0.2991$) and lowest in control, no tumors ($q = 0.0436$).

Now consider a progressive model with $K = 2$ live states, that is, a model in which an animal cannot recover from an endocrine tumor. Suppose A1 holds for the controls but not for the treated animals. For the treated group one has ($Q_{10} = 0$)

$$r_0 = p_0(q_0 - Q_{01}), \qquad r_1 = p_0 Q_{01} + p_1 q_1.$$

The ratios r_k / p_k take the form

$$\frac{r_0}{p_0} = q_0 - Q_{01}, \qquad \frac{r_1}{p_1} = q_1 + Q_{01}\frac{p_0}{p_1}.$$

This is quite different from the A1 relations, in which $Q_{01} = 0$ and $q_k = r_k / p_k$

TABLE 1

Endocrine-Tumor Estimates under A1[0]

Tumor	Prevalence p		Mortality r		Lethality q	
state	c	t	c	t	c	t
0 (no tumor)	0.9936	0.9348	.0433	.1663	.0436	.1779
1 (tumor)	0.0064	0.0652	.0015	.0195	.2344	.2991
Total	1.0	1.0	.0448	.1858	—	—

[a] Derived from Table 2 of [9] by summing over prevalence and mortality (calculated as $r = pq$). Lethality was then calculated as $q = r/p$.

for $k = 0, 1$. Note that in this example A1 would force us to overestimate the lethality among tumor cases q_1 and underestimate it among nontumor cases q_0 in the treatment group. Thus one sees that if the probability of getting leukemia and dying in an interval, Q_{01}, is large, or if it is small and the prevalence p_1 is small, then serious discrepancies between q_k and r_k/p_k may occur.

Table 2 presents what the results would be over a range of Q_{01} values for treated and for control animals. Note that tumor lethality drops below nontumor lethality as Q_{01} increases. If Q_{01} is 0.02 for treated and 0 for control animals, then the smallest lethality would be among treated animals with tumors, indicating that treatment (300 rad of gamma irradiation) may be good for the mice. If instead Q_{01} is near 0.01 for treated and 0.001 for controls, then endocrine tumors appear nonlethal, whereas they would seem comparatively lethal under assumption A1 (see Table 1).

4. CONCLUSION

One can see from the example that inference based on the TM-BT methodology may yield misleading results when assumption A1 is not valid. A test of the hypothesis that lethalities do not depend on treatment [4] is not sensitive to illness transitions which may occur before death during an observation interval. The same problem arises for a test of nonlethality or "rapid lethality" [3]. One could construct the intervals between withdrawals to be small relative to changes in illness state, in order for A1 to be approximately valid. The reader must consider the ultimate use of the model parameters. If one is interested in testing rapid lethality, then this approach may prove useful [3]. However, one needs sufficient knowledge of the pathologies, often unavailable in such a study, to determine the appropriate interval spacing. If one wishes to draw inferences about long-term lethality over intervals which violate A1, then another approach is merited, such as an extended serial-sacrifice, or serial-monitoring, methodology in which individuals are monitored several times while alive [5, 6]. The question remains: how should one monitor the health of mice, or humans, and how can one properly analyse such data?

TABLE 2

Endocrine Tumor Lethalities under A1′

	Treated		Control		
State/Q_{01}	.01	.02	.0005	.001	.0015
0 (no tumor)	.1879	.1979	.0441	.0446	.0451
1 (tumor)	.1557	.0124	.1568	.0791	.0015

I wish to thank Jerzy Neyman for suggesting this project and for continued help and encouragement, and Robert L. Davies for many useful suggestions. Lucien M. LeCam offered helpful comments about identifiability. Stephen W. Lagakos and a reviewer provided insightful remarks. This paper was prepared using the facilities of the Statistical Laboratory, University of California, Berkeley, with support from the National Institute of Environmental Health Sciences (USPHS ES01299).

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