STATISTICS IN MEDICINE
Statist. Med. 17, 971–982 (1998)

AN EXTENDED KAPLAN–MEIER ESTIMATOR AND ITS APPLICATIONS

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SUMMARY

We develop an extension of the Kaplan–Meier estimator for the case of multiple live states. The method can be used to construct prognostic charts for tracking individuals initially in a given condition. It is also the key component in constructing a longitudinal version of the multistate life table. © 1998 John Wiley & Sons, Ltd.

1. INTRODUCTION

A basic task in survival analysis is the estimation of the survival curve from cohort data in the presence of censoring. In the simplest case, with a single live state and a single absorbing state (often death), the non-parametric maximum likelihood estimator is well known to be that of Kaplan and Meier.[1] Standard references include the books by Kalbfleisch and Prentice, Cox and Oakes, and Collett.[2–4]

The multistate case also arises frequently in medical applications, the live states being, for instance, 'healthy' together with one or more 'diseased' states. There may also be more than one absorbing (dead) state. In the biostatistical literature the case of multiple live states is often referred to as multistate (reference 4, p. 275), while the single live state and multiple dead states problem is frequently described as competing risks analysis.[5] For example, Kalbfleisch and Prentice[2] consider the times of first passage from one state to the others, and estimate the distribution function of such times in the presence of censoring. There is also a literature on multistate modelling in situations where the states are at least partly hierarchic.[6] For example, Gray[7] and Finkelstein and Schoenfeld[8] show how information on disease progression may be used to obtain improved estimators of the survival function.

The problem considered here is the estimation of the probabilities $[\pi_{ij}(x, t)]$ that an individual in state i at time x will be in a specified state j at a subsequent time t. The problem may be viewed as one of *prognosis* for an individual who currently has a given condition. Although versions of the formulation given here have been considered previously, the extended Kaplan–Meier estimator we develop appears to be new. We also describe, with examples, two commonly occurring types of application where methodology could profitably be used.

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CCC 0277–6715/98/090971–12$17.50

Received September 1996
Revised April 1997

Multistate problems have been extensively studied in other disciplines, most notably demography[9–18] and the social sciences.[19–33] In contrast with the biostatistical approach, the main tradition in demography has been to work with models and data based on short time intervals. In particular, the period life table (reference 34, p. 11) is in many respects a cross-sectional counterpart to (longitudinal) survival analysis. The demographic *multistate life table*, widely used to model transitions among marital or job status, for example, is similarly period-based (reference 9, p. 354 and reference 18, p. 68). A fundamental problem with the multistate life table is its dependence on a Markov assumption, since the history of an individual prior to the (very short) period of study is not taken into account.[7,18,24,35–38] As we shall see, one can use the estimator introduced here to mitigate the problem.

A similarly period-based methodology was presented by Manton and Soldo,[39] based upon work by Koizumi,[40] and was later popularized by Manton and Stallard (reference 41, p. 7) and Manton and Singer.[42] They considered a population with three live states (healthy, diseased, and disabled) and a dead state, and estimated the age-specific expected proportions in the various live states. Being entirely period-based (for example, they used a period life table rather than a cohort analysis to estimate survival rates), their analysis could not take into account individuals' previous history. As a result, it was not possible to distinguish cohorts on the basis of their state membership at time of birth or at other times; prognosis was only possible for an undifferentiated aggregate cohort. We illustrate how one can use the extended Kaplan–Meier estimator to compare and contrast the prognoses of different cohorts.

2. AN EXTENDED KAPLAN–MEIER ESTIMATOR

2.1. Preliminaries

We begin with the case of a single live state. Let $t_1 < t_2 < \ldots$ represent the observed failure (death) times in a sample from a homogeneous population. Suppose that d_k individuals fail at time t_k and that m_k are censored in the interval $[t_k, t_{k+1})$. Let $s_k = (m_k + d_k) + (m_{k+1} + d_{k+1}) + \ldots$ be the number at risk at time t_k. The Kaplan–Meier estimate of the survivorship function at time t is (reference 2, p. 12)

$$\hat{S}(t) = \prod_{k|t_k<t} \left(\frac{s_k - d_k}{s_k} \right). \tag{1}$$

One estimator for the variance of the estimator is the Greenwood formula (reference 2, p. 14)

$$\hat{\text{var}}[\hat{S}(t)] = \hat{S}^2(t) \sum_{k|t_k<t} \left(\frac{d_k}{s_k(s_k - d_k)} \right). \tag{2}$$

The estimator is appropriate under an assumption of uninformative or random censoring. One version of this (reference 2, p. 121) is

$$\Pr\{Z(t)|C(t)\} = \Pr\{Z(t)|\bar{C}(t)\} \tag{3}$$

where $Z(t)$ indicates the state (alive or dead) at time t, $C(t)$ denotes the event that the individual is censored (unobserved) at time t, and $\bar{C}(t)$ is the complementary event.

For the multistate case, let i, j denote generic live states. Denote the absorbing (dead) state by δ. Let $Z(x)$ denote the individual's state at time x. We have interest in the probabilities

$$\pi_{ij}(x, t) = \Pr\{Z(t) = j | Z(x) = i\} \tag{4}$$

together with $\pi_{i\delta}$. We need a slight generalization of (3). We define *generalized uninformative censoring* by

$$\Pr\{Z(t) = j | Z(x) = i, C(t)\} = \Pr\{Z(t) = j | Z(x) = i, \bar{C}(t)\}. \tag{5}$$

It is easily seen that (5) and (2) are equivalent in the case of a single live state. We can interpret equation (5) as saying that the censoring process is independent of which state the individual is in.

We also need the following notation. Let $N_i = N_i(x)$ be the number of individuals in live state i at time x, and let $n_i(x, t)$ be the number alive and uncensored at time t. Of these $n_i(x, t)$ persons, let $n_{ij}(x, t)$ be the number in state j at time t. Note that the arguments i, x and t are fixed throughout Section 2; we will frequently suppress them in what follows. We use, for instance, the notations N, n and n_j, and refer to the left hand side of (4) as π_j.

2.2. The estimator

It is convenient to begin with the case of no censoring. By conditioning on the event $\{Z(t) \neq \delta\}$, we can rewrite (4) as

$$\pi_j = \pi_{ij}(x, t) = \Pr\{Z(t) = j | Z(t) \neq \delta, Z(X) = i\} \Pr\{Z(t) \neq \delta | Z(x) = i\}. \tag{6}$$

The maximum likelihood estimator (MLE) of π_j is thus the product of the MLEs of the two terms in the right hand side of (6). The former is just n_j/n, since the $\{n_j\}$ are multinomial when conditioned on n. The latter MLE is, in the uncensored case, the empirical survivorship function, that is, the complement of the empirical distribution function of the survival times.

In the presence of censoring, the statistics n and n_j now represent the numbers of *uncensored* individuals alive and in state j, respectively. The MLE of $\Pr\{Z(t) = j | Z(x) \neq \delta, Z(x) = i\}$ can be shown to involve all possible realizations of the process $\{Z(t_m): m = 1, \ldots, r\}$ with $Z(x) = i$, $Z(t) = j$, where the t_m are the censoring times within the interval (x, t). In practice this will generally be intractable. The simple estimator n_j/n is still *consistent*, however. This is so because n_j/n is a consistent estimator of

$$\Pr\{Z(t) = j | Z(x) \neq \delta, Z(x) = i, \text{individual was not censored}\},$$

and by (5) this is equal to $\Pr\{Z(t) = j | Z(x) \neq \delta, Z(x) = i\}$.

Further, under (ordinary) uninformative censoring the MLE of the second term on the right hand side of (6) is the Kaplan–Meier estimator $\hat{S}(x, t)$. Hence the product of these two estimators is consistent for the probability (6).

Thus, finally, we have the *extended Kaplan–Meier estimator*

$$\hat{\pi}_{ij}(x, t) = \frac{n_{ij}(x, t)}{n_i(x, t)} \hat{S}(x, t). \tag{7}$$

It is often convenient to display the results in what one might call a prognostic chart, as illustrated in the next section.

Intuitively, equation (7) has a simple interpretation: firstly, one applies the usual Kaplan–Meier estimator to deal with survival while taking account of censoring (provided censoring is uninformative); secondly, provided that the censoring is uninformative in the generalized sense (5), one multiplies this by the fraction of alive and uncensored individuals who are in state j. In demography, however, although there has been considerable attention to the estimation of the transition probabilities π (references 7, 9, p. 356ff, 18, p. 67ff, 43, 44, p. 122–123, 45), none of the proposed solutions is equivalent to (7) and all suffer from either censoring problems or inconsistency.

If we consider multiple causes of death (that is, there is more than one absorbing state), a simple way to proceed is as follows. First, we combine all the dead states and obtain an initial Kaplan–Meier estimate $\hat{S}(t)$. Next, we use some form of competing risk analysis (or multiple decrement life table; see Schoen (reference 18, chapter 2) to calculate probabilities of the different dead states, conditional on the event that death has occurred. These conditional probabilities are then multiplied by $1 - \hat{S}(t)$. In this way we can partition the 'dead' portion of the prognostic charts according to cause of death.

2.3. Variance of the estimator

We derive the large-sample variance of the estimator (7) for use in the construction of confidence intervals etc. We can estimate the covariances of the several $\hat{\pi}_j$ similarly.

First, for each of the N individuals initially in state i at time x, let p_0 be the chance of being alive and uncensored at time t. Thus n is a binomial random variable with parameters N, p_0. Since we assume that individuals are exchangeable, n_j conditional on n is also a binomial variable with parameters n and p_j, say. We write $r = n_j/n$, suppressing the argument j for simplicity.

Using the standard result

$$\text{var}(r) = E\{\text{var}(r|n)\} + \text{var}\{E(r|n)\} \tag{8}$$

we have

$$\text{var}(r) = E\left\{\frac{p_j(1-p_j)}{n}\right\} + \text{var}(p_j). \tag{9}$$

Since when N is large the coefficient of variation of n is small, we can apply the delta method[46] and write $E(1/n) \approx 1/E(n)$. Using sample values as consistent estimators of the population quantities, we have

$$\text{var}(r) \approx \frac{r(1-r)}{n}. \tag{10}$$

As noted, one estimate of the variance of S is given by the Greenwood formula (2). Further, $\hat{S}$ and r are uncorrelated (though are independent only asymptotically). This is most easily seen in the case of no censoring, because then

$$\hat{S} = \frac{n}{N} \tag{11}$$

and

$$E\{r\hat{S}\} = \frac{E\{E(nr|n)\}}{N}$$

$$= \frac{E\{np_j\}}{N}$$

$$= p_0 p_j \tag{12}$$

while $E(S) = p_0$ and $E(r) = E\{E(r|n)\} = E\{p_j|n\} = p_j$.

Use of the delta method on the product in (7) shows that, asymptotically

$$\operatorname{var}\hat{\pi}_j \sim \hat{S}^2 \operatorname{var}(r) + \{E(r)\}^2 \operatorname{var}(\hat{S})$$

$$= \hat{S}^2 \frac{r(1-r)}{n} + r^2 \operatorname{var}(\hat{S}) \tag{13}$$

where we can use equation (2) as an estimate of $\operatorname{var}(\hat{S})$. We reiterate that the (fixed) arguments i, j and x have been suppressed in this discussion.

3. APPLICATION 1: PROGNOSTIC CHARTS

We illustrate the construction of these charts with an example. Strauss *et al.*[47] studied the prognosis of 11,912 infants with severe developmental disabilities. These were all the children who received medical or other services from the State of California for developmental disabilities before their first birthdays. The study period was 1980–1993. Censoring was primarily type III, or progressive (reference 48, p. 3). Mortality data were obtained from the California Department of Health Services, while other data were obtained from the California Department of Developmental Services.

Preliminary analysis and previous research[49–52] suggested that initially one should partition the children into cohorts on the basis of two key variables. These were tube feeding (a dichotomy according to whether the child required gastrostomy feeding), and a four-point mobility scale (cannot lift head when lying on stomach/can lift head but not chest/can lift head and chest when lying on stomach but has limited ability to roll/has full rolling ability). Further analysis suggested the collapsing of the eight ($= 2 \times 4$) groups into four cohorts as follows:

Cohort A: Tube fed and unable to lift head when lying on stomach; $n = 553$.
Cohort B: Tube fed and lacking full rolling ability, but able to lift head; $n = 296$.
Cohort C: Unable to lift head, but not tube fed; $n = 1849$.
Cohort D: All other children requiring services before first birthday; $n = 9214$.

Figure 1 shows the ordinary Kaplan–Meier survival curves for the four cohorts. (Note that various technical complications arose here and elsewhere in the study because the evaluations were approximately annual rather than continuous, and because the initial evaluations were performed at different ages. We do not deal with these issues here, as they are not relevant to our present topic.) As may be seen, cohort A – the most severely impaired – has much the worst survival prospects, with a median residual survival time of only about three years.

A major focus of the study was on the prognosis for improvement in function. We used the same four categories as before (plus the dead state) to classify children at any subsequent age. For

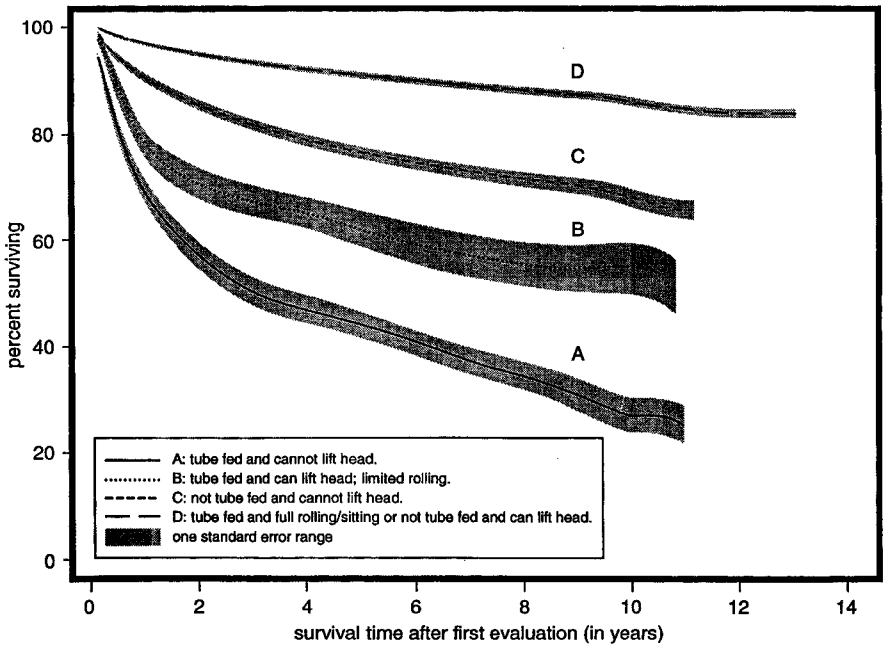

Figure 1. Survival times subsequent to evaluation for four cohorts of children with developmental disability who are evaluated before age 1. Five-year survival probabilities: cohort A, 43 per cent; cohort B, 62 per cent; cohort C, 77 per cent; cohort D, 91 per cent. Median survival times: cohort A, 3·2 years; cohort B, 11·5 years; median survival times for cohorts C and D exceed study period and cannot be computed

example, it is of interest to parents, paediatricians, and others to know the chances that a cohort A child will, at a given subsequent age, be alive but still tube fed and unable to lift his head, or alive and in an improved state.

Figure 2, for children initially in cohort A, was constructed using (7). Thus, the upper curve is the ordinary Kaplan–Meier estimator from Figure 1, while the other curves were constructed by partitioning the survival probability at each age in proportion to the numbers of live uncensored children in each of the categories A, B, C and D. To clarify the use of the chart, we note by way of examples that, by construction, at time 0 (that is, at time of first evaluation) 100 per cent of the children were in the most debilitated state A (tube fed and unable to lift their heads). Two years later, fewer than 60 per cent are expected to have survived. Almost half of these will still be in the most debilitated state. Of those who do improve, however, the majority will be in the least debilitated condition (D). Further, the chances of being in an improved condition appear to level off after two years. (Actually, Figure 2 does not show that an individual's chance of improvement is nearly zero after two years, but rather that the number of such children who improve is balanced by those who subsequently regress back to group A. We required a separate analysis to verify that these numbers were, in this instance, both rather small.)

For comparison, Figure 3 gives the corresponding prognostic chart for cohort C children (initially unable to lift their heads but not tube fed). As may be seen, the prognosis for improvement is much better. Of course, one should not assume that the difference reflects an adverse effect of tube feeding. Strauss *et al.*[53] consider this issue in some detail.

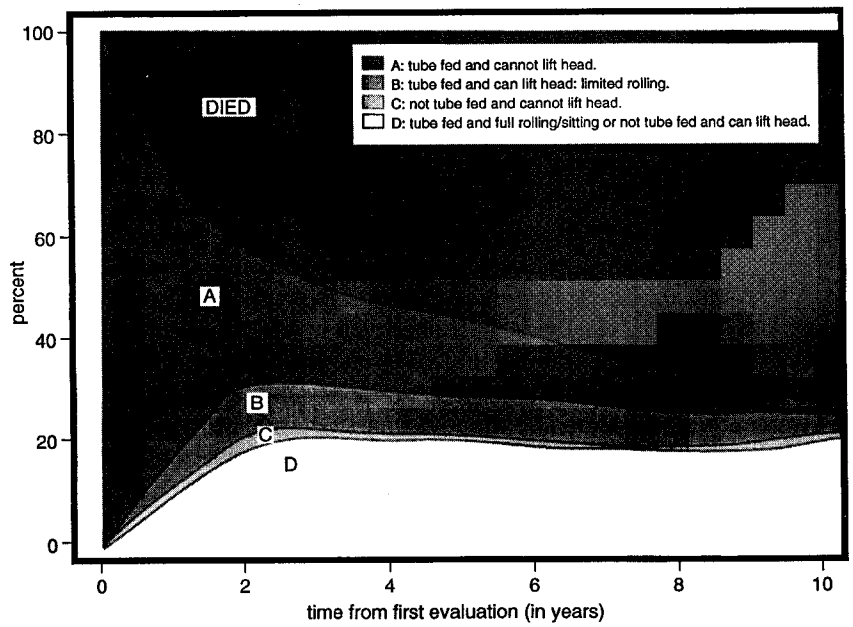

Figure 2. Probabilities of subsequent improvement and of remaining static for children initially in state A. Results apply to a cohort not subject to censoring, so that all surviving members must be in one of the four groups A–D

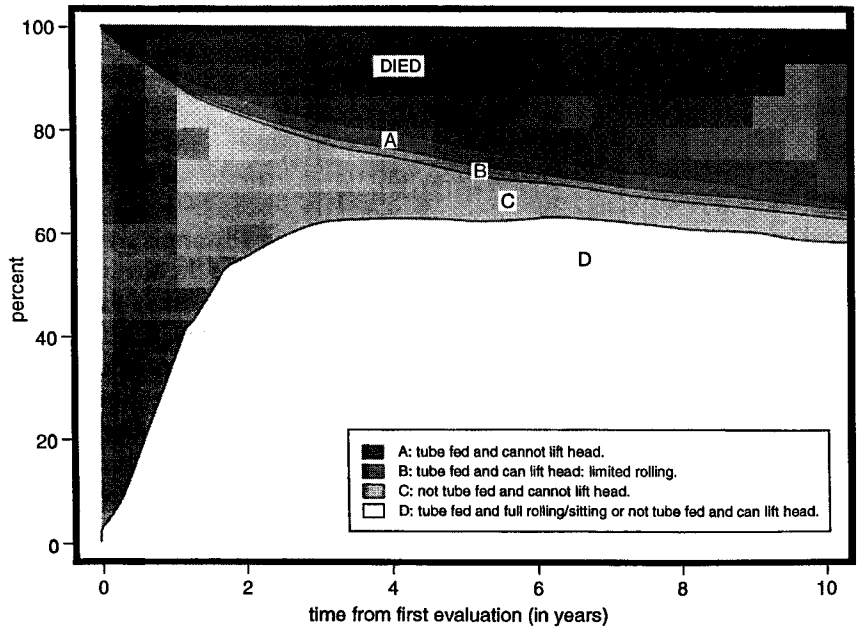

Figure 3. Probabilities of subsequent improvement, regression, or of remaining static for children initially in state B. Results apply to a cohort not subject to censoring, so that all surviving members must be in one of the four groups A–D

When longitudinal data are available, charts of the form of Figures 2 and 3 are useful in numerous medical applications. Some further examples of the sets of live states are healthy/diseased/disabled, smoker/non-smoker, and, for treated cancer patients, remission/relapse.

4. APPLICATION 2: THE LONGITUDINAL MULTISTATE LIFE TABLE

To explain this application we first need some comments on the multistate life table. The multistate table is a generalization of the ordinary life table that models transitions over the lifespan between several states. It was developed by demographers in the 1970s and 1980s.[9,15,16,18,54] When applicable, the method provides estimates of many useful quantities, including the remaining life expectancies of an individual of a given age in a given state, classified by the time expected to be spent in each live state, together with a variety of transition probabilities.

Formally, the underlying model is a continuous time stochastic process that may or may not be Markovian, with an absorbing (dead) state and several transient (live) states. The construction of a multistate life table is not entirely straightforward and some additional assumptions and technical issues arise. Useful recent accounts are given by Schoen (reference 18, Chapter 4) and Keyfitz (reference 9, Chapter 12). To date, most published applications of the method have been in demography and the social sciences, but there are many potential applications in the health field. For example, a multistate analysis with two live states, smoker and non-smoker, would take account of movement between these states. This approach would be preferable to the use of a pair of separate period life tables for smokers and non-smokers because the latter implicitly and unrealistically assumes no transfers. This point has perhaps been insufficiently appreciated in applications.

The current methodology for the multistate table generally uses instantaneous transitions rates, estimated from period-based occurrence/exposure data. Hence, only an individual's current state is taken into account; prior history is ignored. In the multistate setting, unlike the single state case, this requires a Markovian assumption that the transition probabilities depend on the individual's past history only through his current state. As noted previously, the failure of this assumption in practice has been well recognized, and this is perhaps the main obstacle to wider use of the method (reference 8, p. 216).

Like the ordinary life table, the multistate methodology formally applies whether the table is period-based or longitudinal (cohort-based). The latter, however, has the advantage of not relying on the Markov assumption. For example, with longitudinal data one may estimate a matrix of transition probabilities from age 0 to age 10 directly from cohort data. If only one-year period data are available, however, one must compute ten one-year transition matrices (for ages 0 to 1, 1 to 2, and so on) and appeal to the Markov property to justify their multiplication.

Despite its advantages, the cohort approach has not been followed in published applications, probably in part because there has been no suitable proposal of a suitable estimator for long-term transition matrices in the presence of censoring. For example Schoen's (reference 18, p. 77) estimator is inconsistent in the presence of uninformative censoring.

Given longitudinal data over, say, a ten-year study period, one can obtain maximum likelihood estimates of each transition probability $\pi_{ij}(x, t)$, for $t = x + 1, \ldots, x + 10$ by the extended Kaplan–Meier estimator (7). From these, all the life expectancies and related quantities can be derived (reference 9, Chapter 12). Technical note: we used what may be termed a semi-longitudinal multistate table here. The key idea is that if the available data permits estimation of

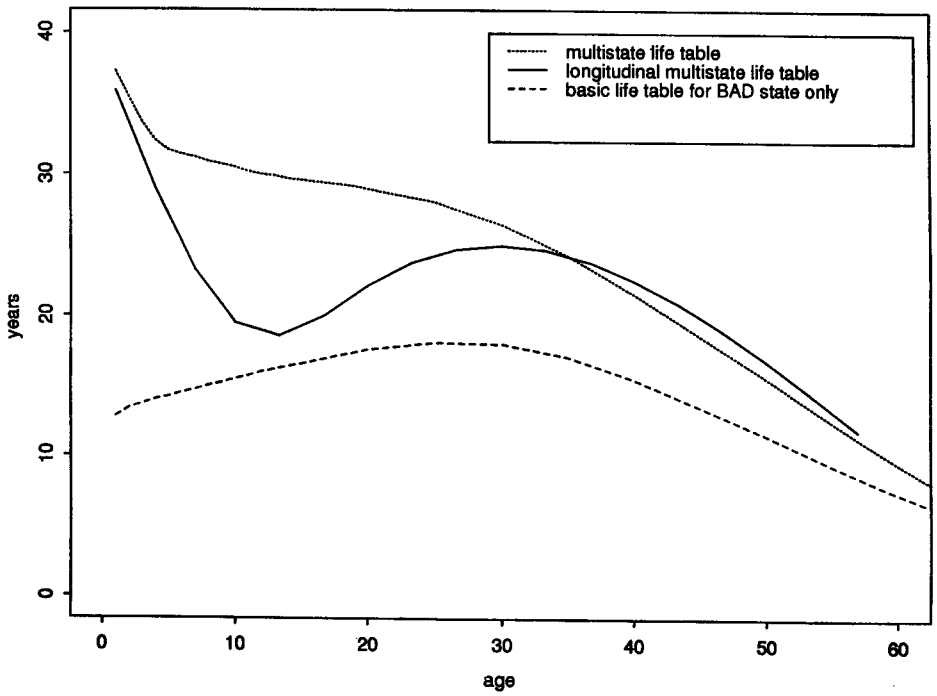

Figure 4. Comparison of remaining life expectancies for those currently in the bad state, under three different life table models. See text for discussion

transition matrices over a ten-year span, say, then matrices of transition probabilities between ages 0 and 30, for example, are computed multiplying the three matrices for transitions between ages 0 and 10, 10 and 20, and 20 and 30. In this way reliance on the Markov assumption is minimized, although not eliminated. Details are given in Shavelle,[55] but are not relevant to our purpose here.

We illustrate with an example based on the same data sources as in the previous section. Here, we focus on a simple dichotomy of the four-point mobility skill variable: can/cannot lift head when lying on stomach. We refer to the two states as 'good' and 'bad'. It is of interest to determine the remaining expected lifetime for a child currently in the bad state, and how much of it will be lived in the two states.

The key inputs for constructing a longitudinal multistate life table are the matrices of transition probabilities

$$\{\pi_{ij}(0, t): i, j = \text{good, bad, or dead}\}$$

for all ages t. We estimated these using the extended Kaplan–Meier estimator, equation (7). We then use standard multistate life table theory (reference 9, Chapter 12) to compute various quantities, such as age- and state-specific remaining life expectancies in each of the live states.

Figure 4 shows total remaining life expectations for person of various ages who are currently in the bad state. The solid line is based on the above longitudinal model. For comparison, we show the corresponding results based on the usual (period) multistate life table methodology. Although

the two methods give comparable results after age 30, the longitudinal method reveals much shorter life expectancies than the period method at earlier ages. This disparity reflects the failure of the Markov assumption inherent in the latter, which seriously overestimates the chances of improvement from the bad state. This occurs because the assumption ignores the 'law of cumulative inertia'[26] – the instantaneous rate for leaving a state often diminishes with increasing duration of stay. Also shown in Figure 4 are life expectancies based on a conventional period life table for persons in the bad state. This would apply to a synthetic cohort of persons who never improve to the good state. The life expectancies are therefore necessarily lower than those derived from the other models.

5. CONCLUSION

We have shown how to extend the Kaplan–Meier estimator to the problem of tracking individuals through several live states. The prognostic chart described in Section 3 may have wide applicability. The estimator also plays a key role in the construction of a longitudinal version of the multistate life table.[55] This methodology appears to have considerable promise in medical applications.

ACKNOWLEDGEMENTS

The authors thank a referee and the editor for helpful suggestions.

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