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APPLICATIONS OF NON-HOMOGENEOUS MARKOV CHAINS TO MEDICAL STUDIES. NONPARAMETRIC ANALYSIS FOR PROSPECTIVE AND RETROSPECTIVE DATA*

by

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Applications of non-homogeneous Markov chains to medical studies. Nonparametric analysis for prospective and retrospective data

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SUMMARY

Recently, AALEN (1978) has shown how the modern theory of stochastic processes may be a useful tool in developing nonparametric estimation and testing procedures of interest in medicine and related fields. The purpose of the present paper is to give a nontechnical review of his results and some extensions of these, and to discuss problems connected with a nonparametric analysis of retrospective data.

1. INTRODUCTION AND EXAMPLES

In many medical investigations one observes certain (random) phenomena (sickness, death, relapse after treatment, etc.) which have a time dimension. The statistical analysis of data collected in such investigations may often be carried out within the framework of stochastic process theory. Models for such processes on the individual level will involve a set of medical statuses (healthy, sick, dead, etc.) and the phenomena to be investigated will consist of stays in these statuses and moves between them.

The models may conveniently be illustrated by labeled boxes, corresponding to the health statuses, and arrows showing the possible direct transitions between the statuses. For example, the simple model underlying the product-limit estimator for the survival distribution (KAPLAN and MEIER, 1958) may be depicted as in Figure 1. At death, the individual moves from state 0 to state 1.

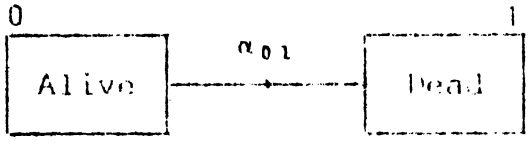

Figure 1. A simple mortality model

By introducing more than one state for "dead" in such a model, we are led to the multiple decrement model, or equivalently to the model of competing risks. This model is shown in Figure 2. A third example of interest in medicine is the following. Assume that we want to analyse the dependence of two events, A and B, say, in the life history of an individual.

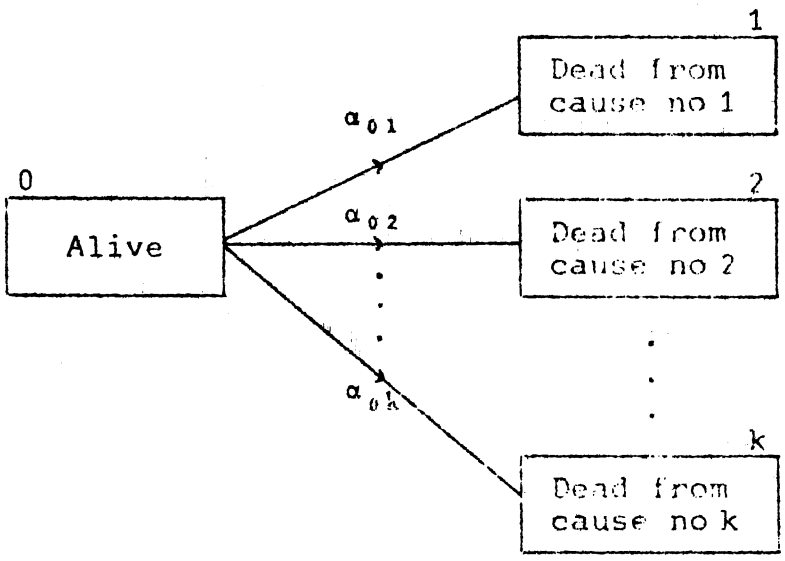

Figure 2. The multiple decrement model

A suitable model for such a study can be the one given in Figure 3. This model is discussed in detail by AALEN et. al. (1980), who use a slight extension of it to investigate the possible influence of menopausal hormonal changes on the outbreak of the chronical skin disease pustulosis palmo-plantaris.

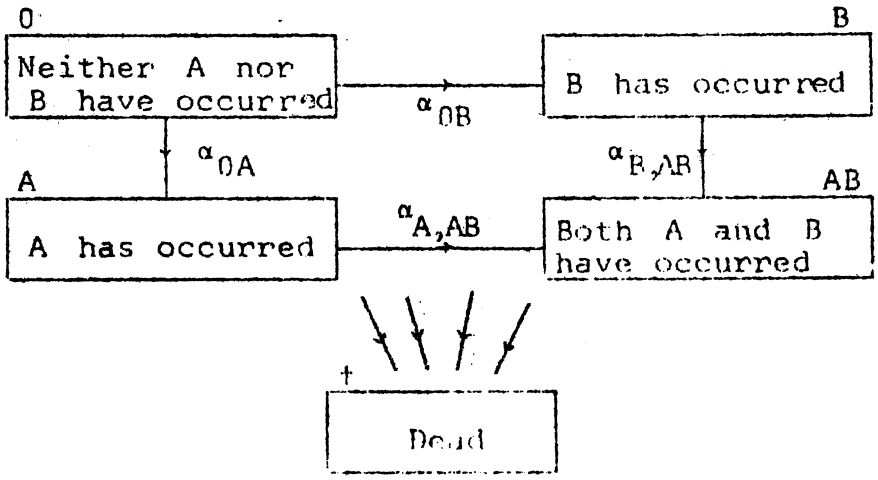

Figure 3. A model for the occurrence of two separate life history events

For more examples, in medical as well as in other contexts, see HOEM (1976, Section 2).

In general one may let the medical statuses correspond to the states i of some state space J of a stochastic process $\{S(t): t \geq 0\}$. A sample path is taken to represent a segment of the life history of an individual, and the time variable t may stand for the age of the individual, for time elapsed since a given treatment, or some such quantity. For most interesting applications in medicine the state space is finite, and to avoid some technical difficulties we will assume that this is the case throughout this paper. Furthermore, we will concentrate on the situation where $S(\cdot)$ is a Markov process. This is a limitation for some of those medical applications where duration-dependence is important.

Let us assume that the transition probabilities

$$P_{ij}(s,t) = P\{S(t) = j \mid S(s) = i\}$$

are absolutely continuous in (s,t), and that the intensities, or forces of transition, defined as

$$\alpha_{ij}(s) = \lim_{t \downarrow s} P_{ij}(s,t)/(t-s)$$

for $i,j \in J$, $i \neq j$, exist and are continuous. Finally, let us postulate that only a finite number of transitions can occur almost surely in any bounded time interval, i.e. there can be no "explosions".

The medical phenomena of interest may now be described by the transition intensities. In the model of Figure 1 $\alpha_{01}(t)$ is the usual death risk (force of mortality) at age t, while the α_{0j}s in Figure 2 are the cause specific hazards or death intensities. In the model of Figure 3, the question whether the occurrence of one of the life history events influences the other, can be studied by comparing the intensities of the Markov chain. For instance, the times of occurrence of A and B will be independent if and only if $\alpha_{0A} \equiv \alpha_{B,AB}$ as well as $\alpha_{0B} \equiv \alpha_{A,AB}$. If, say, $\alpha_{0B} \equiv \alpha_{A,AB}$ while α_{0A} and $\alpha_{B,AB}$ differ on some time interval, this will indicate that B influences A but not the other way around. In summary, the transition intensities are the important quantities of the models, and one of the statistician's main interests in such studies should be to estimate and test the relevant hypotheses concerning these functions.

A number of techniques have been developed for these purposes. There

are the classical methods in demography and actuarial science based on the well-known occurrence/exposure rates (HOEM, 1976). Another possibility, pioneered by GRENANDER (1956), is to assume that the intensities are suitable parametric functions, i.e. $\alpha_{ij}(s) = f_{ij}(s;\underline{\theta})$ for some known functions f_{ij} which depend on an unknown parameter $\underline{\theta} = (\theta_1,\ldots,\theta_p)$. COX (1972) has suggested how one may include covariables (concomitant information) in survival analyses by a "semi-parametric" approach. It should be possible to apply Cox's idea for more general Markov chain models as well, although the present author has seen no such attempts in the literature so far. Finally, AALEN (1978) has recently exploited a nonparametric approach for Markov chains (and more general counting process models), on which the present paper will concentrate. This theory generalizes such well-known methods in biostatistics as the empirical cumulative hazard plot (ALTSHULER, 1970) and the logrank test (PETO and PETO, 1972). The theory is based on the modern theory of time-continuous martingales, stochastic integrals, and counting processes. We will restrict ourselves to a nontechnical review (Section 2).

In the final Section 3 below we consider problems connected with a nonparametric analysis of retrospectively collected data. Our treatment is based on a paper by HOEM (1969), and it is closely related to the discussion by AALEN et. al. (1980).

2. NONPARAMETRIC INFERENCE METHODS. PROSPECTIVE OBSERVATIONAL PLANS

We will call an observational plan <u>prospective</u> if the individuals studied are sampled at random or by some initiating event (like a treatment for a disease) <u>before</u> the events of interest (relapse, death, etc.). The simplest example of such a prospective sampling scheme is the case where at some time 0 one selects a random sample from a homogeneous group of individuals, which are then followed to death. However, the theory reviewed below also covers situations where the persons under observation are followed over different periods of time, as long as the actual observational period for each individual case only depends on the past and on outside random variation. In particular rather general censoring patterns are allowed (AALEN and JOHANSEN, 1978, Section 7).

We now define nonparametric estimation and test procedures. Certain regularity conditions are required in the theoretical derivation of their properties, but the conditions are of a weak and general nature and we need not state them explicitly here.

Let $Y_i(t)$, $i \in J$, be the number of individuals observed to be in state i just before time t, so that $Y_i(t)$ is left continuous, and let $T_{ij}^{(n)}$ be the time of the nth direct transition observed from state i to state j. Then an estimator of the integrated intensity

$$A_{ij}(s,t) = \int_s^t \alpha_{ij}(u)du$$

is given by

$$\hat{A}_{ij}(s,t) = \sum_{\{n:s<T_{ij}^{(n)} \leq t\}} [Y_i(T_{ij}^{(n)})]^{-1} . \tag{2.1}$$

The estimator may be given the following heuristic justification (AALEN, 1976). We split the time interval from s to t by a partitioning $s = t_0 < t_1 < \cdots < t_K = t$ which is so fine that in each subinterval at most one jump occurs, and such that α_{ij} is (approximately) constant on each of the subintervals. Denote this constant value on $\langle t_k, t_{k+1}]$ by $\alpha_{ij}^{(k)}$ and let Δt_k be the length of this subinterval. Then the occurrence/exposure rate $\hat{\alpha}_{ij}^{(k)}$ for $\alpha_{ij}^{(k)}$ is given (almost) by $[Y_i(t_k)\Delta t_k]^{-1}$ if one observes a transition from i to j in the actual subinterval, and it is 0 if no such transition occurs. Consequently a natural estimator for $A_{ij}(s,t) = \sum_k \alpha_{ij}^{(k)} \Delta t_k$ is $\sum_k \hat{\alpha}_{ij}^{(k)} \Delta t_k$, which equals (2.1) approximately.

Using the modern theory of stochastic processes, AALEN (1978) proved that (2.1) is an almost unbiased estimator for $A_{ij}(s,t)$. (Strictly speaking, (2.1) is unbiased for the random process $\int_s^t \alpha_{ij}(u)\, I\{Y_i(u) \geq 1\}du$, where $I\{\cdot\}$ is the indicator function.) Furthermore, an estimator for its variance is given by

$$\sum_{\{n:s<T_{ij}^{(n)} \leq t\}} [Y_i(T_{ij}^{(n)})]^{-2} .$$

As the population size increases, $\hat{A}_{ij}(s,t)$, properly normalized, will asymptotically be distributed as a normal process with independent increments.

Assume that we want to make an overall comparison of two or more intensities $\alpha_{i_r j_r}$, $r = 1,2,\ldots,R$ (where it is quite possible that $i_r = i_h$ or $j_r = j_h$ for some r and h), i.e. we want to test the hypothesis

$$H_0 : \alpha_{i_1 j_1} \equiv \alpha_{i_2 j_2} \equiv \cdots \equiv \alpha_{i_R j_R} .$$

A test for H_0 may be given as follows. Define $\bar{Y}(t) = \sum_r Y_{i_r}(t)$, and let $N_{i_r j_r}$ be the observed number of transitions directly from state i_r to state j_r. Furthermore, denote the time of the nth of any one of these transitions by $U^{(n)}$ and define

$$Z_r = N_{i_r j_r} - \sum_n \frac{Y_{i_r}(U^{(n)})}{\bar{Y}(U^{(n)})} , \tag{2.2}$$

and

$$V_{rh} = \sum_n \frac{Y_{i_r}(U^{(n)})}{\bar{Y}(U^{(n)})} \left(\delta_{rh} - \frac{Y_{i_h}(U^{(n)})}{\bar{Y}(U^{(n)})}\right) .$$

Here δ_{rh} is a Kronecker delta. Note that (2.2) is of the form "observed minus expected", and that $\sum_r Z_r = 0$. Let $\underset{\sim}{V} = \{V_{rh}: r,h = 1,2,\ldots,R-1\}$, and

$$\chi^2 = (Z_1,\ldots,Z_{R-1})\underset{\sim}{V}^{-1}(Z_1,\ldots,Z_{R-1})' . \tag{2.3}$$

Then χ^2 is asymptotically chi-squared distributed with R-1 degrees of freedom under H_0 as the number of persons under observation increases to infinity.

This r-sample test generalizes the well-known log rank test for life testing models (PETO and PETO, 1972, PETO and PIKE, 1973; see also COX, 1972) to our more general setting. For the two-sample case the test statistic (2.3) was studied by AALEN (1978, Section 7). The test for more than two samples was introduced by AALEN et. al. (1980, Section 3) and a formal justification of our statement about its distributional properties will be given in a forthcoming paper (ANDERSEN, BORGAN, and KEIDING, 1980).

In some situations, one may be interested in comparing an intensity α_{ij} with a known function α^0_{ij}. A one-sample statistic for testing $\alpha_{ij} \equiv \alpha^0_{ij}$; asymptotically normally distributed with mean zero and unit variance under the hypothesis, is then given by

$$S = \{N_{ij} - \int Y_i(u)\,\alpha^0_{ij}(u)du\}\{\int Y_i(u)\,\alpha^0_{ij}(u)du\}^{-\frac{1}{2}} , \tag{2.4}$$

where N_{ij} is the observed number of transitions directly from state i to state j in the studied time period. Note that the integral expresses the "expected" number of transitions from i to j under the hypothesis.

The statistic (2.4) is similar to a test given by BRESLOW (1975) for the model of proportional hazards, and to a test studied by HYDE (1977). In the present context it was introduced by AALEN et. al. (1980, Section 3), and its distributional properties will be proved by ANDERSEN et. al. (1980).

3. RETROSPECTIVE OBSERVATIONAL PLANS

If the individuals are sampled <u>after</u> the events of interest, we have a <u>retrospective</u> observational plan. In such cases the intensities must in some sense, be conditional on the sampling criterion (which may be survival, the arrival of a given disease, or some such phenomenon). In the present paper, we will consider four different retrospective sampling schemes. In each case the time variable corresponds to a person's age.

a. <u>Data collected from survivors only</u>

Suppose we have a Markov chain model with state space J, such that $J = L \cup D$. (Here and in what follows we assume that all unions displayed are disjoint.) The states in L correspond to various health statuses for live individuals, while the states in D correspond to death states. Thus, for the three examples in Section 1 we have $L = \{0\}$, $D = \{1\}$; $L = \{0\}$, $D = \{1,2,\ldots,k\}$; and $L = \{0,A,B,AB\}$, $D = \{t\}$; respectively.

If our sampling sheme is to draw all or a random sample of persons with a given age ζ, who live in a restricted area, and collect a retrospectiv account of their individual life histories, data will be missing for individuals who have died or outmigrated before the age ζ. Let us only consider selection by survival. Even before any data areat hand, we then know that all individuals in the sample will be in one of the states in L at age ζ. Consequently, the observations are no longer from the original Markov chain, but from a Markov chain obtained by conditioning on beeing in L at time (age) ζ. (See HOEM, 1969, Section 5, for details.) This Markov chain has transition probabilities

$$P^{L}_{ij}(s,t) = P\{S(t)=j \mid S(s)=i,\ S(\zeta)\in L\} = P_{ij}(s,t)\frac{P_{jL}(t,\zeta)}{P_{iL}(s,\zeta)}$$

for $i,j \in L$ and $s < t \leq \zeta$, where $P_{iL}(s,t) = \sum_{j\in L} P_{ij}(s,t)$.

The transition intensities of the chain are

$$\alpha^{L}_{ij}(s) = \lim_{t \downarrow s} P^{L}_{ij}(s,t)/(t-s)$$

(4.1)

$$= \alpha_{ij}(s)\frac{P_{jL}(s,\zeta)}{P_{iL}(s,\zeta)}$$

for $i,j \in L$, $i \neq j$, and $s < \zeta$.

By the inference procedures described in Section 2 it is possible to estimate the integrated intensities corresponding to the α^{L}_{ij}s and test hypotheses concerning them. In general, the α^{L}_{ij}s will be different from the α_{ij}s, however, which may mean that such inference may be of limited interest.

Define now $\alpha_{iD} = \sum_{j \in D} \alpha_{ij}$ and suppose that $\alpha_{iD} \equiv \mu$ independent of $i \in L$, which means that <u>mortality is non-differential</u>. Then (HOEM, 1969)

$$P_{iL}(s,t) = \exp\{-\int_{s}^{t} \mu(u)du\} \tag{4.2}$$

for all $i \in L$, and, consequently, $\alpha^{L}_{ij} = \alpha_{ij}$ for all $i,j \in L$, $i \neq j$. Thus, for this situation no bias is introduced by the retrospective sampling scheme, and the analysis may be carried out exactly as described in Section 2. (In the present account, we choose to disregard all problems concerning the reliability of the information collected in retrospective studies.)

Normally, one will draw a sample of survivors of different ages, and then the arguments above are valid for each specific age-group. Consequently, if there is non-differential mortality, the analysis may be carried out as before if the age at interview is treated as a fixed censoring time.

b. <u>Data collected from those who have a disease at a given age</u>.

Suppose now that the set L of "live" states may be written as $L = H \cup I$, where a transition from a state in H to one in I corresponds to the occurrence of a particular chronic disease. Thus, we assume that $\alpha_{jH} = 0$ for all $i \in I$. An example of this type of model is the one in Figure 3 If the event A is the occurrence of the chronic disease, we have $H = \{0,B\}$ and $I = \{A,AB\}$.

Let us assume that we draw a random sample of all persons of age ζ who suffer from the disease in question. Then the data will come from a Markov chain with intensities

$$\alpha_{ij}^{I}(s) = \alpha_{ij}(s)\frac{P_{jI}(s,\zeta)}{P_{iI}(s,\zeta)} \tag{4.3}$$

for $i,j \in L$, $i \neq j$ and $s < \zeta$. Again the α_{ij}^{I}s will generally differ from the quantities of interest: viz. the α_{ij}s.

Suppose, however, that the disease considered is nonlethal and that there is non-differential mortality. Then

$$P_{ij}(s,t) = \tilde{P}_{ij}(s,t)\exp\{-\int_s^t \mu(u)du\} \tag{4.4}$$

for $i,j \in L$, where $\tilde{P}_{ij}(s,t)$ denote the transition probabilities of the partial Markov chain with state space $L = H \cup I$ obtained by substituting zero for α_{ij} for all (i,j) with $j \in D$ (HOEM, 1969). Hence, for this case (4.3) reduces to

$$\alpha_{ij}^{I}(s) = \alpha_{ij}(s)\frac{\tilde{P}_{jI}(s,\zeta)}{\tilde{P}_{iI}(s,\zeta)} . \tag{4.5}$$

Clearly $\tilde{P}_{iI}(\cdot,\zeta) \equiv 1$ for all $i \in I$, which means that α_{i_1,i_2} for $i_1,i_2 \in I$ may be estimated without bias from the retrospectively collected data. For the other intensities most attempts at nonparametric estimation lead to rather indirectly interpretable results. For the estimation problems, we refer to the discussion in AALEN et. al. (1980). Here we consider the problem of hypothesis testing.

For the model of Figure 3 it may be of interest to find out whether the occurrence of the event B changes the intensity of morbidity, i.e. one may want to test the hypothesis $\alpha_{0A} \equiv \alpha_{B,AB}$. In the general set-up, the similar hypothesis of non-differential morbidity is

$$H_0: \alpha_{h_1 I} \equiv \alpha_{h_2 I} \equiv \cdots \equiv \alpha_{h_k I} , \tag{4.6}$$

when $H = \{h_1,h_2,\cdots,h_k\}$.

Let $\theta(t)$ be the common value of the $\alpha_{hI}(t)$ in (4.6). As in (4.2) then $\tilde{P}_{hH}(s,t) = \exp\{-\int_s^t \theta(u)du\}$, for all $h \in H$, from which it follows that $\tilde{P}_{hI}(s,t) = 1 - \tilde{P}_{hH}(s,t)$ is independent of $h \in H$. Thus by (4.5), if H_0 holds true, then

$$H_0': \alpha_{h_1 I}^{I} \equiv \cdots \equiv \alpha_{h_k I}^{I}$$

also holds true. Therefore, if we assume non-differential mortality, the hypothesis of non-differential morbidity may be tested directly by

use of the statistic in (2.3) on the retrospective data. The fact that H_0' may hold true even if H_0 does not, may reduce the power of the test. (Note that the hypothesis that only <u>some</u> α_{hI}, $h \in H$, are equal does not imply that the corresponding α^I_{hI}s are equal. The hypothesis must include α_{hI} for <u>all</u> $h \in H$ to get something like H_0'.)

Usually one will also be interested in assessing the influence of the disease on some other phenomena. For instance in the model of Figure 3, one may be interested in testing the hypothesis $\alpha_{0B} \equiv \alpha_{A,AB}$. In the general situation one may want to test

$$\alpha_{h_1,h_2} \equiv \alpha_{i_1,i_2} \tag{4.7}$$

for $h_1,h_2 \in H$, and $i_1,i_2 \in I$, or some other such hypothesis. Hypotheses of this kind cannot be tested directly from the retrospective data without some additional assumptions. In particular, on the assumption that H_0 in (4.6) is valid we have by (4.5) that $\alpha^I_{h_1,h_2} \equiv \alpha_{h_1,h_2}$, $h_1,h_2 \in H$ and it follows that hypotheses like (4.7) may be tested directly under the present observational plan, since $\alpha^I_{i_1,i_2} \equiv \alpha_{i_1,i_2}$ by the resoning below (4.5). Thus, we are led to a stepwise procedure. First one tests H_0 in (4.6). If this hypothesis is rejected one cannot test hypotheses like (4.7). If H_0 is not rejected one may take the point of view to assume that it holds true and test hypotheses concerning intensities for transitions within H against corresponding intensities within I, like (4.7), in the usual way.

This stepwise procedure may be avoided if it is possible to get information regarding α_{h_1,h_2}, $h_1,h_2 \in H$, from other data sources. In such cases this value of the intensity may be tested directly against $\alpha^I_{i_1,i_2} \equiv \alpha_{i_1,i_2}$, $i_1,i_2 \in I$, using the two-sample or one-sample test (depending on the type of information one has about α_{h_1,h_2}) described in Section 2.

It should be noted that the arguments in this subsection cannot easily be extended to the situation where one has a sample of diseased individuals of different ages, cf. (4.5).

c. <u>Sampling among all diseased</u>

Assume now that the set D of death states may be written as $D = D_H \cup D_I$, where D_H contains the death states for people who have never had the chronic disease, and D_I contains the death states for the diseased individuals. One example of such a model is the extension of the model

of Figure 3 shown in Figure 4. Here $D_H = \{\dagger_H\}, D_I = \{\dagger_I\}$,

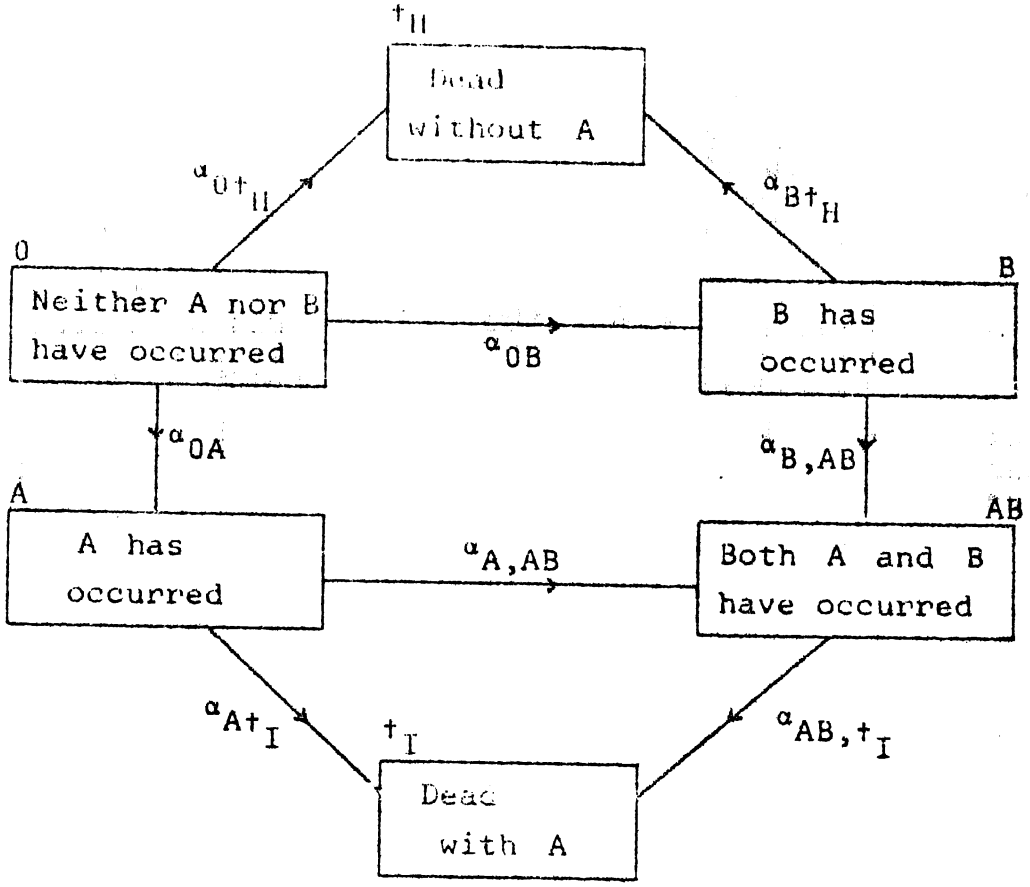

Figure 4. The Markov model of Figure 3, extended with two death states.

$H = \{0,B\}$, and $I = \{A,AB\}$. In general, $\alpha_{hD_I} \equiv 0$ for $h \in H$ and $\alpha_{iD_H} \equiv 0$ for $i \in I$.

The observational plan considered in this subsection, consists in collecting a random sample of people who get the chronic disease sooner or later. This may be the case e.g. for national cancer registers, or for data collected at a given hospital on new cases of the disease in question. With this sampling scheme all the individuals under consideration will end up in one of the states in D_I no later than at the highest possible live age ω. Hence, our observations are from a Markov chain with intensities

$$\alpha^{D}_{ij}(s) = \alpha_{ij}(s)\frac{P_{jD_I}(s,\omega)}{P_{iD_I}(s,\omega)} . \tag{4.8}$$

It is obvious (by definition of ω) that $P_{iD_I}(\cdot,\omega) \equiv 1$ for $i \in I$. Moreover, if we assume non-differential mortality for healthy individuals,

i.e. $\alpha_{hD_H} \equiv \mu$ for all $h \in H$, then

$$P_{hD_I}(s,\omega) = \int_s^\omega \bar{P}_{hI}(s,u)\, e^{-\int_s^u \mu(v)dv}\, \mu(u)du \tag{4.9}$$

for $h \in H$, where $\bar{P}_{ij}(s,t)$ still denote the transition probabilities of the partial Markov chain with state space $L = H \cup I$ (see Subsection 3.b). A formal proof of (4.9) is given in the appendix. By (4.9) and the result stated just below (4.6), H_0 in (4.6) implies that $P_{hD_I}(s,\omega)$ is independent of $h \in H$ in the present situation. By (4.8), therefore, (4.6) entails the hypothesis

$$H_0'' : \alpha^D_{h_1 I} \equiv \cdots \equiv \alpha^D_{h_k I}.$$

The discussion in Subsection 3.b was based on an implication similar to this one. Consequently, if there is non-differential mortality for healthy individuals (alone), the analysis from that subsection is valid here as well. Notice that this result is true under weaker assumptions than before, since we had to assume identical mortality in <u>all</u> "live" states in Subsection 3.b.

d. <u>A process of data selection from the population of diseased</u>

The final sampling scheme we will consider is the one where any given individual has a fixed intensity of being sampled as long as this person has a particular disease and is still alive. For this case it is obvious that patients with long disease histories will have a higher probability of getting sampled, cf. the "waiting time paradox" (FELLER, 1966, Section I. 4). Neither of the sampling schemes discussed above will be adequate.

It is, however, shown by AALEN et. al. (1980) how it for this sampling scheme is possible to model the combined biological and sampling process, and how the analysis may be carried out quite analoguously to that in Subsections 3.b and c of this paper. Moreover, in AALEN et. al. (1980, Section 3) the theory is illustrated by a study concerning the possible influence of menopausal hormonal changes on the intensity of the outbreak of a particular chronical skin disease. The reader who wants to see how the methods in the present paper work in practice, should consult the discussion by AALEN et. al. (1980).

APPENDIX - Proof of (4.9)

It is well-known that $\bar{P}_{ij}(s,t)$ and $P_{ij}(s,t)$ for $i,j \in H$ are the solutions of the Kolmogorov forward differential equations

$$\frac{\partial}{\partial t}\bar{P}_{ij}(s,t) = -\bar{P}_{ij}(s,t)\alpha_j(t) + \sum_{k\in H-j} \bar{P}_{ik}(s,t)\alpha_{kj}(t)$$

and

$$\frac{\partial}{\partial t}P_{ij}(s,t) = -P_{ij}(s,t)(\alpha_j(t)+\mu(t)) + \sum_{k\in H-j} \bar{P}_{ik}(s,t)\alpha_{kj}(t) ,$$

respectively, where $\alpha_j \equiv \sum_{k\in L-j} \alpha_{jk}$. It follows that

$$P_{ij}(s,t) = \bar{P}_{ij}(s,t) \exp\{-\int_s^t \mu(u)du\} \tag{A.1}$$

for $i,j \in H$. Next we will prove that

$$P_{hD_H}(s,t) = \int_s^t \bar{P}_{hH}(s,u) \exp\{-\int_s^u \mu(v)dv\}\mu(u)du \tag{A.2}$$

for $h \in H$. From this (4.9) will follow since $P_{hD_I}(s,\omega) = 1-P_{hD_H}(s,\omega)$ by definition of ω. To prove (A.2) note that

$$P_{hD_H}(s,t+\Delta t) = P_{hD_H}(s,t) + \sum_{k\in H} P_{hk}(s,t)P_{kD_H}(t,t+\Delta t) .$$

Dividing by Δt and letting it approach zero one gets

$$\frac{\partial}{\partial t}P_{hD_H}(s,t) = \sum_{k\in H} P_{hk}(s,t)\alpha_{kD_H}(t) = P_{hH}(s,t)\mu(t) ,$$

since H is finite. From this and (A.1), (A.2) follows, and the proof is complete.

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