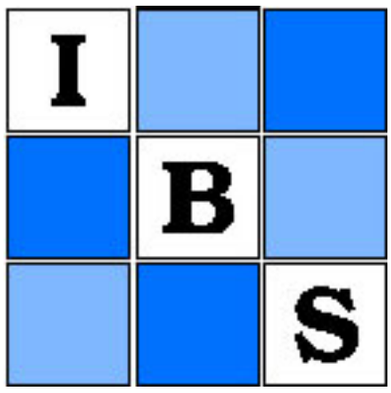

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A Markov Model for Analysing Cancer Markers and Disease States in Survival Studies

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SUMMARY

In studies of serial cancer markers or disease states and their relation to survival, data on the marker or state are usually obtained at infrequent time points during follow-up. A Markov model is developed to assess the dependence of risk of death on marker level or disease state and inferences within this model are based directly on data collected in this haphazard way. An application relating changing levels of serum alpha-fetoprotein to death in hepatocellular carcinoma is discussed in detail.

1. Introduction and Summary

In survival time studies, information on the progress of a disease is often available in the form of a disease state at various points in time. This may be in terms of a cancer marker in cancer clinical trials or some general health measure, such as the Karnofsky scale, in studies of a chronic condition.

This work provides a general method for modelling the relationship between survival time and disease state. Inferences within this model allow potential cancer markers to be identified and also provide measures of relative survival rates across levels of such markers. In terms of disease states, estimated relative survival rates provide direct information on risks associated with each state. In the main the methods will be discussed in relation to cancer marker studies, although it should be understood that they are applicable more generally.

In practical problems of the type described, data on exact transition times are usually not available. In a cancer marker study with three possible cancer marker levels (states) 1, 2, and 3, and a death state 4, say, information on the level will be available only at some baseline time and then at rather infrequent follow-up times. Patients will typically then supply data (time from diagnosis (days), state) of the form

Patient					
1	(0, 2)	(41, 2)	(78, 1)	(95, 3)	(104, 4)
2	(0, 1)	(17, 1)	(52, 4)		
3	(0, 3)	(23, 2)	(58, 3)	(72, 2)	

Time to death, 104 days for patient 1 and 52 days for patient 2, will be known exactly. Note that patient 3 has provided a censored survival time at 72 days. In this application information regarding a patient is not available between marker recordings unless he or she dies so that an observation on a patient's state is made at the censoring time. Methods of inference for the parameters in the model are constructed in the subsequent sections which are appropriate for data collected in this way.

Key words: Cancer markers; Inferences in continuous-time Markov chains; Survival data.

Motivation for this work came from an investigation into the usefulness of serum alpha-fetoprotein (AFP) as a marker in hepatocellular carcinoma. High levels of AFP are indicative of such cancers, particularly in patients with cirrhosis of the liver, at the diagnosis stage (Johnson, Portmann, and Williams, 1978). If presence/absence of cirrhosis is taken into account, however, survival time does not additionally depend on AFP level recorded at start of treatment (Johnson et al., 1981). It is of interest, therefore, to see if changes in AFP level during follow-up are related to risk of death and if so in what way.

Gail (1981) offers several approaches to the analysis of cancer markers and these use the semiparametric regression model of Cox (1972). The haphazard nature of the recording mechanism is dealt with in the Gail work by using an interpolation convention. This interpolation is applied provided a patient has a marker value near, in time, to that required. Patients who do not have a "valid" proximate value are temporarily removed from the data set. Likelihood methods for the Cox model on which the Gail work is based depend entirely on the comparison of the covariate (i.e., marker) values of patients at risk at points in time at which deaths occur. The very nature of the estimation procedure then depends on having "risk" sets of individuals alive, in the study, and with recorded covariates at these times—hence, the need for interpolation and "valid" measurements. The methods discussed in this paper provide an alternative approach to analysis specifically tailored to cancer marker data collected (inevitably) in this haphazard way.

Section 2 describes the Markov model to be used and discusses solutions for the transition probabilities between states. Methods of inference are based on maximum likelihood and these are discussed in Section 3 together with hypothesis testing procedures and methods for model checking. Analysis of the data in the application will be presented in detail in Section 4.

2. Markov Model for k Disease States

The applications set out in the Introduction can be considered as stochastic processes with k transient disease states, $j = 1, \ldots, k$, and a single absorbing state $j = k + 1$ (death). The transient states are assumed to be ordered according to j and transitions can take place from state j to the adjoining states $j - 1$ or $j + 1$ for $j = 2, \ldots, k - 1$, from 1 to 2, and from k to $k - 1$. Transitions can also take place from any of the transient states j to the death state $k + 1$ for $j = 1, \ldots, k$. The system is represented graphically in Figure 1.

Transitions between the transient states occur with rates λ_{ij} defined by

$$\lambda_{ij} = \lim_{dt \to 0} \frac{\Pr\{\text{transition } i \to j \text{ in } [t, t + dt) \mid \text{state } i \text{ at } t\}}{dt}$$

for $i, j = 1, \ldots, k$, $i \neq j$. Transitions to the death state $k + 1$ occur with rates μ_i defined by

$$\mu_i = \lim_{dt \to 0} \frac{\Pr\{\text{transition } i \to k + 1 \text{ in } [t, t + dt) \mid \text{state } i \text{ at } t\}}{dt}$$

for $i = 1, \ldots, k$. We require, for $i = 1, \ldots, k$ and $j = 1, \ldots, k + 1$, the probability functions

$$p_{ij}(t) = \Pr\{\text{state } j \text{ at } t \mid \text{state } i \text{ at time } 0\}$$

in terms of the above rates. Note that the distribution functions $F(t; i)$ for survival times are given by

$$F(t; i) = \Pr(T \leq t \mid \text{state } i \text{ at time } 0) = p_{ik+1}(t),$$

where T is the survival time random variable.

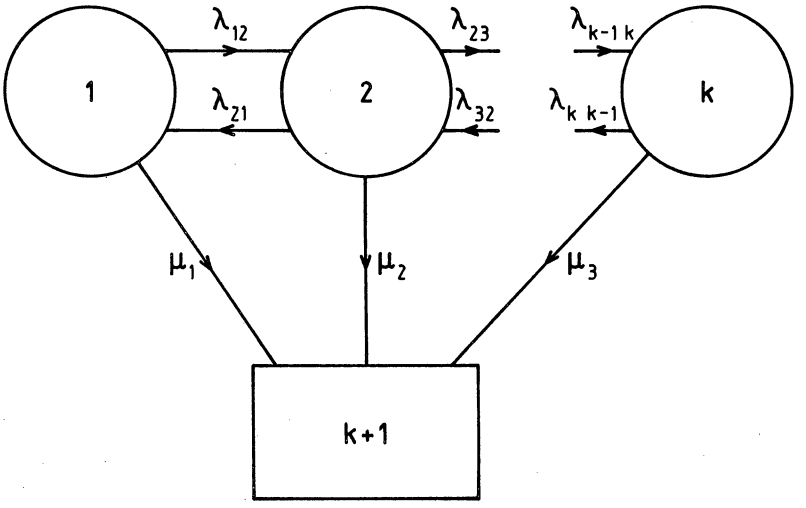

Figure 1. Definition of disease states and transition rates.

Standard methods provide expressions for the $p_{ij}(t)$'s in terms of the transition rates. Kalbfleisch, Lawless, and Vollmer (1983) investigate similar models for aggregate data and in their notation for a general continuous-time Markov chain with stationary transition probabilities, if $\mathbf{Q}$ denotes the $(k+1) \times (k+1)$ transition intensity matrix and $\mathbf{P}(t) = [p_{ij}(t)]$, then the Kolmogorov equations

$$\frac{d}{dt}\mathbf{P}(t) = \mathbf{P}(t)\mathbf{Q}$$

admit the unique solution $\mathbf{P}(t) = \exp(\mathbf{Q}t)$ subject to the boundary condition $\mathbf{P}(0) = \mathbf{I}$. The authors point out that $\mathbf{Q}$ will have distinct eigenvalues $\rho_1, \ldots, \rho_{k+1}$ in practice and if $\mathbf{A}$ is the square matrix whose jth column is the right eigenvector for ρ_j, then

$$\mathbf{P}(t) = \mathbf{A}\ \mathrm{diag}\{e^{\rho_1 t}, \ldots, e^{\rho_{k+1} t}\}\mathbf{A}^{-1}$$

is the unique solution. In the application here, since transitions between the transient states can be only to adjacent states, $\mathbf{Q}$ takes the rather special form

$$\mathbf{Q} = \begin{bmatrix} -(\mu_1 + \lambda_{12}) & \lambda_{12} & 0 & \cdots & 0 & \mu_1 \\ \lambda_{21} & -(\mu_2 + \lambda_{21} + \lambda_{23}) & \lambda_{23} & \cdots & 0 & \mu_2 \\ & \cdots & & & & \\ 0 & 0 & 0 & \cdots & -(\mu_k + \lambda_{kk-1}) & \mu_k \\ 0 & 0 & 0 & & 0 & 0 \end{bmatrix}.$$

For $k = 2$ the solutions $p_{ij}(t)$ are straightforward to evaluate. The eigenvalues of $\mathbf{Q}$ are $\rho_3 = 0$,

$$\rho_1 = \tfrac{1}{2}\{-(\mu_1 + \mu_2 + \lambda_1 + \lambda_2) + [\{(\mu_1 + \lambda_1) - (\mu_2 + \lambda_2)\}^2 + 4\lambda_1\lambda_2]^{1/2}\},$$

and

$$\rho_2 = \tfrac{1}{2}\{-(\mu_1 + \mu_2 + \lambda_1 + \lambda_2) - [\{(\mu_1 + \lambda_1) - (\mu_2 + \lambda_2)\}^2 + 4\lambda_1\lambda_2]^{1/2}\}.$$

The solutions $p_{ij}(t)$ are for $i = 1, 2$, given by

$$p_{ii}(t) = \frac{1}{\rho_1 - \rho_2}[(\mu_i + \lambda_i + \rho_1)e^{\rho_2 t} - (\mu_i + \lambda_i + \rho_2)e^{\rho_1 t}],$$

$$p_{ij}(t) = \frac{\lambda_i}{\rho_1 - \rho_2}(e^{\rho_1 t} - e^{\rho_2 t}) \quad j = 1, 2, \quad i \neq j,$$

and

$$p_{i3}(t) = 1 + \frac{\mu_i + \rho_2}{\rho_1 - \rho_2} e^{\rho_1 t} + \frac{\mu_i + \rho_1}{\rho_2 - \rho_1} e^{\rho_2 t}.$$

The above $(k + 1)$-state model has been considered by many other authors, including Fix and Neyman (1951) and Chiang (1968).

For $k > 2$ it is simple numerically to obtain the eigenvalues $\rho_1, \ldots, \rho_{k+1}$, the eigenvectors making up $\mathbf{A}$ and then $\mathbf{P}(t)$. Computer routines have been written to evaluate $\mathbf{P}(t)$ at any t for the $k = 2$ and general k cases. These have been incorporated in programs to undertake the estimation of the μ and λ parameters as set out in the next section.

3. Statistical Methods

3.1 *Maximum Likelihood Estimation*

The formulation of the problem in terms of the p_{ij} functions in conjunction with the method of maximum likelihood enables the unknown parameters in the model to be estimated. As mentioned earlier, information on an individual's passage through the states will not usually be complete in the sense that we will only know an individual's status at several, possibly prechosen, points in time. The data given in Section 1 will be typical of the kind of data collected. The probability element corresponding to patient 1 there is

$$\begin{aligned} p_1 &= p_{22}(41 - 0)p_{21}(78 - 41)p_{13}(95 - 78)p^*_{34}(104 - 95) \\ &= p_{22}(41)p_{21}(37)p_{13}(17)p^*_{34}(9). \end{aligned}$$

Similarly, for patients 2 and 3, these will be

$$p_2 = p_{11}(17)p^*_{14}(35), \quad p_3 = p_{32}(23)p_{23}(35)p_{32}(14),$$

where $p^*_{i4}(t) = p_{i1}(t - 1)p_{14}(1) + p_{i2}(t - 1)p_{24}(1) + p_{i3}(t - 1)p_{34}(1)$, $i = 1, 2, 3$. In general, let $\tau_{h0} = 0, \tau_{h1}, \ldots, \tau_{hm_h}$ represent the times at which individual h's state is recorded as $y_{h0}, y_{h1}, \ldots, y_{hm_h}$, respectively. In the case of a censored observation the likelihood contribution for that individual is, as a function of the λ's and the μ's ($\boldsymbol{\lambda}$, $\boldsymbol{\mu}$, say),

$$l_h(\boldsymbol{\lambda}, \boldsymbol{\mu}) = \prod_{l=0}^{m_h - 1} p_{y_{hl}y_{hl+1}}(\tau_{hl+1} - \tau_{hl}).$$

For an individual who dies at time τ_{hm_h} the likelihood contribution is

$$l_h(\boldsymbol{\lambda}, \boldsymbol{\mu}) = \prod_{l=0}^{m_h - 2} p_{y_{hl}y_{hl+1}}(\tau_{hl+1} - \tau_{hl}) p^*_{y_{h(m_h-1)}(k+1)}(\tau_{hm_h} - \tau_{h(m_h-1)}).$$

The full likelihood function is then

$$l(\boldsymbol{\lambda}, \boldsymbol{\mu}) = \prod_h l_h(\boldsymbol{\lambda}, \boldsymbol{\mu}),$$

where the product is over all individuals.

In some applications this state may not be known when a patient is censored. If that is true, then a censored data point provides information that a patient is not dead and the final term in that patient's likelihood contribution would then be

$$\sum_{j=1}^{k} p_{y_{hm_h}j}(\tau_{hm_h+1} - \tau_{hm_h}),$$

where t_{hm_h+1} is the censoring time. Computer routines are available which take care of the maximisation process. Further details will be given in conjunction with the application.

With regard to the starting values for the iterative procedure, assume that the time points τ_{hl} represent exact transition times between the states. Let T_i, $i = 1, \ldots, k$, be the total time spent in state i by all individuals and let m_{ij}, $i = 1, \ldots, k$, $j = 1 \ldots, k+1$, be the total number of transitions from state i to state j. The maximum likelihood estimates of the parameters are then

$$\lambda_{ij}^{(0)} = m_{ij}/T_i, \quad \mu_i^{(0)} = m_{ik+1}/T_i, \qquad i = 1, \ldots, k, \quad j = i-1, i+1,$$

and these can be used as starting values in the iterative procedure. Some of their values may be zero ($m_{ij} = 0$) or undefined ($T_i = 0$). In these cases, "average" values

$$\lambda_{ij}^{(0)} = \sum_i \sum_j m_{ij}/\sum_i T_i, \; \mu_i^{(0)} = \sum_i m_{ik+1}/\sum_i T_i$$

should be used.

For general k, the log-likelihood function can be maximised numerically with first and second derivatives being obtained by considering values of the log-likelihood on grids of points. For the $k = 2$ case, however, explicit expressions for the $p_{ij}(t)$'s have been obtained and derivatives of the log-likelihood can easily be written. Formulas for these are available from the author on request.

3.2 *Hypothesis Testing*

In a cancer marker study the hypothesis that there is no relationship between the marker value and survival is

$$H_0: \quad \mu_1 = \mu_2 = \cdots = \mu_k = \mu, \text{ say.}$$

There are several possibilities for constructing a test of H_0 against the general alternative. The easiest method is an application of Wald's test (Rao, 1973, p. 149), which does not require recomputation of the maximum likelihood estimate $(\hat{\boldsymbol{\lambda}}, \hat{\boldsymbol{\mu}})$ under H_0. Suppose

$$\mathbf{I} = \left[\frac{-\partial^2 L}{\partial(\boldsymbol{\lambda}, \boldsymbol{\mu})^2}\right]_{\hat{\boldsymbol{\lambda}}, \hat{\boldsymbol{\mu}}}$$

is the square matrix of minus second-order log-likelihood derivatives of dimension $[2(k-1)+k]^2$ evaluated at the unrestricted maximum likelihood estimates. The elements of $\mathbf{I}^{-1}$, obtained by exact computation ($k = 2$) or numerical methods ($k > 2$), are the estimated variances and covariances of the maximum likelihood estimators. Suppose

$$c_{ij} = \operatorname{cov}(\hat{\mu}_i, \hat{\mu}_j), \quad i, j = 1, \ldots, k,$$

so that

$$\operatorname{cov}(\hat{\mu}_i - \hat{\mu}_k, \hat{\mu}_j - \hat{\mu}_k) = c_{ij} - c_{jk} - c_{ik} + c_{kk} = v_{ij}, \quad i, j = 1, \ldots, k-1.$$

Let $\mathbf{V}_{(k-1)\times(k-1)} = [v_{ij}]$ and $\mathbf{R} = (\hat{\mu}_1 - \hat{\mu}_k, \ldots, \hat{\mu}_{k-1} - \hat{\mu}_k)'$. The statistic $W = \mathbf{R}'\mathbf{V}^{-1}\mathbf{R}$ is asymptotically χ^2_{k-1} under H_0 and can be used to test H_0. For the case $k = 2$ this reduces

to $(\hat{\mu}_1 - \hat{\mu}_2)^2/v_{11}$ while for $k = 3$,

$$W = \frac{(\hat{\mu}_1 - \hat{\mu}_3)^2 v_{22} - 2(\hat{\mu}_1 - \hat{\mu}_3)(\hat{\mu}_2 - \hat{\mu}_3)v_{12} + (\hat{\mu}_2 - \hat{\mu}_3)^2 v_{11}}{v_{11}v_{22} - v_{12}^2}.$$

Additional tests of interest can be undertaken in a similar way although in some cases asymptotically equivalent tests, such as the likelihood ratio procedure, are simpler.

3.3 *Model Checking*

The model in Section 2 makes several quite specific assumptions about the disease process and these are as follows:

(i) homogeneity of the λ and μ parameters across the patient population;
(ii) the Markov assumption, so that transition times from each state are independent of the history of the process prior to entry to that state;
(iii) homogeneity of transition rates through time.

Assumption (i) may be checked by including covariates and treatment indicators $\mathbf{x} = (x_1, \ldots, x_p)'$ on individuals in the modelling process. At the highest level the parameters in the model can be reparametrised with

$$\lambda_{ij}(\mathbf{x}) = \lambda_{ij}^* e^{\boldsymbol{\beta}_{ij}'\mathbf{x}} \quad \text{and} \quad \mu_i(\mathbf{x}) = \mu_i^* e^{\boldsymbol{\beta}_i'\mathbf{x}}.$$

For a single binary x variable this would be equivalent to splitting the data set according to the value of x and obtaining separate estimates of the λ's and the μ's within these subpopulations. Suppose, for example, $k = 2$ and the binary covariate $x = 0, 1$. The eight parameters λ_{01}, λ_{02}, μ_{01}, μ_{02}, λ_{11}, λ_{12}, μ_{11}, and μ_{12}, where the first subscript refers to the covariate value, describe the model. This is equivalent to the above scheme with

$$\begin{aligned} \lambda_{xi} &= \lambda_i e^{\beta_{\lambda i}x} \\ \mu_{xi} &= \mu_i e^{\beta_{\mu i}x} \end{aligned} \qquad i = 1, 2; \quad x = 0, 1.$$

It may then be of interest to test, for example, H_0: $\beta_{\mu 1} = \beta_{\mu 2}$, that the covariate affects the transition rates to the death state from each disease state in the same way. An overall likelihood ratio test of homogeneity can be obtained by comparing the overall log-likelihood with the sum of the log-likelihoods obtained from the two subpopulations.

It does not seem possible to assess assumption (ii) in the absence of data on exact transitions and it is necessary therefore to undertake some interpolation initially in order to estimate exact transition times. Having done this, one can, in theory, assess the Markov assumption by modelling particular transition rates on aspects of the history of the process using a competing-risks Cox model (see Kalbfleisch and Prentice, 1980, pp. 171–172). For example, suppose $k = 2$ and consider the transition $1 \rightarrow 3$, the death state. Let x = time spent in state 2 during last transition from 1. Fitting a model $\lambda_0(t)e^{\beta x}$, where t is time measured from entry to state 2, and testing H_0: $\beta = 0$ would assess the assumption that the transition rate μ_2 is unaffected by the previous sojourn time. Other specific aspects of the Markov assumptions could be tested in a similar way, although a lot of data are needed for these methods to be feasible.

Assumption (iii) can be assessed by fitting the more general model of Faddy (1976), which allows the parameters to be stepwise constant through time. Suppose, for example, that one set of parameters $\boldsymbol{\lambda}^1$, $\boldsymbol{\mu}^1$ apply before some prechosen cutpoint $t = T^*$ and that a second set $\boldsymbol{\lambda}^2$, $\boldsymbol{\mu}^2$ apply after T^*. If $p_{ij}^1(t)$ and $p_{ij}^2(t)$ are the p_{ij} functions based on the first and second sets of parameters, respectively, the likelihood contribution for patient 1 under

this model, taking $T^* = 50$, is

$$p_1 = p_{22}^1(41)\left[\sum_{j=1}^{3} p_{2j}^1(9)p_{j1}^2(28)\right]p_{13}^2(17)p_{34}^{2*}(9).$$

This contribution is obtained by looking at the possible paths, cut at $t = 50$, between state 2 at time 41 days and state 1 at 78 days. Similar contributions can be obtained for each individual and the likelihood for this is again the product of such terms over individuals. A formal test of model assumptions can be obtained by comparing maximised likelihoods. More elaborate generalisations of the basic homogenous Markov model are, of course, possible with several prechosen cutpoints.

4. Application

Data on 81 patients with hepatocellular carcinoma presented to the Liver Unit at Kings College Hospital, London, were available. Treatment was mainly by Adriamycin, although some patients underwent resection or transplantation. AFP was measured on all patients at start of treatment and subsequently at convenient time points during follow-up. The number of measurements on each patient, including that at $t = 0$, varied from 2 to 14 and had average value 5.8. Of the 81 patients, 54 died, so that there were 27 censored observations and the longest survival time was 1031 days. As mentioned previously, presence/absence of cirrhosis at $t = 0$ correlated highly with survival and, having taken account of this, initial AFP level did not have any significant additional effect. Interest here lies in whether rises in AFP level over the $t = 0$ level are associated with increased risk of death.

Suppose $z_i(t)$ represents AFP value recorded on a log scale. The log transformation was included to produce an approximately symmetric distribution of values. Let $x_i(t) = z_i(t)/z_i(0)$ represent the proportionate change in log(AFP) over the baseline ($t = 0$) value. A 5% increase of log(AFP) is then arbitrarily called a "raised" level and an increase less than 5%, or a decrease, is termed a "normal" level. Note that "normal" and "raised" are defined in terms of each patient's $t = 0$ value. A patient starts in state 1 (normal) and continues in that state until the AFP level becomes "raised" as he enters state 2. State 3 is the death state and patients can move to that state from states 1 or 2. A patient in state 2 can return to state 1 if his log(AFP) value falls below the 5% increase over baseline.

Figure 2 shows the underlying structure. The transition rate parameters are also shown. Table 1 presents parameter estimates and standard errors in this three-state model. These were obtained from a computer program incorporating the NAG routine E04EBF, a general-purpose function minimisation routine requiring first and second derivatives of the function (in this case, minus the log-likelihood) to be minimised. The transition rate from state 1 to state 2 is about 6 times greater than that from 2 to 1 and patients, relatively speaking, have a small probability of returning to state 1 having entered state 2. The relative risk of death from state 2 compared to that from state 1 is 8.3, which seems to indicate that increases in AFP level are strongly associated with an increase in the risk of death. Testing the hypothesis H_0: $\mu_1 = \mu_2$ produces a χ_1^2 statistic of 17.98, which is very highly significant. Similar results are produced using a 10% increase to define a "raised" level (see Table 1). In this case the risk of death from state 1 is larger since many high-risk patients whose AFP level increases, but not by the required 10%, stay in state 1. The χ_1^2 statistic for H_0: $\mu_1 = \mu_2$ in the 10% change case is 10.35, again highly significant. Programming the first and second derivatives is quite laborious and requires 2000 lines of FORTRAN 77 code. Alternatively, the NAG routine E04JAF requires just the function to be minimised and computes derivatives numerically and using this, which is very straightforward in terms of

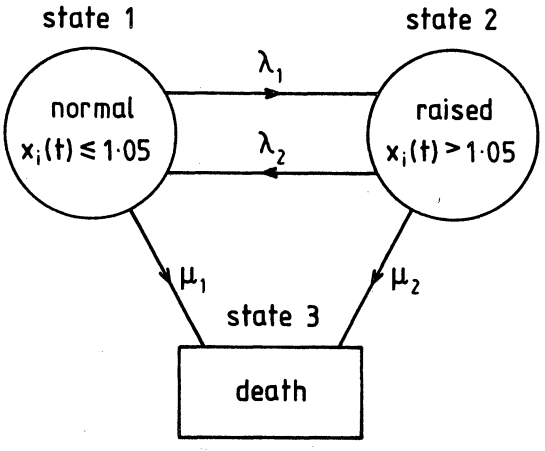

Figure 2. Definition of three-state model.

Table 1
Estimated parameter values and standard errors in three-state models

	Estimate (standard error)	
Parameter	5% change	10% change
λ_1 $(1 \rightarrow 2)$	.0081 (.0013)	.0049 (.0009)
λ_2 $(2 \rightarrow 1)$	.0014 (.0010)	.0008 (.0008)
μ_1 $(1 \rightarrow 3)$	.0010 (.0005)	.0018 (.0006)
μ_2 $(2 \rightarrow 3)$	.0083 (.0015)	.0091 (.0020)

programming, produced estimates that were identical to four decimal places. The estimated standard errors differed very slightly. A four-state model using states normal, raised (> 5% increase), and very raised (> 10% increase) was fitted to the data and results are given in Figure 3.

In view of the numerical properties noted above in the three-state model and the complex nature of the log-likelihood derivatives, this case was fitted using the numerical derivatives routine E04JAF. Movement through the transient states 1, 2, and 3 is reflected by the λ parameters and there are comparable transition rates $\hat{\lambda}_{12}$ and $\hat{\lambda}_{21}$. Having moved to state 2, though, patients have a very high chance of moving quickly to state 3 and a very small chance of then returning to 2. The death rates from states 2 and 3 have relative risks of 4.2 and 8.2 compared to state 1. The test of H_0: $\mu_1 = \mu_2 = \mu_3$ produces a χ^2_2 statistic of 16.40, again highly significant. This confirms the value of AFP increases as a valid marker for hepatocellular carcinoma.

Some simple model checks for the three-state model were undertaken. As mentioned previously, the usefulness of baseline AFP as a diagnostic tool was affected by the presence or absence of cirrhosis and this covariate was also seen to significantly affect survival. It was therefore thought appropriate to include cirrhosis as a covariate in the modelling process. This was done by splitting the patient group according to presence or absence of cirrhosis and fitting the three-state model with 5% cutoff in each of these subgroups. There were 55 patients with and 24 without cirrhosis, and 2 patients had missing information. Parameter estimates and standard errors are given in Table 2.

The estimates are similar to those seen in the whole patient group, in particular the death rates $\hat{\mu}_1$ and $\hat{\mu}_2$. There are some differences in $\hat{\lambda}_1$ and $\hat{\lambda}_2$, and AFP levels in the cirrhosis

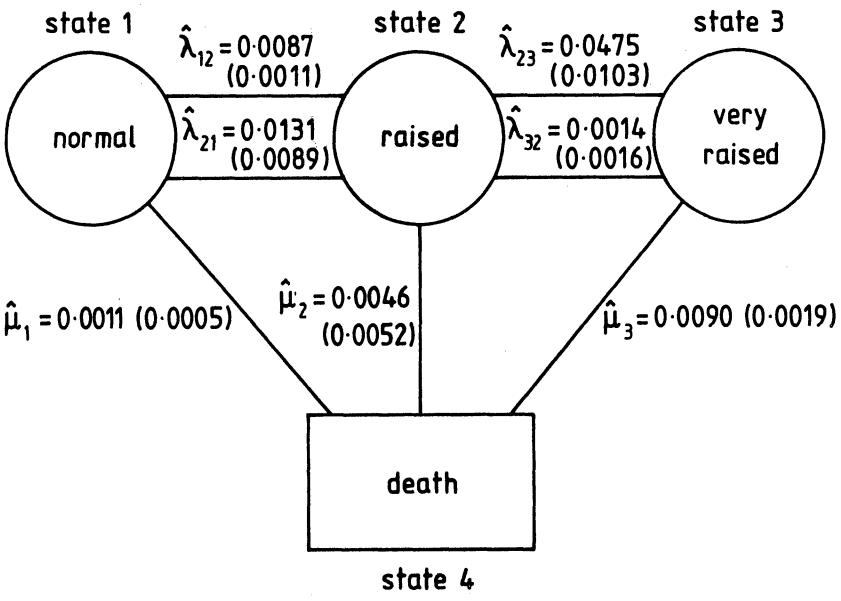

Figure 3. Four-state model and fitted parameter values (standard errors in parentheses).

Table 2
Three-state model for cirrhosis groups

	Estimate (standard error)	
Parameter	Cirrhosis present	Cirrhosis absent
λ_1	.0113 (.0021)	.0045 (.0014)
λ_2	.0014 (.0013)	.0019 (.0021)
μ_1	.0006 (.0007)	.0014 (.0008)
μ_2	.0087 (.0018)	.0075 (.0026)

present group seem more likely to rise quickly and less likely to fall subsequently. A likelihood ratio test of the null hypothesis that the transition rates are the same for the two cirrhosis groups gave a χ^2_4 statistic of 8.60, a result not quite significant at the 5% level. It was not possible to check the Markov assumption by modelling transition rates on aspects of the history of patients, as there was too little data. However, the homogeneity of the λ and μ parameters through time was assessed as set out in the previous section. A value of $T^* = 100$ was chosen, as this approximately divided the observed number of data points into equal groups. The χ^2_4 statistic for the likelihood ratio test comparing the simple model with that with a single cutpoint had value 17.02, which is significant at the 1% level. The tendency is for both the death rates to be increased after T^* ($\hat{\mu}_1^1 = .0008$, $\hat{\mu}_1^2 = .0017$, $\hat{\mu}_2^1 = .0072$, $\hat{\mu}_2^2 = .0104$), while λ_1 is significantly reduced during the second period.

In summary, there is some evidence that the model assumptions are violated and a more complex time-inhomogeneous model could provide a better description of these data. The conclusions regarding the association between increased AFP and risk of death, however, remain the same.

5. Discussion

Myers et al. (1980), in the study of the effects of enzyme levels on survival in prostate cancer, have used methods similar to those described here. The enzyme levels define four "disease" states. These authors, however, use a Markov model with discrete-time parameters

in that they split the time axis into 90-day periods and determine a patient's state at time $t_j = 90j$ by looking at the last measurements available on the enzymes in the preceding 90-day period. The state for every patient at every time point may therefore not be known and a "missing data" state is used to allow for this.

Klein, Klotz, and Grever (1984) have also considered similar problems. These authors consider three states corresponding to less advanced disease, more advanced disease, and death, and model the effect of the marker z in the transition rates so that λ_1, for example, is replaced by $\lambda_1 e^{\beta_1 z}$ and so on. In addition, they allow movement through the states in only one direction corresponding to disease development. For two states, disease and death say, their model and method of analysis can be considered as a continuous version of the model here. There is still some arbitrariness, though, in their approach in that the marker process $z(t)$ is considered as a step function whose value at time t is set equal to the last recorded value. This model is identical to one of the models in Gail (1981) except that Gail allows an arbitrary underlying hazard.

The likelihood function set down in Section 3 is, in fact, not the full likelihood. This would involve probability elements associated with the time points at which measurements are taken. It is assumed that these probabilities, however, do not involve the parameters $\boldsymbol{\lambda}$, $\boldsymbol{\mu}$ of the disease process. This would be the case, for example, if each examination time was chosen on the basis of data obtained at the previous examination time but was not allowed to be influenced by development of the patient's condition between the two. In fact, these seem to be the weakest conditions under which the likelihood is valid. Further investigation of this is continuing in joint work with Jans Grüger and Martin Schumacher.

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Résumé

Dans les études de séries de marqueurs de cancer ou de stades de la maladie et de leur relation avec la durée de survie, la connaissance du niveau du marqueur ou du stade de la maladie n'est habituellement obtenue qu'à de rares moments durant le suivi de l'étude. Un modèle de Markov est développé pour exprimer la relation entre le risque de décés et le niveau du marqueur ou le stade de la maladie, et les procédures statistiques qui en découlent sont directement fondées sur les données telles qu'elles sont, fortuitement recueillies. Une application est exposée en détail, qui relie l'évolution du niveau des alpha-foetoprotéines sériques et le décés dans les hépatocarcinomes.

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