WORK IN PROGRESS: COMMENTS WELCOME

Parametric survival models and decision models: relating continuous hazards to discrete-time transition probabilities

Andrew Briggs*
Helen Campbell
Philip Clarke
Health Economics Research Centre
University of Oxford

Mark Sculpher
Centre for Health Economics
University of York

State transition models of disease often form the basis of health economic evaluations. Such models are most commonly characterised in discrete time periods with transition probabilities of moving between the model states. Where patient level data exist to inform the estimates of transition probabilities, it is often most natural to consider the use of standard survival models to represent these data as outcomes are often subject to censoring. Survival models are based on a hazard rate of the event of interest and the conversion of this rate into a probability represents a potential source of confusion. In this paper, we outline the methods for conversion of hazard functions obtained from parametric and semi-parametric survival models to discrete transition probabilities for a corresponding state-transition model. We consider the different approaches required to capture the influence of covariates and the alternative representations of the baseline hazard. A number of examples of different survival analyses to estimate the time-dependent transitions in a decision model are used to illustrate the approach.

*Corresponding author: Tel: 01865 226847, Email: andrew.briggs@dphpc.ox.ac.uk

Status of work: Work in progress / likely to be substantive changes

Paper presented to the Health Economists' Study Group Conference
Glasgow, June 30th-July 2nd 2004

INTRODUCTION

Economic evaluations of health care interventions often involve the use of decision analytic models. Such models are used to synthesise evidence from a number of sources. Even when primary data are available from a clinical trial, decision models often have an important synthesis role to play in modelling data from the trial (perhaps to enable costs to be estimated in a trial that did not collect resource use information) and/or in extrapolating limited follow-up data to estimate lifetime costs and benefits.

For decision making relating to many health care interventions, there is a fundamental interest in estimating differential costs and consequences between options over a lifetime time horizon (National Institute for Clinical Excellence (NICE) 2004). Given the complexity of many diseases, particularly chronic and progressive ones, state transition models are often employed to represent the evolution of disease over time and the impact of alternative interventions. Such models are most commonly represented in discrete time periods – which often correspond to important economic events, such as treatment cycles or periods between monitoring visits. A popular example of a discrete time transition model is the Markov process. This is a particularly simple form of model, but one that is limited by its lack of memory (the so-called 'Markovian assumption').

It is important to recognise that such models will effectively provide an estimate of survival time (or time to any particular event). For example, the Markov trace of a Markov process model will generate a survival curve when death is included as an absorbing state of the model and the trace can also be used to estimate the 'survival'

time to any particular event of interest. Such curves will be discrete with the time between discrete points on the estimated survivor function given by the length of the Markov cycle. This interpretation of the output of a Markov process emphasises the potential importance of survival time data as a source from which to populate Markov (and other state transition) models.

The use of survival models in the medical field is widespread and well understood. Survival models can handle (non-informative) censoring that frequently occurs in clinical trials. The most popular form of survival model is the semi-parametric Cox proportional hazards model (Cox & Oakes 1984). Since this form of model does not specify the functional form of the hazard function its use for extrapolation of the sort frequently required for decision models is limited. Alternatively, parametric survivor functions can be employed and can be fitted in many popular statistical packages (Cleves, Gould, & Gutierrez 2002;Collett 1994). Furthermore, results from the proportional hazards form of these models gives coefficient estimates that are usually very close to those given by the corresponding Cox model.

The purpose of this paper is to explore the link between the (parametric) survival analysis methods that are commonly employed in the medical statistics literature and the Markov-type discrete transition models that are frequently employed in economic evaluation of medical interventions. In particular, we review how standard survival analyses are based on hazard rates (in continuous time) and how the estimates of such rates can be used to estimate (discrete) time dependent transition probabilities suitable for use in economic evaluation modelling studies.

The next section begins with a review of the standard survival analysis approach, emphasising the general relationships between different aspects of the parametric survival functions that are independent of the particular parametric specification employed. In general terms, we show how the estimated hazard functions are employed to estimate discrete transition probabilities. The following section then presents a series of case studies from our own experience to show how the general principles are applied to specific functions. The final section offers some discussion and highlights some issues for further work.

PARAMETRIC SURVIVAL ANALYSIS

We begin by reviewing the standard form of survival analysis that is commonly presented in many introductory texts (Collett 1994;Parmar & Machin 1997) (but without assuming any more than basic familiarity with calculus). We then show how the general form can be employed to change instantaneous hazard rates into discrete transition probabilities.

Fundamental relationships in survival analysis

We begin by defining a probability density function (pdf) for survival data $f/t0$ with an associated cumulative density function

$$F/t0| \ P/T \Omega t0.$$

The complement of this function is the survivor function

$$S/t0| \ P/T \} t0| \ 14 F/t0.$$

Note that it is therefore straightforward to relate $f/t0$ and $S/t0$

$$f/t0| \ \frac{dF/t0}{dt} | \ \frac{d/14 S/t00}{dt} | \ 4S'/t0. \qquad (1)$$

Define now the hazard function, which is the instantaneous chance of failure at time *t*, conditional on having survived to time *t*, or algebraically

$$h(t) = \lim_{\delta t \to 0} \frac{P(t \le T < t+\delta t \mid T \ge t)}{\delta t}.$$

We note the standard rule for conditional probabilities, that $P(A \mid B) = P(AB)/P(B)$ such that we can re-write the above expression as

$$h(t) = \lim_{\delta t \to 0} \frac{P(t \le T < t+\delta t \mid T \ge t)}{\delta t} \times \frac{1}{S(t)} = \frac{f(t)}{S(t)}. \tag{2}$$

We now define the cumulative hazard function,

$$H(t) = \int_0^t \frac{f(u)}{S(u)} du,$$

noting that the cumulative hazard up to time *t* is not the same as the probability of failure up to time *t* which is given by $F(t)$. Using the result from (1) above, and the standard rules of calculus,* we can express the cumulative hazard as a function of the survivor function

---

* To see how we can get this result consider the chain rule: if $y = f(u)$ and $u = g(x)$, then for $f(.)$ and $g(.)$ as differentiable functions

$$\frac{dy}{dx} = \frac{dy}{du} \times \frac{du}{dx}.$$

It follows that

$$\frac{d \ln S(t)}{dt} = \frac{1}{S(t)} \times \frac{dS(t)}{dt} = \frac{S'(t)}{S(t)}$$

and it should therefore be clear that

$$\int_0^t \frac{S'(t)}{S(t)} = \ln S(t).$$

$$H(t) = \int_0^t \frac{S'(t)}{S(t)} = -\ln S(t)$$

or, alternatively, as the survivor function in terms of the cumulative hazard

$$S(t) = \exp(-H(t)). \quad (3)$$

Estimating discrete time transitions from instantaneous hazard rates

Consider a very simple Markov model with just two states: alive and dead; and therefore, only one transition to estimate: the transition to death. Define the length of the Markov cycle as *u* and let the instantaneous hazard of death at time *t* be represented by *h(t)*, as above. The challenge, therefore, is to estimate the appropriate discrete transition probability between time-points *t*-*u* and *t*, call this $tp(t_u)$ where t_u indicates that *t* is now measured as integer multiples of the cycle length of the model, *u*.

The baseline transition probability of the event of interest can simply be defined as one minus the ratio of the survivor function at the end of the interval to the survivor function at the beginning of the interval:

$$tp(t_u) = 1 - S(t)/S(t-u)$$

which can be rewritten in terms of the cumulative hazard (from Equation (3) above) as

$$tp(t_u) = 1 - \exp(-H(t))/\exp(-H(t-u)) = 1 - \exp(-H(t-u) - H(t)) \quad (4)$$

To see why it is important to move from the arguably more simple specification of the transition probability as the ratio of two points on the survival curve to the specification in Equation (4) consider the application of a treatment effect. It is common to include treatment effects as multiplicative, perhaps as relative risks, or in terms of treatment effects estimated directly from a survival analysis, in terms of a hazard ratio. Such a treatment effect should not be applied directly to the baseline transition probability, rather the treatment effect (call this ϑ) should instead be applied to the hazard. Therefore, if Equation (4) represents the baseline transition probability in the absence of treatment, the treatment transition would be given by

$$
\begin{aligned}
{}_{t}p_{\vartheta}/t_{u}() &= 1 - \exp\left(-\vartheta\left(H/t+u()-H/t()\right)\right) \\
&= 1 - \exp\left(-H/t+u()-H/t()\right)^{\vartheta} \\
&= 1 - \left(\exp\left(-H/t+u()-H/t()\right)\right)^{\vartheta}
\end{aligned}
$$

CASE STUDIES

Having introduced the general framework, we introduce a number of examples from our experience to illustrate the application of the approach. The examples are chosen to show different issues relating to the use of time dependent probabilities in state transition models estimated from standard survival analyses.

Case study 1: Acute MI in patients with acute coronary syndrome

Patient level data were available from an observational source on time to acute myocardial infraction (MI) in 916 patients with acute coronary syndrome. The maximum follow-up time was five years and 51 events were reported during that time. The aim was to estimate the risk of acute MI in a model with yearly transition probabilities in order to extrapolate to a ten-year time-frame.

A parametric Weibull model was employed to model these data. The Weibull pdf is given by

$$f(t) = \varsigma\nu t^{\nu-1}\exp(-\varsigma t^{\nu})$$

where the ς parameter gives the scale of the distribution and the (ancillary) ν parameter defines the shape. From the fundamental relationships of survival analysis described in the previous section, we can easily divide the pdf into component parts

$$h(t) = \varsigma\nu t^{\nu-1}$$
$$S(t) = \exp(-\varsigma t^{\nu})$$
$$H(t) = \varsigma t^{\nu}.$$

Figure 1 shows different time dependent hazard functions that can be modelled using the Weibull function. In particular, the Weibull model nests the exponential as a special case when $\nu = 1$.

Table 1 shows the results of a Weibull survival analysis from STATA v7.0 (the constant _cons is the $\ln(\varsigma)$ value and $p = \nu$ in the STATA output). Note that the 'p' parameter in the table (equivalent to the shape parameter ν in the exposition above) is significantly less that 1, indicating evidence for a decreasing hazard over time.

The corresponding yearly transitions estimated from these data are given in Table 2 and generated from the following equation which is derived from the general form in Equation (4) substituting the expression for the cumulative hazard from the Weibull as given above

$$tp(t_u) = 1 - \exp(-\varsigma(t+u)^{\nu} + \varsigma t^{\nu}).$$

Case study 2: Cause-specific death from early breast cancer following surgery

A patient-level data set was obtained from the Medical Oncology Unit at the Churchill Hospital, Oxford, containing personal and clinical details of breast cancer patients treated at this centre from 1986 onwards. Patients were selected who had operable breast cancer, and who had at least five years of follow-up information subsequent to initial surgery (maximum follow-up was 15 years). The aim was to predict death from early breast cancer for women with different prognostic characteristics.

An initial exploration of the model used the Weibull function, but found that the hypothesis of a constant hazard could not be rejected. Therefore, a straightforward exponential model was employed and the results of this model are presented in Table 3. The pdf for an exponential distribution is given by

$$f(t) = \varsigma \exp^{-}4\varsigma t$$

and this can be split into component parts

$$h(t) = \varsigma$$
$$S(t) = \exp^{-}4\varsigma t$$
$$H(t) = \varsigma t.$$

Although the data set provided information on the use of adjuvant chemotherapy (and hormone therapy) when included in the survival model as dummy cariables, corresponding coefficients were insignificant, and could be biased due to the observational nature of the data. Therefore, the Oxford data were employed to

estimate the baseline transition probabilities of breast cancer death in the absence of adjuvant therapy by setting the chemotherapy and hormone dummies to zero. Thus the baseline transitions were estimated as

$$tp_0 / t_u 0| \ 14 \exp'' \varsigma / t \ 4 \ u 0 4 \ \varsigma t \in$$
$$| \ 14 \exp'' 4 \varsigma u \in$$

where $\ln / \varsigma 0$ is the linear predictor of covariates from Table 3 (omitting treatment effects).

The effect of deciding to give any patient chemotherapy or hormone therapy in the model was then estimated from a systematic review and meta analysis undertaken by the Early Breast Cancer Trialists' overviews (EBCTCG, 1998). Table 4 reports the values used in the model: in summary, it is assumed that hormone treatment has no effect on ER- women, and has a relative risk of 0.72 for women who are ER+. For chemotherapy, the relative risk reduction is related to age, with a relative risk of 0.73 for those aged less than 50 and 0.92 for those over 60. Hence for a 65 year old, ER- woman who is given adjuvant chemotherapy, the estimated transition probability is

$$tp_1 / t_u 0| \ 14 \exp'' 40.92 \varsigma u \in$$

where $\ln / \varsigma 0$ is the same linear predictor of covariates from Table 3 given in the baseline transition probability expression above.

Case study 3: Early and late hip replacement revision

Data were available from the Swedish Hip Registry for all patients receiving either of two alternative prostheses for primary total hip replacement during the period 1992-2000. Altogether nearly 90,000 patient years of information were recorded, together with basic demographic variables and reason for failure. A Weibull model was

employed for the failure probability and this showed evidence of a declining risk of revision during the eight years that data were available. However, this result was somewhat counter-intuitive as one might expect the failure risk to increase with time since replacement as the prostheses gradually wear and loosen with use.

A more detailed analysis, where reason for revision was employed as a dichotomous variable grouping reasons for 'early revision' (such as infection or poor fitting) were differentiated from reasons for 'late revision' (such as wear and loosening), revealed a different story. Fitting Weibull models separately to these two reasons (with the other reason as a censoring variable) revealed a declining revision rate for early revisions and an increasing revision rate for late revisions. Figure 2 shows the result of combining these two models into a single failure probability. The shape of the resulting curve is an approximation to the classic U-shape or 'bath-tub' failure curve commonly employed in engineering models of failure.

Case study 4: A state transition model with time varying covariates for patient history

One issue that arises when applying these more complex models is dealing with time varying covariates. For example a survival analysis of patients with elevated cardiovascular risk may include recent or current levels of blood pressure rather than historic values. While models with time varying covariates can be estimated in statistical packages such as STATA 8.0 the calculation of probabilities must take into account the discontinuities in the hazard that these covariates introduce. For example, if a person's blood pressure changes from one year to the next this is reflected as a jump in the hazard rather than a smooth transition.

One potential method of dealing with these covariates is to assume change covariate occurs at the mid-point of the interval and to separately integrate the cumulative hazard before and after the discontinuity (for example, see Figure 3). The overall hazard would be sum of the integration of the cumulative hazard between *a* and $(a+b)/2$ and the separate integration between $(a+b)/2$ and *b*. It is also possible assume the change at either *a* or *b* as it may be easier to integrate at the beginning or end of each period.

DISCUSSION

In this paper we have illustrated a number of issues relating to the use of parametric survival models to estimate discrete time transitions in decision models. We have not formulated a detailed discussion as, in true HESG tradition, this is work in progress. However, from our own perspective we offer up the following areas for discussion (which, in true HESG tradition, we expect to be ignored!)

- Competing risks: all case studies estimated transitions using competing risks as censoring events: this overestimates the event rate if considered in isolation – however, when added back into a model with the other competing risks the event rates should be correctly estimated?
- Methods described here implicitly relate to dichotomous events (within the framework of competing risks described above) similar to the Millar & Homan paper. An extension to that paper has recently been prepared (Ades et al, manuscript in preparation) pointing out these methods do not work in the

polychotomous context. Do we have the same problem or do the competing risks cover it?

- What is the role for event history analysis (Keiding 1999) in all of this (the multinomial generalisation of the simple dichotomous survival analysis framework)?
- With different reasons for failure in the hip prosthesis case study we added the estimated transitions? Is this correct? We suspect that it is the rates that should be added, but with different shape parameters in the two estimated Weibull equations it was not clear how we should go about this.
- As mentioned above, time dependency is difficult to implement in a simple Markov model when you do not know when a patient started in a state. Micro-simulation is one way around this problem, but allowing for parameter uncertainty in these models is usually computationally intensive. Other options are to build in additional states (tunnel states) or to use higher level modelling language. What are the pros and cons of these different types of models?

Any thoughts on these issues, either before, at or after the conference would be greatly appreciated!

References

Early Breast Cancer Trialists' Collaborative Group 1998, "Tamoxifen for early breast cancer: an overview of the randomised trials.", *Lancet*, vol. 351, no. 9114, pp. 1451-1467.

Cleves, M. A., Gould, W. W., & Gutierrez, R. G. 2002, *An introduction to survival analysis using Stata* Stata Press.

Collett, D. 1994, *Modelling survival data in medical research* Chapman & Hall, London.

Cox, D. R. & Oakes, D. 1984, *Analysis of survival data* Chapman & Hall, London.

Keiding, N. 1999, "Event history analysis and inference from observational epidemiology", *Stat.Med.*, vol. 18, no. 17-18, pp. 2353-2363.

National Institute for Clinical Excellence (NICE) 2004, *Guide to the methods of technology assessment* NICE, London.

Parmar, M. K. B. & Machin, D. 1997, *Survival analysis - A practical approach* John Wiley & Sons ltd., Chichester.

Table 1
Weibull regression for risk of acute MI in patients with acute coronary syndrome

```
Weibull regression -- log relative-hazard form

No. of subjects =          916                     Number of obs   =       916
No. of failures =           52
Time at risk    =      1058651
                                                   LR chi2(0)      =     -0.00
Log likelihood  =   -262.00507                     Prob > chi2     =         .

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       _cons |  -8.028897   .6855026   -11.71   0.000    -9.372457   -6.685336
-------------+----------------------------------------------------------------
       /ln_p |  -.3040257   .1268008    -2.40   0.016    -.5525507   -.0555008
-------------+----------------------------------------------------------------
           p |   .7378419   .0935589                      .5754801    .9460113
         1/p |   1.355304   .1718536                      1.05707     1.73768
------------------------------------------------------------------------------
------------------------------------------------------
```

Table 2
Estimated yearly transition to MI

Year	TP
1	2.47%
2	1.68%
3	1.46%
4	1.34%
5	1.25%
6	1.19%
7	1.14%
8	1.10%
9	1.06%
10	1.03%

Table 3
Coefficients estimated from survival analysis of breast cancer death using a simple exponential model of constant hazard

Explanatory Variable	Coefficient.	SE	P-value
Age at operation	0.031791	0.0060357	<0.001
Tumour size	0.185175	0.0369811	<0.001
Tumour stage 2	0.577657	0.1500816	<0.001
Tumour stage3	1.361642	0.1860969	<0.001
Tumour grade 2	0.379655	0.225727	0.093
Tumour grade 3	0.933166	0.2287583	<0.001
Adjuvant chemotherapy used	-0.10918	0.1808838	0.546
Adjuvant hormone therapy used	-0.20215	0.2235965	0.366
Year of operation 1996	-0.92151	0.3670285	0.012
ER status	-0.44553	0.2348257	0.058
Pred ER	-0.0857	0.2691269	0.75
Constant	-11.55	0.486934	<0.001

Table 4
Effect of adjuvant chemotherapy and hormone treatment on the relative risk of breast cancer death

	Hormone Treatment	**Control**	**Relative risk of treatment compared to control**
ER'-'ve	0.408	0.374	1
ER'+'ve	0.221	0.28	0.72
	Chemotherapy Treatment	**Control**	**Relative risk of treatment compared to control**
Age <50	0.323	0.394	0.73
Age 50-59	0.352	0.385	0.86
Age >60	0.357	0.38	0.92

Source: EBCTG

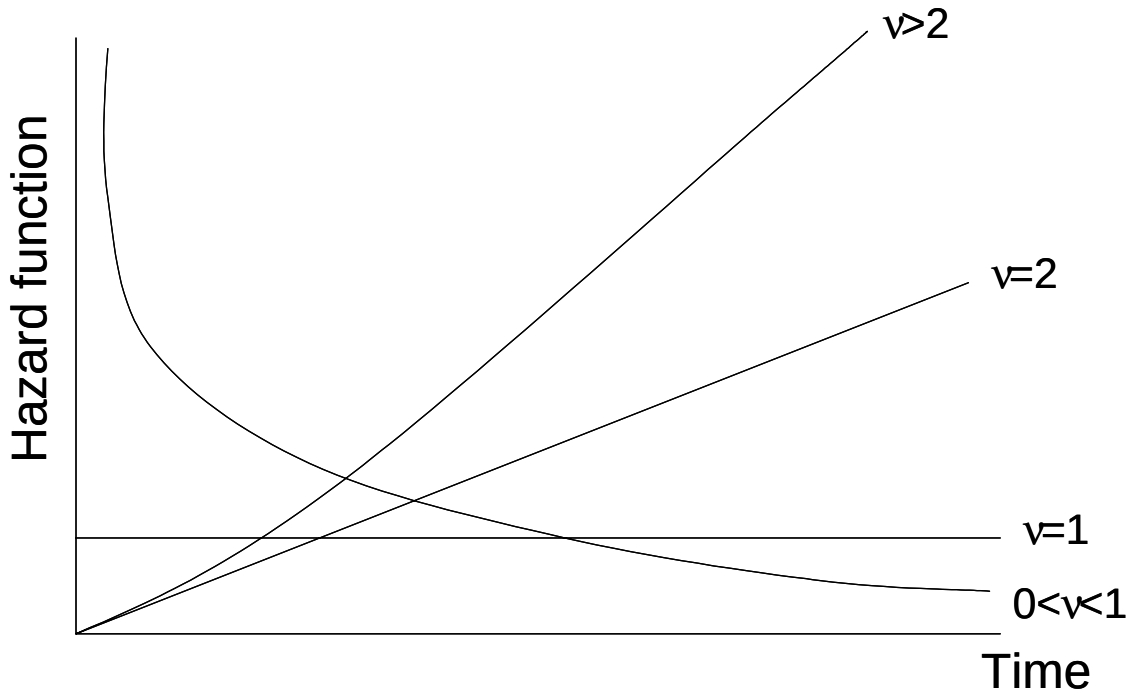

Figure 1
Shapes of the (monotonic) hazard function that can be modelled in a Weibull function with the corresponding values of the shape (gamma) parameter(Collett 1994)

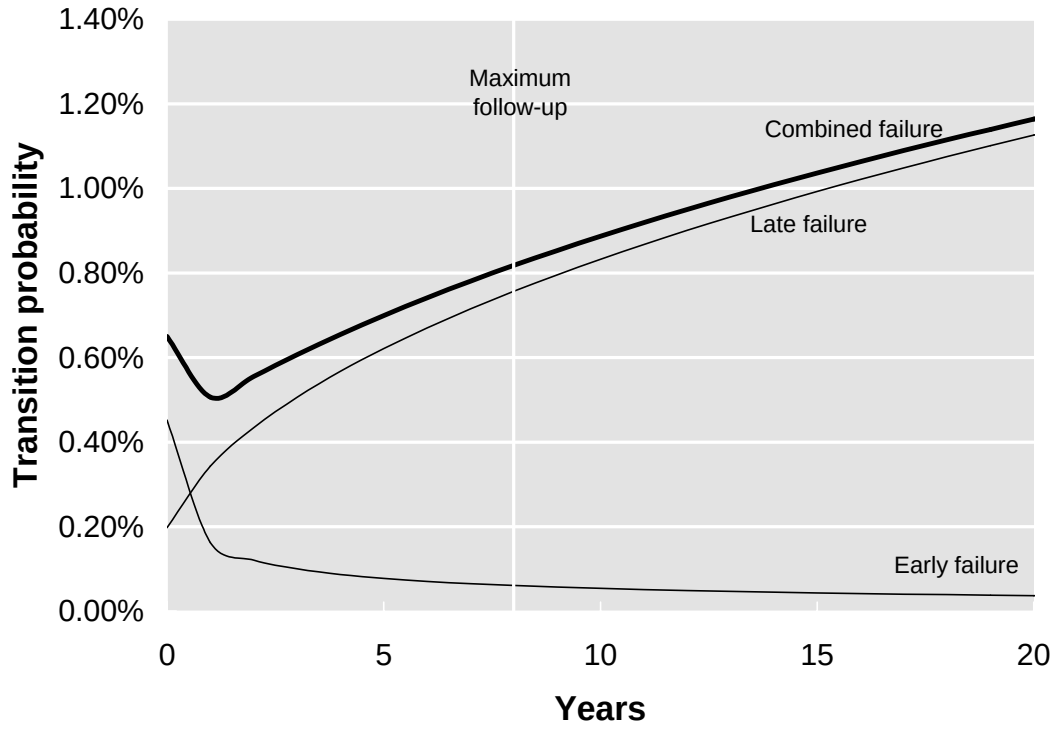

Figure 2
Transition probabilities estimated from the early and late hazard functions separately in order to obtain a 'bathtub' failure curve. The curves shown are for women aged 60 years

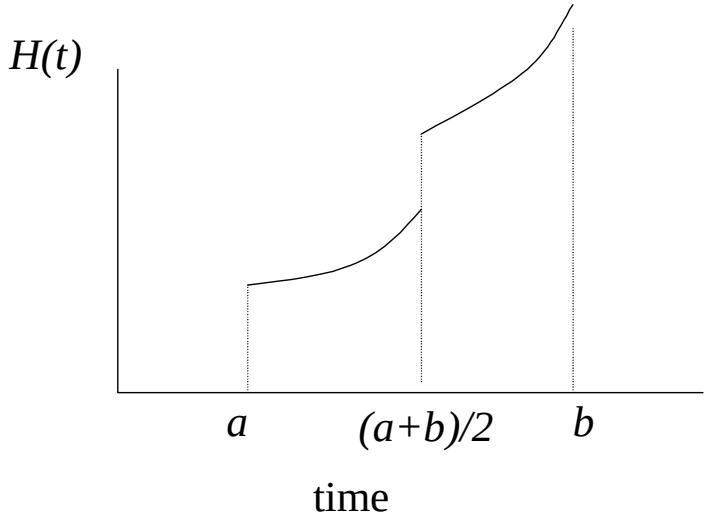

Figure 3
Cumulative hazard with a time-varying covariate