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History of applications of martingales in survival analysis

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Abstract

The paper traces the development of the use of martingale methods in survival analysis from the mid 1970's to the early 1990's. This development was initiated by Aalen's Berkeley PhD-thesis in 1975, progressed through the work on estimation of Markov transition probabilities, non-parametric tests and Cox's regression model in the late 1970's and early 1980's, and it was consolidated in the early 1990's with the publication of the monographs by Fleming and Harrington (1991) and Andersen, Borgan, Gill and Keiding (1993). The development was made possible by an unusually fast technology transfer of pure mathematical concepts, primarily from French probability, into practical biostatistical methodology, and we attempt to outline some of the personal relationships that helped this happen. We also point out that survival analysis was ready for this development since the martingale ideas inherent in the deep understanding of temporal development so intrinsic to the French theory of processes were already quite close to the surface in survival analysis.

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1 Introduction

Survival analysis is one of the oldest fields of statistics, going back to the beginning of the development of actuarial science and demography in the 17th century. The first life table was presented by John Graunt in 1662 (Kreager, 1988). Until well after the Second World War the field was dominated by the classical approaches developed by the early actuaries (Andersen and Keiding, 1998).

As the name indicates, survival analysis may be about the analysis of actual survival in the true sense of the word, that is death rates, or mortality. However, survival analysis today has a much broader meaning, as the analysis of the time of occurrence of any kind of event one might want to study. A problem with survival data, which does not generally arise with other types of data, is the occurrence of censoring. By this one means that the event to be studied, may not necessarily happen in the time window of observation. So observation of survival data is typically incomplete; the event is observed for some individuals and not for others. This mixture of complete and incomplete data is a major characteristic of survival data, and it is a main reason why special methods have been developed to analyse this type of data.

A major advance in the field of survival analysis took place from the 1950's. The inauguration of this new phase is represented by the paper by Kaplan and Meier (1958) where they propose their famous estimator of the survival curve. This is one of the most cited papers in the history of statistics with more than 33,000 citations in the ISI Web of Knowledge (by April, 2009). While the classical life table method was based on a coarse division of time into fixed intervals, e.g. one-year or five-year intervals, Kaplan and Meier realized that the method worked quite as well for short intervals, and actually for intervals of infinitesimal length. Hence they proposed what one might call a continuous-time version of the old life table. Their proposal corresponded to the development of a new type of survival data, namely those arising in clinical trials where individual patients were followed on a day to day basis and times of events could be registered precisely. Also, for such clinical research the number of individual subjects was generally much smaller than in the actuarial or demographic studies. So, the development of the Kaplan-Meier method was a response to a new situation creating new types of data.

The 1958 Kaplan-Meier paper opened a new area, but also raised a number of new questions. How, for instance, does one compare survival curves? A literature of tests for survival curves for two or more samples blossomed in the 1960's and 1970's, but it was rather confusing. The more general issue of how to adjust for covariates was first resolved by the introduction of the proportional hazards model by David Cox in 1972 (Cox, 1972). This was a major advance, and the more than 24,000 citations that Cox's paper has attracted in the ISI Web of Knowledge (by April 2009) is a proof of its huge impact.

However, with this development the theory lagged behind. Why did the Cox model work? How should one understand the plethora of tests? What were the asymptotic properties of the Kaplan-Meier estimator? In order to understand this, one had to take seriously the stochastic process character of the data, and the martingale concept turned out to be very useful in the quest for a general theory. The present authors were involved in pioneering work in this area from the mid-seventies and we shall describe the development of these ideas. It turned out that the martingale concept had an important role to play in statistics. In the 35 years gone by since the start of this development, there is now an elaborate theory, and recently it has started to penetrate into the general theory of longitudinal data (Diggle, Farewell and Henderson, 2007). However, martingales are not really entrenched in statistics in the sense that statistics students are routinely taught about martingales. While almost every statistician will know the concept of a Markov process, far fewer will have a clear understanding of the concept of a martingale. We hope that this historical account will help statisticians, and probabilists, understand why martingales are so valuable in survival analysis.

The introduction of martingales into survival analysis started with the 1975 Berkeley Ph.D. thesis of one of us (Aalen, 1975) and was then followed up by the Copenhagen based cooperation between several of the present authors. The first journal presentation of the theory was Aalen (1978b). General textbook introductions from our group have been given by Andersen, Borgan, Gill and Keiding (1993), and by Aalen, Borgan and Gjessing (2008). An earlier textbook was the one by Fleming and Harrington (1991).

In a sense, martingales were latent in the survival field prior to the formal introduction. With hindsight there is a lot of martingale intuition in the famous Mantel-Haenszel test (Mantel and Haenszel, 1959) and in the fundamental partial likelihood paper by Cox (1975), but martingales were not mentioned in these papers. Interestingly, Tarone and Ware (1977) use dependent central limit theory which is really of a martingale nature.

The present authors were all strongly involved in the developments we describe here, and so our views represent the subjective perspective of active participants.

2 The hazard rate and a martingale estimator

In order to understand the events leading to the introduction of martingales in survival analysis, one must take a look at an estimator which is connected to the Kaplan-Meier estimator, and which today is called the Nelson-Aalen estimator. This estimation procedure focuses on the concept of a hazard rate. While the survival curve simply tells us how many have survived up to a certain time, the hazard rate gives us the risk of the event happening as a

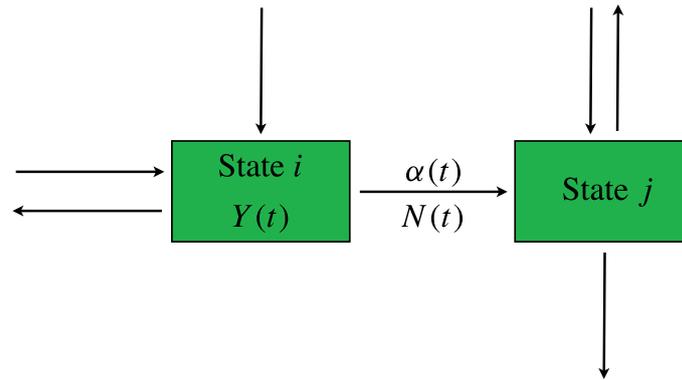


Figure 1: *Transition in a subset of a Markov chain*

function of time, conditional on not having happened previously.

Mathematically, let the random variable T denote the survival time of an individual. The survival curve is then given by $S(t) = P(T > t)$. The hazard rate is defined by means of a conditional probability. Assuming that T is absolutely continuous (i.e., has a probability density), one looks at those who have survived up to some time t , and considers the probability of the event happening in a small time interval $[t, t + dt)$. The hazard rate is defined as the following limit:

$$\alpha(t) = \lim_{\Delta t \rightarrow 0} \frac{1}{\Delta t} P(t \leq T < t + \Delta t \mid T \geq t).$$

Notice that, while the survival curve is a function that starts in 1 and then declines (or is partly constant) over time, the hazard function can be essentially any non-negative function.

While it is simple to estimate the survival curve, it is more difficult to estimate the hazard rate as an arbitrary function of time. What, however, is quite easy is to estimate the cumulative hazard rate defined as

$$A(t) = \int_0^t \alpha(s) ds.$$

A non-parametric estimator of $A(t)$ was first suggested by Wayne Nelson (Nelson, 1969, 1972) as a graphical tool to obtain engineering information on the form of the survival distribution in reliability studies; see also Nelson (1982). The same estimator was independently suggested by Altshuler (1970) and by Aalen in his 1972 master thesis, which was partly published as a statistical research report from the University of Oslo (Aalen, 1972) and later in Aalen (1976a). The mathematical definition of the estimator is given in (2.2) below.

In the 1970's there were close connections between Norwegian statisticians and the Department of Statistics at Berkeley, with the Berkeley professors

Kjell Doksum (originally Norwegian) and Erich Lehmann playing particularly important roles. Several Norwegian statisticians went to Berkeley in order to take a Ph.D. The main reason for this was to get into a larger setting, which could give more impulses than what could be offered in a small country like Norway. Also, Berkeley offered a regular Ph.D. program that was an alternative to the independent type doctoral dissertation in the old European tradition, which was common in Norway at the time. Odd Aalen also went there with the intention to follow up on his work in his master thesis. The introduction of martingales in survival analysis was first presented in his 1975 Berkeley Ph.D. thesis (Aalen, 1975) and was in a sense a continuation of his master thesis. Aalen was influenced by his master thesis supervisor Jan M. Hoem who emphasized the importance of continuous-time Markov chains as a tool in the analysis when several events may occur to each individual (e.g., first the occurrence of an illness, and then maybe death; or the occurrence of several births for a woman). A subset of a state space for such a Markov chain may be illustrated as in Figure 1. Consider two states i and j in the state space, with $Y(t)$ the number of individuals being in state i at time t , and with $N(t)$ denoting the number of transitions from i to j in the time interval $[0, t]$. The rate of a new event, i.e., a new transition occurring, is then seen to be $\lambda(t) = \alpha(t)Y(t)$. Censoring is easily incorporated in this setup, and the setup covers the usual survival situation if the two states i and j are the only states in the system with one possible transition, namely the one from i to j .

The idea of Aalen was to abstract from the above a general model, later termed the multiplicative intensity model; namely where the rate $\lambda(t)$ of a counting process $N(t)$ can be written as the product of an observed process $Y(t)$ and an unknown rate function $\alpha(t)$, i.e.

$$\lambda(t) = \alpha(t)Y(t). \quad (2.1)$$

This gives approximately

$$dN(t) \approx \lambda(t)dt = \alpha(t)Y(t)dt,$$

that is

$$\frac{dN(t)}{Y(t)} \approx \alpha(t)dt,$$

and hence a reasonable estimate of $A(t) = \int_0^t \alpha(s) ds$ would be:

$$\hat{A}(t) = \int_0^t \frac{dN(s)}{Y(s)}. \quad (2.2)$$

This is precisely the Nelson-Aalen estimator.

Although a general formulation of this concept can be based within the Markov chain framework as defined above, it is clear that this really has nothing to do with the Markov property. Rather, the correct setting would be

a general point process, or counting process, $N(t)$ where the rate, or intensity process as a function of past occurrences, $\lambda(t)$, satisfied the property (2.1).

This was clear to Aalen before entering the Ph.D. study at the University of California at Berkeley in 1973. The trouble was that no proper mathematical theory for counting processes with intensity processes dependent on the past had been published in the general literature by that time. Hence there was no possibility of formulating general results for the Nelson-Aalen estimator and related quantities. On arrival in Berkeley, Aalen was checking the literature and at one time in 1974 he asked professor David Brillinger at the Department of Statistics whether he knew about any such theory. Brillinger had then recently received the Ph.D. thesis of Pierre Bremaud (Bremaud, 1973), who had been a student at the Electronics Research Laboratory in Berkeley, as well as preprints of papers by Boel, Varayia and Wong (1975a, 1975b) from the same department. Aalen received those papers and it was immediately clear to him that this was precisely the right tool for giving a proper theory for the Nelson-Aalen estimator. Soon it turned out that the theory led to a much wider reformulation of the mathematical basis of the whole of survival and event history analysis, the latter meaning the extension to transitions between several different possible states.

The mentioned papers were apparently the first to give a proper mathematical theory for counting processes with a general intensity process. As explained in this historical account, it turned out that martingale theory was of fundamental importance. With hindsight, it is easy to see why this is so. Let us start with a natural heuristic definition of an intensity process formulated as follows:

$$\lambda(t) = \frac{1}{dt} P(dN(t) = 1 \mid \text{past}), \quad (2.3)$$

where $dN(t)$ denotes the number of jumps (essentially 0 or 1) in $[t, t + dt)$. We can rewrite the above as

$$\lambda(t) = \frac{1}{dt} E(dN(t) \mid \text{past}),$$

that is

$$E(dN(t) - \lambda(t)dt \mid \text{past}) = 0, \quad (2.4)$$

where $\lambda(t)$ can be moved inside the conditional expectation since it is a function of the past. Let us now introduce the following process:

$$M(t) = N(t) - \int_0^t \lambda(s)ds. \quad (2.5)$$

Note that (2.4) can be rewritten

$$E(dM(t) \mid \text{past}) = 0.$$

This is of course a (heuristic) definition of a martingale. Hence the natural intuitive concept of an intensity process (2.3) is equivalent to asserting that the counting process minus the integrated intensity process is a martingale.

The Nelson-Aalen estimator is now derived as follows. Using the multiplicative intensity model of formula (2.1) we can write:

$$dN(t) = \alpha(t) Y(t) dt + dM(t). \quad (2.6)$$

For simplicity, we shall assume $Y(t) > 0$ (this may be modified, see e.g. Andersen et al., 1993). Dividing over (2.6) by $Y(t)$ yields

$$\frac{1}{Y(t)} dN(t) = \alpha(t) + \frac{1}{Y(t)} dM(t).$$

By integration we get

$$\int_0^t \frac{dN(s)}{Y(s)} = \int_0^t \alpha(s) ds + \int_0^t \frac{dM(s)}{Y(s)}. \quad (2.7)$$

The right-most integral is recognized as a stochastic integral with respect to a martingale, and is therefore itself a zero-mean martingale. This represents noise in our setting and therefore $\widehat{A}(t)$ is an unbiased estimator of $A(t)$, with the difference $\widehat{A}(t) - A(t)$ being a martingale. Usually there is some probability that $Y(t)$ may become zero, which gives a slight bias.

The focus of the Nelson-Aalen estimator is the hazard $\alpha(t)$, where $\alpha(t)dt$ is the instantaneous probability that an individual at risk at time t has an event in the next little time interval $[t, t + dt)$. In the special case of survival analysis we study the distribution function $F(t)$ of a nonnegative random variable, which we for simplicity assume has density $f(t) = F'(t)$, which implies $\alpha(t) = f(t)/(1 - F(t))$, $t > 0$. Rather than studying the hazard $\alpha(t)$, interest is often on the survival function $S(t) = 1 - F(t)$, relevant to calculating the probability of an event happening over some finite time interval $(s, t]$.

To transform the Nelson-Aalen estimator into an estimator of $S(t)$ it is useful to consider the *product-integral* transformation (Gill and Johansen, 1990; Gill, 2005):

$$S(t) = \prod_{(0,t]} \{1 - dA(s)\}.$$

Since $A(t) = \int_0^t \alpha(s)ds$ is the cumulative intensity corresponding to the hazard function $\alpha(t)$, we have

$$\prod_{(0,t]} \{1 - dA(s)\} = \exp\left(-\int_0^t \alpha(s)ds\right),$$

while if $A(t) = \sum_{s_j \leq t} h_j$ is the cumulative intensity corresponding to a discrete measure with jump h_j at time s_j ($s_1 < s_2 < \dots$) then

$$\prod_{(0,t]} \{1 - dA(s)\} = \prod_{s_j \leq t} \{1 - h_j\}.$$

The plug-in estimator

$$\widehat{S}(t) = \prod_{(0,t]} \{1 - d\widehat{A}(s)\} \quad (2.8)$$

is the Kaplan-Meier estimator (Kaplan and Meier, 1958). It is a finite product of the factors $1 - 1/Y(t_j)$ for $t_j \leq t$, where $t_1 < t_2 < \dots$ are the times of the observed events.

A basic martingale representation is available for the Kaplan-Meier estimator as follows. Still assuming $Y(t) > 0$ (see Andersen et al., 1993, for how to relax this assumption) it may be shown by Duhamel's equation that

$$\frac{\widehat{S}(t)}{S(t)} - 1 = - \int_0^t \frac{\widehat{S}(s-)}{S(s)Y(s)} dM(s), \quad (2.9)$$

where the right-hand side is a stochastic integral of a predictable process with respect to a zero-mean martingale, that is, itself a martingale. "Predictable" is a mathematical formulation of the idea that the value is determined by the past, in our context it is sufficient that the process is adapted and has left-continuous sample paths. This representation is very useful for proving properties of the Kaplan-Meier estimator as shown by Gill (1980).

3 Stochastic integration and statistical estimation

The discussion in the previous section shows that the martingale property arises naturally in the modelling of counting processes. It is not a modelling assumption imposed from the outside, but is an integral part of an approach where one considers how the past affects the future. This dynamic view of stochastic processes represents what is often termed the French probability school. A central concept is the local characteristic, examples of which are transition intensities of a Markov chain, the intensity process of a counting process, drift and volatility of a diffusion process, and the generator of an Ornstein-Uhlenbeck process. The same concept is valid for discrete time processes, see Diggle et al. (2007) for a statistical application of discrete time local characteristics.

It is clearly important in this context to have a formal definition of what we mean by the "past". In stochastic process theory the past is formulated as a σ -algebra \mathcal{F}_t of events, that is the family of events that can be decided to have happened or not happened by observing the past. We denote \mathcal{F}_t as the *history at time t*, so that the entire history (or filtration) is represented by

the increasing family of σ -algebras $\{\mathcal{F}_t\}$. Unless otherwise specified processes will be adapted to $\{\mathcal{F}_t\}$, i.e., measurable with respect to \mathcal{F}_t at any time t . The definition of a martingale $M(t)$ in this setting will be that it fulfils the relation:

$$E(M(t) | \mathcal{F}_s) = M(s) \text{ for all } t > s.$$

In the present setting there are certain concepts from martingale theory that are of particular interest. Firstly, equation (2.5) can be rewritten as

$$N(t) = M(t) + \int_0^t \lambda(s) ds.$$

This is a special case of the *Doob-Meyer decomposition*. This is a very general result, stating under a certain uniform integrability assumption that any submartingale can be decomposed into the sum of a martingale and a predictable process, which is often denoted a *compensator*. The compensator in our case is the stochastic process $\int_0^t \lambda(s) ds$.

Two important variation processes for martingales are defined, namely the predictable variation process $\langle M \rangle$, and the optional variation process $[M]$. Assume that the time interval $[0, t]$ is divided into n equally long intervals, and define $\Delta M_k = M(k/n) - M((k-1)/n)$. Then

$$\langle M \rangle_t = \lim_{n \rightarrow \infty} \sum_{k=1}^n \text{Var}(\Delta M_k | \mathcal{F}_{(k-1)/n}) \quad \text{and} \quad [M]_t = \lim_{n \rightarrow \infty} \sum_{k=1}^n (\Delta M_k)^2,$$

where the limits are in probability.

A second concept of great importance is stochastic integration. There is a general theory of stochastic integration with respect to martingales. Under certain assumptions, the central results are of the following kind:

1. A stochastic integral $\int_0^t H(s) dM(s)$ of a predictable process $H(t)$ with respect to a martingale $M(t)$ is itself a martingale.
2. The variation processes satisfy:

$$\left\langle \int H dM \right\rangle = \int H^2 d\langle M \rangle \quad \text{and} \quad \left[\int H dM \right] = \int H^2 d[M]. \quad (3.1)$$

These formulas can be used to immediately derive variance formulas for estimators and tests in survival and event history analysis.

The general mathematical theory of stochastic integration is quite complex. What is needed for our application, however, is relatively simple. Firstly, one should note that the stochastic integral in equation (2.7) (the right-most integral) is simply the difference between an integral with respect to a counting processes and an ordinary Riemann integral. The integral with respect to a counting process is of course just of the sum of the integrand over jump times of the process. Hence, the stochastic integral in our context

is really quite simple compared to the more general theory of martingales, where the martingales may have sample paths of infinite total variation on any interval, and where the Itô integral is the relevant theory. Still the above rules 1 and 2 are very useful in organizing and simplifying calculations and proofs.

4 Stopping times, unbiasedness and independent censoring

The concepts of martingale and stopping time in probability theory are both connected to the notion of a fair game and originate in the work of Ville (1936, 1939). In fact one of the older (non-mathematical) meanings of martingale is a fair-coin tosses betting system which is supposed to give a guaranteed payoff. The requirement of unbiasedness in statistics can be viewed as essentially the same concept as a fair game. This is particularly relevant in connection with the concept of censoring which pervades survival and event history analysis. As mentioned above, censoring simply means that the observation of an individual process stops at a certain time, and after this time there is no more knowledge about what happened.

In the 1960's and 1970's survival analysis methods were studied within reliability theory and the biostatistical literature assuming specific censoring schemes. The most important of these censoring schemes were the following:

- For *type I censoring*, the survival time T_i for individual i is observed if it is no larger than a fixed censoring time c_i , otherwise we only know that T_i exceeds c_i .
- For *type II censoring*, observation is continued until a given number of events r is observed, and then the remaining units are censored.
- *Random censoring* is similar to type I censoring, but the censoring times c_i are here the observed values of random variables C_i that are independent of the T_i 's.

However, by adopting the counting process formulation, Aalen noted in his Ph.D. thesis and later journal publications (e.g. Aalen, 1978b) that if censoring takes place at a stopping time, as is the case for the specific censoring schemes mentioned above, then the martingale property will be preserved and no further assumptions on the form of censoring is needed to obtain unbiased estimators and tests.

Aalen's argument assumed a specific form of the history, or filtration, $\{\mathcal{F}_t\}$. Namely that it is given as $\mathcal{F}_t = \mathcal{F}_0 \vee \mathcal{N}_t$, where $\{\mathcal{N}_t\}$ is the filtration generated by the uncensored individual counting processes, and \mathcal{F}_0 represents information available to the researcher at the outset of the study. However, censoring may induce additional variation not described by a filtration of

the above form, so one may have to consider a larger filtration $\{\mathcal{G}_t\}$ also describing this additional randomness. The fact that we have to consider a larger filtration may have the consequence that the intensity processes of the counting processes may change. However, if this is not the case, so that the intensity processes with respect to $\{\mathcal{G}_t\}$ are the same as the $\{\mathcal{F}_t\}$ -intensity processes, censoring is said to be *independent*. Intuitively this means that the additional knowledge of censoring times up to time t does not carry any information on an individual's risk of experiencing an event at time t .

A careful study of independent censoring for marked point process models along these lines was first carried out by Arjas and Hara (1984). The ideas of Arjas and Hara were taken up and further developed by Per Kragh Andersen, Ørnulf Borgan, Richard Gill, and Niels Keiding as part of their work on the monograph *Statistical Models Based on Counting Processes*; cf. Section 11 below. Discussions with Martin Jacobsen were also useful in this connection (see also Jacobsen, 1989). Their results were published in Andersen et al. (1988) and later Chapter 3 of their monograph. It should be noted that there is a close connection between drop-outs in longitudinal data and censoring for survival data. In fact, independent censoring in survival analysis is essentially the same as *sequential missingness at random* in longitudinal data analysis (e.g., Hogan, Roy and Korkontzelou, 2004).

In many standard statistical models there is an intrinsic assumption of independence between outcome variables. While, in event history analysis, such an assumption may well be reasonable for the basic, uncensored observations, censoring may destroy this independence. An example is survival data in an industrial setting subject to type 2 censoring; that is the situation where items are put on test simultaneously and the experiment is terminated at the time of the r -th failure (cf. above). However, for such situations martingale properties may be preserved; in fact, for type 2 censoring $\{\mathcal{G}_t\} = \{\mathcal{F}_t\}$ and censoring is trivially independent according to the definition just given. This suggests that, for event history data, the counting process and martingale framework is, indeed, the natural framework and that the martingale property replaces the traditional independence assumption, also in the sense that it forms the basis of central limit theorems, which will be discussed next.

5 Martingale central limit theorems

As mentioned, the martingale property replaces the common independence assumption. One reason for the ubiquitous assumption of independence in statistics is to get some asymptotic distributional results of use in estimation and testing, and the martingale assumption can fulfil this need as well. Central limit theorems for martingales can be traced back at least to the beginning of the 1970's (Brown, 1971; Dvoretzky, 1972). Of particular importance for the development of the present theory was the paper by McLeish (1974). The potential usefulness of this paper was pointed out to Aalen by his Ph.D.

supervisor Lucien Le Cam. In fact this happened before the connection had been made to Bremaud's new theory of counting processes, and it was first after the discovery of this theory that the real usefulness of McLeish's paper became apparent. The application of counting processes to survival analysis including the application of McLeish's paper was done by Aalen during 1974–75.

The theory of McLeish was developed for the discrete-time case, and had to be further developed to cover the continuous-time setting of the counting process theory. What presumably was the first central limit theorem for continuous time martingales was published in Aalen (1977). A far more elegant and complete result was given by Rebolledo (1980), and this formed the basis for further developments of the statistical theory; see Andersen et al. (1993) for an overview. A nice early result was also given by Helland (1982).

The central limit theorem for martingales is related to the fact that a martingale with continuous sample paths and a deterministic predictable variation process is a Gaussian martingale, i.e., with normal finite-dimensional distributions. Hence one would expect a central limit theorem for counting process associated martingales to depend on two conditions:

- (i) the sizes of the jumps go to zero (i.e., approximating continuity of sample paths)
- (ii) either the predictable or the optional variation process converges to a deterministic function

In fact, the conditions in Aalen (1977) and Rebolledo (1980) are precisely of this nature.

Without giving the precise formulations of these conditions, let us look informally at how they work out for the Nelson-Aalen estimator. We saw in formula (2.7) that the difference between estimator and estimand of cumulative hazard up to time t could be expressed as $\int_0^t dM(s)/Y(s)$, the stochastic integral of the process $1/Y$ with respect to the counting process martingale M . Considered as a stochastic process (i.e., indexed by time t), this “estimation-error process” is therefore itself a martingale. Using the rules (3.1) we can compute its optional variation process to be $\int_0^t dN(s)/Y(s)^2$ and its predictable variation process to be $\int_0^t \alpha(s)ds/Y(s)$. The error process only has jumps where N does, and at a jump time s , the size of the jump is $1/Y(s)$.

As a first attempt to get some large sample information about the Nelson-Aalen estimator, let us consider what the martingale central limit theorem could say about the Nelson-Aalen estimation-error process. Clearly we would need the number at risk process Y to get uniformly large, in order for the jumps to get small. In that case, the predictable variation process $\int_0^t \alpha(s)ds/Y(s)$ is forced to be getting smaller and smaller. Going to the

limit, we will have convergence to a continuous Gaussian martingale with zero predictable variation process. But the only such process is the constant process, equal to zero at all times. Thus in fact we obtain a consistency result: if the number at risk process gets uniformly large, in probability, the estimation error converges uniformly to zero, in probability. (Actually there are martingale inequalities of Chebyshev type which allow one to draw this kind of conclusion without going via central limit theory.)

In order to get nondegenerate asymptotic normality results, we should zoom in on the estimation error. A quite natural assumption in many applications is that there is some index n , standing perhaps for sample size, such that for each t , $Y(t)/n$ is roughly constant (non random) when n is large. Taking our cue from classical statistics, let us take a look at \sqrt{n} times the estimation error process $\int_0^t dM(s)/Y(s)$. This has jumps of size $(1/\sqrt{n})(Y(s)/n)^{-1}$. The predictable variation process of the rescaled estimation error is n times what it was before: it becomes $\int_0^t (Y(s)/n)^{-1} \alpha(s) ds$. So, the convergence of Y/n to a deterministic function ensures simultaneously that the jumps of the rescaled estimation error process become vanishingly small and that its predictable variation process converges to a deterministic function.

The martingale central limit theorem turns out to be extremely effective in allowing us to guess the kind of results which might be true. Technicalities are reduced to a minimum; results are essentially optimal, i.e., the assumptions are minimal.

Why is that so? In probability theory, the 1960's and 1970's were the hey-day of study of martingale central limit theorems. The outcome of all this work was that the martingale central limit theorem was not only a generalization of the classical Lindeberg central limit theorem, but that the proof was the same: it was simply a question of judicious insertion of conditional expectations, and taking expectations by repeated conditioning, so that the same line of proof worked exactly. In other words, the classical Lindeberg proof of the central limit theorem (see e.g. Feller, 1967) already is the proof of the martingale central limit theorem.

The difficult extension, taking place in the 1970's to the 1980's, was in going from discrete time to continuous time processes. This required a major technical investigation of what are the continuous time processes which we are able to study effectively. This is quite different from research into central limit theorems for other kinds of processes, e.g., for stationary time series. In that field, one splits the process under study into many blocks, and tries to show that the separate blocks are almost independent if the distance between the blocks is large enough. The distance between the blocks should be small enough that one can forget about what goes on between. The central limit theorem comes from looking for approximately independent summands hidden somewhere inside the process of interest. However in the martingale case, one is already studying exactly the kind of process for which the best (sharpest, strongest) proofs are already attuned. No approximations are

involved.

At the time martingales made their entry to survival analysis, statisticians were using many different tools to get large sample approximations in statistics. One had different classes of statistics for which special tools had been developed. Each time something was generalized from classical data to survival data, the inventors first showed that the old tools still worked to get some information about large sample properties (e.g. U statistics, rank tests). Just occasionally, researchers saw a glimmering of martingales behind the scenes, as when Tarone and Ware (1977) used Dvoretzky's (1972) martingale central limit theorem in the study of their class of non-parametric tests. Another important example of work where martingale type arguments were used, is Cox's (1975) paper on partial likelihood; cf. Section 10.

6 Two-sample tests for counting processes

During the 1960's and early 1970's a plethora of tests for comparing two or more survival functions were suggested (Gehan, 1965; Mantel, 1966; Efron, 1967; Breslow, 1970; Peto and Peto, 1972). The big challenge was to handle the censoring, and various simplified censoring mechanisms were proposed with different versions of the tests fitted to the particular censoring scheme. The whole setting was rather confusing, with an absence of a theory connecting the various specific cases. The first connection to counting processes was made by Aalen in his Ph.D. thesis when it was shown that a generalized Savage test (which is equivalent to the logrank test) could be given a martingale formulation. In a Copenhagen research report (Aalen, 1976b) this was extended to a general martingale formulation of two-sample tests which turned out to encompass a number of previous proposals as special cases. The very simple idea was to write the test statistic as a weighted stochastic integral over the difference between two Nelson-Aalen estimators. Let the processes to be compared be indexed by $i = 1, 2$. A class of tests for comparing the two rate functions $\alpha_1(t)$ and $\alpha_2(t)$ is then defined by

$$X(t) = \int_0^t L(s) d(\widehat{A}_1(s) - \widehat{A}_2(s)) = \int_0^t L(s) \left(\frac{dN_1(s)}{Y_1(s)} - \frac{dN_2(s)}{Y_2(s)} \right).$$

Under the null hypothesis of $\alpha_1(s) \equiv \alpha_2(s)$ it follows that $X(t)$ is a martingale since it is a stochastic integral. An estimator of the variance can be derived from the rules for the variation processes, and the asymptotics is taken care of by the martingale central limit theorem. It was found by Aalen (1978b) and detailed by Gill (1980) that almost all previous proposals for censored two-sample tests in the literature were special cases that could be arrived at by judicious choice of the weight function $L(t)$.

A thorough study of two-sample tests from this point of view was first given by Richard Gill in his Ph.D. thesis from Amsterdam (Gill, 1980). The inspiration for Gill's work was a talk given by Odd Aalen at the European

Meeting of Statisticians in Grenoble in 1976. At that time Gill was about to decide on the topic for his Ph.D. thesis, one option being two sample censored data rank tests. He was very inspired by Aalen's talk and the uniform way to treat all the different two-sample statistics offered by the counting process formulation, so this decided the topic for his thesis work. At that time, Gill had no experience with martingales in continuous time. But by reading Aalen's thesis and other relevant publications, he soon mastered the theory. To that end it also helped him that there was organized a study group in Amsterdam on counting processes with Piet Groeneboom as a key contributor.

7 The Copenhagen environment

Much of the further development of counting process theory to statistical issues springs out of the statistics group at the University of Copenhagen. After his Ph.D. study in Berkeley, Aalen was invited by his former master thesis supervisor, Jan M. Hoem, to visit the University of Copenhagen, where Hoem had taken a position as professor in actuarial mathematics. Aalen spent 8 months there (November 1975 to June 1976) and his work immediately caught the attention of Niels Keiding, Søren Johansen, and Martin Jacobsen, among others. The Danish statistical tradition at the time had a strong mathematical basis combined with a growing interest in applications. Internationally, this combination was not so common at the time; mostly the good theoreticians tended to do only theory while the applied statisticians were less interested in the mathematical aspects. Copenhagen made a fertile soil for the further development of the theory.

It was characteristic that for such a new paradigm, it took time to generate an intuition for what was obvious and what really required detailed study. For example, when Keiding gave graduate lectures on the approach in 1976/77 and 1977/78, he followed Aalen's thesis closely and elaborated on the mathematical prerequisites [stochastic processes in the French way, counting processes (Jacod, 1975), square integrable martingales, martingale central limit theorem (McLeish, 1974)]. This was done in more mathematical generality than became the standard later. For example, he patiently went through the Doob-Meyer decompositions following Meyer's *Probabilités et Potentiel* (Meyer, 1966), and he quoted the derivation by Courrège and Priouret (1965) of the following result:

If (N_t) is a stochastic process, $\{\mathcal{N}_t\}$ is the family of σ -algebras generated by (N_t) , and T is a stopping time (i.e. $\{T \leq t\} \in \mathcal{N}_t$ for all t), then the conventional definition of the σ -algebra \mathcal{N}_T of events happening before T is

$$A \in \mathcal{N}_T \iff \forall t : A \cap \{T \leq t\} \in \mathcal{N}_t.$$

A more intuitive way of defining this σ -algebra is

$$\mathcal{N}_T^* = \sigma\{N_{T \wedge u}, u \geq 0\}.$$

Courrège and Priouret (1965) proved that $\mathcal{N}_T = \mathcal{N}_T^*$ through a delicate analysis of the path properties of (N_t) .

Keiding quoted the general definition, valid for measures with both discrete and continuous components, of predictability, not satisfying himself with the “essential equivalence to left-continuous sample paths” that we work with nowadays. Keiding had many discussions with his colleague, the probabilist Martin Jacobsen, who had long focused on path properties of stochastic processes. Jacobsen developed his own independent version of the course in 1980 and wrote his lecture notes up in the *Springer Lecture Notes in Statistics* series (Jacobsen, 1982).

Among those who happened to be around in the initial phase was Niels Becker from Melbourne, Australia, already then well established with his work in infectious disease modelling. For many years to come martingale arguments were used as important tools in Becker’s further work on statistical models for infectious disease data; see Becker (1993) for an overview of this work. A parallel development was the interesting work of Arjas and coauthors on statistical models for marked point processes, see e.g. Arjas and Haara (1984) and Arjas (1989).

8 From Kaplan-Meier to the empirical transition matrix

A central effort initiated in Copenhagen in 1976 was the generalization from scalar to matrix values of the Kaplan-Meier estimator. This started out with the estimation of transition probabilities in the competing risks model developed by Aalen (1972); a journal publication of this work first came in Aalen (1978a). This work was done prior to the introduction of martingale theory, and just like the treatment of the cumulative hazard estimator in Aalen (1976a) it demonstrates the complications that arose before the martingale tools had been introduced. In 1973 Aalen had found a matrix version of the Kaplan-Meier estimator for Markov chains, but did not attempt a mathematical treatment because this seemed too complex. It was the martingale theory that allowed an elegant and compact treatment of these attempts to generalize the Kaplan-Meier estimator, and the breakthrough here was made by Søren Johansen in 1975–76. It turned out that martingale theory could be combined with the product-integral approach to non-homogeneous Markov chains via an application of Duhamel’s equality; cf. (8.2) below. The theory of stochastic integrals could then be used in a simple and elegant way. This was written down in a research report (Aalen and Johansen, 1977) and published in Aalen and Johansen (1978).

Independently of this the same estimator was developed by Fleming and published in Fleming (1978a, 1978b) just prior to the publication of Aalen and Johansen (and duly acknowledged in their paper). Tom Fleming and

David Harrington were Ph.D. students of Grace Yang at the University of Maryland, and they have later often told us that they learned about Aalen's counting process theory from Grace Yang's contact with her own former Ph.D. advisor, Lucien Le Cam. Fleming also based his work on the martingale counting process approach. He had a more complex presentation of the estimator presenting it as a recursive solution of equations; he did not have the simple matrix product version of the estimator nor the compact presentation through the Duhamel equality which allowed for general censoring and very compact formulas for covariances.

The estimator is named the empirical transition matrix, see e.g. Aalen et al. (2008). The compact matrix product version of the estimator presented in Aalen and Johansen (1978) is often called the Aalen-Johansen estimator, and we are going to explain the role of martingales in this estimator.

More specifically, consider an inhomogeneous continuous-time Markov process with finite state space $\{1, \dots, k\}$ and transition intensities $\alpha_{hj}(t)$ between states h and j , where in addition we define $\alpha_{hh}(t) = -\sum_{j \neq h} \alpha_{hj}(t)$ and denote the matrix of all $A_{hj}(t) = \int_0^t \alpha_{hj}(s) ds$ as $\mathbf{A}(t)$. Nelson-Aalen estimators $\widehat{A}_{hj}(t)$ of the cumulative transition intensities $A_{hj}(t)$ may be collected in the matrix $\widehat{\mathbf{A}}(t) = \{\widehat{A}_{hj}(t)\}$. To derive an estimator of the transition probability matrix $\mathbf{P}(s, t) = \{P_{hj}(s, t)\}$ it is useful to represent it as the matrix product-integral

$$\mathbf{P}(s, t) = \prod_{(s,t]} \{\mathbf{I} + d\mathbf{A}(u)\},$$

which may be defined as

$$\prod_{(s,t]} \{\mathbf{I} + d\mathbf{A}(u)\} = \lim_{\max |u_i - u_{i-1}| \rightarrow 0} \prod_i \{\mathbf{I} + \mathbf{A}(u_i) - \mathbf{A}(u_{i-1})\},$$

where $s = u_0 < u_1 < \dots < u_n = t$ is a partition of $(s, t]$ and the matrix product is taken in its natural order from left to right.

The empirical transition matrix or Aalen-Johansen estimator is the plug-in estimator

$$\widehat{\mathbf{P}}(s, t) = \prod_{(s,t]} \{\mathbf{I} + d\widehat{\mathbf{A}}(u)\}, \quad (8.1)$$

which may be evaluated as a finite matrix product over the times in $(s, t]$ when transitions are observed. Note that (8.1) is a multivariate version of the Kaplan-Meier estimator (2.8). A matrix martingale relation may be derived from a matrix version of the Duhamel equation (2.9). For the case where all numbers at risk in the various states, $Y_h(t)$, are positive this reads

$$\widehat{\mathbf{P}}(s, t)\mathbf{P}(s, t)^{-1} - \mathbf{I} = \int_s^t \widehat{\mathbf{P}}(s, u-)d(\widehat{\mathbf{A}} - \mathbf{A})(u)\mathbf{P}(s, u)^{-1}. \quad (8.2)$$

This is a stochastic integral representation from which covariances and asymptotic properties can be deduced directly. This particular formulation is from Aalen and Johansen (1978).

9 Pustulosis palmo-plantaris and k -sample tests

One of the projects that were started when Aalen visited the University of Copenhagen was an epidemiological study of the skin disease pustulosis palmo-plantaris with Aalen, Keiding and the medical doctor Jens Thormann as collaborators. Pustulosis palmo-plantaris is mainly a disease among women, and the question was whether the risk of the disease was related to the occurrence of menopause. Consecutive patients from a hospital outpatient clinic were recruited, so the data could be considered a random sample from the prevalent population. At the initiative of Jan M. Hoem, another of his former master students from Oslo, Ørnulf Borgan, was asked to work out the details. Borgan had since 1977 been assistant professor in Copenhagen, and he had learnt the counting process approach to survival analysis from the above mentioned series of lectures by Niels Keiding. The cooperation resulted in the paper Aalen et al. (1980).

In order to be able to compare patients without menopause with patients with natural menopause and with patients with induced menopause, the statistical analysis required an extension of Aalen's work on two-sample tests to more than two samples. (The work of Richard Gill on two-sample tests was not known in Copenhagen at that time.) The framework for such an extension is k counting processes N_1, \dots, N_k , with intensity processes $\lambda_1, \dots, \lambda_k$ of the multiplicative form $\lambda_j(t) = \alpha_j(t)Y_j(t)$; $j = 1, 2, \dots, k$; and where the aim is to test the hypothesis that all the α_j are identical. Such a test may be based on the processes

$$X_j(t) = \int_0^t K_j(s)d(\widehat{A}_j(s) - \widehat{A}(s)), \quad j = 1, 2, \dots, k,$$

where \widehat{A}_j is the Nelson-Aalen estimator based on the j -th counting process, and \widehat{A} is the Nelson-Aalen estimator based on the aggregated counting process $N = \sum_{j=1}^k N_j$.

This experience inspired a decision to give a careful presentation of the k -sample tests for counting processes and how they gave a unified formulation of most rank based tests for censored survival data, and Per K. Andersen (who also had followed Keiding's lectures), Ørnulf Borgan, and Niels Keiding embarked on this task in the fall of 1979. During the work on this project, Keiding was (by Terry Speed) made aware of Richard Gill's work on two-sample tests. (Speed, who was then on sabbatical in Copenhagen, was at a visit in Delft where he came across an abstract book for the Dutch statistical association's annual gathering with a talk by Gill about the counting process approach to censored data rank tests.) Gill was invited to spend the fall of 1980 in Copenhagen. There he got a draft manuscript by Andersen, Borgan and Keiding on k -sample tests, and as he made a number of substantial comments to the manuscript, he was invited to co-author the paper (Andersen,

Borgan, Gill, and Keiding, 1982).

10 The Cox model

With the development of clinical trials in the 1950's and 1960's the need to analyze censored survival data dramatically increased, and a major breakthrough in this direction was the Cox proportional hazards model published in 1972 (Cox, 1972). Now, regression analysis of survival data was possible. Specifically, the Cox model describes the hazard rate for a subject, i with covariates $\mathbf{Z}_i = (Z_{i1}, \dots, Z_{ip})^\top$ as

$$\alpha(t | \mathbf{Z}_i) = \alpha_0(t) \exp(\boldsymbol{\beta}^\top \mathbf{Z}_i).$$

This is a product of a *baseline* hazard rate $\alpha_0(t)$, common to all subjects, and the exponential function of the linear predictor, $\boldsymbol{\beta}^\top \mathbf{Z}_i = \sum_j \beta_j Z_{ij}$. With this specification, hazard rates for all subjects are proportional and $\exp(\beta_j)$ is the hazard rate ratio associated with an increase of 1 unit for the j th covariate Z_j , that is the ratio

$$\exp(\beta_j) = \frac{\alpha(t | Z_1, Z_2, \dots, Z_{j-1}, Z_j + 1, Z_{j+1}, \dots, Z_p)}{\alpha(t | Z_1, Z_2, \dots, Z_{j-1}, Z_j, Z_{j+1}, \dots, Z_p)},$$

where Z_ℓ for $\ell \neq j$ are the same in numerator and denominator. The model formulation of Cox (1972) allowed for covariates to be time-dependent and it was suggested to estimate $\boldsymbol{\beta}$ by the value $\hat{\boldsymbol{\beta}}$ maximizing the *partial likelihood*

$$L(\boldsymbol{\beta}) = \prod_{i:D_i=1} \frac{\exp(\boldsymbol{\beta}^\top \mathbf{Z}_i(T_i))}{\sum_{j \in R_i} \exp(\boldsymbol{\beta}^\top \mathbf{Z}_j(T_i))}. \quad (10.1)$$

Here, $D_i = I(i \text{ was observed to fail})$ and R_i is the *risk set*, i.e., the set of subjects still at risk at the time, T_i , of failure for subject i . The cumulative baseline hazard rate $A_0(t) = \int_0^t \alpha_0(u) du$ was estimated by the Breslow (1972, 1974) estimator

$$\hat{A}_0(t) = \sum_{i:T_i \leq t} \frac{D_i}{\sum_{j \in R_i} \exp(\hat{\boldsymbol{\beta}}^\top \mathbf{Z}_j(T_i))}. \quad (10.2)$$

Cox's work triggered a number of methodological questions concerning inference in the Cox model. In what respect could the partial likelihood (10.1) be interpreted as a proper likelihood function? How could the large sample properties of the resulting estimators be established? Cox himself used repeated conditional expectations (which essentially was a martingale argument) to show informally that his partial likelihood (10.1) had similar properties as an ordinary likelihood, while Tsiatis (1981) used classical methods to provide a thorough treatment of large sample properties of the estimators $(\hat{\boldsymbol{\beta}}, \hat{A}_0(t))$ when only time-fixed covariates were considered. The

study of large sample properties, however, were particularly intriguing when time-dependent covariates were allowed in the model.

At the Statistical Research Unit in Copenhagen, established in 1978, analysis of survival data was one of the key research areas and several applied medical projects using the Cox model were conducted. One of these projects, initiated in 1978 and published by Andersen and Rasmussen (1986), dealt with recurrent events: admissions to psychiatric hospitals among pregnant women and among women having given birth or having had induced abortion. Here, a model for the intensity of admissions was needed and since previous admissions were strongly predictive for new admissions, time-dependent covariates should be accounted for. Counting processes provided a natural framework in which to study the phenomenon and research activities in this area were already on the agenda, as exemplified above.

It soon became apparent that the Cox model could be immediately applied for the recurrent event intensity, and Johansen's (1983) derivation of Cox's partial likelihood as a profile likelihood also generalized quite easily. The individual counting processes, $N_i(t)$, counting admissions for woman i could then be "Doob-Meyer decomposed" as

$$N_i(t) = \int_0^t Y_i(u) \alpha_0(u) \exp(\boldsymbol{\beta}^\top \mathbf{Z}_i(u)) du + M_i(t). \quad (10.3)$$

Here, $Y_i(t)$ is the at-risk indicator process for woman i (indicating that she is still in the study and out of hospital at time t), $\mathbf{Z}_i(t)$ is the, possibly time-dependent, covariate vector including information on admissions before t , and $\alpha_0(t)$ the unspecified baseline hazard. Finally, $M_i(t)$ is the martingale. We may write the sum over event times in the score $\mathbf{U}(\boldsymbol{\beta}) = \partial \log L(\boldsymbol{\beta}) / \partial \boldsymbol{\beta}$, derived from Cox's partial likelihood (10.1), as the counting process integral

$$\mathbf{U}(\boldsymbol{\beta}) = \sum_i \int_0^\infty \left(\mathbf{z}_i(u) - \frac{\sum_j Y_j(u) \mathbf{z}_j(u) \exp(\boldsymbol{\beta}^\top \mathbf{z}_j(u))}{\sum_j Y_j(u) \exp(\boldsymbol{\beta}^\top \mathbf{z}_j(u))} \right) dN_i(u).$$

Then using (10.3), the score can be re-written as $U_\infty(\boldsymbol{\beta})$, where

$$\mathbf{U}_t(\boldsymbol{\beta}) = \sum_i \int_0^t \left(\mathbf{z}_i(u) - \frac{\sum_j Y_j(u) \mathbf{z}_j(u) \exp(\boldsymbol{\beta}^\top \mathbf{z}_j(u))}{\sum_j Y_j(u) \exp(\boldsymbol{\beta}^\top \mathbf{z}_j(u))} \right) dM_i(u).$$

Thus, evaluated at the true parameter values, the Cox score, considered as a process in t is a martingale stochastic integral, provided the time-dependent covariates (and $Y_i(t)$) are predictable.

Large sample properties for the score could then be established using the martingale central limit theorem and transformed into a large sample result for $\hat{\boldsymbol{\beta}}$ by standard Taylor expansions. Also, asymptotic properties of the Breslow estimator (10.3) could be established using martingale methods. This is because we may write the estimator as $\hat{A}_0(t) = \hat{A}_0(t | \hat{\boldsymbol{\beta}})$, where for

the true value of β we have

$$\widehat{A}_0(t|\beta) = \int_0^t \frac{\sum_i dN_i(u)}{\sum_j Y_j(u) \exp(\beta^\top \mathbf{Z}_j(u))} = A_0(t) + \int_0^t \frac{\sum_i dM_i(u)}{\sum_j Y_j(u) \exp(\beta^\top \mathbf{Z}_j(u))}.$$

That is, $\widehat{A}_0(t|\beta) - A_0(t)$ is a martingale stochastic integral. These results were obtained by Per Kragh Andersen in 1979-80, but a number of technicalities remained to get proper proofs.

As mentioned above, Richard Gill visited Copenhagen in 1980 and he was able to provide the proof of consistency and work out the detailed verifications of the general conditions for the asymptotic results in Andersen and Gill's (1982) *Annals of Statistics* paper. It should be noted that Næs (1982), independently, published similar results under somewhat more restrictive conditions using discrete-time martingale results.

Obviously, the results mentioned above also hold for counting processes $N_i(t) = I(T_i \leq t, D_i = 1)$ derived from censored survival times and censoring indicators, (T_i, D_i) , but historically the result was first derived for the "Andersen-Gill" recurrent events process. Andersen and Borgan (1985), see also Andersen et al. (1993, Chapter VII), extended these results to multivariate counting processes modelling the occurrence of several types of events in the same subjects.

Later, Barlow and Prentice (1988) and Therneau, Grambsch and Fleming (1990) used the Doob-Meyer decomposition (10.3) to define *martingale residuals*

$$\widehat{M}_i(t) = N_i(t) - \int_0^t \exp(\widehat{\beta}^\top \mathbf{Z}_i(u)) d\widehat{A}_0(u). \quad (10.4)$$

Note how $N_i(t)$ plays the role of the observed data while the compensator term estimates the expectation. We are then left with the martingale noise term.

The martingale residuals (10.4) provide the basis for a number of goodness-of-fit techniques for the Cox model. First, they were used to study whether the functional form of a quantitative covariate was modelled in a sensible way. Later, cumulative sums of martingale residuals have proven useful for examining several features of hazard based models for survival and event history data, including both the Cox model, Aalen's additive hazards model and others (e.g., Lin, Wei and Ying, 1993; Martinussen and Scheike, 2006). The additive hazards model was proposed by Aalen (1980) as a tool for analyzing survival data with changing effects of covariates. It is also useful for recurrent event data and dynamic path analysis, see e.g. Aalen et al. (2008).

11 The monograph *Statistical models based on counting processes*

As the new approach spread, publishers became interested, and as early as 1982 Martin Jacobsen had published his exposition in the Springer Lecture Notes in Statistics (Jacobsen, 1982). In 1982 Niels Keiding gave an invited talk “Statistical applications of the theory of martingales on point processes” at the Bernoulli Society conference on Stochastic Processes in Clermont-Ferrand. (One slide showed a graph of a simulated sample function of a compensator, which prompted the leading French probabilist Michel Métivier to exclaim “This is the first time I have seen a compensator”.) At that conference Klaus Krickeberg, himself a pioneer in martingale theory and an advisor to the Springer Series in Statistics, invited Keiding to write a monograph on this topic. Keiding floated this idea in the well-established collaboration with Andersen, Borgan and Gill. Aalen was asked to participate, but had just started to build up a group of medical statistics in Oslo and wanted to give priority to that. So the remaining four embarked upon what became an intense 10-year collaboration resulting in the monograph *Statistical Models Based on Counting Processes* (Andersen et al., 1993). The monograph combines concrete practical examples, almost all of the authors’ own experience, with an exposition of the mathematical background, several detailed chapters on non- and semiparametric models as well as parametric models, as well as chapters giving preliminary glimpses into topics to come: semiparametric efficiency, frailty models (for more elaborate introductions of frailty models see Hougaard, 2002; or Aalen et al., 2008) and multiple time-scales. Fleming and Harrington had published their monograph *Counting Processes and Survival Analysis* with Wiley in 1991 (Fleming and Harrington, 1991). It gives a more textbook-type presentation of the mathematical background and covers survival analysis up to and including the proportional hazards model for survival data.

12 Limitations of martingales

Martingale tools do not cover all areas where survival and event history analysis may be used. In more complex situations one can see the need to use a variety of tools, alongside of what martingale theory provides. For staggered entry, the Cox frailty model, and in Markov renewal process/semi-Markov models (see e.g. Andersen et al., 1993, Chapters IX and X, for references on this work), martingale methods give transparent derivations of mean values and covariances, likelihoods, and maximum likelihood estimators; however to derive large sample theory, one needs input from the theory of empirical processes. Thus in these situations the martingale approach helps at the modelling stage and the stage of constructing promising statistical methodology, but one needs different tools for the asymptotic theory. The reason

for this in a number of these examples is that the martingale structure corresponds to the dynamics of the model seen in real (calendar) time, while the principal time scales of statistical interest correspond to time since an event which is repeated many times. In the case of frailty models, the problem is that there is an unobserved covariate associated with each individual; observing that individual at late times gives information about the value of the covariate at earlier times. In all these situations, the natural statistical quantities to study can no longer be directly expressed as sums over contributions from each (calendar) time point, weighted by information only from the (calendar time) past. More complex kinds of missing data (frailty models can be seen as an example of missing data), and biased sampling, lead also to new levels of complexity in which the original dynamical time scale becomes just one feature of the problem at hand, other features which do not mesh well with this time scale become dominating, with regards to the technical investigation of large sample behaviour. A difficulty with the empirical process theory is the return to a basis of independent processes, and so a lot of the niceness of the martingale theory is lost. Martingales allow for very general dependence between processes.

However, the martingale ideas also enter into new fields. Lok (2008) used martingale theory to understand the continuous time version of James Robins' theory of causality. Similarly, Didelez (2007) used martingales to understand the modern formulation of local dependence and Granger causality. Connected to this are the work of Arjas and Parner (2004) on posterior predictive distributions for marked point process models and the dynamic path analysis of Fosen et al. (2006), see also Aalen et al. (2008). Hence, there is a new lease of life for the theory. Fundamentally, the idea of modelling how the past influences the present and the future is inherent to the martingale formulation, and this must with necessity be of importance in understanding causality.

The martingale concepts from the French probability school may be theoretical and difficult to many statisticians. Jacobsen (1982) and Helland (1982) are nice examples of how the counting process work stimulated probabilists to reappraise the basic probability theory. Both authors succeeded in giving a much more compact and elementary derivation of (different parts of) the basic theory from probability needed for the statistics. This certainly had a big impact at the time, in making the field more accessible to more statisticians. Especially while the fundamental results from probability were still in the course of reaching their definitive forms and were often not published in the most accessible places or languages. Later these results became the material of standard textbooks. In the long run, statisticians tend to use standard results from probability without bothering too much about how one can prove them from scratch. Once the martingale theory became well established people were more confident in just citing the results they needed.

Biostatistical papers have hardly ever cited papers or even books in theoretical probability. However at some point it became almost obligatory

to cite Andersen and Gill (1982), Andersen et al. (1993), and other such works. What was being cited then was worked out examples of applying the counting process approach to various more or less familiar applied statistical tools like the Cox regression model, especially when being used in a little bit non-standard context, e.g., with repeated events. It helped that some software packages also refer to such counting process extensions as the basic biostatistical tool.

The historical overview presented here shows that the elegant theory of martingales has been used fruitfully in statistics. This is another example showing that mathematical theory developed on its own terms may produce very useful practical tools.

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