Søren Johansen

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Institute of Mathematical Statistics
University of Copenhagen

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INSTITUTE OF MATHEMATICAL STATISTICS
UNIVERSITY OF COPENHAGEN

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Abstract

It is shown how one can extend Cox's model for regression analysis of survival data to allow for an arbitrary underlying measure for the intensity.

In this extended model Cox's estimator of the regression parameters and the intensity measure becomes a maximum likelihood estimator. It is shown how one can analyse the extended model as a dynamical exponential family in such a way, that Cox's partial likelihood can be explained by the notion of S-ancillarity.

Key words

Cox's regression model. Multiplicative intensity models.
S-ancillarity. Non-parametric maximum likelihood.

1. Introduction and summary

Cox (1972) introduced the regression model for survival data which can be described as follows: The lifelengths of n individuals are distributed independently with an integrated intensity $\int_0^{t_i} e^{\beta' z_i(u)} \lambda(u)du$ where $\lambda(\cdot)$ and $\beta \in R^k$ are unknown parameters, whereas $z_i(t) \in R^k$ is a vector of known cofactors for the i'th individual at time t.

It was suggested to use the likelihood

$$L_c = \prod_{i=1}^{n} \frac{e^{\beta' z_i(t_i)}}{\sum_{j \in R(t_i)} e^{\beta' z_j(t_i)}}$$

to estimate β. Here t_i is the death time of the i'th individual and $j \in R(t_i)$ if individual j is alive just before time t_i.

Cox also suggested using the discrete measure $\hat{\Lambda}$ given by

$$\hat{\Lambda}(A) = \sum_{t_i \in A} \frac{1}{\sum_{j \in R(t_i)} e^{\beta' z_j(t_i)}}$$

as an estimate of $\int_A \lambda(u)du$.

Various arguments have been given for using this likelihood function, see Cox (1975), Kalbfleisch and Prentice (1980) and Oakes (1981).

Cox has argued that L_c is a partial likelihood in the sense that it is a product of some factors (every second) in a natural factorization of the likelihood function. The main purpose of the present work is to show how a suitable extended model, replacing $\int_A \lambda(u)du$ by the measure Λ, allows one to show that L_c is a partially maximized likelihood, or likelihood profile, in the sense that

$$L_c(\beta) = \max_{\Lambda} L(\beta,\Lambda).$$

Moreover the value of Λ that maximizes $L(\beta,\Lambda)$ is precisely $\hat{\Lambda}$ above, thus an argument can be given for using Cox's likelihood for estimating β without reference to the notion of partial likelihood and the estimates of β and Λ are just the joint maximum likelihood estimates.

We want to exploit the connection between Cox's model and the general multiplicative model for counting processes suggested by Aalen (1978).

A counting process can be considered a continuous family of binary variables and the idea is to consider a continuous family of Poisson variables. This point of view leads to a natural definition of a dynamical exponential family, related to the notion of conditional exponential family, see Heyde and Feigin (1975). For this to work out we shall use the results of Jacod (1975) for multivariate point processes which seems to be the natural tool.

Thus we shall first rephrase the Poisson process as a multivariate counting process, then show how other Poisson-like processes can be constructed by specifying the density with respect to the distribution of the Poisson process.

Then we shall extend the class of Aalen models to allow arbitrary measures, and finally we shall show how this solves the problem of extending the Cox model.

It should be pointed out, however, that although the proposed extension has the property that $\hat{\beta}$ and $\hat{\Lambda}$ are maximum likelihood estimates, it also has the property that the sample paths have only one jump, but this jump could be any size. Hence the discrete measures which we allow for Λ do not necessarily correspond to a reasonable model for survival times, but should be considered an explanation of the usual estimates.

2. The Poisson process as a multivariate counting process

Consider a Poisson process $X(t), t \in R_+ = [0,\infty[$ on some probability space $(\Omega, \mathcal{F}, P)$. Let $\Lambda \in \mathcal{M}^+(R_+)$ denote a Borel measure on $\mathcal{B}(R_+)$, the Borel sets of R_+, with the property that $\Lambda([0,t]) < \infty, t < \infty$. We will assume that $X(0) = 0, X(t)$ has independent increments, is piecewise constant, right continuous and that the distribution of $X(t) - X(s)$ is Poisson with parameter $\Lambda(]s,t])$. We shall call Λ the intensity measure of X.

We define the multivariate counting process N_x, $x \in \mathbb{N} = \{1,2,\ldots\}$ by $N_x(t) = \sum_{s \leqq t} 1\{\Delta X(s) = x\}$ and $N(t) = \Sigma_x N_x(t)$. Thus $N_x(t)$ counts the number of x-jumps of X on $[0,t]$ and $N(t)$ the total number of jumps.

Note that $X(t) = \Sigma_x x N_x(t)$, such that

$$\mathcal{F}_t = \sigma\{X(u), u \leqq t\} = \sigma\{N_x(u), u \leqq t, x \in \mathbb{N}\} \quad .$$

The predictable compensator for the counting process N_x with respect to the family $\{\mathcal{F}_t\}$ is given by

$$\nu_\Lambda([0,t],x) = \int_{[0,t]} \frac{\Lambda(du)^x}{x!} e^{-\Lambda(du)}$$

if $x = 1,2,\ldots$

This notation means that

$$\nu_\Lambda([0,t],1) = \sum_{u \leqq t} \Lambda\{u\} e^{-\Lambda\{u\}} + \Lambda_{cont}([0,t])$$

and

$$\nu_\Lambda([0,t],x) = \sum_{u \leqq t} \frac{\Lambda\{u\}^x}{x!} e^{-\Lambda\{u\}}, \quad x = 2,3,\ldots$$

We also define

$$\nu_\Lambda([0,t],0) = \sum_{u \leq t} e^{-\Lambda\{u\}} .$$

We shall use the distribution P_Λ for the multivariate counting process $\{N_x\}$ in the next section by specifying densities with respect to P_Λ. The representation of X as a multivariate counting process is just a device for transforming the problem, such that the results for counting processes can be applied.

Note that if $\Lambda(A) = \int_A \lambda(u)du$ then $\nu_\Lambda([0,t],x) = 0$ for $x = 2,3,...$ which means that only N_1 has jumps and that $N_1 = X$. Thus for Λ absolutely continuous we get that X is a counting process.

3. The generalized Aalen model for counting processes.

We shall here define a class of models each of which has parameters (β,Λ), $\beta \in R^k$, $\Lambda \in \mathcal{M}^+(R_+)$, with the property that they reduce to Aalen models if Λ is absolutely continuous.

Let Ω be the space of counting processes $\{N_x\}$ which have no common jump point and let $\mathcal{F}_t$ be the σ-field induced by $\{N_x(u), u \leq t\}$.

Let now Y be a non-negative predictable process, i.e. $Y: \Omega \times R_+ \to R_+$ such that Y is measurable with respect to the σ-field generated by $Z: \Omega \times R_+ \to R_+$ with the property that $Z(\cdot,t)$ is measurable $\mathcal{F}_t$ and $Z(\omega,\cdot)$ is left continuous. We shall assume that $Y(u)$ is bounded on $[0,t]$ for all t.

We want to describe a probability measure $P_{Y\Lambda}$ for the counting processes $\{N_x\}$ or X with the property that X has predictable compensator $\int_{[0,t]} Y(u)\Lambda(du)$ with respect to the σ-fields $\{\mathcal{F}_t\}$. The necessary results are taken from Jacod (1975).

We define

$$(3.1) \qquad \nu_{Y\Lambda}([0,t],x) = \int_{[0,t]} \frac{(Y(u)\Lambda(du))^x}{x!} e^{-Y(u)\Lambda(du)}, \quad x \in \mathbb{N}_0$$

then

$$(3.2) \qquad \frac{\nu_{Y\Lambda}(du,x)}{\nu_\Lambda(du,x)} = Y(u)^x \, e^{-(Y(u)-1)\Lambda(du)} .$$

We can now apply Proposition 4.3 and Theorem 5.1 of Jacod (1975) and we find that there exists a probability measure $P_{Y\Lambda}$, which is given by the density $Z(t)$ with respect to P_Λ on $\mathcal{F}_t$, where

$$(3.3) \quad Z(t) = \frac{dP_{Y\Lambda}}{dP_\Lambda}\Big|_{\mathcal{F}_t} = \prod_{u \leq t} \prod_{x \in \mathbb{N}} \left(\frac{\nu_{Y\Lambda}(du,x)}{\nu_\Lambda(du,x)}\right)^{N_x(du)} \left(\frac{\nu_{Y\Lambda}(du,0)}{\nu_\Lambda(du,0)}\right)^{1-N(du)}$$

such that the predictable compensator for N_x is given by $\nu_{Y\Lambda}([0,t],x)$ for the measure $P_{Y\Lambda}$ with respect to the σ-fields $\mathcal{F}_t$. We have used the product integral notation for a measure ν on $\mathcal{B}(R_+)$:

$$\prod_{u \leqq t} (1 - \nu(du)) = \prod_{u \leqq t} (1 - \nu\{u\}) e^{-\nu_{cont}([0,t])} .$$

This notation simplifies the expression given by Jacod and suggests the following interpretation of the process X or $\{N_x\}$. We can think of $\{N_x\}$ as a continuum of multinomial random variables $\{\Delta N_x\}$, such that the distribution of $\{\Delta N_x(u)\}$ at time u given $\mathcal{F}_{u}-$ is multinomial with parameters

$$(1, p_0, p_1, \ldots)$$

where

$$p_x = \nu_{Y\Lambda}(du,x) = \frac{(Y(u)\Lambda(du))^x}{x!} e^{-Y(u)\Lambda(du)}, \quad x \in \mathbb{N}_0 .$$

or alternatively a continuum of Poisson variables $\Delta X(u)$ where the parameter of $\Delta X(u)$ given $\mathcal{F}_u-$ is $Y(u)\Lambda(du)$. The choice (3.1) reduces (3.3) to

$$(3.4) \qquad Z(t) = \prod_{u \leqq t} Y(u)^{X(du)} e^{-\int_0^t (Y(u)-1)\Lambda(du)} .$$

Finally note that since $X = \Sigma_x x N_x$ we find the predictable compensator for X with respect to $\{\mathcal{F}_t\}$ by

$$\Sigma_x x \nu_{Y\Lambda}([0,t],x) = \int_{[0,t]} Y(u)\Lambda(du) .$$

Aalen (1978) formulated the multiplicative intensity model for counting processes as follows: Let X(t) be a counting process with intensity

(3.5) $$Y(t)\lambda(t)$$

where $\lambda(t)$ is locally integrable $\int_0^t \lambda(u)du < \infty$, and Y is predictable with respect to some increasing sequence of σ-fields. We want to make inference about λ from the observation of X and Y.

He suggested using $\int_0^t \frac{X(du)}{Y(u)}$ to estimate $\int_0^t \lambda(u)du$.

If in our generalized Aalen model we assume that Λ is absolutely continuous with density λ then X will indeed be a counting process $(X = N_1)$ and hence the model reduces to Aalens multiplicative intensity model.

The general model depends on the choice of Y, which can depend on the sample path X in a complicated way. From a given Aalen model $Y_0(u)\lambda(u)$ the function Y_0 is only defined on counting processes and one can in general find many Y which equals Y_0 when the measure Λ becomes absolutely continuous.

Thus an Aalen model can in general be extended in many ways.

We can now formulate the general Aalen model as the family

(3.6) $$\{P_{Y\Lambda},\ \Lambda \in M^+(R_+)\} .$$

Let us conclude this section by giving a heuristic argument for the choice (3.1) which contains the Poisson probabilities. The choice is in my opinion justified by the results in the next sections, but intuitively one can argue as follows: If we think of Λ as being approximated by a sequence $\int \lambda_n(u)du$, $n \to \infty$ then if Λ has an atom at t_0, we may have $\lambda_n(t_0) \to \infty$, which would indicate that jumps could pile up around t_0. In the limit we would allow jump sizes larger than one and therefore leave the probabilistic framework of counting processes and work with integer jump size processes, which can be formulated as multivariate counting processes.

We thus have to specify the probabilities of jumps of size x given the past, that is $\nu_{Y\Lambda}(du,x)$. We choose the Poisson probabilities because if $Y=1$ then the jumps are in fact Poisson distributed, and because they give the proper reduction of the likelihood function.

By making the parameters depend on Y and Λ as they do, we make sure that the observation process X has compensator $\int Y(u)\Lambda(du)$, thus generalizing the Aalen model.

The above extension has the property that the increment X(dt) has an exponential family as distribution given F_{t^-}. The "number of parameters" increase continuously. One could call this a dynamical exponential family to emphasize that time enters into the observation scheme and the model building as well as in the analysis in an essential way.

Heyde and Feigin (1975) and Feigin (1976) have introduced the notion of a conditional exponential family via a property of the derivative of the log likelihood.

It appears that the formulation via multivariate point processes is the proper tool to discuss the distribution of the increments directly, even allowing the number of parameters to increase.

4. Statistical analysis of the general Aalen model

Let $x = \{x(t), t \in [0,1]\}$ be the observation of X with jump times $\{t_j\}_1^m$, $0 < t_1 < \ldots < t_m \leqq 1$ and jump sizes $\{x_j\}_1^m$. We want to estimate Λ in the model $\{P_{Y\Lambda}, \Lambda \in M^+(R_+)\}$.

We shall use the method of maximum likelihood as discussed by Kiefer and Wolfowitz (1956), which in this case amounts to finding a $\hat{\Lambda}$ such that

$$P_{Y\hat{\Lambda}}(x) \geqq P_{Y\Lambda}(x), \quad \Lambda \in M^+(R_+) \; .$$

The natural guess is the Nelson-Aalen estimator

$$\hat{\Lambda}(A) = \int_A \frac{X(du)}{Y(u)} = \sum_{t_i \in A} \frac{X_i}{Y(t_i)} \; . \tag{4.1}$$

We find the following expression

$$P_{Y\Lambda}(x) = \prod_{i=1}^{m} \frac{(Y(t_i)\Lambda\{t_i\})^{X_i}}{X_i!} e^{-\int_0^1 Y(u)\Lambda(du)}$$

$$= \prod_{i=1}^{m} \frac{(Y(t_i)\Lambda\{t_i\})^{X_i}}{X_i!} e^{-Y(t_i)\Lambda(t_i)} e^{-\int_B Y(u)\Lambda(du)}$$

where $B = [0,1] \setminus \{t_1,\ldots,t_m\}$.

This is clearly maximized for

$$\Lambda\{t_i\} = X_i/Y(t_i)$$

and

$$\Lambda[0,1] \setminus \{t_1,\ldots,t_m\} = 0$$

which is precisely $\hat{\Lambda}$.

Thus the Nelson-Aalen estimator is the maximum likelihood estimator in the Aalen model. The statistical properties of $\hat{\Lambda}$ have been investigated when Λ is absolutely continuous by Aalen (1978).

5. The extended Cox model

We shall formulate the Cox model as a model for counting processes as follows: Let X_i, $i=1,\dots,n$ be independent counting processes with compensators

$$(5.1) \qquad \int_0^t e^{\beta' z_i(u)} (1-X_i(u^-))^+ \lambda(u)\,du \ .$$

We define $Y_i^\beta(u) = e^{\beta' z_i(u)} (1-X_i(u^-))^+$ and we see that (5.1) is a special case of the Aalen model (3.5).

Cox (1972) suggested estimating β from

$$L_c(\beta) = \prod_i \frac{e^{\beta' z_i(t_i)}}{\sum_{j\in R(t_i)} e^{\beta' z_j(t_i)}} = \prod_{u\leq 1} \prod_i \left(\frac{Y_i^\beta(u)}{\sum_j Y_j^\beta(u)}\right)^{X_i(du)}$$

and to estimate $\int_0^t \lambda(u)\,du$ by

$$\int_0^t \frac{\Sigma_i X_i(du)}{\Sigma_i Y_i^{\hat\beta}(u)} \ .$$

The point of this section is to show that if we extend the Cox model, we obtain a model depending on β and $\Lambda \in M^+(R_+)$, with the property that Cox's estimate for β and Λ are the maximum likelihood estimates. Notice that the way we have defined Y_i allows us to define it for any integer valued process. Thus we consider the model

$$\{ \bigotimes_{i=1}^n P_{Y_i^\beta \Lambda}, \ \Lambda \in M^+(R_+), \ \beta \in R^k \} \ .$$

The probability of an outcome of the processes $X_i(u)$ $u\in[0,1]$, $i=1,\dots,n$, then has the form, see (3.4),

$$(5.2) \qquad L = \prod_i \left\{ \prod_{u\leq 1} \frac{(Y_i^\beta(u)\Lambda(du))^{X_i(du)}}{X_i(du)!} e^{-\int_0^1 Y_i^\beta(u)\Lambda(du)} \right\}$$

$$= \prod_{u \leq 1} \prod_i \left(\frac{Y_i^\beta(u)}{\Sigma_j Y_j^\beta(u)}\right)^{X_i(du)} / X_i(du)!$$

$$\times \prod_{u \leq 1} (\Sigma_j Y_j^\beta(u)\Lambda(du))^{X(du)} e^{-\int_0^1 \Sigma_i Y_i^\beta(u)\Lambda(du)}$$

where $X(u) = \Sigma_i X_i(u)$.

The last factor is exactly the likelihood in the general Aalen model and thus gives the estimate

$$\hat{\Lambda}_\beta(A) = \int_A \frac{X(du)}{\Sigma_i Y_i^\beta(u)}$$

which inserted into (5.2) gives

$$\max_\Lambda L(\beta,\Lambda) = L_c(\beta) \prod_{u \leq 1} \frac{X(du)^{X(du)} e^{-\int_0^t X(du)}}{\prod_i X_i(du)!} .$$

Thus the maximum likelihood estimate of β is found by maximizing $L_c(\beta)$.

Hence we have seen that $(\hat{\beta},\hat{\Lambda})$ are the Cox estimates of β and Λ respectively and in this extended model the estimation procedure can be explained by the method of maximum likelihood without having to invoke a notion of partial likelihood.

If we consider the model as a dynamic exponential family we can analyse it as follows: $\{X_i(du)\}$ are independent given $\mathcal{F}_{u^-}$ with parameters

$$e^{\beta' z_i(du)} (1 - X_i(u^-))^+ \Lambda(du)$$

which shows that

$$U(du) = \Sigma_i z_i(u) X_i(du) \quad \text{and} \quad X(du)$$

are sufficient for β and $\Lambda(du)$.

If we introduce the mixed parametrizations, see Barndorff-Nielsen (1978), i.e. β and $\tau = E(X(du) \mid \mathcal{F}_{u^-})$ then it follows from results about exponential families that these parameters are variation independent and that the likelihood splits into a product of factors depending on β and τ respectively. Thus in this sense X(du) is S-ancillary for β in the conditional experiment of $\{X_i(du)\}$ given $\mathcal{F}_{u^-}$.

Now arguments can be given for conditioning on X(du) when making inference about β. Hence from this dynamic point of view one can "justify" Cox's partial likelihood by the concept of S-ancillarity.

6. Discussion and relation to other approaches

The idea that L_c is a partially maximized likelihood can be found in the paper by Breslow (1974), who fitted an intensity function $\lambda(t)$ which was constant between the observed jump times.

Although this procedure could be a reasonable smoothing it is not derived from a model in a natural way.

The same type of idea has been forwarded by Bay and Mac (1981) who suggested fitting an intensity $\lambda(t)$ which is zero except for an ε-interval just before each observed jump time. This way of estimating λ has the same quality as that suggested by Breslow, but tries to take into account that one really wants a measure $\int\lambda(u)du$ which reflects the fact that jumps are only observed at discrete points of time.

What we have done here is to point out, that these attempts to estimate λ correspond to the idea of extending the model to allow for Λ to be discrete and then apply standard methods. It should also be mentioned that Andersen and Rudemo (1980) have constructed a discrete time model where jumps are Poisson distributed. In this framework it corresponds to the models we get for Λ discrete.

Throughout we have concentrated on extensions which preserve the property that β and Λ becomes the natural estimates. Cox (1972) and Kalbfleisch and Prentice (1980) have discrete versions of the Cox model, but they do not have the same simple estimates. Finally one should perhaps point out that the estimation procedure can be carried out in two steps. First we observe that the estimates of Λ is zero except for atoms at the observed jump points $\{t_i\}$. Thus one only need to consider the likelihood for such t_i. For a discrete Λ, however, the variables $X_i(dt_j)$ are Poisson distributed given the past with mean

$$e^{\beta' z_i(t_j)}(1 - X_i(t_j^-))^+ \Lambda\{t_j\}$$

which shows that the likelihood is nothing but a multiplicative Poisson model (with dependent observations) or a log-linear model. Thus standard programs for estimating in these models can be applied, see Holford (1980). We shall conclude by a few comments of a more negative kind on the proposed model. The sample paths in the extension of the Cox model have the property that they have only one jump, since after the first jump the intensity equals zero. Thus each individual dies only once, but the jump size has no obvious interpretation in relation to the experiment that Cox's model was constructed to describe. To get a feeling for the content of the result it is instructive to consider the simplest possible Cox model, namely for $\beta = 0$. In this case we have i.i.d. waiting times T_i and the natural extension is to consider their distribution F to be an arbitrary probability on R_+.

In this model it is easy to see that $\hat{F}$ is the empirical distribution and hence that the survivor function $\hat{G} = 1 - \hat{F}$. Since we can define the intensity measure $\Lambda(A) = F(du)/(1 - F(u^-))$ we have that $\Lambda\{t\} \leqq 1$, and that

$$G(t) = 1 - F(t) = \prod_{[0,t]} (1 - \Lambda(du)) \ .$$

This shows that in the natural extension we have

$$\hat{G}(t) = \prod_{[0,t]} (1 - \hat{\Lambda}(du)) = \prod_{[0,t]} \left(1 - \frac{N(du)}{n - N(u^-)}\right) = 1 - \hat{F}(t) \ .$$

In the extended Poisson model we get that the survivor function is

$$G(t) = e^{-\int_0^t \Lambda(du)}$$

and hence that the estimate is

$$\hat{G}(t) = e^{-\hat{\Lambda}(t)} \neq \prod_{[0,t]} (1 - \hat{\Lambda}(dt)) \quad .$$

The reason for bringing in this property of the model is to point out the essential difficulty in the extension. If we want the extension of the counting process to be a counting process then we must be sure that the atoms in the intensity measure are bounded by 1. The reason for this is that a counting process is also a dynamical exponential family, namely a family of two point measures where $\Lambda(dt)$ is the probability of succes given the past. For $\beta = 0$ it is easy to consider this extension but for $\beta \neq 0$ the constraint imposed is that

$$e^{\beta' Z_i(t)} \Lambda\{t\} \leqq 1$$

which gives a strange relation between the parameters. By considering a Poisson extension we avoid this and the term appears as a meanvalue instead which does not impose any constraints on the parameters.

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