Chapter 1

MODELS FOR RECURRENT EVENTS IN RELIABILITY AND SURVIVAL ANALYSIS

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Abstract Existing models for recurrent phenomena occurring in public health, biomedicine, reliability, engineering, economics, and sociology are reviewed. A new and general class of models for recurrent events is proposed. This class simultaneously takes into account intervention effects, effects of accumulating event occurrences, and effects of concomitant variables. It subsumes as special cases existing models for recurrent phenomena. The statistical identifiability issue for the proposed class of models is addressed.

Keywords: Counting process; Model identifiability; Renewal process; Repair models.

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1. Introduction

In many studies in public health, biomedicine, reliability, engineering, economics, and sociology, the event of primary interest is recurrent and thus could occur several times during the study period for a study unit or subject. Examples of recurrent events in public health are drug or alcohol abuse of adolescents, outbreak of diseases (e.g., encephalitis), and repeated hospitalization of end stage renal disease patients. In the medical area the recurrent event may be the occurrence of a tumor (cf., Byar (1980); Gail, Santner and Brown (1980); Klein, Keiding and Kamby(1980); Wei, Lin and Weissfeld (1989)), headaches (Leviton, Schulman, Kammerman, Porter, Slack and Graham (1980)), cyclic movements in the small bowel during fasting state (Aalen and Husebye (1991)), depression, seizures of epileptic patients, nausea in patients taking drugs for the dissolution of cholesterol gallstones, and angina pectoris in patients with coronary disease (cf., Lawless (1987); Thall and Lachin (1988)). In the reliability and engineering settings, the breakdown of electro-mechanical systems (e.g., motor vehicles, subsystems in space stations, computers), encountering a software bug in software development, and nuclear power plant meltdowns are examples of recurrent events; while in the economic setting they could be the advent of economic recession, stock market crashes, and labor strikes.

By virtue of the time-sequential fashion in which recurrent events occur, there is an added aspect to these studies which hitherto has not been considered in existing models and which is usually not present in studies where only one endpoint event per subject is observed. This aspect is the ability to perform interventions on the subject upon event occurrence. For example, when a subject abuses alcohol, intervention in the form of psychological methods (e.g., confinement or enforced hospitalization; correction of faulty home environment), physiological methods (e.g., conditional reflex therapy; elevation of blood sugar level; convulsive therapy; serotherapy and hemotherapy), or through family-based or institutional-based methods (e.g., closer supervision by family members; Alcoholics Anonymous) is performed. Similarly, a heart attack patient would for instance be advised to alter existing lifestyle (e.g., eating habits; reduce stress level); while the reoccurrence of a tumor might lead to its removal and some prophylactic treatment (e.g., continuation of retinoid prophylaxis (cf., Byar (1980))). In reliability and engineering, the breakdown of the system will entail repair or replacement of the failed subsystem or component, and the replacement will usually be an improved version of the old subsystem or component. In an economic setting, when the stock market crashes or a recession occurs, the government intervenes by

instituting new guidelines. The primary purpose of such interventions is to prolong, if not eliminate, the reoccurrence of the event. Hence such interventions can be viewed as improving the subject or unit. Improvement is usually possible since one could use the information that has accumulated on or before the event occurrence and the knowledge that has been discovered or acquired between event occurrences to assist in the formulation of new intervention strategies. It should be realized, however, especially in the medical and public health settings which usually deal with human subjects, that though the intervention may bring about improvements, other factors such as the weakening effect on the subject of accumulating event occurrences and the adverse effects of aging and other time-dependent covariates may outweigh the intervention improvement. Thus, when all these effects are considered, the time to the next occurrence of the event may still be smaller, in a stochastic sense, relative to the preceding interoccurrence time. It is therefore imperative that any modeling scheme should attempt to take into consideration the effects of the interventions simultaneously with the effects of accumulating event occurrences and relevant concomitant variables.

2. Mathematical Framework

Let us formalize the description of mathematical models for recurrent phenomena by considering an experimental unit (for example, a patient in a clinical trial) experiencing successive occurrences of a recurrent event. Let $\mathbf{X} = (X_1, \ldots, X_q)^{\mathrm{t}}$, where $^{\mathrm{t}}$ denotes vector/matrix transpose, be a vector of covariates (e.g., age, race, sex) for this unit, which may be time-dependent. Denote by $T_1, T_2, T_3, \ldots$ the successive interoccurrence times of the event, and by $S_1, S_2, S_3, \ldots$ the successive calendar times of event occurrences, so

$$S_0 \equiv 0, S_1 = T_1, S_2 = T_1 + T_2, S_3 = T_1 + T_2 + T_3, \ldots . \tag{1}$$

Let $\mathbf{F} = \{\mathcal{F}_s : s \geq 0\}$ represent an increasing, right-continuous collection of σ-fields for this unit, that is, a filtration (cf., Fleming and Harrington (1992); Andersen, Borgan, Gill and Keiding (1993)), so in particular $\mathcal{F}_s$ contains information about the number of times that the recurrent event has occurred in the time interval $[0, s]$, the covariate information, and information concerning the types of interventions performed upon event occurrences.

A probabilistic model for the successive occurrences of the recurrent event is a specification of the collection of joint distribution functions of $\{S_1, S_2, S_3, \ldots\}$. Because of the dynamic nature or time-sequential feature of the setting and as a consequence of the interventions that are performed, such specifications are facilitated by restating the model in

terms of hazard functions or failure intensities. Let $\{N(s) : s \geq 0\}$ be the process which represents the number of occurrences of the recurrent event during the period $[0, s]$, and $\{Y(s) : s \geq 0\}$ denote the risk process so $Y(s) = 1$ if the unit is still under observation at time s, and $Y(s) = 0$ if the unit is not under observation at time s. Let $\{A(s) : s \geq 0\}$ be a predictable nondecreasing process such that the process $\{M(s) : s \geq 0\}$, where

$$M(s) = N(s) - A(s), \quad s \geq 0,$$

is a square-integrable local martingale. We assume that $A(s) = \int_0^s \mathrm{d}\Lambda(w)$, where $\{\Lambda(s) : s \geq 0\}$ is a predictable nondecreasing process satisfying

$$\mathrm{d}\Lambda(w) = Y(w)\alpha(w)\mathrm{d}w, \tag{2}$$

where $\{\alpha(w) : w \geq 0\}$ is a predictable nonnegative process (see Aalen (1978)). It will have the intuitive and practical interpretation that, for $h > 0$ and sufficiently small, the quantity $Y(s)\alpha(s)h$ represents the approximate conditional probability, given $\mathcal{F}_{s-}$, of the recurrent event occurring in the time interval $[s, s + h)$. The probabilistic model for the recurrent phenomena is then completely determined by specifying the failure intensity rate process $\{\alpha(s) : s \geq 0\}$ (cf., Jacod (1975); Aalen (1978); Bremaud (1981); Arjas (1989); Andersen, Borgan, Gill and Keiding (1993)). As implied by its measurability with respect to $\mathcal{F}_{s-}$, the intensity process $\alpha(s)$ may depend on the covariate of the unit and the number of event occurrences during the period $[0, s]$.

3. Existing Models

By specifying the $\{\alpha(s) : s \geq 0\}$ process, a variety of classes of models for the recurrent event are generated. We review in this subsection some of the models considered in the literature. Let $\psi : \Re \to \Re_+$ be a known nonnegative (link) function. In most cases this is taken to be the exponential function given by

$$\psi(u) = \exp\{u\}. \tag{3}$$

Let $\alpha_0(\cdot)$ be some unknown hazard rate function. The simplest model considered is obtained by taking

$$\alpha(s) = \alpha_0(s - S_{N(s-)})\psi(\mathbf{X}^{\mathrm{t}}\beta), \tag{4}$$

where $\beta = (\beta_1, \beta_2, \ldots, \beta_q)^{\mathrm{t}}$ is a regression coefficient vector. Since $s - S_{N(s-)}$ represents the elapsed time since the last event occurrence, this model assumes that the interoccurrence times are identically distributed. Borrowing from the parlance of reliability, one says that upon an event

occurrence, the intervention leads to a 'perfect repair' of the unit. With ψ given in (3), this model is the extension of the Cox (1972) proportional hazards model, or Aalen (1978) and Andersen and Gill (1982) multiplicative intensity model, to the recurrent event situation. This model has been considered in Prentice, Williams and Peterson (1981), Lawless (1987), and Aalen and Husebye (1991), and under this model the resulting data could be analyzed using partial likelihood methods for making inference about β, and through the use of the Nelson-Aalen estimator for making inference about the cumulative baseline hazard function $\mathcal{A}_0(\cdot) = \int_0^{\cdot} \alpha_0(s)\mathrm{d}s$ (cf., Kalbfleisch and Prentice (1980); Cox and Oakes (1984); Fleming and Harrington (1992); Andersen, Borgan, Gill and Keiding (1993)). This model has the disadvantage of ignoring the (non-zero) correlations among the interoccurrence times (cf., Prentice and Kalbfleisch (1979); Aalen and Husebye (1991)), which could have serious implications especially in the presence of intervention. Two possible approaches could be used to partially alleviate this deficiency. The first approach is to introduce a time-dependent covariate $X_{q+1}(t)$, possibly defined to be $X_{q+1}(t) = \log\{1 + N(t-)\}$, which is augmented to the covariate vector to obtain $\mathbf{X}^* = (\mathbf{X}^{\mathrm{t}}, X_{q+1})^{\mathrm{t}}$, while the regression vector is also augmented to become $\beta^* = (\beta^{\mathrm{t}}, \beta_{q+1})$, (note that β_{q+1} is not time-dependent). In model (4), the linear form $\beta^{*\mathrm{t}}\mathbf{X}^*$ is then used in the link function. Such an approach, however, suffers from the defect that it could not allow non-proportional intervention effects. The second approach is to incorporate in the model an unobservable random frailty in model (4) via

$$\alpha(s|Z) = Z\alpha_0(s - S_{N(s-)})\psi(\beta^{\mathrm{t}}\mathbf{X}), \tag{5}$$

where Z has some parametric distribution which is usually taken to be a gamma distribution with shape and scale parameters (η, η). Through such a model, dependencies among the interoccurrence times are incorporated, although whether they are the appropriate dependencies is not clear. In models where only one event per subject is observed, incorporating frailties is very useful in generating models which account for subject heterogeneities, aside from being able to model positive dependence among the failure times of the subjects. An excellent exposition on the stochastic process approach to modeling frailties together with the appropriate methods of analyses could be found in Andersen, Borgan, Gill and Keiding (1993, Ch. IX). Other very useful references are those by Clayton (1978), Clayton and Cuzick (1985), Hougaard (1984, 1986a, 1986b, 1987), Oakes (1982, 1986a, 1986b, 1989), Nielsen, Gill, Andersen and Sorensen (1992), and Vaupel (1990).

Another model for recurrent data considered in the literature is obtained by taking

$$\alpha(s) = \alpha_0(s)\psi(\beta^{\mathrm{t}}\mathbf{X}). \tag{6}$$

This has been considered in Prentice, Williams and Peterson (1981), Brown and Proschan (1983) and Lawless (1987). It amounts to assuming that the intensity of event occurrence for a subject or unit that just experienced an event occurrence is identical to the intensity just prior to the event occurrence. In reliability terminology, the subject or unit is said to have been 'minimally repaired' through the intervention. Partial likelihood methods are also applicable in making inference about β under this model. A limitation of this model is the restrictive way in which intervention effects can be modeled, since the model basically states that there is *no* improvement on the subject or unit relative to its state just prior to the event occurrence even after the intervention. As in (4) one may be able to alleviate the just-mentioned limitation in (6) through the incorporation of a time-dependent covariate which enters in the link function, or through the introduction of an unobservable random frailty.

A generalization of the Markovian model of Gail, Santner and Brown (1980), derived via theories of carcinogenesis, postulates that

$$\alpha(s) = (m - N(s-) + 1)\alpha_0(s - S_{N(s-)})\psi(\beta^{\mathrm{t}}\mathbf{X}), \tag{7}$$

where m is some unknown positive integer parameter with the interpretation of being the original number of tumor sites, so that $N(s) \leq m$. This model could also be viewed as another extension of (4) through the use of the time-dependent covariate $X_{q+1}(s) = \log(m - N(s-) + 1)$ with $\beta_{q+1} = 1$. This model takes into account the effect of the number of event occurrences through the multiplicative term $m - N(s-) + 1$, and since this is a decreasing function of $N(s-)$, this is a model where the effect of an increasing number of event occurrences on the subject or unit leads to its improvement, which may not be the case in many biomedical-type settings. At this stage we point out the fruitful interplay between models that arise in biomedical settings and reliability by observing that the model in (7) can also be viewed as the Jelinski and Moranda (1972) software reliability model with covariates, where m will have the interpretation as being the original number of bugs in the software. The basic limitation of the model in (7) is again the restrictive way in which intervention effects can be incorporated.

Another model usable for recurrent data, but which was primarily developed for modeling the tumor occurrences at multiple sites after breast cancer, is that of Klein, Keiding and Kamby (1989) which utilizes the generalized multivariate Marshall-Olkin distribution. For the bivariate

case, the joint survivor function of (T_1, T_2) is assumed to be

$$S(t_1, t_2) = \exp\{-\mathcal{A}_1(t_1) - \mathcal{A}_2(t_2) - \mathcal{A}_{12}(\max(t_1, t_2))\}$$

where, for $j \in \{1, 2, 12\}$, we have

$$\mathcal{A}_j(t) = \int_0^t \alpha_j(u)\mathrm{d}u \quad \text{with} \quad \alpha_j(t) = \alpha_{0j}(t)\exp\{\beta_{0j} + \beta_j^{\mathrm{t}}\mathbf{X}\}.$$

It is not clear, however, how this model could be restated in the stochastic process framework that we have adopted, and this modeling scheme seems difficult to implement in the situation where event occurrences and interventions are happening in a time-sequential fashion. Furthermore, the appeal of this model in the tumor occurrence setting is it allows the modeling of simultaneous occurrences, but this is not the case in the recurrent model we are considering since we are assuming that for a given subject or unit the events are occurring one at a time.

The class of *marginal* models developed for multivariate failure time data could also be used in the recurrent data setting. Such models specify the marginal distributions or hazard functions of the interoccurrence times T_k's. Among these models is the one examined by Wei, Lin and Weissfeld (1989) which postulates that the hazard rate function of T_k is

$$\alpha_k(t) = \alpha_{0k}(t)\exp\{\beta_k^{\mathrm{t}}\mathbf{X}_k(t)\}, \quad k = 1, 2, \ldots; \tag{8}$$

or the log-linear model of Lin and Wei (1991) given by

$$\log(T_k) = \beta_k^{\mathrm{t}}\mathbf{X}_k + \epsilon_k, \quad k = 1, 2, \ldots, \tag{9}$$

where $\mathbf{X}_k$ are (possibly time-dependent in (8)) covariates which are relevant for the kth event, and ϵ_k's are random error terms. Aalen and Husebye's (1991) variance component model which specifies that

$$g(T_k) = \mu + U + \epsilon_k, \quad k = 1, 2, \ldots, \tag{10}$$

where U and ϵ_k's are independent, U is zero-mean normal with variance σ_u^2, and the ϵ_k's are iid zero-mean normal random variables with variance σ_ϵ^2, also belongs to this marginal class of models. The appeal of these models is the ease of analyses since existing methods for the Cox model and the accelerated failure time model are immediately applicable. The disadvantage of these models when dealing with recurrent data is that the dependencies among the T_k's are not explicitly taken into account, and one would be hard-pressed to model the intervention effects and the possibly weakening effects of accumulating event occurrences. Furthermore, the time-dynamic aspect of the model is ignored.

Finally, another modeling approach utilized primarily in the reliability area, but which could be adopted to recurrent models in biomedical settings is that of specifying the form of the cumulative mean function (CMF) of $N(s)$, without specifying the full probabilistic specification of the process. This approach is exemplified in Lawless and Nadeau (1995), where they presented simple and robust methods for the estimation of the CMF. The robust estimators are related to estimators developed under the Poisson process model. The specific model considered in that paper, which also incorporates covariates, is given by

$$m(t) = m_0(t)P(t)\psi(\beta^{\mathrm{t}}\mathbf{X}(t)), \quad t \geq 0, \tag{11}$$

where $m_0(\cdot)$ is a baseline mean function, and $P(\cdot)$ is some known function. The cumulative mean function is (in the continuous-time case) defined to be

$$M(t) = \int_0^t m(u)\mathrm{d}u.$$

Some of the robust inference procedures for this model were developed using estimating equation theory. The model in (11) is restrictive in that the intervention effects it could model can only be contained in the $P(\cdot)$ function, and the link function.

These are the different varieties of models that have been utilized in dealing with recurrent data in the biomedical, reliability, engineering, economics, and sociological settings. Though many of these models are quite general, none of them satisfy the three requirements enunciated in Section 1, which is to have a model that takes into account the three effects *simultaneously*. One may argue that all of these effects could be incorporated through the use of time-dependent covariates in the Cox model, but one should realize that the type of effects that could be modeled through such an approach are limited to be of the proportional type. In the next section we advocate a different scheme of modeling the intervention effects, which is through a change in the time origin of the baseline hazard function just after intervention. It will also be demonstrated that most of the models mentioned above are subsumed in the proposed class of models.

4. A New Class of Models

To describe our proposed class of models, we assume the existence of a complete probability space $(\Omega, \mathcal{F}, \mathbf{P})$ with an associated filtration

$$\mathbf{F} = \{\mathcal{F}_s : s \in [0, \tau]\},$$

where $0 < \tau \leq \infty$ is the upper endpoint of the study period. All relevant random entities are defined on $(\Omega, \mathcal{F})$. In particular, the interoccurrence

times $T_1, T_2, \ldots$, the calendar times $S_1, S_2, \ldots$ of event occurrences, and the observable processes $\{N(s) : s \in [0,\tau]\}$ and $\{Y(s) : s \in [0,\tau]\}$ are defined in $(\Omega, \mathcal{F})$.

Our proposed class of models postulates that the intensity rate process $\{\alpha(s|\mathbf{X}) : s \in [0,\tau]\}$ for a subject or unit with covariate vector $\mathbf{X} = (X_1, \ldots, X_q)^{\mathrm{t}}$, which may be time-dependent, is of the form

$$\alpha(s|\mathbf{X}) = \alpha_0[\mathcal{E}(s)]\rho[N(s-)]\psi(\beta^{\mathrm{t}}\mathbf{X}). \tag{12}$$

In (12), $\alpha_0(\cdot)$ is an unknown baseline hazard rate function; $\rho(\cdot)$ is a nondecreasing or nonincreasing function from $\mathbb{N} = \{0, 1, 2, \ldots\}$ into $\Re_+ = [0, \infty)$ which may depend on unknown parameters with the norming condition $\rho(0) = 1$; $\psi(\cdot)$ is a nonnegative link function from $\Re = (-\infty, \infty)$ into $\Re_+$ which is of known form (usually taken to be the exponential function); $\beta = (\beta_1, \beta_2, \ldots, \beta_q)^{\mathrm{t}}$ is an unknown regression coefficient vector; and $\{\mathcal{E}(s) : s \in [0,\tau]\}$ is an observable predictable process satisfying the conditions:

(I) $\mathcal{E}(0) = e_0$ almost surely (a.s.), where e_0 is a nonnegative real number;

(II) $\mathcal{E}(s) \geq 0$ a.s.;

(III) for $s \in [S_{k-1}, S_k)$, $\mathcal{E}(s)$ is a.s. monotone and differentiable with $\mathcal{E}'(s) \in (0, 1]$.

This predictable observable process, called the *effective age* of the unit, is where the improvement effects accruing from the performed intervention is modeled. Note that condition (III) implies $\mathcal{E}(S_k-) \leq \mathcal{E}(S_{k-1}) + T_k$, $k = 1, 2, \ldots$, which means that the unit's effective age just before the kth event occurrence, which is represented by $\mathcal{E}(S_k-)$, is at most the unit's effective age just after the $(k-1)$th event occurrence, which is $\mathcal{E}(S_{k-1})$, plus the time between the $(k-1)$th and the kth event occurrences, which is T_k. Thus, in the context of the effective age of the unit, the effect of intervention is to make the unit age at a slower rate relative to the elapsed calendar time. We point out that a different interpretation is needed or other conditions need to be imposed if the baseline hazard rate function $\alpha_0(\cdot)$ is a decreasing hazard rate function, as in the case for instance when dealing with infants having ear infection since infants will usually exhibit a decreasing hazard rate. In these types of situations, the improvement effects might be modeled by changing the sign of the derivative and allowing $\mathcal{E}(0)$ to be non-zero. Our modeling the intervention effects as a change in the unit's effective age differs from models which have been considered in the literature, since most of the models in the literature incorporate such effects in the regression component. The

initial motivation of our modeling approach came from reliability repair models where when a system or component fails, either the system or component is restored to its state just prior to its failure, or is replaced by a new component, so the process of repair leads to a change in the unit's effective age. In biomedical settings, such a model is also plausible since interventions that can be considered as good are meant to slow or decelerate the reoccurrence of the event.

In model (12), the function $\rho(\cdot)$, represents the effect of accumulating event occurrences. In many biomedical situations, this will usually be assumed to be a nondecreasing function of $N(s-)$ since it is natural to assume that the event occurrences have a weakening effect on the unit or subject. In some situations however, such as the Markovian model by Gail, Santner and Brown (1980) in (7) where this function will be $\rho(k) = m - k + 1$, the occurrences of events lead to improvements on the unit. This nonincreasing feature is also prevalent in reliability models where at each event occurrence, faults or defects in the system or component are eliminated, which leads to improvements. Thus, generally, we will simply require that this function be monotonic, either nondecreasing or nonincreasing depending on the context or situation at hand. The link function in the model clearly serves the purpose of containing the effects of the concomitant variables. In this model (12), the intervention effects, the effects of accumulating event occurrences, and the effects of the covariates are therefore taken into account simultaneously. Furthermore, there is an interplay among these effects to the extent that just after intervention, in an overall sense, the unit need not always be better relative to its state just before the event occurrence because the improvement effects might be outweighed by the other two effects.

We now illustrate the generality of the proposed class of models by considering specific forms of $\mathcal{E}(\cdot)$ and $\rho(\cdot)$.

Example 4.1: By letting $\rho(k) \equiv 1$, $k \in \mathbf{Z} \equiv \{0, 1, 2, \ldots\}$, and $\mathcal{E}(s) = s - S_{N(s-)}$, then $\alpha(s|\mathbf{X}) = \alpha_0(s - S_{N(s-)})\psi(\beta^{\mathrm{t}}\mathbf{X})$, which is the extended Cox model in (4) considered by Prentice, Williams and Peterson (1981), Lawless (1987), and Aalen and Husebye (1991). ‖

Example 4.2: By letting $\rho(k) \equiv 1$, $k \in \mathbf{Z}$, and $\mathcal{E}(s) = s$, $s \in [0, \tau]$, we obtain $\alpha(s|\mathbf{X}) = \alpha_0(s)\psi(\beta^{\mathrm{t}}\mathbf{X})$, which is the model in (6), a model examined by Prentice, Williams and Peterson (1981), Brown and Proschan (1983) and Lawless (1987). ‖

Example 4.3: Gail, Santner and Brown's (1980) Markovian model becomes a special case of model (12) by taking $\mathcal{E}(s) = s - S_{N(s-)}$ and $\rho(k) = m - k + 1$, and as mentioned in the preceding section, this model

coincides with the Jelinski and Moranda (1972) software reliability model with the additional feature that a covariate has been incorporated. ‖

Example 4.4: Let $I_1, I_2, I_3, \ldots$ be a sequence of iid Bernoulli random variables with success probability p. [For technical reasons, it is assumed that the I_i's are measurable with respect to $\mathcal{F}_0$.] Define the process $\{\eta(s) : s \in [0, \tau]\}$ via

$$\eta(s) = \sum_{i=1}^{N(s)} I_i.$$

Also, let $0 \equiv \tau_0 < \tau_1 < \tau_2 < \ldots$ be defined according to

$$\tau_k = \min\{j > \tau_{k-1} : I_j = 1\}, \quad k = 1, 2, 3, \ldots.$$

By setting $\rho(k) \equiv 1$ and $\mathcal{E}(s) = s - S_{\tau_{\eta(s-)}}$, we obtain

$$\alpha(s|\mathbf{X}) = \alpha_0(s - S_{\tau_{\eta(s-)}})\psi(\beta^{\mathrm{t}}\mathbf{X}). \tag{13}$$

This is the Brown and Proschan (1983) minimal repair model used in reliability modeling, and it can be viewed as a mixture of the perfect repair and the minimal repair models in the preceding examples. If the success probability p is made to depend on the time of the event occurrence, then the Block, Borges and Savits (1985) model obtains (see also Hollander, Presnell and Sethuraman (1992) and Presnell, Hollander and Sethuraman (1994)). Note that in this example, the τ_k's represent the event occurrences in which intervention causes the unit to be 'as good as new' (in the reliability terminology, a *perfect* repair), and such perfect repairs happen independently at each event occurrence with probability p. Furthermore, note that $S_{\tau_{\eta(s-)}}$ is the time of the last perfect repair prior to time s. ‖

Example 4.5: Let $\{A_j : j = 0, 1, 2, \ldots\}$ and $\{\Theta_j : j = 0, 1, 2, \ldots\}$ be two sequences satisfying

$$A_0 = 0, \Theta_0 = 1, A_j \geq 0, \Theta_j \in (0, 1], \text{ and } A_j \leq A_{j-1} + \Theta_{j-1}T_{j-1},$$

for $j = 1, 2, 3, \ldots$. If we let $\rho(k) \equiv 1$, and

$$\mathcal{E}(s) = A_{N(s-)} + \Theta_{N(s-)}(s - S_{N(s-)}), \tag{14}$$

then model (12) reduces to the general repair model, but with the added feature of having incorporated covariates in the model. The model without covariates was introduced and studied in Dorado, Hollander and Sethuraman (1997), where they interpreted the sequence $\{A_j\}$ as the successive effective ages just after event occurrences, while the sequence

$\{\Theta_j\}$ was given the interpretation of being life supplements. In our context, these life supplements could then be viewed as the improvement effects attributable to the interventions that were performed. Notice that in this model, the intensity is still fully determined by the baseline hazard rate function $\alpha_0(\cdot)$ and the covariates through the link function $\psi(\cdot)$. In contrast, in our proposed model, by introducing the term $\rho[N(s-)]$, which could model the effects of the accumulating event occurrences, the intensity process is not totally governed by the baseline hazard rate function.

Even with the restriction $\rho(k) \equiv 1$ however, notice that this general repair model subsumes the preceding three examples. Furthermore, as shown in Dorado, Hollander and Sethuraman (1997), this model also subsumes as special cases some models that are utilized in the reliability and engineering contexts. For instance, Kijima's (1989) Model I is obtained by setting $\Theta_i = 1, i \geq 0$, and $A_j = \sum_{i=1}^{j-1} D_i T_i, j \geq 1$, where $\{D_j\}_{j\geq 1}$ is a sequence of independently distributed random variables taking values in $[0, 1]$, and which is independent of the other random entities. Kijima's (1989) Model II is obtained via the general repair model by taking $\Theta_j = 1, j \geq 0$, and $A_j = \sum_{k=1}^{j-1}(\prod_{i=k}^{j-1} D_i)T_k, j \geq 1$. $\|$

Example 4.6: Last and Szekli (1998) introduced a model for the failure process of a repairable system. Their model is as follows: Let $\bar{F}$ be a survivor function, and for a given $a \geq 0$, let

$$\bar{F}_a(t) = \frac{\bar{F}(t+a)}{\bar{F}(a)}$$

be the residual survivor function at time a. Given an initial age A_0, the first interfailure time T_1 is distributed according to the survivor function $\bar{F}_{A_0}$. The (calendar) time to the occurrence of the first failure is therefore $S_1 = S_0 + T_1 = T_1$ since $S_0 = 0$. Upon failure the unit is repaired with a random degree $Z_1 \leq 1$ which could possibly depend on information up to S_1, and the new effective age of the unit becomes $A_1 = (1 - Z_1)(S_1 + A_0)$. Here, the Z_1 is allowed to be negative, which would correspond to destructive repair. The next interfailure time T_2 is distributed according to the survivor function $\bar{F}_{A_1}$, and the calendar time at which the second failure occurs is $S_2 = S_1 + T_2$. Upon this second failure, the unit is repaired with a random degree Z_2, and the new effective age of the unit becomes $A_2 = (1 - Z_2)(A_1 + T_2)$. Again, Z_2 is allowed to take a negative value, and it could also depend on information up to S_2. Continuing in this fashion, the nth interfailure time has survivor function $\bar{F}_{A_{n-1}}$, and the calendar time at which the nth event occurs is given by $S_n = S_{n-1} + T_n$. The effective age of the unit just after the nth event becomes $A_n = (1 - Z_n)(A_{n-1} + T_n)$.

If, in the Dorado, Hollander and Sethuraman (1997) model, hereafter referred to as the DHS model, we set $\Theta_j = 1$ for all j, and $A_{j+1} = (1 - Z_{j+1})(A_j + T_{j+1})$, and if furthermore we assume that the Z_i's cannot be negative, then the Last and Szekli (1998) model, hereon referred to as the LS model, is obtained. Thus, the LS model is almost subsumed by the DHS model, but not completely because in the former model the Z_i's could be negative. Last and Szekli (1998) showed that their model contains many proposed models in the literature, including those of Baxter, Kijima and Tortorella (1996) and Stadje and Zuckerman (1991). Notice, however, that the LS model is subsumed by our proposed model by simply taking

$$\mathcal{E}(s) = A_{N(s-)} + \left(s - S_{N(s-)}\right),$$

further illustrating the generality of our proposed class of models even in the case without covariates. ‖

Example 4.7: We consider some more examples where $\rho(\cdot)$ is not identically unity. The simplest such specification is to take $\rho[N(s-)] = \rho_0^{N(s-)}$, where $\rho_0 \in \Re$. If we then take $\mathcal{E}(s) = s - S_{N(s-)}$, then the model postulates that the effect of accumulating event occurrences is a proportional increase (if $\rho_0 > 1$) in the intensity rate relative to the preceding intensity rate. This could serve as a simple and natural model for the weakening of the subject caused by the stresses of event occurrences. Under this specification the intensity process becomes

$$\alpha(s|\mathbf{X}) = \alpha_0(s - S_{N(s-)})\rho_0^{N(s-)} \exp\{\beta^{\mathrm{t}}\mathbf{X}\}. \tag{15}$$

It is of course possible to couple this specification to the other forms of $\mathcal{E}(s)$ considered in the preceding examples, and by doing so the class of models becomes quite rich and wide-ranging. ‖

Example 4.8: Our final example is a generalization of the Gail, Santner and Brown (1980) model. This extension is obtained by taking

$$\rho[N(s-)] = \max\{B^0 - g[N(s-)], 0\}, \tag{16}$$

where B^0 is some positive real number, and $g(\cdot)$ is some nondecreasing function. One could interpret the parameter B^0 as an initial measure of defectiveness (or in the biomedical setting, event occurrence proneness) of the subject, and $g(\cdot)$ specifies the rate at which this unit is becoming stronger as the event occurrences accumulate. If we then take $\mathcal{E}(s) = s - S_{N(s-)}$, then the resulting model has the interesting property that the subject's defects contribute to the event occurrence intensity according to the baseline hazard rate function $\alpha_0(\cdot)$. The special case

of this model wherein we take $g[N(s-)] = N(s-)$ and $\alpha_0(s) = \alpha_0$, where α_0 is some positive constant, leads to the Jelinski-Moranda model (Jelinski and Moranda, 1972) in software reliability with covariates having been incorporated, or to the Gail, Santner and Brown (1980) tumor occurrence model. ‖

If model (12) holds, then the compensator of the counting process $\{N(s) : s \in [0,\tau]\}$ is given by $\{A(s|\mathbf{X}) : s \in [0,\tau]\}$, where

$$A(s|\mathbf{X}) = \int_0^s Y(s)\alpha_0[\mathcal{E}(s)]\rho[N(s-)]\psi(\beta^{\mathrm{t}}\mathbf{X})\mathrm{d}s, \tag{17}$$

where $\{Y(s) : s \in [0,\tau]\}$ is the at-risk process for this subject. To describe models with frailties, let there be n subjects or units in the study which are being subjected to the same type of intervention, with the ith, $(i = 1, 2, \ldots, n)$, subject having covariate $\mathbf{X}_i = (X_{1i}, \ldots, X_{qi})^{\mathrm{t}}$. Denote by $\{N_i(s) : s \in [0,\tau]\}$ and $\{Y_i(s) : s \in [0,\tau]\}$ the observable processes for the ith subject counting the number of event occurrences and the at-risk indicator, respectively. The intensity rate process of the ith subject is modeled via

$$\alpha_i(s|\mathbf{X}_i) = \alpha_0[\mathcal{E}_i(s)]\rho[N_i(s-)]\psi(\beta^{\mathrm{t}}\mathbf{X}_i), \quad i = 1, \ldots, n, \tag{18}$$

so the compensator of $N_i(\cdot)$, $(i = 1, \ldots, n)$, is

$$A_i(s|\mathbf{X}_i) = \int_0^s Y_i(u)\alpha_0[\mathcal{E}_i(u)]\rho[N_i(u-)]\psi(\beta^{\mathrm{t}}\mathbf{X}_i)\mathrm{d}u.$$

This model could be enhanced by introducing an unobservable frailty in order to incorporate associations among the subjects and the interoccurrence times of events. For example, we could specify the intensity process of the ith subject to be

$$\alpha_i(s|\mathbf{X}_i, Z) = Z\alpha_0[\mathcal{E}(s)]\rho_i[N_i(s-)]\psi(\beta^{\mathrm{t}}\mathbf{X}_i), \quad i = 1, \ldots, n, \tag{19}$$

where Z is an unobservable nonnegative variable with a parametric distribution. Note that, as in the case where only one event is observed per subject, the model is nonidentifiable with respect to scaling. To eliminate this nonidentifiability, the form of the distribution for the frailty needs to be restricted, for instance to a gamma distribution with the same shape and scale parameters. By incorporating a frailty component, the proposed class of models for recurrent data becomes richer. Through the incorporation of this frailty component, one may also be able to use the enriched model to validate the original frailty-less model.

Through the above examples and with the option of incorporating frailties in the models, we see that the proposed class of models is very

general and encompasses many of the models considered in the literature. Furthermore, its development is based on the intuitive consideration that a model should incorporate the improvement induced by the intervention performed upon event occurrence and the effects on the subject of accumulating event occurrences. The class of models proposed in this paper could also be applied in many areas, aside from the health and medical sciences, wherein a *dynamic* modeling of the intensity rates of event occurrence is desired, such as those in Hollander, Presnell and Sethuraman (1992) and Presnell, Hollander and Sethuraman (1994) for the minimal repair models; in Hollander and Peña (1995) in the context of dynamically modeling the lifetime of a coherent system; and in Dorado, Hollander and Sethuraman (1997).

5. Statistical Identifiability Issue

An important issue that needs to be resolved pertaining to this new class of models is that of identifiability. Here we consider the statistical model where the observable is

$$\{(N(s), Y(s), \mathbf{X}(s)),\ s \in [0,\tau]\}, \tag{20}$$

where τ is an upper endpoint of the study period. The family of compensator processes of $\{N(s), s \in [0,\tau]\}$, which determines the family of probability measures of the statistical model, is given by

$$\mathrm{d}A^{\theta}(s) = Y(s)\alpha_0[\mathcal{E}(s)]\rho[N(s-);\eta]\psi[\mathbf{X}(s)^{\mathrm{t}}\beta]\mathrm{d}s, \tag{21}$$

where $\theta = (\alpha_0(\cdot), \eta, \beta)$ is the relevant parameter vector, $\rho(\cdot;\cdot)$ is a function of known form with $\rho(0;\eta) = 1$, and $\psi(\cdot)$ is a link function of known form. We assume that $\mathbf{X}(0)$ could take the value $\mathbf{0}$, for if this is not so, then one could achieved this condition by subtracting an appropriate quantity. Furthermore, we assume that $\psi(\cdot)$ is continuous at zero and is not an even function. The relevant notion of identifiability is defined as follows:

Definition 5.1: Let

$$\theta^{(1)} = (\alpha_0^{(1)}(\cdot), \eta^{(1)}, \beta^{(1)}) \quad \text{and} \quad \theta^{(2)} = (\alpha_0^{(2)}(\cdot), \eta^{(2)}, \beta^{(2)})$$

be two parameter values. If

$$\begin{aligned} \theta_\tau^{(1)} &\equiv \{(\alpha_0^{(1)}(s), \eta^{(1)}, \beta^{(1)}), s \in [0,\tau]\} \\ &= \{(\alpha_0^{(2)}(s), \eta^{(2)}, \beta^{(2)}), s \in [0,\tau]\} \equiv \theta_\tau^{(2)} \end{aligned}$$

whenever, for almost all sample paths of $\{(N(s), Y(s), \mathbf{X}(s)) : s \in [0,\tau]\}$,

$$\mathrm{d}A^{\theta^{(1)}}(s) = \mathrm{d}A^{\theta^{(2)}}(s), s \in [0,\tau], \tag{22}$$

then we say that the statistical model is identifiable. ‖

We now establish the following theorem which addresses the identifiability of the statistical model.

Theorem 1 *If*

(i) for each $\theta = (\alpha_0(\cdot), \eta, \beta)$*, the support of* $\mathcal{E}(T_1)$ *contains* $[0, \tau]$*, where* T_1 *is the time to the occurrence of the first event; and*

(ii) $\rho(\cdot, \cdot)$ *satisfies the property that*

$$\left\{\forall k \in \{0, 1, 2, \ldots\} \left[\rho(k; \eta^{(1)}) = \rho(k; \eta^{(2)})\right]\right\} \rightarrow \left\{\eta^{(1)} = \eta^{(2)}\right\},$$

then the statistical model is identifiable in the sense of Definition 5.1.

Proof: From (22), for $s \in [0, \tau]$,

$$\begin{aligned} &\alpha_0^{(1)}[\mathcal{E}(s)]\rho[N(s-); \eta^{(1)}]\psi[\mathbf{X}(s)^{\mathrm{t}}\beta^{(1)}] \\ &= \alpha_0^{(2)}[\mathcal{E}(s)]\rho[N(s-); \eta^{(2)}]\psi[\mathbf{X}(s)^{\mathrm{t}}\beta^{(2)}]. \end{aligned} \tag{23}$$

Setting $s = 0$, and since $\mathcal{E}(0) = e_0$ by Condition (I), $N(0-) = 0$, and $\rho(0; \eta) = 1$, it follows that

$$\alpha^{(1)}(e_0)\psi[\mathbf{X}(0)^{\mathrm{t}}\beta^{(1)}] = \alpha^{(2)}(e_0)\psi[\mathbf{X}(0)^{\mathrm{t}}\beta^{(2)}].$$

This equality holds true for almost all $\mathbf{X}(0)$, in particular, it should hold when $\mathbf{X}(0) = \mathbf{0}$. This would imply that $\alpha^{(1)}(e_0) = \alpha^{(2)}(e_0)$, and consequently, we must have

$$\psi[\mathbf{X}(0)^{\mathrm{t}}\beta^{(1)}] = \psi[\mathbf{X}(0)^{\mathrm{t}}\beta^{(2)}]. \tag{24}$$

Take $\mathbf{X}(0) = (x, 0, \ldots, 0)^{\mathrm{t}}$, so that (24) becomes $\psi(x\beta_1^{(1)}) = \psi(x\beta_1^{(2)})$ for all x. Because $\psi(\cdot)$ is non-trivial, then if either one of $\beta_1^{(1)}$ or $\beta_1^{(2)}$ is zero, then necessarily the other must also be zero. Thus, consider the case where both of these coefficients are nonzero. Without loss of generality, assume that $|\beta_1^{(1)}| \geq |\beta_1^{(2)}|$, and denote by $r = \beta_1^{(2)}/\beta_1^{(1)}$, so $|r| \leq 1$. With $y = x\beta_1^{(1)}$, we therefore have the identity

$$\psi(y) = \psi(ry).$$

Iterating this identity, we obtain for every $m \in \{1, 2, \ldots\}$,

$$\psi(y) = \psi(ry) = \psi(r^2 y) = \ldots = \psi(r^m y) = \ldots.$$

Suppose $|r| < 1$. Since $\psi(\cdot)$ is continuous at 0, then by letting $m \rightarrow \infty$, we must have $\psi(y) = \psi(0)$ for every y which will imply that $\psi(\cdot)$ is a

constant function. This is a contradiction, hence $|r| = 1$. Since $\psi(\cdot)$ is not an even function, then $r = 1$, or $\beta_1^{(1)} = \beta_1^{(2)}$. Analogously, we must have $\beta_j^{(1)} = \beta_j^{(2)}$ for $j = 2, 3, \ldots, q$.

From (23) it now follows that for $s \in [0, \tau]$,

$$\alpha_0^{(1)}[\mathcal{E}(s)]\rho[N(s-); \eta^{(1)}] = \alpha_0^{(2)}[\mathcal{E}(s)]\rho[N(s-); \eta^{(2)}]. \tag{25}$$

Recalling that T_1 represents the time to occurrence of the first event, and since $N(s-) = 0$ for $s \leq T_1$, we therefore obtain, by also using the condition that $\rho(0; \eta) = 1$, that

$$\alpha_0^{(1)}[\mathcal{E}(s)] = \alpha_0^{(2)}[\mathcal{E}(s)], s \in [0, \tau].$$

Since the support of $\mathcal{E}(T_1)$ contains $[0, \tau]$ by condition (i) of the Theorem, then it follows that $\alpha_0^{(1)}(s) = \alpha_0^{(2)}(s), s \in [0, \tau]$.

Finally, from (23) and using the just-established results that $\alpha_0^{(1)}(s) = \alpha_0^{(2)}(s), s \in [0, \tau]$ and $\beta^{(1)} = \beta^{(2)}$, we obtain

$$\rho[N(s-); \eta^{(1)}] = \rho[N(s-); \eta^{(2)}].$$

By condition (ii) of the theorem, it follows that $\eta^{(1)} = \eta^{(2)}$. This completes the proof of the identifiability of the statistical model in the sense of Definition 5.1. ||

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