Survival models and health sequences

Peter McCullagh*

December 12, 2013

Abstract

Survival studies often generate not only a survival time for each patient but also a sequence of health measurements at annual or semi-annual check-ups while the patient remains alive. Such a sequence of random length accompanied by a survival time is called a survival process. Ordinarily robust health is associated with longer survival, so the two parts of a survival process cannot be assumed independent. This paper is concerned with a general technique—time reversal—for constructing statistical models for survival processes. A revival model is a regression model in the sense that it incorporates covariate and treatment effects into both the distribution of survival times and the joint distribution of health outcomes. The revival model also determines a family of conditional survival distributions given the observed history, which describes how the subsequent survival distribution is modified by the progression of health outcomes.

Keywords: covariate confounding; interference; preferential sampling; quality-of-life; revival process; semi-revival time; time reversal; treatment effect

1 Survival studies

A survival study is one in which patients are recruited according to a well-defined protocol, and their health status monitored on a regular or intermittent schedule until the terminal event, here assumed to be fatal. Covariates such as sex and age are recorded at the time of recruitment, and, if there is more than one treatment level, the assignment is presumed to be randomized. In a simple survival study, the health status $Y(t)$ at time $t$ is a bare-bones binary variable, dead or alive, and the entire process is then summarized by the length of time $T > 0$ spent in state 1, i.e. the survival time. In a survival study with health monitoring, $Y(t)$ is a more detailed description of the state of health or quality of life of the individual, containing whatever information—pulse rate, cholesterol level, cognitive score or CD4 cell count—is deemed relevant to the study. The goal may be to study the effect of treatment on survival time, or to study its effect on quality of life, or to predict the subsequent survival time of patients given their current health history.

*Department of Statistics, University of Chicago, 5734 University Ave, Chicago, Il 60637, U.S.A. E-mail: pmcc@galton.uchicago.edu
Survival studies with intermittent health monitoring are moderately common, and likely to become more so as health records become available electronically for research purposes. Within the past few years, several issues of the journal *Lifetime Data Analysis* have been devoted to problems connected with studies of exactly this type. For a good introduction, with examples and a discussion of scientific objectives, see Diggle, Sousa and Chetwynd (2008), Kurland, Johnson, Egleston and Diehr (2009) or Farewell and Henderson (2010). Section 8 of van Houwelingen and Putter (2012) is recommended reading.

In practice, the patient’s health status is measured at recruitment \(t = 0\), and regularly or intermittently thereafter while the patient remains alive. To emphasize the distinction between the observation times and observation values, each time is called an appointment date, the set of dates is called the appointment schedule; an appointment cancelled is a non-appointment, and cancellation is assumed to be uninformative given the survival time. Apart from covariate and treatment values, a complete uncensored observation on one patient \((T, t, Y[t])\) consists of a survival time \(T > 0\), an appointment schedule \(t \subset [0, T]\), and the health status measurements \(Y[t]\) at these times. To accommodate patients whose record is incomplete, a censoring indicator variable is also included. In that case, the censoring time is usually, but not necessarily, equal to the date of the most recent appointment.

A statistical model for a survival study is a family of probability distributions for the record of each patient, all three components included. At a minimum, therefore, it is necessary to model the survival time and the state of health jointly, and to consider how the joint distribution might be affected by treatment. Ordinarily, robust health is associated with longevity, but if both are affected by treatment, there is no guarantee that the two effects are in similar directions.

In the sense that the health status is measured over time on each patient, a survival study is a particular sort of longitudinal study. Certainly, temporal and other correlations are expected and must be accommodated. But the distinguishing feature, that each sequence is terminated by failure or censoring, gives survival-process models a very distinct character. For a good survey of the goals of such studies and the modeling strategies employed, see Kurland, Johnson, Egleston and Diehr (2009).

The goal of this paper is not so much to recommend a particular statistical model, as to suggest a general mathematical framework for the construction of survival-process models, permitting easy computation of the likelihood function and parameter estimates, and straightforward derivation of predictive distributions for individual survival times. For example, the paper has nothing to say on the choice between proportional hazards and accelerated lifetimes for accommodating treatment effects. Apart from reservations concerning the use of time-evolving covariates, all standard survival models are acceptable within the framework. Nor has the paper anything to contribute to the choice between Bayesian and non-Bayesian methods of analysis; prior distributions are not discussed, so either approach can be used. Administrative complications of the sort that are inevitable in medical and epidemiological research will be ignored for the most part, so no attempt is made to provide a complete turnkey package. For example, the paper has little to say about how best to handle incomplete records other than to recognize that censor-
ing and delayed reporting are issues that must be addressed—again using standard well-developed methods. Since most of the computations needed for model fitting and parameter estimation are relatively standard and need not involve specialized Markov chain or Monte Carlo algorithms, detailed discussion of computational techniques is omitted. The emphasis is on statistical principles, strategies for model formulation, sampling, and the distinction between time-dependent variables and time-evolving variables in the definition of treatment effects.

2 Latent-variable models

There are numerous examples in the medical and biostatistical literature of studies involving both successive measurements on each patient, such as CD4 lymphocyte cell counts, together with survival time (Lagakos, 1976; DeGruttola and Tu, 1994; Faucett and Thomas 1996; Guo and Carlin, 2004; Fieuws, Verbeke, Maes and Varenretherghe, 2008). Geriatric studies seldom focus exclusively on survival time, but tend to emphasize variables related to quality of life, such as overall physical and mental health, mobility, independence, memory loss, mental acuity, and so on. In the statistical literature, survival studies with health monitoring are called longitudinal studies with time-to-event data (Henderson, Diggle and Dobson, 2000; Xu and Zeger, 2001; Tsiatis and Davidian, 2004; Wu, Liu, Yi and Huang, 2012). Although there are variations in model formulation and implementation, all authors are agreed on the need for a joint distribution covering both survival time and the progression of health outcomes.

Motivated by several examples of a medical nature, Tsiatis and Davidian (2004) and Diggle, Sousa and Chetwynd (2008) provide a good explanation of the ins and outs of joint modelling. The inevitability of an association—positive or negative—between the measured health outcome and the survival time is one of the key model components. Beginning with Wulfsohn and Tsiatis (1997), the standard modelling strategy uses a bivariate zero-mean temporal process $\eta_i = (\eta_{0i}, \eta_{1i})$, independent and identically distributed for distinct patients, which affects the health outcome directly and additively and also the force of mortality $h_i$ in a component-wise manner. The longitudinal health variable, also called the outcome variable, is modelled as a temporal stochastic process,

$$Y_i(t) = \mu(t) + \eta_{0i}(t)$$

in which $\mu$ is the mean function. Given $\eta$, the survival time for patient $i$ is the time to the first event in the Poisson process whose intensity at time $t$ is

$$h_i(t) = h_0(t) \times \exp(\eta_{1i}(t) + x_i'\beta),$$

where $h_0(t)$ is an arbitrary intensity common to all patients, and $x_i'\beta$ is the covariate effect. For $\eta_1 \equiv 0$, this is the proportional hazards model (Cox, 1972). The dependence between $\eta_0$ and $\eta_1$ has the desired effect of inducing a dependence between the survival time and health outcomes (Henderson, Diggle and Dobson, 2000, section 2.2; Rizopoulos, 2000; Sweeting and Thompson, 2011).
Since $\eta_i(t)$ is not observed, (thus not included in the history $H_t$ generated by the observations up to time $t$), some authors prefer to replace $\eta_i(t)$ with $\alpha Y_i(t)$, effectively treating the longitudinal variable as a time-evolving covariate in the proportional hazards model (Tsiatis and Davidian 2004; Sweeting and Thompson, 2011). This is not entirely satisfactory because $\eta_i$ is ordinarily envisaged as a relatively smooth function whereas $\eta_0$ invariably has a white noise component.

The conventional strategy for model construction seems natural enough for recurrent non-fatal events, but probability distributions constructed in this way are extraordinarily complicated when applied to single-event survival data. Tsiatis and Davidian (2004, section 3) provide an explicit likelihood function for the latent-variable model, giving a careful, correct discussion of assumptions. They point out that the latent-variable model defines health-status trajectories extending beyond death, and this fact alone invites counterfactual speculation, which they do not dismiss but wisely decline to embrace. Moreover, some authors distinguish between the observed health trajectory and the ‘true’ health trajectory (Guo and Carlin, 2004), whereas others on the logical positivist side of the philosophical spectrum consider such a distinction neither appropriate nor inappropriate, but simply meaningless.

What is missing from the latent-variable formulation is an explicit recognition of the fact that health outcomes are observable on patients only while they remain alive. To speak of post-mortem health values, or to define such values mathematically, is needless, pointless, and faintly ridiculous. Death is the fundamental characteristic of a survival process, and death is not to be confused with truncation or censoring. It can be incorporated into the model by flatlining, i.e. by re-defining the observable outcome process as $Y'(t) = Y(t) \times I(T < t)$, so that $Y'(t) = 0$ for $t \geq T$. Alternatively, but not exactly equivalently, the observable process is the restriction of $Y$ to the patient’s lifetime, which is the random domain $(-\infty, T)$. Both restriction and flatlining imply that $T$ is a function of the observable process, though not of its finite restriction $Y'[t]$, so the need for a joint distribution becomes less clear.

In the simplest case where the latent process is Gaussian, $\eta_0 \sim \text{GP}(0, K_0)$ on $\mathbb{R}$, the distributions for each finite subset $t \subset \mathbb{R}$ are Gaussian:

$$Y[t] \sim N(\mu[t], K_0[t]).$$

This is not to be confused with the distribution of the observable process $(t, Y'[t])$ at either a fixed or randomly generated set of appointment dates. For fixed $t$, the implied restriction to survivors $\{i: T_i > \text{max}(t)\}$ is an instance of truncation or preferential sampling (McCullagh, 2008; Diggle, Menezes and Su, 2010), and the distribution among survivors is not Gaussian. For random $t$, the sequence of health records $Y'[t]$ is a point in the space $\bigcup_{n \geq 0} \mathbb{R}^n$ of finite-length real-valued sequences, which is not a vector space. In either case, $Y'[t]$ is not Gaussian.

In order to avoid some of these difficulties, both philosophical and computational, the suggestion put forward in this paper is to approach the problem from a different angle—literally in reverse. Time reversal is discussed as one of several options in Table 2 of Kurland, Johnson, Egleston and Diehr (2009), it is mentioned in section 8.3 of van Houwelingen and Putter (2012), and Figure 1 of van
den Hout, Muniz-Terrera and Matthews (2011), so the idea is not new. This paper explores the probabilistic and statistical implications of time-reversal, with a focus on exchangeability and distributional factorization for the entire survival process. The implications for sampling, the consequences for survival prediction, and the interpretation and estimation of treatment effects are also considered.

3 Time reversal

3.1 The survival process

A survival process $Y$ is a stochastic process defined for real $t$, in which $Y_i(t)$ is the state of health or quality of life of patient $i$ at time $t$, usually measured from recruitment. In a simple survival process, the state space $R = \{0, 1\}$ is sufficient to encode only the most basic of vital signs, dead or alive; more generally, the state space is any set large enough to encode the observable state of health or quality of life of the patient at one instant in time. Flatlining is the distinguishing characteristic of a survival process, i.e. $♭ \in R$ is an absorbing state such that $Y(t) = ♭$ implies $Y(t') = ♭$ for all $t' \geq t$. Whatever the state space may be, a survival process clearly cannot be stationary.

Survival time is the time to failure: $T_i = \sup_{t \geq 0} \{t : Y_i(t) \neq ♭\}$; it is presumed that $Y(0) \neq ♭$ at recruitment, so $T_i \geq 0$. This definition is quite general, and does not exclude immortality, i.e. $T = \infty$ with positive probability. In all of the models considered here, however, survival time is finite with probability one.

In constructing a probability distribution for the record of one patient, it is essential to bear in mind that the three observable components $(T, t, Y[t])$ cannot be independent. First, $T > 0$ is a positive random variable, and the appointment schedule $t$ is a finite subset of the random interval $[0, T)$, which implies that $t$ is also a random variable. Moreover $T > \max(t)$ implies that the appointment schedule for any patient is informative about his or her survival time. Likewise, since the number of health-status measurements coincides with $\#t$, it also should be strongly correlated with survival. Second, if better health status is associated with longer survival, we should expect patients who are initially frail to have shorter health-status records than patients who are initially healthy. In other words, even if the trajectories for distinct individuals may be identically distributed, the first component $Y(0)$ of a short health-status record should not be expected to have the same distribution as the first component of a longer record. On the contrary, any model such that record length is independent of record values must be regarded as highly dubious for survival studies.

Despite these complications, we aim to construct a statistical model that has the right sorts of symmetries and is not self-contradictory or otherwise inappropriate in any of the senses discussed above. Progress in this direction requires a few
assumptions, and in this paper, the first assumption is that
\[ t \perp Y \mid T. \] (1)

In other words, given the survival time, the appointment schedule is independent of the patient’s state of health as summarized in \( Y \). This condition does not require appointments to be made regularly or kept sedulously, but it does demand that the probability of an appointment being missed while the patient lives should not depend on the state of health, except through \( T \). A similar assumption is made explicitly or implicitly by most authors: see Henderson, Diggle and Dobson (2000, section 2.1). The assumption is mathematically natural, but it is not one to be taken for granted.

While the conditional independence assumption is mathematically clear-cut, the situation in practice may be considerably more muddy. Consider, for example, the CSL1 trial organized by the Copenhagen Study Group for Liver Diseases in the 1960s to study the effect of prednizone on the survival of patients diagnosed with liver cirrhosis. In this instance \( Y(\cdot) \) is a composite blood coagulation index called the prothrombin level: details can be found in Andersen, Hansen and Keiding (1991). Beginning at death, the reverse-time mean intervals between appointments are 77, 210 and 251 days, while the medians are 21, 165 and 292 days. In other words, half of the patients who died had their final appointment within the last three weeks of life. It is evident that the appointment intensity increases as \( s \to 0 \) in reverse time, which is not, in itself, a violation of (1). However, one might surmise that the increased intensity is related to the patient’s state of health or perception thereof. Condition (1) implies that the appointment intensity in reverse time does not depend on the blood coagulation index, and it is then unclear to what extent the condition may be violated by patient behaviour.

Although we refer to \( Y(\cdot) \) generically as the patient’s state of health, this description is not to be taken literally. The actual meaning depends on what has in fact been measured: in general, \( Y(\cdot) \) is only one component or one aspect of patient health.

### 3.2 The revival process

On the assumption that the survival time is finite, the time-reversed process
\[ Z_i(s) = Y_i(T_i - s) \]
is called the revival process. Thus, \( Z_i(s) \) is the state of health of patient \( i \) at time \( s \) prior to failure, and \( Z_i(T_i) = Y_i(0) \) is the value at recruitment. By construction, \( Z(s) = b \) for \( s < 0 \), and \( Z(s) \neq b \) for \( s > 0 \). Although \( Z \) is defined in reverse time, the temporal evolution via the survival process occurs in real time: by definition, \( Z(\cdot) \) is not observable component-wise until the patient dies.

The transformation \( Y \mapsto (T, Z) \) is clearly invertible; it may appear trivial, and in a sense it is trivial. Its one key property is that the revival process \( Z \) and the random variable \( T \) are variation independent. In the statistical models considered here, variation independence may be exploited through the revival assumption, which
states that the revival process and the survival time are statistically independent. More generally, \( Z \perp T \mid X \) if covariates are present.

To understand what the revival assumption implies, consider two patients \( i, j \) with identical covariate values \( x_i = x_j \), whose survival times are \( T_i = 5 \) and \( T_j = 20 \) time units respectively. Exchangeability implies that their health status values at revival time \( s \), \( Z_i(s) \) and \( Z_j(s) \), are identically distributed, and the revival assumption implies that both are independent of the survival times. The revival assumption is trivially satisfied by survival models with simple follow-up, where \( Y(t) \) is binary.

The revival assumption provides a convenient starting point for model construction: it is not critical to any part of the theory presented here. The more fundamental assumption is that the appointment schedule should be conditionally independent of the revival process given the survival time, i.e. \( t \rightarrow T \rightarrow Z \) in standard graphical-model notation. The revival assumption is a simplification implying that the edge connecting \( Z \) with \( T \) is omitted. Covariates, if there are any, are regarded as a fixed function on the patients.

### Table 1: Average prothrombin levels indexed by \( T \) and \( t \).

| Survival time (\( T \)) | 0–1 | 1–2 | 2–3 | 3–4 | 4–5 | 5–6 | 6–7 | 7–8 | 8+ |
|--------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 0–1                      | 58.0|     |     |     |     |     |     |     |     |
| 1–2                      | 72.5| 66.4|     |     |     |     |     |     |     |
| 2–3                      | 72.6| 73.2| 66.0|     |     |     |     |     |     |
| 3–4                      | 69.8| 71.2| 68.5| 54.2|     |     |     |     |     |
| 4–5                      | 68.5| 75.7| 72.5| 74.6| 57.7|     |     |     |     |
| 5–6                      | 70.5| 77.3| 73.5| 57.1| 64.5| 60.9|     |     |     |
| 6–7                      | 81.8| 73.6| 81.1| 80.6| 79.4| 75.5| 75.8|     |     |
| 7–8                      | 84.4| 88.8| 88.1| 92.1| 85.2| 81.2| 84.3| 88.1|     |
| 8+                       | 77.3| 73.6| 87.0| 74.1| 92.0| 80.3| 89.2| 79.4| 84.7|

The chief motivation for time reversal has to do with the effective alignment of patient records for comparison and signal extraction. Are the temporal patterns likely to be more similar in records aligned by age (time since birth or recruitment), or are they likely to be more similar in records aligned by reverse age (time remaining to failure)? Ultimately, the answer must depend on the context, but the context of survival studies suggests that the latter may be more effective than the former. Table 1 shows the averaged \( Y \)-values indexed by \( T \) and \( t \) for the prothrombin example discussed in more detail in section 6. It should be borne in mind that each cell is the average of 8–266 non-independent high-variability measurements, the larger counts occurring in the upper left cells. Alignment by reverse time is equivalent to counting leftwards from the main diagonal. Despite certain anomalies in the table of averages, e.g. row 6, column 4, it is clear that reverse-time is a more effective way of organizing the data to display the main trends in the mean response: the forward- and reverse-time sums of squares (equally weighted) are 543.0 and 1132.8 respectively, both on eight degrees of freedom. A standard least-squares analysis shows that the prothrombin mean values are not additive in \( T, t \), but they are approximately additive in \( T, T - t \), i.e. expressible approximately as \( \alpha(T) + \beta(T - t) \).
Figures 8.3 and 8.4 of van Houwelingen and Putter (2012), which are not substantially different from Fig. 2 of this paper, offer strong confirmation of this viewpoint in one further survival study involving white blood cell counts for patients suffering from chronic myeloid leukemia. For an application unrelated to survival, see example B of Cox and Snell (1981).

Model construction by time reversal may appear peculiar and unnatural in biological work, where the accepted wisdom is that an effect such as death cannot precede its supposed causes, such as ill health. However, the contrarian viewpoint—that proximity to death is the chief cause of ill health—seems neither less compelling nor more helpful. The author’s attitude is that metaphysical discussion along such lines is seldom productive and best avoided.

3.3 Exchangeability

In the presence of covariates such as sex, age at recruitment or treatment status, exchangeability is understood in the sense of McCullagh (2008, section 2) i.e. it applies to each subset of patients having the same covariate value. For any such set of patients, it implies that the survival times $T_{i_1}, \ldots, T_{i_n}$ are identically distributed, the record lengths $\#t_{i_1}, \ldots, \#t_{i_n}$ are identically distributed, the health-status variables $Y_{i_1}(t), \ldots, Y_{i_n}(t)$ are identically distributed, and likewise for the revival values at any fixed revival time $s$. In this paper, therefore, baseline health status is the first component of $Y$, not a covariate. This is essential for revival models: it is immaterial that $Y(0)$ is measured prior to randomization and treatment assignment. Exchangeability does not imply that $Y(0)$ is independent of the record length $\#t_i$.

Assuming that the record is complete, the observation for one patient consists of a survival time $T$, a finite appointment schedule $t \subset [0, T)$, and a sequence of length $\#t$ taking values in the space of medical records, here denoted by $\mathcal{R}$. For simplicity of notation in what follows, it is assumed that the appointment date is included in $\mathcal{R}$. Then the sample space for the observation $(T, Y|t)$ on one patient is

$$\mathcal{S} = (0, \infty) \times \bigcup_{k=0}^{\infty} \mathcal{R}^k$$

in which the second component is the space of finite-length $\mathcal{R}$-valued sequences.

For $n$ patients $i_1, \ldots, i_n$, the observations are independent if the joint distribution on $\mathcal{S}^n$ factors in the usual way:

$$P_{i_1, \ldots, i_n}(A_1 \times \cdots \times A_n) = \prod_{j=1}^{n} P_{i_j}(A_j),$$

where each $P_i$ is a probability distribution on $\mathcal{S}$, and $A_1, \ldots, A_n \subset \mathcal{S}$ are arbitrary events. In that circumstance, it is sufficient to describe the marginal distributions $P_i$ on $\mathcal{S}$, which may depend on covariates $x_i$. The observations on patients are infinitely exchangeable if $P_{i_1, \ldots, i_n}$ is the marginal distribution of $P_{i_1, \ldots, i_n, i_{n+1}}$, and all joint distributions are unaffected by permutation of patients, who are always assumed to be distinct individuals.
The implications of exchangeability are the same whether the record for each patient is expressed in terms of the survival process $Y$ or the revival process $Z$. Together with the revival assumption, that $Z$ and $T$ are independent, it implies that $Z_{i1}(s), \ldots, Z_{in}(s)$ are identically distributed independently of the survival times $T_{i1}, \ldots, T_{in}$.

### 3.4 Covariates

In the absence of specific information to the contrary, responses for distinct units are presumed to be distributed exchangeably. In the great majority of situations, specific information does exist in the form of covariates or classification variables or relationships. A covariate is a function $i \mapsto x_i$ on the units, in principle known for all units whether they occur in the sample or not. A covariate implies a specific form of inhomogeneity such that equality of covariates implies equality of response distributions: $x_i = x_j$ implies $Y_i \sim Y_j$. In practice, approximate equality of $x$-values also implies approximate equality of distributions. Likewise, a relationship is a function on pairs of units such that $R(i, i') = R(j, j')$ implies $(Y_i, Y_{i'}) \sim (Y_j, Y_{j'})$ for distinct pairs provided that the two pairs also have the same covariate values: $(x_i, x_{i'}) = (x_j, x_{j'})$. Geographic distance and genetic distance are two examples of symmetric relationships. The overarching principle is that differences in distribution, marginal or joint, must be associated with specific inhomogeneities in the experimental material or observational units.

The status of certain variables in specific survival studies may appear genuinely unclear. The conventional rationalization, in which certain variables used for prediction are notionally ‘fixed’ or non-random and treated as covariates, is not especially helpful for survival studies. Consider, for example, marital status as one variable in a geriatric study in which the goal is to study both quality of life and survival time. However it is defined, quality of life is a multi-dimensional response, a combination of mobility, independence, optimism, happiness, family support, and so forth. Marital status is a temporal variable known to be associated with survival and with quality of life; one goal may be to predict survival given marital status, or even to recommend a change of status in an effort to improve the quality of life. Another example of a similar type is air quality and its relation to the frequency and severity of asthmatic attacks (Laird, 1996). Should such a variable be regarded as a covariate or as one component of the response? For survival studies, and for longitudinal studies generally, the answer is very clear and very simple: every time-evolving variable is necessarily part of the response process.

By definition, a temporal variable $x$ is a function defined for every $t \geq 0$. A temporal variable is a covariate if it is also a function on the units, meaning that the entire function is determined and recorded at baseline. Usually this means that $x$ is constant in time, but there are exceptions such as patient age: see also section 3.5. Marital status and air quality, however, are not only temporal variables, but variables whose trajectories evolve over real time; neither is available as a covariate at baseline.

With marital status as a component of the survival process, the joint distribution may be used to predict the survival time beyond $t$ of an individual whose
marital history and other health-status measurements up to \( t \) are given. For that purpose, it is necessary to compute the conditional distribution of \( T \), or more generally of \( Y \), given the observed history \( \mathcal{H}_t \) up to time \( t \). For such calculations to make mathematical sense, marital status must be a random variable, a function of the process \( Y \). Thus, the statement ‘marital status is a random process’ is not to be construed as a sociological statement about the fragility of marriage or the nature of human relations; it is merely a mathematical assertion to the effect that probabilistic prediction is not possible without the requisite mathematical structure of \( \sigma \)-fields \( \mathcal{H}_t \subset \mathcal{H}_t' \) for \( t \leq t' \) and probability distributions.

### 3.5 Treatment

Treatment refers to a scheduled intervention or series of interventions in which, at certain fixed or random times, the prescription for patient \( i \) is switched from one arm to another. Thus, \( a_i(t) \) is the treatment arm scheduled for patient \( i \) at time \( t > 0 \). In general, but crucially for revival models, a null level is needed for \( t \leq 0 \), including the baseline \( t = 0 \). The entire temporal trajectory \( a_i(t) \) for \( t > 0 \) is determined by randomization and recorded at baseline. It does not evolve over real time in response to the doctor’s orders or the patient’s perceived needs, so it is not a time-evolving variable. For \( i \neq j \), the random variables \( a_i(\cdot), a_j(\cdot) \) need not be independent. In the sense that it is recorded at baseline, \( a_i(\cdot) \) is a covariate; in the sense that it is a temporal function, it is a time-dependent covariate.

In practice, the distribution of \( a(\cdot) \) is such that a switch of treatment arm is seldom scheduled more than once, and then only immediately after recruitment. Nonetheless, more general formulation is retained to underline the fact that treatment is a scheduled intervention such that \( a_i(t) \neq a_i(0) \), and thus not constant in time. Unlike the survival process, the treatment schedule does not evolve in real time.

It should be understood that each treatment arm is a specification for the drug type, dose level, frequency and manner of ingestion given the prevailing medical circumstances. Consider a hypertension study in which blood pressure \( Y(\cdot) \) in conventional units is measured at regular appointments. Thus, \textit{one blue pill to be taken three times daily while blood pressure exceeds 180, and one white pill twice daily if the pressure is between 160 and 180} is a treatment arm in which the actual dose level at time \( t' \) depends on the outcome \( Y(t) \) at the most recent appointment \( t \leq t' \). Another treatment arm might reverse the colours or adjust the doses. In this setting, \( a_i(t) \) denotes the assigned treatment arm, not the active drug or the dose administered on this date, so \( a_i(\cdot) \) is ordinarily constant for \( t > 0 \), even for dynamic chemotherapy strategies such as those discussed by Rosthøj, Keiding and Schmiegelow, (2012). For a compliant patient, the drug type and ingested dose can, in principle, be determined from the treatment arm and previously recorded \( Y \)-values. The important point is that each treatment arm be fully specified in advance, and the assignment be randomized at recruitment.

Let \( \bar{a}_i(s) = a_i(T_i - s) \) be the treatment arm expressed in revival time, so that, in the standard setting, \( \bar{a}_i(s) \) is null for \( s \geq T_i \). The revival assumption, that \( Z \perp \perp T \mid \bar{a} \), is trivial because \( T \) is a function of \( \bar{a} \). In the case of treatment, however,
the crucial assumption is lack of interference, i.e. the treatment assigned to one individual has no effect on the response distribution for other individuals, and the treatment assigned at one point in time has no effect on the response distribution at other times. For the latter, the statement is as follows. For each finite subset \( s \subset \mathbb{R}^+ \), the conditional distribution of \( Z[s] \) given the treatment schedule and survival time depends only on the treatment arms \( \bar{a}[s] \) prevailing at the scheduled times, i.e.

\[
Z[s] \perp \perp \bar{a} \mid \bar{a}[s].
\]

This is a strong assumption denying carry-over effects from earlier treatments or later treatments. It implies in particular that \( Z(s) \perp T \mid \bar{a}(s) \), which is primarily a statement about the one-dimensional marginal distributions.

It is common practice in epidemiological work for certain time-evolving variables to be handled as covariates, as if the entire trajectory were recorded at baseline. This approach is perfectly reasonable for a variable such as air quality in an asthma study where lack of cross-temporal interference might be defensible. It has the advantage of leading to simple well-developed procedures for effect estimation using marginal moments (Zeger and Liang, 1986; Zeger, Liang and Albert, 1988; Laird, 1996). The same approach is less convincing for an evolving variable such as marital status in a survival study, because the entire trajectory—suitably coded for \( t > T_i \)—would often contain enough information to determine the survival time.

4 Survival prediction

4.1 Simple Gaussian revival process

Consider first the simplest model in which observations for distinct patients are independent and identically distributed, and the revival assumption holds. To simplify matters further, problems related to parameter estimation are set aside. In other words, the survival time is distributed according to \( F \), and the revival processes is distributed independently with known distribution \( G \). Given the joint distribution, we are free to compute whatever conditional or marginal distribution is needed to address the inferential target.

It is natural in clinical settings to consider the question of how the trajectory of \( Y \) in \([0, t]\) affects the subsequent survival time. However the question is phrased, any suggestion of a causal mechanism is unwarranted: ultimately the answer is determined by the appropriate conditional distribution. The problem is to predict the survival time of an individual for whom the survival process at times \( t = (t_1 < \cdots < t_k) \) is given, i.e. to compute the conditional distribution given the information available. It is understood that \( t \) is a set of appointments, which implies that \( Y(t_k) \neq b \), and hence that \( T > t_k \).

To avoid a potential ambiguity of notation, it is worth re-stating the nature of the information provided for prediction. If \( t \) were known to be the complete appointment record, and if appointments were scheduled at unit intervals, we could reasonably deduce from the absence of subsequent appointments that \( \max(t) < T < \max(t) + 1 \). However, the information given is that contained in \( H(t_k) \), namely
that the patient has had \( k \) appointments in the interval \([0, t_k]\), producing a partial record \( Y[t]\). Thus, no upper bound for \( T \) can be inferred from the observed subset.

For positive real numbers \( s = (s_1 > \cdots > s_k) \), let \( g_k(z; s) \) be the joint density at \( z \in \mathbb{R}^k \) of the health-status values

\[
Z[s] = (Z(s_1), \ldots, Z(s_k)) = (Y(T - s_1), \ldots, Y(T - s_k)).
\]

Under the revival model, the joint density of \((T, t, Y[t])\) at \((t, t, y)\) is

\[
f(t) \times p(t \mid T = t) \times g_Y(y; t - t) \tag{2}
\]

where \( f = F' \) is the survival density, and \( p(\cdot \mid t) \) is a probability distribution on finite subsets of \([0, t]\). Then the conditional survival density given \( t, Y[t] = y \) is proportional to \( g_Y(y; t - t) \). Ordinarily, this is not the conditional distribution needed for survival prediction because the conditioning event implies that \( \text{max}(t) \) is the patient’s final appointment. In the usual clinical setting, a patient who has been examined at certain times \( t' \) in the past may, if fortune favours, have many subsequent appointments. The natural conditioning event is thus \( t = (t', \ldots) \) and \( Y[t'] = y \), in which the set \( t' \) of past appointments is a subset of all eventual appointments. In other words, the predictive survival distribution has a density at \( t \) proportional to

\[
f(t) \times p((t', \ldots) \mid T = t) \times g_Y(y; t - t') \tag{3}
\]

where \((t', \ldots)\) denotes the set of finite ordered subsets of \([0, t]\) in which \( t' \) is the leading subsequence.

If appointments are scheduled administratively on a fixed timetable, the second factor is constant in \( t \). Likewise, but for different reasons, if second and subsequent appointments occur as a uniform Poisson process in \((0, t)\), the second factor is constant in \( t \). Diverse arguments of this sort confirm intuition that the second factor is ignorable in practical work. In general, however, if appointments do not occur uniformly throughout the patient’s lifetime, the second factor is not constant in \( t \), meaning that the configuration of past appointments is informative for subsequent survival. Nonetheless, in all subsequent calculations we proceed as if the second factor is constant, in effect assuming that appointments are scheduled administratively.

A simple numerical example illustrates the idea. Suppose \( T \) is exponentially distributed with mean 10 years, and the revival process for \( s > 0 \) is a real-valued Gaussian process with mean \( E(Z(s)) = \beta s/(1 + s) \) and covariance function \( \delta_{ss'} + \exp(-|s - s'|) \) for \( s, s' > 0 \). The observed health-status values at \( t = (0, 1, 2, 3) \) are \( y = (6.0, 4.5, 5.4, 4.0) \).

For \( \beta = 0 \), the conditional density is such that \( T - 3 \) is exponential with mean 10; for various values of \( \beta \) in the range \( 0 \leq \beta \leq 8 \), the conditional density is shown in Fig. 1. Evidently, the conditional distribution depends on both the observed outcomes and on the model parameters: the median residual lifetime is not monotone in \( \beta \). In applications where the mean function is estimated with appreciable uncertainty, the predictive distribution is an appropriately weighted convex combination of the densities illustrated.
The conditional survival distribution given $Y[t]$ depends not only on the current or most recent value of $Y$, but linearly on the entire vector in a way that is generally more complicated than \[ g. \] In particular, the conditional distribution does not have the structure of a regression model in which the longitudinal variable enters as a time-dependent covariate without temporal interference. Thus, on the assumption that the joint model is adequate, issues related to covariate confounding do not arise.

4.2 The predictive density ratio

The ratio of the conditional survival density at $t$ to the marginal density is proportional to the factor $g(y; t - t)$, in which $y, t$ are fixed, and $t$ the variable. This modification factor—the Radon-Nikodym derivative—depends only on the revival process, not on the distribution of survival times. On a purely mathematical level, it is precisely the likelihood function in the statistical model for the $k$-dimensional variable $Y[t]$ whose density at $y$ is $g(y; t - t)$ for some value of the temporal offset parameter $t > t_k$.

In a Gaussian revival model, both the mean vector $\mu[t - t]$ for fixed $t$, and the covariance matrix $\Sigma$ of $Y[t] = Z[t-t]$ may depend on $t$. In the simpler circumstance where $\Sigma$ is independent of $t$, $\log g$ is a quadratic function of $y - \mu[t - t]$, so the dependence of the likelihood on $t$ stems from the lack of constancy of the mean function. Clearly $g$ has its maximum at the value $\hat{t} \geq t_k$ that minimizes $\|y - \mu[t - t]\|^2$ in the appropriate norm, which could occur at more than one internal point or at the extremes. For a locally stationary point, maximum or minimum, $\hat{\mu}' \Sigma^{-1} (y - \hat{\mu}) = 0$, where $\hat{\mu} = \mu[t - t]$ and $\mu'$ is the derivative.

In the very special case where $\mu(s) = \alpha + \beta s$ is linear in reverse time, and the covariances are independent of $s$ for $s > 0$, the log density ratio factor

$$-\frac{1}{2}(y - \mu[t - t])' \Sigma^{-1} (y - \mu[t - t]),$$

is also quadratic in $t$. After substituting $\alpha + \beta(t - t)$ for the mean function, and expressing the log density ratio as a quadratic in $t$, it can be seen that the predictive
density ratio at \( t > \max(t) \) is the density at \( \beta t \) of the Gaussian distribution with mean

\[-\alpha + 1' \Sigma^{-1} (y + \beta t) / (1' \Sigma^{-1} 1) = \bar{y} - \alpha + \beta \bar{t}\]

and variance \( 1 / (1' \Sigma^{-1} 1) \). Ignoring the dependence on the data that comes from parameter estimation, the dependence of the predictive density ratio on the data for one patient comes through the weighted averages

\[
\bar{y} = 1' \Sigma^{-1} y / (1' \Sigma^{-1} 1), \quad \bar{t} = 1' \Sigma^{-1} t / (1' \Sigma^{-1} 1)
\]

for this particular individual.

In applications to geriatric studies with \( Y \) representing some measure of physical health or mental acuity, it is reasonable to consider a revival model in which the mean \( \mu(s) \) is monotone increasing with an asymptote as \( s \to \infty \). The inverse linear model \( \mu(s) = \beta s / (\gamma + s) \) with asymptote \( \beta \), and semi-asymptote \( \mu(\gamma) = \mu(\infty) / 2 \), is a natural choice. In that case, the likelihood function is bounded as \( t \to \infty \), so the tail behaviour of the predictive distribution is the same as that of the unconditional survival distribution.

### 4.3 Exchangeable Gaussian revival process

In a more general Gaussian model, the revival values for distinct patients are exchangeable but not necessarily independent. Revival models have much in common with plant growth-curve models in which \( Z_i(s) = \mu + \eta_0(s) + \eta_i(s) \) is a sum of two independent zero-mean Gaussian processes, and the mean \( \mu \equiv \mu(s) \) is constant across individuals, and possibly constant in time. Usually the common trajectory \( \eta_0(\cdot) \) is moderately smooth but not stationary, perhaps fractional Brownian motion with \( \eta_0(0) = 0 \). The individual deviations are independent and identically distributed and they incorporate measurement error, so \( \eta_i(\cdot) \) is the sum of a continuous process and white noise. Thus, the Gaussian process is defined by

\[
E(Z_{is}) = \mu(s)
\]

\[
\text{cov}(Z_{is}, Z_{i's'}) = K_0(s, s') + \sigma^2 \delta_{ii'} \delta_{ss'}
\]

for some suitable covariance functions \( K_0, K_1 \), each of which can be expected to have a variance or volatility parameter and a range parameter. In the case of fractional Brownian motion, for example, \( K(s, t) \propto s^{\nu} + t^{\nu} - |s - t|^{\nu} \) for some \( 0 < \nu < 2 \), which governs the degree of smoothness of the random function.

For an new patient such that \( Y[t] = y \), the conditional survival density \( \Pr(T \in dt \mid \text{data}) \) given the data, including the outcomes for the new patient, is computed in the same way as above. The final factor in (3) is the density at the observed outcomes of the Gaussian joint distribution whose means and covariances are specified above. This involves all \( n + 1 \) patients including the new patient.

### 4.4 Illustration by simulation

Figure 2 shows simulated data for 200 patients whose survival times are independent exponential with mean five years. While the patient lives, annual appointments are
kept with probability $5/(5 + t)$, so appointment schedules in the simulation are not entirely regular. Health status is a real-valued Gaussian process with mean $E(Z(s)) = 10 + 10s/(10 + s)$ in reverse time, and covariances

$$\text{cov}(Z(s), Z(s')) = (1 + \exp(-|s - s'|/5) + \delta_{ss'})/2$$

for $s, s' > 0$, so there is an additive patient-specific effect in addition to temporal correlation. Values for distinct patients are independent and identically distributed. This distribution is such that health-status plots in reverse time aligned by failure show a stronger temporal trend than plots drawn in the conventional way. The state of health is determined more by time remaining before failure than time since recruitment. These trends could be accentuated by connecting successive dots for each individual, as in Fig. 2 of Sweeting and Thompson (2011), but this has not been done in Fig. 2.

![Figure 2: Simulated health status sequences aligned by recruitment time (left) and the same sequences aligned by failure time (right)](image)

Since the survival times are exponential with mean five, independent of covariates and treatment, the root mean squared prediction error using covariates only is five years. For fixed $k \geq 2$, and a patient having at least $k$ appointments, the conditional survival distribution given the first $k$ health-status values has a standard deviation depending on the observed configuration, but the average standard deviation is about 2.5 years, and the root mean squared prediction error is about 2.7 years. For this setting, the longitudinal variable is a reasonably effective predictor of survival, and the prediction error is almost independent of $k$ in the range 2–5. This summary does not tell the full story because certain $y$-configurations lead to very precise predictions whereas others lead to predictive distributions whose standard deviation exceeds five years.

The parameter settings used in this simulation may not be entirely representative of the range of behaviours of the conditional survival distribution given $Y[t]$. If the ratio of the between-patient to within-patient variance components is increased, the average variance of the conditional survival distribution decreases noticeably with $k$. For such settings, prediction using the entire health history is more effective than prediction using the most recent value.
4.5 Recurrent health-related events

In certain circumstances the health outcome $Y$ is best regarded as a point process, recording the occurrences of a specific type of non-fatal event, such as epileptic or asthmatic attacks or emergency-room visits. In other words, $Y_i \subset \mathbb{R}$ is the set of times at which patient $i$ experiences the event. Then $t = (0, t_k)$ is a bounded interval, and the observation $Y[t] = Y \cap t$ is the set of events that occur between recruitment and the most recent appointment. This observation records the actual date of each event, which is more informative than the counting process $\#Y[(0, t_1)], \ldots, \#Y[(0, t_k)]$ evaluated at the appointment dates. If there are recurrent events of several types, $Y$ is a marked point process, and $Y[t]$ is the set of all events of all types that occur in the given temporal interval. The paper Schaubel and Zhang (2010) is one of several papers in the October 2010 issue of Lifetime Data Analysis, which is devoted to studies of this type.

In this situation, the frequency of the recurrent event may be constant over time, or it may vary in a systematic way. For example, the frequency may increase slowly but systematically as a function of either age or time since recruitment. Alternatively, the frequency may be unrelated to age at recruitment, but may increase in the last year of life as death approaches. In the former case, time reversal is ineffective; in the latter case, the revival processes for different individuals have a common pattern, and time reversal is an effective device for exploiting this commonality.

We consider here only the simplest sort of recurrent-event process in which the revival process is Poisson, there is a single event type, and the subset $Y \cap t = y$ of observed event times is finite. The mean measure of the revival process is $\Lambda$, which is non-atomic with intensity $\lambda$ on the positive real line. The density ratio at $t > \sup(t)$ is the probability density at the observed event configuration $t - y$ as a subset of the reverse-time interval $t - t$, i.e.,

$$g(y; t - t) = \exp(-\Lambda(t - t)) \prod_{y \in Y} \lambda(t - y).$$

In particular, if the intensity is constant for $s > 0$, the density ratio is constant, and the event times are uninformative for survival. In other words, it is the temporal variation of the intensity function that makes the observed configuration $y$ informative for patient survival.

For a specific numerical example, let $\lambda(s) = (2 + s^2)/(1 + s^2)$ be the revival intensity, and let $t = (0, 2)$ be the observation window. The revival intensity, monotone decreasing with an asymptote of one, implies that the recurrent events are moderately common at all ages, but their frequency increases as failure approaches. Figure 3 shows the likelihood as a function of $t \geq 2$ for three event configurations, $y_0 = \emptyset$, $y_1 = \{0.5, 1.2\}$ and $y_2 = \{0.2, 1.3, 1.9\}$. Since the likelihood function is defined only up to an arbitrary multiplicative constant, the curves have been adjusted so that they are equal at $t = 20$, or effectively at $t = \infty$. In place of the predictive survival distributions, we show instead the ratio of the predictive hazard functions to the marginal hazards as dashed lines on the assumption that the marginal failure distribution is exponential with mean 5. Because of the form of the revival intensity, which is essentially constant except near the origin, the
Figure 3: Likelihood functions (solid lines) for three point configurations, with predictive hazard ratios (dashed lines)

predictive hazard functions are very similar in shape to the likelihood functions.

5 Parameter estimation

5.1 Likelihood factorization

The joint density for the observations in a revival model factors into two parts, one involving only survival times, the other involving only the revival process. More generally, if the revival assumption fails, the second factor is the conditional distribution of the revival process given $T = t$, so both factors depend on $t$. Although both factors may involve the same covariates and treatment indicators, the parameters in the two parts are assumed to be unrelated, i.e. variation independent. Thus the likelihood also factors, the first factor involving only survival parameters such as hazard modifiers associated with treatment and covariates, the second factor involving only health-status parameters such as temporal trends and temporal correlations. In other words, the two factors can be considered separately and independently, either for maximum likelihood estimation or for Bayesian operations.

The first stage in parameter estimation is to estimate the survival distribution $F$ together with treatment and covariate effects if needed. Whether the model for survival times is finite-dimensional or infinite-dimensional, this step is particularly simple because the first factor involves only the survival times and survival distribution. The standard assumption of independent survival times for distinct patients simplifies the problem even further. Exponential, gamma and Weibull models are all feasible, as is Cox’s (1972) proportional hazards model. Censored records are handled in the standard way, for example by using the Kaplan-Meier estimator if there are no covariates. The literature on this topic is very large, and this paper has nothing further to add.

The second stage, which is to estimate the parameters in the revival process, is also straightforward, but only if all records are complete with no censoring. Serial
dependence is inevitable in a temporal process, and there may also be independent persistent idiosyncratic effects associated with each patient, either additive or multiplicative. Gaussian revival models are particularly attractive for continuous health measurements because such effects are easily accommodated with block factors for patients and temporal covariance functions such as those included in the simulation in Fig. 2.

Thus the second stage involves mainly the estimation of variance components and range parameters in an additive Gaussian model. One slight complication is that the revival process is not expected to be stationary, which is a relevant consideration in the selection of covariance functions likely to be useful. Another complication is that the health status may be vector-valued, \( Y(t) \in \mathbb{R}^q \), so there are also covariance component matrices to be estimated. If the covariance function is separable, i.e.

\[
\text{cov}(Z_{ir}(s), Z_{ir'}(s')) = \Sigma_{r,r'} K(s, s')
\]

for some \( q \times q \) matrix \( \Sigma \), maximum-likelihood estimation is straightforward. But separability is a strong assumption implying that temporal correlations for all health variables have the same pattern, including the same decay rate, which may not be an adequate approximation. Nevertheless, this may be a reasonable starting point.

The second stage requires all health records to be aligned at their termini. Accordingly, a record that is right censored \((T_i > c_i)\) cannot be properly aligned. The simplest option is to ignore censored records entirely in the second stage, on the grounds that their information content is limited, and the estimating equations based complete records remain unbiased. This conclusion follows from the fact that the second factor is the conditional distribution given survival time. Thus, provided that the censoring mechanism is a selection based on patient survival time, the estimating equations derived from complete records are unbiased. For this purpose, it is not necessary that \( Z \) and \( T \) be independent. The inclusion of censored records is thus more a matter of statistical efficiency than bias, and the information gained may be disappointing in view of the additional effort required.

### 5.2 Incomplete records

If we choose to include in the likelihood the record for a patient censored at \( c > 0 \), we need the joint probability of the event \( T > c \), the density of the subset \( t_c = t \cap [0, c] \), and the outcome \( Y[t_c] \) at \( y \). On the assumption that censoring is uninformative, i.e. that the distribution of the subsequent survival time for a patient censored at time \( c \) is the same as the conditional distribution given \( T > c \) for an uncensored patient, the joint density is

\[
\int_{t \geq c} f(t) p(t_c \mid t) g(y; t - t_c) \, dt
\]

on the space of finite-length records. The second factor, the density of the appointment dates in \([0, c] \) for a patient surviving to time \( t > c \), is presumed not to depend on the subsequent survival time \( t - c \), in which case it may be extracted from the integral. It may be reasonable to assume that the distribution of appointment
schedules is known, for example if appointments are scheduled administratively at regular intervals, in which case the second factor may also be discarded from the likelihood. Since the survival probability $1 - F(c)$ is included in the first-stage likelihood, the additional factor needed in the analysis of the revival model is

$$\frac{1}{1 - F(c)} \int_{t > c} f(t) g(y; t - t_c) \, dt$$

in which $t_c$ may regarded as a fixed subset of $[0, c]$. Unfortunately, the integral involves both the survival density $f(t) = F'(t)$ and the density of the revival process, so the full likelihood no longer factors. For an approximate solution, $f$ may be replaced with the estimate obtained from the first-stage analysis of survival times.

For a revival parameter $\theta$, a censored record contributes less information than an uncensored record of similar length. The log likelihood derivative generated by a complete record $(t, t, y)$ is

$$U_\theta(t, t, y) = \frac{g'_\theta(y; t - t)}{g_\theta(y; t - t)}$$

where $g'_\theta$ is the derivative with respect to the parameter of the revival density. The log likelihood derivative for an incomplete record is the predictive expected value

$$\bar{U}_\theta(c, t_c, y) = \int_{t > c} U_\theta(t, t_c, y) f_\theta(t | Y[t_c] = y) \, dt.$$ 

In other words, $\bar{U}_\theta = E(U_\theta | Y[t_c] = y)$ for fixed $t_c$ and $Y[t_c] = y$. The Fisher information measures are

$$i(\theta) = \text{var}(U_\theta(t, t, y))$$

$$\bar{i}(\theta) = \text{var}(\bar{U}_\theta(c, t_c, y) = \text{var}(E(U_\theta | Y[t_c] = y))$$

$$i(\theta) - \bar{i}(\theta) = E \text{var}(U_\theta | Y[t_c] = y),$$

where all moments refer to the joint distribution of $T, Y[t_c]$ for fixed $t_c$. It is not easy from these formulae to gauge the loss of information associated with censoring, partly because some parameters are affected more severely than others.

### 5.3 Treatment effect: definition and estimation

Consider a survival study in which each eligible patient is randomized to one of two or more treatment arms $i \mapsto a_i$, which remains constant for $t > 0$. Health status is measured at recruitment—at $t = 0$, pre-randomization—and subsequently thereafter on a fixed appointment schedule until the patient dies. In addition to treatment and baseline health status, covariates $x_i$ such as sex, and age (at recruitment) are also recorded: all covariates are constant in time.

We consider here only the simplest sort of revival model for the effect of treatment on patient health, ignoring entirely its effect on survival time. Health status in the revival process is assumed to be Gaussian, independent for distinct patients, and the treatment is assumed to have an effect only on the mean of the process, not on its variance or covariance. Consider two patients, one in each treatment arm,

$$a_i(t) = \bar{a}_i(T_i - t) = 1, \quad a_j(t) = \bar{a}_j(T_j - t) = 0$$
such that $x_i = x_j$. The revival assumption asserts that the random variable $Z_i(s) - Z_j(s)$ is distributed independently of the pair $T_i, T_j$. By definition, the treatment effect as defined by the revival model is the difference of means

$$\tau_{10}(s) = E(Z_i(s)) - E(Z_j(s)) = E(Y_i(T_i - s)) - E(Y_j(T - s))$$

at revival time $s$. This is not directly comparable with either of the conventional definitions

$$\gamma_{10}(t) = E(Y_i(t)) - E(Y_j(t)) \quad \text{or} \quad \gamma'_{10}(t) = E(Y_i(t) - Y_j(t) \mid T_i, T_j > t)$$

in which the distributions are compared at a fixed time following recruitment. The expectation in a survival study—that healthy individuals tend to live longer than the frail—implies that $E(Y(t) \mid T)$ must depend on the time remaining to failure. In that case, the conventional treatment definition $\gamma'_{10}(t)$ depends explicitly on the difference between the two survival times. In other words, it does not disentangle the effect of treatment on patient health from its effect on survival time.

If the revival assumption fails, i.e. if $Z$ is not independent of $T$, then, in the simplest setting where the dependence on $T$ is linear and additive, the difference of means

$$E(Z_i(s) \mid T) - E(Z_j(s) \mid T) = \tau_{10}(s) + \gamma(T_i - T_j).$$

contains both a treatment effect and an effect due to the difference in survival times. In other words, the failure of the revival assumption does not necessarily complicate the interpretation of treatment effects. By contrast with standard practice in the analysis of randomized trials with longitudinal responses, (Fitzmaurice, Laird and Ware 2011, section 5.6), it is most unnatural in this setting to work with the conditional distribution given the baseline outcomes $Y_i(0) \equiv Z_i(T_i)$. That is one reason for the recommendation in section 3.3 that the baseline response be regarded as an integral part of the outcome sequence, not as a covariate. Exchangeability implies distributional equality $Z_i(T_i) \sim Z_j(T_j)$ for individuals having the same covariate values, but it does not imply equality of conditional distributions given $T$. On the presumption that treatment assignment is independent of baseline response values, we also have $Z_i(T_i) \sim Z_j(T_j)$ conditionally on treatment, whether or not $a_i, a_j$ are equal. Consequently, in order to satisfy the exchangeability assumption, it is necessary to introduce a null, pre-randomization, treatment level, $a_i(0) = a_j(0)$, common to all subjects.

5.4 Revival review

The easiest way to check the revival assumption is to formulate and fit a specific alternative model in which the revival process is not independent of the survival time. We consider here only the simplest design in which all records are complete, there are no covariates or treatment assignment, observations for distinct patients are independent, and the revival model is a family of Gaussian process. One way to do this is to replace (5) with

$$E(Z_i(s) \mid T) = \mu(s, T_i)$$
for some suitable family of functions $\mu(s,T)$, leaving the covariances unchanged. For example, if $x$ denotes patient age at recruitment, the revival mean might be modeled as

$$E(Z_i(s) \mid T) = \mu(s) + \beta_1 x_i + \beta_2 T_i$$

depending additively on patient age and survival time. If $\beta_1 = \beta_2$, the dependence is on age at failure rather than age at recruitment. More general models involving multiplicative interactions between $s$ and $T_i$ may also be considered.

Consider, for instance, the non-linear Gaussian revival model with mean

$$\mu(s) = \alpha + \beta s/(\gamma + s),$$

which is such that $\mu(0) = \alpha$, $\mu(\infty) = \alpha + \beta$, and $\mu(\gamma) = \frac{1}{2}(\mu(0) + \mu(\infty))$, so that $\gamma > 0$ is the semi-revival time. Within this family, the revival trajectory for one patient could be different from that of another, depending on their survival times. In other words, $\alpha, \beta, \gamma$ could depend on $T$ or $x+T$, either of which is a violation of the revival assumption. One of the simplest models of this type is the time-accelerated revival model in which the semi-revival time is inversely related to survival,

$$\mu(s,T) = \mu_0(sT) = \alpha + \beta sT/(\gamma + sT).$$

As a practical matter, it would be more effective to replace $\gamma$ with $\gamma_0 + \gamma_1/T$ or $\exp(\gamma_0 + \gamma_1/T)$ to generate a test of the revival assumption. Likewise, we could replace $\alpha$ with $\alpha_0 + \alpha_1 T$, asserting that the outcome sequences for long-lived patients are elevated by a constant amount at all revival times. Similarly, if $\beta$ is replaced with $\beta_0 + \beta_1 T$, the the asymptote is elevated in proportion to the additional lifetime.

Any modification of this sort is a violation of the revival assumption, so the survival time and the revival process are no longer independent. However, the factorization of the likelihood function remains intact, so the analysis remains relatively straightforward. For example, a likelihood ratio statistic to test the revival assumption can be constructed by fitting two nested models to the revival process, one satisfying the revival assumption, the other involving $T$.

6 A worked example: cirrhosis study

6.1 Prednizone and prothrombin levels

In the period 1962–1969, 532 patients in Copenhagen hospitals with histologically verified liver cirrhosis were randomly assigned to two treatment arms, control and prednizone. Only 488 patients for whom the initial biopsy could be reevaluated using more restrictive criteria were retained, yielding 251 and 237 patients in the prednizone and placebo groups respectively. Variables recorded at entry include sex, age, and several histological classifications of the liver biopsy. Clinical variables were also collected, including information on alcohol consumption, nutritional status, bleeding, and degree of ascites. However, these covariates
were not included in the dataset used here, which was downloaded from the R library [http://cran.r-project.org/web/packages/joineR](http://cran.r-project.org/web/packages/joineR) maintained by Philipson Sousa, Diggle, Williamson, Kolamunnage-Dona and Henderson. At the end of the study period, the mortality rate was 292/488, or approximately 60%.

![Prothrombin mean trajectories in forward time and in reverse time](image)

Figure 4: Prothrombin mean trajectories in forward time and in reverse time

We focus here on the prothrombin index, a composite blood coagulation index related to liver function, measured initially at three-month intervals and subsequently at roughly six- to twelve-month intervals. The individual prothrombin trajectories are highly variable, both in forward and in reverse time, which tends to obscure patterns and trends. In Figure 4a the mean trajectory is plotted against time from recruitment for four patient groups placebo/prednisone and censored/not censored, with the solid lines denoting censored individuals. Naturally, only those patients who are still alive are included in the average for that time. Figure 4b shows the same plots in reverse time. While there are certain similarities in the two plots, the differences in temporal trends are rather striking. In particular, prothrombin levels in the six months prior to censoring are fairly stable, which is in marked contrast with levels in the six months prior to failure.

One of the most basic forms of Gaussian revival model is such that

\[ Z_i(s) = \alpha + \beta T_i + \tau_{0}(s) + \eta_0(s) + \eta_1(s) + \epsilon_i + \epsilon'_i \]

in which \( \tau \) is the treatment effect given the survival time. The inclusion of \( T_i \) is warranted in view of the increasing trend along the diagonals and sub-diagonals of Table 1. The remaining four terms are independent zero-mean Gaussian processes, \( \eta_0(\cdot), \eta_1(\cdot) \) denoting temporal processes having a degree of continuity, and \( \epsilon, \epsilon' \) having independent and identically distributed components. Additive models of this sort are used for plant and animal growth curves in which \( \eta_0(s) \) is the temporal trajectory of the population average, \( \eta_i(s) + \epsilon_i \) is the idiosyncratic deviation associated with individual \( i \) at time \( s \), and \( \epsilon' \) represents further deviations sometimes pejoratively called measurement error.
Since $Z$ is Gaussian, the model may be specified by its first two moments
\[
E(Z_i(s) \mid T) = \alpha + \beta T_i + \tau_{\alpha_i(s)}
\]
\[
\text{cov}(Z_i(s), Z_j(s') \mid T) = \sigma_0^2 K_0(s, s') + \sigma_1^2 \delta_{ij} K_1(s, s') + \sigma_2^2 \delta_{ij} \delta_{ss'} + \sigma_3^2 \delta_{ij} \delta_{ss'}. \tag{6}
\]
The precise choice of covariance function is seldom critical provided that the correlation range is reasonable and the behaviour at the origin is appropriate for the degree of continuity desired. For $\eta_i$, it is essential to use a proper covariance function, and for illustration purposes we choose $K_1(s, s') = \exp(-|s - s'|/\lambda)$ with range $\lambda > 0$; this choice guarantees temporal continuity of the idiosyncratic deviations. The value used for the range in subsequent calculations is $\lambda = 1.5$ years, which implies an autocorrelation of 0.51 at a lag of one year. For the mean trajectory $\eta_0$, we use a generalized process with kernel 1, i.e. $K_0(s, s') = -|s - s'|$, equivalent to the limiting exponential covariance function with infinite range. To say the same thing in another way, the joint distribution of temporal increments of $\eta_0$ is the same as the joint distribution of temporal increments of Brownian motion.

To some extent, these distributional choices are arbitrary. In particular, there is no compelling reason to expect either $\eta_0$ or $\eta_i$ to be stationary, particularly near the origin. As it happens, the fit of the model can be significantly improved by using non-stationary covariance functions, but we press ahead for the moment to explore the consequences of inappropriately using a stationary model. For the population average trajectory $\eta_0(s)$, a smoother quadratic spline kernel such as $|s - s'|^2 \log |s - s'|$ or even a cubic spline $|s - s'|^3$ might be preferred, particularly for aesthetic purposes and graphical depiction. To accommodate these higher-order splines the kernel must be increased to include span(1, s). Very rarely does the log likelihood contain much information about the degree of smoothness, but these data exhibit a slight preference for the rougher linear spline function.

In the revival process setting, treatment is a three-level factor, ‘null’ for pre-randomization and ‘control’ or ‘prednizone’ thereafter. Ordinarily, sex and age should be included as covariates in the mean model, but these were not included in the dataset available. Thus, the parameter space for the mean model has dimension four, while the covariance parameter space has dimension 5 (including one range parameter). For the smoother spline kernels, reverse time must be included in the mean model or explicitly in the kernel (Clifford and McCullagh, 2006).

In the likelihood computations discussed below, only the 292 prothrombin trajectories for non-censored patients are used, making 1634 values in total. All four variance components were found to be significantly positive, the REML values being (35.2, 207.3, 218.8, 173.3) in the order shown in (6). The treatment effect estimates for control and prednizone versus null are (2.24, 13.39) with standard errors 1.42, 1.45. Thus, even in the control group, there is a suggestion of a small increase in average prothrombin index immediately after recruitment. Figure 4a suggests that any such change might be gradual, but we do not pursue that here. The prednizone-versus-control contrast has a larger standard error (1.66) because it is a contrast between different patients, thus involving the between-patients variance component $\sigma_2^2$.

As measured by the residual likelihood ratio, the revival covariance model (6) fits
appreciably better than the forward-time version. First note that $\delta_{ij}|s-s'|$ is equal to $\delta_{ij}|t-t'|$ but $|s-s'| \neq |t-t'|$ for different patients, so time reversal affects only the first of the four variance components. The greater similarity of the trajectories in reverse time accounts for the fact that the maximized residual log likelihood is 46.2 units larger for the revival model (6) than the forward-time version. The family of distributions with both $K_0(s,s')$ and $K_0(t,t')$ included can be fitted to the data, if only as a test of the adequacy of assumptions. The conclusions to be drawn from this are encouraging: the fitted coefficient of $K_0(t,t')$ is small (2.31), and the increase in log likelihood (1.24) is insignificant.

The fitted coefficient of $T_i$ is small in absolute terms ($1.80 \pm 0.48$ prothrombin units per year), but sufficient to show that the revival assumption is not quite satisfactory in this setting. Individuals who fail early have slightly lower mean trajectories than those who survive beyond the first year, and the trend continues beyond that. The need for this term may be a consequence of age dependence, where age is best defined at death rather than at recruitment.

![Figure 5: Three Bayes estimates of $\eta_0(s)$ for the prothrombin data](image)

The population-average prothrombin trajectory is a continuous random function $\eta_0(\cdot)$, whose Bayes estimate is the conditional expected value

$$\hat{\eta}_0(s) = E(Z_u(s) - \mu_u(s) | \text{data})$$

(7)

of the centered revival process for an extra-sample patient $u$. When parameter estimates are inserted for computation, this is called the empirical Bayes estimate. The Bayes estimate is a linear function of the observed $y$-values; its nature as a function of $s$ depends on $K_0$, and for the three functions mentioned above it is a spline of degree one, two or three. Apart from the degree of smoothness, the broad features of the three estimates shown in Fig. 5 are the same, namely a constant value followed by an abrupt decline in the last six months of life. All three versions exhibit low-amplitude oscillations, which are probably spurious; their appearance here is
most likely an artifact of fitting a stationary model to a non-stationary process. The
fit of the model can be improved significantly by using a non-stationary model such
as \( K_0(s, s') = -|\log(s+\delta) - \log(s'+\delta)| \) with a small positive offset of about one day,
and if this is done, the oscillations in the Bayes estimate are greatly reduced. The
cubic spline model on the log scale is particularly effective in eliminating oscillations.
A similar effect can be achieved by using a suitable non-linear mean function such as
inverse linear or the type considered by van den Hout, Muniz-Terrera and Matthews
(2011).

![Graph of log modification factors for the predictive survival density for patient 402.](image)

Figure 6: Two log modification factors for the predictive survival density for pa-
tient 402. The smoother curve comes from a smooth non-stationary covariance
function, the rougher one from a Brownian motion model for the revival process.

### 6.2 Effect of prothrombin on prognosis

Over a period of 5 years and one month following recruitment, patient \( u \) had eight
appointments yielding prothrombin values as follows:

| \( t_u \) (days) | 0  | 126 | 226 | 392 | 770 | 1127 | 1631 | 1855 |
|-----------------|----|-----|-----|-----|-----|------|------|------|
| \( Y_u[t_u] \)   | 49 | 93  | 122 | 120 | 110 | 100  | 72   | 59   |

This is in fact the record for patient 402 who was assigned to prednizone and subse-
sequently censored at 2661 days. As determined on day 1855, the survival prognosis
for this patient depends on preceding sequence of measurements. Relative to the
unconditional survival density for a patient on the prednisone arm, the conditional
survival density at time \( t \) is modified multiplicatively by a factor proportional to the
joint conditional density of the random variable \( Z_u[t - t_u] \) at the observed point \( y_u \)
given the data observed for all other patients: see section 4. This factor, which is
non-zero only for \( t > \max(t_u) \), depends to a substantial extent on the nature of the
survival model, for example on whether the conditional mean \( E(Z_u(s) \mid T) \) depends
on $s$ or the survival time, whether $K_0(s, s')$ is stationary, whether it is smooth, and so on. Figure 6 shows this modification factor computed for two fitted models, one stationary and one not, with covariance functions

$$
K_0(s, s') = -|s - s'|, \quad K_0(s, s') = |\log(s + \delta) - \log(s' + \delta)|^3.
$$

Direct comparison of these models via the likelihood is not entirely straightforward because the kernel of the non-stationary model span $\{1, \log(s + \delta)\}$ depends on the offset. Nevertheless, if $\delta$ is regarded as fixed at one day, the models may be compared, and the maximized likelihoods are approximately equal. Both fitted models have the same conditional mean space, constant in $s$, but including treatment and survival time; the kernels include span $\{1, \log(s + \delta)\}$ to make the likelihoods comparable.

Figure 6 shows that the ratio of the predictive survival density to the marginal density is moderately sensitive to the assumed form for the revival covariance function $K_0$. The spurious oscillations are attributable to the unwarranted stationarity assumption. In this example, the smoother non-stationary covariance function is better in terms of the plausibility of its predictions. According to the fitted model, the decrease in the last two prothrombin values leads to a higher predicted risk for the next year, but the prothrombin values have little effect on the prognosis beyond that time. These prognostic distributions are specific to patient 402: another patient who has the same sequence of prothrombin values, but who is on the null treatment level, has a different prognostic distribution with a less elevated initial risk.

The code used for fitting the various models and generating Figures 5 and 6 is available at www.stat.uchicago.edu/~pmcc/reports

Acknowledgements

Comments by D.R. Cox, W. Dempsey, D. Farewell, R. Gibbons, N. Keiding and S.M. Stigler on an earlier version of this paper are gratefully acknowledged. Walter Dempsey helped with the computation in section 6 and the preparation of Figure 4.

7 References

Andersen, P.K., Hansen, L.H. and Keiding, N. (1991) Assessing the influence of reversible disease indicators on survival. *Statistics in Medicine* 10, 1061-1067.

Clifford, D. and McCullagh, P. (2006). The regress function. *R Newsletter* 6, 6–10.

Cox, D.R. (1972) Regression models and life tables (with discussion). *J. Roy. Statist. Soc. B* 34, 187–220.

Cox, D.R. and Snell, E.J. (1981) *Applied Statistics*. London: Chapman and Hall.

DeGruttola, V. and Tu, X.M. (1994) Modeling progression of CD-4 lymphocyte count and its relation to survival time. *Biometrics* 50, 1003–1014.

Diggle, P.J., Liang, K.-Y. and Zeger, S.L. (1994) *Analysis of Longitudinal Data*. Oxford Science Publications: Clarendon Press.
Diggle, P.J., Farewell, D. and Henderson, R. (2007) Analysis of longitudinal data with drop-out: objectives, assumptions and a proposal (with discussion). *Applied Statistics* **56**, 499–550.

Diggle, P.J., Sousa, I. and Chetwynd, A. (2008) Joint modeling of repeated measurements and time-to-event outcomes: The fourth Armitage lecture. *Statistics in Medicine* **27**, 2981–2998.

Diggle, P., Menezes, R. and Su, T-L. (2010) Geostatistical inference under preferential sampling (with discussion). *Appl. Statist.* **59**, 191–232.

Farewell, D. and Henderson, R. (2010) Longitudinal perspectives on event history analysis. *Lifetime Data Analysis* **6**, 102–117.

Faucett, C.L. and Thomas, D.C. (1996) Simultaneously modeling censored survival data and repeatedly measured covariates: a Gibbs sampling approach. *Statistics in Medicine* **15**, 1663–1685.

Fieuws, S., Verbeke, G., Maes, B. and Vanreentghem (2008) Predicting renal graft failure using multivariate longitudinal profiles. *Biostatistics* **9**, 419–431.

Fitzmaurice, G.M., Laird, N.M. and Ware, J.H. (2011) *Applied Longitudinal Data Analysis, 2nd edition*. New York: Wiley.

Guo, X. and Carlin, B. (2004) Separate and joint modeling of longitudinal and event time data using standard computer packages. *American Statistician* **58**, 1–10.

Henderson, R., Diggle, P. and Dobson, A. (2000) Joint modeling of longitudinal measurements and event time data. *Biostatistics* **1**, 465–480.

Kurland, B.F., Johnson, L.L., Egleston, B.L. and Diehr, P.H. (2009) Longitudinal data with follow-up truncated by death: match the analysis method to the research aims. *Statistical Science* **24**, 211-222.

Lagakos, S.W. (1976) A stochastic model for censored-survival data in the presence of an auxiliary variable. *Biometrics* **32**, 551-559.

Laird, N. (1996) Longitudinal panel data: an overview of current methodology. In *Time Series Models in Econometrics, Finance and Other Fields*, D.R. Cox, D.V. Hinkley and O.E. Barndorff-Nielsen, eds. Chapman & Hall Monographs on Statistics and Applied Probability 65.

McCullagh, P. (2008). Sampling bias and logistic models (with discussion). *J. Roy. Statist. Soc.* B **70**, 643–677.

Rizopoulos, D. (2010) JM: An R package for the joint modeling of longitudinal and time-to-event data. *Journal of Statistical Software* **35**, 1–33.

Rosthøj, Keiding, N. and Schmiegelow, N. (2012) Estimation of dynamic treatment strategies for maintenance therapy of children with acute lymphoblastic leukaemia: an application of history-adjusted marginal structural models. *Statistics in Medicine* **31**, 470–488.
Sweeting, M.J. and Thompson, S.G. (2011) Joint modeling of longitudinal and time-to-event data with application to predicting abdominal aortic aneurysm growth and rupture. *Biometrical Journal* **53**, 750–763.

Tsiatis, A.A., DeGruttola, V. and Wulfsohn, M.S. (1995) Modeling the relationship of survival to longitudinal data measured with error., applications to survival and CD4 counts in patients with AIDS. *J. Amer. Statist. Assoc.* **90**, 27–37.

Tsiatis, A.A, and Davidian, M. (2004) Joint modeling of longitudinal and time-to-event data: an overview. *Statistica Sinica* **14**, 809–834.

van den Hout, A., Muniz-Terrera, G. and Matthews, F. (2011) Smooth random change-point models. *Statistics in Medicine* **30** 599–610.

van Houwelingen, H.C. and Putter, H. (2012) *Dynamic Prediction in Clinical Survival Analysis*. Monographs on Statistics and Applied Probability 123; CRC Press.

Xu, J. and Zeger, S.L. (2001) Joint analysis of longitudinal data comprising repeated measures and times to events. *Applied Statistics* **50**, 375–387.

Wulfsohn, M.S. and Tsiatis, A.A. (1997) A joint model for survival and longitudinal data measured with error. *Biometrics* **53**, 330–339.

Zeger, S.L. and Liang, K.-Y. (1986) Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* **42**, 121–130.

Zeger, S.L., Liang, K.-Y. and Albert, P. (1988) Models for longitudinal data: a generalized estimating equation approach. *Biometrics* **44**, 1049–1060.