Bernoulli **17**(3), 2011, 895–915
DOI: 10.3150/10-BEJ303

A martingale approach to continuous-time marginal structural models

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Marginal structural models were introduced in order to provide estimates of causal effects from interventions based on observational studies in epidemiological research. The key point is that this can be understood in terms of Girsanov's change of measure. This offers a mathematical interpretation of marginal structural models that has not been available before. We consider both a model of an observational study and a model of a hypothetical randomized trial. These models correspond to different martingale measures – the observational measure and the randomized trial measure – on some underlying space. We describe situations where the randomized trial measure is absolutely continuous with respect to the observational measure. The resulting continuous-time likelihood ratio process with respect to these two probability measures corresponds to the weights in discrete-time marginal structural models. In order to do inference for the hypothetical randomized trial, we can simulate samples using observational data weighted by this likelihood ratio.

Keywords: counting processes; marginal structural models; martingale measures; event history analysis; Aalen's additive hazard model

1. Introduction

We will consider the following scenario: A patient has a disease. In order to avoid an event (e.g., death), a specific treatment can be given. The given treatment will typically depend on the patient's previous health condition.

We would like to estimate the effect of a given treatment on the time until the occurrence of the event. A natural way to do so is to implement some sort of randomized trial. This means that we would have to set up an experiment on a group of patients where the treatment was initiated by randomization independently of each patient's previous health condition. Such a study typically requires significant resources that may not be available. In order to take advantage of another type of data, we could try to base our estimates of the treatment effect on an observational study. Suppose we have observations of a group of patients where the given treatments were chosen by doctors. As a first attempt, one could try to compute the relative short-term risk between the group given treatment and the group not given treatment at a particular time. This could be done using Cox proportional hazards regression techniques. However, such a naive analysis would most likely introduce a bias compared to the estimate based on the randomized trial. The reason is that the health condition of the patient not already in treatment will be a predictor of both treatment and death; that is, it is likely to be a confounder [19].

We can easily imagine two opposite scenarios where this confounder would complicate estimates: Due to considerable costs, reduced life quality or possibly drug resistance, one could decide that the treatment should not be initiated until the patients are sufficiently ill. A naive

marginal analysis based on data from an observational study would then quickly lead us to believe that the treatment effect was less than the true treatment effect. Conversely, if we decided only to initiate treatment for patients with good health conditions and not for the ones with poor conditions, then a naive marginal analysis would quickly lead us to believe that the treatment effect was better than the true treatment effect.

In order to solve this problem, one might suggest that we compute an estimate of the treatment effect conditionally on the health condition of the patient. However, in several situations, it is likely that the previous treatment will improve the patient's general intermediate health condition. This improvement will in itself typically postpone the time of death. The conditional effect estimate we described would only incorporate the direct treatment effect, not the effect that is due to an improvement of the patient's intermediate health condition.

There is also another source of bias that we have to consider in order to lay hands on the causal effect of treatment; that is, censoring. We assume that a patient may drop out of the study at a time and not return; that is, we have right censoring. The given treatment, calender time and the patient's health condition might lead to such a drop out. If we do a naive analysis based on the patients that are still in the study, then we introduce a selection bias [9].

We are forced to move outside the standard Cox regression framework since we have to deal with the mentioned time-dependent confounder effects due to a patient's underlying health condition. In order to provide a meaningful estimate of the treatment effect, with a simple interpretation, we could try to construct a rich model that also describes the dynamics of the underlying biological processes. Such mechanisms are likely to be very complicated and there might not be sufficient knowledge or data available. For this reason we could try to fit a marginal model of a suitable randomized trial for our scenario. This will be our strategy in what follows.

One attempt to provide a marginal estimate of the causal treatment effect this way is presented by Robins in [15]. This method uses marginal structural models and relies on the additional assumption that there are no unmeasured confounders; that is, there does not exist an unobserved process that is a predictor of both censoring and treatment, both censoring and the event or both treatment and the event, given the observed covariates. If every such process is measured, then the marginal structural model (MSM) approach provides a proper adjustment of the marginal effect estimates. The idea is to apply some clever weights to the observations. This weighting results in a pseudo-population that is different from the observed population. The key property of this pseudo-population is that the selection bias and the treatment confounding due to the patient's health condition become negligible. Now, one can proceed with a weighted Cox regression to obtain a marginal estimate of the effect of treatment. The method has been used several times on epidemiological studies. In [8] it was used to estimate the effect of Zidovudine on the survival of HIV-positive men in the Multicenter AIDS Cohort Study. Moreover, the method was also used in [19] to give an estimate of the hazard ratio for the effect of highly active antiviral treatment (HAART) on progression to AIDS or death for HIV patients in Switzerland.

The method introduced by Robins deals with longitudinal data in discrete time. We will consider continuous-time versions of the marginal structural models for event history data. The idea is to characterize reasonable models of a randomized trial, the randomized trial measures, using martingale theory. This offers a mathematical interpretation of marginal structural models that has not been available before.

We characterize a class of of reasonable models of randomized trials in terms of local independence. Such a model corresponds to a particular martingale measure. The continuous-time

likelihood ratio process between this measure and the observational probability measure corresponds to the weights in a discrete-time marginal structural model. In order to do inference for this new measure, we can simulate samples using the observed data weighted by this likelihood ratio.

Another approach to causal inference within our scenario is to use the so-called structural nested models. These models were also introduced by Robins; see [16,17]. Lok has developed continuous-time versions of such models using counting processes and martingale theory; see [13].

2. Observable processes and local independence

Before we come to the main results, we will spend some time establishing terminology. Even if the mathematics involved is fairly standard stochastic process theory, it is perhaps not so commonly used in event history analysis. A very good background reference on stochastic processes that we will use frequently is [11].

2.1. Observable processes

In Section 3 we will consider a stochastic model of a single patient. There are typically many factors that are important for describing how the disease of that individual develops in time. We will consider models where all the possible observations of one patient are represented by stochastic integrals against Poisson processes. More formally, let $d, n \in \mathbb{N}$ and consider a probability space $(\Omega, \mathcal{F}, Q)$ with mutually orthogonal counting processes $N_t^1, \ldots, N_t^n$ on the interval $[0, T]$ and a filtration $\{\mathcal{F}_t\}_t$ that is generated by their joint history and some initial information $\mathcal{F}_0$. The counting processes are assumed to be Poisson processes in the sense that

$$\overline{N}_t^1 := N_t^1 - t, \ldots, \overline{N}_t^n := N_t^n - t$$

define Q-martingales, the compensated Poisson processes. The probability measure Q will only play a role as a reference measure, as we will mainly be interested in probability measures that are absolutely continuous with respect to Q. This will sometimes be referred to as the *Poisson measure*.

We let H be a bounded and $\mathcal{F}_t$-predictable $d \times n$-matrix-valued process and let X_0 denote a bounded $\mathcal{F}_0$-measurable random vector. Now, define the d-dimensional *observable process*:

$$X_t := X_0 + \int_0^t H_s \, \mathrm{d}N_s.$$

All the possible observations of a patient in our approach will be processes of this form. Counting processes are trivially included in this class, but we also allow slightly more complicated jump processes. One example could be measurements of blood values. Each time the blood value is updated, it would be given by a jump and correspond to a jump time of the underlying counting process. The size and direction of the jump would then be given by the value of the predictable integrand H at the jump time.

2.2. Separability

We will say that two observable processes X and Y are *separable* if they allow the representations:

$$X_t = X_0 + \int_0^t H_s^X \, \mathrm{d}N_s^X,$$

$$Y_t = Y_0 + \int_0^t H_s^Y \, \mathrm{d}N_s^Y,$$

where N^X and N^Y are independent components of the multivariate process N, X_0 and Y_0 are bounded $\mathcal{F}_0$-measurable random vectors and H^X and H^Y are bounded matrix-valued processes that are predictable with respect to the histories of N^X and N^Y, respectively. Separability is a technical assumption that provides well-behaved factorizations of likelihoods. This is used in the proof of Theorem 1. Heuristically, it means that the processes X and Y do reflect different random phenomena. Separability is even stronger than orthogonality since the processes are independent with respect to the Poisson measure Q. However, since we will deal with other probability measures that are absolutely continuous with respect to the Poisson measure, separable processes can not necessarily be treated as independent.

2.3. A martingale measure

As we mentioned earlier, our samples will consist of paths of observable processes. These samples will be distributed according to some probability measure P such that a given family of predictable and non-negative processes define the jump intensities for $N^1, \ldots, N^n$ with respect to $\mathcal{F}_t$. Since we assume that the observations are distributed according to P, we will refer to such a measure as an *observational measure*.

More formally, we let $\lambda^1, \ldots, \lambda^n$ be non-negative $\mathcal{F}_t$-predictable processes and we assume that P is a probability measure such that:

(1) P and Q coincide on $\mathcal{F}_0$,
(2) $P \ll Q$, i.e., P is absolutely continuous with respect to the Poisson measure,
(3) The equation

$$M_t^i := N_t^i - \int_0^t \lambda_s^i \, \mathrm{d}s$$

defines a square-integrable P-martingale with respect to $\mathcal{F}_t$ for every i.

These properties characterize the probability measure P uniquely if such a measure exists, [11], Theorem III 1.26.

2.4. Non-influence

We will need a notion of non-influence between observable processes. There are several formal definitions that are meant to capture this; see [7]. Independence, or even conditional indepen-

dence, is too strong to be of interest for the method we have in mind. The non-influence relation we will consider is *local independence*. Heuristically, a process X is locally independent of a process Y if information about the past of Y does not contribute to a better prediction of the short-term behavior of X.

In the setting of event history analysis, this concept has been studied thoroughly by Didelez [6]. Schweder [18] used this concept in a study of composable Markov processes. Aalen *et al.* made use of local independence in order to study the effect of menopause on the risk of developing a certain skin disease in [3].

2.5. Local independence

Let X, Y, Z be observable processes that are mutually separable. The processes $X_t - X_0$, $Y_t - Y_0$ and $Z_t - Z_0$ are obviously independent with respect to the probability measure Q. However, the situation is typically more complex with respect to the measure P, since the jump intensities $\lambda_t^1, \ldots, \lambda_t^n$ could depend on all the information in $\mathcal{F}_{t-}$. We therefore introduce the following concept.

Definition 1. *Let $\mathcal{F}_t^{X,Y,Z}$ denote the filtration generated by N^X, N^Y, N^Z and let $\mathcal{F}_t^{X,Z}$ denote the filtration generated by N^X and N^Z. We say that X is locally independent of Y, given Z, if there exists an $\mathcal{F}_t^{X,Z}$-predictable process μ such that*

$$N_t^X - \int_0^t \mu_s \, \mathrm{d}s$$

defines a local P-martingale with respect to $\mathcal{F}_t^{X,Y,Z}$. If this is the case, then we write:

$$Y \nrightarrow X | Z.$$

2.6. Independent censoring

Local independence generalizes a much-used concept in event history analysis, that is, *independent censoring*. Suppose we can follow a group of individuals in a clinical trial. We would like to compute the probability for an individual to survive longer than time t. However, an individual might be censored at some time before the event due to the end of the study or a "drop-out". Inference is much simpler if the censoring does not influence the instantaneous risk of the event. Therefore, it is common to assume independent censoring. This means that an individual at risk has the same instantaneous risk of an event as he would in the situation without censoring. More formally, this means that if T_D is the time of the event and T_C is the time of censoring, then the compensator of the process $D_t := I(t \geq T_D)$ with respect to the joint event and censoring history only depends on the event history. This is essentially the same as saying that D is locally independent of the process defined by $C_t := I(t \geq T_C)$.

2.7. Local independence before a stopping time

Sometimes we may not be interested in dependencies that are considered trivial. This could be dependencies due to an absorbing state (e.g., death). We will see that we can rule out such trivial dependencies if we consider local independence before a stopping time τ.

Definition 2. *Let τ be an $\mathcal{F}_t$-adapted stopping time. We say that X is locally independent of Y before τ and given Z if there exists an $\{\mathcal{F}_t^{X,Z}\}_t$-predictable process μ such that*

$$N^X_{t\wedge\tau} - \int_0^{t\wedge\tau} \mu_s \, \mathrm{d}s$$

defines a local P-martingale with respect to $\{\mathcal{F}_t^{X,Y,Z}\}_t$. If this is the case, then we write:

$$Y \nrightarrow_\tau X|Z.$$

If we let τ denote the time of the first jump of N^Y then it is not very hard to see, using the explicit representation of $\mathcal{F}_t^{X,Y,Z}$-predictable processes in [5], Theorem A.2, that for every $\mathcal{F}_t$-predictable process γ there exists an $\mathcal{F}_t^{X,Z}$-predictable process $\tilde{\gamma}$ such that $\gamma_S \cdot I(S \leq \tau) = \tilde{\gamma}_S \cdot I(S \leq \tau)$ P-a.s. for every $\mathcal{F}_t$-adapted stopping time S. This means that $Y \nrightarrow_\tau X|Z$; that is, stopping at the first jump of N^Y rules out every local dependence of Y.

2.8. Local independence graphs

Didelez also considered graphical models based on local independence; see [6]. These graphs will prove to be very useful in order to represent complex models.

Definition 3. *We say that a directed graph $G = (E, V)$ is a local independence graph if the vertexes correspond to observable processes that are mutually separable and such that*

$$(X, Y) \notin E \quad \Longrightarrow \quad X \nrightarrow_\tau Y|V \setminus \{X, Y\}.$$

Several examples of such graphs will appear below.

3. Models of clinical trials

3.1. A patient model

We will now describe a model of a single patient that participates in a clinical study. We suppose that N is of the form $(N^A, N^C, N^D, N^L)'$, where N^A, N^C, N^D are univariate counting processes and N^L is a multivariate counting process. These counting processes count various events that are important for the development of the disease.

3.1.1. *The event process*

We let $T_D = \inf\{t > 0 \mid N_t^D = 1\}$ and let

$$D_t := \int_0^t I(s \leq T_D)\, \mathrm{d}N_s^D$$

be the *event process*. It jumps from 0 to 1 at the time the event occurs. The event could be death or the progression to AIDS for an HIV patient.

3.1.2. *Measurements of the underlying biological process*

The state of an underlying biological process reflecting the patient's health condition at time t is given by

$$L_t := L_0 + \int_0^t H_s^L\, \mathrm{d}N_s^L,$$

where L_0 is a bounded $\mathcal{F}_0$-measurable random vector and H^L is a matrix-valued, bounded and $\mathcal{F}_t^L$-predictable process. The process L could be measurements of various blood values.

3.1.3. *Right censoring*

We assume that the patient can be right censored, that is, we will not be able to observe the patient after some stopping time T_C. This can happen because the study ends, but it can also be a "drop-out" due to poor health or recovery. We assume that $T_C := \inf\{s > 0 \mid N_s^C \neq 0\}$ and define the censoring process

$$C_t := \int_0^t I(s \leq T_C)\, \mathrm{d}N_s^C.$$

3.1.4. *The treatment process*

One can switch between two treatments of the patient at the stopping time T_A. This could typically be to initiate treatment for a patient at risk. We let $T_A := \inf\{s > 0 \mid N_s^A \neq 0\}$ and define the treatment process

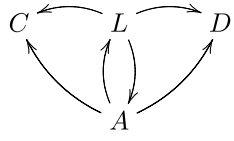
$$A_t := \int_0^t I(s \leq T_A)\, \mathrm{d}N_s^A.$$

This means that the patient will not initially be in treatment. This somewhat limiting assumption can be dropped, but then the considerations around the hypothetical randomized trial at baseline will be much more involved.

3.2. Local independences with respect to the observational measure

The process D influences the other processes. However, we consider these dependencies as trivial. We will consider local independence before T_D, because then we will automatically have that $D \nrightarrow_{T_D} A|C \cup L$, $D \nrightarrow_{T_D} C|A \cup L$ and $D \nrightarrow_{T_D} L|A \cup C$.

We also assume that the censoring does not carry any information about the short term behavior of the other process that we would not obtain if we left C out of the analysis. In terms of local independence this means that $C \nrightarrow_{T_D} A|D \cup L$, $C \nrightarrow_{T_D} D|A \cup L$ and $C \nrightarrow_{T_D} L|A \cup D$. We summarize these local independencies in the following local independence graph:



(3.1)

3.3. Randomized trial measures

Our ultimate goal is to provide estimates of the causal effect of a particular treatment based on observations of patients in an observational study.

Hypothetically, one could carry out some randomized trial where the given treatment did not depend on the previous health condition of the patient. If we had observations from such a trial, we could easily provide simple estimators for the causal treatment effect that would not require information about the underlying biological mechanisms. This is, however, not the case for us. So, based on observations from the observational study, we will try to simulate a counterfactual or hypothetical randomized trial. We assume that we have measurements of all the relevant processes and variables. Especially, we assume that the process L is complete in the sense that it gives rise to every event that affects both the short-term behavior of the treatment and the event, both the censoring and the event or both the censoring and the treatment, given the full covariate history. This assumption means that all the confounder processes are measured and is usually referred to as *no unmeasured confounders*.

In order to provide causal interpretation of simple estimators, we should at least require the hypothetical trial to satisfy the following:

(1) Both the underlying biological process and the event process should dynamically behave in the same way in the counterfactual trial and the observational study, given the full covariate history.
(2) One should not allow drop-out due to poor health or recovery, that is, the censoring should not be directly affected by the underlying health process, given the event and treatment history.
(3) Since we consider time-dependent treatments, we have to generalize the notion of a randomized trial slightly. In our counterfactual trial, the patient's previous health condition or censoring should not be relevant for the short-term behavior of the treatment process. Heuristically, this means that the randomization should act locally in time.

The counterfactual trial corresponds to a probability measure $\tilde{P}$ on the space $(\Omega, \mathcal{F})$. We will refer to such a measure as a *randomized trial measure*. It carries the frequencies of the potential observations in the counterfactual randomized trial. The above requirements can now be translated into the following:

(1) The process M^i is a local $\tilde{P}$-martingale with respect to the filtration $\{\mathcal{F}_t\}_t$ for every $i \in D \cup L$. This means that both the processes N^L and N^D have the same intensity with respect to the randomized trial measure $\tilde{P}$ as with respect to the observational measure P. Moreover, we assume that the observational measure and the randomized trial measure coincide at baseline, that is,

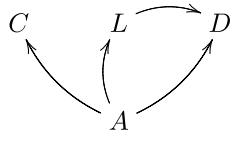
$$E_P[H] = E_{\tilde{P}}[H]$$

for every bounded $\mathcal{F}_0$-measurable random variable H.

(2) The censoring should be locally independent of the underlying health process L with respect to $\tilde{P}$, given the event and treatment history.

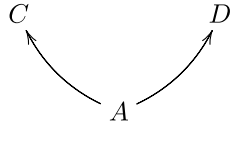
(3) The treatment process should be locally independent of the underlying health process L and censoring C with respect to $\tilde{P}$, given the event history.

We summarize the local independence structure with respect to the randomized trial measure $\tilde{P}$ in the following local independence graph:



A construction of reasonable randomized trials is given in Theorem 2. Before we come to that, we will consider censoring in the counterfactual trial. In order to estimate the total treatment effect, we will consider a marginal model where L is unobserved. One natural choice of effect measure in the hypothetical experiment could be the hazard of the event process with respect to the filtration $\{\mathcal{F}_t^{A,D}\}_t$. In order to estimate the hazard with respect to this filtration, we could try to estimate the hazard of the event before censoring with respect to the filtration $\{\mathcal{F}_t^{A,C,D}\}_t$. If, in addition, the event process was locally independent of the censoring, given the treatment process, then these hazards would coincide before censoring; that is, we would have independent censoring. This would imply that the censoring would not cause bias in the sense that if we did not pay attention to the underlying biological process, then the hazard of the event would not depend on whether the patient had been censored or not. We will see in the next theorem that this is the case for the randomized trial measures.

Theorem 1. *If P is a randomized trial measure then we have $C \nrightarrow_{T_D} A \cup D$, that is, we have independent censoring in the marginalized model without L. This gives the following local independence graph*:



Proof. The likelihood ratio process

$$S_t := \frac{\mathrm{d}P|_{\mathcal{F}_t}}{\mathrm{d}Q|_{\mathcal{F}_t}}$$

is a Q-martingale with respect to $\mathcal{F}_t$. This is shown in [11], Theorem III 3.4. The n-dimensional Poisson process N has the martingale representation property with respect to the filtration; see [11], Theorem III 4.37, so there exist predictable processes $u^1, \ldots, u^n$ such that:

$$S_t = 1 + \sum_{i=1}^{n} \int_0^t u_s^i \, \mathrm{d}\overline{N}_s^i,$$

where $\overline{N}_s^i := N_s^i - s$.

Now, let

$$\mu_s^i := I(S_{s-} > 0)\left(\frac{u_s^i}{S_{s-}} + 1\right)$$

and note that

$$1 + \sum_{i=1}^{n} \int_0^t S_{s-}(\mu_s^i - 1) \, \mathrm{d}\overline{N}_s^i = 1 + \int_0^t I(S_{s-} > 0) \, \mathrm{d}S_s = S_t, \qquad Q\text{-a.s.} \tag{3.2}$$

The last equality follows from [11], Lemma III 3.6.

Let $M_t^{(i)} := N_t^i - \int_0^t \mu_s^i \, \mathrm{d}s$ and note that since $\Delta\overline{N}_s^i$ is bounded, [11], Lemma III 3.14, says that the quadratic (co)variation process $[\overline{N}^i, S]$ has locally integrable variation, so its compensator $\langle \overline{N}^i, S \rangle$ is well defined. We can compute that

$$\langle \overline{N}^i, S \rangle_t = \int_0^t S_{s-}(\mu_s^i - 1) \, \mathrm{d}\langle \overline{N}^i, \overline{N}^i \rangle_s = \int_0^t S_{s-}(\mu_s^i - 1) \, \mathrm{d}s,$$

so we get from Girsanov's theorem (see [11], Lemma III 3.14) that

$$\overline{N}_t^i - \int_0^t \frac{1}{S_{s-}} \, \mathrm{d}\langle \overline{N}^i, S \rangle_s = \overline{N}_t^i - \int_0^t (\mu_s^i - 1) \, \mathrm{d}s = M_t^{(i)}$$

is a local P-martingale with respect to $\{\mathcal{F}_t\}_t$ for every $i \leq n$.

Now

$$M_t^{(i)} - M_t^i = \int_0^t \lambda_s - \mu_s^i \, \mathrm{d}s$$

defines a continuous finite variation P-martingale, so $\mu^i = \lambda^i$ P-a.s. a.e. and $S = \mathcal{E}(K)$, where $K_t := \sum_{i=1}^n \int_0^t (\lambda_s^i - 1) \, \mathrm{d}\overline{N}_s^i$ and $\mathcal{E}$ is the stochastic exponential. Let $K_t^C := \int_0^t (\lambda_s^C - 1) \, \mathrm{d}\overline{N}_s^C$ and $K_t^L := K_t^C - K_t$. Since $[K^L, K^C] = 0$ Q-a.s., we have that:

$$\mathcal{E}(K) = \mathcal{E}(K^C + K^L) = \mathcal{E}(K^C + K^L + [K^C, K^L]) = \mathcal{E}(K^C)\mathcal{E}(K^L). \tag{3.3}$$

The last equality follows from [14], Theorem II 38.

We now consider filtrations corresponding to the σ-algebras: $\mathcal{G}_t := \mathcal{F}^{A,D}_{t\wedge T_D}$, $\mathcal{G}^C_t := \mathcal{F}^{A,C,D}_{t\wedge T_D}$, $\mathcal{G}^L_t := \mathcal{F}^{A,D,L}_{t\wedge T_D}$ and $\mathcal{G}^{C,L}_t := \mathcal{F}_{t\wedge T_D}$. Moreover, we let $\tilde{\lambda}^D$ denote the $\mathcal{G}_t$-predictable projection of λ^D; see [11], Theorem I 2.28. It is the unique $\mathcal{G}_t$-predictable process such that

$$E[\lambda^D_S|\mathcal{G}_{S-}] = \tilde{\lambda}^D_S$$

for every $\mathcal{G}_t$-predictable stopping time S.

The local independence relations:

(1) $L \nrightarrow_{T_D} C|A \cup C$;
(2) $C \nrightarrow_{T_D} L|A \cup D$;
(3) $C \nrightarrow_{T_D} A|L \cup D$;
(4) $C \nrightarrow_{T_D} D|A \cup L$

and (3.3) provide a factorization

$$\frac{\mathrm{d}P|_{\mathcal{G}^{C,L}_{t-}}}{\mathrm{d}Q|_{\mathcal{G}^{C,L}_{t-}}} = S^L_t \cdot S^C_t,$$

where S^L is $\mathcal{G}^L_t$-predictable and S^C is $\mathcal{G}^C_t$-predictable. Bayes' theorem now gives that, whenever F is $\mathcal{G}^L_{t-}$-measurable and bounded, then

$$E[F|\mathcal{G}_{t-}] = E[F|\mathcal{G}^C_{t-}] \tag{3.4}$$

P-a.s. Therefore, if we let F be bounded and $\mathcal{G}^C_t$-predictable, then we can compute:

$$\begin{aligned} E\left[\int_0^T F_s\tilde{\lambda}^D_s\,\mathrm{d}s\right] &= \int_0^T E[F_s\tilde{\lambda}^D_s]\,\mathrm{d}s = \int_0^T E[F_s E[\lambda^D_s|\mathcal{G}_{s-}]]\,\mathrm{d}s \\ &= \int_0^T E[F_s E[\lambda^D_s|\mathcal{G}^C_{s-}]]\,\mathrm{d}s = \int_0^T E[E[F_s\lambda^D_s|\mathcal{G}^C_{s-}]]\,\mathrm{d}s \\ &= E\left[\int_0^T F_s\lambda^D_s\,\mathrm{d}s\right]. \end{aligned}$$

If we let $\tilde{M}^D_t = D_t - \int_0^t \tilde{\lambda}^D_s\,\mathrm{d}s$ and $M^D_t = D_t - \int_0^t \lambda^D_s\,\mathrm{d}s$, then we can compute:

$$\begin{aligned} E\left[\int_0^T F_s\,\mathrm{d}\tilde{M}^D_s\right] &= E\left[\int_0^T F_s\,\mathrm{d}D_s\right] - E\left[\int_0^T F_s\tilde{\lambda}^D_S\,\mathrm{d}s\right] \\ &= E\left[\int_0^T F_s\,\mathrm{d}D_s\right] - E\left[\int_0^T F_s\lambda^D_S\,\mathrm{d}s\right] \\ &= E\left[\int_0^T F_s\,\mathrm{d}M^D_s\right] = 0, \end{aligned}$$

so $\tilde{M}^D$ is a P-martingale with respect to the filtration $\mathcal{G}_t^C$. Now, since $\mathcal{G}_t \subset \mathcal{G}_t^L$, we have that $\tilde{\lambda}^D$ is $\mathcal{G}_t^L$-predictable:

$$\begin{aligned}\tilde{M}_t^D &= E[\tilde{M}_{T_D}^D|\mathcal{G}_t^C] = E[\tilde{M}_{T_D}^D I(T<t) + \tilde{M}_{T_D}^D I(T\geq t)|\mathcal{G}_t^C] \\ &= \tilde{M}_{T_D}^D I(T<t) + E[\tilde{M}_{T_D}^D I(T\geq t)|\mathcal{G}_t^C] \\ &= \tilde{M}_{T_D}^D I(T<t) + E[\tilde{M}_{T_D}^D|\mathcal{F}_t^{A,C,D}]I(T\geq t) \\ &= E[\tilde{M}_{T_D}^D|\mathcal{F}_t^{A,C,D}],\end{aligned}$$

that is, $\tilde{M}^D$ is a P-martingale with respect to the filtration $\{\mathcal{F}_t^{A,C,D}\}_t$.

Finally, we note that

$$N_{t\wedge T_D}^A - \int_0^t \lambda_s^A I(s\leq T_D)\,\mathrm{d}s \tag{3.5}$$

defines a P-martingale with respect to $\mathcal{F}_t$. Since λ_s^A is $\mathcal{F}_t^{A,D}$-predictable, we also see that (3.5) defines a martingale with respect to $\{\mathcal{F}_t^{A,C,D}\}_t$. □

4. Existence of randomized trial measures

We have now come to the construction of randomized trial measures. The idea is to construct a reasonable randomized trial measure $\tilde{P}$ from the observational measure P such that $\tilde{P} \ll P$. The absolute continuity is important since this provides a natural method for simulating the empirical expectation of random variables as if the data was sampled from the counterfactual trial, while actually using P-distributed samples. To get an idea of how this is done, let $J \in \mathbb{N}$, let H be a bounded random variable and let $\omega_1, \ldots, \omega_J$ be J independently P-distributed samples from Ω. The law of large numbers then yields:

$$\lim_{J\to\infty} \frac{1}{J}\sum_{j=1}^{J} \frac{\mathrm{d}\tilde{P}}{\mathrm{d}P}(\omega_j)H(\omega_j) = E_P\left[\frac{\mathrm{d}\tilde{P}}{\mathrm{d}P}H\right] = E_{\tilde{P}}[H], \qquad P\text{-a.s.}$$

Heuristically, this means that the likelihood ratio can be viewed as a transformation from the observational study into the counterfactual scenario.

There might exist several reasonable counterfactual trials, each corresponding to a choice of a well-behaved treatment and censoring strategies. Given a non-negative $\mathcal{F}_t^{A,D}$-predictable process $\tilde{\lambda}^A$ and a non-negative $\mathcal{F}_t^{A,C,D}$-predictable process $\tilde{\lambda}^C$, we can consider the problem of finding a randomized trial measure $\tilde{P}$ that has $\tilde{\lambda}^A$ as the $\mathcal{F}_t$-intensity of N^A and $\tilde{\lambda}^C$ as the $\mathcal{F}_t$-intensity of N^C. This suggests that $\tilde{\lambda}^A$ is the treatment strategy and $\tilde{\lambda}^C$ is the censoring strategy in the counterfactual trial. We will consider the counterfactual treatment strategy given by the P-intensity of N^A with respect to $\mathcal{F}_t^{A,D}$. The counterfactual censoring strategy will be given by the P-intensity of N^C with respect to $\mathcal{F}_t^{A,D,C}$. This gives a randomized trial measure

with a likelihood ratio that heuristically corresponds to the *stabilized weights* one usually considers in the discrete time marginal structural models; see [15]. The problem of finding such a randomized trial measure is a martingale problem. Note that this problem might not have a solution. The next theorem shows that if the counterfactual strategies are not too different from the observed intensities, then there exists a unique corresponding randomized trial measure $\tilde{P}$.

Theorem 2. *Suppose that there exist positive numbers θ_1 and θ_2 such that*:

$$\lambda_s^A - \theta_1\sqrt{\lambda_s^A} \le E_P[\lambda_s^A | \mathcal{F}_{s-}^{A,D}] \le \lambda_s^A + \theta_1\sqrt{\lambda_s^A} \tag{4.1}$$

and

$$\lambda_s^C - \theta_2\sqrt{\lambda_s^C} \le E_P[\lambda_s^C | \mathcal{F}_{s-}^{A,C,D}] \le \lambda_s^C + \theta_2\sqrt{\lambda_s^C} \tag{4.2}$$

for almost every s P-a.s. Let $\tilde{\lambda}^A$ denote the P-intensity of N^A with respect to the filtration $\{\mathcal{F}_t^{A,D}\}_t$ and let $\tilde{\lambda}^C$ denote the P-intensity of N^C with respect to the filtration $\{\mathcal{F}_t^{A,C,D}\}_t$.

The equation

$$\begin{aligned} R_t := &\prod_{s\le t}\left(\frac{\tilde{\lambda}_s^A}{\lambda_s^A}\right)^{\Delta N_s^A} \exp\left(\int_0^t \tilde{\lambda}_s^A - \lambda_s^A \,\mathrm{d}s\right) \\ &\times \prod_{s\le t}\left(\frac{\tilde{\lambda}_s^C}{\lambda_s^C}\right)^{\Delta N_s^C} \exp\left(\int_0^t \tilde{\lambda}_s^C - \lambda_s^C \,\mathrm{d}s\right) \end{aligned} \tag{4.3}$$

defines a square-integrable P-martingale with respect to the filtration $\{\mathcal{F}_t\}_t$. Moreover,

$$\mathrm{d}\tilde{P} = R_T \,\mathrm{d}P$$

defines a randomized trial measure on $(\Omega, \mathcal{F})$ such that the martingale dynamics of the biological processes D and L coincide for the two probability measures $\tilde{P}$ and P, that is,

$$L_t - \int_0^t H_s^L \lambda_s^L \,\mathrm{d}s \quad \textit{and} \quad D_t - \int_0^t \lambda_s^D I(s \le T_D)\,\mathrm{d}s$$

also define $\tilde{P}$-martingales with respect to $\{\mathcal{F}_t\}_t$.

Proof. We define

$$K_t := \int_0^t \left(\left(\frac{\tilde{\lambda}_s^A}{\lambda_s^A} - 1\right)\mathrm{d}M_s^A + \int_0^t \left(\frac{\tilde{\lambda}_s^C}{\lambda_s^C} - 1\right)\right)\mathrm{d}M_s^C.$$

By the innovation theorem, we have that

$$\tilde{\lambda}_s^A = E_P[\lambda_s^A | \mathcal{F}_{s-}^{A,D}] \quad \text{and} \quad \tilde{\lambda}_s^C = E_P[\lambda_s^C | \mathcal{F}_{s-}^{A,C,D}] \qquad P\text{-a.s., } s\text{-a.e.} \tag{4.4}$$

By (4.1) and (4.2) we have that

$$\left(\frac{\tilde{\lambda}_s^A}{\lambda_s^A} - 1\right)^2 \lambda_s^A + \left(\frac{\tilde{\lambda}_s^C}{\lambda_s^C} - 1\right)^2 \lambda_s^C \leq \theta_1 + \theta_2, \qquad P\text{-a.s., } s\text{-a.e.}$$

We therefore obtain that:

$$\langle K, K\rangle_t = \int_0^t \left(\left(\frac{\tilde{\lambda}_s^A}{\lambda_s^A} - 1\right)^2 \lambda_s^A + \left(\frac{\tilde{\lambda}_s^C}{\lambda_s^C} - 1\right)^2 \lambda_s^C\right) \mathrm{d}s \leq (\theta_1 + \theta_2) \cdot t.$$

Since $\langle K, K\rangle$ is bounded on the interval $[0, T]$, [12], Theorem II.1, yields that the stochastic exponential $R := \mathcal{E}(K)$, given by the SDE:

$$R_t = 1 + \int_0^t R_{s-}\, \mathrm{d}K_s \tag{4.5}$$

is square-integrable.

Now

$$\tilde{\mathrm{d}}P = R_T\, \mathrm{d}P$$

defines a probability measure $\tilde{P}$ on $(\Omega, \mathcal{F})$.

Note that we have:

$$M^D - \int_0^{\cdot} \frac{1}{R_{s-}}\, \mathrm{d}\langle M^D, R\rangle_s = M^D \quad \text{and} \quad M^l - \int_0^{\cdot} \frac{1}{R_{s-}}\, \mathrm{d}\langle M^l, R\rangle_s = M^l$$

P-a.s. for every $l \in L$. Moreover, Girsanov's theorem (see [11], Lemma III 3.14) gives that these processes define local $\tilde{P}$-martingales with respect to the filtration $\{\mathcal{F}_t\}_t$.

Moreover,

$$\langle M^A, R\rangle_t = \int_0^t R_{s-}\left(\frac{\tilde{\lambda}_s^A}{\lambda_s^A} - 1\right) \mathrm{d}\langle M^A, M^A\rangle_s = \int_0^t R_{s-}(\tilde{\lambda}_s^A - \lambda_s^A)\, \mathrm{d}s,$$

so again by Girsanov's theorem, we have that

$$M_t^A - \int_0^t \frac{1}{R_{s-}}\, \mathrm{d}\langle M^A, R\rangle_s = M_t^A - \int_0^t \tilde{\lambda}_s^A - \lambda_s^A\, \mathrm{d}s = N_t^A - \int_0^1 \tilde{\lambda}_s^A\, \mathrm{d}s$$

defines a $\tilde{P}$-martingale with respect to the filtration $\{\mathcal{F}_t\}_t$. Analogously, we have that

$$M_t^D - \int_0^t \frac{1}{R_{s-}}\, \mathrm{d}\langle M^D, R\rangle_s = N_t^D - \int_0^t \tilde{\lambda}_s^D\, \mathrm{d}s$$

defines a local $\tilde{P}$-martingale with respect to the filtration $\{\mathcal{F}_t\}_t$.

Finally, we note that by [11], Theorem I 4.60, the SDE (4.5) has the explicit solution given by (4.3). Expressions of this form are well known in the literature on marked point process; see, for instance, [10]. □

Remark 1. Note that the condition (4.1) heuristically means that the short-term "risk" of starting treatment, given the previous full history,

$$\lim_{h\to 0} h^{-1} P(t \leq T_A < t+h | \mathcal{F}_t),$$

is not too different from the short-term "risk" of starting treatment when we do not pay attention to the underlying health process or censoring, that is,

$$\lim_{h\to 0} h^{-1} P(t \leq T_A < t+h | \mathcal{F}_t^{A,D}).$$

Similarly, condition (4.2) heuristically means that the short-term "risk" of being censored, given the previous full history, is not too different from the short-term "risk" of being censored when we do not pay attention to the underlying health process. In words, this means that the previous history of the health process L alone can not at any time yield too high of a short-term "risk" of starting treatment or being censored.

5. Weighted additive hazard regression

Suppose that we have observations of m independent individuals until death or censoring from an observational study and want to estimate the total effect of treatment. Ideally, we would like to base our estimate on some randomized trial. However, such a trial might not be available. The marginal structural approach now suggests that we simulate a counterfactual randomized trial, using the data we already have. We would then like to estimate the counterfactual hazard, that is, the hazard that the patient would have if he, contrary to the fact, had participated in the randomized trial. In this way we could compare the total effect of being in treatment versus never being in treatment.

We assume that the observations from each individual are P-distributed. The observations of the patient would have been $\tilde{P}$-distributed if he, contrary to the fact, participated in the hypothetical randomized trial.

We assume that the counterfactual intensity follows Allen's additive hazard regression model, see [1,2]. To formalize this, let β^0 and β^1 be functions on $[0, T]$. We assume that we only have instantaneous effect and that the hazard for the event, with respect to the treatment and event history, is given by:

$$\beta_t^0 + \beta_t^1 A_{t-}.$$

One way to estimate the hazard from the counterfactual trial is to weight the observations by the corresponding likelihood ratios. We will prove that a suitable weighted variant of Aalen's additive hazard regression gives consistent estimators of $\int_0^t \beta_s^0 \, \mathrm{d}s$ and $\int_0^t \beta_s^1 \, \mathrm{d}s$ from independent

P-distributed observations. This requires some notation. Let $Y_s^1, \dots, Y_s^m$ be the "at-risk" indicators and $A_t^1, \dots, A_t^m$ be the "at-treatment" indicators for the m independent individuals. We define the $m \times 2$-matrix:

$$X_t^{(m)} = \begin{pmatrix} Y_t^1 & Y_t^1 \cdot A_{t-}^1 \\ \vdots & \vdots \\ Y_t^m & Y_t^m \cdot A_{t-}^m \end{pmatrix}.$$

Moreover, let $R_t^1, \dots, R_t^m$ be the individual likelihood ratios at time t and let

$$R_{t-}^{(m)} = \begin{pmatrix} Y_t^1 R_{t-}^1 & 0 & \dots & 0 \\ 0 & Y_t^2 R_{t-}^2 & & \vdots \\ \vdots & & \ddots & 0 \\ 0 & 0 & \dots & Y_t^m R_{t-}^m \end{pmatrix}.$$

Finally, let $D_t^1, \dots, D_t^m$ be event processes for the m individuals before t. The observed events are now given by the vector

$$D_t^{(m)} = \begin{pmatrix} \int_0^t Y_s^1 \, \mathrm{d}D_s^1 \\ \vdots \\ \int_0^t Y_s^m \, \mathrm{d}D_s^m \end{pmatrix}.$$

Theorem 3. *We assume that*:

(1) *The P-intensity of D with respect to the filtration $\mathcal{F}_t$, λ^D is dominated by an integrable function G.*

(2) (*Positivity*) *Both the "at-risk" groups in the counterfactual trial are always present, that is,*

$$E_{\tilde{P}}[Y_s A_{s-}] > 0 \quad \textit{and} \quad E_{\tilde{P}}[Y_s(1 - A_{s-})] > 0$$

for every $s \in [0, T]$.

(3) *There exist integrable and left-continuous functions with right limits β^0 and β^1 such that $\beta = (\beta^0, \beta^1)^{\mathrm{T}}$ and such that*

$$D_t^{(m)} - \int_0^t X_s^{(m)} \beta_s \, \mathrm{d}s$$

is a $\tilde{P}$-martingale with respect to the filtration $\mathcal{F}_t^{A,C,D}$, i.e., $Y_t(\beta_t^0 + \beta_t^1 A_{t-}^1)$ is the $\tilde{P}$-intensity of D w.r.t. the filtration $\mathcal{F}_t^{A,C,D}$.

We let

$$J_s^{(m)} := I\left(\sum_{i=1}^m R_{t-}^i Y_t^i (1 - A_{t-}^i) > 0 \text{ and } \sum_{i=1}^m R_{t-}^i Y_t^i A_{t-}^i > 0\right),$$

$$\hat{B}_t^{(m)} := \int_0^t J_s^{(m)} \left(X_s^{(m)\mathrm{T}} R_{s-}^{(m)} X_s^{(m)}\right)^{-1} X_s^{(m)\mathrm{T}} R_{s-}^{(m)} \,\mathrm{d}D_s^{(m)}$$

and

$$B_t := \int_0^t \beta_s \,\mathrm{d}s.$$

Now $\hat{B}^{(m)}$ is a consistent estimator of B_t in the sense that:

$$\lim_m P\left(d\left(\hat{B}^{(m)}, B\right) \geq \epsilon\right) = 0$$

for every $\epsilon > 0$, where d denotes the Skorokhod metric; *see* [11] *or* [4].

Proof. We define:

$$Y_t^{(m)} = \begin{pmatrix} Y_t^1 \\ \vdots \\ Y_t^m \end{pmatrix}, \qquad \lambda_t^{(m)} = \begin{pmatrix} \lambda_t^1 \\ \vdots \\ \lambda_t^m \end{pmatrix} \quad \text{and} \quad M_t^{(m)} = \begin{pmatrix} D_t^1 - \int_0^t \lambda_s^1 \,\mathrm{d}s \\ \vdots \\ D_t^m - \int_0^t \lambda_s^m \,\mathrm{d}s \end{pmatrix}.$$

We will often drop the index (m) in order to simplify the notation. Another simplification of the notation we will use is $E[\cdot]$ for the expectation with respect to P and $\tilde{E}[\cdot]$ for the expectation with respect to $\tilde{P}$.

First we prove that

$$\lim_m P\left(\sup_{t \leq T} \left| \int_0^t J_s (X_s^{\mathrm{T}} R_{s-} X_s)^{-1} X_s^{\mathrm{T}} R_{s-} \lambda_s \,\mathrm{d}s - B_t \right| \geq \epsilon\right) = 0 \tag{5.1}$$

for every $\epsilon > 0$. Define:

$$V := \begin{pmatrix} 1 & 0 \\ -1 & 1 \end{pmatrix} \quad \text{and} \quad S_t := \begin{pmatrix} \sum_{i=1}^m R_{t-}^i Y_t^i (1 - A_{t-}^i) & 0 \\ 0 & \sum_{i=1}^m R_{t-}^i Y_t^i A_t^i \end{pmatrix}.$$

The matrix V is invertible and, using the fact that the Y^i and the A^i are indicators, we have:

$$V^{\mathrm{T}} X_t^{\mathrm{T}} R_{t-} X_t V = S_t,$$

that is, $X_t^{\mathrm{T}} R_{t-} X_t$ is congruent to the diagonal matrix S_t. A simple matrix computation gives that

$$(X_t^{\mathrm{T}} R_{t-} X_t)^{-1} = V S_t^{-1} V^{\mathrm{T}},$$

when $J_s > 0$.

Now, we see that:

$$J_t (X_t^{\mathrm{T}} R_{t-} X_t)^{-1} X_t^{\mathrm{T}} R_{t-} \lambda_t = J_t V (H)_t^0 H_t^1,$$

where

$$H_t^0 = \frac{\sum_{i=1}^m R_{t-}^i Y_t^i (1 - A_{t-}^i) \lambda_t^i}{\sum_{i=1}^m R_{t-}^i Y_t^i (1 - A_{t-}^i)} \quad \text{and} \quad H_t^1 = \frac{\sum_{i=1}^m R_{t-}^i Y_t^i A_{t-}^i \lambda_t^i}{\sum_{i=1}^m R_{t-}^i Y_t^i A_{t-}^i}.$$

Since $\tilde{E}[Y_t A_{t-}] > 0$, the law of large numbers implies that H_t^0 converges in probability to

$$\frac{\tilde{E}[Y_t (1 - A_{t-}) \lambda_t^D]}{\tilde{E}[Y_t (1 - A_{t-})]} = \tilde{E}[\lambda_t^D | Y_t (1 - A_{t-}) = 1].$$

Analogously, since $E[Y_t (1 - A_{t-})] > 0$, we have that H_t^1 converges in probability to

$$\frac{\tilde{E}[Y_t A_{t-} \lambda_t^D]}{\tilde{E}[Y_t A_{t-}]} = \tilde{E}[\lambda_t^D | Y_t A_{t-1} = 1].$$

By a similar argument, we see that $\{J_s^{(m)}\}$ converges in probability to 1 for almost every s.

Since the P-intensity of D with respect to $\mathcal{F}_s^{A,C,D}$ coincides with $E[\lambda_s^D | \mathcal{F}_{s-}^{A,C,D}]$ P-a.s. for almost every s, we have that:

$$\tilde{E}[\lambda_D | Y_t (1 - A_{t-}) = 1] = \beta_t^0 \quad \text{and} \quad \tilde{E}[\lambda_t^D | Y_t A_{t-} = 1] = \beta_t^0 + \beta_t^1.$$

This means that

$$J_s (X_t^{\mathrm{T}} R_{t-} X_t)^{-1} X_t^{\mathrm{T}} R_{t-} \lambda_t \tag{5.2}$$

converges in probability to β_t when m increases. Note that

$$E\left[\sup_t \left| \int_0^t J_s V \begin{pmatrix} H_s^0 \\ H_s^1 \end{pmatrix} \mathrm{d}s - \int_0^t \beta_s \, \mathrm{d}s \right| \right] \le \int_0^T E\left[\left| J_s V \begin{pmatrix} H_s^0 \\ H_s^1 \end{pmatrix} - \beta_s \right| \right] \mathrm{d}s,$$

so by the dominated convergence theorem, we obtain (5.1).

We will now prove that

$$\begin{aligned} Z_t &:= \hat{B}_t - \int_0^t J_s (X_s^{\mathrm{T}} R_{s-} X_s)^{-1} X_s^{\mathrm{T}} R_{s-} \lambda_s \, \mathrm{d}s \\ &= \int_0^t (X_s^{\mathrm{T}} R_{s-} X_s)^{-1} X_s^{\mathrm{T}} R_{s-} \, \mathrm{d}M_s \end{aligned}$$

converges weakly to 0. Note that:

$$\begin{aligned}\langle Z, Z\rangle_t &= \int_0^t J_s (X_s^{\mathrm{T}} R_{s-} X_s)^{-1} X_s^{\mathrm{T}} R_{s-}\, \mathrm{d}\langle M, M\rangle_s R_{s-} X_s (X_s^{\mathrm{T}} R_{s-} X_s)^{-1} \\ &= \int_0^t J_s V S_s^{-1} V^{\mathrm{T}} X_s^{\mathrm{T}} R_{s-}\, \mathrm{d}\langle M, M\rangle_s R_{s-} X_s V S_s^{-1} V^{\mathrm{T}} \\ &= V \int_0^t J_s S_s^{-2} U_s\, \mathrm{d}s\, V^{\mathrm{T}},\end{aligned}$$

where

$$U_s = \begin{pmatrix} \sum_{i=1}^m R_{s-}^{i2} Y_s^i (1 - A_{s-}^i)\lambda_s^i & 0 \\ 0 & \sum_{i=1}^n R_{s-}^{i2} Y_s^i A_{s-}^i \lambda_s^i \end{pmatrix}.$$

Now,

$$E\left[\sup_t \left| \int_0^t V J_s S_s^{-2} U_s V^{\mathrm{T}}\, \mathrm{d}s \right| \right] \le \int_0^T E[|V J_s S_s^{-2} U_s V^{\mathrm{T}}|]\, \mathrm{d}s,$$

so, by the dominated convergence theorem, $\{\langle Z^{(m)}, Z^{(m)}\rangle\}$ converges uniformly in probability to 0.

We define

$$Z_t^{(\epsilon,m)} := \int_0^t I\big(|J_s (X_s^{\mathrm{T}} R_{s-} X_s)^{-1} X^{\mathrm{T}} R_{s-} Y_s| \ge \epsilon\big) J_s (X_s^{\mathrm{T}} R_{s-} X_s)^{-1} X^{\mathrm{T}} R_{s-}\, \mathrm{d}M_s$$

and see that

$$0 \le \big\langle Z^{(\epsilon,m)}, Z^{(\epsilon,m)}\big\rangle_t \le \big\langle Z^{(m)}, Z^{(m)}\big\rangle_t.$$

Since both

$$\big\{\big\langle Z^{(\epsilon,m)}, Z^{(\epsilon,m)}\big\rangle\big\}_m \quad \text{and} \quad \big\{\big\langle Z^{(m)}, Z^{(m)}\big\rangle\big\}_m$$

converge uniformly in probability to 0, the central limit theorem for martingales ([11], Theorem VIII 3.22) implies that $\{Z^{(m)}\}_m$ converges weakly to 0.

We have that

$$\hat{B}_t^{(m)} = Z_t^{(m)} + \int_0^t J_s (X_s^{\mathrm{T}} R_{s-} X_s)^{-1} X_s^{\mathrm{T}} R_{s-} \lambda_s^{(m)}\, \mathrm{d}s,$$

so the sequence $\{\hat{B}^{(m)}\}_m$ is the sum of two C-tight sequences. Jacod and Shiryaev [11], Corollary VI 3.33, implies that the sequence itself is also C-tight. By Slutsky's theorem, the finite-dimensional distributions on the form $\mathcal{L}(\hat{B}_{t_1}^{(m)}, \ldots, \hat{B}_{t_j}^{(m)})$ converge weakly to the Dirac measures: $\delta_{B_{t_1},\ldots,B_{t_j}}$. This means that $\{\hat{B}^{(m)}\}_m$ converges in law and therefore in probability to B. □

6. Concluding remarks

We have shown that marginal structural modeling can be understood in terms of change of probability measures. The author believes that this is an elucidating point of view that is natural in the framework of modern probability theory.

As stressed by several authors, there is a very important and highly non-trivial assumption one has to make in order to interpret effects from marginal structural models as causal. This is the assumption of *no unmeasured confounders*, or equivalently: *all confounders are measured*. This means that every process that affects the short-term behavior of both the treatment and the censoring or both the treatment and the event must be observed. In this equivalent form, it becomes more apparent that this is just an assumption about completeness of the model. This completeness assumption is not that mysterious. When modeling various phenomena in the natural sciences, one typically assumes that all the important variables are contained in the model. This is also necessary in the MSM approach. However, it is important to note that this is not generally a statistically testable assumption. It is also not a condition that would follow from a mathematical argument without further assumptions about the model.

Heuristically, the MSM approach provides an adjustment of the the treatment effect bias caused by the measured confounders. In the marginal structural model approach, instead of modeling the underlying and potentially very complicated biology, one models a randomized trial. The problem of computing marginal effects then splits into two parts. The first problem is to model the marginal intensity of the event in the simulated "randomized trial". If one knew the corresponding likelihood ratio process, then this would be obtainable using, for instance, the weighted additive hazard regression from the previous section. In order to compute this likelihood ratio, one has to deal with the second part of our problem. That is to model the dynamics of the treatment and censoring processes given the full and the marginal history in the observational study. This is a crucial point. We have chosen not to deal with this problem in the current paper. However, one could use regression techniques to do this at least approximately. In the discrete time setting, one typically uses pooled logistic regressions see [8,19]. In the continuous-time setting it is probably more natural to use additive hazard or Poisson regression to estimate the censoring and treatment intensities, both with respect to the full covariate history and marginal covariate history. This will be the topic of future work. Once these intensities are known, one can compute the likelihood ratio process using (4.3).

Acknowledgements

Supported by the Research Council of Norway. Project: 170620/V30. I would like to thank Odd O. Aalen, Vanessa Didelez and Jon Michael Gran for helpful discussions related to this project.

References

[1] Aalen, O., Borgan, Ø. and Gjessing, H. (2008). *Survival and Event History Analysis: A Process Point of View*. New York: Springer. MR2449233

[2] Andersen, P.K., Borgan, Ø., Gill, R.D. and Keiding, N. (1993). *Statistical Models Based on Counting Processes*. New York: Springer. MR1198884
[3] Aalen, O.O., Borgan, Ø., Keiding, N. and Thormann, J. (1980). Interaction between life history events. Nonparametric analysis for prospective and retrospective data in the presence of censoring. *Scand. J. Statist.* **7** 161–171. MR0605986
[4] Billingsley, P. (1999). *Convergence of Probability Measures*, 2nd ed. New York: Wiley. MR1700749
[5] Brémaud, P. (1981). *Point Processes and Queues*. New York: Springer. MR0636252
[6] Didelez, V. (2008). Graphical models for marked point processes based on local independence. *J. Roy. Statist. Soc. Ser. B* **70** 245–264. MR2412641
[7] Florens, J.-P. and Fougere, D. (1996). Noncausality in continuous time. *Econometrica* **64** 1195–1212. MR1403234
[8] Hernán, M.A., Brumback, B. and Robins, J.M. (2000). Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology* **11** 561–570.
[9] Hernán, M.A., Hernández-Díaz, S. and Robins, J.M. (2004). A structural approach to selection bias. *Epidemiology* **15** 615.
[10] Jacod, J. (1974). Multivariate point processes: Predictable projection, Radon–Nikodým derivatives, representation of martingales. *Z. Wahrsch. Verw. Gebiete* **31** 235–253. MR0380978
[11] Jacod, J. and Shiryaev, A.N. (2003). *Limit Theorems for Stochastic Processes*, 2nd ed. *Grundlehren der Mathematischen Wissenschaften [Fundamental Principles of Mathematical Sciences]* **288**. Berlin: Springer. MR1943877
[12] Lépingle, D. and Mémin, J. (1978). Sur l'intégrabilité uniforme des martingales exponentielles. *Z. Wahrsch. Verw. Gebiete* **42** 175–203. MR0489492
[13] Lok, J.J. (2008). Statistical modeling of causal effects in continuous time. *Ann. Statist.* **36** 1464–1507. MR2418664
[14] Protter, P.E. (2005). *Stochastic Integration and Differential Equations*, 2nd ed. *Stochastic Modelling and Applied Probability* **21**. Berlin: Springer. MR2273672
[15] Robins, J.M., Hernán, M.A. and Brumback, B. (2000). Marginal structural models and causal inference in epidemiology. *Epidemiology* **11** 550–560.
[16] Robins, J. (1992). Estimation of the time-dependent accelerated failure time model in the presence of confounding factors. *Biometrika* **79** 321–334. MR1185134
[17] Robins, J.M. (1998). Structural nested failure time models. In *The Encyclopedia of Biostatistics* 4372–4389. Chichester: Wiley.
[18] Schweder, T. (1970). Composable Markov processes. *J. Appl. Probab.* **7** 400–410. MR0264755
[19] Sterne, J.A., Hernán, M.A., Ledergerber, B., Tilling, K., Weber, R., Sendi, P., Rickenbach, M., Robins, J.M. and Egger, M. (2005). Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: A prospective cohort study. *Lancet* **366** 378–384.

Received March 2009 and revised June 2010