Monitoring time to event in registry data using CUSUMs based on excess hazard models

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Abstract

An aspect of interest in surveillance of diseases is whether the survival time distribution changes over time. By following data in health registries over time, this can be monitored, either in real time or retrospectively. With relevant risk factors registered, these can be taken into account in the monitoring as well. A challenge in monitoring survival times based on registry data is that data on cause of death might either be missing or uncertain. To quantify the burden of disease in such cases, excess hazard methods can be used, where the total hazard is modelled as the population hazard plus the excess hazard due to the disease.

We propose a CUSUM procedure for monitoring for changes in the survival time distribution in cases where use of excess hazard models is relevant. The procedure is based on a survival log-likelihood ratio and extends previously suggested methods for monitoring of time to event to the excess hazard setting. The procedure takes into account changes in the population risk over time, as well as changes in the excess hazard which is explained by observed covariates. Properties, challenges and an application to cancer registry data will be presented.

Keywords: Excess risk, relative survival, survival time monitoring, risk-adjusted monitoring.

1 Introduction

In health registries, such as cancer registries, patients are routinely registered at diagnosis, and outcome data like survival times are often added later. Based on such data, an aspect of interest could be to monitor whether the distribution of the time to an outcome of interest changes over time, for instance if the survival times of cancer patients change over time while adjusting for known risk factors. Such monitoring could be of interest both for real-time monitoring of incoming data and for retrospective analyses to pinpoint when in time important changes took place. A common challenge in monitoring survival times based on such registry data is that time to death, but not necessarily cause of death, is registered. To quantify the burden of disease in such cases, excess hazard methods can be used. With excess hazard models, the total hazard is modelled as the population hazard plus the excess hazard due to the disease. The population hazard is found from national life tables.

Approaches for monitoring of ordinary time to event data were first proposed by Biswas and Kalbfleisch (2008), Sego, Reynolds Jr and Woodall (2009), Gandy, Kvaløy, Bottle and Zhou (2010) and Steiner and Jones (2010). These have since been extended to things like frailty models (Begun, Kulinskaya and MacGregor, 2019; Keshavarz, Asadzadeh and Niaki, 2021), cure models (Oliveira, Valença, Medeiros and Marçula, 2016), illness-death models (Liu, Lai, Wang, Zhu and Liu, 2023) and queue models (Kuang, Das, Sir and Pasupathy, 2023). Impact of estimation error in time to event data

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monitoring was studied by Zhang, Xu, He and Hou (2016) and effectiveness versus periodic evaluations was studied by Massarweh, Chen, Rosen, Dong, Richardson, Axelrod, Harris, Wilson and Petersen (2021). Applications have been demonstrated in, for instance, monitoring of perioperative mortality (Lai, Li, Liu, Tsung, Lai, Wang, Zhang, Zhu and Liu, 2021; Chen, Chidi, Dong, Richardson, Axelrod, Petersen and Massarweh, 2023).

We propose a CUSUM procedure for monitoring for changes in the time to event distribution when the use of excess hazard models is relevant. The procedure is based on a survival log-likelihood ratio and extends the literature discussed above to monitoring of time to event in the excess hazard setting. The procedure takes into account changes in the population risk over time, as well as changes in the excess hazard which are explained by observed covariates. Properties, challenges and an application to cancer registry data will be presented.

The structure of the paper is as follows: Section 2 introduces the setup and notation and presents the proposed method. In Section 3, numerical simulations and experiments are carried out to demonstrate the use of the method and how it performs under different scenarios, including studying the impact of estimation error. An application of the method on a real data set obtained from the Norwegian Cancer Registry is illustrated in Section 4. Finally, Section 5 provides some concluding remarks. R-code implementing the proposed methods and for running the simulations in Section 3 can be found at `https://github.com/jihut/cusum_relative_survival_simulations`.

2 CUSUM chart based on excess risk models

2.1 Setup and Notation

The setting considered is monitoring time to event data under the assumption of an additive hazard model $h(t) = h_P(t) + h_E(t)$. Here, $h_P(\cdot)$ denotes the population hazard that is assumed to be known and usually found from population life tables, while $h_E(\cdot)$ denotes the excess hazard. We would like to monitor for changes in $h_E(\cdot)$ over calendar time.

Let $B_1 \leq B_2 \leq \ldots$ denote the calendar times at which individuals enter. Also, let $Z_1, Z_2, \ldots$ denote the corresponding vectors of demographic variables affecting $h_P(t)$ and $X_1, X_2, \ldots$ the covariate vectors affecting $h_E(t)$. The demographic variables, often age, gender and birth year, may or may not be a subset of the covariates. Furthermore, let T_i denote the time to event and C_i the censoring time for individual i. We then define the time at risk up to calendar time t for individual i as $A_i(t) = \min(T_i, C_i, \max(t - B_i, 0))$ and the event indicator $\delta_i(t) = I(T_i = A_i(t))$.

Let $h_{0i}(\cdot) = h_P(\cdot, Z_i) + h_{E,0}(\cdot, X_i)$ be the in-control hazard rate. The known population hazard $h_P(\cdot)$ might change over calendar time, but this is suppressed in the notation. The excess hazard rate in the in-control (baseline) situation is assumed to be constant over calendar time. At some calendar time η, the hazard switches to some out of control hazard rate $h_{1i}(\cdot) = h_P(\cdot, Z_i) + h_{E,1}(\cdot, X_i)$ and we would like to quickly detect this change. Finally, let the cumulative hazard be $H_{ji}(t) = \int_0^t h_{ji}(s)ds$ for $j = 0, 1$.

2.2 The proposed CUSUM procedure

Following Gandy et al. (2010), we define a continuous time CUSUM procedure based on the survival likelihood ratio. Moustakides (1986) has shown optimality properties for CUSUMs based on likelihood ratios. The (partial) likelihood based on h_{ji} up to calendar time t is (Aalen, Borgan and Gjessing, 2008)

$$L_j(t) = \prod_{i:B_i \leq t} h_{ji}(T_i)^{\delta_i(t)} \exp[-H_{ji}(A_i(t))].$$

2

The (partial) log-likelihood ratio between the in- and out-of-control likelihood up to calendar time t thus becomes

$$R(t) = \sum_{i:B_i \leq t} \delta_i(t) \log\left(\frac{h_{1i}(T_i)}{h_{0i}(T_i)}\right) - \sum_{i:B_i \leq t} [H_{1i}(A_i(t)) - H_{0i}(A_i(t))].$$

$R(t)$ is the continuous time analogue to a cumulative sum. By restarting this sum whenever it drops to 0, we get the continuous time CUSUM control chart

$$\Psi(t) = R(t) - \min_{s \leq t} R(s)$$

that signals at a time $\tau = \inf\{t : \Psi(t) > c\}$ for some threshold $c > 0$.

What differs from the procedure in Gandy et al. (2010) is that we here work with an excess risk model, and this in particular implies that it is more challenging to determine c and that we need to keep track of the population hazard in the first term of $R(t)$. Usually, the population hazard can be found in national life tables. Also, in most practical applications, one has to estimate $h_{E,0}(\cdot, X_i)$. The most common excess hazard models in relative survival are based on the proportional hazard model, i.e. $h_{E,0}(\cdot, X_i) = h_0(\cdot)\exp(\beta X_i)$, where h_0 corresponds to the baseline excess hazard. For our purposes, a piecewise constant baseline excess hazard model, estimated by a GLM-approach with Poisson error structure (Dickman, Sloggett, Hills and Hakulinen, 2004), and a semiparametric excess hazard model with a smooth nonparametric estimate of $h_0(\cdot)$, fitted by an EM-algorithm (Perme, Henderson and Stare, 2009), will be the relevant models in the upcoming sections.

2.3 Out-of-control alternatives

In this section, we consider different alternative models for the out-of-control hazard $h_{1i}(\cdot)$. As motivated in the previous sections, the main focus here is to monitor the change in the excess hazard part related to the disease of interest. Therefore, the standard proportional alternative on the overall hazard considered in Gandy et al. (2010), which implies monitoring change in the total hazard, is not suitable for the current purpose. However, based on the same idea, a proportional alternative directly on the excess hazard, i.e. $h_{E,1}(\cdot, X_i) = \rho h_{E,0}(\cdot, X_i)$ for some $\rho > 0$, can be considered. The corresponding log-likelihood ratio at a given calendar time t becomes

$$R(t) = \sum_{i:B_i \leq t} \delta_i(t) \log\left(\frac{h_P(T_i, Z_i) + \rho h_{E,0}(T_i, X_i)}{h_P(T_i, Z_i) + h_{E,0}(T_i, X_i)}\right) - (\rho - 1) \sum_{i:B_i \leq t} [H_{E,0i}(A_i(t))]. \tag{1}$$

A number of simulated scenarios and illustrations with this model was presented in the master thesis of Tran (2022). A similar, but more enhanced simulation study inspired by real data will be presented here.

The proportional alternative implies assuming a larger change in absolute value of the hazard for patients with a higher hazard. However, this might not always be reasonable, and an alternative model for the change could be an additive model where the hazard changes by the same absolute amount for all patients. This motivates an additive out-of-control alternative for the excess hazard. Assuming that we work with non-negative excess hazard, which is usually the case when dealing with cancer patients, the additive alternative is given as $h_{E,1}(\cdot, X_i) = \max(0, h_{E,0}(\cdot, X_i) + \gamma)$ for some $-\infty < \gamma < \infty$ so that

$H_{E,1}(t, X_i) = \int_0^t \max(0, h_{E,0}(\cdot, X_i) + \gamma) du$ and

$$R(t) = \sum_{i:B_i \leq t} \delta_i(t) \log \left(\frac{h_P(T_i, Z_i) + \max(0, h_{E,0}(T_i, X_i) + \gamma)}{h_P(T_i, Z_i) + h_{E,0}(T_i, X_i)} \right)$$
$$- \sum_{i:B_i \leq t} \left(\left(\int_0^{A_i(t)} \max(0, h_{E,0}(u, X_i) + \gamma) du \right) - H_{E,0}(A_i(t), X_i) \right). \tag{2}$$

The use of the maximum function is to ensure that we do not get a negative excess hazard in the out-of-control scenario for some individuals when $\gamma < 0$. In the case where $\gamma > 0$, the maximum function can be omitted and the log-likelihood ratio simplifies to

$$R(t) = \sum_{i:B_i \leq t} \delta_i(t) \log \left(\frac{h_P(T_i, Z_i) + h_{E,0}(T_i, X_i) + \gamma}{h_P(T_i, Z_i) + h_{E,0}(T_i, X_i)} \right) - \gamma \sum_{i:B_i \leq t} A_i(t). \tag{3}$$

The setup can in theory be extended to non-negative excess hazard as well by rather requiring that the total hazard is non-negative, i.e. $h_{1i}(\cdot) = \max(h_P(\cdot, Z_i) + h_{E,0}(\cdot, X_i) + \gamma, 0)$. For situations where $h_{1i}(T_i) = 0$, the corresponding observations will have no events. The hazard term can thus be omitted for these. However, we will not pursue this somewhat odd situation any further.

Further, as considered in Gandy et al. (2010) for ordinary hazard models, time-transformation alternatives can be used to model changes in the hazard. We consider the following linear accelerated time alternative specified as $H_{E,1}(u, X_i) = H_{E,0}(ku, X_i)$ for some $k > 0$. This leads to the following log-likelihood ratio for the linear accelerated time alternative:

$$R(t) = \sum_{i:B_i \leq t} \delta_i(t) \log \left(\frac{h_P(T_i, Z_i) + k h_{E,0}(kT_i, X_i)}{h_P(T_i, Z_i) + h_{E,0}(T_i, X_i)} \right) - \sum_{i:B_i \leq t} [H_{E,0i}(kA_i(t)) - H_{E,0i}(A_i(t))]. \tag{4}$$

This parameterization implies in most cases an easy interpretation of the alternative - a value of $k < 1$ yields $H_{E,1i}(u) = H_{E,0i}(ku) < H_{E,0i}(u)$, which implies that the survivor function is larger at the same time point u in the out-of-control setting compared to the in-control scenario, and the other way around for $k > 1$. One could also choose the parameterization $h_{E,1}(u, X_i) = h_{E,0}(ku, X_i)$, but the interpretation is less clear as it will in general depend on the shape of $h_{E,0}(u, X_i)$ as a function of u and thus will not be considered further here.

A possible challenge with the linear accelerated time alternative occurs if the monitoring system is used to monitor survival up to a certain time point, for instance 10 year survival, and a $k > 1$ alternative is of interest. Then, estimation of the hazard function up to $10k$ years will be required for calculating $h_{E,0}(ku, X_i)$ and $H_{E,0}(ku, X_i)$. If nonparametric modelling is used, this requires that survival data up to $10k$ years must be available for estimating the hazard function. If survival data beyond 10 years are not available, a parametric hazard model can be used, but this will require extrapolations beyond the range of the data used to estimate the model.

2.4 Criteria for determining the signal threshold

The signal threshold c needs to be tuned to achieve the desired performance of the CUSUM charts. Usually, the threshold is chosen so that the charts achieve a certain performance under the in-control alternative. For example, one could relate c with the in-control average run length defined as ARL $= E(\tau \mid \eta = \infty)$, which corresponds to the expected time until the charts cross the threshold c when the hazard never changes to the out-of-control state. Then, c is chosen such that the in-control ARL is equal to a desired value. Another common strategy is to choose c such that the probability of a false signal until a given time point t_m follows a desired level α, i.e. $p_{\text{hit}} = P(\tau \leq t_m \mid \eta = \infty) = \alpha$.

Gandy et al. (2010) explored the setting of choosing c with respect to the expected number of events until hitting or the probability that the number of events at hitting time point does not exceed a given amount when in-control, i.e. $E(N(\tau) \mid \eta = \infty)$ and $P(N(\tau) \leq N_{\max} \mid \eta = \infty)$. In the overall hazard change studied in Gandy et al. (2010), c can be analytically computed using a method based on a discrete time Markov chain with finite state space when the mentioned quantities are specified. However, this methodology does not apply for the setting of monitoring the excess hazard as the jump of the chart is no longer constant across observations. Nevertheless, it is possible to approximate the current setting to a situation where the Markov chain method is applicable whenever the population hazard is much smaller compared to the excess hazard. This was examined in the master thesis of Tran (2022), where the thresholds obtained from the method yield approximately the desired performances in circumstances where the excess hazard dominates the population hazard.

In the excess hazard scenarios studied in the present paper, it is seemingly not possible to compute c analytically. In the remaining sections, the thresholds will thus be calculated via different simulation approaches depending on the setting.

2.5 Simulating the signal threshold

In the following, an overview of the general approach to simulate the threshold c based on a predefined p_{hit} is described.

Algorithm 1 Simulating c based on a chosen p_{hit}

1: Specify the start time of the monitoring process, specify t_m, $p_{\text{hit}} = \alpha$ for some $\alpha \in (0,1)$ and the number of simulations N. Assume that the arrivals of observations follow a homogeneous Poisson process with intensity λ_a and the interim censoring time C_i^* an exponential distribution with censoring rate λ_{C^*}.
2: **for** $j = 1, ..., N$ **do**
3: Simulate the number of observations n up to the time point t_m with the assumed arrival process. Obtain $B_1, \cdots, B_n$.
4: **for** $i = 1, ..., n$ **do**
5:   Simulate X_i and Z_i.
6:   Simulate T_{Ei} based on $h_{E,0}(\cdot, X_i)$ and T_{Pi} based on $h_P(\cdot, Z_i)$.
7:   Simulate interim censoring time $C_i^* \sim \text{Exp}(\lambda_{C^*})$. Calculate final censoring time $C_i = \min(C_i^*, t_m - B_i)$.
8:   Calculate $T_i = \min(T_{Ei}, T_{Pi}, C_i)$.
9: **end for**
10: Run CUSUM chart and let $W_j = \max_{0 \leq t \leq t_m} \Psi_j(t)$, where $\Psi_j(t)$ is the CUSUM chart run for this specific iteration.
11: **end for**
12: Calculate c as the $\alpha \cdot 100\%$ upper quantile of the values $W_1, \cdots, W_N$.

We will consider two different scenarios for simulating the covariates X_i and Z_i. For the first simulations performed in Section 3, we assume that the true covariate distribution is known and therefore simulate X_i and Z_i directly from these distributions. In real-life applications, this is usually not the case. We then opt for a nonparametric bootstrap procedure that estimates the baseline/in-control distribution in such scenarios. Also, the interim censoring rate is estimated by counting the number of observations in the baseline period that are censored and the corresponding observed time is less than the maximum follow-up time.

2.6   Monitoring and updating schemes

The proposed method is best suited for detecting changes in the setting that all observations in the system will experience the out-of-control hazard whenever $t > \eta$, e.g. if a new regime for post-operative treatment is introduced for all patients. However, in certain cases, only the individuals arriving after the change point η will be affected by the change in the hazard, for instance if a new surgery procedure is introduced. Our method should still be able to detect the change in this latter scenario, but there will be more delay in detecting the change.

With the definition $A_i(t) = \min(T_i, C_i, \max(t - B_i, 0))$, we assume that information on the status of a patient is available continuously, from arrival and onwards. This is realistic if cases are registered to the database more or less in real time and information about censoring or events is swiftly added. For instance, this will be the case when the method is used for retrospective analysis, as in our example coming later. Another scenario could be that information about each case becomes available only after censoring or an event. For this scenario, Gandy et al. (2010) suggested to redefine $A_i(t)$ such that the observation contributes to the likelihood ratio only after an event or censoring has occurred:

$$A_i(t) = \min(T_i, C_i)I(\min(T_i, C_i) + B_i \leq t).$$

It is clear that the chart will not have a continuous drift, but only jumps in value whenever an observation has experienced an event or censoring. The same result can be applied here, but for the purpose of the real data set considered in the later section, this version will not be considered in the remainder of the text.

Another situation that could appear is when the information is only available at certain time points. An example is when a patient is diagnosed in the middle of a year, but the observation is only included in the database at the end of the year. A possible solution is to again redefine $A_i(t)$ so that the observation is included in the system periodically, e.g. at the start of every new year so that

$$A_i(t) = \min(T_i, C_i, t - B_i)I(\lceil B_i \rceil \leq t),$$

where $\lceil \cdot \rceil$ is the ceiling function.

Similarly to the above, we can extend the first situation where the information of an observation is only available periodically after the observation experiences an event or has been censored, e.g. when a patient either dies or drops out of a study in the middle of a year and the database is updated with the given observation at the start of the new year. Then, $A_i(t)$ can be defined as follows:

$$A_i(t) = \min(T_i, C_i)I(\lceil \min(T_i, C_i) + B_i \rceil \leq t).$$

Another scenario is when the entire database is updated in regular intervals, adding all information accumulating since the last update. Then, an option would be to run the CUSUM retrospectively by running the CUSUM for the last period once the data for that period become available. This would of course lead to a certain delay in signalling versus when running the chart in real-time.

In some cases, it is of interest to just monitor for survival up to a certain time after diagnosis t_D, for instance $t_D = 5$ years survival in cancer patients. A benefit with such monitoring is that we only need baseline data over a time period long enough to be able to estimate $h_{E,0}(\cdot)$ up to t_D. Furthermore, with this set-up, there is no restriction as to how long we can run the monitoring as we will only need to evaluate $h_{E,0}(t)$ for $t \leq t_D$. Thus, it is not required to have an estimate of $h_{E,0}(t)$ for $t \geq t_D$. Estimation of the in-control model is further discussed in the next subsection.

2.7 Estimating the in-control model

In practical applications, the true in-control excess hazard will be unknown and has to be estimated from baseline data. To run the monitoring procedure, we need to be able to evaluate $h_{E,0}(t)$ and $H_{E,0}(t)$ for any survival time t that could be observed during the monitoring. In practice, this means that if nonparametric estimates of $h_{E,0}(t)$ and $H_{E,0}(t)$ are used, baseline data for at least as long period as the maximum monitoring period would be required to estimate these functions, if the monitoring is run without any upper limit on the time to event of interest. If a parametric estimate is used, one could in principle use the estimated model beyond the event horizon observed in the baseline data.

When estimating the in-control excess hazard, the estimation error will propagate to the achieved in-control performance. The impact of this, as well as the impact of model misspecifications, will be illustrated in Section 3.5.

3 Simulation study

In this section, properties of the suggested procedures are studied by simulations.

3.1 Simulation set-up

For the following, we will use a proportional excess hazard model, i.e. $h_{E,0}(\cdot, X_i) = h_0(\cdot) \exp(\beta X_i)$. Inspired by data from the Norwegian Cancer Registry, Table 5 in Appendix A presents the covariates that we will consider in the simulations, with corresponding parameter values.

The interim censoring time is set to be exponentially distributed with the rate parameter equal to 0.000275. The monitoring is run for 10 years (in one case 5 years) and is using the population hazard of Norway from the beginning of 2010 to the end of 2019. The baseline excess hazard is chosen to be a piecewise constant function of the form $h_0(t) = \exp\left[\sum_k \chi_k I_k(t)\right]$, where $I_k(t) = 1$ whenever t lies in the k-th band of the 10-year follow-up interval. Here, we partition the follow-up interval into yearly bands during the first five years before defining one single band for $t \in [5, 10]$. Inspired by the cancer data, we will use $\chi = (-1.4, -1.6, -1.8, -2.0, -2.1, -3.0)$.

In most simulations, we assume that both the distributions of the covariates and the parameter vectors β and χ are known. Thus, the charts are calculated using the true parameters, and hence the true functional form of h_0. However, the impact of estimation error will be studied in Section 3.5.

Arrival of patients is simulated as a homogeneous Poisson process with arrival rate λ_a. To determine the threshold c, we use the false signal probability during the 10 years of monitoring as criteria. The threshold is then computed by simulating 1000 or 10 000 CUSUMs from the in-control model, and we tune the threshold to achieve the desired false alarm signal probability, which we specify to either 0.05 or 0.01.

After the signal threshold c is determined, the signal probabilities for various out-of-control situations are simulated by simulating 1000 or 10 000 CUSUMs.

We study three different scenarios for the shift from in-control to out-of-control: i) All patients are in the out-of-control situation from the beginning ($\eta = 0$), ii) All patients change to the out-of-control hazard at some time point η years (either $\eta = 2.5$ or $\eta = 5$), iii) Only patients arriving after some time point η^* have the out-of-control hazard (either $\eta^* = 2.5$ or $\eta^* = 5$).

3.2 Proportional alternative

This subsection considers different scenarios with the proportional alternative represented by (1). The charts are computed using the correct value of ρ that determines the various out-of-control situations.

The first simulation setup examines the scenario of four different values of ρ in a situation with a moderate yearly arrival rate of $\lambda_a = 250$.

The results from the described simulation setup are given in Table 1. One can observe that in the situation when the excess hazard is in the out-of-control state from the start, almost all simulations yield a signal during the 10-year monitoring period for the largest shifts, i.e. $\rho = 0.80$ and $\rho = 1.20$. When the change is less pronounced like $\rho = 0.90$ and $\rho = 1.10$, the signal ratio is reduced, and of course, lower for the 0.01 false alarm probability versus 0.05. If the shift happens in the monitoring period, it is natural that the signal ratio is further decreased as there is less time for the charts to signal. Finally, the situation where only the individuals arriving after 5 years will experience the out-of-control state yields the smallest signal ratio. As expected, the proposed CUSUM charts have less power to detect these shifts.

		Signal Ratio		
	Scenario	$\eta = 0$	$\eta = 5$	$\eta^* = 5$
ρ	$P(\tau \leq 10 \mid \eta = \infty)$			
0.80	0.01 $(c = 6.41)$	95.34%	78.39%	42.97%
	0.05 $(c = 5.02)$	98.50%	89.85%	64.17%
0.90	0.01 $(c = 4.37)$	43.57%	21.49%	9.21%
	0.05 $(c = 3.41)$	65.28%	42.61%	24.44%
1.10	0.01 $(c = 4.32)$	36.09%	17.39%	8.02%
	0.05 $(c = 3.36)$	59.78%	37.78%	21.40%
1.20	0.01 $(c = 6.12)$	91.20%	67.78%	32.45%
	0.05 $(c = 4.80)$	96.75%	83.95%	54.09%

Table 1: The table reports proportions of cases when the CUSUM signals in a setting where individuals arrive over calendar time according to a Poisson process with rate $\lambda_a = 250$, and the out-of-control model is $h_{1i}(\cdot) = h_P(\cdot, Z_i) + \rho h_{E,0}(\cdot, X_i)$ with the latter having a piecewise constant baseline excess hazard. Different shifts in terms of ρ and different shift points η are considered. For the shift after 5 years of monitoring, both the setting that the shift affects all individuals ($\eta = 5$) and the setting when the shift only affects new individuals ($\eta^* = 5$) are considered. $10\,000$ simulations are performed for each combination of ρ and scenario of shift, and for finding thresholds c.

Next, a situation with a much larger arrival rate, similar to what is observed in the cancer registry data used in Section 4, is considered by letting $\lambda_a = 3700$. To balance out the increased power due to the larger amount of arrived individuals, we just run the CUSUM for 5 years and examine less prominent changes in the excess hazard by investigating values of ρ that differ less from unity compared to the previous situation. From Table 2, the power of the monitoring system is relatively high if the excess hazard changes by 10% for both scenarios of η. On the other hand, even with the much larger amount of arrivals, just above half of the charts will signal when the false alarm signal probability is 0.05 and the excess hazard changes by 5%. In order to detect shifts quickly in these scenarios, more observations are needed to increase the power.

3.3 Additive alternative

In this subsection, we perform a similar experiment as in the preceding for the additive alternative given by (2). By letting $\lambda_a = 3700$, we examine three values of γ: -0.002, 0.002 and 0.005. It turns out that combining the general simulation setup described earlier with $\gamma = -0.002$ yields individual

		Signal Ratio		
	Scenario	$\eta = 0$	$\eta = 2.5$	$\eta^* = 2.5$
ρ	$P(\tau \leq 10 \mid \eta = \infty)$			
0.90	0.01 $(c = 8.00)$	97.3%	84.9%	26.0%
	0.05 $(c = 6.23)$	99.2%	94.0%	46.0%
0.95	0.01 $(c = 6.06)$	37.2%	16.4%	3.0%
	0.05 $(c = 4.96)$	54.8%	33.3%	8.5%
1.05	0.01 $(c = 6.08)$	33.3%	13.8%	3.3%
	0.05 $(c = 4.69)$	57.6%	37.1%	10.1%
1.10	0.01 $(c = 7.63)$	96.0%	84.6%	22.2%
	0.05 $(c = 6.06)$	98.5%	92.5%	42.0%

Table 2: The table reports proportions of cases when the CUSUM signals in a setting where individuals arrive over calendar time according to a Poisson process with rate $\lambda_a = 3700$, and the out-of-control model is $h_{1i}(\cdot) = h_P(\cdot, Z_i) + \rho h_{E,0}(\cdot, X_i)$ with the latter having a piecewise constant baseline excess hazard. The CUSUM is run for 5 years. Different shifts in terms of ρ and different shift points η are considered. For the shift after 2.5 years of monitoring, both the setting that the shift affects all individuals ($\eta = 2.5$) and the setting when the shift only affects new individuals ($\eta^* = 2.5$) are considered. 1000 simulations are performed for each combination of ρ and scenario of shift, and for finding thresholds c.

		Signal Ratio		
	Scenario	$\eta = 0$	$\eta = 5$	$\eta^* = 5$
γ	$P(\tau \leq 10 \mid \eta = \infty)$			
-0.002	0.01 $(c = 4.93)$	61.8%	49.3%	5.0%
	0.05 $(c = 3.78)$	79.3%	70.7%	17.6%
0.002	0.01 $(c = 4.78)$	60.6%	46.9%	5.6%
	0.05 $(c = 3.83)$	76.6%	64.7%	13.5%
0.005	0.01 $(c = 6.81)$	100.0%	100.0%	22.5%
	0.05 $(c = 5.50)$	100.0%	100.0%	40.0%

Table 3: The table reports proportions of cases when the CUSUM signals in a setting where individuals arrive over calendar time according to a Poisson process with rate $\lambda_a = 3700$, and the out-of-control model is $h_{1i}(\cdot) = h_P(\cdot, Z_i) + \max(0, h_{E,0}(\cdot, X_i) + \gamma)$ with the latter having a piecewise constant baseline excess hazard. Different shifts in terms of γ and different shift points η are considered. For the shift after 5 years of monitoring, both the setting that the shift affects all individuals ($\eta = 5$) and the setting when the shift only affects new individuals ($\eta^* = 5$) are considered. 1000 simulations are performed for each combination of γ and scenario of shift, and for finding thresholds c.

out-of-control excess hazards that are non-negative so that (3) can also be used for faster calculations. For moderate shifts like 0.002 in absolute value, we can see from Table 3 that the power of the charts is moderate when using the threshold giving a 5% probability of false signal. On the other hand, increasing the effect of change to 0.005 leads to signals for all simulated charts for the cases where all individuals are affected by the shift. We also notice that the $\gamma = -0.002$ and $\gamma = 0.002$ cases achieve roughly the same power. As before, the situation where only new arrivals are affected by the change has the smallest signal ratios for all values of γ.

3.4 Linear accelerated time alternative

		Signal Ratio		
	Scenario	$\eta = 0$	$\eta = 5$	$\eta^* = 5$
k	$P(\tau \leq 10 \mid \eta = \infty)$			
0.90	0.01 ($c = 7.83$)	100.0%	100.0%	44.7%
	0.05 ($c = 6.50$)	100.0%	100.0%	62.8%
0.95	0.01 ($c = 7.29$)	99.9%	99.7%	10.6%
	0.05 ($c = 5.89$)	99.9%	100.0%	25.4%
1.05	0.01 ($c = 7.18$)	99.9%	99.6%	14.3%
	0.05 ($c = 5.97$)	100.0%	99.9%	26.2%
1.10	0.01 ($c = 8.49$)	100.0%	100.0%	35.3%
	0.05 ($c = 6.47$)	100.0%	100.0%	64.2%

Table 4: The table reports proportions of cases when the CUSUM signals in a setting where individuals arrive over calendar time according to a Poisson process with rate $\lambda_a = 3700$, and the out-of-control model is $h_{1i}(\cdot) = h_P(\cdot, Z_i) + k h_{E,0}(k\cdot, X_i)$ with the latter having a piecewise constant baseline excess hazard. Different shifts in terms of γ and different shift points η are considered. For the shift after 5 years of monitoring, both the setting that the shift affects all individuals ($\eta = 5$) and the setting when the shift only affects new individuals ($\eta^* = 5$) are considered. 1000 simulations are performed for each combination of γ and scenario of shift, and for finding thresholds c.

For the last setup in this section, we investigate the performance of the linear accelerated time alternative (4) with four different values of k. When $k > 1$, we extend the upper limit of the last band of $h_0(t) = \exp\left[\sum_k \chi_k I_k(t)\right]$ covering the time interval between 5 and 10 years to $10k$ years. Table 4 shows that almost all charts signal for the situations when $\eta = 0$ and $\eta = 5$ across all four values of k. For $\eta^* = 5$, we can still observe that the procedure struggles more to capture these changes.

3.5 Estimation error and model misspecification

In the preceding simulation studies, the true covariate parameters and functional form of the baseline excess hazard are used when computing the CUSUM charts. In practice, these are all unknown quantities and need to be estimated as discussed in Section 2.7. To illustrate the effect of estimation error in achieving e.g. the specified in-control false probability or average run length, we perform the simulation setup presented in Algorithm 2.

Furthermore, we will also consider some model misspecification aspects. One would presume that the observed in-control false signal probability will be further off from the nominal value if the specified form of the baseline is not correct, e.g. when using a piecewise constant baseline excess hazard model

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Algorithm 2 Simulation setup to illustrate effect of estimation error and model misspecification

1: We consider a specific underlying proportional excess hazard model $h_{E,0}(\cdot, X_i) = h_0(\cdot)\exp(\beta X_i)$ with h_0 being a parametric baseline excess hazard function.
2: From the true model, we simulate a data set to be used for estimating the in-control model.
3: Based on the simulated data set, we estimate an in-control model (which could be an estimated "true" model, e.g. a model with a piecewise constant baseline if the true excess hazard is on this form, or an estimated "wrong model", e.g. with a smooth baseline if the true excess hazard is piecewise constant.)
4: We treat the estimated model as a true model and simulate the threshold c to obtain a certain rejection probability under this assumed true model by simulating observations from the in-control model. Two possibilities regarding the covariate distribution will be considered here: In the first approach, the true covariate distribution is assumed to be known, the second uses a nonparametric bootstrap procedure on the simulated data set from step 2.
5: We use the estimated model from step 3 with the threshold from step 4 and run the CUSUM many times on data simulated from the true model specified in step 1. The achieved rejection probability is calculated using these runs.
6: Steps 2 to 5 are repeated many times in order to characterize the distribution of the in-control false signal probability obtained under the estimated model.

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when the true excess hazard is a continuous function. Consequently, we will consider two different types of baseline excess hazard in this subsection: A piecewise constant baseline and a flexible smooth nonparametric baseline hazard. Both methods can be found in the R package `relsurv` via the `rsadd`-function, see e.g. Perme and Pavlic (2018). A note regarding the smoothing procedure to obtain continuous nonparametric estimates of the baseline excess hazard is given in Appendix B.

In addition, we also investigate for each combination of estimation procedure and true excess hazard if the results obtained from bootstrapping the covariate distributions from the data set obtained in step 2 of Algorithm 2 differ from simulating directly from the true covariate distributions. We will only perform the simulation using the proportional alternative, but the idea is the same for the remaining out-of-control situations.

3.5.1 Piecewise constant baseline

In this part of the simulation, we consider the same piecewise constant baseline excess hazard setup presented previously in this section. The arrival rate is set to $\lambda_a = 3750$, the proportionality constant relating the out-of-control and in-control scenario is $\rho = 0.90$. We let the desired in-control false probability during the first five years of monitoring be equal to $P(\tau \leq 5 \mid \eta = \infty) = 0.05$. Steps 2 to 5 are performed 1000 times to obtain the distribution of in-control false probability under a given combination of estimation method and covariate simulation. For each iteration, 1000 simulations are also done in order to obtain the threshold value c. Figure 1 shows the results when the model estimation is performed using the piecewise baseline excess hazard model. This resembles the situation where the estimated baseline excess hazard is correctly specified. We can observe that both the median and mean in-control signal ratio, regardless if the covariate distributions are simulated using bootstrap or the true distributions, only differ slightly from the desired nominal value of 5% due to the effect of the estimation error of β and χ.

On the other hand, when examining the results of the same procedure using the smooth baseline excess hazard estimate, we see that the median and mean in-control signal ratio, independent of the scenario considered in step 4, are further away from the nominal value. Not only do we have the

(a) True covariate distribution used in step 4. Mean signal ratio is 5.73%, median signal ratio is 4.30%.

(b) Bootstrapping used to estimate the covariate distribution. Mean signal ratio is 5.65%, median signal ratio is 4.30%.
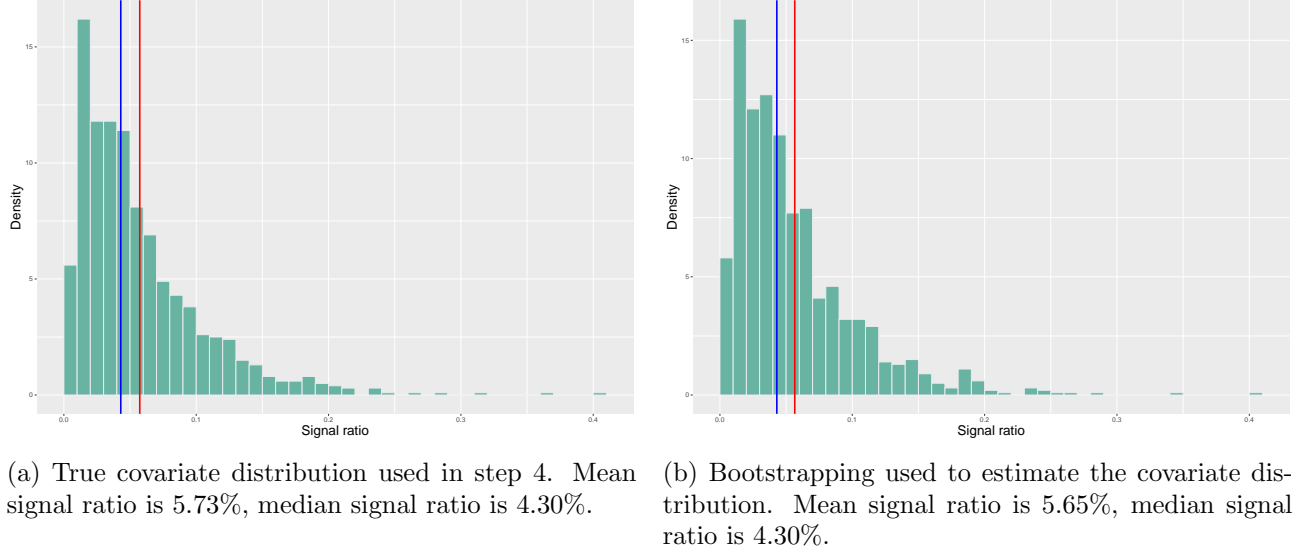
Figure 1: Histograms of the achieved rejection probabilities under in-control scenario with the true baseline excess hazard following a piecewise constant function. The model estimation is done using the model with piecewise constant baseline in step 3. Here, the blue vertical line represents the median and the red line corresponds to the mean signal ratio.

estimation error in the covariate parameters that affects the results, the incorrect specification of the form of the baseline excess hazard when using the smooth baseline estimate leads to larger deviation from the desired false signal ratio. Therefore, if the true baseline excess hazard is indeed a piecewise constant function, approximating it with a continuous and smooth function might cause undesired behaviour in the monitoring procedure.

3.5.2 Weibull baseline

In theory, the previous true form of baseline excess hazard favors the model with piecewise constant baseline as it is difficult for the estimated smoothed nonparametric baseline excess hazard to capture the stepwise behaviour. We now illustrate the opposite scenario by considering a Weibull baseline as the true form, where

$$h_0(t) = abt^{a-1}.$$

Inspired by the data from the Norwegian Cancer Registry, we let $a = 0.65$ and $b = 0.25$. Otherwise, the other quantities remain the same as in the piecewise constant baseline scenario. Results are reported in Figure 3. Compared to the situation with a piecewise constant baseline as the true form, the differences between the 5% nominal value and the mean and median signal ratio are now increased as expected due to the misspecification of the baseline excess hazard in the model estimation.

Figure 4 reports the results obtained when using the smooth nonparametric baseline excess hazard estimate. The obtained in-control signal ratio is slightly closer towards the desired value of 5%, but the difference in absolute value is still larger compared to the piecewise constant model from above. We suspect that this is a consequence of the choice of the smoothing parameters in the experiment. This example shows a potential issue with the nonparametric baseline excess hazard estimate (Perme et al., 2009) - the smoothing parameters will have a large impact on how the charts will perform compared to the required in-control performance. An ideal situation is to obtain the full continuous
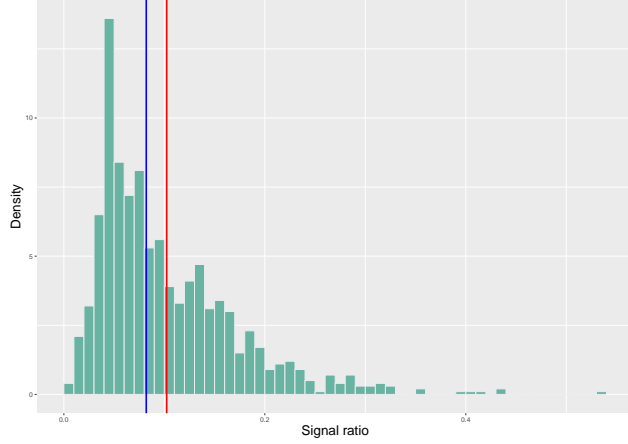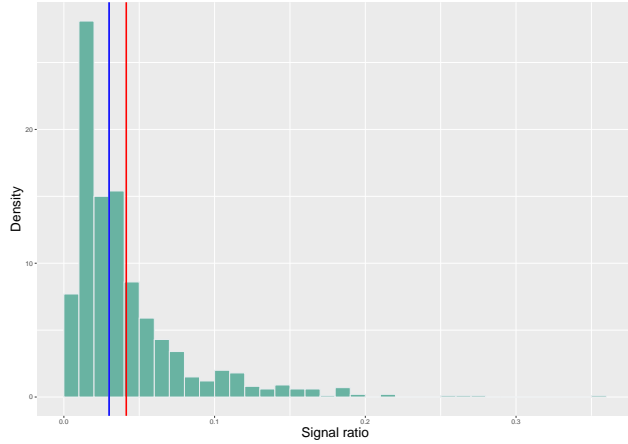
(a) True covariate distribution used in step 4. Mean signal ratio is 10.23%, median signal ratio is 8.20%.
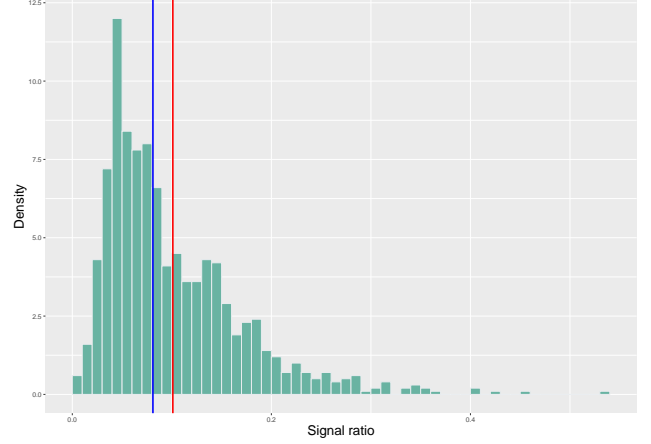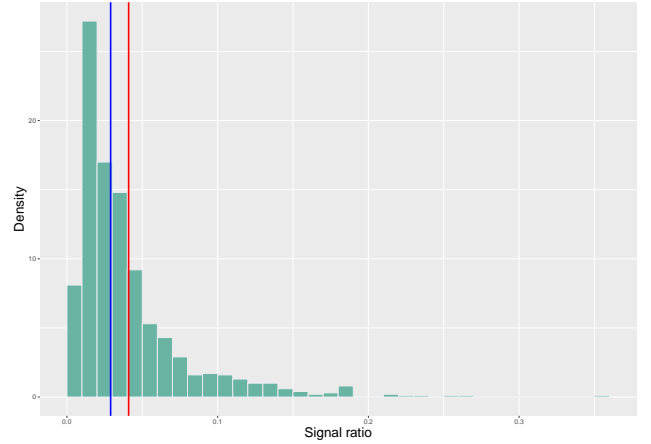
(b) Bootstrapping used to estimate the covariate distribution. Mean signal ratio is 10.10%, median signal ratio is 8.10%.

Figure 2: Histograms of the achieved rejection probabilities under in-control scenario with the true baseline excess hazard following a piecewise constant function. The model estimation is done using a smooth nonparametric baseline excess hazard in step 3. Here, the blue vertical line represents the median and the red line corresponds to the mean signal ratio.

(a) True covariate distribution used in step 4. Mean signal ratio is 4.14%, median signal ratio is 3.00%.

(b) Bootstrapping used to estimate the covariate distribution. Mean signal ratio is 4.09%, median signal ratio is 2.90%.

Figure 3: Histograms of the achieved rejection probabilities under in-control scenario with the true baseline excess hazard following the hazard function of the Weibull distribution. The model estimation is done using the model with piecewise constant baseline in step 3. Here, the blue vertical line represents the median and the red line corresponds to the mean signal ratio.
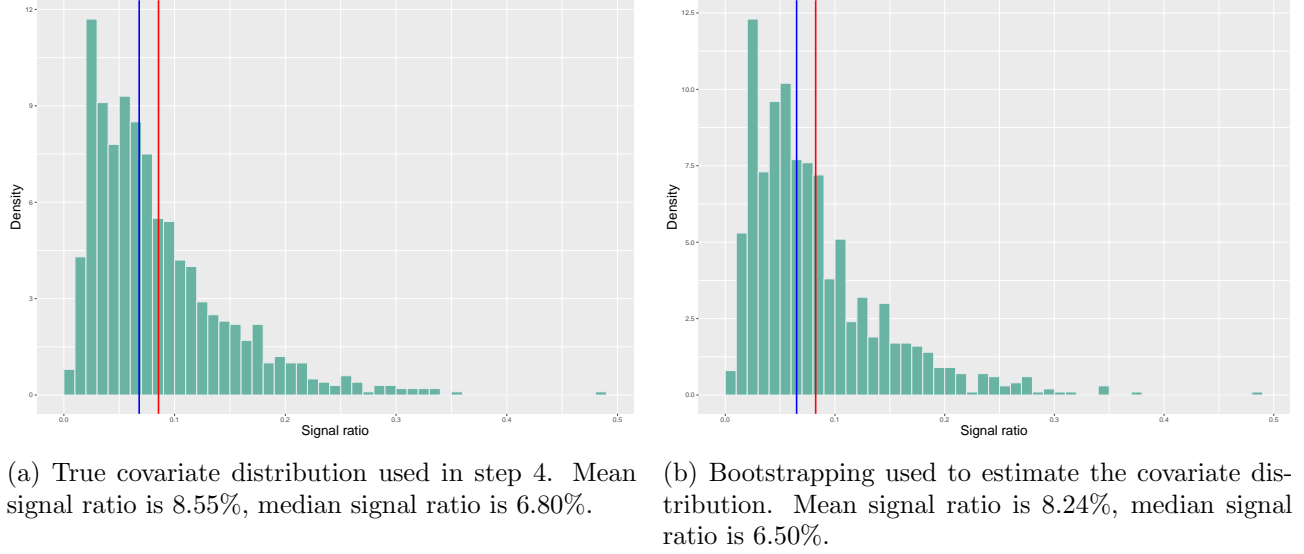
(a) True covariate distribution used in step 4. Mean signal ratio is 8.55%, median signal ratio is 6.80%.

(b) Bootstrapping used to estimate the covariate distribution. Mean signal ratio is 8.24%, median signal ratio is 6.50%.

Figure 4: Histograms of the achieved rejection probabilities under in-control scenario with the true baseline excess hazard following the hazard function of the Weibull distribution. The model estimation is done using a smooth nonparametric baseline excess hazard. Here, the blue vertical line represents the median and the red line corresponds to the mean signal ratio.

estimate of h_0 at the last E-step of the EM-algorithm when fitting the Cox-type excess hazard model to avoid another smoothing operation on top of the already smoothed estimates. However, this is not possible, and one could argue that this combination might give rise to oversmoothing. Nonetheless, this simulation setup illustrates the challenges of a nonparametric baseline in the model estimation when using the proposed monitoring scheme.

4   Application to colorectal cancer data monitoring

In this section, we apply the proposed methods to a subset of a data set of 171 087 patients diagnosed with colorectal cancer in Norway between the start of 1953 and the end of 2020. We will here only consider data from 1970 and onwards. We will also focus on patients that have received major surgery, have a cancer stage grading of 1-3 and with specified and known position of the tumor, i.e. patients treated with a curative intention. With reference to Table 5, this means that the relevant subset is the patients in surgery group 0, with SEER stadium equal to localised or regional and with ICD indicator equal to 0, 1 or 2. Furthermore, a recent focus in studies of colorectal cancer has been regarding early-onset colorectal cancer, the occurrence of the disease among younger patients (see e.g REACCT Collaborative, Zaborowski, Abdile, Adamina, Aigner et al. (2021) for an overview). Inspired by this fact, we divide the data into patients up to 50 years and patients above 50 years of age. This leaves us with 5321 patients in the younger age group and 86 360 patients in the older age group.

In this example, we explore monitoring in bands of 10 years, i.e. we choose a baseline period of 10 years and use this period to monitor for the next 10 years. More specifically, we define the first baseline period to be between 1970-1980. The patient cohort diagnosed in this period is used to fit an excess hazard model that will represent $h_{E,0}(\cdot, X_i)$ in the CUSUM chart. The covariate vector X_i here contains gender, ICD indicator, morphology type and SEER stadium.

We will here only consider a piecewise constant baseline excess hazard model. With these results as the in-control period, we run the CUSUM charts for the next 10 years, i.e. the time period between

1980-1990. Subsequently, this period is then used as the baseline period for the new monitoring period of 1990-2000, and this is done until we monitor the period between 2010 and 2020.

4.1 Proportional alternative

First, we consider the proportional alternative. For each combination of age group and monitoring period, the chart is computed using four different values of ρ: 0.80, 0.90, 0.95 and 1.05, i.e. three scenarios corresponding to decreased and one to increased excess hazard. Figure 5 shows the calculated charts for different combinations of monitoring time period and ρ in the two age groups. The dashed lines are the thresholds obtained by simulations using the bootstrap procedure mentioned in Section 3.5. It is clear from both plots that the charts fluctuate and do not signal for any combinations of age group and time period when considering the increased burden of disease scenario of $\rho = 1.05$.

All charts signal for all the $\rho < 1$ scenarios, indicating that improvement versus the previous decade is observed for all the periods considered. For the elders, a striking observation is that in the 1990s, no improvement was seen during the first five years. An explanation for this could be that possible advancements in diagnosis and treatment of colon cancer during the 1980s were not reflected in changes in outcomes during the first half of the 1990s. On the other hand, the chart signals fastest in the period 2010-2020. This could indicate early advances in this period, but the faster signal could also possibly be partly explained by more patients arriving during this time interval. For the younger, there seems to be an indication of a better treatment advance in the period 2000-2010 versus the previous decade than in the other periods. The generally later signals for the younger could be explained by much fewer patients in this group.

4.2 Additive alternative

Next, we investigate the setting of an additive alternative. As in the previous setting, we also here use three shift parameters that correspond to decreasing and one corresponding to increasing excess hazard, i.e. the values of γ considered are -0.020, -0.010, -0.005 and 0.005. The results are depicted in Figure 6. We observe that none of the charts yield a signal for the $\gamma = 0.005$ case that implies a worse outcome over time in this additive setting, although for the younger patients, the charts are actually close to a signal in the periods 1980-1990 and 1990-2000.

For the remaining values of γ, all the charts related to the old age group signal with an increasing trend. The behaviors of the charts across all the values of γ are very similar to the proportional alternative, with the latest two monitoring periods appearing to have the largest improvement.

Looking at the charts obtained from the younger age group, no signals are now obtained in the first two monitoring periods for $\gamma < 1$ unlike the conclusions from the proportional alternative. The values of the charts for the periods 2000-2010 and 2010-2020 when $\gamma = -0.010$ and $\gamma = -0.005$ are also much closer. In addition, for the largest shift $\gamma = -0.020$, the chart for the period 2010-2020 starts decreasing again after signalling at around 5 years. Therefore, the evidence of a larger reduction of -0.020 in the excess hazard is much weaker for this period compared to the evidence for smaller changes like -0.010 and -0.005. This shows the effect of setting a value of the change parameter to a larger change than the observed.

4.3 Linear accelerated time alternative

Finally, we try a linear accelerated time alternative with the following four values of the acceleration parameter k: 0.80, 0.90, 0.95 and 1.05. Therefore, this corresponds again to three improvement alternatives and one worsening situation. For the older age group, we see a similar behaviour as in the previous models, although with a later signal in the case with the smallest improvement of $k = 0.95$.
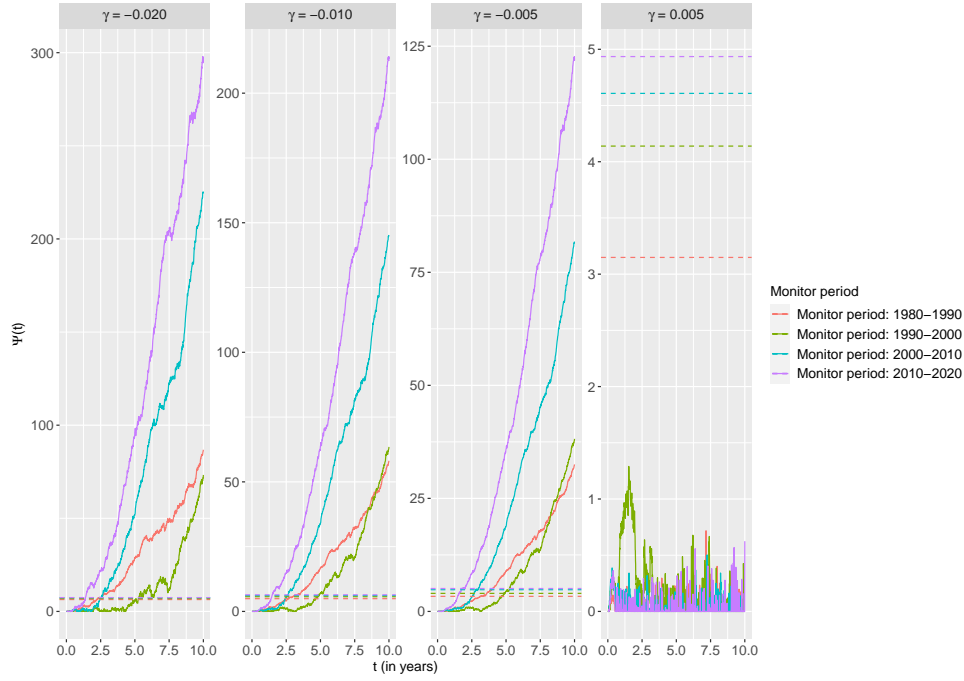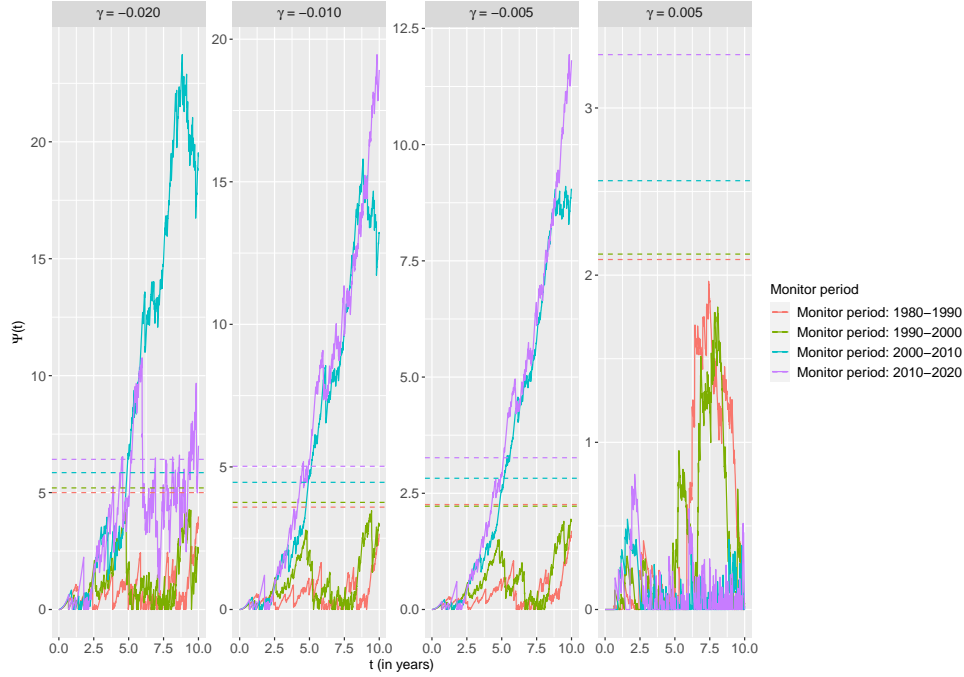
15
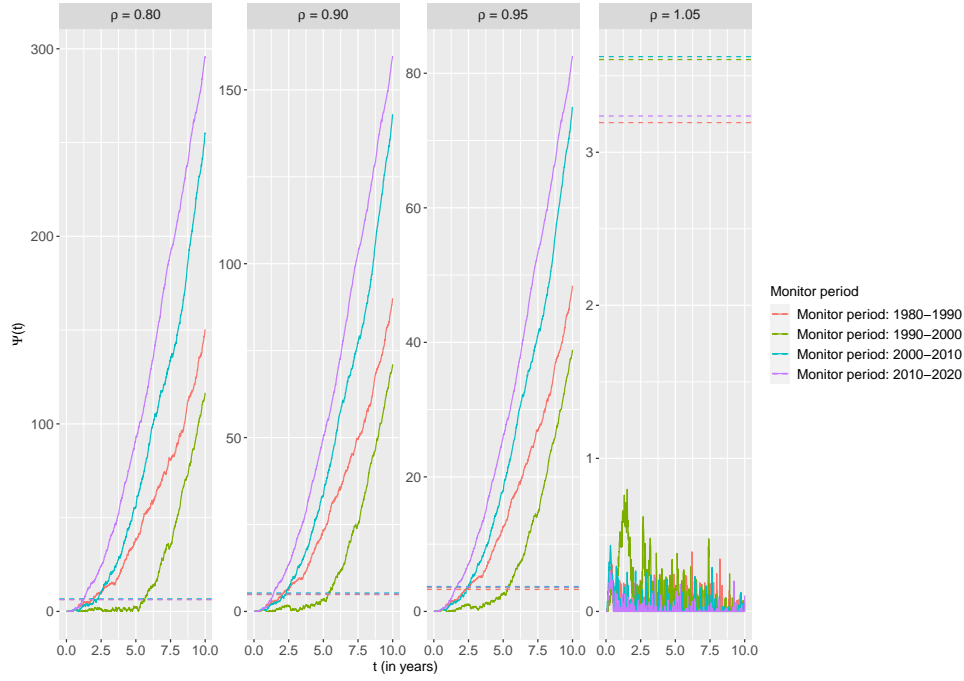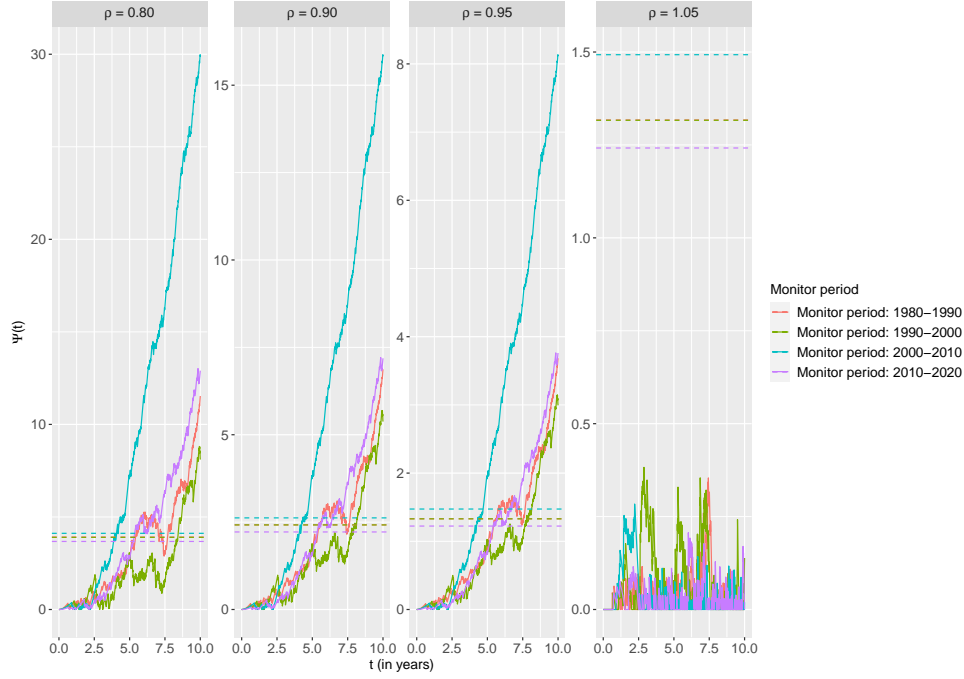
(a) Age > 50

(b) Age ≤ 50

Figure 5: CUSUM charts using the proportional alternative for each age group monitoring 10-year survival in four different time periods with the estimated output from the piecewise constant baseline excess hazard model fitted on the preceding 10-year time period as the in-control. Four different values of ρ are explored here.
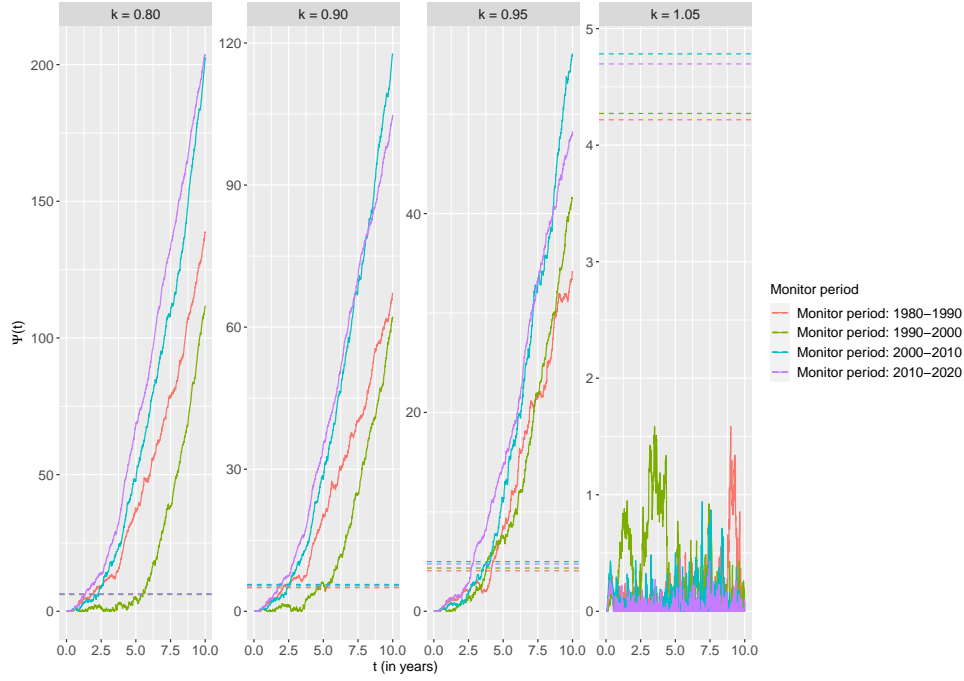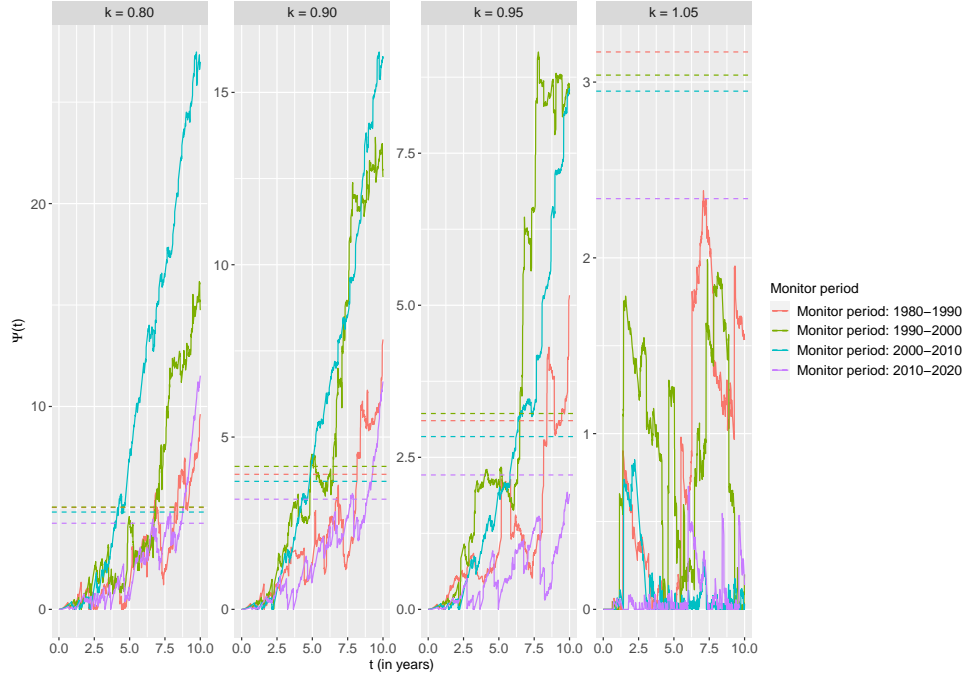
(a) Age > 50

(b) Age ≤ 50

Figure 6: CUSUM charts using the additive alternative for each age group monitoring 10-year survival in four different time periods with the estimated output from the piecewise constant baseline excess hazard model fitted on the preceding 10-year time period as the in-control. Four different values of γ are explored here.

(a) Age > 50

(b) Age ≤ 50

Figure 7: CUSUM charts using the linear accelerated time alternative for each age group monitoring 10-year survival in four different time periods with the estimated output from the piecewise constant baseline excess hazard model fitted on the preceding 10-year time period as the in-control. Four different values of k are explored here.

The most interesting observation from the results regarding the younger age group is the charts corresponding to the periods 1990-2000 and 2010-2020. With the additive alternative, the charts monitoring towards improvement for 1990-2000 did not signal at all. However, with the linear accelerated time alternative, all charts for this period signal for all values of $k < 1$, as was also the case for the corresponding charts with the proportional model. Further, the charts for 2010-2020 have a much later response than what was observed for the additive and proportional alternative. Also, when $k = 0.95$, the chart does not even signal. This is another example of how different alternatives can potentially lead to different conclusions.

5 Summary

We have presented a CUSUM-based method for monitoring changes in excess hazard for situations where the population hazard is known. This complements the literature on monitoring based on time to event models. The proposed method can be used either for real-time monitoring or for retrospective analyses. The method can be adapted to various data updating schemes.

We have considered proportional, additive and linear accelerated time change models and studied properties by simulations and in an application to cancer registry data. In particular, we have also considered the impact of estimation error and some forms of model misspecifications. Simulations indicate that with a decent amount of baseline data, the impact of estimation error is not critical. However, model misspecifications might be a more severe issue. Applications to data illustrate that careful considerations need to be made when specifying the type of changes in the excess hazard to monitor against.

Disclaimer
The study has used data from the Cancer Registry of Norway. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Cancer Registry of Norway is intended nor should be inferred.

A Summary table of the covariates in the simulation setup of Section 3

Table 5: Overview of the covariates used in the simulations, with the corresponding parameter value used and proportion of observations simulated to be in each category for the categorical covariates. Age is simulated from a normal distribution with mean 75 and standard deviation 10, truncated at 50 and 105. See Tran (2022) for details about the medical interpretations of the covariates.

Variable	β	Proportion
Gender = Male	·	50.00%
Gender = Female	0.005	50.00%
ICD indicator = 0	·	27.00%
ICD indicator = 1	0.500	44.00%
ICD indicator = 2	0.200	28.00%
ICD indicator = 3	0.300	1.00%
Morphology type = Adenocarcinoma	·	90.00%
Morphology type = Mucinous carcinoma	−0.050	10.00%
SEER stadium = Distant	·	20.00%
SEER stadium = Localised	−3.000	20.00%
SEER stadium = Regional	−1.750	55.00%
SEER stadium = Unknown	−1.000	5.00%
Surgery group = 0	·	82.75%
Surgery group = 1	1.500	17.15%
Surgery group = 2	2.500	0.10%

B Smoothing procedure for the semiparametric excess hazard model in the CUSUM method

An important note regarding the semiparametric excess hazard model is that the user can specify a smoothing parameter `bwin`. Originally, the estimation of the model is done using the EM-algorithm by Dempster, Laird and Rubin (1977). Perme et al. (2009) proposed to apply kernel smoothing to the nonparametric baseline excess hazard estimates at each E-step of the algorithm. The argument `bwin` therefore controls the bandwidth in the smoothing process, with larger values implying larger bandwidth, and therefore smoother estimates. In the end, only the estimates of h_0 at the times to event are returned. However, in order to apply the proposed CUSUM procedures, $h_0(t)$ is required at all possible values of $t \in [0, 10]$ for continuous monitoring if the main interest is the 10-year excess survival. To get a continuous estimate of $h_0(t)$, we must again apply some sort of manual smoothing on top of the returned estimates at the times to event. For this purpose, smoothing splines (see e.g. James, Witten, Hastie and Tibshirani (2013)) are used with the baseline excess hazard estimates as the response variable and the times to event as the sole predictor. Therefore, there are two extra sources that can impact the upcoming results: The smoothing parameter `bwin` at each E-step of the EM-algorithm when fitting the model and the effective degrees of freedom from the smoothing splines procedure. To get somewhat sensible results, we have decided to set `bwin` and the effective degrees of

freedom to 25. It is therefore important to note that a different combination of these two parameters will lead to a different result than what we have obtained in Section 3.5.

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