

Application of gap time analysis with flexible hazards to pulmonary exacerbations in the EPIC Observational Study

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Cystic fibrosis and other chronic lung disease clinical trials often use time to first pulmonary exacerbation (PE_x) or total PE_x count as endpoints. Use of these outcomes may fail to capture patterns or timing of multiple exacerbations and how covariates influence risk of future exacerbations. Analysis of gap times between PE_x provides a useful framework to understand risks of subsequent events, particularly to assess if there is a temporary increase in hazard of a subsequent PE_x following the occurrence of a PE_x. This may be useful for estimating the amount of time needed to follow patients after a PE_x and predicting which patients are more likely to have multiple PE_x. We propose a smoothed hazard for gap times to account for elevated hazards after exacerbations. A simulation study was conducted to explore model performance when misspecified and was able to appropriately estimate parameters in all situations with an underlying change-point with independent or correlated recurrent events. Models with different change-point structures and trends are compared using Early Pseudomonas Infection Control Observational Study data, using a quasi-likelihood modification of Akaike information criterion; a model with a change-point provided a better fit than a model without one. The analysis suggests that the change-point may be 1.8 years (SE 0.09) after the end of a PE_x. Models including covariates in the hazard function revealed that having one or two copies of the $\Delta F508$ mutation, female sex, and higher numbers of previous PE_x were significantly associated with increased risk of another PE_x.

Key words: Change-point hazard model; Gap time model; Pulmonary exacerbations

1 Introduction

Cystic fibrosis (CF) is a genetic disorder affecting approximately 30,000 individuals in the U.S. and 70,000 worldwide (Treggiari *et al.*, 2009), making it the most common life-shortening inherited disorder in Caucasians (Yan and Fine, 2008), though it affects all races and ethnicities. One of the hallmarks of CF is pulmonary exacerbations (PE_x), which are periods of increased sputum production, chest congestion, coughing, fatigue, and decreased lung function (Rosenfeld *et al.*, 2001). In addition to being associated with significant medical costs, pulmonary exacerbations cause significant lung and respiratory damage, reduced quality of life, and, over time, increased mortality (Parkins *et al.*, 2012, Rosenfeld *et al.*, 2001, VanDevanter *et al.*, 2016). It has been suggested too that occurrence of PE_x is associated with greater subsequent declines in lung function (Waters *et al.*, 2012). Thus, PE_x are important clinical outcomes in CF that warrant further evaluation.

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Given the importance of pulmonary exacerbations in CF, obtaining a better understanding of the risk for recurrent exacerbations over time may be useful for preventing future events. A carryover effect after each PEx, in which the occurrence of one event produces a temporary increase in hazard or risk of a future event, has been previously studied (Çiğşar and Lawless, 2012), and is the focus of our work. The study that motivates this work is the Early Pseudomonas Infection Control (EPIC) observational study, a multicenter study that enrolled and followed over 1700 patients diagnosed with cystic fibrosis (Treggiari *et al.*, 2009, Rosenfeld *et al.*, 2012). Data are available from the earliest registry entry or pulmonary exacerbation.

Existing approaches to modeling PEx as a study endpoint include analysis of time to first exacerbation, one randomly selected exacerbation, or number or rate of exacerbations (Ferkol *et al.*, 2006, Ramsey *et al.*, 1999, Saiman *et al.*, 2003, Sanders *et al.*, 2010, VanDevanter and Konstan, 2010). These approaches exclude exacerbation data if only considering the first exacerbation or a randomly selected exacerbation, and they fail to address timing of exacerbations or dependence between events when only considering total number or rate. With few exceptions (Espel *et al.*, 2017, Mayer-Hamblett *et al.*, 2018), most previous studies that have considered recurrent PEx in the analysis only included a subset of all exacerbations, such as the number of PEx in a baseline period (Sequeiros and Jarad, 2010, Smith *et al.*, 1999, VanDevanter *et al.*, 2016). All such approaches fail to incorporate some aspect of the PEx disease process.

Our particular interest with this data is in testing whether there is a temporary increase in hazard of a subsequent PEx following the occurrence of a PEx. Understanding how the hazard of having a PEx changes over time could be useful for (i) better estimating the amount of time needed to follow patients after a PEx, (ii) predicting which patients are more likely to have multiple PEx, and (iii) in future work, identifying predictors observable at the end of a PEx that suggest whether the patient will have another in a short time, and if so, that treatment may be needed. The lengthy follow-up period of the EPIC study allows for studying and testing this important problem.

Models that explicitly incorporate a change in the hazard of an event have been proposed in the literature, including the classical change-point model allowing for a sudden change in the hazard of an event. However, this model is most appropriate when there is expected to be a sharp change in the level of the hazard, which is not necessarily the case in many biological processes. Muller and Wang (1994) proposed a smoothed approximation change-point model in which the “point of most rapid change” is defined as the maximum of the first derivative of the hazard. We propose a parametric function for the hazard that still estimates the point of most rapid decline but converges to the classical change-point in the limit when one of the parameters approaches zero (Zelterman *et al.*, 1994); we therefore refer to this model as a smoothed change-point model.

In this paper, we propose a recurrent-events model with a smooth, flexible hazard to address the question of whether there is an increased risk of having a future PEx after the conclusion of a prior PEx. To our knowledge, this is the first application of a gap time analysis to address this important clinical question and therefore represents a significant contribution to the literature. Our approach incorporates two important characteristics. First, it allows for the estimation of the “point of most rapid change” (Muller and Wang, 1994, p. 226) with a flexible hazard. For brevity, we refer to this as a smooth change-point model, although our model only coincides with the classical change-point hazard model in a limiting sense. The smoothness of our adaptation of the classical model is achieved through the use of a logistic cumulative distribution function to approximate the indicator function implicit in the classical change-point hazard model: when the scale parameter of this CDF approaches zero, the model converges to the classical change-point model (Zelterman *et al.*, 1994). Second, our approach allows for the hazard to depend on event history, thereby allowing individuals’ hazards to increase over time in association with the number of previous PEx. This relaxes the usual independent and identically distributed assumptions of renewal processes (Cook and Lawless, 2007, Heggland and Lindqvist, 2007) through the use of robust covariance estimation. Analyzing exacerbations within our proposed framework uses all exacerbation data, rather than restricting to only one exacerbation, a subset, or a total count (Cook and Lawless, 2007, Heltshe *et al.*, 2016, Twisk *et al.*, 2005, Waters *et al.*, 2015).

The remainder of the paper is structured as follows. The motivating example from the EPIC observational study is detailed in Section 2. Section 3 describes the smoothed change-point model (3.1) and the likelihood construction (3.2). Simulation studies investigating model misspecification and the effect of correlated versus independent events are described in Section 4. The data analysis is summarized in Section 5, including model results (5.1), covariate effects (5.2), and goodness of fit (5.3). The paper concludes with discussion of these results and other applications of this model in Section 6.

2 Early Pseudomonas Infection Control (EPIC) Observational Study

Data on the gap times between PEx were drawn from the EPIC Observational Study, where data was collected through the Cystic Fibrosis Foundation Patient Registry (CFFPR). This study enrolled CF patients who had either no prior isolation of *Pseudomonas aeruginosa*, or at least a two-year period with no isolation of *P. aeruginosa* (Treggiari *et al.*, 2009). Data collected in the EPIC observational study are longitudinal and include demographic and risk factor data, respiratory cultures, clinical encounter information, and clinical outcomes, such as bacterial infections or pulmonary exacerbations (PEx). PEx are an important clinical outcome defined by the requirement of IV antibiotics or hospitalization for respiratory symptoms (Cystic Fibrosis Foundation, 2016). If an individual started a PEx within one week of the end of their last exacerbation, those events were treated as a single exacerbation (VanDevanter *et al.*, 2016). The exacerbation data are recorded in age to the nearest hundredth of a year, meaning that PEx that begin and end within 0.02 years of one another are treated as a single exacerbation. It is more conservative to combine PEx that start and end within one week of one another into a single exacerbation rather than combining PEx within a larger time window, because this provides us with greater capabilities to model the risk directly after PEx, particularly when PEx are closely spaced in time. PEx duration was not included in the model, since our interest lied in hazards directly after a PEx concluded.

The beginning of follow-up was defined as an individual's earliest registry entry or pulmonary exacerbation; a registry entry could have occurred before their enrollment in the EPIC Observational Study. End of follow-up in the study was defined as a patient's latest CF registry encounter or pulmonary exacerbation. These data include observational data through 2014.

Predictors of clinical interest considered in our analyses were determined *a priori* and included genotype and sex. Our genotype of interest was defined by the number of confirmed $\Delta F508$ (F508del) mutations (0, 1, or 2), where 0 included both those with 0 known copies and those with unknown status with respect to this mutation. Homozygosity of $\Delta F508$ ($\Delta F508/\Delta F508$), the most common CF-causing mutation (Cystic Fibrosis Foundation, 2016) is associated with increased risk of infection and lower lung function in CF (Rosenfeld *et al.*, 2012, Sanders *et al.*, 2010).

Gap times between PEx were defined as years between the end of one PEx and the start of the next PEx. Durations of PEx are excluded from gap times, since an individual is not at risk for another exacerbation before their current exacerbation has ended. Kaplan-Meier curves (Figure 1) suggest that gap times may have different distributions depending on the number of previous exacerbations.

3 Gap time analysis model with smoothed change-point

3.1 Model of recurrent exacerbations with smoothed change-point hazard

The classical change-point hazard (Matthews and Farewell, 1985, Müller and Wang, 1994) can be written as $h(t) = \lambda_0(t)\mathbf{I}(t > \omega) + \lambda_1(t)\mathbf{I}(t \leq \omega)$ for some change-point $\omega \geq 0$, where the indicator function \mathbf{I} is equal to 1 when true and 0 otherwise. The hazard is equal to $\lambda_0(t)$ when the gap time is greater than some change-point ω and the hazard is defined as $\lambda_1(t)$ when the gap time is less than ω . In this context, $\lambda_1(t)$ represents the hazard of having a future PEx immediately after a PEx ends, and $\lambda_0(t)$ represents that baseline hazard of having a PEx that all individuals are assumed to return to.

However, the change-point is unlikely to be this “sharp” in a biological process, so a hazard rate that allows for more flexibility in its shape is required to test our specific hypotheses of interest related to the EPIC observational data. We therefore replace this change-point hazard formulation with a smooth function, $G(t; \omega, \sigma) = \{1 + \exp[-(t - \omega)/\sigma]\}^{-1}$, where σ is the smoothing parameter associated with the change-point. The logistic cumulative distribution function (CDF) is a natural choice for G since it has closed-form integrals and since it is a symmetric location-scale family CDF. Therefore, it can smoothly approximate our function of interest if the location parameter is set equal to ω while the scale parameter approaches 0 (Zelterman *et al.*, 1994). Indeed, any such CDF could equally serve this purpose, including the normal distribution function; however, the specific choice of CDF used to smoothly approximate the indicator is not expected to impact results substantially. Thus, we write the change-point hazard

$$h(t) = \frac{\lambda_0}{1 + \exp\left(-\frac{t-\omega}{\sigma}\right)} + \frac{\lambda_1}{1 + \exp\left(\frac{t-\omega}{\sigma}\right)} \quad (1)$$

3.2 Likelihood construction

If times between exacerbations have the distribution defined by the smoothed change-point hazard in (1), then each subject has a renewal process $N_i(t)$, which assumes independence between event times within a subject, $i = 1, \dots, M$. We take the approach of constructing the likelihood based on this assumed “working” independence correlation structure, and then adjust the standard errors of the resulting estimates using a robust estimator for the covariance matrix (Croux *et al.*, 2003). Since the likelihood construction assumes independence between events, after maximizing the working-independence likelihood (3), robust standard errors from sandwich estimators may be obtained to account for within-subject correlation.

For each subject, let n_i be the number of exacerbations observed. Let z_i be the time from the end of the last exacerbation to their last recorded event, and let $t_{i,1}, t_{i,2}, \dots, t_{i,k_i}$ denote the k_i gap times between exacerbations for individual i . Each subject’s likelihood contribution will depend on whether $n_i = 1$ or $n_i \geq 2$. Note that subjects with no events would not contribute to the likelihood since they have no information on times between exacerbations and are considered to be waiting for their first exacerbation. For an individual with exactly one exacerbation recorded during follow-up time, their only contribution to the likelihood would come from the gap time after the end of their first exacerbation z_i , which would contribute to the survival function. Thus, the likelihood contribution for this subject would be $L_i = S(z_i) = \exp(-H(z_i))$.

Otherwise, for an individual with more than one exacerbation recorded over the course of their follow-up time, the gap time(s) between exacerbations for individual i , $t_{i,1}, t_{i,2}, \dots, t_{i,k_i}$, would contribute to the likelihood as observed event times. Then, the gap time from the end of their last exacerbation to their last recorded event, z_i , would contribute the survival function. Thus, a subject with more than one exacerbation would contribute:

$$L_i = S(z_i) \prod_{j=1}^{k_i} f(t_{i,j}) = \exp(-H(z_i)) \prod_{j=1}^{k_i} h(t_{i,j}) \exp(-H(t_{i,j})). \quad (2)$$

The model may be generalized to allow inclusion of covariates in a proportional hazards framework and non-independent and identically distributed gap times; note that the assumptions of independent and identically distributed observations have been violated, so this cannot be classified as a renewal process. Since we have clinical rationale to believe that individuals’ hazards of having another exacerbation differ based on their sex, number of copies of $\Delta F508$ and number of previous exacerbations, we propose modifying (1) to allow for greater flexibility in hazards at each gap time j and to allow for covariates to affect the hazards as well.

Let \mathbf{x}_i be a vector of fixed covariates for individual i . The hazard function for the j th gap time, $j = 1, \dots, J$, and the i th subject will be equal to

$$h_{ij}(t) = \left[\frac{\lambda_{0j}}{1 + \exp\left(-\frac{t-\omega}{\sigma}\right)} + \frac{\lambda_{1j}}{1 + \exp\left(\frac{t-\omega}{\sigma}\right)} \right] \exp(\mathbf{x}_i' \boldsymbol{\beta}), \quad (3)$$

where the baseline (λ_{0j}) and post-event (λ_{1j}) hazards may depend on previous exacerbations and may include fixed covariates, e.g. gender, that act multiplicatively in both hazards. Further generalizations of this work could extend to time-dependent covariates. When no covariates are included, $\boldsymbol{\beta}$ is restricted to 0.

4 Simulation studies

First, a simulation study was conducted under eight scenarios to determine that (i) the model is estimating the correct change-point when one exists, (ii) that when there is no change-point, the model provides evidence of that, and (iii) to assess the effect of censoring on estimating parameters of the change-point model. For each of the scenarios, 1000 data sets with 1000 subjects in each were simulated with one gap time per subject. Each of these data sets was then analyzed with the simplest model that included a smoothed change-point hazard (1). When applicable in the scenarios, the two hazards, λ_1 and λ_0 , were set equal to 0.7 and 0.2, respectively, to reflect the relatively low event rate observed in our data set and to be similar to the hazard rates in the model without trend parameters or covariates. The change-point ω was set equal to 2.0, which was similar to the change-point estimated from our data.

The five scenarios with no censoring were specified as follows:

- (i) Simulation U1: a “sharp” change-point ($\sigma = 0$)
- (ii) Simulation U2: a smoothed change-point where $\sigma = 0.2$
- (iii) Simulation U3: a smoothed change-point where $\sigma = 0.35$
- (iv) Simulation U4: a smoothed change-point where $\sigma = 0.5$
- (v) Simulation U5: no change-point (exponential distribution with a hazard rate of 0.7)

The results of these simulations are shown in Table 2, and the comparison of the true parameter values and the parameters estimated from the simulated data are graphed for these five simulations in the supplement in Figure S1. Note that in scenarios U1 and U5, numerical issues prevented estimation of standard errors using the information matrix, so we recommend bootstrapping for inference when standard error estimates seem unreasonable or when a sharp change-point is suspected.

In simulation scenario U1, we aimed to test whether the model would be able to estimate the change-point well when there was a “sharp” change-point. The change-point was well estimated, with model estimates of the smoothing parameter tending towards zero.

In simulation scenarios U2, U3, and U4, in which the model was correctly specified, the results were largely unbiased with small empirical standard errors.

The results under simulation scenario U5 suggest that the model performs as expected when are fitting a model containing parameters that have no meaning in the data-generating mechanism. Specifically, under an exponential model, several possible configurations of parameters in the change-point hazard model could produce an equivalent fit to the data. For example, setting the change-point equal to 0, the smoothing parameter and one of the hazard rate parameters could take any value; the remaining hazard rate parameter would then correspond to the exponential rate parameter. This results in a situation where the model is not identifiable. The estimates under this simulation scenario, particularly for the change-point, consequently were observed to have very large standard errors. Bias in estimating λ_1 was slightly higher in this scenario than in others, but it was still relatively small.

Next, to determine the effect of censoring on parameter estimation, three simulations were run under different rates of censoring. The two hazards, λ_1 and λ_0 , were set equal to 0.7 and 0.2, the change-point ω was set equal to 2.0, and the smoothing parameter σ was set equal to 0.5 (1).

- (i) Simulation C1: censoring rate of 10%
- (ii) Simulation C2: censoring rate of 25%
- (iii) Simulation C3: censoring rate of 40%

Each of these data sets was then analyzed with the smoothed change-point hazard model. The results of these simulations are also shown in Table 2, and the comparison of the true parameters and estimated parameters are graphed for these three simulations in Figure S1.

The results of simulations C1, C2, and C3 suggest that censoring does not prevent accurate estimation of the hazards, change-point, or smoothing parameter, although standard errors increased incrementally as censoring rates increased. There are slight biases in estimation of the change-point and smoothing parameter as censoring rates increase, but likely not large enough to change clinical interpretation.

Finally, a separate simulation study was conducted in which recurrent events were simulated from a smoothed-change-point hazard model for 200 individuals in 1000 data sets with parameters $\lambda_0 = 0.2$, $\lambda_1 = 0.7$, $\omega = 2.0$, and $\sigma = 0.5$. These data were simulated under nine scenarios with three follow-up times and three frailty variances. The follow-up times considered were 7.6 years (50th percentile) and 9.7 years (75th percentile) to allow for different event rates across scenarios. Three variance structures were considered for the frailty from which the data were simulated: independent recurrent events, a low frailty variance (0.10), and a higher frailty variance (0.45).

The results of these simulations are summarized in Table 3. Bias is not shown since we are fitting a marginal model while simulating data from a conditional model: we would only expect unbiased parameter estimation in the zero frailty variance case, which we do see from these results. Variance estimation was good in all scenarios, with robust standard errors improving slightly over model-based. Results shown in the supplement also consider a shorter follow-up time and smaller sample size to examine the impact of fewer observed events. Here we found that rate of numerical failures was low (<1%) for the larger of the two follow-up times considered, suggesting that performance of the proposed methods may be impacted when too few events are observed.

5 Application to EPIC study

A total of 1772 subjects with CF were included in the dataset, 9 of whom were excluded from the analysis because they received a lung transplant during the course of the study. Ideally, we would treat these patients as censored at the time of lung transplant, but lung transplant data were not specific enough to determine when transplants occurred with respect to PEx. Individuals with at least one exacerbation recorded as longer than 60 days were also removed ($n = 16$), since these durations were considered to be clinically unlikely and possibly due to data entry errors. Others were removed because of missing start or end times for exacerbations or follow-up ($n = 15$). Of the remaining study population, 1017 individuals with at least one exacerbation during follow-up comprised the analysis cohort. Summary demographic information on the individuals comprising the analytic data set is given in Table 1. A total of $N = 1017$ individuals had at least one nonzero gap time. Approximately half of the included individuals were male. The median follow-up time was 14.37 years, and individuals experienced a median of 3 PEx.

5.1 Model Development

While the model in (3) could be made more flexible by allowing the “baseline” hazard λ_{0j} to depend on number of previous events, we were concerned about overparameterizing the model, so this parameter is

assumed constant for the purposes of the EPIC data analysis, $\lambda_{0j} = \lambda_0$. Future work may investigate this or other possibilities for increased flexibility. On the other hand, since we hypothesized that the hazard for time to next PEx would increase as an individual's cumulative number of exacerbations increased, this parameter λ_{1j} depends on previous PEx. Thus trend parameters, that multiply the hazard directly after an exacerbation, are included in the intensity function (3) as follows.

$$\lambda_{1j} = \begin{cases} \lambda_1, & j = 1 \\ \lambda_1 \exp(\gamma_j), & 1 < j < J \\ \lambda_1 \exp(\gamma_J), & j \geq J, \end{cases} \quad (4)$$

where the factors of $\exp(\gamma_j)$ multiplying the hazard of a recurrent PEx prior to return to baseline risk level allow for either an increase ($\gamma_j > 0$) or decrease ($\gamma_j < 0$) relative to the hazard for the first gap time. We vary J in order to balance model complexity and goodness of fit: increasing J allows more flexibility, but there will be less data to estimate the γ_j values as j increases, since fewer participants will have experienced j PEx for larger values of j .

The EPIC analysis is conducted in two stages: the first focuses on evaluating the change-point and trend parameters of the model and the second one on assessing covariates. To compare models and assess fit in the EPIC data, we used a QIC, a modification of Akaike's Information Criterion (AIC) that is commonly utilized in a generalized estimating equations (GEE) framework in which response data are correlated (Pan, 2001). It can be employed in a straightforward manner in cases such as this, where working independence is assumed. QIC is calculated similarly to AIC; the likelihood used in AIC is replaced by a quasi-likelihood, and an adjustment is made to the penalty term to account for the fact that the GEE estimator has different asymptotic properties than the MLE used for AIC.

These models were each fit to the EPIC study data by maximizing the working-independence likelihood with model-based standard errors and robust standard errors from sandwich estimators. Bootstrapped standard errors were also considered, but were very similar to robust standard errors and are therefore omitted. Based on model fit statistics (Figure 2), a model with 10 trend parameters was selected as the optimal model. We chose a candidate set of models with up to 15 trend parameters on the basis of acceptable model parsimony. We observed that 10 trend parameters was approximately at the "elbow" of the QIC criterion, as beyond this point there was relatively little distinction in fit between models.

Results for all models are presented in Table S1, and hazards are plotted over time in the supplement in Figure S2. Note that we also considered generalizations of the model in which we allowed the change-point or smoothing parameter to vary by gap time (results not shown), but the results did not differ appreciably from the results presented here.

To determine the significance of the change-point itself while avoiding the pitfalls associated with non-identifiability of parameters under the null, we performed a separate bootstrap likelihood ratio test. This compared our final model (alternative hypothesis H_1) to a model without a change-point (null hypothesis H_0). We fit each to the observed data, obtaining estimates \hat{M}_0 and \hat{M}_1 respectively and calculating the likelihood ratio test statistic (LRT) based on the difference between these models. We repeated this B times and generated data $y_{1b}, y_{2b}, \dots, y_{nb}$ using observed covariate values but estimates \hat{M}_0 . Finally, we compared the value $-2 * (\ell_0 - \ell_1)$ with the simulated null distribution based on $-2 * (\ell_{01} - \ell_{11}), -2 * (\ell_{02} - \ell_{12}), \dots, -2 * (\ell_{0B} - \ell_{1B})$. Thus, the bootstrap p -value will be the proportion of times the simulated null value of the test statistic is less than the observed value. Using $B = 1000$ bootstrap samples, we observed $p < 0.001$, suggesting that our model fits the data significantly better than a model with no smoothed change-point and flexible hazard. This same p -value was observed when we accounted for correlation within patients by incorporating a cluster-resampling step (Cheng et al., 2013) into the parametric bootstrap procedure described above.

5.2 Effect of covariates

Table 4 presents the results of fitting the best-fitting model to the EPIC data with both genotype and sex included as covariates affecting hazard rate parameters. The addition of covariates had no strong effect on the estimation of the change-point, which was estimated at 1.862 years.

There was a borderline significant difference in hazard multipliers between having 1 copy of $\Delta F508$ and no copies of $\Delta F508$ ($p = 0.076$) and for having 2 copies of $\Delta F508$ compared to no copies ($p = 0.040$). Each increase in number of $\Delta F508$ copies increased the hazard multiplier, suggesting higher risks of having a future PEx for those with greater numbers of mutation copies. There was also a significant difference in the post-PEx hazards for males and females ($p = 0.002$), with females having a hazard that was 1.117 (95% CI: 1.041, 1.198) that of males' hazards of a future PEx.

5.3 Goodness of fit

To assess model fit, a parametric bootstrap was performed (Pewsey, 2018) based on the results of the final selected model, which included a smoothed change-point hazard, 10 trend parameters, and genotype and sex as covariates. Parameters were simulated from the multivariate normal distribution using the parameter estimates and their estimated variance-covariance matrix. Each of the 1017 individuals' follow-up times and covariates were treated as fixed. Then, gap times between exacerbations were simulated until the cumulative sum of the gap times surpassed the follow-up time; the last gap time simulated was considered to be censored. Kaplan-Meier curves for the simulated gap times 1-6 were plotted alongside the Kaplan-Meier curves for the full data and model fit for direct comparison.

This process was repeated 200 times, and the Kaplan-Meier curves for one randomly selected covariate combination—females with 1 copy of $\Delta F508$ —are shown in Figure 2 alongside the Kaplan-Meier curves for the EPIC data and model fit. Kaplan-Meier curves for the other five covariate combinations are shown in Figures S3-S7. These figures can then be examined to easily compare the simulated parametric bootstrap curves to the EPIC data and model fit. There is some deviation among the EPIC data, model fit, and parametric bootstrap curves, but when it occurs, it is usually much further into the tails of the distributions in question, where we have less data available on which to judge model fit. The simulated curves completely cover the data and model fit curves in many of the figures, suggesting that the model fits the data well.

6 Discussion

In this paper, we have proposed a smoothed flexible hazard for modeling gap times between exacerbations in order to address the clinical question of whether there is a period of elevated risk of further exacerbations following the current exacerbation's conclusion. Our parametric approach takes full advantage of the recurrent events structure of the data in the sense that the times of all PEx for a subject are included in the analysis, rather than only using information on time to the first PEx or the total number of events as in previous studies. Applying our proposed approach to data from the EPIC observational study, we were able to determine how hazards of having a future PEx in children with cystic fibrosis change over time and how these flexible hazard rates are associated with genotype, sex, and number of previous PEx. We were able to conclude that while the proposed model fits the data significantly better than a model without a change-point, the clinical significance of this finding is unclear due to the lengthy change-point time estimated: it was anticipated based on clinical considerations that any elevation in hazard following a PEx would last weeks or months rather than almost 2 years as estimated using our model. These results may be useful in informing clinical practice related to estimating the amount of time needed to follow patients after a PEx, and predicting which patients are more likely to have multiple PEx.

In simulation studies, the proposed model estimated the hazard rates, change-point, and smoothing parameter well in all situations when data were simulated from a model with a change-point. When there was no change-point, as expected, standard errors were much larger suggesting that a change-point could take

on a wide range of values. In a real data analysis this would indicate that there is no change-point. There were slight biases when the smoothing parameter was large, but the medians of the parameter estimates were largely unbiased in these situations. The larger the smoothing parameter, the less dramatically the hazard decreases at the change-point, so estimation of a change-point may have less relevance in such situations. Numerical issues prevented estimation of standard errors using the information matrix in simulation scenarios U1 and U5, so we recommend bootstrapping for inference when estimates seem unreasonable or when a sharp change-point is suspected. [In further simulation scenarios in which recurrent events were simulated from a smoothed-change-point hazard with varying follow-up times and frailty variances, variance estimation remained accurate, particularly when using cluster-robust standard errors. These simulations also suggested that the method's performance may be negatively impacted by reduced follow-up time \(i.e., high censoring rates\), which is a common concern in any time-to-event model.](#)

The EPIC observational study represents an important data source for exploration these changing hazards in CF patients since the study had a median follow-up time of 14.4 years per patient, allowing for sufficient data to investigate existence of a change-point. Based on QIC, model M5 provided the best fit to the data. The results of the model showed a clear period of increased risk of a future PEx of approximately 1.86 (SE = 0.09) years. Increasing numbers of copies of $\Delta F508$ mutation and female sex were significantly associated with increased hazard rates. Therefore, there is evidence of a change-point in these data, but since the estimated change-point is approximately 2 years after an exacerbation ends, its clinical relevance may be questionable; had the change-point been much smaller, it could have affected which patients clinicians should closely monitor post-PEx and for how long. However, the hazards are flexible in that they may increase or decrease over time, so the fact that they decrease after an exacerbation suggests clustering of exacerbations (Winklemann, 1995) and provides an adaptable framework for modeling recurrent events.

[The question of model selection was raised during peer review, as in the EPIC data analysis QIC did not reveal a clear minimizing candidate model. Further investigation \(results not shown\) revealed very little dependence of the estimates of \$\lambda_0\$, \$\lambda_1\$, \$\omega\$, \$\sigma\$ on the number of trend parameters. This means that we would obtain very similar conclusions as to the existence and length of a window of increased risk following PEx regardless of how many trend parameters were included. While this may not be true generally, it is reassuring in the analysis of the EPIC data set given the lack of a clear minimizing QIC value.](#)

Two sensitivity analyses were conducted using the best-fitting model with covariates included. First, to determine if the definition of a PEx affected the results, the analysis was repeated with multiple PEx within 14 days (0.04 years) of completing treatment defined as a single exacerbation (in contrast to the period of 7 days (0.02 years) used in the primary analysis). Minimal differences were observed relative to the model based on the 7 day definition. A second sensitivity analysis was conducted to determine if the sample was biased towards sicker patients, since patients with more exacerbations contribute more observations to the likelihood than patients with no or few exacerbations. This analysis was restricted to the 315 individuals who had at least 5 exacerbations (30.9% of analysis cohort). The results of the model fitted to this sub-population were similar to those based on the full sample; the only exception was the change-point, which was estimated at 1.456 years compared to the estimate of 1.86 years from the full sample. So while sicker patients may have contribute more to the likelihood compared to patients with fewer PEx, clinical interpretations of the model do not change.

There are a few limitations of the analysis and results in this paper. First, these results cannot necessarily be generalized to the entire CF population; this was a fairly young cohort with relatively mild disease and a low PEx rate. Next, this model does not account for the duration of exacerbation, which includes the length of treatment. A 14 day treatment is considered fairly standard, but there is some variation around this standard that was not accounted for. If treatment duration were of particular interest, it could be accounted for by extending the modeling framework of an alternating renewal process (Alvarez, 2006), with adaptations of the generalized Cox model (Hu *et al.*, 2011), or with a nonparametric approach (Bhattacharya, 2018). Additionally, due to the enrollment mechanism for the CF registry, we cannot include accurate information about time to first PEx in our model since we were not able to evaluate what a true time zero would be for the patients. This is because we do not know exactly how people are entered into the database and

why; however, as this was not related to our research questions, this was not of concern for this analysis. Our covariates were limited to only include number of copies of $\Delta F508$ and sex due to their importance in previous CF research and treatment; future work will explore other factors that could affect risk of pulmonary exacerbations, including time-varying covariates, such as *Pseudomonas aeruginosa* infection. Future work could also allow covariates to affect other parameters in the model including the change-point or the smoothing parameter. Finally, as an alternative to our GEE-like approach that treats gap times as independent and uses robust standard errors, future work could include a frailty in the model to account for within-subject correlation (Hougaard, 1995, Wienke, 2010), although this could introduce numerical difficulties in computing and maximizing the marginal likelihood.

A gap time model with a smoothed change-point hazard such as we have proposed in this paper has potential applications in understanding a variety of diseases or disorders characterized by a progressive nature. Examples include recurrent opportunistic infections in people living with HIV, recurrent ischemic attacks in individuals with cerebrovascular disease, repeated pyogenic infections in chronic granulomatous disease, recurrent asthma attacks in children (Eshaghi *et al.*, 2016), persistent epileptic seizures (Kwan and Brodie, 2000), periods of acute respiratory worsening in idiopathic pulmonary fibrosis (Raghu *et al.*, 2011), and exacerbations of chronic obstructive pulmonary disease (COPD) (Garcia-Aymerich *et al.*, 2003). These models could also accommodate disease processes that improve over time or with treatment, since they allow flexibility in the direction of trends.

7 Availability of Data and Materials

Simulated datasets and the code used to fit the model will be publicly available in the supplementary materials.

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Conflict of Interest *The authors have declared no conflict of interest.*

Table 1 Demographic information about the $N = 1017$ individuals with at least one pulmonary exacerbation (PEX) recorded in the EPIC observational study, presented with frequencies (percents) or medians (interquartile ranges).

Variable	N (%)	Variable	Median (IQR)
Sex		Age at first PEX (years)	0.28 (1.5)
female	518 (50.9%)	Age at final visit (years)	15.45 (4.4)
male	499 (49.1%)	Follow-up time (years)	14.37 (5.1)
Number of copies of F508del		Total number of PEX	3.00 (4.0)
0	86 (8.5%)	Length of gap time (years)	
1	369 (36.3%)	after 1st PEX	1.94 (3.9)
2	562 (55.3%)	after 2nd PEX	1.15 (2.1)
PEX recorded		after 3rd PEX	0.90 (1.4)
1	325 (32.0%)	after 4th PEX	0.73 (1.1)
2	178 (17.5%)	after 5+th PEX	0.38 (0.6)
3	123 (12.1%)		
4	76 (7.5%)		
5+	315 (31.0%)		

Table 2 This table displays the results of the eight simulation scenarios. Data were simulated from a sharp change-point ($\sigma = 0$) in simulation U1, a smoothed change-point with $\sigma = 0.2$ in simulation U2, a smoothed change-point with $\sigma = 0.35$ in simulation U3, a smoothed change-point with $\sigma = 0.5$ in simulation U4, and no change-point (an exponential distribution) in simulation U5. Simulations C1, C2, and C3 were all simulated from the same parameters ($\lambda_0 = 0.2$, $\lambda_1 = 0.7$, $\omega = 2.0$, and $\sigma = 0.5$), but with different levels of censoring. Simulation C1 had a censoring rate of 10%, simulation C2 had a censoring rate of 25%, and simulation C3 had a censoring rate of 40%. Each of these simulated data sets were analyzed with a model that included a smoothed change-point hazard. *Average estimated standard errors that could not be estimated due to numerical issues are marked with asterisks.

Simulation	Parameter	Mean	Median	Empirical SE	Avg. Estimated SE*	Bias	
U1	λ_0	0.2	0.200	0.199	0.013	*	0.000
	λ_1	0.7	0.705	0.705	0.026	*	0.005
	ω	2	1.989	1.991	0.039	*	-0.011
	σ	0	0.051	0.043	0.033	*	0.051
U2	λ_0	0.2	0.200	0.200	0.014	0.014	0.000
	λ_1	0.7	0.703	0.703	0.031	0.031	0.003
	ω	2	1.994	1.995	0.103	0.103	-0.006
	σ	0.2	0.206	0.196	0.089	0.083	0.006
U3	λ_0	0.2	0.201	0.200	0.015	0.015	0.001
	λ_1	0.7	0.706	0.703	0.044	0.041	0.006
	ω	2	1.987	1.991	0.157	0.155	-0.013
	σ	0.35	0.353	0.336	0.132	0.123	0.003
U4	λ_0	0.2	0.201	0.200	0.015	0.016	0.001
	λ_1	0.7	0.713	0.702	0.070	0.061	0.013
	ω	2	1.962	1.980	0.254	0.238	-0.038
	σ	0.5	0.508	0.487	0.187	0.174	0.008
U5	λ_0	-	8.856	0.706	163.37	*	*
	λ_1	0.7	0.642	0.694	0.263	*	-0.058
	ω	-	3.542	1.239	9.535	*	*
	σ	-	4.730	1.402	7.773	*	*
C1	λ_0	0.2	0.200	0.200	0.020	0.019	0.000
	λ_1	0.7	0.716	0.702	0.073	0.065	0.016
	ω	2	1.954	1.982	0.269	0.251	-0.046
	σ	0.5	0.504	0.478	0.198	0.187	0.004
C2	λ_0	0.2	0.199	0.198	0.034	0.033	-0.001
	λ_1	0.7	0.727	0.702	0.108	0.077	0.027
	ω	2	1.928	1.974	0.361	0.302	-0.072
	σ	0.5	0.521	0.467	0.276	0.235	0.021
C3	λ_0	0.2	0.193	0.195	0.057	0.051	-0.007
	λ_1	0.7	0.740	0.703	0.138	0.098	0.040
	ω	2	1.909	1.975	0.454	0.384	-0.091
	σ	0.5	0.555	0.464	0.385	0.300	0.055

Table 3 This table displays the results of the nine simulation scenarios with three follow-up times (4.3 years, or the 25th percentile of follow-up time after the first PEx in the EPIC-OBS data set; 7.6 years, or the 50th percentile; 9.7 years, or the 75th percentile) and three frailty variances (no variance, low variance, and high variance). One thousand trials of recurrent event data with 1000 individuals in each data set were simulated from a smoothed change-point in all scenarios with parameters ($\lambda_0 = 0.2$, $\lambda_1 = 0.7$, $\omega = 2.0$, and $\sigma = 0.5$). Empirical standard deviations (ESD), asymptotic normal standard error (ANSE), asymptotic robust standard error (ARSE) and the percentage of trials that had numerical issues due to a negative hessian are reported (Fails).

Follow-up time	Frailty variance	Parameter	Mean	Median	ESD	ANSE	ARSE	Fails
7.6	0	λ_0	0.200	0.199	0.014	0.014	0.014	0
		λ_1	0.702	0.699	0.025	0.025	0.025	
		ω	2.000	2.004	0.104	0.102	0.103	
		σ	0.502	0.497	0.095	0.091	0.093	
7.6	0.1	λ_0	0.171	0.171	0.014	0.014	0.014	0.2
		λ_1	0.786	0.781	0.042	0.038	0.039	
		ω	1.818	1.830	0.123	0.118	0.120	
		σ	0.598	0.587	0.102	0.097	0.100	
7.6	0.45	λ_0	0.112	0.113	0.012	0.012	0.012	0.7
		λ_1	1.217	1.181	0.174	0.148	0.158	
		ω	1.086	1.137	0.272	0.246	0.261	
		σ	0.819	0.808	0.116	0.111	0.117	
9.7	0	λ_0	0.200	0.200	0.011	0.011	0.011	0.4
		λ_1	0.702	0.701	0.023	0.022	0.022	
		ω	1.999	2.000	0.090	0.091	0.092	
		σ	0.502	0.498	0.080	0.079	0.080	
9.7	0.1	λ_0	0.174	0.174	0.010	0.010	0.011	0
		λ_1	0.788	0.782	0.037	0.033	0.034	
		ω	1.831	1.842	0.111	0.105	0.107	
		σ	0.592	0.584	0.087	0.083	0.086	
9.7	0.45	λ_0	0.116	0.116	0.009	0.009	0.009	0
		λ_1	1.252	1.216	0.167	0.135	0.143	
		ω	1.077	1.123	0.264	0.227	0.239	
		σ	0.836	0.822	0.112	0.099	0.105	

Table 4 This table displays the parameter estimates from our final model. This model was a smoothed change-point model with 10 trend parameters and covariates for genotype and sex.

	Estimate	SE (robust)	95% robust	
			LCL	UCL
λ_0	0.092	0.011	0.073	0.117
λ_1	0.286	0.026	0.239	0.342
ω	1.862	0.093	1.688	2.053
σ	0.479	0.062	0.371	0.618
$\exp(\gamma_1)$	1.591	0.109	1.392	1.819
$\exp(\gamma_2)$	2.076	0.149	1.803	2.389
$\exp(\gamma_3)$	2.549	0.185	2.210	2.939
$\exp(\gamma_4)$	2.902	0.224	2.495	3.376
$\exp(\gamma_5)$	3.436	0.295	2.904	4.067
$\exp(\gamma_6)$	3.668	0.343	3.055	4.405
$\exp(\gamma_7)$	3.884	0.394	3.184	4.738
$\exp(\gamma_8)$	4.301	0.456	3.494	5.295
$\exp(\gamma_9)$	4.302	0.540	3.364	5.503
$\exp(\gamma_{10})$	7.655	0.561	6.631	8.837
$\exp(\beta_{G1})$	1.154	0.093	0.985	1.351
$\exp(\beta_{G2})$	1.174	0.092	1.007	1.369
$\exp(\beta_F)$	1.117	0.040	1.041	1.198

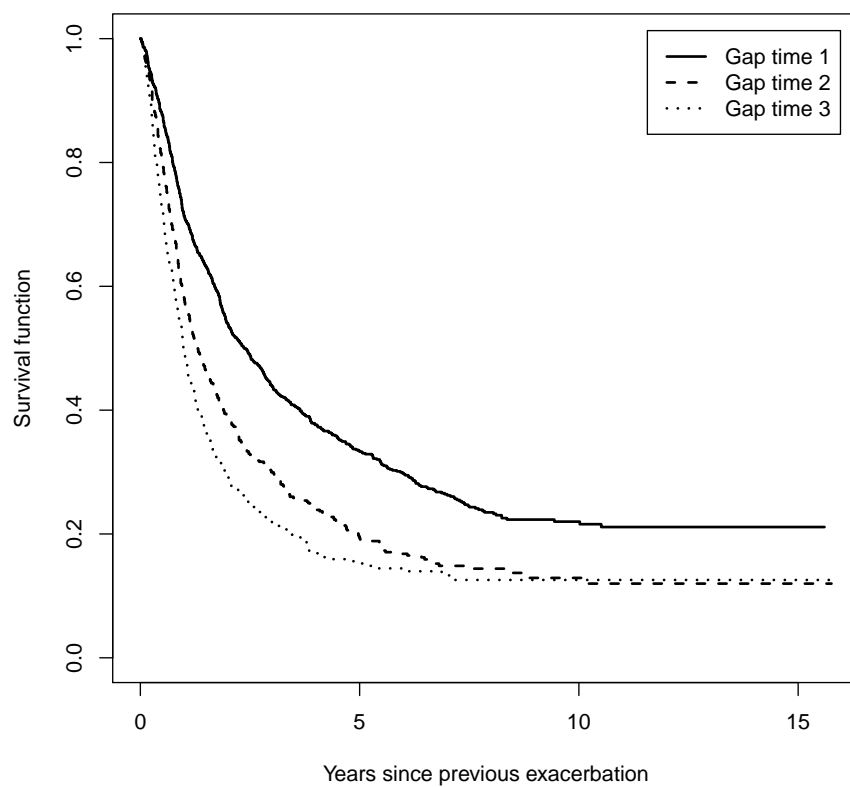


Figure 1 Kaplan-Meier estimates of the survival curves for the 1st gap time (between the first and second exacerbations; $N = 692$ individuals with PEx, 325 individuals censored), the 2nd gap time (between the second and third exacerbations; $N = 514$ PEx, 168 censored), and the 3rd gap time (between the third and fourth exacerbations; $N = 391$ PEx, 118 censored).

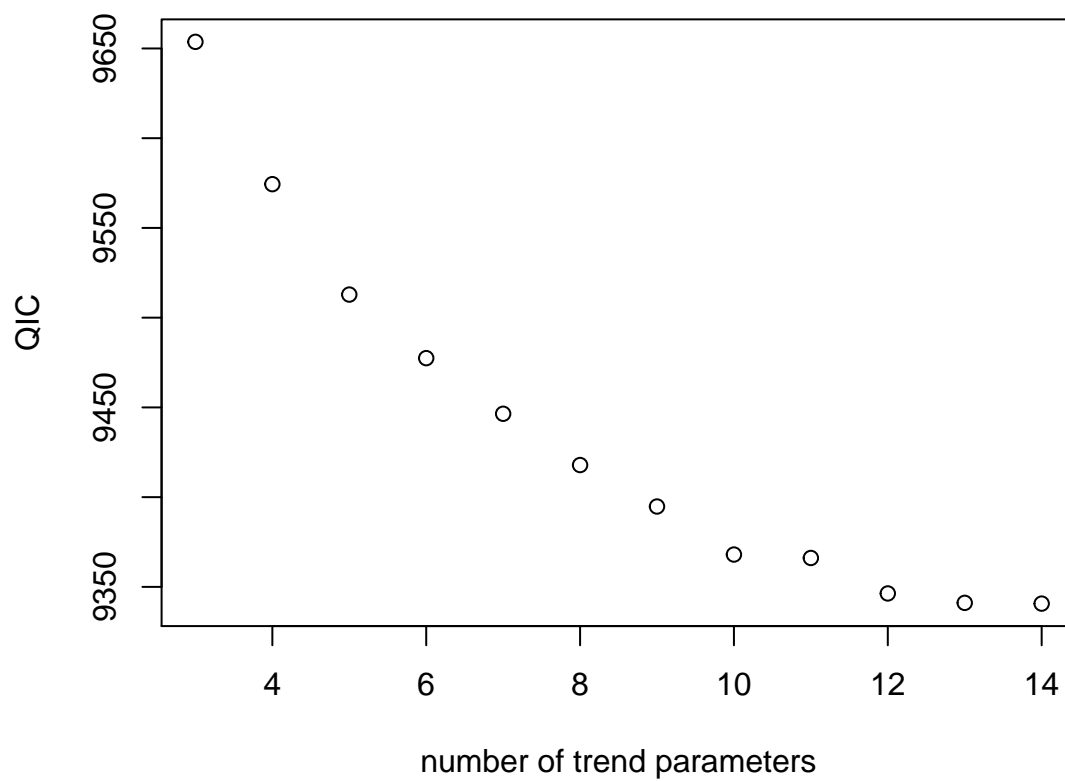


Figure 2 Model fit comparisons on the basis of QIC. The x -axis shows the number of trend parameters included while the y -axis shows the associated quasi-information criterion values for each model. The optimal model was chosen at the “elbow” around 10 trend parameters.

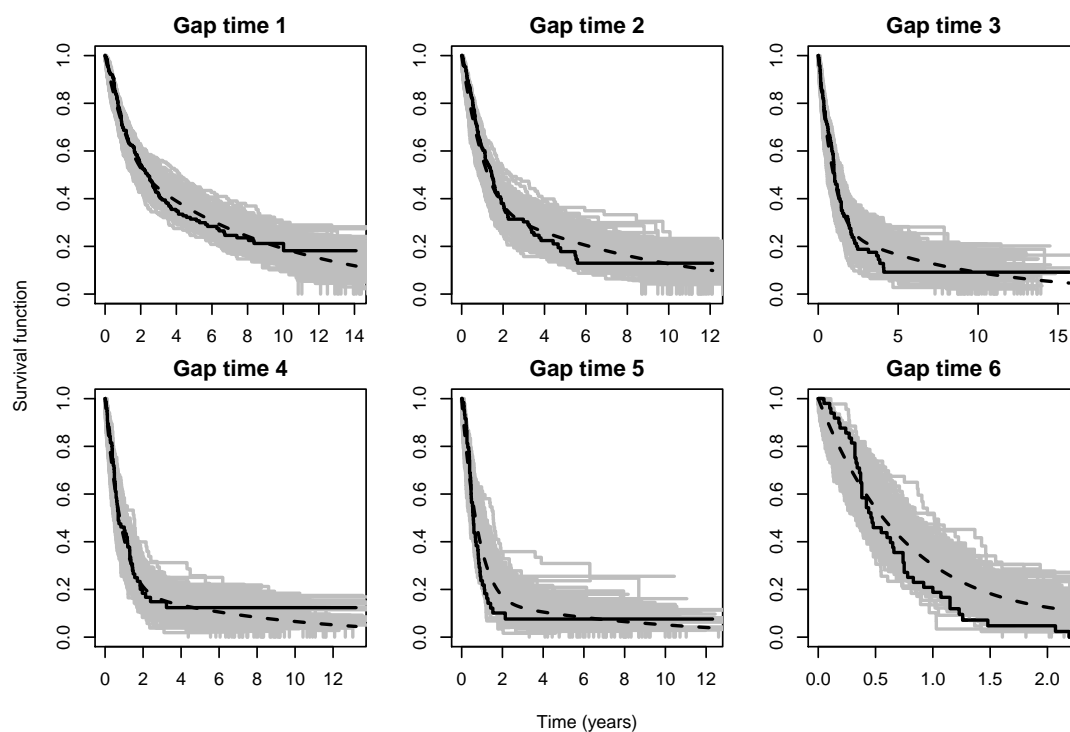


Figure 3 Kaplan-Meier estimates of survival curves of the parametric bootstrap results for females with 1 copy of $\Delta F508$. Note that the x-axis differs in each panel. Kaplan-Meier curves for the simulated results in the parametric bootstrap (gray) are compared to the survival curve of the data (black) and the model fit (dashed). The high coverage of the parametric bootstrap curves over the model fit and the data suggest that the model fits the data well.

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