This article introduces the pammtools package, which facilitates data transformation, estimation and interpretation of Piece-wise exponential Additive Mixed Models. A special focus is on time-varying effects and cumulative effects of time-dependent covariates, where multiple past observations of a covariate can cumulatively affect the hazard, possibly weighted by a non-linear function. The package provides functions for convenient simulation and visualization of such effects as well as a robust and versatile function to transform time-to-event data from standard formats to a format suitable for their estimation. The models can be represented as Generalized Additive Mixed Models and estimated using the R package mgcv. Many examples on real and simulated data as well as the respective R code are provided throughout the article.

Keywords: survival analysis, time-varying effects, time-dependent covariates, cumulative effects, distributed lags, exposure-lag-response associations, functional data analysis, generalized additive mixed models.

1. Introduction

This article introduces the pammtools package (https://adibender.github.io/pammtools/), which provides functions to facilitate the estimation and interpretation of a class of models for time-to-event data analysis, which we call Piece-wise exponential Additive Mixed Models (PAMMs; Bender, Groll, and Scheipl 2018a). PAMMs are a semi-parametric extension of the Piece-wise Exponential Model (PEM) (Friedman 1982) that allow for penalized estimation of very flexible survival models with (time-varying, non-linear) covariate effects, random effects and cumulative effects of time-varying covariates, also known as distributed lags and exposure-lag-response associations (Gasparrini 2014). In short, PAMMs directly transfer the flexibility and performance available in current implementations of generalized additive regression models (GAMs) to time-to-event models.

Using PAMMs for time-to-event data analysis involves three main steps

1. **Data pre-processing**: This can be more or less involved, depending on the type of effects one wants to estimate (especially when the goal is to estimate cumulative effects) and depending on the type of software/package one wants to use for estimation (cf. Section 3).

2. **Estimation**: This step is currently performed outside of pammtools. In this article we use mgcv (Wood 2011) for estimation but any other package that implements
GAMMs or variants thereof can also be used, e.g., model-based boosting via \texttt{mboost} (Hothorn and Bühlmann 2006; Hofner, Mayr, Robinzonov, and Schmid 2012). Most post-processing and visualization functions in \texttt{pammtools} are customized to work with \texttt{mgcv::gam} objects, however.

3. \textbf{Model post-processing}: This includes calculation of estimated hazard rates, cumulative hazards and survival probabilities, which all need to take into account the specific data structure of PAMMs, as well as model/effect visualization, which can also become relatively complex, again, especially in the case of cumulative effects.

In the following, Section 2 briefly describes the piece-wise exponential additive mixed model and introduces the notation used throughout this article. Section 3 demonstrates the data transformations necessary to fit PAMMs in different scenarios, i.e., for data with and without time-dependent covariates (TDCs) and depending on the type of effects to be estimated. In Section 4, we discuss some application examples on real and simulated data to illustrate the estimation, visualization and interpretation of the different effect types in (1), facilitated by convenience functions provided in \texttt{pammtools}. Throughout, the results obtained by PAMMs are compared to estimates obtained from other established models when applicable.

For the code examples, the following packages will be used:

\begin{verbatim}
devtools::install_github("adibender/pammtools")
library(dplyr); library(tidyr); library(purrr); library(ggplot2)
library(survival); library(mgcv); library(pammtools)
\end{verbatim}

2. Piece-wise Exponential Additive Mixed Models

In this article, we consider models for time-to-event analysis with hazard rates given by (1) and in the log-linear form by (2). Note that in (2) the log-baseline hazard was split in two terms such that $\log(\lambda_0(t)) = \beta_0 + f_0(t)$.

$$
\lambda_i(t; x_i, Z_i, \ell_i) = \lambda_0(t) \exp \left[ \sum_{p=1}^{P} f_p(x_{i,p}, t) + \sum_{m=1}^{M} g(z_{i,m}, t) + b_{\ell_i} \right]
$$

$$
\log(\lambda_i(t; x_i, Z_i, \ell_i)) = \beta_0 + f_0(t) + \sum_{p=1}^{P} f_p(x_{i,p}, t) + \sum_{m=1}^{M} g(z_{i,m}, t) + b_{\ell_i}
$$

Let $T_i$ and $C_i$, the true event and censoring times of subject $i$, respectively. Then, $(t_i, \delta_i)$ is the observed event time tuple for subject $i$ with event time $t_i = \min(T_i, C_i)$ and status indicator $\delta_i = 1(T_i \leq C_i)$, $x_i$ is the vector of time-constant covariates $x_{i,p}, p = 1, \ldots, P$ and $Z_i = \{z_{i,m} : m = 1, \ldots, M\}$ is the set of $M$ time-dependent covariate vectors (exposure histories) $z_{i,m} = \{z_{i,m}(t_{z_m,q_m}) : q_m = 1, \ldots, Q_m\}$, where $t_{z_m}$ the (exposure) time points at which covariate $z_m$ was observed. It is important to stress the difference between $t$, which denotes the time scale on which the event times are observed and $t_z$, which denotes the time scale
on which time-dependent covariate $z$ is observed. The two scales $t$ and $t_z$ do not need to be identical or even overlap, nor do they have to be measured in the same units (see Section 3.3 and 4.3 for examples).

In the following paragraphs, we briefly describe the individual components in (2). A tutorial style exposition of the model without the $g(z, t)$ terms is given in Bender et al. (2018a) and a very general framework for models with cumulative effects $g(z, t)$ is described and evaluated in Bender, Scheipl, Hartl, Day, and Küchenhoff (2018b).

The terms $f_p(x_{i,p}, t)$ denote time-varying effects (TVEs) of time-constant covariates $x_{..p}$, and our notation subsumes the entire range of effects of this kind, i.e., from time-constant linear effects all the way to non-linear and non-linearly time varying effect surfaces and everything in between. A selection of possible TVEs along with their specification for estimation with mgcv::gam are summarized in Table 1. Note that models with multiple time-varying effects may need to impose additional identifiability constraints (Wood 2017, Ch. 5.6.3), see ?mgcv::ti and the examples in Section 4.2. Also note that (non-linear, non-linearly time-varying) interaction effects of multiple covariates can be specified and estimated in the same way in this framework.

The terms $g(z_{i,m}, t)$ are potentially (non-linearly) time-varying, potentially cumulative effects of time dependent covariates $z_{..m}$. Such terms are discussed in more detail in Sections 3.2 (data transformation) and 4.3 (modeling).

The term $b_\ell i$ denotes random effects (a log-normal frailty) associated with group $\ell = 1, \ldots, L$ to which subject $i$ belongs. Extensions to more complex random effect structures for nested or crossed groups or spatial effects are possible within the presented framework as well (e.g. Wood and Scheipl 2017). For an example of a random effect model estimated via PAMMs see the frailty vignette. In the following, we omit the random effect term to focus on time-varying and cumulative effects rather than hierarchical models.

Table 1: Selection of possible $f(x_{i,p}, t)$ effect specifications in PAMMs, including the R code when fitted using mgcv::gam. Here $x$ denotes any covariate of interest in the data set and $t$ a representation of time in each interval. This could be for example the interval end-points $t_j := \kappa_j$ or interval mid-points $t_j := (\kappa_{j-1} + (\kappa_j - \kappa_{j-1})/2)$.

| $f(x_{i,p}, t)$ | Description | Specification in mgcv::gam |
|-----------------|-------------|---------------------------|
| $\beta_p x_{i,p} \cdot x_{i,p}$ | Linear, time-constant effect | ... + x + ... |
| $f_p(x_{i,p})$ | Smooth nonlinear, time-constant effect | ... + s(x) + ... |
| $\beta_p x_{i,p} + \beta_p t \cdot x_{i,p} \cdot t$ | Linear, linearly time-varying effect | ... + x + x:t ... |
| $f_p(x_{i,p}) \cdot t$ | Smooth, linearly time-varying effect | ... + s(x, by=t) + ... |
| $x_{i,p} \cdot f_p(t)$ | Linear, smoothly time-varying effect | ... + s(t, by=x) + ... |
| $f_p(x_{i,p}, t)$ | Smooth, smoothly time-varying effect | ... + te(x,t) + ... |
To estimate model (1) using PAMMs, the time under risk is divided into \( J \) intervals with interval cut points \( \kappa_0 < \ldots < \kappa_J \) that define intervals \((\kappa_{j-1}, \kappa_j], j = 1, \ldots, J\). The smooth hazard \( \lambda(t) \) is approximated by piece-wise constant hazards \( \lambda(t) = \lambda(t_j) \forall t \in (\kappa_{j-1}, \kappa_j] \) where \( t_j \in (\kappa_{j-1}, \kappa_j] \) denotes any fixed timepoint in the \( j \)-th interval, (typically \( t_j := \kappa_j \)), such that

\[
\log(\lambda_i(t; x_i, Z_i)) \approx \lambda_{ij} := \log(\lambda_i(t_j; x_i, Z_i)) \forall t \in (\kappa_{j-1}, \kappa_j], i = 1, \ldots, n \\
\approx \beta_0 + f_0(t_j) + \sum_{p=1}^{P} f_p(x_{i,p}, t_j) + \sum_{m=1}^{M} g(z_{i,m}, t_j)
\]

Piecewise constant hazard rates imply a piecewise exponential distribution of event times, thus: PEM and PAMM, but note that any shape of the conditional hazard rate can be approximated arbitrarily closely by a sufficiently dense step function.

In the classical PEM, the number of intervals \( J \) as well as the positioning of cut points \( \kappa_j \) are important parameters that affect the quality of the approximation (Demarqui, Loschi, and Colosimo 2008). This is less important for PAMMs as long as \( J \) is not so small and \( \kappa_j \) are sufficiently dense in areas where \( \lambda(t; x, Z) \) varies more quickly. In agreement with Whitehead (1980), we recommend to use the unique observed event and/or censoring times as cut-points, which automatically leads to improved approximation with increasing \( n \) and high \( \kappa_j \) density in the relevant parts of the follow-up. The default in \texttt{pammttools} is to use the uniquely observed event times. For large data sets, an exception to this rule might be preferable if computational resources are insufficient for the resulting data size. GAMMs for big data (cf. Wood, Goude, and Shaw (2015) and \texttt{mgcv} : \texttt{bam}) are very useful in this context to reduce both memory load and computation time.

Regardless of the splitting scheme, once the interval split points \( \kappa_j \) are chosen, the data has to be transformed to what we call the piece-wise exponential data (PED) format (cf. Bender \textit{et al.} (2018a) and the data-transformation vignette) with

- interval specific event indicators \( \delta_{ij} = \begin{cases} 1, & \text{if } t_i \in (\kappa_{j-1}, \kappa_j] \land \delta_i = 1, \\ 0, & \text{else} \end{cases} \)

and

- offsets \( o_{ij} = \log(t_{ij}) \), where \( t_{ij} = \min(\kappa_j - \kappa_{j-1}, t_i - \kappa_{j-1}) \)

After this data transformation, the model can be estimated using Poisson regression with offsets \( o_{ij} \) under the working assumption \( \delta_{ij} \overset{i.i.d.}{\sim} \text{Po}(\mu_{ij}) \) with \( \mu_{ij} = \lambda_{ij} t_{ij} \) and \( \lambda_{ij} \) as defined in (3), even though the working assumption of independent \( \delta_{ij} \) is clearly violated (see Holford (1980); Whitehead (1980); Laird and Olivier (1981); Friedman (1982) for the original justification of the PEM and Cai, Hyndman, and Wand (2002); Kauermann (2005); Argyropoulos and Unruh (2015); Bender \textit{et al.} (2018b) for penalized and mixed model based approaches).

### 3. Data pre-processing

Using pseudo-Poisson responses for time-to-event analysis requires a specific augmented data format called piece-wise exponential data (PED) in the following. \texttt{pammttools} provides convenience functions that perform this data augmentation to create the required additional covariates (e.g., \( t_j := \kappa_j \), event indicators \( \delta_{ij} \) and the offsets \( o_{ij} \)).

In the context of PAMMs, data transformation depends on the type of covariates that are present (time-constant (TCC) vs. time-dependent (TDC)) and the type of effects one wants to
estimate (time-constant or time-varying for TCCs and concurrent or cumulative for TDCs). In PAMMs, time-varying effects of TCCs are simply interactions of the covariates with (a function of) time. Therefore, no special treatment is required. Thus, we differentiate the following situations

- TCCs with potentially time-varying effects \( f(t, x) \), see Section 3.1
- TDCs with concurrent (time-varying) effects \( f(t) z(t) \), see Section 3.2
- TDCs with cumulative effects \( \int_{t_z}^{T} h(t, t_z, z(t_z)) \, dt_z \), see Section 3.3

For all data transformations listed above, \texttt{pammtools} provides a single function \texttt{as_ped} (mnemonic: \texttt{as piece-wise exponential data}), with a formula based interface, which contains specials \texttt{concurrent} and/or \texttt{cumulative} in the presence of TDCs.

### 3.1. Time-constant covariates

In this section we illustrate the transformation of standard time-to-event data without TDCs to the PED format. All examples in this section will use the \texttt{tumor} data available in \texttt{pammtools}. The application of \texttt{as_ped} and its output are illustrated in \texttt{R-chunk 1} for the first 2 rows for each category of the \texttt{sex} variable of the \texttt{tumor} data, using a rather crude 200-day partition of the follow up.

```r
R-chunk 1

```
In the \texttt{as_ped} call in \texttt{R}-chunk 1

- the left hand side (LHS) of the \texttt{formula} specifies the event time and status information. Currently \texttt{pammtools} only supports right-censored data.
- the right hand side (RHS) of the \texttt{formula} specifies covariates that should be kept after data transformation. This can be useful when the data contains many variables but only a few will be used to estimate the hazard. As usual, a dot (\texttt{\textperiodcentered.}) can be used to include all variables.
- the follow up is partitioned at the split points \(\kappa_j\) provided through the \texttt{cut} argument. The start (\texttt{tstart}) and stop (\texttt{tend}) times are created as well as an \texttt{interval} column.
- the \(\delta_{ij}\), which will serve as the outcome of the Poisson regression, are stored in the column \texttt{ped_status} and are 1 only in the interval in which the subject experienced an event (if uncensored), which is also the final interval for that subject.
- the offset variable is calculated, e.g., subject \texttt{id = 3} was censored at 579 days, therefore \(o_{i=3,j=3} = \log(\min(579 - 400, 600 - 400)) = \log(179) = 5.187386\).
- subjects with event times \(t_i > \kappa_J\) will be administratively censored at \(\kappa_J\) (see \texttt{id = 1}).

The output data has class \texttt{ped} and \texttt{pammtools} contains several \texttt{S3} methods that dispatch on \texttt{ped} objects. Examples are provided in Section 4, especially Section 4.4.

In \texttt{R}-chunk 2, \texttt{as_ped} is applied to all observations of the \texttt{tumor} data. As the \texttt{cut} argument is not explicitly specified, all unique \(t_i\) where \(\delta_i = 1\) will be used as interval split points. The argument \texttt{max_time = 3034} indicates that the last interval should end at 3034 days, which means that all observations with \(t_i > 3034\) will be considered censored at \(\kappa_J = 3034\). This can be useful to limit the follow-up to a reasonable range with enough observations (i.e., events), which can make estimation of models faster and more robust, especially with respect to time dependent terms. Here, \texttt{max_time} was set to the last observed event time in order to facilitate comparisons to the Aalen model in Section 4.2.

\begin{verbatim}
R-chunk 2

ped_tumor <- tumor %>% as_ped(Surv(days, status)~., max_time =3034)

\end{verbatim}

The data set \texttt{ped_tumor} will be used for illustration of the estimation and interpretation of time-constant effects and (non-linearly) time-varying effects in Sections 4.1 and 4.2, respectively.

### 3.2. Time-dependent covariates with concurrent effects

Transformation of data containing time-dependent covariates involves a little more work, as, usually, the interval split points \(\kappa_j\) are now the union of the user-specified split points and the time points at which (changes in) the time-dependent covariate(s) were recorded.

In this section, we use the \texttt{pbc} data (Therneau and Grambsch 2001), provided by the \texttt{survival} package (see \texttt{?pbc} and \texttt{R}-chunk 3), ignoring the potentially dependent competing risks, focusing only on the endpoint death (see also \texttt{vignette("timedep", package="survival")}). Note that by loading \texttt{pbc}, two data sets are loaded, the first, \texttt{pbc}, contains survival information and time-constant covariates (and values of time-dependent covariates recorded at beginning of the follow-up) and \texttt{pbcseq}, which stores information on time-dependent covariates.
The variables defining the structure of the data are

- the subject indicator (id),
- the time to event (time),
- the event indicator (status),
- the time of exposure/time at which TDCs were observed (day).

Note that only the first 312 observations in pbc also have time-dependent information in pbcseq, therefore we only use this part of the data.

R-chunk 3

```r
# Note that this code loads two data sets, pbc and pbcseq
data("pbc", package="survival")
# event time information
pbc <- pbc %>%
  filter(id <= 312) %>%
  mutate(status = 1L*(status == 2)) %>%
  select(id:status, trt:sex, bili, protime)
pbc %>% slice(1:6)
# A tibble: 6 x 8
  id  time status trt age  sex bili protime
1  1     400     1   1   58.8 f  14.5  12.2
2  2    4500     0   1   56.4 f  1.10  10.6
3  3    1012     1   1   70.1 m  1.40  12.0
4  4    1925     1   1   54.7 f  1.80  10.3
5  5    1504     0   2   38.1 f  3.40  10.9
6  6    2503     1   2   66.3 f  0.800 11.0
# TDC information
pbcseq <- pbcseq %>%
  select(id, day, bili, protime)
pbcseq %>% slice(1:6)
# A tibble: 6 x 4
  id  day  bili protime
1  1    0 14.5  12.2
2  1    1 192  21.3
3  2    0 1.10  10.6
4  2    2 182  0.800
5  2    2 1.00  11.6
6  2    2 768  1.90
```

To combine these data sets and to transform them into the PED format we again use the as_ped function, however, the first argument is a list of data sets and the variables that should be treated as concurrent variables are specified using the concurrent formula special, as illustrated in R-chunk 4.

R-chunk 4
In R-chunk 4 as_ped

- uses the union of unique event times and all measurement times of the TDCs as interval split points,
- merges the expanded data set with the data set containing information on TDCs by ID and time (time and day) and
- fills in the values of TDCs for any time-points that did not occur in tz_var by carrying the respective previous value of the TDC forward.

The last point of course implies the assumption that the values of the TDCs remain constant between observation points, which can be questionable, especially for longer periods between updates.

For analysis of this data and a comparison to results from an extended Cox model see Bender et al. (2018a) and the pamtools vignette on time-dependent covariates.

3.3. Time-dependent covariates with cumulative effects

Some additional effort is required to create PED with TDCs that will be modeled as cumulative effects. If mgcv::gam is used for estimation, we need to construct covariate matrices for each TDC with a cumulative effect, as well as additional covariate matrices representing either time and/or time of exposure and/or the latency of exposure and the lag-lead matrix defining the time window $T(t)$. 
Let’s consider a model with one cumulative effect \( g(z,t) \) of TDC \( z \), such that a general representation of the cumulative effect is given by

\[
g(z,t) = \int_{\mathcal{T}(t)} h(t,t_z,z(t_z))dt_z
\]  

In (5)

- the tri-variate function \( h(t,t_z,z(t_z)) \) defines the so-called partial effects of the TDC \( z(t_z) \) observed at exposure time \( t_z \) on the hazard at time \( t \) (Bender et al. 2018b). Other specifications commonly used in the literature are special cases of the general partial effect definition given above, e.g.,
  - \( h(t - t_z)z(t_z) \) is the WCE model of Sylvestre and Abrahamowicz (2009) and
  - \( h(t - t_z,z(t_z)) \) corresponds to the DLNM model of Gasparini (2014)
- the cumulative effect \( g(z,t) \) at follow-up time \( t \) is the integral of the partial effects over exposure times \( t_z \) contained within \( \mathcal{T}(t) \)
- \( \mathcal{T}(t) \) denotes the lag-lead window (or window of effectiveness). The most common definition is \( \mathcal{T}(t) = \{ t_{z,q} : t \geq t_{z,q}, q = 1, \ldots, Q \} \), which means that all exposures that were observed prior to \( t \) or at \( t \) can affect the hazard at time \( t \).

Thus, when transforming the data to a format suitable to fit such effects using \texttt{mgcv::gam}, the required covariate matrices will be created depending on

- the specific definition of the partial effect \( h() \),
- the grid of exposure times \( t_z \) and
- the lag-lead window \( \mathcal{T}(t) \)

As before, the \texttt{as_ped} function can be used to transform the data into the right format by extending the RHS of the \texttt{formula} using the formula special \texttt{cumulative}. The most important arguments to \texttt{cumulative} are:

- \texttt{...}: a place holder where the individual components (variables) of the partial effects can be specified. See Table 2 for a selection of possible partial effect specifications and how to represent them in \texttt{cumulative} (for their specification in \texttt{mgcv::gam} see Section 4.3)
- \texttt{tz_var}: the name of the variable that contains exposure times \( t_z \) of TDC \( z \)
- \texttt{ll_fun}: a boolean function of follow-up time \( t \) and exposure time \( t_z \), which defines \( \mathcal{T}(t) \) in Equation (5) (see also Figure 2)

For illustration of the data transformation using \texttt{as_ped} and \texttt{cumulative}, consider the simulated data \texttt{simdf_elra} contained in \texttt{pammtools} (see example in \texttt{?sim_pexp} for data generation):

```r
data("simdf_elra", package = "pammttools")
simdf_elra %>% slice(1:3)
```

# A tibble: 3 x 9
  id  time status x1  x2 tz1  z.tz1 tz2  z.tz2
  <int> <dbl> <int> <dbl> <dbl> <list> <list> <list> <list>
1  1  3.22  1    1.59  4.61 <int [10]> <dbl [10]> <int [11]> <dbl -
2  2 10.00  0  -0.530  0.178 <int [10]> <dbl [10]> <int [11]> <dbl -
3  3  0.808  1  -2.43  3.25 <int [10]> <dbl [10]> <int [11]> <dbl -
```
It contains
- the follow-up time \( t \) (time),
- the event indicator \( \text{status} \) (censoring only occurs at the end of the follow up at \( t = 10 \)),
- two time constant covariates \( x_1 \) (x1) and \( x_2 \) (x2) and
- two TDCs \( z_1 \) (z1.tz1), \( z_2 \) (z2.tz2) observed at two different exposure time grids \( t_{z_1} \) (tz1) and \( t_{z_2} \) (tz2).

Let’s further assume that two different lag-lead windows \( T_1(t) = \{t_{z_1,q_1} : t \geq t_{z_1,q_1}, q_1 = 1,\ldots,Q_1\} \) and \( T_2(t) = \{t_{z_2,q_2} : t \geq t_{z_2,q_2} + 2, q_2 = 1,\ldots,Q_2\} \) (the latter defined by \( \text{ll}_2 \leftarrow \text{function}(t, tz) \ t \geq tz + 2 \) are associated with the cumulative effects of the respective TDCs. The latter corresponds to a lag time of 2 days, so, for example, the value of \( z_2(3) \) only affects the hazard for follow-up times \( t \geq 5 \).

Table 2 shows a selection of partial effect specifications for this setting and the respective specification using the formula special \text{cumulative}. Note that
- the variable representing follow-up time \( t \) in \text{cumulative} (here \( \text{time} \)) must match the time variable specified on the LHS of the formula (\text{Surv(time, status)}) provided to \text{as_ped}
- if the latency \( t - t_z \) should be used instead of \( t_z \), the variables representing exposure time \( t_z \) (here \( \text{tz1} \) and \( \text{tz2} \)) must be wrapped within \text{latency()}
- by default, \( T(t) \) is defined as \text{function}(t, tz) \( t \geq tz \), thus for \( T_1(t) \) there is no need to specify the lag-lead window explicitly. To define a custom lag-lead window, provide the respective function to the \text{ll_fun} argument in \text{cumulative} (see \text{ll}_2 in Table 2)
- \text{cumulative} does not distinguish between partial effects \( h(t - t_z, z(t_z)) \) and \( h(t - t_z)z(t_z) \) as the required data transformations are identical
- more than one \( z \) variable can be provided to \text{cumulative}, which can be convenient if multiple covariates share time components and will be integrated over the same lag-lead windows
- multiple \text{cumulative} terms with different exposure times \( t_{z_1}, t_{z_2} \) and/or different lag-lead windows for different covariates \( z_1, z_2 \) can be specified, as illustrated in Table 2
- to tell \text{cumulative} which of the variables provided is the exposure time \( t_z \), the \text{tz_var} argument must be specified within each \text{cumulative} term. The follow-up time component \( t \) (\( \text{time} \)) will be recognized from the LHS of the formula

| cumulative effect(s) | data transformation (\text{pammttools}) |
|----------------------|-----------------------------------------|
| \( \int_{T_1} h(t - t_{z_1}, z_1(t_{z_1})) \) | \text{cumulative(latency(tz1), z1.tz1, tz_var="tz1")} |
| \( \int_{T_1} h(t, t - t_{z_1}, z_1(t_{z_1})) \) | \text{cumulative(time, latency(tz1), z1.tz1, tz_var="tz1")} |
| \( \int_{T_1} h(t, t_{z_1}, z_1(t_{z_1})) \) | \text{cumulative(time, tz1, z1.tz1, tz_var="tz1")} |
| \( \int_{T_1} h(t, t_{z_1}, z_1(t_{z_1})) + \int_{T_2} h(t - t_{z_2}, z_2(t_{z_2})) \) | \text{cumulative(time, tz1, z1.tz1, tz_var="tz1")} + \text{cumulative(latency(tz2), z2.tz2, tz_var="tz2", ll_fun=ll_2)} |
One possible data transformation call for the `simdf_elra` data is given in R-chunk 5.

```r
ped_simdf <- simdf_elra %>% as_ped(Surv(time, status) ~ x1 + x2) +
  cumulative(time, latency(tz1), z.tz1, tz_var="tz1") +
  cumulative(latency(tz2), z.tz2, tz_var="tz2"), cut = 0:10)
str(ped_simdf)
```

The newly created matrix valued variables have

- different number of columns (10 vs. 11), reflecting the different exposure time grids \( (t_{z_1,1}, \ldots, t_{z_1,Q_1}=10 \text{ and } t_{z_2,1} = -5, \ldots, t_{z_2,Q_2} = 5) \).

- different components, depending on the partial effect and `cumulative` specification, respectively. Thus, for \( z.tz1 \) a time matrix `time_tz1` was created as well as a latency matrix `tz1_latency`, whereas only the latency matrix `tz2_latency` was created for the partial effects associated with \( z.tz2 \).

- different lag-lead specifications, which can be extracted and visualized using convenience functions `get_laglead` and `gg_laglead`. Applied to a `ped` object, they retrieve the lag-lead definition used during data transformation (cf. Figure 1). More complex specifications of \( T(t) \) can be generated easily (cf. Figure 2), where a lead time of \( t_{lead} = 5 \) is included in addition to a lag time of \( t_{lag} = 2 \).
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---

**gg_laglead(ped_simdf)**

Figure 1: Lag-lead windows created by `as_ped` in R-chunk 5. When viewed row-wise, the black squares indicate the intervals at which the respective exposure times \( t_z \) can affect the hazard. For example, in the left panel, exposure at time \( t_z = 5 \) can affect the hazard in intervals \((5, 6]\) through \((9, 10]\) (\texttt{as_ped} is conservative and \( t \geq t_z \) is only true if the relationship is true for the interval start time). When viewed column-wise, one can obtain the exposure times contained within \( \mathcal{T}(t) \). For example, \( \mathcal{T}(t = 5) = \mathcal{T}(\{\kappa_{j-1} = 4, \kappa_j = 5\}) = \{t_z = 1, \ldots, t_z = 4\} \).

```r
my_ll_fun <- function(t, tz, tlag = 2, tlead = 5) {
  t >= tz + tlag & t < tz + tlag + tlead
}
gg_laglead(0:10, tz=-5:5, ll_fun = my_ll_fun)
```

---

Figure 2: Illustration of a more complex definition of the lag-lead window \( \mathcal{T}(t) \) with \( t_{lag} = 2 \) and \( t_{lead} = 5 \). For example, exposure at time \( t_z = -1 \), starts to affect the hazard at time \( t = t_z + t_{lag} = -1 + 2 = 1 \), i.e., interval \((1, 2]\), as \( t \) in the specification of the lag-lead function refers to the start time of the interval. Similarly, exposure at time \( t_z \) lasts until \( t = t_z + t_{lag} + t_{lead} = -1 + 2 + 5 = 6 \), i.e., interval \((5, 6]\). Note that we used the condition \( t < t_z + t_{lag} + t_{lead} \) to ensure that the condition is true for the end time of the interval.
4. Modeling and Interpretation

With data in PED format (see Section 3), the subsequent modeling step is relatively straightforward, as any software for Generalized Additive (Mixed) Models (or similar) can be used. In this article, the model estimation is performed outside the `pammtools` package using `mgcv` (Wood 2011). In the following sections, we demonstrate how to fit different models using the `mgcv::gam` formula syntax, with special attention given to cumulative effects.

4.1. Time-constant effects

We start with a standard survival model with time-constant effects of time-constant covariates and compare the results to the Cox PH model using the tumor data (?tumor) contained in the `pammtools` package.

The data used in this section has already been transformed into the correct format in Section 3.1 (see R-chunk 2). Therefore, we can directly apply `mgcv::gam` to the transformed data as shown in R-chunk 6. Note that we must specify `family = poisson()` and `offset = offset` for the model to be estimated correctly. For an overview of estimates the `mgcv` functions `summary.gam` and `plot.gam` can be used. Note that the log-baseline hazard displayed in Figure 3 does not contain the intercept term $\beta_0$ and cannot be interpreted usefully as it relates to a patient with age 0. Note that `gg_smooth` replicates the plots produced by `plot.gam` and visualizes all effects as smooth lines, while for PAMMs, representations of the (log-)hazard should be plotted as step functions (see Figure 4).

R-chunk 6

```r
pam_tumor <- gam(
  formula = ped_status ~ s(tend) + sex + age + charlson_score + transfusion +
  + complications + metastases + resection,
  data = ped_tumor, family = poisson(), offset = offset, method = "REML"
)
# default summary
summary(pam_tumor)
...
```

Parametric coefficients:

| Estimate  | Std. Error | z value | Pr(>|z|) |
|-----------|------------|---------|----------|
| (Intercept) | -9.837979  | 0.364656 | -26.979  | < 2e-16 *** |
| sexfemale  | 0.185245   | 0.107953 | 1.716    | 0.086167 .  |
| age        | 0.021019   | 0.005034 | 4.175    | 2.98e-05 *** |
| charlson_score | 0.149562  | 0.041992 | 3.562    | 0.000368 *** |
| transfusionyes | 0.254105  | 0.110703 | 2.295    | 0.021711 *  |
| complicationsyes | 0.581987 | 0.109125 | 5.333    | 9.65e-08 *** |
| metastasesyes | 0.166650  | 0.116752 | 1.427    | 0.153467  |
| resectionyes | 0.260660  | 0.112118 | 2.325    | 0.020079 *  |

---

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Approximate significance of smooth terms:

| edf | Ref.df | Chi.sq | p-value |
|-----|--------|--------|---------|
| 3.761 | 4.679 | 19.33  | 0.00139 **  |

...
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```r
gg_smooth(ped_tumor, pam_tumor, terms="tend") + xlab("time")
```

![Log-baseline hazard of the PAM estimated on the tumor data with time-constant effects](image)

Figure 3: Log-baseline hazard of the PAM estimated on the tumor data with time-constant effects (cf. **R**-chunk 6).

**pammtools** provides convenience functions to extract the fixed coefficients including confidence intervals (**tidy_fixed**, cf. **R**-chunk 7) as well as a plot function for the fixed effect coefficients (**gg_fixed**), which returns a **ggplot** object. Note that by default, the output of both functions omits the intercept term, which can be added by setting `intercept=TRUE`. When comparing the results with the Cox PH model (cf. **R**-chunk 7), the estimated effects are, not surprisingly, very similar.

**R-chunk 7**

```r
coxph_tumor <- coxph(
  formula = Surv(days, status) ~ sex + age + charlson_score + transfusion +
  + complications + metastases + resection,
  data = tumor)
# compare coefficient estimates
imap(list(PAM = pam_tumor, COX = coxph_tumor),
  ~ tidy_fixed(.x) %>% select(variable, coef) %>% rename(!.y := coef)) %>%
reduce(left_join)
```

| variable       | PAM    | COX    |
|----------------|--------|--------|
| sexfemale      | 0.185  | 0.185  |
| age            | 0.0210 | 0.0209 |
| charlson_score | 0.150  | 0.147  |
| transfusionyes | 0.254  | 0.255  |
| complicationsyes | 0.582 | 0.571  |
| metastasesyes | 0.167  | 0.164  |
| resectionyes   | 0.261  | 0.256  |
4.2. Time-varying effects

Time-varying effects of time-constant covariates \(f(t) \cdot x\) can generally be divided in two groups:

- stratified hazards for categorical \(x\)
- time-varying coefficients for continuous \(x\)

Interactions between continuous and categorical covariates are possible as well in order to allow for the time-varying effect of a continuous variable to vary over the different levels of a categorical variable.

**Stratified hazards model**

Consider the variable complications for the case of stratified hazards. Suppose that patients experiencing major complications during surgery are under increased risk immediately afterwards, and that this increase subsides after some time. If this is the case, the PH assumption of the Cox model is not fulfilled, or more generally, the effect of complications is time-varying. One solution to this problem are stratified hazards models (e.g., Klein and Moeschberger (1997, Ch. 9.3)) with separate baseline hazards for the levels of a categorical covariate. The estimated log-hazards are presented in R-chunk 8 and Figure 4. Note that we use tidy_smooth to extract the data used by plot.gam for visualization of 1D smooth effects. The hazards in the two groups are vastly different with the expected drop in the log-hazard within the first 500 days for patients with major complications.

```
R-chunk 8

pam_strata <- bam(
  formula = ped_status ~ complications + s(tend, by = complications) + sex +
              age + charlson_score + transfusion + metastases + resection,
  data = ped_tumor, family = poisson(), offset = offset, discrete = TRUE)
summary(pam_strata)

... Parametric coefficients:

  Estimate  Std. Error   z value     Pr(>|z|)
(Intercept)  -9.959335 0.363745  -27.380 < 2e-16 ***
 complicationsyes  0.443763 0.122720   3.616  0.000299 ***
  sexfemale  0.190760 0.108295   1.761  0.078157 .
  age  0.020753 0.005018   4.136  3.53e-05 ***
  charlson_score  0.159937 0.042035   3.805  0.000142 ***
  transfusionyes  0.234964 0.111398   2.109  0.034924 *
  metastasesyes  0.175349 0.116637   1.503  0.132744

Approximate significance of smooth terms:

  edf Ref.df    Chi.sq p-value
s(tend):complicationsno  4.434  5.481  11.05   0.0746 .
s(tend):complicationsyes  5.087  6.181  91.59  <2e-16 ***
...```

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Varying coefficients

Let’s now include all covariates available in the tumor data, with possibly non-linearly time-varying effects, where the effects of continuous covariates are assumed to vary non-linearly in time, but linearly in the covariate, i.e., \( f_p(t)x_p \). The model specification is given in R-chunk 9. Note that categorical covariates are included using `by = as.ordered(...)`, which (together with `ti`) ensures identifiability of the model (cf. \( ?mgcv::gam.models \) and \( ?mgcv::ti \)). For the effects of `age` and `charlson_score` the basis functions of the smooths are multiplied with the respective covariate values, thus no further identifiability constraints are necessary.

R-chunk 9

```r
pam_tumor_tve <- bam(
  formula = ped_status ~ ti(tend) + complications + ti(tend, by = as.ordered(complications)) + metastases + ti(tend, by = as.ordered(metastases)) + sex + ti(tend, by = as.ordered(sex)) + transfusion + ti(tend, by = as.ordered(transfusion)) + resection + ti(tend, by = as.ordered(resection)) + s(tend, by = charlson_score) + s(tend, by = age),
  data = ped_tumor, family = poisson(), offset = offset, method = "fREML", discrete = TRUE)
```

The model output is presented in R-chunk 10. The effects of variables `metastases`, `transfusion` and `resection` were estimated as linearly time-varying effects (edf=1), however, they must be interpreted as relative changes (ceteris paribus, c.p.) compared to the baseline hazard `ti(tend)`, which itself is non-linear.
The usual visualization of the log-hazard contributions \( f_p(t)x_p \) over the follow-up could be used for the interpretation of the estimates (similar to figure 4). However, for models with time-varying effects (that are linear in the covariates), an alternative visualization, which is also useful for comparisons to the non-parametric additive Aalen model (Martinussen and Scheike 2006), will be used here.

The default visualization of covariate effect estimates for the Aalen model in the \texttt{timereg} package is the so-called cumulative coefficient \( B_p(t) = \int_0^t \beta_p(s)ds \). Since the Aalen model is additive, i.e., \( \lambda(t|x) = \lambda_0(t) + \beta_1(t)x_1(t) + \cdots \), this cumulative coefficient can be nicely interpreted as the cumulative hazard difference at time \( t \) for a 1 unit increase of the covariate/compared to its reference level (c.p.), i.e., \( B(t) = \Lambda(t|x + 1) - \Lambda(t|x) \). Thus, to obtain a PAMM analog of the cumulative coefficient, we can calculate the difference between the respective cumulative hazards. Although \( B(t) \) is not directly estimated for PAMMs as it is for the Aalen model, \texttt{pammtools} provides the function \texttt{get_cumu_coef} that performs these calculations (including simulation based confidence intervals), as illustrated in \texttt{R}-chunk 11.

The cumulative coefficients of the PAMM and Aalen model are presented in Figure 5. The cumulative hazard difference between a patient with complications (compared to one without, c.p.), increases at the beginning, directly after the operation when complications occurred, while after approximately 500 days, the cumulative hazard difference remains constant (i.e. \( \beta_p(t) = f_p(t) \approx 0 \forall t > 500 \)). Similarly, the effect of metastases has a plausible interpretation: At \( t = 0 \), as much as possible of the cancerous tissue including metastases is removed, thus the hazard in both groups is almost the same in the beginning, however, the risk of cancer
returning after some time due to cancerous tissue that was not removed is higher in patients with metastases, which notably increases their hazard for $t > 1500$ compared to patients without metastases. For the cumulative coefficients based on PAMMs, confidence intervals were estimated by Monte Carlo estimation based on 100 draws from the model coefficients’ posterior distribution (Argyropoulos and Unruh 2015; Wood 2017). Overall, the estimates obtained from the PAMM estimates are very close to the estimates obtained from the Aalen model with respect to the cumulative coefficients as well as their confidence intervals.

R-chunk 11

```r
# here cumu_hazard denotes the cumulative hazard differences
get_cumu_coef(pam_tumor_tve, ped_tumor, terms = c("age", "sex")) %>%
group_by(variable) %>% slice(1:2)
```

| method | variable | time | cumu_hazard | cumu_lower | cumu_upper |
|--------|----------|------|-------------|------------|------------|
| bam    | age      | 1.   | 0.000000458 | 0.0000000896 | 0.000000883 |
| bam    | age      | 2.   | 0.000000916 | 0.000000180  | 0.00000177  |
| bam    | sex (female) | 1.  | -0.00000177 | -0.0000116   | 0.00000858  |
| bam    | sex (female) | 2.  | -0.0000352  | -0.000231    | 0.000172    |

Figure 5: Comparison of cumulative coefficients estimated with PAMMs and the additive Aalen model respectively (the effect of resection is not displayed for conciseness). For PAMMs these are defined as cumulative hazard differences, e.g. $B_{PAMM}(t) := \Lambda(t|\text{sex = "female"}) - \Lambda(t|\text{sex = "male")}$. Note the different scales on the vertical axes of the panels.
4.3. Cumulative effects

In this section, we illustrate the estimation of cumulative effects using \texttt{mgcv::gam} (or \texttt{mgcv::bam}) with suitably formatted data sets (see Section 3.3), as well as their visualization. We use simulated data that allows us to discuss different aspects and model classes covered by our general approach. The simulation of the various data sets with different specifications of cumulative effects is described in Appendix A, specifically sections A.3.1, A.3.2 and A.3.3.

**Weighted cumulative exposure**

Consider model (6) with a smooth log-baseline hazard function $f_0(t)$ and a cumulative covariate effect of exposure histories $z_i$. In the following example, the associated partial effect is non-linear in the latency $t - t_z$, the time since the exposure was observed, and linear in the values of $z(t_z)$, such that

$$\lambda_i(t|z_t) = \exp \left( \beta_0 + f_0(t) + 0.5x_{1,i} + \sqrt{x_{2,i}} + \int_{T(t)} h(t - t_z)z_i(t_z)dt_z \right)$$

(6)

Section A.3.1 describes how to simulate data from this model using the \texttt{pammtools} function \texttt{sim_pexp} (cf. \texttt{R-chunk 19}). Given this data (\texttt{simdf_wce}), we can proceed with the analysis of the data, first by transforming it to the PED format using the \texttt{as_ped} function as shown in Section 3.3 and applied to the simulated data in \texttt{R-chunk 12}. Note that the created matrix columns have 41 columns, because this was the length of the exposure time grid used in the data simulation step.

```
R-chunk 12

time_grid <- seq(0, 10, by = 0.5)
ped_wce <- as_ped(
  data = simdf_wce,
  formula = Surv(time, status) ~ x1 + x2|
    cumulative(latency(tz), z.tz, tz_var="tz", ll_fun = ll_fun),
  cut = time_grid)
str(ped_wce[,1])
```

```
$ tz_latency: num [1:7460, 1:41] 5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 ...  
$ z.tz : num [1:7460, 1:41] 1.86 1.86 1.86 1.86 1.86 ...  
$ LL : num [1:7460, 1:41] 0.25 0.25 0.25 0.25 0.25 0.25 0.25 0.25 0.25 0.25 ...  
...  
```

\texttt{R-chunk 13} shows the model specification necessary to fit the correctly specified model. Note that we use the correct lag-lead window, as we provide the true \texttt{ll_fun} (cf. \texttt{R-chunk 18}) to the data transformation function in \texttt{R-chunk 12}. The estimated weight function $\hat{h}(t - t_z)$ is fairly close to the true function used in the simulation, as displayed in Figure 6.
R-chunk 13

```r
mod_wce <- gam(
  formula = ped_status ~ s(tend) + s(x1) + s(x2) + s(tz_latency, by = z.tz * LL),
  data = ped_wce, family = poisson(), offset = offset, method = "REML")
summary(mod_wce)
```

| Estimate | Std. Error | z value | Pr(>|z|) |
|----------|------------|---------|----------|
| (Intercept) | -1.77996   | 0.04739 | -37.56   | <2e-16 *** |

Approximate significance of smooth terms:

| edf | Ref.df | Chi.sq | p-value |
|-----|--------|--------|---------|
| s(tend) | 6.366 | 7.385 | 328.49 | < 2e-16 *** |
| s(x1) | 1.420 | 1.728 | 449.38 | < 2e-16 *** |
| s(x2) | 3.021 | 3.758 | 199.97 | < 2e-16 *** |
| s(tz_latency):z.tz * LL | 3.566 | 4.182 | 43.46  | 1.23e-08 *** |

Figure 6: Left: Partial effect \( \hat{h}(t - t_z) \) estimated in R-chunk 13, depicted for all possible latencies for the particular data. Dashed lines indicate the latencies that contribute to the cumulative effect at interval \( (4.5, 5] \). Middle: Partial effects for each combination of \( t \) and \( t_z \). The vertical stripes at each interval are subsets of the partial effect depicted in the left panel. Right: Cumulative effect \( g(z, t) \) at all time points of the follow up. Each point is the sum of the vertical stripes depicted in the middle panel. The point at \( t = 5 \) indicates the sum of weighted partial effects of the highlighted vertical stripe (interval \( (4.5, 5] \)) in the middle panel.

**Distributed Lag Non-linear Model**

The WCE approach from the previous section assumes that the effect of \( z \) is non-linear with respect to the latency and linear in \( z \). Relaxing the latter assumption and allowing the partial effect to also vary non-linearly over \( z(t_z) \) (cf. eq. (9)) leads to what is often referred to as
the distributed lag non-linear model (DLNM; Gasparrini 2014).

\[ \lambda_i(t|z_i) = \exp \left( \beta_0 + f_0(t) + 0.5x_{1,i} + \sqrt{x_{2,i}} + \int_{T(t)} h(t - t_z, z_i(t_z))dt_z \right) \]  

(7)

Data transformation and model estimation for this data (simdf_dlnm; cf. Section A.3.2 for data simulation and Figure 14 for the true partial effects used for simulation) is given in R-chunk 14. Note that the formula provided to as_ped is actually the same as the one used to transform the simdf_wce data in R-chunk 12, as the created covariate matrix for z.tz will be the same in both cases, thus we could have also used the ped_wce data for estimation of the DLNM model. However, the specification of the term in the call to gam is different: te(tz_latency, z.tz, by = LL) for the DLNM vs. s(tz_latency, by = z.tz * LL) for the WCE.

R-chunk 14

```r
ped_dlnm <- as_ped(
  formula = Surv(time, status) ~ x1 + x2|
  cumulative(latency(tz), z.tz, tz_var = "tz", ll_fun = ll_fun),
  data = simdf_dlnm, cut = time_grid)
# ped_dlnm$tz_latency <- ped_dlnm$tz_latency * ped_dlnm$LL
mod_dlnm <- bam(
  formula = ped_status ~ s(tend) + s(x1) + s(x2) +
  te(tz_latency, z.tz, by = LL, k = c(10,10)),
  data = ped_dlnm, family = poisson(), offset = offset,
  method = "fREML", discrete = TRUE)
summary(mod_dlnm)
... 
```

Figure 7 depicts the estimated partial effect surface (left hand panel) as well as one-dimensional slices through the surface with respect to the latency \( t - t_z \in \{1,5,10\} \) (middle panel) and the covariate \( z(t_z) \in \{-1.5,0,1.5\} \) (right panel). Note that, equivalently to the true partial effect in Figure 14, the depicted effects are relative to an observation with exposure history \( z(t_z) = -1 \forall t_z \), thus the effects pass through zero at \( z(t_z) = -1 \forall t_z \). We use pammtools convenience functions gg_partial and gg_slice to create the individual figures. Internally, they use make_newdata to create a data set based on ped_dlnm and the variable specification provided through the ellipsis arguments (…). If specified, the effects will be calculated relative to covariate values provided as the reference argument (here `reference = list(z.tz = -1)`), which must be a list with single value specifications for each covariate that should be changed in the comparison data set.

Figure 8 again shows the partial effect surface from Figure 7 (left panel), as well as the partial effects for each combination of \( t \) and \( t_z \), with \( z(t_z) = 1 \forall t_z \). This visualization shows more directly which partial effects will contribute to the cumulative effect at time \( t \) (see also the dashed lines in the left panel). Finally, the right panel of Figure 8 depicts the total cumulative effect \( g(z,t) \) for the partial effects displayed in the middle panel.
# Define reference values
ref <- list(z.tz = -1)

# Partial effect surface
p_partial_dlnm <- gg_partial(ped_dlnm, mod_dlnm, term = "z.tz", reference = ref, z.tz = seq(-3, 3, by = 0.1), tz_latency = seq(0, 12, by = .25), LL = c(1))

# Slices over exposures with fixed exposure time values
p_slice_tz <- gg_slice(ped_dlnm, mod_dlnm, term = "z.tz", reference = ref, z.tz = seq(-3, 3, by = 0.25), tz_latency = c(1, 5, 10), LL = c(1)) + geom_vline(xintercept = 1.5, lty = 3)

# Slices over exposure times with fixed exposure values
p_slice_z.tz <- gg_slice(ped_dlnm, mod_dlnm, term = "z.tz", reference = ref, z.tz = c(-1.5, 0, 1.5), tz_latency = seq(0, 12, by = 0.25), LL = c(1)) + geom_vline(xintercept = 6, lty = 3) + scale_colour_brewer(palette = "Dark2") + scale_fill_brewer(palette = "Dark2")

Figure 7: Partial effect $h(t - t_z, z(t_z))$ estimated by model `mod_dlnm` in R-chunk 14. Note, all effects were calculated relative to $z(t_z) = -1 \forall t_z$. Left: Partial effect surface for a range of values for latency $t - t_z$ and covariate $z(t_z)$. Middle: Slices through partial effect surface for latencies 1, 5 and 10. Right: Slices through the partial effect surface for $z(t_z) \in \{-1.5, 0, 1.5\}$.

Figure 8: From left to right: Bivariate partial effect surface estimate $h(t - t_z, z(t_z))$, partial effects for different combinations of $t$ and $t_z$ with $z(t_z) = 1, \forall t_z$ and the resulting cumulative effect $g(z, t)$.
General Exposure-lag-response Associations

In Sections 4.3.1 and 4.3.2 we discussed the most common specifications of cumulative effects in the literature. Our general specification of cumulative effects in eq. (5) has the advantage that it includes the other approaches as special cases and while also supporting alternative (and more complex) models. Thus, depending on the context, alternative specifications of the partial effects are possible, e.g.,

- \( h(t, t-t_z)z(t_z) \) or alternatively \( h(t, t_z)z(t_z) \), a smoothly time-varying WCE (the latter formulation was used in Bender et al. (2018b) in combination with a categorical \( z(t_z) \))
- \( h(t, t-t_z, z(t_z)) \), a smoothly time-varying DLNM, which was demonstrated by means of a simulation study in Bender et al. (2018b, sec. 4)

For a last illustration, consider the following model:

\[
\lambda_i(t|z_i) = \exp \left( \beta_0 + f_0(t) + 0.5x_{1,i} + \sqrt{x_{2,i}} + \int_{T(t)} h(t, t_z)z(t_z)dt_z \right)
\]  

(8)

which looks very similar to the WCE model in Section 4.3.1, but the assumption that the partial effect only depends on the latency \( t-t_z \) is softened. Data simulation from model (8) is given in R-chunk 21 and the true bivariate partial effect \( h(t, t_z) \) as well as the resulting cumulative effect \( \int_{T(t)} h(t, t_z)z(t_z)dt_z \) are depicted in Figure 15.

The data transformation and model estimation for this data is shown in R-chunk 15. The estimated effects are visualized in Figure 9. Although the bivariate partial effect surface (left panel) was estimated quite well, there is some underestimation for \( t > 5 \), thus, necessarily, the cumulative effect (right panel) for \( t > 5 \) is also underestimated.

R-chunk 15

```r
# transform simulated data to PED format
ped_tv_wce <- as_ped(Surv(time, status)~ x1 + x2| cumulative(time, tz, z.tz, tz_var = "tz", ll_fun = ll_fun), data = simdf_tv_wce, cut = time_grid)

# estimate the model
mod_tv_wce <- gam(ped_status ~ s(tend) + s(x1) + s(x2) + te(time_mat, tz, by = z.tz*LL), data = ped_tv_wce, family = poisson(), offset = offset, method = "REML")
summary(mod_tv_wce)
...
```

Approximate significance of smooth terms:

| Smooth Term   | edf | Ref.df | Chi.sq | p-value |
|---------------|-----|--------|--------|---------|
| s(tend)       | 6.726 | 7.754   | 267.0  | <2e-16 *** |
| s(x1)         | 1.002 | 1.004   | 320.7  | <2e-16 *** |
| s(x2)         | 2.689 | 3.351   | 169.5  | <2e-16 *** |
| te(time_mat,tz):z.tz*LL | 10.856 | 13.482 | 176.8  | <2e-16 *** |
...
# partial effect (in lag-lead window)
p_partial_elra <- gg_partial_ll(ped_tv_wce, mod_tv_wce, term="z.tz",
time_mat = seq(0,10, by = 0.5), tz = seq(-5, 5, by = 0.25), z.tz=c(1),
reference = list(time_mat = c(5)), time_var = "time_mat")+
geom_contour(aes(z = fit), color = "grey30")

# cumulative effect
p_cumu_elra <- gg_cumu_eff(ped_tv_wce, mod_tv_wce, term = "z.tz", z1=1) +
geom_line(data=cumu_df_elra, aes(x = t, y = cumu_eff), col = 2)
ggridExtra::grid.arrange(p_partial_elra, p_cumu_elra, nrow=1, widths=c(1.5, 1))

Figure 9: Left: Estimated bivariate partial effect surface \( \hat{h}(t, t_z) \) for all combinations of \( t \) and \( t_z \) within \( T(t) \). Right: Resulting cumulative effect estimation for \( z(t_z) = 1 \forall t_z \).

4.4. Convenience functions, survival probabilities and other quantities

For communicating and checking the results of complex time-to-event models, it is often necessary to calculate covariate effects in terms of conditional hazards, cumulative hazards or survival probabilities. *pammtools* provides convenience functions to quickly calculate these quantities for different covariate specifications, along with uncertainty estimates. The suggested workflow for these calculations is to create a dataset with the covariate specifications of interest and then use one of the *add_* functions (see `?add_hazard` for an overview). For illustration we will use the *tumor* data model discussed in section 4.2.

Creating new data

*pammtools* provides several functions that facilitate the creation of data sets with customized covariate specifications:

- **int_info** provides interval information (start and stop times, interval length) for a given interval split point specification or extracting the split-points used during the creation of a *ped* object

```r
# extract interval information
int_info(ped_tumor) %>% slice(1:5)
```

# A tibble: 5 x 5
tstart tend intlen intmid interval

```
• **sample_info** extracts the mean and modal values for continuous and categorical variables respectively (if applied to an object of class `ped`, variables representing interval information are omitted)

```r
# sample means/modi
sample_info(tumor)
```

```r
# A tibble: 1 x 9
  days status charlson_score age sex transfusion complications
  <dbl> <dbl>        <dbl> <dbl> <fct>  <fct>        <fct>
1 1017. 0.483       2.78  62.0 male no no
# ... with 2 more variables: metastases <fct>, resection <fct>
```

```r
sample_info(ped_tumor)
```

```r
# A tibble: 1 x 7
  charlson_score age sex transfusion complications metastases
  <dbl>        <dbl> <fct>  <fct>  <fct>
1 2.78 62.0 male no no yes
# ... with 1 more variable: resection <fct>
```

```r
ped_tumor %>% group_by(sex) %>% sample_info()
```

```r
# A tibble: 2 x 7
# Groups: sex [2]
  charlson_score age sex transfusion complications metastases
  <dbl>        <dbl> <fct>  <fct>  <fct>
1 2.96 63.3 male no no yes
2 2.52 60.1 female no no yes
# ... with 1 more variable: resection <fct>
```

• **ped_info** combines `int_info` and `sample` info to return a data frame with all unique intervals of the `ped` object and all covariates set to their sample mean/modus.

```r
# interval and sample info
ped_info(ped_tumor) %>% slice(1:3)
```

```r
# A tibble: 3 x 12
  tstart tend intlen intmid interval charlson_score age sex
  <dbl> <dbl> <dbl> <dbl> <fct> <fct> <dbl> <fct> <fct>
1  0.    1.  1.00  0.50 <(0,1] 2.78  62.0 male
2  1.    2.  1.50  1.50 <(1,2] 2.78  62.0 male
```
# make_newdata is a flexible function for creating new data sets from `ped` or `data.frame`-objects. Specific covariate values can be provided through the ellipsis argument (...) as key-value-pairs, while all unspecified variables will be set to their sample means or modes.

```r
# make arbitrary new data
make_newdata(tumor, age=seq_range(age, n=3))
```

```
# A tibble: 3 x 9
days status charlson_score age sex transfusion complications
<dbl> <dbl> <dbl> <dbl> <fct> <fct> <fct>
1 1017. 0.483 2.78 14. male no no
2 1017. 0.483 2.78 55. male no no
3 1017. 0.483 2.78 96. male no no
# ... with 2 more variables: metastases <fct>, resection <fct>
```
### pammtools: Piece-wise exponential Additive Mixed Modeling tools

```r
# A tibble: 12 x 9

| days | status | charlson_score | age | sex  | transfusion | complications | metastases | resection |
|------|--------|----------------|-----|------|-------------|---------------|------------|-----------|
| 1060 | 0.483  | 2.96           | 50  | male | no          | no            | no         | no        |
| 954  | 0.484  | 2.52           | 50  | female | no         | no            | no         | no        |
| 1060 | 0.483  | 2.96           | 55  | male | no          | no            | no         | no        |
| 954  | 0.484  | 2.52           | 55  | female | no         | no            | no         | no        |
| 1060 | 0.483  | 2.96           | 60  | male | no          | no            | no         | no        |
| 954  | 0.484  | 2.52           | 60  | female | no         | no            | no         | no        |
| 1060 | 0.483  | 2.96           | 50  | male | no          | no            | no         | no        |
| 954  | 0.484  | 2.52           | 50  | female | no         | no            | no         | no        |
| 1060 | 0.483  | 2.96           | 55  | male | no          | no            | no         | no        |
| 954  | 0.484  | 2.52           | 55  | female | no         | no            | no         | no        |
| 1060 | 0.483  | 2.96           | 60  | male | no          | no            | no         | no        |
| 954  | 0.484  | 2.52           | 60  | female | no         | no            | no         | no        |
```

# same can be performed on ped data

```r
make_newdata(ped_tumor, age=seq_range(age, n=3))
```

# A tibble: 3 x 14

```r
tstart tend intlen interval id offset ped_status charlson_score
<dbl> <dbl> <dbl> <fct> <dbl> <dbl> <dbl> <dbl>
1 0 1 1 (0,1] 393. 0. 0. 2.73
2 0 1 1 (0,1] 393. 0. 0. 2.73
3 0 1 1 (0,1] 393. 0. 0. 2.73
```

# note that other interval related variables are adjusted as well

```r
make_newdata(ped_tumor, tend=unique(tend)[1:2])
```

```r
tstart tend intlen interval id offset ped_status charlson_score
<dbl> <dbl> <dbl> <fct> <dbl> <dbl> <dbl> <dbl>
1 0 1 1 (0,1] 392.6801 0.0000000 0 2.72929
2 1 2 1 (1,2] 392.6801 0.0000000 0 2.72929
3 2 3 1 (2,3] 392.6801 0.0000000 0 2.72929
4 3 5 2 (3,5] 392.6801 0.6931472 0 2.72929
```

```r
ped_tumor %>% group_by(transfusion) %>% make_newdata(tend=unique(tend)[1:2])
```

```r
tstart tend intlen interval id offset ped_status charlson_score
<dbl> <dbl> <dbl> <fct> <dbl> <dbl> <dbl> <dbl>
1 0 1 1 (0,1] 400.6291 0 0 2.68491
2 1 2 1 (1,2] 375.0737 0 0 2.82758
```
Adding hazards, cumulative hazards and survival probabilities

Using these flexibly created new data sets, we employ `mgcv`’s `predict` function to calculate estimated log-hazards as well as secondary quantities like conditional survival probabilities from an estimated PAMM model (see also `?add_term`):

- hazard (`add_hazard`)/log-hazard (`add_hazard(..., type = "link")`):

  ```r
  new_df <- make_newdata(ped_tumor, tend = unique(tend)) %>% slice(1:5)
  new_df %>% add_hazard(pam_tumor_tve, type = "link") %>%
  select(tend, hazard:ci_upper)
  # A tibble: 5 x 5
  tend hazard se ci_lower ci_upper
  <dbl> <dbl> <dbl> <dbl> <dbl>
 1 1. -8.31 0.171 -8.65 -7.97
 2 2. -8.31 0.171 -8.65 -7.97
 3 3. -8.31 0.170 -8.65 -7.97
 4 5. -8.31 0.170 -8.65 -7.97
 5 6. -8.31 0.170 -8.65 -7.97
  # ... with 1 more variable: surv_lower <dbl>
  ```

- cumulative hazard (`add_cumu_hazard`):

  ```r
  new_df %>% add_cumu_hazard(pam_tumor_tve) %>% add_surv_prob(pam_tumor_tve) %>%
  select(interval, cumu_hazard:surv_upper)
  # A tibble: 5 x 7
  interval cumu_hazard cumu_lower cumu_upper surv_prob surv_upper
  <fct> <dbl> <dbl> <dbl> <dbl> <dbl>
 1 (0,1] 0.000246 0.000175 0.000346 1.000 1.000
 2 (1,2] 0.000492 0.000350 0.000693 1.000 1.000
 3 (2,3] 0.000739 0.000525 0.00104 0.999 0.999
 4 (3,5] 0.00123 0.000876 0.00173 0.999 0.999
 5 (5,6] 0.00148 0.00105 0.00208 0.999 0.999
  # ... with 1 more variable: surv_lower <dbl>
  ```

Thus, the `add_*` functions add the calculated quantities directly to the data. The resulting augmented data sets can then be used for visualizations:
5. Implementation details

In our implementation, we follow the principles of *tidy* data analysis (Wickham 2014), which implies that most functions take a data set as their first argument and all plot convenience functions are accompanied by respective functions that return the data used for plotting in a tidy format. All graphics in this article have been created using *ggplot2* (Wickham 2016b) and the visualization functions in *pammtools* also return *ggplot*-objects. Internally and in example code, we use *dplyr* (Wickham, Francois, Henry, and Müller 2017) and *tidyr* (Wickham 2016a) for data manipulation and *purrr* (Henry and Wickham 2018) for functional programming, *checkmate* (Lang 2017) and *testthat* (Wickham 2011) were used for defensive programming during the iterative development via *devtools* (Wickham, Hester, and Chang 2018). The flexible, formula based specification used to transform different data types to the PED format is facilitated by the *Formula* package (Zeileis and Croissant 2010). We compared the PAMM estimates to the Cox PH model, estimated using the *coxph* routine provided by the *survival* package (Therneau and Grambsch 2001), and to the Aalen model using the *aalen* routine provided by the *timereg* package (Martinussen and Scheike 2006). Simulation of time-to-event data from the *PEXP* distribution is facilitated by the *msm* package (Jackson 2011). The companion website (https://adibender.github.io/pammtools/) was created using *pkgdown* (Wickham and Hesselberth 2018). This article was compiled using *knitr* (Xie 2015) based on *pammtools* v0.1.2 (Bender and Scheipl 2018).
6. Discussion

Summary

The R package pammtools facilitates the estimation, interpretation and visualization of flexible time-to-event regression analysis using GAMMs. In particular, in Section 3 we demonstrate how data of different complexity, including data with time-dependent covariates, can be transformed into a format suitable for such analyses. Special attention was given to the modeling and interpretation of time-varying effects (cf. Section 4.2) and cumulative effects (cf. Sections 3.2 and 4.3). In addition, Supplement A demonstrates how time-to-event data with complex time-varying and cumulative effects can be simulated, which will simplify future research on complex time-to-event models.

Limitations

Currently the package only supports data transformation for right-censored time-to-event data. While the PED format created by the as_ped function could be provided to any function or statistical software distribution that supports estimation of Poisson GA(M)Ms, most post-processing functions and convenience plot functions are customized to work with the R package mgcv. Although much effort went into making the respective functions robust, these efforts are limited by the fact that the estimation process is currently performed outside of pammtools. Feedback, bug reports and feature requests are welcomed at https://github.com/adibender/pammtools/issues or by contacting the authors.

Outlook

Future releases of pammtools will primarily focus on further improvement of the user interface and robustness of the implementation. We plan to extend the current framework to allow different censoring and truncation scenarios (left-truncation, left-censoring), as well as to support more complex outcomes like competing risk events or multi-state models.
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A. Simulating time-to-event data

For convenience, the *pammtools* package contains a lightweight, but versatile function for the simulation of time-to-event data, with potentially smooth, smoothly time-varying effects. For the simulation of survival times we use the Piece-wise exponential distribution \( t \sim \text{PEXP}(\lambda_i,t) \), which is implemented in the *R* package *msm* (Jackson 2011). Here \( \lambda \) is a vector of hazards at time points \( t \) and \( \lambda \) can be specified conveniently using a *formula* notation.

In Section A.1, we empirically demonstrate that even crude PEXP hazards can be used to simulate survival times from continuous distributions. In Section A.2 we illustrate the simulation of survival times based on hazard rates that flexibly depend on time-constant covariates. Lastly, Section A.3 shows how to simulate from hazards with cumulative effects of TDCs.

A.1. Motivation

We use a simple Weibull baseline hazard model to illustrate that the function indeed simulates event times from the desired distribution, even though the hazards \( \lambda \) are assumed to be piece-wise constant between two time-points in \( t \). Figure 10 depicts the hazard rate and survivor function of a Weibull distribution with \( T \sim WB(\alpha = 1.5, \lambda = 10) \).

![Figure 10: Hazard rate (left) and survivor function (right) of the WB(1.5, 10) distribution.](image)

Figure 11 shows the baseline hazard estimated by a PEM with 10 intervals based on the true Weibull hazard and survival probability, respectively.

![Figure 11: PEM estimates of the baseline hazard \( \lambda(t) \) (left panel) and survival probability \( S(t) \) (right panel). Red lines indicate the true Weibull hazard and survival probability, respectively.](image)
on \( n = 1000 \) survival times simulated from \( WB(1.5, 10) \). Although the approximation of the underlying smooth hazard is relatively crude, the survival function calculated from this step hazard is very close to the true survivor function (cf. right panel of Figure 11). Finally, Figure 12 depicts the distribution of survival times (Kaplan-Meier estimates) for \( n = 1000 \) survival times simulated directly from the correct Weibull distribution (\( rweibull(n, 1.5, 10) \)) on the one hand and from the \( PEXP \) distribution (based on the crude hazard in Figure 11) on the other hand.

Figure 12: Comparison of Kaplan-Meier survival probability estimates based on survival times simulated directly from the Weibull distribution \( WB(1.5, 10) \) and based on survival times simulated from the \( PEXP \) distribution based on the hazards depicted in Figure 11. The Black line indicates the true Weibull survival probability on \( t \in [0, 10] \).

### A.2. Flexible, covariate dependent simulation of survival times

To simulate survival times from the \( PEXP \) distribution conveniently, \texttt{pammtools} provides the \texttt{sim_pexp} function. Similar to the \texttt{as_ped} function, it uses a formula interface, which allows to specify complex hazards relatively easily. For example, in \texttt{R}-chunk 16 we simulate data from

\[
\log(\lambda(t|x_1, x_2)) = -3.5 + f_0(t) - 0.5x_1 + \sqrt{x_2},
\]

where \( f_0(t) \) is a Gamma(8,2) density function. Any existing or previously defined function can be used in the \texttt{formula} argument to \texttt{sim_pexp}. The argument \texttt{cut} defines the time-points at which the piece-wise constant hazard will change its value. In \texttt{R} chunk 16 for example, the hazard will change its value at \( t = 1, t = 2, \ldots \) with \( f_0(t) \) (and other time-varying effects) evaluated at the respective interval end-points. \texttt{sim_pexp} returns the original data augmented by the simulated survival times (\texttt{time}) as well as a \texttt{status} column.

```r
R-chunk 16

# basic data
set.seed(7042018)
# create data set with covariates
n <- 1000
df <- tibble::tibble(x1 = runif(n, -3, 3), x2 = runif(n, 0, 6))
# baseline hazard function
f0 <- function(t) {dgamma(t, 8, 2) * 6}
# simulate data from \( PEXP \)
Note that the simulation could be easily extended to contain time-varying effects, e.g. by defining a function

```r
f_tx <- function(t, x) sqrt(x)*log(t)
```

and calling

```r
sim_pexp(~ -3.5 + f0(t) -0.5*x1 + f_tx(t, x2), data = df, cut = 0:10)
```

### A.3. Simulation of survival times with cumulative effects

**Weighted cumulative exposure**

In this section we demonstrated how to simulate data with hazard rate

$$\log(\lambda(t|x_1, x_2, z)) = -3.5 + f_0(t) - 0.5x_1 + \sqrt{x_2} + \int_{T(t)} h(t - t_z)z(t_z)dt_z.$$ 

which constitutes a so-called Weighted cumulative exposure model (Sylvestre and Abrahamowicz 2009). This data is used in section 4.3.1 to illustrate estimation and visualizations of such effects. The static part of the data set as well as the baseline hazard and TCC effects are identical to the previous section (cf. R-chunk 16). For the cumulative effect, we define the exposure time grid (i.e., the time points $t_z$ at which the TDC was observed) and use the function `add_tdc` (mnemonic: *add time-dependent covariate*) to add the information on the exposure times and the $z(t_z)$ to the data (cf. R-chunk 17).

```r
# define follow-up time grid for simulation
# (arbitrary, but check that enough events are observed over follow-up)
time_grid <- seq(0, 10, by = 0.5)

# baseline hazard
f0 <- function(t) {
dgamma(t, 8, 2) * 6
}

# define time grid on which TDC is observed
# (arbitrary, but lag-lead matrix will depend on it)
tz <- seq(-5, 5, by = .25)

# define function that generates nz exposures $z(t_{z,1}), ..., z(t_{z,Q})$
rng_z = function(nz) {
as.numeric(arima.sim(n = nz, list(ar = c(.8, -.1))))
}

## add TDCs to data set
df <- df %>% add_tdc(tz, rng_z)
```
The partial effect $h(t - t_z)$ (see function `f_wce`) and the lag-lead window $\mathcal{T}(t)$ (see function `ll_fun`) are defined in R-chunk 18 and depicted in Figure 13. The left panel of Figure 13 shows the latency-dependent weight function $h(t - t_z)$ for the exposures $z(t_z)$. The middle panel shows the lag-lead window with partial effects. Note that $h(t - t_z)$ only depends on the latency, not the specific combination of $t$ and $t_z$. Nonetheless, the cumulative effect $g(z, t)$ (right panel) varies over $t$ even for constant exposure $z(t_z) = z$ since it is integrated over different windows of effectiveness $\mathcal{T}(t)$.

R-chunk 18

```r
# define lag-lead function: integrate over the preceding 12 time units
ll_fun <- function(t, tz) ((t - tz) >= 0) & ((t - tz) <= 12)
# gg_laglead(0:10, -5:5, ll_fun)

# partial effect h(t - tz) * z
f_wce <- function(t, tz, z) {
  0.5 * (dnorm(t - tz, 6, 2.5)) * z
}
```

Figure 13: Left: Partial effect $h(t - t_z)$ defined in R-chunk 18 for different latencies $t - t_z$. Middle: The lag-lead window $\mathcal{T}(t)$ and respective partial effects for each combination of $t$ and $t_z$. Combinations of $t$ and $t_z$ outside the specified lag-lead window in dark gray. Partial effects of exposures at different time-points $t, t_z$ are the same if the latency $t - t_z$ is the same, i.e. $h(5 - 1) = h(6 - 2) = h(4)$. Right: Cumulative effect $g(z, t)$ for constant $z(t_z) = 1 \forall t_z$.

Given the above setup with cumulative effects $g(z, t) = \int_{\mathcal{T}(t)} h(t - t_z)z(t_z)dt_z$, we can now simulate the data using the `sim_pexp` function as displayed in R-chunk 19.
R-chunk 19

```r
simdf_wce <- sim_pexp(
  formula = -3.5 + f0(t) -0.5*x1 + sqrt(x2)
  | fcumu(t, tz, z.tz, f_xyz=f_wce, ll_fun=ll_fun),
  data = df, cut = time_grid)
```

**Bivariate, smooth partial effects**

In this section we illustrate an extension of the previous simulation, where the exposure \( z(t_z) \) affects the hazard non-linearly as denoted in eq. 9.

\[
\log(\lambda(t|x_1,x_2,z)) = -3.5 + f_0(t) - 0.5x_1 + \sqrt{x_2} + \int_{T(t)} h(t-t_z,z(t_z))dt_z
\]  

Using the `sim_pexp` function, we can extend the previous simulation (cf. Section A.3.1) by changing the partial effect function as illustrated in R-chunk 20 (function `f_dlnm`). Figure 14 depicts the bivariate, smooth partial effect \( h(t-t_z,z(t_z)) \) and the resulting cumulative effects \( g(z,t) \) for a simplified exposure history with constant \( z(t_z) = 1 \) all \( t_z \).

R-chunk 20

```r
# partial effect h(t - tz) * z
f_dlnm <- function(t, tz, z) {
  20 * ((dnorm(t - tz, 6, 2.5)) * (dnorm(z, 1.25, 2.5) - dnorm(-1, 1.25, 2.5)))
}
simdf_dlnm <- sim_pexp(
  formula = -4.5 + f0(t) -0.5*x1 + sqrt(x2)
  | fcumu(t, tz, z.tz, f_xyz=f_dlnm, ll_fun=ll_fun),
  data = df, cut = time_grid)
```

Figure 14: **Left:** Partial effect \( h(t-t_z,z(t_z)) \) used for the simulation of survival times (data `simdf_dlnm`) in R-chunk 20. **Right:** The cumulative effects \( g(z,t) \) resulting from constant exposure histories \( z(t_z) = 1 \) all \( t_z \).
Bivariate smooth of time and exposure time

Here we simulate the data used in Section 4.3 with hazard

\[
\log(\lambda(t|x_1,x_2,z)) = -3.5 + f_0(t) - 0.5x_1 + \sqrt{x_2} + \int_{\mathcal{T}(t)} h(t,t_z)z(t_z)dt_z.
\]

The simulation code is given in R-chunk 21 with updated partial effect function \(f_{\text{elra}}\). Figure 15 depicts the bivariate, smooth partial effect \(h(t,t_z)\) (left panel) and the resulting cumulative effect \(g(z,t)\) for a simplified exposure history with \(z(t_z) = 1\)∀\(t_z\) (right panel).

R-chunk 21

```r
# partial effect \(h(t,tz) \ast z\)
f_elra <- function(t, tz, z) {
  5*(-(dnorm(tz, -1, 2.5)) * (dnorm(t, 5, 1.5) - dnorm(5, 5, 1.5))) * z
}
simdf_tv_wce <- sim_pexp(formula = ~ -4.5 + f0(t) - 0.5*x1 + sqrt(x2) | fcumu(t, tz, z.tz, f_xyz = f_elra, ll_fun = ll_fun),
data = df, cut = time_grid)
```

Figure 15: Left: Bivariate partial effect surface \(h(t,t_z)\), combinations of \(t\) and \(t_z\) that lie outside the lag-lead window \(\mathcal{T}(t)\) are omitted. Right: The cumulative effect resulting from the partial effect depicted in the left panel for a simplified exposure profile with \(z(t_z) = 1\)∀\(t_z\).