The R package **predint**
Prediction intervals for overdispersed binomial and Poisson data, or based on linear random effects models in R

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Abstract

A prediction interval is a statistical interval that should encompass one (or more) future observation(s) with a given coverage probability and is usually computed based on historical control data. The application of prediction intervals is discussed in many fields of research, such as toxicology, pre-clinical statistics, engineering, assay validation or for the assessment of replication studies. Anyhow, the prediction intervals implemented in \texttt{predint} descent from previous work that was done in the context of toxicology and pre-clinical applications. Hence the implemented methodology reflects the data structures that are common in these fields of research. In toxicology the historical data is often comprised of dichotomous or counted endpoints. Hence it seems natural to model these kind of data based on the binomial or the Poisson distribution. Anyhow, the historical control data is usually comprised of several studies. These clustering gives rise to possible overdispersion which has to be reflected for interval calculation. In pre-clinical statistics, the endpoints are often assumed to be normal distributed, but usually are not independent from each other due to the experimental design (cross-classified and/or hierarchical structures). These dependencies can be modeled based on linear random effects models. Hence, \texttt{predint} provides functions for the calculation of prediction intervals and one-sided bounds for overdispersed binomial data, for overdispersed Poisson data and for data that is modeled by linear random effects models.

Keywords

Bio-assay, historical control data, bootstrap calibration, assay validation and qualification
1 Introduction

A prediction interval is a statistical interval $[L, U]$ that should encompass $M \geq 1$ future observations $y^*$ simultaneously with coverage probability

$$P(L \leq y^* \leq U) = 1 - \alpha.$$ 

Similarly, lower prediction bounds $L$ should result in the coverage probability

$$P(L \leq y^*) = 1 - \alpha$$

and upper prediction bounds $U$ should have a coverage probability of

$$P(y^* \leq U) = 1 - \alpha.$$ 

The computation of prediction intervals or bounds is based on the assumption that both, the historical observations $y$ as well as the future observations $y^*$ descent from the same data generating process.

The application of the prediction intervals implemented in `predint` is of use in several fields of research, such as the detection of anti-drug antibodies [Hoffmann and Berger, 2011, Menssen and Schaarschmidt, 2021] or the validation of an actual control group by historical control data in toxicology [Menssen and Schaarschmidt, 2019]. Further applications of prediction intervals can be found in industry [Ryan, 2007], in experiments for method comparison (bridging) or assay validation [Francq et al., 2019] or in the context of the evaluation of replication studies [Spence and Stanley, 2016].

All the applications mentioned above have in common, that the historical data used for the calculation of prediction intervals is comprised of several clusters, rather than of one unstructured sample. For example, in pre-clinical experiments for the detection of anti-drug antibodies, it is of interest to distinguish between 'responders' whose anti-drug antibody reaction exceeds a critical level and 'non-responders' whose reaction is uncritical low. One approach for the detection of such a critical level is the application of an upper prediction bound that is calculated based on the observed anti-drug antibody reaction of a set of known 'non-responders'.

Such experiments are usually run based on blood samples obtained from different patients
The prediction intervals implemented in `predint`, that are based on random effects models, are similar to the methodology proposed in [Menssen and Schaarschmidt, 2021]. But, additionally to the historical experimental design, two of the three implementations are also able to take the design of the future data into account, rather than only the number of future observations as proposed in [Menssen and Schaarschmidt, 2021]. Furthermore, the implemented methodology is applicable to a broad range of experimental designs such as cross-classified and/or hierarchical structures as well as balanced or unbalanced data (see section 2.1).

Another example where clustered data occurs are bio-assays with a toxicological background. These experiments are usually comprised of an untreated control group that is compared to several groups of model organisms treated with a chemical compound of interest. In that field of research prediction intervals are of interest in order to validate the outcome of an actual (or future) control group. Hence, such intervals are calculated based on observations obtained from historical control groups of previous experiments [Menssen and Schaarschmidt, 2019, Valverde-Garcia et al., 2018]. Since many endpoints in toxicology are either dichotomous (e.g. rats with a tumor vs. rats without a tumor) or counted observations (e.g. numbers of eggs per hen), it seems natural to model them based on the binomial or the Poisson distribution, respectively. Anyhow, the model has to take the clustering into account and hence also possible overdispersion, meaning that the variance of the data exceeds the variance that can be modeled based on 'simple' binomial or Poisson distribution. One reason for the presence of overdispersion are positive correlations between experimental units in each cluster. Therefore, overdispersion is considered to be almost always present in biological data [Demetrio et al., 2014, McCullagh and Nelder, 1989].

Prediction intervals for $M = 1$ future observation based on overdispersed binomial data were proposed in [Menssen and Schaarschmidt, 2019]. Anyhow, the prediction intervals for that...
type of data that are implemented in \texttt{predint} are based on a slightly different approach, meaning that they are also applicable in the case where a simultaneous prediction interval that should cover $M > 1$ future observations is needed (see section \ref{simultaneous}).

To the authors knowledge, prediction intervals for $M \geq 1$ future observations that can be computed based on clustered count data that exhibits overdispersion were not available in an \texttt{R} package hosted on CRAN. This gap is filled by the prediction interval proposed in section \ref{prediction}

\section{Theory}

\subsection{Linear random effects models}

A general linear random effects model is given by

$$
Y = 1\mu + ZU + e
$$

where $Y = (Y_1, \ldots, Y_N)^T$ is a vector of random variables representing $n = 1, \ldots, N$ observations. The overall mean is represented by $\mu$. $U$ is a stacked vector consisting of random effects sub-vectors $U_c$. Hence, each $U_c$ represents all $f = 1, \ldots, F_c$ levels associated with a particular random factor out of the $c = 1, \ldots, C$ random factors that influence the observations. $Z$ is a design matrix of dimensions $N \times F$ where $F = \sum_c F_c$ denotes the total length of $U$.

The random errors associated with the observations are represented by $e$. The individual random effects can be represented as $Z_c U_c$ such that

$$
ZU = \begin{pmatrix} Z_1 & \cdots & Z_C \end{pmatrix} \begin{pmatrix} U_1 \\ \vdots \\ U_C \end{pmatrix} = \sum_{c=1}^C Z_c U_c
$$

with each

$$
U_c = \begin{pmatrix} U_{c1} \\ \vdots \\ U_{cF_c} \end{pmatrix}
$$
All random effects are assumed to be normal distributed $U_c \sim N(0, I\sigma^2_c)$ as well as the errors $e \sim N(0, I\sigma^2_{C+1})$. Furthermore it is assumed that

$$\text{cov}(\mu, U_{cF_c}) = 0 \quad \forall \quad c = 1, \ldots, C + 1$$

$$\text{cov}(U_{cF_c}, U_{c'F_{c'}}) = 0 \quad \forall \quad c = 1, \ldots, C + 1, \quad c' = 1, \ldots, C + 1 : c \neq c'$$

This model implies that the observations follow a multivariate normal distribution

$$Y \sim MVN(1\mu, V) \quad (1)$$

with variance-covariance matrix

$$V = \sum_{c=1}^{C} Z_c Z_c^T \sigma^2_c + I \sigma^2_{C+1} \cdot$$

It is assumed that both, the historical as well as the future random variables are independent from each other, but descent from the same data generating process. Hence, also the future random variable $Y^*$ that represents $m = 1, \ldots, M$ future observations is multivariate normal

$$Y^* \sim MVN(1\mu, V^*) \quad (2)$$

with variance-covariance matrix

$$V^* = \sum_{c=1}^{C} Z^*_c Z^*_c^T \sigma^2_c + I^* \sigma^2_{C+1} \cdot$$

Please note, that the number of random effects per random factor might differ between the historical and the future data (e.g. 5 hospitals, each with 3 patients vs. 3 hospitals, each with 4 patients). Consequently, the number of observations might differ between the historical and the future data ($Y$ is of length $N$ and $Y^*$ is of length $M$) as well as the variance-covariance matrices $V$ and $V^*$, since they depend on different effects design matrices $Z_c$ and $Z^*_c$. This implies that, $Y$ and $Y^*$ usually do not follow the same multivariate normal distribution (see eq. 1 and 2), but, nevertheless, descent from the same data generating process which depends only on the mean $\mu$ and the variance components $\sigma^2_c$.

In this setup, the error margin of the prediction is

$$D = Y^* - 1\mu$$
with

\[ D \sim MVN(0, \text{var}(D)) \]
\[ \text{var}(D) = \text{var}(Y^* - 1\mu) = \text{var}(Y^*) = V^* \]

which, in the case of a prediction for only \( M = 1 \) future observation simplifies to

\[ V^* = \sum_{c=1}^{C+1} \hat{\sigma}_c^2 \]

If a prediction interval for \( M \geq 1 \) future observations should be computed based on observed historical data \( y \) and the fitted model

\[ y = 1\hat{\mu} + Z\hat{U} + \hat{e} \]

the estimated prediction variance becomes

\[ \hat{\text{var}}(D) = \hat{\text{var}}(Y^* - 1\hat{\mu}) = V^* + J\hat{\text{var}}(\hat{\mu}) \]

with \( J \) as a square matrix with all entries set to one.

A prediction interval that should cover \( M > 1 \) future observations \( y^* \) simultaneously with coverage probability \( 1 - \alpha \) is given by

\[ [L, U] = \hat{\mu} \pm mvt_{1-\alpha/2, df, \hat{\text{var}}(D)} \]

with \( mvt_{1-\alpha/2, df, \hat{\text{var}}(D)} \) as the \( 1 - \alpha/2 \)-quantile of the multivariate t-distribution. Please note, that a prediction interval for \( M = 1 \) future observation simplifies to

\[ [L, U] = \hat{\mu} \pm t_{1-\alpha/2, df} \sqrt{\sum_{c=1}^{C+1} \hat{\sigma}_c^2 + \hat{\text{var}}(\hat{\mu})}. \]

\[ \text{Menssen and Schaarschmidt [2021]} \] gave an overview about several methods for the computation of the prediction intervals given in equations 3 and 4 of which their bootstrap calibrated prediction interval serves as the basis of the intervals implemented in \texttt{predint}.\
2.2 Overdispersed binomial data

In several bio-assays run in the field of toxicology, the endpoints are dichotomous (e.g. rats with tumors vs. rats without tumors). A natural approach for modeling such data is the binomial assumption

\[ y_h \sim \text{bin}(n_h, \pi) \]  
\[ \text{var}(y_h) = n_h\pi(1 - \pi) \]  

with \( E(y_h) = n_h\pi \). In this notation \( \pi \) is the binomial proportion, \( n_h \) is the size of \( h = 1 \ldots H \) clusters (e.g. number of individuals in the \( h \)th historical control group) and \( y_h \) are the number of successes obtained from the individuals of the \( h \)th cluster (e.g. rats with tumors).

Anyhow, most of the biological data that is assumed to be binomial has higher variability than expected and hence exhibits overdispersion [Demetrio et al., 2014, McCullagh and Nelder, 1989].

There are two approaches to model overdispersion: The quasi-binomial (or quasi-likelihood) approach or modelling based on the beta-binomial distribution. The first approach assumes a dispersion parameter that constantly inflates the variance for all observations, such that

\[ \text{var}(y_h)^{QB} = \phi n_h\pi(1 - \pi) \]  

with \( E(y_h) = n_h\pi \) and \( \phi > 1 \).

For the latter, the data is assumed to be beta-binomial distributed

\[ \pi_h \sim \text{beta}(a, b) \]  
\[ y_h \sim \text{bin}(\pi_h, n_h) \]  
\[ \text{var}(y_h)^{BB} = n_h\pi(1 - \pi)[1 + (n_h - 1)\rho] \]  

with \( E(\pi_h) = \pi = a/(a + b) \), \( E(y_h) = n_h\pi \) and \( \rho = 1/(1 + a + b) \). It is noteworthy, that \([1 + (n_h - 1)\rho]\) depends on the cluster size \( n_h \) and becomes a constant, if all of the \( H \) clusters have the same size \( n_h = n_h' = n \). In this case the quasi-likelihood approach and the model that is based on the beta-binomial distribution both result in overdispersion that constantly inflates the binomial variance of the different clusters.
Several methods for the calculation of prediction intervals based on one binomial sample were proposed in literature [Hahn et al., 2017]. Anyhow, none of these methods reflect the fact that the historical data is usually comprised of several clusters. Furthermore, these methods do not consider for possible overdispersion and hence, yield coverage probabilities far below the nominal level, if overdispersion is present in the data [Menssen and Schaarschmidt, 2019].

The prediction intervals for dichotomous data that are implemented in predint are derived from an asymptotic prediction interval for \( M = 1 \) future observation, which is based on one unclustered binomial sample [Hahn et al., 2017]. Its calculation is based on the assumption that

\[
\frac{\hat{y}^* - Y^*}{\sqrt{\text{var}(\hat{y}^* - Y^*)}} = \frac{n^*\hat{\pi} - Y^*}{\sqrt{\text{var}(n^*\hat{\pi} - Y^*)}} = \frac{n^*\hat{\pi} - Y^*}{\sqrt{\text{var}(n^*\hat{\pi}) + \text{var}(Y^*)}}
\]

approximately follows a standard normal distribution

\[
\frac{n^*\hat{\pi} - Y^*}{\sqrt{\text{var}(n^*\hat{\pi}) + \text{var}(Y^*)}} \approx N(0,1).
\]

In this notation \( \hat{y}^* \) is the expected future observation, \( Y^* \) is the future random variable, \( \hat{\pi} \) is the estimate for the binomial proportion obtained from the historical sample of size \( n \) and \( n^* \) is the size of the future cluster. The corresponding prediction interval for \( M = 1 \) future observation is given by

\[
[l, u] = n^*\hat{\pi} \pm z_{1-\alpha/2} \sqrt{n^*\hat{\pi}(1-\hat{\pi})\left(1 + \frac{n^*}{n}\right)}
\]  

(7)

with \( \text{var}(Y^*) = n^*\hat{\pi}(1-\hat{\pi}) \) and \( \text{var}(n^*\hat{\pi}) = n^2[\hat{\pi}(1-\hat{\pi})/n] \). As mentioned above, this interval was proposed for the application to one historical set of unclustered observations. Therefore, this prediction interval does not account for clustering and hence, neglects the possible effect of overdispersion that might occur in the data.

Prediction intervals for \( M = 1 \) future observation, that account for the clustered structure of the historical data, can be calculated based on both, the quasi-binomial approach or the beta-binomial distribution. A prediction interval that is based on the quasi-binomial assumption can be obtained by substituting \( \text{var}(Y) \) with \( \text{var}(Y)^{QB} = \phi n^*\hat{\pi}(1-\hat{\pi}) \) and \( \text{var}(n^*\hat{\pi}) \) with \( \text{var}(n^*\hat{\pi})^{QB} = n^2\phi\hat{\pi}(1-\hat{\pi})/N \) in eq. 7. Hence, the interval is defined as

\[
[l, u] = n^*\hat{\pi} \pm z_{1-\alpha/2} \sqrt{\phi n^*\hat{\pi}(1-\hat{\pi})\left(1 + \frac{n^*}{N}\right)}.
\]  

(8)
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with \( N = \sum_{h=1}^{H} n_h \).

A prediction interval for one future observation that is based on the beta-binomial distribution is computed if \( \hat{\text{var}}(Y) \) is substituted by \( \hat{\text{var}}(Y)^{BB} = n^*\hat{\pi}(1 - \hat{\pi})[1 + (n^* - 1)\hat{\rho}] \) and \( \hat{\text{var}}(n^*\hat{\pi}) \) by \( \hat{\text{var}}(n^*\hat{\pi})^{BB} = \frac{n^*\hat{\pi}(1 - \hat{\pi})}{N} + \frac{N - 1}{N}n^*\hat{\pi}(1 - \hat{\pi})\hat{\rho} \) in eq. 7. The resulting prediction interval is given as

\[
[l, u] = n^*\hat{\pi} \pm z_{1-\alpha/2}\sqrt{n^*\hat{\pi}(1 - \hat{\pi})[1 + (n^* - 1)\hat{\rho}] + \left[\frac{n^*\hat{\pi}(1 - \hat{\pi})}{N} + \frac{N - 1}{N}n^*\hat{\pi}(1 - \hat{\pi})\hat{\rho}\right]}
\]

Please note, that prediction intervals that should cover \( M > \) future observations simultaneously, can be obtained by the application of the bootstrap-calibration procedure described below in section 2.4.

### 2.3 Overdispersed Poisson data

In several bio-assays, such as avian reproduction, the variable of interest is comprised of count data [Valverde-Garcia et al., 2018]. A natural approach for modeling counts is to assume them to be Poisson distributed

\[
y_h \sim \text{Pois}(\lambda)
\]

\[
E(y_h) = \text{var}(y_h) = \lambda.
\]

Here, \( y_h \) are the observations per cluster, \( h = 1 \ldots H \) is the index for the clusters and \( \lambda \) is the Poisson mean. Similar to dichotomous data, overdispersion is usually present and can be modeled based on the quasi-Poisson (quasi-likelihood) approach that grounds on a constant dispersion parameter inflating the Poisson-variance [Demetrio et al., 2014], such that

\[
\text{var}(y_h)^{QP} = \phi\lambda
\]

with \( \phi > 1 \) and \( E(y_h) = \lambda \). Another approach for modeling overdispersed Poisson data is the negative-binomial distribution where the means of the historical studies follow a gamma
distribution with parameters $a$ and $b$, such that

\[
\lambda_h \sim \text{gamma}(a, b) \\
y_h \sim \text{Pois}(\lambda_h)
\]

\[
\text{var}(y_h)^{NB} = \lambda + \kappa \lambda^2 = (1 + \kappa \lambda) \lambda
\]

with $E(y_h) = \lambda = a/b$ and $\kappa = 1/a$ \cite{Gsteiger:2013}. Please note that in the case in which several counted observations $y_h$ simply vary around their expected value $\lambda$, both, the quasi-Poisson and the negative-binomial assumption are not in contradiction with each other (with regard to their variance formula). This is because both, $\phi$ and $(1 + \kappa \lambda)$ are constant in this case. Hence,

\[
\text{var}(y_h)^{NB} = \text{var}(y_h)^{QB} = (1 + \kappa \lambda) \lambda = \phi \lambda. \tag{10}
\]

Several methods for the calculation of prediction intervals for one future observation based on one Poisson distributed historical sample are reviewed in \cite{Hahn:2017}. An asymptotic prediction interval for $M = 1$ future observation $y^*$ which is based on one unclustered Poisson distributed sample is based on the assumption that

\[
\frac{\hat{y}^* - Y^*}{\sqrt{\text{var} (\hat{y}^* - Y^*)}} = \frac{\hat{\lambda} - Y^*}{\sqrt{\text{var} (\hat{\lambda} - Y^*)}} = \frac{\hat{\lambda} - Y^*}{\sqrt{\text{var}(\hat{\lambda}) + \text{var}(Y^*)}} \tag{11}
\]

is approximately standard normal

\[
\frac{\hat{\lambda} - Y^*}{\sqrt{\text{var}(\hat{\lambda}) + \text{var}(Y^*)}} \overset{\text{appr.}}{\sim} N(0, 1).
\]

The corresponding asymptotic prediction interval is given by

\[
[l, u] = \hat{\lambda} \pm z_{1-\alpha/2} \sqrt{2\hat{\lambda}}.
\]

Please note that this interval is a simplified version (ignoring offsets) of the one that is reviewd in \cite{Hahn:2017}. Its adaption to overdispersed data comprised of $h = 1, \ldots, H$ clusters results in

\[
[l, u] = \hat{\lambda} \pm z_{1-\alpha/2} \sqrt{\hat{\phi} \hat{\lambda} \left(1 + \frac{1}{H}\right)} \tag{12}
\]

with $\hat{\phi} > 1$. Simultanious prediction intervals for $M > 1$ future observations can be obtained by the application of the bootstrap calibration procedure described in the next section.
2.4 Bootstrap calibration

The bootstrap-calibration of statistical intervals dates back to the late 1980ies. The original approach proposed by Loh [1987] was aimed to find a better value for the $\alpha$ with which an interval is calculated in order to bring the coverage probability of the calibrated interval as close as possible to the nominal $1 - \alpha$. This approach is reviewed in Efron and Tibshirani [1994] and is sometimes called alpha-calibration.

Contrary to alpha-calibration, the bootstrap-calibration procedure used for the calculation of the prediction intervals implemented in \texttt{predint}, is aimed to find a coefficient $\delta$ that directly replaces the $t$- or $z$-quantiles in eq. 4, 8, 9 and 12 resulting in prediction intervals for $M \geq 1$ future observations

$$[L, U] = \hat{y}^* \pm \delta \sqrt{\hat{\text{var}}(\hat{y}^*) + \hat{\text{var}}(Y^*)}$$  \hspace{1cm} (13)

for which the coverage probability is as close as possible to the nominal level

$$P(L \leq y^* \leq U) = 1 - \alpha$$ \hspace{1cm} (14)

In this notation, $y^*$ is the vector of the $m = 1, \ldots, M$ future observations, $\hat{y}^*$ is the estimate for the expected future observation and $\sqrt{\hat{\text{var}}(\hat{y}^*) + \hat{\text{var}}(Y^*)}$ is the prediction error.

Please note, that all prediction intervals implemented in \texttt{predint} are of the form given in eq. 13. For interval calculation, the estimates that correspond to $\hat{y}^*$, $\hat{\text{var}}(\hat{y}^*)$ and $\hat{\text{var}}(Y^*)$, which off cause depend on the chosen model, are simply plugged in. Bootstrap calibrated prediction intervals can be obtained depending on the following algorithm:

1. Fit a random effects model to the historical data set $y$ in order to obtain the estimates $\hat{y}^*$, $\hat{\text{var}}(\hat{y}^*)$ and $\hat{\text{var}}(Y^*)$

2. Draw $B$ parametric bootstrap samples $y_b^*$ that follow the same experimental design as the future data

3. Additionally, draw $b = 1, \ldots B$ further bootstrap samples $y_b$ that follow the same experimental design as the historical data.

4. Fit the initial model to $y_b$ in order to obtain $\hat{y}_b^*$, $\hat{\text{var}}(\hat{y}_b^*)$ and $\hat{\text{var}}(Y_b^*)$. 
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5. Choose a start-value for $\delta$.

6. Calculate prediction intervals based on the bootstrapped estimates as

$$[L, U]_b = \hat{y}^*_b \pm \delta \sqrt{\hat{\text{var}}(\hat{y}^*_b) + \hat{\text{var}}(Y^*_b)}.$$  

7. Calculate the coverage probability for the prediction intervals that correspond to the particular $\delta$ as

$$\hat{\Psi}_\delta = \frac{\sum_{b=1}^{B} I_\delta}{B}$$  \hspace{1cm} (15)$$

with $I_\delta = 1$ if $y^*_b \in [L, U]_b$ and $I_\delta = 0$ if $y^*_b \notin [L, U]_b$.

8. Alternate $\delta$ and repeat step six and seven until $\hat{\Psi}_\delta$ is satisfactory close to the nominal $1 - \alpha$. Use this particular value of $\delta$ for the calculation of the calibrated prediction interval.

9. Calculate the calibrated prediction interval based on the chosen $\delta$ and the parameter estimates from the initial model as shown in equation [13].

Please note, that for all prediction intervals implemented in **predint** the search for $\delta$ in step 8 of the calibration algorithm depends on the following bisection:

1. Define start values $\delta_{min}$ and $\delta_{max}$ such that the corresponding bootstrap coverage probabilities $\hat{\Psi}_{\delta_{min}}$ and $\hat{\Psi}_{\delta_{max}}$ estimated following eq. [15] are

$$\hat{\Psi}_{\delta_{min}} < 1 - \alpha$$

$$\hat{\Psi}_{\delta_{max}} > 1 - \alpha.$$  

2. Start the first of $g = 1, \ldots, G$ bisection steps by defining

$$\delta_1 = \frac{\delta_{min} + \delta_{max}}{2}$$

3. Calculate the corresponding bootstrap coverage probability $\hat{\Psi}_{\delta_1}$ according to eq. [15]

4. If $\hat{\Psi}_{\delta_1} < 1 - \alpha$, calculate

$$\delta_2 = \frac{\delta_1 + \delta_{max}}{2}$$

If $\hat{\Psi}_{\delta_1} > 1 - \alpha$, calculate

$$\delta_2 = \frac{\delta_1 + \delta_{min}}{2}$$
5. Calculate the bootstrap coverage probability \( \hat{\Psi}_{\delta} \) according to eq. 15.

6. Repeat this iteration process until \( |1 - \alpha - \hat{\Psi}_{\delta_G}| < t \) or a maximum number of bisection steps \( G_{\text{max}} \) was done.

7. Use this particular \( \delta_G \) for the calculation of the calibrated interval (replace \( \delta \) by \( \delta_G \) in eq. 13).

### 3 Methodology implemented in predint

#### 3.1 Prediction intervals

Since all functions for the calculation of prediction intervals (see tab. 1) depend on the same calibration approach and the intervals are of the same form (see eq. 13), all functions share a common framework in terms of applicability. The arguments common to all functions for interval calculation are given in tab. 2.

| Function name     | Functionality                                |
|-------------------|----------------------------------------------|
| lmer_pi_unstruc() |                                |
| lmer_pi_futvec()  | PI based on random effects models            |
| lmer_pi_futmat()  |                                |
| beta_bin_pi()     | PI for overdispersed binomial data           |
| quasi_bin_pi()    |                                |
| quasi_pois_pi()   | PI for overdispersed count data              |

Prediction intervals are calculated with `alternative="both"`, which is the default setting. Anyhow, if lower prediction bounds are of interest, `alternative` has to be set to "lower". Upper prediction bounds are computed with `alternative="upper"`. Please note, that bootstrap calibration of prediction bounds is done by adopting eq. 15, where \( L = -\infty \), if `alternative` is set to "upper", or \( U = \infty \) if `alternative` is set to "lower".

If not specified explicitly, all functions calculate prediction intervals (or bounds) with...
Table 2: Arguments common to all functions for interval calculation

| Argument   | Functionality                                      |
|------------|---------------------------------------------------|
| alternative| Prediction intervals or bounds $L, U$             |
| alpha      | Definition of $\alpha$                           |
| nboot      | Number of bootstrap samples $B$                   |
| delta_min  | Lower start value for bisection $\delta_{min}$   |
| delta_max  | Upper start value for bisection $\delta_{max}$   |
| tolerance  | Tolerance for bisection $t$                       |
| traceplot  | Graphical overview about the bisection           |
| n_bisec    | Max. number of bisection steps $G_{max}$         |

The coverage probability $1 - \alpha = 0.95$ which can be altered by setting `alpha` to any value between 0 and 1. The number of bootstrap samples can be specified by `nboot` which is set to 10000 by default. Start values for the bisection are provided by the arguments `delta_min` and `delta_max` which are set to default values of 0.01 and 10. The maximum number of bisection steps is controlled via `n_bisec` and is per default 30.

A graphical overview about the bisection process is given if `traceplot=TRUE` (see fig. 1). In such a plot, the calibration values $\hat{\delta}_g$, calculated during the bisection, are given on the x-axis. The y-axis shows the difference between the observed bootstrap coverage probabilities $\hat{\Psi}_{\delta_g}$ and the nominal level $1 - \alpha$. The bisection stops if $1 - \alpha - \hat{\Psi}_{\delta_g} \in 0 \pm t$ or, if this is not the case, after the maximum number of steps defined via `n_bisec`. In rare occasions it might happen, that the estimated coverage probabilities $\hat{\Psi}_{\delta_g}$ do not converge to the nominal level $1 - \alpha$. This happens if $\hat{\Psi}_{\delta_{G_{max}}} \notin [(1 - \alpha) - t, (1 - \alpha) + t]$ with $t$ controlled via `tolerance`. In this case the value for $\delta_{G_{max}}$ from the last bisection step is chosen for interval calculation in eq. 13.

The user can decide either to use the calculated interval or to change the search-interval for $\delta$ by changing `lambda_min` and `lambda_max`. Alternatively one might increase the tolerable level around the nominal coverage probability $(1 - \alpha)$ via `tolerance`.

Please note, that due to the discreteness of dichotomous or count data, the true coverage probability of the interval might not approach the desired $1 - \alpha$ in some occasions. Consequently, also the bisection might not converge to the nominal level. In such cases the calibrated
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Figure 1: Graphical overview about the bisection steps

Prediction interval corresponding to the last of the $G_{max}$ bisection steps, should be the one with coverage probability closest to the nominal level.

3.1.1 Prediction intervals based on linear random effects models

Prediction intervals, that are based on random effects models fit with `lme4::lmer()` to the historical data, can be computed using `lmer_pi_unstruc()`, `lmer_pi_futvec()` or `lmer_pi_futmat()`. These intervals depend on the historical mean $\hat{\mu}$ which is extracted from the fitted model with `lme4::fixef()`, its estimated variance $\hat{\text{var}}(\hat{\mu})$ drawn from the fitted model with `lme4::vcov.merMod()` and $\hat{\text{var}}(Y^*)$, the sum of the variance components extracted from the fitted model with `lme4::VarCorr()`. Substituting these estimates into eq. 13 results in a bootstrap calibrated
prediction interval

\[ [L, U] = \hat{\mu} \pm \delta \sqrt{\text{var}(\hat{\mu}) + \sum_{c=1}^{C+1} \hat{\sigma}_c^2}. \quad (16) \]

This interval can be applied either in the case where a prediction for one future observation is needed, as well as in the case where \( M > 1 \) future observations should be predicted.

In the examples below, \texttt{c2_dat1} will serve as an example for a historical data set. It descents from a two way completely cross-classified design with three replications per random factor and three replications per interaction term and is therefore comprised of 27 observations.

\[
\begin{array}{l}
R> c2\_dat1 \\
\end{array}
\]

\[
\begin{array}{l}
y_{ijk} \quad a \quad b \\
1 \quad 105.27359 \quad 1 \quad 1 \\
2 \quad 101.40640 \quad 1 \quad 1 \\
3 \quad 94.01300 \quad 1 \quad 1 \\
4 \quad 97.82988 \quad 2 \quad 1 \\
5 \quad 94.30743 \quad 2 \quad 1 \\
6 \quad 92.52234 \quad 2 \quad 1 \\
7 \quad 102.17317 \quad 3 \quad 1 \\
8 \quad 99.74908 \quad 3 \quad 1 \\
9 \quad 100.64042 \quad 3 \quad 1 \\
10 \quad 95.49433 \quad 1 \quad 2 \\
11 \quad 92.30937 \quad 1 \quad 2 \\
12 \quad 99.88281 \quad 1 \quad 2 \\
13 \quad 103.82970 \quad 2 \quad 2 \\
14 \quad 99.95517 \quad 2 \quad 2 \\
15 \quad 107.13102 \quad 2 \quad 2 \\
16 \quad 107.42282 \quad 3 \quad 2 \\
17 \quad 105.25822 \quad 3 \quad 2 \\
18 \quad 108.82881 \quad 3 \quad 2 \\
19 \quad 107.30048 \quad 1 \quad 3 \\
\end{array}
\]
A random effects model that reflects the experimental design of \texttt{c2\_dat1}, can be fitted with

\begin{verbatim}
R> # install.packages("lme4")
R> library(lme4)
R> fit <- lmer(y_{ijk}|(1|a)+(1|b)+(1|a:b), data=c2\_dat1)
\end{verbatim}

In all three functions, the fitted model has to be specified via \texttt{model}. Please note, that at the current state, only models in which the random effects are specified as \texttt{(1|random effect)} are supported.

The bootstrap sampling of future observations $y_{ib}^*$ is the same in all three functions, if a prediction interval for $M = 1$ future observation is needed. This is because, internally, the future data is bootstrapped from the fitted model via \texttt{lme4::bootMer()} of which one observation per bootstrap data set is randomly chosen to serve as $y_{ib}^*$ in step 2 of the calibration process. Hence all three functions yield the same prediction interval in this case.

\begin{verbatim}
R> set.seed(1234)
R> lmer_pi_unstruc(model=fit, m=1, alternative="both", nboot=10000)
\end{verbatim}

\begin{verbatim}
m hist_mean quant_calib pred_se lower upper 1 1 102.3971 2.273359 5.923724 88.93033 115.8638
\end{verbatim}
The output of the three functions is a **data.frame** where \( m \) is the number of future observations the prediction interval should cover (in this case one). The historical mean \( \hat{\mu} \) is given by **hist_mean** and **quant_calib** is the bootstrap calibrated coefficient used for the calculation of the interval (\( \delta \) in eq. [13]). **pred_se** is the estimated standard error of the prediction (\( \sqrt{\text{var}(\hat{\mu}) + \text{var}(Y^*)} \) in eq. [13]) and **lower** and **upper** are the lower and the upper bounds of the prediction interval.

The only difference between the three functions is the way how the bootstrap samples \( y_b^* \) are drawn, if a prediction interval for \( M > 1 \) future observations is needed. In the examples below, **predint::c2_dat3** will serve as a future data set that descents from the same data generating process, but has only two observations per random factor and hence eight observations in total.

```r
R> c2_dat3

     y_ijk a b
 1  97.47232 1 1
 2  95.44895 1 1
 3 100.18817 2 1
 4  99.36843 2 1
 5  99.08363 1 2
 6 101.11561 1 2
```
`lmer_pi_unstruc()` is a direct implementation of the prediction interval described in [Menssen and Schaarschmidt (2021)](https://example.com). Hence, if \( M > 1 \) the bootstrapped future observations \( y^*_b \) are sampled in two steps. Firstly, bootstrap samples that have the same experimental structure as the historical data are sampled using `lme4::bootMer()`. Then, \( M \) observations are drawn randomly from the bootstrapped data in order to serve as \( y^*_b \) in the calibration. Therefore, only the number of future observations, but not the experimental design of the future data set is considered.

A prediction interval for \( M = 8 \) future observations can be obtained, if \( m \) is set to 8 or if the future data set `c2_dat3` is directly specified via `newdat`.

```
R> set.seed(1234)
R> lmer_pi_unstruc(model=fit, m=8, alternative="both", nboot=10000)
   m  hist_mean quant_calib  lower  upper
1  8  102.3971    3.366016  82.45774 122.3364
```

```
R> set.seed(1234)
R> lmer_pi_unstruc(model=fit,
               newdat=c2_dat3,
               alternative="both",
               nboot=10000)
   y_ijk  a  b  hist_mean quant_calib  pred_se lower  upper cover
1  97.47232 1 1  102.3971    3.366016  5.923724 82.45774 122.3364  TRUE
2  95.44895 1 1  102.3971    3.366016  5.923724 82.45774 122.3364  TRUE
3 100.18817 2 1  102.3971    3.366016  5.923724 82.45774 122.3364  TRUE
4  99.36843 2 1  102.3971    3.366016  5.923724 82.45774 122.3364  TRUE
5  99.08363 1 2  102.3971    3.366016  5.923724 82.45774 122.3364  TRUE
6 101.11561 1 2  102.3971    3.366016  5.923724 82.45774 122.3364  TRUE
7  97.05361 2 2  102.3971    3.366016  5.923724 82.45774 122.3364  TRUE
8  97.81136 2 2  102.3971    3.366016  5.923724 82.45774 122.3364  TRUE
```
If `newdat` is specified, the output is a `data.frame` in which the first columns represent the data set specified via `newdat`. `hist_mean`, `quant_calib`, `pred_se`, `lower` and `upper` are the same as above. `cover` gives a statement whether the observation is covered by the interval or not.

Contrary to `lmer_pi_unstruc`, `lmer_pi_futvec()` accounts for the experimental design of the future data and is applicable if the experimental design of the future data is part of the design of the historical experiment(s). If a prediction interval for $M > 1$ future observations is needed, a vector of row numbers that define the experimental structure of the future data based on the historical data set has to be specified.

\begin{verbatim}
R> futvec <- c(1, 2, 4, 5, 10, 11, 13, 14)
\end{verbatim}

defines the rows in `c2_dat1` that correspond to the experimental design of `c2_dat3` (two observations per random factors a and b and their interaction). In other words, if the observations defined by the row numbers given in `futvec` are subsetted from `c2_dat1`, these subset will appear to descent from the same experimental design as `c2_dat3`.

\begin{verbatim}
R> c2_dat1[futvec, ]
   y_ijk a b
1  105.27359 1 1
2  101.40640 1 1
4   97.82988 2 1
5   94.30743 2 1
10  95.49433 1 2
11  92.30937 1 2
13 103.82970 2 2
14  99.95517 2 2
\end{verbatim}

Internally, the bootstrap samples corresponding to the future observations are sampled with `lme4::bootMer()`. Then for each of the bootstrap samples, a subset that is comprised of the observations in the rows defined by `futvec` is drawn and serves as $y_{b}^{*}$ in the calibration. A prediction interval for the 8 future observations in `c2_dat3` can be obtained with
R> set.seed(1234)
R> lmer_pi_futvec(model=fit, futvec=futvec, alternative="both", nboot=10000)

   m hist_mean quant_calib pred_se lower upper
1 8 102.3971   3.30748 5.923724 82.80448 121.9897

If the future data should appear in the output, it can be specified via newdat but, of course its data structure has to correspond to the structure defined by futvec.

R> set.seed(1234)
R> lmer_pi_futvec(model=fit,
    futvec=futvec,
    newdat=c2_dat3,
    alternative="both",
    nboot=10000)

 y_ijk a b hist_mean quant_calib pred_se lower upper cover
1 97.47232 1 1 102.3971 3.287969 5.923724 82.92006 121.8741 TRUE
2 95.44895 1 1 102.3971 3.287969 5.923724 82.92006 121.8741 TRUE
3 100.18817 2 1 102.3971 3.287969 5.923724 82.92006 121.8741 TRUE
4 99.36843 2 1 102.3971 3.287969 5.923724 82.92006 121.8741 TRUE
5 99.08363 1 2 102.3971 3.287969 5.923724 82.92006 121.8741 TRUE
6 101.11561 1 2 102.3971 3.287969 5.923724 82.92006 121.8741 TRUE
7 97.05361 2 2 102.3971 3.287969 5.923724 82.92006 121.8741 TRUE
8 97.81136 2 2 102.3971 3.287969 5.923724 82.92006 121.8741 TRUE

Despite its user friendliness `lmer_pi_futvec()` has one drawback: It is only applicable if the experimental design of the future data is included in the experimental design of the historical data. In other words, `lmer_pi_futvec()` is not applicable if the number of observations per random factor is bigger in the future data than in the historical data (e.g. if data will be observed from four future laboratories but the historical data contains only three historical ones).

This problem can be overcome by using `lmer_pi_futmat()`, which is the only function in which the $M > 1$ future observations are directly bootstrapped from the experimental design.
of the future data. As already stated in section 2.1, a prediction interval for $M > 1$ future observations depends on the numbers of observations per random factor in the future data set. Hence, the variance-covariance matrices $V$ and $V^*$ for the historical and the future observations differ from each other if $N \neq M$.

The bootstrap sampling used in \texttt{lmer_pi_futmat()} is based on the following algorithm which is implemented in \texttt{lmer bs()} (see section 3.2):

1. Obtain the estimates for the mean $\hat{\mu}$ and the variance components $\hat{\sigma}_c^2$ based on the model fit to the historical data set.

2. Define the design matrices $Z^*_c$ each of dimensions $M \times F^*_c$, with $M$ as the number of future observations and $F^*_c$ as the number of observations per random factor in the future data set.

3. Draw random samples that correspond to the random effects, such that $U^*_c \sim N(0, I\hat{\sigma}_c^2)$ and $e^* \sim N(0, I\hat{\sigma}_{C+1}^2)$.

4. Calculate the bootstrap sample as $y = \hat{\mu} + \sum_{c=1}^C Z^*_c U^*_c + e^*$.

5. In order to obtain $B$ bootstrap samples, repeat step 1 to 4 for $b = 1, \ldots, B$ times.

If the future data is handed over via \texttt{newdat}, the bootstrap depends on a list containing the design matrices $Z^*_c$ that was created using \texttt{lme4::lFormula()}. Hence each random factor in \texttt{newdat} needs at least two replications. A prediction interval for \texttt{c2_dat3} is given with

\begin{verbatim}
R> set.seed(1234)
R> lmer_pi_futmat(model=fit,
                newdat=c2_dat3,
                alternative="both",
                nboot=10000)

   y_ijk  a  b hist_mean  quant_calib  pred_se  lower  upper  cover
1  97.47232  1  1  102.3971  3.326992  5.923724  82.6889 122.1053  TRUE
2  95.44895  1  1  102.3971  3.326992  5.923724  82.6889 122.1053  TRUE
3 100.18817  2  1  102.3971  3.326992  5.923724  82.6889 122.1053  TRUE
\end{verbatim}
Sometimes a random factor in the future data set might not have any replicate e.g. if the historical data descents from trials that were done in several different laboratories, but the experiments for the future observations were carried out in another one. This is the case in `c2.dat4`, where the factor `b` has only one observation.

```r
R> c2_dat4
   y_i jk a b
 1  102.8583 1 1
 2  101.1324 1 1
 3  104.9425 2 1
 4  101.2299 2 1
 5  104.6727 2 1
 6  105.3402 2 1
```

Here, the future data can not be specified via `newdat` since `lme4::lFormula()` can not handle such cases. Alternatively, a list that contains the design matrices $Z_c^*$ can be provided via `futmat_list`. Please note, that the order of the design matrices has to correspond to the order by which the random factors are handled in the initial model that was fit to the historical data with `lme4::lmer()`. A list of design matrices corresponding to `c2.dat4` is given by

```r
R> fml <- vector(length=4, "list")
R>
R> names(fml) <- c("a:b", "b", "a", "Residual")
R>
R> fml[["a:b"]]<- matrix(nrow=6, ncol=2,
       data=c(1,1,0,0,0,0,
```
```r
R> fml["a"] <- matrix(nrow=6, ncol=2,
                   data=c(1,1,0,0,0,0,
                          0,0,1,1,1,1))
R>
R> fml["Residual"] <- diag(6)
R>
R> fml

$a:b$

[,1] [,2]
[1,] 1 0
[2,] 1 0
[3,] 0 1
[4,] 0 1
[5,] 0 1
[6,] 0 1

$b$

[,1]
[1,] 1
[2,] 1
[3,] 1
[4,] 1
[5,] 1
[6,] 1
```
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```r
$a

[,1] [,2]
[1,] 1 0
[2,] 1 0
[3,] 0 1
[4,] 0 1
[5,] 0 1
[6,] 0 1

$Residual

[,1] [,2] [,3] [,4] [,5] [,6]
[1,] 1 0 0 0 0 0
[2,] 0 1 0 0 0 0
[3,] 0 0 1 0 0 0
[4,] 0 0 0 1 0 0
[5,] 0 0 0 0 1 0
[6,] 0 0 0 0 0 1
```

The corresponding prediction interval is given by

```r
R> set.seed(1234)
R> lmer_pi_futmat(model=fit,
    futmat_list=fml,
    alternative="both",
    nboot=10000)
```

| m | hist_mean | quant_calib | pred_se | lower | upper |
|---|-----------|-------------|---------|-------|-------|
| 1 | 6         | 102.3971    | 3.034316| 84.42263 | 120.3715 |
3.1.2 Prediction intervals for overdispersed binomial data

Prediction intervals for overdispersed binomial data can be calculated based on the quasi-likelihood approach using `quasi_bin_pi()` or based on the beta-binomial assumption using `beta_bin_pi()`. Because overdispersion appeals as a constant if the cluster size is the same, `qb_dat1` will serve as an example for the historical data on which prediction intervals will be calculated based on both assumptions. The data set is comprised of the numbers of success (e.g. rats with tumors) vs. the number of failures (e.g. rats without a tumor) obtained in 10 clusters, each comprised of 50 experimental units (e.g. rats).

```R
R> qb_dat1

   succ fail
 1    0 50
 2    9 41
 3   13 37
 4    1 49
 5    4 46
 6    5 45
 7   13 37
 8    7 43
 9    7 43
10    6 44
```

Based on the quasi-likelihood approach, `quasi_bin_pi()` calculates bootstrap calibrated prediction intervals for $M \geq 1$ future numbers of success $y_m^*$

$$[l, u]_m = n_m^* \hat{\pi} \pm \delta \sqrt{\phi n_m^* \hat{\pi} (1 - \hat{\pi}) \left( 1 + \frac{n_m^*}{\sum_{h=1}^{H} n_h} \right)}.$$

with $n_m^*$ as the size of $m = 1, \ldots, M$ future clusters.

Please note, that the calculation of prediction intervals depend on the future cluster size $n_m^*$ and hence, the calculated prediction intervals are different, if the size of the future clusters differs between each other.
The historical data set has to be specified `histdat` and needs to be a `data.frame` with two columns, of which one describes the numbers of success and the other the numbers of failures. Then, internally, the estimation of $\hat{\phi}$ and $\hat{\pi}$ is done based on a generalized linear model, fit with `glm(cbind(histdat[,1],histdat[,2]) ~ 1, family=quasibinomial(), data=histdat)`. The bootstrap data used in step two and three of the calibration process described above, is sampled using the `rqbinom()` function which is described in detail in section 3.2.

A prediction interval for the number of success in one future cluster of size 50 can be obtained with

```r
R> set.seed(1234)
R> quasi_bin_pi(histdat=qb_dat1, newsize=50, nboot=10000)
```

| total | hist_prob | quant_calib | pred_se | lower | upper  |
|-------|-----------|-------------|---------|-------|--------|
| 50    | 0.13      | 0.9855859   | 10.72381| 0     | 17.06923|

The resulting output is a `data.frame` in which `total` indicates the future cluster size $n^*$, `hist_prob` is the estimate for the historical binomial proportion $\hat{\pi}$, `quant_calib` is the bootstrap calibrated coefficient used for the calculation of the interval ($\delta$ in eq. 13), `pred_se` is the prediction error $\sqrt{\hat{\phi}n_m^*\hat{\pi}(1-\hat{\pi})(1 + n_m^*/\sum_{h=1}^{H} n_h)}$ and the prediction interval is given by `lower` and `upper`.

Prediction intervals that simultaneously cover $M = 3$ future numbers of success which are observed in clusters of size 40, 50 and 60 can be calculated with

```r
R> set.seed(1234)
R> quasi_bin_pi(histdat=qb_dat1, newsize=c(40, 50, 60), nboot=10000)
```

| total | hist_prob | quant_calib | pred_se | lower | upper  |
|-------|-----------|-------------|---------|-------|--------|
| 40    | 0.13      | 1.434355    | 8.75595 | 0     | 17.75915|
| 50    | 0.13      | 1.434355    | 10.72381| 0     | 21.88175|
| 60    | 0.13      | 1.434355    | 12.68858| 0     | 25.99993|

If the future data should appear in the output, it can be specified via `newdat`. Please note, that the future data has to be of the same structure as the historical one (two variables,
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one for success and one for failures). Defining `qb_dat2` via `newdat` results in the following output.

```r
R> qb_dat2

   succ fail
 1    0   40
 2    6   44
 3    8   52
R> set.seed(1234)
R> quasi_bin_pi(histdat=qb_dat1, newdat=qb_dat2, nboot=10000)

   succ fail total hist_prob quant_calib pred_se lower upper cover
 1    0   40   40  0.13   1.434355   8.75595  0 17.75915 TRUE
 2    6   44   50  0.13   1.434355  10.72381  0 21.88175 TRUE
 3    8   52   60  0.13   1.434355  12.68858  0 25.99993 TRUE
```

In this output, three further variables occur: The first two variables are the data set specified via `newdat`. `total` is the clustersite \( n_m \) and `cover` gives a statement, if the prediction intervals cover their corresponding future observation (first column of the output).

Bootstrap calibrated prediction intervals that are based on the beta-binomial assumption, can be computed with `beta_bin_pi()`. The resulting prediction intervals are given as

\[
[l, u]_m = n_m^* \hat{\pi} \pm \delta \sqrt{n_m^* \hat{\pi}(1 - \hat{\pi}) \left[ 1 + (n_m^* - 1) \hat{\rho} \right] + \left[ \frac{n_m^*^2 \hat{\pi}(1 - \hat{\pi})}{N} + \frac{N - 1}{N} \right] n_m^* \hat{\pi}(1 - \hat{\pi}) \hat{\rho}}.
\]

Internally, the estimate of the binomial proportion is given as \( \hat{\pi} = \sum_{h=1}^{H} y_h / \sum_{h=1}^{H} n_h \) and the estimate for the intra-class correlation \( \hat{\rho} \) is calculated following Lui et al. [2000]. The bootstrap calibration is done using the algorithm given in section 2.4 with \( y_b \) and \( y_b^* \) sampled using `rbinom()` which is described in section 3.2. Please note, that for the user, the functionality of `beta_bin_pi()` is exactly the same as of `quasi_bin_pi()`, meaning that the handling of historical and future data does not differ from each other. Furthermore, the output of both functions has the same format.

A prediction interval for the number of success in one future cluster of size 50 can be obtained with
R> set.seed(1234)
R> beta_bin_pi(histdat=qb_dat1, newsize=50, nboot=10000)

          total hist_prob quant_calib pred_se lower upper
1          50   0.13       2.429453  4.395622  0 17.17896

Simultaneous prediction intervals for the numbers of success out of three clusters of size 40, 50 and 60 can be obtained by

R> set.seed(1234)
R> beta_bin_pi(histdat=qb_dat1, newsize=c(40, 50, 60), nboot=10000)

          total hist_prob quant_calib pred_se lower upper
1          40   0.13       3.405039  3.643114  0 17.60495
2          50   0.13       3.405039  4.395622  0 21.46727
3          60   0.13       3.405039  5.144237  0 25.31633

If a future data set (in this case predint::bb_dat2) is available, it can be specified via newdat

R> set.seed(1234)
R> beta_bin_pi(histdat=qb_dat1, newdat=bb_dat2, nboot=10000)

          succ fail total hist_prob quant_calib pred_se lower upper cover
1          11  29   40   0.13       3.405039  3.643114  0 17.60495  TRUE
2           1  49   50   0.13       3.405039  4.395622  0 21.46727  TRUE
3           3  57   60   0.13       3.405039  5.144237  0 25.31633  TRUE

3.1.3 Prediction intervals for overdispersed Poisson data

Bootstrap calibrated prediction intervals for overdispersed Poisson data are implemented in quasi_pois_pi() and are calculated as

\[ [l, u] = \hat{\lambda} \pm \delta \sqrt{\hat{\phi}\hat{\lambda}\left(1 + \frac{1}{H}\right)} \]  (17)
with δ as the calibrated coefficient used in eq. 13. Please note, that the sampling of bootstrap data $y_b$ and $y^*_b$ in step two and three of the calibration process is done based on \texttt{rqpois()}, which will be described below in section 3.2. The data set \texttt{qp.dat1} contains sampled data that mimics historical observations (e.g. eggs per hen over two years) obtained from several clusters (e.g. studies).

\begin{verbatim}
> qp.dat1
[1] 46 62 30 59 74 53 32 27 59 47
\end{verbatim}

A prediction interval for one future observation is given by

\begin{verbatim}
> set.seed(1234)
> quasi_pois_pi(histdat=data.frame(qp.dat1), m=1, nboot=10000)

   m hist_mean quant_calib pred_se lower upper
1 1   48.9   2.253848   16.23642 12.30559 85.49441
\end{verbatim}

Please note, that the historical data specified via \texttt{histdat} needs to be a \texttt{data.frame}. The number of future observations that should be covered by the prediction interval can be specified by \texttt{m}. A prediction interval for $M = 3$ future observations can be obtained by

\begin{verbatim}
> set.seed(1234)
> quasi_pois_pi(histdat=data.frame(qp.dat1), m=3, nboot=10000)

   m hist_mean quant_calib pred_se lower upper
1 3   48.9   3.092852   16.23642     0 99.11683
\end{verbatim}

If the future data is already available (here \texttt{qp.dat2}), it can be specified via \texttt{newdat}

\begin{verbatim}
> qp.dat2
[1] 44 74 36
> set.seed(1234)
> quasi_pois_pi(histdat=data.frame(qp.dat1),
        newdat=data.frame(qp.dat2),
        nboot=10000)
\end{verbatim}
### 3.2 Functions for data sampling and bootstrapping

Since, all prediction intervals implemented in `predint` are based on bootstrap calibration, functions for the sampling of new observations from the models described above are necessary. An overview about these functions is given in table 3.

| Function name | Functionality                                      |
|---------------|---------------------------------------------------|
| lmer_bs()     | Bootstrapping from random effects models          |
| rbbinom()     | Sampling of beta-binomial data                    |
| rqbinom()     | Sampling of quasi-binomial data                   |
| rqpois()      | Sampling of quasi-Poisson data                    |

#### 3.2.1 Bootstrapping from random effects models

In principle, bootstrapping from linear random effects models fit with `lme4::lmer()` can be done with `lme4::bootMer()`. Anyhow, the bootstrap samples obtained with `lme4::bootMer()` are bound to have the same experimental structure (same numbers of observations per random factor) as the original data set the model was fit to.

As already stated in section 2.1, a simultainious prediction intervall for \( M > 1 \) future observations depends on the numbers of observations per random factor in the future data set. Hence, the variance-covariance matrices \( V \) and \( V^* \) for the historical and the future observations usually differ from each other.

A bootstrap function, that is able to sample new data sets based on the estimated mean and variance components drawn from a random effects model fit with `lme4::lmer()`, in which the bootstraped data does not have to be of the same structure as the initial data, is
provided via \texttt{lmer\_bs()} and is based on the sampling algorithm described in section 3.1.1. \texttt{lmer\_bs()} depends on the following arguments: \texttt{model, newdat, futmat\_list} and \texttt{nboot}. \texttt{model} defines the random effects model fit with \texttt{lme4::lmer()}. Please note, that \texttt{lmer\_bs()} only works for models in which random effects are specified as \texttt{(1 | random effect)}. \texttt{nboot} defines the number of bootstrap samples \( B \). If \texttt{newdat} is defined, the design matrices \( Z_c^* \) are computed using \texttt{lme4::lFormula}. But, as described before, \texttt{lme4::lFormula} requires at least to observations per random factor. If this is not the case, a list containing the design matrices can be supplied via \texttt{futmat\_list}. Based on the fitted model

\begin{verbatim}
R> fit <- lmer(y_ijk~(1|a)+(1|b)+(1|a:b), c2_dat1)
\end{verbatim}

100 bootstrap samples that have the same experimental structure as \texttt{c2.dat3} can be sampled with

\begin{verbatim}
R> lmer_bs(model=fit, newdat=c2_dat3, nboot=100)
\end{verbatim}

Alternatively new data can be sampled based on a list that contains the design matrices \( Z_c^* \) that can be specified via \texttt{futmat\_list}

\begin{verbatim}
R> lmer_bs(model=fit, futmat\_list=fml, nboot=100)
\end{verbatim}

with \texttt{fml} defined above in section 3.1.1.

### 3.2.2 Sampling of beta-binomial data

If the data is assumed to be beta-binomial distributed, such that

\[
\pi_i \sim \text{beta}(a, b) \\
y_i \sim \text{bin}(\pi_i, n_i) \\
\text{var}(y_i)^{BB} = n_i \pi (1 - \pi) [1 + (n_i - 1) \rho]
\]

with \( i = 1, \ldots, I \) clusters of size \( n_i \) and intra-class correlation coefficient

\[
\rho = \frac{1}{1 + a + b},
\]
it can be sampled using the following mechanism:

Based on given values for $\pi$ and $\rho$, the parameters of the beta-distribution $a$ and $b$ can be calculated as

\[
\begin{align*}
    a + b &= \frac{1 - \rho}{\rho} \\
    a &= \pi(a + b) \\
    b &= (a + b) - a.
\end{align*}
\]

with $\pi = E(\pi_i) = a/(a + b)$. Then, the binomial proportions for each cluster are sampled from the beta distribution

$$\pi_i \sim Beta(a, b)$$

and the numbers of successes for each cluster are sampled to be

$$y_i \sim Bin(n_i, \pi_i)$$

for a given cluster size $n_i > 1$. Please note, that this sampling mechanism only works if $\rho$ is bigger than zero but smaller than one.

This approach is implemented in `rbbinom()` in which `n` refers to the number of clusters $I$, `size` refers to the cluster size $n_i$, `prob` refers to the expected binomial proportion $\pi$ and `rho` to the intra class correlation coefficient $\rho$.

A data set with ten clusters, each comprised of 50 experimental units, an expected success probability of 0.1 and an intra class correlation of 0.06 can be sampled as

```
R> rbbinom(n=10, size=50, prob=0.1, rho=0.06)
```

### 3.2.3 Sampling of quasi-binomial data

Quasi-binomial data sampling is based on the assumption that the binomial variance is inflated by a dispersion parameter that is constant for all $i = 1, \ldots I$ clusters

$$var(y_i) = \phi n_i \pi (1 - \pi).$$

This type of data can be sampled from the beta-binomial distribution using the following mechanism:
For a given cluster size $n_i > 1$ and a given dispersion parameter $\phi$, the sum of the parameters of the beta-distribution differs between the $i = 1, \ldots, I$ clusters and is given by

$$ (a + b)_i = \frac{\phi - n_i}{1 - \phi}. $$

Subsequently, $a_i$ and $b_i$ can be calculated individually for each cluster, based on a predefined value between 0 and 1 for $\pi$

$$ a_i = \pi(a + b)_i $$
$$ b_i = (a + b)_i - a_i. $$

Then, the binomial proportions for each cluster are sampled from individual beta distributions

$$ \pi_i \sim \text{Beta}(a_i, b_i) $$

and the numbers of success for each cluster are sampled to be

$$ y_i \sim \text{Bin}(n_i, \pi_i). $$

Please note, that this sampling mechanism works only, if $\phi > 1$ and $\phi < n_i$. Both, a dispersion parameter of $\phi < 1$ as well as $\phi > n_i$ result in negative $(a + b)_i$ in eq. 18 and hence in negative values for $a_i$ and $b_i$ as well. Furthermore, $\phi = 1$ and $\phi = n_i$ result in $(a + b)_i = 0$. Anyhow, the beta-distribution is only defined if their parameters are positive numbers greater than zero.

An implementation of this sampling process is provided via \texttt{rqbinom()} which depends on the arguments \texttt{n}, \texttt{size}, \texttt{prob} and \texttt{phi}. Similar to \texttt{rbinom()}, \texttt{n} refers to the number of clusters $I$, \texttt{size} to the size of the clusters $n_i$ and \texttt{prob} to the expected binomial proportion $\pi_i$. \texttt{phi} defines the dispersion parameter $\phi$.

A data set with ten clusters, each comprised of 50 experimental units, an expected success probability of 0.1 and a dispersion parameter of three can be sampled as

R> rqbinom(n=10, size=50, prob=0.1, phi=3)

### 3.2.4 Sampling of quasi-Poisson data

The sampling of quasi-Poisson data is based on the assumption, that the dispersion parameter constantly inflates the variance of the observations obtained in $i = 1, \ldots, I$ clusters, such
that

$$\text{var}(y_i) = \lambda (1 + \lambda \kappa) = \phi \lambda$$

as described above (see eq. 10). Hence overdispersed Poisson data with constant overdispersion can be sampled from the negative-binomial distribution as follows: Define $\kappa$ as

$$\kappa = \frac{\phi - 1}{\lambda}$$

for given values of $\phi > 1$ and $\lambda > 0$. Then calculate

$$a = \frac{1}{\kappa}$$
$$b = \frac{1}{\kappa \lambda}$$

and sample the poisson means for each cluster from the gamma distribution, such that

$$\lambda_i \sim \text{Gamma}(a, b).$$

Subsequently, the observations are sampled from the Poisson distribution

$$y_i \sim \text{Pois}(\lambda_i).$$

This sampling process is implemented in \texttt{rqpois()} which depends on the arguments \texttt{n}, \texttt{lambda} and \texttt{phi}. Similar to \texttt{rbbinom()} and \texttt{rqbinom()}, \texttt{n} refers to the number of clusters $I$. The expected value for the observations $E(y_i) = \lambda$ is defined by \texttt{lambda} and the dispersion parameter $\phi$ by \texttt{phi}. Hence, a data set with ten clusters, an expected value of five and dispersion parameter of three can be sampled as

R> rqpois(n=10, lambda=5, phi=3)

4 Summary

The \texttt{predint} package is the first R-package available from CRAN that provides prediction intervals for $M \geq 1$ future observations based on random effect models, overdispersed binomial data or based on overdispersed poisson data. Although the implemented methodology evolved from applications in the context of toxicology and pre-clinical statistics \cite{Menssen and Schaarschmidt 2019, Menssen and Schaarschmidt 2021}, it might be applicable in a broad range of other research fields.
4.1 Interpretation of the implemented prediction intervals

A prediction interval for $M = 1$ future observation can be interpreted as a \textit{pointwise} prediction interval. This kind of interval should cover one future observation in $(1 - \alpha)\%$ of the cases. If such an interval is applied based on a univariate distribution, it directly approximates the central $(1 - \alpha)\%$ of this distribution. This is because both, the historical as well as the future observation(s) are believed to be independent realisations of exactly the same distribution. Hence, in the long run, its borders $L$ and $U$ converge to the $\alpha/2$ and the $1 - \alpha/2$ quantiles of the underlying distribution (see Francq et al. 2019 Fig. 1).

In this special case, such an prediction interval can be interpreted as a $\beta$-content tolerance interval that covers the central $(1 - \alpha)\%$ of the distribution. A univariate prediction interval for $M = 1$ future observation, that is based on one normal distributed sample, is reviewed in Hahn et al. [2017] and implemented in the BivRegBLS package of Francq et al. [2020] in order to be displayed in a Bland-Altman plot.

Anyhow, if the underlying data is comprised of several clusters (e.g. due to repeated measurements), the sample is not comprised of independent observations anymore. These dependencies can be taken into account, if the data is modeled by a random (or mixed) effects model (see section 2.1). This approach leads to the assumption that the historical and the future data usually do not follow exactly the same distribution, although they descent from the same data generating process (see eq. 1 and 2). In this case, one has to be extremely careful, if the prediction interval for $M = 1$ future observation is aimed be interpreted as a $\beta$-content tolerance interval, since the distribution of a future sample changes with its experimental design.

Simultaneous prediction intervals should cover all of $M > 1$ future observations and hence are applicable to a broad field of applications in which, at the moment, the application of tolerance intervals seems to be favoured (e.g. in toxicology or antidrug-antibody detection). Furthermore, the problem that in random (or mixed) effects models the historical and the future observations usually follow different distributions, should also influence the calculation and interpretation of $\beta\gamma$-tolerance intervals (which should cover the central $100\gamma\%$ of the underlying distribution with coverage probability $\beta$). Hence, further theoretical work will
follow on that topic.

4.2 The future of predint

It is planned, that the future research on prediction intervals (as well as on other intervals) will be included in predint, if it fits into the initial scope of this package (the use of historical control data for the validation of actual observations).

Hence, the implemented methodology for random effects models will be extended to be also applicable in the context of models with mixed effects. This kind of models are of use, if a data set contains several factors of interest, such as the strain or the sex of rats as well as several random factors, representing the experimental design. At the moment, it seems to be common to split such a data set according to the factors of interest (e.g. female rats of a given strain) and assume that these subsets are samples of independent observations [Igl et al., 2019, Menssen and Schaarschmidt 2019, Elmore and Peddada 2009]. As stated above, an alternative approach that is based on the complete data set is the application of mixed effects models. But, prediction intervals that are based on such models are not available in an R package so far. Therefore, it is planned to fill this gap. Furthermore, it is planned to implement tolerance intervals for both, random and mixed effects models.

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