Bootstrapping using rTPC

Daniel Padfield

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A brief example of how bootstrapping can help visualise and estimate model uncertainty when fitting models to TPCs using rTPC, nls.multstart, car and the tidyverse.

Things to consider

- (Non-parametric) bootstrapping is a robust way of computing parameter and model prediction confidence intervals.
- Case resampling involves resampling the actual data with replacement and then refitting the model to the new, simulated datasets.
- When there are fewer data points-per-curve, resampling the whole dataset with replacement may result in some resampled datasets not having any points beyond the optimum temperature.
- In these instances, residual sampling creating new datasets from mean centred residuals of the original model fit provides an alternative to case resampling.
- Both resampling methods will be sensitive to the number of unique data points and the mathematical model being used.
- Bootstrapping can allow differences between explicitly modelled and calculated parameters to be evaluated. If calculated properly, non-overlapping confidence intervals of parameters can indicate significant differences between curves.

load packages
library(boot)
library(car)
library(TPC)
library(nls.multstart)
library(broom)
library(tidyverse)
library(patchwork)
library(minpack.lm)

Case resampling: Resampling the original data with replacement

Bootstrapping involves simulating "new" datasets produced from the existing data by sampling with replacement. The same model is then fitted separately on each individual bootstrapped dataset. Doing this over and over allows us to visualise uncertainty of predictions and produce confidence intervals of estimated parameters.

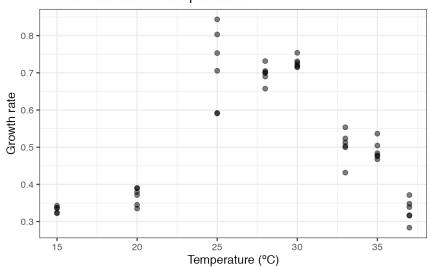
First, we will demonstrate this case resampling approach using data from a recent paper by Padfield $et\,al.$ (2020), that measures the thermal performance of the bacteria, $Pseudomonas\,fluorescens$, in the presence and absence of its phage, $\phi 2$. In this study, each single growth rate estimate is a technical replicate, coming from an isogenic strain of bacteria either inoculated with, or without, the phage. As such, all the data points within each phage treatment can be used to estimate the same curve and there is no rep column as in the chlorella_tpc dataset. We can visualise one of the curves (bacteria in the absence of phage), using ggplot2.

```
# load in data
data("bacteria_tpc")

# keep just a single curve
d <- filter(bacteria_tpc, phage == 'nophage')

# show the data
ggplot(d, aes(temp, rate)) +
    geom_point(size = 2, alpha = 0.5) +
    theme_bw(base_size = 12) +
    labs(x = 'Temperature (°C)',
        y = 'Growth rate',
        title = 'Growth rate across temperatures')</pre>
```

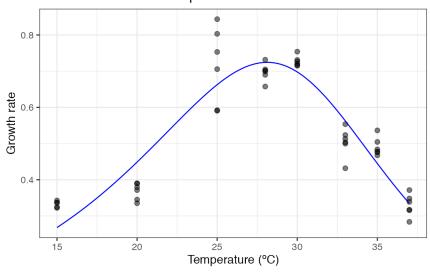
Growth rate across temperatures



As in the study, we can fit the Sharpe-Schoolfield model to the data and plot the predictions using the approaches in vignette(rTPC) and $vignette(fit_many_models)$.

```
# fit Sharpe-Schoolfield model
d_fit <- nest(d, data = c(temp, rate)) %>%
 mutate(sharpeschoolhigh = map(data, ~nls multstart(rate~sharpeschoolhigh 1981(temp = temp, r tref,e,e
h, th, tref = 15),
                        data = .x,
                        iter = c(3,3,3,3),
                        start_lower = get_start_vals(.x$temp, .x$rate, model_name = 'sharpeschoolhigh_19
81') - 10,
                        start_upper = get_start_vals(.x$temp, .x$rate, model_name = 'sharpeschoolhigh_19
81') + 10,
                        lower = get lower lims(.x$temp, .x$rate, model name = 'sharpeschoolhigh 1981'),
                        upper = get upper lims(.x$temp, .x$rate, model name = 'sharpeschoolhigh 1981'),
                        supp errors = 'Y',
                        convergence count = FALSE)),
         # create new temperature data
         new data = map(data, \sim tibble(temp = seq(min(.x$temp), max(.x$temp), length.out = 100))),
         # predict over that data,
         preds = map2(sharpeschoolhigh, new data, ~augment(.x, newdata = .y)))
# unnest predictions
d preds <- select(d fit, preds) %>%
 unnest (preds)
# plot data and predictions
ggplot() +
 geom line(aes(temp, .fitted), d preds, col = 'blue') +
 geom point(aes(temp, rate), d, size = 2, alpha = 0.5) +
 theme bw(base size = 12) +
  labs(x = 'Temperature (^{\circ}C)',
      y = 'Growth rate',
       title = 'Growth rate across temperatures')
```

Growth rate across temperatures



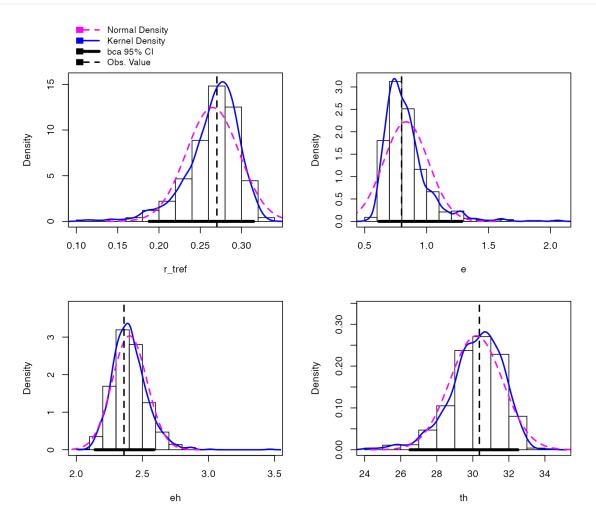
Here we have the best fit to the data. If we want confidence bands around this prediction, we can get those by resampling the data a number of times. The R package **car** contains the function **Boot()** that provides a wrapper for the widely used function **boot::boot()** that is tailored to bootstrapping regression models.

nls_multstart() is designed to fit models across a wide possible parameter space, but as it samples multiple start parameters for each model, using it with bootstrapping becomes computationally expensive. Instead, we refit the model using **minpack.lm::nlsLM()**, using the coefficients of **nls_multstart()** as the start values. The **Boot()** function then refits the model 999 times and stores the model coefficients.

```
# refit model using nlsLM
fit_nlsLM <- minpack.lm::nlsLM(rate~sharpeschoolhigh_1981(temp = temp, r_tref,e,eh,th, tref = 15),
                        data = d,
                        start = coef(d_fit$sharpeschoolhigh[[1]]),
                        lower = get_lower lims(d$temp, d$rate, model name = 'sharpeschoolhigh 1981'),
                        upper = get_upper lims(d$temp, d$rate, model name = 'sharpeschoolhigh 1981'),
                        weights = rep(1, times = nrow(d)))
# bootstrap using case resampling
boot1 <- Boot(fit_nlsLM, method = 'case')</pre>
# look at the data
head(boot1$t)
           r tref
#> [1,] 0.2618013 0.8782097 2.282569 29.48463
#> [2,] 0.2632917 0.7003234 2.616369 32.04360
  [3,] 0.2790073 0.8043182 2.279580 30.03292
  [4,] 0.3130349 0.7243579 2.264205 30.35111
  [5,] 0.2941174 0.7344628 2.281169 30.62331
#> [6,] 0.2701428 0.7191663 2.513140 31.64732
```

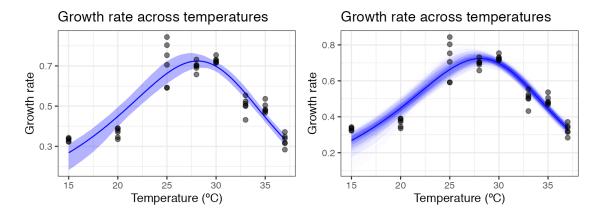
The parameters of each bootstrapped refit are returned. All methods that are available for **boot()** and **Boot()** are supported for these objects. This includes the **hist.boot()** to look at the distribution of each parameter.

```
hist(boot1, layout = c(2,2))
```



We can easily create predictions for each of these models and through this confidence intervals around the original fitted predictions. We can then plot (1) the bootstrapped fits and (2) the confidence regions around the model predictions.

```
# create predictions of each bootstrapped model
boot1 preds <- boot1$t %>%
 as.data.frame() %>%
 drop_na() %>%
 mutate(iter = 1:n()) %>%
 group_by_all() %>%
 do(data.frame(temp = seq(min(d\$temp), max(d\$temp), length.out = 100))) %>%
 mutate(pred = sharpeschoolhigh_1981(temp, r_tref, e, eh, th, tref = 15))
# calculate bootstrapped confidence intervals
boot1 conf preds <- group by(boot1 preds, temp) %>%
  summarise(conf lower = quantile(pred, 0.025),
            conf upper = quantile(pred, 0.975)) %>%
  ungroup()
# plot bootstrapped CIs
p1 <- ggplot() +
 geom line(aes(temp, .fitted), d preds, col = 'blue') +
  geom_ribbon(aes(temp, ymin = conf_lower, ymax = conf_upper), boot1_conf_preds, fill = 'blue', alpha =
0.3) +
  geom point(aes(temp, rate), d, size = 2, alpha = 0.5) +
  theme bw(base size = 12) +
  labs(x = 'Temperature (^{\circ}C)',
       y = 'Growth rate',
       title = 'Growth rate across temperatures')
# plot bootstrapped predictions
p2 <- ggplot() +
 geom_line(aes(temp, .fitted), d_preds, col = 'blue') +
 geom line(aes(temp, pred, group = iter), boot1_preds, col = 'blue', alpha = 0.007) +
 geom_point(aes(temp, rate), d, size = 2, alpha = 0.5) +
 theme bw(base size = 12) +
  labs(x = 'Temperature (°C)',
       y = 'Growth rate',
       title = 'Growth rate across temperatures')
p1 + p2
```



This method works well here, because there are many points beyond the optimum temperature and multiple independent points at each temperature.

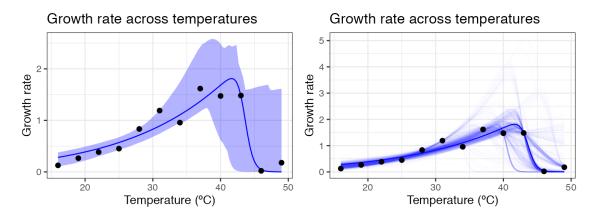
This method becomes more problematic when there is a small sample size and the coverage of temperature values beyond the optimum temperature is small. This means that many of the bootstrapped models will not have any points beyond the optimum, which is problematic for mathematical models that expect a unimodal shape. The effect of this can be seen by case resampling a curve from the <code>chlorella_tpc</code> dataset used throughout these vignettes. Here we again fit the model using <code>nls_multstart()</code>, refit the model using <code>nlsLM()</code>, then bootstrap the model using <code>Boot()</code>.

```
# load in chlorella data
data('chlorella_tpc')
d2 <- filter(chlorella_tpc, curve_id == 1)</pre>
# fit Sharpe-Schoolfield model to raw data
d_fit <- nest(d2, data = c(temp, rate)) %>%
 mutate(sharpeschoolhigh = map(data, ~nls multstart(rate~sharpeschoolhigh 1981(temp = temp, r tref,e,e
h, th, tref = 15),
                        data = .x,
                       iter = c(3,3,3,3),
                       start lower = get start vals(.x$temp, .x$rate, model name = 'sharpeschoolhigh 19
81') - 10,
                       start upper = get start vals(.x$temp, .x$rate, model name = 'sharpeschoolhigh 19
81') + 10,
                        lower = get lower lims(.x$temp, .x$rate, model name = 'sharpeschoolhigh 1981'),
                        upper = get upper lims(.x$temp, .x$rate, model name = 'sharpeschoolhigh 1981'),
                        supp errors = 'Y',
                        convergence count = FALSE)),
         # create new temperature data
         new data = map(data, ~tibble(temp = seq(min(.x$temp), max(.x$temp), length.out = 100))),
         # predict over that data,
         preds = map2(sharpeschoolhigh, new data, ~augment(.x, newdata = .y)))
# refit model using nlsLM
fit_nlsLM2 <- nlsLM(rate~sharpeschoolhigh_1981(temp = temp, r_tref,e,eh,th, tref = 15),</pre>
                       data = d2,
                       start = coef(d fit$sharpeschoolhigh[[1]]),
                       lower = get_lower_lims(d2$temp, d2$rate, model_name = 'sharpeschoolhigh 1981'),
                       upper = get_upper_lims(d2$temp, d2$rate, model_name = 'sharpeschoolhigh 1981'),
                        control = nls.lm.control(maxiter=500),
                        weights = rep(1, times = nrow(d2)))
# bootstrap using case resampling
boot2 <- Boot(fit_nlsLM2, method = 'case')</pre>
#> Number of bootstraps was 988 out of 999 attempted
```

```
Number of bootstraps was 994 out of 999 attempted
```

We can then create predictions for each bootstrapped model and calculate 95% confidence intervals around the predictions. Models that don't fit and return NA for the parameter estimates are dropped.

```
# unnest predictions of original model fit
d_preds <- select(d_fit, preds) %>%
 unnest (preds)
# predict over new data
boot2_preds <- boot2$t %>%
 as.data.frame() %>%
 drop_na() %>%
 mutate(iter = 1:n()) %>%
 group_by_all() %>%
 do(data.frame(temp = seq(min(d2$temp), max(d2$temp), length.out = 100))) %>%
 mutate(pred = sharpeschoolhigh 1981(temp, r tref, e, eh, th, tref = 15))
# calculate bootstrapped confidence intervals
boot2 conf preds <- group by (boot2 preds, temp) %>%
  summarise(conf lower = quantile(pred, 0.025),
            conf upper = quantile(pred, 0.975)) %>%
 ungroup()
# plot bootstrapped CIs
p1 < - ggplot() +
 geom line(aes(temp, .fitted), d preds, col = 'blue') +
 geom_ribbon(aes(temp, ymin = conf_lower, ymax = conf_upper), boot2_conf preds, fill = 'blue', alpha =
0.3) +
 geom point (aes (temp, rate), d2, size = 2) +
  theme bw(base size = 12) +
  labs(x = 'Temperature (^{\circ}C)',
      y = 'Growth rate',
       title = 'Growth rate across temperatures')
# plot bootstrapped predictions
p2 <- ggplot() +
 geom_line(aes(temp, .fitted), d_preds, col = 'blue') +
 geom_line(aes(temp, pred, group = iter), boot2_preds, col = 'blue', alpha = 0.007) +
 geom_point(aes(temp, rate), d2, size = 2) +
 theme bw(base size = 12) +
 labs(x = 'Temperature (^{\circ}C)',
       y = 'Growth rate',
       title = 'Growth rate across temperatures')
p1 + p2
```



As can be seen, bootstrapping-with-replacement with only a single point at each temperature can lead to a large variety of fits. In the second panel, we can see the variation of the curve fits, clustering around 4 possible paths for the decrease in rate beyond the optimum temperature. This occurs because in many instances there are no points sampled at the very high temperatures, leading to this clustering in curve fits.

Residual resampling

Case resampling is the most common way of thinking about bootstrapping. However, bootstrapping ordinary least squares regression models is often done using bootstrapping residuals. This method - where the values of the predictors in a study remain fixed during resampling - is

especially useful in a designed experiment where the values of the predictors are set by the experimenter. This is commonly the case when measuring thermal performance curves.

Re-sampling residuals, at its heart, follows a simple set of steps:

- 1. Fit the model and for each data point, i , retain the fitted values $\hat{y_i}$ and the residuals, $\hat{e_i}=y_i-\hat{y_i}$
- 2. For each data pair, (x_i, y_i) , where x_i is the measured temperature value, we add a randomly re-sampled residual, \hat{e} to the fitted value $\hat{y_i}$. This becomes the new y_i value, such that $y_i = \hat{y_i} + \hat{e}$. The new response variable is created based on the random re-allocation of the variation around the original model fit
- 3. The model is refit using the newly created y_i response variable
- 4. Repeat steps 2 and 3 a number of times

This method makes the assumption that the original model fit is a good representation of the data, and that the error terms in the model are normally distributed and independent. If the model is incorrectly specified – for example, if there is unmodelled non-linearity, non-constant error variance, or outliers – these characteristics will not carry over into the re-sampled data sets.

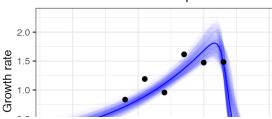
car::Boot() has an argument that allows us to easily implement residual resampling instead of case resampling.

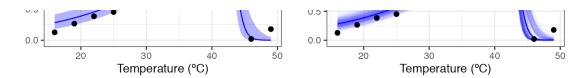
```
# bootstrap using residual resampling
boot3 <- Boot(fit_nlsLM2, method = 'residual')</pre>
# predict over new data
boot3_preds <- boot3$t %>%
 as.data.frame() %>%
 drop_na() %>%
 mutate(iter = 1:n()) %>%
 group_by_all() %>%
 do(data.frame(temp = seq(min(d2\$temp), max(d2\$temp), length.out = 100))) %>%
 ungroup() %>%
 mutate(pred = sharpeschoolhigh_1981(temp, r_tref, e, eh, th, tref = 15))
# calculate bootstrapped confidence intervals
boot3 conf preds <- group by(boot3 preds, temp) %>%
  summarise(conf lower = quantile(pred, 0.025),
            conf upper = quantile(pred, 0.975)) %>%
  unaroup()
# plot bootstrapped CIs
p1 <- ggplot() +
 geom_line(aes(temp, .fitted), d_preds, col = 'blue') +
  geom_ribbon(aes(temp, ymin = conf_lower, ymax = conf_upper), boot3_conf_preds, fill = 'blue', alpha =
0.3) +
  geom_point(aes(temp, rate), d2, size = 2) +
  theme_bw(base_size = 12) +
 labs(x = 'Temperature (°C)',
      y = 'Growth rate',
       title = 'Growth rate across temperatures')
# plot bootstrapped predictions
p2 <- ggplot() +
 geom_line(aes(temp, .fitted), d_preds, col = 'blue') +
 geom_line(aes(temp, pred, group = iter), boot3_preds, col = 'blue', alpha = 0.007) +
 geom_point(aes(temp, rate), d2, size = 2) +
 theme_bw(base_size = 12) +
 labs(x = 'Temperature (^{\circ}C)',
       y = 'Growth rate',
       title = 'Growth rate across temperatures')
p1 + p2
```

Growth rate across temperatures

2.0 drowth rate 1.5 drowth 1.0 drowth 2.0 dr

Growth rate across temperatures



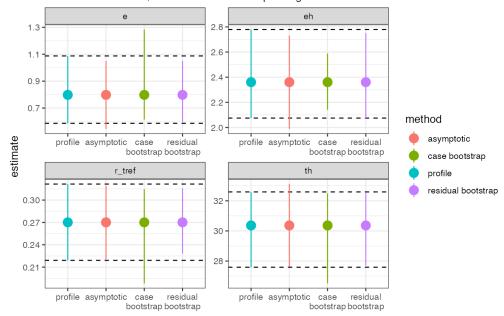


Calculating confidence intervals of estimated and calculated parameters

Bootstrapping can be used to estimate confidence intervals of the parameters explicitly modelled in the regression. We can compare these approaches to profiled confidence intervals (using **confint-MASS**) and asymptotic confidence intervals (using **nlstools::confint2()**). For the bootstrapped parameter distributions, **confint.boot()** supports the calculation of BCa, basic, normal, and percentile confidence intervals. We use BCa here, and we will calculate all CIs on the two models done previously in this vignette. First with the bacteria TPC.

```
# First for the bacteria
# get parameters of fitted model
param bact <- broom::tidy(fit nlsLM) %>%
  select(param = term, estimate)
# calculate confidence intervals of models
ci bact1 <- nlstools::confint2(fit nlsLM, method = 'asymptotic') %>%
  as.data.frame() %>%
  rename(conf lower = 1, conf upper = 2) %>%
  rownames to column(., var = 'param') %>%
  mutate(method = 'asymptotic')
ci bact2 <- confint(fit nlsLM) %>%
  as.data.frame() %>%
  rename(conf lower = 1, conf upper = 2) %>%
  rownames to column(., var = 'param') %>%
  mutate(method = 'profile')
#> Waiting for profiling to be done...
# CIs from case resampling
ci bact3 <- confint(boot1, method = 'bca') %>%
  as.data.frame() %>%
 rename(conf_lower = 1, conf_upper = 2) %>%
  rownames_to_column(., var = 'param') %>%
 mutate(method = 'case bootstrap')
# CIs from residual resampling
ci_bact4 <- Boot(fit_nlsLM, method = 'residual') %>%
  confint(., method = 'bca') %>%
 as.data.frame() %>%
 rename(conf_lower = 1, conf_upper = 2) %>%
 rownames_to_column(., var = 'param') %>%
 mutate(method = 'residual bootstrap')
ci_bact <- bind_rows(ci_bact1, ci_bact2, ci_bact3, ci_bact4) %>%
  left_join(., param_bact)
#> Joining, by = "param"
# plot
ggplot(ci_bact, aes(forcats::fct_relevel(method, c('profile', 'asymptotic')), estimate, col = method)) +
 geom_hline(aes(yintercept = conf_lower), linetype = 2, filter(ci_bact, method == 'profile')) +
 geom_hline(aes(yintercept = conf_upper), linetype = 2, filter(ci_bact, method == 'profile')) +
 geom_point(size = 4) +
 geom_linerange(aes(ymin = conf_lower, ymax = conf_upper)) +
  theme_bw() +
  facet_wrap(~param, scales = 'free') +
  scale_x_discrete('', labels = function(x) stringr::str_wrap(x, width = 10)) +
  labs(title = 'Calculation of confidence intervals for model parameters',
       subtitle = 'For the bacteria TPC; dashed lines are CI of profiling method')
```

For the bacteria TPC; dashed lines are CI of profiling method

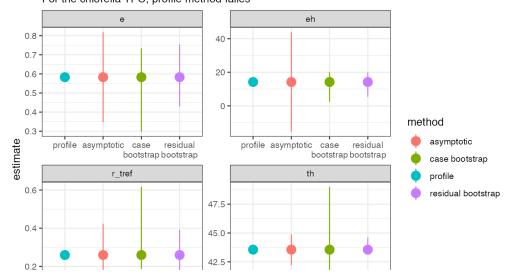


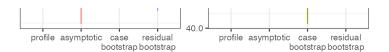
Each panel is a different explicitly modelled parameter. The dashed lines represent the 95% intervals for the profiling method. In general, the different bootstrap methods are similar to the profiled intervals, but not all parameters are the same. For example, r_tref and e give wider (and asymmetric) confidence intervals using the case resampling method. The residual method gives estimates that are more similar to those calculated from profiling.

Now for the TPC from the *Chlorella* dataset.

```
# Second for Chlorella data
# get parameters of fitted model
param_chlor <- broom::tidy(fit_nlsLM2) %>%
 select(param = term, estimate)
# calculate confidence intervals of models
ci_chlor1 <- nlstools::confint2(fit_nlsLM2, method = 'asymptotic') %>%
 as.data.frame() %>%
 rename(conf_lower = 1, conf_upper = 2) %>%
 rownames to column(., var = 'param') %>%
 mutate(method = 'asymptotic')
ci chlor2 <- nlstools::confint2(fit nlsLM2, method = 'profile')</pre>
#> Waiting for profiling to be done...
#> Error in prof$getProfile(): number of iterations exceeded maximum of 50
# profiling method fails
ci chlor2 <- mutate(ci chlor1, method = 'profile',</pre>
                    conf lower = NA,
                    conf upper = NA)
# CIs from case resampling
ci chlor3 <- confint(boot2, method = 'bca') %>%
 as.data.frame() %>%
 rename(conf lower = 1, conf upper = 2) %>%
 rownames to column(., var = 'param') %>%
 mutate(method = 'case bootstrap')
# CIs from residual resampling
ci chlor4 <- confint(boot3, method = 'bca') %>%
 as.data.frame() %>%
 rename(conf_lower = 1, conf_upper = 2) %>%
 rownames_to_column(., var = 'param') %>%
 mutate(method = 'residual bootstrap')
ci_chlor <- bind rows(ci_chlor1, ci_chlor2, ci_chlor3, ci_chlor4) %>%
 full_join(., param_chlor)
#> Joining, by = "param"
ggplot(ci_chlor, aes(forcats::fct_relevel(method, c('profile', 'asymptotic')), estimate, col = method))
 geom_point(size = 4) +
 geom_linerange(aes(ymin = conf_lower, ymax = conf_upper)) +
 theme bw() +
 facet_wrap(~param, scales = 'free') +
  scale_x_discrete('', labels = function(x) stringr::str_wrap(x, width = 10)) +
  labs(title = 'Calculation of confidence intervals for model parameters',
       subtitle = 'For the chlorella TPC; profile method failes')
```

Calculation of confidence intervals for model parameters For the chlorella TPC; profile method failes



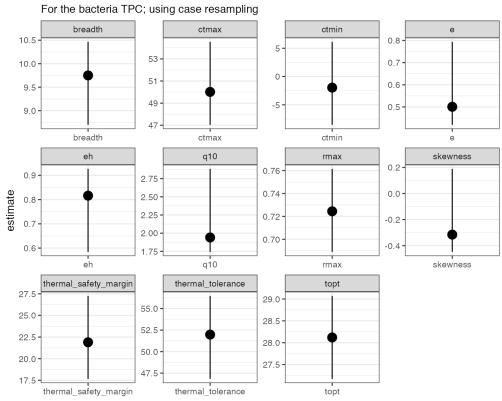


For this curve, the profiling method failed and the asymptotic method has very wide confidence intervals for <code>eh</code> . Consequently, it is hard to know how the bootstrapping methods do as these cannot be benchmarked against the profiling method. Even so, we can see that the intervals for <code>eh</code> and <code>th</code> for the case resampling method are very wide (as can be seen from the plot of the model predictions earlier). Meanwhile, the residual resampling method again gives more symmetric estimates, but we don't know if they are conservative (give narrower CIs) which would increase the rate of false positives if used for inference.

We can also bootstrap confidence intervals for the extra parameters calculated in **calc_params()**. We will do this for the bacteria TPC and the case resample.

```
extra_params <- calc_params(fit_nlsLM) %>%
         pivot_longer(everything(), names_to = 'param', values_to = 'estimate')
 \texttt{ci} = \texttt{extra} \texttt{params} \leftarrow \texttt{Boot}(\texttt{fit} \texttt{nlsLM}, \texttt{f} = \texttt{function}(\texttt{x}) \texttt{\{unlist}(\texttt{calc} \texttt{params}(\texttt{x})) \texttt{\}}, \texttt{labels} = \texttt{names}(\texttt{calc} \texttt{params}(\texttt{fit})) \texttt{\}}, \texttt{labels} = \texttt{names}(\texttt{calc} \texttt{params}(\texttt{fit})) \texttt{\}}, \texttt{labels} = \texttt{names}(\texttt{calc} \texttt{params}(\texttt{fit})) \texttt{\}}, \texttt{labels} = \texttt{names}(\texttt{fit}) \texttt{}, \texttt{labels} = \texttt{names}(\texttt{labels}) \texttt{}, \texttt{labels} = \texttt{labels} = \texttt{labels} = \texttt{labels} = \texttt{labels} = \texttt{labels}
it_nlsLM)), R = 200, method = 'case') %>%
          confint(., method = 'bca') %>%
          as.data.frame() %>%
          rename(conf lower = 1, conf upper = 2) %>%
          rownames to column(., var = 'param') %>%
          mutate(method = 'case bootstrap')
ci extra params <- left join(ci extra params, extra params)
#> Joining, by = "param"
ggplot(ci extra params, aes(param, estimate)) +
          geom\ point(size = 4) +
          geom linerange(aes(ymin = conf_lower, ymax = conf_upper)) +
          theme bw() +
          facet wrap(~param, scales = 'free') +
          scale x discrete('') +
          labs(title = 'Calculation of confidence intervals for extra parameters',
                                   subtitle = 'For the bacteria TPC; using case resampling')
```

Calculation of confidence intervals for extra parameters



You can see that the confidence intervals around certain parameters, such as e, eh, q10, and skewness are very asymmetrical. This is because they are modelled from a subsample of the original dataset (for example, e is calculated from fitting a modified Boltzmann equation to all the points at or below the optimum temperature as calculated from the model predictions). If interested in these parameters, we recommend

using mathematical models that contain them explicitly in the formulation.

NB The Padfield *et al.* analysis actually uses a Bayesian approach to fit thermal performance curves, quantify uncertainty, and estimate derived parameters. This approach is powerful and flexible, and becoming easier to use with the incredible development of the R package **brms** (https://github.com/paul-buerkner/brms). Examples of using **brms** to model thermal performance curves can be found on the GitHub repository (https://github.com/padpadpadpad/Padfield_2019_ISME_bact_phage_temperature) of the paper

Further reading

- John Fox (author of car) on bootstrapping regression models in R
 - https://statweb.stanford.edu/~owen/courses/305a/FoxOnBootingRegInR.pdf (https://statweb.stanford.edu/~owen/courses/305a/FoxOnBootingRegInR.pdf)
- A.C. Davison & D.V. Hinkley (2003) Bootstrap Methods and their Application. https://www.cambridge.org/core/books/bootstrap-methods-and-their-application/ED2FD043579F27952363566DC09CBD6A (https://www.cambridge.org/core/books/bootstrap-methods-and-their-application/ED2FD043579F27952363566DC09CBD6A)
- Schenker, N., & Gentleman, J. F. (2001). On judging the significance of differences by examining the overlap between confidence intervals. The American Statistician, 55(3), 182-186.
- Puth, M. T., Neuhäuser, M., & Ruxton, G. D. (2015). On the variety of methods for calculating confidence intervals by bootstrapping. Journal
 of Animal Ecology, 84(4), 892-897.

Developed by Daniel Padfield, Hannah O'Sullivan.

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