

Bioinactivation FE User Manual

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Document Revisions

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1 Abbreviations and symbols

t	Elapsed time since inoculation.
N	Microbial count.
N_0	Microbial count at the moment of inoculation.
S	Fraction of survivors (N/N_0).
T	Temperature.
T_{ref}	Reference temperature.
\log_{10}	Decimal logarithm.
D	D-value of Bigelow model.
D_R	D-value at the reference temperature.
z	z-value of Bigelow, Mafart and Geeraerd model.
b	Parameter of Peleg model.
n	Parameter of Peleg model.
k_b	Parameter of Peleg model.
T_c	Critical temperature of Peleg model.
δ	Scale factor of the Weibull distribution for Mafart model (δ -value).
δ_R	δ -value at the reference temperature.
p	Shape factor of the Weibull distribution for Mafart model.
k_{max}	Maximum rate of inactivation for Geeraerd model.
k	Instantaneous rate of inactivation for Geeraerd model.
α	Parameter of Geeraerd model including the shoulder effect.
γ	Parameter of Geeraerd model including the tail effect.
C_c	Dummy substance limiting the microbial inactivation in Geeraerd model.
N_{res}	Residual microbial count in Geeraerd model.



2 Introduction

Industrials usually apply dynamic heat treatments to food products in order to ensure their health safety. However, the lack of in-deep knowledge of the response of the pathogens to the sterilization treatments applied usually results in unnecessary overprocessing which reduces the organoleptic properties of the final product.

Current consumer demands for minimally processed products (fresh-like) require the optimization of the heat processes applied to the products, while guaranteeing health safety. This can only be accomplished with a detailed knowledge of the response of the microbial populations to the treatments applied.

Predictive microbiology serves a key role in this aspect. This branch of the microbiology tries to model the evolution of the microbial cells under known environmental conditions using mathematical models. However, the parameters of these models cannot be determined analytically. Thus, experiments in laboratory conditions must be performed in order to estimate their values. Consequently, inactivation curves cannot be predicted with complete certainty. Instead, prediction intervals at the desired confidence level must be generated.

Published research have shown that non-isothermal heat treatments like those commonly applied in industry can only be described using inactivation models whose model parameters have been estimated using dynamic experiments. However, the estimation of model parameters using from the dynamic experimental data requires their determination directly from the system of differential and algebraic equations. This requires advanced mathematical procedures.

The bioinactivation package for the R programming language (Garre, Fernández, & Egea, 2015) implements several features for the modeling of microbial inactivation either isothermal or non-isothermal. It includes functions for the estimation of model parameters from isothermal or non-isothermal data, as well as for the prediction of the inactivation process (inactivation curves or prediction intervals). Nevertheless, knowledge of programming in R is required to access these functions.

Bioinactivation SE (Simplified Environment) (Garre, Fernández, Lindqvist, & Egea, 2017) was published providing a simplified interface to selected functions of the bioinactivation package, namely the estimation of model parameters from non-isothermal experiments and the generation of prediction intervals of the inactivation process. Due to the positive feedback received from the community, it was decided to develop Bioinactivation FE, which includes an interface to every function in the bioinactivation package. Moreover, several improvements in the user interface were implemented based on the user feedback.

The layout of Bioinactivation FE has been developed using the *shiny* package of R (Chang, Cheng, Allaire, Xie, & McPherson, 2015). This package provides a framework for the creation of web applications which can run R code. Hence, the user does not need to have R installed in his computer to use Bioinactivation FE. The only requirements are an internet connection and a web browser. Hence, it can even be used using a smartphone.

Bioinactivation FE is hosted in the following link:

<https://opada-upct.shinyapps.io/bioinactivationFull/>

A permanent link to this page is kept on the Department of Food Microbiology of the Universidad Politécnica de Cartagena, under the “Recursos” (“Resources”) section.

Bioinactivation FE can also be used on computers without internet connection. In this case, however, the software must be installed locally. Please contact the maintainers of the software as indicated in the section *Alberto Garre, Pablo S. Fernandez, Roland Lindqvist, Jose A. Egea, Bioinactivation: Software for modelling dynamic microbial inactivation, Food Research International, Volume 93, March 2017, Pages 66-74, ISSN 0963-9969, http://dx.doi.org/10.1016/j.foodres.2017.01.012.*

Contact.

Bioinactivation FE is free to use. However, when using it in scientific publications, please cite it as:

Alberto Garre, Pablo S. Fernandez, Roland Lindqvist, Jose A. Egea, Bioinactivation: Software for modelling dynamic microbial inactivation, Food Research International, Volume 93, March 2017, Pages 66-74, ISSN 0963-9969, http://dx.doi.org/10.1016/j.foodres.2017.01.012.



3 Features included in Bioinactivation FE

Bioinactivation FE implements an interface to most functions of the bioinactivation package for R, which is publicly in the Comprehensive R Archive Network (CRAN) under the following link:

<https://cran.rstudio.com/web/packages/bioinactivation/index.html>

Bioinactivation FE includes the following features:

- Calculation of survivor curves during isothermal or non-isothermal thermal treatments.
- Model fitting of isothermal experiments.
- Model fitting of dynamic inactivation experiments using non-linear regression or an MCMC algorithm.
- Generation of prediction intervals of the dynamic inactivation process based on the adjustment performed.
- Editable plots of the predicted survivor curves or fitted curves.
- Several measurements (ME, RMSE, log-likelihood, AIC, BIC, A_f and B_f) of the predicted/fitted curve with respect to the experimental data.
- Plot of the residuals.
- Shapiro-Wilk normality test of the residuals.
- Output of the adjusted curve as a text file.

4 Units

Bioinactivation SE does not require the user to input the values in any specific unit system. The output is generated in the same unit system defined by the user.

5 Layout of Bioinactivation FE

Figure 1 illustrates the layout of Bioinactivation FE as it is loaded by the web browser. It is divided in a side bar and a main body. The side bar allows switching between the different sections of the application:

- Generation of predictions.
- Fitting of isothermal experiments.
- Fitting of non-isothermal experiments.

Moreover, there is an about page with miscellaneous information and a link to the original article, where the mathematical basis of the bioinactivation package are illustrated.

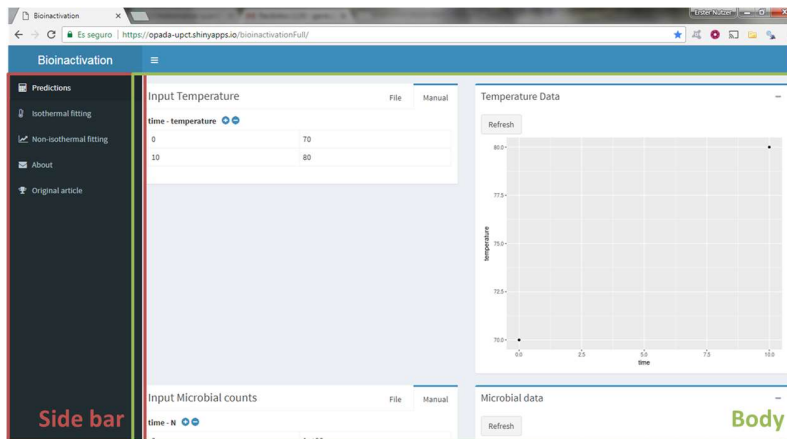


Figure 1: Overview of the layout of Bioinactivation FE

The body of the application is divided in several boxes, which are color coded according to their function (Figure 2):

- **Blue boxes** are for user input.
- **Green boxes** are for showing and editing plots.
- **Yellow boxes** provide statistical results.
- **Red boxes** are for output of the results to other formats.

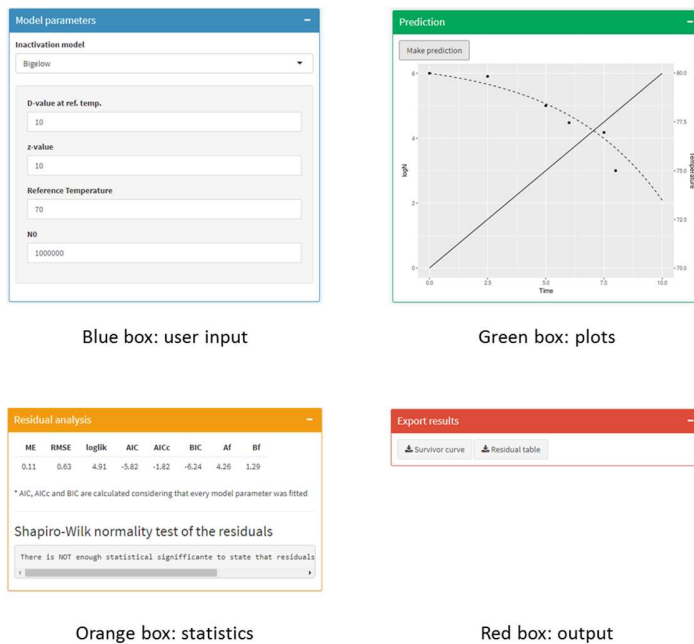


Figure 2: Color code of the boxes in Bioinactivation FE

6 Modules of Bioinactivation FE

Bioinactivation FE is divided in three different modules. They are accessible from the buttons in the sidebar.

6.1 Prediction module

The prediction module allows to simulate the response of the microbial cells to a thermal treatment, provided that the model parameters describing its kinetics are known. The first step for this is the input of the temperature profile. Bioinactivation FE supports two type of input: manual or by a csv file. **¡Error! No se encuentra el origen de la referencia.** illustrates the two boxes available. In box ① the actual data input takes place, whereas box ② illustrates the data interpreted by Bioinactivation FE. By default, the table ③ has two rows, but this number can be increased or reduced using the blue “+” and “-” signs. Once the data input is finished, the “Refresh” button ④ must be clicked. The data is then saved by the software and illustrated in box ②. In Bioinactivation, the temperature profile is linearly interpolated between the points supplied by the user. Note that isothermal experiments can be predicted by setting the same temperature in every entry.

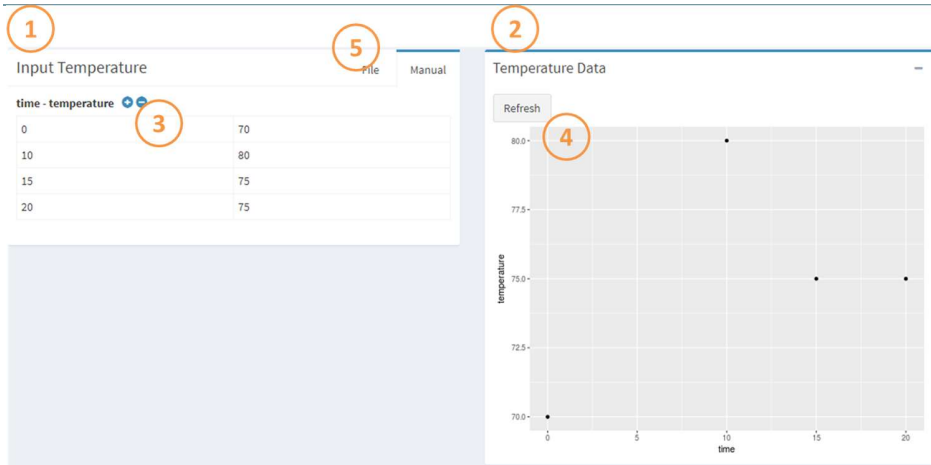


Figure 3: Widgets for inputting the thermal profile for prediction

Moreover, the temperature profile can be input as a text file by clicking the “File” tab ⑤. The layout of box ① is, then, changed to the one illustrated in Figure 4. The user can select a file by clicking the “Browse...” button ①. Three column separator characters are supported by Bioinactivation FE: comma (,), semicolon (;) and tabs (\t). The one used in the uploaded file can be selected using the radio buttons ②. Furthermore, Bioinactivation FE supports decimal points indicated by points (.) or comma (,). The selected one must be indicated in the radio buttons ③.

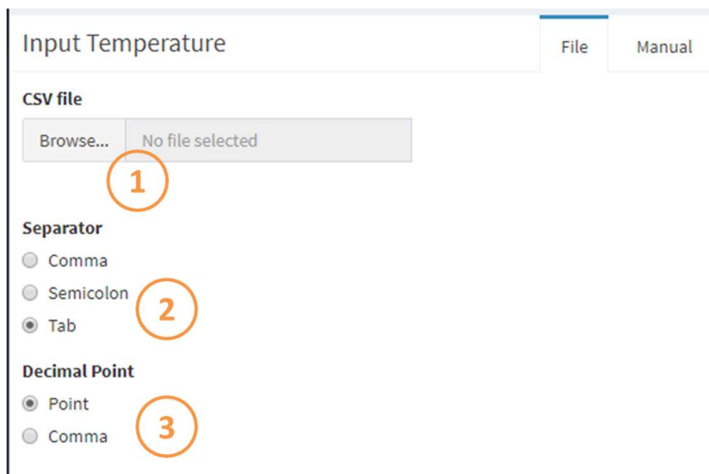


Figure 4: File input

Bioinactivation FE is able to compare the microbial response predicted with the data obtained in the lab. This information must be provided in the two boxes shown in Figure 5. The layout of these boxes is identical to the one of the temperature profile (Figure 3).

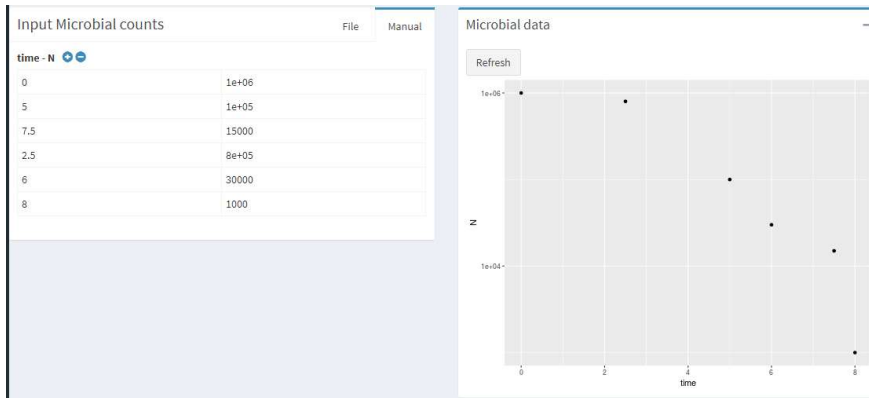


Figure 5: Layout of the microbial data input

The next step for the generation of predictions is the input of the mode parameters. Figure 6 depicts the box implemented in Bioinactivation FE for this purpose. The inactivation model describing the microbial response can be selected with the selection box ①. The contents of the well box ② change according to the model selected, showing a text label ③ for each model parameters, as well as a text input ④ where the value of the model parameter is input by the user.

The screenshot shows a 'Model parameters' form with the following fields and callouts:

- Inactivation model:** A dropdown menu showing 'Bigelow' (callout ①).
- D-value at ref. temp.:** A text input field containing '10' (callout ②).
- z-value:** A text input field containing '10' (callout ③).
- Reference Temperature:** A text input field containing '70' (callout ④).
- N0:** A text input field containing '1000000'.

Figure 6: Layout for input of model parameters

Once all the data has been input, the microbial response to the thermal treatment can be simulated. For that, the button “Make prediction” (① in Figure 7) must be clicked. After a short loading time, the predicted survivor curve is plotted as a dotted line, whereas the

temperature profile is drawn as a solid line in ②. Several aesthetics of the plot can be edited by interacting with the widgets in box ③. The temperature profile can be omitted from the plot by unticking the check box ④.

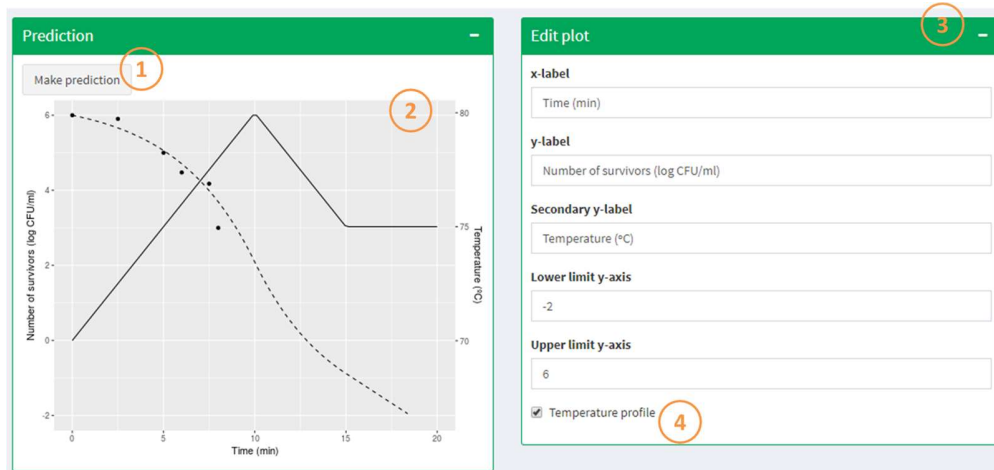


Figure 7: Layout of boxes for prediction

Bioinactivation FE provides several statistics comparing the predicted survivor curve and the microbial data input by the user. Box ① provides a table with the data observed and predicted at each time point, as well as the residual. Box ② reports several statistics measures of the residuals ③ as well as the results of a Shapiro-Wilk normality test of the residuals ④.

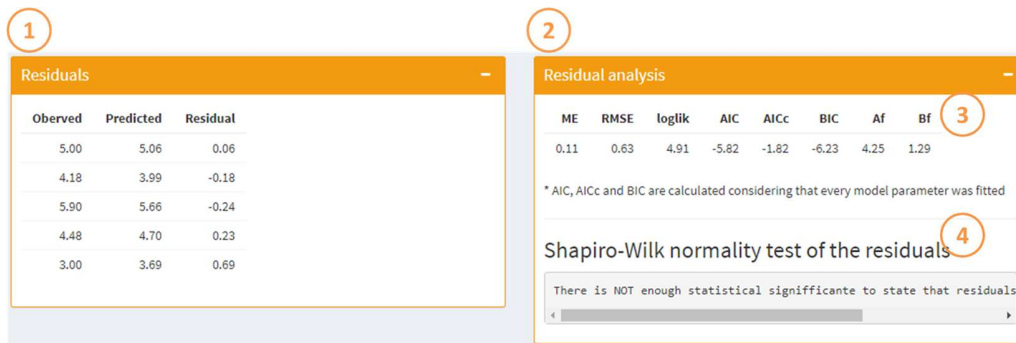


Figure 8: Layout of the boxes comparing the prediction and data

The survivor curve and the residual tables calculated by Bioinactivation FE can be output as text files for further editing using external software. Figure 9 illustrates the layout of the box implemented for this purpose. Button ① generates a .csv file with the survivor curve simulated, whereas button ② does the same for the residual table.

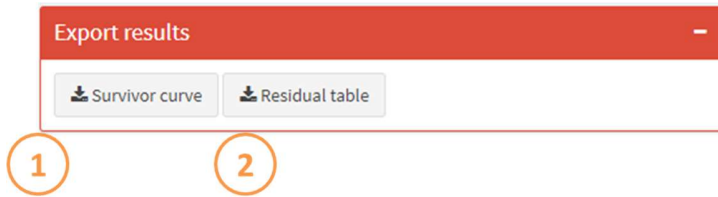


Figure 9: Box for the output of prediction results

6.2 Isothermal fitting module

The isothermal fitting module allows to characterize the microbial response based on the data isothermal inactivation generated in the lab. The data is input in the boxes illustrated in Figure 10. The data is input in box ① as either a table or a file ⑤. In any case, the data must have three columns:

- time: the elapsed time of the experiment.
- logS: the number of log-reductions of the microbial count ($\log S = \log N - \log N_0$).
- temperature: the isothermal temperature held during the experiment.

By default, the table for data input has nine entries. This number can be modified by clicking the blue “+” and “-” buttons ③. Once the data input is finished, the “Refresh” button ④ must be clicked to save the progress. The input data are, then, shown in box ②.

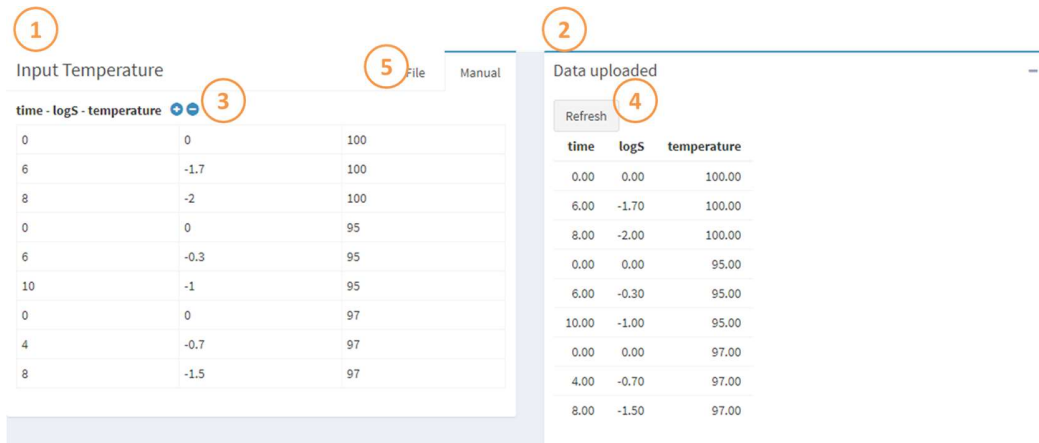


Figure 10: Boxes for the data input of isothermal inactivation data

Bioinactivation FE uses a one-step non-linear regression algorithm for estimating the values of the model parameters. This algorithm requires the definition of initial guesses of the model parameters. These are implemented in the box shown in Figure 11. The inactivation model can be chosen in the selection box ①. The model parameters of the selected model are then shown below, with a text label ② followed by a text input ③, where the guess of

the model parameters must be input. Bioinactivation allows the user to select which parameters to fit and which ones to keep fixed during the model fit. The user can switch between both behaviors by ticking the checkbox ④.

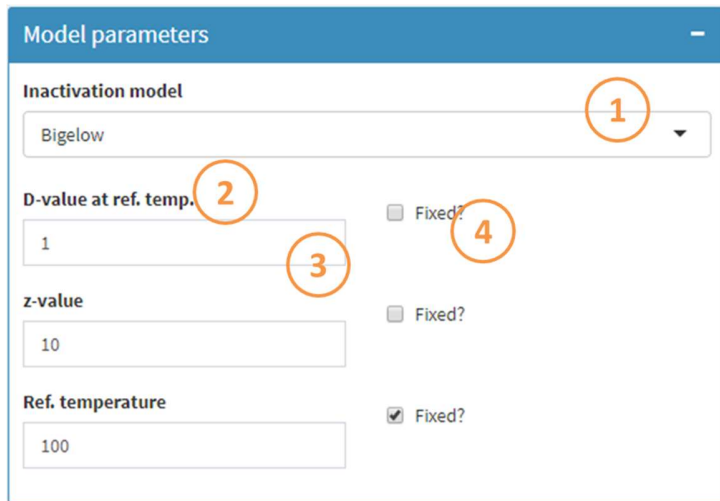


Figure 11: Input of guesses of the parameters for fitting of isothermal experiments

Once the user has input all the information required for the fit, the model parameters can be estimated. Figure 12 shows the box where this action takes place. The user must click the “Fit model” button ①. After a short calculation time, the predicted curve at each isothermal temperature, as well as the data obtained in the lab, are illustrated ②.

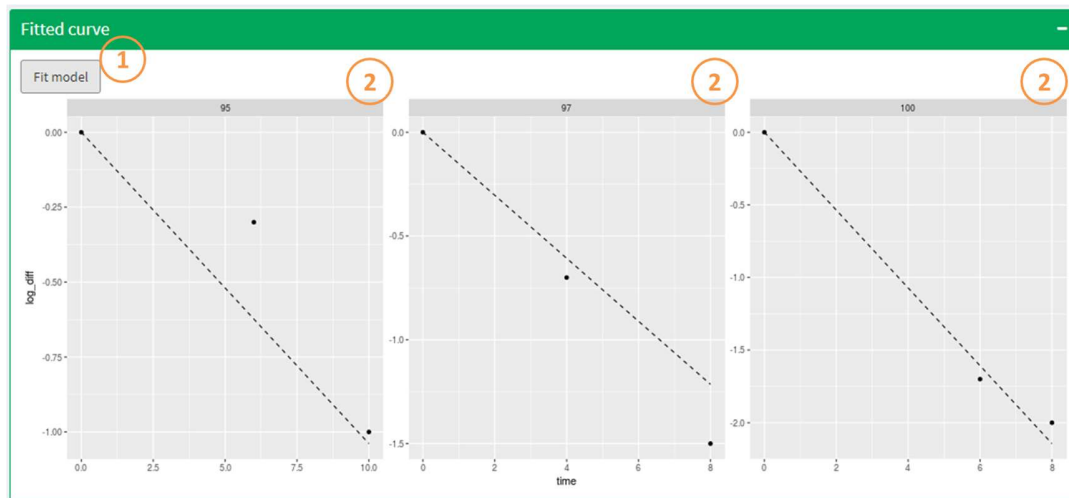


Figure 12: Box for model fitting of isothermal experiments

Figure 13 illustrates the boxes showing the results of the model fit. Estimates of the value of the model parameters and their standard deviations, as well as a the limits of a confidence interval at the 95% confidence level calculated are provided in ②. Moreover, several

statistical indexes describing the goodness of the mode fit are supplied in ③. In box ④, a residual plot is shown in ⑤, where the dots are colored by temperature. Furthermore, the results of a Shapiro-Wilk normality test of the residuals is reported in ⑥.

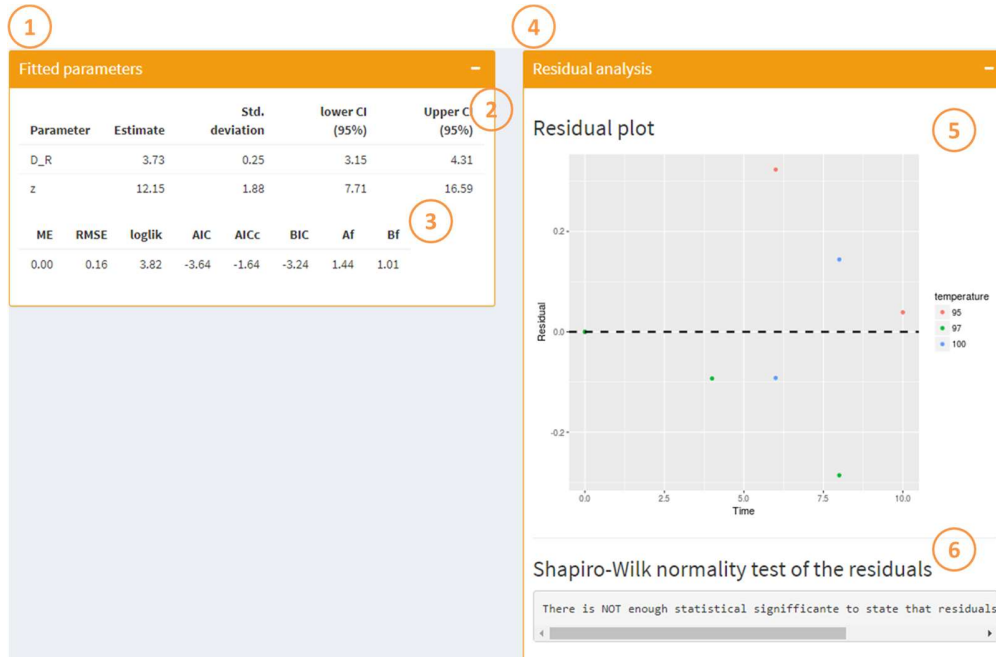


Figure 13: Boxes showing the results of the isothermal model fit

6.3 Non-isothermal fitting module

6.3.1 Fitting of non-isothermal inactivation experiments

The non-isothermal fitting module includes every feature that was previously included in Bioinactivation SE: the model fitting of non-isothermal experiments and the generation of prediction intervals. The first step is the input of the temperature profile used during the experiment, as well as the microbial counts obtained during the experiment. Bioinactivation FE supports two type of input: manual or by a csv file. Figure 14 illustrates the two boxes available. In box ① the actual data input takes place, whereas box ② illustrates the data interpreted by Bioinactivation FE. By default, the table ③ has two rows, but this number can be increased or reduced using the blue “+” and “-” signs. Once the data input is finished, the “Refresh” button ④ must be clicked. The data is then saved by the software and illustrated in box ⑤. In Bioinactivation, the temperature profile is linearly interpolated between the points supplied by the user.

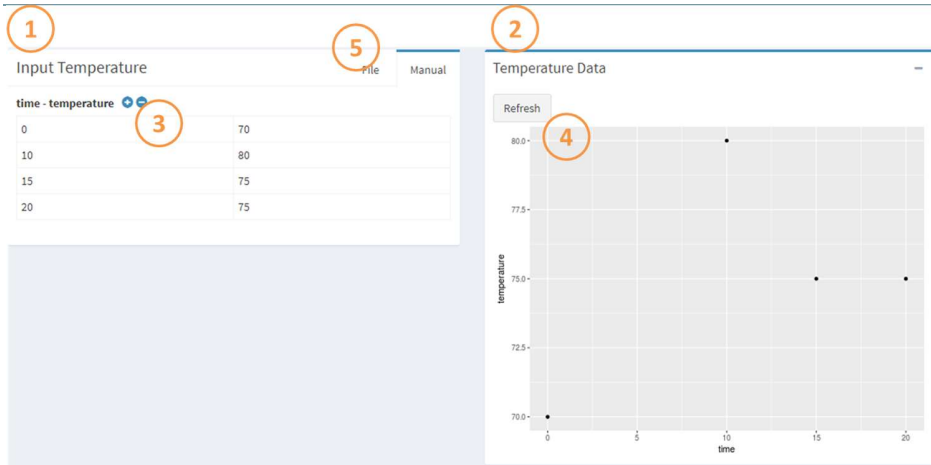


Figure 14: Widgets for inputting the thermal profile for non-isothermal fitting

Moreover, the temperature profile can be input as a text file by clicking the “File” tab (5). The layout of box (1) is, then, changed to the one illustrated in Figure 15. The user can select a file by clicking the “Browse...” button (1). Three column separator characters are supported by Bioinactivation FE: comma (,), semicolon (;) and tabs (\t). The one used in the uploaded file can be selected using the radio buttons (2). Furthermore, Bioinactivation FE supports decimal points indicated by points (.) or comma (,). The selected one must be indicated in the radio buttons (3).

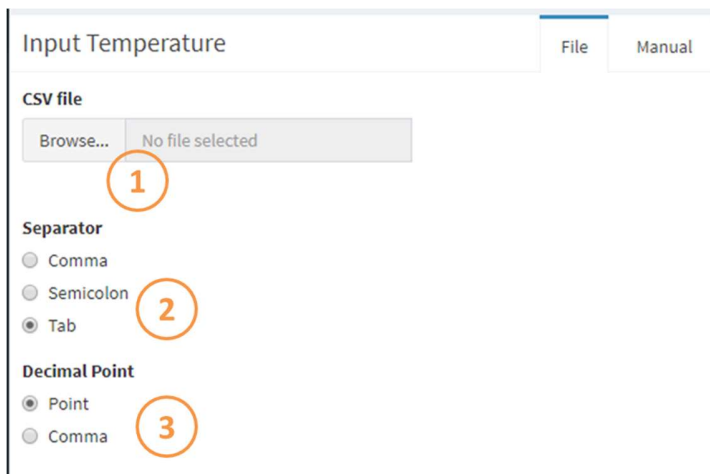


Figure 15: File input

Bioinactivation FE is able to compare the microbial response predicted with the data obtained in the lab. This information must be provided in the two boxes shown in Figure 16. The layout of these boxes is identical to the one of the temperature profile (Figure 14Figure 3).

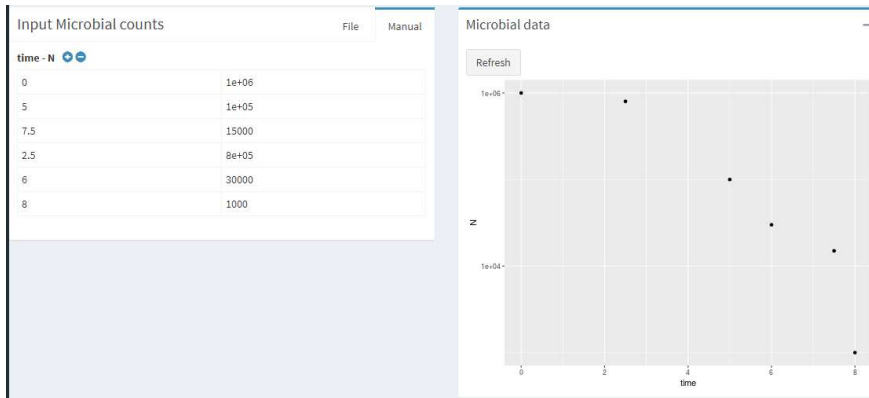


Figure 16: Layout of the microbial data input

The model fitting algorithms implemented in Bioinactivation require the definition of initial guesses of the model parameters. This step is performed in the box illustrated in Figure 17. The inactivation model can be selected in ①. The contents of the box below are updated according to the model selected, showing a text label ② for each model parameter followed by a text input where initial guess ③, lower bound ④ and upper bound ⑤ can be defined. Bioinactivation allows the user to fix or fit any model parameter at will (including the initial microbial count) by interacting with the check box ⑥.

The screenshot shows the 'Model parameters' configuration window. At the top, there is a dropdown menu for the 'Inactivation model' set to 'Bigelow', marked with a circled 1. Below this, several parameters are listed with their respective input fields and checkboxes:

- D-value at ref.temp.** (marked with a circled 2): Initial guess (10, marked with a circled 3), Lower bound (7, marked with a circled 4), Upper bound (20, marked with a circled 5), and a 'Fixed?' checkbox (unchecked, marked with a circled 6).
- z-value**: Initial guess (10), Lower bound (7), Upper bound (20), and a 'Fixed?' checkbox (unchecked).
- Reference temperature**: Initial guess (70), Lower bound (60), Upper bound (90), and a 'Fixed?' checkbox (checked).
- Decimal logarithm of N0**: Initial guess (6), Lower bound (5), Upper bound (7), and a 'Fixed?' checkbox (checked).

Figure 17: Definition of initial guesses of the model parameters for dynamic fit

The selection of the initial guesses and bounds for the model parameters can be based on literature review or preliminary simulations. In order to assist during this procedure, Bioinactivation implements a box (Figure 18) comparing the survivor curve obtained

when the initial guess and bounds are used against the experimental data input. The user should be aware that using model parameters too deviated from the experimental data may result in the model failing to converge.



Figure 18: Boxes to define the settings of the fitting algorithm

Box ② in Figure 18 allows the user to define several settings of the fitting algorithm. The user can select between a non-linear regression algorithm and an Adaptive Monte Carlo algorithm (MCMC) implemented in the FME package (Soetaert & Petzoldt, 2010) using the selection box ③. If the MCMC algorithm is used, the users must select the number of iterations of the algorithm (① in Figure 19). Once the algorithm is selected, the model fitting algorithm can be run by clicking the “Fit the model” button ②. This process can take some time, so a progress bar is shown while the calculation is taking place. Once it is finished, the output is shown as illustrated in Figure 20. The predicted survivor curve is plotted as a dotted line, whereas the temperature profile is drawn as a solid line in ①. Several aesthetics of the plot can be edited by interacting with the widgets in box ②. The temperature profile can be omitted from the plot by unticking the check box ③.

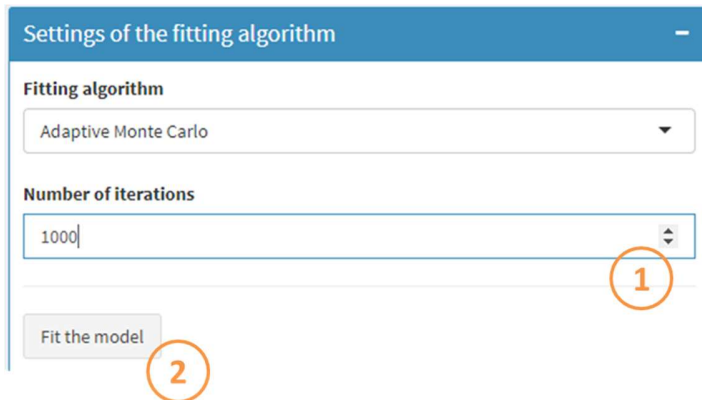


Figure 19: Settings of the MCMC algorithm

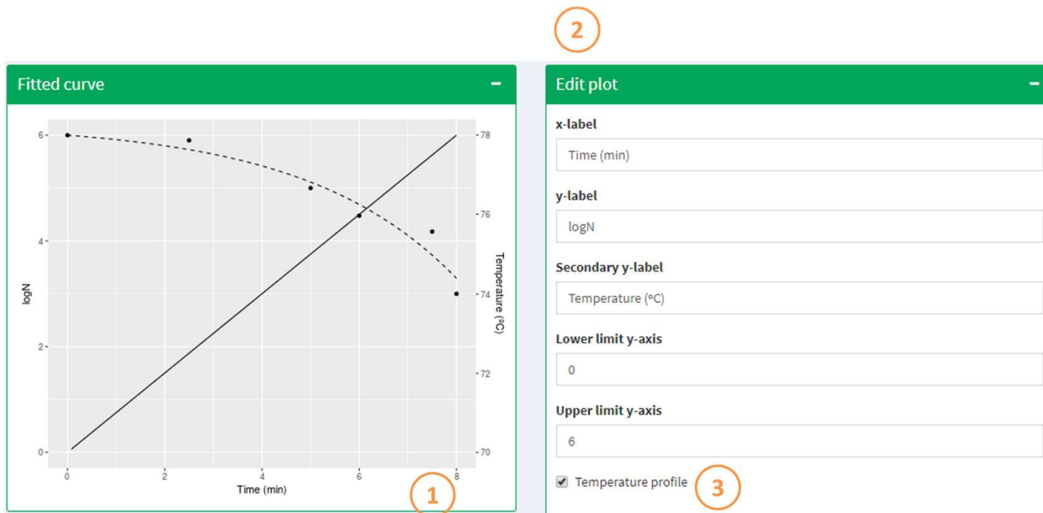


Figure 20: Output of non-isothermal fitting

Bioinactivation FE provides estimates of the values and standard deviations of the model parameters, as well as confidence intervals at the 95% confidence level in the box illustrated in Figure 21. Furthermore, several indexes evaluating the goodness of the fit and the convergence of the fitting algorithm are output. Figure 22 illustrates the residual plot ① generated by the application, as well as the results of a Shapiro-Wilk normality test of the residuals ② and an estimate of the parameter correlation ③. Moreover, if the MCMC algorithm was selected for the fit, additional plots are generated to assess the convergence of the algorithm (Figure 23). Bioinactivation FE allows the user downloading the results calculated for further processing using external software, as shown in Figure 24.

Fitted parameters							
Parameter	Estimate	Std. deviation	lower CI (95%)	Upper CI (95%)			
D_R	14.14	3.75	7.38	19.86			
z	7.09	2.82	7.11	18.40			
ME	RMSE	loglik	AIC	AICc	BIC	Af	Bf
-0.00	0.37	4.78	-5.56	-1.56	-5.98	2.36	1.00

Figure 21: Parameter estimates reported by the non-isothermal fitting module

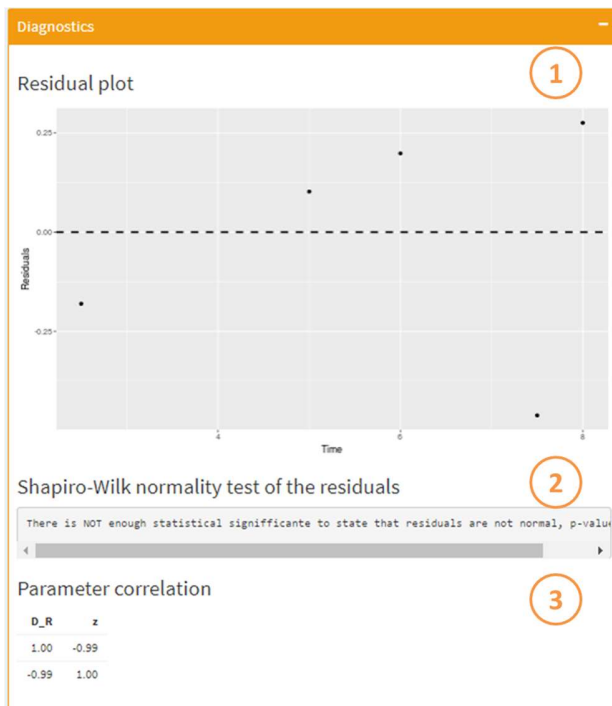


Figure 22: Illustration of the output generated by Bioinactivation SE evaluating the goodness of the non-isothermal fitting

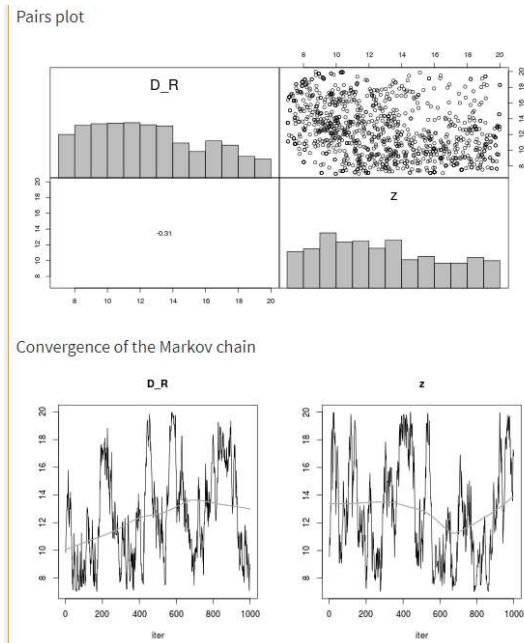


Figure 23: Output generated by Bioinactivation FE to assess the convergence of the MCMC algorithm

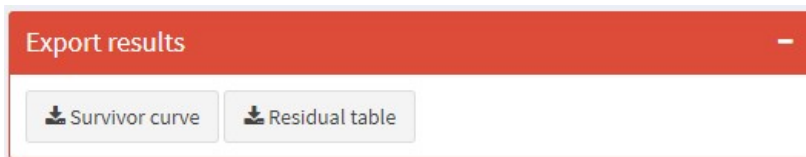


Figure 24: Box for the output of the results of the non-isothermal fit

6.3.2 Generation of prediction intervals

Bioinactivation FE provides the users with functionality to generate prediction intervals of the microbial response using the variance of the model parameters estimated using the non-isothermal data. For that, the user must first input the temperature profile using the box illustrated in Figure 25. The layout of this box is the same as described previously in Figure 14. Note that isothermal profiles can be simulated by setting every entry of the table to the same temperature.

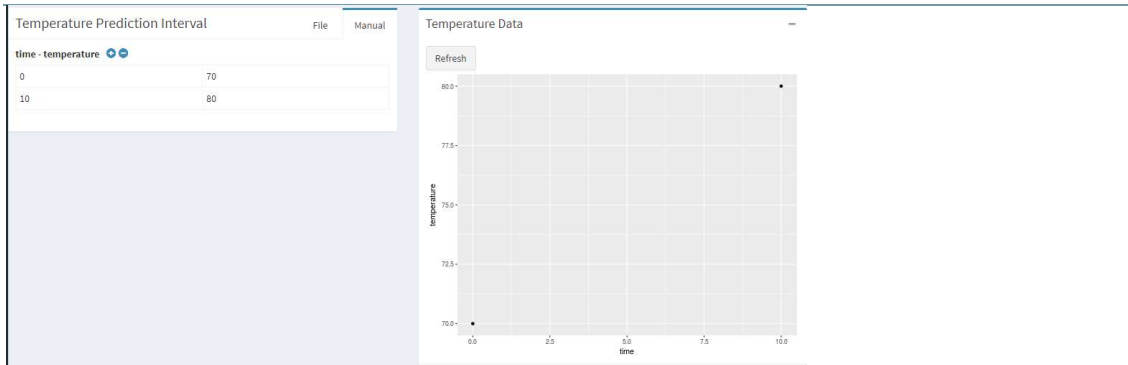


Figure 25: Input of the temperature profile for the calculation of prediction intervals

The user has the freedom to edit several settings of the algorithm for the calculation of prediction intervals. Figure 26 illustrates the box implemented for this purpose. The user can select the quantiles at which the prediction interval is calculated using the slider ①. By default, a symmetrical interval at the 90% confidence is calculated. Moreover, the number of iterations of the MCMC algorithm can be input using ②. Once the setting has been set, the prediction interval can be estimated by clicking the “Calculate interval” button ③.

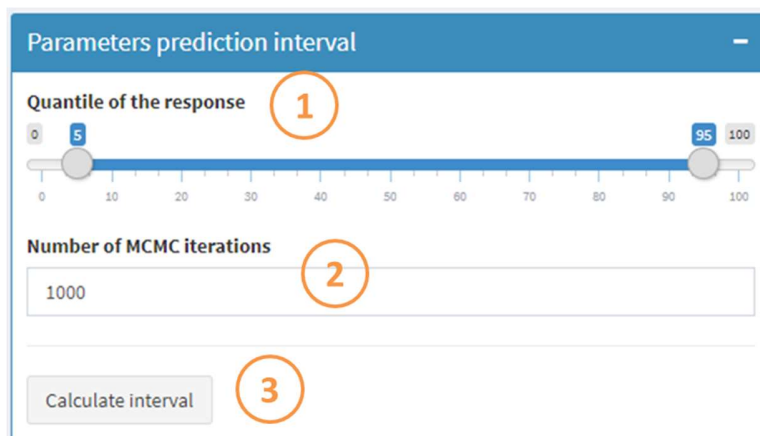


Figure 26: Box for setting the parameters of the algorithm for calculating prediction intervals

The estimation of the prediction interval can be time consuming. Hence, a progress bar is shown while the calculation is taken place. Once it is done, the results are shown in the two boxes illustrated in Figure 27. Box ① plots the prediction interval estimated. This plot can be edited by interacting with the widgets in box ②.

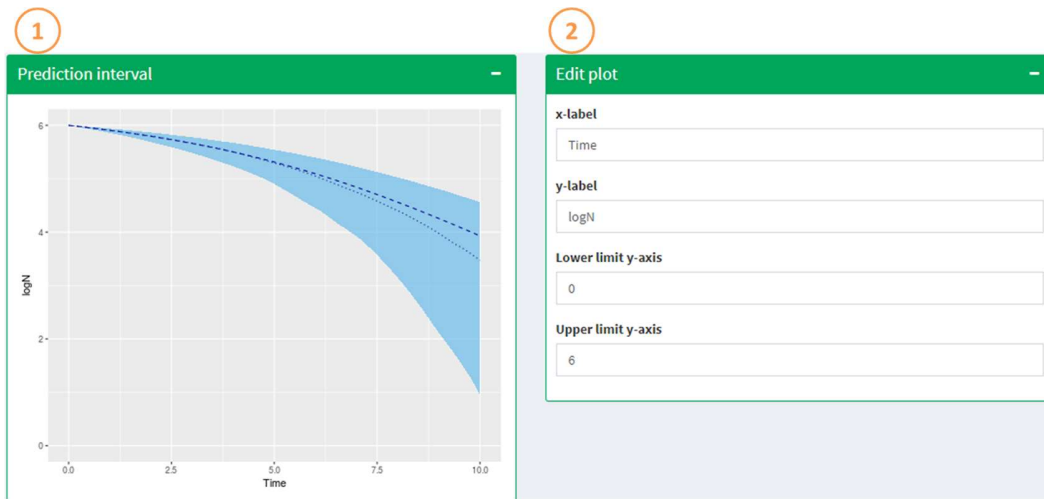


Figure 27: Output of the prediction interval



7 Citation

When using Bioinactivation FE in scientific papers, please refer it as:

Alberto Garre, Pablo S. Fernandez, Roland Lindqvist, Jose A. Egea, Bioinactivation: Software for modelling dynamic microbial inactivation, Food Research International, Volume 93, March 2017, Pages 66-74, ISSN 0963-9969, <http://dx.doi.org/10.1016/j.foodres.2017.01.012>.

8 Contact

For issues not covered in this manual, please contact:

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- Peleg, M., & Cole, M. (1988). Reinterpretation of microbial survival curves. *Critical Reviews in Food Science*, 380, 353-380.

Appendix A: Inactivation models included in Bioinactivation SE

This section presents the constitutive equations of each inactivation model implemented in Bioinactivation SE. Each one of them has been implemented in differential form, to be able to describe dynamic inactivation. For further detail on each model, please consult the original papers referenced.

9.1 Bigelow model

The model defined by Bigelow (1921) is described by the following system of differential and algebraic equations:

$$\frac{d\log_{10}N(t)}{dt} = -\frac{1}{D(T)} \quad (1)$$
$$\log_{10}D(T) = \log_{10}D(T_{ref}) - \frac{T - T_{ref}}{z}$$

9.2 Peleg model

The model defined by Peleg (1988) is described by the following system of differential and algebraic equations:

$$\frac{d\log_{10}S(t)}{dt} = -b(T)n \left(\frac{\log_{10}S}{b(T)} \right)^{\frac{n-1}{n}} \quad (2)$$
$$b(T) = \ln(1 + e^{k_b(T-T_c)})$$

9.3 Mafart model

The model defined by Mafart et al. (2002) is described by the following system of differential and algebraic equations:

$$\frac{d\log_{10}S(t)}{dt} = -p \left(\frac{1}{\delta(T)} \right)^p t^{p-1} \quad (3)$$
$$\log_{10}\delta(T) = \log_{10}\delta(T_{ref}) - \frac{T - T_{ref}}{z}$$



9.4 Geeraerd model

The model defined by Geeraerd et al. (2009) is described by the following system of differential and algebraic equations.

$$\frac{dN}{dt} = -\alpha \cdot k_{max} \cdot \gamma \cdot N(t)$$

$$\frac{dC_c}{dt} = -k_{max}(T) \cdot C_c$$

$$\alpha = \frac{1}{1 + C_c} \quad (4)$$

$$\gamma = 1 - \frac{N_{res}}{N}$$

$$k_{max}(T) = k_{max} 10^{-(T-T_{ref})/z}$$

9.5 Arrhenius model

A model based on the log-linear model with a secondary Arrhenius model has been implemented in Bioinactivation.

$$\frac{dN}{dt} = -k(T) \cdot N$$

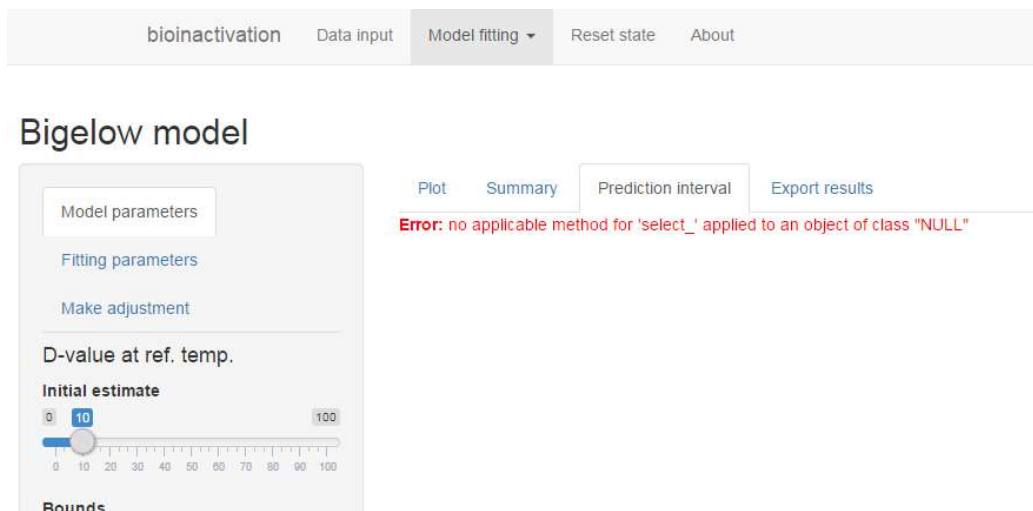
$$k(T) = k_{ref} \cdot e^{-\frac{E_a}{8.31} \left(\frac{1}{T} - \frac{1}{T_{ref}} \right)} \quad (5)$$

Appendix B: Common error messages and known bugs

1 Error in Prediction interval

ERROR DESCRIPTION

The tab *Prediction interval* of the *Model input* page shows the message **Error: no applicable method for 'select_' applied to an object of class 'NULL'**.



REASON

The adjustment has not been performed yet.

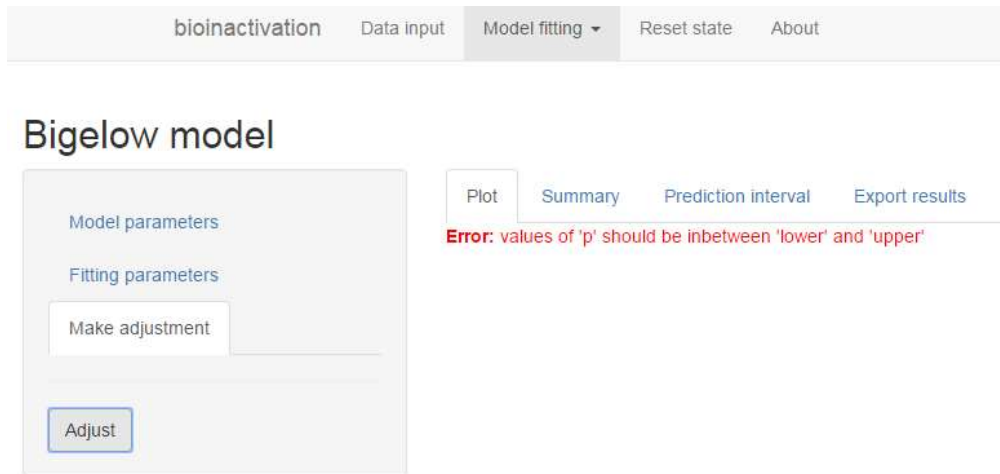
SOLUTION

Perform the model fitting.

2 Wrong bounds selected

ERROR DESCRIPTION

The tab *Plot* (or *Summary*) of the *Model input* page shows the message **Error: values of 'p' should be inbetween 'lower' and 'upper'** after launching the model adjustment.



REASON

The initial estimate of at least one model parameter (not considered known) is not within the admissible bounds defined by the user.

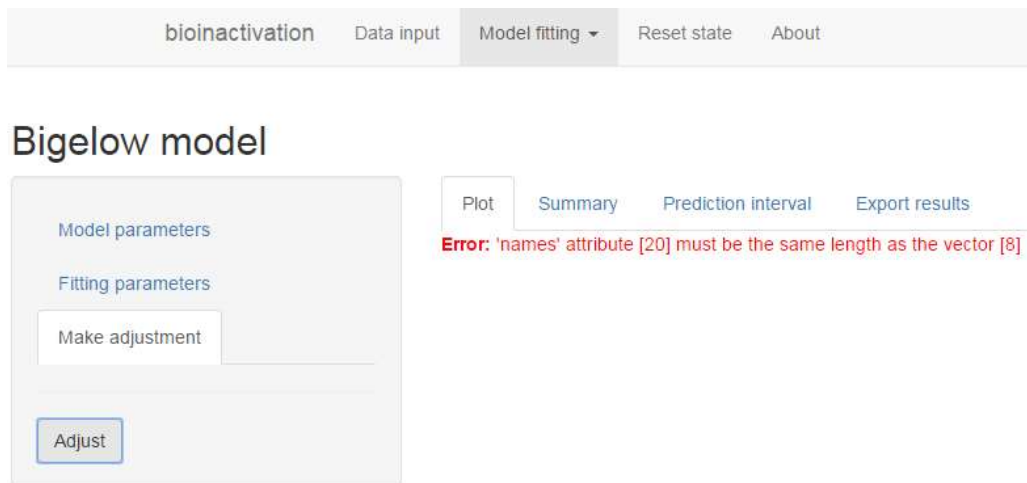
SOLUTION

Readjust the initial estimates and bounds of the model parameters.

3 Error after performing nlr adjustment

ERROR DESCRIPTION

The tab *Plot* (or *Summary* or *Prediction interval*) of the *Model input* page shows the message **Error: 'names' attribute [X] must be the same length as the vector [Y]** after launching a model adjustment using the nlr algorithm.



REASON

The nlr algorithm failed to converge.

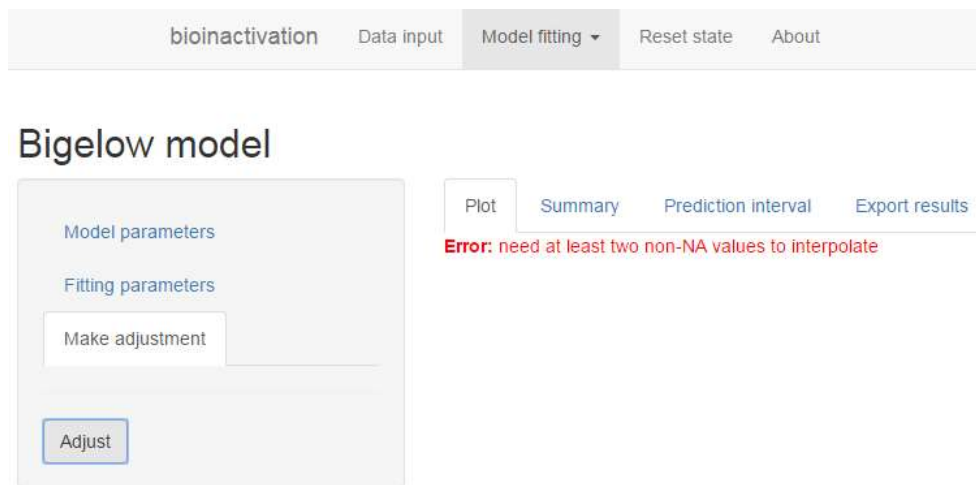
SOLUTION

Make sure that the reference temperature has been fixed to a value. If it has, repeat the adjustment with different initial estimates of the model parameters. If that fails, try fixing some of them to reasonable values. If the error persists, use the nlr algorithm.

4 Error after performing MCMC adjustment

ERROR DESCRIPTION

The tab *Plot* (or *Summary* or *Prediction interval*) of the *Model input* page shows the message **Error: need at least two non-NA values to interpolate** after launching a model adjustment using the MCMC algorithm.



REASON

The MCMC algorithm failed to converge.

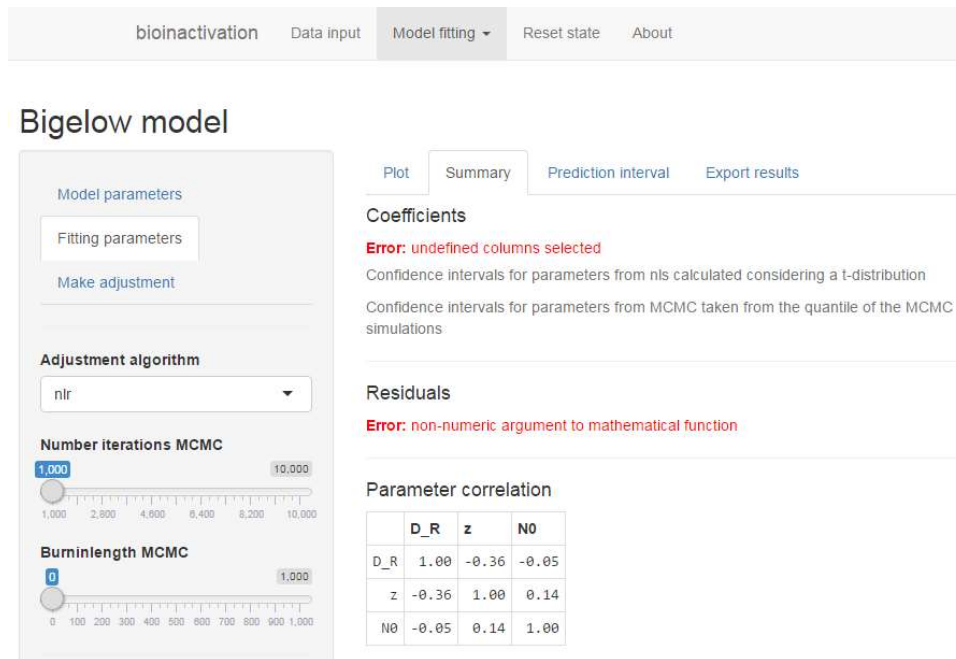
SOLUTION

Make sure that the reference temperature has been fixed to a value. If it has, repeat the adjustment with different initial estimates of the model parameters. If that fails, try fixing some of them to reasonable values. If the error persists, use the nlr algorithm.

5 Error in summary tables

ERROR DESCRIPTION

The places where the coefficient and residuals tables should be located show error messages but the survivor curve has been generated.



The screenshot shows the 'Bigelow model' configuration window. On the left, there are controls for 'Model parameters', 'Adjustment algorithm' (set to 'nlr'), 'Number iterations MCMC' (set to 1,000), and 'Burninlength MCMC' (set to 0). On the right, the 'Summary' tab is active, displaying 'Coefficients' and 'Residuals' sections. The 'Coefficients' section shows an error: 'Error: undefined columns selected'. The 'Residuals' section shows an error: 'Error: non-numeric argument to mathematical function'. Below these, a 'Parameter correlation' table is displayed.

	D_R	z	N0
D_R	1.00	-0.36	-0.05
z	-0.36	1.00	0.14
N0	-0.05	0.14	1.00

REASON

The adjustment algorithm has been modified.

SOLUTION

Modify the selection box where the fitting algorithm is selected or relaunch the model fitting.



6 Negative values are estimated for the confidence interval of the model parameters after nlr adjustment

ERROR DESCRIPTION

The application estimates negative values for the lower bounds of the confidence intervals of the model parameters after performing a nlr adjustment.

REASON

The calculation of confidence intervals for the model parameters based on a nlr model adjustment is based on the hypothesis that the model parameters follow a t-distribution with the mean and standard deviations estimated by the adjustment algorithm. If the standard deviation is large, or the mean is close to zero, the confidence interval estimated may contain negative values.

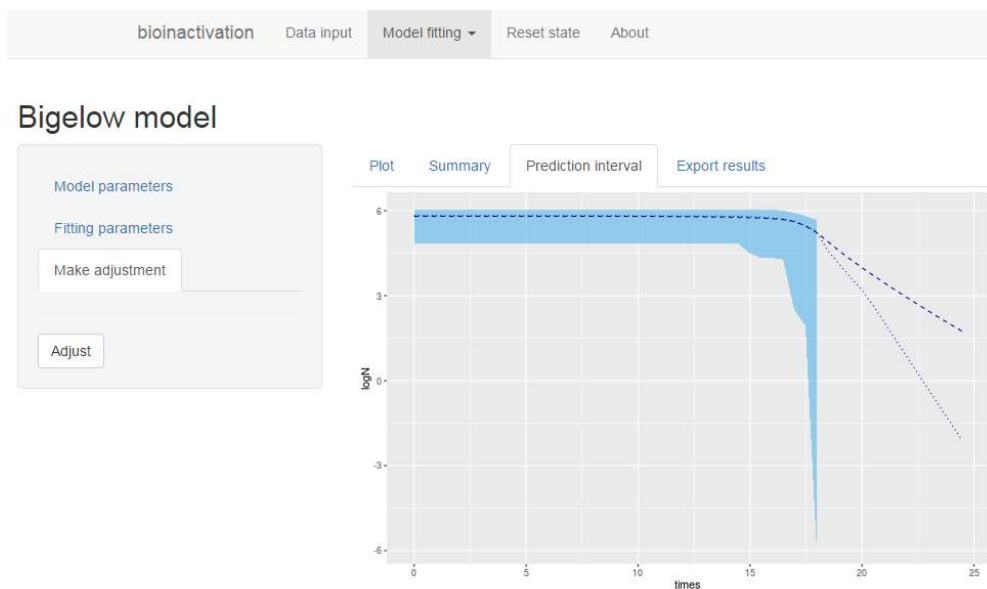
SOLUTION

Use the MCMC algorithm.

7 Strange prediction interval calculated after nlr adjustment

ERROR DESCRIPTION

The prediction interval calculated by the tool looks strange, with some blank areas after performing a nlr adjustment.



REASON

The hypothesis followed for the calculation of prediction intervals from the results of the nlr adjustment is similar to those use for the calculation of confidence intervals of the model parameters. This may produce failed iterations of the Monte Carlo algorithm used for the generation of the prediction interval.

SOLUTION

Use the MCMC algorithm.