

Getting started with BatchReactor®

Use Case 2: Simulation of bioreactions

Software & Services In Process Simulation

We guide You to efficiency



ProSim




Introduction

This document describes a method to model bioreactions using BatchReactor® software.

The challenge tied to the modeling of bioreactions results from the complexity of bioreaction schemes and kinetics. With the advanced mode available in Simulis Reactions, the user can import libraries of bioreaction kinetic models that can be easily modified and adjusted to a wide range of bioreactions.

As an example, this document showcases how to simulate the classical rate of biomass growth using the model of Monod.

Here are the steps to follow:

-  Step 1: Selection of the compounds
-  Step 2: Configuration of the bioreaction
-  Step 3: Specification of the equipment and the operating scenario

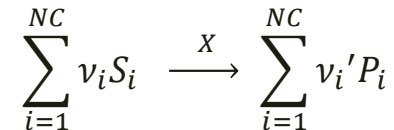
Before reading this document, it is recommended to consult “Getting Started with BatchReactor® - Use Case 1”

Description of the model

A bioreaction corresponds to an autocatalyzed reaction, since the biomass has both roles of catalyst and product of the reaction:



The bioreaction stoichiometry can be described as follows:



With:

NC	Number of components
S	Substrates (<i>i.e.</i> , glucose, oxygen and other limiting or non-limiting substrates...)
P	Products (<i>i.e.</i> , biomass growth, products of interest and other by-products)
X	Biomass (<i>e.g.</i> , micro-organisms catalysing the bioreaction)
v_i, v_i'	stoichiometric coefficients (positive value for products and negative value for substrates)

The global bioreaction rate can be defined as follows:

$$r_G = \frac{1}{v_i} r_{S_i} = \frac{1}{v_i'} r_{P_i}$$

With:

r_G	Global reaction rate of the bioreaction (positive value)
r_{S_i}	Specific rate of consumption of the substrate S_i (negative value)
r_{P_i}	Specific rate of formation of the product P_i (positive value)

Description of the model

Using the advanced mode available in Simulis Reactions, the user can import a library of bioreaction kinetic models. Two different formalisms are available, where it is possible to combine elementary kinetic models ($r(C_{Si})$) to take into account multiple different uptake/inhibition kinetics:

Product of elementary kinetic models (Option 1):
$$r_G = \left(\alpha \cdot \mu_{max} \prod_{i=1}^{NLS} r(C_{Si}) + \beta \right) \cdot C_X$$

Sum of elementary kinetic models (Option 2):
$$r_G = \left(\alpha \cdot \sum_{i=1}^{NLS} \mu_{max,i} \cdot r(C_{Si}) + \beta \right) \cdot C_X$$

With:

α	The growth-related coefficient
β	The non-growth-related coefficient
μ_{max}	The maximum growth rate
C_{Si}, C_X	Substrate, inhibitor or biomass concentration

The elementary kinetic models $r(C_{Si})$ are selected from a standard list that can be enriched by the user



Model index	Description	Equation of the term $r(C_{Si})$
1	Monod	$\frac{C_S}{K_S + C_S}$
2	Hill	$\frac{C_S^N}{K_S^N + C_S^N}$
3	Contois	$\frac{C_S}{K_S C_X + C_S}$
Etc...

Description of the model

APPLICATION EXAMPLE: this simple application example is based on the modeling of biomass growth, corresponding to the following equation:



The bioreaction stoichiometry can be described as follows: $S \xrightarrow{X} X$

The global rate of bioreaction is represented by the model of Monod:

$$r_G = \mu \cdot C_X = \mu_{max} \left(\frac{C_S}{K_S + C_S} \right) C_X$$

With:

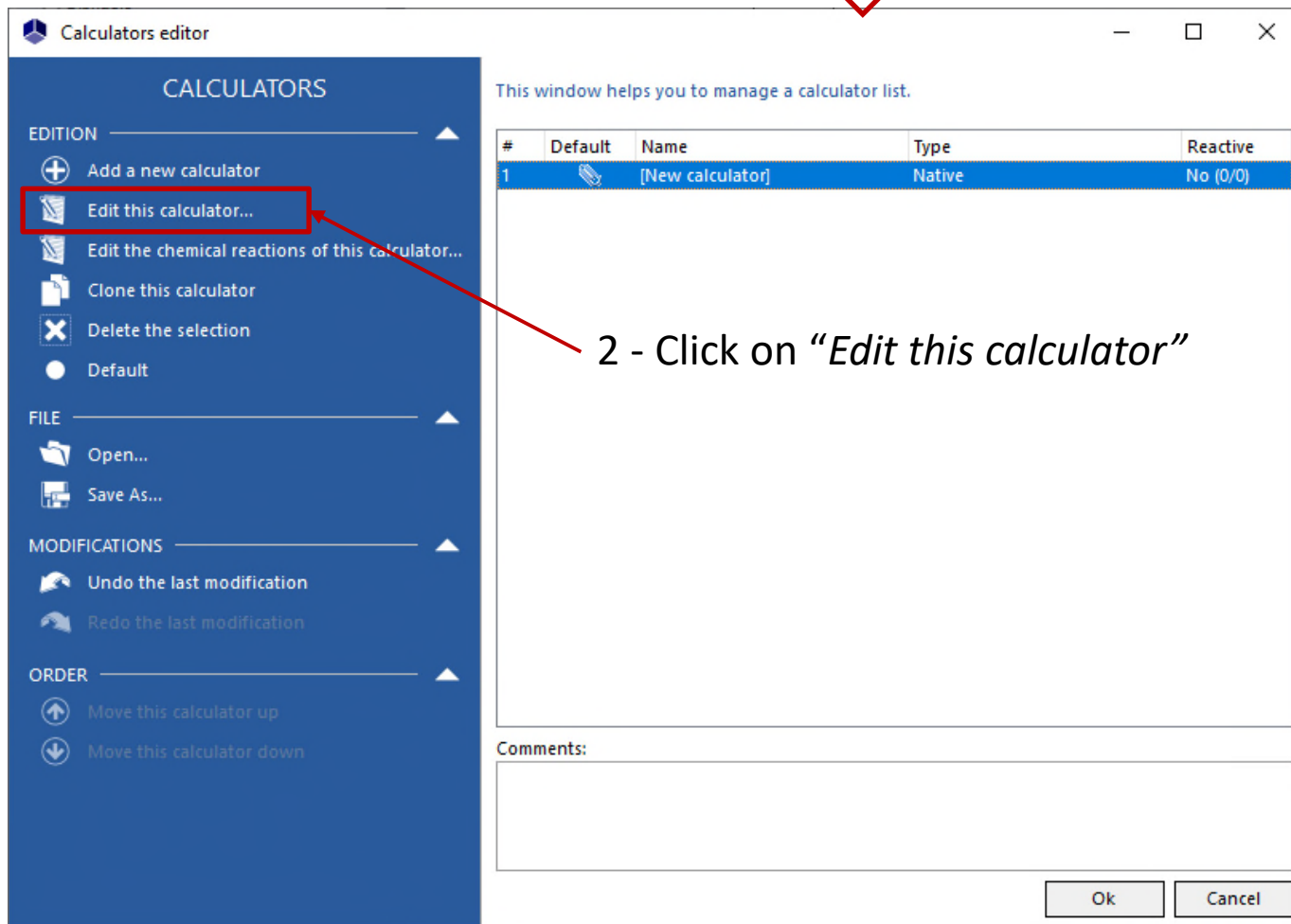
Model parameters	Definition	Value
μ_{max}	Maximum growth rate	4.10^{-5} s^{-1}
K_S	Saturation constant	2.8 g/L
C_S, C_X	Concentration of substrate (S) and biomass (X)	Process variables



The global rate is defined here in: g of biomass/(L.s). Since the stoichiometric coefficients are provided in molar, the global molar rate is obtained with the equation: $r_{G,molar} = \frac{r_{G, mass}}{M_{Biomass}}$

Step 1: Selection of the compounds

1 - Click on the “*Edit the thermodynamics and compounds*” icon to access the “*Calculators editor*” window



Step 1: Selection of the compounds

This application example requires to import the following compounds:



WATER



SUBSTRATE (modeled as “Glucose”):

- Import of the “Glucose” from the compounds database
- Modification of the name: SUBSTRATE
- Modification of the CAS number^(*): 1111-11-1



BIOMASS (modeled as “Glucose”):

- Import of the “Glucose” from the compounds database
- Modification of the name: BIOMASS
- Modification of the CAS number^(*): 2222-22-2

^(*): CAS Registry Numbers® are the intellectual property of the American Chemical Society; and are used by ProSim SA with the express permission of CAS. CAS Registry Numbers® have not been verified by CAS and may be inaccurate

Step 1: Selection of the compounds

Once this step is done, the compounds are displayed as follows in the “Compounds” tab:

The screenshot shows the 'Thermodynamic calculator editor' window. The 'COMPOUNDS' tab is selected and highlighted with a red box. The window contains a table of compounds, a left sidebar with various tools, and a right sidebar with compound management options.

#	IUPAC Name	CAS Registry Number®
1	WATER	7732-18-5
2	SUBSTRATE	1111-11-1
3	BIOMASS	2222-22-2

Below the table is a 'Comments :' text area. At the bottom, a disclaimer states: 'CAS Registry Numbers® are the intellectual property of the American Chemical Society; and are used by ProSim S.A. with the express permission of ACS. CAS Registry Numbers® have not been verified by ACS and may be inaccurate.'

The left sidebar includes sections for FILE (Open..., Save as...), PACKAGE, SERVICES (Calculate, Export as a PSF file, Diagrams, Residue..., Export as a PVT file, Stream..., Sigma profiles), MODIFICATIONS, and CONFIGURATION (Name: [Nouveau calculator], Comments, Calculator type: Native, Show the expert mode).

The right sidebar includes sections for COMPOUNDS (FILE: Open..., Save as..., Publish...; PACKAGE: Show the package manager..., Import a package..., Build a package with this list...; EDIT: Select compounds..., Edit this compound..., Add a new compound, Remove all the compounds, Clone this compound, Update the compounds, Delete the selection) and SERVICES (Create a pseudo-compound..., Temperature dependent properties, Editor array, Compare with the original). 'Ok' and 'Cancel' buttons are at the bottom right.



For more information about compounds selection, please refer to “Getting started with Simulis Thermodynamics, use case 1”

Step 1: Selection of the compounds

1 - In the “Model” tab, select the “ideal” thermodynamic profile:

The screenshot shows the 'Thermodynamic calculator editor' window. The 'MODEL' tab is selected and highlighted with a red box. The 'Profile' dropdown menu is also highlighted with a red box and set to 'Ideal'. Other settings include 'Approach type' as 'From activity coefficients', 'Equation of state' as 'Perfect gas', 'Activity coefficient model' as 'Ideal', and 'Pure liquid fugacity standard state' as 'Vapor pressure'. The 'THERMODYNAMIC MODEL' panel on the right shows the 'Water-hydrocarbons model' selected with 'Sol A' at 6.25043 and 'Sol B' at 4015.3. The 'Ok' button at the bottom right is highlighted with a red box and a red arrow pointing to it from the text '2 - Click on “Ok” to confirm'.

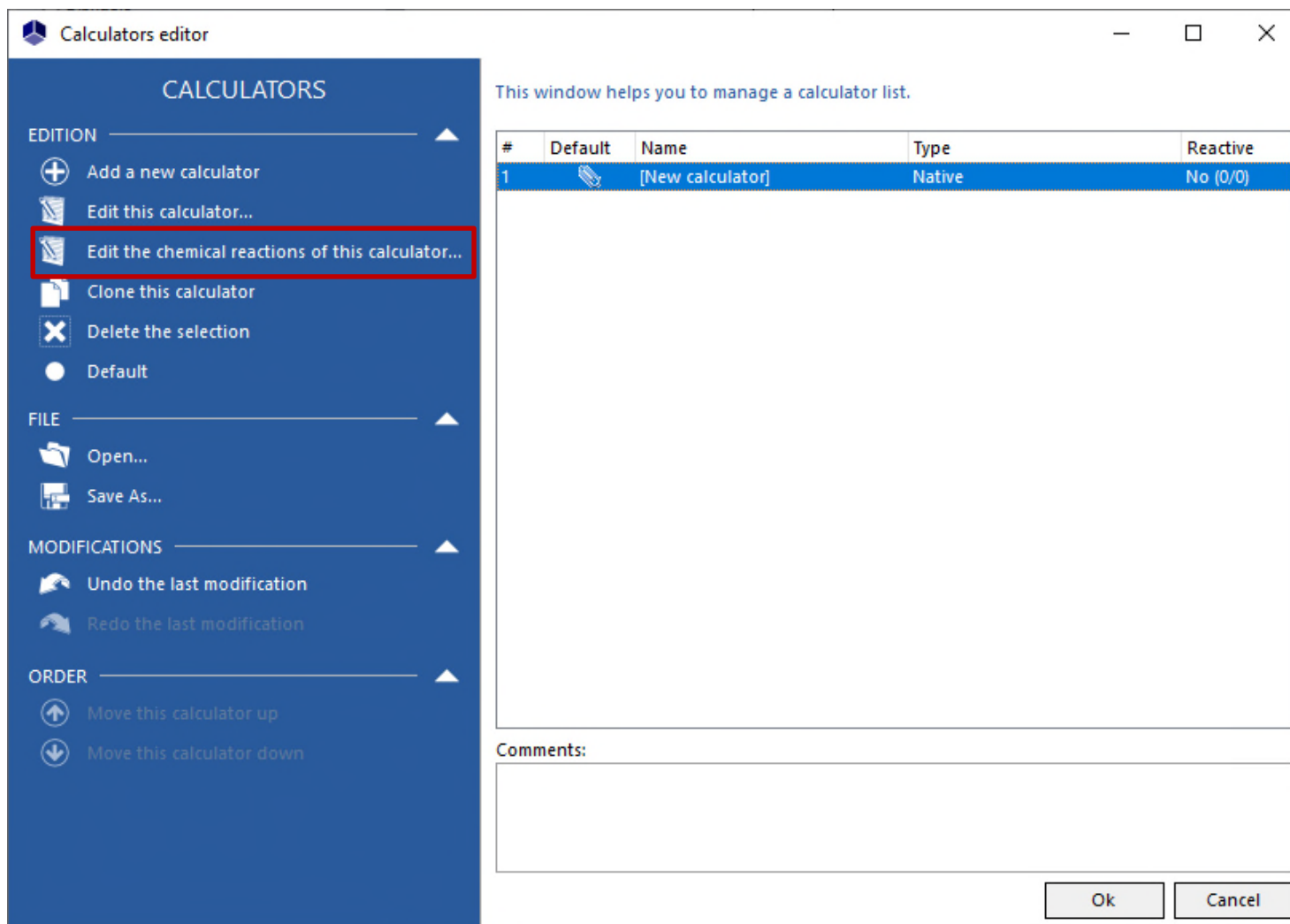
2 - Click on “Ok”
to confirm



For more information about thermodynamic model configuration, please refer to “*Getting started with Simulis Thermodynamics, use case 1*”

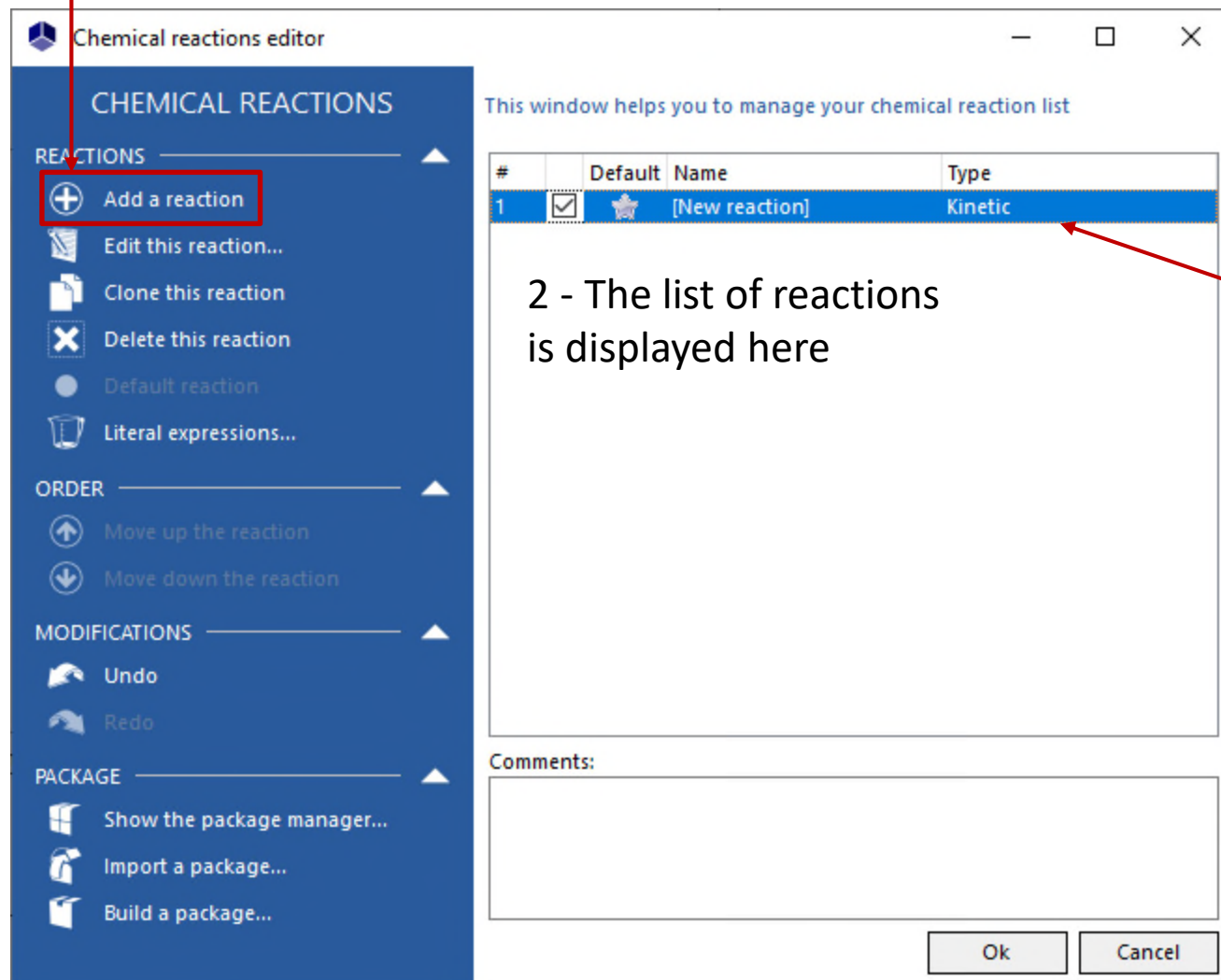
Step 2: Configuration of the bioreaction

Back on the “*Calculators editor*” window, click on “*Edit the chemical reactions of this calculator*”



Step 2: Configuration of the bioreaction

1 - Select "Add a reaction"



Step 2: Configuration of the bioreaction

1 - Check the “kinetic” box

The screenshot shows the 'Chemical reaction editor' window. On the left sidebar, under 'CHEMICAL REACTION', the 'Kinetic' option is selected and highlighted with a red box. A red arrow points from the text '1 - Check the “kinetic” box' to this box. In the main panel, the 'General' tab is selected and highlighted with a red box. A red arrow points from the text '2 - Select the “General” tab' to this box. Below the tabs, there are several input fields: 'Name' (containing 'Biomass growth'), 'Physical state' (a dropdown menu set to 'Liquid'), 'User ID', and 'Comments'. Three red arrows point from the text '3 - Specify the general information' to these three fields. At the bottom right, there are 'Ok' and 'Cancel' buttons.

Chemical reaction editor

CHEMICAL REACTION

REACTION ——— ▲

● Equilibrium

● **Kinetic**

● Instantaneous

TOOLS ——— ▲

PDF Export (Print)

MODIFICATIONS ——— ▲

Undo

Redo

HELP ——— ▲

Technical help...

This window helps you to define the context of your chemical reaction

ID: {D829F2AA-B82C-4B3C-88FE-5A5A425D5EDB}

General Reaction heat Kinetic

☒ Activated

Name

Biomass growth

Physical state

Liquid ▼

User ID

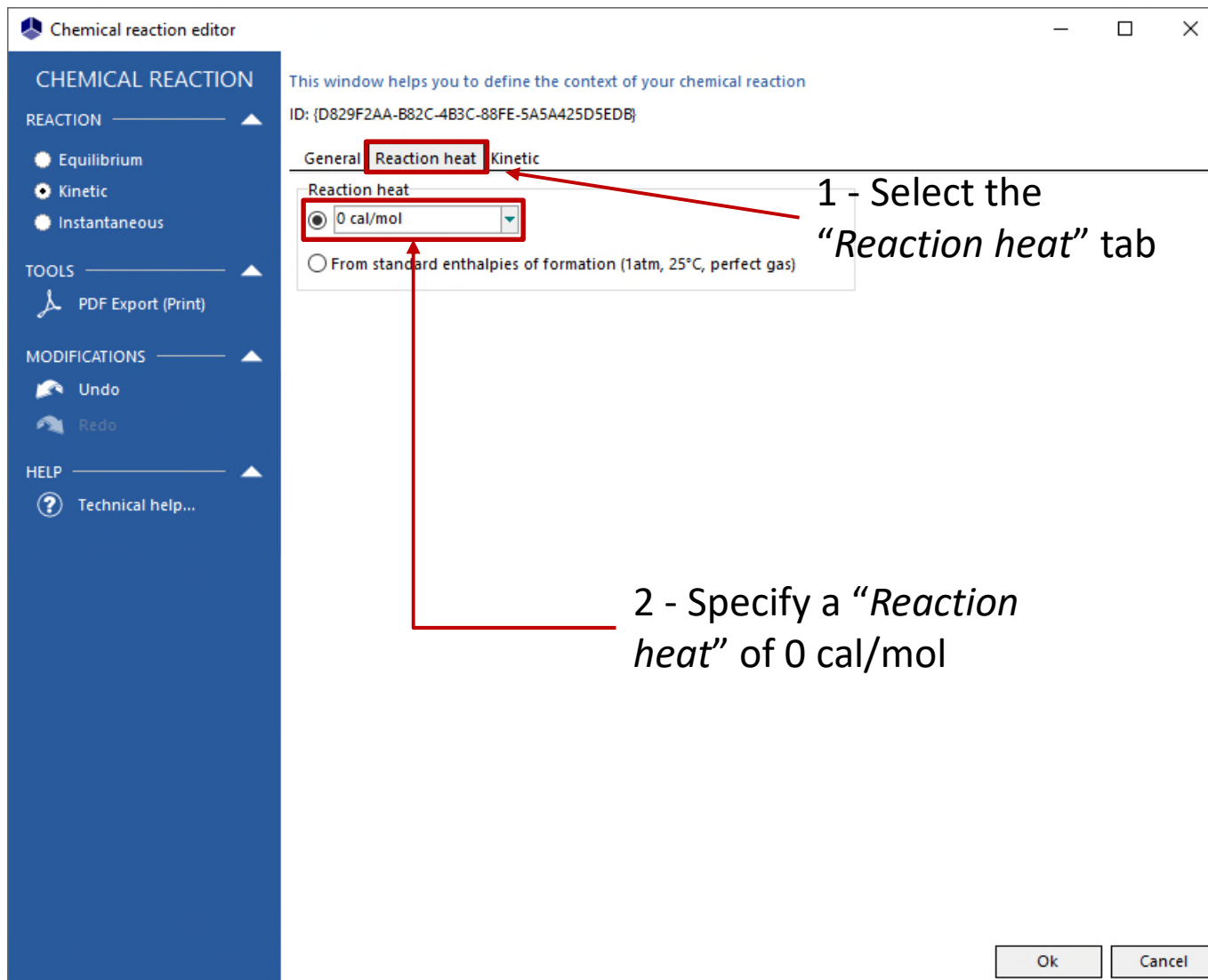
Comments

3 - Specify the general information

2 - Select the “General” tab

Ok Cancel

Step 2: Configuration of the bioreaction



Step 2: Configuration of the bioreaction

Access the **Advanced mode** to provide a custom kinetic model for the bioreaction

1 - Select the "Kinetic" tab

The screenshot shows the 'Chemical reaction editor' window. On the left is a blue sidebar with sections: 'CHEMICAL REACTION' (containing 'REACTION' with radio buttons for Equilibrium, Kinetic, and Instantaneous), 'TOOLS' (containing 'PDF Export (Print)'), 'MODIFICATIONS' (containing 'Undo' and 'Redo'), and 'HELP' (containing 'Technical help...'). The main area has a title bar and a subtitle 'This window helps you to define the context of your chemical reaction'. Below this is a tab bar with 'General', 'Reaction heat', and 'Kinetic'. The 'Kinetic' tab is selected and highlighted with a red box. Below the tabs, there are two fields: 'Rate model' with a dropdown menu showing 'User "interpreted"' (highlighted with a red box) and 'Activation energy' with a text box showing '0 cal/mol'. At the bottom right of the main area is a vertical stack of tabs: 'Equation', 'Code', 'Compounds', 'Constants', and 'Model'. The 'Model' tab is highlighted with a red box. At the very bottom are 'Ok' and 'Cancel' buttons.

2 - Select the "User interpreted" rate model (**Advanced mode**)

It is not necessary to configure these tabs when using the advanced mode

These tabs will enable to provide the **bioreaction stoichiometry** and the **global rate of bioreaction**

Step 2: Configuration of the bioreaction

Access the **Advanced mode** to provide a custom kinetic model for the bioreaction

Chemical reaction editor

CHIMICAL REACTION

REACTION ▲

- Equilibrium
- Kinetic**
- Instantaneous

TOOLS ▲

PDF Export (Print)

MODIFICATIONS ▲

Undo

Redo

HELP ▲

Technical help...

This window helps you to define the context of your chemical reaction

ID: {8D122076-5699-468B-B888-3C1FCEB47FFB}

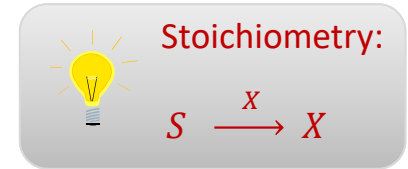
General | Reaction heat | **Kinetic**

Rate model: User "interpreted" | Activation energy: 0 cal/mol

Properties		Stoichiometry and orders		
Name	CAS Registry Number® or ID	Stoichiometry	Direct	Reverse
WATER	7732-18-5	0	0	0
SUBSTRATE	1111-11-1	-1	1	0
BIOMASS	2222-22-2	1	0	0

Equation | Code | **Compounds** | Constants | Model

Ok Cancel



2 - Indicate the bioreaction stoichiometry:

- "-1" for the substrate
- "1" for the biomass

1 - Select the "compounds" tab

Step 2: Configuration of the bioreaction

Access the **Advanced mode** to provide a custom kinetic model for the bioreaction

Chemical reaction editor

CHIMICAL REACTION

REACTION

- Equilibrium
- Kinetic**
- Instantaneous

TOOLS

- PDF Export (Print)

MODIFICATIONS

- Undo
- Redo

HELP

- Technical help...**

This window helps you to define the context of your chemical reaction

ID: {D829F2AA-B82C-4B3C-88FE-5A5A425D5EDB}

General | Reaction heat | **Kinetic**

Rate model: User "interpreted"

Activation energy: 0 cal/mol

Interpreted code ☒ Show the script errors

```

1 ' CHECK PROCEDURE
2
3 function CheckRate
4   CheckRate = True
5 end function
6
7 ' CALCULATION PROCEDURE
8 ' --- Data ---
9 ' T: Variant - Temperature (K).
10 ' P: Variant - Pressure (atm).
11 ' z: Variant - Molar fractions.
12 '
13 ' --- Results ---
14 ' Rate: Variant - rate in mol/l/s.
15 ' dRatedT: Variant - rate derivative with the respect
16 ' dRatedP: Variant - rate derivative with the respect
  
```

PARAMETERS

- User parameters...

LIBRARY

- Load...
- Publish...

EDITION

- Copy
- Paste

FILES

TEST

Test

Equation | **Code** | Constants | Model

Ok Cancel



Bioreaction rate :

$$r_G = \mu_{max} \left(\frac{C_S}{K_S + C_S} \right) C_X$$

2 - Select "Technical help" to get information about the library of kinetic models dedicated to bioreactions

1 - Select the "Code" tab

Step 2: Configuration of the bioreaction

Access the **Advanced mode** to provide a custom kinetic model for the bioreaction



Technical help...

It is necessary to look at the “*Technical help*” to get information about the suitable kinetic models for the bioreaction along with the parameters to provide

Selection of the suitable model



Bioreaction rate :

$$r_G = \mu_{max} \left(\frac{C_S}{K_S + C_S} \right) C_X$$

Selection of the model for the global rate of bioreaction



(Option 1): $r_G = \left(\alpha \cdot \mu_{max} \prod_{i=1}^{NLS} r(C_{Si}) + \beta \right) \cdot C_X$

Selection of the elementary kinetic model
 $r(C_{Si})$

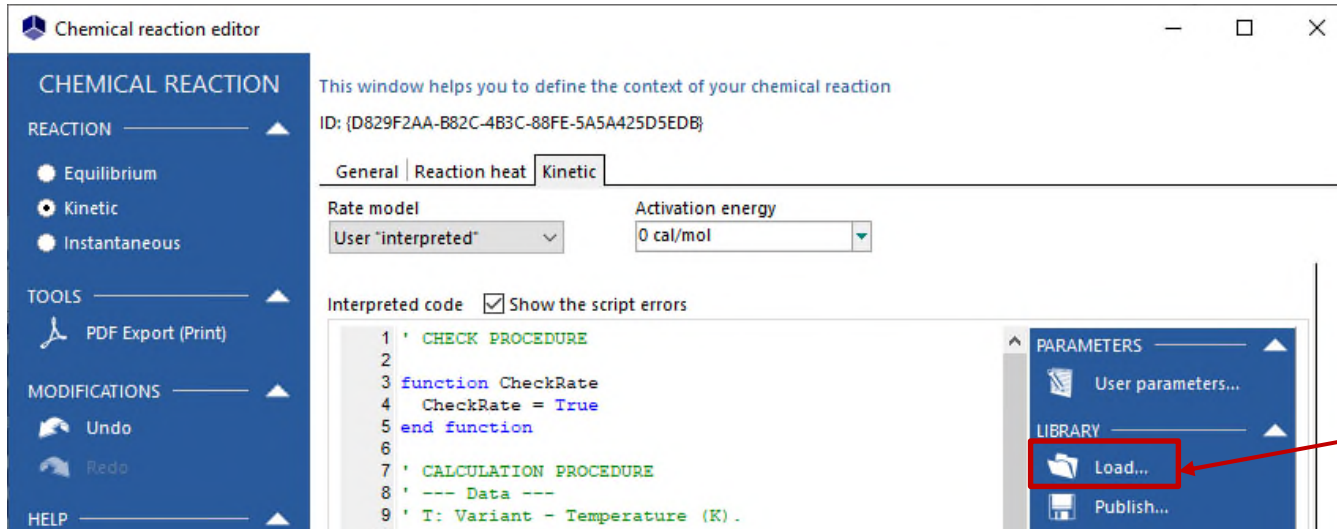
1 elementary term



Model index	Description	Equation of the term $r(C_{Si})$
1	Monod	$\frac{C_S}{K_S + C_S}$

Step 2: Configuration of the bioreaction

Access the **Advanced mode** to provide a custom kinetic model for the bioreaction



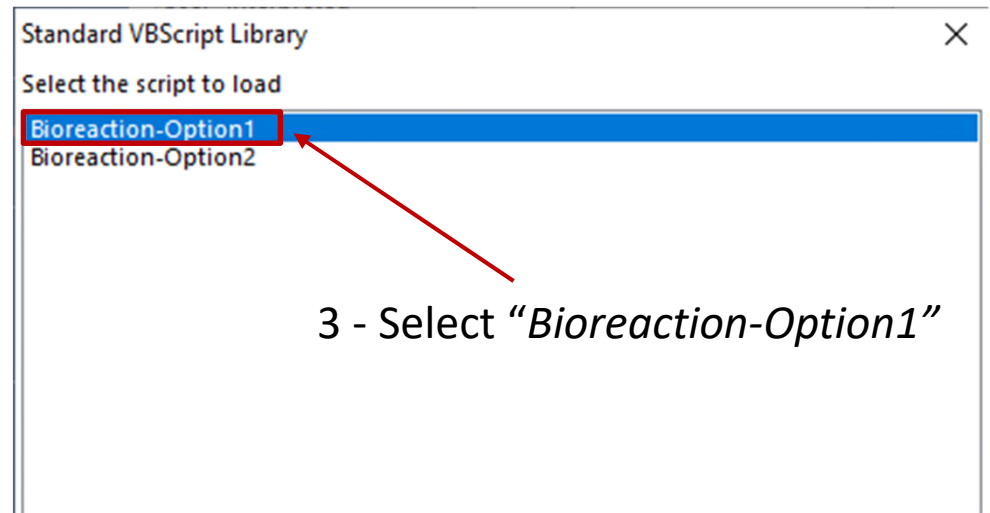
Bioreaction rate :

$$r_G = \mu_{max} \left(\frac{C_S}{K_S + C_S} \right) C_X$$

1 - Click on
"Load"



2 - The library of available scripts
is displayed here



3 - Select "Bioreaction-Option1"

Step 2: Configuration of the bioreaction

Access the **Advanced mode** to provide a custom kinetic model for the bioreaction

Chemical reaction editor

CHIMICAL REACTION

REACTION

- Equilibrium
- Kinetic**
- Instantaneous

TOOLS

PDF Export (Print)

MODIFICATIONS

Undo

Redo

HELP

Technical help...

This window helps you to define the context of your chemical reaction

ID: {D829F2AA-B82C-4B3C-88FE-5A5A425D5EDB}

General | Reaction heat | **Kinetic**

Rate model: User "interpreted"

Activation energy: 0 cal/mol

Interpreted code ☒ Show the script errors

```

1 ' -----
2 '
3 ' ----- USER GUIDE -----
4 '
5 ' 1) Click on "User parameters"
6 '
7 ' 2) Specify the model global parameters (REQUIRED):
8 '   - Number of elementary kinetic terms (>1)
9 '   - Alpha, the growth-related coefficient (-)
10 '  - Beta, the non-growth-related coefficient (s-1)
11 '  - Maximum growth rate (s-1)
12 '  - CAS number of "X", the Biomass compound (WITH NO)
13 '  - CAS number of "Reference", the reference compound
14 '
15 ' 3) Specify the elementary kinetic terms parameters (1)
16 '   - Index of the elementary kinetic model
  
```

PARAMETERS

User parameters...

LIBRARY

Load...

Publish...

EDITION

Copy

Paste

FILES

TEST

Test

Equation | **Code** | Constants | Model

Ok Cancel



Bioreaction rate :

$$r_G = \mu_{max} \left(\frac{C_S}{K_S + C_S} \right) C_X$$

2 - Click on
"User parameters"

1 - The script is loaded here

Step 2: Configuration of the bioreaction

Access the **Advanced mode** to provide a custom kinetic model for the bioreaction

1 - Specify the model input parameters:

- 1 elementary kinetic term, corresponding to the model #1 (Monod)
- $\alpha = 1$
- $\beta = 0$
- $\mu_{max} = 4.10^{-5} \text{ s}^{-1}$
- $K_S = 2.8 \text{ g/L}$
- CAS number^(*) of the biomass (X) and the compound of reference: 2222222
- CAS number^(*) of the substrate (S): 1111111



Bioreaction rate :

$$r_G = \mu_{max} \left(\frac{C_S}{K_S + C_S} \right) C_X$$

User parameters

PARAMETERS

- Add
- Delete
- Move up
- Move down
- Copy
- Paste

HELP

- Technical help...

List of parameters

#	Description	Value
1	Number of terms	1
2	Alpha (-)	1
3	Beta (s-1)	0
4	Max growth rate (s-1)	4E-005
5	CAS of X	2222222
6	CAS of Reference	2222222
7	Term #1: Model index (OPTIONAL)	1
8	Term #1: CAS of S (OPTIONAL)	1111111
9	Term #1: CAS of I (OPTIONAL)	0
10	Term #1: Ks (g/L) (OPTIONAL)	2.8
11	Term #1: Ki (g/L) (OPTIONAL)	0
12	Term #1: N (OPTIONAL)	0
13	Term #1: Tmin (K) (OPTIONAL)	1
14	Term #1: Tmax (K) (OPTIONAL)	1000
15	Term #2: Model index (OPTIONAL)	0
16	Term #2: CAS of S (OPTIONAL)	0

Ok Cancel

2 - Click on “Ok” to confirm and go back to the main flowsheet

(*) CAS Registry Numbers® are the intellectual property of the American Chemical Society; and are used by ProSim SA with the express permission of CAS. CAS Registry Numbers® have not been verified by CAS and may be inaccurate

Step 3: Specification the equipment and the operating scenario

1 - Scenario:

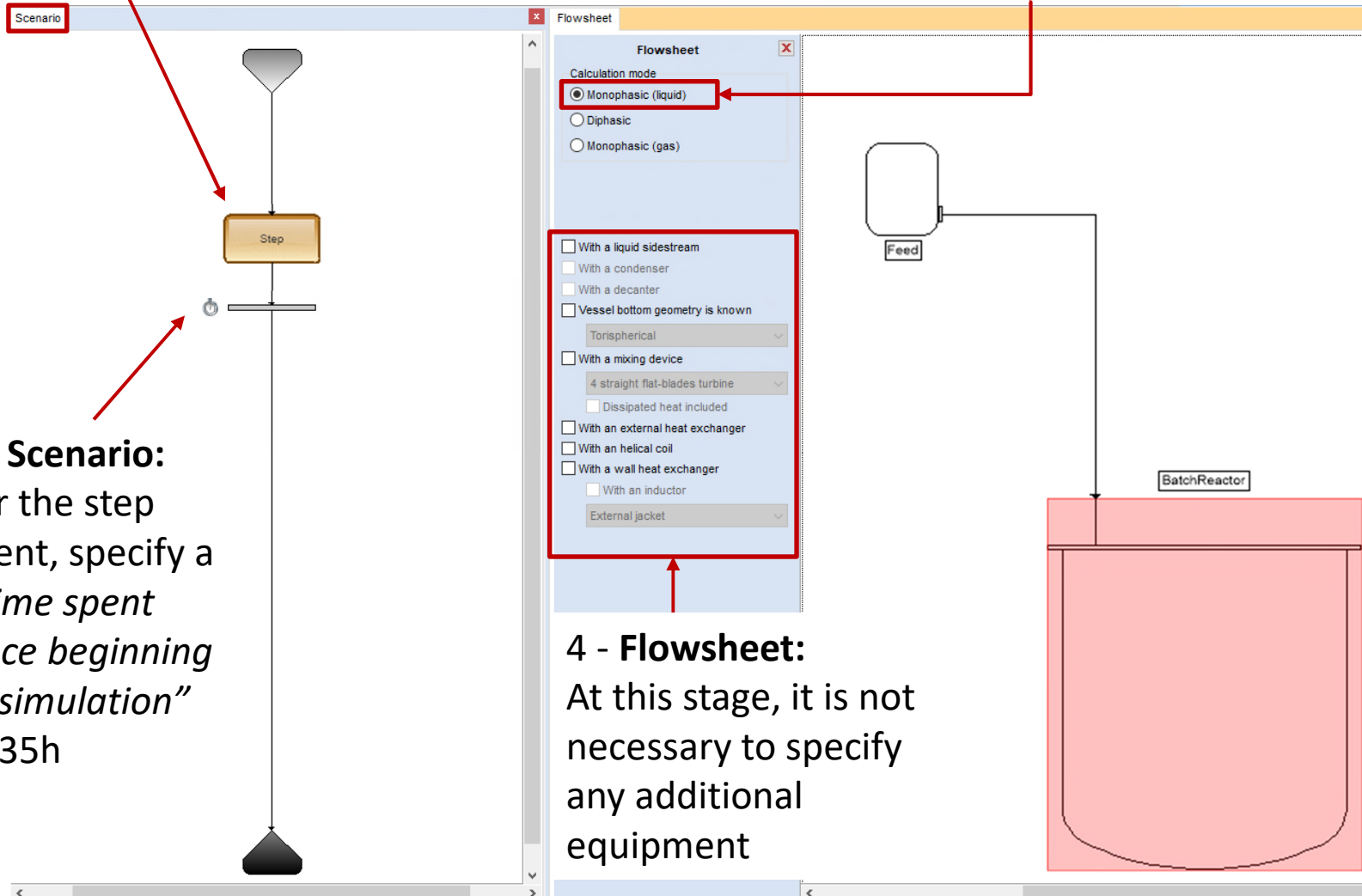
Add 1 “Constant heat duty” step

3 - Flowsheet:

Check the “Monophasic (liquid)” calculation mode

2 - Scenario:

For the step event, specify a “Time spent since beginning of simulation” of 35h

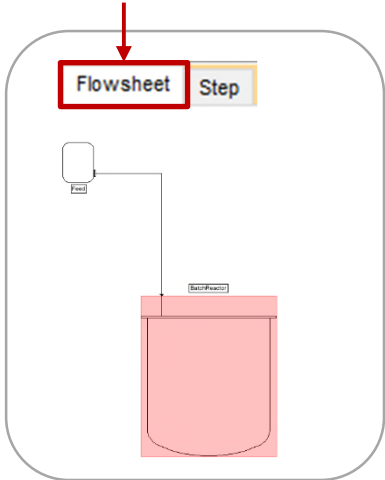


4 - Flowsheet:

At this stage, it is not necessary to specify any additional equipment

Step 3: Specification the equipment and the operating scenario

1 - Select the “*Flowsheet*” tab and double click on the reactor to specify the initial conditions



The 'Reactor' configuration window is shown with the 'BatchReactor' name. The 'Parameters' tab is active, displaying various settings for the reactor. A schematic diagram of the reactor is shown on the right, with an 'Initial load' label at the bottom of the vessel. Red boxes highlight the 'Fixed temperature' (298.15 K) and 'Fixed pressure' (101325 Pa) settings. A red arrow points from the 'Initial load' label in the schematic to the 'Initial load' specification window.

Reactor Name: BatchReactor

Parameters | Notes | Advanced parameters | Validation

Feeds

Reactor temperature [TR]
Fixed temperature: 298.15 K
Alarms [TR]
Minimum: 273.15 K
Maximum: 1000 K

Reactor pressure [PR]
Fixed pressure: 101325 Pa
Alarms [VR]
Minimum: 1E-5 m3
Maximum: 1 m3

Initial load

Liquid productions

Restore Technology OK Cancel

The 'Initial load' specification window is shown with the 'Initial load specification' tab. The 'Fractions' and 'Mass' tabs are selected. A table lists the compounds and their fractions. The 'Total volume load' is set to 1 l.

Initial load specification

Fractions Mass

Compound	Fraction
WATER	0.9625
SUBSTRATE	0.035
BIOMASS	0.0025

Total volume load: 1 l

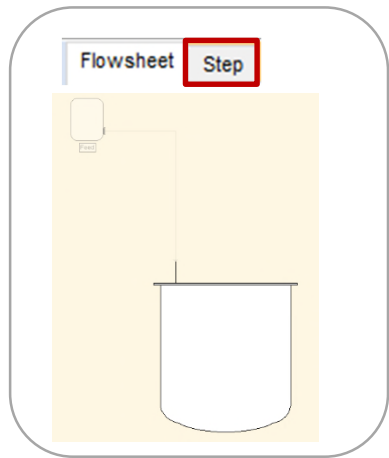
Restore OK Cancel

2 - Specify the initial conditions:

- $T = 298.15 \text{ K}$
- $P = 101325 \text{ Pa}$
- Initial mass composition: 96.25% Water, 3.5% Substrate, 0.25% Biomass
- Initial load: 1L

Step 3: Specification the equipment and the operating scenario

1 - Double click on the “Step” in the operating scenario or select the “Step” tab and double click on the reactor to specify the operating conditions



2 - Specify the operating conditions:

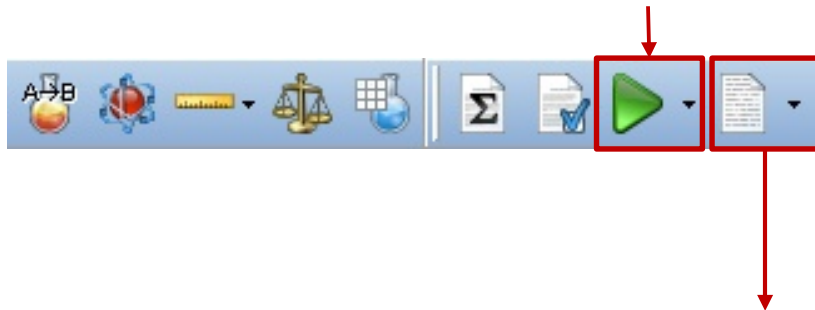
- No feed
- Heat duty = 0 J/s
- Pressure = 101325 Pa



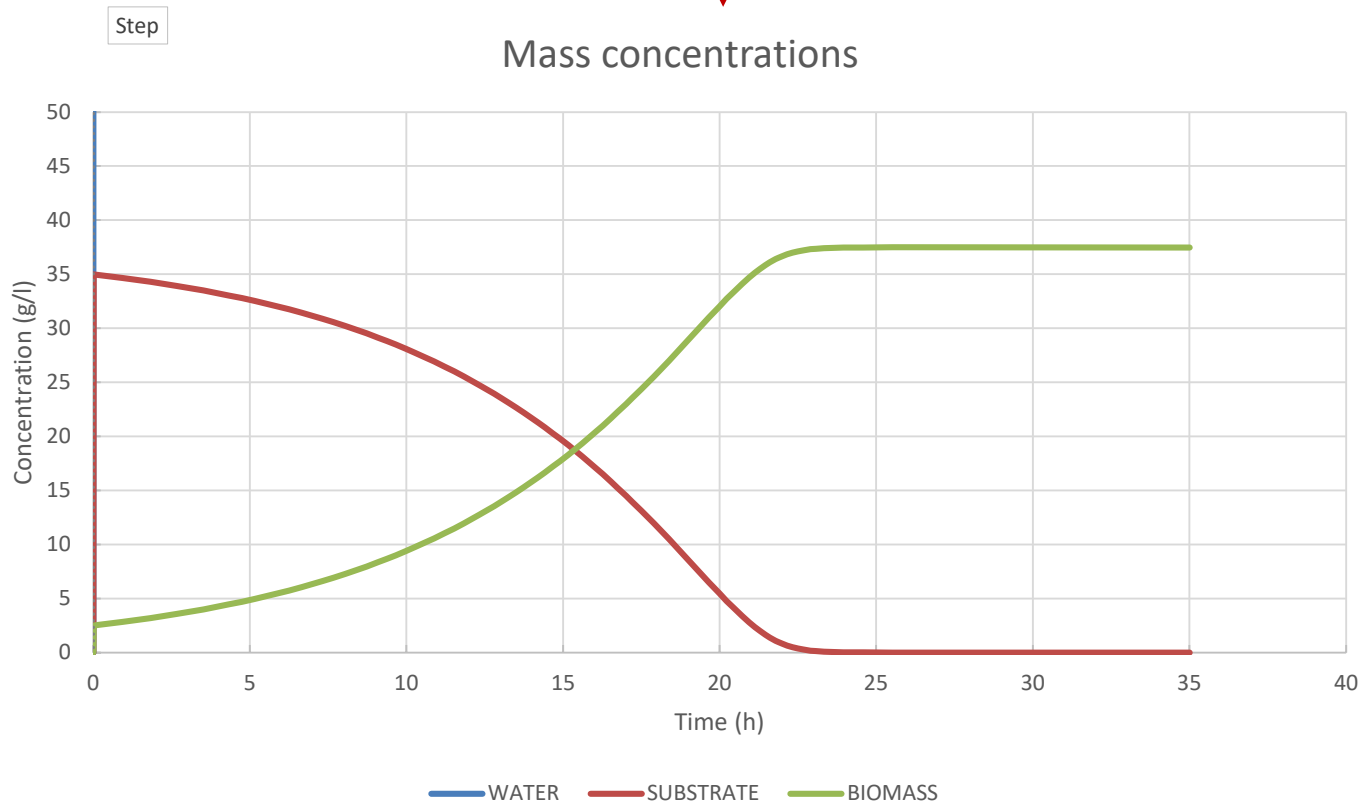
For more information about these steps, please refer to “*Getting started with BatchReactor, use case 1*”

Results

1 - Click on the green arrow to run the simulation



2 - Once the simulation is done, click on the “Results” icon to access the simulation report





ProSim SA

51, rue Ampère
Immeuble Stratège A
F-31670 Labège
France

Phone: +33 (0) 5 62 88 24 30



ProSim

Software & Services In Process Simulation

We guide You to efficiency

www.prosim.net

info@prosim.net



ProSim, Inc.

325 Chestnut Street, Suite 800
Philadelphia, PA 19106
U.S.A.

Phone: +1 215 600 3759