

Getting started with Simulis Reactions®

Use Case 2: Modeling of bioreactions using the
advanced mode

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Introduction

This document describes a method to model bioreactions using the advanced mode of Simulis Reactions.

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 model 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 model

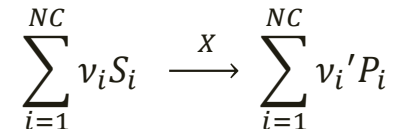
Before reading this document, it is recommended to consult “*Getting Started with Simulis Reactions - Use Case 1*”

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)
ν_i, ν_i'	stoichiometric coefficients (positive value for products and negative value for substrates)

The global bioreaction rate can be defined as follows:

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

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:

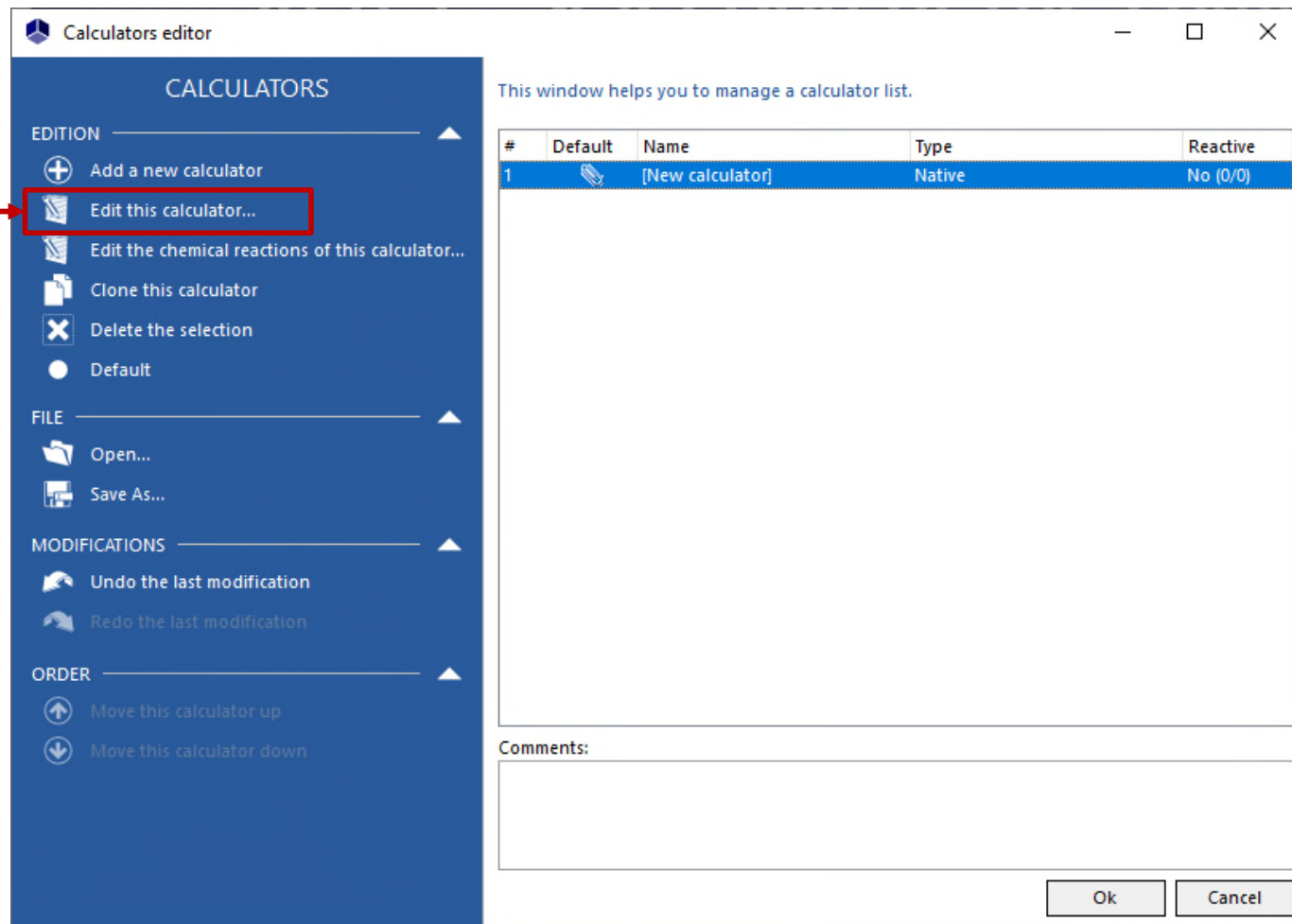
Model parameters	Definition	Value
μ_{max}	Maximum growth rate	$4 \cdot 10^{-5} \text{ s}^{-1}$
K_S	Saturation constant	2.8 g/L
C_S, C_X	Concentration of substrate (S) and biomass (X)	Process variables



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

From the “*Calculators editor*” window, select “*Edit this calculator*”



Step 1: Selection of the compounds

This application example requires to import the following compounds, with the modifications described hereafter:

 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 active, displaying a table with the following data:

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

The interface also includes a left sidebar with 'CALCULATOR' options (FILE, PACKAGE, SERVICES, MODIFICATIONS, CONFIGURATION) and a right sidebar with 'COMPOUNDS' options (FILE, PACKAGE, EDIT, SERVICES, ORDER). The 'COMPOUNDS' sidebar includes actions like 'Import compounds...', 'Edit this compound...', 'Create a new compound', 'Remove all the compounds', 'Clone this compound', 'Update the compounds', 'Delete the selection', 'Create a pseudo-compound...', 'Temperature dependent properties...', 'Editor array', 'Compare with the original', and 'Compare the compounds'. At the bottom, there are 'Ok' and 'Cancel' buttons.



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:

Thermodynamic calculator editor

This window helps you to define the context of your thermodynamic calculator

COMPOUNDS **MODEL** PARAMETERS

Name:

Category:

Profile:

Approach type:

Equation of state:

Alpha function:

Mixing rules:

Activity coefficient model:

Pure liquid fugacity standard state:

Liquid molar volume:

Transport properties:

Enthalpy calculation:

User-defined thermodynamic model:

Model index:

Comments:

THERMODYNAMIC MODEL

DOCUMENTATION

- Thermodynamic assistant
- Thermodynamic help

ADDITIONAL PARAMETERS

MODEL INFORMATION

WATER-HYDROCARBON

PURE WATER

Ok Cancel

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 model

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

Calculators editor

CalcULATORS

EDITION

- Add a new calculator
- Edit this calculator...
- Edit the chemical reactions of this calculator...**
- Clone this calculator
- Delete the selection
- Default

FILE

- Open...
- Save As...

MODIFICATIONS

- Undo the last modification
- Redo the last modification

ORDER

- Move this calculator up
- Move this calculator down

This window helps you to manage a calculator list.

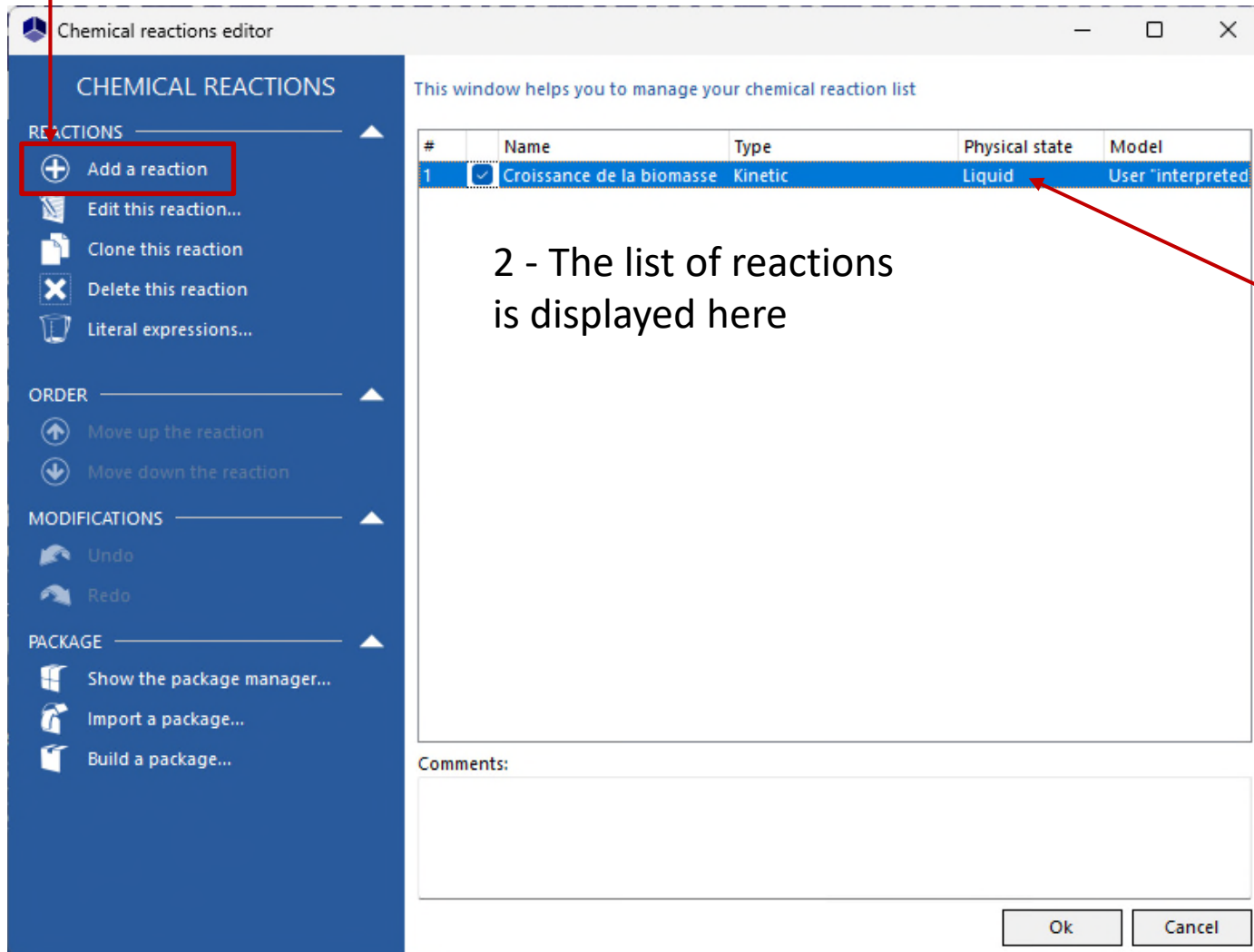
#	Default	Name	Type	Reactive
1		[New calculator]	Native	No (0/0)

Comments:

Ok Cancel

Step 2: Configuration of the bioreaction model

1 - Select "Add a reaction"



The screenshot shows the 'Chemical reactions editor' window. On the left, a blue sidebar contains a 'REACTIIONS' section with a red box around the 'Add a reaction' button. Below it are options for editing, cloning, deleting, and literal expressions. Further down are 'ORDER' and 'MODIFICATIONS' sections. At the bottom is a 'PACKAGE' section. The main area displays a table of reactions with the following data:

#	Name	Type	Physical state	Model
1	Croissance de la biomasse	Kinetic	Liquid	User interpreted

Below the table is a 'Comments:' text area and 'Ok' and 'Cancel' buttons at the bottom right.

2 - The list of reactions is displayed here

3 - Double click on the new reaction to configure it

Step 2: Configuration of the bioreaction model

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: {E2445F8E-EFD6-40A9-98BD-FA7A3277942B}

General VBScript Kinetic parameters Equilibrium constant Interface Notes

Name Croissance de la biomasse

User ID

Physical state Liquid

Reaction heat Supplied by the user 0 cal/mol

Concentration model Molar concentration

Rate model User "interpreted"

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

Ok Cancel

1 - Select the "General" tab

2 - Indicate a name (optional)

3 - Indicate the reaction phase

Step 2: Configuration of the bioreaction model

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: {E2445F8E-EFD6-40A9-98BD-FA7A3277942B}

General VBScript Kinetic parameters Equilibrium constant Interface Notes

Name Croissance de la biomasse Activated

User ID

Physical state Liquid

Reaction heat Supplied by the user 0 cal/mol

Concentration model Molar concentration

Rate model User "interpreted"

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

Ok Cancel

4 - Specify a "Reaction heat" of 0 cal/mol

Step 2: Configuration of the bioreaction model

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



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

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: {E2445F8E-EFD6-40A9-98BD-FA7A3277942B}

General **VBScript** **Kinetic parameters** Equilibrium constant Interface Notes

Name Croissance de la biomasse Activated

User ID

Physical state Liquid

Reaction heat Supplied by the user 0 cal/mol

Concentration model Molar concentration

Rate model User "interpreted"

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

Ok Cancel

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

Step 2: Configuration of the bioreaction model

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

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: {E2445F8E-EFD6-40A9-98BD-FA7A3277942B}

General VBScript Kinetic parameters Equilibrium constant Interface Notes

Name Croissance de la biomasse Activated

User ID

Physical state Liquid

Reaction heat Supplied by the user 0 cal/mol

Concentration model Molar concentration

Rate model User "interpreted"

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

Ok Cancel



Stoichiometry:



2 - Indicate the bioreaction stoichiometry:

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

Step 2: Configuration of the bioreaction model

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

1 - Select the "VBScript" tab

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

Name	Molar fraction
WATER	0,00000
SUBSTRAT	0,00000
BIOMASSE	0,00000

Step 2: Configuration of the bioreaction model

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 model

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

The screenshot shows the 'Chemical reaction editor' window. On the left, the 'CHEMICAL REACTION' panel has 'Kinetic' selected. The 'VBScript' tab is active, and the 'Load...' button in the 'LIBRARY' section is highlighted with a red box. The main text area contains a user guide with instructions: '1) Click on "User parameters"' and '2) Specify the model global parameters (REQUIRED): - Number of elementary kinetic terms (>1) - Alpha, the growth-related coefficient (-)'. A red arrow points from the 'Load...' button to the 'Standard VBScript Library' dialog box shown below.

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

The 'Standard VBScript Library' dialog box is shown, titled 'Select the script to load'. It contains a list of scripts: 'Bioreaction-Option1' and 'Bioreaction-Option2'. 'Bioreaction-Option1' is highlighted with a blue background and a red box. A red arrow points from the text '3 - Select "Bioreaction-Option1"' to this highlighted option.

3 - Select "Bioreaction-Option1"

Step 2: Configuration of the bioreaction model

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

Chemical reaction editor

REACTOR 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: {E2445F8E-EFD6-40A9-98BD-FA7A3277942B}

General **VBScript** Kinetic parameters Equilibrium constant Interface Notes

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
13 '   - CAS number of "Reference", the reference comp
...

```

PARAMETERS

- User parameters...**

LIBRARY

- Load...
- Publish...

EDITION

- Copy
- Paste

TEST

- Test

T= 298,15 K P= 101325 Pa

Name	Molar fraction
WATER	0,00000
SUBSTRAT	0,00000
BIOMASSE	0,00000

Ok Cancel



Bioreaction rate:

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

5 - Click on
"User parameters"

4 - The script is loaded here

Step 2: Configuration of the bioreaction model

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 index #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:

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

2 - Click on “Ok” to confirm... The bioreaction is now correctly configured!

User parameters

PARAMETERS

- + Add
- X 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 compound 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

(*) 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



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