PLA 3.0

BIOLOGICAL ASSAY SIMULATION PACKAGE
GETTING STARTED GUIDE

Technical Preview

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STEGMANN SYSTEMS

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1 INTRODUCTION

Welcome to the Getting Started Guide of the Biological Assay Simulation Package.

This guide gives a general overview of this add-on and describes the basic tasks. It is intended for users who want to learn how to work with this add-on.

Note:
It is assumed that users are familiar with the general handling of the PLA 3.0 user interface.

1.1 About the Biological Assay Simulation Package add-on

The Biological Assay Simulation Package add-on allows you to create simulations of Quantitative response assays (QRAs). It provides the following document types:

- Use the **QRA simulator** document type to simulate and generate Quantitative response assays. You can generate new assays from scratch or based on assays in your database.

- Use the **QRA collector** document type if you want to aggregate multiple assays in preparation for the simulation.

The process consists of the following steps:

1. Setting up the simulation logic

2. Simulating the assays

3. Generating the assay documents

1.2 Installation

The Biological Assay Simulation Package is delivered as an add-on to the PLA 3.0.6 framework and does not require a separate installation. To make the functionality of the Biological Assay Simulation Package available for use, you have to activate the add-on in your database.

Procedure

To activate the add-on:

1. Log in to PLA 3.0.6.

2. Open the **System** menu, and click ❖ **Add-on management**.
   Result: The **Add-on** tab opens.

3. By default, only the add-on names are displayed on the **Add-ons** tab. The available versions are collapsed. Expand the add-on, right-click the version you want to activate, and click **Activate**.
   Result: The add-on is added to the repository (🗄) and activated in the database (🗄).

2 SETTING UP THE SIMULATION LOGIC

2.1 Create a QRA simulator document

To create a QRA simulator document:

1. In the **Navigator**, right-click the folder in which you want to create the document, and select New.

2. In the **Create a new document** dialog, on the **Available document types** tab, navigate to Biological Assay Simulation Package (Draft) > QRA Simulator (draft), and select the 'New QRA simulator' document type.

3. To confirm your selection, click **Create**.
   Result: The **Content** editor opens, displaying your new document.

4. Enter a document name and save the document.

   Tip: We recommend you enter a meaningful document name, as this makes it easier for you to search for the document later.

2.2 Read source documents

If you want to use existing assays for simulation, you can read the required settings from these source documents, thus transferring them to the QRA simulation document.

   Note: Reading settings from source documents is the standard use case. As an advanced user, you can also set up the QRA simulator document manually, without using a source document.

You can use the following types of source documents:

- Use a template, if you only need information about the assay setup, for example, the number of samples, dilution sequence, and the number of replicates.

- Use a Quantitative response assay document, if you also need information about the observations and the model fit of the assay.

- Use a QRA collector document, if you want to replicate the behavior of a group of assays.

Procedure

To read settings from your source documents, you use the **Content** editor of your QRA simulator document.

1. Under **Input settings**, select the type of document from which you want to read the settings. In the following example, 'Online Example - 3PL (Document-93) is used as the source document.

Element		Value
☐ **QRA Simulator**	○	*QRA simulator document*
Name	T	QRA simulator document
☐ **Input settings**	○	*Source: Online Example - 3PL (Document-93)*
Logarithm base	≡	Binary logarithm (base 2)
Response transformation	≡	No response transformation
Source document ∨	✎	*Online Example - 3PL (Document-93)*
☐ **Out** Source document	○	*Target folder: not selected (current folder), Number of assays to simulate: 1*
Sim Source template		
Source collector	⊞	*Click Here to Open the Observation Data Editor*

Figure 1: Selection of a source for the QRA collector document

> ⓘ **Tip:** If you want to use a QRA collector document, select **Source collector**, and click ⭐ to fast create the document. Make sure that all assays referenced in the QRA collector document use the same assays setup and show similar responses and fit parameters.

☐ **Input settings**	○	*Source: No source data used for reading*
Logarithm base	≡	Binary logarithm (base 2)
Response transformation	≡	No response transformation
Source collector ▾	✎	... ⭐

Figure 2: Fast creation of a QRA collection document

2. To transfer the settings from the source document to the QRA simulator document, on the action bar, click ➡ **Read**.

2.3 Configure the observations

You can change the settings read from your source documents if you require. To do so, you use the **Observations** editor.

Usually, each row in this editor corresponds to the measurements of a single sample and dose combination. If multiple rows are created for the same sample and dose pair, the generated observations are merged. For each row, observations are generated by drawing from a normal distribution. You can configure the mean, variance, and sample size of the drawn sample.

The columns in the **Observations** editor are:

- **Assay element:** Contains the name of the assay element. Upon generation, all rows with the same assay element are be assigned to a single sample.

- **Dose:** Each measurement must be associated with a dose. The dose is used for calculating the mean of the normal distribution. The dose is also used to assign measurements to a specific dose step in the generated Quantitative response assays. If multiple rows with the same dose are created for a single assay element, the generated observations are assigned to the same dose step.
  You can use this setting, for example, to force the resulting observations to contain an outlier at a specific dose.

- **Replicate:** Number of observations that are created for this row.

- **Mean:** Mean of the observations for this sample and dose pair. Can be used as a mean for the normal distribution generating the new observations.

- **Variance:** Variance of the observations for this sample and dose pair, used as the variance for the normal distribution generating the new observations. If left empty, zero is used as a variance, that is, all replicates are equal to the used mean.

- **Parameters:** All other columns contain parameters and their variance. The parameters, together with the dose, can be used to calculate the mean for the normal distribution used for generating new observations. If a parameter variance is given, new curve parameters are determined for each new assay using a normal distribution. All rows of an assay element use the same parameters.

  📝 **Note:** Depending on the model, some parameter columns must remain empty. For example, for an assay using a 4-parameter logistic model, only the columns **A**, **B**, **C**, **D**, and their variances are needed. All other columns should remain empty.

  📝 **Note:** If both parameters and a mean are given for a specific observation row, the setting **Simulation priority** determines how the observations are generated.

2.4 Configure the content

Use the **Content** editor to configure the following global settings for the simulation:

Input settings

- **Logarithm base:** Used for transforming the values from the **Dose** column if a curve is used to determine the mean.

- **Response transformation:** If the assay/template used with the simulator has a response transformation, for example, a logarithmic transformation of the response data, the inverse of this transformation is applied to the simulated data before generating documents.

Output settings

- **Simulation priority:** If both a curve and a mean are defined for an observation row, this setting controls which of these settings is used to determine the mean used for the simulation.

- **Center data:** If this setting is active (set to yes), generated observations for each row are shifted so that the mean of the created observations is identical to the target mean for this row.

- **Force variance homogeneity:** If this setting is active (set to yes), simulation of the observations does not use the variance defined in each observation row but uses a (weighted) average of all entries in the variance column instead.

  Note: Even if the variance of your observations is homogenous, estimated variances from historic assays can show significant differences due to sampling bias. Use this setting to remove this bias. If the variance of your observations is typically non-homogenous, activating this setting biases the created assays by flattening out the variance profile.

- **Number of simulated assays:** Determines the number of assay replicates to be simulated.

3 SIMULATING THE ASSAYS

After configuring the observations and the content of your QRA simulation document, you can create the simulated assays: On the action bar, click ➡ **Process**.

Response values are drawn from a normal distribution. Mean, variance, and the number of replicates are determined by the configuration of the observations and the content of the document. If the used mean should be calculated from a curve, the corresponding observation columns need to be filled and all other parameter columns need to be empty.

The corresponding columns are:

- Linear model: Slope and Intercept
- 4PL-model: A, B, C, and D
- 5PL-model: A, B, C, D, and G

If parameter variances are defined, new model parameters are determined for each assay replicate using a normal distribution. Parameters need to be identical for all rows belonging to a single assay element.

📝 **Note:** If the parameter columns and the **Mean** column contain data, the setting **Simulation priority** controls, which method is used to determine the target mean for each replicate.

After performing the **Process** action, you can inspect the generated observations using the dashboard and/or the report.

Checklist | **Results** | Info | Activity Stream

TECHNOLOGY PREVIEW 03/2022 – This data was generated with the upcoming Biological Assay Simulation Package for PLA 3.0.6 (or higher). The package has not been released and has not been finally verified for production use. Contact Stegmann Systems (support@bioassay.de or https://support.bioassay.de) to report issues or suggest additional features.

RESULTS

Element: std

Dose	0.	-1.00000	-2.00000	-3.00000	-4.00000	-5.00000	-6.00000	-7.00000	-8.00000	-9.00000	-10.00000	-11.0
Step	1	2	3	4	5	6	7	8	9	10	11	
Response	0.73545	0.72638	0.69430	0.58185	0.50994	0.34895	0.22962	0.10738	0.10840	0.12484	0.12048	0.1
	0.75741	0.73716	0.71579	0.63093	0.50713	0.34745	0.22872	0.14313	0.13421	0.11898	0.14578	0.0
	0.74976	0.76271	0.66634	0.66176	0.51943	0.37492	0.22935	0.13292	0.12483	0.12216	0.12781	0.1

Element: tst1

Dose	0.	-1.00000	-2.00000	-3.00000	-4.00000	-5.00000	-6.00000	-7.00000	-8.00000	-9.00000	-10.00000	-11.0
Step	1	2	3	4	5	6	7	8	9	10	11	
Response	0.74724	0.70464	0.59929	0.48320	0.34751	0.22351	0.13375	0.12943	0.12648	0.11679	0.11734	0.1
	0.70156	0.71963	0.59865	0.66579	0.35483	0.22716	0.13466	0.11967	0.12311	0.13276	0.12086	0.1
	0.71519	0.70081	0.65522	0.57915	0.33868	0.21371	0.14783	0.13566	0.09702	0.12940	0.11170	0.1

Dashboard · Content · Observations · Attachments · Audit Trail · Calculate (Draft) · Read (Draft) · Generate (Draft) · Report... · Signatures...

New · Defined · Calculated

4 GENERATING THE ASSAY DOCUMENTS

Procedure

To create Quantitative response assay documents from the simulated data, complete the following steps:

1. Configure the following output settings in the **Content** editor of your QRA simulation document:

   ◆ **Target folder:** Select where the assays should be located in your folder structure. If you do not specify a target folder, the assays are stored in the same folder as the QRA simulator document.

   ◆ **Template:** Reference the template you want to use for generating the new assays.

Element		Value
⊟ **QRA Simulator**	∘	*QRA simulator document*
Name	T	QRA simulator document
⊞ **Input settings**	∘	*Source: Online Example - 3PL (Document-93)*
⊟ **Output settings**	∘	*Target folder: Biological assays simulation (Folder-81), Number of assays to simulate: 1*
Target folder	🖉	*Biological assays simulation (Folder-81)*
Simulation priority	☰	Prefer mean
Center data	☰	no
Force variance homogeneity	☰	no
Number of simulated assays	ℤ	1
Template	🖉	*Daily Assay for Product X (Basic Bioassay Protocol Example Template) (Template-1)*
Simulation data	▦	*Click Here to Open the Observation Data Editor*

2. To create Quantitative response assay documents from the simulated data, on the action bar, click ➡ **Generate**.