

# Development of a population PKPD model using MONOLIX - Case Study III

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# 1 Introduction

The aim of this tutorial is to show how to develop a pharmacokinetic-pharmacodynamic (PKPD) model using MonolixSuite applications. It is based on a clinical study of a hypothetical test drug used in the treatment of immunosuppression and as an anti-inflammatory agent. The trial was conducted in 20 patients, who received 100 mg of the drug infused during 6 hours with rate 16.7 mg/h. Measurements of the drug and histamine concentrations were collected at times  $t = (0.5, 1, 3, 5, 6, 8, 12, 15, 18, 24, 30)$  hours post dose and are given in  $\mu\text{g/mL}$ . Histamine was used as a biomarker and describes the response to the drug.

A PKPD model describes two types of observations, which depend on each other. Here, the PD part of the model - histamine used as a biomarker - depends on the PK part given by the drug concentration. There are three approaches to model PKPD observations:

- **Simultaneous (also called joint)**: All parameters of a joint PKPD model are estimated at the same time.
- **Intermediate (also called population sequential)**: At the first stage a PK model is developed and its parameters are estimated. At the second stage the population PK parameters are fixed to their estimated values and the PD population parameters are estimated. Note that individual PK parameters are not fixed, they are sampled from their conditional distributions.
- **Sequential**: At the first stage the PK model is developed and both the population and individual PK parameters are estimated. At the second stage, the individual PK parameters are fixed (defined as regressor variables in Monolix) and the population PD parameters are estimated.

Monolix contains [PKPD libraries](#) of models and the SAEM algorithm can deal easily with the simultaneous modeling approach. However, in real examples it is often easier to start with the intermediate approach and then use its results as initial values for the joint PKPD model. For the tutorial purposes all three approaches are described.

The following MonolixSuite applications are used:

- [Datxplorer](#) to visualize and explore the data to give the first insights into the structural model and covariates relationships.
- [Monolix](#) to develop models, estimate parameters and generate statistical tests and diagnostic plots.
- [Sycomore](#) to manage the modeling workflow and compare models.

The workflow starts with the data exploration to obtain insight into possible structural models. Then, a detailed description of the intermediate approach is presented, followed by the simultaneous PKPD approach. In case of the sequential method, modifications of the data set and the model file are required and will be explained in detail. Finally, all models are compared. This tutorial focuses on how to model multiple types of observations (such as PK and PD) and analysis of the statistical part of the model (distribution of individual parameters and error model) is not explained. Please refer to the previous case studies of the series for examples of statistical model development.

## 2 Data file and data exploration

### Data file

Figure 1 shows a sample of a csv file compatible with all applications of the MonolixSuite and Table 1 contains a complete description of all variables of the data set under study. All column types available in the MonolixSuite are described in the [data set documentation](#).

	A	B	C	D	E	F	G
1	CID	TIME	OBS	OBSID	AMT	RATE	MDV
2	1	0	0	CONC	100	16.7	1
3	1	0.5	94.324	CONC	0	0	0
4	1	1	202.81	CONC	0	0	0
5	1	3	428.36	CONC	0	0	0
6	1	5	678.33	CONC	0	0	0
7	1	6	590.98	CONC	0	0	0
8	1	8	450.33	CONC	0	0	0
9	1	12	233.45	CONC	0	0	0
10	1	15	156.33	CONC	0	0	0
11	1	18	86.048	CONC	0	0	0
12	1	24	30.676	CONC	0	0	0
13	1	30	11.06	CONC	0	0	0
14	1	0	13.008	HIST	0	0	0
15	1	0.5	13.808	HIST	0	0	0
16	1	1	8.6859	HIST	0	0	0
17	1	3	6.2601	HIST	0	0	0
18	1	5	4.0602	HIST	0	0	0
19	1	6	4.4985	HIST	0	0	0
20	1	8	3.2736	HIST	0	0	0
21	1	12	2.6026	HIST	0	0	0
22	1	15	2.3422	HIST	0	0	0
23	1	18	3.8008	HIST	0	0	0
24	1	24	7.1397	HIST	0	0	0
25	1	30	8.9367	HIST	0	0	0
26	2	0	0	CONC	100	16.7	1
27	2	0.5	72.945	CONC	0	0	0
28	2	1	154.01	CONC	0	0	0

Figure 1: A sample of a csv file compatible with all MonolixSuite applications.

Column name	Description	Requirement
CID	identifier of the individual tagged as <b>ID</b>	mandatory
TIME	time of observation record (blood sampling time) tagged as <b>TIME</b>	mandatory
OBS	PK and PD observed data tagged as <b>OBSERVATION</b>	mandatory
OBSID	observation data identifier: CONC - drug concentration; HIST - histamine concentration <b>OBSERVATION ID</b>	mandatory
AMT	dose amount at dosing time (zero for observation records) tagged as <b>AMOUNT</b>	mandatory
RATE	rate of infusion tagged as <b>INFUSION RATE</b>	mandatory
MDV	identifier to ignore an observation information tagged as <b>IGNORED OBSERVATION</b>	optional

Table 1: Description of the data set variables.

In Monolix multiple observations are placed in the same column tagged as **OBSERVATION** and are distinguished by identifiers given in an additional column tagged **OBSERVATION ID**. Different observations correspond to different observation identifiers, which can be integers or strings. In this case study PK observation is marked as "CONC" and PD observation as "HIST", see Figure 2 for a Datxplore interface screen-shot.

### Data exploration

Data exploration starts with opening Datxplore, choosing a "New project" and loading the csv file. All columns, apart from CID for the identifier, have typical headers and are tagged automatically. After tagging the first column as ID, the data set is accepted by clicking the button ACCEPT.

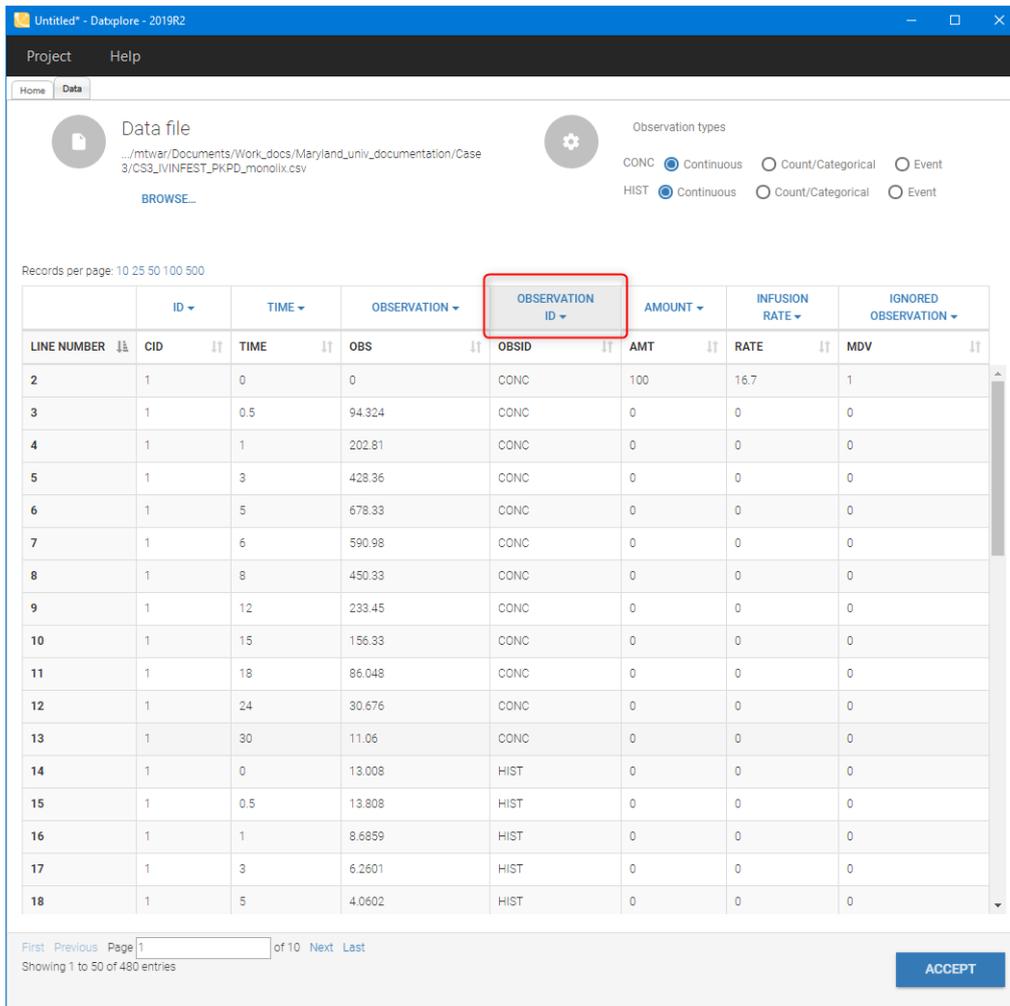


Figure 2: Tagging of the data set in Datxplorer: columns are tagged according to the variable types and the data is accepted by clicking the button ACCEPT.

Figure 3 presents plots of the time evolution of the drug (on the left) and histamine (on the right) concentrations. The plots are generated automatically and are available in the Data Viewer in the Plots tab of Datxplorer.

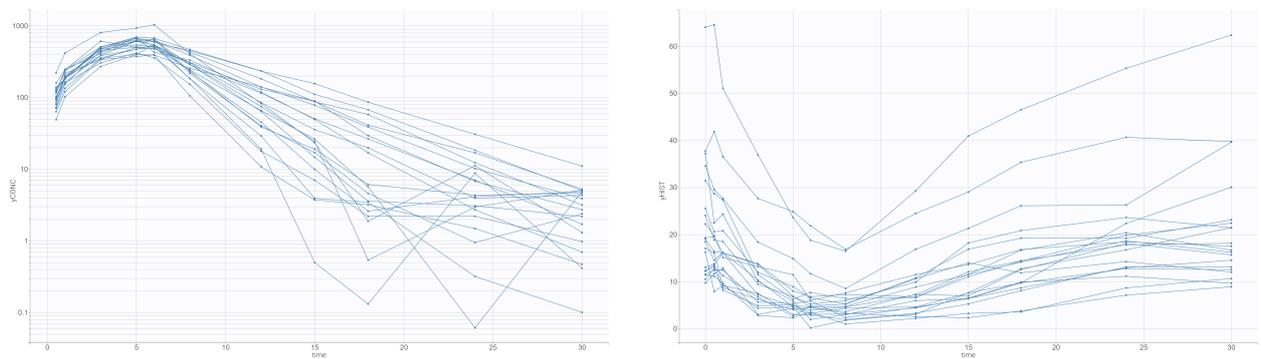


Figure 3: Datxplorer viewer: time evolution of the drug concentration (on the left) and histamine concentration (on the right).

- The elimination slope for the drug seems to follow a linear decrease in the log scale, so the one compartment model can be the starting point for the base structural model.
- Histamine concentration is inhibited by the drug and from the plots it is hard to see if there is

a time delay between the drug concentration and the response.

- Analysis of the PD vs. PK plot, see Figure 4, shows a clockwise hysteresis. The red curve highlights one individual, and the "Selection" feature in the STRATIFICATION, in the right panel of the interface, can be used to visualize individuals separately. The hysteresis indicates clearly that the histamine concentration decreases with a delay with respect to the drug presence. This behavior can be modeled by a direct response model with delay, which requires a [delayed ODD equation](#), or by an [effect compartment](#) or an [indirect model with a turnover](#). The last two models are available in the PKPD Monolix library.

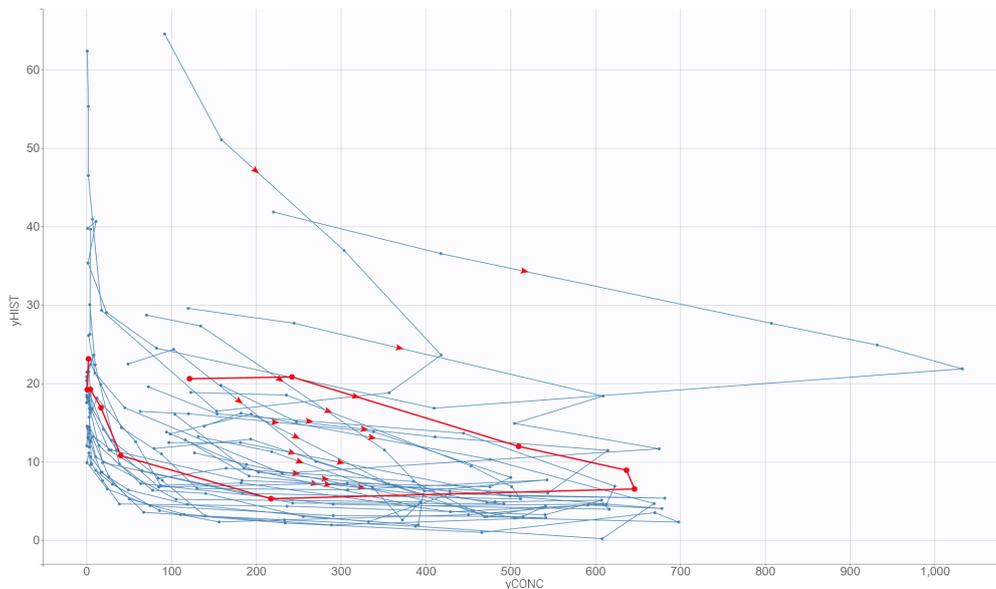


Figure 4: Datxplore viewer: hysteresis type relationship between drug concentration vs. histamine concentration (PD vs. PK). The curve highlights one individual and red arrows show the direction of time.

### 3 Intermediate approach

This section describes how to develop a PKPD model using the intermediate approach. This method has two stages:

1. First, the PK model is developed and its population parameters are estimated.
2. Then the PD model is fitted with the population PK parameters fixed to their estimated values, which is done in the Monolix interface.

It has to be noted that in this approach the individual PK parameters are assumed unknown at the second stage and are sampled from their conditional distributions.

The modeling workflow is as follows:

- Load the data set and tag the columns.
- Load a PK model, set initial values and run the tasks (parameter estimation, standard errors, conditional distribution, Likelihood)
- Go to the "Initial estimates" tab and fix all parameters by clicking "FIX PARAMETERS:all".
- Go to the "Structural model" tab and select a PKPD model from the library.

- Set initial values for the PD parameters and run the tasks.

First, the Datxplorer project is exported directly to Monolix from the top panel Export > Export to Monolix. The Monolix application opens with all required data information already setup.

### 3.1 PK model

The data exploration in Datxplorer showed that the elimination slope (in the log scale) seems to be constant, which suggests a one compartment structural model. In the PK library, infusion is chosen as the administration method, then one-compartment model and linear elimination. File infusion\_1cpt\_VCl.txt with (V,Cl) parametrization is selected and in the "Initial estimates" tab the "AUTO-INIT" procedure finds the best initial parameter values for the data, see Figure 5.

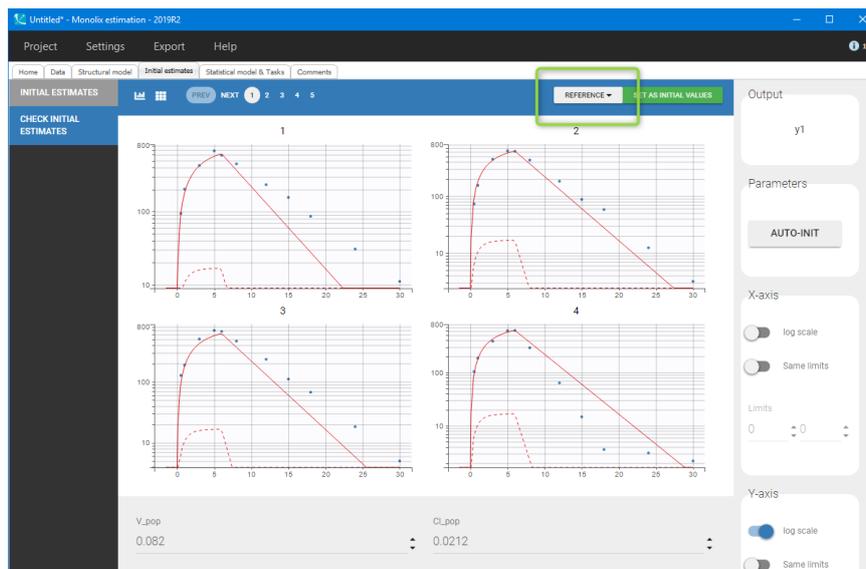


Figure 5: Graphical guide to choose initial parameters: the drug concentration data points for several individuals (in blue), the reference model prediction using the default values (dashed line in red) and the model prediction based on the "auto-init" estimates (solid line in red). Log scale is chosen on the y-axis for better visualization of the elimination phase.

Initial values are accepted by clicking the green box "SET AS INITIAL VALUES" and this brings the user to the next tab with the statistical part of the model. The base model uses:

- **Residual error model** - default combined1 model with an additive and a proportional term,
- **Parameter distributions** - default log-normal distributions for all parameters, and no correlations between random effects.

Before running any Monolix task, the project has to be saved, for example as "project\_PKPDint\_01.mlxtran" (menu: Project > Save), so that result files will be saved in a folder next to the project file.

### Monolix tasks and goodness of fits

Running a task in Monolix is done by clicking on the corresponding button in the "Tasks" section. Monolix tasks and methods were described in details in the Case studies number 1 and 2 and are explained in the Monolix documentation [Monolix tasks documentation](#). Here, for readability, all tasks are performed by clicking on the button RUN and only relevant result are analyzed. The analysis of the goodness of the structural model is done through the diagnostic plots.

- **Individual fits**, see Figure 6, show good predictions for all individuals. Misfits at small concentrations are probably due to a high constant residual error.

- Points on the **Observations vs. predictions** plot, see Figure 7, are mostly symmetrically distributed. This case study contains a small number of individuals, and the slightly larger number of points above the  $y=x$  line might result from random errors.

Because the aim of this tutorial is to show PKPD modeling, the PK model is considered satisfactory and not investigated further.

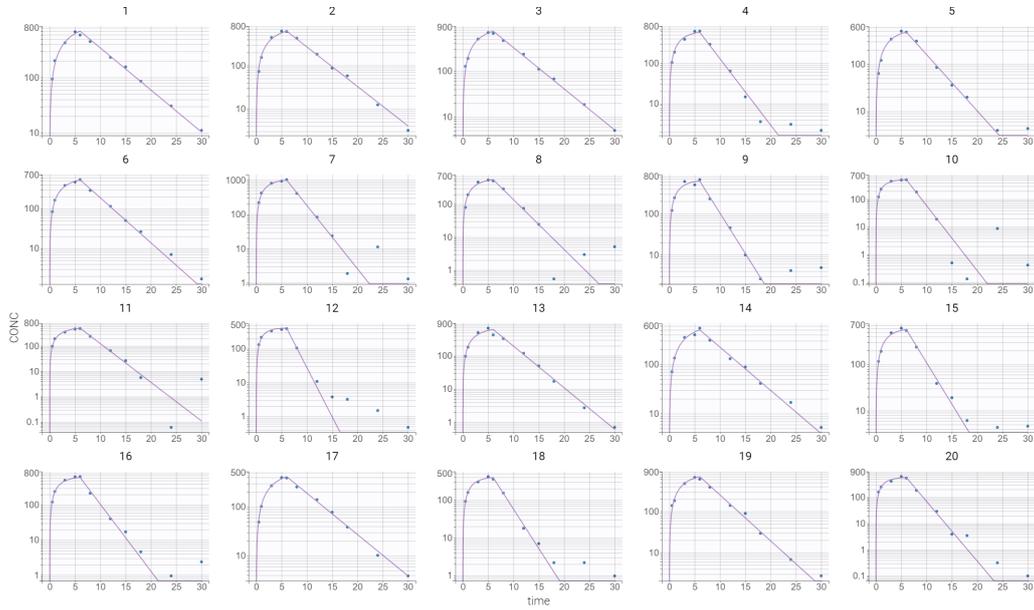


Figure 6: Individual fits for the drug concentration in the first step (PK model) of the intermediate approach.

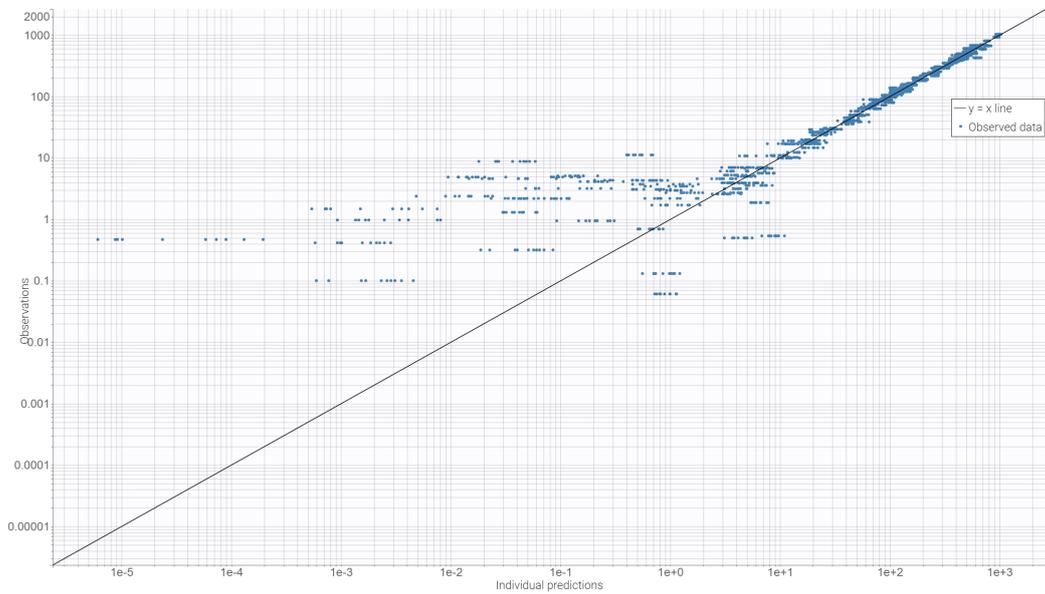


Figure 7: Observations vs. predictions for the drug concentration in the first step (PK model) of the intermediate approach.

## Results

The population parameters are displayed in the "POP.PARAM" sub-tab in the Results tab - volume  $V$  is in  $mL$  and clearance  $Cl$  in  $ml/h$  (according to the data. All parameters have relative standard

errors < 20%, which gives a good confidence. These values are going to be fixed in the PD model. The individual parameters are displayed in the "INDIV.PARAM" sub-tab in the "Results" tab. Figure 8 presents tables with the values of all parameters. Description of the complete list of results can be found in the [Monolix output documentation](#).

	VALUE	S.E. (R.S.E.%)
<b>Fixed Effects</b>		
$V_{pop}$	0.0738	0.00512 (6.93%)
$Cl_{pop}$	0.0244	0.00146 (6%)
<b>Standard Deviation of the Random Effects</b>		
$\omega_V$	0.305	0.0496 (16.2%)
$\omega_{Cl}$	0.265	0.0431 (16.2%)
<b>Error Model Parameters</b>		
a	3.04	0.298 (9.8%)
b	0.0883	0.00682 (7.72%)

id	V	Cl
1	0.0884	0.0156
2	0.0907	0.019
3	0.0761	0.0158
4	0.0691	0.0259
5	0.102	0.028
6	0.0946	0.0246
7	0.0359	0.0153
8	0.0745	0.026
9	0.0549	0.0248
10	0.0565	0.0308
11	0.0816	0.0285
12	0.0601	0.04
13	0.0761	0.0219
14	0.115	0.0235
15	0.0649	0.0268
16	0.0573	0.0252
17	0.144	0.0278
18	0.0817	0.0399
19	0.0736	0.0187
20	0.0532	0.0279

Figure 8: Results: estimated population parameters (on the left) and individual parameters (on the right) for the PK part of the model.

### Fixing parameters

In the intermediate approach population PK parameters are fixed during the development of the PD model. This operation is managed directly in the interface in the "Initial estimates" tab, see Figure 9:

- click USE LAST ESTIMATES:all
- click FIX PARAMETERS VALUES:all

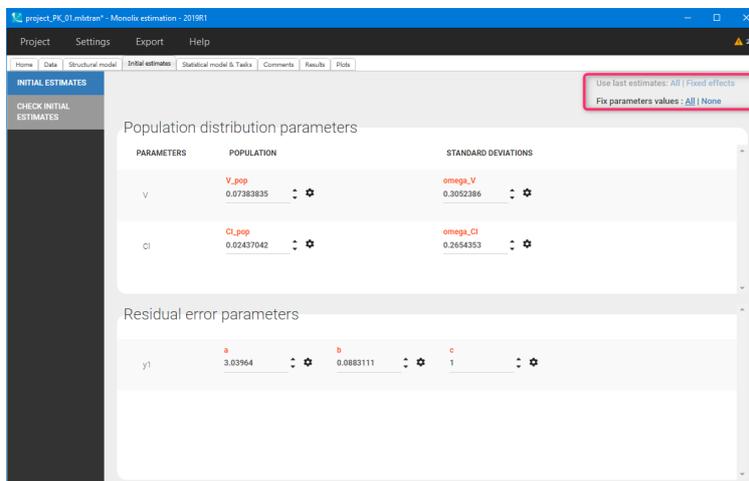


Figure 9: Fixing the PK population parameters directly in the Monolix interface during the intermediate approach of the PKPD model development.

## 3.2 PD model

The data exploration showed that the drug inhibits the production of histamine and that there is a hysteresis between PK and PD observations. It suggests a time delay between the two processes. Several PD models of the Monolix library can be tested in this case study. We will concentrate on the following one, which is compatible with the known mechanism of action of the drug:

Indirect turnover model with production inhibition given by an ODE equation

$$C_c = \text{pkmodel}(V, k)$$
$$\frac{dR}{dt} = k_{in} \left( 1 - I_{\max} \frac{C}{C + IC50} \right) - k_{out} R,$$

where  $k_{in}$ ,  $k_{out}$  are the rates of the response production and loss respectively, and  $I_{\max}$  denotes the strength of the inhibition. Figure 10 shows the definitions of this model written in the mlxtran language.

```
[LONGITUDINAL]
input = {V, Cl, R0, kout, Imax, IC50}

EQUATION:

;===== PK part of the model

; Parameter transformations
k = Cl/V

; PK model definition
Cc = pkmodel(V,k)

;===== PD part of the model

;initial values
R_0 = R0

;parameter transformation
kin = R0 * kout

;ODE for the response
ddt_R = kin * (1 - Imax * Cc/(Cc+IC50)) - kout * R

OUTPUT:
output = {Cc, R}
```

Figure 10: Structural model definition in the mlxtran language used in the intermediate PKPD modeling.

In the following, a detailed description of the turnover model only is presented. Other models, with possible correlations, can be evaluated and compared in the Sycomore application.

### Indirect model with a turnover

After estimating the PK model and fixing its population parameters, the structural model is chosen from the PKPD library, see Figure 11. In the structural model tab, a mapping between the data set observation ids (CONC and HIST) and the model outputs (Cc and R) is done automatically. If the mapping is incorrect, it can be manually changed.

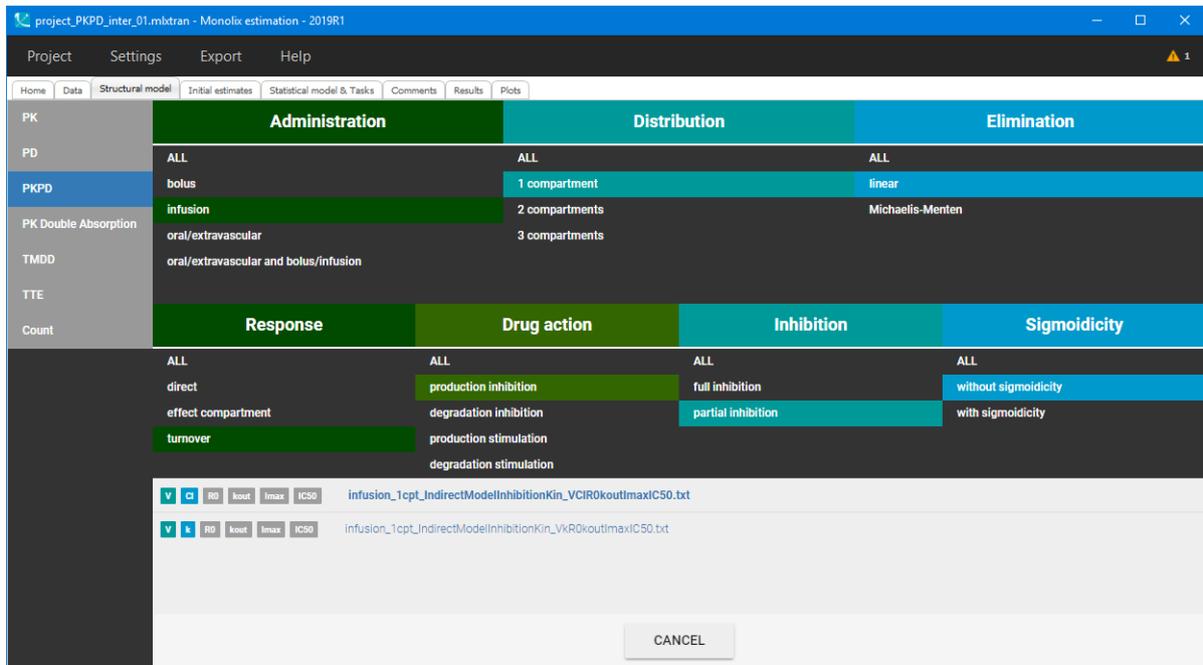


Figure 11: Structural model definition using Monolix PKPD library.

Because the models from the PK and PKPD library use the same PK parameter names, the PK parameter values set and fixed previously are remembered. The next step is the selection of the initial estimates for the PD parameters, see Figure 12. Plots in the "Initial estimates" tab can be switched between PK and PD by scrolling the list OUTPUT in the right panel at the top.

The initial fit is improved by setting the following values for the PD population parameters:

- parameter R0 denotes the histamine concentration at time = 0, and is changed to  $R0_{pop} = 20$ ,
- IC50 controls the inhibition effect and is set  $IC50 = 100$ , the typical PK concentration in this data set.
- Imax is increased to strengthen the inhibition effect  $Imax = 0.99$
- kout controls the speed of the effect and the recovery, it is kept at  $kout_{pop} = 1$



Figure 12: Initial estimates of the indirect model with a turnover for the PD part of the model for selected individuals. The green frame highlights fixed PK parameters, and the red frame points out PD parameters that have been modified.

The project is saved as "project\_PKPDint\_01.mlxtran" (menu: Project > Save). All tasks are performed by clicking on the button RUN. The individual fits show a good agreement with the data and observations vs. predictions plot does not suggest any mis-specifications, see Figures 13 and 14 respectively.

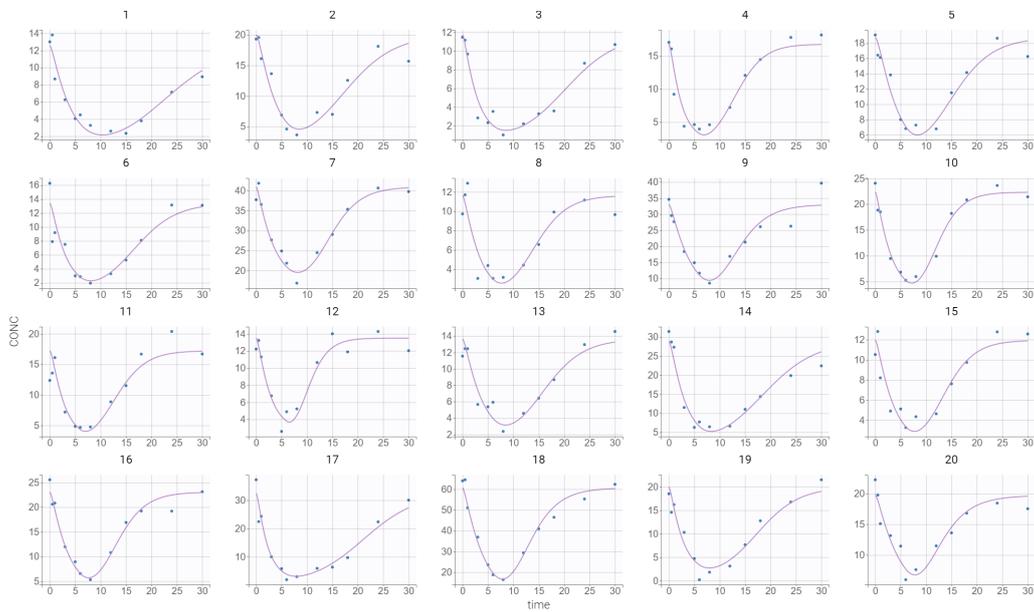


Figure 13: Individual fits for the histamine concentration (PD) in case of the intermediate approach.

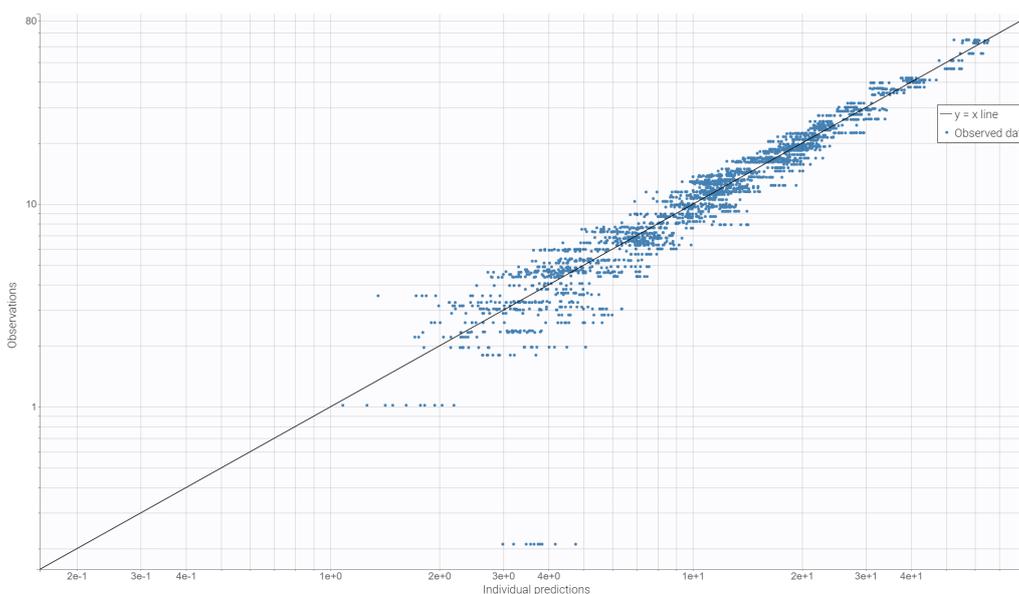


Figure 14: Observations vs. predictions for the histamine concentration in case of the intermediate approach.

## 4 Simultaneous PKPD model

In the intermediate modeling approach, the PK model is fitted with only a subset of the data (the PK data only). But if the PK data is poor, using the PD data as well will bring more information to estimate the PK parameters, as the PK influences the PD. In Monolix, modeling multiple observation types together is very easy thanks to the Monolix [PKPD library](#) which includes the typical response models. Moreover, the results of the intermediate method can be used as a starting point for the joint (simultaneous) PKPD model.

The workflow for the simultaneous PKPD model (when done after an intermediate approach) is:

- Estimate the PKPD model parameters using the Intermediate method, as in the previous section.
- Go to "Initial estimates" tab and do two actions: click on USE LAST ESTIMATES:all and FIX PARAMETERS VALUES:none. This permits to set good initial values for the joint PKPD model estimation and unfix the population PK parameters.
- Save the project under a new name and run the tasks.

Passage through the intermediate approach is not obligatory. In Monolix it is possible to start a new project to develop a joint PKPD model. In this case a PKPD model is chosen from the library and the user has to set the initial estimates.

## 5 Sequential PKPD model

The last approach is the sequential method. It is the less practical method, because it involves a modification of the data set and the model file from the library. Here, a PK model is developed exactly as in the intermediate approach. The difference is that now both type of parameters, population and individual, are fixed. The values of individual parameters for all individuals have to be added to the data set - each parameter is in a separate column tagged as [REGRESSOR](#).

## 5.1 Data file preparation

The modification of the data file has two parts:

- in the column IGNORED OBSERVATION (mdv) the PK data is ignored: MDV=1 for lines where OBSID=CONC (PK data), and MDV=0 for lines where OBSID=HIST (PD data), see blue and green frames in Figure 15,
- the estimated individual PK parameters are given for each individual in two new columns: one for V and one for Cl; in Monolix they are tagged as regression variables using the column-type REGRESSOR, see red frames.

**Remark:** In Monolix, the column MDV with ignored observation is not obligatory. The PK output, based on the prediction with fixed individual parameters, can be visible in diagnostic plots.

LINE NUMBER	CID	TIME	OBS	OBSID	AMT	RATE	MDV	m_V	m_Cl
10	1	15	156.33	CONC	0	0	1	0.0884	0.0156
11	1	18	86.048	CONC	0	0	1	0.0884	0.0156
12	1	24	30.676	CONC	0	0	1	0.0884	0.0156
13	1	30	11.06	CONC	0	0	1	0.0884	0.0156
14	1	0	13.008	HIST	0	0	0	0.0884	0.0156
15	1	0.5	13.808	HIST	0	0	0	0.0884	0.0156
16	1	1	8.6859	HIST	0	0	0	0.0884	0.0156
17	1	3	6.2601	HIST	0	0	0	0.0884	0.0156
18	1	5	4.0602	HIST	0	0	0	0.0884	0.0156

Figure 15: Sample of the PD data set in Datxplore for sequential PKPD modeling: PK data is ignored using IGNORED OBSERVATION column (blue and green frames) and the individual PK parameters are defined as REGRESSORS (red frames).

### Structural model

A PKPD model is defined as a new project in Monolix using the modified data file. The procedure is: open Monolix, choose a NEW PROJECT and BROWSE the data file. The columns with individual PK parameters are tagged as regressors and the data file is accepted by clicking the button ACCEPT.

The structural model is a PKPD model, chosen from the PKPD library, with the indirect turnover response. In this case, contrary to the previous two methods, the model has to be modified to set the PK parameters as constant, read from the data set. From the "Structural model" tab, the txt file with the model is opened in the Mlxeditor. First, the parameters V and Cl are defined as regressors, see the blue frame in Figure 16, second, the PK concentration output is removed, see the red frame. Then the new model is saved and loaded into Monolix by clicking the BROWSE link. Note that for regressors the mapping between the data set columns and regressors in the model is done by order (order of the column in the data set and order of the parameters in the model "input" line), not by name.

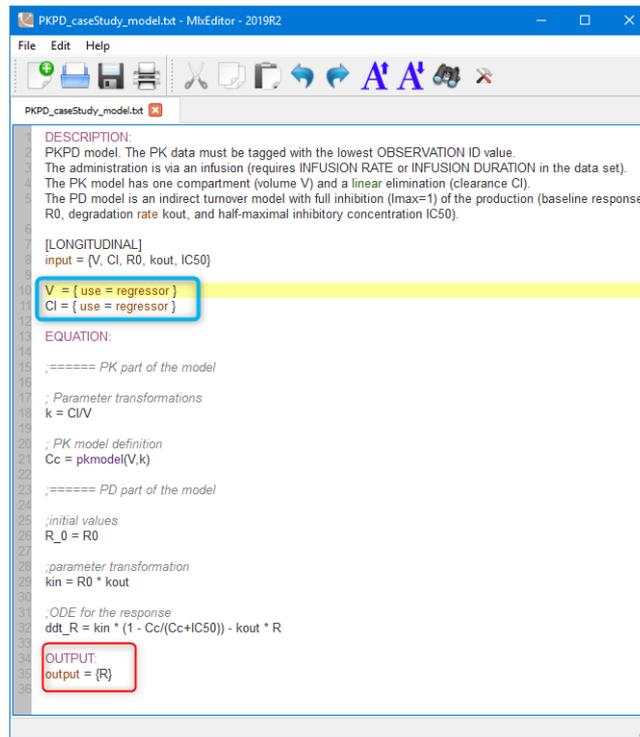


Figure 16: Modification of the structural model definition, loaded from the PKPD library, to include individual PK parameters as constants.

After choosing the structural model, the initial estimates are selected as in the previous approach and the Monolix tasks can be run.

## 6 Summary of results

The aim of this case study was to show how to use MonolixSuite applications to develop a population PKPD model of a hypothetical drug administered by infusion and having an indirect inhibitory effect on the response. Three different methods to model multiple observations types were shown. First, the intermediate approach with fixed PK parameters in the PD model was described in detail. Then, its results were used to initialize the simultaneous PKPD model development. Finally, the sequential approach was described.

Figure 17 shows the comparison of the VPC plots for the three approaches. There are no significant difference. The comparison of the parameter values, Figure 18, shows that the confidence in the estimates is the highest (the smallest standard errors) in the simultaneous approach.

From the computational time point of view, the intermediate or sequential approaches allow for faster parameter estimation. However, the simultaneous approach can be more accurate if PK data set is sparse or there is a strong dependence between the PK and PD parts.

Monolix allows to also easily model more than 2 types of observations, as well as any combination of continuous and non-continuous (categorical, count or time-to-event) outputs.

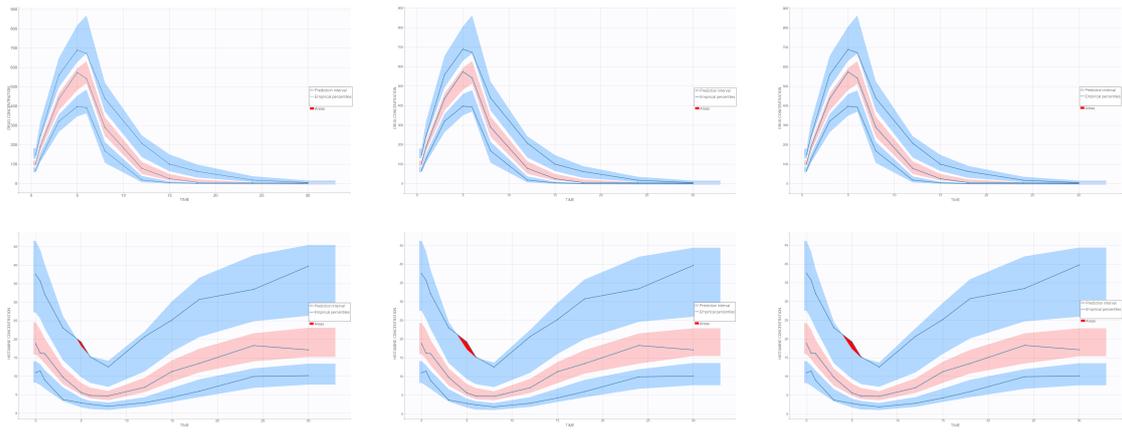


Figure 17: VPC plot for the drug concentration (on top) and response - histamine concentration (on bottom) for the sequential method (on the left), intermediate method (in the middle) and simultaneous approach (on the right).

Project Name	project_PK_01	project_PKPD_01	project_PKPD_inter_01	project_PKPDturnover_sim_01			
-2*LL (Importance sampling)	1922.16	1095.9	3017.29	3017.4			
BICc (Importance sampling)	1949.72	1140.77	3066.06	3096.69			
<b>Fisher tasks</b>							
<b>Fixed effects</b>	S.A.	S.A.	S.A.	S.A.			
R0_pop		19.75	10.21%	19.87	10.22%	19.81	10.12%
kout_pop		0.399	8.77%	0.405	13.57%	0.406	8.33%
lmax_pop		0.95	3.35%	0.969	8.61%	0.969	3.06%
IC50_pop		74.89	15.86%	69.15	33.66%	71.41	15.28%
V_pop	0.0738	6.93%		0.0738		0.0739	6.93%
Cl_pop	0.0244	6%		0.0244		0.0244	6.04%
<b>Standard deviation</b>	S.A.	S.A.	S.A.	S.A.	S.A.	S.A.	S.A.
omega_IC50		0.439	32.21%	0.361	23.95%	0.405	23.8%
omega_lmax		0.0696	39.7%	1.36	102.88%	1.29	39.28%
omega_R0		0.452	16.12%	0.448	15.87%	0.448	15.83%
omega_kout		0.306	23.36%	0.274	23.04%	0.275	22.35%
omega_Cl	0.265	16.23%		0.265		0.267	16.29%
omega_V	0.305	16.25%		0.305		0.305	16.26%
<b>Residual error parameters</b>	S.A.	S.A.	S.A.	S.A.	S.A.	S.A.	S.A.
a2		0.776	17.09%	0.819	16.07%	0.822	16.1%
b2		0.0732	16.72%	0.071	17.21%	0.0704	17.19%
a	3.04	9.8%		3.04		3.02	9.76%
b	0.0883	7.72%		0.0883		0.0886	7.73%
<b>Figures</b>							

Figure 18: Comparison in Sycomore application between different methods of PKPD modeling. Note that the likelihood values cannot be compared because different subset of the data are used in the different approaches.