Dataset Formatting

If we are collecting blood samples around a single dose of a drug that is given at multiple doses. How do we tell Monolix the number of doses preceding the sampling dose? Do we have to enter every single dose preceding the sampling dose?	You can encode each dose in the dataset, or encode multiple doses with the SS and II columns (steady-state) and enter the number of doses before steady-state in the interface. https://dataset.lixoft.com/description/description-of-column-types-used-to-define-the-dose-regimen/
Can we enter negative values for time? We have samples collected not exactly at time 0 (where the dose is given)?	Yes
Can monolix take nonmem datasets as inputs?	Most of the time yes, be careful of a few differences described here: https://dataset.lixoft.com/faq/translating-your-dataset-from-nonmem-format-to-the-monolix-suite-format/
Why is Excel not accepted to format the data?	Only text files are accepted. You can export your Excel dataset as a csv file for example.
Is it possible to integrate infusion duration	Yes, you need a RATE or INFUSION

information ? Specifically if it is different for subjects	DURATION column in your dataset. The infusion duration can be different for each individual. You can then select a model with "administration = infusion" in the library models for instance.
Can we enter the drug and metabolite in the same sheet? How to enter more than one metabolite?	Yes, parent and metabolite can be entered in the same OBSERVATION column and distinguished with different ids in a column OBSERVATION ID. You can enter several metabolites the same way with a different id in OBSERVATION ID for each analyte.
Can we enter more than one administration route?	Yes, several administration routes can be distinguished with a column ADMINISTRATION ID.
Why would some of the data need to be censored? And what is LLOQ?	LLOQ is an acronym for lower limit of quantification. Analytical methods used to quantify drug concentration in blood plasma samples cannot quantify drug plasma concentration below a certain limit called lower limit of quantification. That is also a typical example of censored data - data below the limit of quantification. This kind of data is called censored because the exact plasma concentration is not known, all that is known is that it's somewhere between 0 and LLOQ value.
Is it possible to include observations with censored time points, e.g., samples taken between 12 and 24 h?	No, this is currently not possible.
Is the customized header also available if we update monolix to the next version?	Yes, preferences are kept for the next version.
Could DVID be used for concentrations measured at 2 different sites of the body (e.g. blood and lymphocytes)?	Yes, the OBSERVATION ID (DVID) column is used to distinguish different types of measurements, including coming from different sites.
Could DVID be used for drug and metabolite?	Yes
If we have a concentration at time = 0, can we add in the same line an amount and a dv or do we need to create a "t0" and a t0.1" for example ?	You can either have both amount and concentration on the same line, or on two different lines with the same time.
In the data sets shown it looks like samples are collected at the same time points across individuals. What adjustments must be made if time points are collected	You simply have to indicate the exact measurement times in your data set. The data is in long format, with different lines for different individuals.

heterogeneously, and how should data points be aligned? (For example, in the case of Covid vaccination when timing and initiation of 1st, 2nd and booster doses is very heterogeneous)?	
Can monolix take character such as sex: M, F as covariate?	Yes, any string of characters.
Hi, will you distinguish body weight as continuous or categorical covariates?	It should be continuous.
In the amount column, if different amounts are given, related to different weights of individuals or different dosages, how should this be indicated to the software?	Each dose amount must be indicated separately with the corresponding dosing time and the corresponding id.
Does AMT in the dataset mean the amount of drug measured? or dose?	AMT column in the dataset is a dose column, it means administered amount of drug.
Is it possible to remove or ignore data points directly from monolix or should they be annotated in advance (before loading csv files)?	Yes, with the Filter module (tab Data), by removing some lines.
Is it possible to load data from RDS files?	No
How to change data units using monolix PK analysis?	Monolix doesn't keep track of data units, you will have to do it yourself. However, we will show you how to handle different data units in amount and observation columns in session 3.
Is there a solution for drug concentrations that are higher than the assay quantitation limit ?	Censored observations that are above an upper limit of quantification can be indicated with -1 in the CENSORING column, and the ULOQ in the OBSERVATION column.
Does an empty cell mean the same as the dot in the cell (for example for DV and AMT columns)?	Yes
If I use only PD data, with all TIME=0, then PK and PD data still need to be in the DV column with DVID variable settings, correct?	If you have no PK data, just put the PD data in the data set and no OBSERVATION ID (DVID) column. OBSERVATION ID column is just needed to distinguish different types of observations, if relevant.
Is there an automated way to add columns with individual PK parameter estimates for the sequential approach, or do we have to do it outside the MonolixSuite?	This has to be done outside Monolix for the moment. We are working on a new data formatting module for the next version.
If I have missing values in either the	If the value is missing, at the moment of

concentration or effect, and I put a ".", how am I sure that Monolix is treating them as missing? Do I add MDV?	accepting a dataset you will see a warning that Monolix found lines with missing observations (if there is no dose either on the line) and that these lines will be ignored. You do not need the MDV column.
If the exposure goes up and down over time, can it still be tagged as time to explore the exposure-time relationship?	Yes. It is also possible to tag it as REGRESSOR. The values will be displayed on the x-axis of the plots, instead of time, in increasing order.

Data visualization

What is the difference between a regression and a spline? Will there be problems when evaluating splines with censored data?	In the Monolix GUI, regression is a linear regression (straight line), while spline can have a more complex shape. We use simulated censored data to avoid bias due to censoring.
Is the loop seen on PD vs PK plot what we call 'hysteresis clockwize effect'?	Clockwise or anticlockwise depending on the case, but yes.
Can you plot pk and pd vs time on the same axes?	No that is not possible

Structural model

Are there ready-to-load models for log transformed concentrations or do you have to modify the model in the text editor?	No, models from the Monolix library do not use log-transformed concentration, but you can easily edit them to add this transformation.
If I have data that have drug and metabolite, for structural model, would I use the PK or ParentMetabolite library? If I model it using the PK library, how would I relate the two (drug, metabolite) after getting the best fit?	If you want to model both at the same time, you should use the parent-metabolite library. I recommend to first fit the parent data only using the PK library, click "use last estimates", and select a model from the parentMetabolite library. The estimated values from the parent only run will be remembered.
How do you recommend to model subcutaneous administration?	Subcutaneous administration could be modeled the same as oral administration, since it is an extravascular route of administration. In this case, you could model it with first order absorption using

	absorption macro, if, for example, your formulation is a solution. The macro will also combine an infusion with the 1st-order absorption if you have a column tagged as ‘infusion rate’ or ‘infusion duration’ in your dataset (see more details here: https://mlxtran.lixoft.com/model-libraries/library-of-pk-models/) However, if you are modeling long acting injectables, more complex models (for example double absorption models with transit compartments) would probably fit the data better. You would still be able to write this model with multiple absorption macros for absorption and then compartment/peripheral/elimination macros.
If we modify a model from the library is it going to overwrite the default model or create a new customized model file?	With the new version (Monolix2021R1) you will be forced to save the model as a new file and not overwrite the model from the library.
In the Monolix PK library it seems that the models do not indicate the number of compartments explicitly in the model names.	They do. For instance in "oral1_1cpt_kaVCl", "1cpt" indicates a one compartment model (no peripheral compartment).
I wonder if there is a model including F (bioavailability) in addition to ka (absorption rate constant) for oral administration in your library.	Only for the models that combine oral and iv/bolus administrations, otherwise F is not identifiable. However you can easily edit the model to add it.
How do you include Tlag when you are coding your model?	You can add Tlag as an argument in the macro that handles doses (PK macro or depot macro if you are using ODEs).
Is there any method implemented to help determine the number of transit compartments needed for modeling the delay in monolix?	When taking a model from the library, the number of compartments is estimated. The estimated input parameters are Mtt and Ktr and n can be calculated from Mtt=(n+1)/Ktr. You do not need to implement the transit compartments by yourself.
Are there any demos or library models for DDI and CYP450 enzymes?	No, not yet.
How do we generate the Exposure parameters and their steady states from the parameters estimated in the popPK analysis	You can add additional lines in the structura model to calculate them and use the "table" statement to output them. Check: https://monolix.lixoft.com/faq/how-to-compute-auc-using-in-monolix-and-mlxtran/
Question related to the PK/PD models. Is it possible to compute AUC and introduce this	Yes it is possible, you can add ddt_AUC = CC in the EQUATION: section, with Cc the

parameter into some parameter under the PD part of the model? Like x = y*AUC?	concentration variable.
Is it possible to develop whole body or minimal PBPK models in Monolix?	Yes, any model that can be written in ODEs can be used in Monolix. There is no built-in library for such models so you need to write them yourself.
Are there some differences between a model with Q and Cl instead of microparameters (k12/k21/ke) in terms of computational time and/or results?	In terms of computational time, there is no difference. The results are the same if correlation is included between all parameters, but not if the omega matrix is diagonal (no correlations).
Is it possible to extract data from the fit? Let's say I would like to change some parameter conditions, whenever y reaches a certain threshold?	You can use if/else statements in the model, with conditions on the ODE variables (concentration prediction for example). If you wan You can use the predicted concentration to define a threshold in an if/else statement, but not the simulated observations (with residual error). You can also use the observed data for the threshold, for this you have to duplicate the observations in a new column tagged as REGRESSOR, to read this column in the model and use it for the if/else condition.
Are there examples for time dependent CL and parallel linear and MM CL?	We do have a small video on this topic: https://www.youtube.com/watch?v=9RrM8NnS0AM The time-varying component can be added on the linear term (Cl) or on the non-linear term (Vmax) depending on your situation.
How to write the code for parallel linear and nonlinear elimination?	You can combine two elimination macros, one for linear with k or Cl, and the other for nonlinear with Vm and Km.Like this: compartment(cmt=1, volume=V, concentration=Cc) iv(cmt=1) elimination(cmt=1, Cl) elimination(cmt=1, Vm, Km)
Is the order of parameters in pkmodel important?	The order of the parameter keywords doesn't matter. For instance pkmodel(ka,V,Cl) is the same as pkmodel(V,ka,Cl).
What is the macro for an IM administration?	IM corresponds to an extravascular administration with IM absorption rate, so you can use the absorption macro.
I have a treatment and control group and I	The individual parameters in the control

am using a model in which a parameter is used for the treatment group but not for the control group. In the individual parameter table, it still shows values for that parameter in the control group. Is it still estimating something for that group?	group are actually sampled randomly from the population distribution, since there is no individual data to guide their estimation. Only the data from the treatment group will guide the population and individual parameter estimations.
Why is there no V2 in your peripheral compartment?	A peripheral compartment can be defined via (k12,k21) or (Q,V2). The two parametrizations are related by k12=Q/V1 and k21=Q/V2.
Is there any way to have lag time and transit at the same time?	No, this is not possible via the macros. You would have to write the ODE's by yourself using depot(Tlag) in the PK: section.
Can you combine a PK model with macros and a PD model with ODEs if performing PKPD modeling?	Yes, definitely !
Could you please explain the function of iv a little bit?	The iv macro applies the doses to some compartment, either as iv bolus or as iv infusion. The choice is done automatically depending on the dosing information in the dataset: if there is a column tagged as INFUSION RATE or INFUSION DURATION, it is used to apply iv infusions. Otherwise the doses are applied as bolus.
How is the regressor mapping done in Monolix?	Mapping between data set columns and model input is done: - by name if match (e.g “Tlag” as column header and “Tlag” as model parameter) - by column/parameter order otherwise (e.g “Tlag_mode” in dataset and “Tlag” in model)
Is there a way to view the ODE format of a model that was specified by macros? (e.g. for a sanity check)	No it is not possible. In addition it does not always correspond to an ODE system, since when possible it uses the analytical solution.
Can you convert the library models that are written with PK macros into diff equations?	No, that is not possible.
Why is there no cmt label on the peripheral compartment?	It is implicitly defined by the numbering of k12: peripheral(k12,k21) means a peripheral compartment with number "2" connected to the compartment with number "1".
Can we add a second elimination route from the peripheral compartment?	Yes, you can combine several elimination macros, from different compartments or from the same compartment.
Do you plan to develop a list of macros or a	We plan to provide a library of PBPK

library for PBPK models? (macros would keep the code more readable)	models, hopefully for the early 2023 version. This may be done together with additional macros also.
Could I have a model more complex than 3 compartments?	You can have any number of compartments.
Ac_0=0 is only when we have a Cc=0 at t=0? What if we are in a steady state?	If you know the starting concentration, you can set the initial condition to that value, Ac_0=50 for instance. If you don't know the initial value, you can start the ODE integration at a negative time with Ac_0=0 and add many doses to reach the steady-state.
Is there any way to censor an initial value (for example : an initial concentration below LOQ)?	The initial concentration can be censored like any censored data in the dataset with the CENSORING column.
What does stiff ODE solver mean?	It means that the stiff solver will be used, which is more appropriate for some ODE systems compared to the default non-stiff solver. More details here: https://mlxtran.lixoft.com/longitudinal/how-do-i-model-an-ode/
In the equation: “ddt_Ac = ka*Ad - Cl/V*Ac” could Cl/V be replaced with ke?	Yes, you can parameterize the model with ke and estimate ke instead of Cl.
Is it possible to incorporate a variable which is a function of time in ddt_Ac? For example: ddt_Ac= ka*Ad - Cl/V*Ac + “a*t” ?	Yes, "t" is the keyword for time and it can be used in the equations.
If Vmax is dependent on time t, can it be expressed with an equation with t and also at the same time be part of the ddt_Cc?	Yes, this is possible.
Can we keep ODE equations but get rid of the depot line?	If you want to apply a dose to an ODE model, you need the depot() macro. If you have no dose to apply, you can leave the depot() line out.
How can we write comments when writing ODEs in mlxtran?	; is the character to start a comment
Is Tlag fit or specified by the user, and if fit, what is the standard initial value?	You can either include Tlag in the input list of the model, in that case it is estimated, and you should choose the initial value (the standard initial value is 1 for all parameters but it should be changed), or you can specify Tlag in the structural model (Tlag=<number>) and not estimate it.
Is there a need to use brackets to arrange	Brackets, no. Parenthesis yes, if you need

mathematical operations while writing ODE?	to define which operation should be done first (as in any mathematical program).
If I have depot(target = Ad) and Ad_0 = 0, will depot overwrite the initial condition for Ad?	If there is a dose at time 0 in the dataset, the depot macro will add the dose amounts on top of the initial condition for Ad. If Ad_0=0 and depot(target=Ad), then Ad(time=0) = 0 + doseAmount.
Using the depot macro, can you describe a 0-order absorption or a transit compartment absorption while using a model described by ODEs?	Yes, the depot macro can be used with arguments Tk0 for 0-order absorption, or Ktr and Mtt for transit compartments absorption. https://mlxtran.lixoft.com/pk/depot-macro/
What do you mean by regressor?	REGRESSOR columns define variables (possibly time-varying) that will be available for calculations in the structural model. More here: https://dataset.lixoft.com/description/description-of-column-types-used-to-define-regressions/
Do you have examples of lifespan models?	https://mlxtran.lixoft.com/examples/lifespan-based-indirect-response-models/
I don't understand what Ac in depot(target = Ac, ka) is doing. Moreover, the differential equation ddt_Ad = -ka *Ad is removed. Does it mean that the drug is administered both as IV and Oral?	The depot() macro takes the doses in the dataset and adds them to the ODE variable. The target= argument indicates on which ODE variable should be added. When there is no "ka" parameter, the dose is added on the target variable as a bolus. When "ka" is present, we actually add a hidden depot compartment, add the dose as a bolus on the depot compartment and transfer it with rate ka to the variable defined in the "target=" argument. So in the examples, only oral administration was considered.
Where can we find the document on keywords used in mlxtran?	Macro keywords are all summarized in the cheatsheet available on https://mlxtran.lixoft.com/. All keywords (also mathematical functions etc) are detailed here: https://mlxtran.lixoft.com/language-reference/what-are-the-keywords/
Can we write a model with a substrate and an inhibitor (a customized DDI model)? Is there any example using mlxtran for reference?	Sure, this can be done. We do not have such a model on the example page but it would be quite straightforward to write from equations published in an article.
Can you use two types of administration in pkmodel if they are in to the same compartment (for example IV bolus followed	IV bolus and IV infusion yes, but not a mix of extravascular and intravascular.

by IV infusion)?	
When using other macros than pkmodel (and using only these macros), as currently exemplified, is the solution analytical used (=faster) or is it converted to ODE (slower)?	It depends on the model defined. For 1 to 3 compartment models with linear PK (linear elimination, no transit compartments), the analytical solution is used.
How to set lower/upper bounds for parameters which I want to estimate?	You can set a logitnormal distribution on the parameter in the interface, with custom bounds (default is [0,1]).
Is conditional dosage with ifelse statement also possible? E.g. if WT<45 kg -> dose X or WT>45 kg -> dose Y.	For estimation in Monolix, the best would be to define the final dose in the dataset. For simulations in Simulx, you can define individual doses and weights with the correct relationship.
Does double absorption relate to enterohepatic recirculation?	Double absorption is even larger than enterohepatic recycling. For instance extended release formulations can show two peaks.
I tried to code an IM administration. When I used absorption (adm=3,.....) it didn't work but when I used absorption (type=3,.....) it worked well. What is the difference between "type" and "adm" ?	Both are aliases so both should work. There are probably other differences between your two models.
Can we define an absorption model with a weibull distribution ? And other time-dependent absorption constant?	Yes, an example is given here: https://mlxtran.lixoft.com/examples/transit-compartments-weibull-absorption/
What is the difference between using depot along with ODEs vs compartment, IV, and absorption? Would the latter work with ODEs?	Both are possible. Usually iv()/absorption() and compartment() are used when the rest of the model is also defined via macros() and depot() when the rest of the model is defined via ODEs. But in practice it is also possible to do iv(), absorption(), compartment() + ODEs.
Is it possible to model a double absorption and also consider bioavailability?	Yes, you can combine the factors like this: p=F*F1 or p=F*(1-F1) with F the bioavailability and F1 the fraction of drug in each absorption.
Which structural model do you recommend for modeling the effect of an antibiotic drug (static concentration) on bacterial growth over time?	We have a specific video on this topic: https://www.youtube.com/watch?v=Q3wmyxTHg8s
Do you also have a model library capturing tolerance in PD effect?	Not in the library, but we do have an example here: https://mlxtran.lixoft.com/examples/auto-induction-model/

In the effect compartment model, do we actually estimate Ce or it is a mathematical artifact to better relate Cc and E?	We estimate only the transfer rate ke0 to the effect compartment, Ce is computed based on this.
Can I just use a PD model and not consider the time dependent properties? In this case, t is not used; so how to input data with the data mapping? Does time have to be an input in the data mapping? Which columns to map for concentration and effect data?	If your data is not over time, you can set TIME=0 for all observations (or any other value actually), or you can have no TIME column. The column containing concentrations should be tagged as REGRESSOR. If there is no time, “time” will still appear on the x-axes on plots, but actually the REGRESSOR values will be used instead. An example is given here: https://www.youtube.com/watch?v=xFOR73swhcg&ab_channel=Lixoft
Is it possible to create multiple PD models (i.e. PD-1, PD-2) where the input to PD-2 model is from PD-1 model?	Yes of course, and your model can have as many outputs as you want.
If I develop a model with a combination of macros and ODEs, can I see the full ODE system including the ones specified with the macros? Can the structural model be exported to other formats such as SBML?	No, you will see the model only as it is written (with macros and ODEs).
For ODE models what are the non-stiff and stiff solvers? Also, is there a library of scientific functions that we can call, for gamma function, error function etc?	Library of functions: https://mlxtran.lixoft.com/language-reference/usual-mathematical-functions-in-mlxtran/. More infos on the ODE solvers here: https://mlxtran.lixoft.com/longitudinal/how-do-i-model-an-ode/
After writing a PBPK model, can I use the PD library to join a PD model to the PBPK model or should I write it as well?	You can open a PD model from the library in mlxEditor to copy the PD equations and paste them in your PBPK model. This video shows how to combine models: https://www.youtube.com/watch?v=5r_7_Z1bWq8&ab_channel=Lixoft
For the calculation of AUC between 50 and 100, can't we use if(t > 50 & t < 100) and calculate AUC_50_100 in one go?	This is not a good practice because then ddt_AUC=0 for a long time and this will lead the ODE solver to do large steps and possibly miss the condition in the if statement.
In the PD model with sigmoid response, if the saturatable Cc has a baseline that varies among individuals, how would the ODEs be like?	Baseline can be treated as a parameter and estimated for each individual.
In the example shown, R is the response and R0 is just the initial value, why is R0 used in the "INPUT" instead of R?	R, the response, is not a parameter that will be estimated, but it is a variable defined with an equation in the model, it will be

	calculated based on the estimated parameters. One of these estimated parameters is R0, the initial value for the variable R.
How to put an intermittent hemodialysis effect on drug disposition as a variable in the dataset?	You would need to write the model that sums the hemodialysis and systemic clearance just for the times when hemodialysis is happening, and read these times from the data as a REGRESSOR column.
How to carry out the study of a combination of drugs? For example the administration of a different drug A and B to the same individual and the same sampling time.	It is explained in detail in this video: https://youtu.be/Chei_lZiAhc
If I have both blood drug concentration data and tissue drug concentration data, how can I do the PK modeling?	This would correspond to a compartmental model with blood concentration in the central compartment and tissue concentration in the peripheral compartment. To output the latter for tissue, you can write: peripheral(concentration = Cp, k12, k21) and then add the Cp in the output list, next to the Cc for the central compartment.
If I have a dataset with inconsistent sampling times, is it possible to calculate AUC between two administered doses rather than between two time points?	In Monolix you calculate AUC in the structural model. The keyword tDose gives the time of the last administered dose, so if the first dose was at zero, it would work. Otherwise, for any dose times you need to use syntax presented during the third session of the Spring School. Take a look also here for other examples: https://monolix.lixoft.com/faq/how-to-compute-auc-using-in-monolix-and-mlxtran/
Can we model PD effects with a circadian rhythm?	Yes that is possible, you can use the function sin or cos in mlxtran. It is done in this case study: https://monolix.lixoft.com/case-studies/vanoxerine-c-qtc-case-study/

Statistical model

What does it mean to add a covariate to a parameter? That it may change based on the value of that covariate?	The parameter distribution captures the variability of the parameter value within the population. Part of this variability may be explained by patient characteristics, for

	instance the volume of distribution may tend to be larger for patients with a larger weight. Adding a covariate on a parameter means that we will assume that the parameter variability is partly explained by this covariate value and partly un-explained (and captured in the random effects).
What if we have multiple covariates and these covariates are correlated to each other in a complex way. How can we take care of something like that?	This is not possible in the interface of Monolix, but you can implement complex covariate effects directly in the structural model.
Is the exponential covariate model the only one applicable in Monolix? Is there any possibility to model the clearance as: Cl_i= Cl_pop +number/ covariate or should I use my covariate as a regressor and edit in the mlxtran?	The relationship implemented automatically in the interface is h(P_i) = h(P_pop) + beta*cov, with h the transformation corresponding to the distribution of the parameter, and cov can be transformed. So if Cl is described with log-normal distribution, log(Cl_i) = log(Cl_pop)+beta*cov in the interface. If Cl is described with a normal distribution it would be possible to have the relationship you describe.
Can we select WT normalization to median or mean value?	The default normalization is by weighted mean (mean weighted by the number of observations). You can edit the formula to choose any normalization value.
Do you always need to use log transformed values for WT or was that just in the case of normalizing to a typical value?	It depends on the relationship you want to implement, but the normalized power law shown by Monika is the standard relationship for continuous covariate effect.
Does Monolix calculate statistics for my data to get the estimate for mean/median?	Yes, you can see the statistics in the window for covariate transformation, when hovering on the covariate of interest.
When there are several values (i.e. body weight changed over time) observed for a covariate for a subject during the study period, Monolix uses only the first value in a single occasion. How to let Monolix consider all the values instead of only the first value?	You need to tag the column as REGRESSOR instead of covariate and then describe the parameter-covariate relationship in the structural model.
What is the difference between the error models?	The equations of the error models are different, leading to different shapes in the prediction intervals. Figures are shown here: https://monolix.lixoft.com/graphics/obs-vs-pred/ and the equations here: https://monolix.lixoft.com/data-and-models/

	errormodel/
In the equation of the combined error model, there is an "e" at the end, what does that mean?	it represents a random variable with normal distribution. Check the slides from the theoretical introduction in the first session.
Is the combined2 residual error model equal to the additive + exponential model?	It is equal to additive + proportional. The equation is: y = Cc + sqrt(a^2+(b*Cc)^2) * eps = Cc + a*eps1 + Cc*b*eps2 with eps, eps1 and eps2 standard normal random variables (mean = 0 and standard deviation = 1).
How do I know which error model is best to choose? Why did you decide to choose "combined1"?	Combined1 is often a good start, if the estimates for a or b are small (small compared to the data set observations values) it will indicate to drop the constant or proportional term. If the estimates are not small but are correlated, it is often an indication to choose combined2 instead. You can also have a look at the tab Results > Proposal, which makes suggestions about the best error model to use.
Does the value for "b" in Error Model Parameters represent residual error variability?	Yes, b is the proportional term of the residual error.
Can a different error model (for example: Poisson) be coded in Mlxtran?	No that is not possible
I have a question - How do we report error model parameters (a, b) for publication?	Parameters of the error model are population parameters. The usual practice is to report a as standard deviation of the residual error, in case of a constant error model, and b*100 as %CV of the residual error in case of a proportional error model.
For the observation model, I think the distribution should be changed to lognomal, right?	It depends. If the distribution is changed to lognormal, then we assume an exponential error model: log(y) = log(Cc) + a*eps <=> y = Cc * exp(a*eps). The exponential error model is convenient when used for simulations because it generates only positive concentrations. However from a modeling point of view, it is often less appropriate for PK data, compared to a proportional or combined error model.
How to decide if the observation distribution is normal or lognormal?	The choice is tricky. Most PK models use a normal distribution.
How do you set upper and lower bounds on parameters?	You can change the parameter distribution to "logitnormal" and then change the bounds of the logit function (by default they

	are [0,1]).
Since PK parameters are lognormally distributed, how do they have SE/RSE? Or are these for the log(CL/Vd) instead of the actual CL/Vd?	We first estimate the SE on the log(CL) and then transform it back to the SE of CL using a multiplication by the Jacobian.
Does the correlation matrix assume correlations between etas, without specifying it in the model?	By default we assume a diagonal omega matrix (no correlation between the etas). The correlation matrix shown in the Result tab (section SE) is the correlation between the estimates of the population parameters, not the correlation between the etas.
How to model correlation between beta parameters with other parameters?	Correlations are implemented between random effects. Beta parameters are fixed effects and have no inter-individual variability, thus it makes no sense to have correlations on betas.
How does latent covariate work? Could we add covariates that have binomial distributions with this feature?	Yes, you could. The usage of latent covariates is explained in the following video: https://www.youtube.com/watch?v=4zZHSriEvv4
In Monolix we can estimate the proportion of latent covariates plcat1 and plcat2 in the population for example for some parameter but how to estimate what is the value for this parameter under plcat1 and its other value under plcat2?	If you, for example, have a latent covariate included on some parameter p, then the value for plcat1 would be the estimated p_pop value and the value for plcat2 would be p_pop * exp(beta_plcat2).
I see that random effects are assigned to all parameters. After the 1st run, do you recommend that random effects may be removed from some parameters?	There is no automatic recommendation for random effects yet. You can try removing the random effects that have a small estimated standard deviation. It may be necessary to run the estimation without simulated annealing to identify correctly small standard deviations: https://monolix.lixoft.com/tasks/population-parameter-estimation-using-saem/simulated-annealing/
Is it a good practice to start modeling considering random effects in all parameters and then "remove them wisely" and analyze the possible improvements? Or the other way around?	Yes, it is a convenient approach that we usually adopt, if the number of parameters is not too high. If there are many parameters to estimate it might be too long to also estimate all the random effects, so it might be better to set random effects on only part of the parameters from the start.
Is it possible to edit the equation in the individual model manually? For example, let the equation estimating individual values for	It is not possible with the individual models defined automatically in the interface, but you can define the individual models

V2 use the eta of V1.	manually in the structural model. Examples of custom individual models are given here: https://monolix.lixoft.com/faq/complex-parameter-covariate-relationships-time-dependent-covariates/
In the individual parameter report, there are only individual mean and mode. How can we have the conditional distribution values?	There are two types of files. The values sampled from the cond distrib are in the file "simulated...".
How could allometric scaling for covariates be done in monolix?	Let's assume that you have dog data and you implement V = Vpop * (WTdog)*beta * exp(eta). First you can fix beta=1 or 0.75 for instance. Then if you want the volume of a human, just set WT=WThuman. Note that Vhuman = Vdog*(WTh/WTd)^beta = Vpop * WTd^beta * (WTh/WTd)^beta = Vpop * WTh^beta
When can we say we have a strong/good correlation between covariates?	Small p-values for correlations are highlighted with colors in the interface. P-values colored in red can be considered as strong.
How small p-value means the correlations, Is there a specific cutoff value for p-values that indicates a strong correlation? or is it a relative value for a specific case?	There is no clear cut-off, adding a covariate effect or a correlation between random effects corresponding to a small p-value might lead to a better model (smaller BICc, beta or correlation parameter well estimated) or not depending on the cases. Sometimes adjusting the statistical model based on a not-so-small p-value works as well. Looking at the proposal is another hint to decide if the statistical model should be adjusted or not.
If Monolix suggests adding several covariate, then how to know with which one to start, or should be add them simultaneously?	This is up to you. You can add them one by one based on the p-value in the Tests tab for instance, or all at once.
When is it necessary to add a covariate log linearly or using power law (allometric scaling)?	These are typical options but you can also define more complex parameter-covariate relationships by defining them directly in the structural model file. We will show this on Friday.
Is it better to force log(WT) as a covariate, even if Monolix suggests (through statistical tests) that an untransformed WT is a better covariate?	Monolix suggestions in the "proposal" tab are suggestions based on one set of sampled parameters. It can be that by "bad luck" with these sampled parameters WT is better than log(WT), but I would personnaly prefer to include log(WT) for physiological reasons, even if Monolix suggests WT.

In the exercise, why logWT rather than WT alone?	LogWT uses a log-transformation of WT centered by a typical value. Thus the covariate effect is implemented with a non-linear power law which is more standard, and the centering leads to a value of V_pop easier to interpret, since it is the volume for a typical individual (with typical WT).
Is SCM similar to stepwise covariate search (i.e., forward addition and backward elimination)?	SCM is the classic stepwise covariate search method (forward selection followed by backward selection).
What is the difference between locked out and not selected covariates?	Not selecting a covariate will not add the covariate on any parameter. With lock-out you can choose not to add a covariate on specific parameters.
Is it not better to change one thing at a time? e.g. run the logWT on the CL then compare both error models?	This is up to you. It is more usual to do changes one by one, such that the impact of each change can be assessed. But doing one thing at a time takes more runs hence more time, for the sake of the training we prefer to do it faster in a single run. And actually it is unlikely that adding a covariate effect will change much the properties of the error model.
What if one covariate masks the effect of another one? Do we look at the BICC to decide which covariate to use?	It is up to you, you can choose according to the BICc, or you can prefer the covariate effect that makes more sense biologically.
Why the preference for BICC over AIC in the hands-on example?	We usually compare BICc, but AIC could work as well.
Should we compare the absolute value of the BICc?	The absolute BICc value is not important. It is the difference between two models that matters.
I've seen studies where log(concentration) was used as DV instead of concentration. What is your advice concerning this practice when using Monolix/SAEM? Can it be useful with some datasets ? And if yes when? Or a contrario can it be counter productive?	This transformation does not need to be defined in the dataset, it can be done on the observations and model output directly in the GUI by changing the error model distribution to lognormal. Monolix always works in the gaussian space. Changing the distribution to lognormal allows to assume an exponential error model: log(y) = log(Cc) + a*eps <=> y = Cc * exp(a*eps). The exponential error model is convenient when used for simulations because it generates only positive concentrations. However from a modeling point of view, it is often less appropriate for PK data, compared to a proportional or

	combined error model.
Just to confirm, the omega that Monolix gives is small omega, not the squared big omega, correct?	Yes, the omega parameters are standard deviations of the random effects, not variances.
Does monolix give the sd of ω ? Because in simulx when I want to add the distribution of pop parameters it needs sd for the parameters and ω.	In Simulx you need to enter the sd if you want to sample new population parameters from a distribution, in order to take into account uncertainty. Monolix gives the standard errors of the population estimates (fixed effects or omega parameters), not the standard deviations. Note that if you export a Monolix project into Simulx, an element mlxPopUncertain is automatically generated to sample population parameters from the variance-covariance matrix to take into account uncertainty.
I understand why PK parameters have lognormal distribution (because physiological parameters can not be negative) but why does the omega parameter have a lognormal distribution and not a normal distribution?	Omega is the sd of the random effects V = Vpop * exp(eta) with eta a random variable with mean=0 and sd=omega. So omega does not have a distribution (except if we consider the uncertainty of omega in the variance-covariance matrix. There we assume a lognormal distribution to avoid sampling negative omega values, which would not make sense).
I have a question regarding yesterday's "homework" - I chose to center WT on 70 kg instead of mean. My covariate was log(WT/70) instead of log(WT/67.8332). I got quite a different model. Is it normal that such a small change so visibly impacts the results? For example - my best & only cov was this logtransformed WT on V1, and V1 was 141 instead of 25. Beta was 0.8 instead of -0.18. Is it ok?	It seems indeed like an unexpectedly large change in the results. It is hard to say more without having a look at the project. I recommend having a further look at the results to compare the fits and the BICc to check if the model has been well estimated with correct results. If it is the case, and other parameters such as ka_pop also have large differences, it may be a flip-flop. This is explained here: https://www.youtube.com/watch?v=jIKBuTfAn8E&ab_channel=Lixoft
How can we fix the beta terms for covariates?	Beta parameters can be fixed in the Initial estimated tab if you click on the settings icon next to the parameter name.
Is there a particular strategy in Monolix to handle highly correlated covariates?	Highly correlated covariates will be taken into account in Proposal, so if you have two highly correlated covariates, Proposal will suggest adding just one of those two.
Since I guess R0 has a logit distribution, is it better to have R0=1 rather than R0=100?	You can specify the limits in the logitnormal distribution, and change them from 0-1 to 0-100. Click on the icon next to the

	"logitnormal" distribution in the drop-down menu
I have a PKPD model from the literature with parameters and their RSE%. How to correctly select proper omegas for those parameters in Monolix? Could my initial guess for omegas be the %RSE or I should try another approach?	These are two different things. RSE describes the uncertainty of population parameters. Omega parameters are standard deviations of random effects. They are also population parameters, which you can estimate. The default value (1) is usually a good initial value to estimate the omegas.
In the example with ClwithWT, you have to call table(ClwithWT) for the value, otherwise monolix shows you the value of Cl, is that right?	Yes you would use table = {ClwithWT} in the output section of the model
Is there a trick to add a time-varying covariate to the model, and make the model run fast because when I tried it, it took a very long time to finish running.	No, non-constant regressors (for example a time-varying covariate) make the analytical solutions not available, so the run will be slow compared to the analytical solution if it was available.
Should regressors have only increasing values? In the case of blood pressure for exemple, for one patient, at several times, the pressure can increase and decrease, so which covariate should be chosen?	Regressors can have increasing or decreasing values with time. Covariates have to be constant in time. Detailed information can be find here: https://monolix.lixoft.com/data-and-models/regressor/
How to test covariates significance using SAMBA if one of the covariates is time-varying?	Monolix, and automatic model building algorithms, cannot handle time varying covariates yet.
Could we use the same categorical values for different categorical covariates? For example: Treatment (responder = 1, non-responder = 0); Sex (Male = 0, Female = 1)	Yes, covariates can have the same categories as others and stay independent.

Estimation

Can we use other parameter estimation algorithms? FOCEI, laplacian, etc?	Only SAEM is implemented in Monolix, and Nelder-Mead for parameters without inter-individual variability. SAEM is very efficient for both simple and complex problems. If SAEM does not converge, probably the model is not identifiable and using a different algorithm would not help.

Does Monolix solve problems of identifiability?	If a parameter is not identifiable, several diagnostics will hint to it: high relative standard errors indicating poor confidence in the estimated parameter, parameter estimation that keeps drifting and warning message that the convergence criteria have not been achieved, very different estimates obtained when running the "convergence assessment" tool.
Can auto-initialization be done in R using lixoftConnectors?	Yes, the function is called fillInitialParametersByAutoInit().
Which algorithms are used in the backend for auto-init calculation? Could you please provide the reference?	We use a custom algorithm whose details are confidential. The general idea is a deterministic fit using the Nelder-Mead algorithm on the pooled data.
What's the algorithm for picking initial values? How good is the algorithm in treating local minimums?	The details of the algorithm are confidential. In short, we use a deterministic algorithm on the pooled data. It may stay stuck in a local minimum. It is a help but you don't have to accept the auto-init result as a starting point if you think these values are not appropriate. For complex models, our experience is that working on a single representative individual works very well.
When we use autoint, does it apply only for new parameters, and not for the parameters for which we have used the previous estimates as new initial values?	The autoinit will work on all parameters except those which are marked as "fixed" (in the "initial estimates" tab, small wheel button next to each parameter value). So the initial values that came from previous estimates will be updated. If they were already good the autoinit should not change them much.
Does SAEM always find the global minimum, or some local minimum?	We cannot guarantee that the algorithm will converge to the global minimum. One of the ways to assess if the algorithm converged to the global or local minimum is the convergence assessment tool available in Monolix. More on that here: https://monolix.lixoft.com/tasks/algorithms-convergence-assessment/
SAEM is stochastic by nature. How is reproducibility ensured?	The random seed is fixed in the project settings. Thus when you rerun SAEM on the same project you will always get the same results.
How reproducible are the modeling results in Monolix? Can someone else reproduce my results on another computer?	Yes, results are completely reproducible. More on that here: https://monolix.lixoft.com/faq/reproducibility/

For individual estimates, which ones are recommended to use: Mode or Mean or SAEM?	It depends on the goal. For individual fits and pred vs obs plots, use the mode (EBEs, most probable parameter value). For diagnostic plots showing the parameters or random effects (e.g param versus covariate), use the sample from the conditional distribution, as they avoid bias due to shrinkage. The "SAEM" is just an approximate mean calculated on fewer samples. It should never be used.
Is the M3 method for BQL available in Monolix?	Yes, the M3 method is the method implemented automatically in Monolix. You only need to use a censoring column in your data set to mark censored data.
Can you please explain the M3 method and how it is implemented in Monolix? or any link related to it? Thanks!	It means that Monolix will use in the likelihood the probability p(observation<LOQ). More information here: https://monolix.lixoft.com/data-and-models/censoreddata/
Can we develop a model in Monolix if we have only trough level concentrations in steady-state available?	You can, but you will have to fix two out of three (ka,V,Cl) parameters in the model.
Do we have any number to decide the model? AIC and BIC?	Yes, AIC and BIC are provided
What does BIC mean?	BIC is an acronym for Bayesian information criterion. It is a criterion for model selection based on the likelihood function. Lower values are preferred.
Which metric is more important in comparing models in Sycomore: -2*LL or BICc?	BICc is preferred as it includes a penalty for the number of parameters in the model.
Can someone provide an intuitive explanation of BICc and why a lower value is better?	Like the other information criteria, BICc = -2*LL + penalty. The penalty involves the number of parameters in the model, and the number of observations. The goal is to maximize LL (log-likelihood), and thus to minimize BICc. The penalty is there to select models that capture well the data (high LL) with fewer parameters, to avoid over-parameterization.
You said that the BICc was not significatively different between 1 and 2 cpt but there is no statistical rule to state that contrary to the -2LL value, is that right ? Is any decrease of the BIC, even as small as 0.1 or 0.2 sufficient to select the model with	Indeed, there is no statistical rule, it is only a rule of thumb. The decision should not be made only based on the BICc value but also the diagnostic plots, parameter identifiability (RSE), etc.

the lowest BIC ?	
Can monolix perform statistical comparison and indicate whether the model improvement is significant or not?	A statistical comparison can be done using the LL values via a likelihood ratio test. It is done when using the automatic covariate search procedures (covered in tomorrow's session). But it cannot be done automatically between any model because there are several requirements (e.g nested models) which cannot be tested automatically.
There is no OFV?	The OFV (-2*LL) is provided in the Results tab along with AIC, BIC and BICc
If the RSE% value is colored in orange, what are you supposed to do?	The orange color means that the RSE is quite high, so the parameter is estimated with quite poor confidence. What to do depends on how you want to use your model afterwards. One option is to remove the random effects on this parameter, to make it easier to estimate.
Can Monolix 2021 perform bootstrap?	Bootstrap option is available through the Rsmlx R package. http://rsmlx.webpopix.org/
In the case where log-parameters are estimated, the parameter estimates and SE are reported in Monolix output as non-transformed values. If I want to transform the variance-covariance matrix back to log-space, then I should use the Jacobian (I think the transformation is J*VarCov*Jinverse). Can I get that Jacobian directly from Monolix? How about the objective function, or the Hessian?	The Jacobian is not outputted by Monolix. If you would like to transform back and forth, you need to calculate the Jacobian by yourself. It is a diagonal matrix, and the terms on the diagnocal are the derivatives so d(log(x))/dx = 1/x for instance.
If I want to run an external evaluation of the model fixing the population parameters, which value of individual prediction given by monolix should I use to calculate MPE and RMSE? A) ind pred Saem B) ind pred mean	ind pred mean
What should I do if the robustness of Vd in the convergence indicator was not good?	It may indicate that Vd is difficult to estimate, maybe because the data is not rich enough, or maybe because of correlations with other parameters.
Do we often need to adjust the settings for parameter estimation algorithms and	No, most of the time you do not need to adjust the settings. In case you reach the

convergence criteria before running?	maximum number of iterations and convergence has not been reached (there will be a warning), you can increase the maximum number of iterations. This is the main setting that may need to be changed sometimes.
How can I confirm that the Tlag parameter should be in the final model ?	Tlag is useful in the model if it is estimated to a significantly positive value with a good standard error.
Is information sampling like identifiability or sensitivity of parameters?	"Importance sampling" is a way to calculate the likelihood. Maybe you are referring to the "convergence assessment" which allows you to start several runs from different initial values. The convergence assessment indeed allows to check the identifiability and sensitivity of the parameters.
When the dataset contains insufficient concentrations to describe the absorption and distribution phase, would it be possible that the “auto-init” function generates a set of initial values for typical parameters that are not plausible?	Yes if the data is not rich enough the autoinit might find wrong/inadequate values. In that case you should choose good initial values yourself.
How do we know if the sample size is adequate to predict accurately the parameters and capture random/covariate effect?	If the data is rich enough to estimate robustly the parameters, they will be associated with small relative standard errors.
Of course this is a monolix course, but if you'd like to answer, is simulated annealing available as an option in NONMEM SAEM method too?	To my knowledge, a document explaining how to do something close to simulated annealing in Nonmem is available, but it involved a lot of manual steps and was not very straightforward.
How does Monolix obtain individual subject parameter estimates after obtaining the population estimates? It reuses the data?	Yes, individual estimates are based on the population estimates and the individual data.
I've been in a situation before where the pop fit described individual data better than the individual fits - any ideas why that may be the case?	Note that the estimation of population estimates also estimates values for the individual estimates, but they are less precise than the EBEs estimated in the dedicated task. So the individual fits you see in the plots after running even only SAEM are not population fits. Population fits can be displayed along with the individual fits by selecting the corresponding option in Display. The situation you describe sounds strange indeed. Maybe the population fits seem better than individual fits from a visual

	point of view, but the likelihood from individual fits should actually be better.
If the simulation annealing option is enabled, how would you determine whether etas could be really kept in the statistical model?	Deciding which eta needs to be included or not in the model is a difficult question. One option is to remove the simulated annealing to see if they are going to very small values. We also have a prototype procedure implemented in the Rsmlx package to detect which parameters need random effect or not. You can test it at http://rsmlx.webpopix.org/userguide/buildvar-2/
Does high shrinkage mean poor results?	High shrinkage indicates that the data is too sparse (does not contain enough information) to reliably estimate individual parameters.
Is it possible to get quantiles of the conditional distributions (for each individual) instead of the mode?	In the result folder we provide the mean and sd. If you need the quantiles, you need to increase the cond distrib task setting "number of simulated parameters" to a high number (more than the number of iterations of the task) to recover all samples from the conditional distribution in the result folder and calculate the quantiles by yourself.
Is it not possible to run conditional estimation distribution in NONMEM? Or does it require an extra step of coding?	To my knowledge, conditional distribution has been implemented in recent Nonmem versions. However its implementation may be less efficient than in Monolix.
Does this mean that when looking at the conditional distribution you don't have to worry about shrinkage at all? e.g. when using monolix vs nonmem shrinkage isn't an issue?	When using the samples from the conditional distribution to look at the diagnostic plots (for instance param versus covariate), shrinkage is not an issue. For the estimation of the population parameters, the SAEM algorithm does not use the EBE, so here again the shrinkage is not an issue.
If data is sufficient to estimate individual parameters (EBEs), then conditional estimation and conditional mode (EBEs) should provide similar shrinkage values?	Yes, in that case the conditional distributions (which represent the uncertainty for each individual) will be very narrow and using a random sample from this distribution or the mode (EBE) of the distribution should lead to very similar shrinkage values.
How should you change your model if one of the tests indicates non-normal distribution?	The test checking normality is quite sensitive, so if all other results seem good it might not necessarily be an issue. In this case you should have a further look at the

	distribution of the parameter or the scatterplot of residuals (depending on the object checked by the test) to see if describing parameters/observations with another distribution could be more appropriate.
Can we save different sets of parameters for different scenarios, species, etc.? And then call upon any particular set for a simulation?	Different sets of parameters would rather be defined as Simulx elements (shown tomorrow) rather than in the model file.
How are BLQ values handled in Monolix? Are there any options besides censoring?	They are either considered as censored (i.e "probability to have a measurement < LOQ") or just ignored.
How to extract some individual PK parameters? Do they get saved in csv or text files in the results?	Yes, the EBEs are in the result folder /IndividualParameters/estimatedIndividualParameters.txt, columns *_mode
What is the criteria you use to assess accuracy among the joint, intermediate and sequential PKPD approaches?	"Accuracy" is maybe not the best term here. With the joint approach, you use all the data at the same time so you are using the maximum available information, so your parameter values will be better.
What tools does Monolix offer to evaluate PK/PD models?	All the diagnostic plots shown yesterday are also available for PK/PD. Sycomore for LL and BICc comparison also.
In the hands-on solution 1, it's indicated to disable simulated annealing, but I understood it's important to keep this option enabled to avoid a fast decrease of the omega parameters during the exploratory phase to find the global minimum?	For the first run we keep the option on to help the SAEM find the global minimum. If the omega parameters decrease during estimation, and are small, you can then try a run with simulated annealing disabled, starting from the last estimates so that you stay close to the global minimum. Please take a look here for more details; https://monolix.lixoft.com/tasks/population-parameter-estimation-using-saem/
For the manual sensitivity analysis, the parameter is only changed but the model is not re-run, correct?	If you ask about the convergence assessment, Monolix runs the estimation task for each set of new initial parameters.
After disabling simulated annealing, I had an error message "(stopped at the maximum number of iterations/auto-stop criteria have not been reached)". This message indicates that this model should be not taken into account or it is ok ?	It does not necessarily mean that the model is incorrect. When running SAEM the maximal iterations numbers are set to default values, which are sufficient in most of the cases. For some problems, complex models, sparse dataset, not optimal initial values, the SAEM algorithm might need more iterations. You can increase them in the task settings. Please take a look also in the online documentation

	https://monolix.lixoft.com/tasks/population-parameter-estimation-using-saem/

Diagnostic plots

Some journals do not accept graphs/plots exported from Monolix for image quality reasons. Is it possible to regenerate all those Monolix plots on R ?	It is possible to do it using lixoftConnectors package. To find out more, you can take a look at the following video: https://www.youtube.com/watch?v=fzHLYDu2GjI Moreover, exporting the plots of Monolix in svg format should yield a good image quality.
What is the difference between censored data, simulated censored and corrected censored when plotting VPCs?	This video explains well the simulated censored data: https://www.youtube.com/watch?time_continue=2&v=gEwCrPpW0tU&feature=emb_title In the VPC you can either choose to display censored data as LOQ or as simulated censored.
Can you overlay simulations for two treatment groups on the same plot in Simulx?	Unfortunately not in the GUI (graphical user interface). But you can use the R package RsSimulx to do so: https://simulx.lixoft.com/rssimulx/
Can the VPC be applied to censored data in monolix?	The VPC uses censored data by default, you can choose to remove them in the section Display next to the plot.
Can the number of simulations be modified for the generation of VPCs?	Yes, this can be changed in the plot settings (settings icon next to the Plots task)
How can we use pc-vpc in monolix?	By default the VPC is not corrected, there is an option in the Display section next to the plot to display the pcVPC
Can you edit the text in the X and Y axis title?	On most of the plots the axes labels can be changed, in the panel Display next to the plot.
For the distribution of the residuals: is it possible to obtain statistical indications of the normality?	Yes, this information is available in the tab "Results/Tests/Residuals".
Is there any specific package in R to facilitate plotting the Monolix charts?	The MonolixSuite API lixoftConnectors include functions to generate the same plots as in the interface. See here: https://www.youtube.com/watch?v=fzHLYD

	u2GjI&feature=youtu.be
Why do some PK profiles have 1 compartment and others have 2 compartments for the same drug?	The 2nd compartment is not necessarily visible for all individual data. It is more visible for high doses.
What to do when the misspecification concerns high concentration?	Usually this shows in the Obs vs Pred in linear scale.
What is the VPC, what is the implication and how is it generated in Monolix?	VPC stands for visual predictive check. It is a useful diagnostic plot which summarizes the data into percentiles, and compares them to the same percentiles computed from model simulations. You can learn more about it here: https://youtu.be/bVpHPmufcbo
What could be the reason for the negative value on the y axis of VPC?	If you have censored data without a lower limit set to zero, the simulations of these observation times can result in negative values. In addition, if there is a constant term in the residual error model with a normal distribution on the observations, negative observations can also be simulated.

Sycomore

Does Sycomore take into account nested models ?	Sycomore will not detect automatically if the models are nested or not.
Can you show how to run Sycomore with 3 models at once, what results are expected?	Simply add one more model on the left panel. Everything else is the same.
Can Monolix workflow be loaded in Pirana?	No
I already have Monolix installed and cannot find Sycomore in there?	All applications are installed at the same time, including Sycomore.
Is it possible to use Sycomore with PKanalix for NCA, CA?	No, Sycomore can only read Monolix projects.

Simulx

Will mlxR continue to be updated ?	You need to switch to RsSimulx, which will be maintained.

Is Simulx included in the Monolix license?	It is included in the free academic license, but not in the commercial one. The installation process installs all applications, but then depending on your license (if you paid for Monolix, Simulx or for both) you will have access to the application.
Does Simulx calculate sample size for the clinical trial?	It does not by default, but you can use lixoftConnectors R package to simulate trials with different sample sizes, calculate their powers and optimize the sample size.
I tried to calculate AUC 0-12 in Simulx. Simulx gives me an output of AUC at times 0-1-2-3 etc. If I did it correctly, what does AUC at time 4 mean ? AUC 0-4?	Yes, if you did that correctly, AUC at time 4 means AUC0-4.
What is the difference between MlxpopuncertainSA and the population parameter generator in R simpopmlx?	The exact values could be different as they are not implemented in the same way, but they will give the same population parameters distribution.
What if have so heavy data that exporting from Monolix to Simulx causes a crash? Can we load individual files from Monolix to Simulx?	Yes, you can define individual parameters elements as an external using a table with individual parameters values.
Previously addLines was not working unless exported from monolix, I hope this issue has been solved.	Yes, it is solved.
Where does the model shown in the lecture come from? The one in the material of lecture 4 is different from the one which is shown.	In the lecture materials, there is a folder called "monolix project" which Pauline exported to Simulx
There are papers which only upload their .mlxtran and model.txt files with no data. Does Simulx help simulate such models?	You could use mlxtran file, model file and estimates, if they are published, to simulate such models. But even if there is no mlxtran and model.txt file available, but the estimates and model details are published, you could recreate the model in Simulx. You can take a look at the relevant video: https://www.youtube.com/watch?v=Jn-F2UEfNJ8
Do I have to specify the block, like longitudinal, if I add an additional model line in simulx?	No, additional lines will be in the EQUATION section by default.
Is there a tool or software available to organize information from Simulx projects, similar to Sycomore for Monolix? If there is not, are you planning to develop a software that can help with Simulx projects	Currently there is no application equivalent to Sycomore for Simulx, but we plan to develop it in the future.

organization?	
Is there a way to import parameters from another source (Excel ?) or model into Simulx ? If yes, what is the format to use ?	Yes, they should be in a txt file with comma separated values, containing id column and one column per each parameter.
How do I start Simulix if I can only see the monolix icon on my desktop?	Type "simulx" in the search, or go to C:/ProgramData/Lixoft/MonolixSuite2021R1/lib where you find the .exe files
Will there be an explanation on when to use simpopmlx and where to use mlx-popuncertainSA?	Simpopmlx is part of the mlxR package that is no longer maintained. It was a workaround to generate population parameters to be used with Simulx2020 which did not provide mlx_popUncertainSA. With Simulx2021 you should always use mlx_popUncertainSA.
How does Monolix sample new covariate vectors if the covariates include categorical columns?	Take a look here: https://simulx.lixoft.com/definition/covariates/
How could we output Peak/(fixed) MIC ratio in Monolix or Simulx?	It is explained in this feature of the week video : https://youtu.be/Q3wmyxTHg8s
Is it possible to define a treatment in Simulx with a parameter like weight without actually having that parameter as a covariate in the model?	Simulx uses only covariates added in the model. If you do not want to use it, the workaround is to add it in the model and fix the corresponding beta parameter to zero.
Can I use Monolix or Simulx for bootstrap? If yes, how?	You can use the R package Rsmlx which offers a bootmlx function. http://rsmlx.webpopix.org/userguide/bootmlx/
What is the difference between mlx_yPK and mlx_Cc? Why do we need to predict two PK outcomes?	mlx_yPK outputs plasma concentration with the added residual error, while mlx_Cc outputs a "smooth" plasma concentration prediction..
Quite often we need to predict concentration profiles for individuals based on actual dosing and actual dosing time. Is it possible to do it with Simulx GUI?	You can define different dosing times manually for different individuals. If you are asking if the dosing time can have some "uncertainty", then the answer is unfortunately not in the GUI. You could simulate this kind of dosing time uncertainty in R, for example, and import the simulated dosing times in Simulx.
With Simulx, is it better to put the dose in mg or in mg/kg?	For Simulx there is no difference. It depends what you want to simulate.
Which model details from a paper are needed to recreate the model in Simulx, except parameter estimates?	Everything that is needed for you to write the model file. If the model is simple enough, you can often assume the model

	details from the parameter names.
The link regarding covariates (https://simulx.lixoft.com/definition/covariates/) states that “an auto fill option allows to automatically fill one or several of the categories” for categorical covariates. Is this implementation accounting for correlations between continuous and categorical covariates or are the categorical covariates just randomly sampled to fulfill the defined fraction?	Currently, Simulx cannot simulate correlated covariates. However, you can generate them in, for example R, and define in Simulx a covariate element as "external" with this table.
How and where units in amount in Simulx and concentrations in Monolix can be defined? Is there a way to scale them properly?	Simulx, as Monolix, does not take care of units by itself. The units depend on your parameter values, and you need to know what should be the value of a dose in agreement with the units. However, there are several possibilities of scaling the units in the model, we covered them in yesterday's session.
Can we upload an external file of treatment nonadherence to predict PKPD using Simulx?	It is not possible to load an external file of treatment nonadherence, but you can upload an external file of individual dosing regimen that can include nonadherence.
How does the repeat option differ from the occasion section?	The repeat option allows to define only a treatment element with a dosing regimen that repeats several times in regular cycles. Occasions are applied to all simulated objects. Take a look here: https://simulx.lixoft.com/definition/occasions/ and here: https://simulx.lixoft.com/definition/treatments/
So, Simulx takes care of matching the time points from an external Treatment file and its internal ODE time?	An external text file to define treatment is a text file with: columns id (optional), occasions (optional), time (mandatory), amount (mandatory), tinf or rate (optional), washout (optional). So the doses are given at times specified in this file.
Where can I find an example of an external treatment file that differs between individuals?	You can export a Monolix project with different dosing times between individuals to Simulx and save it. A folder will be created next to the project with an ExternalFiles subfolder in which you can find the example treatment files. You can also in Simulx the demo project named treatment_external_byAgeGroup.smlx (demos 3.1).

Is there an easy way to convert days to hours when entering the treatment interval for simulx?	You cannot do it inside the Simulx GUI, you would have to do the calculation beforehand.
What does the intercept represent in this case?	The intercept is the value that will be added to each dose. Please, take a look at this video: https://youtu.be/LHBcVSaQfcU or in this documentation page: https://simulx.lixoft.com/definition/treatments/
Why use mlx_cc and not mlx_Y as mlx_Y considers the effect of residual error?	mlx_cc corresponds to the model prediction, while with the "y" it is the model observation: model prediction + error model. We use mlx_Cc for the sake of the demo, because smooth predictions are easier to check.
How to perform sensitivity of a fixed parameter? Simulx manual sensitivity would be the option to go for? or convergence assessment?	Both would work depending on what you mean by "manual sensitivity". Convergence assessment runs the Monolix estimation task several times for different initial values of the parameters, including for fixed parameters if they have been selected for sensitivity. In Simulx, in the Exploration tab, you can modify the parameter values and see how the model prediction changes - it is just a calculation of the model prediction for new parameter values (it is a fast calculation so you can see the result in real time).
Is it possible to post-process PK simulations to extract an AUC (e.g. to assess AUC above a defined value)?	You can either define the AUC calculation in the model directly (additional line ddt_AUC=Cc for instance) and then define an output element for AUC. Or you can export your data with Export > Export simulated data and import the MonolixSuite-formatted data into PKanalix to calculate AUC using the usual NCA rules (see the spring school next week).
Is there a documentation page on lixoft website that provides the specification of the external output file to be used in Simulx?	Yes, for each element, there are all possible options described in the Simulx documentation. For example, for the treatment element, you would find the description here: https://simulx.lixoft.com/definition/treatments/, under section External.
If I understood correctly, checking the box "same individuals in groups" should be useful for crossover designs?	Yes, for instance. For crossovers, you can also define occasions and two groups, one for each sequence.

Could you please show us parametric boostrap and non-parametric boostrap of clinical simulations for efficacy?	I am not sure what you mean exactly. Doing replicates of a clinical trial simulation is a kind of parametric bootstrap: different individuals and simulated observations are generated for each trial. Non-parametric bootstrap usually refers to re-sampling an existing data set (simulated or not), but here it would be much more cumbersome to do and less powerful.
How can I recreate population uncertainty in Simulx? Using the RSE, omega or IIV values for particular parameters?	After importing a monolix project, the elements mlx_PopUncertainSA/lin are created automatically. When they are selected in the Simulation tab together with replicates, they can be used to generate samples of population parameters from their uncertainty distribution. If you do not have a Monolix project, you would need to sample by yourself the pop param and then give them as an external file when creating a pop param element, as you cannot give RSE values directly in Simulx.
Can I run the simulation for a hypothetical situation, e.g I don't have PD data but I have parameter values for PD?	Yes, Simulx works as an independent application and you can create a simulation scenario from scratch, see here: https://simulx.lixoft.com/overview/new-project/
Can I generate random weight for simulation?	You can define a covariate as a distribution, or generate random values, for example in R, write them in a table and define a covariate as "external" with that table.
Is it possible to scale by WT and also another covariate ,for example if homozygous 0.075 mg kg, else 0.1 mg kg?	It is not possible to combine dose scaling by different covariates in Simulx. You woud have to use external tables for covariates and doses, with the scaling already done in these tables.
I am wondering if I have it right about the values set for probability in the sampled population. In the exercise, we only want to sample RA patients, so we set the value as “1” which stands for 100% of the population is RA patient.	Yes, it is correct.
Usually what is the acceptable successful rate before getting into the clinical trial?	We have no answer for this. It probably depends on the type of drug, ratio of benefit/risk, the pharma company...
Does Simulx have a way to simulate until steady state is achieved?	You would need to define a treatment element with an appropriate number of

For example to obtain AUCss, Cmaxss, etc	doses, for example using a regular method to define multidose, leading to steady state. Then, you can define an output only on the time interval that is of interest to you.

Time-to-event

For time-to-event data, how to handle a scenario in which an event also has a specific intensity? For e.g., I have time of seizure and intensity of seizure (mild, moderate, ...)	You could build a joint model with two outputs for event and intensity, where the intensity probability would be predicted at all times and correspond to the intensity of a potential seizure if it happens...
Aside from the inbuilt TTE models, can one define a new hazard function for example lognormal distributed TTE?	Of course you can always write your own model. You can reuse a model from the library to have the basic syntax ready, and edit the hazard function to replace it by your own.
Is it better to apply a covariate on the hazard or on one of the parameters (Te, p...)?	It is hard to say, on the hazard it is convenient as for some models the covariate parameters allow to compute the hazard ratio (cf https://www.youtube.com/watch?v=1ChymTGMaMY), but on the parameters it can be appropriate as well.
How do we handle continuous covariates in TTE models?	Since we use a parametric approach in Monolix, continuous covariates can be handled the same way as for continuous models: you can add a covariate effect on a parameter of the hazard or the hazard itself (cf https://www.youtube.com/watch?v=1ChymTGMaMY)
How can you calculate the hazard ratio from the model?	You can take a look at this video https://youtu.be/1ChymTGMaMY It explains proportional hazard models and how to calculate the hazard ratio.
Can you directly link h to the different survival functions implemented on Monolix or do you have to write your own (or copy it) ?	The link is done directly in the structural model in the definition of EVENT (used to calculate the survival function).

Other

Datxplore and Sycomore also came with the MonolixSuite. What are these programs used for?	Datxplore is for data visualization. Sycomore is for managing and comparing different Monolix runs.
Does FDA accept Monolix-based analysis for regulatory submission?	Yes, more details here: https://monolix.lixoft.com/faq/submission-of-monolix-analysis-to-regulatory-agencies/
So with no modeling challenge this year, is there another way to train ourselves after the spring school?	We have several case studies available online, for which we provide the datasets to train: https://monolix.lixoft.com/case-studies/
How is Monolix different compared to WinNonLin ?	WinNonLin is mostly for non-compartmental analysis. The NLME module of Winnonlin can also do population PK/PD modeling. It is however harder to learn compared to MonolixSuite.
What are the advantages provided by Monolix vs Nonmem?	Monolix has a clear user-friendly interface, with interactive plots that help diagnose the model, and the algorithms are also faster and more powerful.
What is the roadmap for the future in terms of reporting? Is there any plan to build some "integrated" report in a single file (Word, PDF or whatever) for a particular run that would summarize all the inputs/settings and the results/outputs?	Yes, we are working on this for the next release planned for early 2023.
Can Monlix do the model comparison to assess which model produces a better fit such as without Tlag or with Tlag, 1-compartment vs. 2-compartment model?	Yes, in MonolixSuite there is a tool called Sycomore, whose purpose is to make comparison of different models easier. We will extensively use Sycomore during the course of these few days, so stay tuned.
Do you plan to implement an "optimal sample design" based on a model (optimisation of sample times for PK and/or PD data) ? This could be really useful (something like PFIM but with a more "user-friendly' interface).	This is not on our short-term roadmap, but is in our "to do" list for the future.
Do you have on your website an updated list of publications using Monolix for PK analysis ?	There are so many publications with Monolix that we do not keep a list of all of them!
Will it be possible to show how to subset data and use the subsetted dataset for modeling?	This will probably not be covered in the spring school but you can watch our videos https://www.youtube.com/watch?v=lBFVZ0ZSnwY&ab_channel=Lixoft

What is the working directory of monolix runs? How can we set the working directory?	Before running, do a "File > Save as" (top menu). The results will be created in a folder next to the saved .mlxtran. You can change the folder in the project settings. If you do not save, the results are going into the Temp folder on your computer.
I want to compare two models (for example after adding Tlag), is it possible to add a new tab to the current project to switch between two projects?	A Monolix window can show only one model at a time. However you can open several Monolix windows if you wish, or use Sycomore to compare models side by side.
How can I delete a Monolix project?	A Monolix project (.mlxtran file) is actually a text file. You can delete it manually on your computer like you would for any text file. You should also manually remove the associated results folder if you have run some task. In Sycomore, you can untick it in the left panel.
What if you want to randomly select individuals by IDs?	Random selection of ids is not possible in Monolix.
I couldn't find the new ggplot functions in LixoftConnectors, are they currently available?	Yes, they are available. You need to install the lixoftConnectors of the 2021 version. All the plotting functions start with "plot", for instance plotObservedData().
Can we have an idea of computer properties (workstation) you used at Lixoft for PK/PD modeling of average sample size (100 patients / 5 samples by patient) in terms of processors and RAM or other useful components ?	For the RAM, 16 GB is good. For the processor, it all depends how long you are ready to wait for your results.
Can you provide any article that has DDI equations for reference ?	We do not have this available at hand.
What are the drawbacks (if any) of normalizing the data (here the PD data normalized to the baseline) versus using the raw data and estimate the baseline level (the main advantage being to have one parameter less to estimate as far as I understand)?	It would probably depend on the situation: data and model, and also on the questions you would like to answer using your model.
Do you plan to include unit management in next versions?	Units for models from the Monolix libraries are on the list of future features. Maybe in the next release.

In the hands-on 1, I realized the 2cmt_Tlag and I compared the initial values of this model and yours (pk_2cmt_Tlag) proposed in the hands-on solution 1 and they are the same. I continued with my model and restarted with no eta on Q and V2 and I compared again with your model and now I haven't the same results, not the same correlation and not the same initial values. What can explain this difference?	The results may change if the models have been run on different machines, and different operating systems . The calculation depends on the seed, sequence of random numbers, which can be generated differently.
Why don't we use a model without eta on Q, V2 and ka in the hands-on 2? I tried this model and the model without eta on Q and V2, and the BICc is a little bit lower with the model without eta on Q, V2 and ka.	Good catch! We didn't want to make the hands-on too long, so we skipped this part but this is definitely a good option too.
Why didn't you use all last estimates in the model pk_2cmt_Tlag_noSimAnn to realize the model pk_2cmt_Tlag_noEtakaV2 ? I thought it was better to click on it every time before a new run, is this not the case ?	In this case, the initial values were already pretty good, so using "use last estimates" didn't change much. There are often many different modeling "paths" which are equally good and modeling is not a deterministic science.
GUI corresponds to ?	Graphical User Interface
Are the data used in this spring school related to publications ? Can we trust the models or are they totally random (Warfarin / mAB)?	The warfarin and mAB examples use real data, but the modeling choices are ours and not published.
Do you have an up to date listing of the publications of your team ?	A list with links to our publications is here: https://lixoft.com/lixoft-university/