Challenge solution webinar

Q&A session

Questions	Answers
What didn't you use transit compartments instead of lag time?	We have also tested transit compartments (after the webinar). The Mtt parameter converges to the same value as Tlag, and Ktr to a very large value. The LL improvement is small and the predictions close to those of a model with Tlag. Note that models with Tlag runs faster due to the existence of analytical solutions.
Would adding dose group as a covariate achieve different results?	Dose could be added as a continuous covariate on the absorption parameters leading to a dose-dependent ka for instance. However defining the dose-dependent ka in the structural model using amtDose gives more flexibility to define the shape of the relationship (here Michaelis-Menten). In general, it is better to find a true mechanism which could explain the data.
Are there specific materials (books etc.) that address the writing/rationale/coding/ mathematics of "general" (and complex) PK, PK-PD models and in pharmacometrics in general?	You can have a look at the CPT tutorials, for instance: “Basic Concepts in Population Modeling, Simulation, and Model-Based Drug Development” (Part I to part III)
Why don't you use pcVPC instead of VPC, as there are many different doses?	Indeed, using the pcVPC makes sense such that the upper percentile (for instance) takes into account the entire data set and not only the upper doses. Both are complementary.
Why is the reason of using -2×loglikelihood and not BIC when comparing models?	The -2LL will always improve when the model becomes more complex (as more complex models have more flexibility to fit the data). The likelihood ratio test (i.e 3.84 point difference) is valid only for nested models. Information criteria such as the BIC take into account a penalty for the number of parameters to help choose a parsimonious model, and do not require nested models.
Is the saturation expressed as a Michaelis Menten equation ?	Yes
When looking at the PK data of the parent drug, it seems that there were 2 peaks for oral route. Was this explored instead of the saturating absorption process?	Some individuals may seem to have two peaks because of measurement noise, but this was not a consistent trend across individuals.
Do you use a threshold for BICc decrease to keep or remove a covariate? If yes, which value is used?	In the automated approach using BICc there is no threshold, it just has to be better.

Can you comment on your covariate search: how does the regulatory view this via Monolix?	The automated approaches are precisely documented on our website and are acceptable from regulatory point of view. The SCM implementation is the same as in other software. The COSSAC method has been shown to perform equally well on a large number of true data sets (see https://ascpt.onlinelibrary.wiley.com/doi/10.1002/psp4.12612)
Why covariate analysis is performed on the PK model only and not on the joint final model?	For computational time reasons, it is convenient to start the covariate search once the PK structural model is ok. But it could be done at the end on the joint model also.
In real time, if provided with a formatted dataset, how long would this task have taken for the typical Monolix modeler to conduct the first step (IV, oral parent and covariate search) and the next steps (IV, oral parent and metabolite)?	It really depends on the experience of the modeler! It is quite fast to test different ideas of models on the same data in Monolix. For such relatively small data sets which run fast, a Lixoft modeler (not knowing the solution of course) would need around one day to build the PK parent model, and would then let the covariate search run overnight.
Please could you confirm that we need to use plasma concentration in molar unit (umol/L) and not as usual in ng/mL when fitting simultaneously parent and metabolite to account for difference in molecular weight?	Yes. When one molecular species is transformed into another one, or when two molecular species binds together (for instance in TMDD models) it is important to work in molar units because 1 nmol of parent transform into 1 nmol of metabolite. On the opposite, if parent and metabolite have different molecular weight, we cannot say that 1 ng of parent transforms into 1 ng of metabolite.
A more detailed explanation on F? (in relation to not including IIV in the previous estimation of the parent drug).	F is the absolute bioavailability of the oral formulation. Because we have both IV and oral data, we are able to estimate F. However, as each individual has received either the oral or the iv dose but not both, it is not possible to distinguish the variability on F and on V. We thus remove the random effects on F, as they are not identifiable.
Is the modelling procedure the same if the metabolite is not a direct metabolite?	It depends on the prior knowledge we have about the intermediate steps. In first approximation, you can consider that the metabolite (although not direct) is produced from the parent, as we have done here.
Following this challenge, what advise will you give to be a stepwise approach to use the pk model in solving the challenge?	We advise to follow the stepwise approach shown here: start with very simple model and make it more complex based on seen misspecifications. Before running a new complex model, the model behavior can be explored in Simulx to check if it has a chance to resolve the misspecification. PKanalix (NCA) can also be used to spot for instance that the Tmax is changing with the dose.
Is the estimated value for the fixed effect the median value or the mean value?	The fixed effect (e.g V_pop) is the median of the population distribution.
Can you show final BICc please?	The BICc for the final model is 12164. The BICc of the model provided by the winner is 12460.

Could you give us link to access the SPECIFIC video recordings of the last spring school?	The spring school videos were available only during the time of the spring school (i.e until April 16th).
How do we get uniform outputs, I select Cc and duration with interval it gives different time interval for example for 10 days with 1 hr sampling, I get for 10 days but sampling is some random number like 5 or 6 hrs	The output is uniform if you have set it so. However, for the output distribution plot, we bin the data so there can be a bin every 5 or 6 hr for instance. The binning can be change on the right panel.
We have to keep in mind that probably with TID a lot of patients will forget doses.	You are right, to be comprehensive we should add a non-compliance probability. This can be done in the treatment definition in Simulx.
Why didn't you consider a loading dose to reach SS more quickly?	We kept simple dosing regimen for the challenge, but it is a good idea.
Was the 10 mmHg difference placebo-treatment given by the clinicians or is it because our efficacy effect size was found to be a reduction of ~10?	The 10 mmHg difference was given by the clinicians.
Have you tried with classical sample size calculator for clinical trials based on the arithmetic difference and sd between the 2 groups ?	No this was not tried, as the goal was to show the use of Simulx.
In "Replicates" in the clinical trial simulation for power calculation, is this related to inter-individual variablity in the model? Or by clicking it, additional datasets were generated using a kind of bootstrapping approach?	Replicates will simulate new populations of individual parameters. In each replicate there is variability between individuals. When calculating summary statistics (for instance the average change from baseline) for one clinical trial simulation (one replicate), this summary statistic is has some uncertainty associated to the fact that it is calculated on a limited number of individuals (as in a true clinical trial). We can assess this uncertainty by running replicates.
Could you give the publication reference that advocates the use of BICc instead of other criterions ?	Delattre, M., Lavielle, M. & Poursat, M. A. A note on BIC in mixed-effects models. *Electron. J. Stat.* **8**, 456–475 (2014).