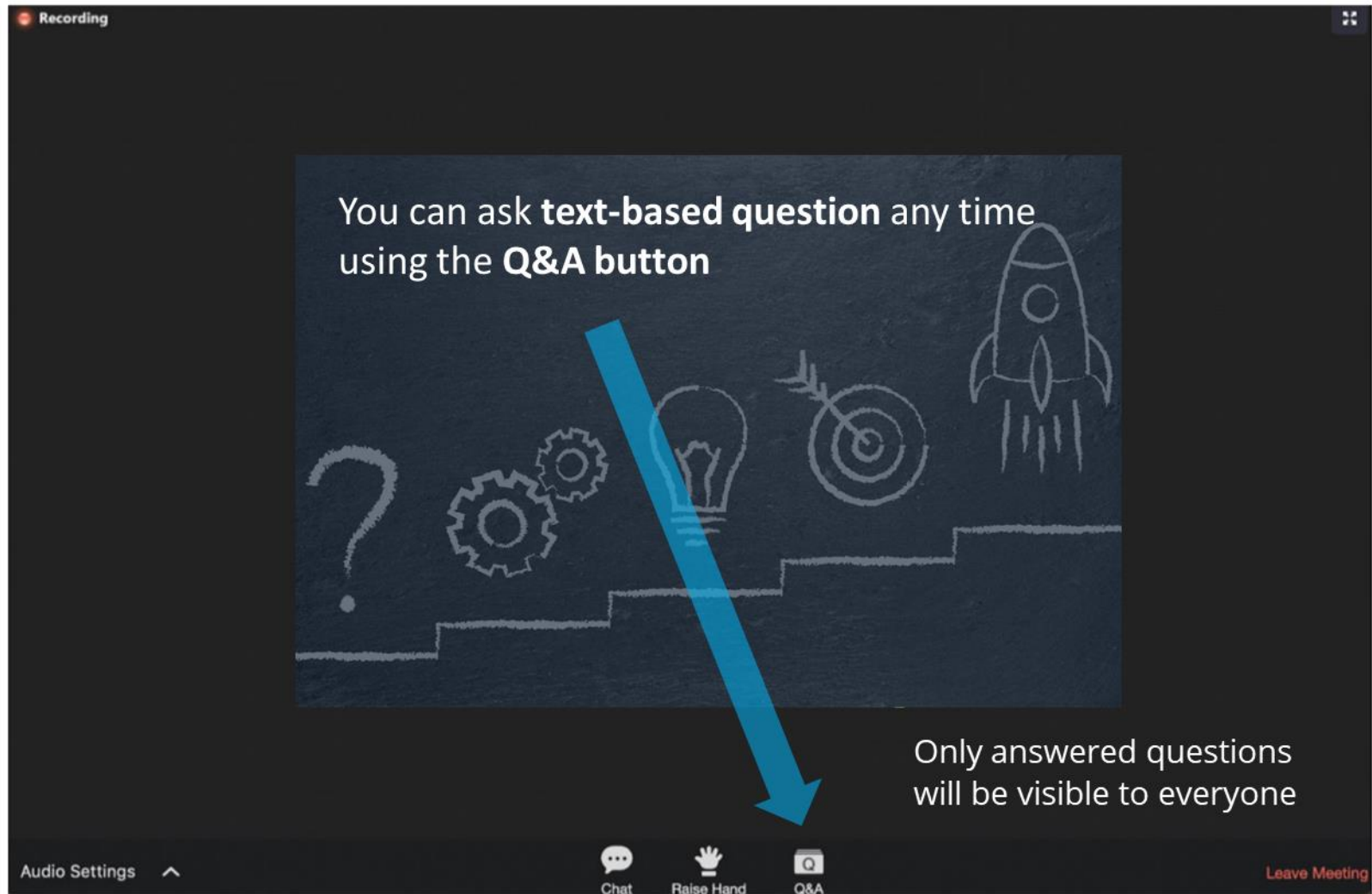


- The webinar starts at **2:00 pm Basel Time**
8:00 am East Coast Time
- Everyone is placed on mute during the webinar
- Webinar material (including presentation) can be downloaded here:
<https://training.intiquan.com/MIDDmodules/M2.2.zip>
- The webinar will be recorded
 - Recording will be made available on the following link:
<https://training.intiquan.com/MIDDmodules/M2.2.mp4>
 - Recording available ~1 day after the webinar



Q&A during Webinar



Recording

You can ask **text-based question** any time using the **Q&A button**

Only answered questions will be visible to everyone

Audio Settings ^

Chat Raise Hand Q&A

Leave Meeting

The screenshot shows a webinar interface with a dark background. At the top left, there is a 'Recording' indicator. The main content area features a chalkboard-style illustration with a sequence of icons: a question mark, two interlocking gears, a lightbulb, a target with an arrow, and a rocket. A large blue arrow points from the text 'Q&A button' to the 'Q&A' button in the bottom toolbar. The bottom toolbar includes 'Audio Settings', 'Chat', 'Raise Hand', 'Q&A', and a 'Leave Meeting' button.

Module 2.3

~~Advanced~~ NLME PKPD modeling – Part 2

IntiQuan Webinar Series on efficient support of
Model Informed Drug Development (MIDD)

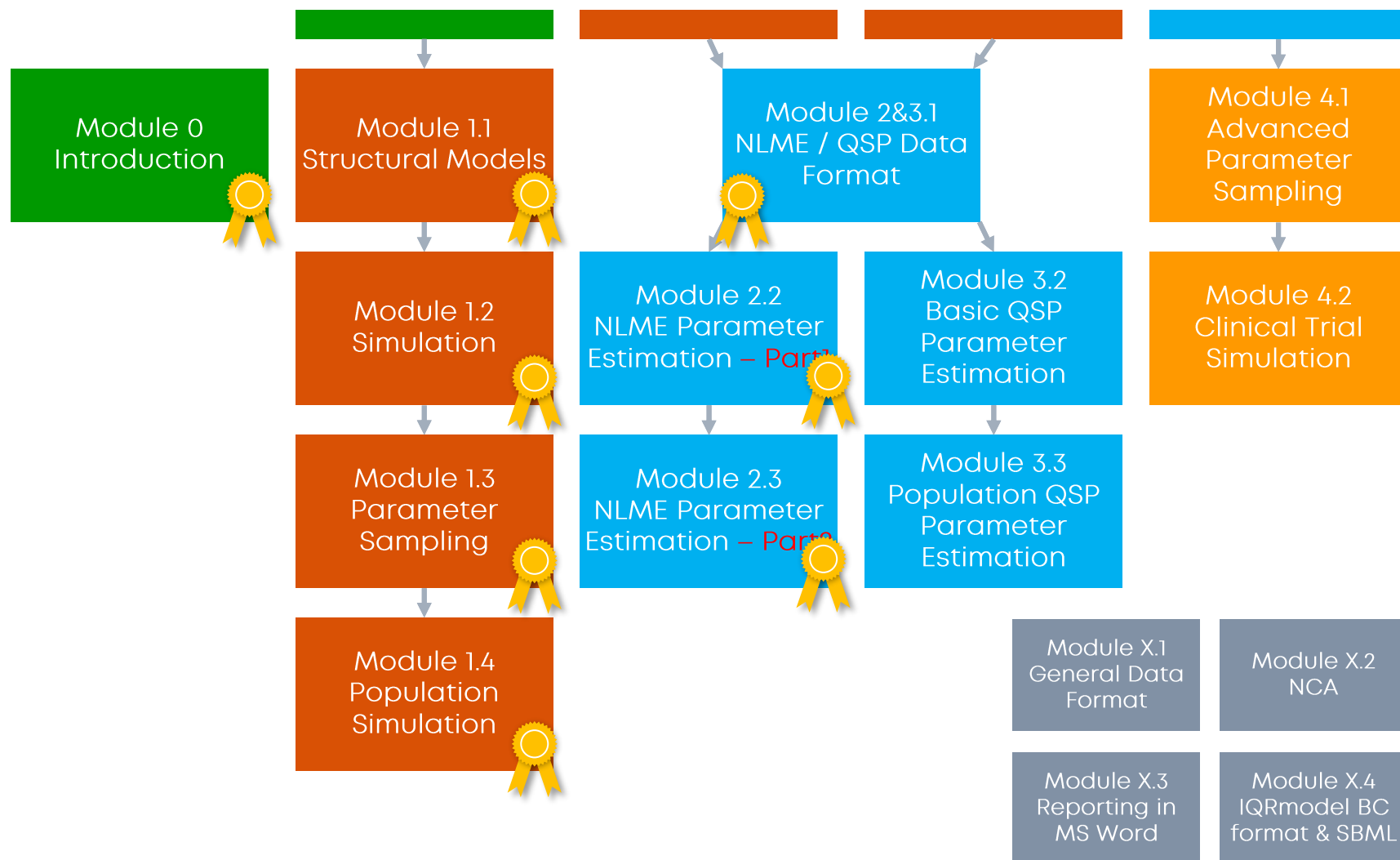
Outline

1. Background
2. PKPD model examples
3. Tools
4. Example workflows
5. Special elements
6. Conclusions
7. Outlook webinar modules
8. Q&A

Background

Overview of Webinar Modules

IntiQuan Webinar Series on efficient support of Model Informed Drug Development (MIDD)



Goals of this module

- **You will have seen examples on how to**
 - ✓ Implement PKPD model examples (joint, sequential)
 - ✓ Generate VPCs & pcVPCs with flexible stratification
 - ✓ Generate bootstraps
 - ✓ Perform covariate analyses
 - ✓ Set up complete workflows - from data to report
- **Giving you the possibility to use the approaches in own projects**

Download of webinar material

- The Webinar material is available as a convenient download
- After installation of IQR Tools, simply type the following

```
library(IQRtools)  
install_MIDDmodule("2.3")
```

- Or download directly from:

```
https://training.intiquan.com/MIDDmodules/M2.3.zip
```


Modules 2.2, 2.3, & 2.4 require presence of NONMEM and/or MONOLIX on the system to fully run the examples

Convenient setup of IQR Tools options, including interfacing with NONMEM and MONOLIX on the system through the IQR Tools options setup:

```
library(IQRtools)
setup_IQRtools()
```

```
49 # UNIX setup
50 # -----
51 # Name of the NONMEM executable or shell script. Required calling syntax:
52 # "command controlfile outputfile"
53 # NONMEM Version 7.2/7.3/7.4 have been tested with IQR Tools.
54 .PATH_SYSTEM_NONMEM <- list(
55   # First entry is used as default version
56   NM743 = 'nmfe74'
57 )
58
59 # MacOS setup
60 # -----
61 # Name of the NONMEM executable or shell script. Required calling syntax:
62 # "command controlfile outputfile"
63 # NONMEM Version 7.2/7.3/7.4 have been tested with IQR Tools.
64 .PATH_SYSTEM_NONMEM <- list(
65   NM74 = "nmfe74"
66 )
67
68 # WINDOWS setup
69 # -----
70 # Path to NONMEM (Version 7.2/7.3/7.4 have been tested) batch files. The info
71 # is provided as a list. By default the first entry is used but the user can
72 # switch when calling the IQRnlmeProject function.
73 .PATH_SYSTEM_NONMEM <- list(
74   NM74 = "C:/nm74g64/run/nmfe74.bat"
75 )
```

NONMEM7™

The program for Nonlinear
Mixed Effects Modeling



Parallel NONMEM runs handled by IQR Tools as well – can be set up in options as well.
Requires a shell/batch script available on systems command line with the following calling syntax:

command NRCORES controlfile outputfile"

IQdesktop

- Helps getting the complete environment set up in ~0 min
- Is freely available
- Requires admin rights on your computer (to install docker)
- *Bring your own NONMEM and/or MONOLIX licenses*
- ...

- More information:
<https://iqdesktop.intiquan.com>

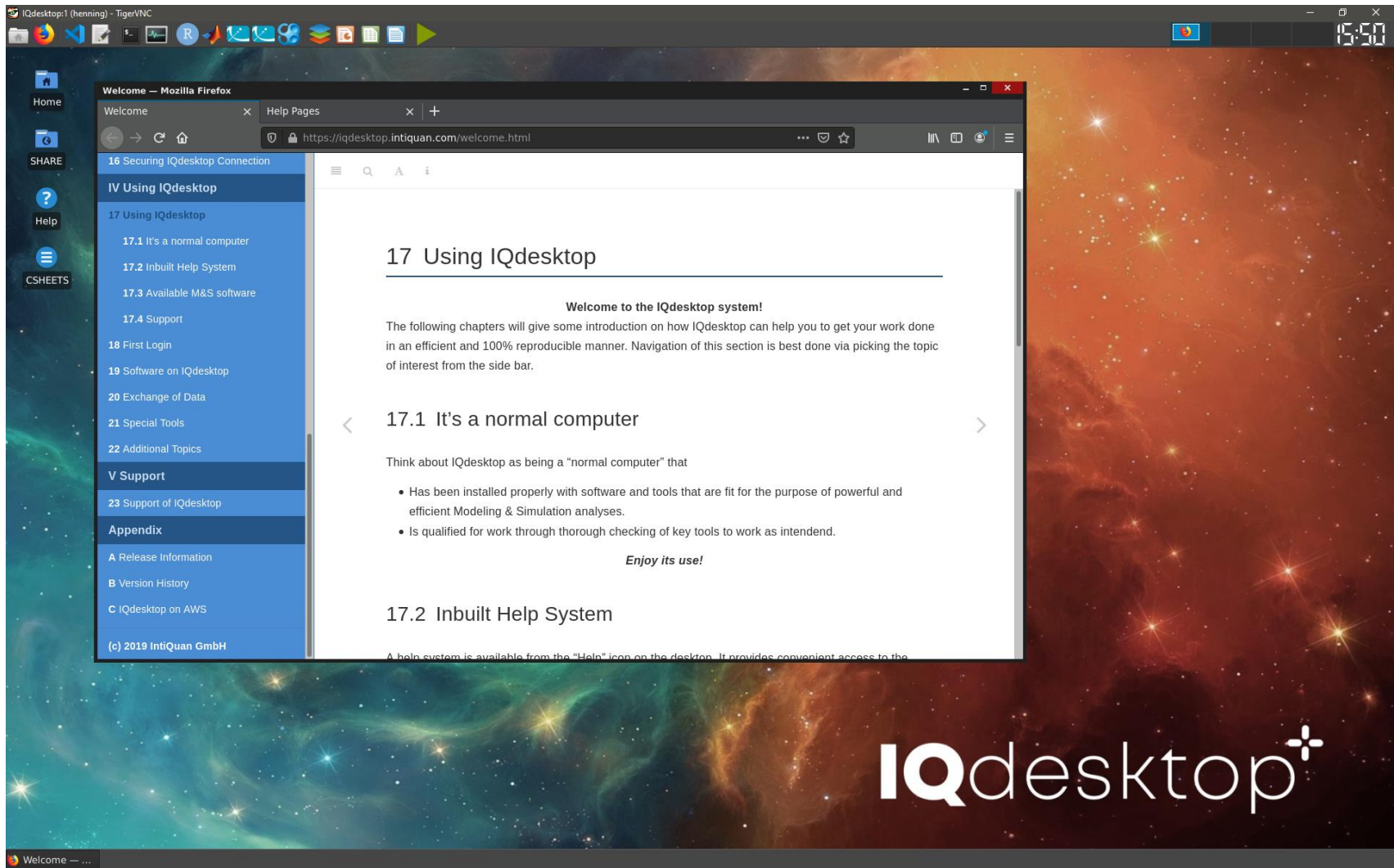
■ Installation guide

- [Windows](#)
- [macOS](#)
- [Linux](#)
- [Cloud](#)

https://iqdesktop.intiquan.com/doc/IQDesktop_Installation_Windows.mp4

A.1 Release V2.1.1 - 30 April 2021

- **Image name:** `intiquan/iqdesktop:2.1.1`
- **Base system:** Ubuntu 18.04
- **Connections:** VNC, SSH (incl. screen)
- **Modeling & Simulation & specific Development Tools**
 - IQR Tools (Version 1.7.0)
 - IQnca (Version 1.0.0)
 - IQReport (Version 1.51)
 - IQSlides (Version 0.3.2)
 - R default (Version 3.6.3)
 - CRAN snapshot dated 2020-03-15
 - URL: <https://cran.intiquan.com/snapshot/2020-03-15>
 - R exploratory (Version 4.0.3)
 - CRAN snapshot dated 2020-12-21
 - URL: <https://cran.intiquan.com/snapshot/2020-12-21>
 - IQR Tools, IQnca, and IQSlides not installed on R 4.0.3
 - MATLAB (Version R2021A) + Simbiology and relevant toolboxes
 - NONMEM (Version 7.4.3)
 - NONMEM (Version 7.5.0)
 - MONOLIX (Version 2019R1)
 - MONOLIX (Version 2020R1)
 - CellDesigner (Version 4.4.2)
 - PsN (Version 5.0.0) (no gls and qa)
 - RHEM (Version 0.1.2)
 - Rstudio (Version 1.2.5042)
 - Jenkins 2.249.2 CI/CD server (including suggested plugins)
 - Population Isoboles R package (1.0.0)
- **Changes**
 - Update to MATLAB R2021A
 - Update to IQSlides 0.3.2



<https://iqdesktop.intiquan.com>

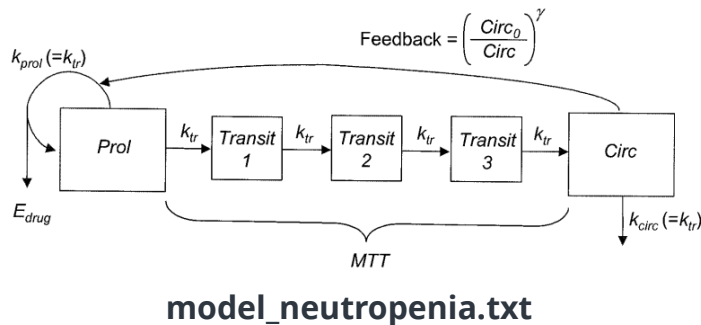
https://iqdesktop.intiquan.com/doc/IQDesktop_Installation_Windows.mp4

PKPD model examples

PK/PD Model Example

Individual parameters provided in dataset

- Structural PD model: based on Friberg et al (<https://pubmed.ncbi.nlm.nih.gov/12488418/>)
- PK model: 2 compartments IV



```
# Structural model (PK/PD)
model <- IQRmodel("model_neutropenia.txt")

# Data - Individual PK parameters defined in dataset
data <- data_IQRest(
  datafile = "dataNLME.csv",
  covNames = c("WT", "HT"),
  # Define regressors (PK) parameters in the same order
  # In the dataset and in the model
  regressorNames = c("Vp", "Vc", "CL", "Q")
)

# Model specification - without covariates
modelSpec <- modelSpec_IQRest(

  # Typical subject parameters
  POPvalues0 = c(CIRC0 = 7.21, MTT = 124, SLOPU = 28.9, GAMMA = 0.239),
  POPestimate = c(CIRC0 = 1, MTT = 1, SLOPU = 1, GAMMA = 1),

  # Between subject variability
  IIVdistribution = c(CIRC0 = "L", MTT = "L", SLOPU = "N", GAMMA = "L"),
  IIVvalues0 = c(CIRC0 = 0.5, MTT = 0.5, SLOPU = 10, GAMMA = 0.1),
  IIVestimate = c(CIRC0 = 1, MTT = 1, SLOPU = 1, GAMMA = 2),

  # Error model
  errorModel = list(OUTPUT1 = c(type="abs", abs0 = 0.1))
)
```

PK/PD Model Example

Individual parameters provided in dataset

- Individual PK parameters provided in dataset
 - => Used as *regressors*

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W
1	IXGDF	USUBJID	ID	TIME	TIMEPOS	TAD	NAME	DV	UNIT	YTYPE	AMT	ADM	EVID	MDV	CENS	TINF	RATE	Vp	Vc	CL	Q	WT	HT
2	1	1	1	1	0	0	0 Dose	0 mg		.	206	1	1	1	0	0.5	412	454	272	236	102	84	183
3	2	1	1	1	0	0	0 Neutroph	8.1 10^9/L		1	0.	.	0	0	0	0	0	454	272	236	102	84	183
4	3	1	1	192	192	192	Neutroph	3.3 10^9/L		1	0.	.	0	0	0	0	0	454	272	236	102	84	183
5	4	1	1	336	336	336	Neutroph	5.5 10^9/L		1	0.	.	0	0	0	0	0	454	272	236	102	84	183
6	5	1	1	456	456	456	Neutroph	12.3 10^9/L		1	0.	.	0	0	0	0	0	454	272	236	102	84	183
7	6	2	2	0	0	0	Dose	0 mg		.	165	1	1	1	0	0.5	330	471	153	202	102	84	167
8	7	2	2	0	0	0	Neutroph	11.9 10^9/L		1	0.	.	0	0	0	0	0	471	153	202	102	84	167
9	8	2	2	432	432	432	Neutroph	9.7 10^9/L		1	0.	.	0	0	0	0	0	471	153	202	102	84	167
10	9	3	3	0	0	0	Dose	0 mg		.	172	1	1	1	0	0.5	344	635	250	222	102	78	175
11	10	3	3	0	0	0	Neutroph	6.4 10^9/L		1	0.	.	0	0	0	0	0	635	250	222	102	78	175
12	11	3	3	312	312	312	Neutroph	5.3 10^9/L		1	0.	.	0	0	0	0	0	635	250	222	102	78	175

- Order of regressors has to be the same in model and dataset. Here:

Vp, Vc, CL, Q

***** MODEL PARAMETERS

Define parameters

```
CIRC0      = 7.21  # Baseline circulating neutrophils (10^9 cells/L)
MTT        = 124   # Mean transit time (hours)
SLOPU      = 28.9  # Slope of drug effect (mL/ug)
GAMMA      = 0.239 # Exponent (.)
```

Define regression parameters

```
Vp         = 1     # Peripheral volume (L)
Vc         = 1     # Central volume (L)
CL         = 1     # Clearance (L/hour)
Q          = 1     # Intercompartmental clearance (L/hour)
```

model_neutropenia.txt

Tools

VPC & pcVPC

Example 1

- The function `vpc_IQRnlmeProject` generates information for VPC and pcVPC
 - An IQRnlmeProject (path) is provided as input (can be NONMEM, MONOLIX, or NLMIXR project)
- Function `plotVPC_IQRdataVPC` is used to plot the results of the VPC generation

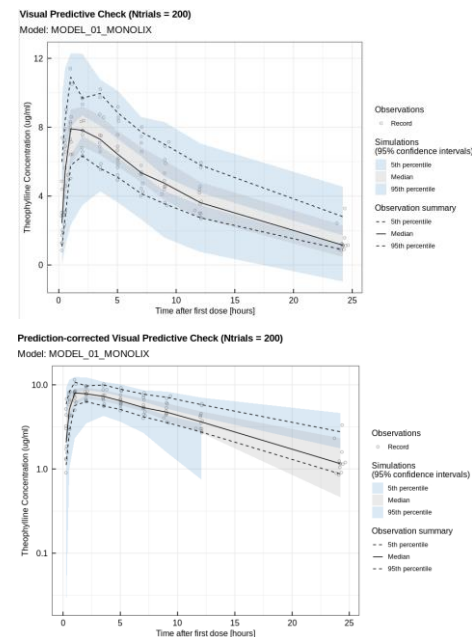
```
# Define model to generate the VPC for
NLMEMODEL <- "MODEL_01_MONOLIX"

# ----- #
# Simple VPC ----
# ----- #

# Generate the VPC information
# Dataset is used that was used for modeling
vpc <- vpc_IQRnlmeProject(
  project = NLMEMODEL,           # Point to NLME Model (IQRnlmeProject)
  Ntrials = 200,                 # Number of trials to simulate
  FLAGpreparePC = TRUE,          # If TRUE then information for a pcVPC will be
                                # generated in addition
  ncores = 10                    # Parallelization on 10 cores
)

# Plot the VPC
plotVPC_IQRdataVPC(vpc)

# Plot the pcVPC on logY axis
plotVPC_IQRdataVPC(vpc, FLAGpc = TRUE, FLAGlogY = TRUE)
```

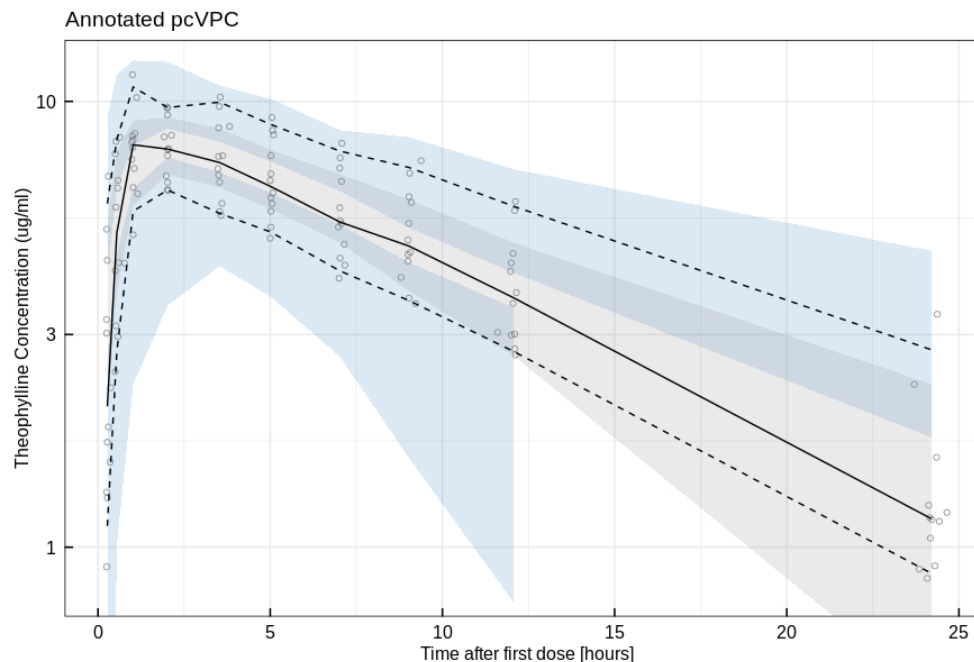


VPC & pcVPC

Example 1

- The function `plotVPC_IQRdataVPC` returns an object of type `IQRoutputFigure`
 - The field "content" contains the `ggplot2` object, allowing to postprocess each plot

```
# Modify output as desired
out <- plotVPC_IQRdataVPC(vpc, FLAGpc = TRUE, FLAGlogY = TRUE)
out$OUTPUT1$content[[1]] +
  coord_cartesian(ylim=c(0.8,12)) +
  ggtitle("Annotated pcVPC")
```



example_vpc_1.R

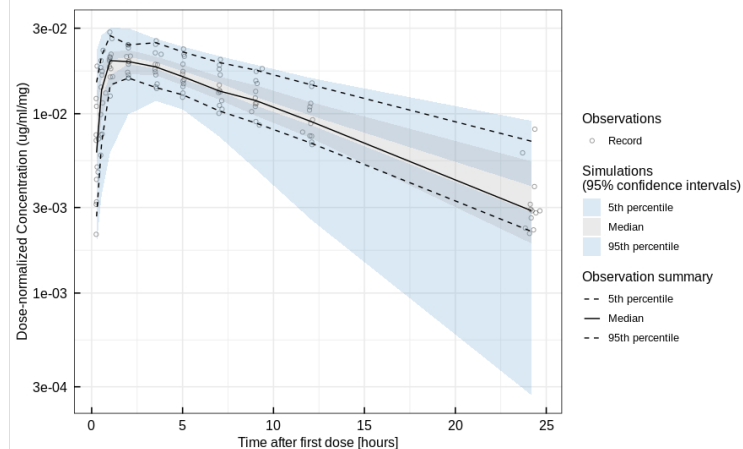
VPC & pcVPC

Example 1

- The function `vpc_IQRnlmeProject` can take a modified / different dataset for VPC generation
 - Here used to implement a dose-normalized VPC
 - Also, useful to predict new data and compare model to this data

Visual Predictive Check (Ntrials = 200)

Model: MODEL_01_MONOLIX



```
# Get dataset used for modeling
data <- getData_IQRnlmeProject(NLMEModel)

# Normalize doses and observations
data$DV <- data$DV/data$DOSE
data$AMT <- data$AMT/data$DOSE
data$UNIT <- paste0(data$UNIT, "/mg")
data$NAME[data$EVID==0] <- "Dose-normalized Concentration"

# Generate the VPC for changed dataset
vpc <- vpc_IQRnlmeProject(
  project = NLMEModel,           # Point to NLME Model (IQRnlmeProject)
  dataVPC = data,                # Provide modified data
  Ntrials = 200,                 # Number of trials to simulate
  ncores = 10,                  # Parallelization on 10 cores
  FLAGaddResidualNoise = FALSE  # Switch of residual error ...
                                # try with set to TRUE ...
                                # not a good idea here ... pcVPC better ...
                                # or normalize to a higher dose than 1 mg!
)

# Plot the VPC
plotVPC_IQRdataVPC(vpc, FLAGlogY = TRUE)
```

example_vpc_1.R

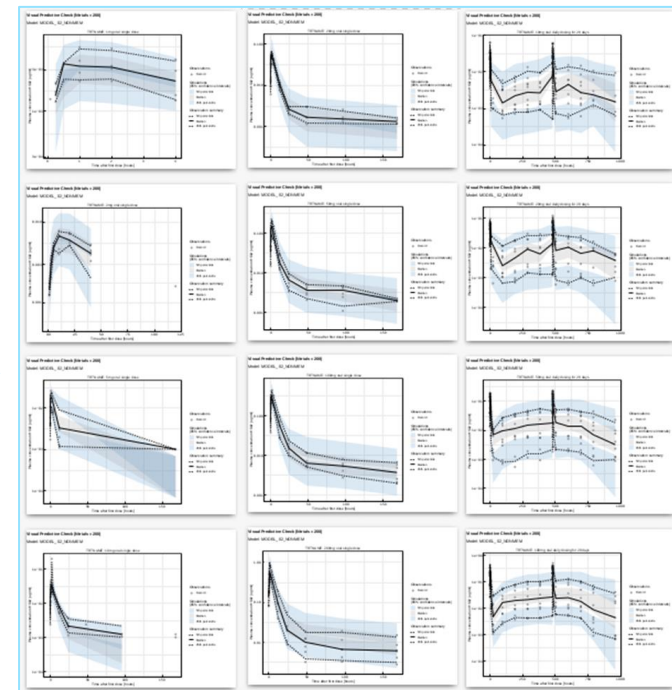
VPC & pcVPC

Example 2

- The function `plotVPC_IQRdataVPC` allows stratification based on columns available in the dataset for which the VPC is generated
 - Results can be exported directly to PDF

```
# -----#  
# Stratify by TRTNAME ----#  
# -----#  
  
# Plot the VPC  
plotVPC_IQRdataVPC(vpc, stratifyBy = "TRTNAME", FLAGlogY = TRUE)  
  
# Plot and export to PDF  
plotVPC_IQRdataVPC(vpc, stratifyBy = "TRTNAME", FLAGlogY = TRUE, filename =  
"VPC_TRTNAME.pdf")  
  
# -----#  
# Stratify by Regimen ----#  
# -----#  
  
# Plot the VPC  
plotVPC_IQRdataVPC(vpc, stratifyBy = "REGIMEN", FLAGlogY = TRUE)  
  
# Plot the pcVPC  
plotVPC_IQRdataVPC(vpc, stratifyBy = "REGIMEN", FLAGpc = TRUE, FLAGlogY = TRUE)
```

example_vpc_2.R



Bootstrap

- The function `bootstrap_IQRnlmeProject` generates bootstrap information
 - An IQRnlmeProject (path) is provided as input (can be NONMEM, MONOLIX, or NLMIXR project)

```
# Define model to generate the bootstrap for
NLMEMODEL <- "MODEL_01_MONOLIX"
NLMEMODEL <- "MODEL_01_NONMEM"

# -----#
# Simple bootstrap ----
# -----#

# Generate the bootstrap
bootstrap_IQRnlmeProject(
  projectPath = NLMEMODEL,      # Define the NLME model to do the bootstrap for
  bootstrapPath = "Output",    # Define output path
  Nsamples = 100,              # Number of samples (small for example)
  group = "SEX",               # Stratify by column "SEX"
  Nparallel = 10,              # Number of parallel model executions
  FLAGremoveRESULTSORIG = TRUE # Remove original results to keep size on disk low
)
```

example_bootstrap.R

- Bootstrap data can be stratified using the "group" argument, based on one or more columns in the original modeling dataset

Bootstrap

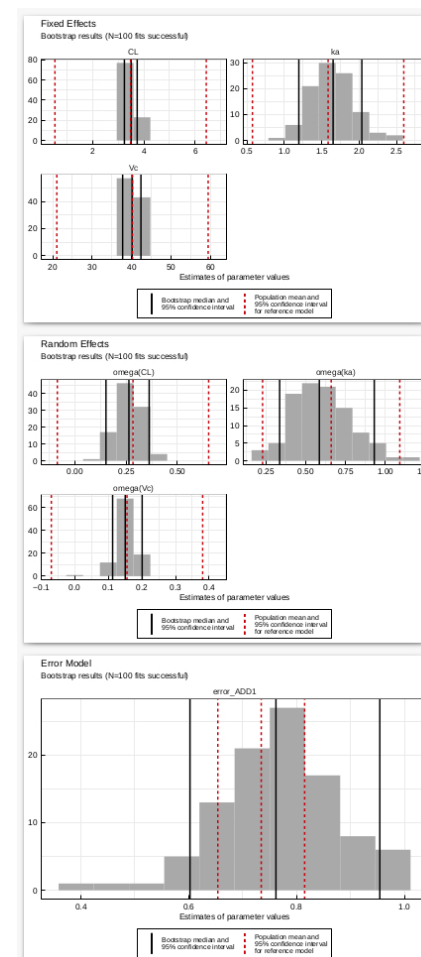
- Results are post-processed and presented in tabular and graphical form

Bootstrap results

Parameter	Model estimate	Bootstrap median	Model 95% CI	Bootstrap 95% CI
CL	3.485	3.506	[0.5396,6.43]	[3.243,3.741]
ka	1.586	1.653	[0.574,2.599]	[1.195,2.037]
Vc	40.25	40.15	[21.05,59.44]	[37.75,42.39]
omega(CL)	0.2836	0.2638	[-0.08455,0.6518]	[0.1522,0.3624]
omega(ka)	0.6598	0.5853	[0.2279,1.092]	[0.3354,0.931]
omega(Vc)	0.1556	0.1504	[-0.06957,0.3808]	[0.1129,0.2007]
error_ADD1	0.7345	0.7618	[0.654,0.815]	[0.6025,0.9544]

N=100 bootstrap samples were evaluable (objective function different from "NA").

Number of significant digits: 4



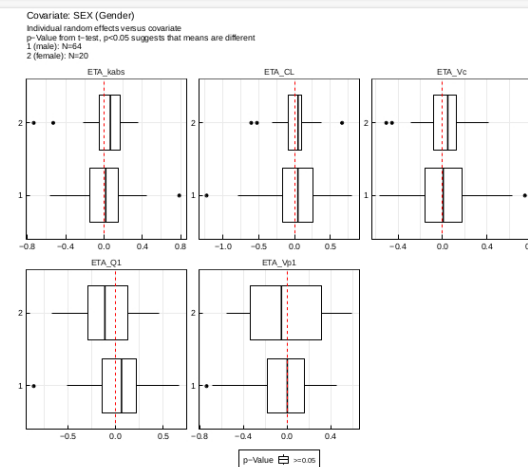
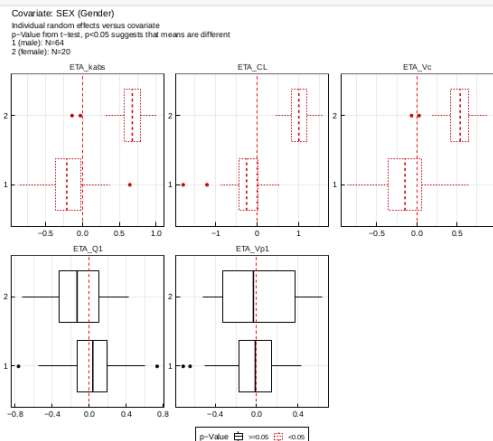
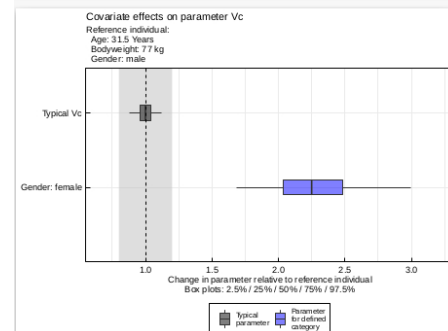
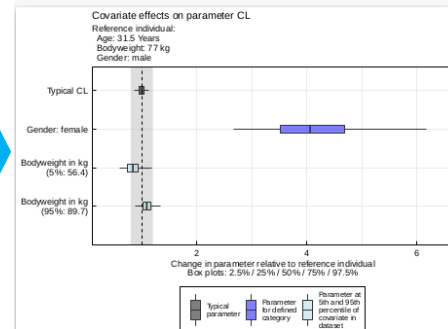
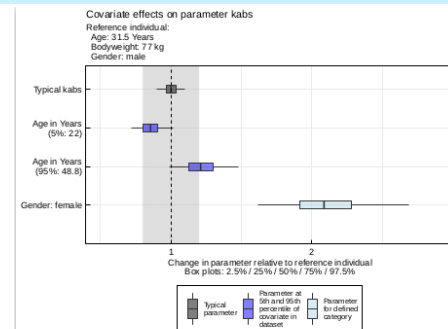
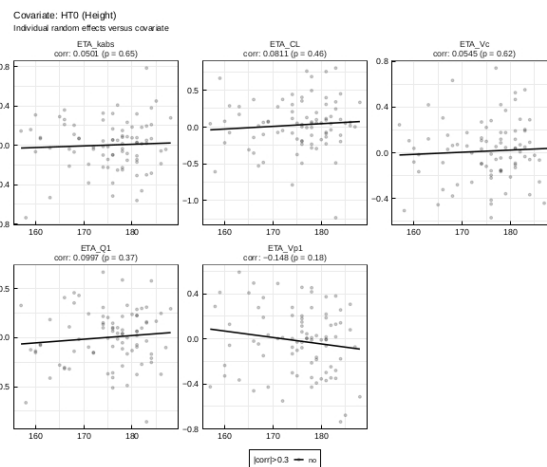
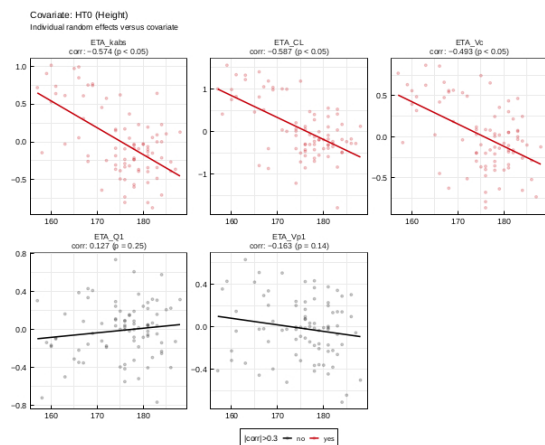
Covariate search

- Stepwise covariate search not (yet) implemented in public version of IQR Tools
- Reason:
 - We mainly use SAEM as parameter estimation method
 - Objective function values obtained from NONMEM upon parallel runs are highly variable (same model, same initial guesses, same computer, same dataset, same seed, same everything) - it is an underlying problem in NONMEM
 - Better since 7.5.0 but not fully solved yet
 - => It does not make sense to implement a method that might result in a different covariate model each time it is run again => "not reproducible"
 - Note: using FOCEI this issue does not exist - but convergence often is very poor
- Suggested approach at covariate analysis:
 - Based on information content in the data, rather than only objective function
 - Full-covariate-type-of modeling approach
 - Assessment of correlations of random effects and covariates
 - Physiologic plausibility
 - Identifiability of covariate coefficients (based on standard error)
 - Potential clinical relevance of covariate (based on impact of typical parameter)

Covariate search

- Upon presence of covariates in the dataset, IQR Tools automatically generates informative diagnostics

Impact of covariates on parameter



Summary

- All standard functionality available
- Flexible handling of customization since all based in R

Example workflows

Population PK workflow - from data to report

- Functionality available in IQR Tools allows for implementation of full analysis workflows that are reproducible at any point in time
 - Reproducible conduct of a popPK
 - Fully scripted
 - From data preparation to final report
 - Fake data
 - Focus on workflow - not on completeness

The screenshot shows the SAS Universal Viewer interface. On the left, a tree view displays the workflow structure: 03_workflows, 01_PopPK_Data2Report, Data, DataSource (highlighted), Models, Output, Report, and Scripts. On the right, a list of files is shown: dm.xpt, ex.xpt, lb.xpt, pc.xpt, and vs.xpt. Below this, a data table is displayed with columns: STUDYID, DOMAIN, USUBJID, PC38Q, PCTESTCD, PCTEST, PCORRES, PCORRESU, and PCSTRESC. The table contains 6 rows of data.



The screenshot shows the IQR Tools interface. On the left, a tree view displays the workflow structure: 03_workflows, 01_PopPK_Data2Report, Data, DataSource, Models, Output, Report (highlighted), and Scripts. On the right, a list of files is shown: very_basic_report.docx and very_basic_report.rmd. Below this, a report preview is displayed. The report includes a table of parameters, a table of model coefficients, and a plot of predicted versus observed values.

PARAMETER	VALUE	SE	MIN	MAX	COMMENT
CL	0.147	11.1%	-	-	Clearance (L/hour)
V1	2.1	5.8%	-	-	Central volume (L)
Q1	0.444	12.3%	-	-	Intercompartmental clearance (L/hour)
V1F	2.1	11.1%	-	-	Peripheral volume (L)

INTER-INDIVIDUAL VARIABILITY	VALUE	SE	MIN	MAX	COMMENT
omega(O1)	0.283	21.8%	1.2%	-	LogNormal
omega(O2)	0.117	21.1%	0.1%	-	LogNormal
omega(O3)	0.147	21.1%	0.1%	-	LogNormal
omega(O4)	0.147	21.1%	0.1%	-	LogNormal
omega(O5)	0.289	28.2%	11.2%	-	LogNormal

CORRELATION OF RANDOM EFFECTS	VALUE	SE	MIN	MAX	COMMENT
omega(O1, O2)	0.831	17.4%	-	-	Correlation coefficient

PARAMETER CORRELATION COEFFICIENT	VALUE	SE	MIN	MAX	COMMENT
omega(O1, O2)	0.155	24%	-	-	Age in years on Y1 (centered around 27.5 years)

RESIDUAL VARIABILITY	VALUE	SE	MIN	MAX	COMMENT
sigma(O1)	0.121	47.5%	10%	-	Additive Error (Loglik) - Plasma Concentration
sigma(O2)	0.155	5.96%	-	-	Proportional Error (Residual) - Plasma Concentration

Objective function: 1474
AIC: 1498
BIC: 1500

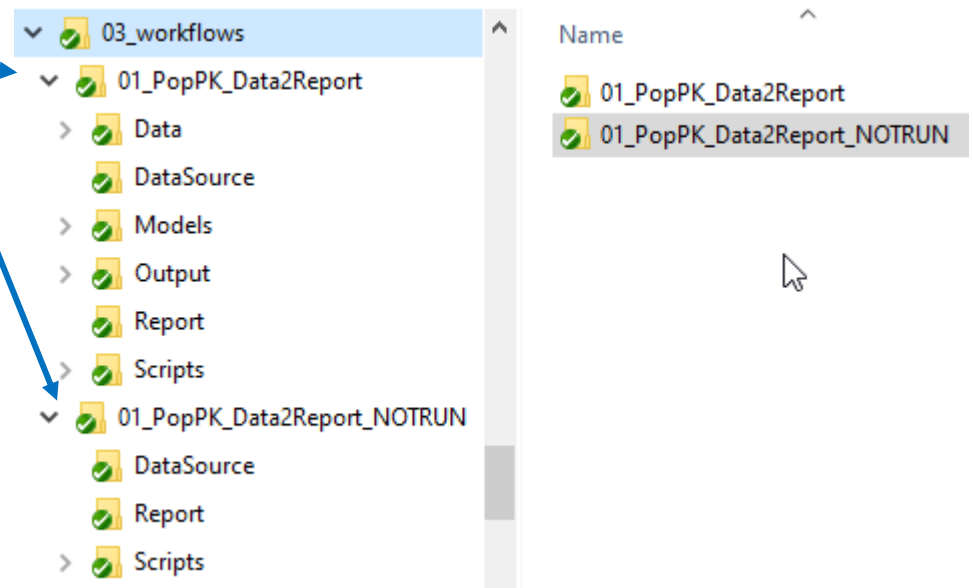
Model: Output.FINALMODEL.SIS.FINALMODEL

Figure 1: Prediction corrected VPC for final selected model. The plot shows the percentage of observations below the predicted values (P50, P25, P75) against the time after first dose (hours). The observed data points are shown as black dots, and the predicted values are shown as a shaded area.

Population PK workflow - from data to report

- Example material contains the PopPK workflow twice

1. Fully executed
2. Only key files that need to be present to regenerate all results



Examples/03_workflows

Population PK workflow - from data to report

- "Base" material for the workflow analysis

Source data

01_PopPK_Data2Report_NOTRUN

- DataSource
 - dm.xpt
 - ex.xpt
 - lb.xpt
 - pc.xpt
 - vs.xpt
- Report
- Scripts
 - Resources

Scripts performing the analysis

01_PopPK_Data2Report_NOTRUN

- DataSource
- Report
- Scripts
 - SCRIPT_00_RUNALL.R
 - SCRIPT_01_importData.R
 - SCRIPT_02_createNLMEdata.R
 - SCRIPT_03_exploreNLMEdata.R
 - SCRIPT_10_PK_base.R
 - SCRIPT_20_PK_covariate.R
 - SCRIPT_25_PK_covariance.R
 - SCRIPT_30_FinalModel.R
 - SCRIPT_40_Comparison_Tables.R
 - SCRIPT_99_report.R
- Resources

Report in RMD (Markdown format)

01_PopPK_Data2Report_NOTRUN

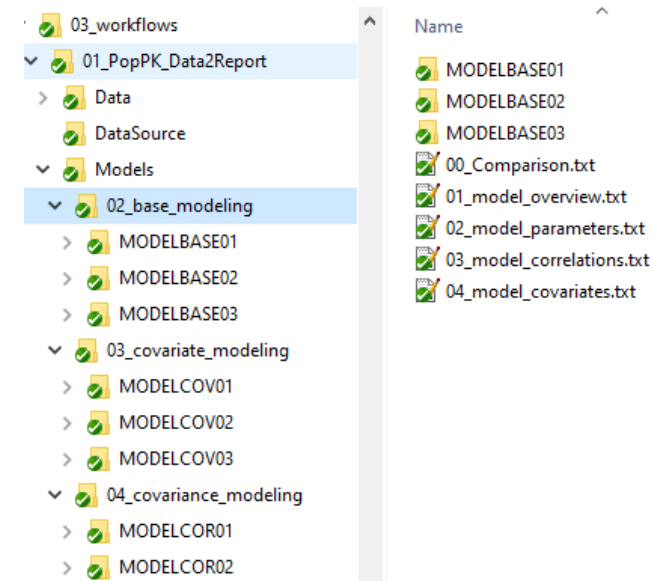
- DataSource
- Report
 - very_basic_report.rmd
- Scripts
- Resources

Conversion of RMD files to Word requires presence of IQReport (<https://iqreport.intiquan.com>)

```
27 !TAB[Demographics table - continuous,size:10](../Output/03_exploreNLMEdata/TAB01_summaryCovPF.txt)
28 !TAB[Demographics table - categorical,size:10](../Output/03_exploreNLMEdata/TAB02_summaryCatPF.txt)
29 !LANDSCAPE
30 !TAB[size:7](../Output/03_exploreNLMEdata/TAB03_summaryObsPF.txt)
31 Correlation of potential covariates are shown in Appendix @FIG(fig_contcor), @FIG(fig_catcor), and @FIG(fig_contcatcor).
32 !PORTRAIT
33
34 # Model Results
35 * All tested models shown in Appendix @TAB(taball)
36 * Key model results shown in @TAB(tabkey)
37 * Final selected model results shown in @TAB(tabfinal)
38   * Prediction corrected VPC shown in @FIG(figvpc)
39   * Diagnostics shown in @SEC(diagnostics)
40   * Final model control file in Appendix @TEXT(txtcontrol)
41   * Final model output file in Appendix @TEXT(txtoutput)
42
43
44 !TAB[Key model results,label:tabkey,size:10](../Output/FINALMODELS/TAB_01_comparison.txt)
45
46 !TAB[Final selected model,label:tabfinal,size:10](../Output/FINALMODELS/03_FINALMODEL/project_parameters_table.txt)
47
48 !FIG[Prediction corrected VPC for final selected model,label:figvpc](../Output/FINALMODELS/FIG001_poVPC_FINALMODEL_1.pdf)
49
50 !APPENDIX
51
52 # Data Specification {#dataspec}
53 !PDF[scale:90](../Data/01_dataNLME_PK/dataNLME_define.pdf)
54 !LANDSCAPE
55
56 # Data Programming
57 !TAB[Manually selected ignored observation records,label:data,size:8](../Output/02_createNLMEdata/01_datacleaning/01_Man
```

Advantages of workflow based analyses

- Full documentation of analysis
- 100% reproducible at any point in time
 - On the same system => ensured through use of virtualized computer systems (e.g. IQdesktop)
 - By any person (not only the initial analyst)
- Easy structuring of model development in folders
 - Base model
 - Base model
 - Covariate model
 - Covariance model
 - Etc.
- Full audit trail available
 - Through use of version control (e.g. git)
- Can be followed and reused with minor modifications



Special elements

Conclusions

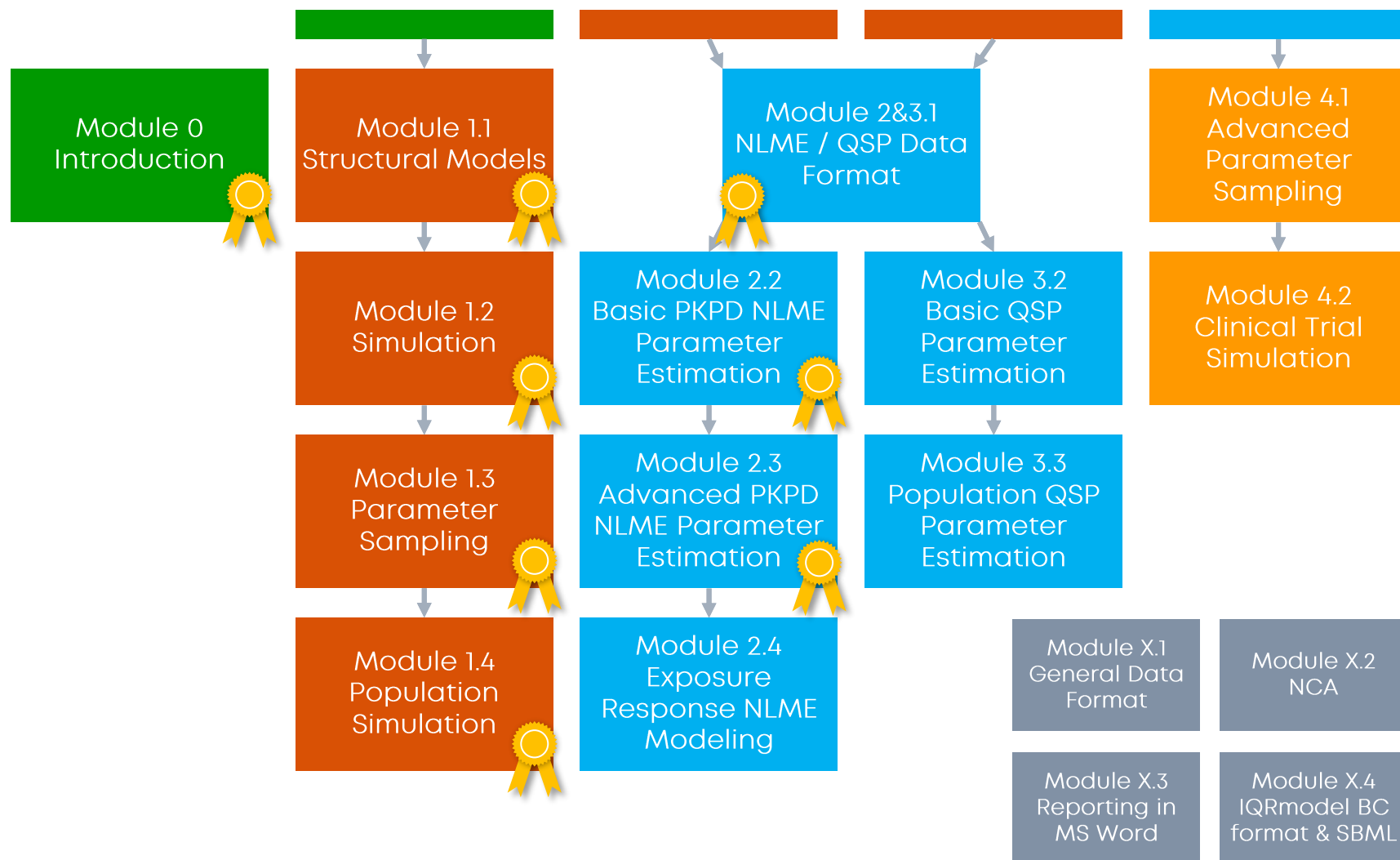
Conclusions

- IQR Tools supports powerful script based set up of full analyses
 - From data to final report in Word
 - PK, PKPD, QSP, etc.
- High flexibility
- 100% reproducibility
- Adequate setup with version control ensures
 - Audit trail
 - Full analysis can be executed by anyone (not only by the initial analyst)

Outlook webinar modules

Overview of Webinar Modules

IntiQuan Webinar Series on efficient support of Model Informed Drug Development (MIDD)



Q&A session

Thank
You

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