wega Breakfast AI in GxP Environment

March, 2021

Key messages

THE NATURE OF AI METHODS NEEDS NEW VALIDATION CONCEPTS

WERUM HAS INITIATED A GAMP GROUP AND IS CONTRIBUTING TO THE CREATION OF A GUIDELINE FOR VALIDATING AI IN THE PHARMACEUTICAL INDUSTRY

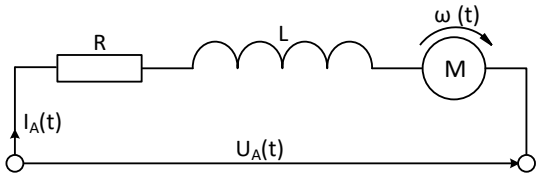
WERUM HAS DEVELOPED A PRODUCT WHICH USES AN AI METHOD TO CONTROL A CHROMATOGRAPHY PROCESS

MOST OF THE VALIDATION CONCEPTS ARE IMPLEMENTED IN THIS PRODUCT

The nature of AI methods: Black Box Models

In white box models there is a clear algorithm to map input to output

Example: model of electrical engine for the derivation of a differential equation

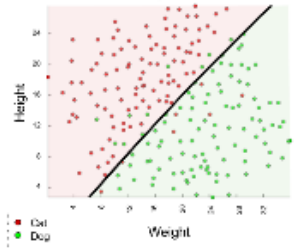


$$UAt=URt+ULt+\phi E\omega t$$

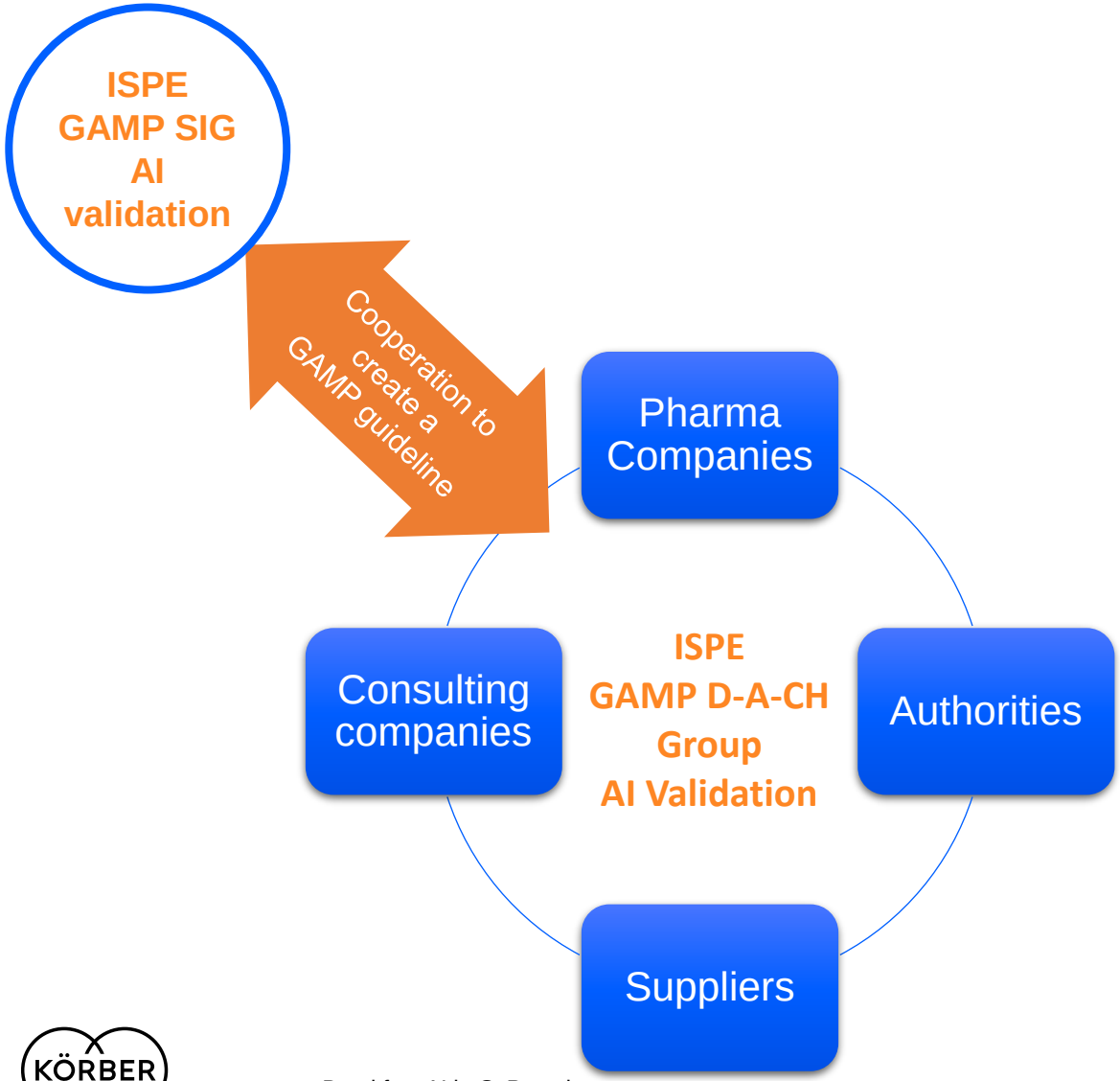
A black box model predicts an output based on input data and trained knowledge

Example: Recognition of cats

Could be cats with probability 95%



GAMP D-A-CH Group: AI Validation



Facts:

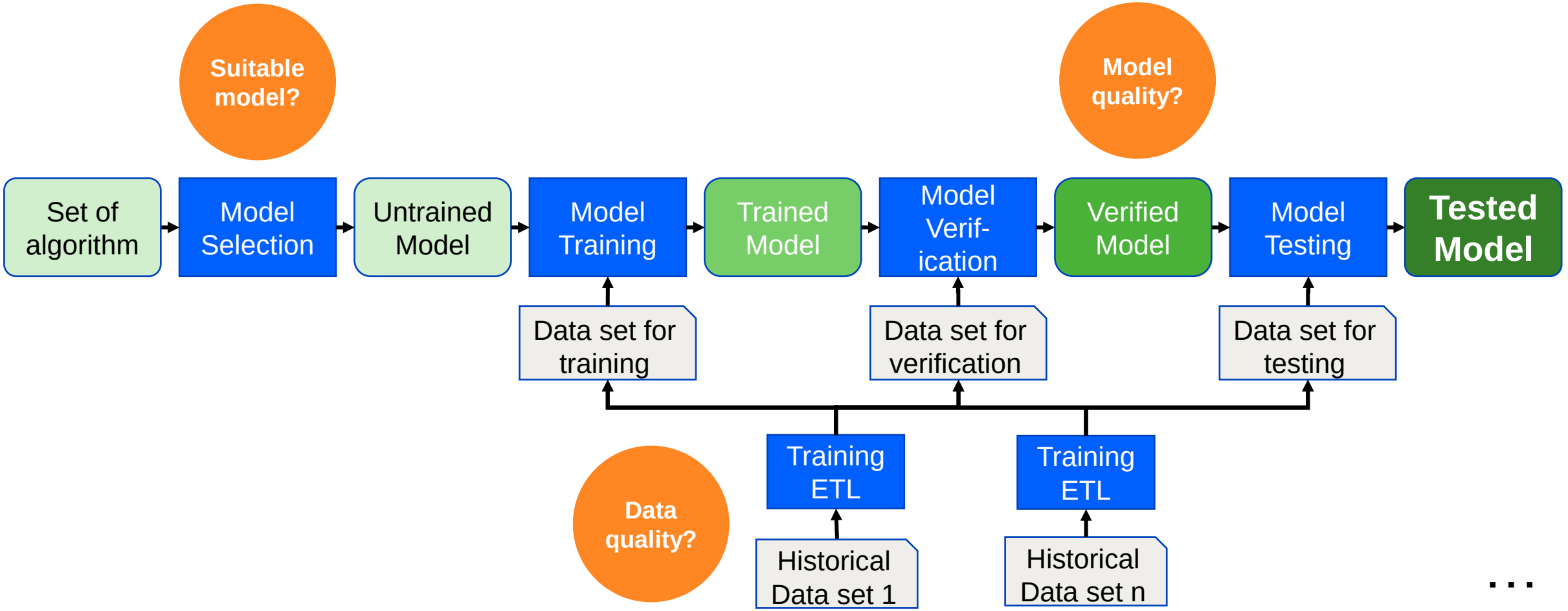
- Founded September 2019 at the GAMP DACH Forum in Frankfurt
- Approx. 22 Members

Goal:

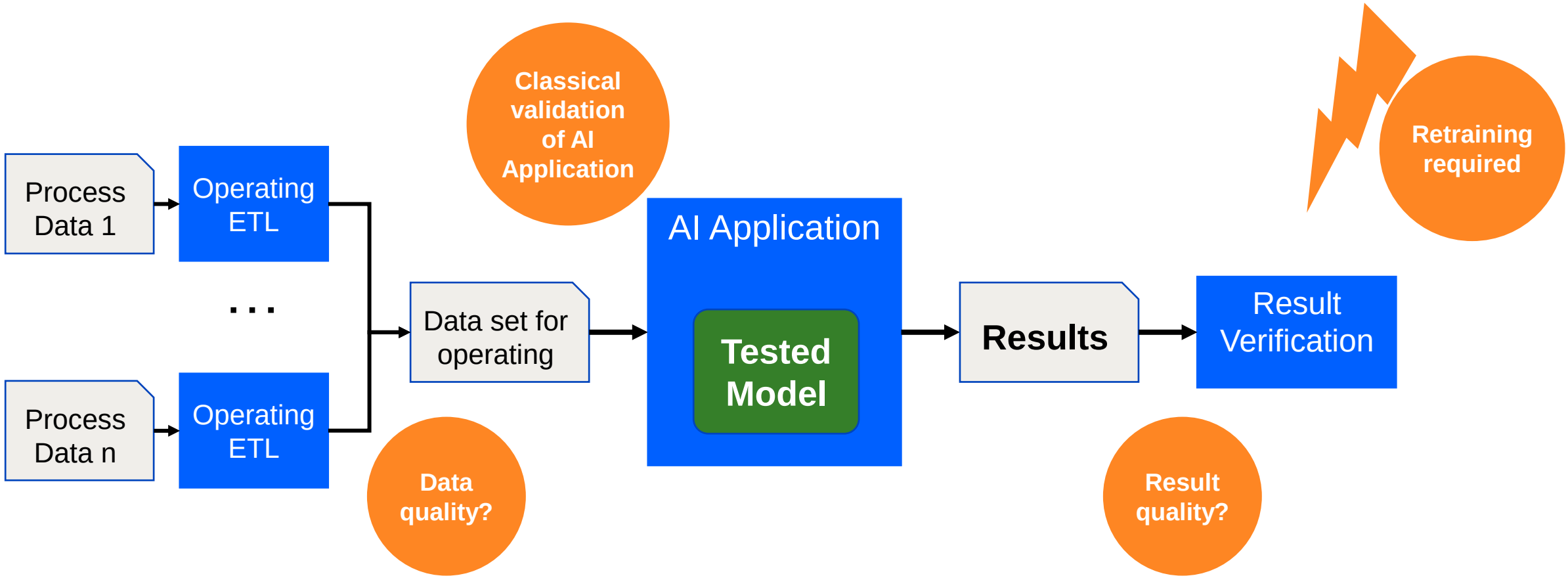
- Create guidance on how to make use of AI in a GxP-compliant manner.

Guideline TABLE OF CONTENTS

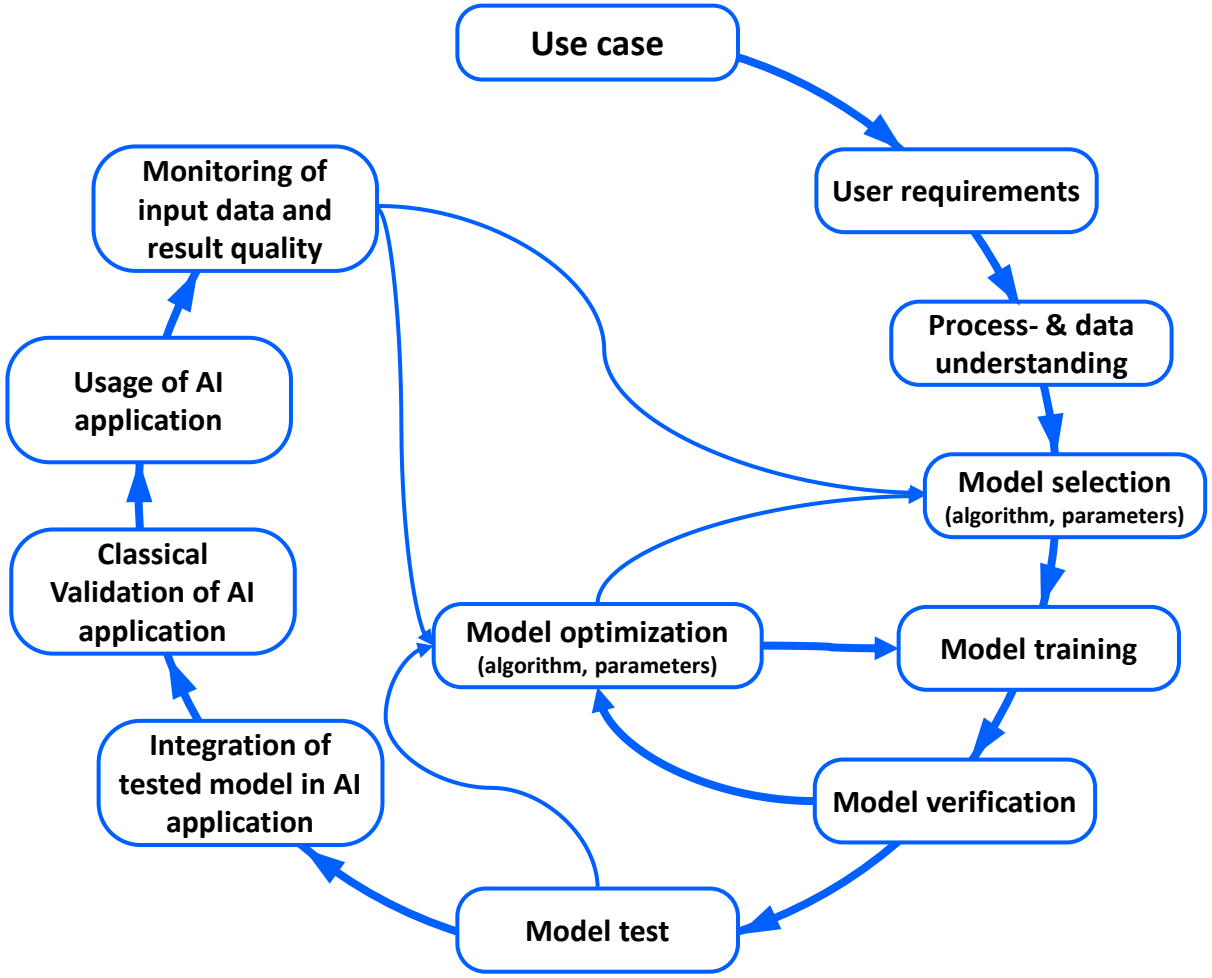
Elements to build the model for an AI Application



Elements of AI application in operation



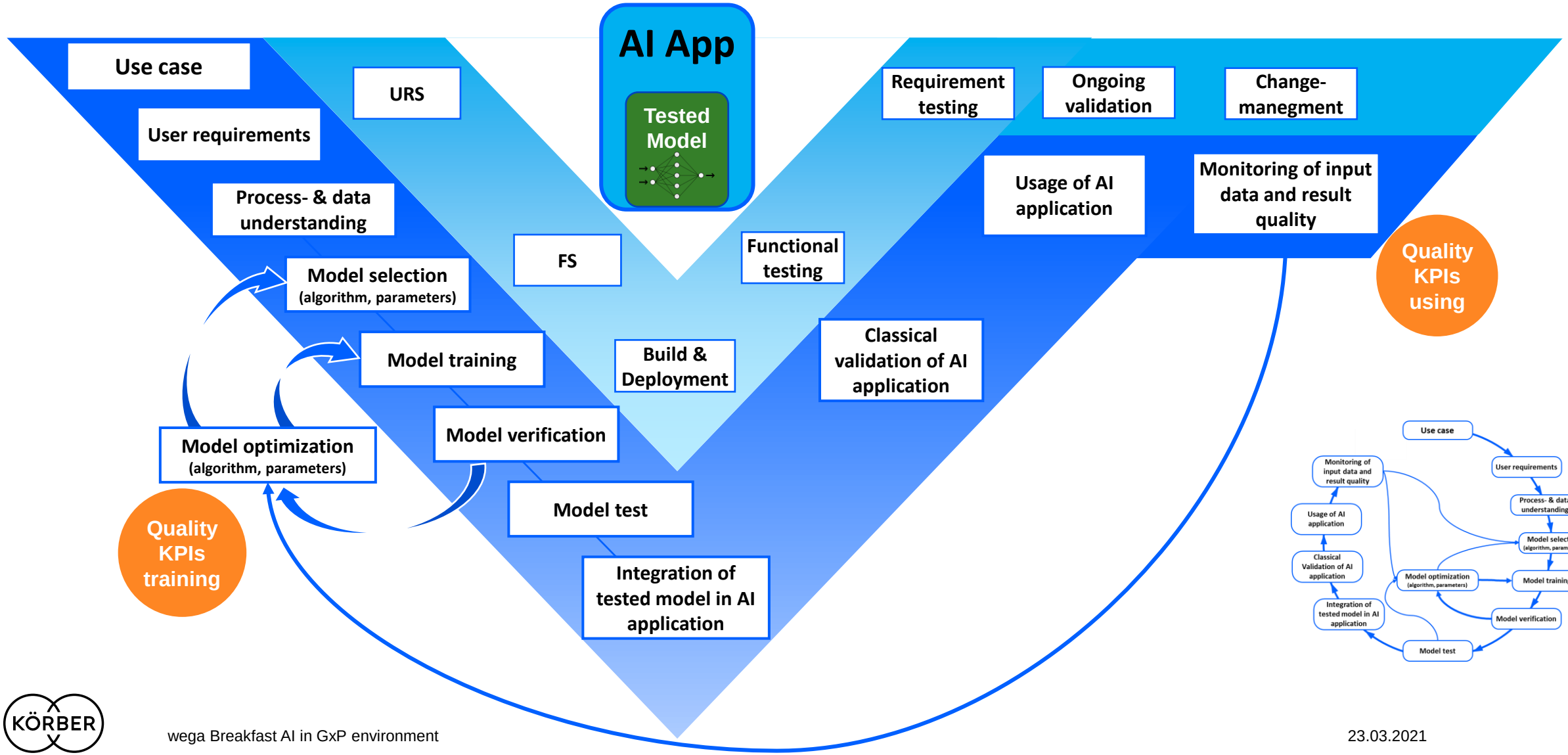
AI model life cycle



Documented quality controls are associated with each step

Combining validation of AI model with AI application

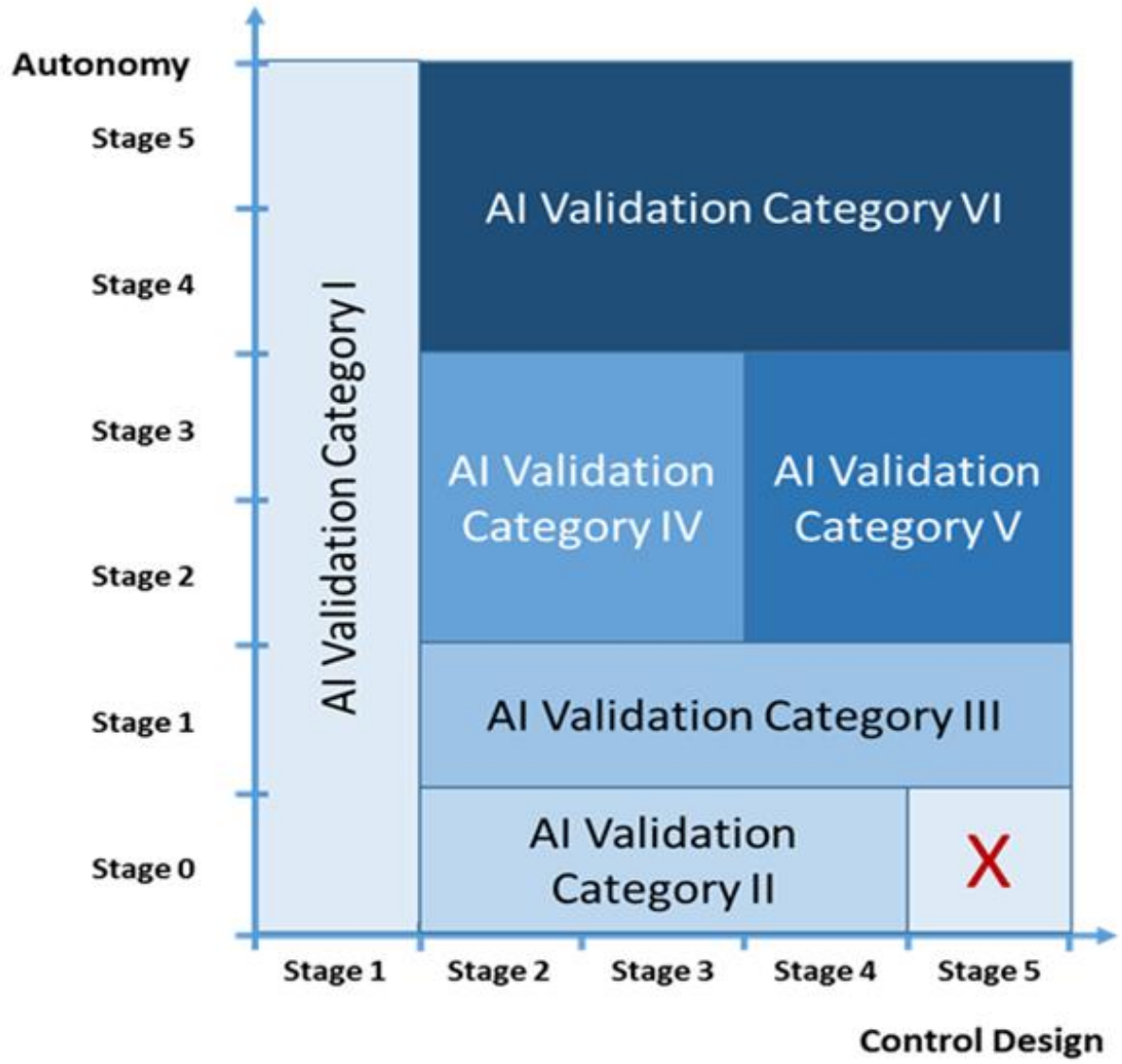
Validation of classical software and data driven software



AI Maturity Model

Goal

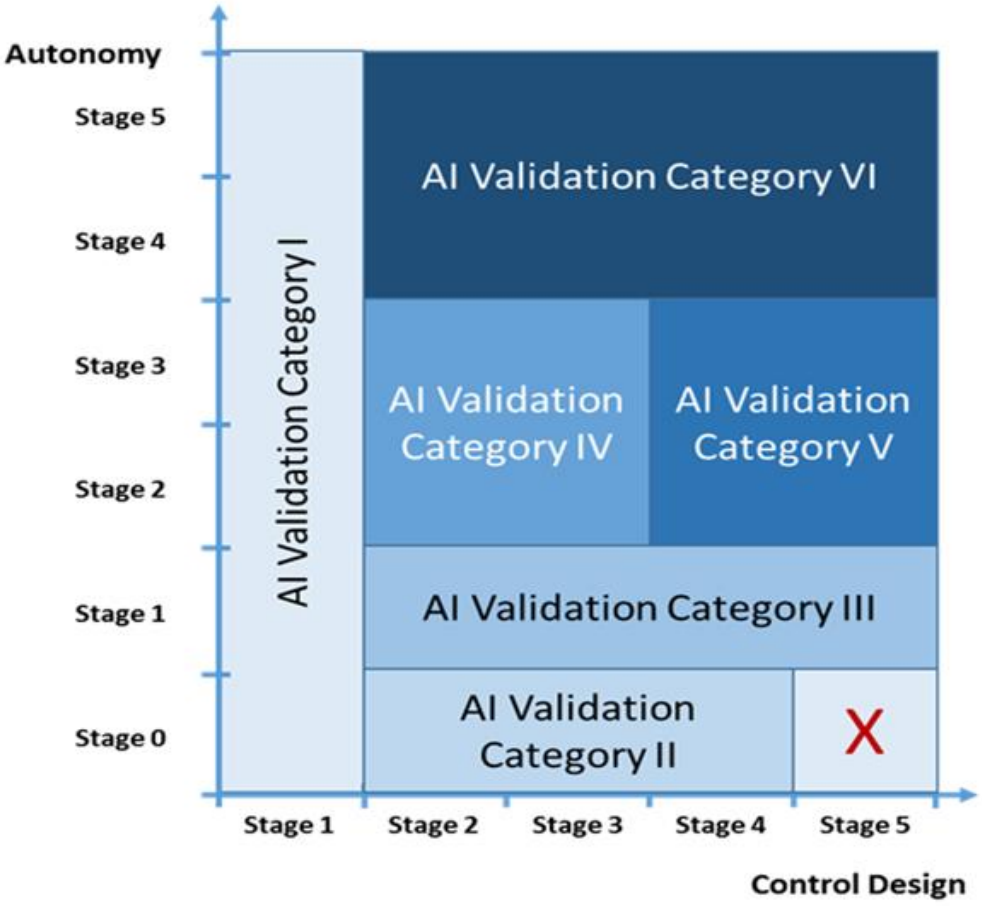
Validation categories depending on control designs and level autonomy of the AI system



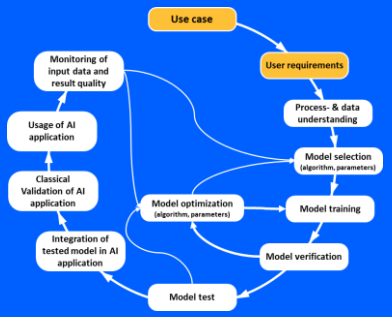
AI Validation Categories

Stringency of the validation procedure should be based on the AI autonomy and maturity

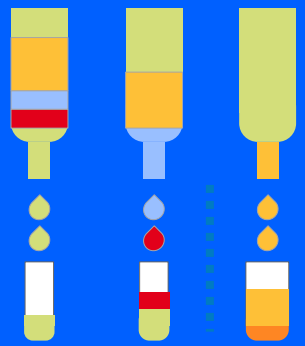
AI Val. Categories	Description
I	No Validation required
II	Validation of computerized system, but no dedicated focus on AI
III	Additionally: • Documented justification why a model was selected. • Training data verification • Model quality assurance after training • Input data monitoring in operation
IV	Additionally: • Monitoring of model quality in operation • Controlling quality KPIs and notification process
V	Additionally: • Periodical re-test with defined test data set • Assurance of self-control
VI	Currently no validation concept available



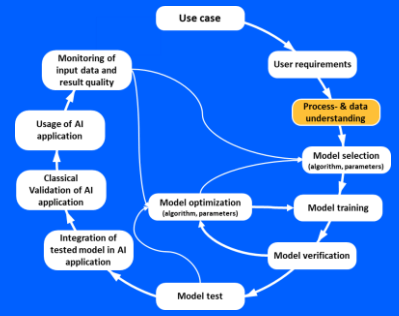
Use case – Chromatography Column



Process	biopharmaceutical API production, upstream process
Current Situation	decision for start of main fractioning process done by human experts based on HPCL data
Goal	add technical decision support to optimize yield
Challenge	use historical data to predict best initial time for future fractioning process



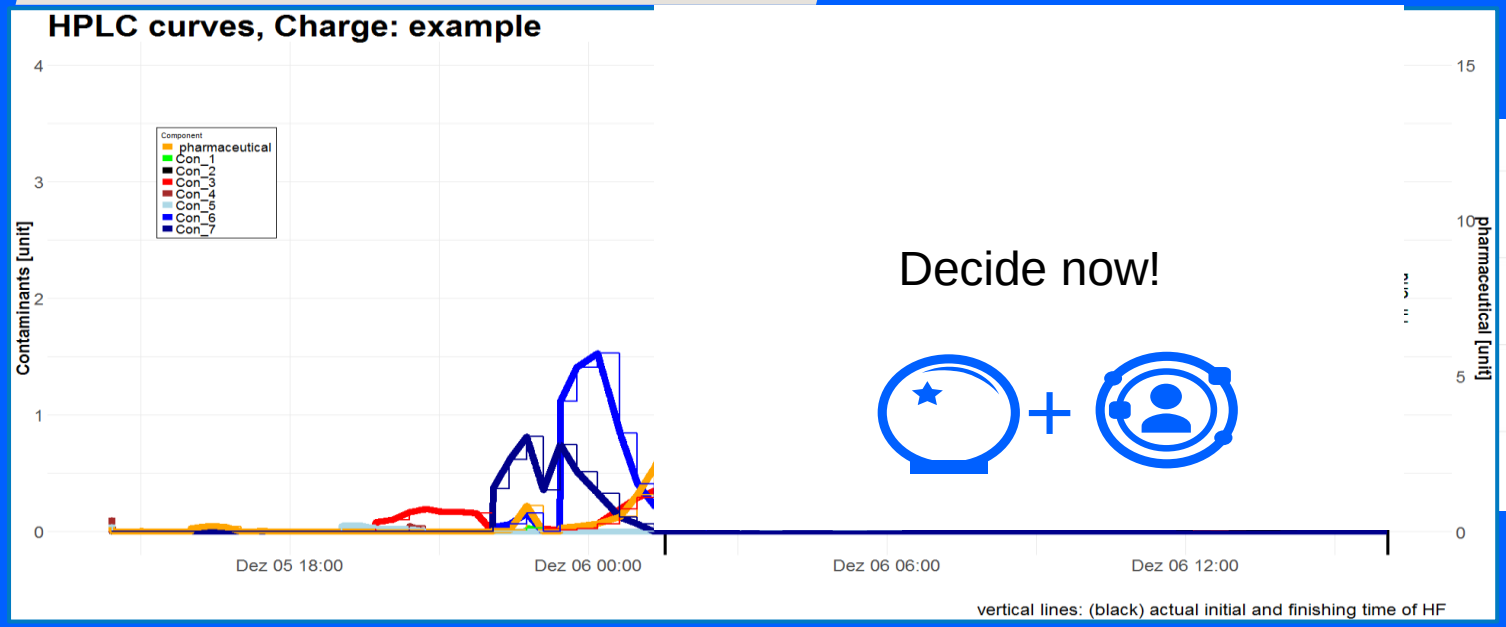
Process- & data understanding



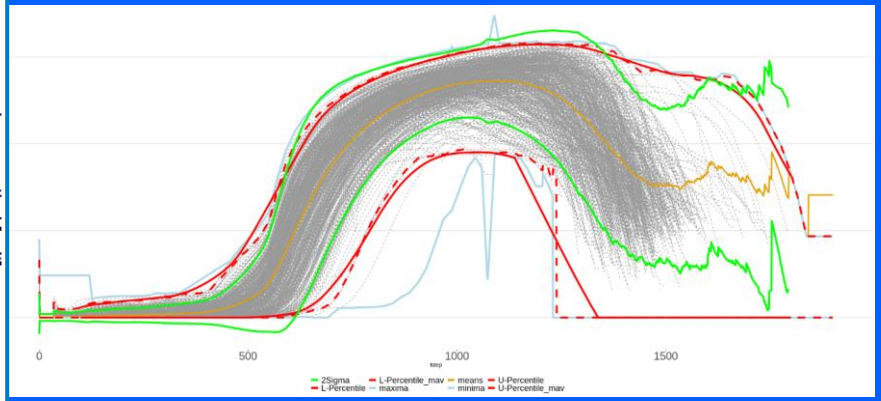
Start main extraction:
It would be simple if the **operator** would know the whole story

… but he doesn't…

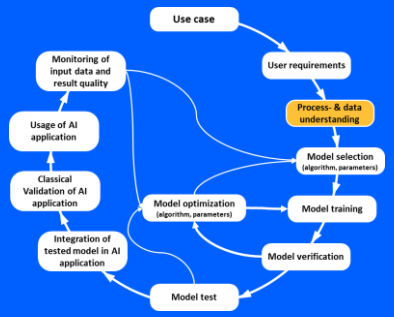
… and there are variations from batch to batch:



Decide now!



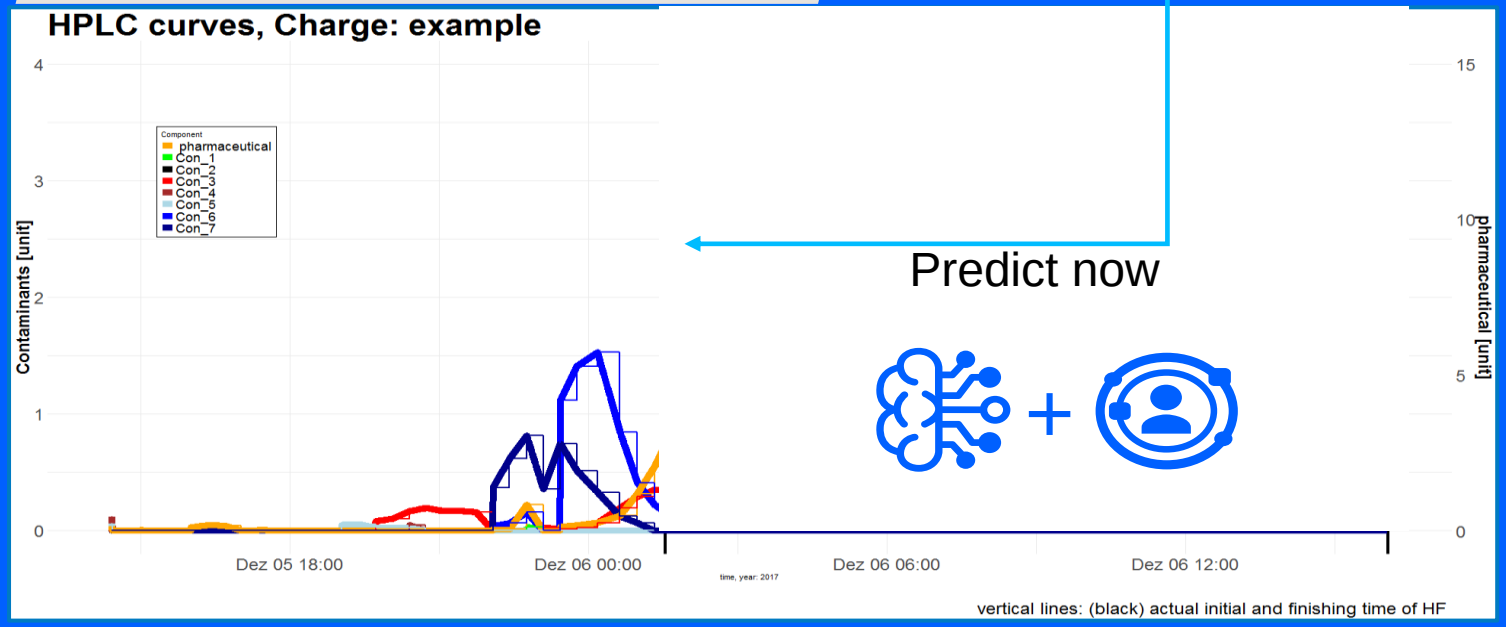
Process- & data understanding

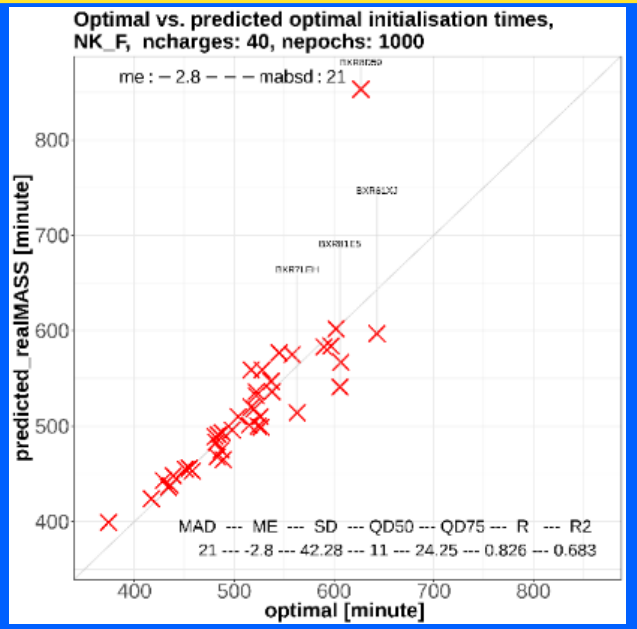


The idea:
Use AI to predict all curves based on the information…

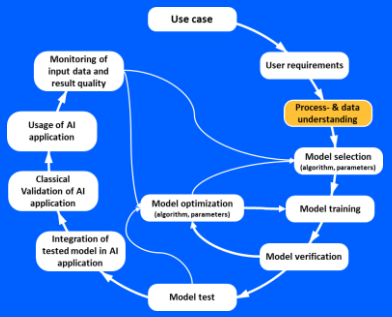
… available up to a certain early date before and calculate the start time

Result quality
surprisingly good and mostly better than manual

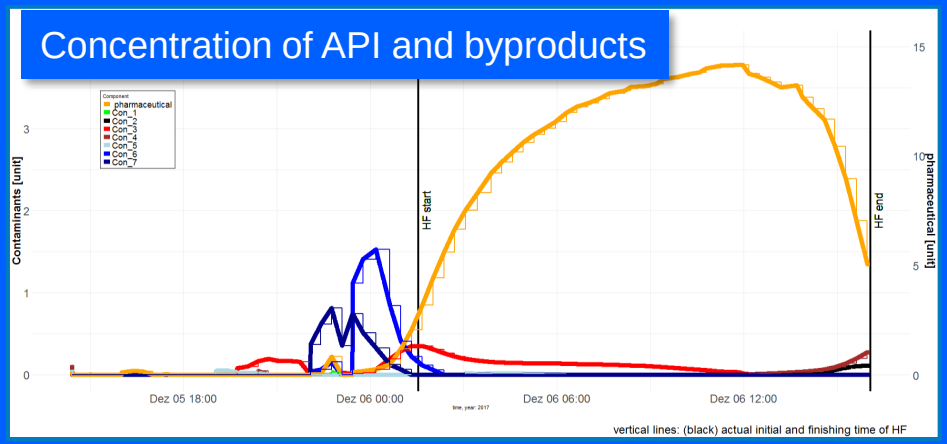




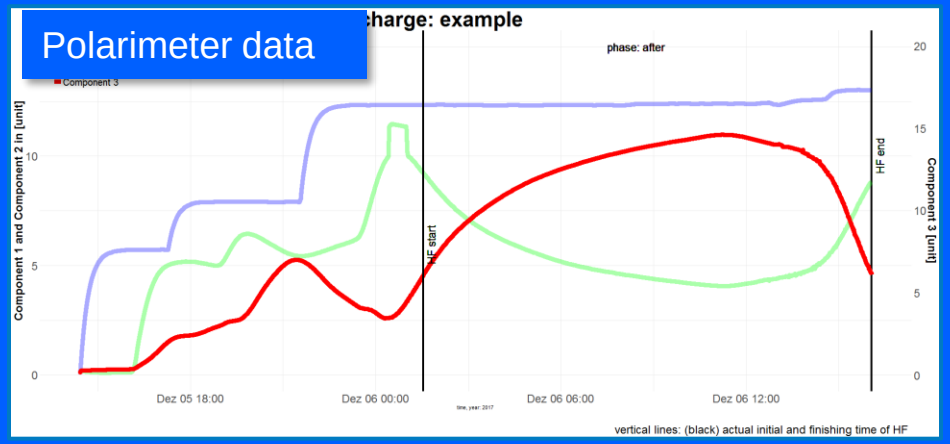
Process- & data understanding



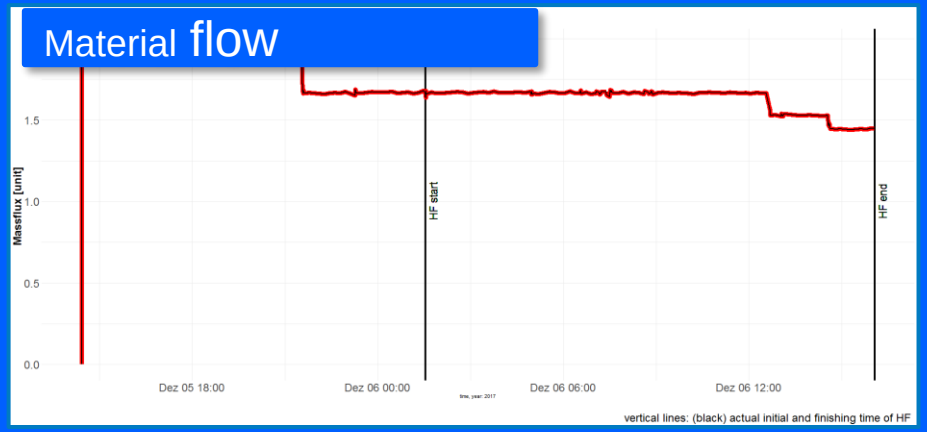
Concentration of API and byproducts



Polarimeter data

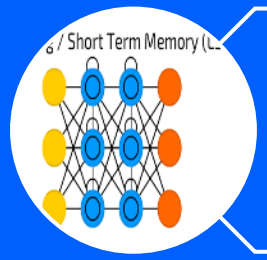


Material flow

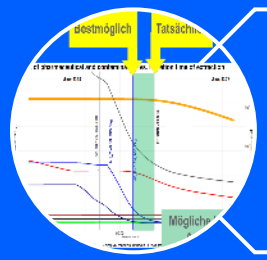


Metadata
- Limits for impurity
- time dependency

What were the next steps?



Create a model to predict the curves at a point of time before extraction start



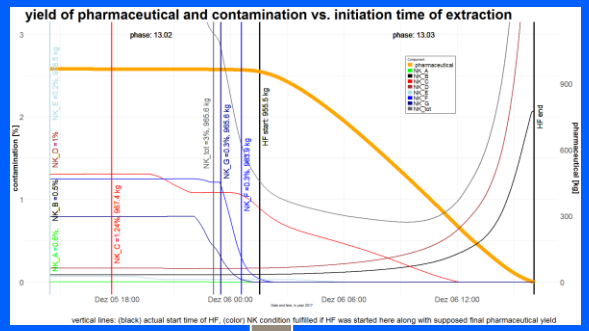
Use the predicted curves to calculate the best extraction start

Today: Notify operator about the predicted extraction start

(Future: Start extraction automatically)

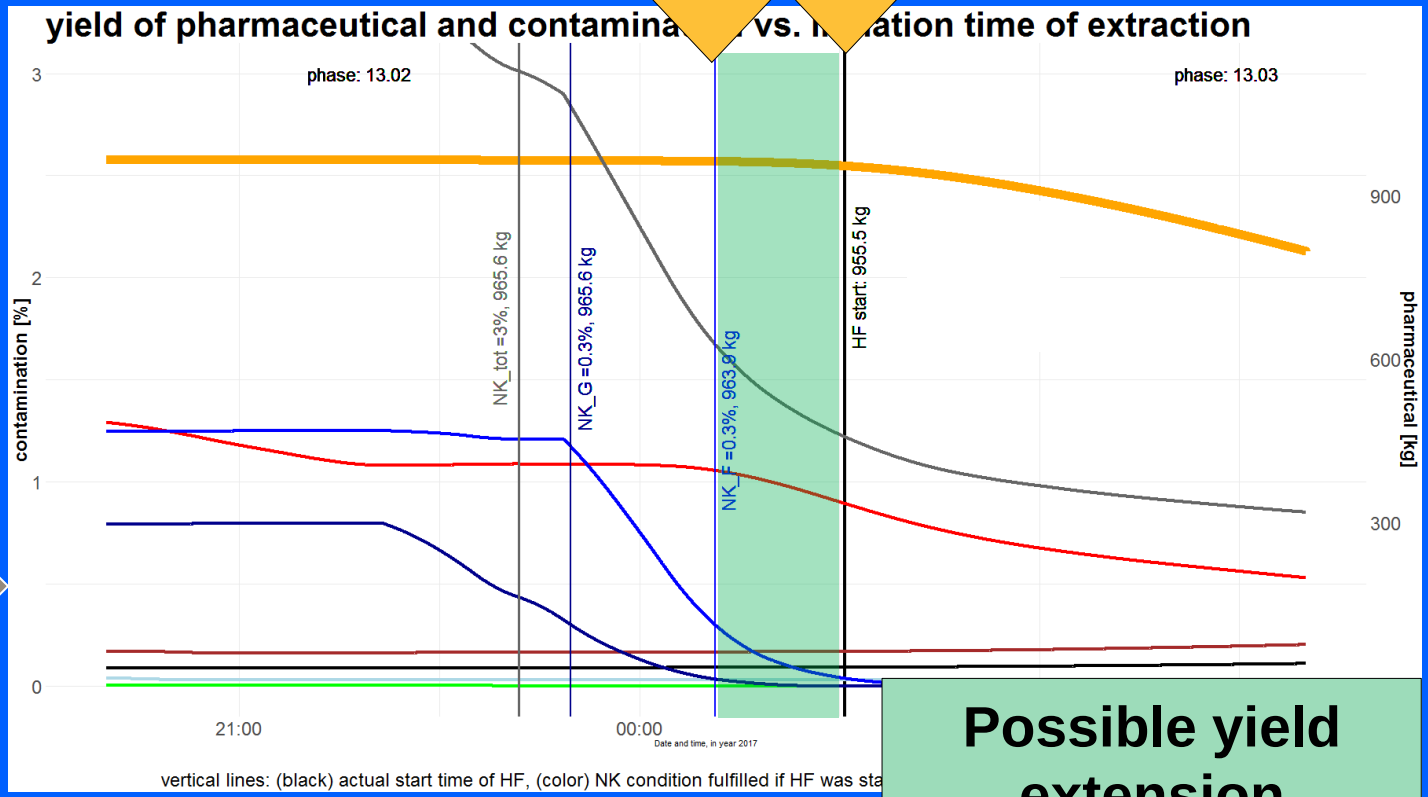
- **Produce best yield**
- **Keep impurity below the defined limits**

Possible Benefit



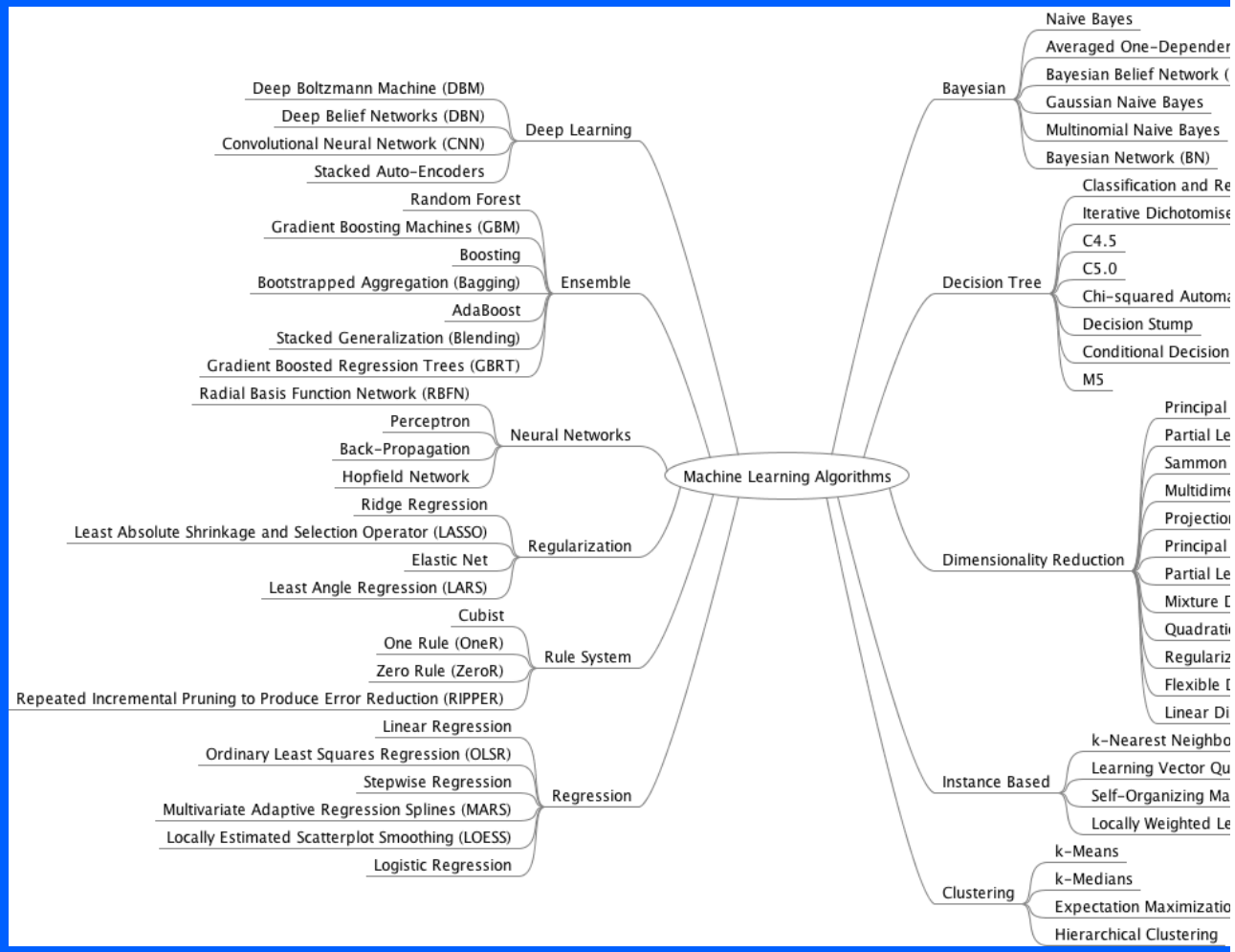
Optimal

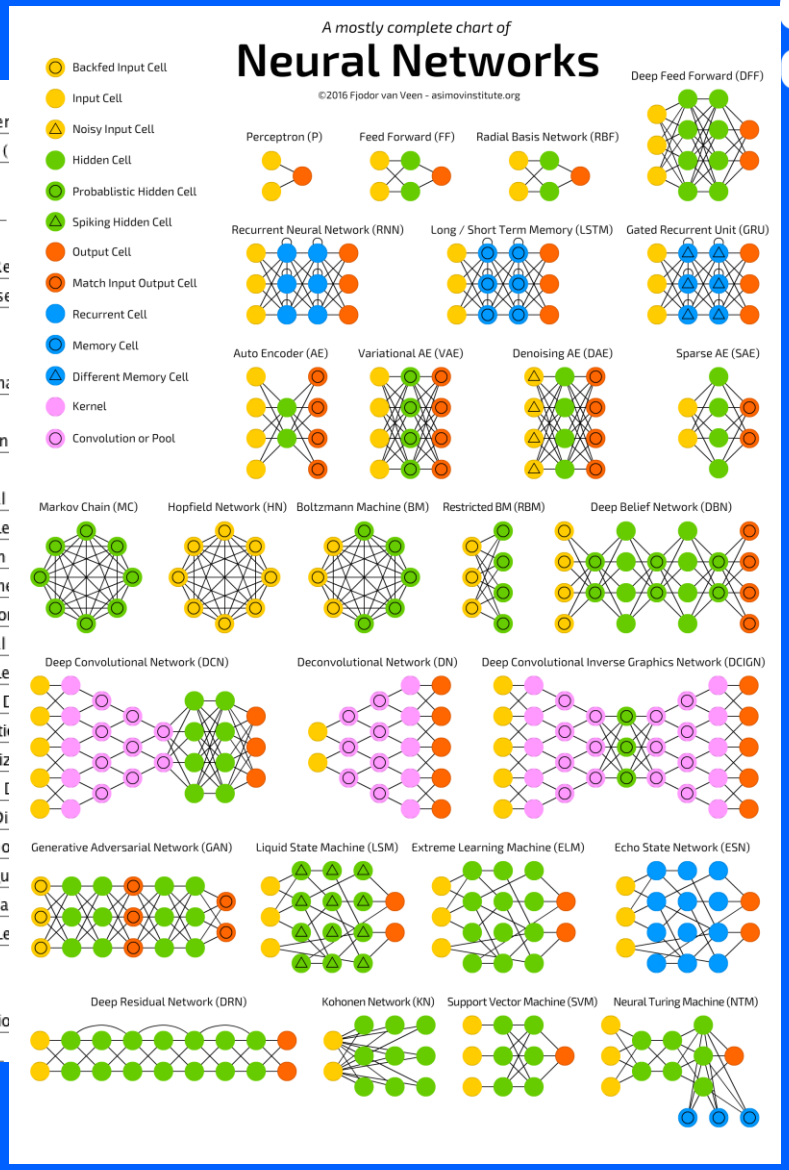
Actual

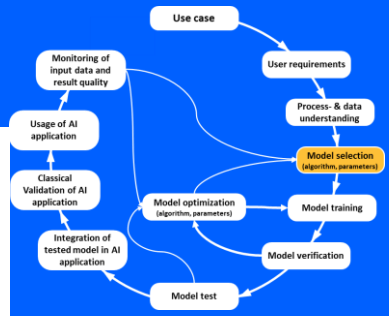


Possible yield extension

Model Selection

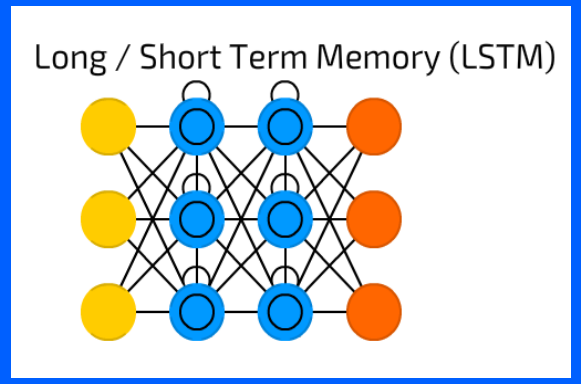






Neural Net:
Experiments with Parameter Variation to get best Result Quality

A neural network is built like the human brain and performs in a similar way

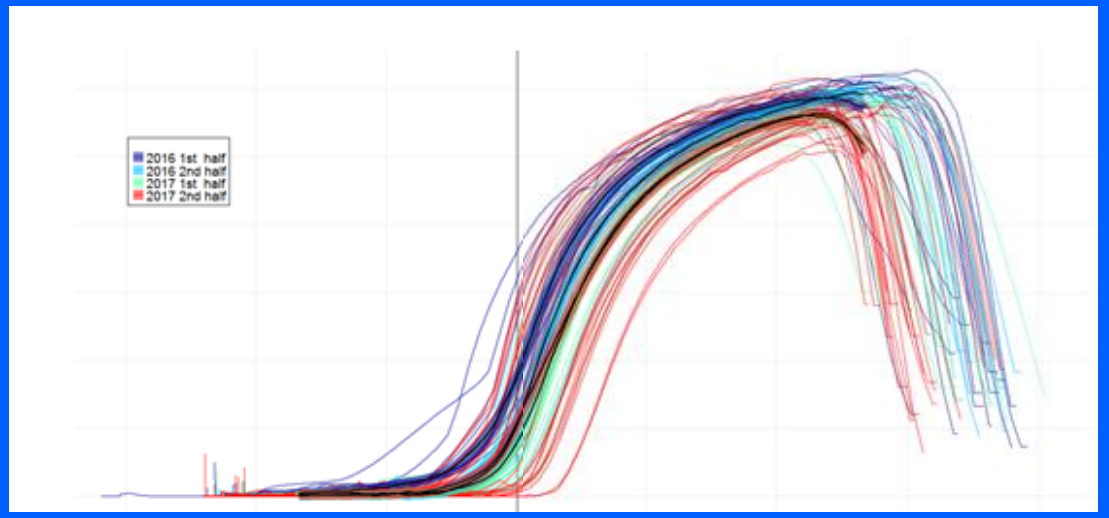


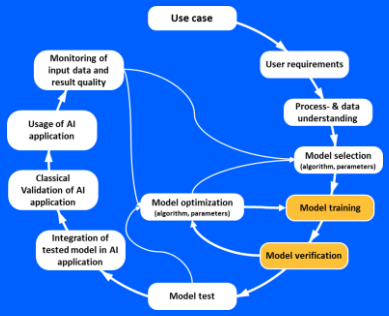
The chosen neural network is well suited to process graphics and time series (image recognition, translation, etc.)

Facts

- **>200 training runs with varying parameters were performed**
- **Number of inner levels 4**
  Number of neurons per level 32
  Number of iterations per run 1000
- **The result of each training run was verified and marked with the MAD value**
- **At the end the configuration with the best MAD value was selected.**

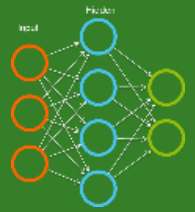
Training of the neural net



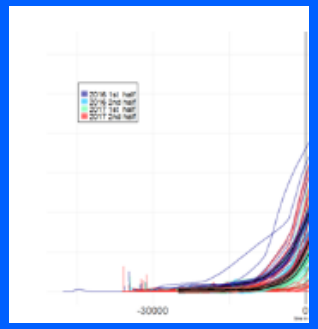


Creates a model

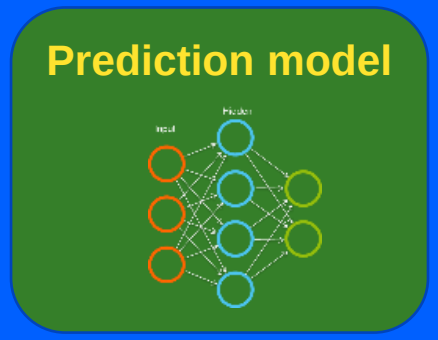
Prediction model



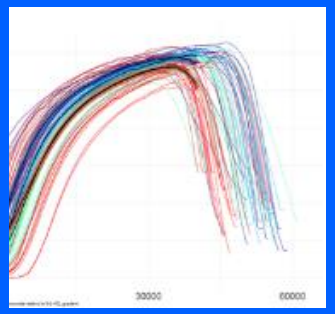
Verifying the Forecast Model

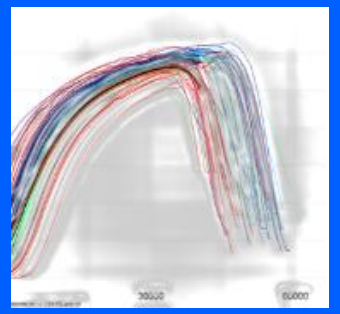


Take x% of the data to verify the prediction model

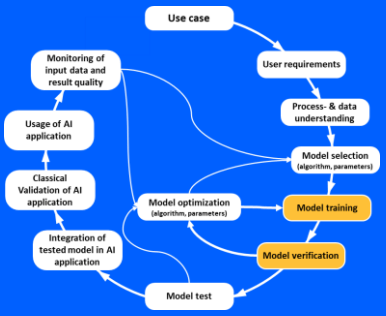


Existing curves

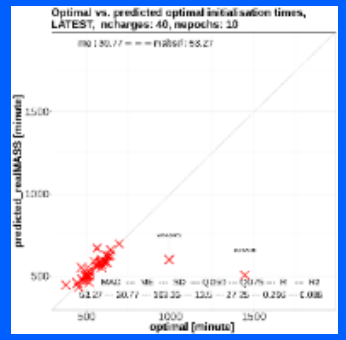




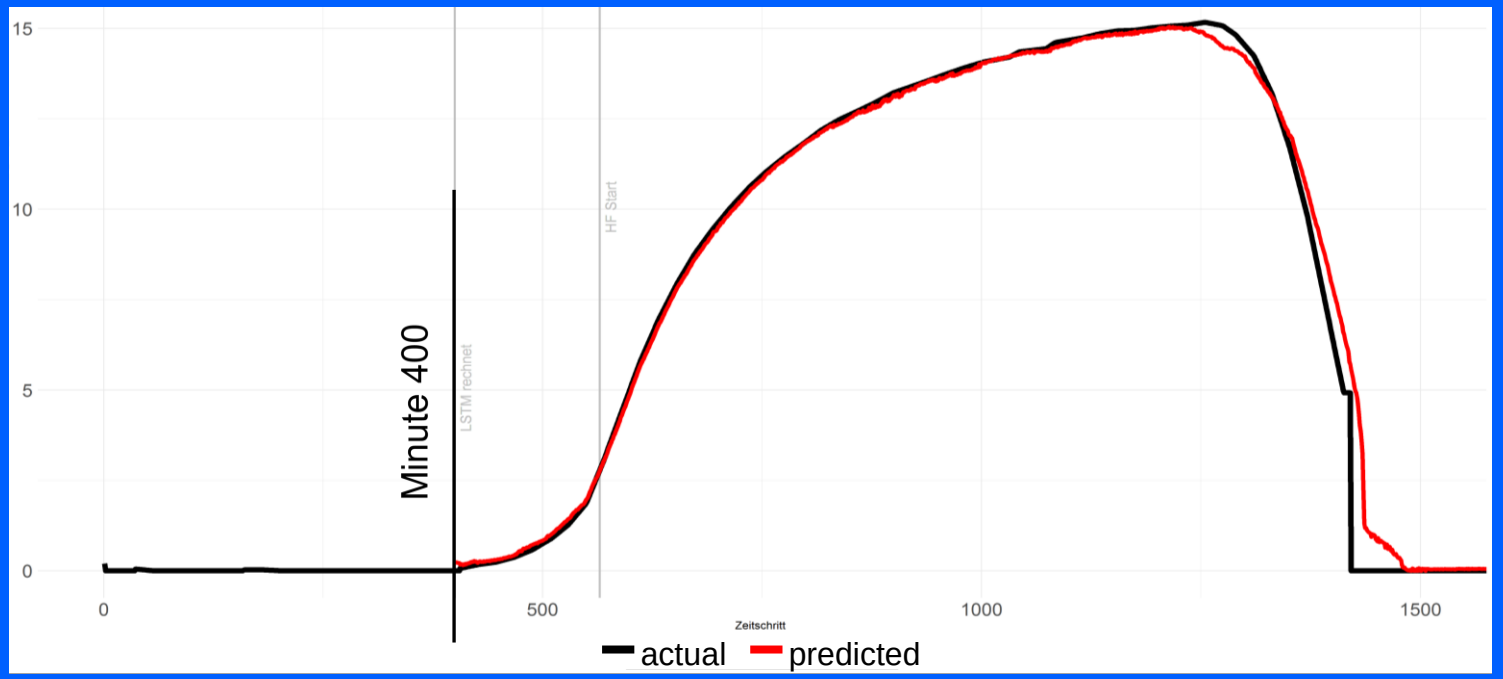
Predicted curves



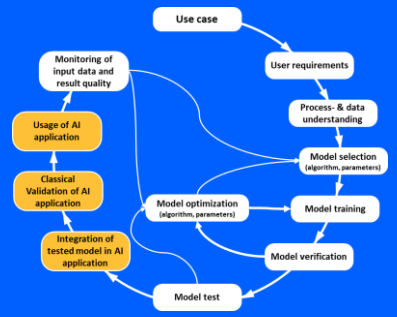
Compare both to determine result quality

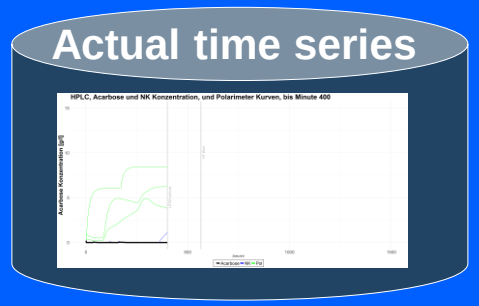


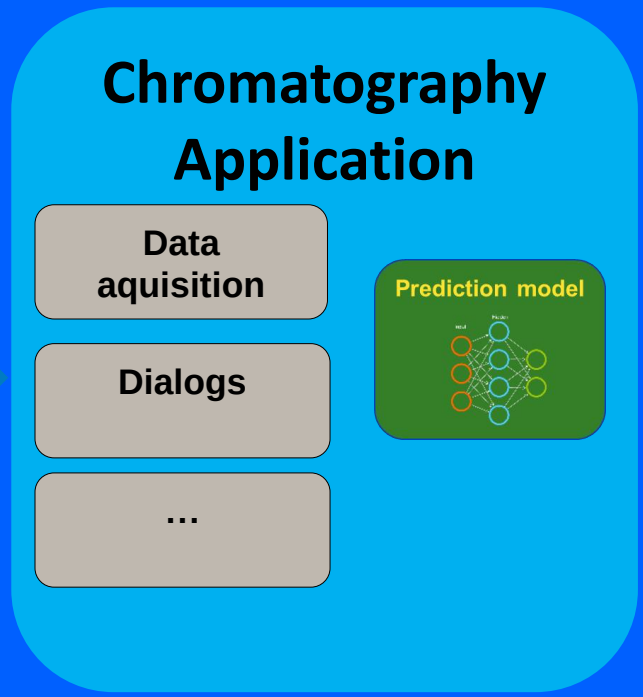
Predicted Curve and Actual Curve at 400 minutes



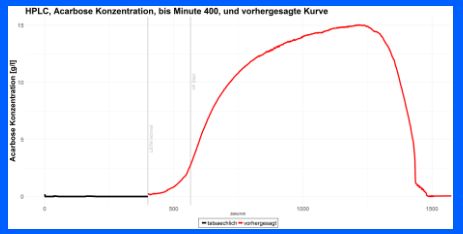
Usage of the Model in Application





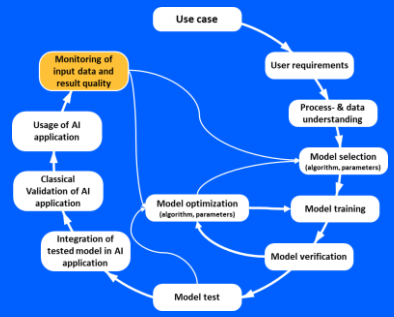


Prediction: API concentration curve
Calculation: Best time to extract API



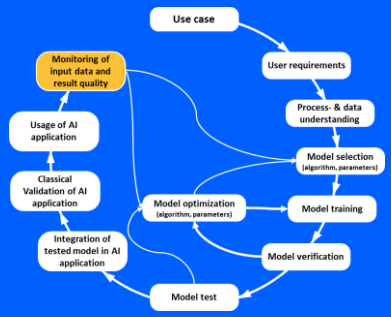
Goal: Best yield with defined purity

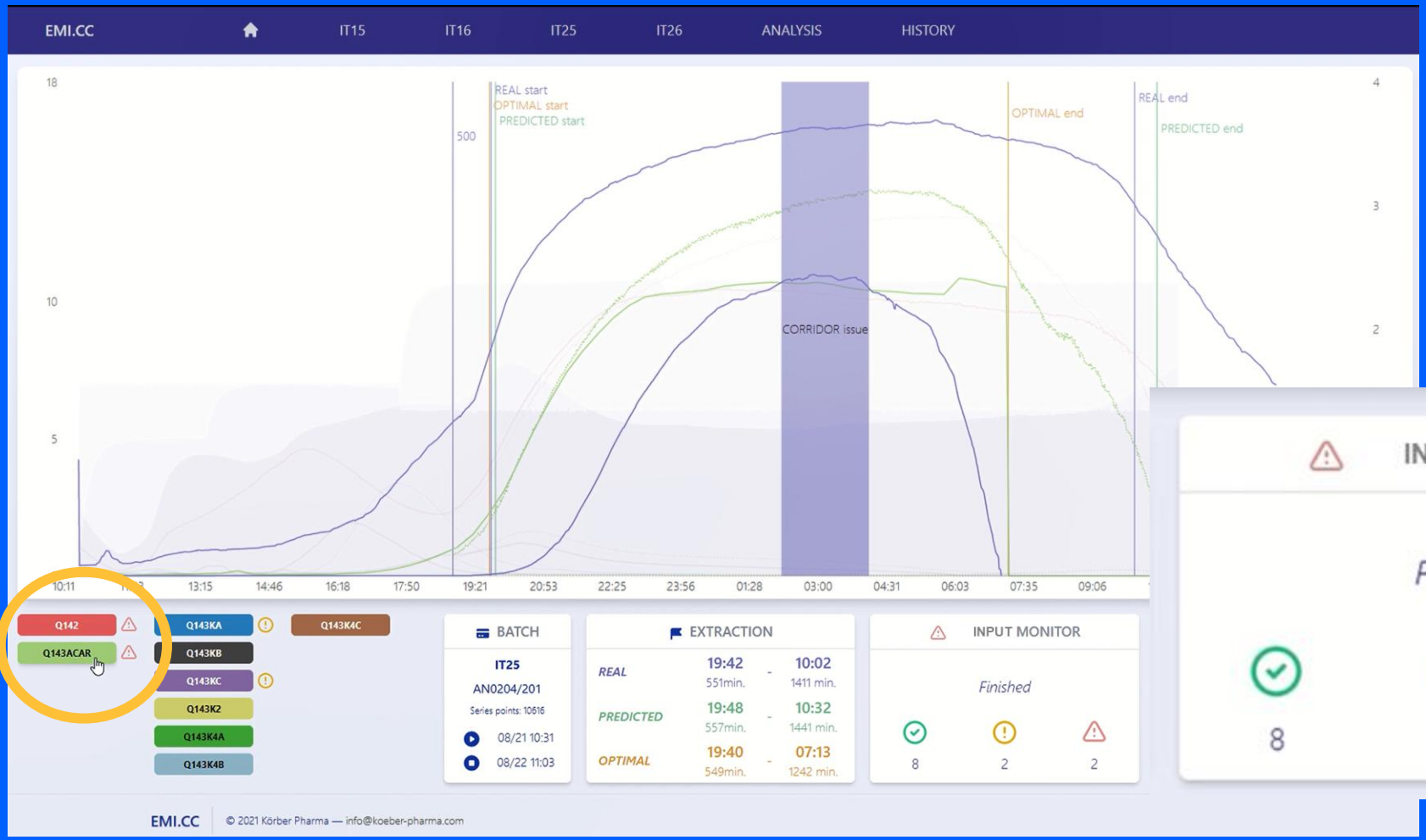
Create Trust with Transparency

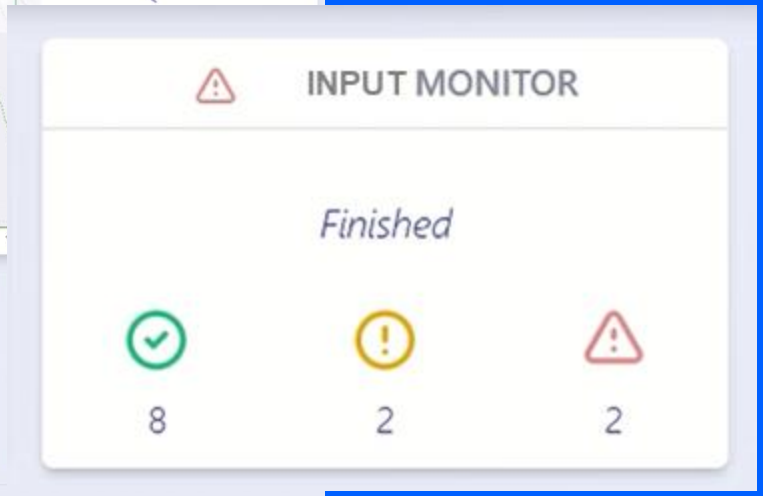


Monitoring of Incoming Data

Trainings Corridor

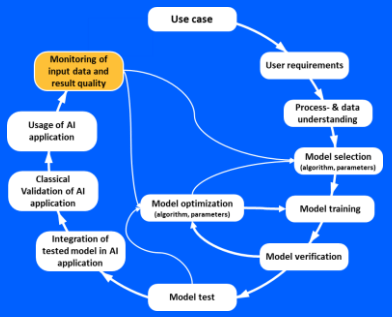






Monitoring of Result Quality

Compare predicted yield with actual yield



SPC: Result Quality KPI

Initiated Retraining if Result Quality shows a trend

Summary

- **To create trust in AI needs more than classical validation**
- **Quality of data is most important**
- **AI model validation is focused on model selection and training**
- **Real time monitoring is needed to check input and output data continuously**
- **We have ideas and we have already implemented them to create a better understanding. But we are at the beginning**
- **We still need a broader community accepting a validation approach**

Thank you for your interest

Questions

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