Continuous Process Development, a New Work Flow Supported by Process Simulation

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Batch Processes have and will continue to fulfill an important role in the manufacture of Active Drug Substance; they allow multiple recipes to be executed in the same core equipment. However, the compromise is, batch fails to deliver the precision, speed of manufacture and intensification of a flow process.

Here, I present how at GSK, we are converting our standard batch manufacturing facilities to flow technologies. We expect that this approach not only changes the way the Factory looks, and costs, but how it is built, deployed and operated.

To accelerate tech. transfer and enable greater robustness, we are supporting API process development by deep process understanding and process simulation.

We believe that the implementation of high performance flow processes in manufacture will allow us to deliver more medicines of value to patients, both in affordability and function

Past and Future Objectives

Continuous Manufacturing

2003 Started Programme

2016 Gain First Commercial Credibility for 3 Stage Process.

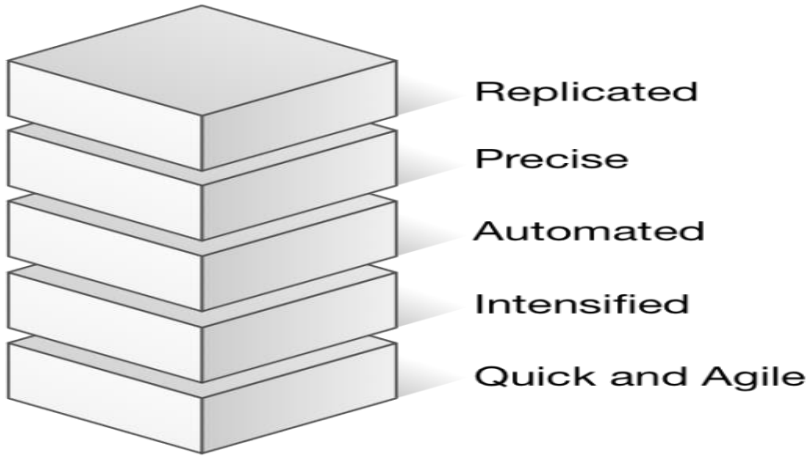
First Clinical Campaign of Organometallic Flow Process.

2016 Build Operational Experience.

Control Strategy.

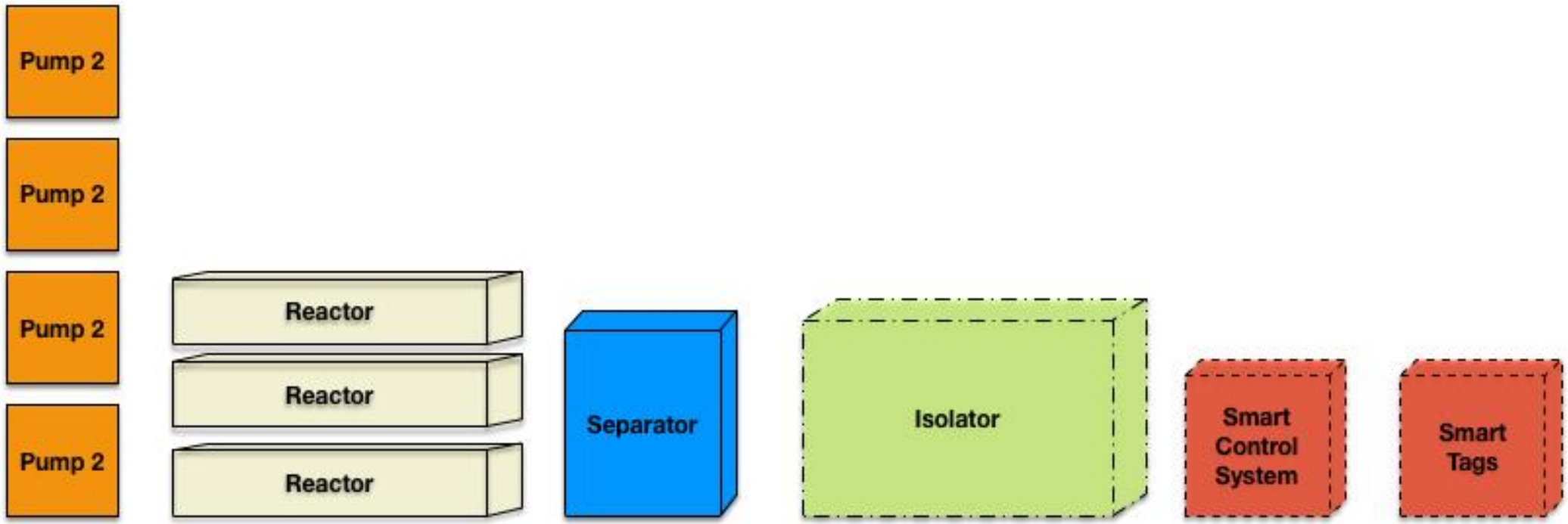
Business Processes.

2016-2021 Design/Build the Space to house the next Phase of Projects



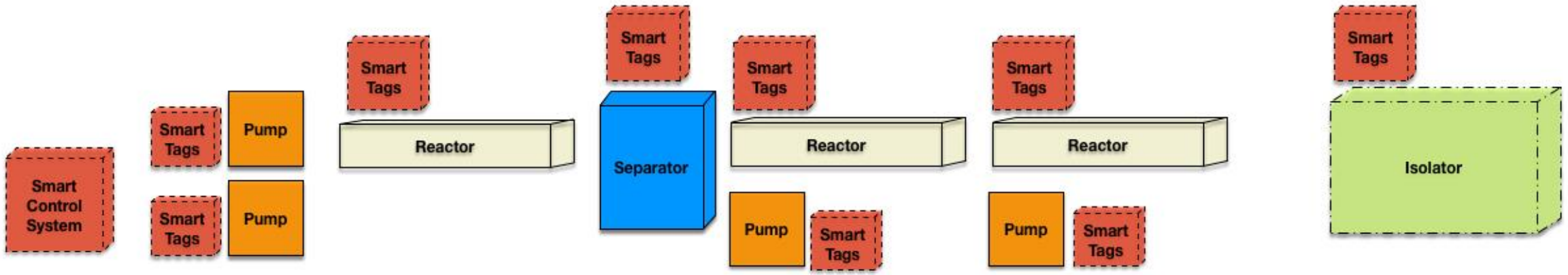
Engineering Starting Point. A Library

Feed, Reactors, Separators, and Isolators. Modular. Replicated. Smart.



Arrange Library Components to Execute Recipe.

Enable the Library Components to handshake with the Control Architecture.



Solution

Current. 2015. Best of Lab/Plant. Modularisation at Controllable sub-unit level. Separated Feeds.

GSK Drug Substance Process Ambitions

To allow an efficient transition from Batch to Flow, we need to change the way we approach development

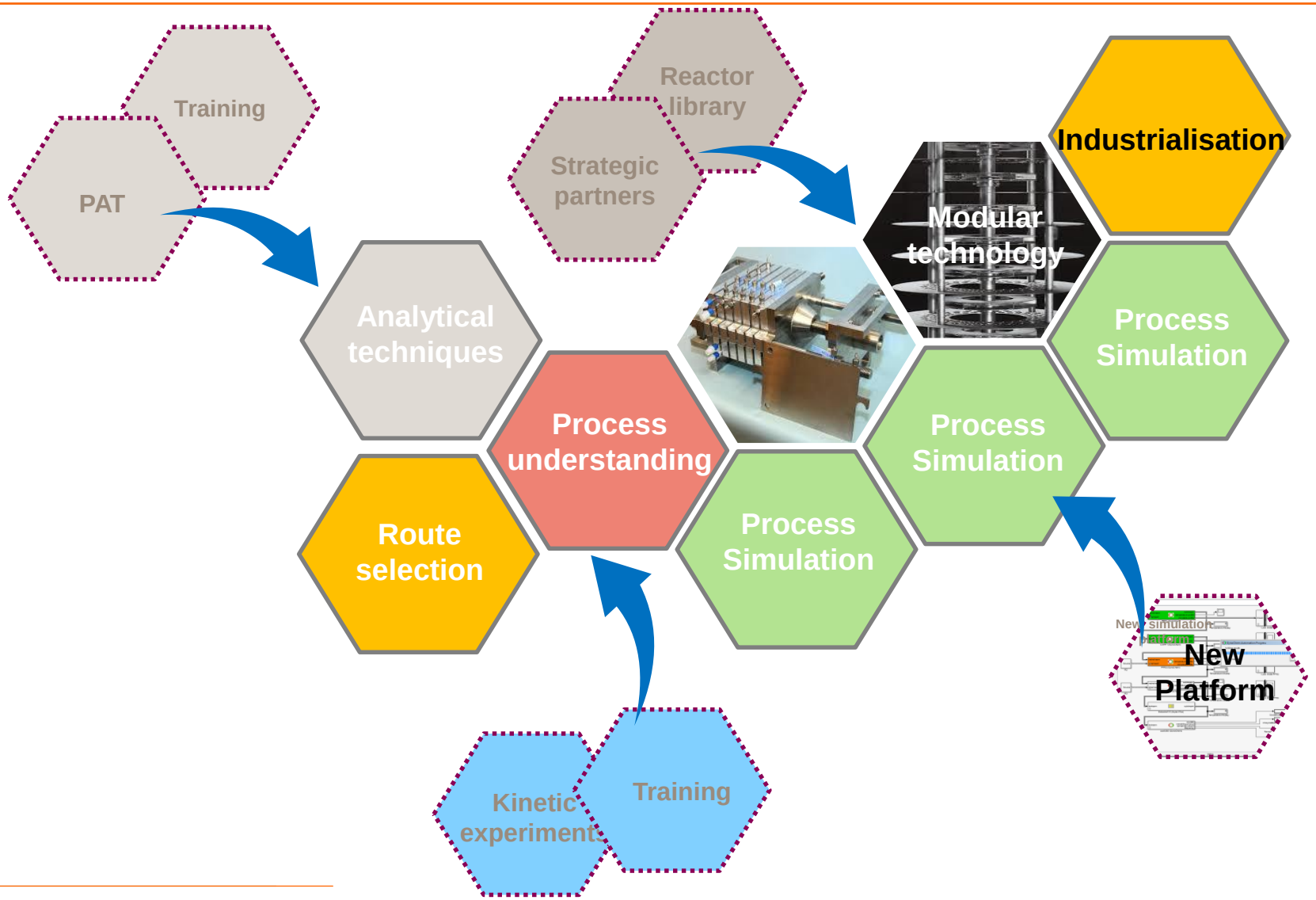
Pharma has been working on a knowledge and trial & error principal. Development has been governed by statistical models and small scale increment until manufacturing scale.

To support this strategy, simulation has to be integrated at the centre of process development to

- Accelerate process development
- Provide more robustness in the development phase
- Ensure an understanding from scale to scale

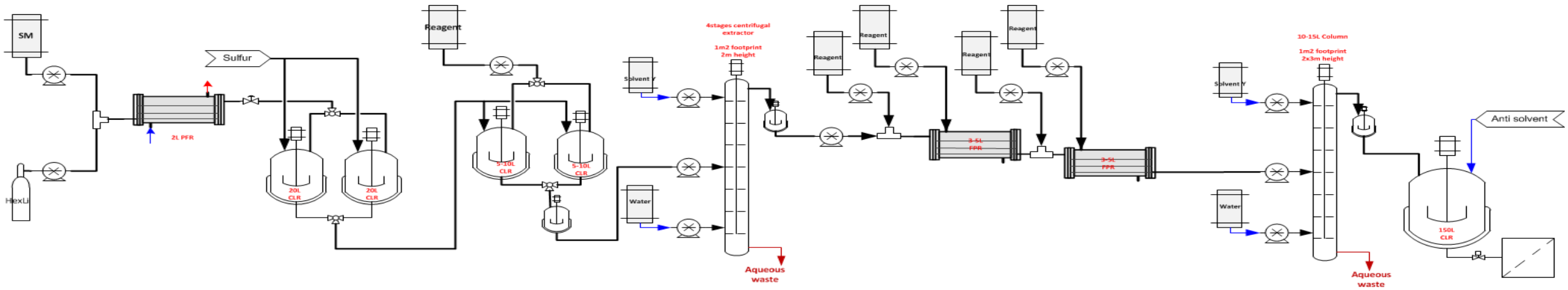
New Work Flow Application

From Hardware to Virtual World



GSK Ambitions in Simulation

What for Today and the Future

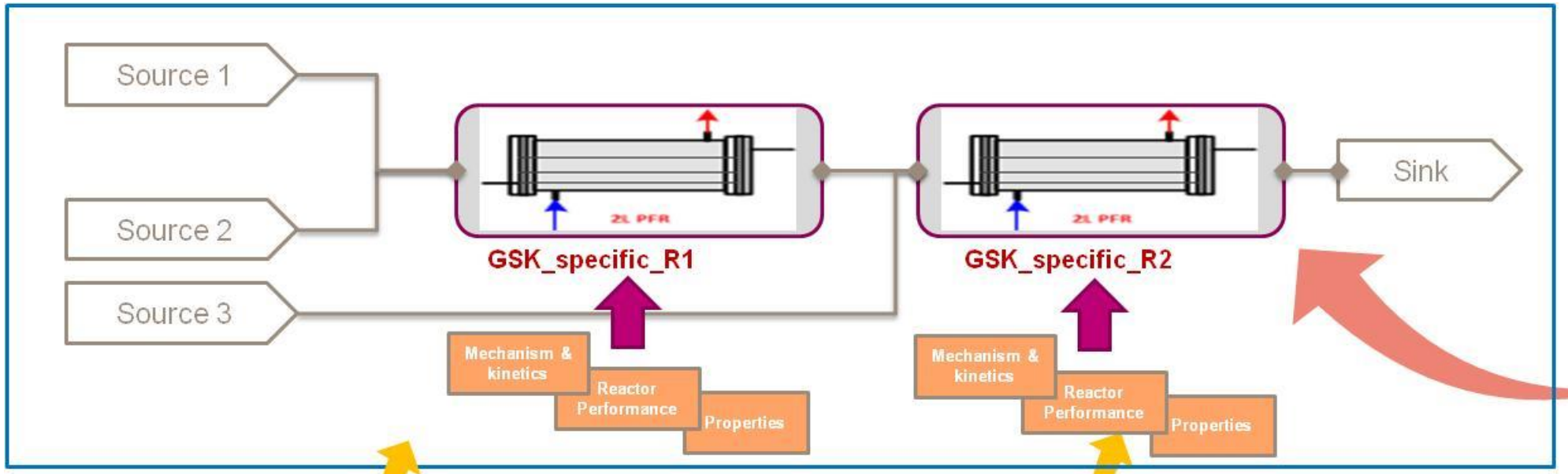


- **Current simulation capability for batch and flow**
  - Kinetic and thermodynamic modelling
  - Reactor performance model

- **Application**
  - Application of single unit ops
  - Integration of high complexity models into flow sheet interfaces

Flow Sheet Interface

gPROMS



Mechanism definition & Parameter regression

DATA

Specific model decoupled from the flow sheet only for parameter regression

Reactor Performance

DATA

Performance data embedded within a separate file
The specific file can be called from the reactor model

Equipment Library

Reactors

- PFR
- CSTR
- Batch

Work up

- Extraction
- Evaporation

Crystallisation

- Batch

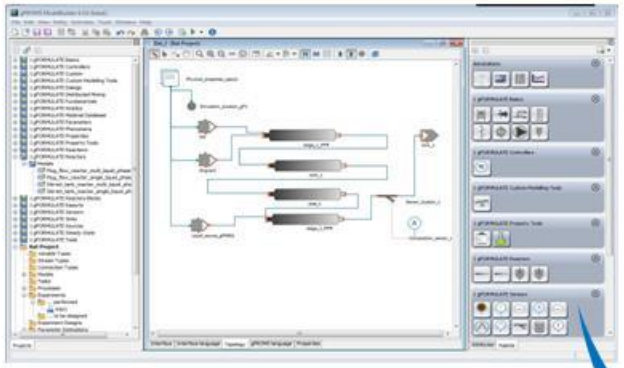
Simulation Application: Design Space and QbD

Mechanism definition & Parameter regression

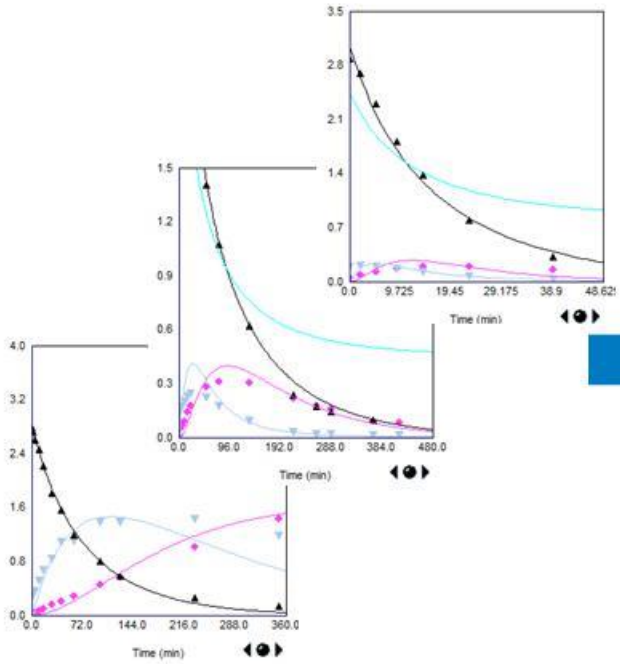
DATA

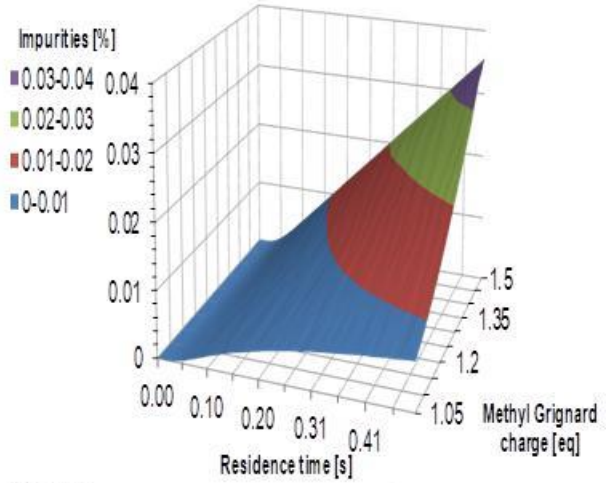
Kinetic orientated exps
- Calorimetry
- Concentration time course at various temperature, concentration, mixing time

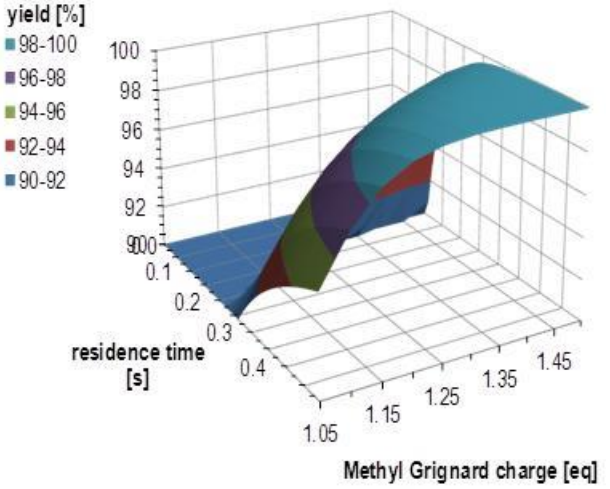
Specific model decoupled from the flow sheet only for parameter estimation



Parameter estimation

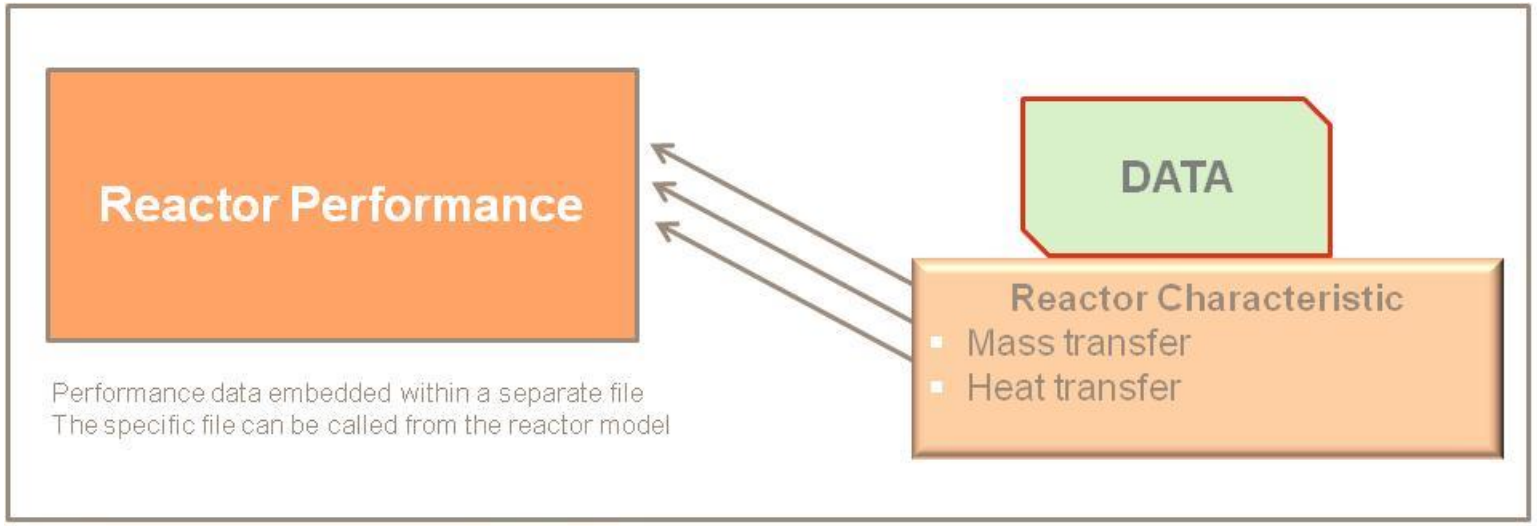


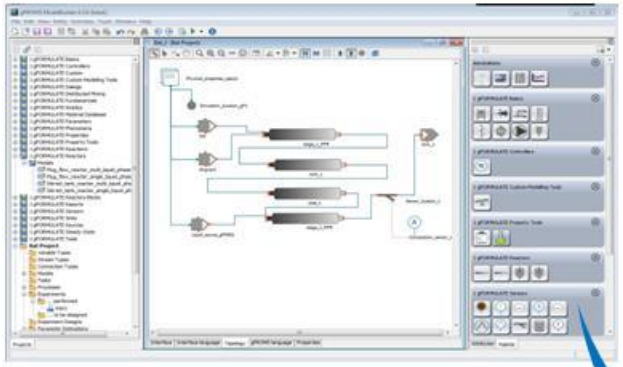




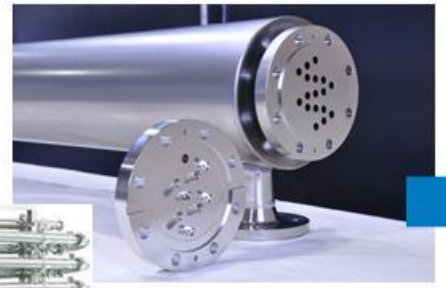
Working conditions & Design space of operation

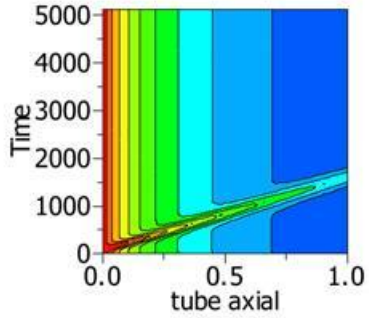
Simulation Application: Reactor Definition

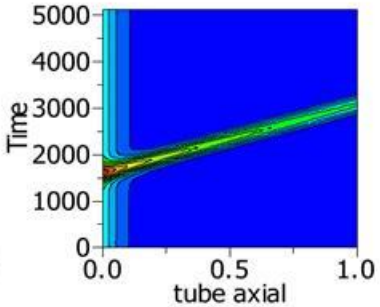


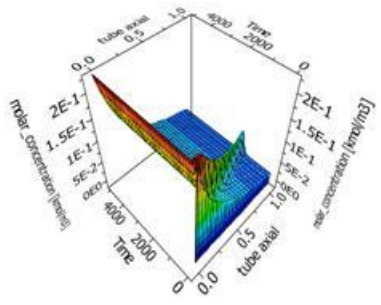


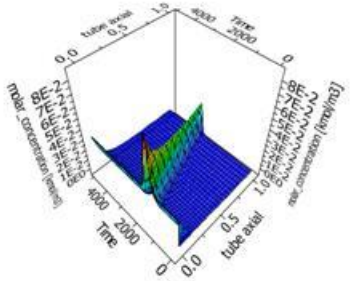
Reactor Design







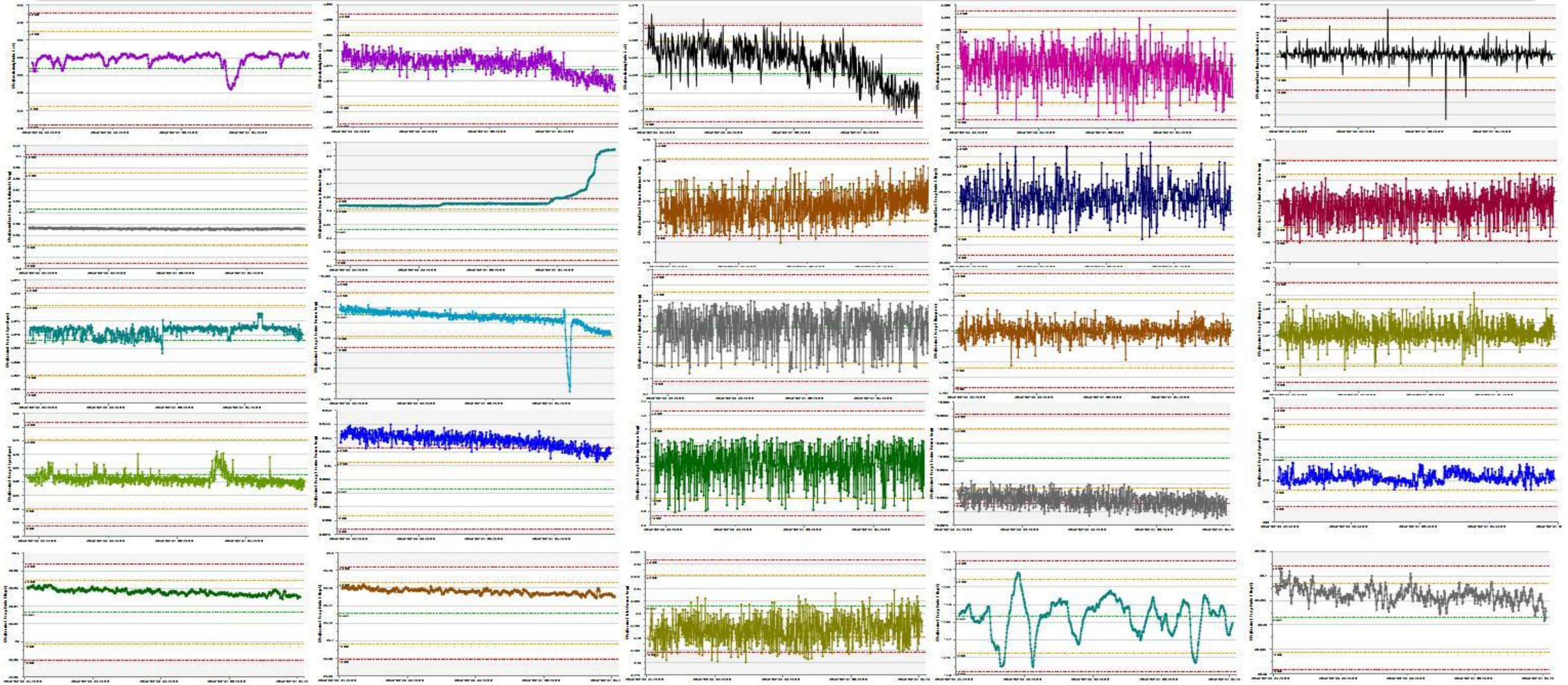




Propagation of disturbance through the reactors over time and in space. Kinetics and dispersion impacts the results.

Simulation Application: Multivariate Monitoring

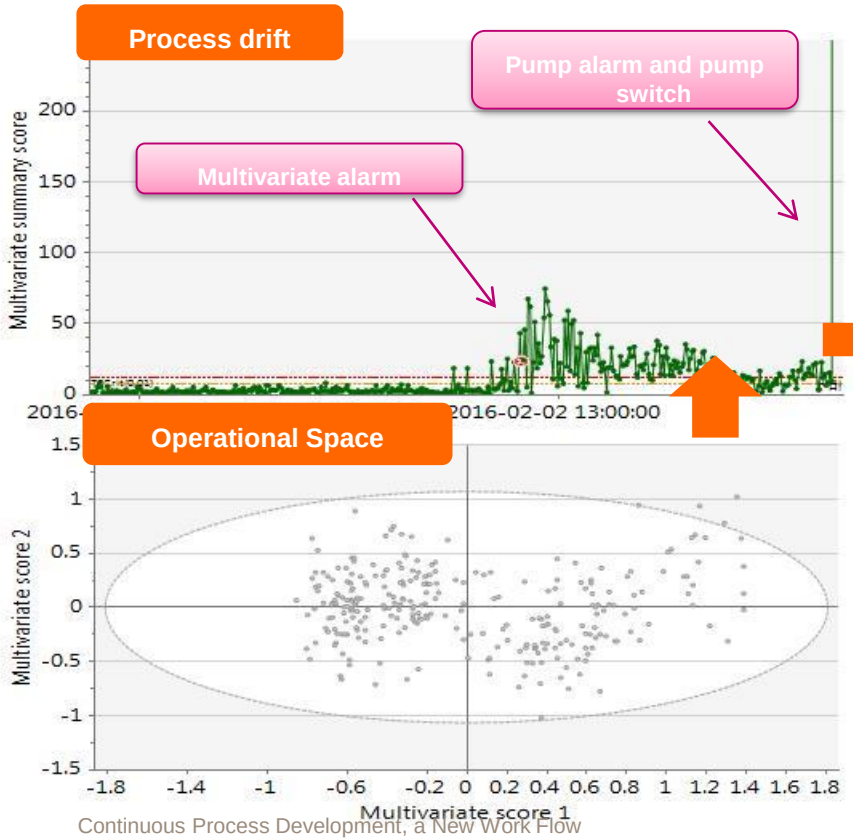
Process performance is monitored by process sensors: conductivity, temperature, pressure, flow rates, pump pressure and pump speeds

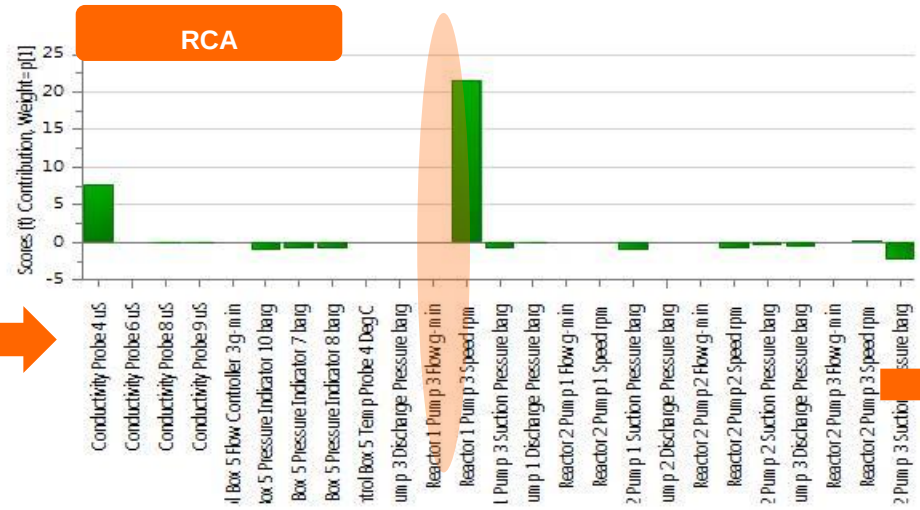


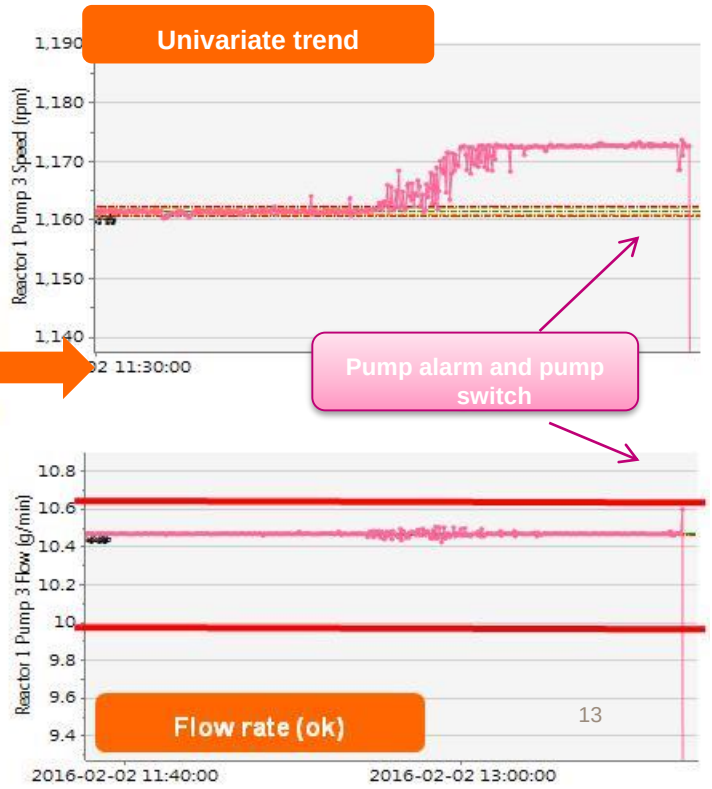
Simulation Application: Multivariate Monitoring

Enhance manufacturability

- Define operational space at state of control by multivariate monitoring
- Monitor process trend multivariately in real time
- If process drift, identify root cause and perform preventative maintenance, e.g. Pump switch







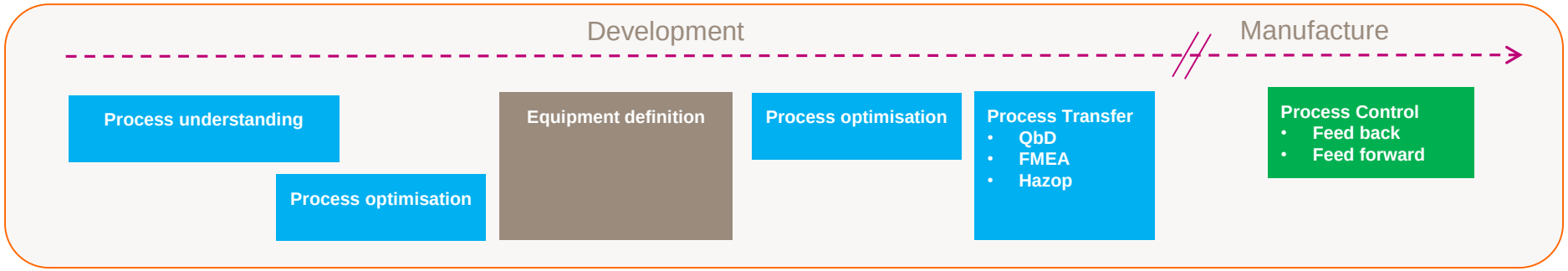
- Multivariate alarm: 12:48
- Univariate alarm: 13:52
- Action: pump switch at 13:52

→ **diverting to waste and/or shut down prevented**

Where We are and Next Step

We are…..

- Individual simulation enabling parameter regression
  - Mechanistic model and kinetic parameters
- Individual simulation enabling reactor characterisation
  - Mass and heat transfer characterisation
- Insilico Optimisation and QbD
- Monitoring of well being of the process during operation



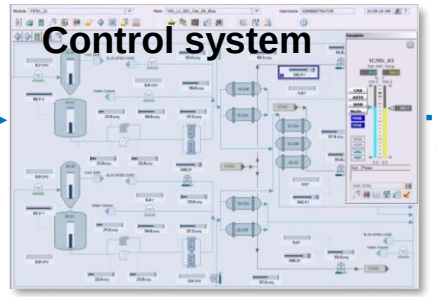
Where We are and Next Step

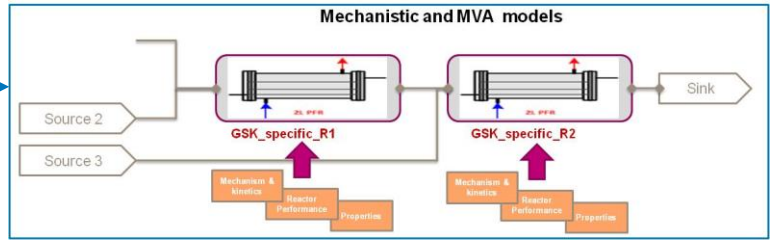
We would like to be…..

- Direct interaction between complex none linear model and control system
  - Feedback / feed forward

Process parameters output

Changes





- Complex model being part of the control strategy

A Space

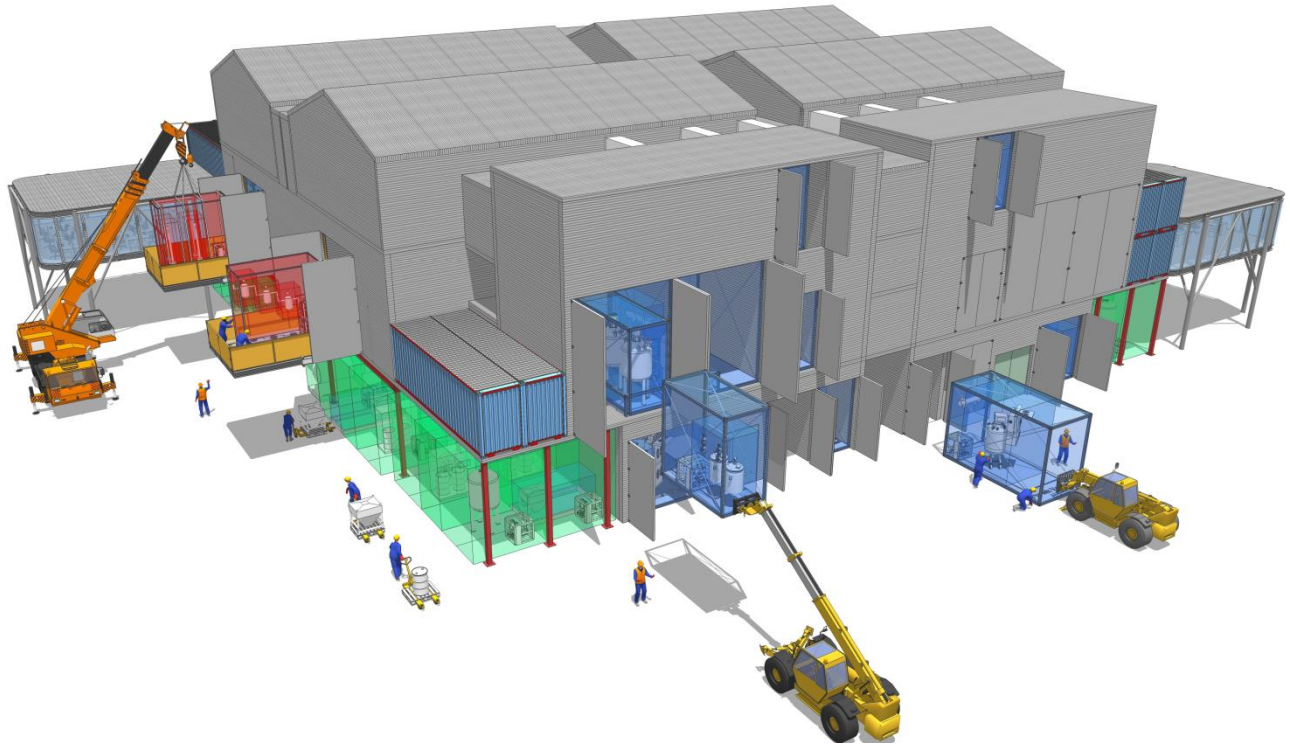
Design a host space that allows Rapid & Compliant Introduction of Equipment.

Maximises benefits of Modular Parts.

Designs Replicated.

Responsive to Demand.

Automated to drive Compliance and Productivity



Thank You.