Advanced process control of a pharmaceutical granulation process - a digital design approach

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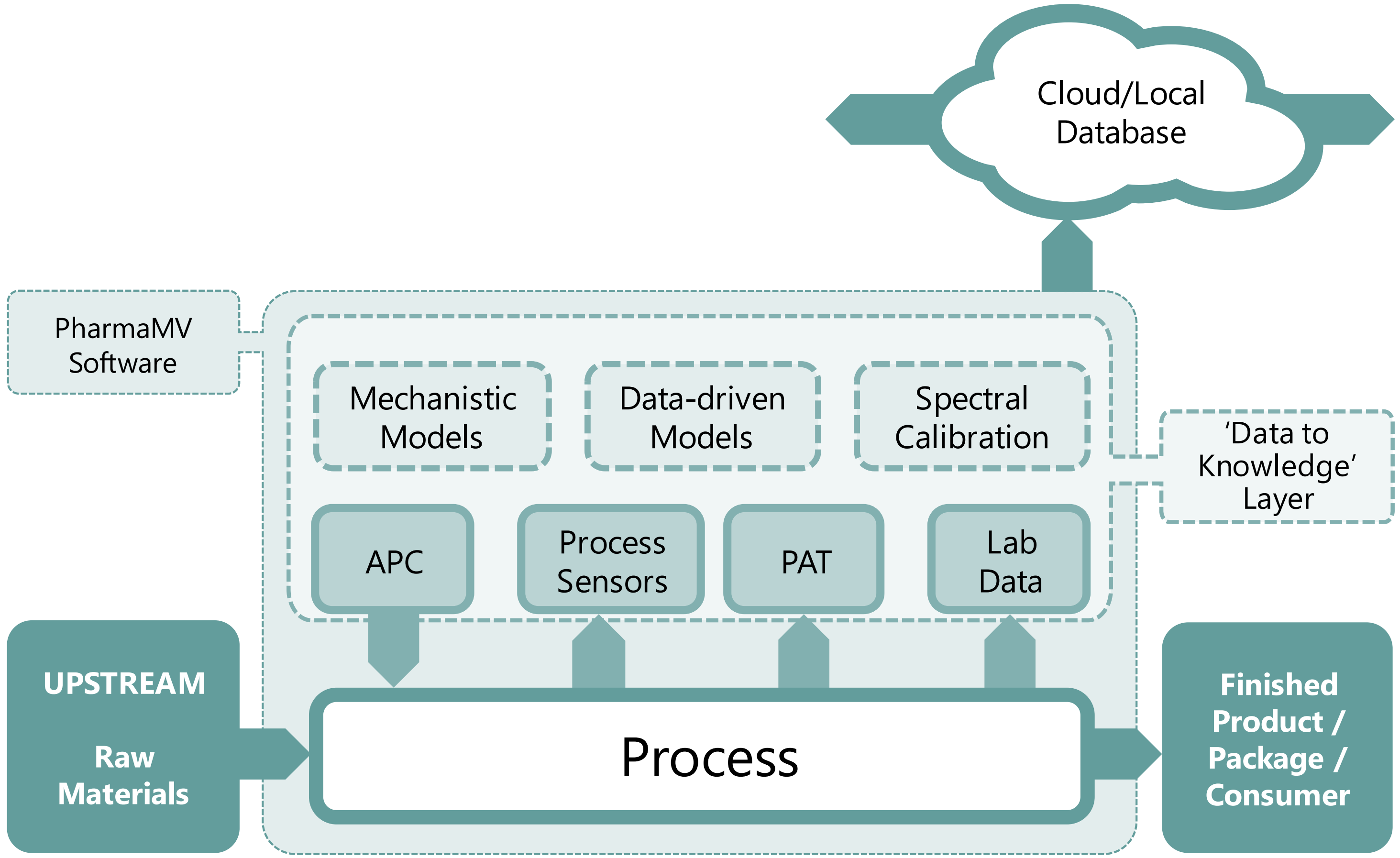
PharmaMV
Process Control & Monitoring

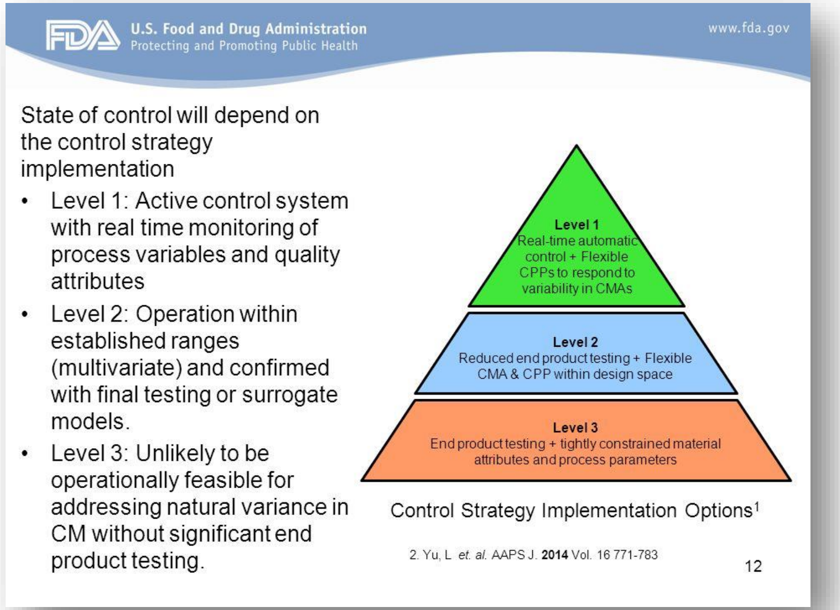
- In the lab, PharmaMV can act as a SCADA/HMI to pull control and monitoring of discrete pieces of equipment into a single interface
    - allowing **ALL** data to be accessed from a single interface and used in modelling and process understanding
- In routine manufacturing, PharmaMV sits on top of a SCADA **pooling** **parametric** and **PAT data** and using this to **control** process parameters to CQA's



Model Predictive Control – Level 1 Control Strategy
What does it mean?

APC or Model Predictive Control understands process constraints and complex process interactions:

- Build multivariate **Models** between Critical Process Parameters (CPP) and Critical Quality Attributes (CQAs)
- **Predict** and compensate for the impact of known disturbances such as raw material variability (CMAs)
- Predict, Advise, Make co-ordinated **control** moves on multiple CPPs
- Exploit all opportunities to maximise product quality and process robustness


U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

State of control will depend on the control strategy implementation

- Level 1: Active control system with real time monitoring of process variables and quality attributes
- Level 2: Operation within established ranges (multivariate) and confirmed with final testing or surrogate models.
- Level 3: Unlikely to be operationally feasible for addressing natural variance in CM without significant end product testing.

Control Strategy Implementation Options[1]

2. Yu, L. *et. al.* AAPS J. **2014** Vol. 16 771-783

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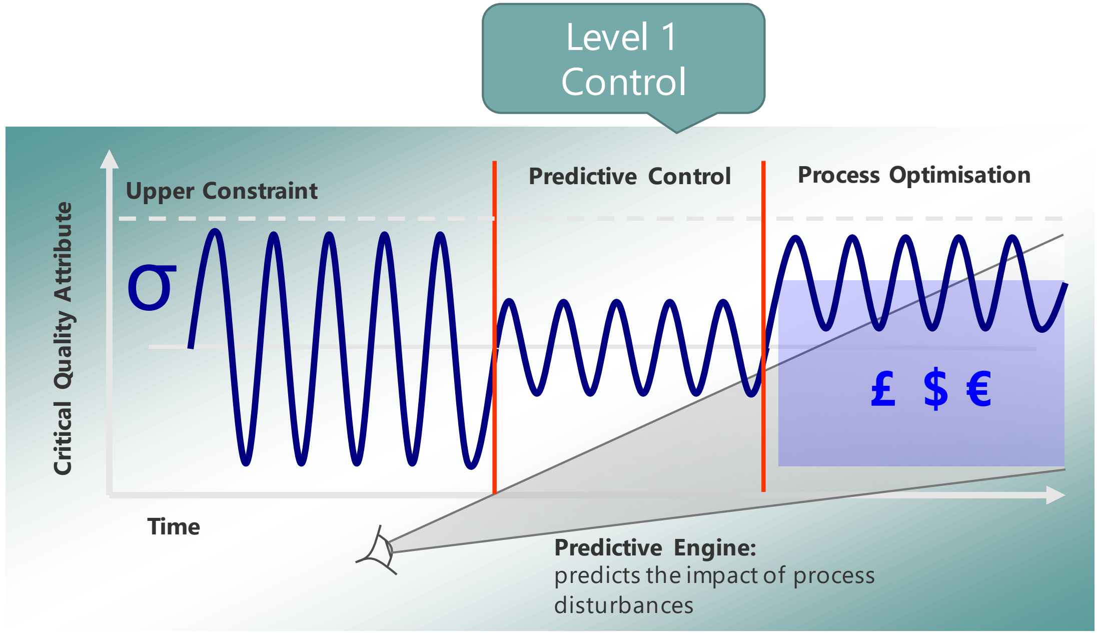

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ADVANCED DIGITAL DESIGN OF PHARMACEUTICAL THERAPEUTICS

Application of hybrid models for Advanced Process Control of a Twin Screw Wet Granulation Processes

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1. Perceptive Engineering Ltd., Daresbury, UK
2. Process Systems Enterprise (PSE) Ltd., London, UK
3. AstraZeneca plc, UK

Digital Design for Advanced Process Control

A consortium for taking technology from medium to high TRL!

Pharma Primes

AstraZeneca

Bristol-Myers Squibb

gsk GlaxoSmithKline

Pfizer

SMEs

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The Cambridge Crystallographic Data Centre

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ADDoPT Scope:

Digital Design to go from Molecule to Medicine

Improve / optimise for impact

Product and Process Design

Upstream

Materials properties
Surface chemistry
Release profiles
Manufacturing classification
Particle attributes
Processing rules
Formulation
Quality systems

Product Performance

Downstream

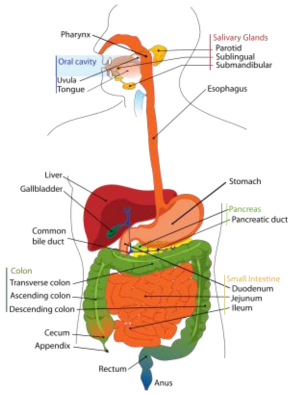
Secondary Manufacturing

Active Ingredient (API)
Excipient
Lubricant

→ Wet granulation
Drying

→ Milling
Blended
Compaction
Coating

→ 

→ 

ADDoPT scope

Processes **Products** **Patients**

Design and control of optimised development & manufacturing processes
through data analysis and first principle models

Digital Design Based Workflow

Experimental Work %

Modelling %

Experimental Work

- **Data Collection**
  - API concentration, Moisture, PSD, etc..
- **Data Integration**
  - Integrate PAT and Process Data

Modelling

- **Model Development & Scale up**
  - TWSG model development, scale up and validation (parameter estimation)
- **Calibration Modelling**
  - Implement a Calibration Model in Real-Time
- **Virtual Dynamic Response Testing**
  - Apply process response tests for granulation process modelling

Simulation

- **Controller Development**
  - Develop the model and simulate the MPC

Experimental Work

- **Controller Commission**
  - Commission and Evaluate the Controller's performance

- Minimal experimental work to determine system's properties (feed rate operating range, liquid to solid ratio, API concentration, PSD) on different scales.
- PSE's gPROMS FormulatedProducts platform is used to develop a mechanistic Twin Screw Wet Granulator Model.
- Combining Perceptive's PharmaMV & PSE's gPROMS FormulatedProducts platforms, provides a fast and cost effective hybrid approach for developing a closed loop controller.

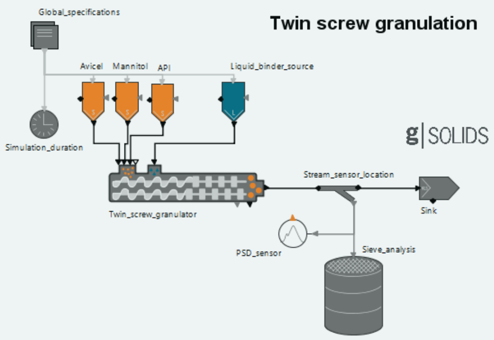
Digital Design Workflow: gPROMS/PharmaMV Integration

The Virtual Process

The Controller

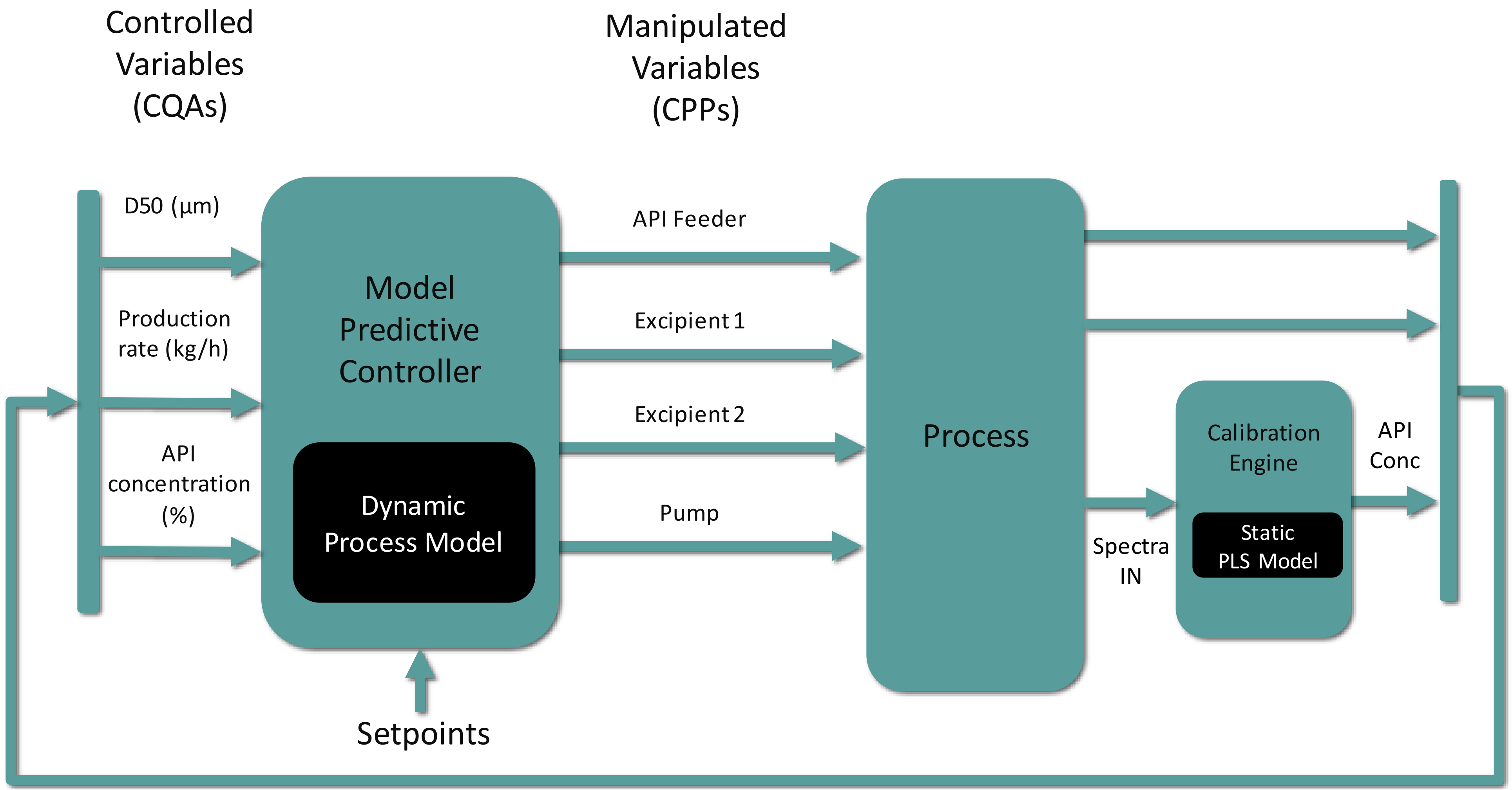
Manipulated Signals

gPROMS FORMULATED PRODUCTS



Measured Signals

Data Driven Workflow:
Production rate based Model predictive control development



Data Driven Workflow:
Twin Screw Wet Granulation Control

- Model Predictive Control is used to maintain CQAs to set point:
  - API concentration
  - D50 measured from the sieve analyser.
  - Production rate
- API concentration and D50 are driven to their set points while maintaining the production rate.

APC Development Workflow

APC_Development_Workflow

Twin Screw Wet Granulation- APC Development Workflow

Mode: OFF

Development Workflow

1. Open-Loop

Feeder and Pump set points

Descriptor	Value
API CSP	1.68
Mannitol CSP	8.26
Avicel CSP	5.05
Pump CSP	1.80

2. Process Response Test

Set Response Test Parameters

Descriptor	Value
Amplitude Avicel	2
Mean Avicel	5.05
Amplitude Mannitol	2
Mean Mannitol	8.26
Amplitude API	2

3. Adaption

Adapter Configuration

Descriptor	Value
Adaption Time	1

4. Closed Loop (APC)

Controlled Variables

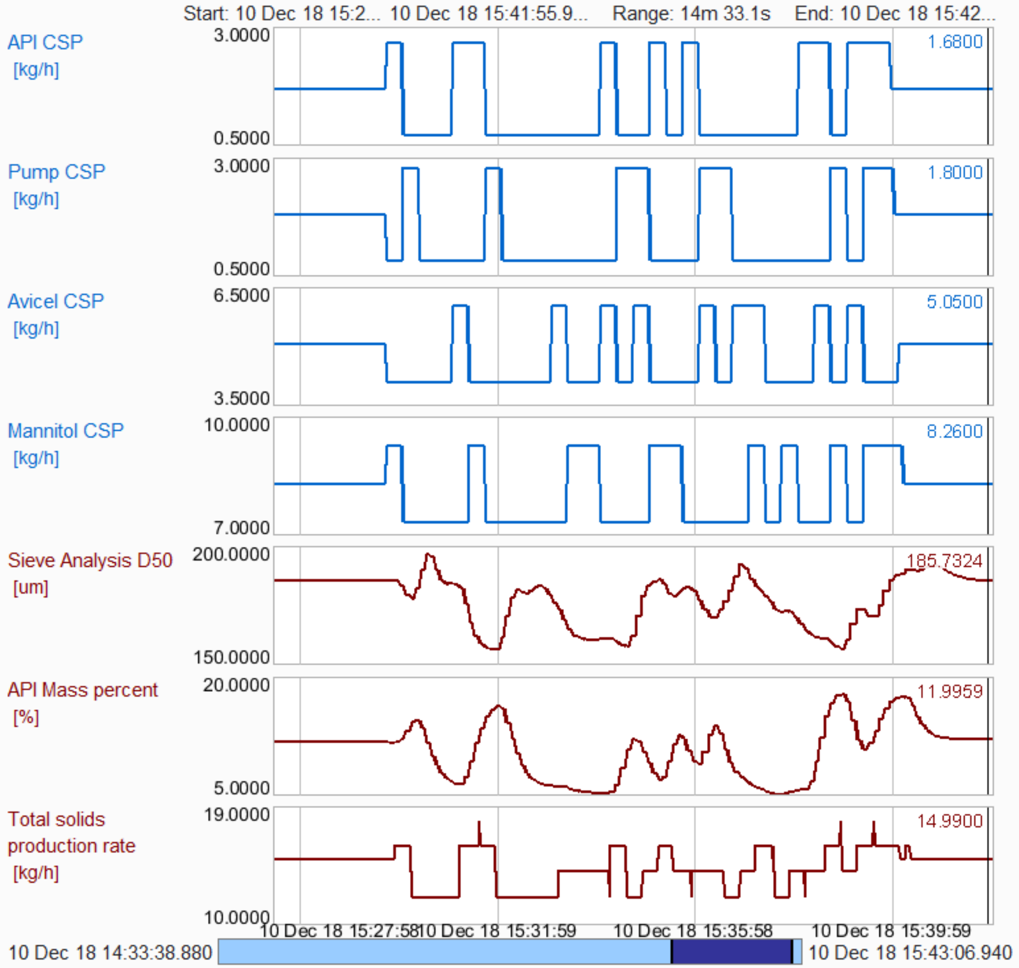
Descriptor	Value
Concentration SP	0
D50 SP	0
Total Solids SP	0

Off

Active MPC Model

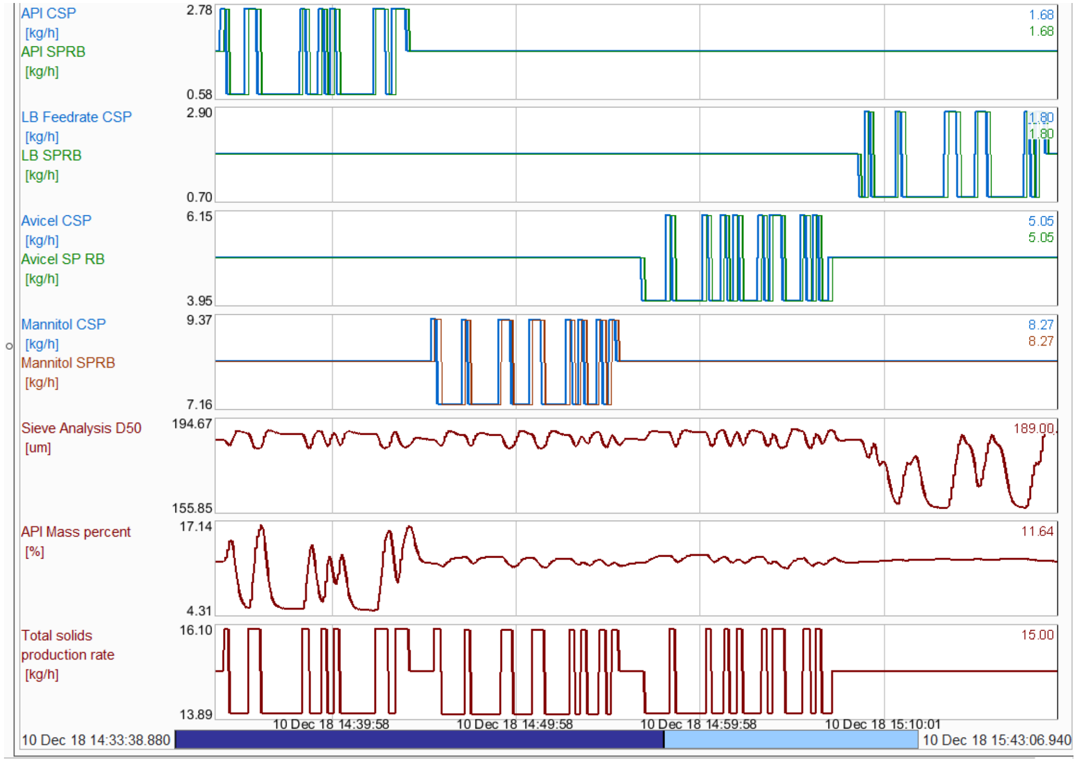
Tag	Value
4= Current Adapted Mo...	0

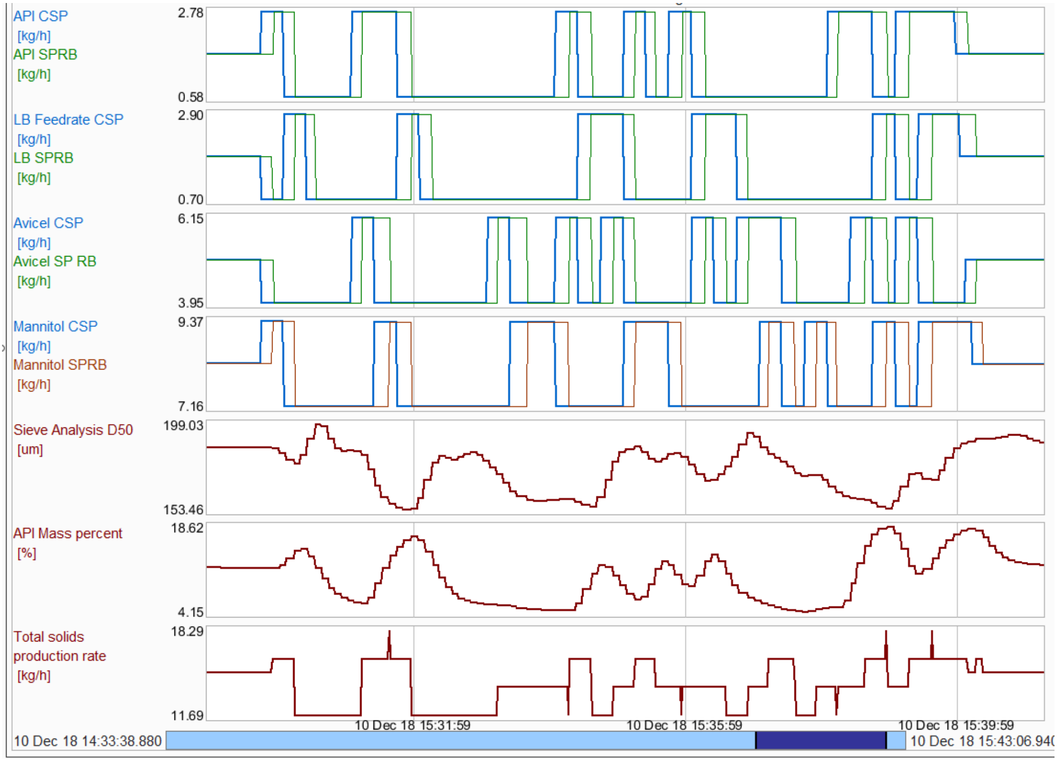
Process and MPC Overview



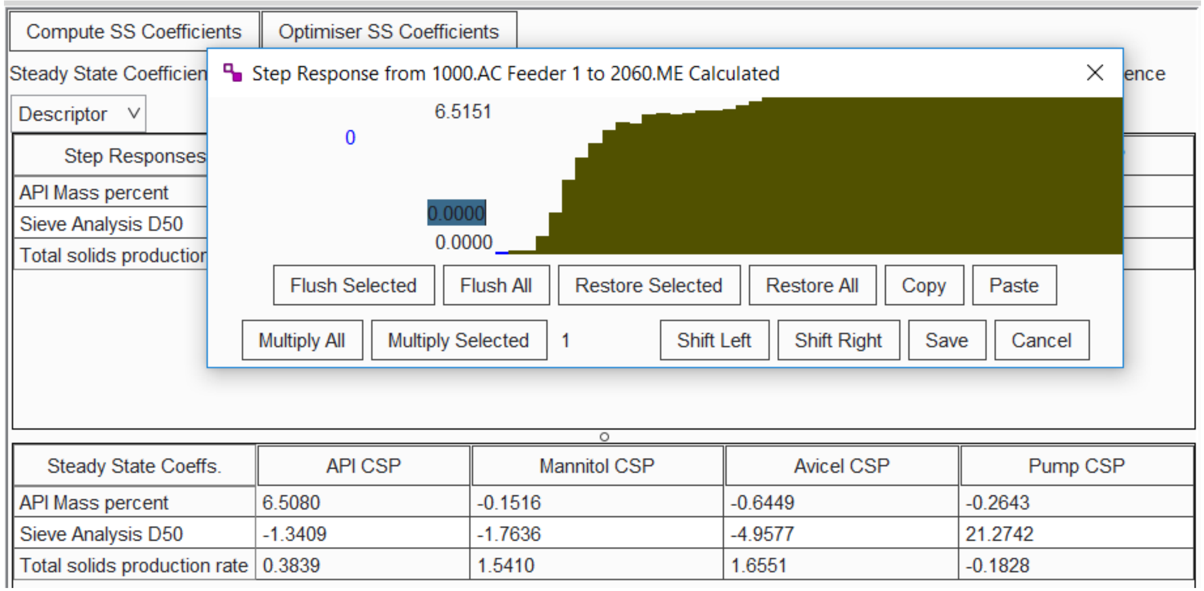
Statistical Model Development – PRBS step testing

- To identify a statistical model, Pseudo Random Binary Sequence (PRBS) step testing is applied to the gPROMS FormulatedProducts flowsheet model using PharmaMV.
- The screenshot below shows the step tests on the feeders and the corresponding response of API mass percent (%), d50 and total solids production rate.
- This data is statistically rich, allowing an accurate control model to be developed.



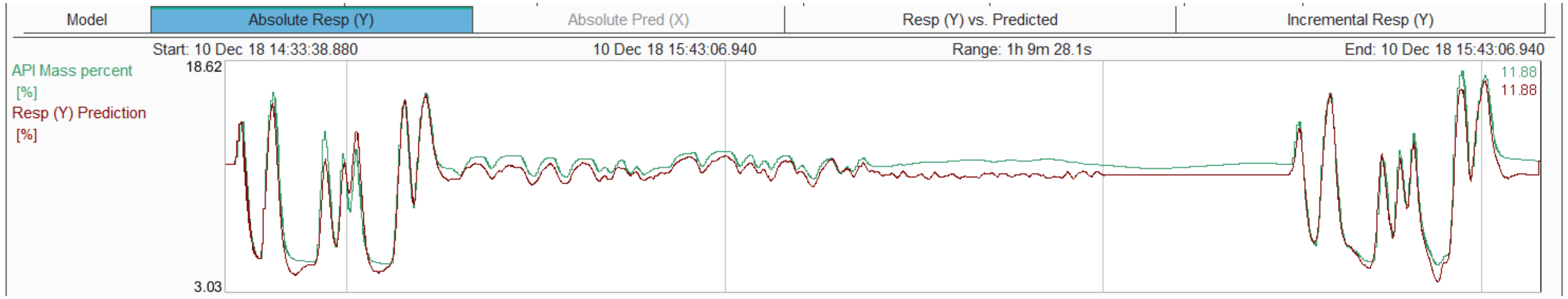


Statistical Model Development – Identification



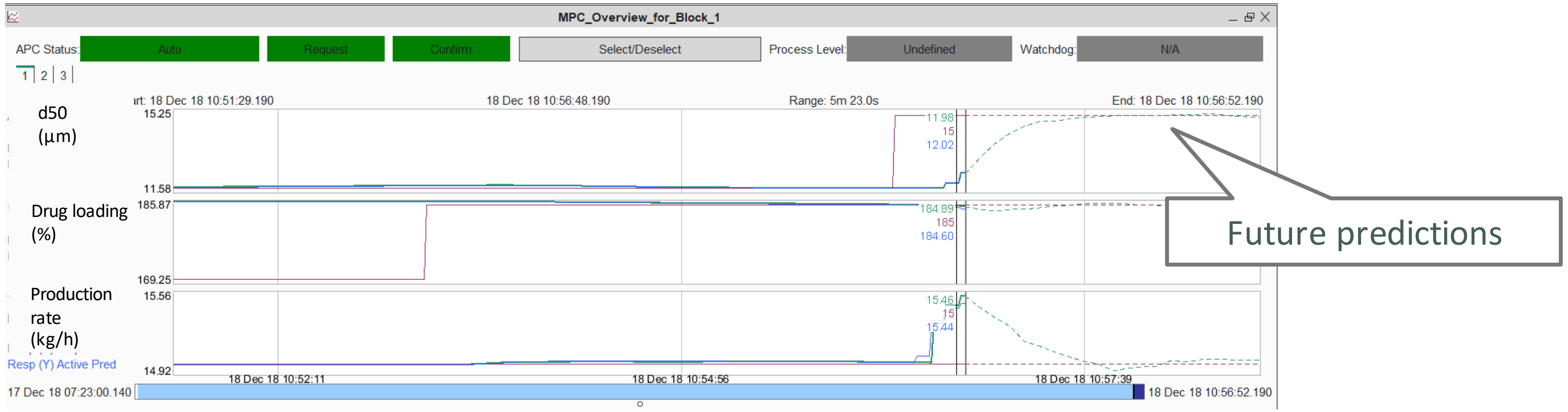
Steady State Coeffs.	API CSP	Mannitol CSP	Avicel CSP	Pump CSP
API Mass percent	6.5080	-0.1516	-0.6449	-0.2643
Sieve Analysis D50	-1.3409	-1.7636	-4.9577	21.2742
Total solids production rate	0.3839	1.5410	1.6551	-0.1828

The statistical model is identified using the Recursive Least Squares (RLS) algorithm. The screenshot above shows the response of the API mass percent to a step change in the API feed rate.

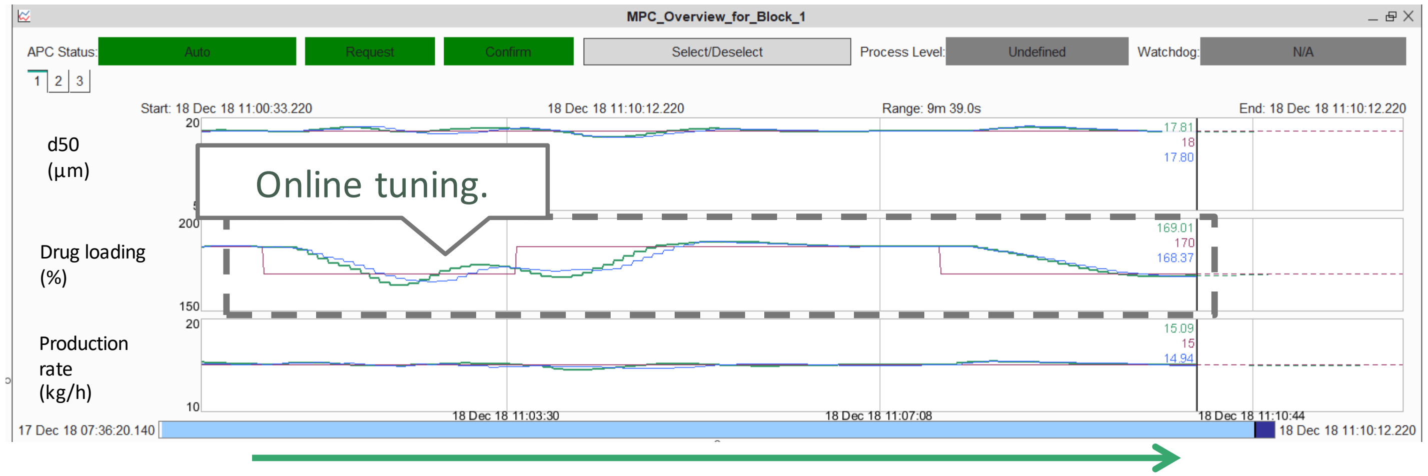


A comparison between the API mass percent and the model prediction shows good model performance

Twin Screw Wet Granulation Control – Overview



Post model development, the controller is commissioned and tuned using the flowsheet "Digital Twin".



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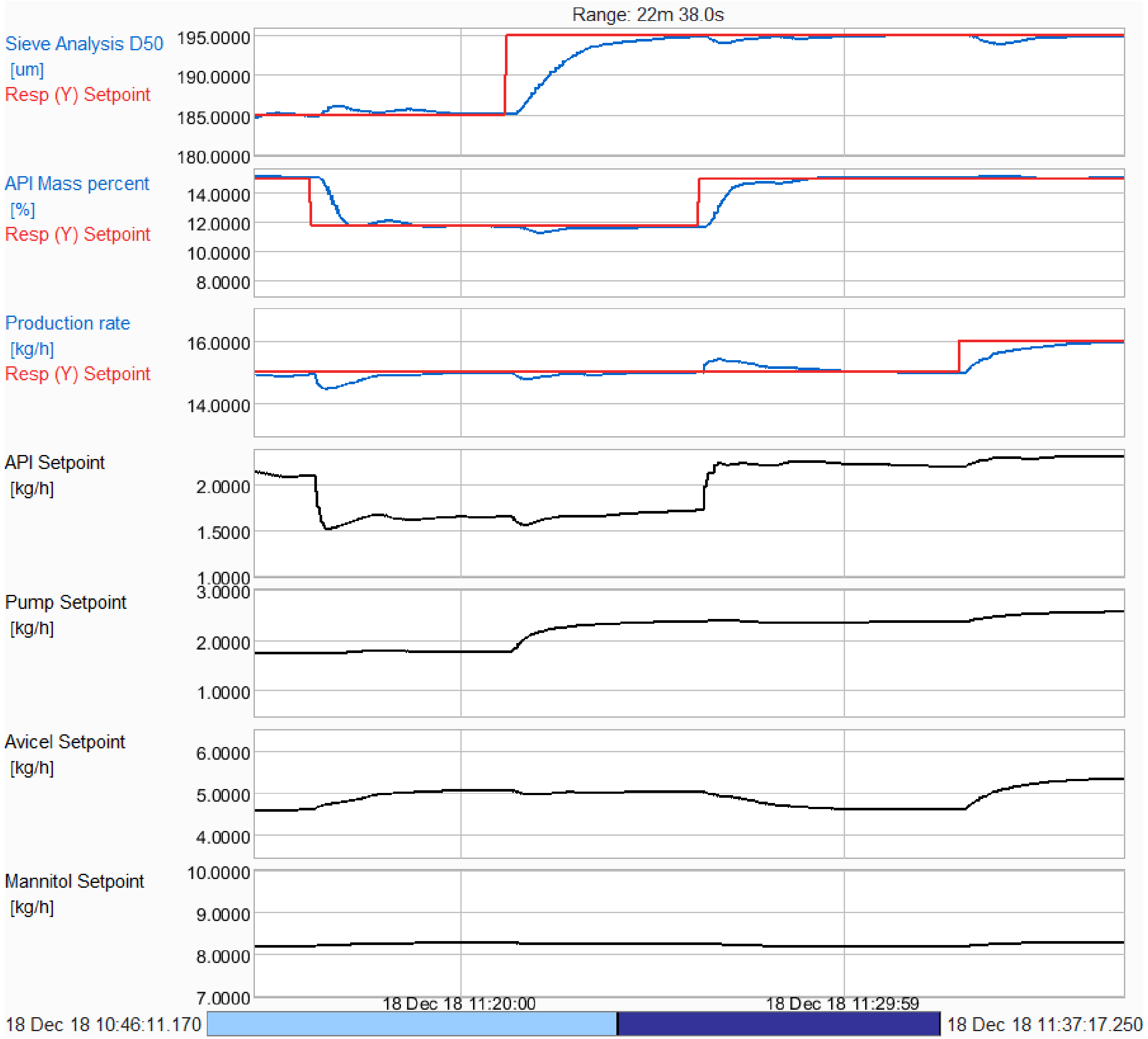
Twin Screw Wet Granulation Control – Results



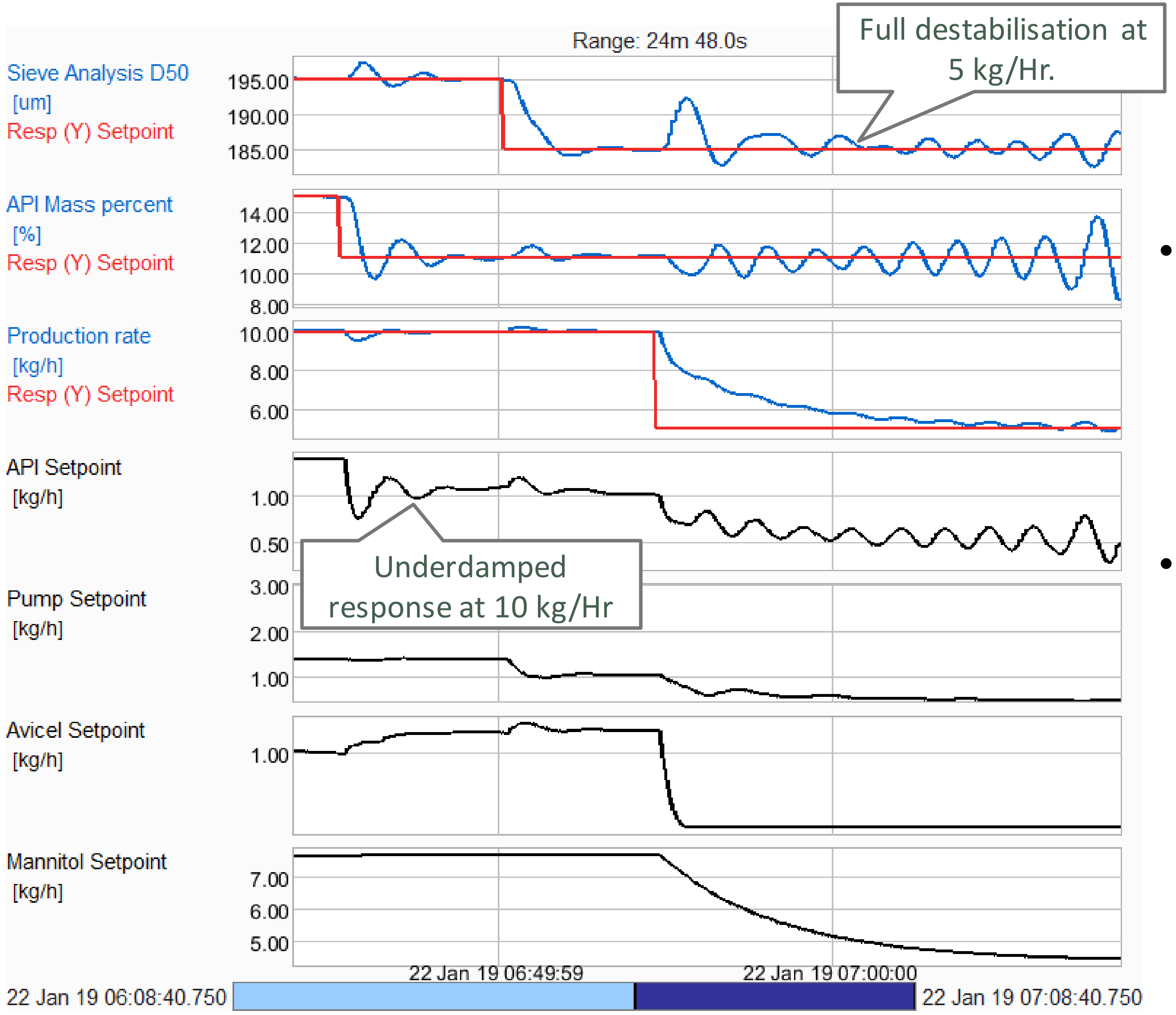
- Through smooth manipulations of the feed rates and the pump set point, the API Mass percent, d50 and the production rate have been controlled for various set point changes.

Considerations when scaling-up/changing product in TSWG Advanced Process Control

- For continuous processes, scale up = higher throughput or running the process for a longer duration. Considerations for higher throughputs are:
  - Lower residence times – although desirable, it is important to ensure that the rate of wetting and nucleation as well as consolidation and growth occurs effectively.[1]
  - Ensuring through monitoring, all critical quality attributes remain within desired tolerance limits.
  - Presence of a robust controller that can deal with changing process dynamics.
- Considerations for changing product are to ensure replaced elements have similar material characteristics, eg. PSD of individual components of the formulation.

[1] A.S. El Hagrasy, J.R. Hennenkamp, M.D. Burke, J.J. Cartwright, J.D. Litster, Twin screw wet granulation: Influence of formulation parameters on granule properties and growth behavior, Powder Technology, Volume 238, 2013, Pages 108-115, ISSN 0032-5910, https://doi.org/10.1016/j.powtec.2012.04.035. (http://www.sciencedirect.com/science/article/pii/S003259101200277X)

Twin Screw Wet Granulation Control – Performance Analysis



- At a lower production rate (10 kg/h), the controller's responses are underdamped due to model error.
- On further dropping the production rate (5 kg/h) the controller completely de-stabilizes.

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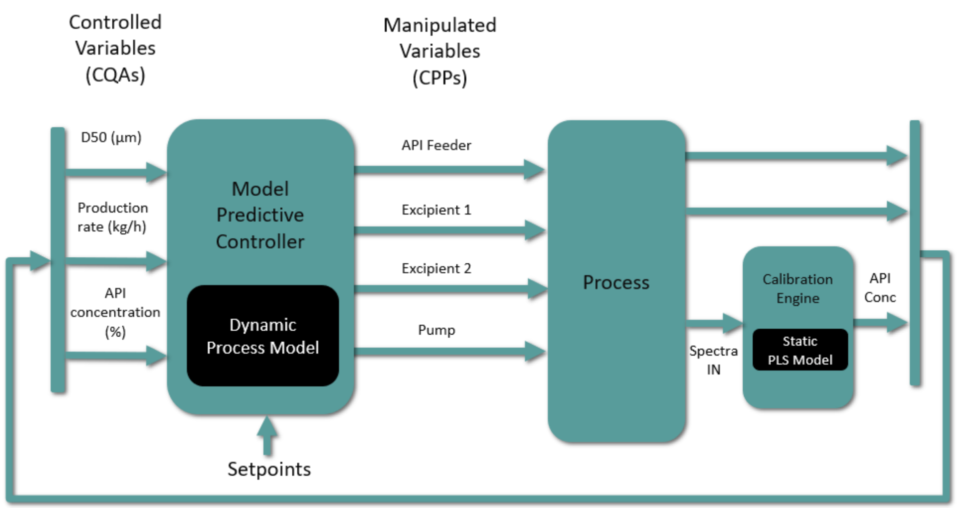
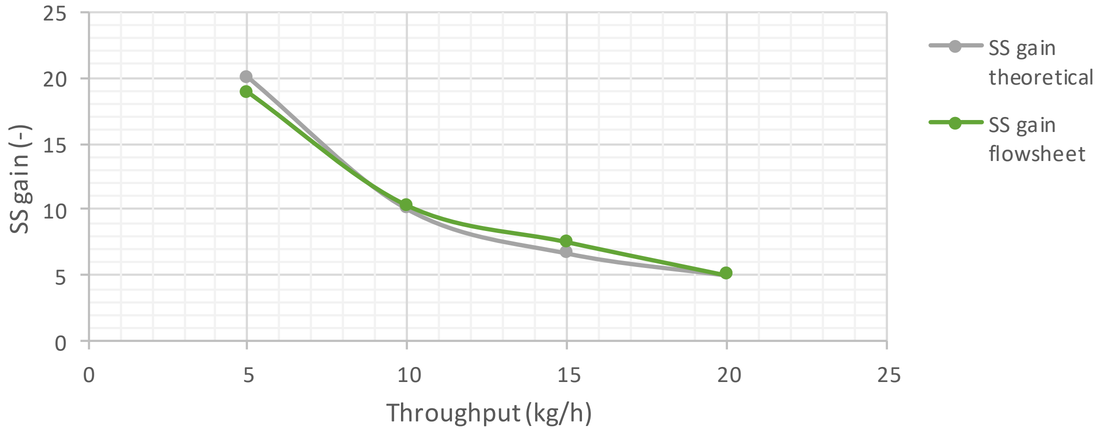
Twin Screw Wet Granulation Control – Performance Analysis

Instability can be attributed to the following reasons:

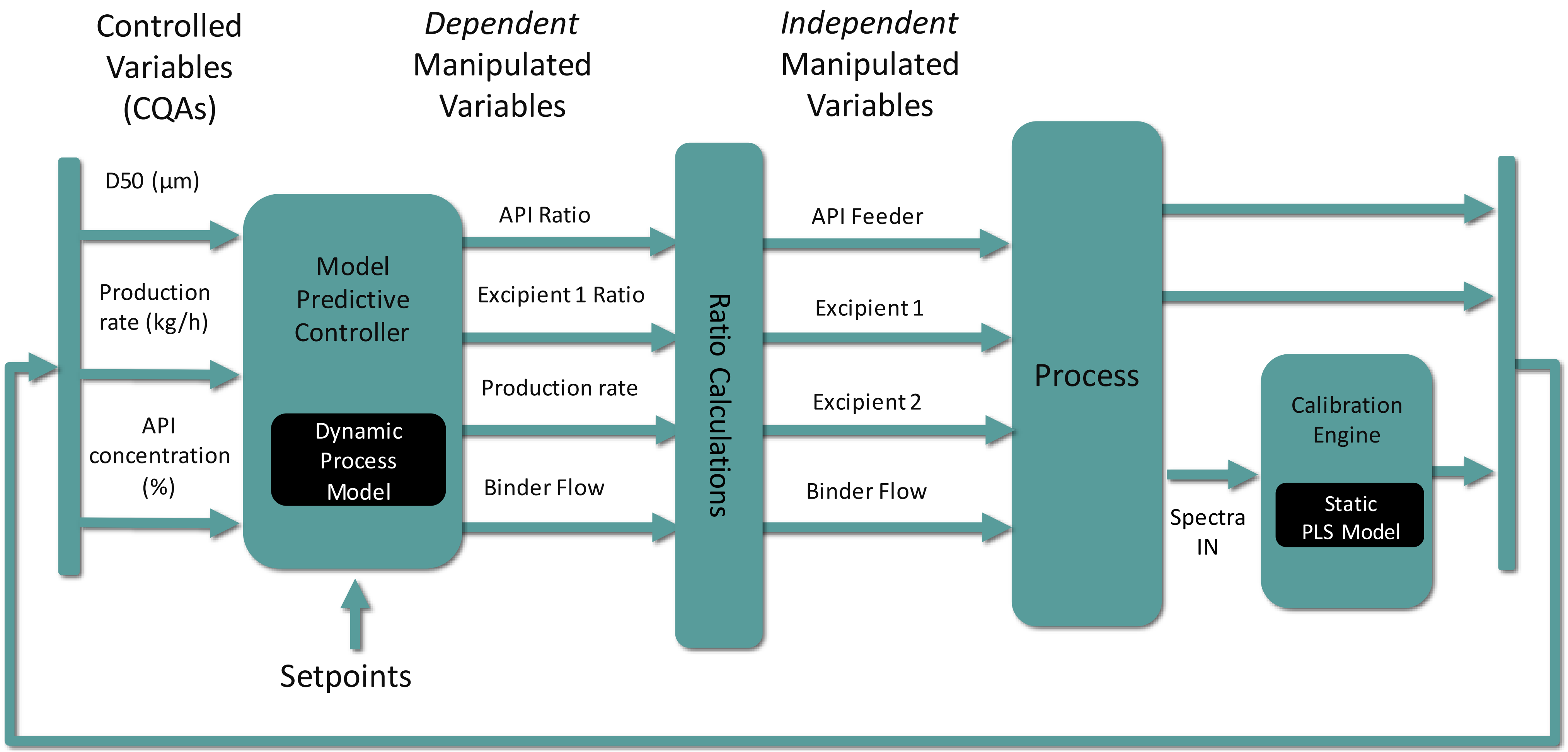
1. The current MPC structure directly controls the feeder mass flows. These are not independent.
2. As the throughput in the process increases the process gains decrease and vice versa.
3. The linear MPC does not account for the decrease in gain.
4. The input dependency destabilises the controller when the throughput changes.

The mechanistic model is used to explore improved APC control strategies



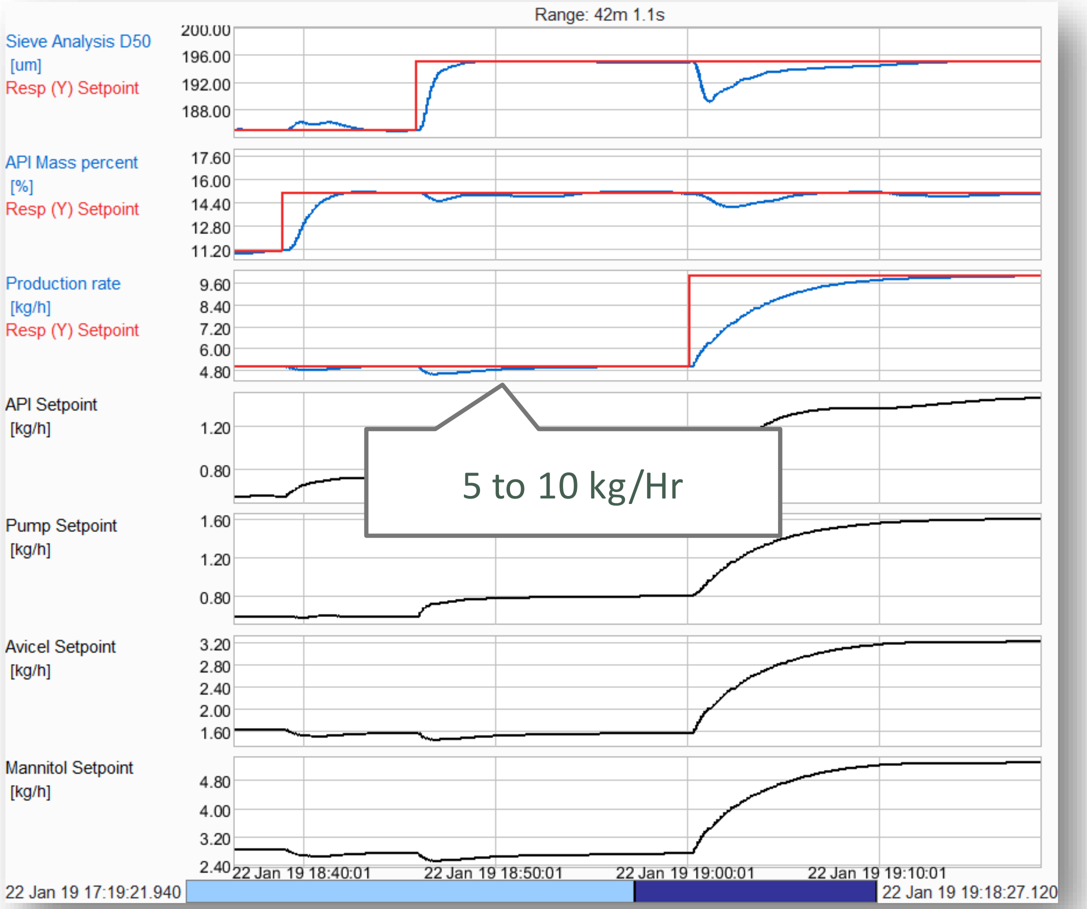


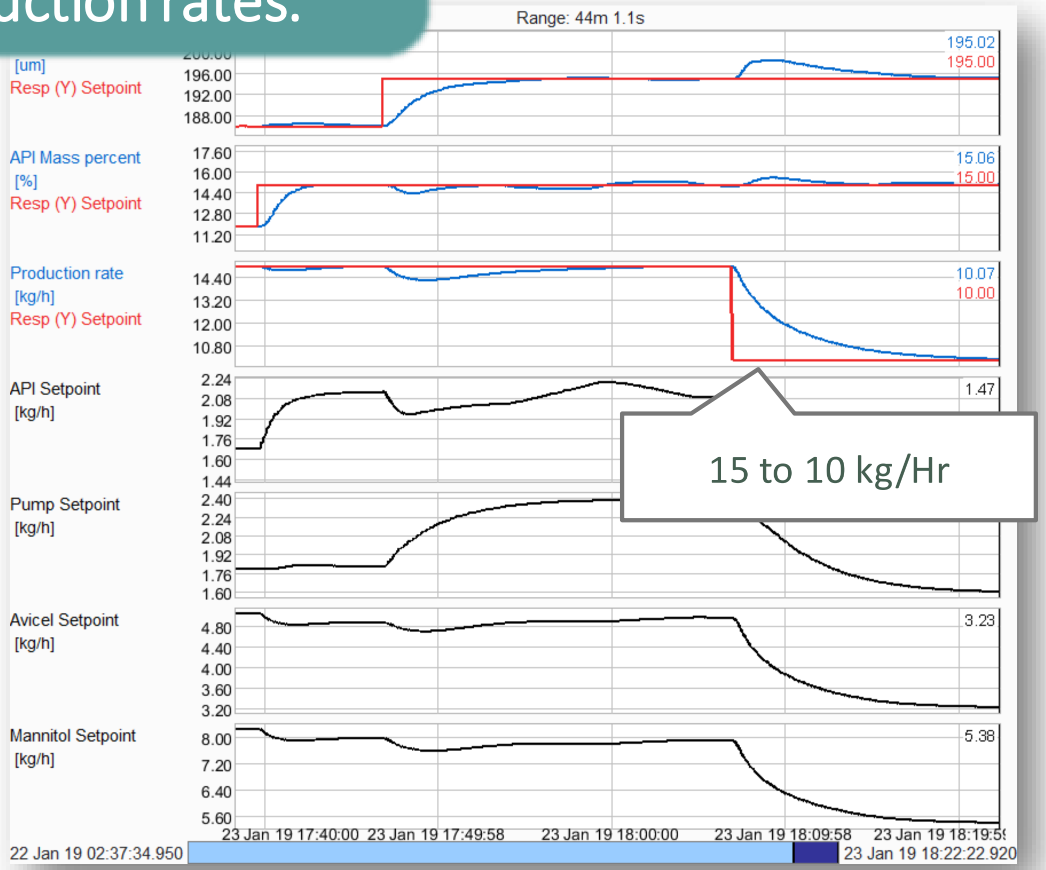
Twin Screw Wet Granulation Control
Modified Control Structure: Ratio Control



Twin Screw Wet Granulation Control – Ratio control results

The digital twin has been used as a design tool to ensure stable control of the CQAs for all production rates.

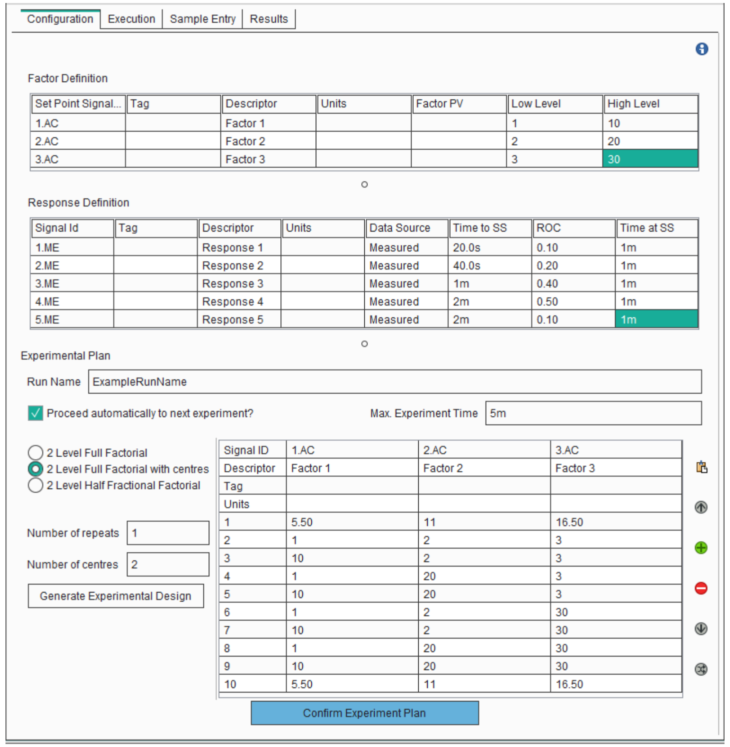




Another approach - Machine Learning

Motivations and Benefits

Process Development Approaches

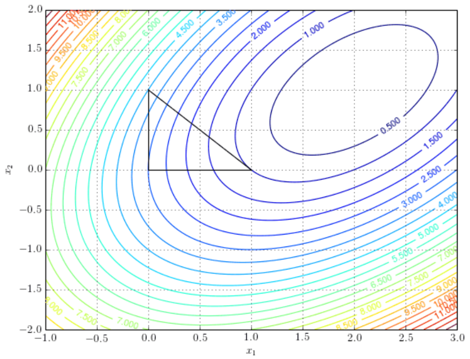


Traditional "One at a Time" approach

- Trial and error optimisation of the reaction
- Significant human input – depends of the know-how of the chemist

Quality by Design Approach

- Application of Design of Experiments
- Automation can be used to execute pre-defined experimental conditions
- Extensive experimental effort required



ML – Recursive Learning Approach

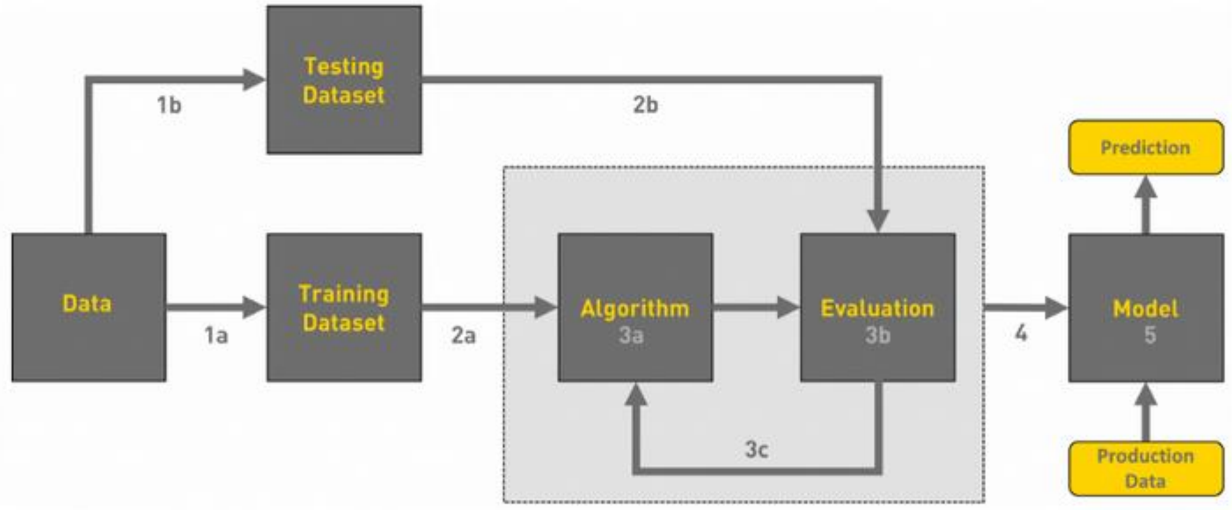
- Automation and online analysis combined with a "curiosity" algorithm
- Outperforms a human to get to the optimum
- No human interaction required after initialisation

**An Autonomous Self-Optimizing Flow Reactor for the Synthesis of Natural Product*
The Journal of Organic Chemistry 2018 83 (23), 14286-14299

Teaching the machine

Data is everywhere.....or is it?

SMART DATA GENERATION



Overview of the Workflow of ML

CONTROL

Can we use machine learning to generate "Smart Data" for process understanding, control AND optimisation?

https://towardsdatascience.com/workflow-of-a-machine-learning-project-ec1dba419b94

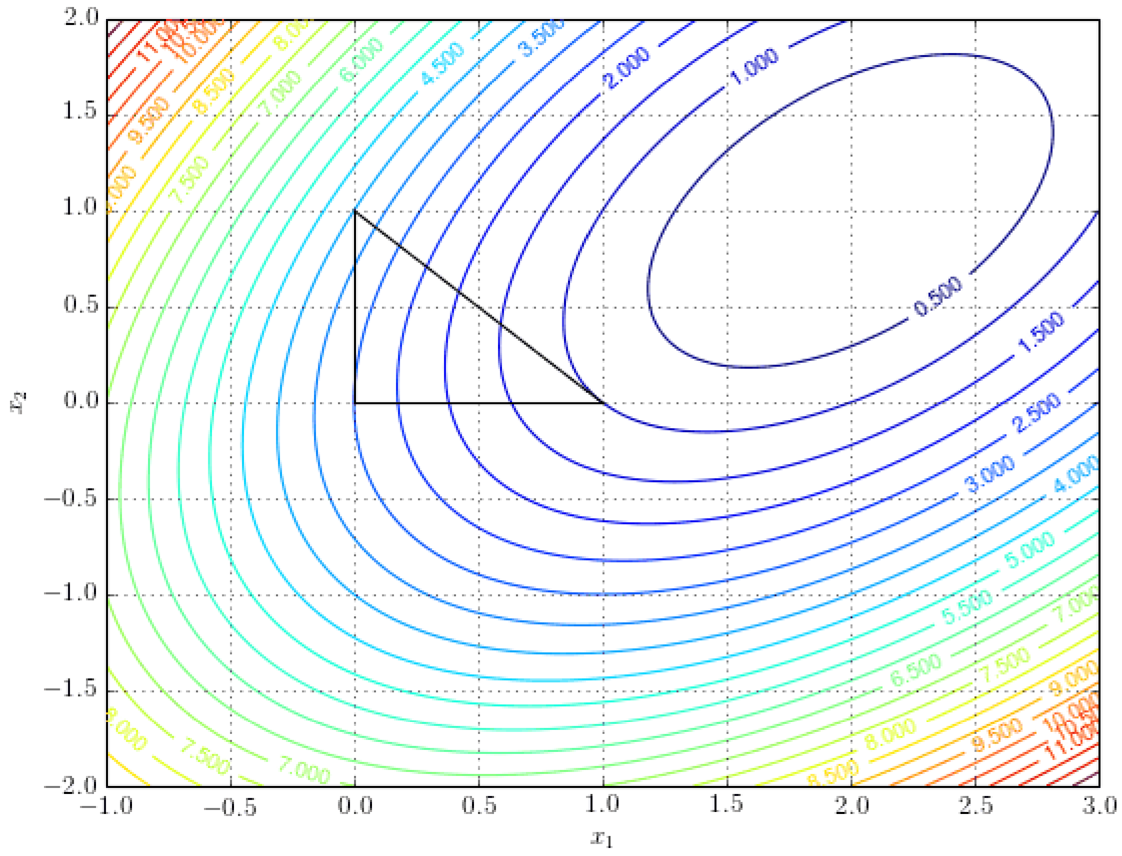
Simple Overview

Simple easy to understand algorithm

- Treats the process as a black-box
- Explores the objective function's domain with n-dimensional simplexes
- Ranks the n + 1 vertices of a simplex according to their objective function values and replaces the worst of them with a new (always better) vertex

Gets stuck in local minima/maxima
Only single objective*

*can be "tricked" to be multi-objective with clever crafting of an objective function – Still has problems



Another Approach – Machine Learning (Nelder Mead)

For the Secondary Manufacturing World

Self Optimising Twin Screw Wet Granulator

Mode: Open Loop

Development Workflow

1. Open-Loop

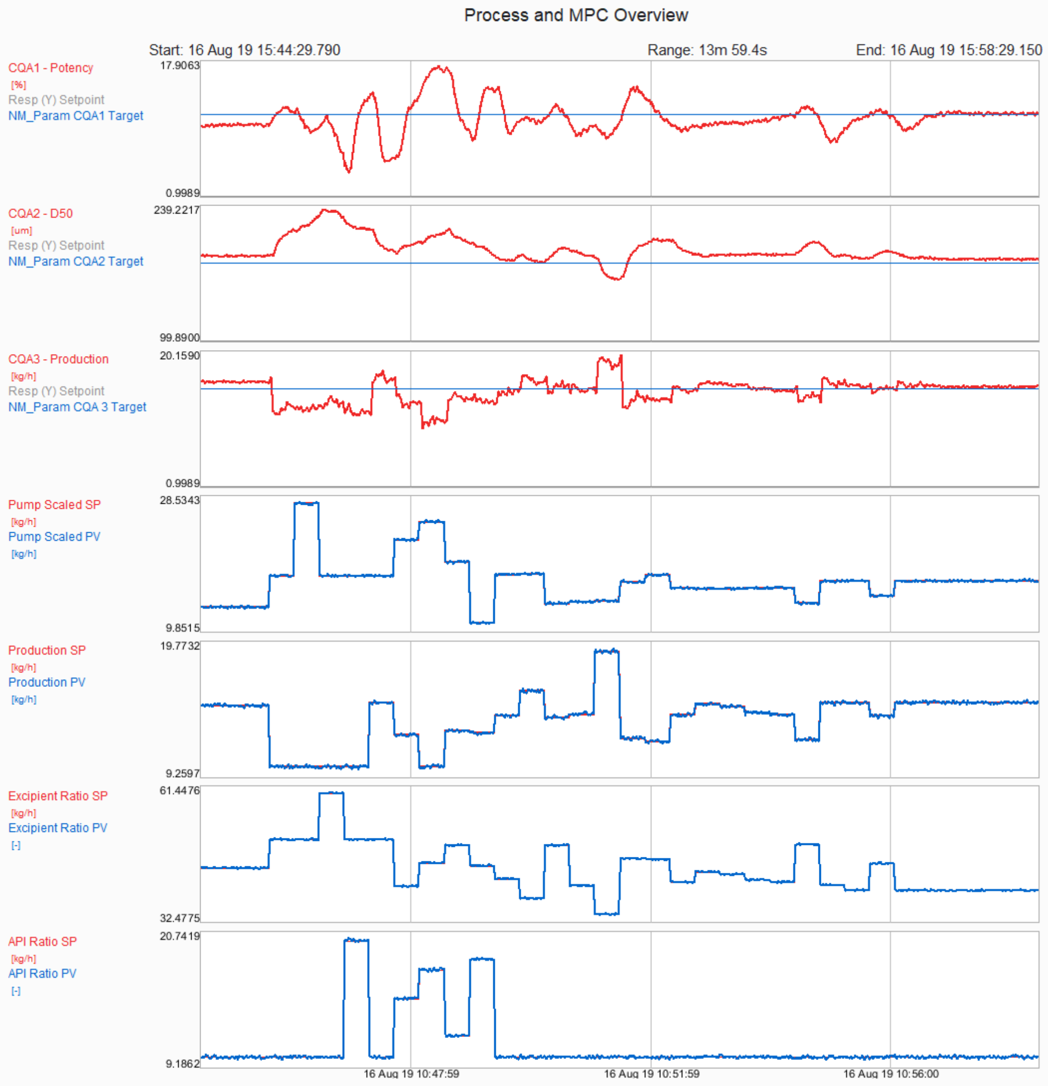
Self Optimising Adaption

Self Optimising

Closed loop

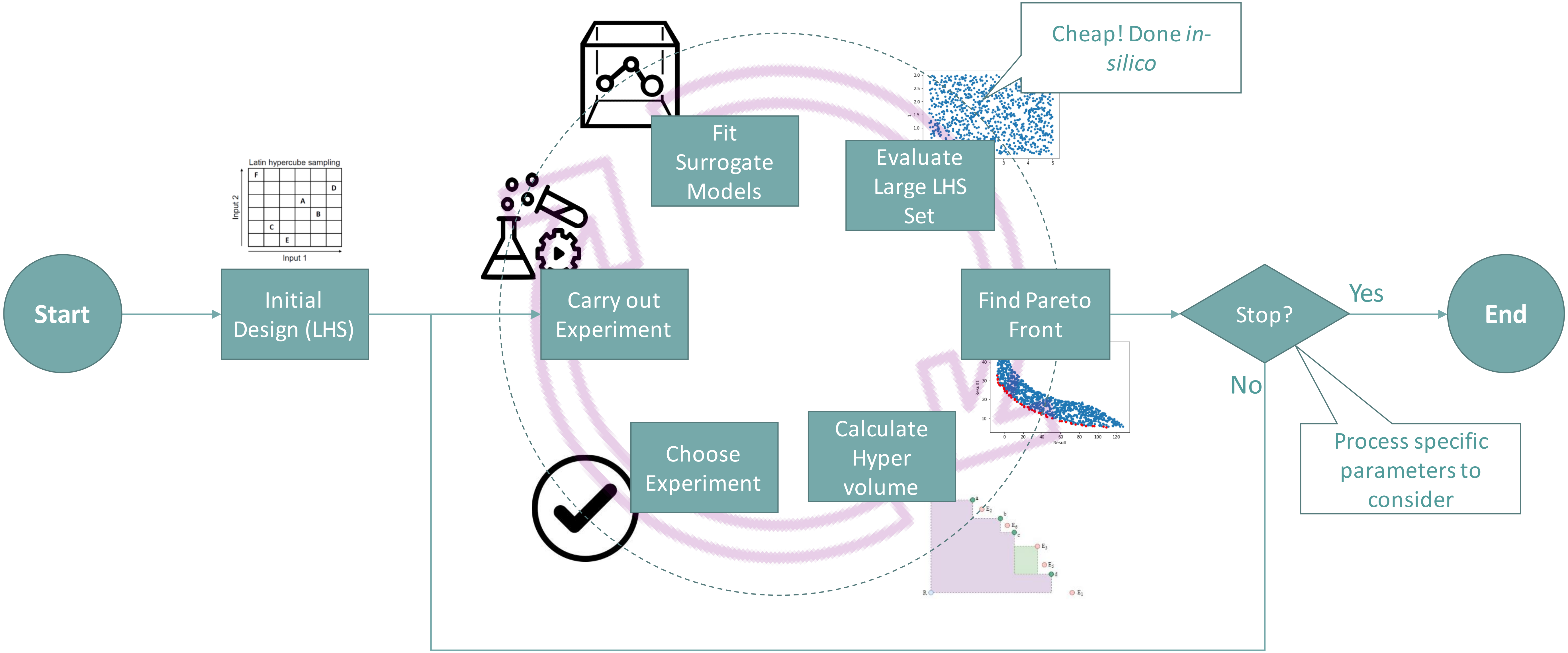
Nelder Mead Optimisation Variables

Descriptor	Value
NM_Param CQA1 Target	11.25
NM_Param CQA2 Target	180
NM_Param CQA 3 Target	14.95
NM_Param Optimiser Kick Off Value	2
NM_Param Evaluation Time	10
NM_Param Time Interval	2
NM_Param Pump Initial Step	10
NM_Param ExpRatio Initial Step	10
NM_Param APIRatio Initial Step	10
NM_Param ProdRatio Initial Step	5
NM_Param Pump Min	1
NM_Param Pump Max	35
NM_param_ExpRatio Max	1
NM_Param ExpRatio Max	100
NM_Param APIRatio Min	10
NM_Param APIRatio Max	20
NM_Param Prod Min	10
NM_Param Prod Max	20
NM_Param Segment Time	25
NM_Param Max Iterations	10
NM_Param No Improv Thresh	0.01
NM_Param No Improv Break	2
NM_Param alpha [reflection factor]	1
NM_Param gamma [expansion factor]	2
NM_Param rho [contraction factor]	0.50
NM_Param sigma [shrinkage factor]	0.50
Optimiser_Running	0



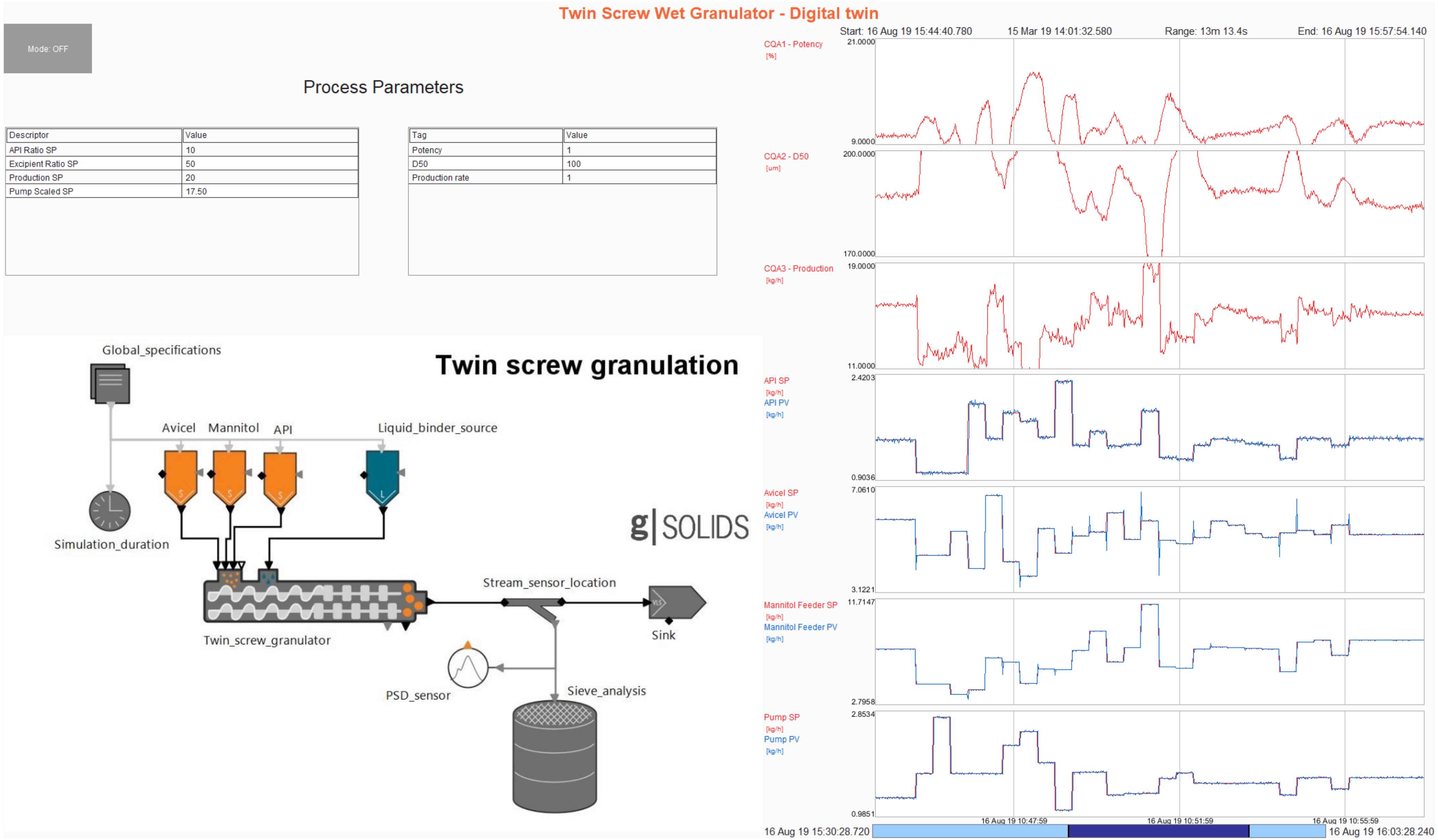
True Multi-objective Optimisation

Gaussian Search



Another Approach – Machine Learning (Gaussian Search)

For the Secondary Manufacturing World

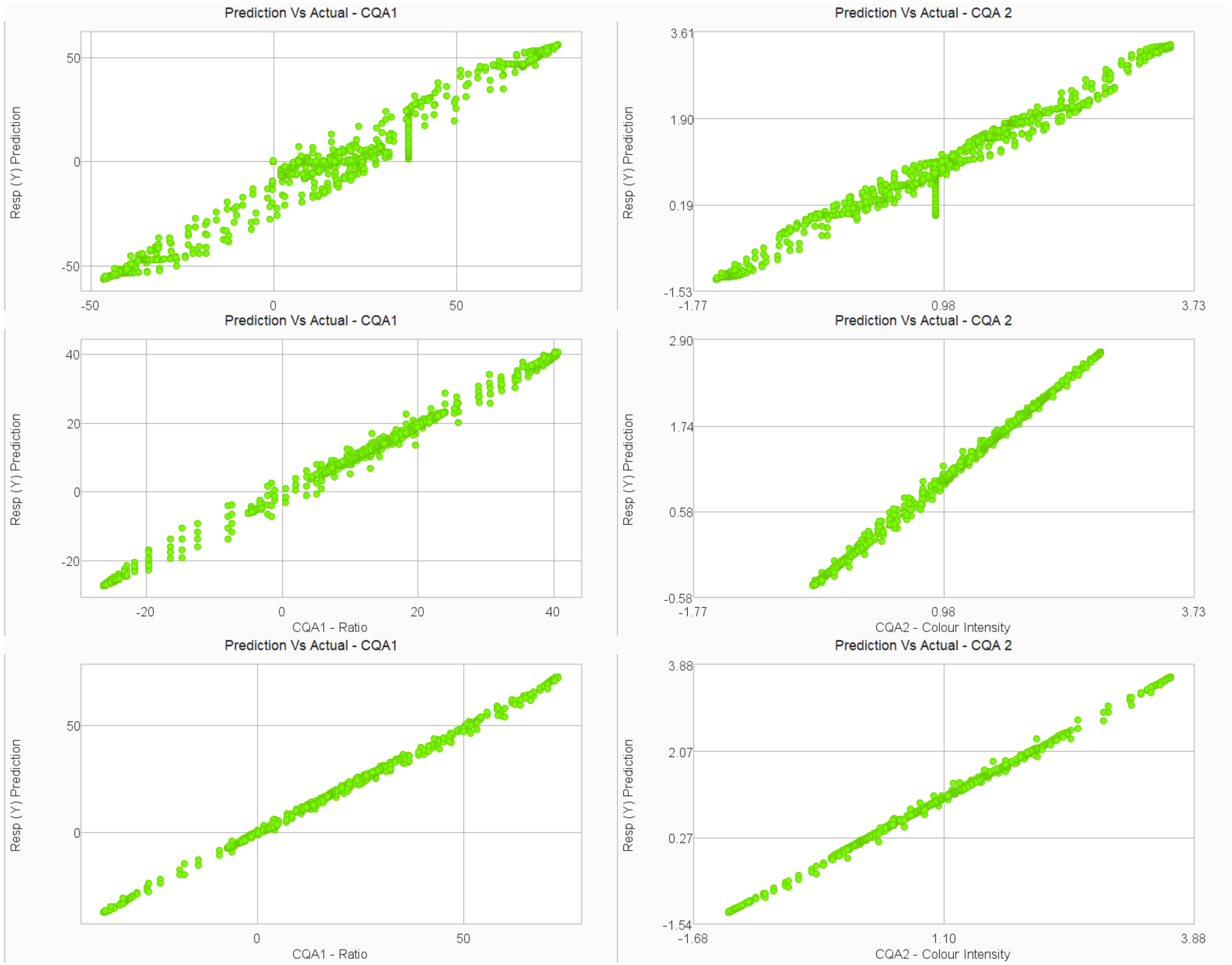


Process Control

MPC Model

RMSEP

	CQA1	CQA2
DoE	6.8	0.12
NM	1.05	0.030
GS	0.51	0.013



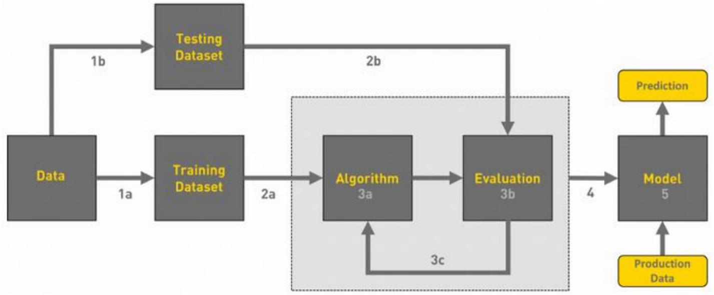
Comparison

Does the ML do what we want?

	Automated DoE	Nelder Mead	Gaussian Search
Optimised Process	✗	✓ "Single Objective" Pseudo-MultiObjective Possible	✓ "MultiObjective"
Static Process Model	✓ Anova and Linear Model at Best (Further Modelling Step)	✓ (Further Modelling Step)	✓ Linear and/or Non-Linear for Each Objective
PAT Calibration	✗ Unlikely	✓	✓
Rich enough Data for MPC	✗	✓ Sometimes	✓

Process development?

SMART DATA GENERATION



Overview of the Workflow of ML

CONTROL

DoE/ Self Opt

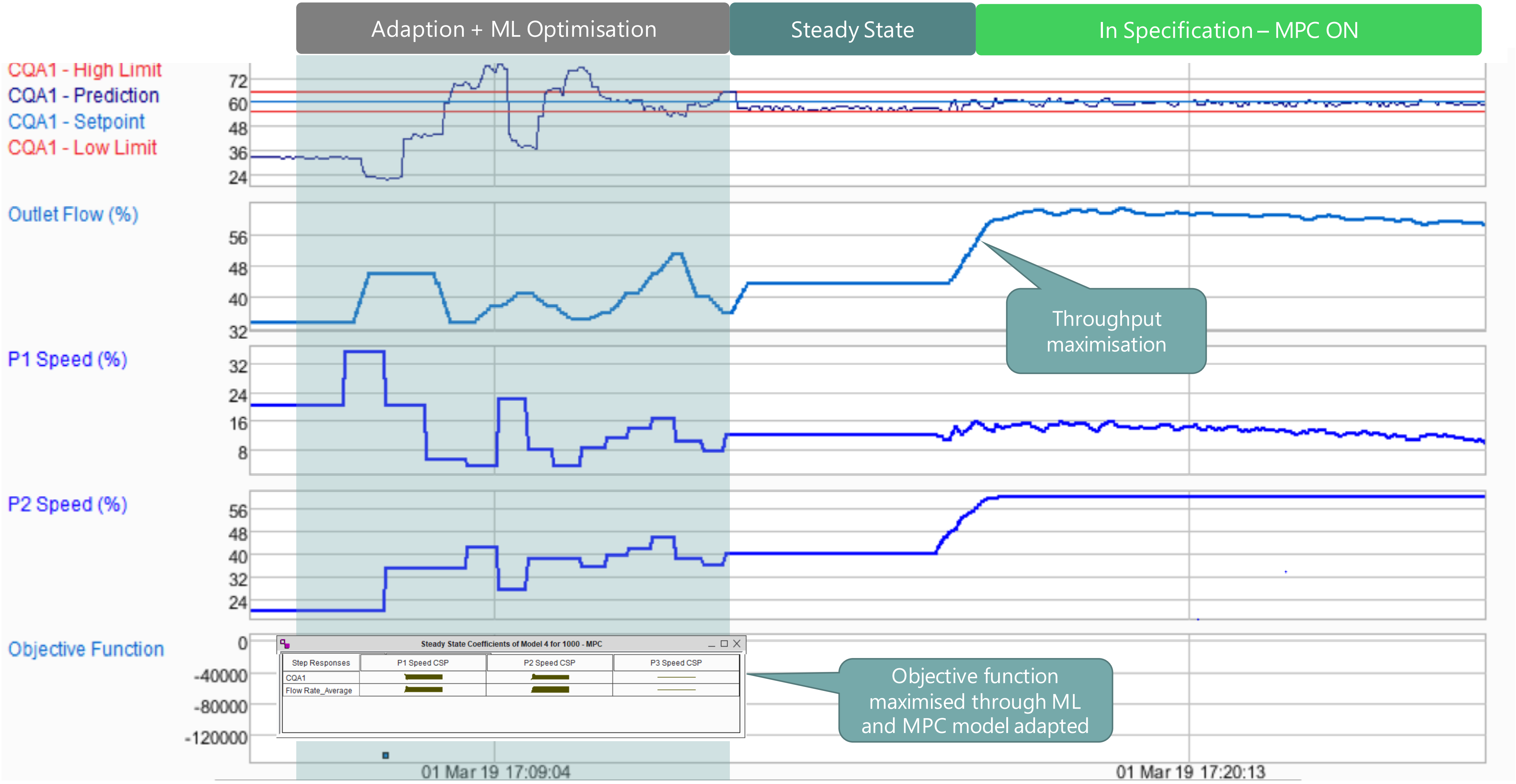
Static Process Models

Model Predictive Control

?

Combined Advanced Process Control And Machine Learning

Example



Machine Learning and Digital Design Tools for APC

Summary

APC is a well proven and efficient technique for improving product quality and process robustness

Mechanistic models provide a powerful tool for in silico development of APC

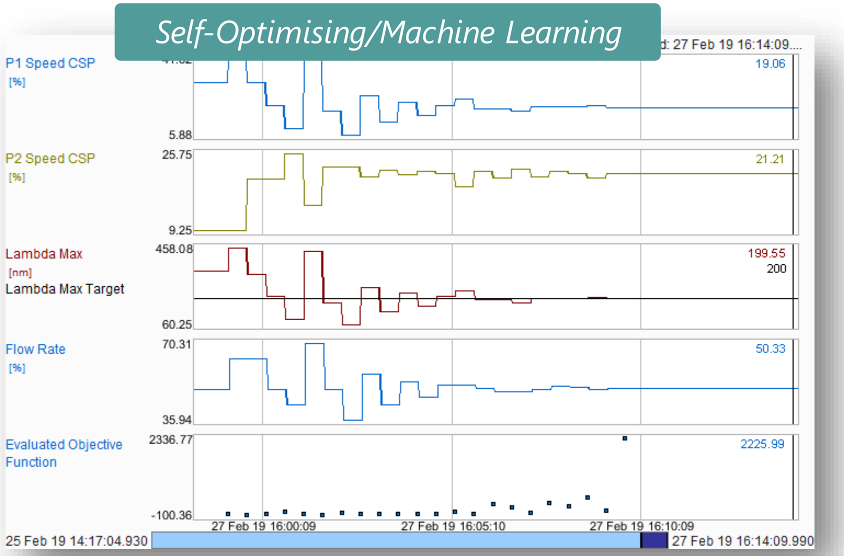
Within process development a QbD approach alone doesn't yield sufficient data to take full advantage of Advanced Process Control

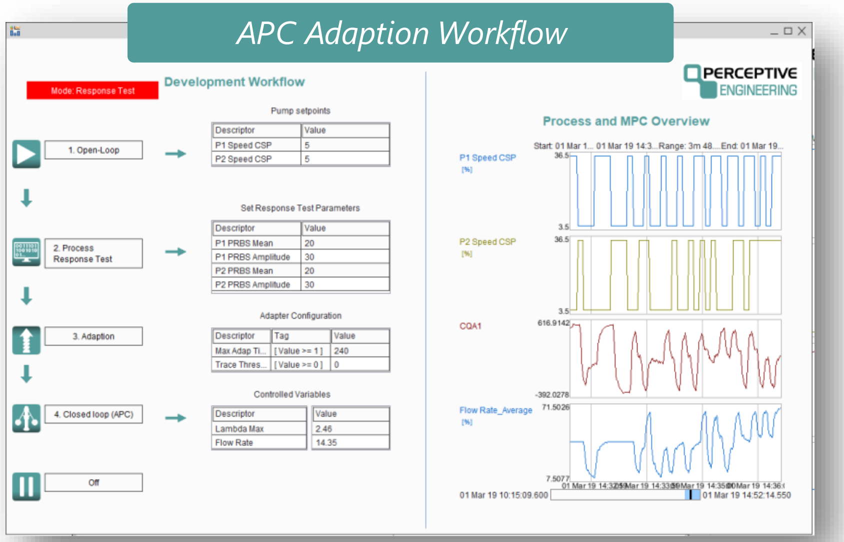
ML has brought along with it a whole new set of terminology for existing techniques.

- The potential of these techniques is significant provided they are selected with care.

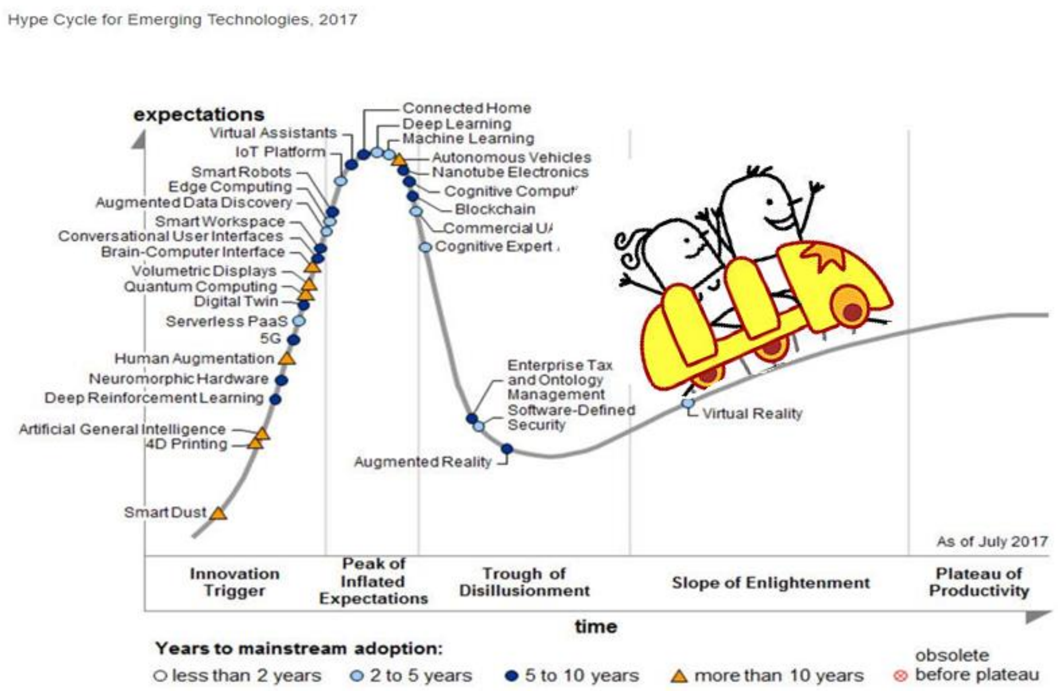
Using optimisation techniques borrowed from AI and adaptive control modelling we can generate data from single experimental runs which can be used for:

PAT Calibration | Advanced Process Control | Static Process Models | Process Optimisation





Thanks for listening.
- Acknowledgements



Perceptive Engineering:

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- Gavin Reynolds

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Thank you!

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