A Comparison of Machine Learning and Advanced Process Control tools for Pharmaceutical Process Development

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Perceptive Engineering
2-Minute Capability Pitch

Solely focussed on software and solutions applying Advanced Process Control techniques

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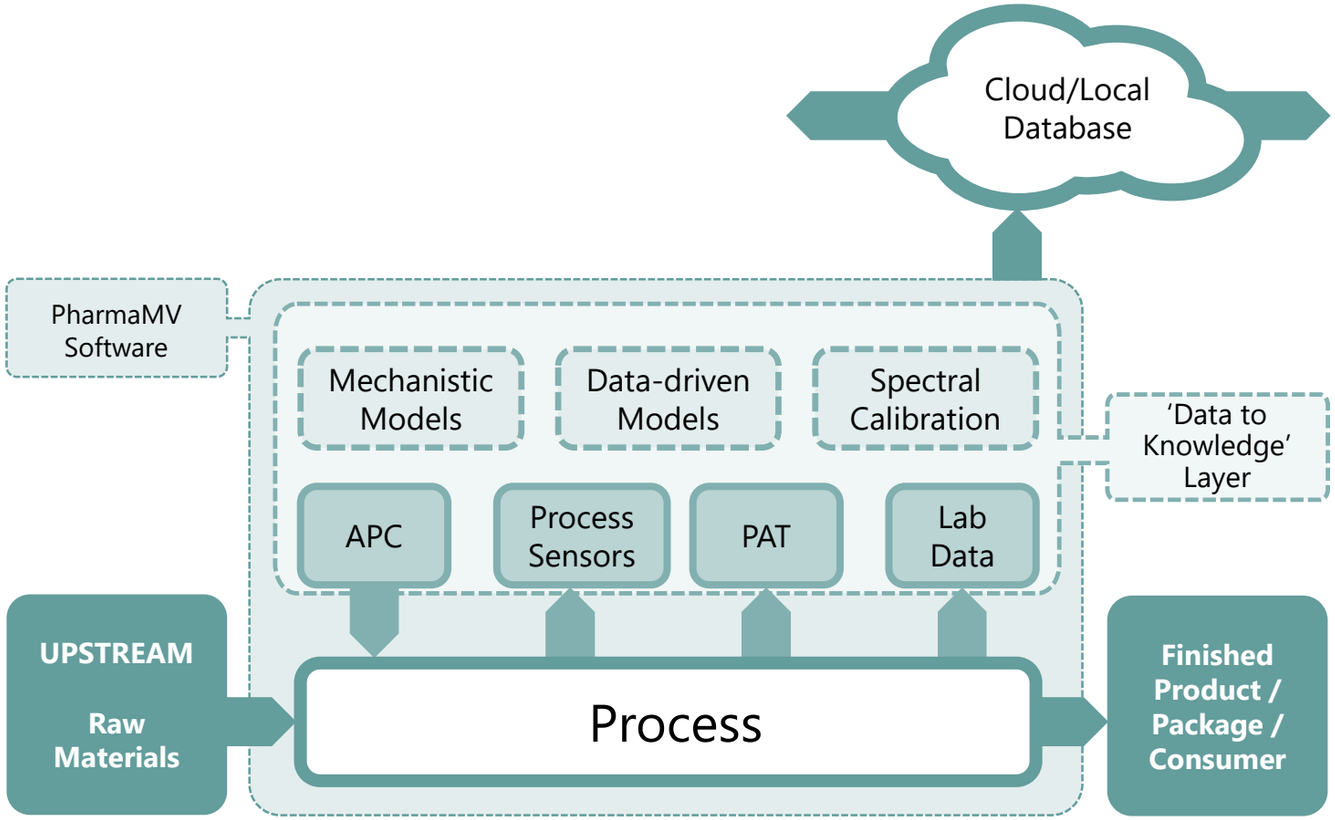
PharmaMV
Process Control & Monitoring

- 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

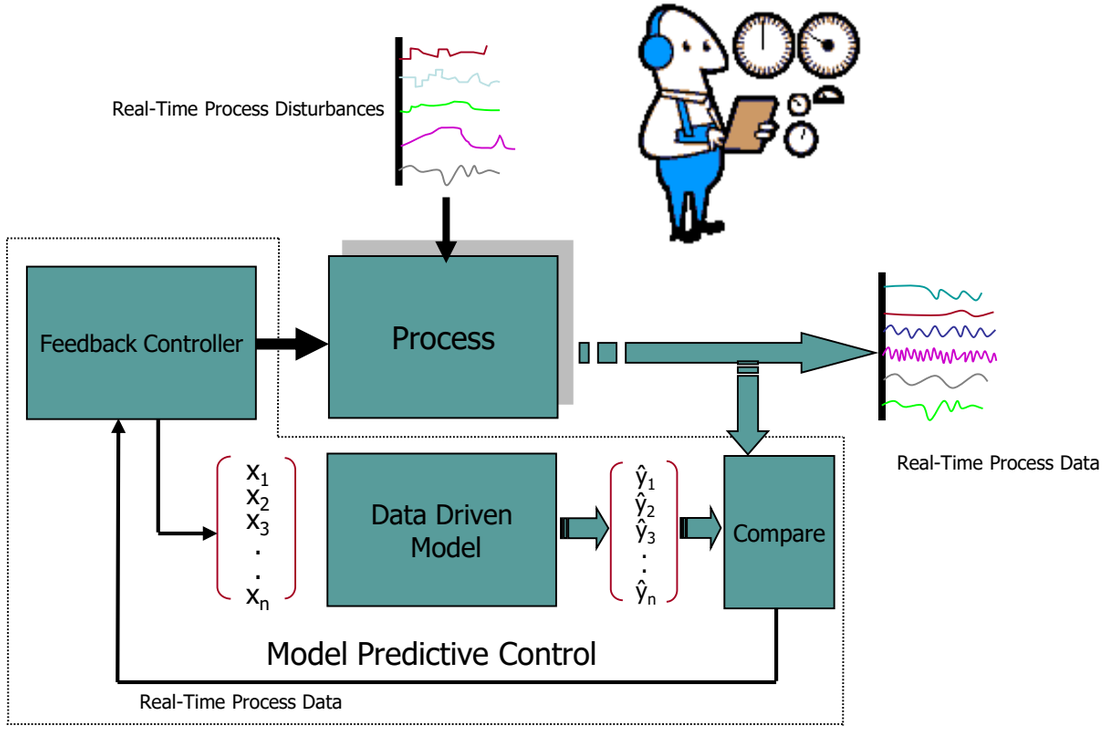
- In routine manufacturing, PharmaMV sits on top of a SCADA **pooling parametric** and **PAT data** and using this to **control** process parameters to CQA's



Model Predictive Control

Simple Overview

- A key **data driven** technology in the Advanced Process Control toolbox
- Understand process constraints and complex process interactions
- Build multivariate correlation between process inputs and process inputs = Process Model
- Predict impact of known disturbances on operation
- Predict, Advise, Make co-ordinated moves on multiple actuators
- Exploit all opportunities to improve quality and optimise the process



Artificial Intelligence, Industry 4.0, IIOT, ML….

Artificial Intelligence, Industry 4.0, IIOT, ML….

What is it? Why do we care . . .

Vendors sell IIOT as "**leveraging power from DATA!**" but that often just means:

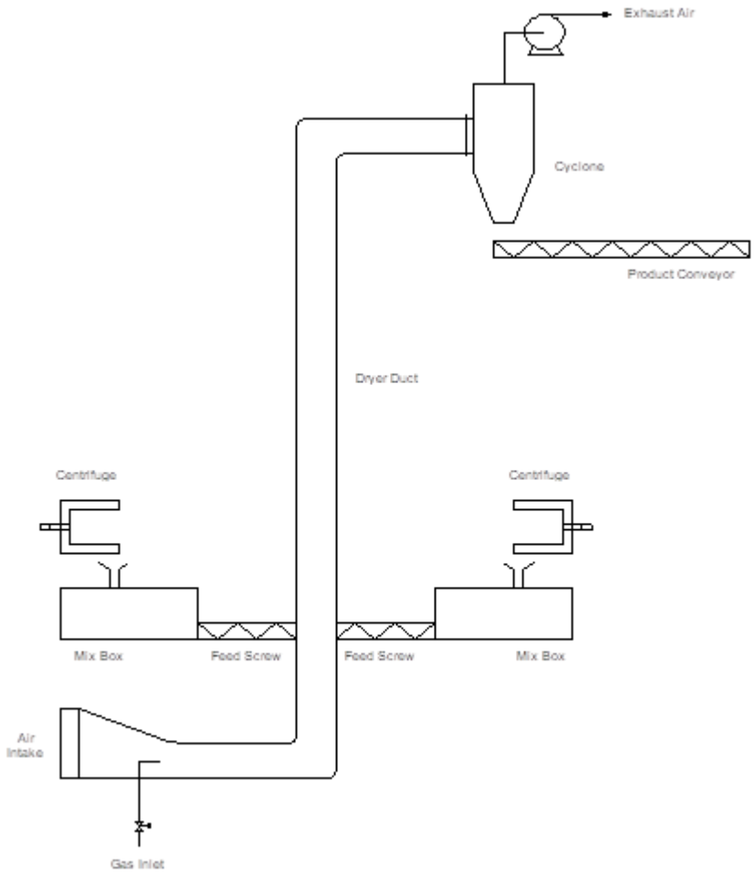
$$If\ f(x) < limit:$$

$$then:$$

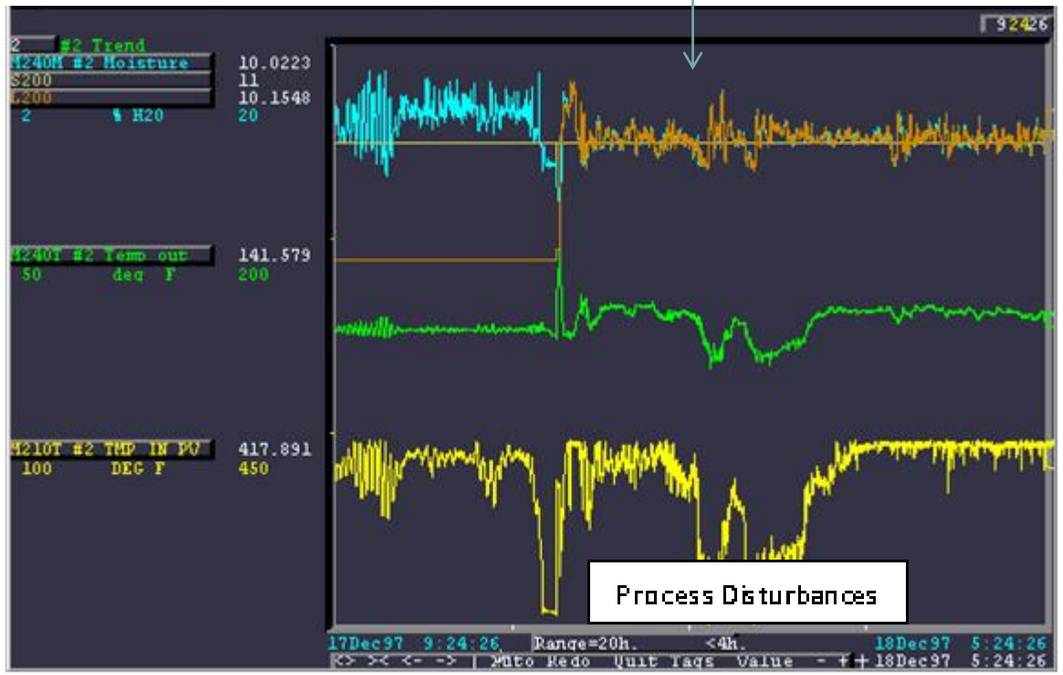
$$else:$$

Artificial Intelligence

Example – Starch Dryer

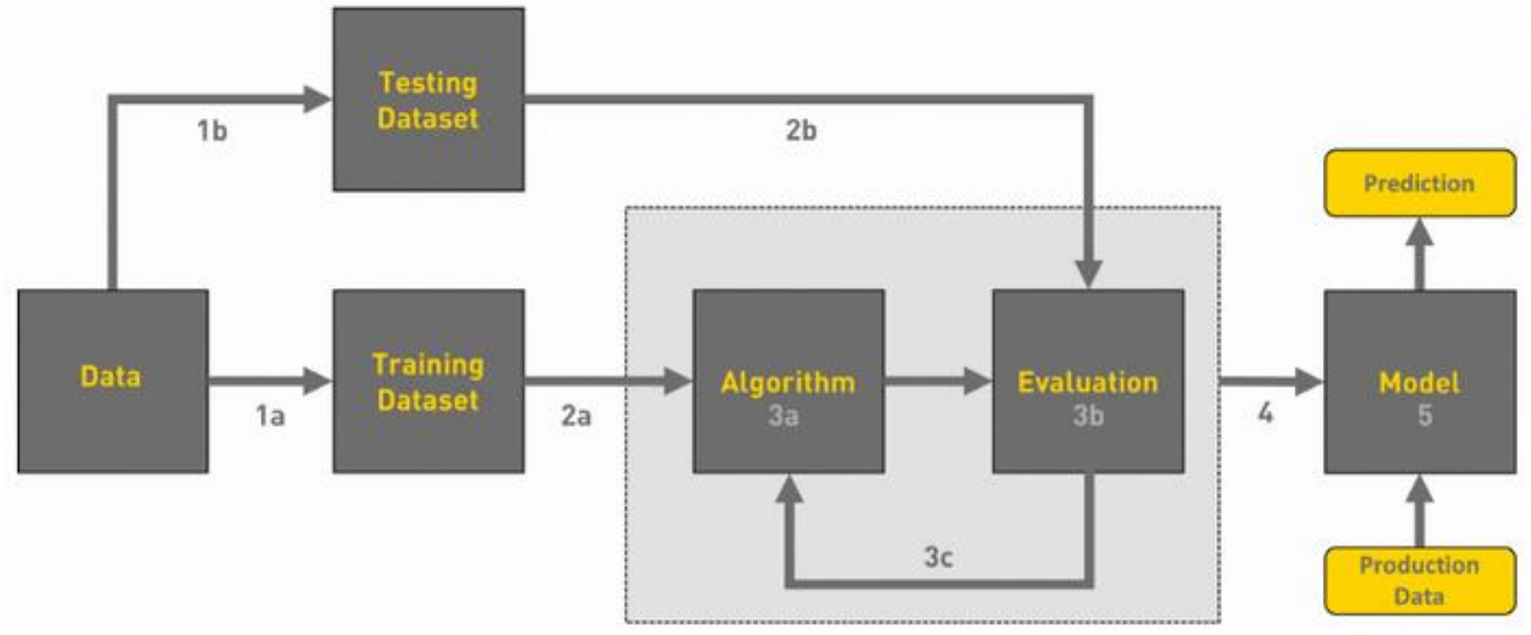


Model Prediction (Orange)



Teaching the machine

Data is everywhere…..or is it?



Overview of the Workflow of ML

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

Motivations and Benefits

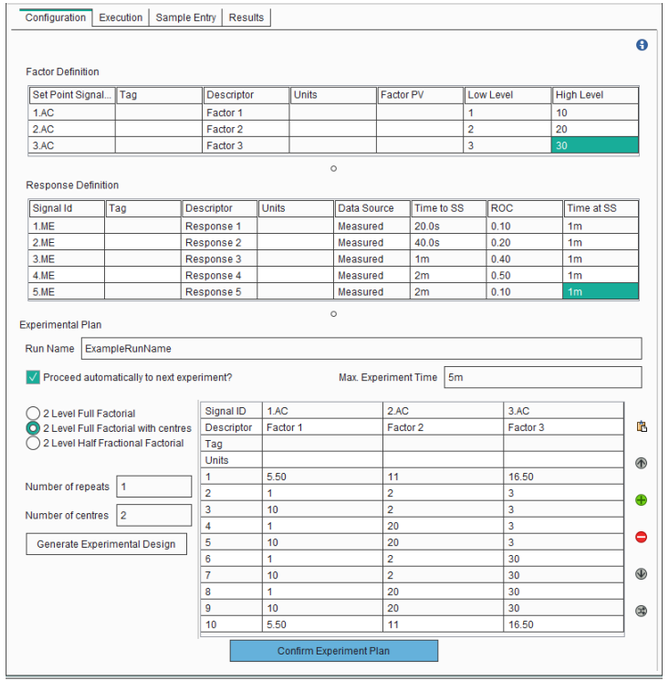
Process Development Approaches

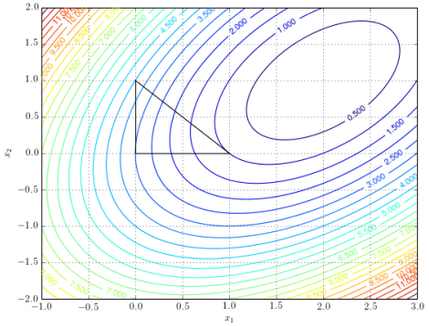
Traditional "One at a Time" approach

- 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





Machine 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
  - **Smart Data** generation

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

ROYAL SOCIETY OF CHEMISTRY

Themed collection

Synthesis 4.0: Towards an Internet of Chemistry

Microreactor Technology

DOI: 10.1002/anie.201006107

Intelligent Microflow: Development of Self-Optimizing Reaction Systems**

*Munawwer Rasheed and Thomas Wirth**

Chem Soc Rev

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TUTORIAL REVIEW

Towards dial-a-molecule by integrating continuous flow, analytics and self-optimisation

Victor Sans*[a] and Leroy Cronin*[b]

Cite this: Chem. Soc. Rev., 2016, 45, 2032

The employment of continuous-flow platforms for synthetic chemistry is becoming increasingly popular in research and industrial environments. Integrating analytics in-line enables obtaining a large amount of information in real-time about the reaction progress and selectivity via manual or automated feedback optimisation, possible to influence the reaction progress, catalytic activity and stability, etc. Furthermore, it is thus constituting a dial-a-molecule approach employing digital synthesis. This contribution gives an overview of the most significant contributions in the field to date.

Received 21st October 2015

DOI: 10.1039/c5cs00793c

www.rsc.org/chemsocrev

Angewandte Reviews

S. V. Ley et al.

Machine-Assisted Chemistry | Special Issue 150 Years of BASF

DOI: 10.1002/anie.201410744

Organic Synthesis: March of the Machines

Steven V. Ley, Daniel E. Fitzpatrick, Richard. J. Ingham, and Rebecca M. Myers*

EurJOC European Journal of Organic Chemistry

SHORT COMMUNICATION

DOI: 10.1002/ejoc.201500980

Automated Serendipity with Self-Optimizing Continuous-Flow Reactors

Zacharias Amara,*[a] Emilia S. Streng,[a] Ryan A. Skilton,[a] Jing Jin,[a] Michael W. George,[a,b] and Martyn Poliakoff*[a]

Reaction Chemistry & Engineering

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REVIEW

Online monitoring and analysis for autonomous continuous flow self-optimizing reactor systems

D. C. Fabry, E. Sugiono and M. Rueping*

Cite this: React. Chem. Eng., 2016, 1, 129

In this review the recent progress in the field of self-optimizing reactor systems for continuous flow chemistry is presented. Particular focus is directed to the implementation of monitoring tools and realization of computer-controlled reaction optimizations without human interaction.

Received 21st September 2015, Accepted 5th November 2015

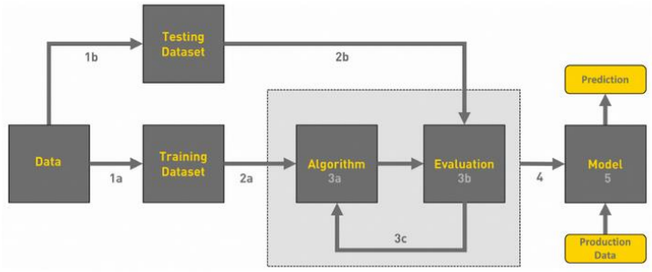
DOI: 10.1039/c5re00038f

rsc.li/reaction-engineering

Process development

Smart Data Generation

SMART DATA GENERATION



Overview of the Workflow of ML

CONTROL

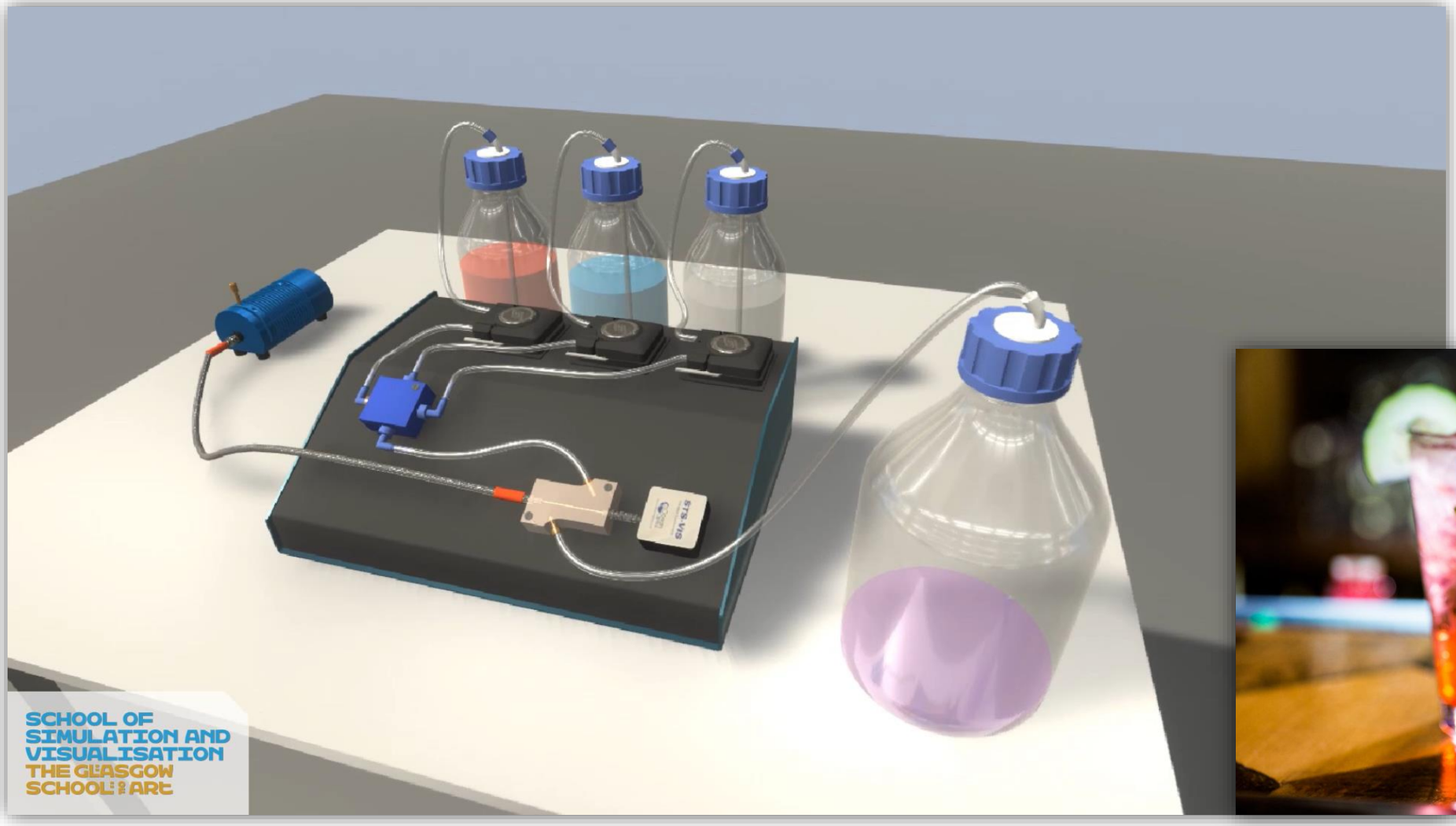
CAN A TRULY INTELLIGENT SYSTEM DO ALL OF THESE?
SHOULD IT?
IS IT MACHINE LEARNING?

Machine Learning & APC Example – Self-Optimising Continuous Process

© Perceptive Engineering

Self-Optimising Reactor Example

Continuous Flow Process – Digital Twin



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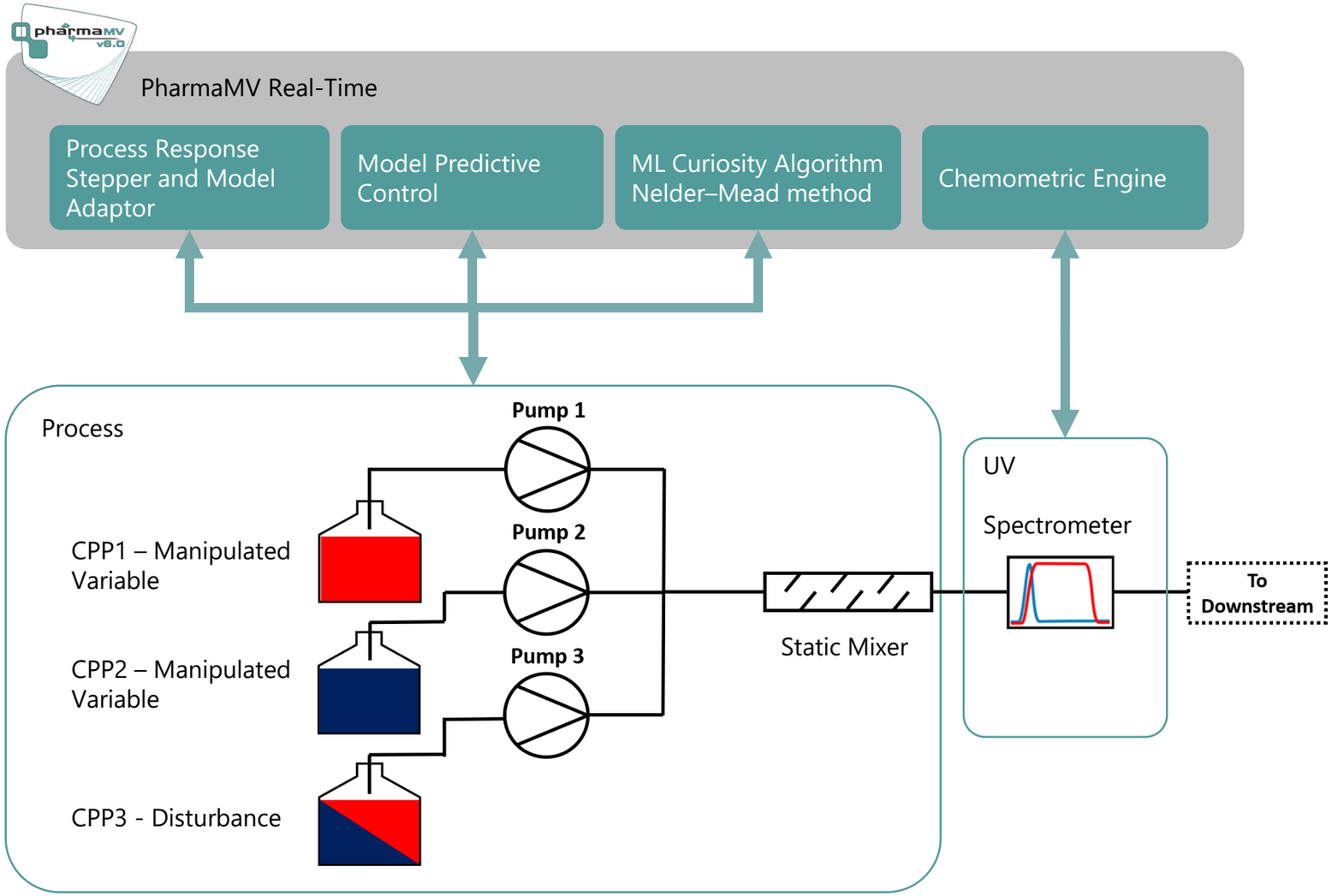
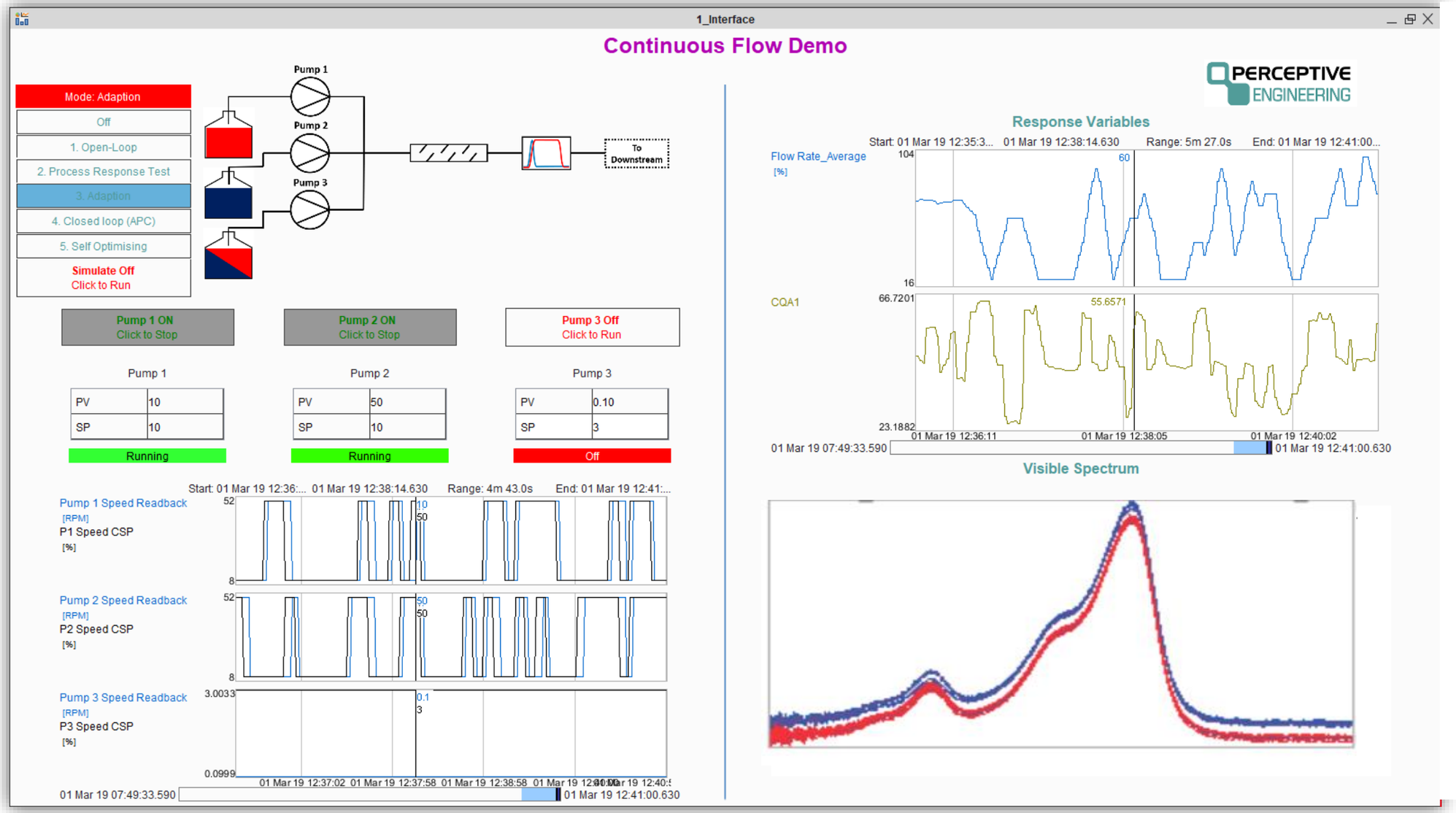
Self-Optimising Reactor Example

Continuous Flow Process



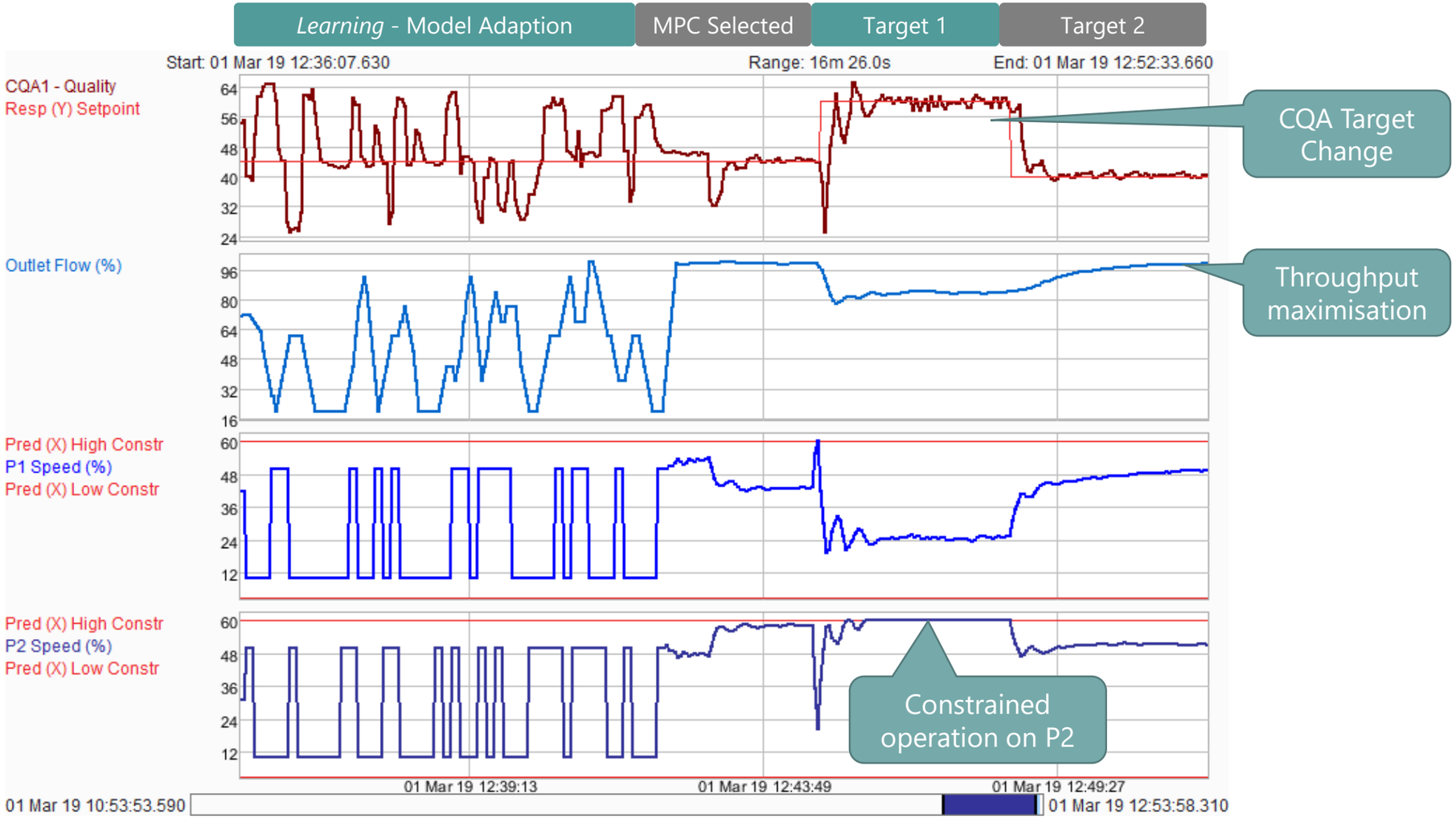
Self-Optimising Reactor Case-Study

Continuous Flow Dashboard



Model Predictive Control

Example *Adaption*, Control and Optimisation



Machine Learning. . . Nelder Mead Method

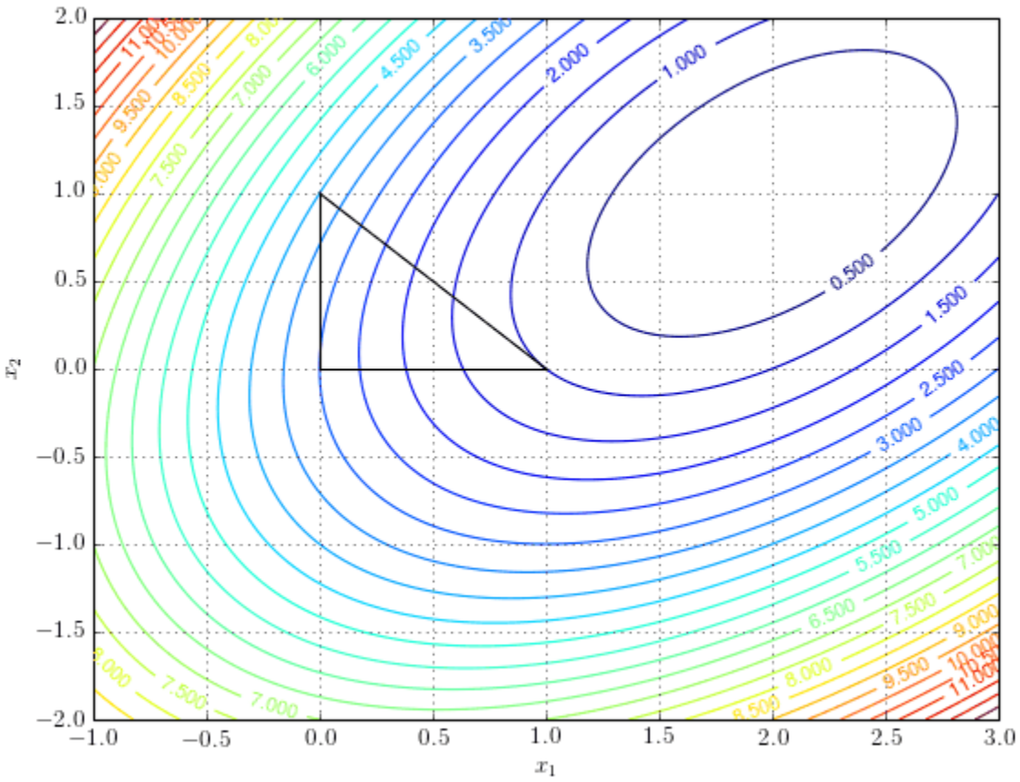
Simple Overview

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

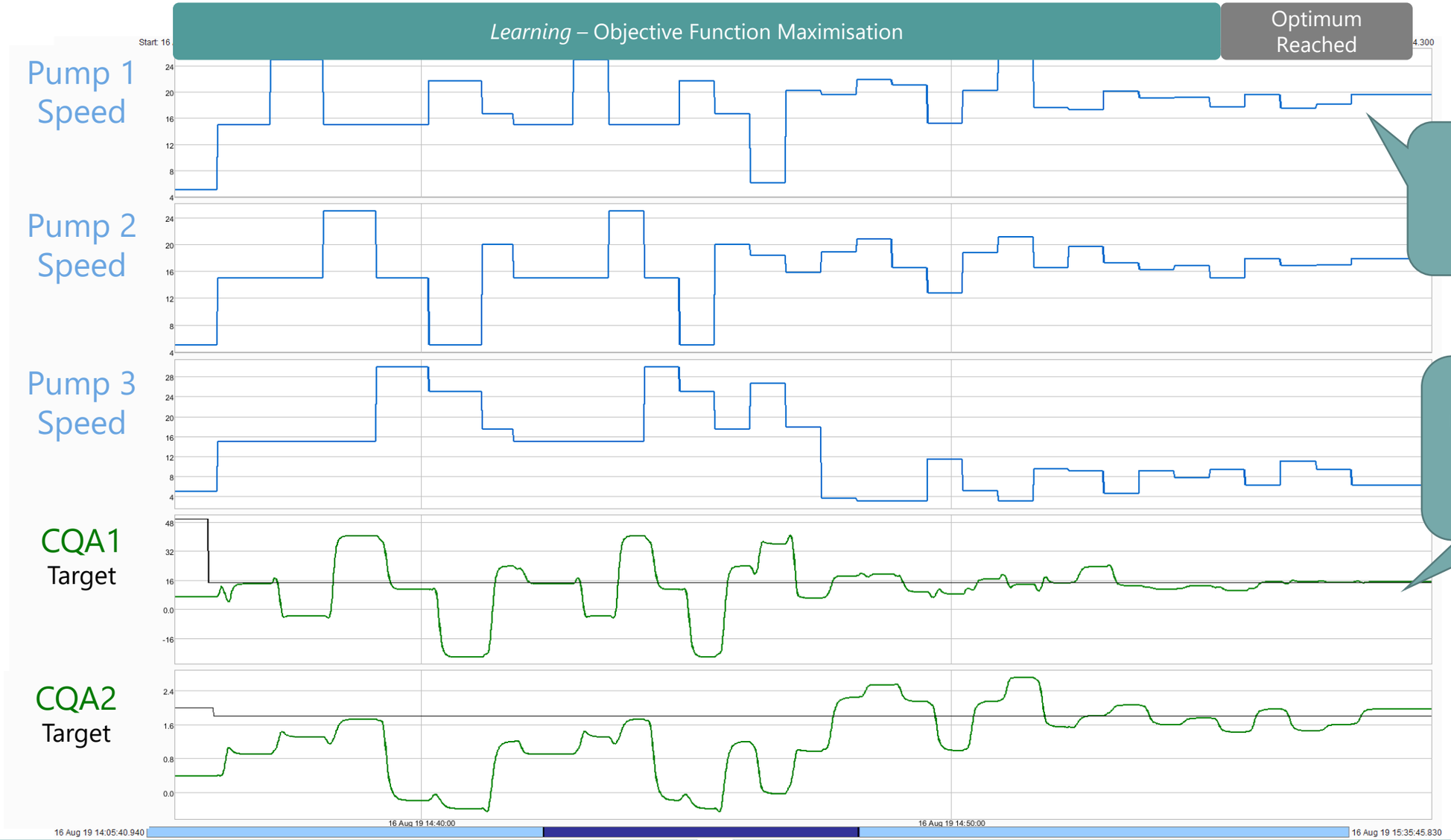
Gets stuck in local minima/maxima
Only single objective*

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



ML Method - Nelder Mead Optimisation

Example

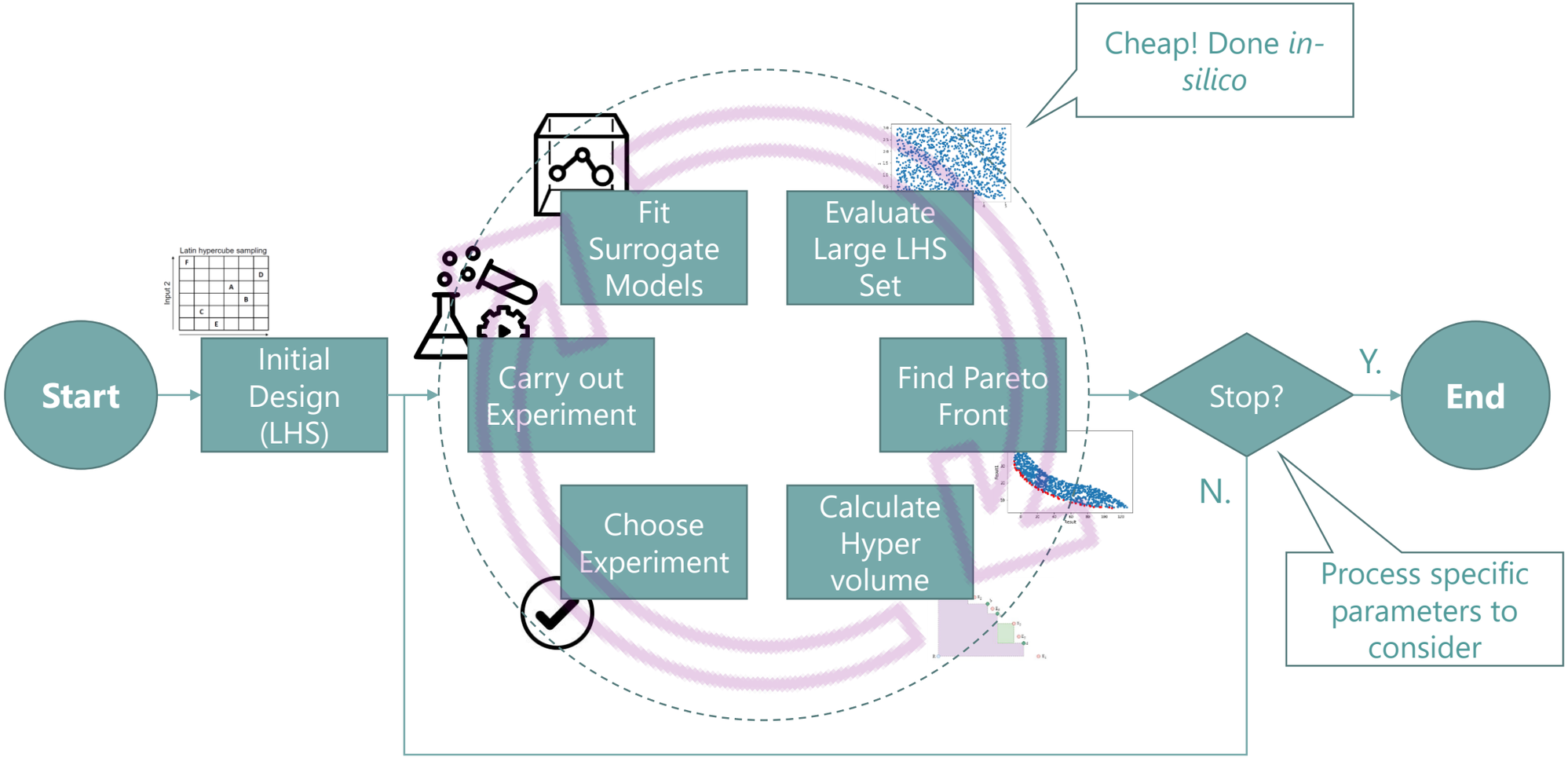


28 Steps required to reach the optimum.

Significantly more material consumed compared to APC.

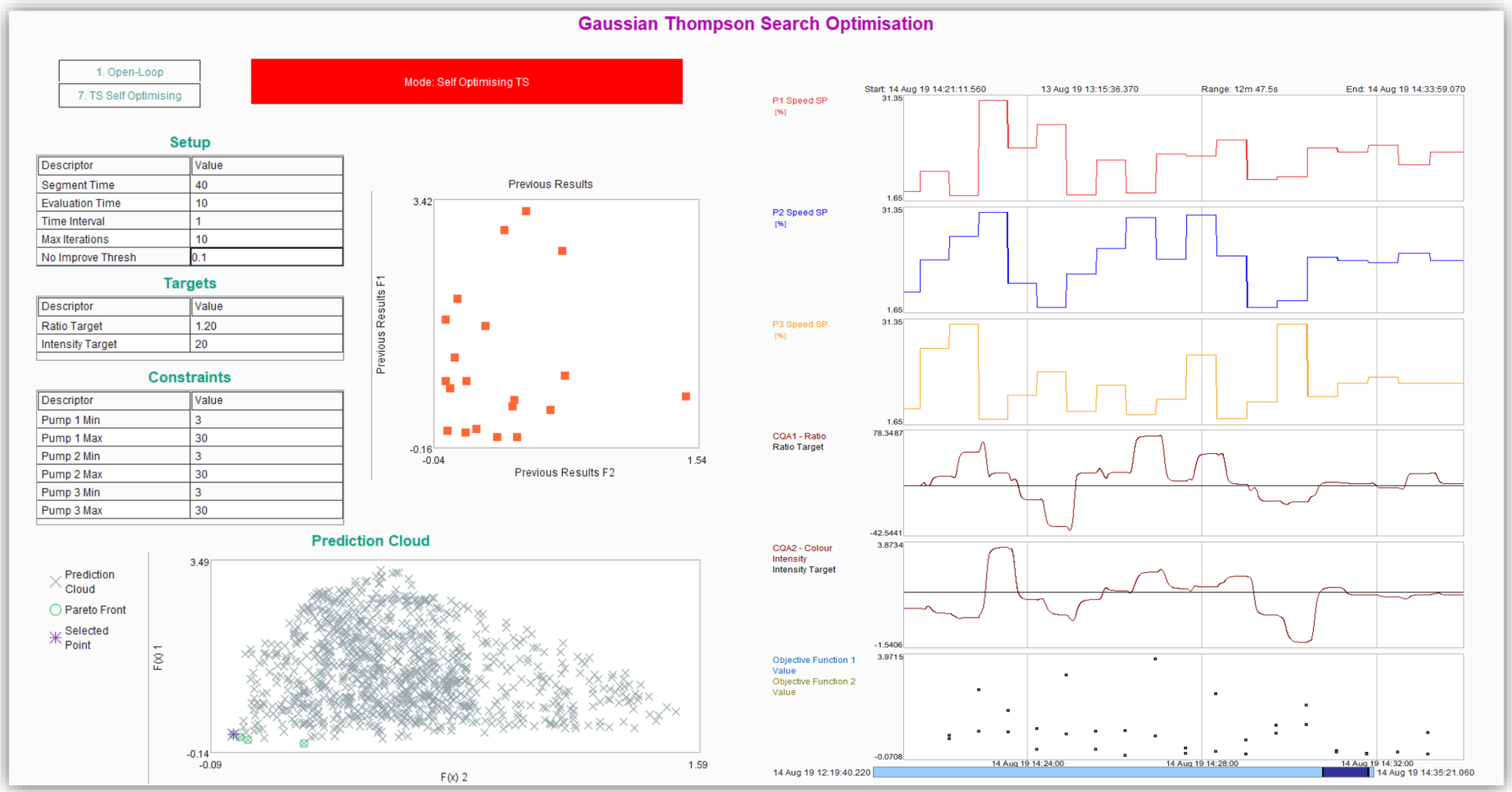
True Multi-objective Optimisation

Gaussian Search



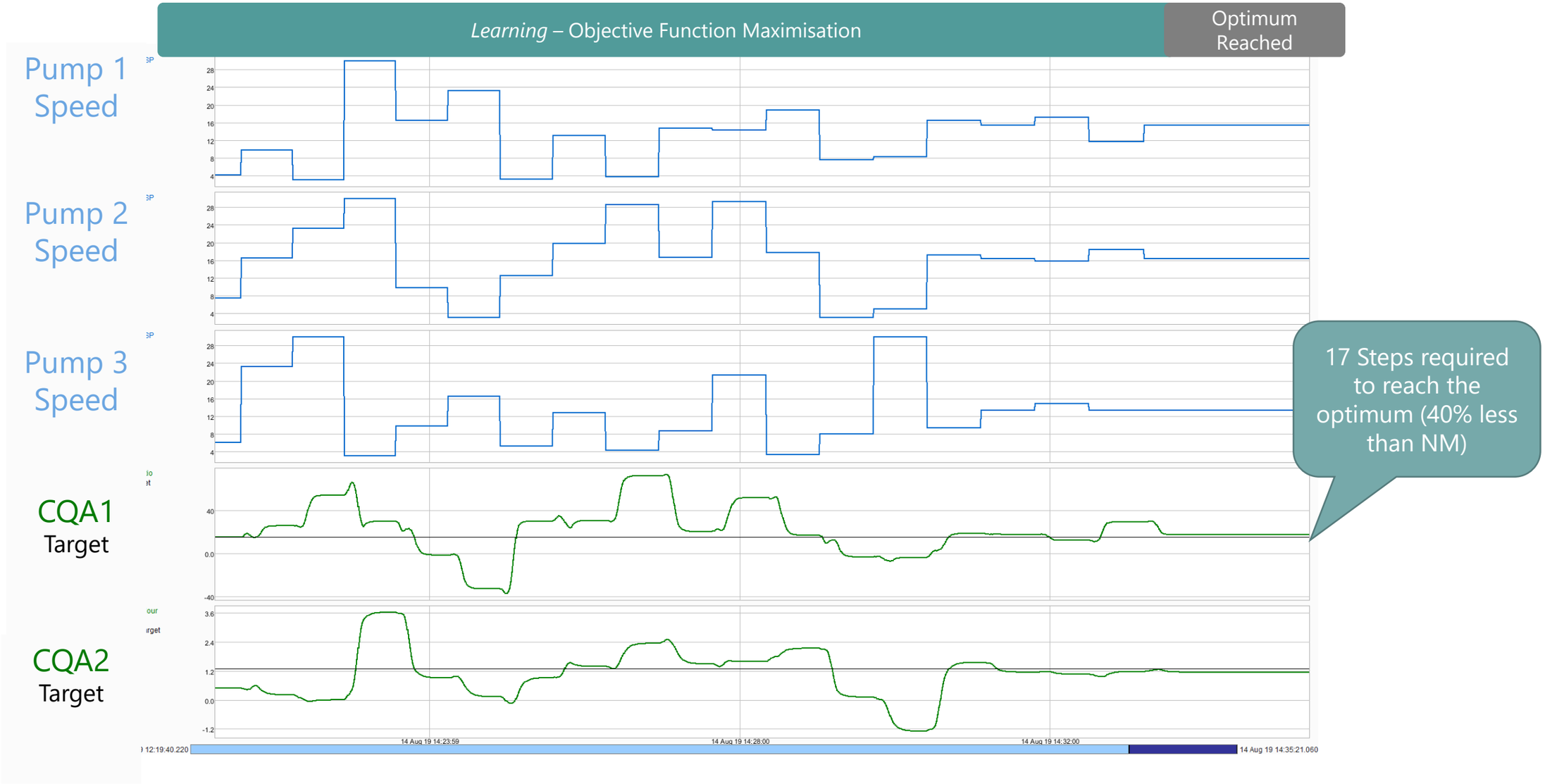
True Multi-objective Optimisation

Gaussian Search Dashboard



True Multi-objective Optimisation

Gaussian Search

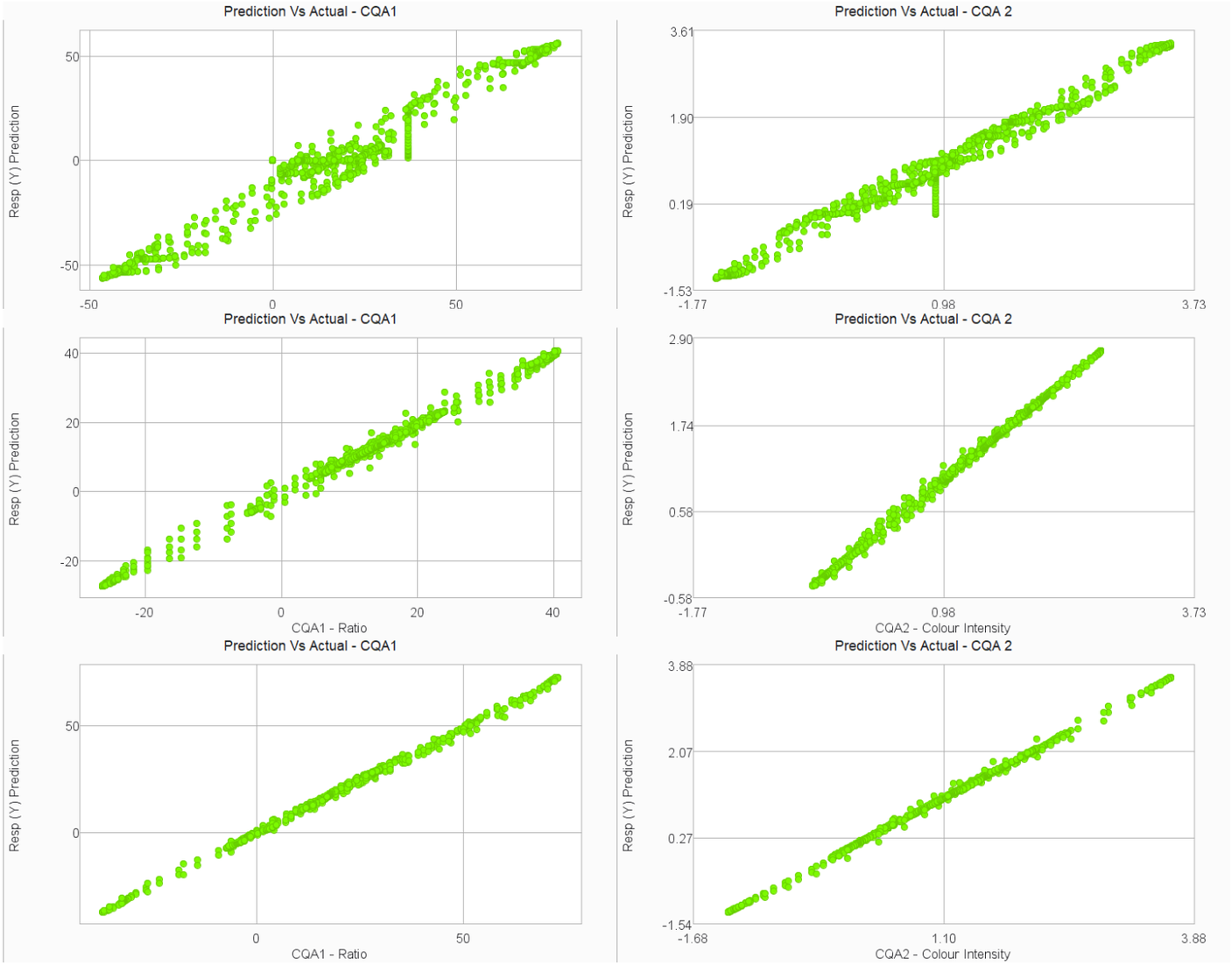


Smart Data Generation

Can the data be used to develop a model for control?

Model Uncertainty -RMSEP

	CQA1	CQA2
DoE	6.8	0.12
Nelder Mead	1.05	0.030
Gaussian Search	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
Resource Frugal?	✗	✗	✓
Rich enough Data for MPC?	✗	✓ Sometimes	✓

Challenging the Machine Learning Algorithms

What if?

The process conditions change?

Wear, fouling etc
Unmeasured disturbances and faults

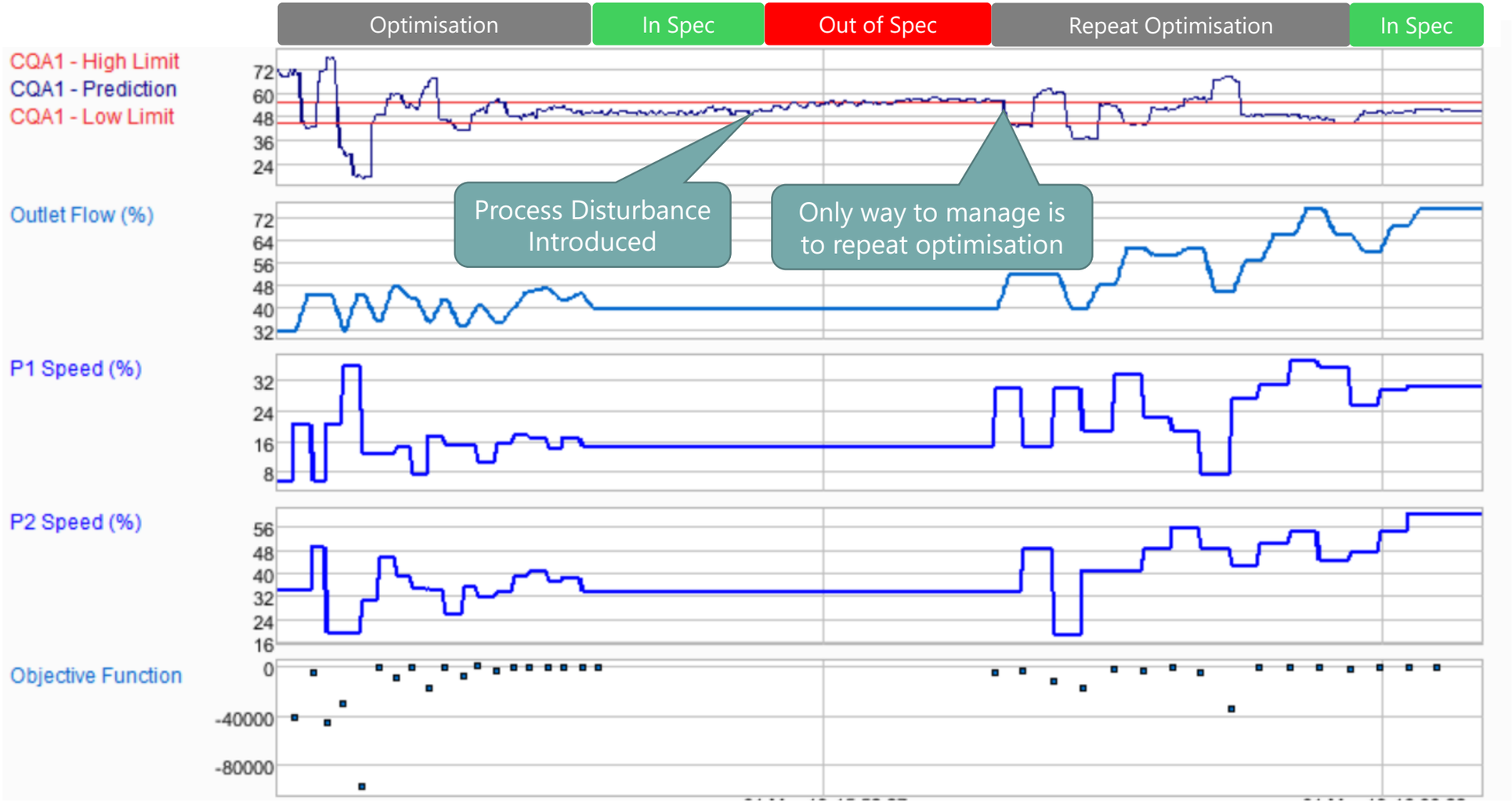
We change our Objectives,

such as a new setpoint?

The raw material properties change?

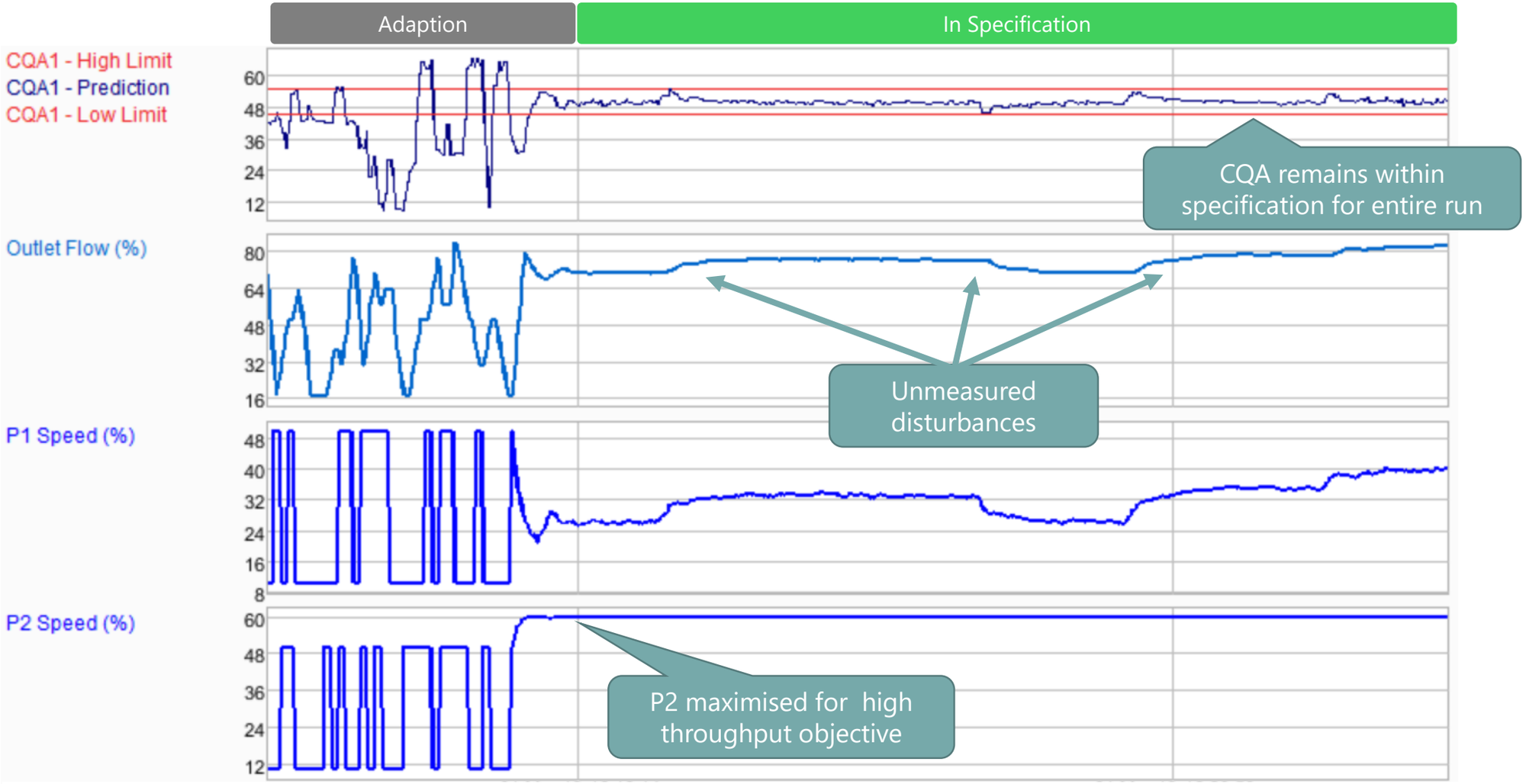
Machine Learning as a controller?

Effect of Process Disturbances



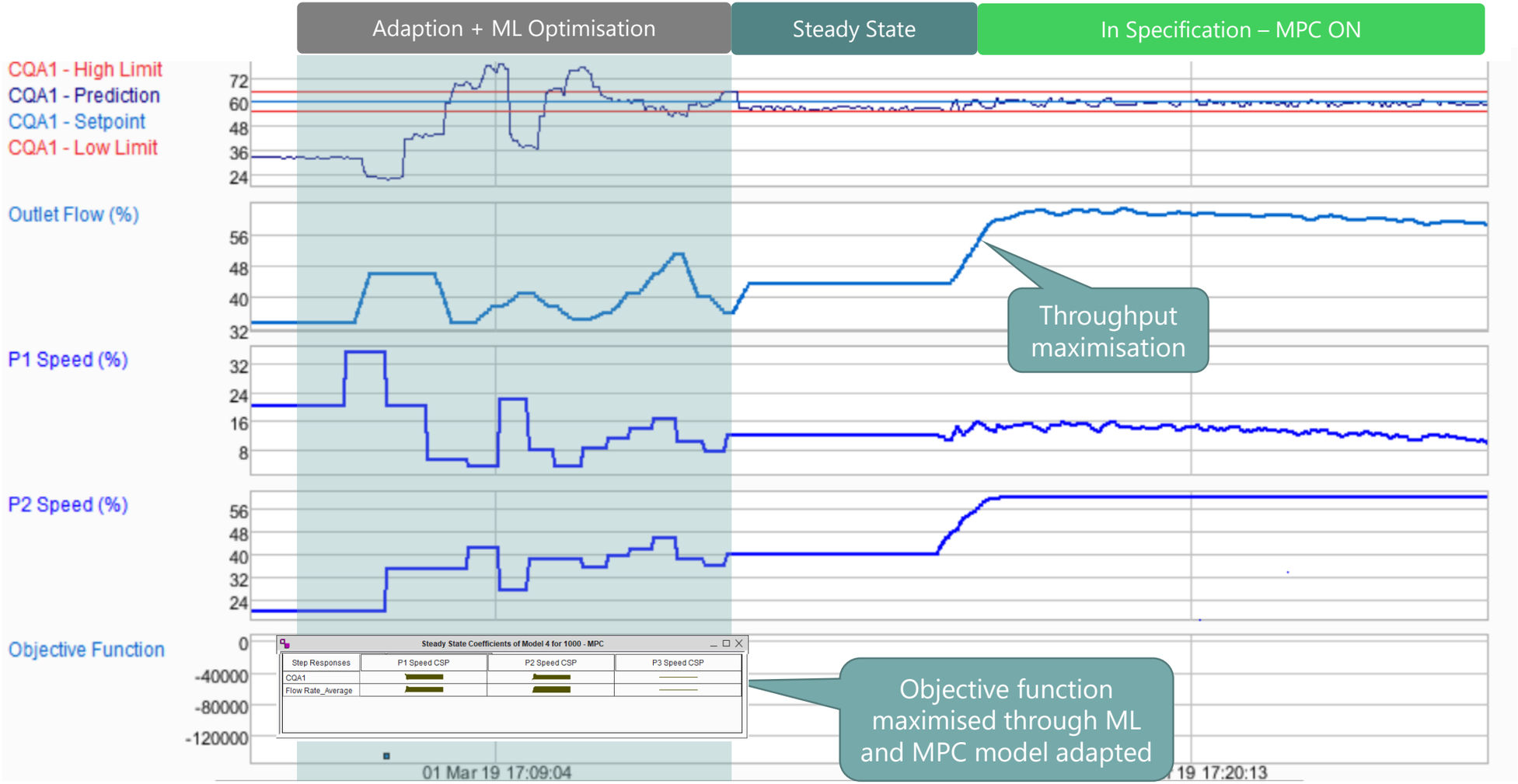
Model Predictive Control

Effect of Process Disturbances



Combined Advanced Process Control And Machine Learning

Example



A Comparison of Machine Learning and APC

Summary

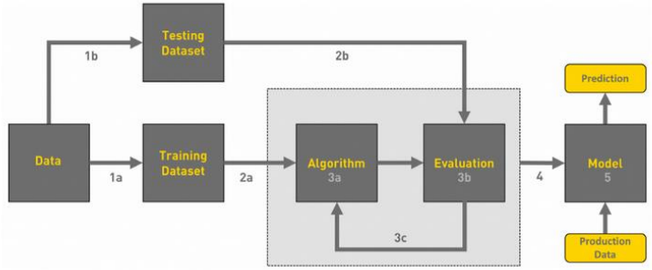
Within process development typical QbD approach doesn't yield enough data to take full advantage of Machine Learning or Advanced Control and the benefits it can bring

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

SMART DATA GENERATION

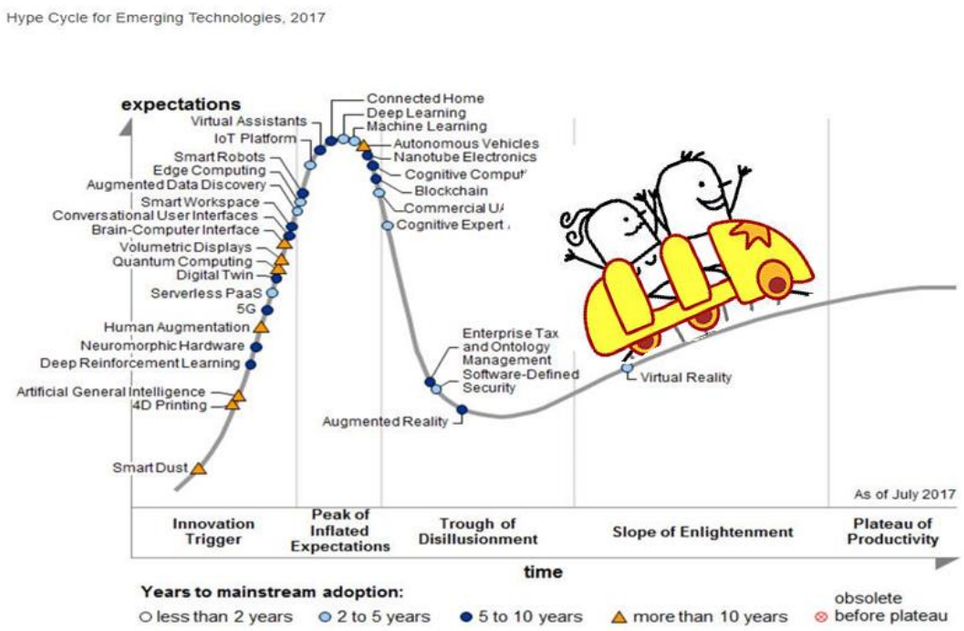


Overview of the Workflow of ML

CONTROL

A Comparison of Machine Learning and APC

Thanks for listening.



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