Improving Pharmaceutical drug product processing through Advanced Process Control and Multi-Variate Monitoring

John Mack – Engineering Director
Perceptive Engineering

PERCEPTIVE ENGINEERING

Perceptive Engineering Company

Who we are:

- 30 Employees
- Offices in the UK, Singapore, Ireland

What We Do:

- We develop software for the automation industries:
  - PAT, Advanced Process Control, Monitoring and Optimisation.

Academic and Innovation Alliances

- Universities of Cambridge, Manchester, Newcastle, Rutgers, Limerick, Strathclyde, Leeds, Surrey
- Centre for Process Innovation (CPI), Centre for Continuous Manufacturing and Crystallisation (CMAC), Institute of Chemical and Engineering Sciences (ICES Singapore), Synthesis & Solid State Pharmaceutical Centre (SSPC)
- Industrial partnerships with Siemens and GEA

Sci-Tech Daresbury UK

Singapore

The PharmaMV Platform
- Philosophy

A software platform for Advanced Process Control in the Pharmaceutical Industry:

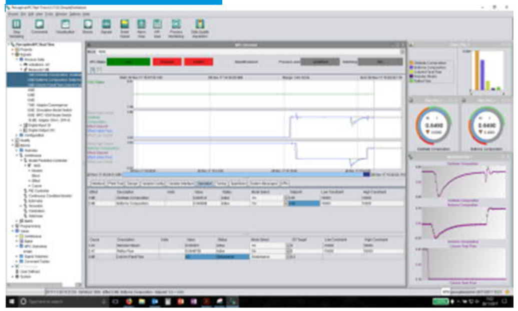
Some of the challenges....

- Management of “Instrument and Data” Integrity
- Capability to deal with Batch and Continuous Processes
- Interconnectivity – Use of existing industrial standards.
- Delivering Fault tolerant Monitoring, Control, Optimization.
- Traceable User Actions and support for 21CFR Part 11.

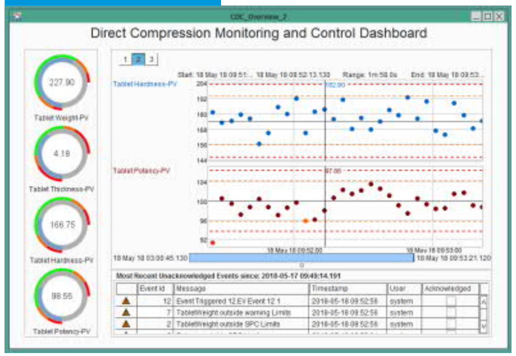
Blending the Pharmaceutical Scientist and Automation Engineering disciplines

PharmaMV - Key Benefits
Process Modelling, Monitoring and Control

Advanced Process Control



Statistical Process Control Dashboard



Advanced Process Control

- Model Predictive Control of Critical Quality Attributes using PAT derived or soft-sensor models.
- Integration with GEA Dynamic Process Control

Process Modelling

- Creation and execution of dynamic process, chemometric, mechanistic and soft-sensor models.

Data Visualisation

- Uni-variate and multi-variate visualisation tools including SPC charts, contribution/score plots, trends
- Data visualisations can be added to web-enabled dashboards and reports.

Multi-Variate Statistical Process Control

- Multivariate process monitors using Principal Component Analysis, Partial Least Squares
- MVSPC Plots with SPE & T2 statistics provided for real time monitoring.
- Implementation of Real-time release

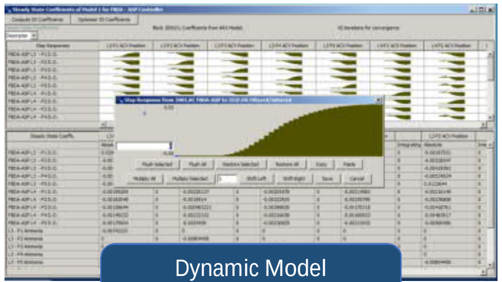
Process Modelling
Setting the scene for “Statistical” and “Mechanistic” Models

Statistical, Empirical or Data Driven Models

- Control: Dynamic Models
- Calibration: Static Models

Created from

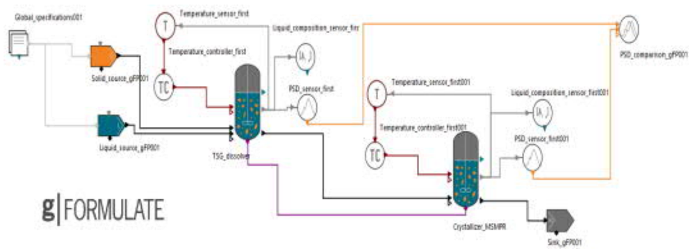
- Designed Plant Tests
- Historical Process Data



Dynamic Model for Control

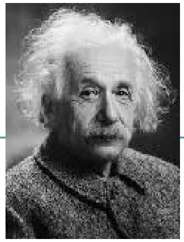
Mechanistic Models

- A model is one where the basic elements of the model have a direct correspondence to the underlying mechanisms in the system being modelled (1)
- Parameterised from experimental data

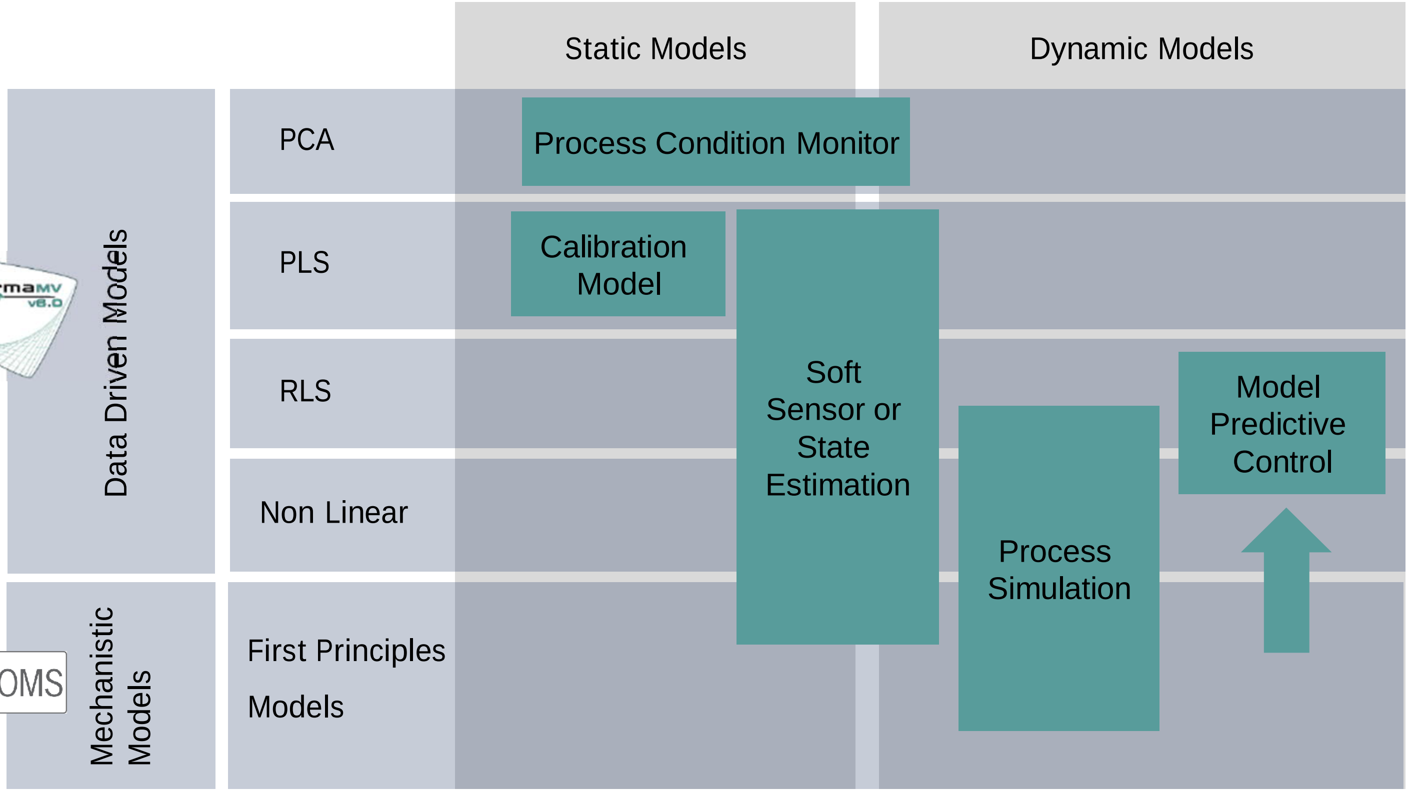


Flowsheet model

(1) https://grey.colorado.edu/oreilly/index.php/Mechanistic_Model



Process Modelling
“The Unified Theory of Everything”

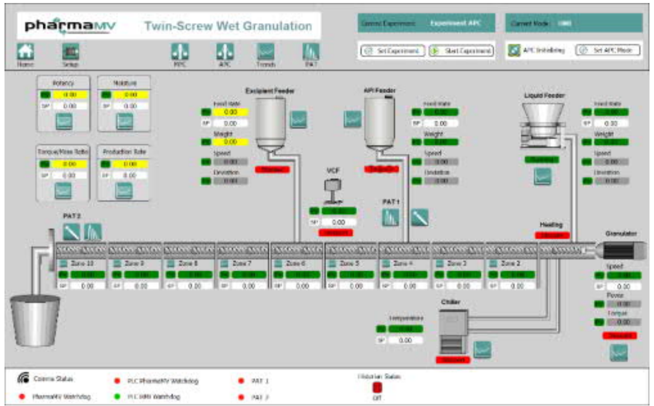


APC Case Study: TSWG

PerceptiveAPC Platform
Case Study: Twin-Screw Wet Granulator APC

Closed loop control of Critical Quality Attributes

- Twin Screw-Wet Granulation Example (GSK)
- Model Predictive Control, PAT and Chemometrics



What are the considerations when delivering robust control?

- Uncertainty
- Data Quality Monitoring
- Measurement redundancy?

gsk

Twin Screw Wet Granulator APC Network Topology

Integrate PAT and Process Data

Apply Process Response Tests

Structure the controller

Build a dynamic process model

Tune and commission the controller

Evaluate the Benefits

Twin Screw Wet Granulator OPC Server

Siemens WinCC Operator Interface

Embedded Displays

Network

PerceptiveAPC Real-Time APC

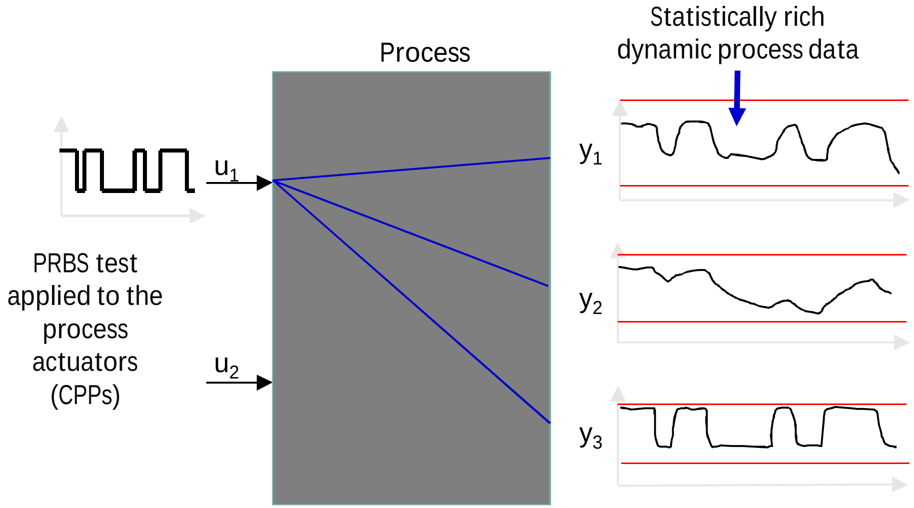
PAT (Granulator outlet) SentroSuite/Sentrodriver

Twin Screw Wet Granulator APC
Process Response Testing

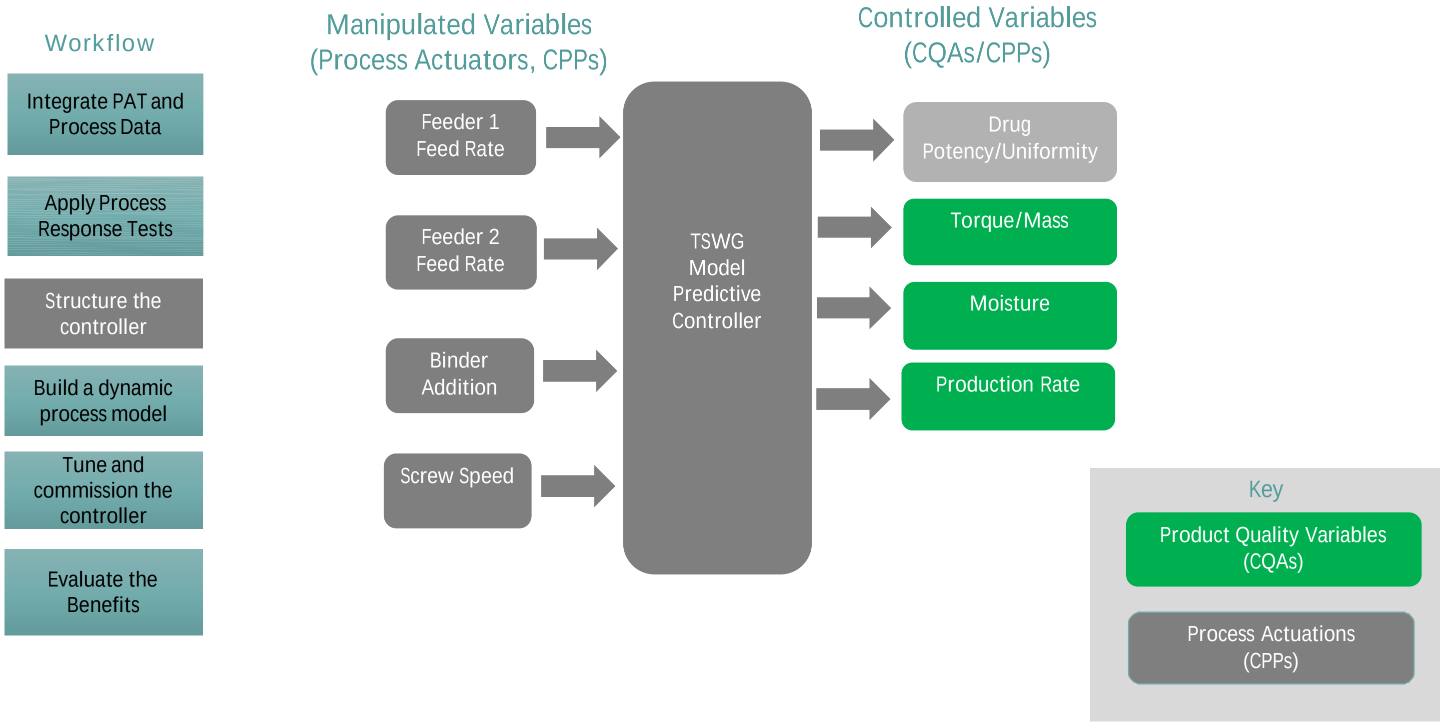
Workflow

- Integrate PAT and Process Data
- Apply Process Response Tests
- Structure the controller
- Build a dynamic process model
- Tune and commission the controller
- Evaluate the Benefits

- To build an accurate, robust dynamic model, we need to perturb the process to excite the dynamics using a Pseudo Random Binary Sequence "PRBS"
  - Good dynamic excitation
  - Minimal number of test runs required



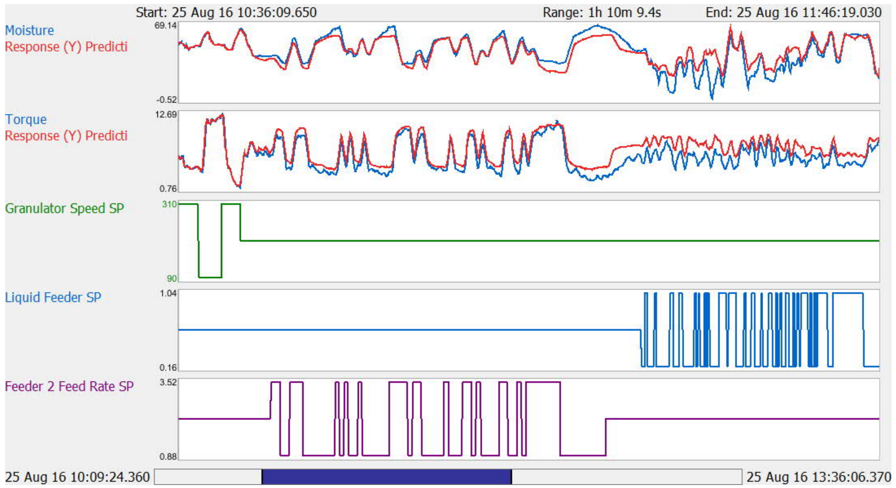
Twin Screw Wet Granulator APC
MPC Controller – Structure



Twin Screw Wet Granulator APC
Dynamic Process Model Development

Workflow

- Integrate PAT and Process Data
- Apply Process Response Tests
- Structure the controller
- Build a dynamic process model
- Tune and commission the controller
- Evaluate the Benefits



Process Response Data and Dynamic Predictions

Step Responses	Feeder 1 Feed Rate SP	Feeder 2 Feed Rate SP	Liquid Feeder SP	Granulator Speed SP
Granulator Torque				
Moisture Prediction				
Production Rate				

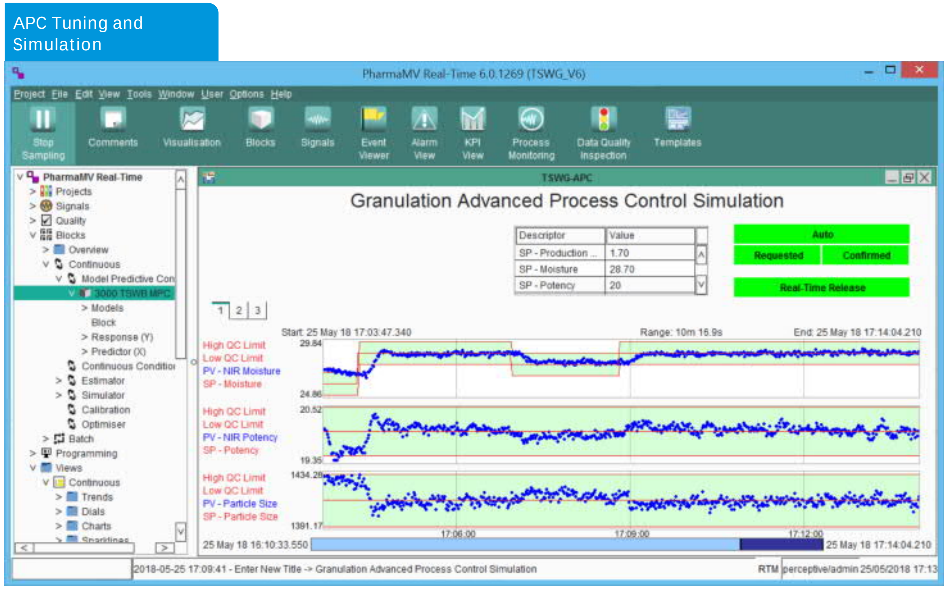
Dynamic Model

Twin Screw Wet Granulator APC
Simulation and Tuning

The controller is tuned in simulation to minimise the process run time and raw material required...

Workflow

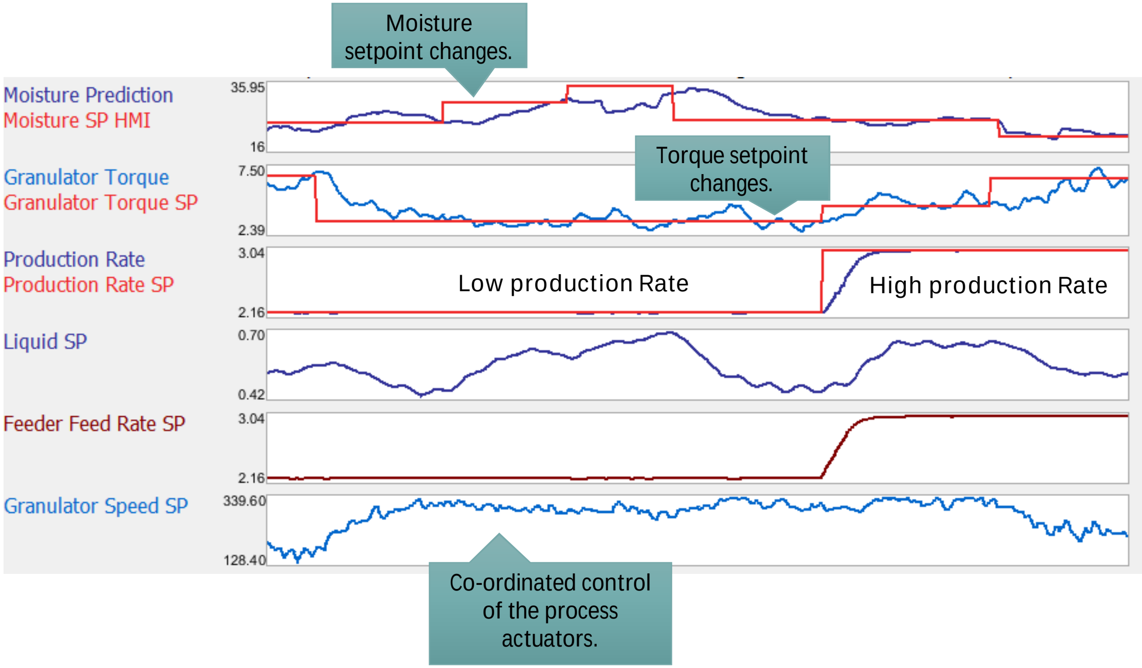
- Integrate PAT and Process Data
- Apply Process Response Tests
- Structure the controller
- Build a dynamic process model
- Tune and commission the controller
- Evaluate the Benefits



Twin Screw Wet Granulator APC Evaluation: Closed Loop Control

Workflow

- Integrate PAT and Process Data
- Apply Process Response Tests
- Structure the controller
- Build a dynamic process model
- Tune and commission the controller
- Evaluate the Benefits



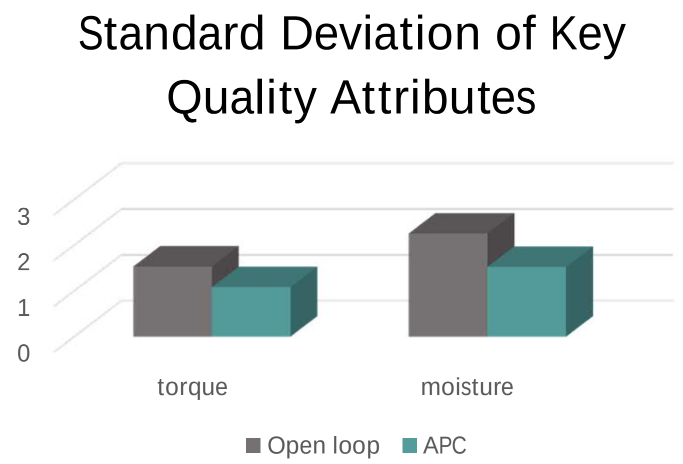
Twin Screw Wet Granulator APC
Evaluate the Benefits

Workflow

- Integrate PAT and Process Data
- Apply Process Response Tests
- Structure the controller
- Build a dynamic process model
- Tune and commission the controller
- Evaluate the Benefits

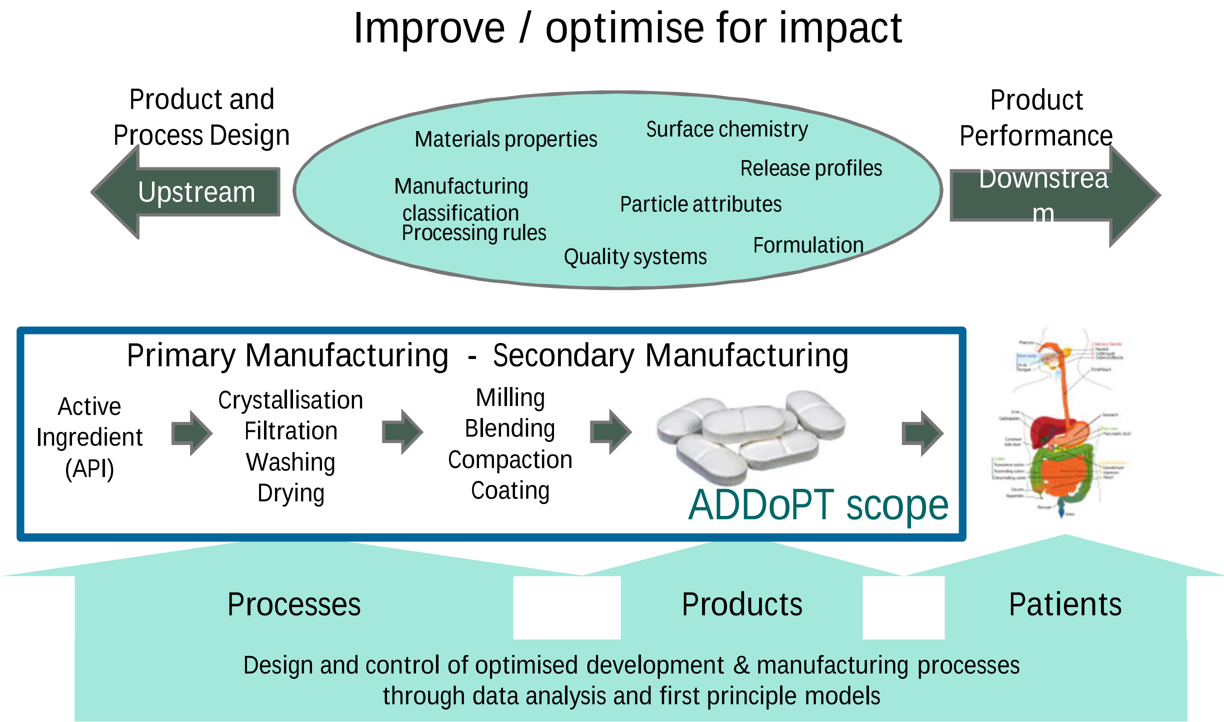
The TSWG process can be controlled by combining PAT with APC:

- Co-ordinated control of process actuators (CPPs)
- Minimise the variability in product quality (30% improvement)
- Respond to variations in raw material and other factors



Digital Design Based Approach - ADDoPT

ADDoPT Scope:
Digital Design to go from Molecule to Medicine



A consortium for taking technology from medium to high TRL!

Pharma Primes

AstraZeneca
Bristol-Myers Squibb
gsk GlaxoSmithKline
Pfizer

SMEs

PSE
PERCEPTIVE ENGINEERING LTD
Britest

Research

UNIVERSITY OF CAMBRIDGE
UNIVERSITY OF LEEDS
University of Strathclyde Glasgow
The Cambridge Crystallographic Data Centre
Hartree Centre
Science & Technology Facilities Council

MPC development workflow
Data driven v Digital Design approaches

Experimental Work %

Modelling %

Experimental Work

pharmaMV v5.2

Data Integration
Integrate PAT and Process Data

DoE Testing
Apply Experimental Tests to generate Calibration Data

Modelling

Calibration Modelling
Implement a Calibration Model in Real-Time

Experimental Work

Dynamic Response Testing
Apply process response tests for process Dynamics

Modelling and Simulation

Controller Development
Develop the model and simulate the MPC

Experimental Work

Controller Commission
Commission and Evaluate the Controller's performance

Data Driven Workflow

Modelling %

Experimental Work

Data Collection
Solubility, Concentration, PSD, MSZW, etc..

Data Integration
Integrate PAT and Process Data

Modelling

Model Development & Scale up
Crystallisation 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 growth modelling

Simulation

Controller Development
Develop the model and simulate the MPC

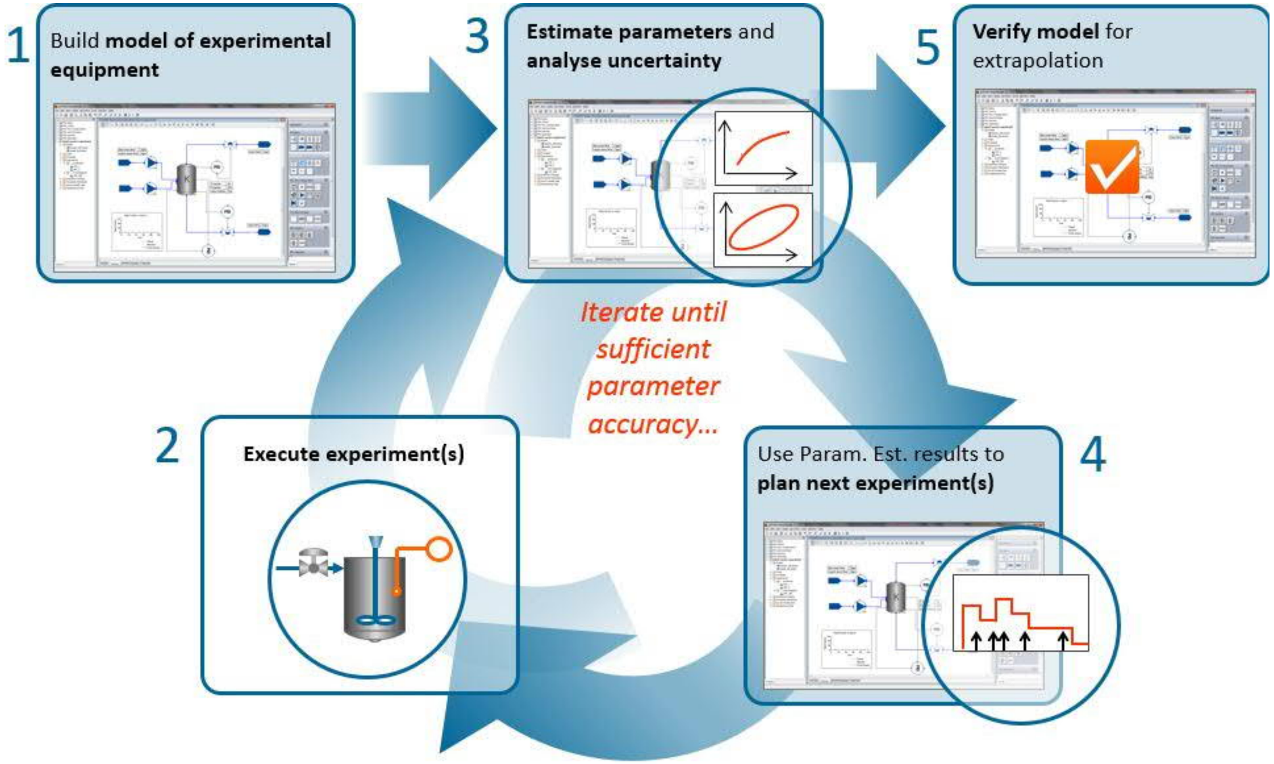
Experimental Work

Controller Commission
Commission and Evaluate the Controller's performance

Digital Workflow

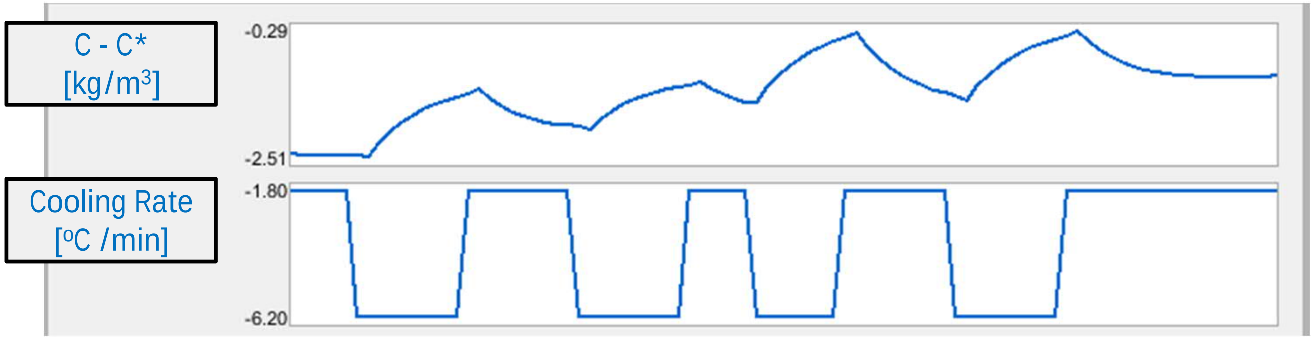
ADDoPT

Digital Design Workflow: Mechanistic model development

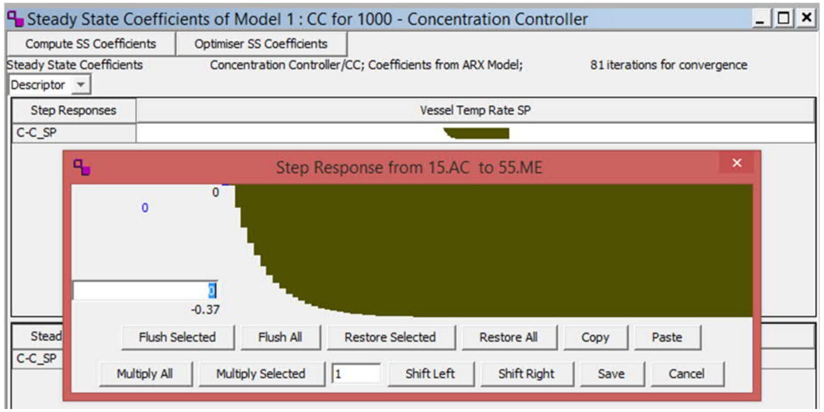


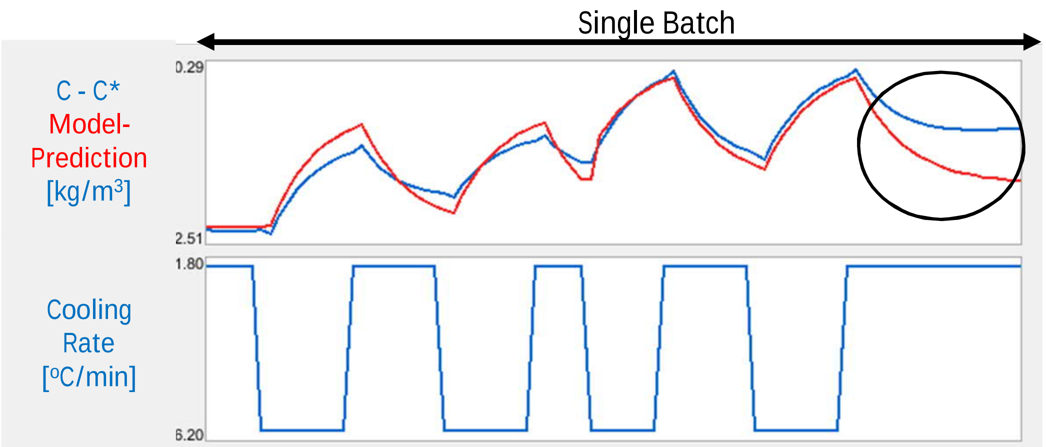
Statistical Model Development – Response Testing

- To identify a statistical model, Pseudo Random Binary Sequence (PRBS) step testing is applied to the flowsheet model using PharmaMV.
- The screenshot below shows the step tests on the cooling rate (ºC/min) and the corresponding response of C – C* (C* = set point concentration).
- This data is rich enough to identify an accurate statistical model for MPC controller.



Statistical Model Development – Identification





- The statistical model is identified using the Recursive Least Squares (RLS) algorithm. The screenshot on the left shows the C-C* response to a step change in the cooling rate.
- The crystallisation process is non-linear towards the end of the batch as there is less material to crystallise out – this is the reason why the linear model under-predicts the concentration for the last step change (black circle).

ADDOPT

Case Study Summary

- Benefits of digital design based workflow
  - Cost-effective development of an advanced control solution.
  - Reduced experimental effort in developing process models and control strategies.
  - Reduced wastage of the API material.
  - Minimal interruption in the process production time for step-testing/model development.
  - The research in model development can ultimately be used to improve production in commercial manufacturing plants.

Current Research Projects

PROSPECT CP Twin Screw Wet Granulation Pharmaceutics Formulation Platform for Process Development and Metrological Studies

PROJECT UPDATE

Test Bed for Innovation in Solid Formulation Manufacturability

- Twin screw granulation with associated PAT tools
- Generate process understanding to support the development of new products & processes
- Establish control strategies for commercial manufacturing processes
- Assess new and existing process analytical tools in real-life manufacturing

PROGRESS IN 2017 AND PLANS FOR 2018

- Foundational capability being built, in place Q1-Q2 2018, fully digitally-enabled
- Commissioning Q2 2018, learning project to be contracted to begin Q3 2018
  - Demonstrate utility of infrastructure
  - Implement emerging tools and engineering approaches
  - Propose and verify control strategy for exemplar product

Linking in-process analysis to finished product attributes

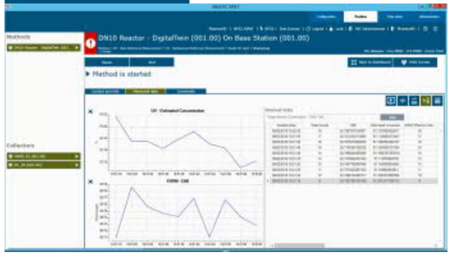
CPI – PROSPECT CP
Automation Update

Automated by a fully Industry 4.0 enabled software platform for data fusion:

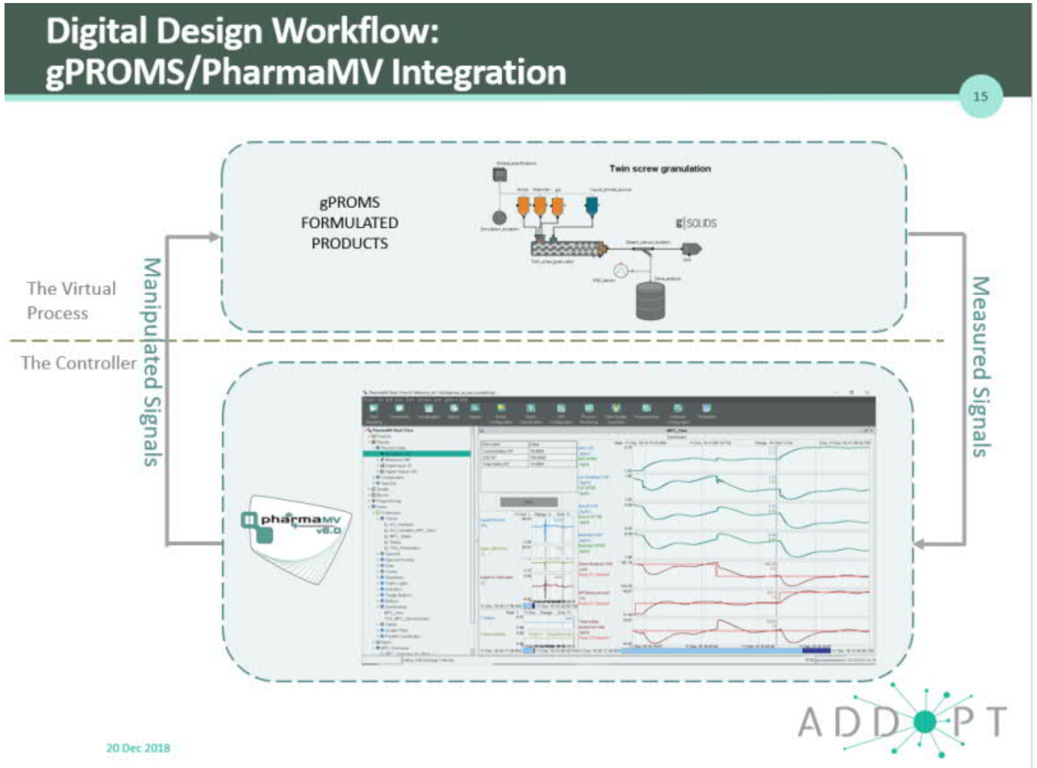
- Online execution of DoE, process response tests and development of empirical models.
- User-friendly workflows for model development.
- Chemometric techniques are applied to provide estimation of Critical Quality Attributes (CQAs).
- Flexible Advanced Process Control strategies to demonstrate closed loop control with feed-forward compensation for variability in raw material properties.
- Multi-Variate Analysis can be applied to detect process abnormalities to maximise process robustness.

PharmaMV Automated DoE Execution

Siemens SIPAT



Ongoing Research
ADDoPT Case Study - TSWG



Improving Pharmaceutical processing using APC and MVA Summary

Industrial processes can be controlled by combining PAT with APC, backed up with robust data quality monitoring:

- Co-ordinated control of process actuators (CPPs)
- Minimise the variability in product quality (moisture, granule size distribution and content uniformity)
- Respond to variations in raw material and other factors
- Risk-based system design
- Back up PAT with data driven soft-sensors for CQA prediction

Digital Design approaches can be used :

- Mechanistic models can be built using (very) small-scale experiments and then scaled up.
- Reduced wastage of the API material.
- Controller robustness and process non-linearities can be explored
- Hybrid models can be used as soft-sensors
  - Use a statistical model to “soak up” residual errors

Thanks for Listening
- Acknowledgements

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ADDoPT Partners:

Thank-you

Any Questions?

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