ADVANCED DIGITAL DESIGN OF PHARMACEUTICAL THERAPEUTICS

Mechanistic Model-based Digital Design framework for individual and integrated manufacturing steps

David Slade (Process Systems Enterprise)

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ADDoPT scope – a reminder

Improve / optimise for impact

Product and Process Design

Upstream

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

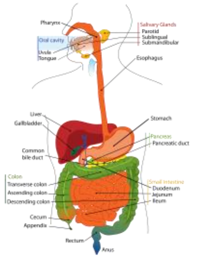
Product Performance

Downstream

Primary Manufacturing - Secondary Manufacturing

Active Ingredient (API) → Crystallisation, Filtration, Washing, Drying → Milling, Blending, Compaction, Coating →

→



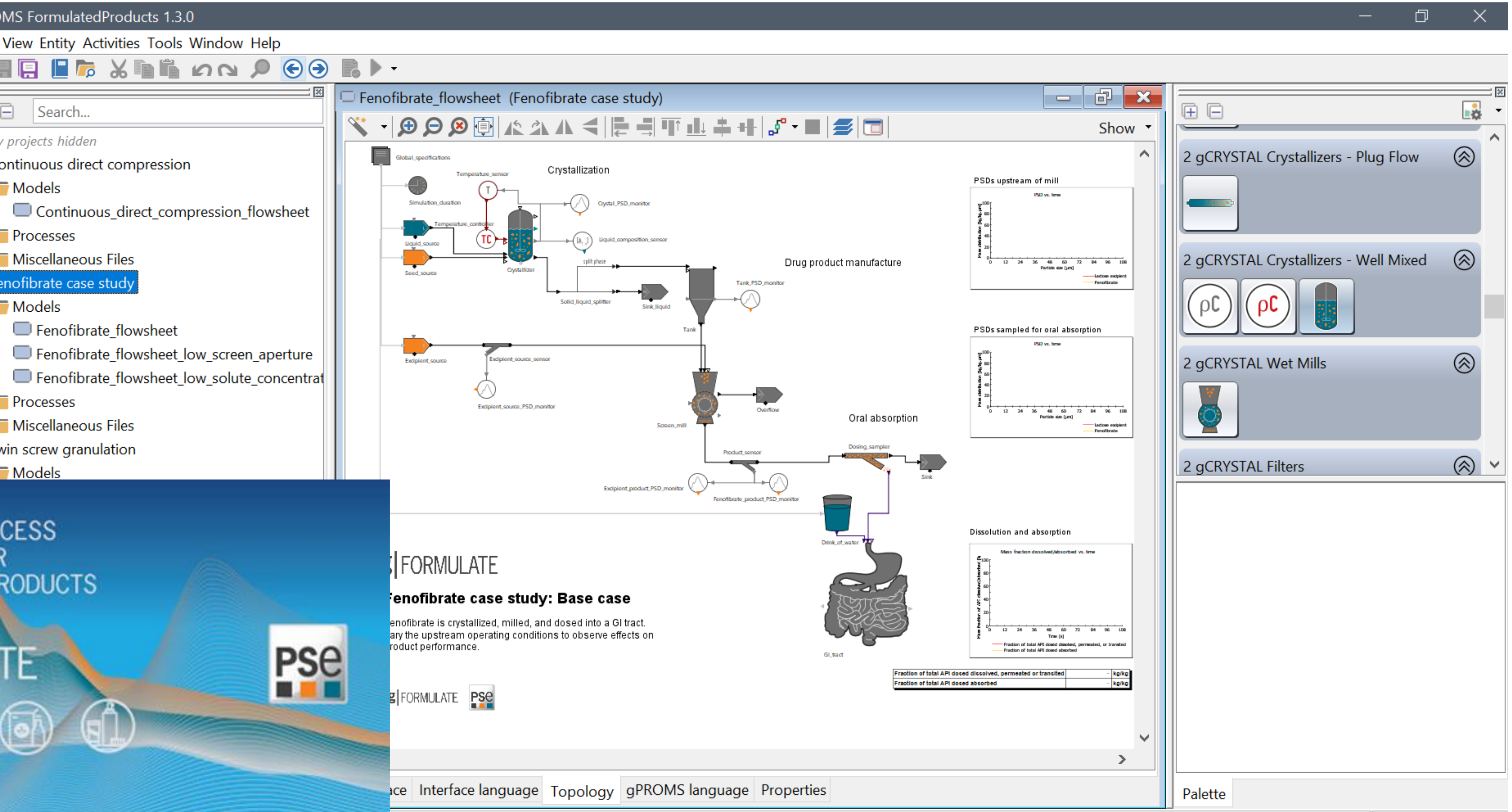
Processes | **Products** | **Patients**

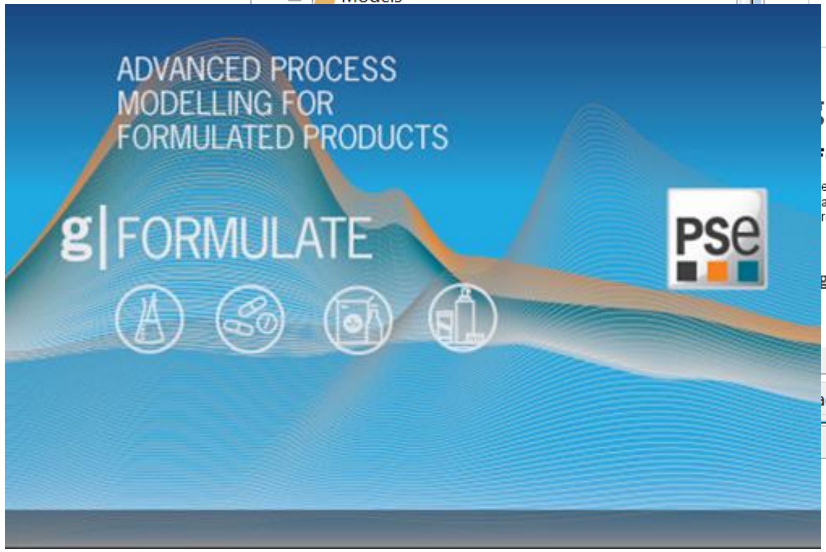
Design and control of optimised development & manufacturing processes through data analysis and first principle models

- A systems-based approach to pharmaceutics
- **Horizontal integration: Manufacture → Product Performance (breaking down silos)**
- **Vertical integration: Length Scales & Design → Operation**

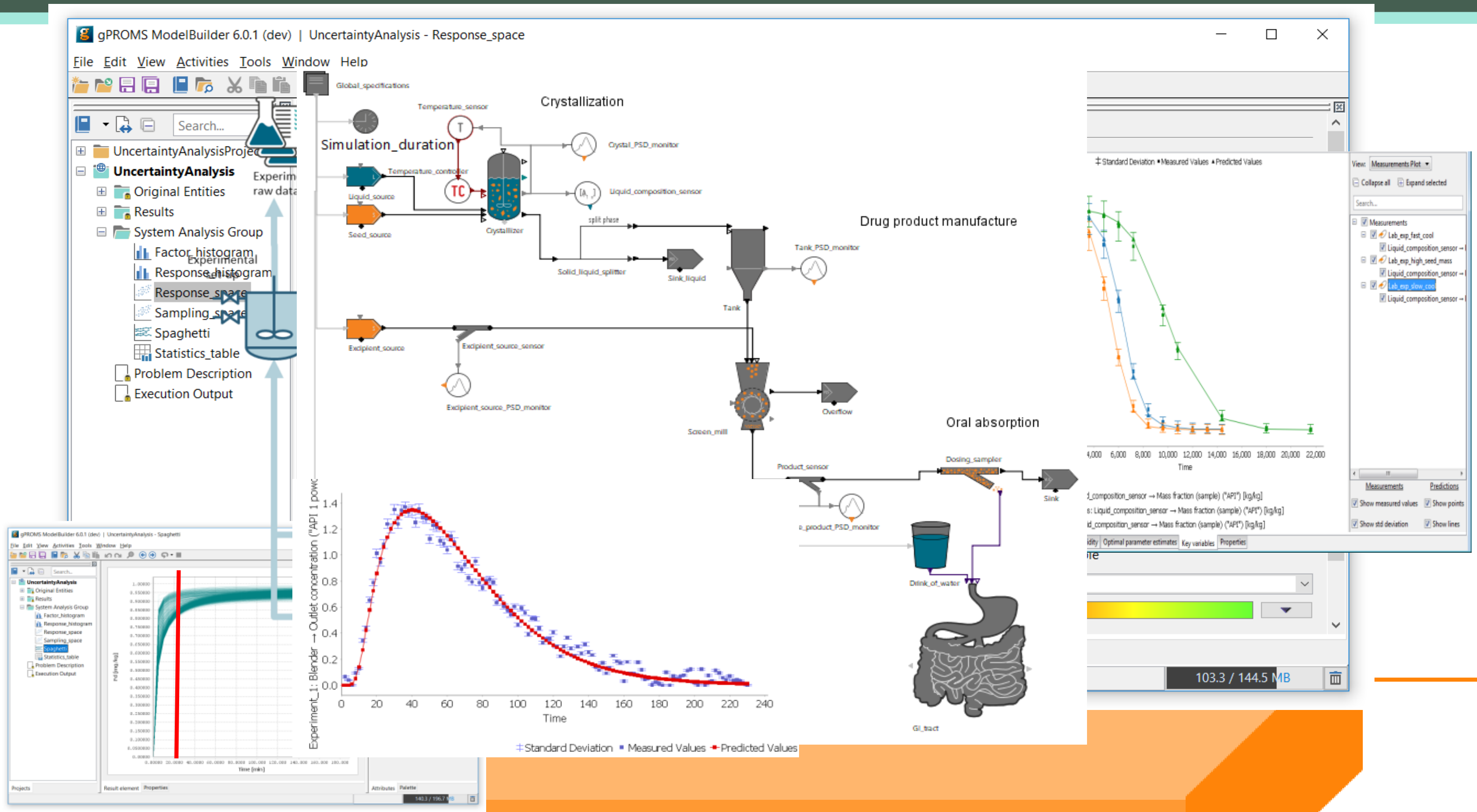
ADDOPT

gPROMS FormulatedProducts – a new PSE product enabled by ADDoPT





Enabling platform - gPROMS



Platform

gPROMS

Advanced Process Modelling platform
Advanced Materials Modelling platform

A single powerful software platform

- R&D → engineering design → operations
- Formulation → manufacture → product performance

Platform functionality

Process modelling

Equation-oriented solution power

Custom model construction

Steady-state and dynamic simulation

Powerful optimisation, including mixed-integer

Advanced parameter estimation

Global system analysis

High-performance computing

Materials modelling

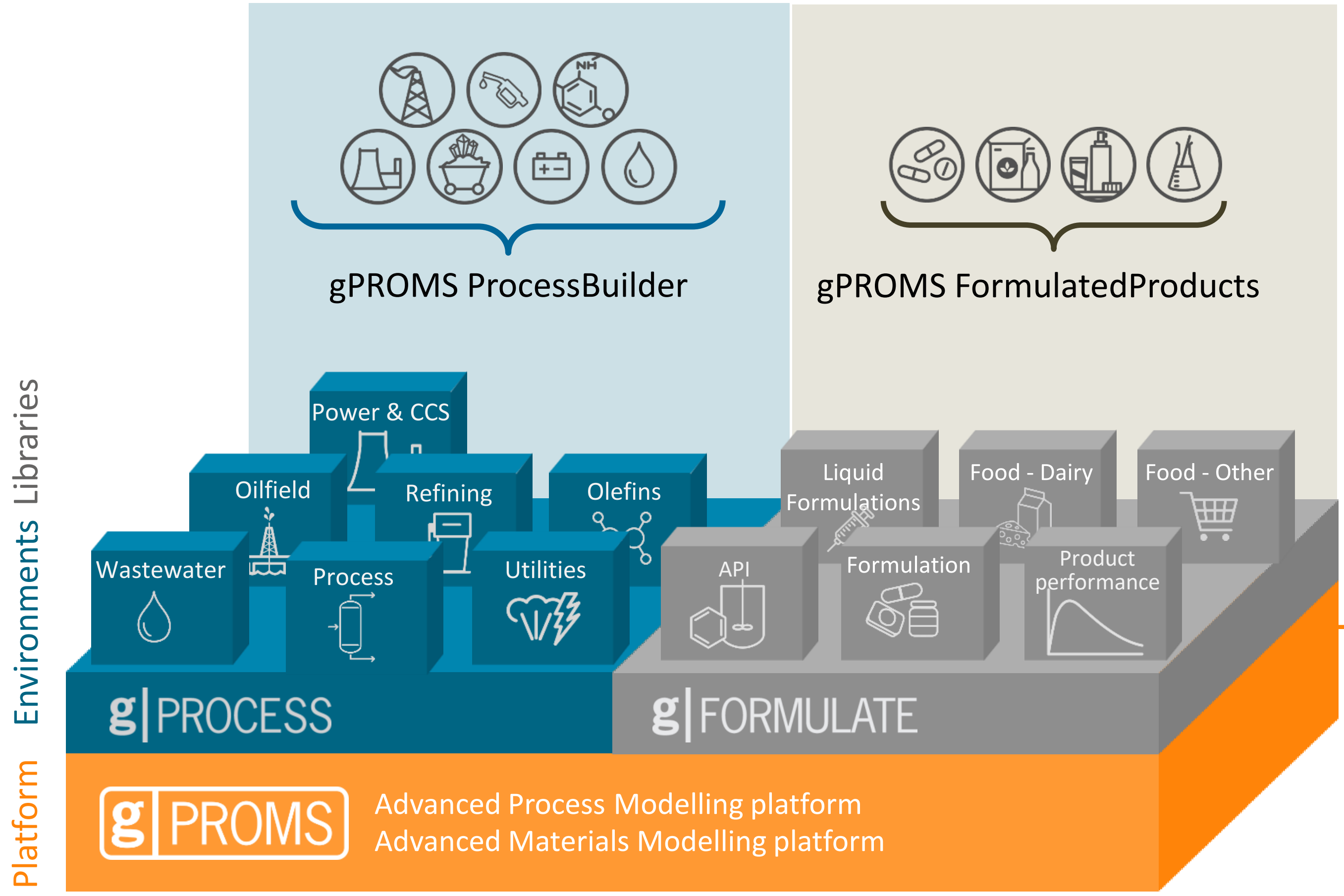
Molecular & ionic species

Complex species & mixtures

Gas, liquid, solid phases

Phase & reaction equilibrium

Enabling platform - gPROMS



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Model libraries in gPROMS FormulatedProducts

g|FORMULATE

Active Ingredient Manufacture

- Membrane separation
- Heat treatment
- Evaporation
- Solar pond operations
- Well-mixed crystallizer
- CSTR
- AFD
- PFR
- VL & VLL Flash
- Plug flow crystallizer
- Wet mill
- Distillation
- Extraction
- Pressure filter
- Centr. filter
- nD pop balance crystallization framework

Formulation Manufacture

- Feeder
- Dry mill
- Fluid-bed drying
- Tablet press
- Roller compactor
- Jet mill
- Conveying
- Agglomerator
- Spray drying
- Tablet coater
- High shear wet granulator
- Twin screw granulator
- Continuous blenders
- Fluid-bed granulation
- Hot melt extruder
- Film coater
- 2D pop balance granulation framework
- Lyophilization
- Bin flow / segregation

Product Performance

- In-vitro dissolution and precipitation
- Oral absorption in GI tract
- Pharmacokinetics
- Solid form stability
- Parenteral stability

g|PROMS

- Properties DB
- Data import and processing
- Global Sensitivity Analysis
- Parallelisation of GSA and PE
- Multizonal (gFP:CFD)
- Multizonal (gFP:DEM)
- External model validation
- Extension of gSAFT databank

g|WAPPs

g|OES

Available in gPROMS FormulatedProducts 1.2

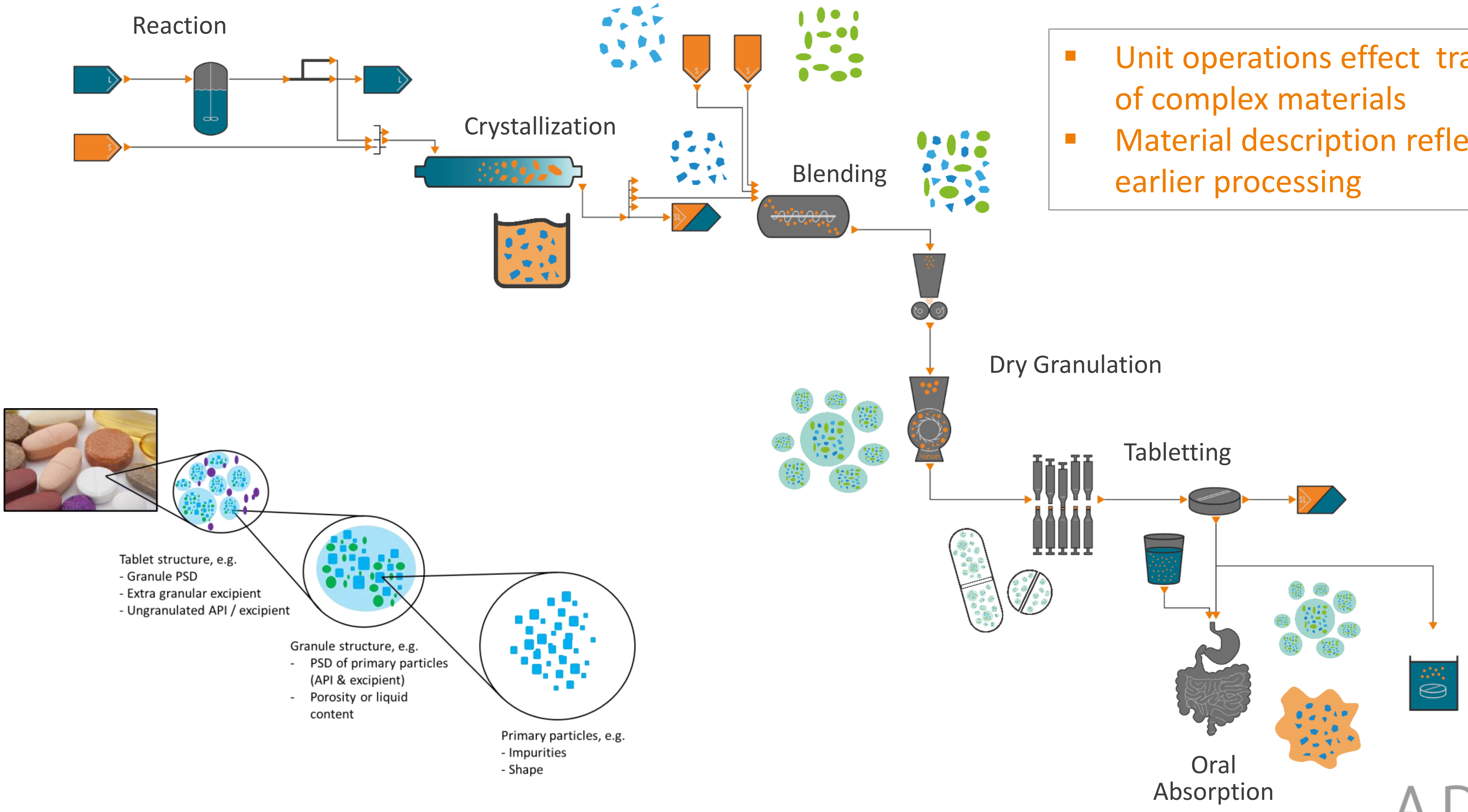
Introduced with gPROMS FormulatedProducts 1.3

On roadmap

ADDOPT

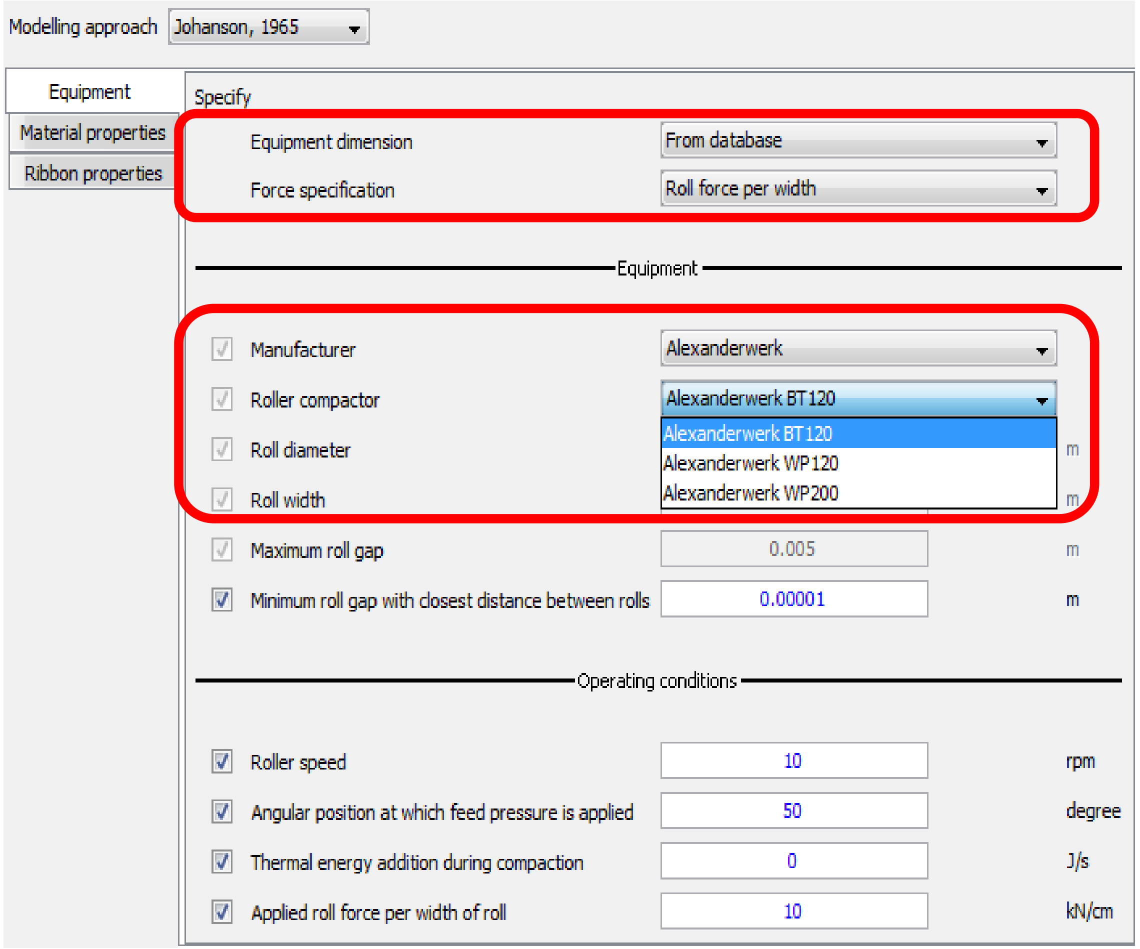
Tracking material structure evolution across the system

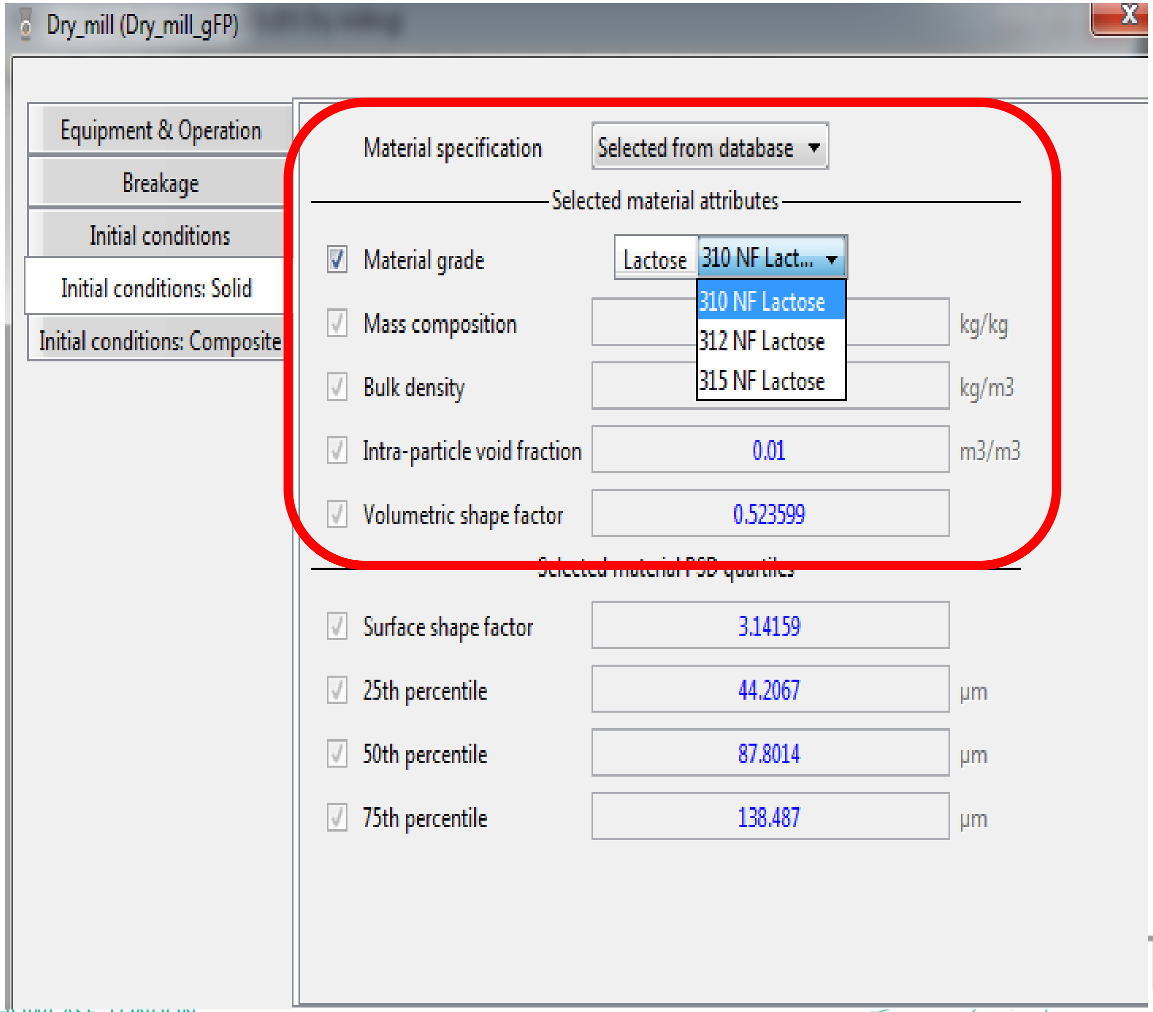
- Unit operations effect transformations of complex materials
- Material description reflects earlier processing



Properties and equipment databases

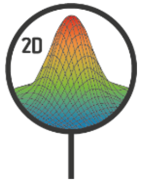
- Flexible database structure compatible with
  - PSE provided databases

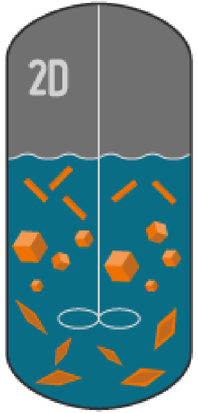




Example of models developed in ADDoPT using the latest science & workflows

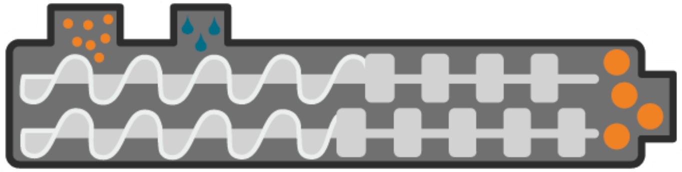
Ability to model the particle size and shape evolution during crystallization processes supported by new Morphological Crystallizer and Morphological PSD sensor models





Twin screw granulation - case study with AZ establishes **model validation workflows and requirements, value proposition**

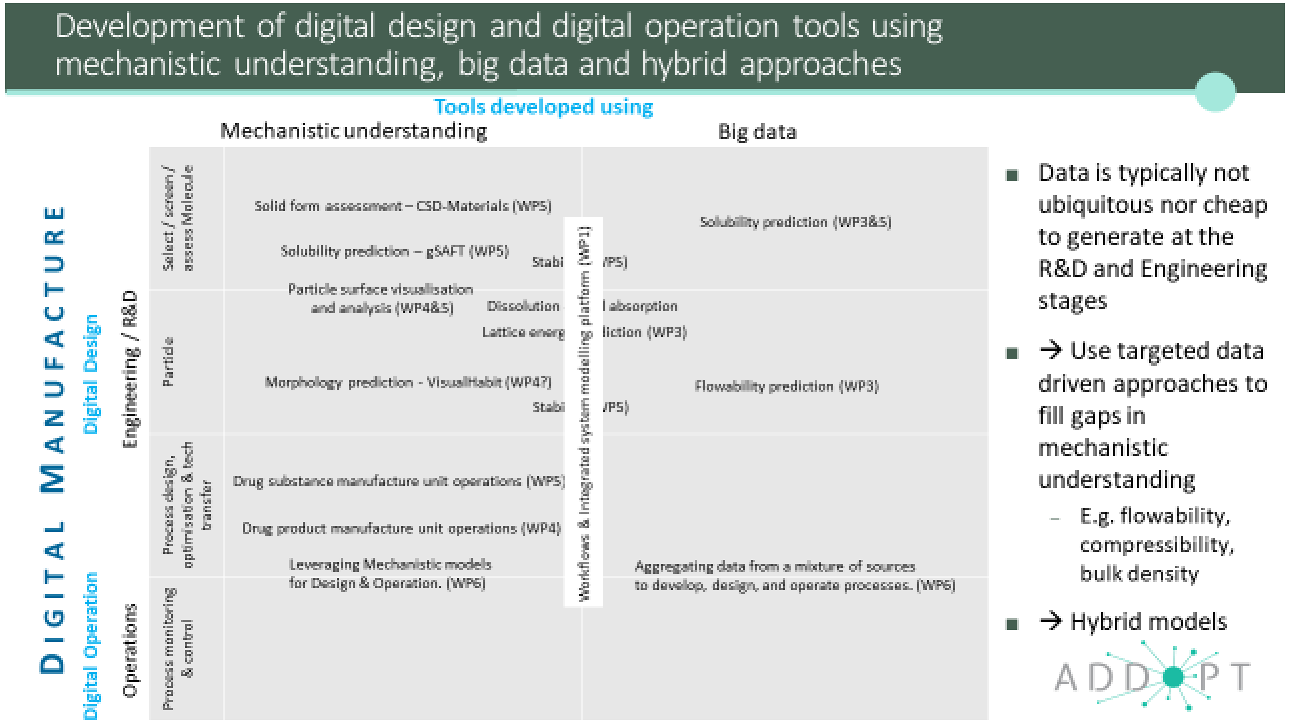
- Perform fewer, more targeted experiments.
- Determine optimal screw configuration for desired granule PSD.



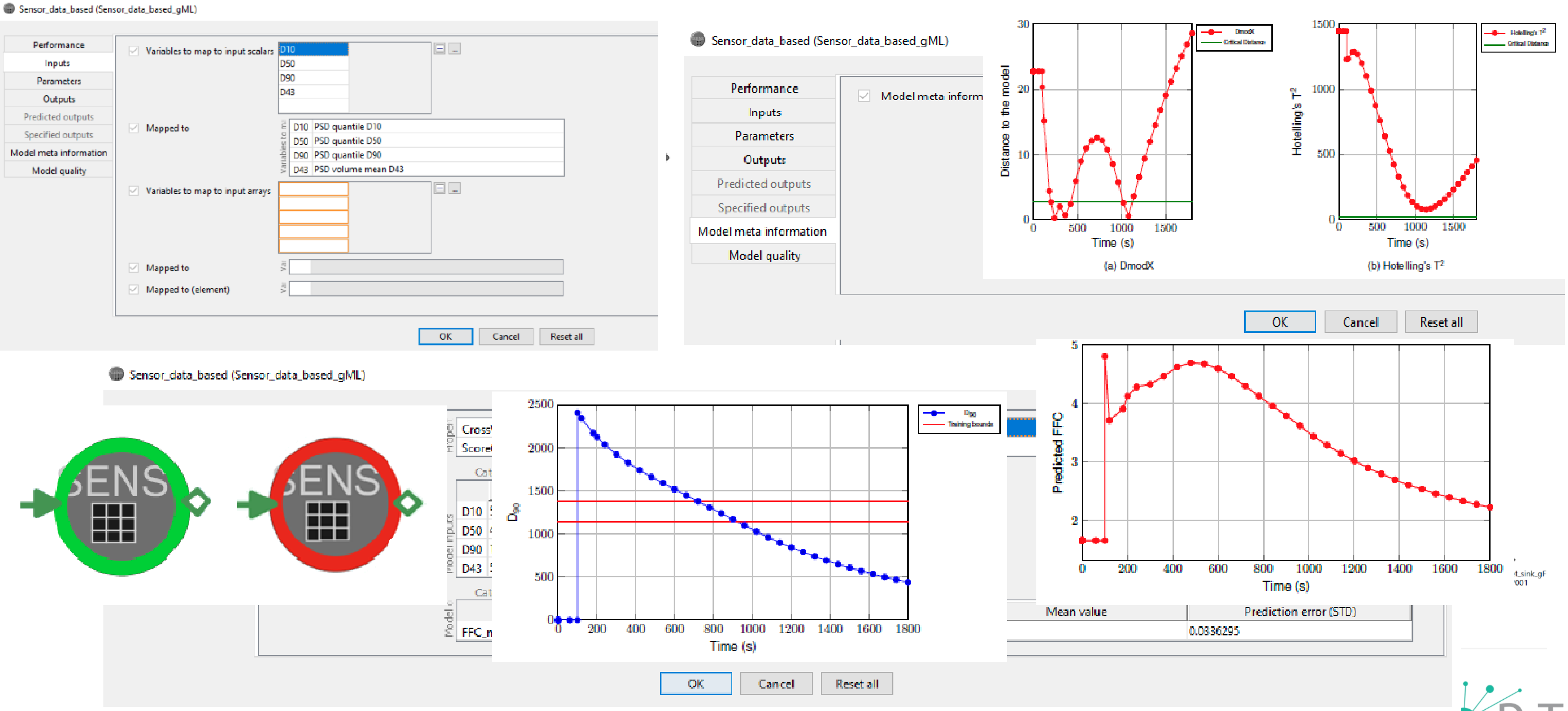
Models from academia and industry implemented and applied using new framework, establishing workflows complimentary to existing or challenging current practice

Hybrid modelling

- Combining mechanistic and data driven models
- Rationale for this approach outlined earlier today

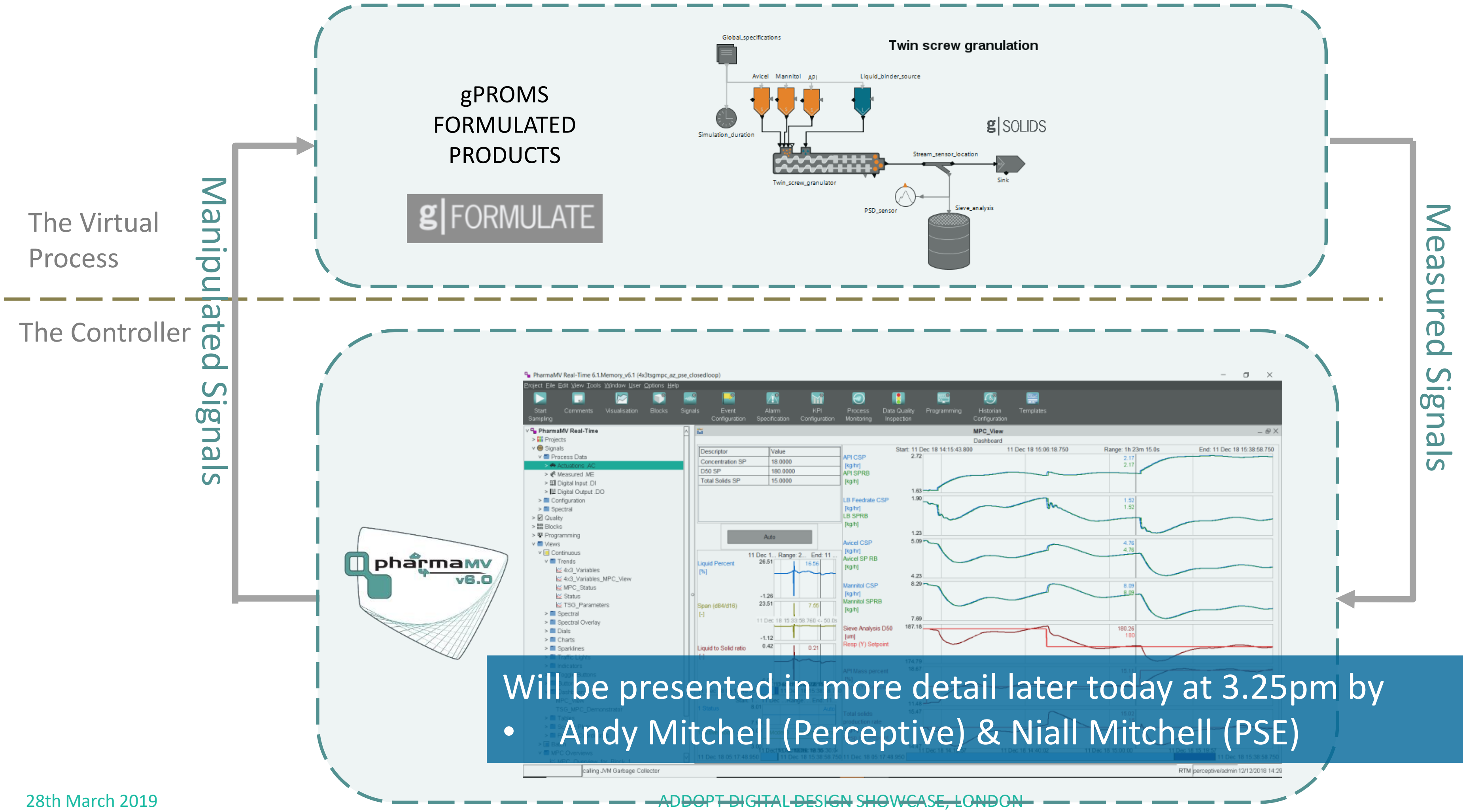


An interface for hybrid data-driven & mechanistic models



PharmaMV integration

Integration of gPROMS FormulatedProducts and PharmaMV



Will be presented in more detail later today at 3.25pm by

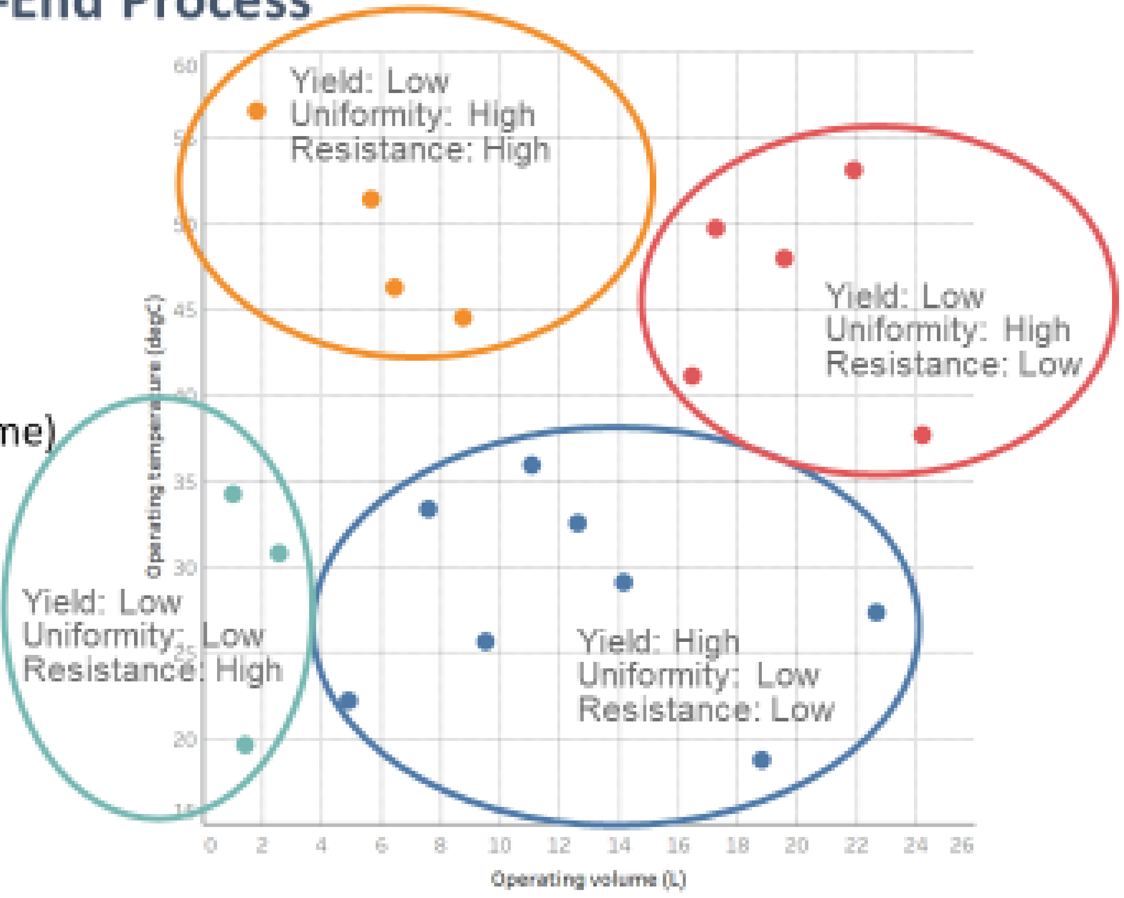
- Andy Mitchell (Perceptive) & Niall Mitchell (PSE)

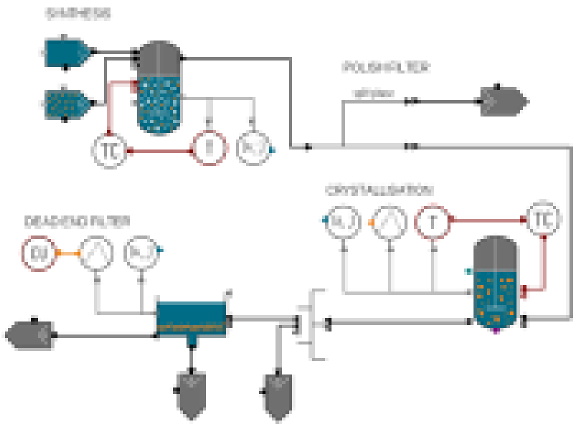
Applying the gPROMS FormulatedProducts systems framework
CMAC Digital Design example

CMAC A Design Tool for End-to-End Process

Multi unit operation and objective design space

- Using validated model to explore design space
- Linking operations to see the impact between processes
- Limit operating space by considering quality (content uniformity), manufacturing (filtration time) and economic (yield)
- 11.6 days (only experiment run time), 250 kg experimental vs 4 hr simulations



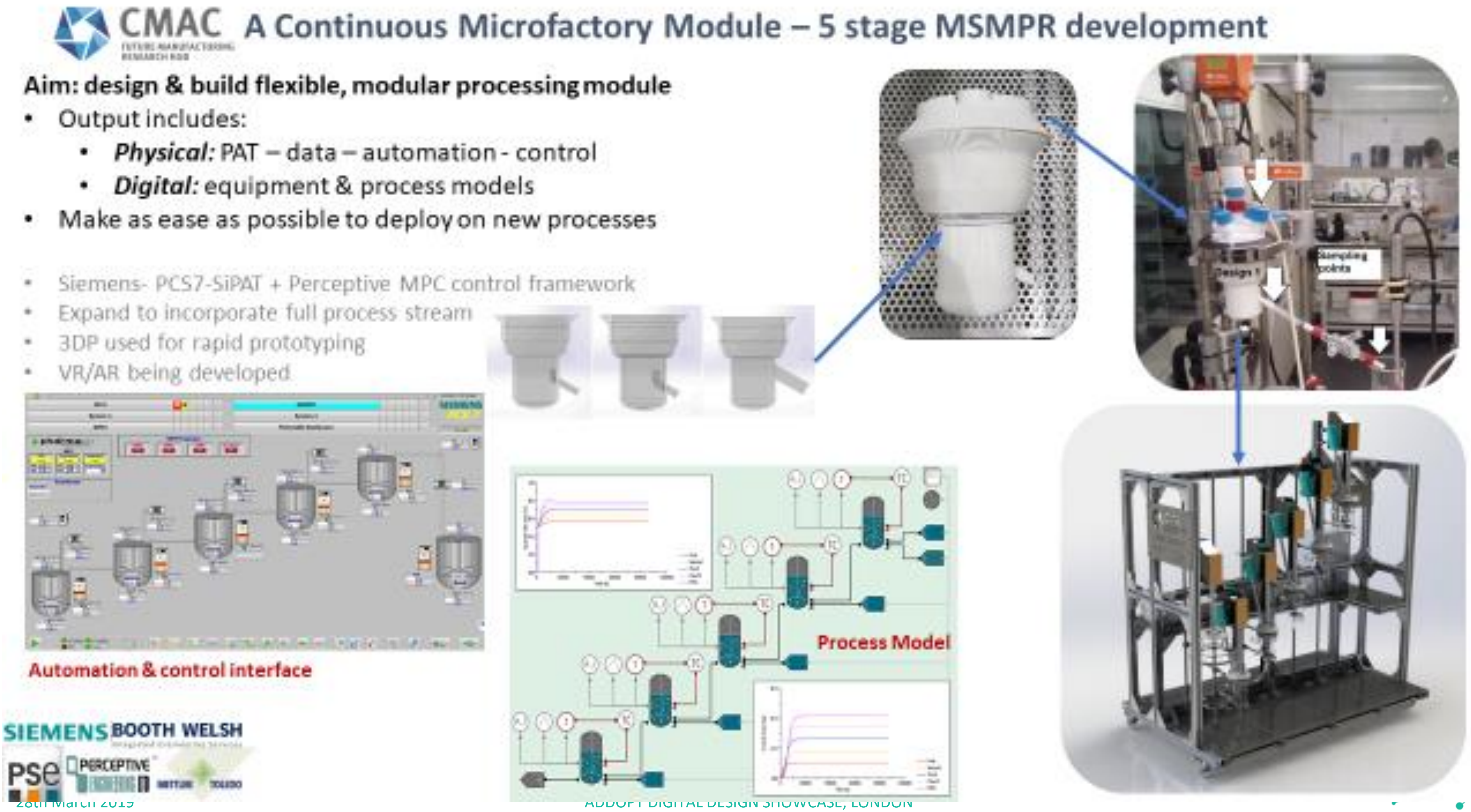


EPSRC

Applied also to

- RTD across mulitple unit ops &
- Effect of Disturbances

Applying the gPROMS FormulatedProducts systems framework CMAC Digital Design and Digital Operation example



Further case studies


Mechanistic Modelling of Powder Feeding

Drivers

Approach

A Process Model for Twin Screw Granulation

Using models to optimise implementation of new technology platforms

A cutting-edge modelling approach can dramatically reduce experimental burden without sacrificing process understanding

Drivers

Twin screw granulation offers a flexible and effective continuous formulation route, but the near-infinite potential variations in screw elements and set-up that provide such useful configurability also make it highly challenging to cover all the options in a solely practically-based approach to platform optimisation.

The purpose of this case study was to see to what extent modelling could be used to reduce the number of practical trials needed without sacrificing the amount of process understanding obtainable across the full range of design space. A lower experimental burden (cost of materials and time in experimental design, execution and analysis) equates to increased efficiency in development and cost reduction.

Approach

An early version of an advanced mechanistic model using a population balance based approach to describe the complex set of simultaneous rate processes occurring within a twin screw granulator was implemented within a worksheet environment by PSE for evaluation to see how close it was to utility as part of a normal AZ development workflow.

Key Features

- An advanced mechanistic model has been evaluated in a flowsheet environment facilitating rapid, virtual experimentation in place of expensive and time-consuming practical experimentation
- A sufficiently predictive model was achieved using just 5 trials instead of 24
- The study demonstrates the potential for early, virtual process platform optimisation

The tool was used on a retrospective example to assess the potential for reduced experimental requirements. Whilst the case study was fairly limited in scope - a practical design space including two screw configurations was used to predict behaviour in a third – a sufficiently successful demonstration would be a significant step forward and a good indicator of future utility in further process understanding work.

An ADDoPT Case Study featuring collaboration between PSE and AZ

Talks today from

- Next: Marta Moreno-Benito, Pfizer, *Solid Drug Product and Process Design using Multi-Scale Interconnected Flowsheet Modelling and Global System Analysis*

- 4.05pm: Gavin Reynolds, AZ, *Application of hybrid models for Advanced Process Control of a Twin Screw Wet Granulation Process*

Demo booths in lobby:

- Morphological crystallizer, jet mill, integrated system

Anyone from PSE…

Summary

A mechanistic model-based digital design framework, gPROMS FormulatedProducts, has been created for

- Horizontal integration: Manufacture → Product Performance (breaking down silos)
- Vertical integration: Length Scales & Design → Operation

Enabling the creation of a Digital Twin of both complex formulated products and their manufacturing processes

These Digital Twins can be used for virtual DoEs (design space exploration), tech transfer and as a basis for Digital Operation

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