



ADVANCED DIGITAL DESIGN OF PHARMACEUTICAL THERAPEUTICS

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

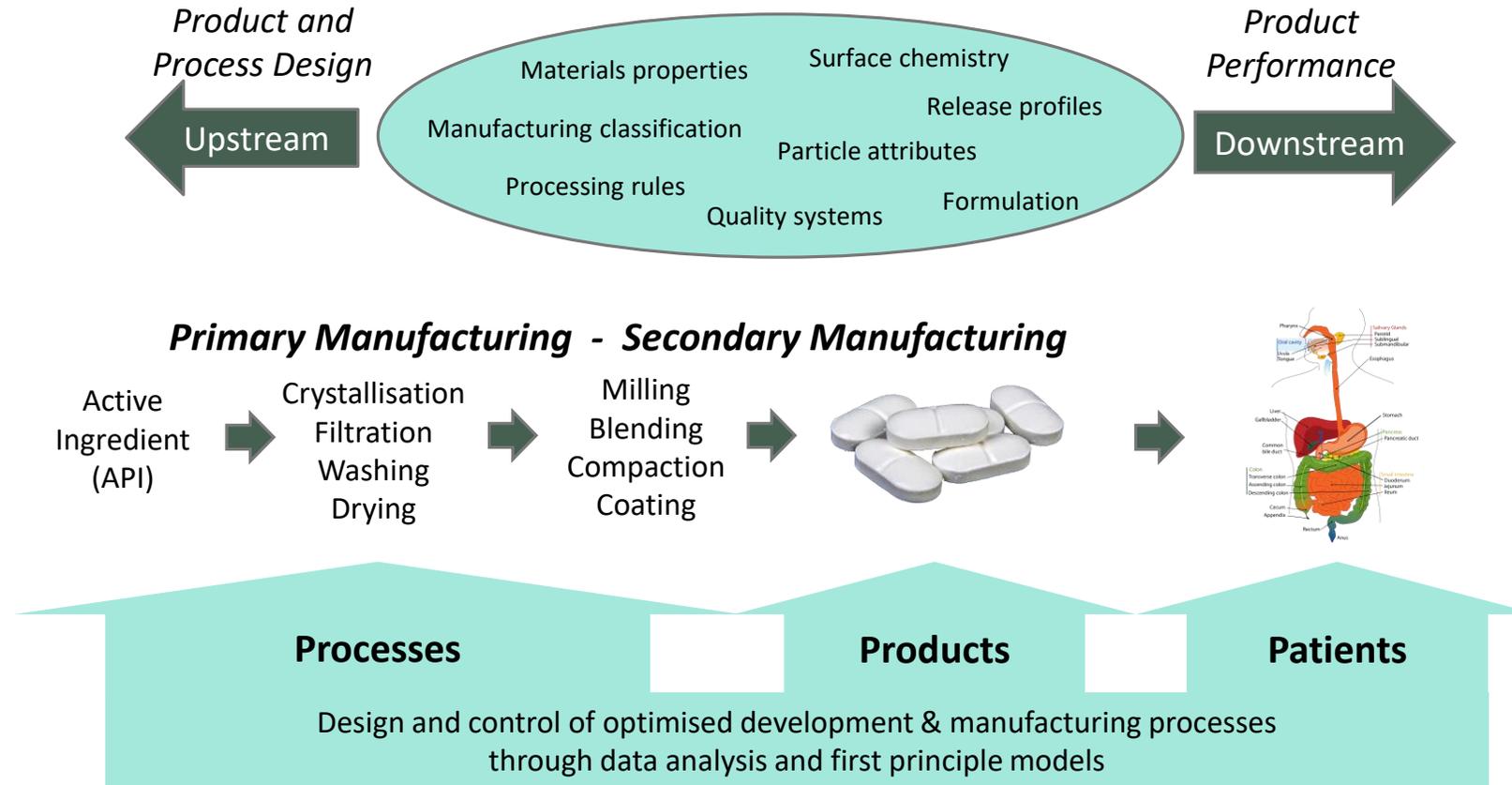
David Slade (Process Systems Enterprise)

Alastair Florence (CMAC, University of Strathclyde)



ADDoPT scope – a reminder

Improve / optimise for impact



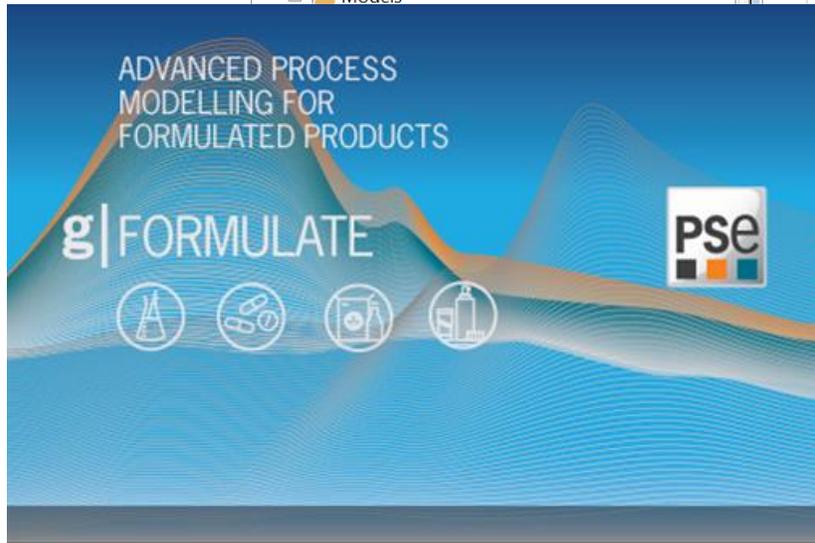
- A systems-based approach to pharmaceuticals
- **Horizontal integration: Manufacture → Product Performance (breaking down silos)**
- **Vertical integration: Length Scales & Design → Operation**

gPROMS FormulatedProducts – a new PSE product enabled by ADDoPT

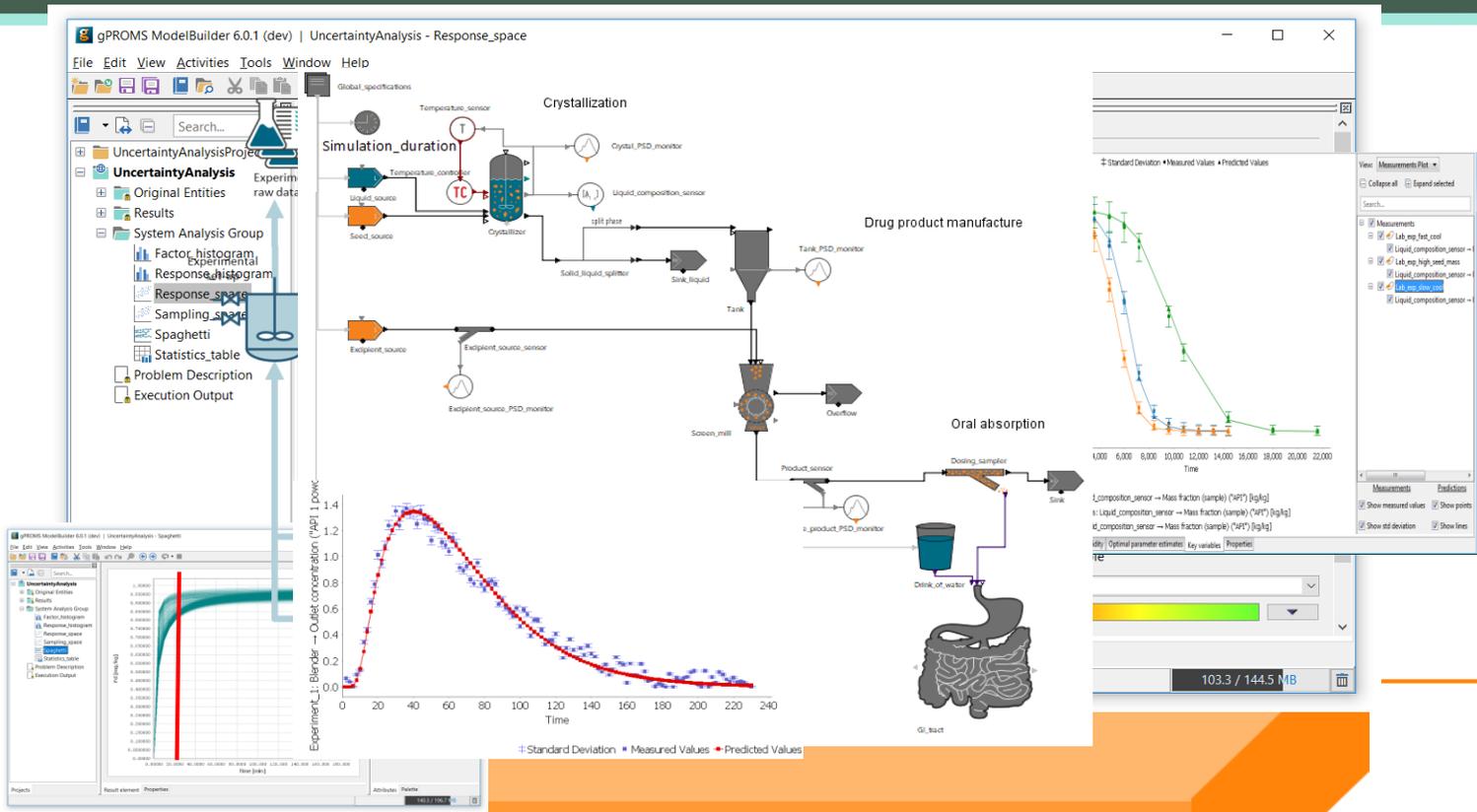
The screenshot displays the gPROMS FormulatedProducts 1.3.0 software interface. The main window shows a detailed process flowchart for a Fenofibrate case study, including stages like Crystallization, Drug product manufacture, and Oral absorption. The flowchart includes various sensors and control points. To the right of the flowchart are three plots: 'PSDs upstream of mill', 'PSDs sampled for oral absorption', and 'Dissolution and absorption'. The 'Dissolution and absorption' plot shows the mass fraction of API dissolved, permeated, or transferred over time. Below the plots is a table with the following data:

Fraction of total API dosed dissolved, permeated or transferred	kg/kg
Fraction of total API dosed absorbed	kg/kg

The left sidebar shows a library of projects, with 'Fenofibrate case study' selected. The bottom of the interface has a menu bar with options like 'Interface language', 'Topology', 'gPROMS language', and 'Properties'. A 'Palette' window on the right lists components like '2 gCRYSTAL Crystallizers - Plug Flow', '2 gCRYSTAL Crystallizers - Well Mixed', '2 gCRYSTAL Wet Mills', and '2 gCRYSTAL Filters'.



Enabling platform - gPROMS



Platform



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

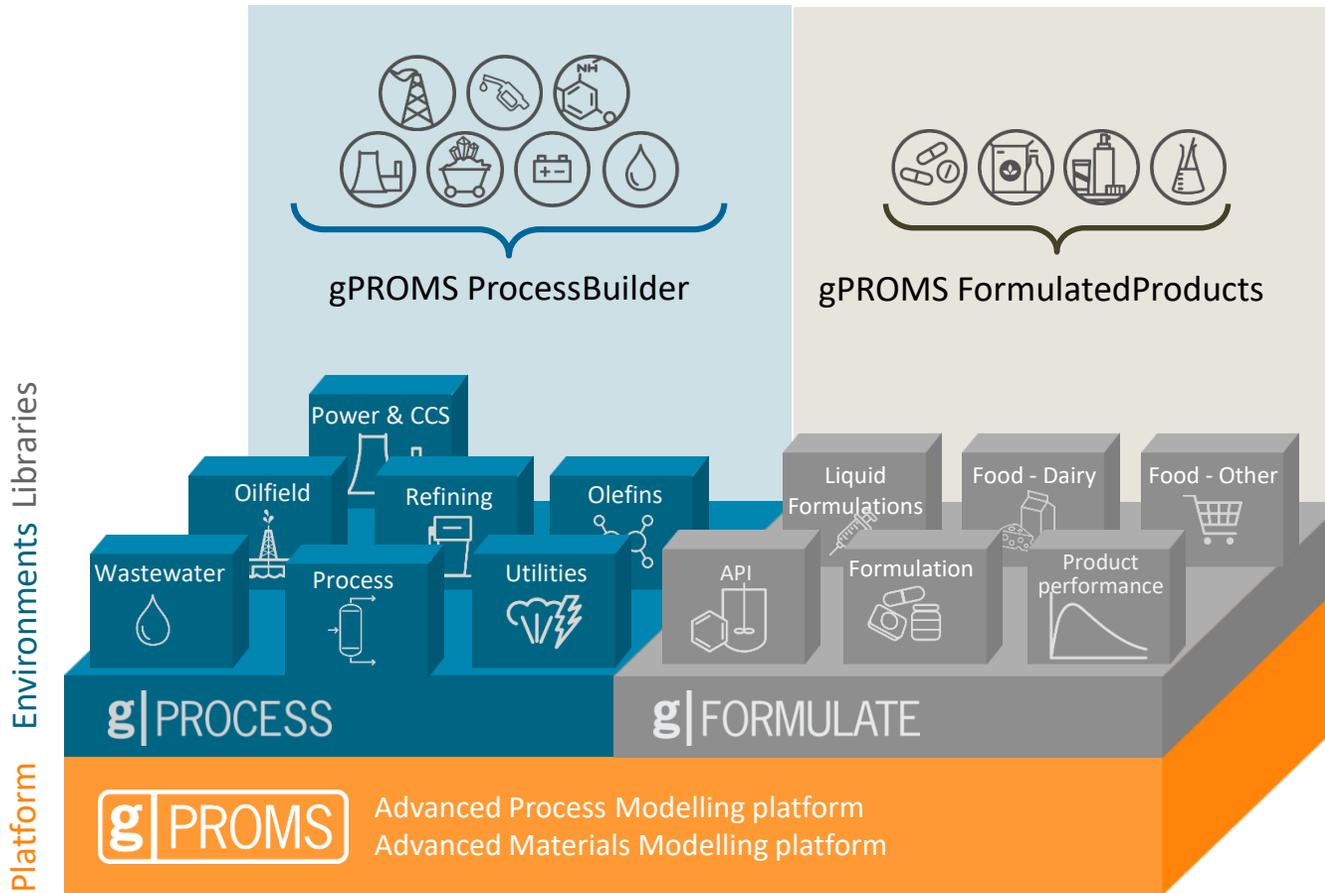
Gas, liquid, solid phases

Phase & reaction equilibrium



Enabling platform - gPROMS

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Platform functionality

Process modelling

- Equation-oriented solution power
- Custom model construction
- Steady-state and dynamic simulation
- Powerful optimisation, including mixed-integer
- Advanced parameter estimation
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Materials modelling

- Molecular & ionic species
- Complex species & mixtures
- Gas, liquid, solid phases
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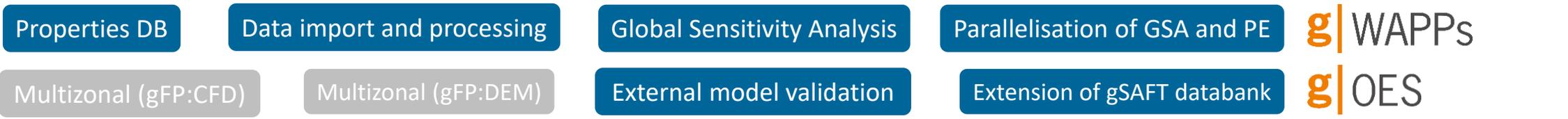
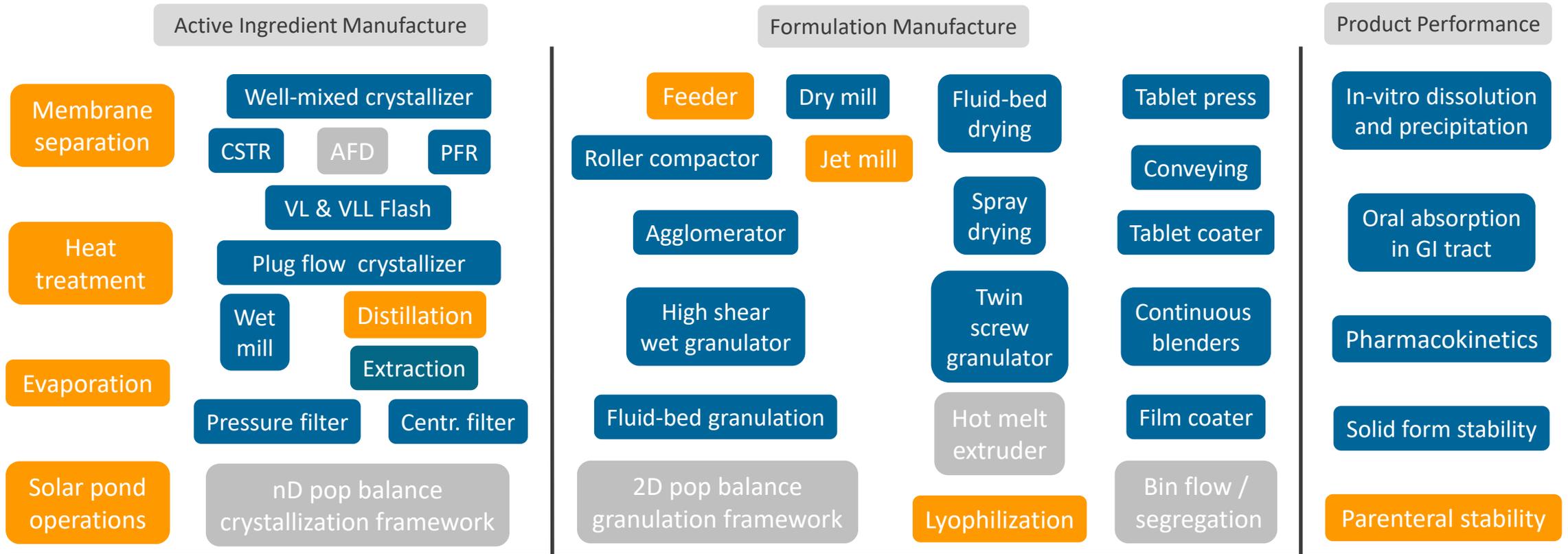
A single powerful software platform

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

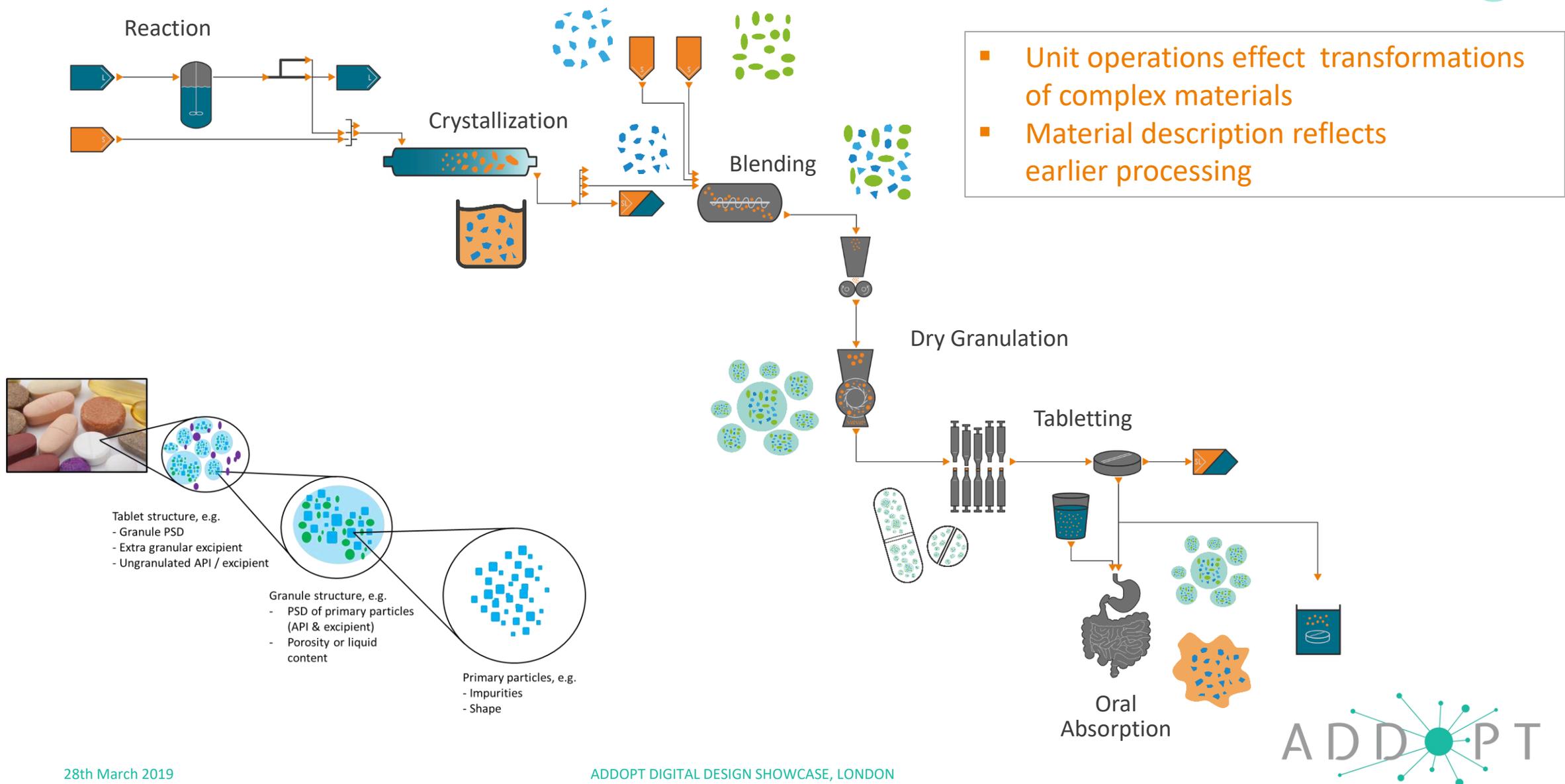
Model libraries in gPROMS FormulatedProducts

g|FORMULATE

g|PROMS



Tracking material structure evolution across the system



Properties and equipment databases

- Flexible database structure compatible with
 - PSE provided databases

Modelling approach: Johanson, 1965

Equipment	Specify
Material properties	Equipment dimension: From database
Ribbon properties	Force specification: Roll force per width

Equipment

<input checked="" type="checkbox"/> Manufacturer	Alexanderwerk
<input checked="" type="checkbox"/> Roller compactor	Alexanderwerk BT120
<input checked="" type="checkbox"/> Roll diameter	Alexanderwerk BT120 m
<input checked="" type="checkbox"/> Roll width	Alexanderwerk WP200 m
<input checked="" type="checkbox"/> Maximum roll gap	0.005 m
<input checked="" type="checkbox"/> Minimum roll gap with closest distance between rolls	0.00001 m

Operating conditions

<input checked="" type="checkbox"/> Roller speed	10 rpm
<input checked="" type="checkbox"/> Angular position at which feed pressure is applied	50 degree
<input checked="" type="checkbox"/> Thermal energy addition during compaction	0 J/s
<input checked="" type="checkbox"/> Applied roll force per width of roll	10 kN/cm

Dry_mill (Dry_mill_gFP)

Equipment & Operation	Material specification: Selected from database
Breakage	
Initial conditions	
Initial conditions: Solid	
Initial conditions: Composite	

Selected material attributes

<input checked="" type="checkbox"/> Material grade	Lactose 310 NF Lact...
<input checked="" type="checkbox"/> Mass composition	310 NF Lactose kg/kg
<input checked="" type="checkbox"/> Bulk density	312 NF Lactose kg/m3
<input checked="" type="checkbox"/> Intra-particle void fraction	0.01 m3/m3
<input checked="" type="checkbox"/> Volumetric shape factor	0.523599

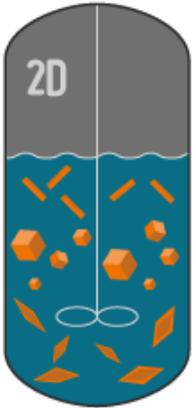
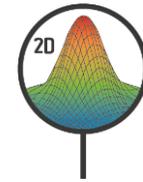
Selected material PSD quantiles

<input checked="" type="checkbox"/> Surface shape factor	3.14159
<input checked="" type="checkbox"/> 25th percentile	44.2067 μm
<input checked="" type="checkbox"/> 50th percentile	87.8014 μm
<input checked="" type="checkbox"/> 75th percentile	138.487 μm

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

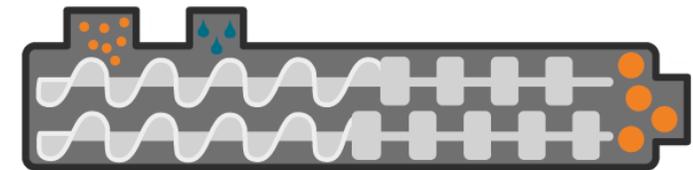
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Ability to model the particle size and shape evolution during crystallization processes supported by new Morphological Crystallizer and Morphological PSD sensor models



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

Development of digital design and digital operation tools using mechanistic understanding, big data and hybrid approaches

		Tools developed using	
		Mechanistic understanding	Big data
DIGITAL MANUFACTURE Digital Design Engineering / R&D	Select / screen / assess Molecule	Solid form assessment – CSD-Materials (WP5) Solubility prediction – gSAFT (WP5) Particle surface visualisation and analysis (WP4&5) Morphology prediction - VisualHabit (WP47)	Solubility prediction (WP3&5) Stability (WP5) Dissolution / absorption / elution (WP3) Flowability prediction (WP3)
	Particle	Dissolution / Lattice energy Stability (WP5)	
	Process design, optimisation & tech transfer	Drug substance manufacture unit operations (WP5) Drug product manufacture unit operations (WP4) Leveraging Mechanistic models for Design & Operation. (WP6)	Aggregating data from a mixture of sources to develop, design, and operate processes. (WP6)
	Operations Process monitoring & control		

- Data is typically not ubiquitous nor cheap to generate at the R&D and Engineering stages
- → Use targeted data driven approaches to fill gaps in mechanistic understanding
 - E.g. flowability, compressibility, bulk density

■ → Hybrid models




An interface for hybrid data-driven & mechanistic models

Sensor_data_based (Sensor_data_based_gML)

Performance

Inputs

Parameters

Outputs

Predicted outputs

Specified outputs

Model meta information

Model quality

Variables to map to input scalars

D10
D50
D90
D43

Mapped to

Variables to m: D10 PSD quantile D10
D50 PSD quantile D50
D90 PSD quantile D90
D43 PSD volume mean D43

Variables to map to input arrays

Mapped to

Mapped to (element)

OK Cancel Reset all

Sensor_data_based (Sensor_data_based_gML)

Performance

Inputs

Parameters

Outputs

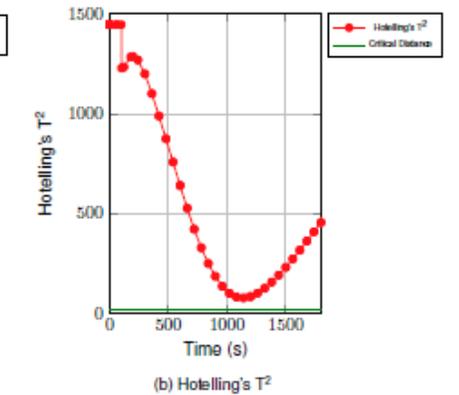
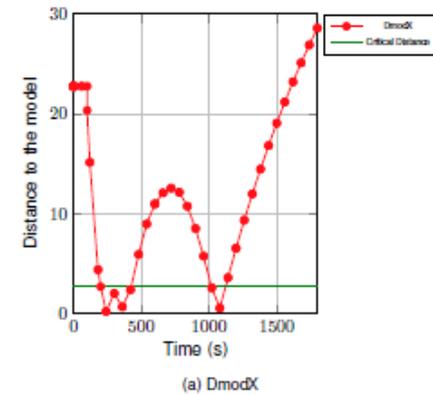
Predicted outputs

Specified outputs

Model meta information

Model quality

Model meta inform



OK Cancel Reset all

Sensor_data_based (Sensor_data_based_gML)

Model inputs

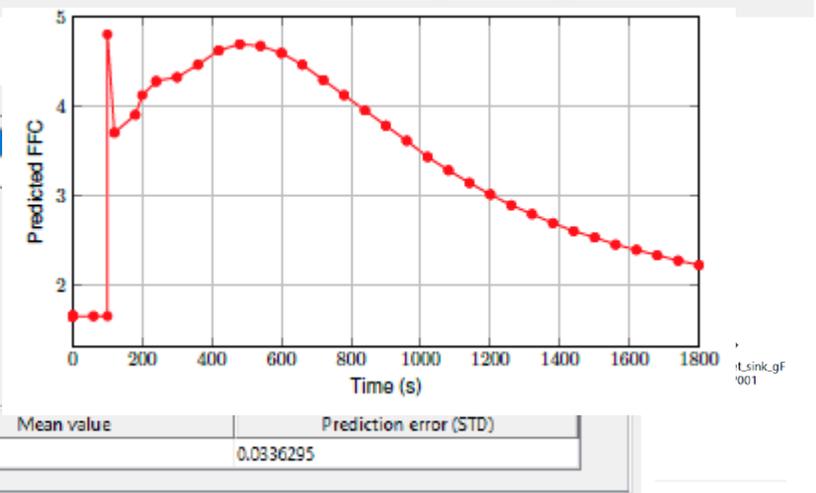
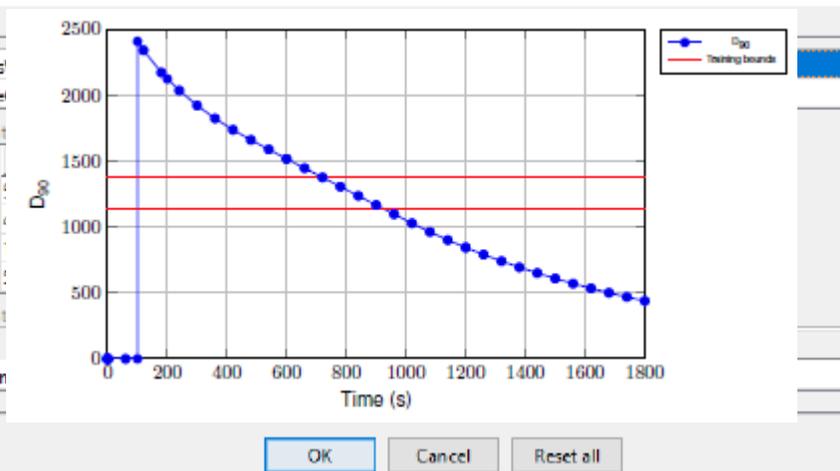
D10
D50
D90
D43

Model outputs

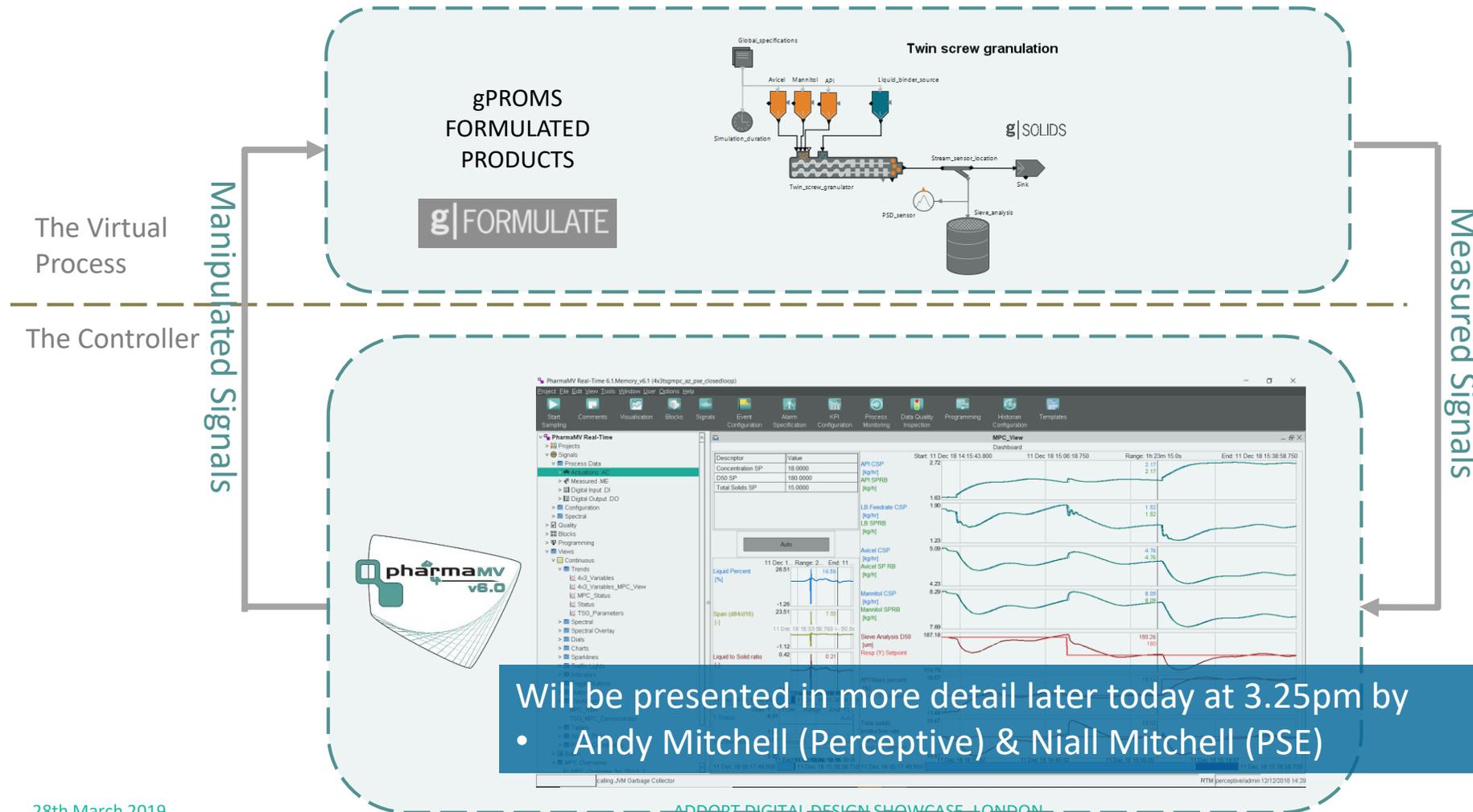
Cross Score

Cat

FFC_n



Integration of gPROMS Formulated Products and PharmaMV



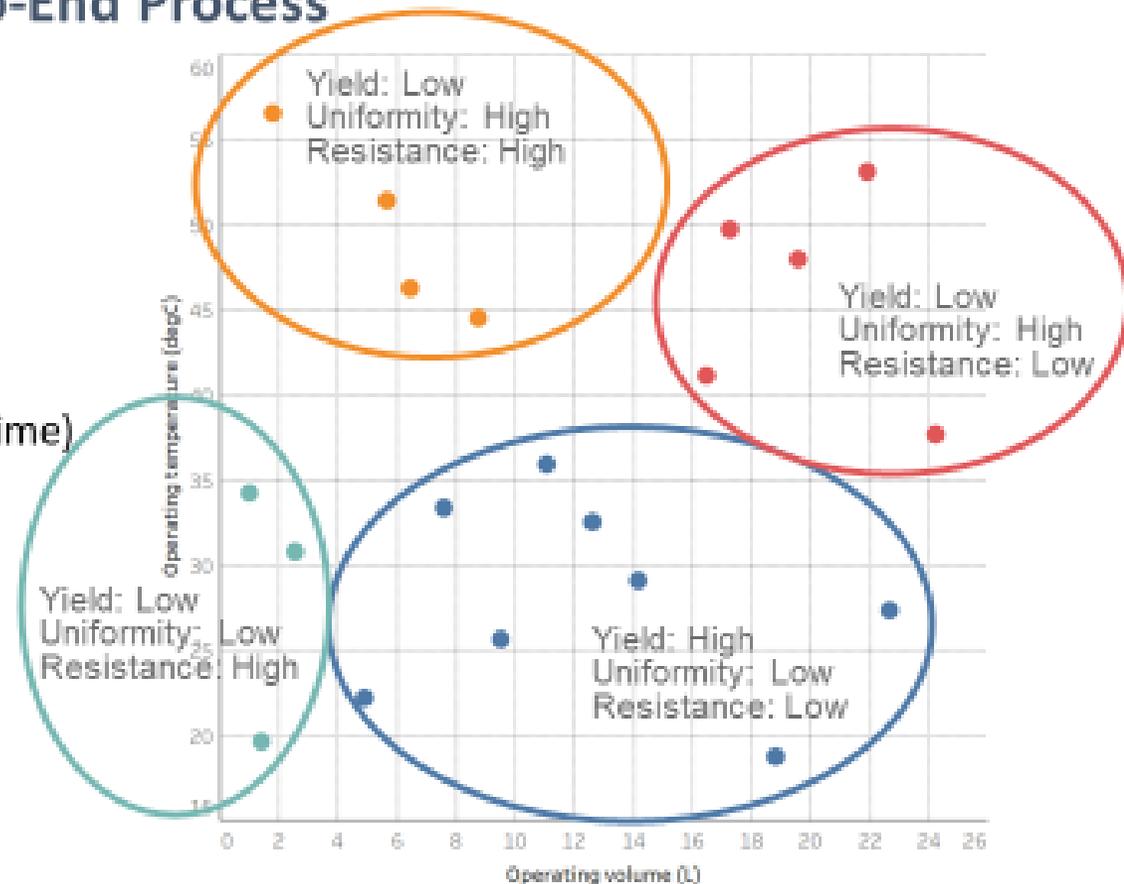
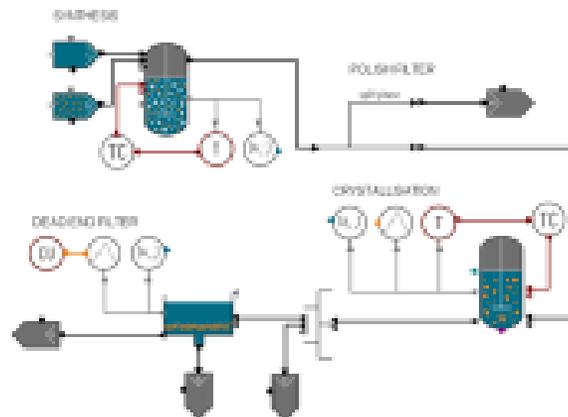
Applying the gPROMS Formulated Products systems framework

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



Applied also to

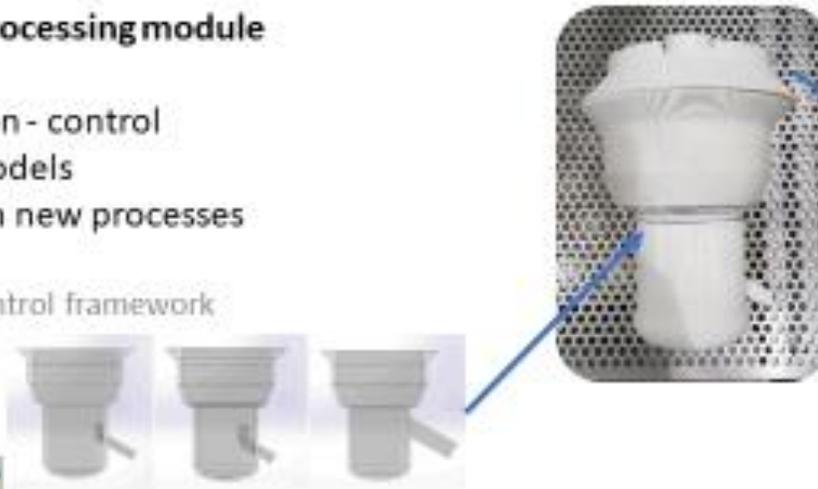
- RTD across multiple unit ops &
- Effect of Disturbances

Applying the gPROMS Formulated Products systems framework CMAC Digital Design and Digital Operation example

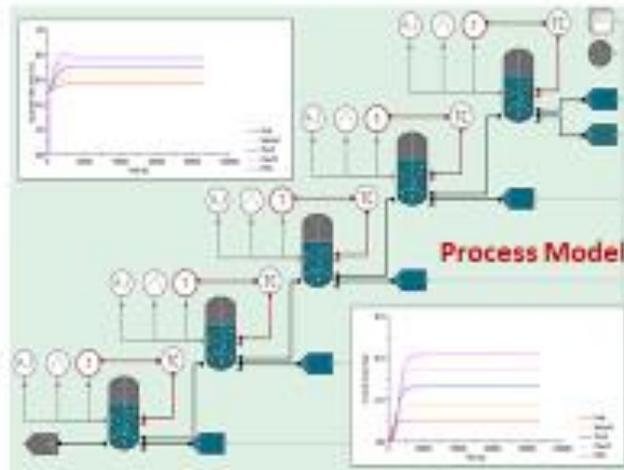
CMAC A Continuous Microfactory Module – 5 stage MSMPR development

Aim: design & build flexible, modular processing module

- Output includes:
 - **Physical:** PAT – data – automation - control
 - **Digital:** equipment & process models
- Make as ease as possible to deploy on new processes
- Siemens- PCS7-SiPAT + Perceptive MPC control framework
- Expand to incorporate full process stream
- 3DP used for rapid prototyping
- VR/AR being developed



Automation & control interface



Mechanistic Modelling of Powder Feeding

Predicting flow performance

A Process Model for Twin Screw Granulation

Using models to optimise implementation of new technology platforms

Drivers

Powder feeders are an integral part of pharmaceutical industry solid dose processing trains and are particularly challenging to design. Feeder performance is often less straightforward when dealing with pharmaceutical ingredients (API) due to their challenging flow properties. An accessible predictive model of performance would enhance both development and manufacture, increase speed of development, reducing costs, and improving process reliability.

Approach

A model based upon the best available public domain literature for granulation has been incorporated into a user-friendly software tool primarily focused on pharmaceutical granulation with some degree of comfort in its use by modelling specialists.

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 software environment by PSE for evaluation to see how close it was to utility as part of a normal AZ development workflow.

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

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

28th March

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...

A mechanistic model-based digital design framework, gPROMS Formulated Products, 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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