



ADVANCED PROCESS MODELLING FORUM

LONDON

20–21 APRIL 2016

gPROMS FormulatedProducts

Integrated design of formulated products & their manufacturing processes

Sean Bermingham, Head of PSE Formulated Products



A new PSE product ...

An illustration of a software interface titled "g|FORMULATE". The title is in large, white, sans-serif font. Below it, the text "ADVANCED PROCESS MODELLING" is displayed in a smaller, white, sans-serif font. The background is a blue gradient with wavy, light-grey lines. Various icons are scattered across the screen, including a person icon with "PID" text, a gear icon, a mail icon, a lock icon, a dog icon, a bottle icon, a funnel icon, and two exclamation mark icons. In the top right corner, there is a white rectangular box containing the "PSE" logo and its color-coded squares.

g|**FORMULATE**

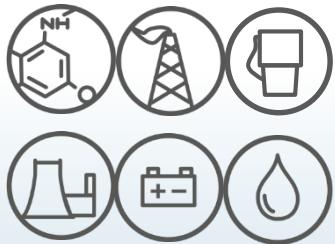
ADVANCED
PROCESS
MODELLING

PSE

... in the gPROMS Product Family



"Fluids processing world"



g|PROCESS
gPROMS
ProcessBuilder
Process MLs

g|WATER

Water MLs

g|UTILITIES

Utilities MLs

g|CCS

CCS MLs

g|POWER

Power MLs

g|OILFIELD

Oilfield MLs

"Formulated products world"

g|FORMULATE
gPROMS
FormulatedProducts



Crystallisation MLs

g|CRYSTAL

Solids MLs

g|SOLIDS

Oral absorption MLs

g|COAS

g|FLARE *

Flare &
depressurisation MLs

g|FUELCELL

Fuel cell MLs

General
mathematical
modelling

g|MODEL

gPROMS ModelBuilder
provides essentially
the full platform
functionality

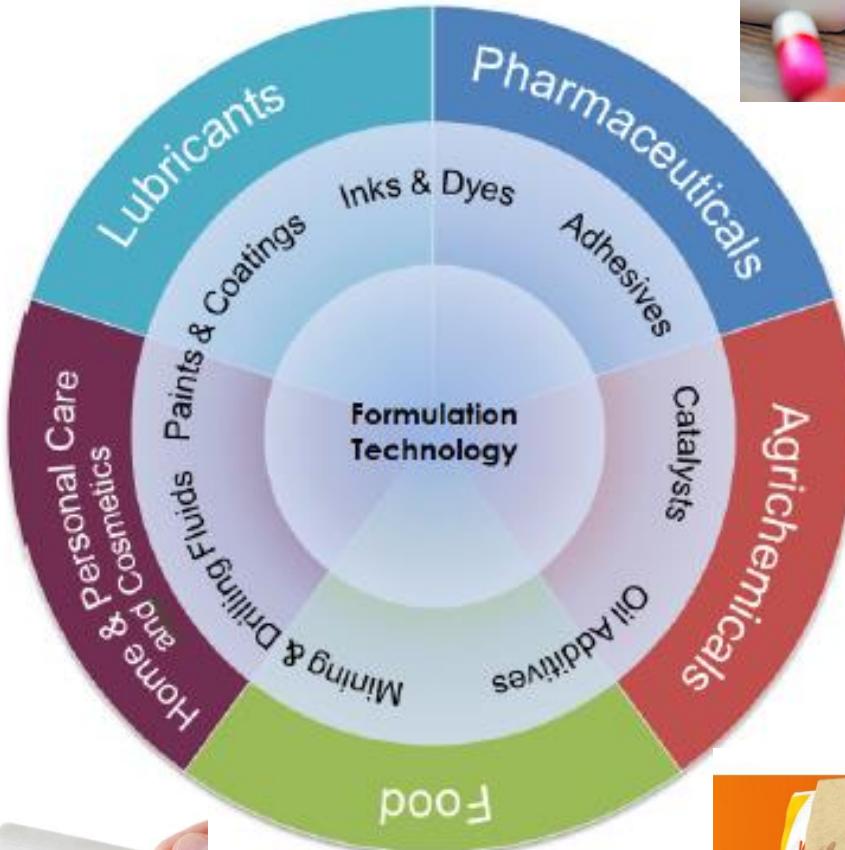
g|PROMS

The gPROMS platform
Equation-oriented modelling & solution engine

g|SAFT

* Primarily used internally by PSE for delivery of services

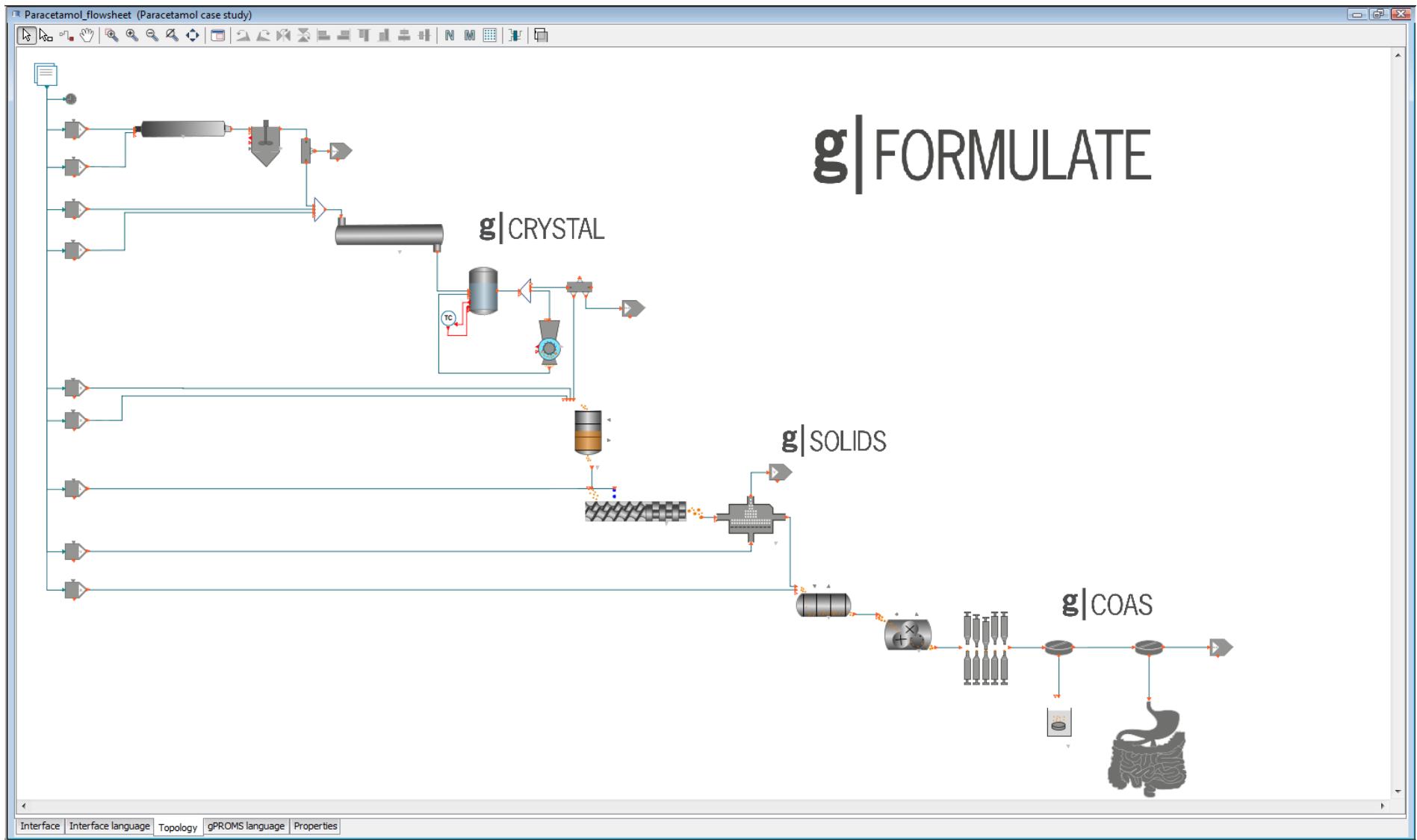
Formulated products world?



Holistic, systems-based approach to design of formulated products and their manufacturing processes



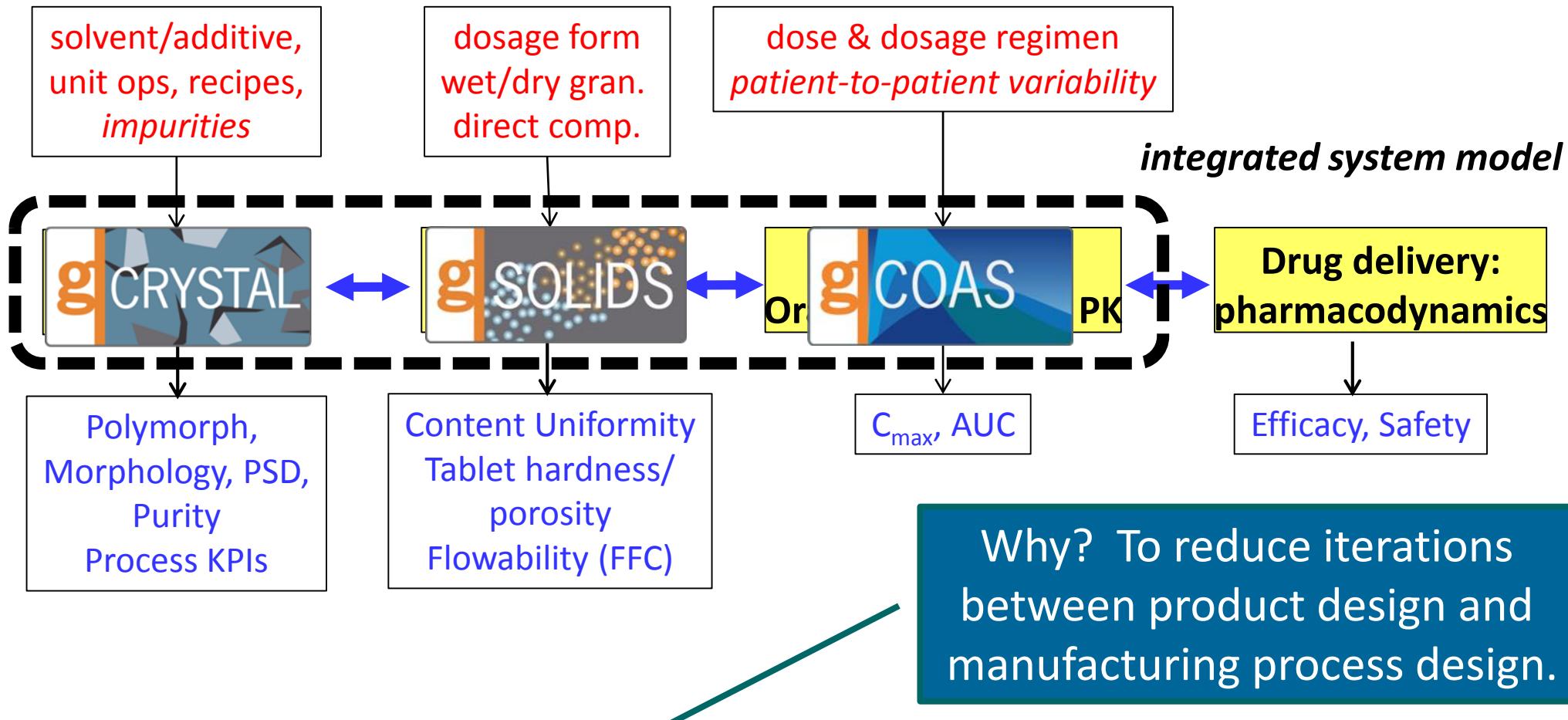
g|FORMULATE



ADVANCED PROCESS MODELLING FORUM 2016

An example of such a systems based approach

Systems-based Pharmaceutics



- Use an integrated system model to quantify effects of CPPs & disturbances on CQAs, process economics, operability, safety

Uptake of PSE's standalone mechanistic modelling tools



1.0

2.0

3.0

4.0

4.1

4.2



1.0

2.0

3.0

3.1

4.0

4.1



An increasing number of organisations are using two or more of these tools and wish to use them in an integrated manner

2011

2012

2013

2014

2015

1.0



1.3



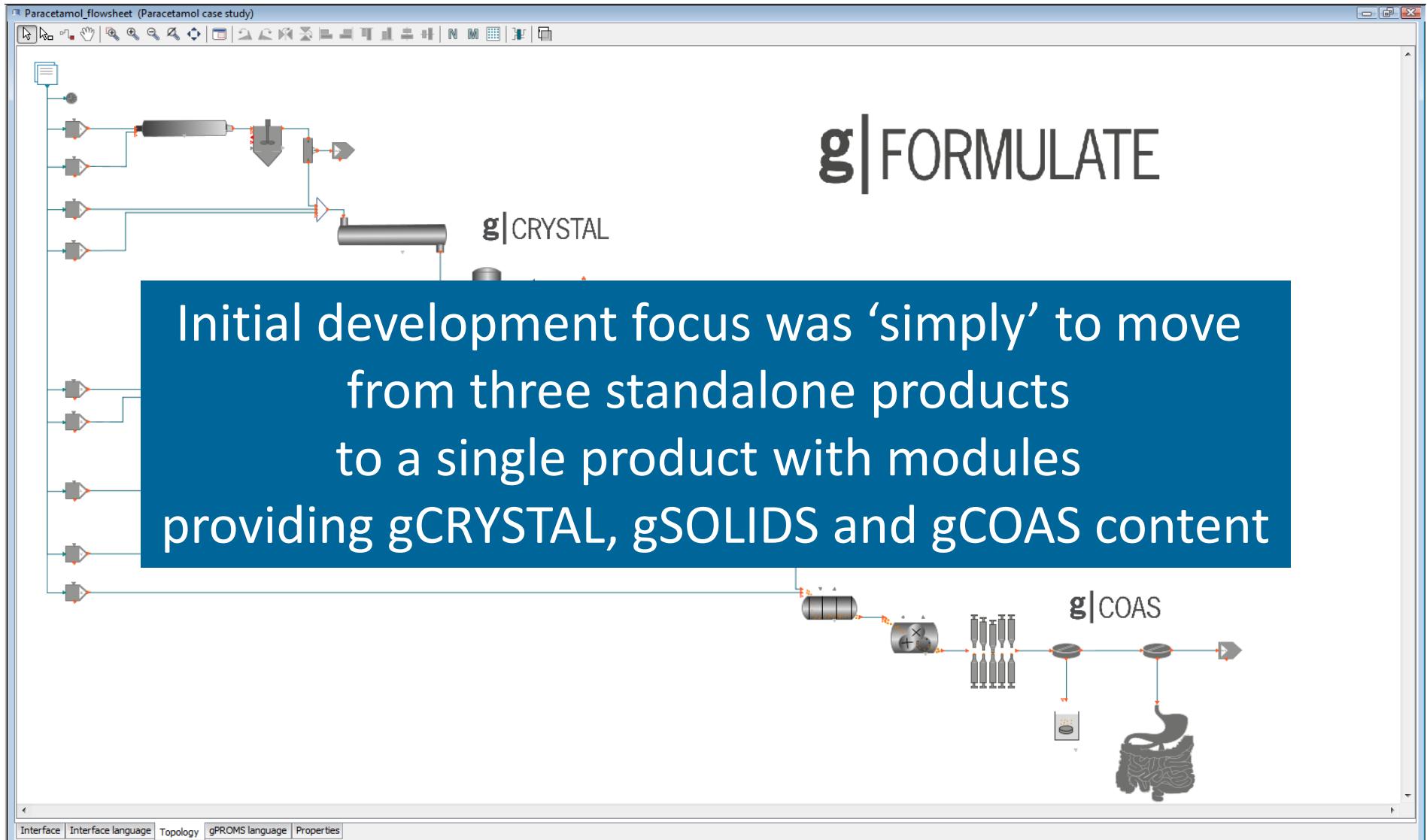
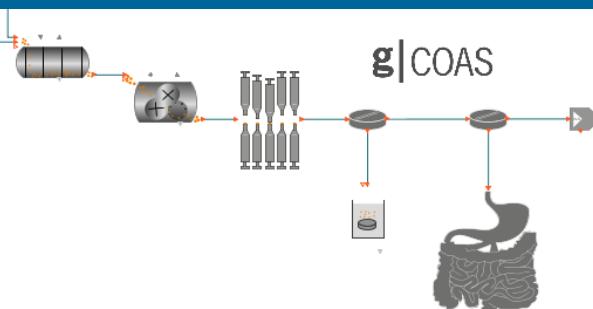
ADVANCED PROCESS MODELLING FORUM 2016

Development of this product started in 2014



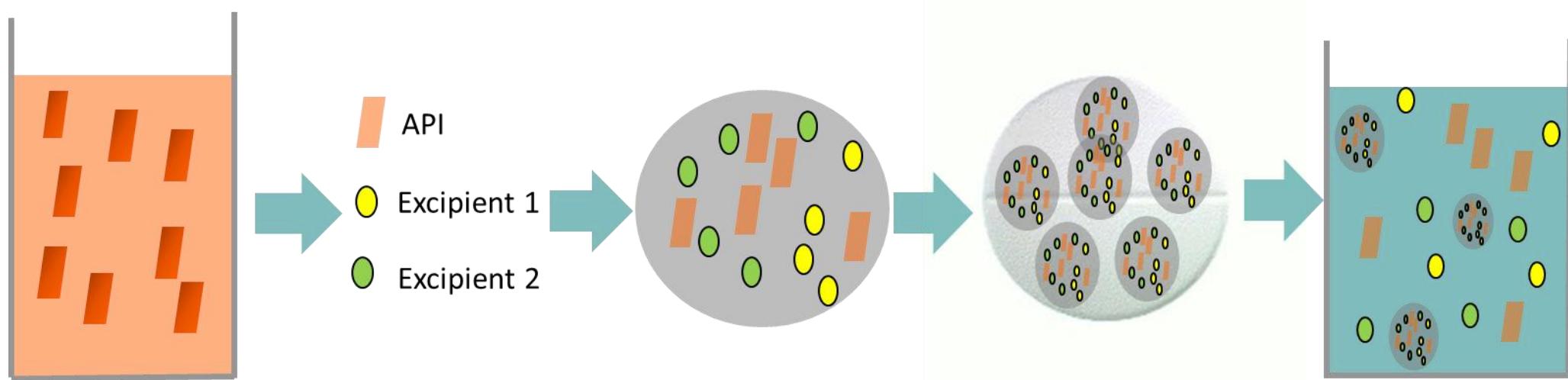
g|FORMULATE

Initial development focus was 'simply' to move from three standalone products to a single product with modules providing gCRYSTAL, gSOLIDs and gCOAS content



Introduces major architecture changes

- Superficially: connecting gCRYSTAL, gSOLIDS and gCOAS
- Internally many changes, in particular architecture to describe
 - evolution of distributed phases
 - existence of composite phases



Crystallization

Blending

Granulation

Tabletting

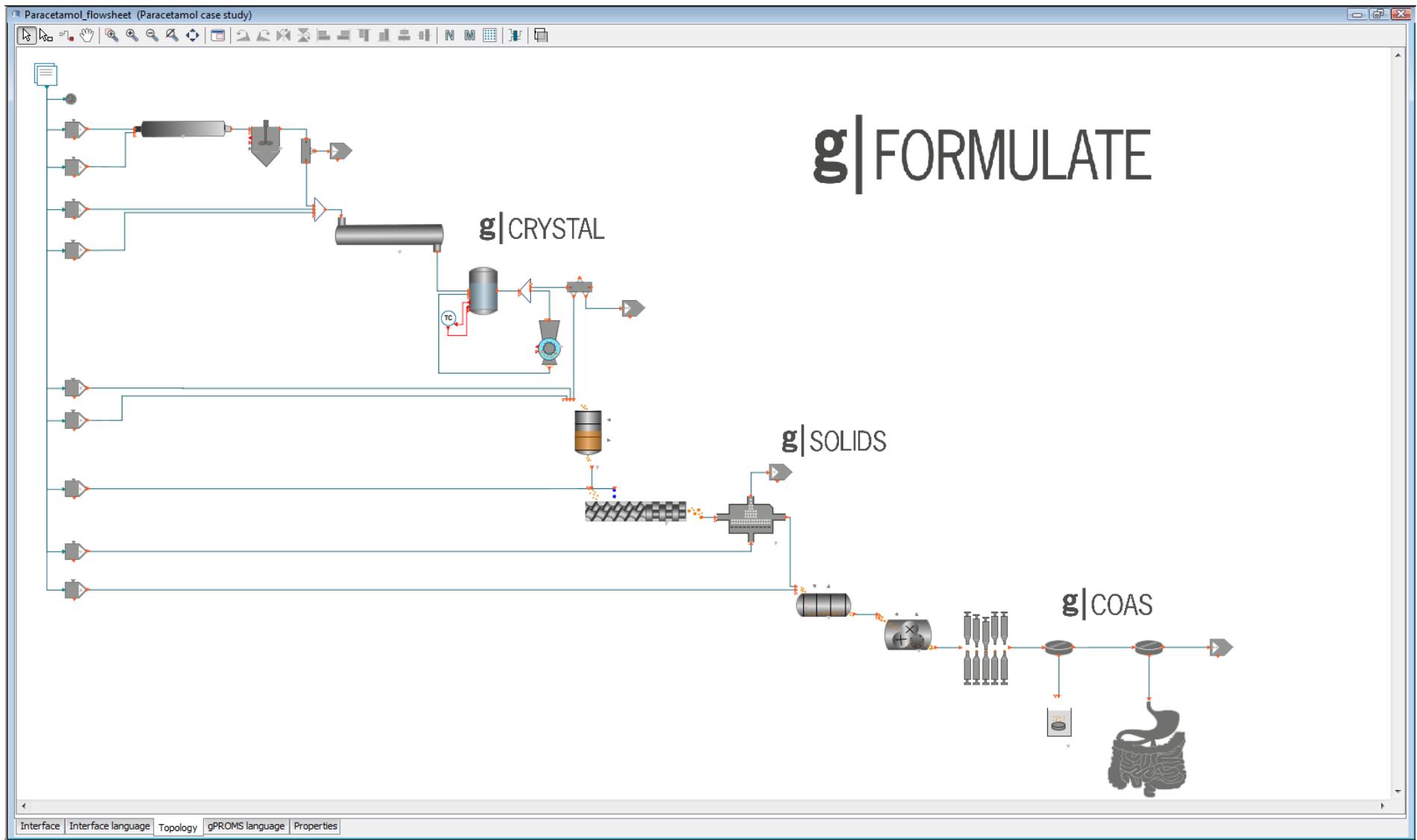
Disintegration
and dissolution

- This handling of distributed and composite phases
is not limited to solid phases

Holistic, systems-based approach to design of formulated products and their manufacturing processes

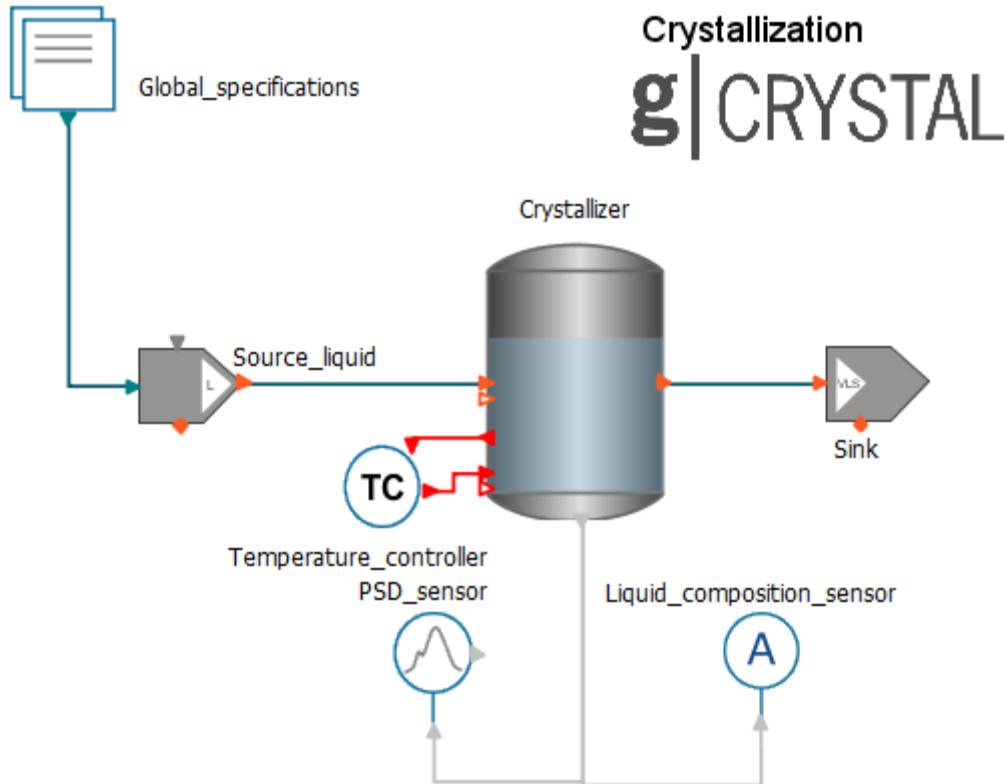


g|FORMULATE

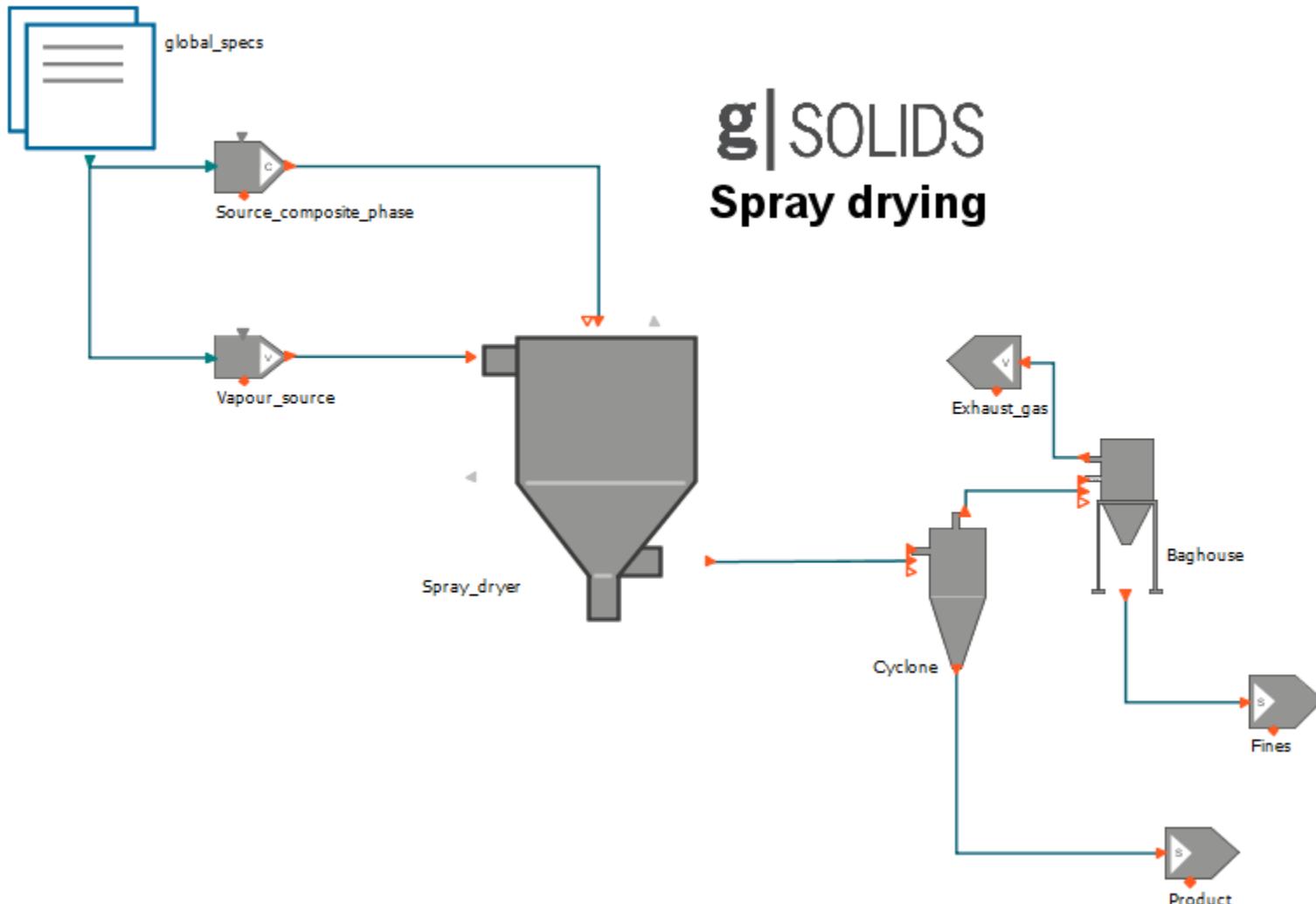


ADVANCED PROCESS MODELLING FORUM 2016

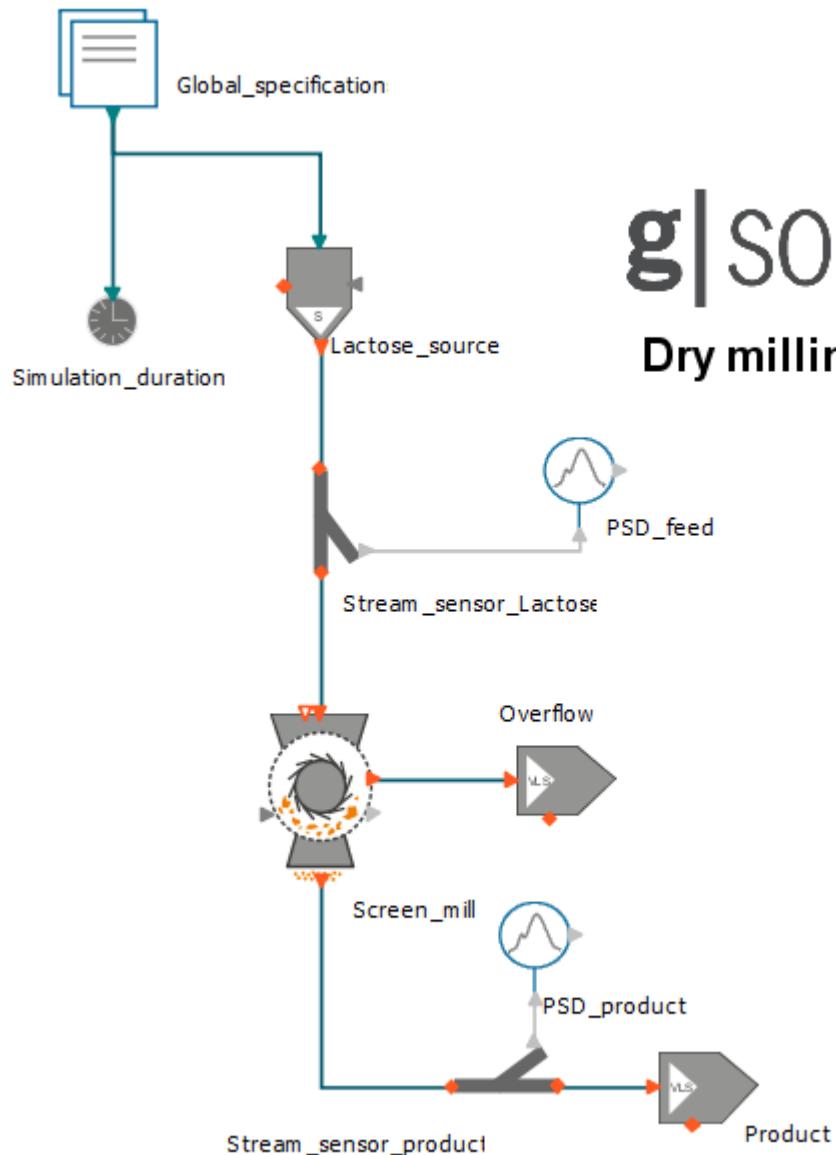
Also supports optimal design of system components



Also supports optimal design of system components

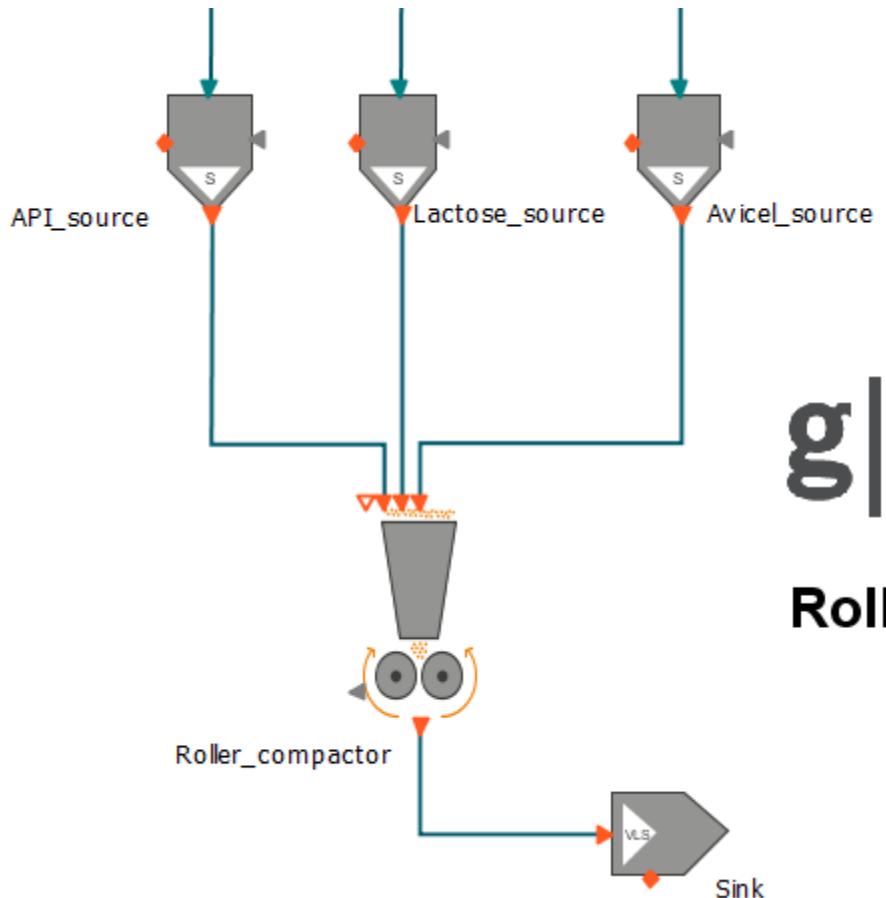


Also supports optimal design of system components



g|SOLIDS Dry milling

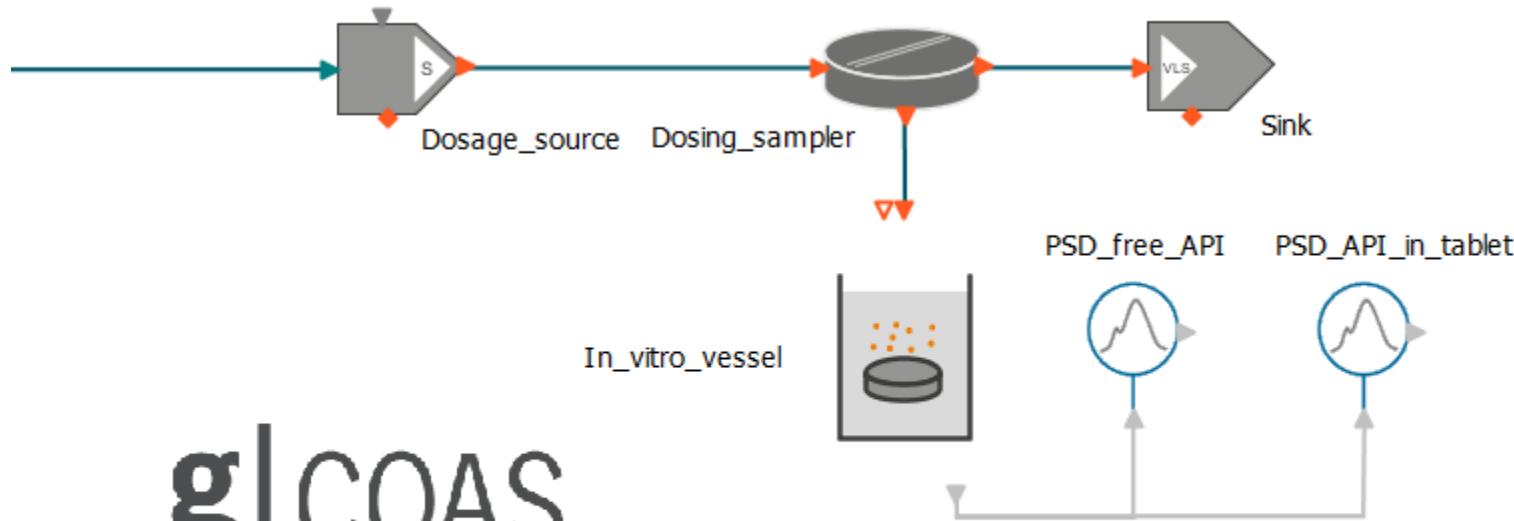
Also supports optimal design of system components



g|SOLIDS

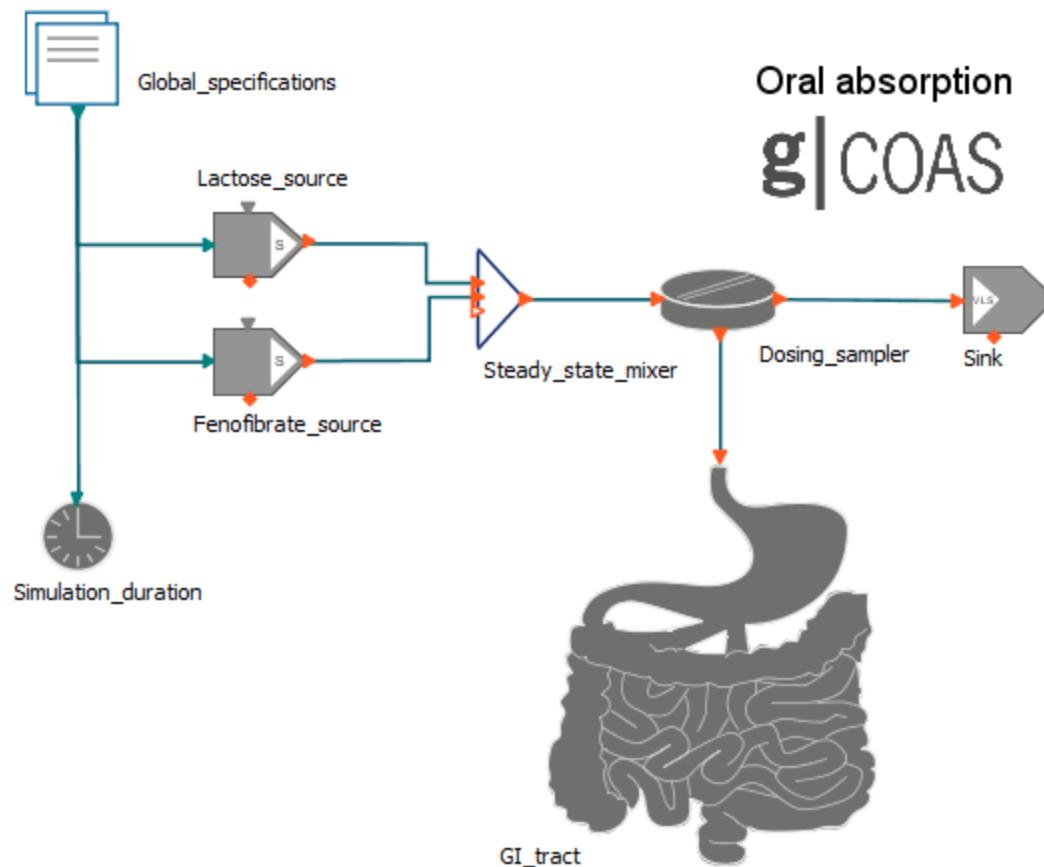
Roller compaction

Also supports optimal design of system components

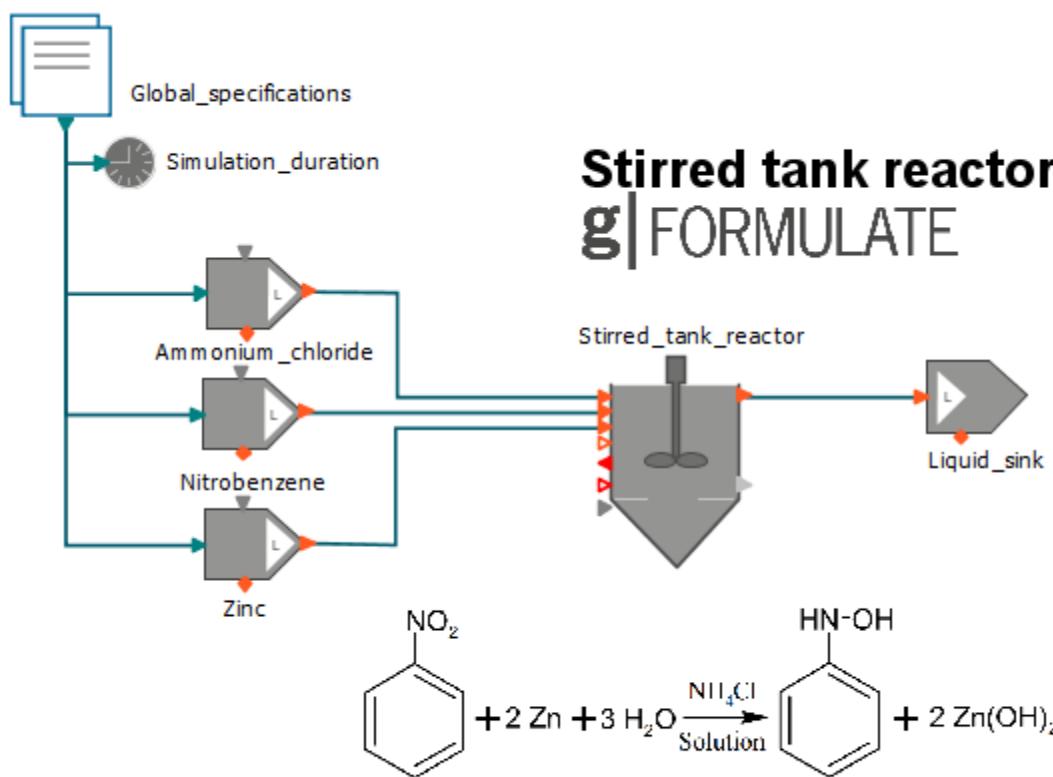


g|COAS
In vitro dissolution

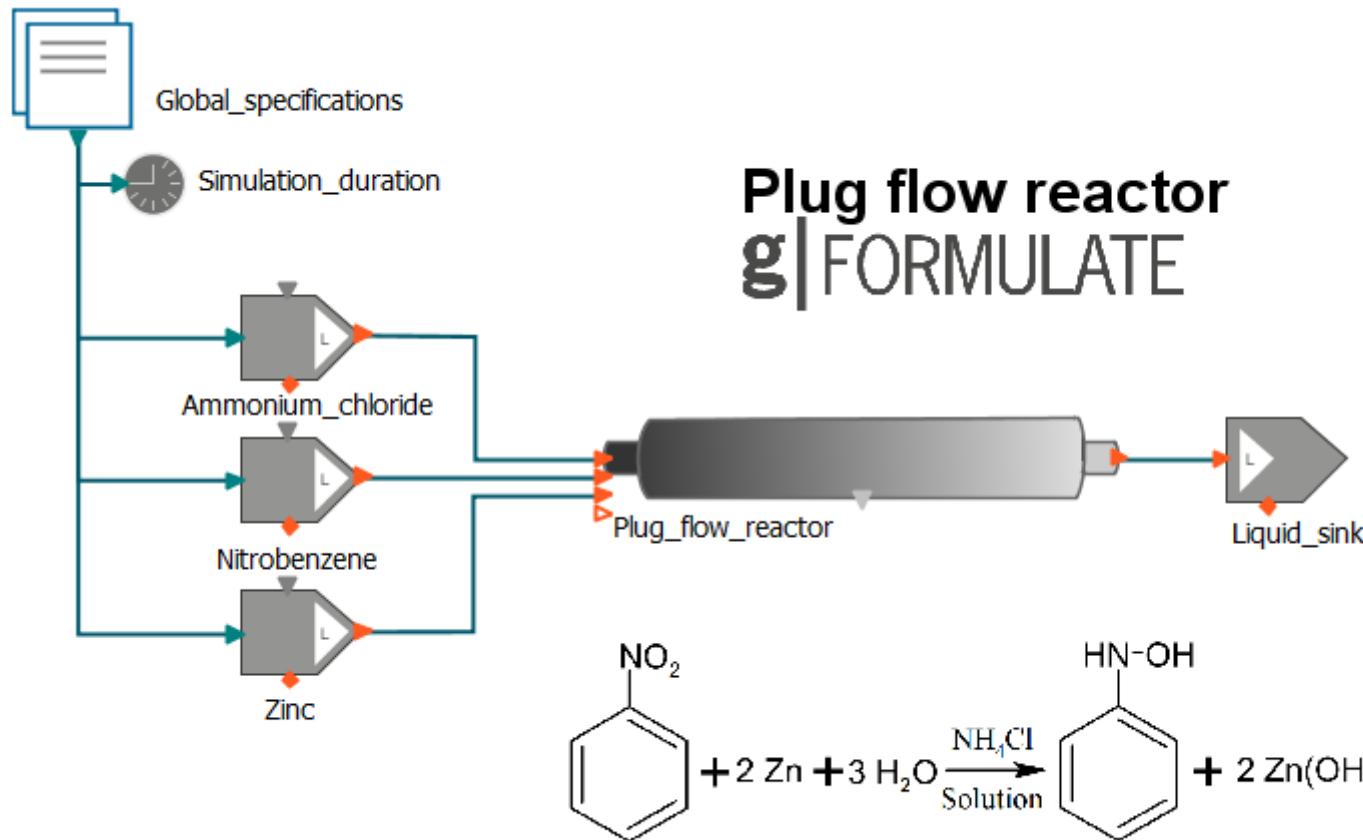
Also supports optimal design of system components



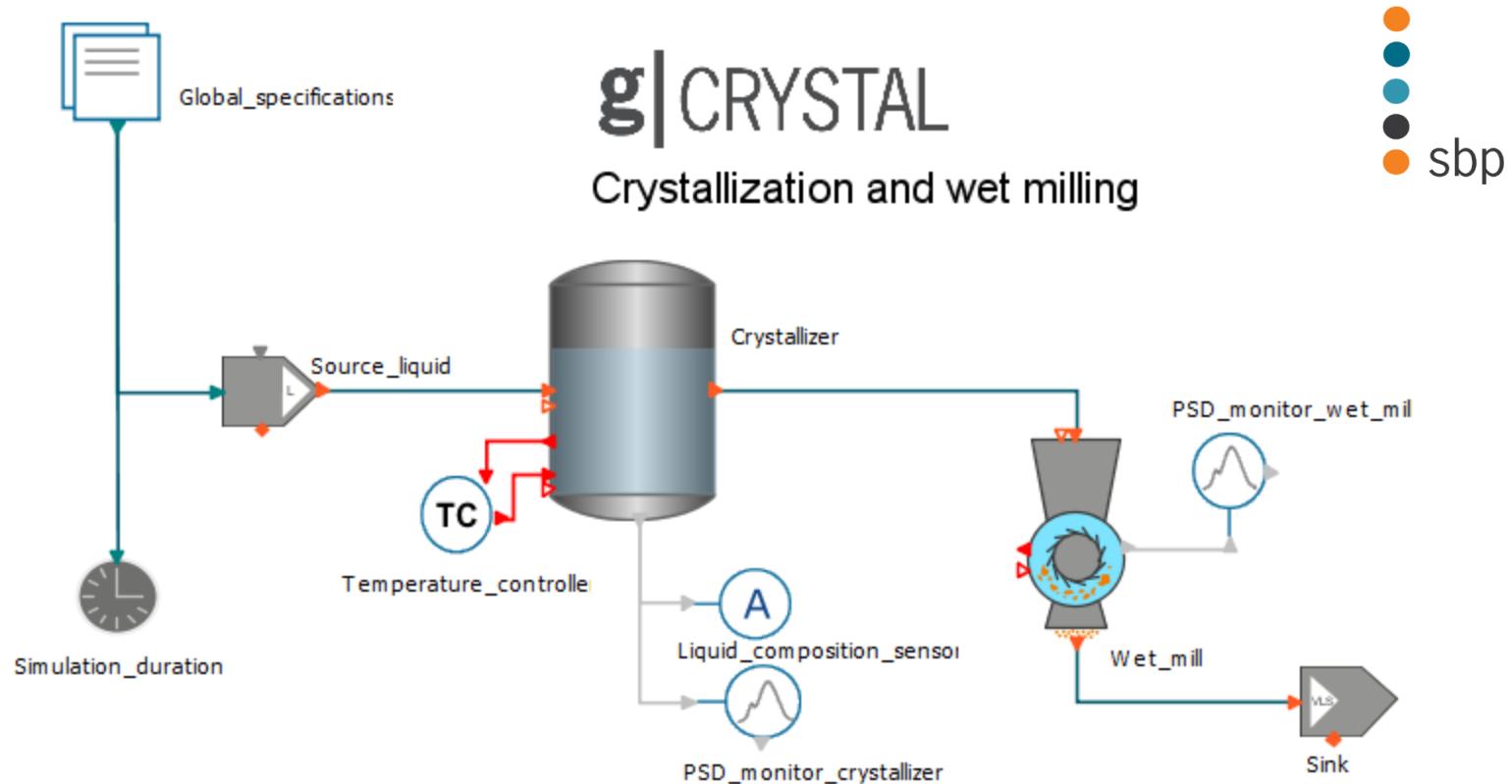
And introduces many new models



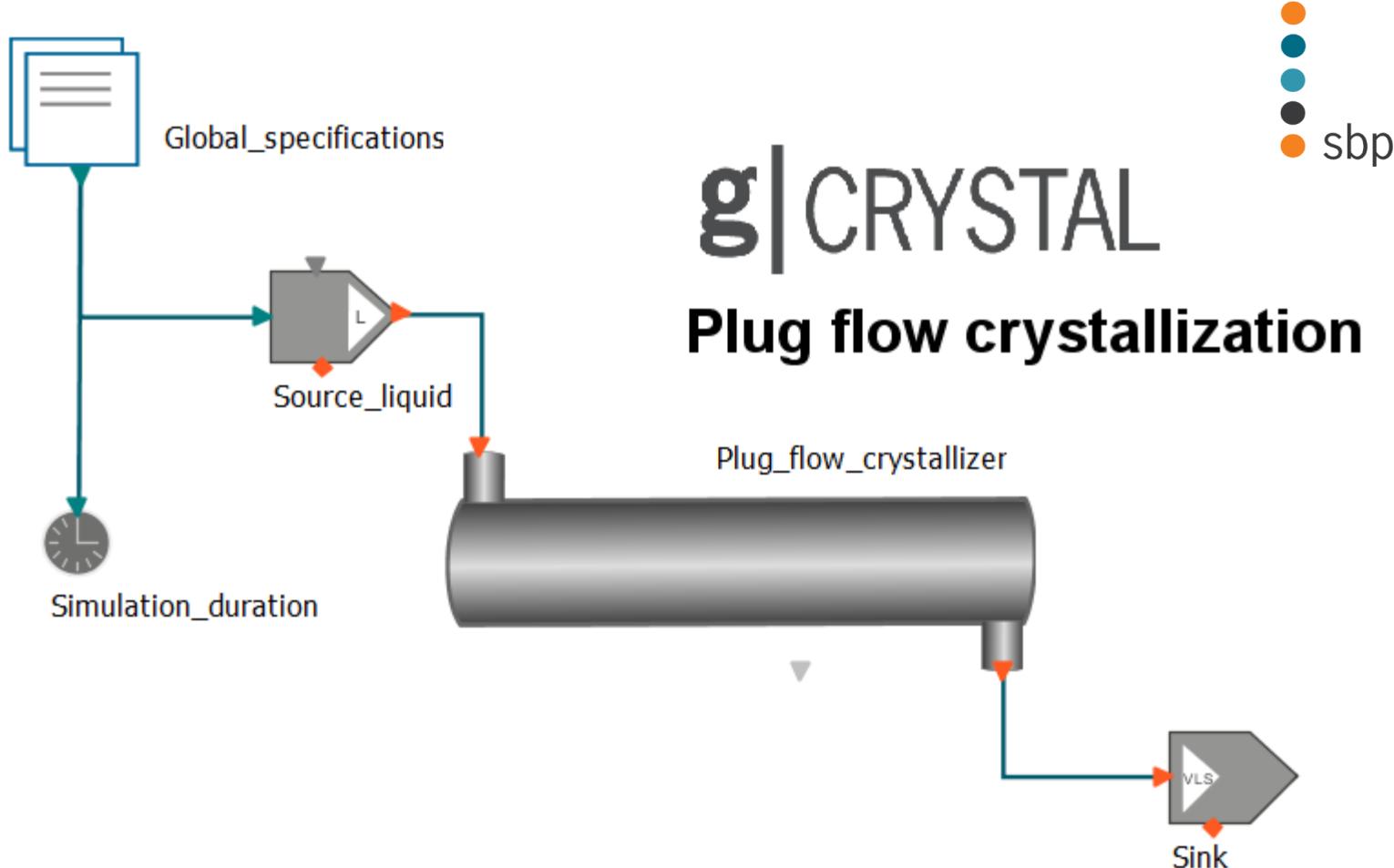
And introduces many new models



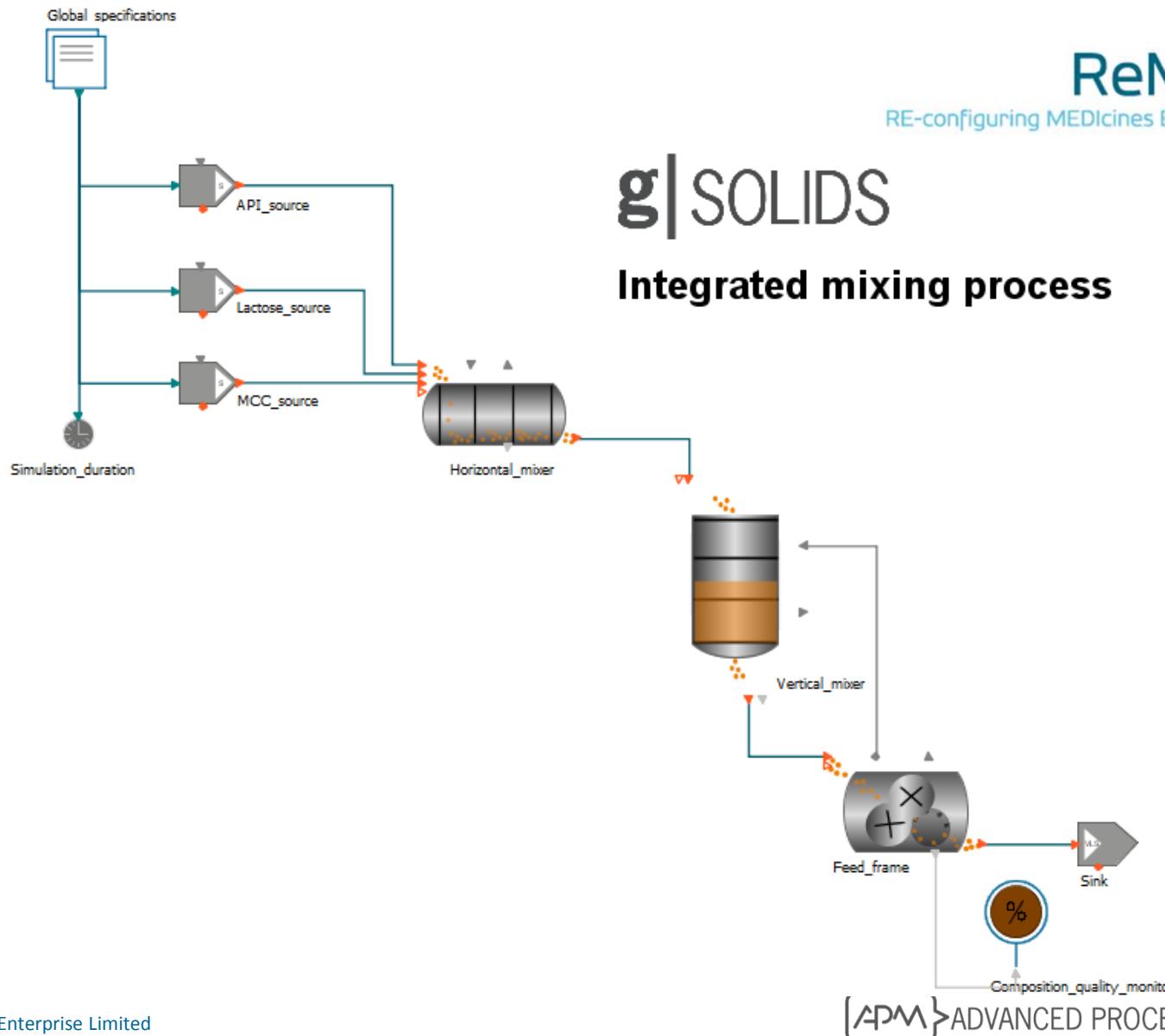
And introduces many new models



And introduces many new models



And introduces many new models

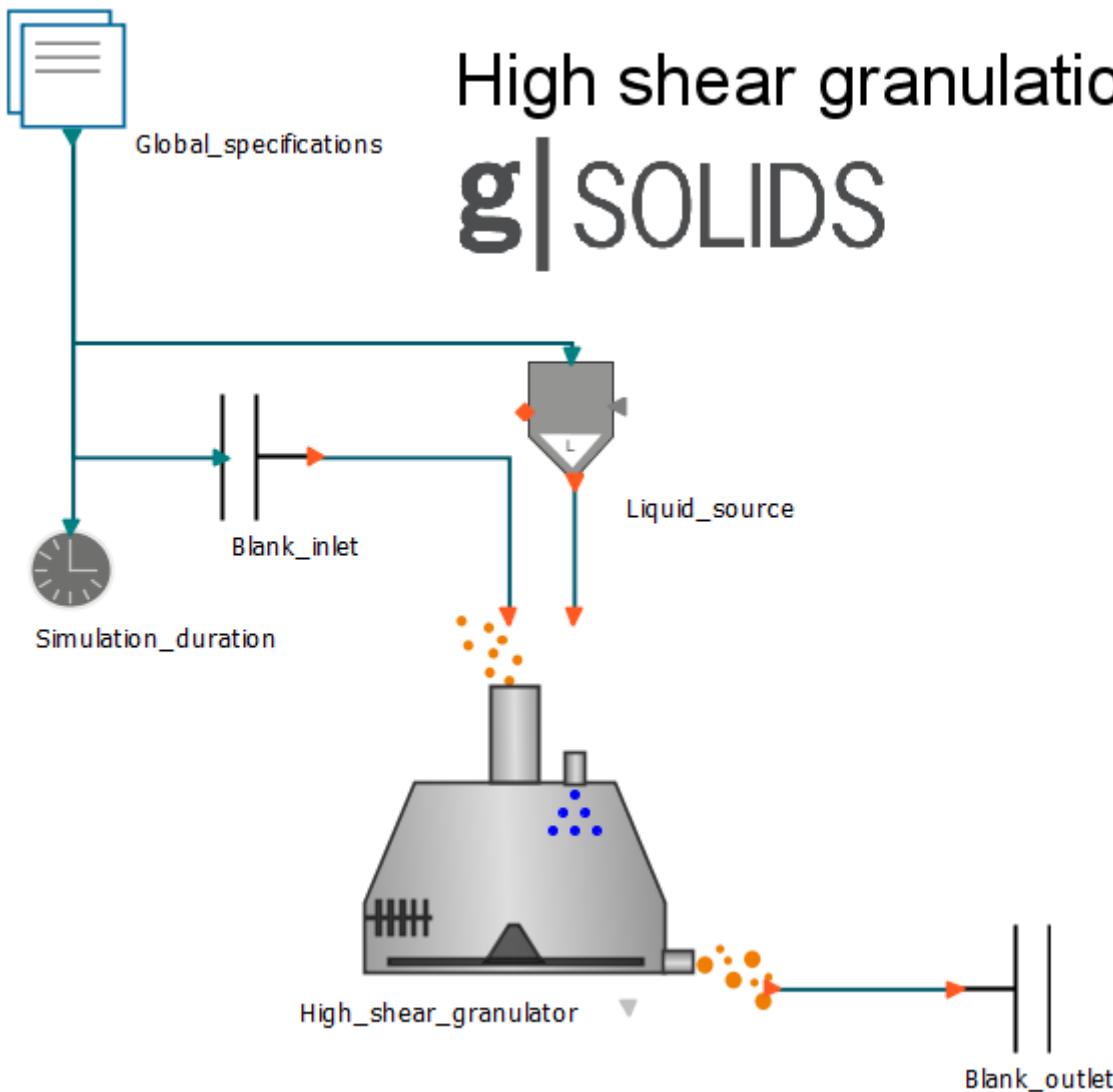


ReMediES
RE-configuring MEDIcines End-to-end Supply

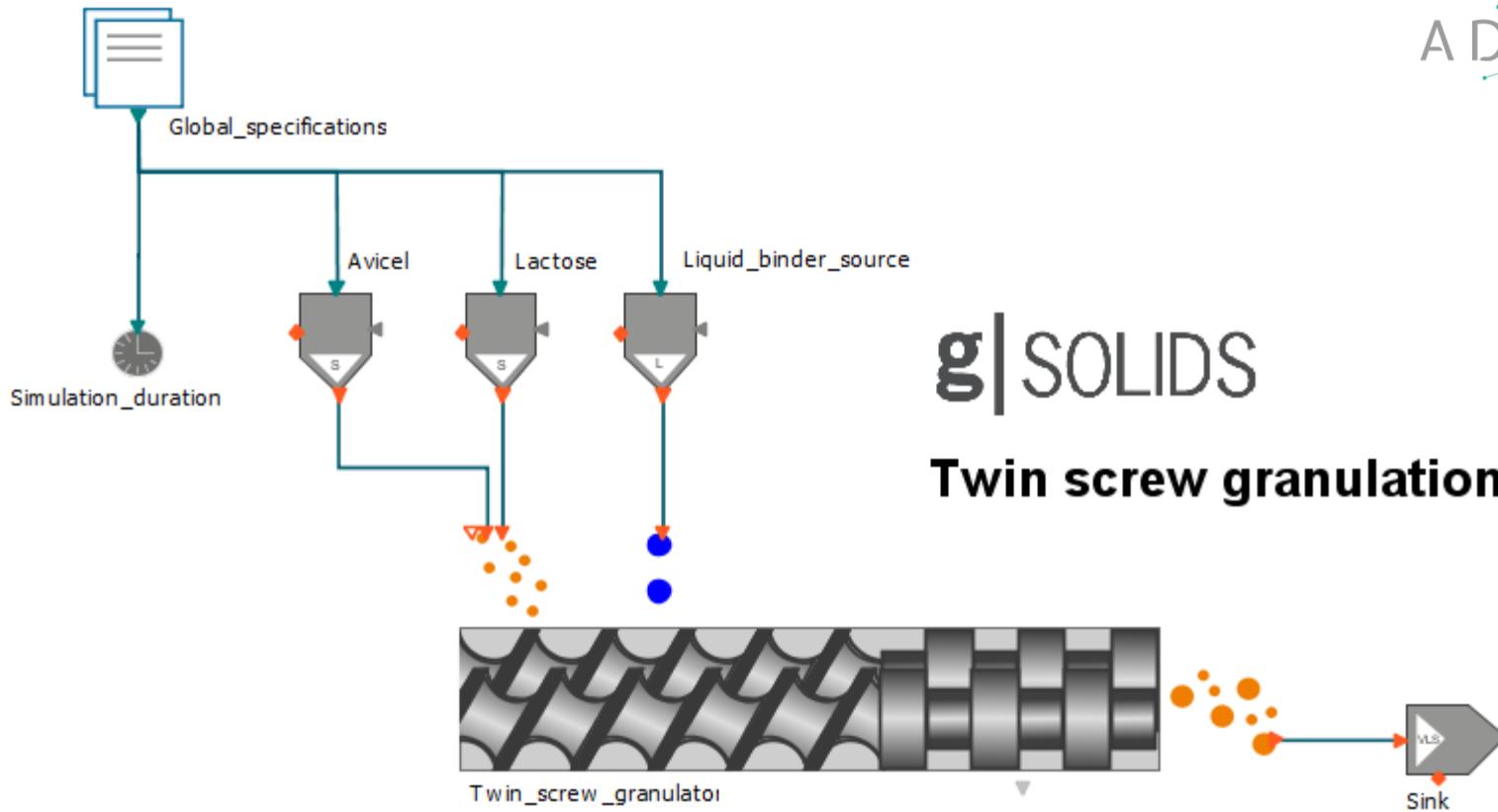
g|SOLIDs Integrated mixing process

And introduces many new models

High shear granulation g|SOLIDs



And introduces many new models



g|SOLIDS

Twin screw granulation

- FormulatedProducts specific developments
 - Property package for species that may exist in solid (and fluid) phases
 - Databases
 - Material properties
 - Equipment dimensions and operating conditions
 - Physiology

- gPROMS platform developments
 - Switching units of measurement
 - Support for parameter estimation and optimisation
 - Global System Analysis
 - Uncertainty analysis
 - Sensitivity analysis

- Flexible database structure compatible with
 - PSE provided databases
 - 3rd party databases
 - corporate databases, etc.

Materials



Dosage forms



Equipment



Physiology



- Significant increase in usability
 - single repository for validated data
 - less looking up of data
 - fewer transcription errors

Significant increase in usability Material database



Pre-database

source_sieve_data (Source_solid_distributed)

Is the flowrate controlled? No

PSD specification Specified from sieve analysis

Density specifications Specify bulk density and intra-particle void

Sieves specified in Descending order

Flowrate specified as Mass

Specify

Single solid phase leaving source Coffee

Mass flowrate 1 kg/s

Mass fraction Uniform for entire array 1 kg/kg

Temperature 298.15 K

No. of sieves 4

Sieve analysis data

Sieve analysis results

No. of sieves	Screen size ...	Weight on s...
1	1000	0.2
2	800	0.2
3	600	0.2
4	400	0.2
5		

Weight on pan 0.2 kg

Bulk density 600 kg/m³

Intra-particle void 0 m³/m³

OK Cancel Reset all Help

Using database

solid_source_1 (Source_only_solid_distributed_gWIZ)

Conditions

Specify

Material Fast Flo Lactose

Material grade 315 NF Lactose

PSD D25 23.69 Micron

PSD D50 27.146 Micron

PSD D75 31.651 Micron

Bulk density 280.0 kg/m³

OK Cancel Reset all

- Material list filtered by species available
- User now only needs to specify values for flowrate and temperature
- Custom material still a possibility: pre-database functionality

Significant increase in usability Equipment database



Pre-database

Roller_compactor (Roller_compactor_gWIZ)

Specify

Equipment	User input
Material properties	Roll force per width
Ribbon properties	

Equipment

Roll diameter	1	m
Roll width	1	m
Maximum roll gap	0.01	m
Minimum roll gap with closest distance between rolls	0.00001	m

Operating conditions

Roller speed	10	rpm
Angular position at which feed pressure is applied	50	degree
Thermal energy addition during compaction	0	J/s
Feed material bypass fraction	0.0	
Applied roll force per width of roll	10	kN/cm

OK Cancel Reset all Help

Using database

Roller_compactor (Roller_compactor)

Modelling approach Reynolds et al, 2010

Specify

Equipment	From database
Material properties	Roll force per width
Ribbon properties	

Equipment

Manufacturer	Alexanderwerk	
Roller compactor	Alexanderwerk WP 120	
Roll diameter	0.12	m
Roll width	0.04	m
Maximum roll gap	0.005	m

Operating conditions

Roller speed	20	rpm
Angular position at which feed pressure is applied	The specified value (20) is greater than the stipulated range.	
Thermal energy addition during compaction	0	J/s
Applied roll force per width of roll	10	kN/cm

OK Cancel Reset all Help

- User now only specifies operating conditions, which are verified against bounds also provided by the database
- Custom equipment still a possibility: pre-database functionality

Manage risk by quantifying impact of uncertainty

Environmental inputs
External disturbances
Commercial environment

Variability

System



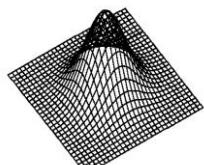
Innovate UK collaborative R&D project on
Global Systems Analysis
AstraZeneca, Britest, GSK, Pfizer, PSE
2014/06 – 2016/05

Model



Decisions

- Design
- Operational



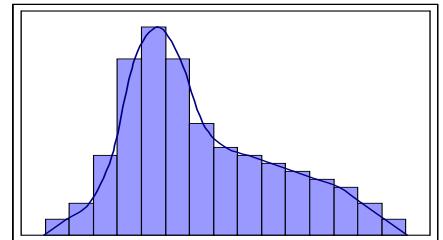
Model parameters

Uncertainty



KPIs

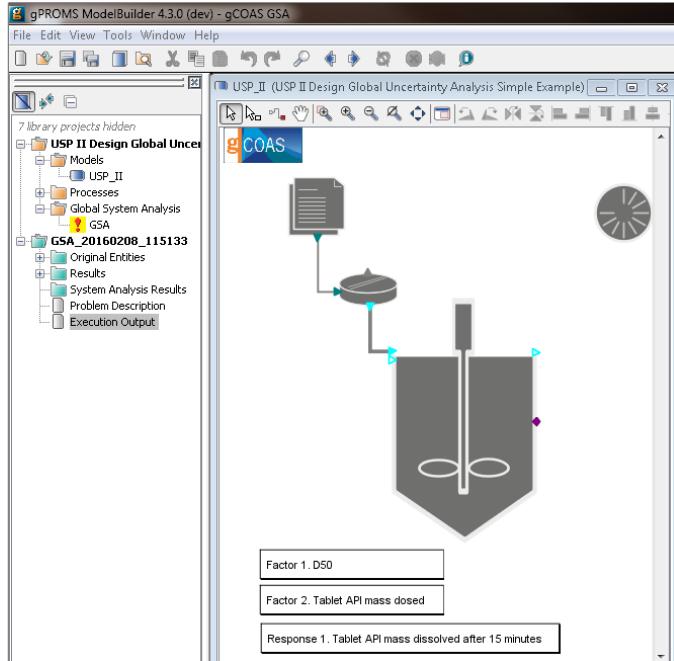
- CQAs
- Process operability
- Process safety
- Environmental impact
- Economic performance



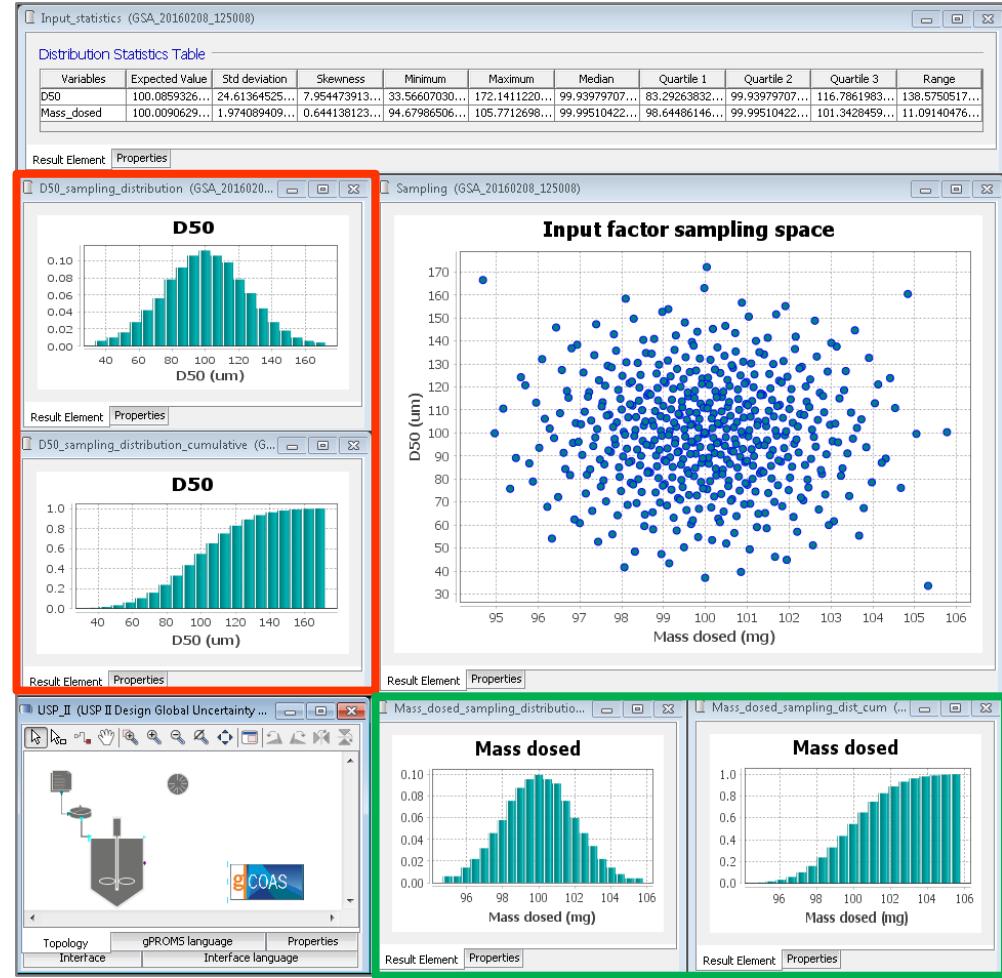
**Risk associated
with model-based
decisions**

Tablet dissolution

Biorelevant dissolution testing

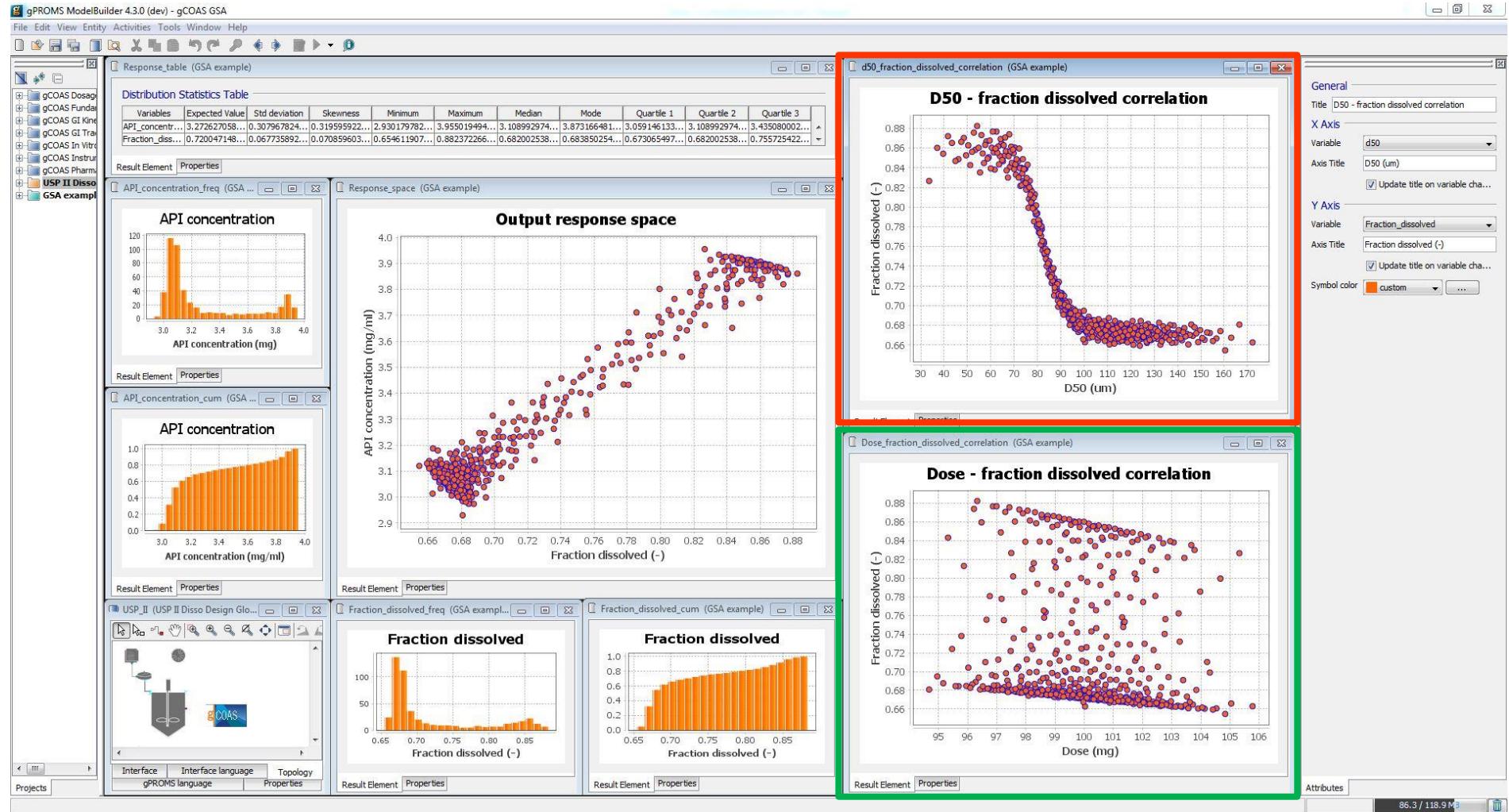


Factor sampling space – **D50** and **dose mass**

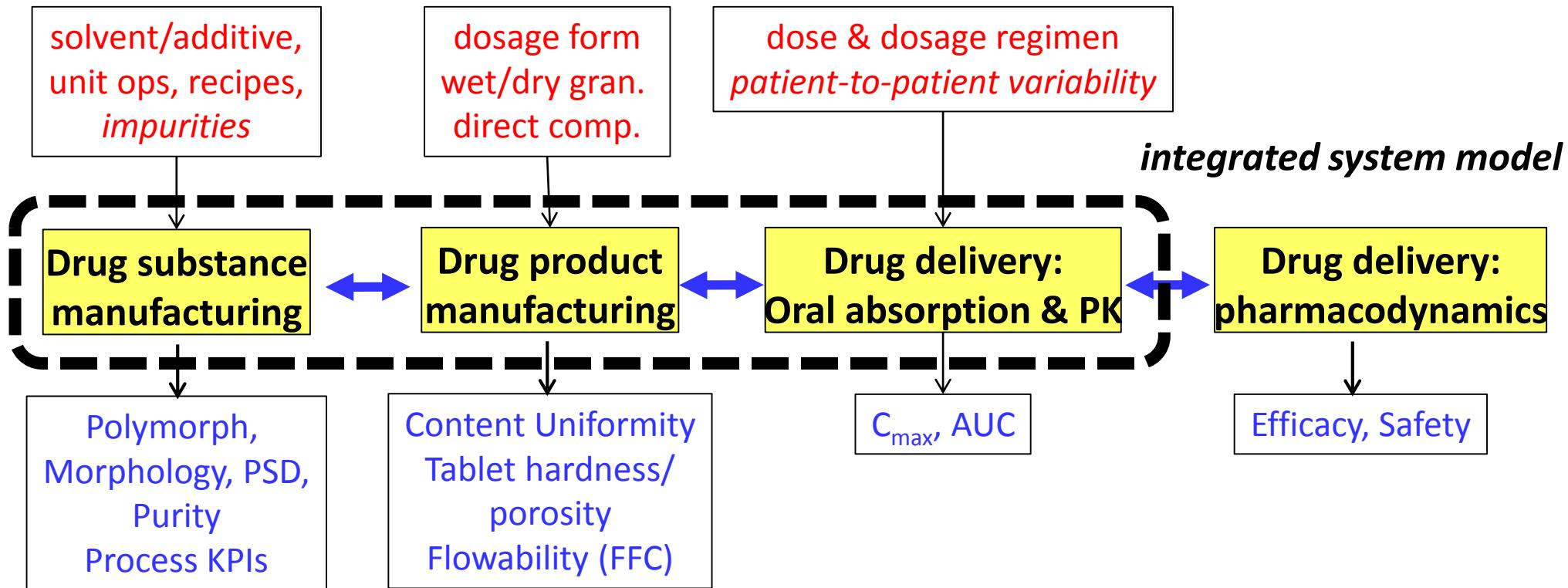


Tablet dissolution

Response space – showing effect of **D50** and **dose mass** on fraction dissolved



Systems-based Pharmaceutics



- Explore decision space effectively & efficiently
 - formal optimisation to eliminate trial-and-error
- Manage risk by quantifying impact of uncertainty

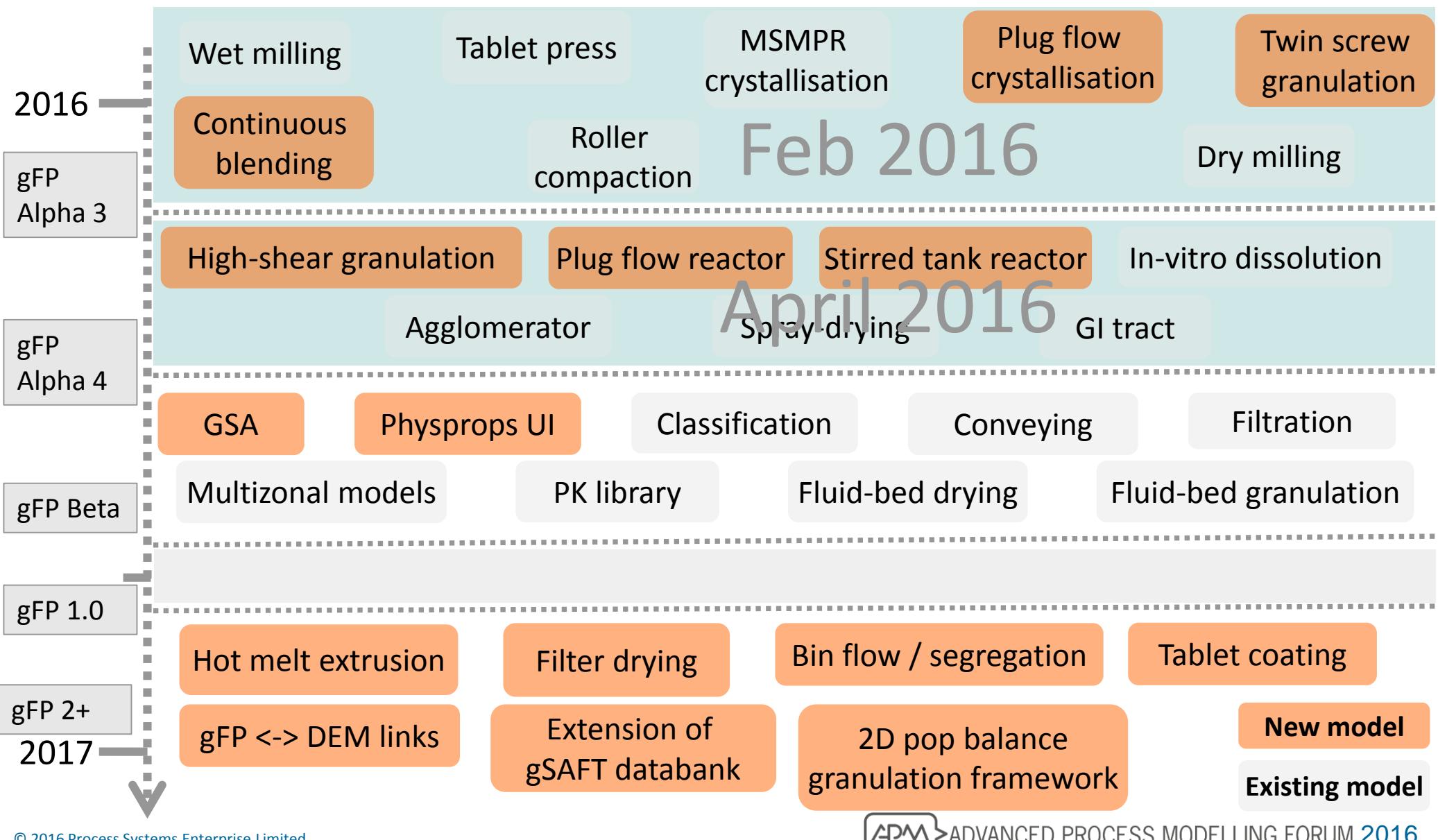
How? Use sensitivity analysis to quantify effect of upstream disturbances on variability in downstream performance.

Roadmap

gPROMS FormulatedProducts



Scope and timelines



Conclusions

gPROMS FormulatedProducts

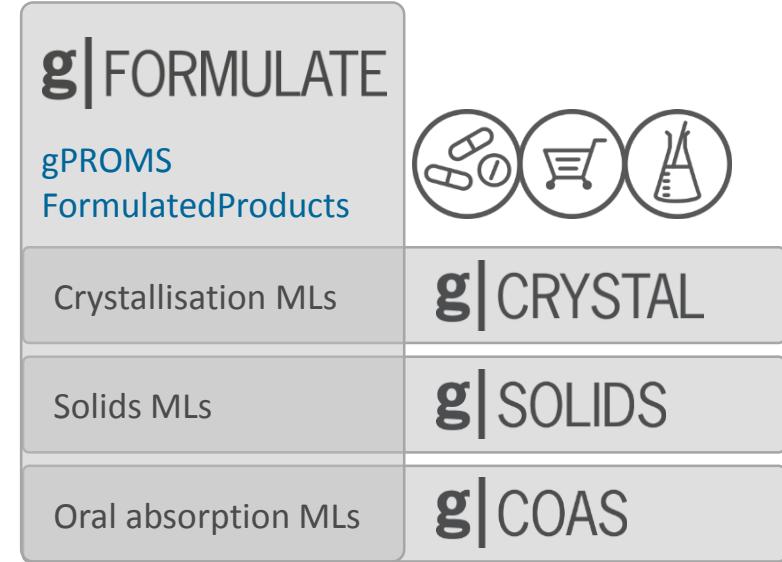


gPROMS FormulatedProducts contains functionality previously offered by four different PSE products



■ gCRYSTAL, gSOLIDs and gCOAS

- no longer standalone products
- now modules (libraries, examples and documentation) within gPROMS FormulatedProducts



■ Custom modelling

- and other ModelBuilder functionality

■ Hence reduces number of (installers for) PSE products from four to one, with significant advantages to both

- users of these products
- IT departments

An extendible platform for realising the vision of systems-based approaches for formulated products



- Systems-based Pharmaceutics Alliance
 - Phase 1: Eli Lilly and Pfizer; \$1,200k; Oct 2013 – Oct 2015
 - Phase 2: Eli Lilly, Pfizer, ... ; \$1,200k+; Dec 2015 – Dec 2017



- Digital Design: £444k; 3 FTE over 2 years till Jun 2016
 - Global System Analysis
 - AstraZeneca, Britest, GSK and Pfizer



- **£400k; 1.6 FTE over 4 years till Jan 2018**
 - Continuous drug product manufacture
 - AstraZeneca, GSK, GEA, Britest, Perceptive Engineering and ~20 others

- **ADD-PT** £3,600k; 10 FTEs over 4 years till March 2019 – 480 person-months
 - Multi-scale modelling, Solubility, Sensor models, Big data and support for Operations
 - AstraZeneca, BMS, GSK, Pfizer, Britest, Perceptive Engineering, CCDC, STFC, U. Leeds, U. Strathclyde, Cambridge U.

An extendible platform for realising the vision of systems-based approaches for formulated products



- Increased focus on models for food industries

- Manufacture (Thu PM meeting)
 - product performance



- Complex liquids: emulsions, dispersions, gels, ...

- Other product performance aspects

- e.g. product stability

Acknowledgments



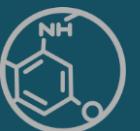
gPROMS FormulatedProducts

Acknowledgments



- Formulated Products team
- Software Technology Group
- Formulated Products Advisory Board

Thank you



Transitioning from gCRYSTAL, gSOLIDS and gCOAS



gPROMS FormulatedProducts

■ Licensing

- existing customers will be issued with a new set of licences covering their existing functionality

■ Backward compatibility

- physical property specifications – yes
- specifications of unit operation and other models – partial

■ PSE's recommendation

- use FormulatedProducts 1.0 for new applications
- for existing applications
 - continue using gCRYSTAL, gSOLIDS or gCOAS until we have introduced necessary platform functionality to fully address backward compatibility
 - Work with the Formulated Products team to manually convert models

Features

gPROMS FormulatedProducts

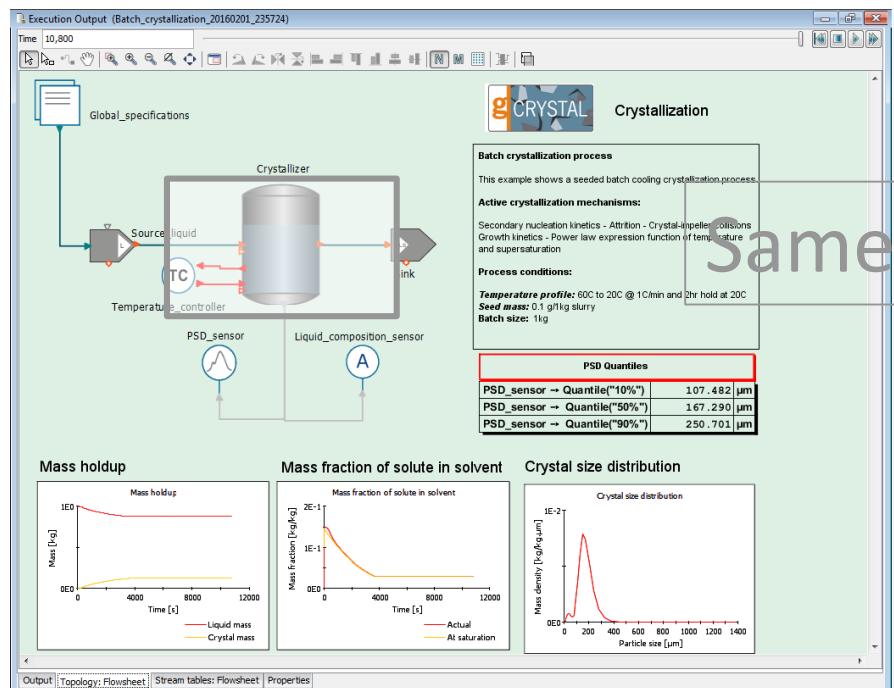


gPROMS FormulatedProducts features

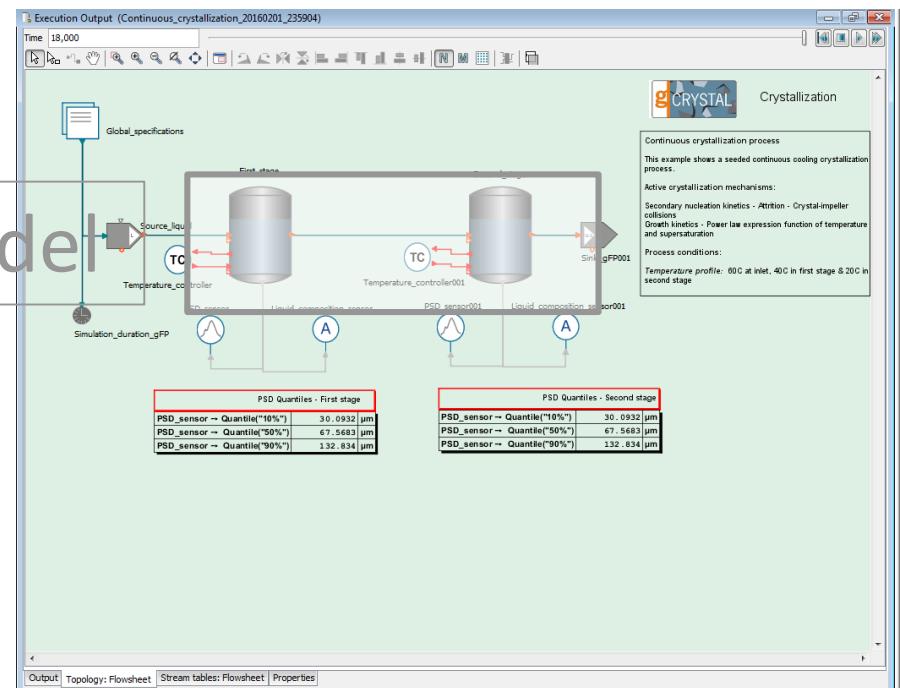
Batch and continuous operation



Batch crystallization



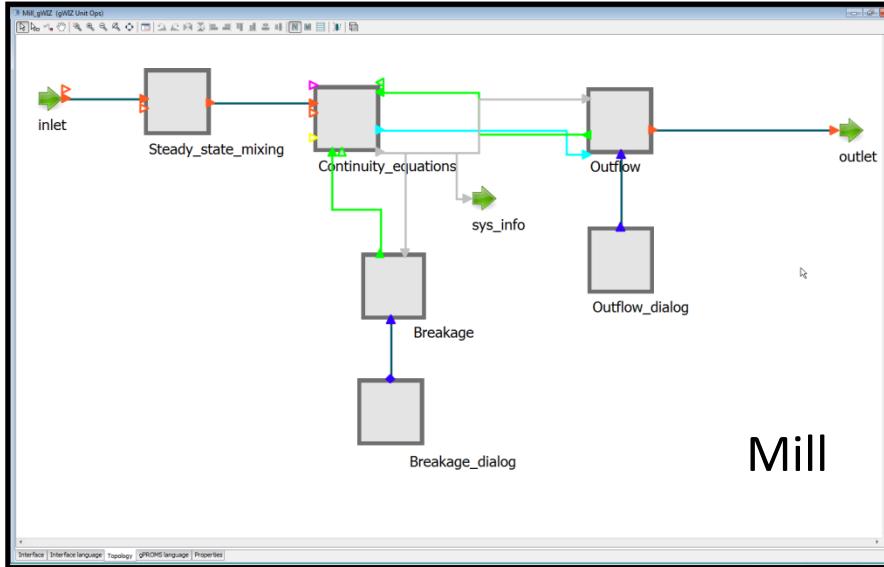
Continuous crystallization



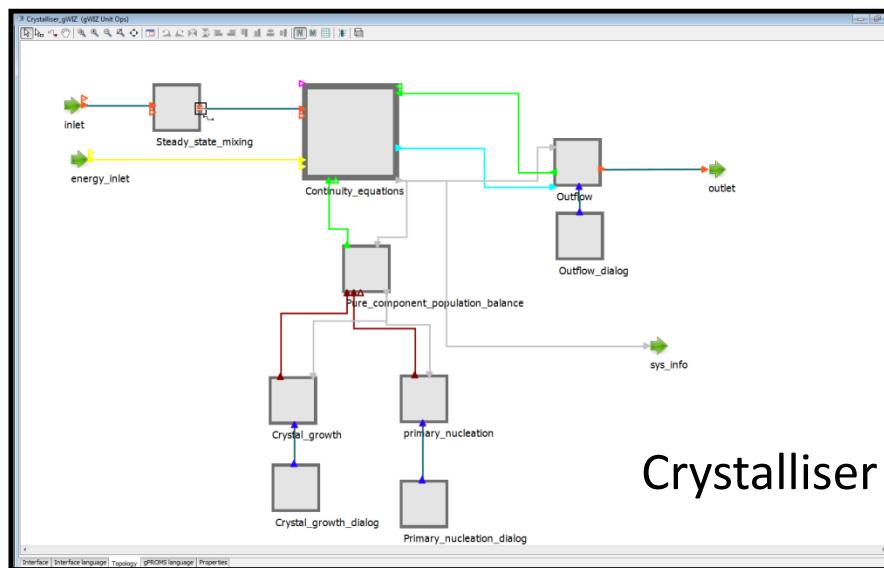
Same model

gPROMS FormulatedProducts features

Consistent internal structure across all models



- “Mix and match” physical phenomena between different library models



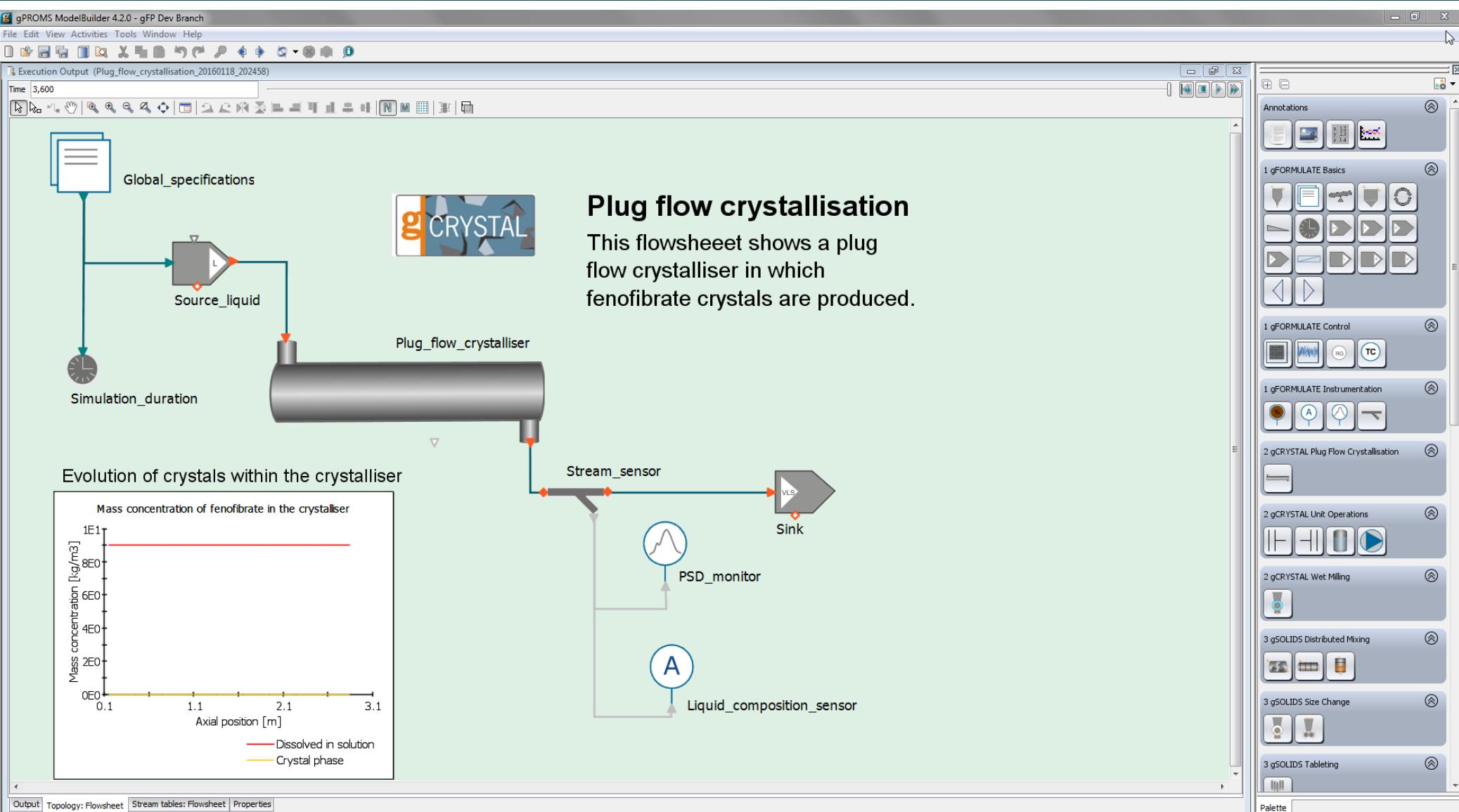
- Consistency in code base, user interfaces and databases

Example applications



gPROMS FormulatedProducts

gPROMS FormulatedProducts Plug flow crystallisation



gPROMS FormulatedProducts

Wet milling



gPROMS ModelBuilder 4.2.0 - gFP Dev Branch

File Edit View Activities Tools Window Help

Execution Output (Crystallisation_and_wet_milling_recycle_20160118_202607)

Time 36,000

Annotations

1. gFORMULATE Basics

2. gFORMULATE Control

3. gFORMULATE Instrumentation

2. gCRYSTAL Plug Flow Crystallisation

2. gCRYSTAL Wet Milling

3. gSOLIDS Distributed Mixing

3. gSOLIDS Size Change

3. gSOLIDS Tableting

Crystallisation and wet milling

Global_specifications

Source_liquid

Crystalliser

Temperature_controller (TC)

Liquid_composition_sensor (A)

PSD_monitor_crystalliser

PSD_monitor_wet_mill

Wet_mill

Phases_to_recycle

Simulation_duration

Mass holdup

Mass [kg]

Time [s]

Mass holdup

Mass density [kg/kg μ m]

Particle size [μ m]

Crystal size distribution

Mass holdup

Mass [kg]

Time [s]

Mass holdup

Mass fraction [kg/kg]

Time [s]

Mass fraction of solute in solvent

Actual

At saturation

Mass density [kg/kg μ m]

Particle size [μ m]

Crystal size distribution

Output Topology: Flowsheet Stream tables: Flowsheet Properties

450.5 / 557.1 MB

gPROMS Formulated Products Continuous manufacture



Execution Output (Integrated_mixing_process_random_20160118_203617)

Time: 360

Global specifications

Disturbance

API_source

Lactose_source

MCC_source

Horizontal_mixer

Vertical_mixer

Feed_frame

Sensor

Sink

Simulation_duration

g SOLIDS

Integrated mixing process

The flowsheet shows a direct compression mixer process. Several sources feed material (API and excipients) into a horizontal mixing tank which then fills a vertical pipe.

The pipe directly feeds into a feed frame tablet press, the operation of which dictates the flow rate out of the vertical pipe. The concentration of API leaving the feed frame is predicted.

The acceptance of a tablet can be based on the specification requirements of API concentration. The acceptable range shown in the graph below shows how disturbances or changes in the flow rates from the feeders can cause a tablet to go off-spec.

API flows

Excipient flows

API concentration

Annotations

1. gFORMULATE Basics

2. gCRYSTAL Plug Flow Crystallisation

3. gCRYSTAL Unit Operations

4. gCRYSTAL Wet Milling

5. gSOLIDS Distributed Mixing

6. gSOLIDS Size Change

7. gSOLIDS Tableting

Output Topology: Flowsheet Stream tables: Flowsheet Properties

228.5 / 613.3 MB

gPROMS FormulatedProducts Twin screw granulation



gPROMS ModelBuilder 4.2.0 - gFP Dev Branch

File Edit View Activities Tools Window Help

Execution Output (Twin_screw_granulation_20160118_201832)

Time 180

Annotations

1 gFORMULATE Basics

1 gFORMULATE Control

1 gFORMULATE Instrumentation

2 gCRYSTAL Plug Flow Crystallisation

2 gCRYSTAL Unit Operations

2 gCRYSTAL Wet Milling

3 gSOLIDs Distributed Mixing

3 gSOLIDs Size Change

3 gSOLIDs Tableting

Palette

Global_specifications

Avicel

Lactose

Liquid_binder_source

Simulation_duration

Twin_screw_granulator

Stream_sensor

Sink

PSD_monitor

Twin screw granulation

The flowsheet shows a twin screw wet granulation process in which microcrystalline cellulose and lactose powders are granulated using water.

Screw configuration

- "Conveying"
- "Kneading, 60 F"

Outlet flow rates

Outlet mass flow rates, by phase

Mass flow rate [kg/s] vs Time [s]

Phase	Mass flow rate [kg/s]
Lactose powder	~0.0001
Avicel powder	~0.0001
Liquid binder	~0.0001
Granulate	~0.0001

Granule size distribution

Mass distribution [kg/kgum] vs Granule size [μm]

Mass distribution [kg/kgum] vs Granule size [μm]

Output Topology: Flowsheet Stream tables: Flowsheet Properties

309.5 / 538.6 MB

gPROMS FormulatedProducts Tablet disintegration

