



ADVANCED DIGITAL DESIGN OF PHARMACEUTICAL THERAPEUTICS

# Solid Drug Product and Process Design using Multi-Scale Interconnected Flowsheet Modelling and Global System Analysis

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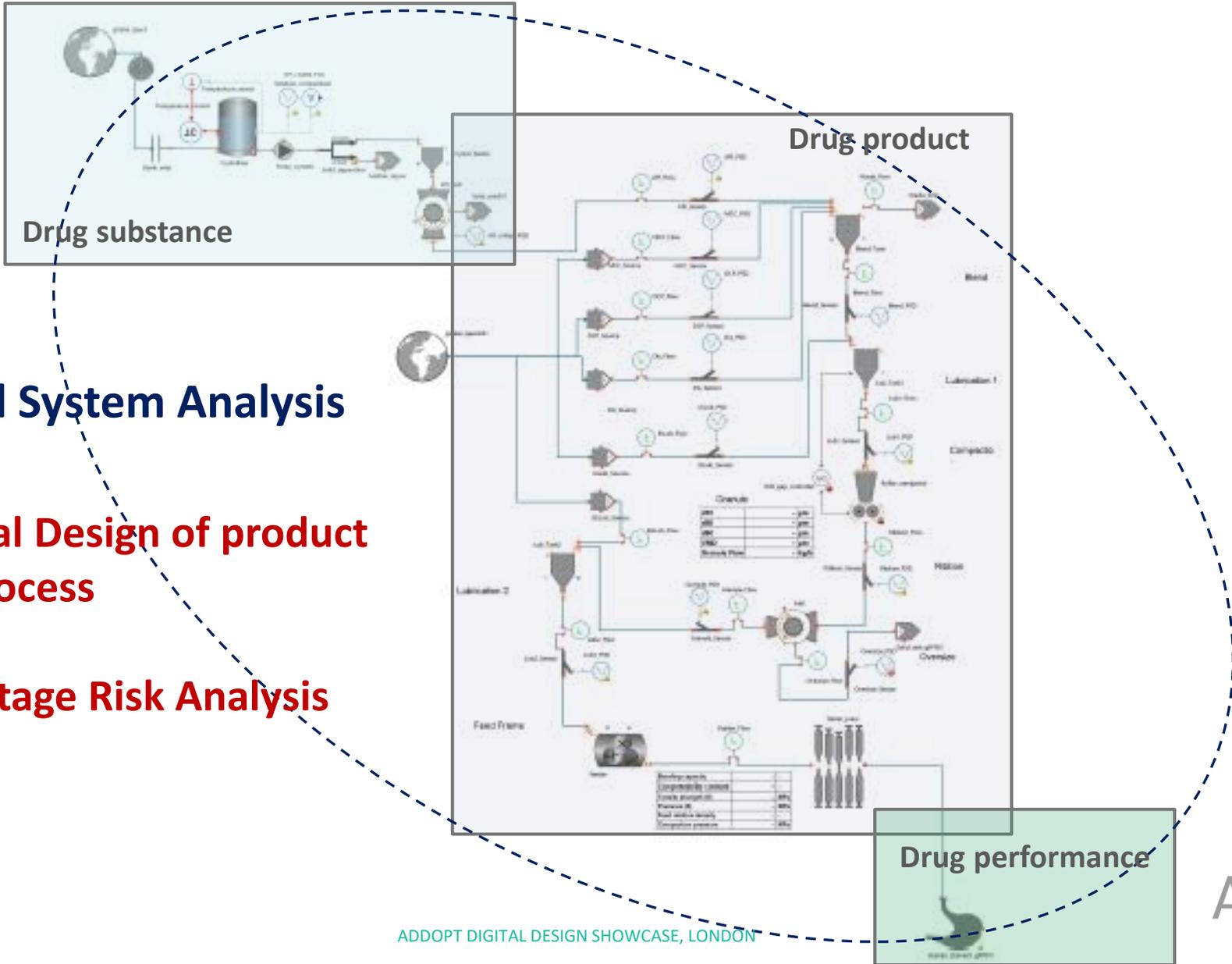
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# Systems-based approach in Pharmaceutical Industry



**Global System Analysis**

**Optimal Design of product and process**

**Early Stage Risk Analysis**



Model interconnection

Global System Analysis (GSA) methodology

GSA of individual unit operations

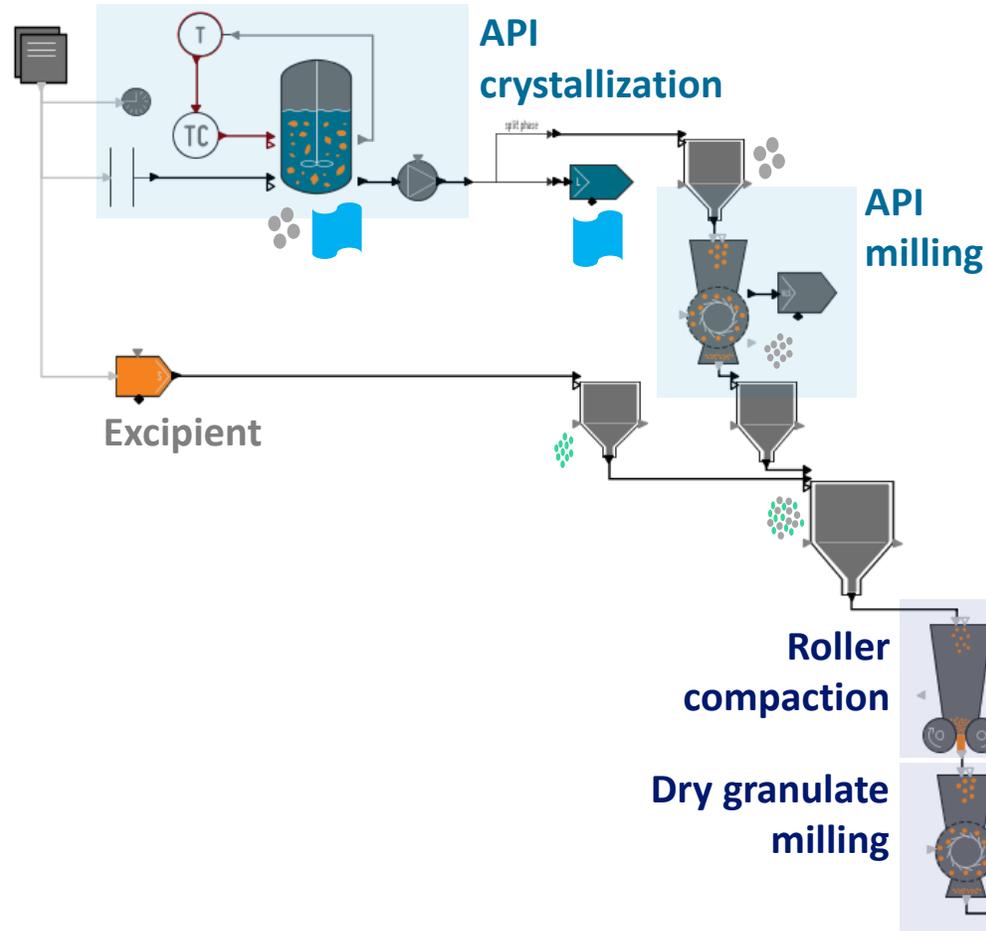
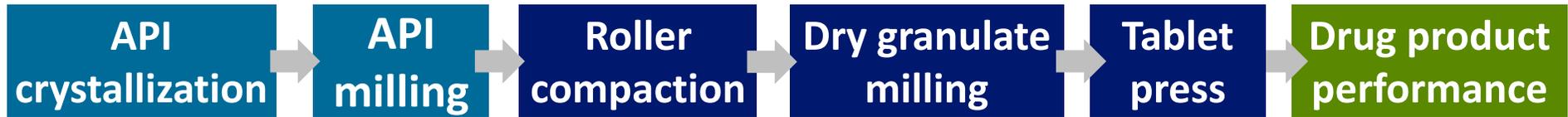
- Batch cooling crystallization model
- API milling model
- Roller compaction model
- Dry granulate milling model
- Tablet press model
- In vitro dissolution model

GSA of the interconnected flowsheet

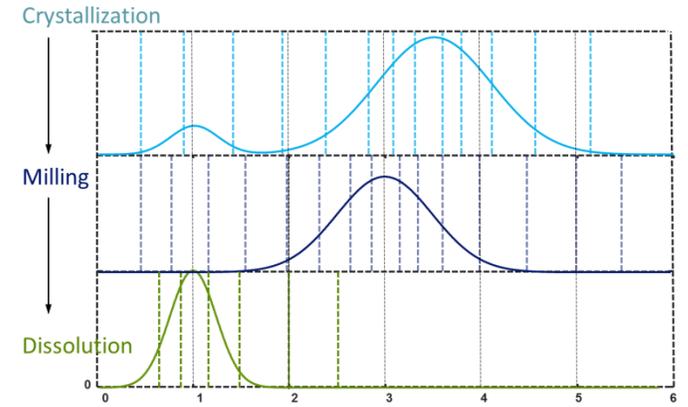
Further applications

Conclusions

# Interconnected flowsheet



Particle Size Distribution



Drug product performance



## GSA algorithm

- Define the uncertainty distribution of model parameters and inputs
- Define a **Monte Carlo simulations** scheme
- Calculate the statistics (**mean, variance and distributions**) from the model output
- Calculate the **Sobol indices** using ANOVA decomposition

## Methodology for solving interconnected flowsheets

Input variables and parameters  
(range, uncertainty distribution)

GSA of individual unit operations

Dominant input variables and  
parameters and their range

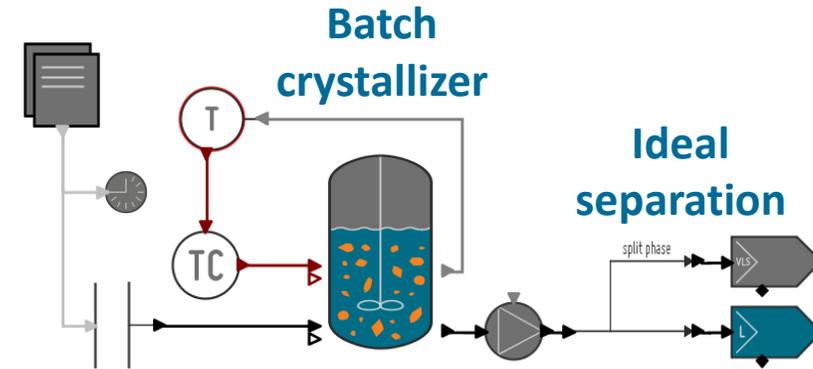
GSA of interconnected flowsheet

Dominant input variables and  
parameters of the interconnected  
system

# GSA of API crystallization

## Batch cooling crystallization model

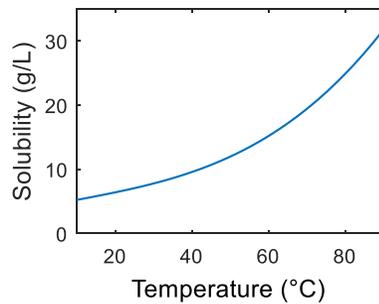
Processing decisions	Range / Value	Sensitivity ind. d50 API crystal
Initial temperature (°C)	50 – 90	0.040
Cooling rate (°C/min)	-1.333 (90->10 in 1h) – -0.1667 (50->10 in 4h)	0.000
Initial seed mass fraction (g/g)	$0.2e^{-6} - 50e^{-6}$	0.836
Impeller frequency (rpm)	10 – 100	0.000
Absolute supersat. (g API/g tot.)	0 – 0.05	0.128



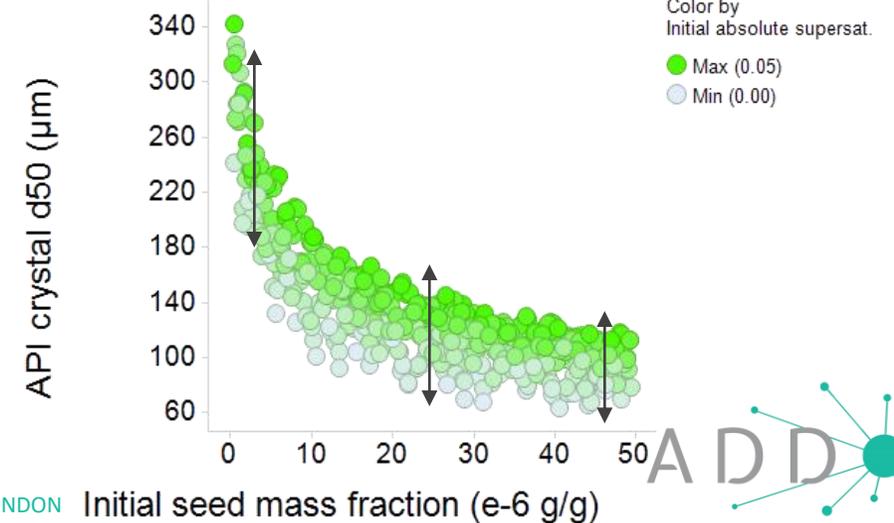
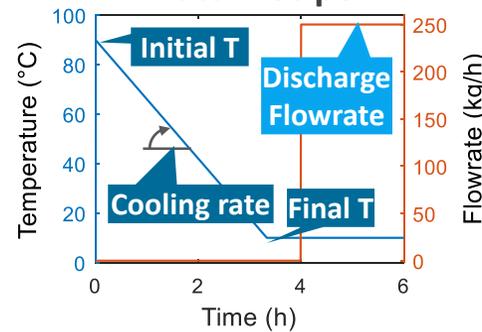
Primary nucleation: *Power law kinetics (relative supersat.)*

Growth & dissolution: *Classical two-step kinetics; Garside et al. (1990)*

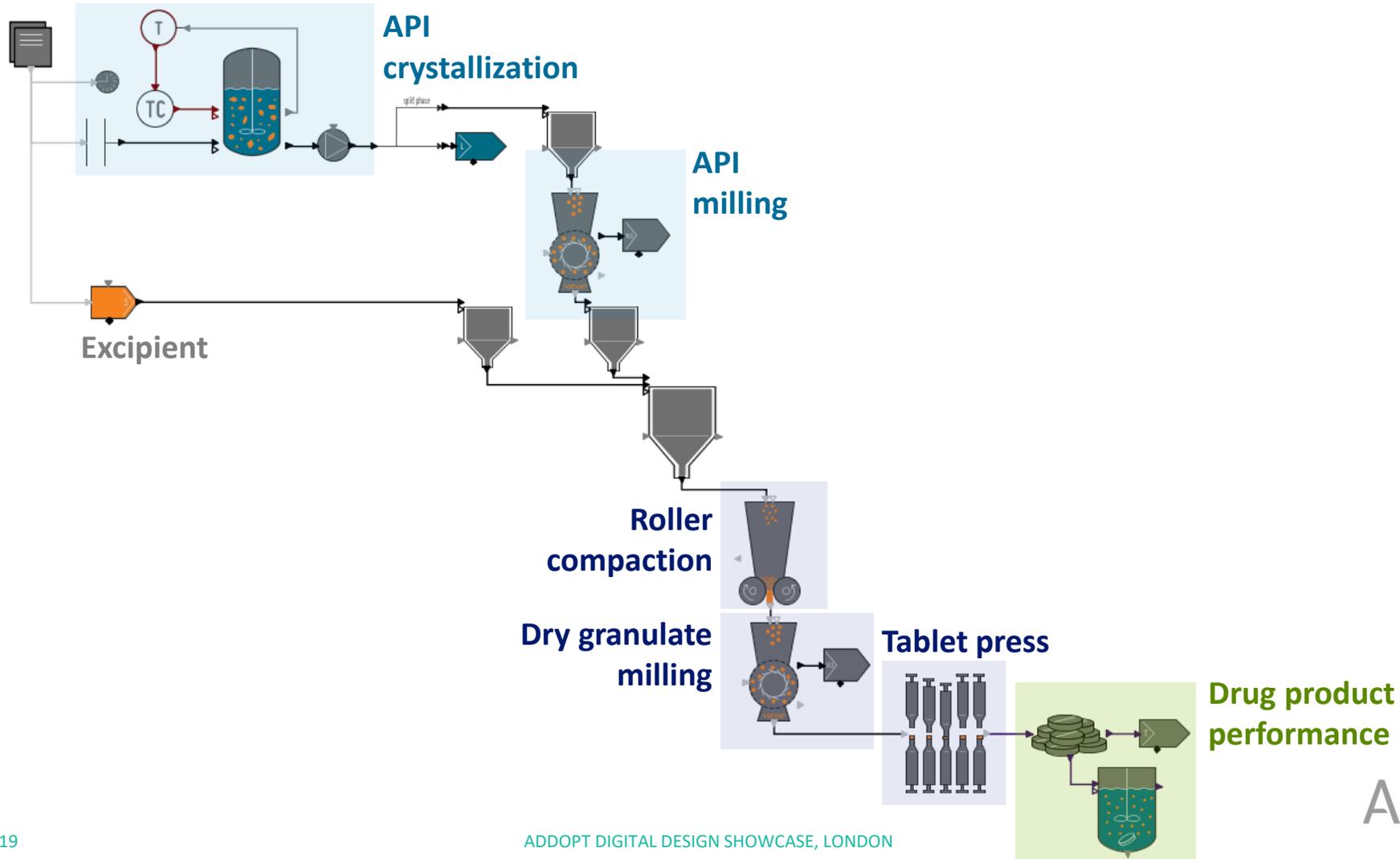
Solubility curve



Batch recipe

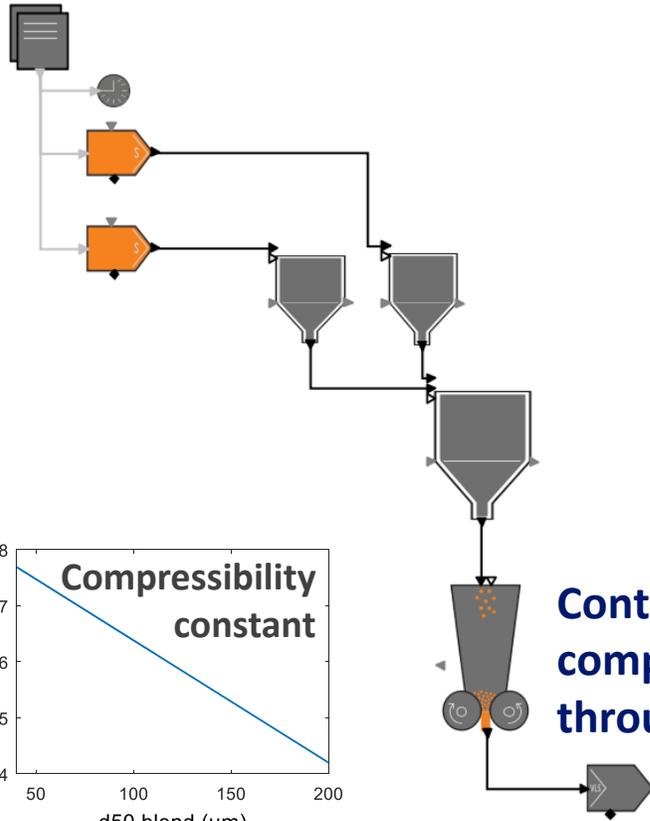


# GSA of the interconnected flowsheet

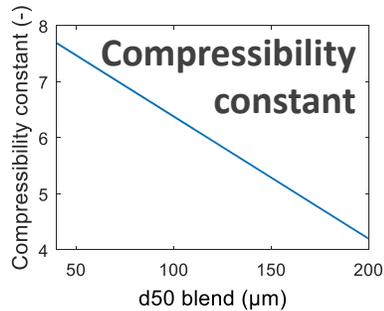


# GSA of Roller compaction

## Roller compaction model

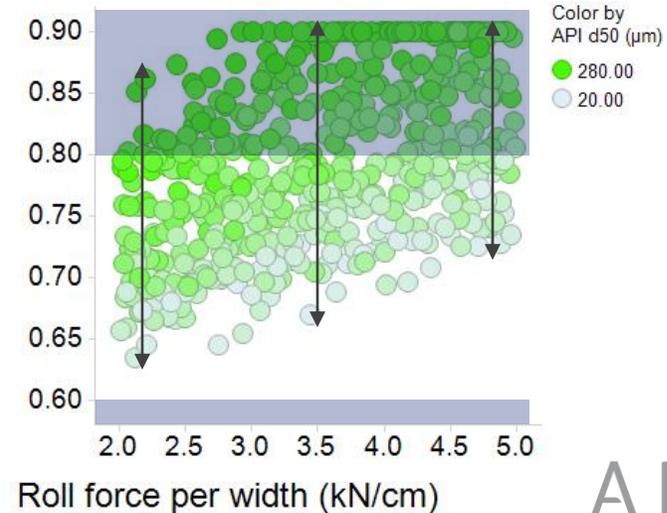


Processing decisions	Range / Value	Sensitivity ind. ribbon solid fraction
API PSD location ( $\mu\text{m}$ )	20 – 280	0.646
Mass throughput (kg/h)	6 – 24	0.063
Roll force per width (kN/cm)	2 – 5	0.262
Roller speed (rpm)	2 – 8	0.073



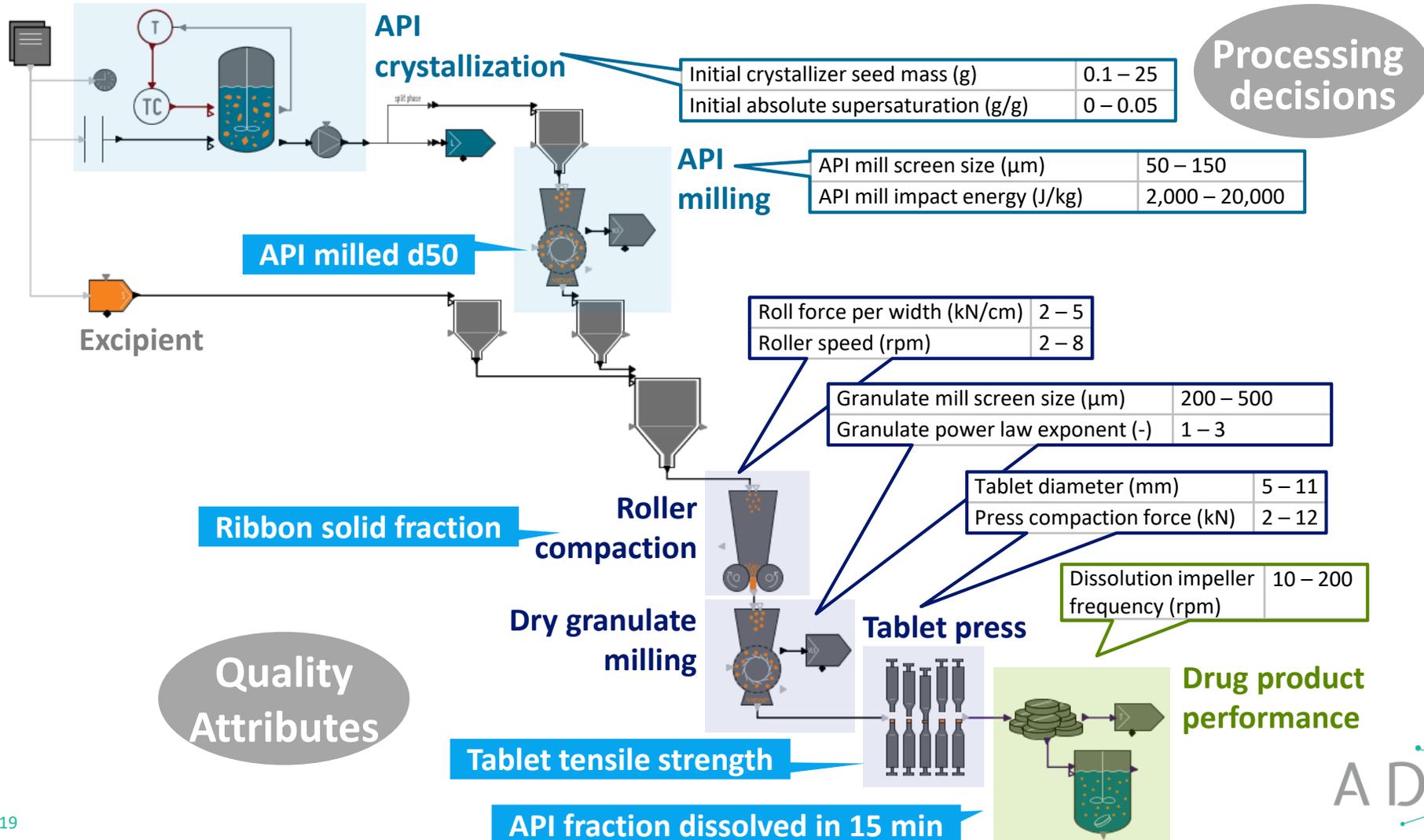
**Continuous roller compactor - throughput control**

Ribbon solid fraction (g/g)



Nip angle, maximum pressure & granule density:  
*Johanson (1965) and Reynolds et al. (2010)*

# GSA of the interconnected flowsheet



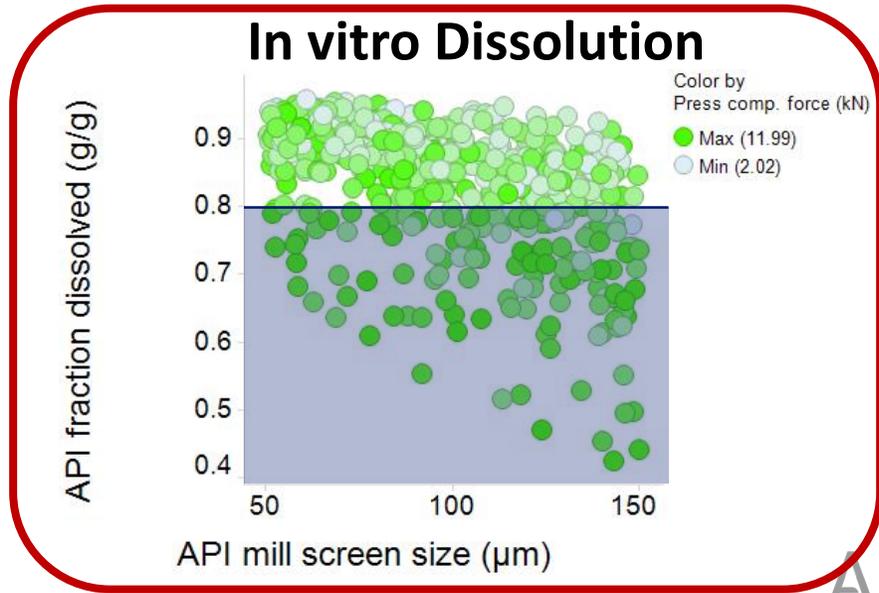
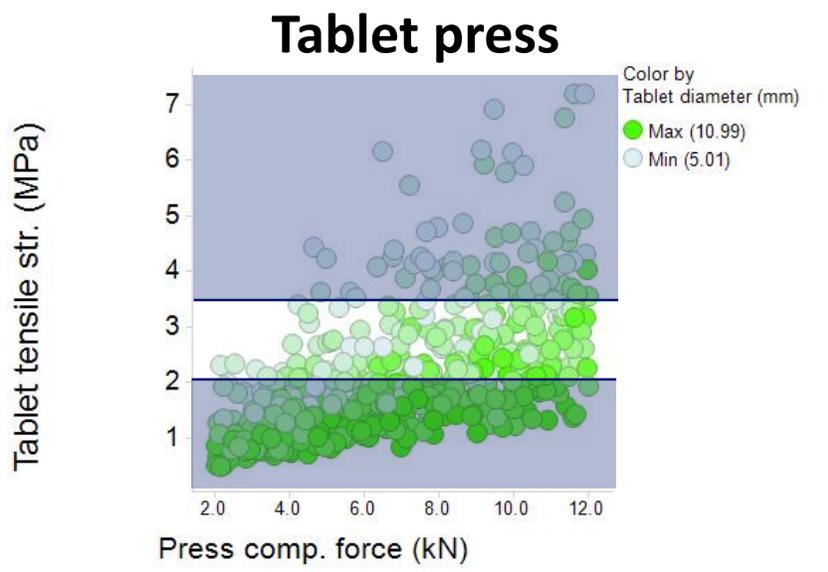
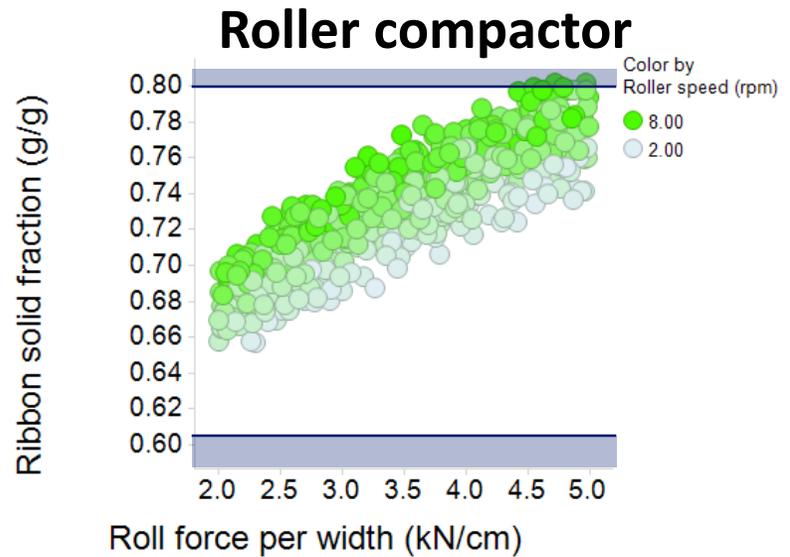
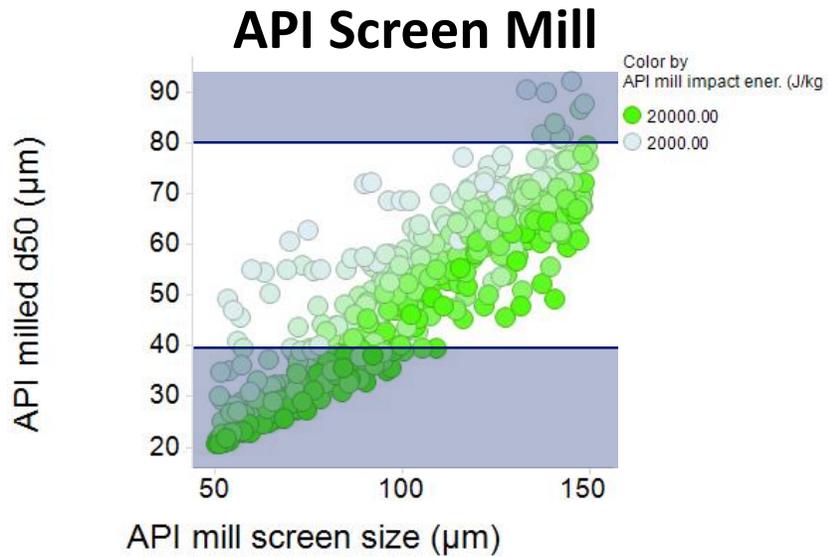
# GSA of the interconnected flowsheet

## Sensitivity Indices

Attributes	Units	Min	Max	API crystal d50	API milled d50	Ribbon solid fraction	Granulate d50	Tablet tensile strength	API fraction dissolved
Processing decisions									
Initial crystallizer seed mass	g	0.1	25	0.940	0.070	0.005	0.000	0.009	0.014
Initial absolute supersaturat.	g/g	0	0.05	0.060	0.008	0.001	0.000	0.001	0.002
API mill screen size	µm	50	150		0.843	0.055	0.000	0.089	0.241
API mill impact energy	J/kg	2,000	20,000		0.160	0.010	0.000	0.018	0.046
Roll force per width	kN/cm	2	5			0.849	0.000	0.131	0.176
Roller speed	RPM	2	8			0.175	0.000	0.036	0.036
Granulate mill screen size	µm	200	500				0.698	0.000	0.000
Granulate power law exponent	-	1	3				0.490	0.000	0.000
Tablet diameter	mm	5	11					0.377	0.249
Press compaction force	kN	2	12					0.398	0.298
Dissolution impeller frequency	RPM	10	200						0.019



# GSA of the interconnected flowsheet

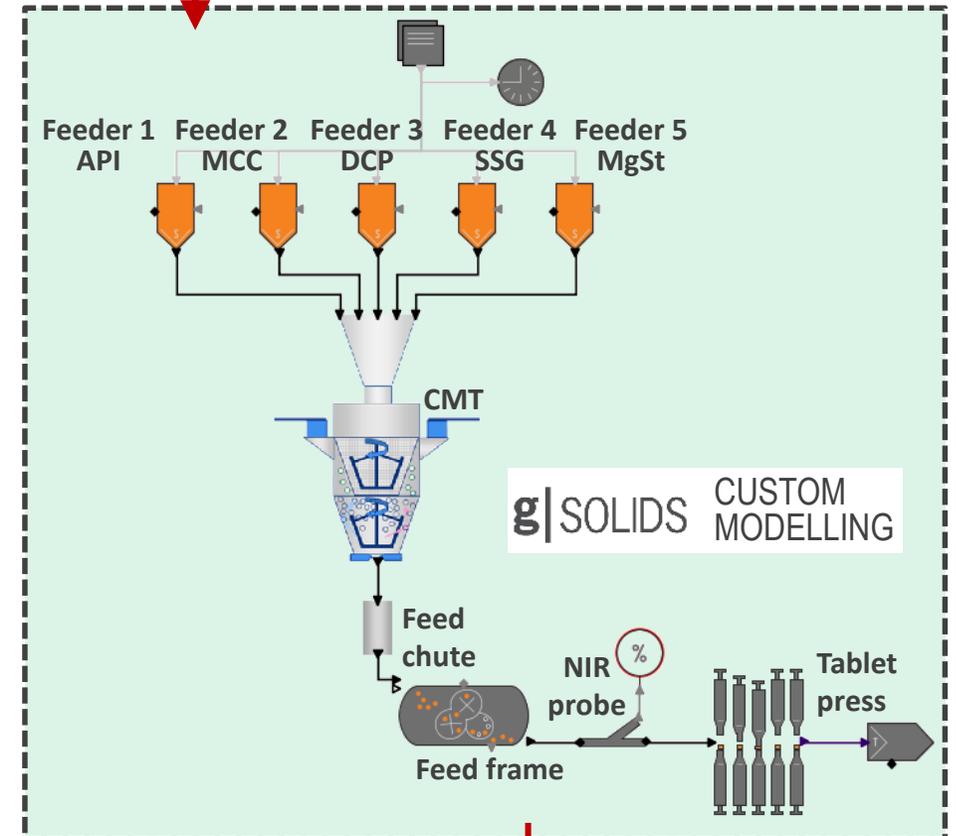
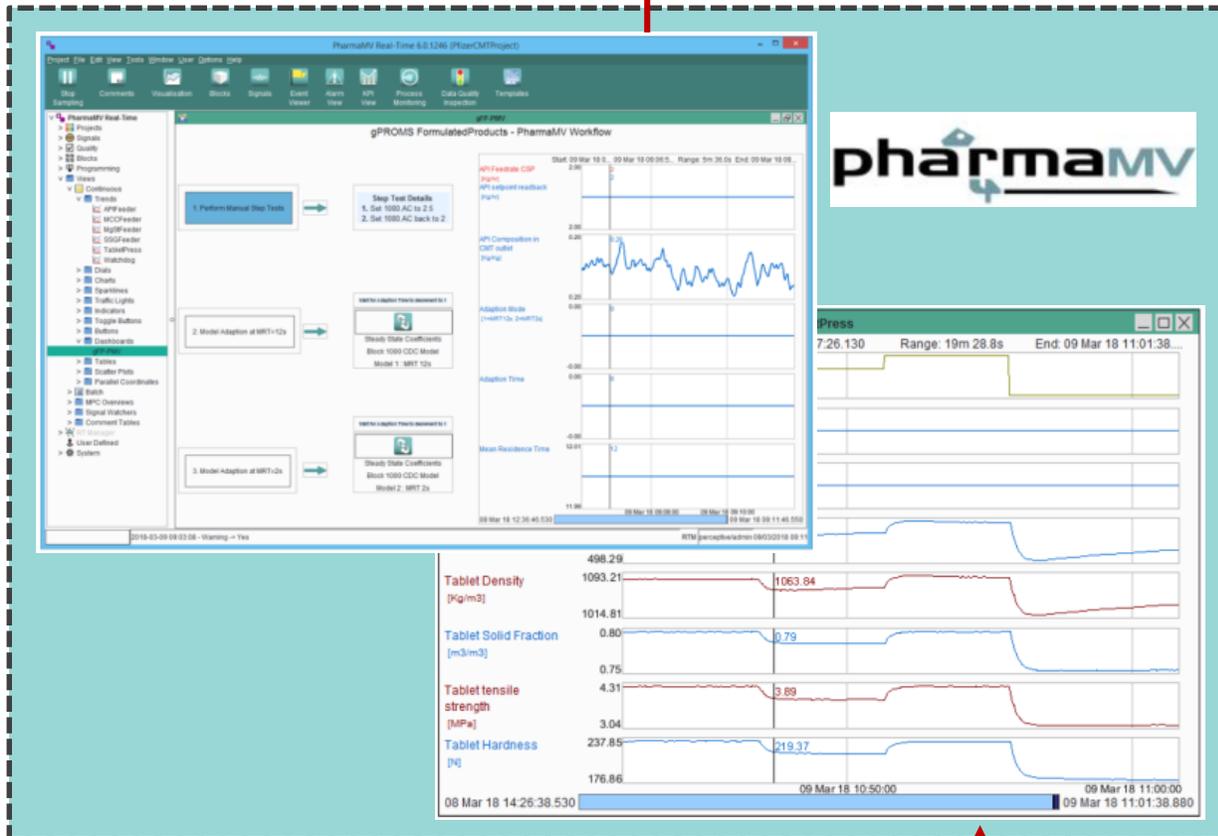


# Further applications – Process control & monitoring

Control & monitoring platform

Virtual process

Manipulated signals



Measured signals



- The analysis of interconnected flow sheet models is used to identify the critical process parameters from API crystallization to tablet compaction affecting critical quality attributes and performance of solid drug product.
- Execution of large number of simulation (Virtual DOE) and expansion to use “HPC environment” capabilities are powerful features.
- Hybrid modelling combining mechanistic and statistical models can describe material properties and process behavior.
- Seamless, integrated *in silico* modeling from API and drug product manufacture to oral absorption will become part of work-flow, to improve process robustness and product quality.
- The same models used for digital design of the drug formulation and manufacturing process can be used for digital operation.

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Many thanks for your attention!

