D3P: Digital Design of Drug Product Application of Global Systems Analysis to a Tablet Manufacturing Process

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Advanced Process Modelling Forum, London

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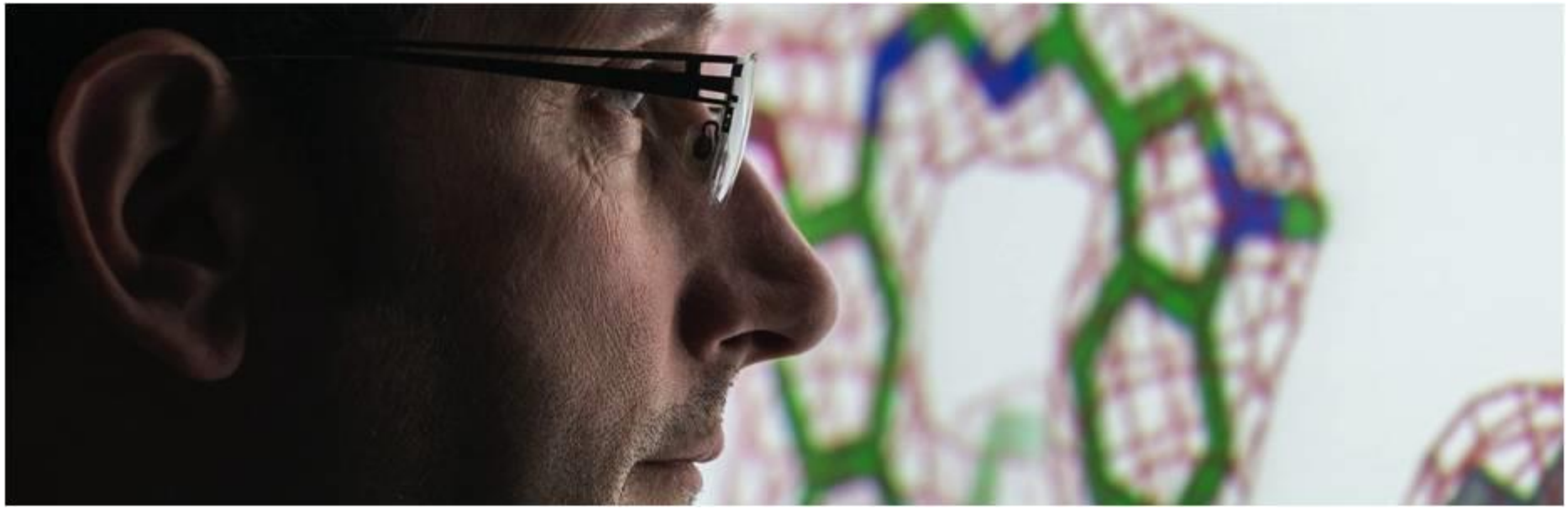


Overview

- Introduction
  - D3P Project Overview
  - Concepts
- Case Study – Application to a Tablet Manufacturing Process
- Summary

Introduction: D3P

Digital Design of Drug Products

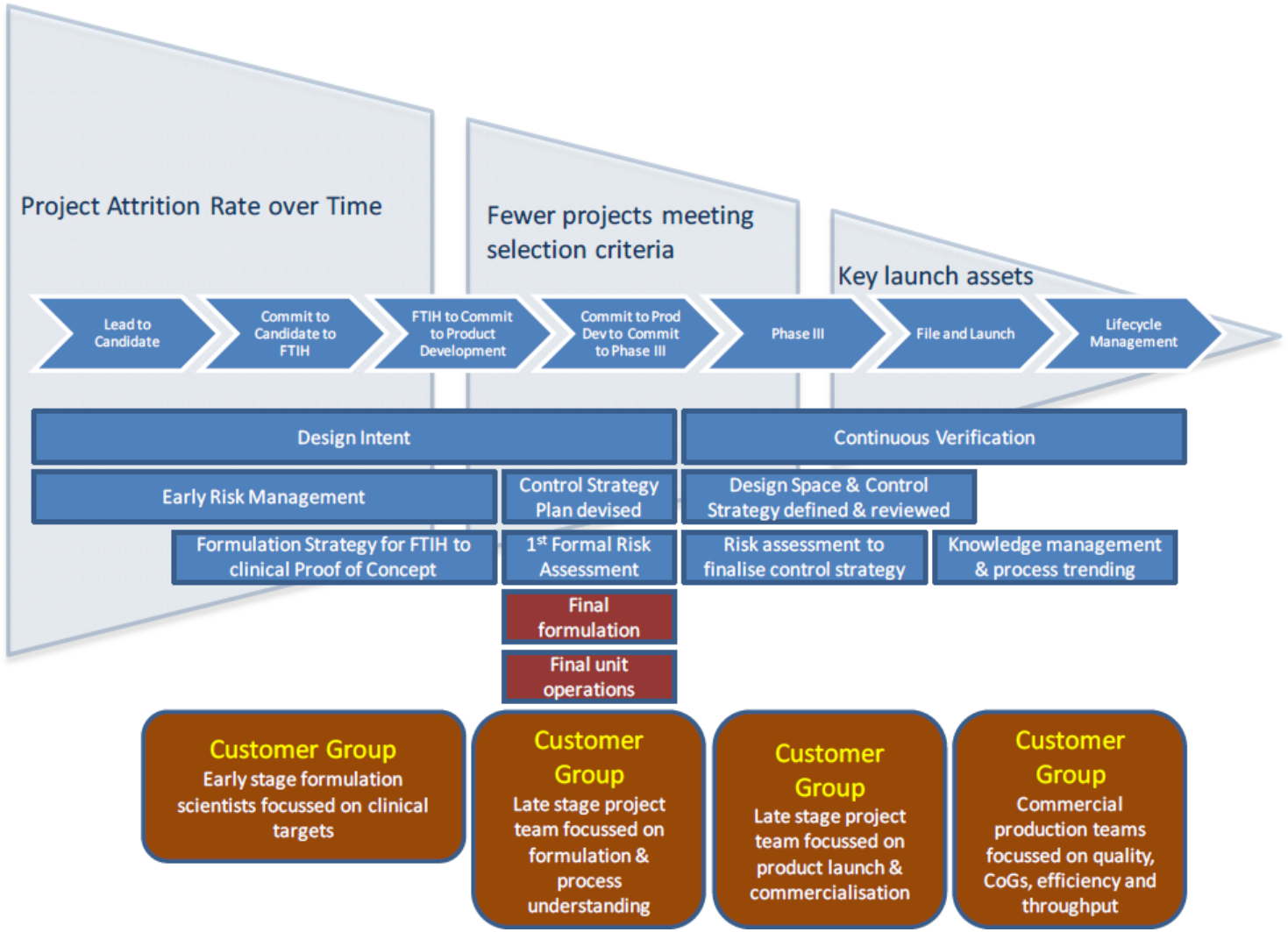
Innovate UK funded project

Two-year programme, from June 2014

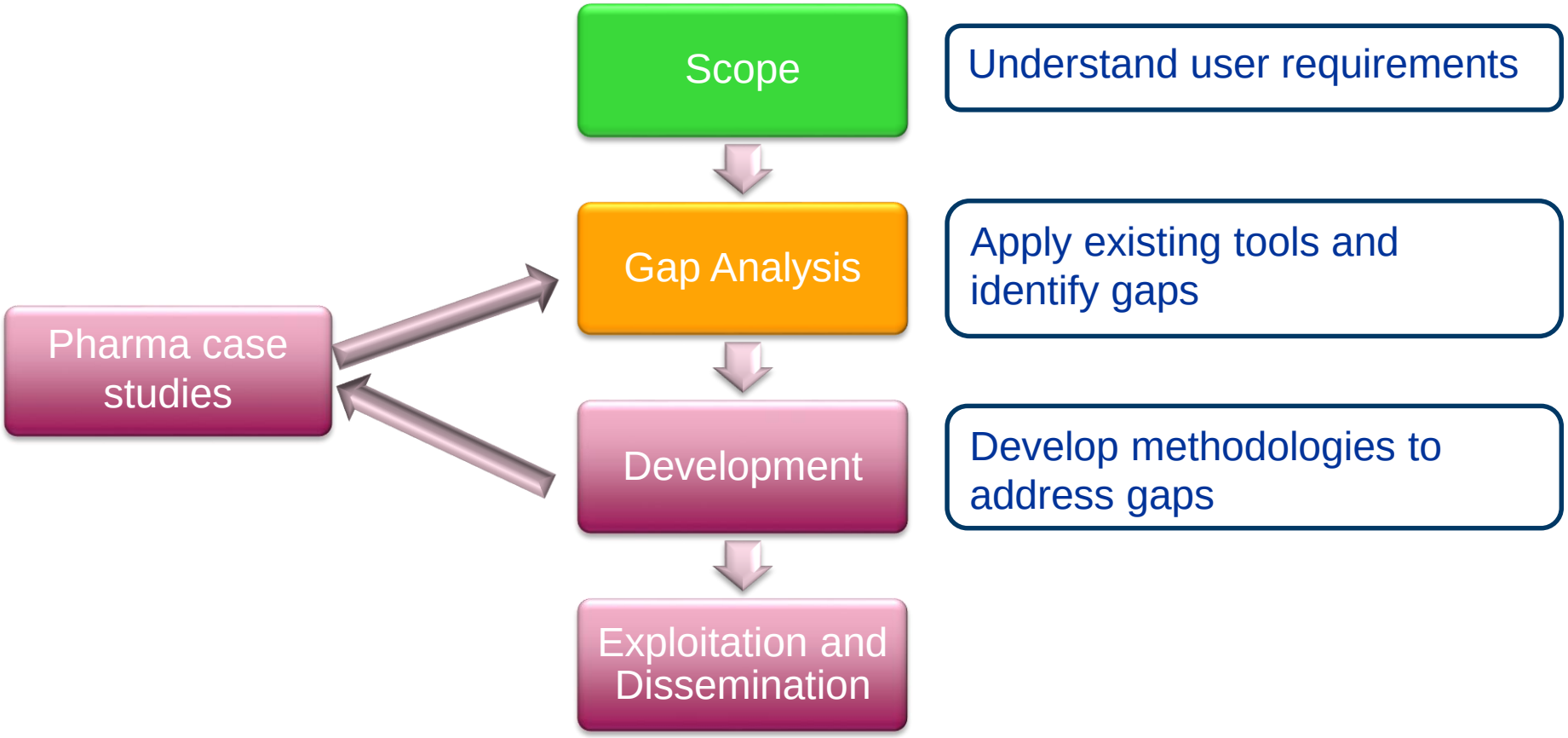
Consortium members:

Project aim

Integration of qualitative and quantitative tools to create a ‘Design Space Explorer’ to improve the design and manufacture of formulated drug products.



Project Structure



Qualitative Tools

- What CQAs need to be considered?
- What processes are important?
- What material properties, intermediate properties and process parameters are linked to the product CQAs?
- How are these properties transformed through the process?

- Generate qualitative **understanding**
- May be sufficient to aid early **decision making**
- Provides a **scope** for a more detailed quantitative model
- Can highlight the key **requirements** for an in-silico model

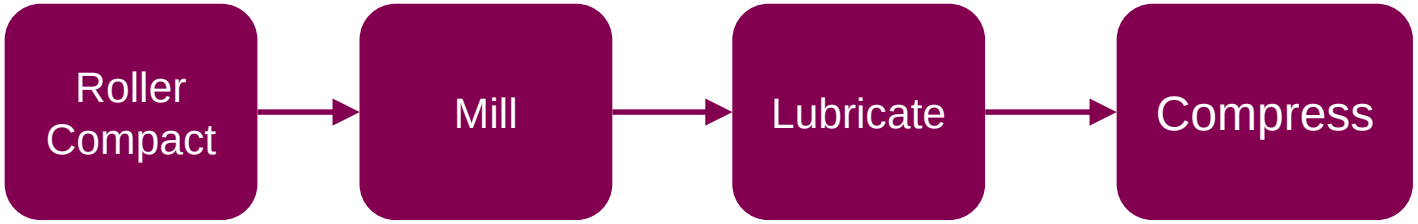
Quantitative Tools

- Mechanistic models linking the influence of material properties and process parameters on product quality attributes
- PSE already have a suite of process models and an environment for implementation of new models
- Running simulations and interpreting results can be very time consuming

- Automated interrogation of process models to quantify uncertainty and sensitivity will provide a new paradigm for utilising these tools for decision making during drug product development and establishing robust control strategies

Case Study: Application to a tablet manufacturing process

Scope



Quality Attributes

Potential CQAs	Risk	Model Response
Dissolution		
Degradation		
Appearance		Tablet tensile strength
Assay		
Content Uniformity		Granule flow (weight uniformity)
Hardness		Tablet tensile strength
Manufacturability		Tablet tensile strength and granule flow

‘Virtual Experimental Design’: Factors to investigate

FACTORS

Roller Compactor
- Roll Force
- Roll Gap
- Side Seal Leakage

Mill
- Screen Size

Lubrication
- Number of Revolutions

Tablet Press
- Pressure

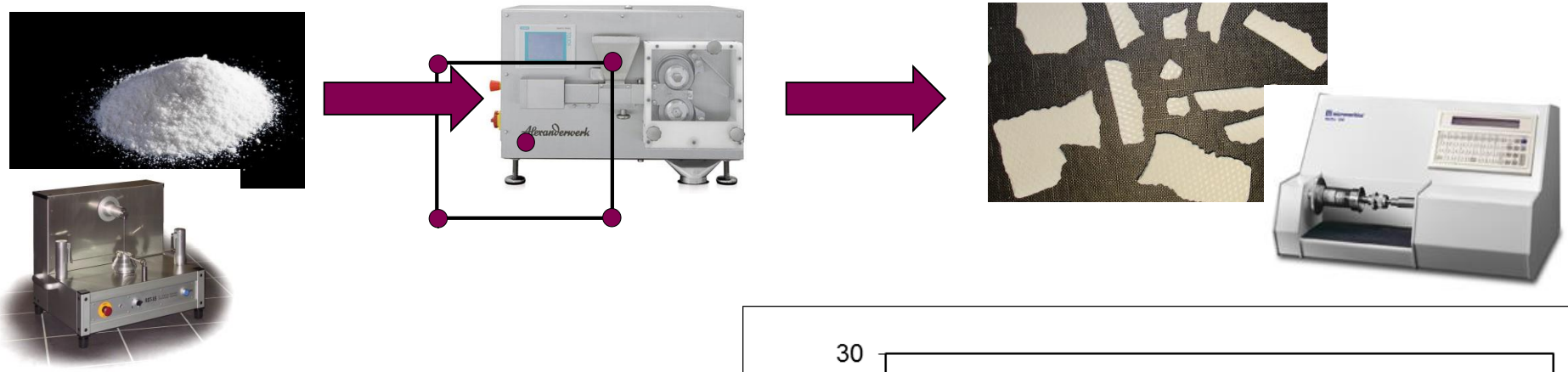
RESPONSES

Ribbon
- Porosity

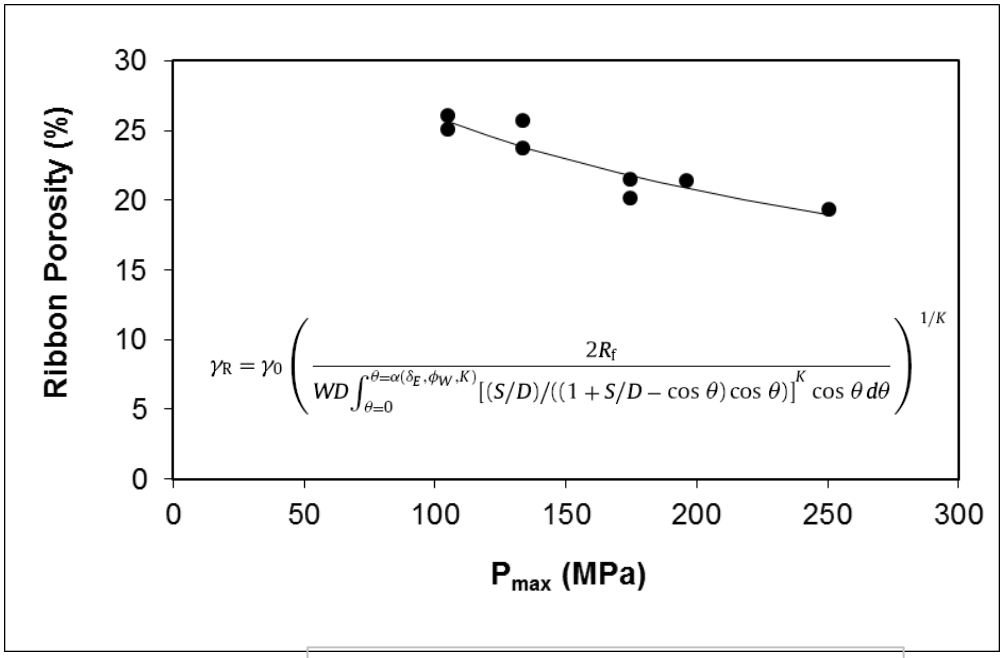
Granule
- D10
- D50
- D90
- D43
- FFC

Tablet
- Tensile Strength
- Porosity

Building the model: Roller Compactor

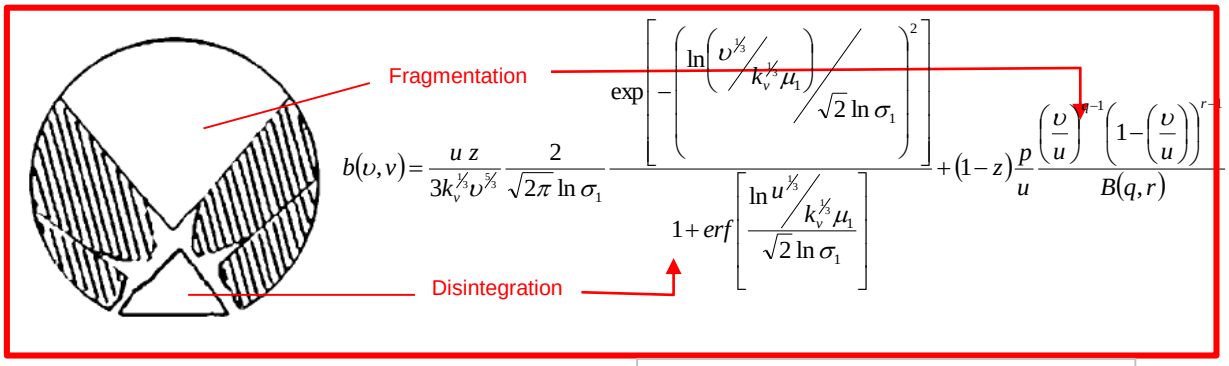


- The powder compaction properties are calibrated to RC experimental data.
- P_{max} is dependent on these parameters, so the model needs to be solved iteratively to determine γ_0 and K.



Reynolds (2010), Comp. Chem. Eng. 34, 1049

Building the model: Milling

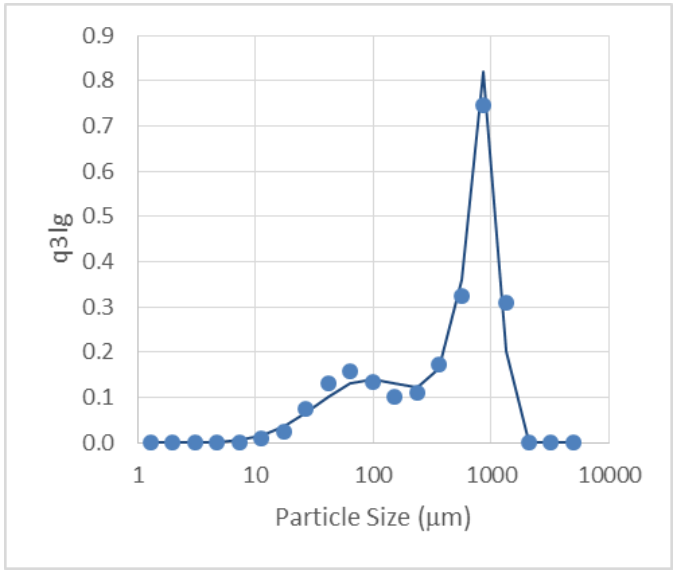


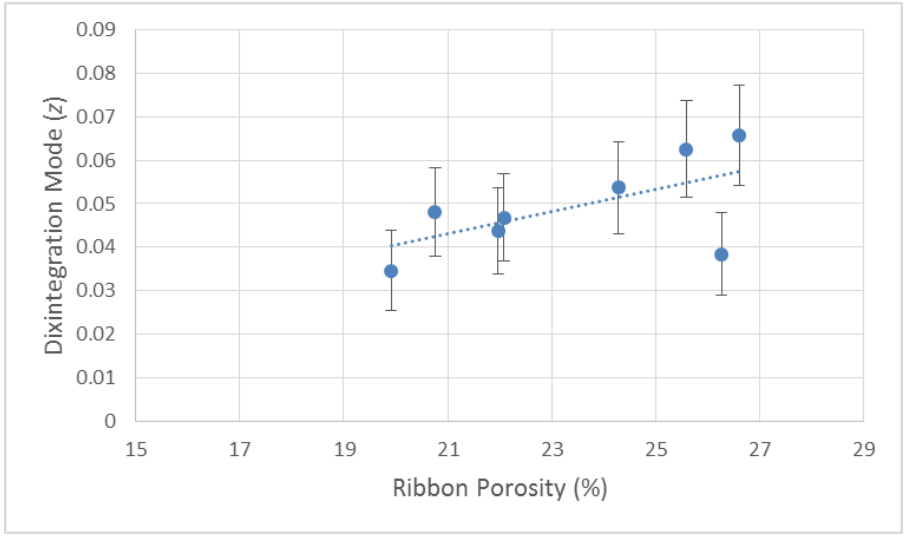
$$b(\upsilon,v)=\frac{u\,z}{3k_v^{1/3}\upsilon^{5/3}}\frac{2}{\sqrt{2\pi}\ln\sigma_1}\frac{\exp\left[-\left(\ln\left(\upsilon^{1/3}/k_v^{1/3}\mu_1\right)/\sqrt{2}\ln\sigma_1\right)^2\right]}{1+erf\left[\ln u^{1/3}/k_v^{1/3}\mu_1/\sqrt{2}\ln\sigma_1\right]}+(1-z)\frac{p}{u}\frac{\left(\frac{\upsilon}{u}\right)^{q-1}\left(1-\left(\frac{\upsilon}{u}\right)\right)^{r-1}}{B(q,r)}$$

Reynolds (2010), Chem. Eng. J. 164, 383

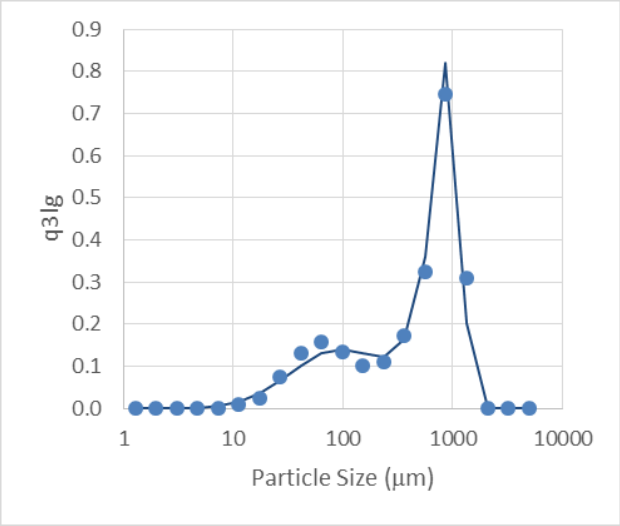
Model

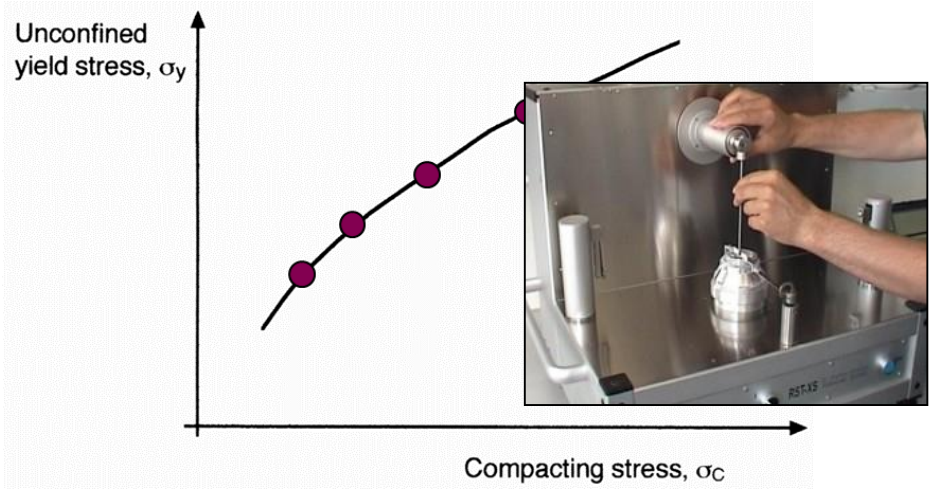
- Fine mode can be described with the size of initial powder.
- Size of coarse mode can be calculated based on screen size and dimensions of mill.
- Ratio between fine and coarse mode is a function of material properties and process parameters.



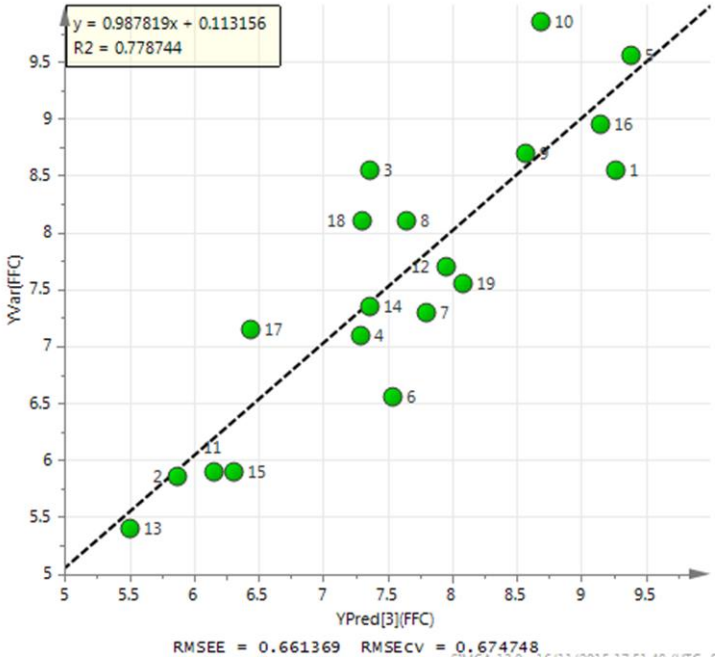


Building the model: Granule Flowability

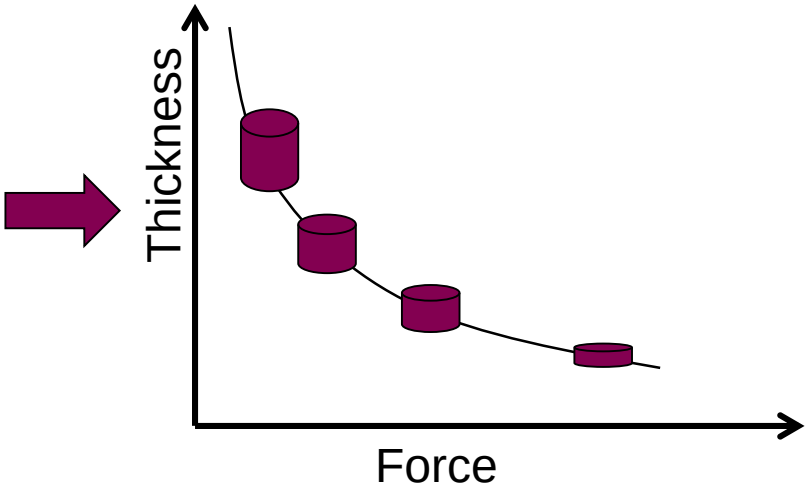




- PLS Model based on particle size metrics (d10, d50, d90 and d4,3) to predict FFC (4kPa)

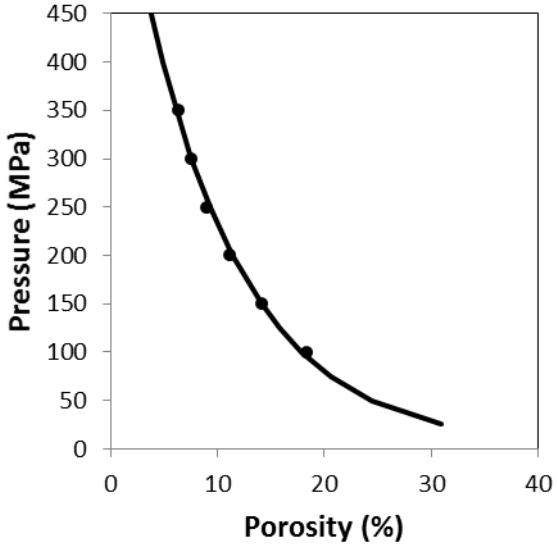


Building the model: Tablet Press

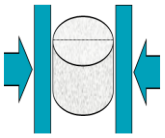


- A simple compaction model is implemented to determine tablet porosity from the tablet dimensions and punch force.

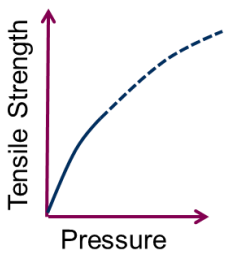
$$P = \frac{F}{A} \qquad P = P_0 \exp\left[-K\,\varepsilon\right]$$

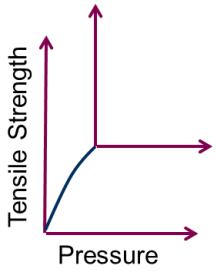


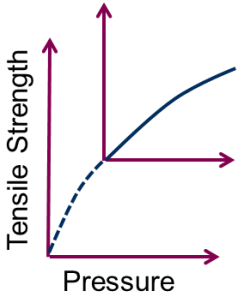
Building the model: Tensile Strength



Roller Compact → Mill → Lubricate → Compress







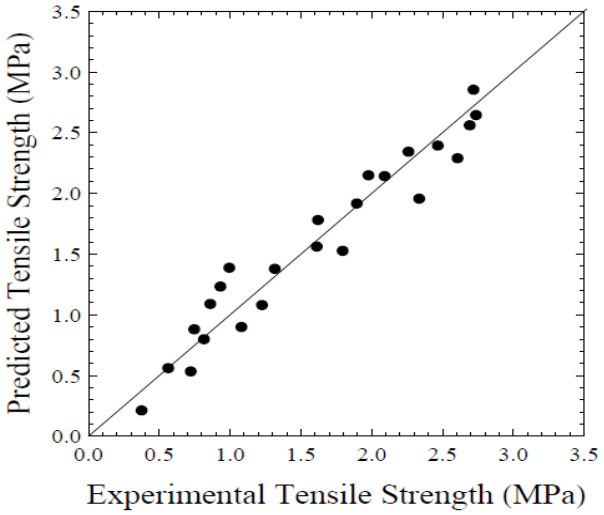
$$T_{tablet} = \overline{T}e^{-k_b\varepsilon_{tablet}} - \overline{T}e^{-k_b\varepsilon_{ribbon}}$$

Tablet porosity

Ribbon porosity

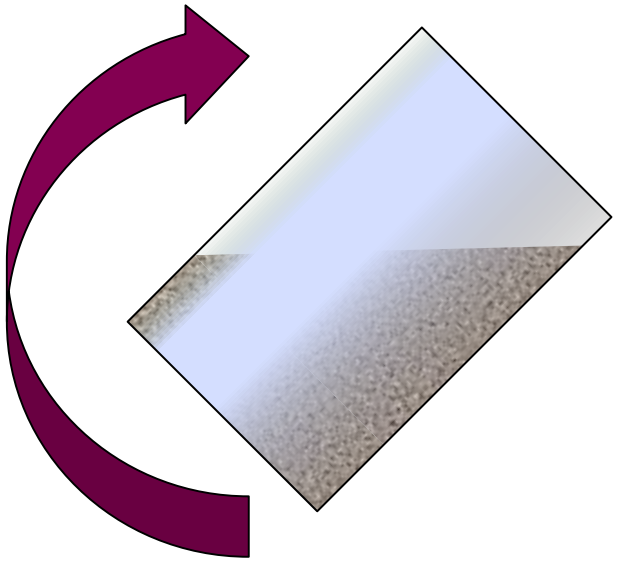
Parameter estimation

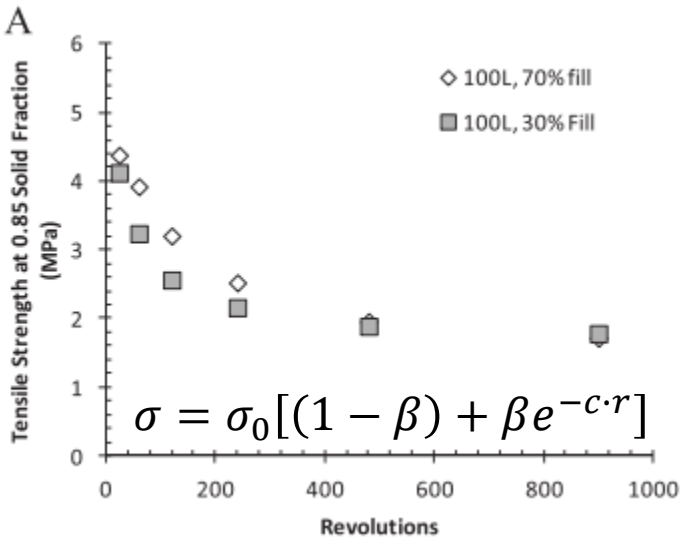
- Compaction profiles for several ribbon porosities



Gavi & Reynolds (2014), *Comp Chem Eng* 71, pp 130-140

Building the model: Lubrication

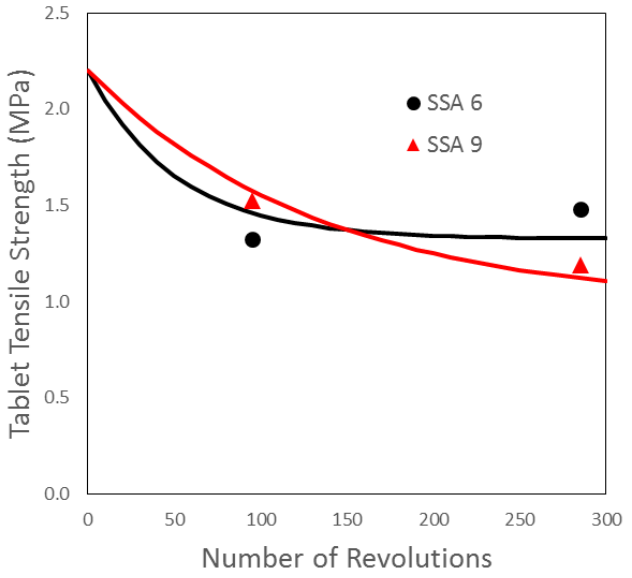




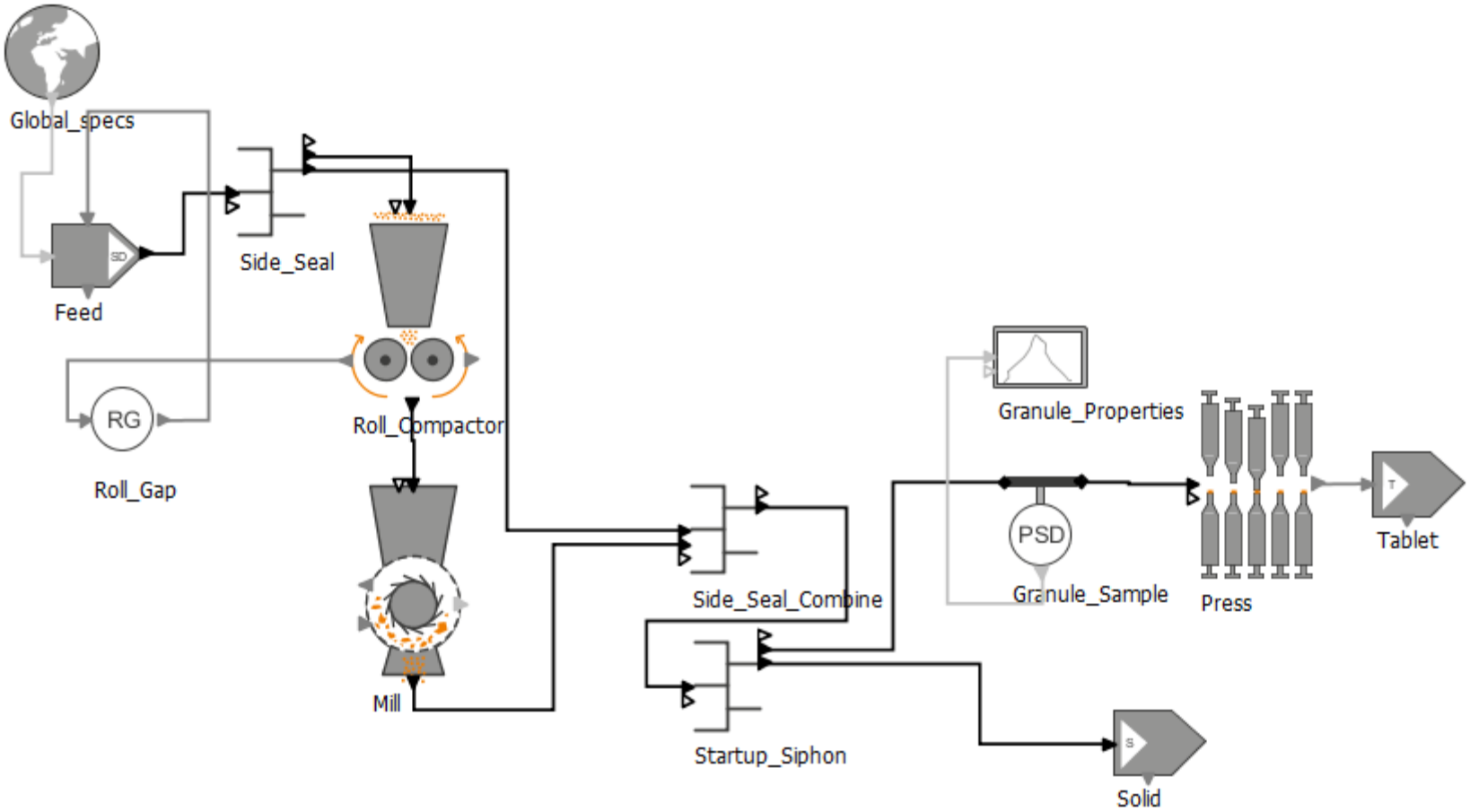
Kushner & Schlack (2014), *Int J Pharm* 475, pp 147-155

Parameter estimation:

- β and c estimated separately for lubricant SSA of 6m^2/g and 9m^2/g
- Describe extent and rate of overlubrication

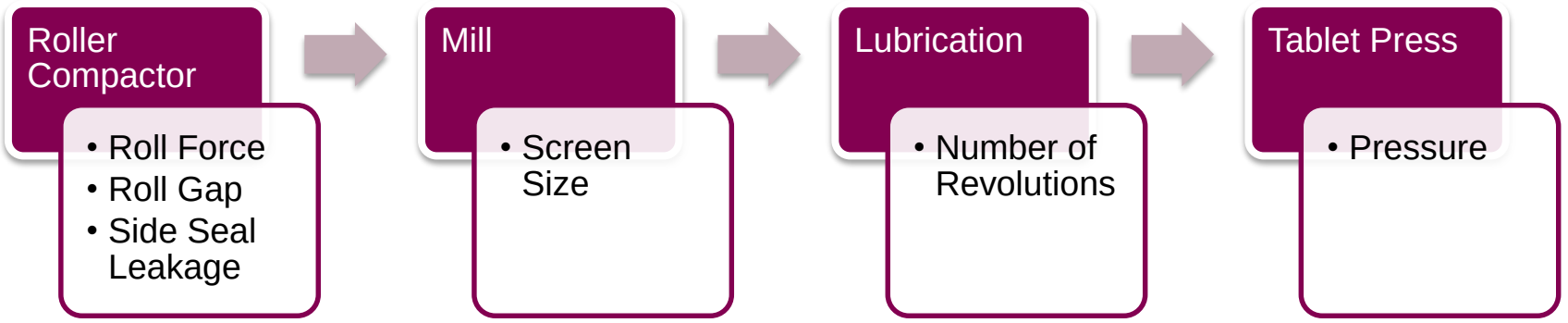


gSolids implementation

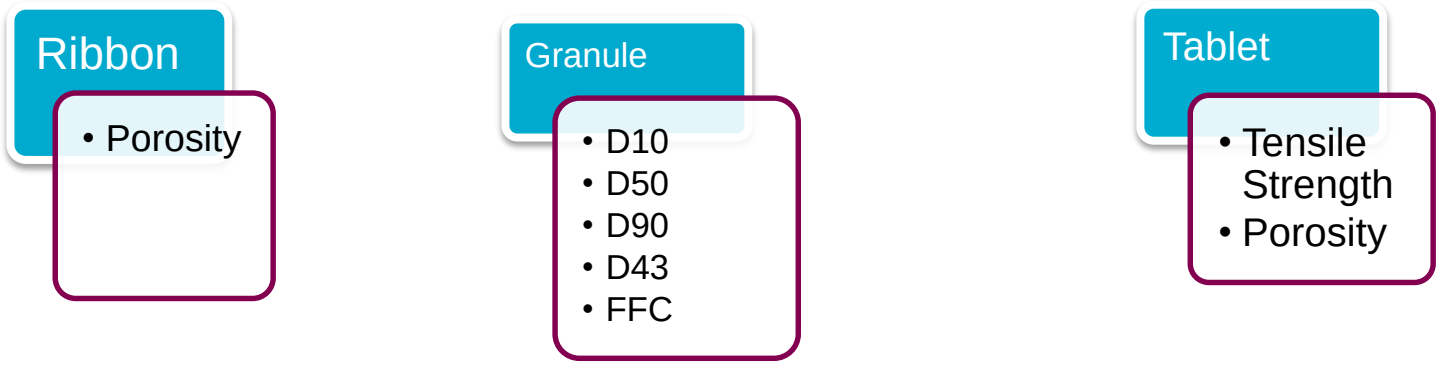


‘Virtual Experimental Design’: Factors to investigate

FACTORS

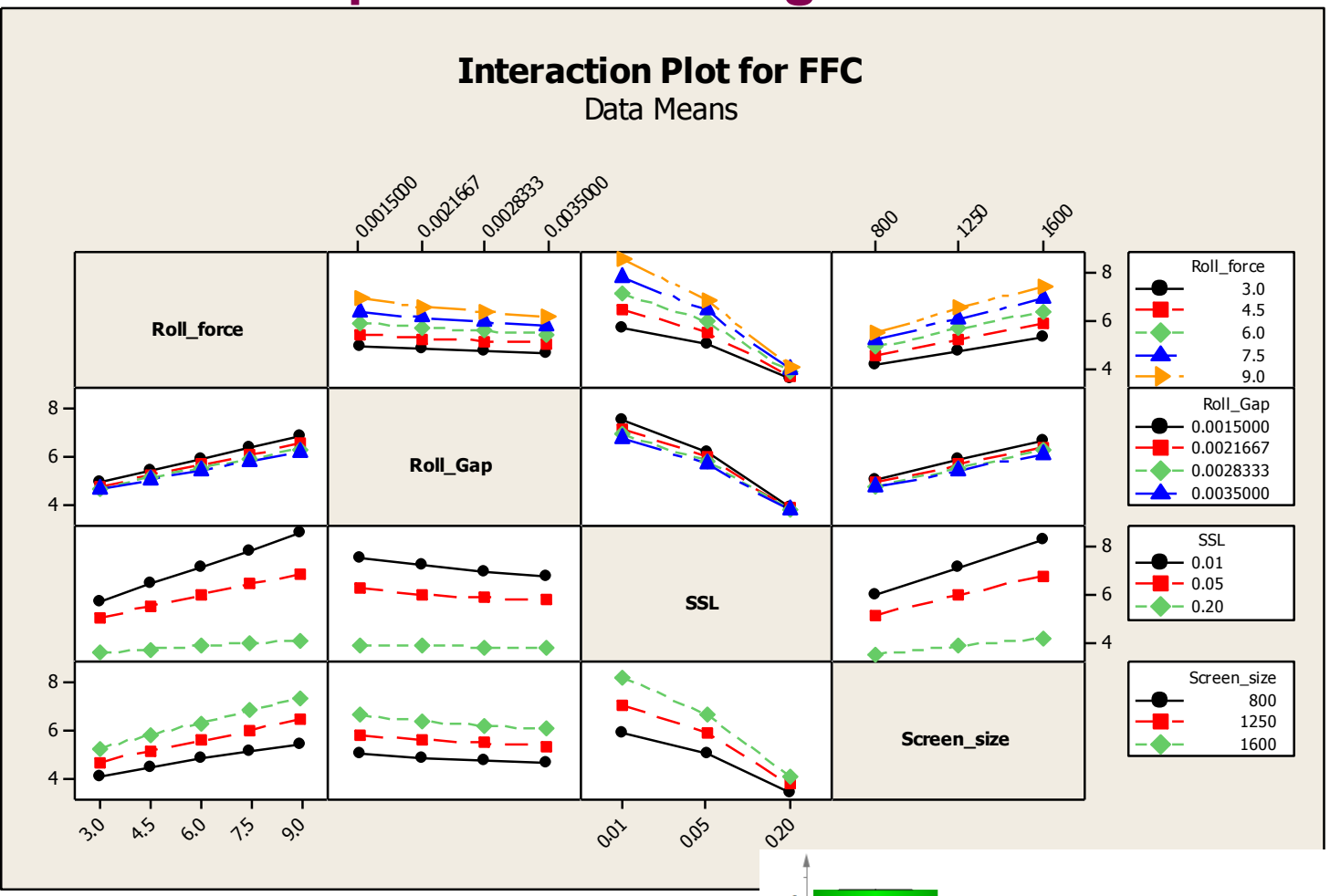


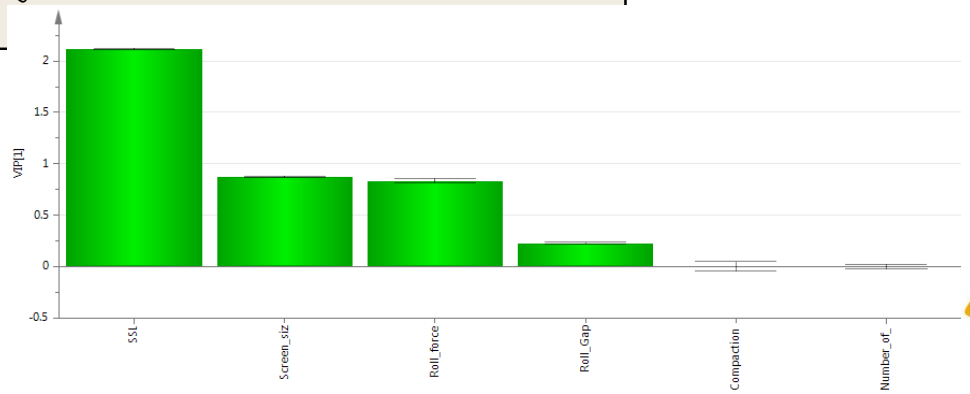
RESPONSES



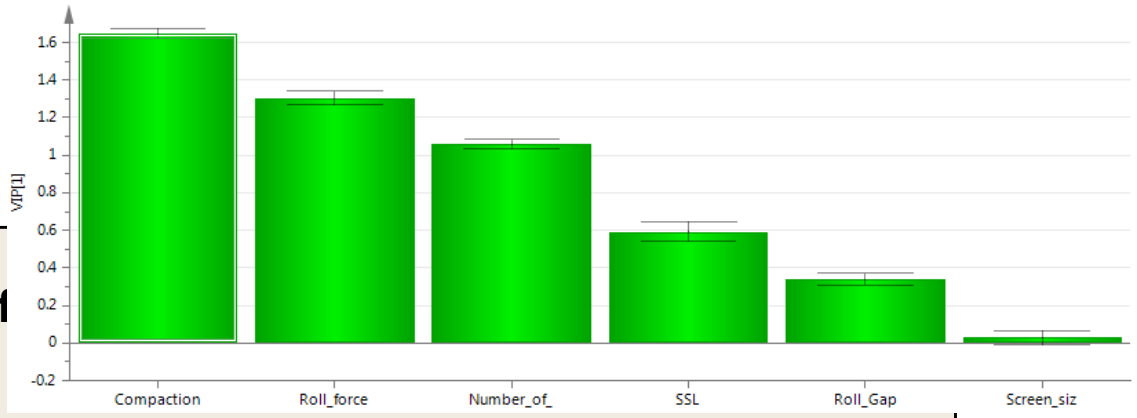
The results presented in the following slides are the result of over 3000 automated simulations performed by varying these factors.

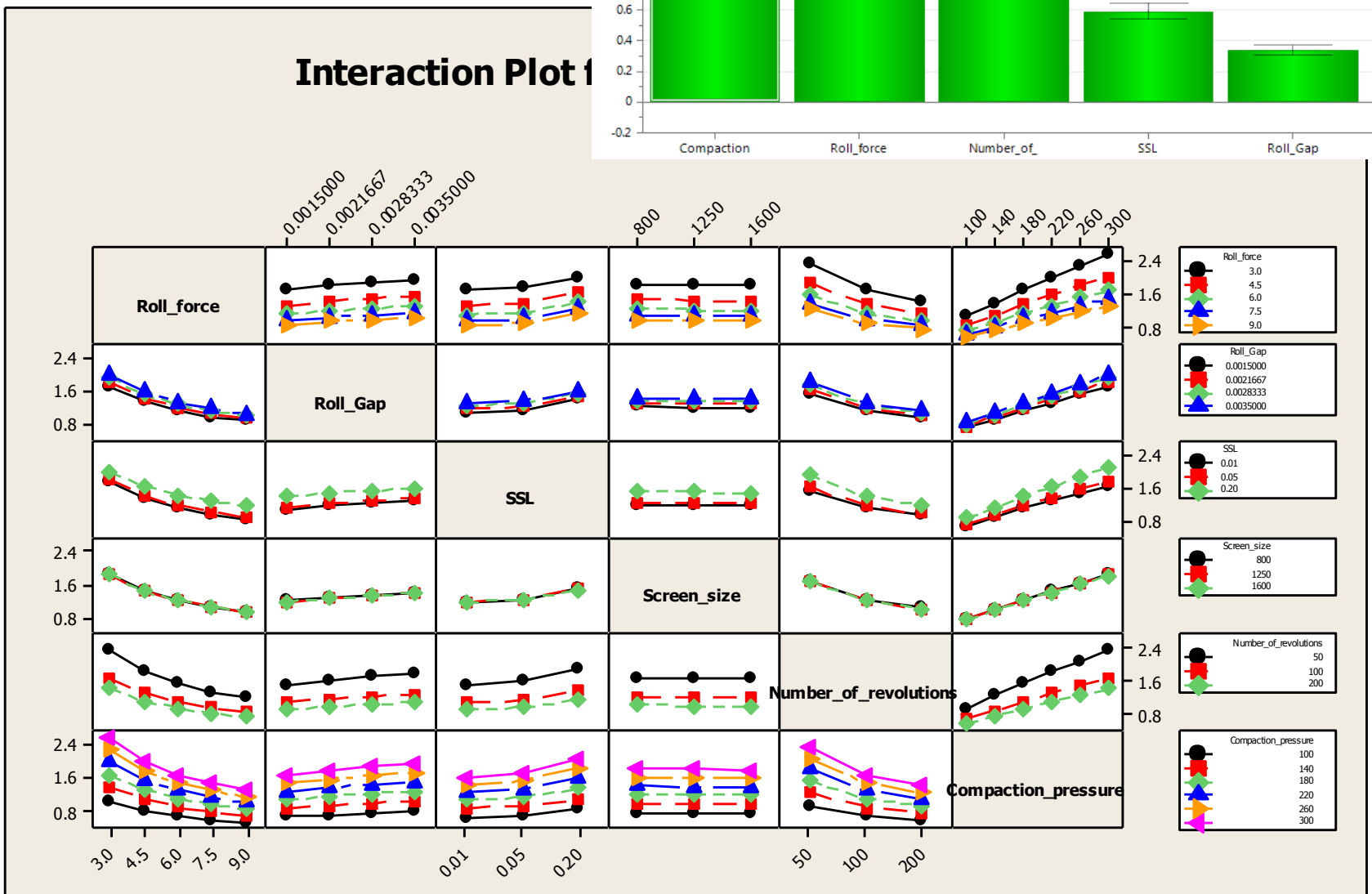
‘Virtual Experimental Design’: FFC



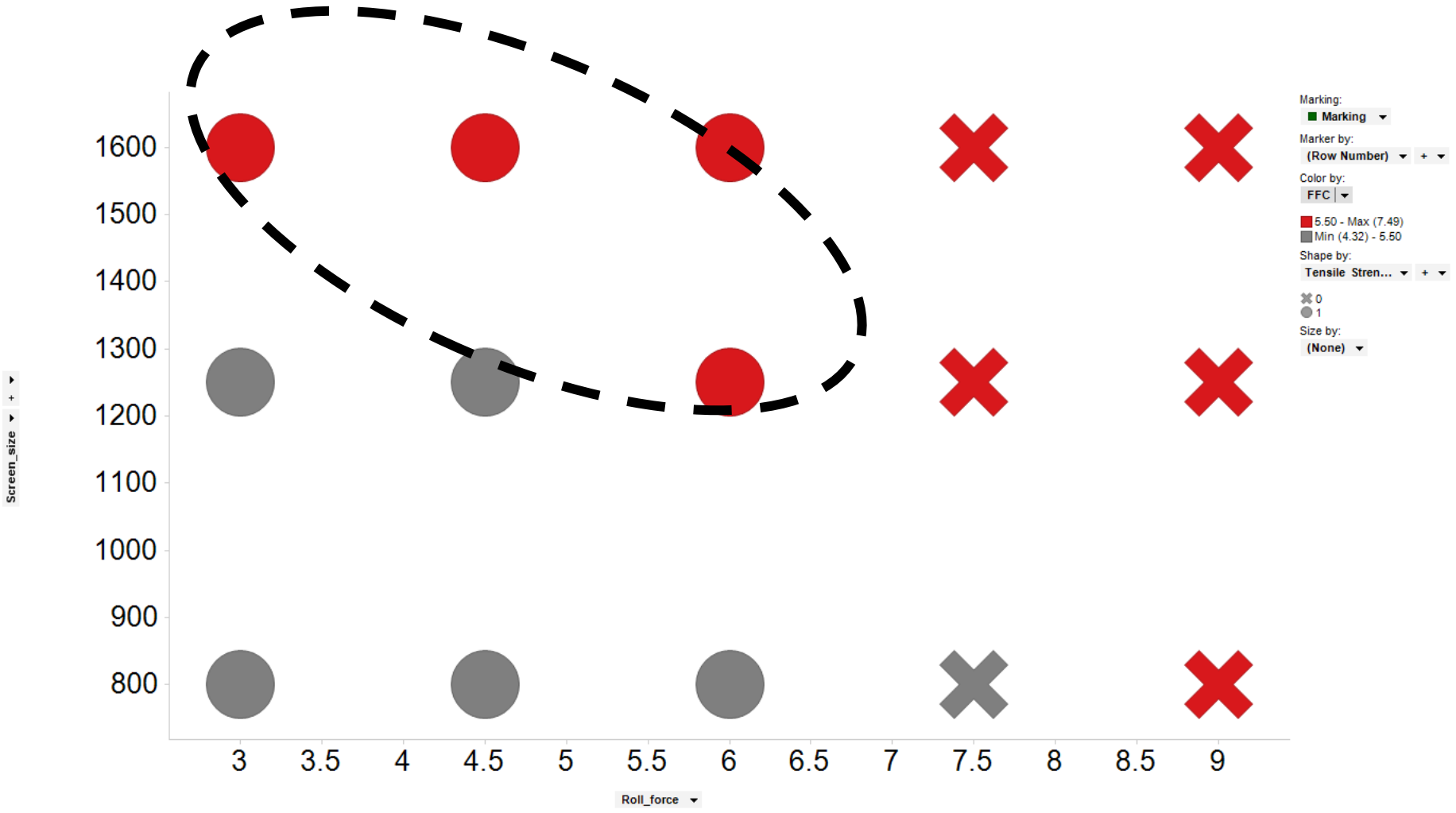


‘Virtual Experimental Design’: Tensile Strength

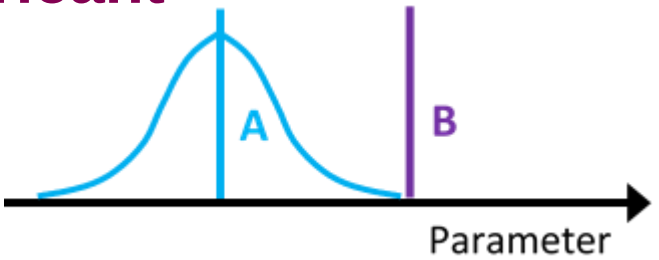




‘Virtual Experimental Design’: Operating Space

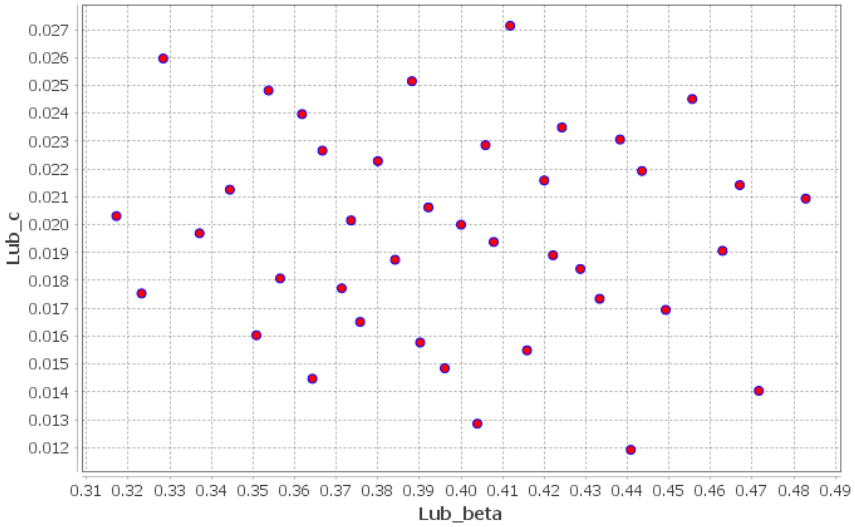


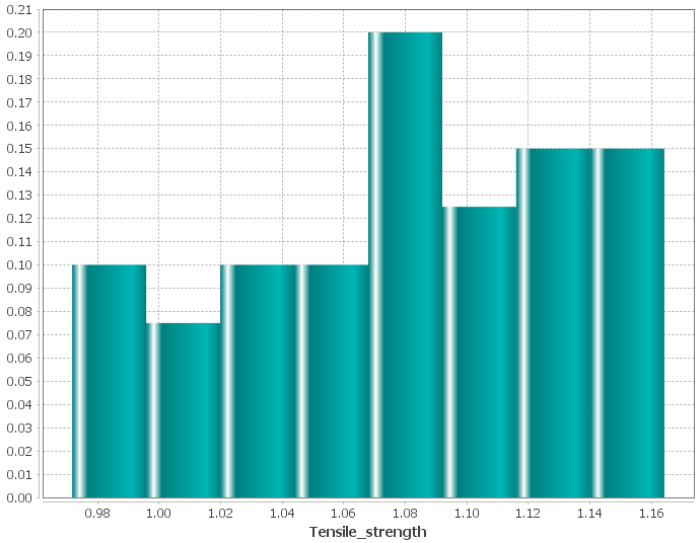
Uncertainty Analysis: Variability in lubricant



What is the impact on tablet tensile strength from variability in lubricant specific surface area?

Lubrication parameters varied using a normal distribution with mean equivalent to 6 m^2/g and span (3 standard deviations) up to the parameters for 9 m^2/g.





COV: ~ 5% Variation in tablet tensile strength

Summary

Summary

- Qualitative tools for process understanding can be used to define the scope and framework for a quantitative model
- Automated interrogation or ‘virtual experimental design’ of a system model is an efficient way to rapidly quantify the importance and criticality of material properties and process parameters on product quality attributes
- Uncertainty analysis can be used to understand the impact of variability of raw material properties on product quality attributes

Acknowledgements

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Confidentiality Notice