

# Modeling and Simulation of Cohesive Powders: An Industrial Perspective

Bill Ketterhagen

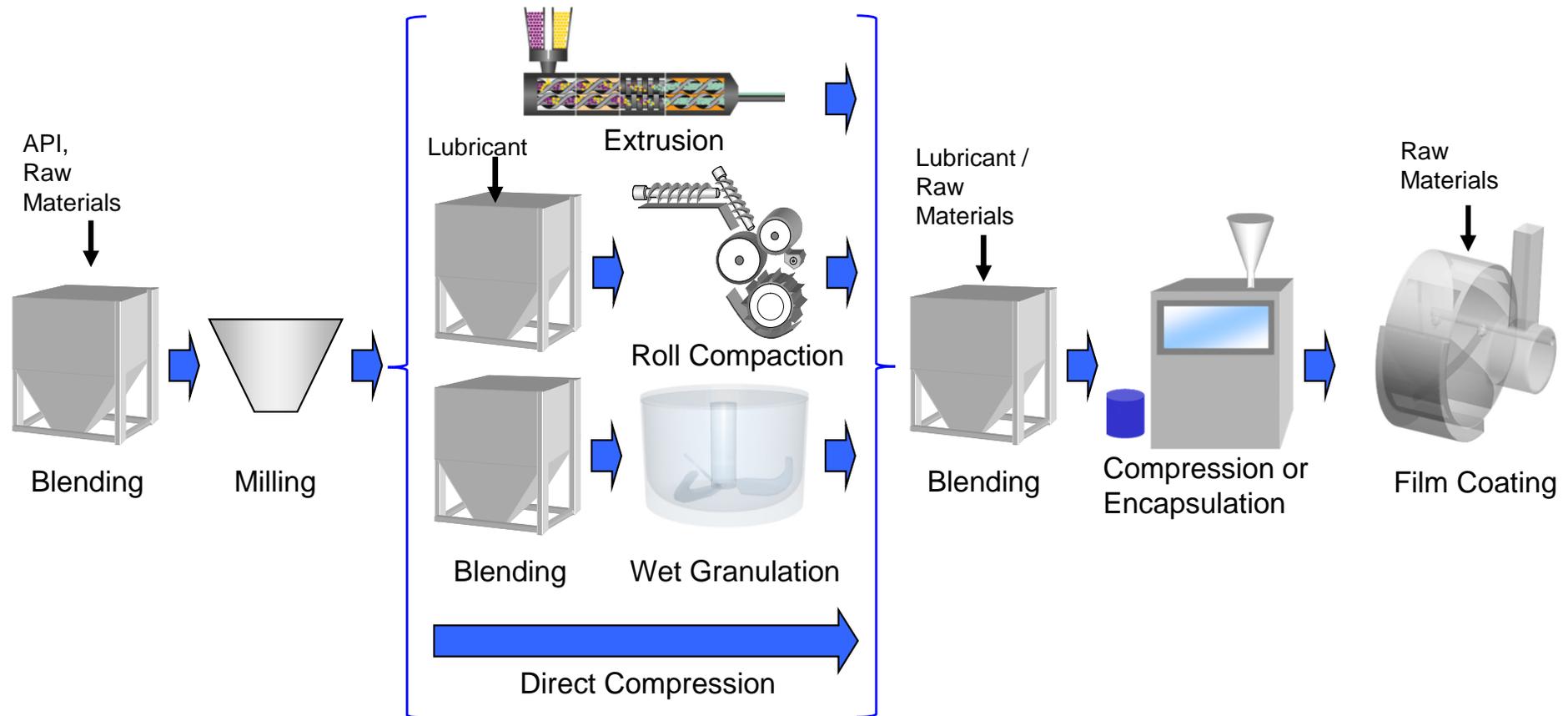
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IFPRI Cohesion Workshop

Philadelphia, PA

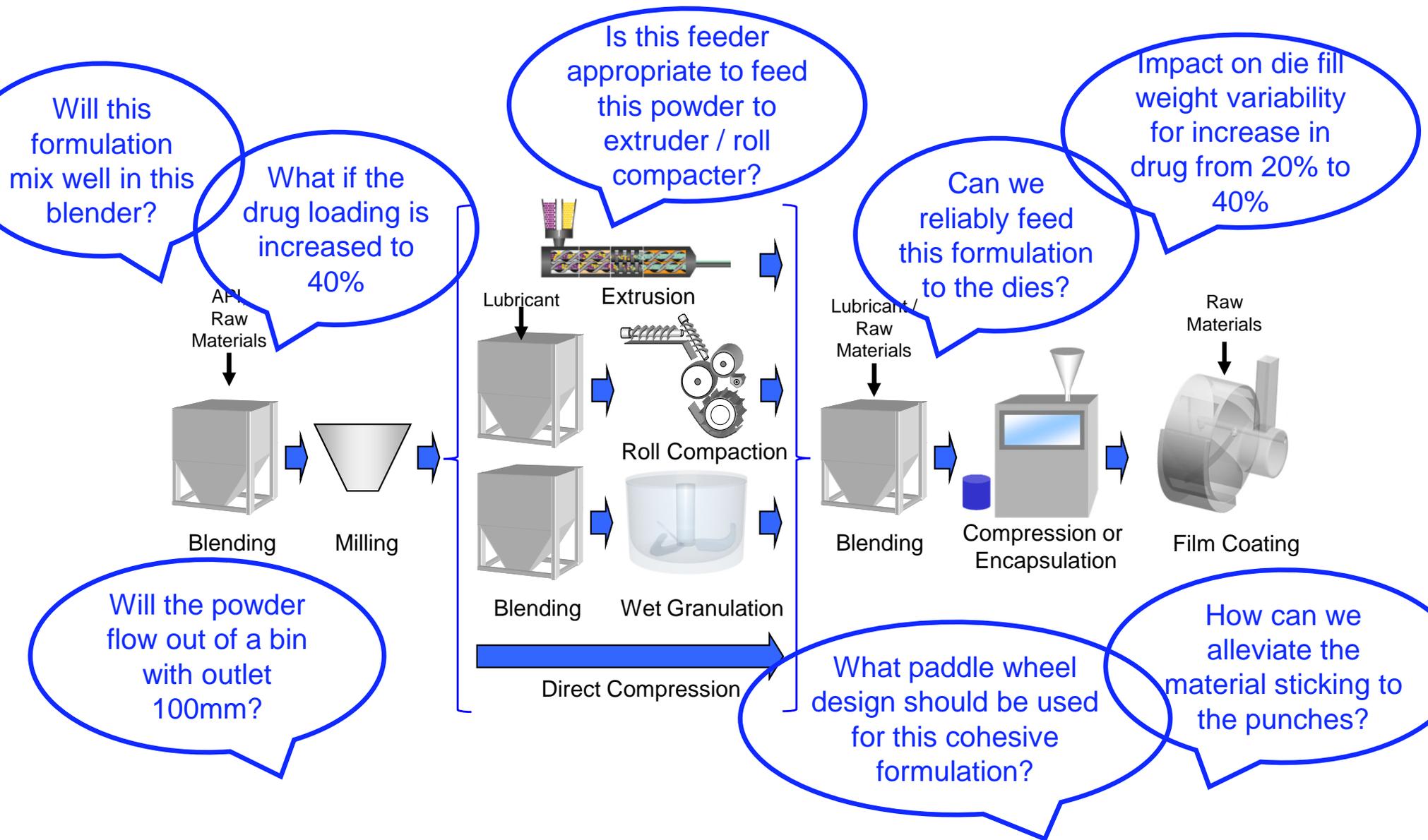
abbvie

# Common Drug Product Unit Operations



- Drug product process development
  - Unit operations a primary focus
    - Powder cohesion → Can affect powder behavior and process performance
  - Powder transfer steps: ➡
    - Powder cohesion → Significantly impacts transfer steps, especially impactful in scale-up

# Some Typical Questions Asked during Development and Scale-Up



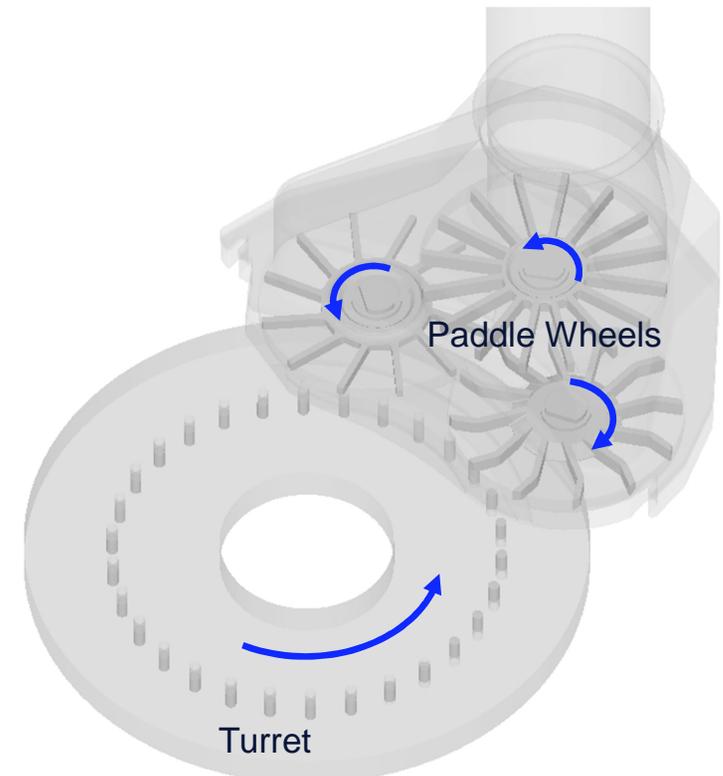
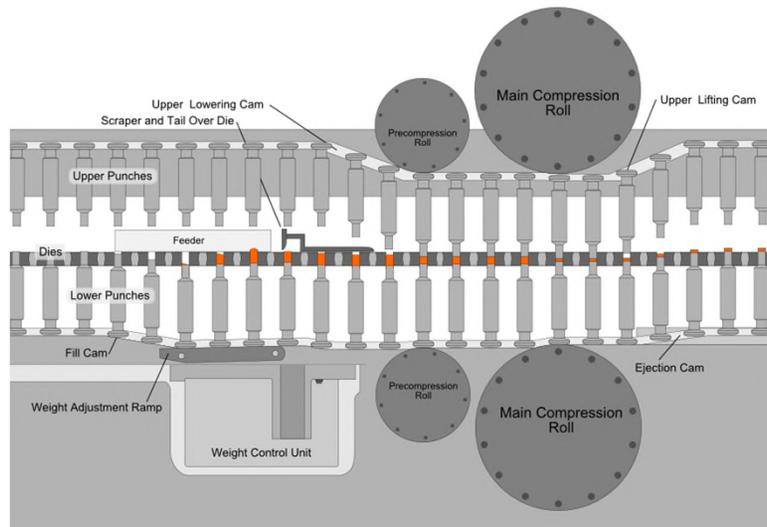
**Many questions about processing, flow, and feeding of cohesive powders!**

# Tablet Compression

- The feeding of powders to the tablet dies is an important last step prior to compaction. During compaction, tablet...
  - Mass is fixed
  - Content is fixed
- Difficult to determine what powder flow phenomena may be occurring under various conditions



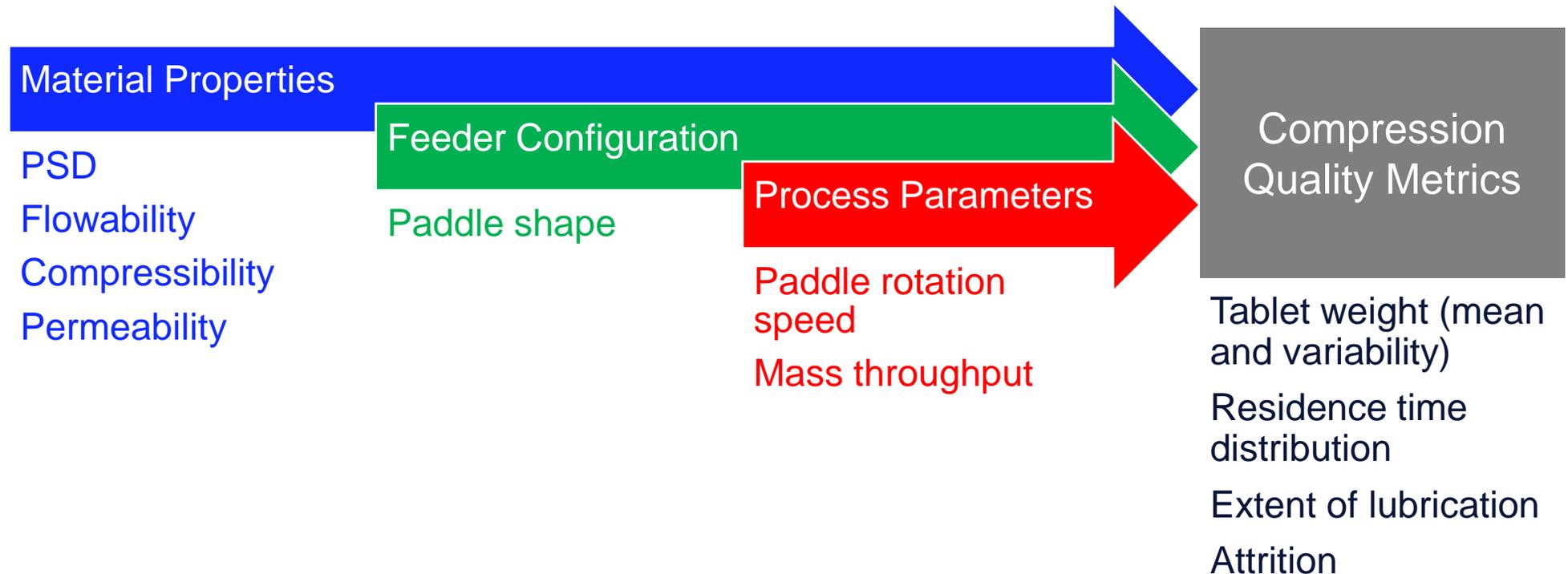
Feed Tube



Turret

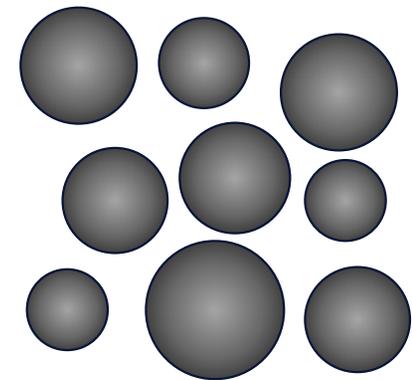
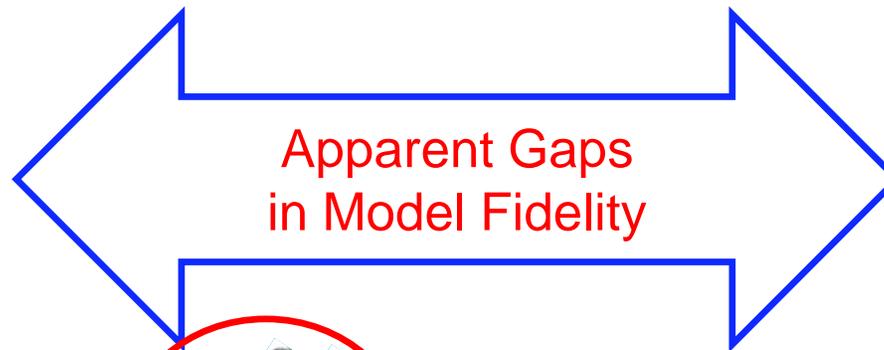
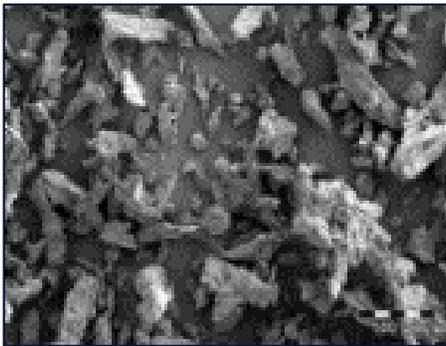
# Tablet Compression

- Seek to improve understanding of feeding process
- Streamline feeder setup and selection of process parameter ranges



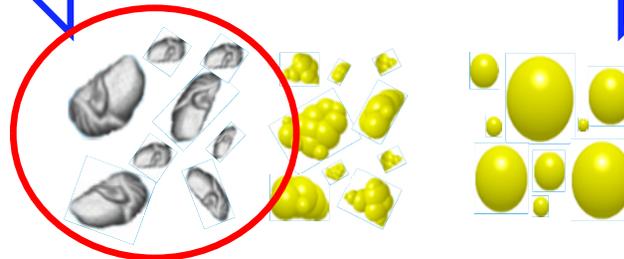
# Application of DEM to Fine Powders

- DEM can be a useful tool to better understand the behavior of bulk solids
  - Explore process design space computationally
  - Guide process development with **actionable predictions**
    - Use modeling to make the next decision in the development process **more quickly, confidently, efficiently**



## Majority of Powders

- Complex shapes, asperities, roughness
- Wide PSD (~1000-fold range)
- Anisotropic surface properties
- Heterogeneous composition

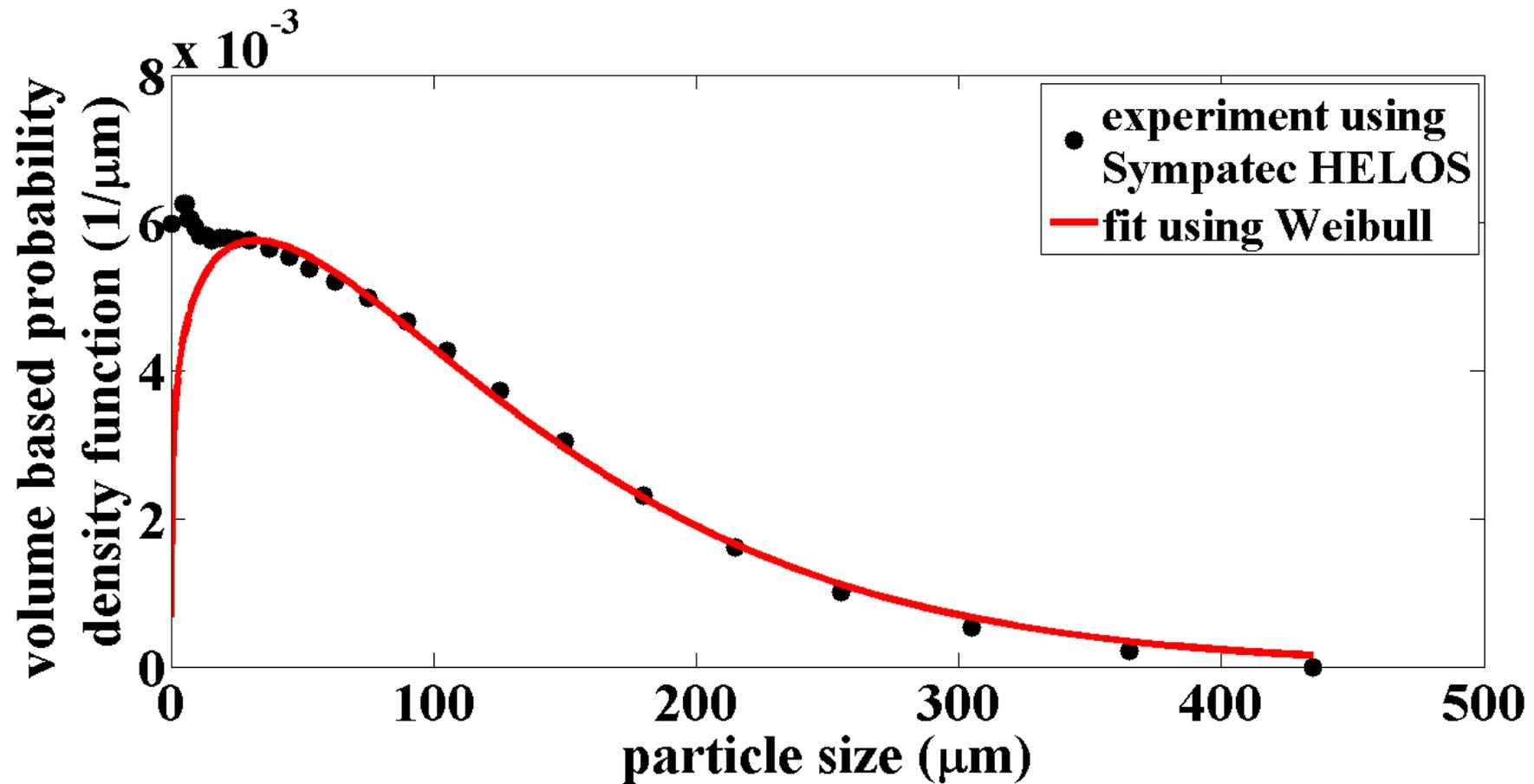


## Majority of DEM Models

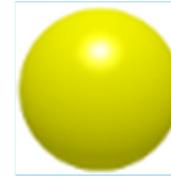
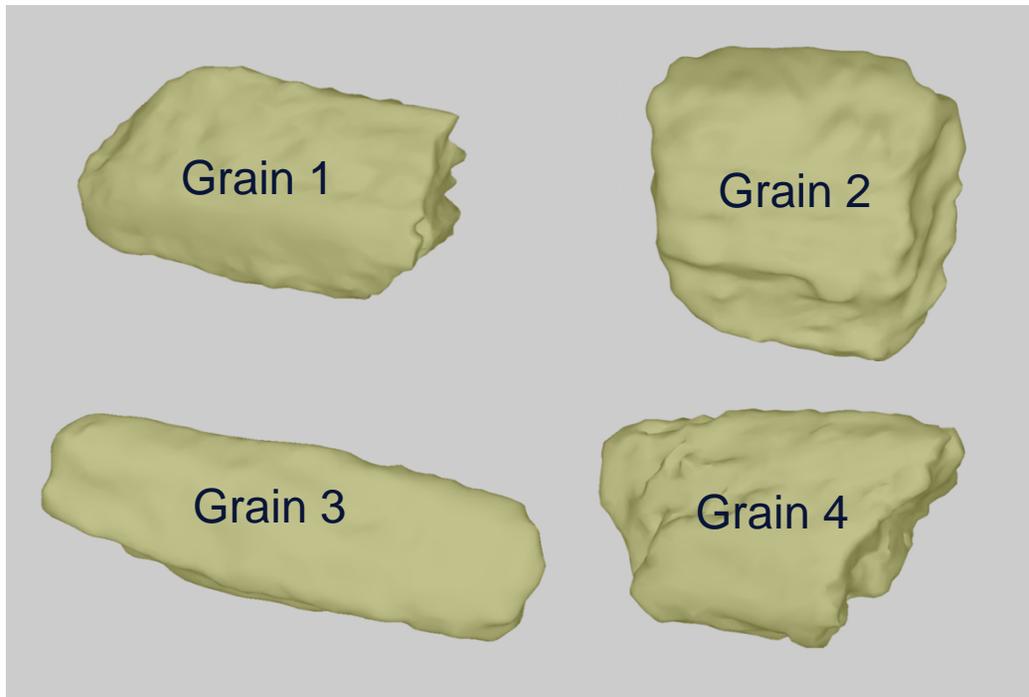
- Simplified shapes
- Narrow PSD (~10-fold range)
- Simplified physical models

# Particle Size Distribution

- Test material: L-proline
  - Moderately cohesive, poorly flowing powder, FFC ~ 3



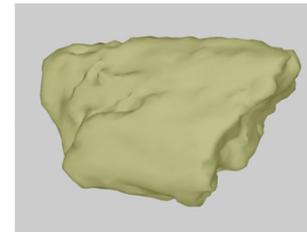
# MicroCT Imaging of Particles



Spherical approximation



Glued-spheres approximation  
(e.g. EDEM)

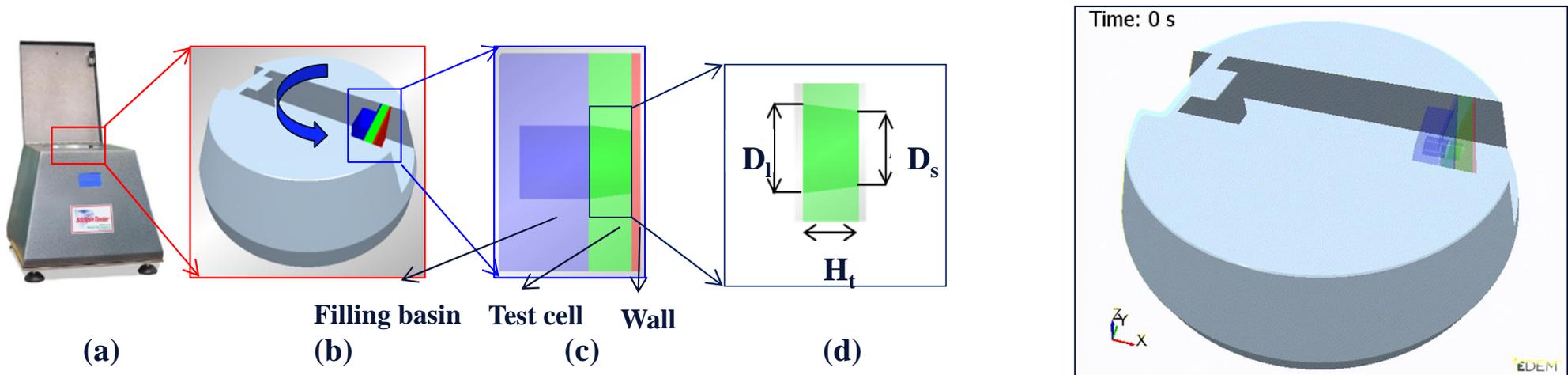


Actual representation  
using polyhedrons  
(e.g. Rocky-DEM)

CAD models of actual particle shapes are obtained through microtomography

# The SSSpinTester (Material Flow Solutions)

- Uses centrifugal forces to compress then measure the **unconfined yield strength (UYS)** of fine powders.
  - UYS is predictive of powder flowability, e.g., hopper discharge.
- Very fast analysis using very small amount of material (~0.5 g).
- Limitation: Only applicable to powders with moderate cohesiveness.

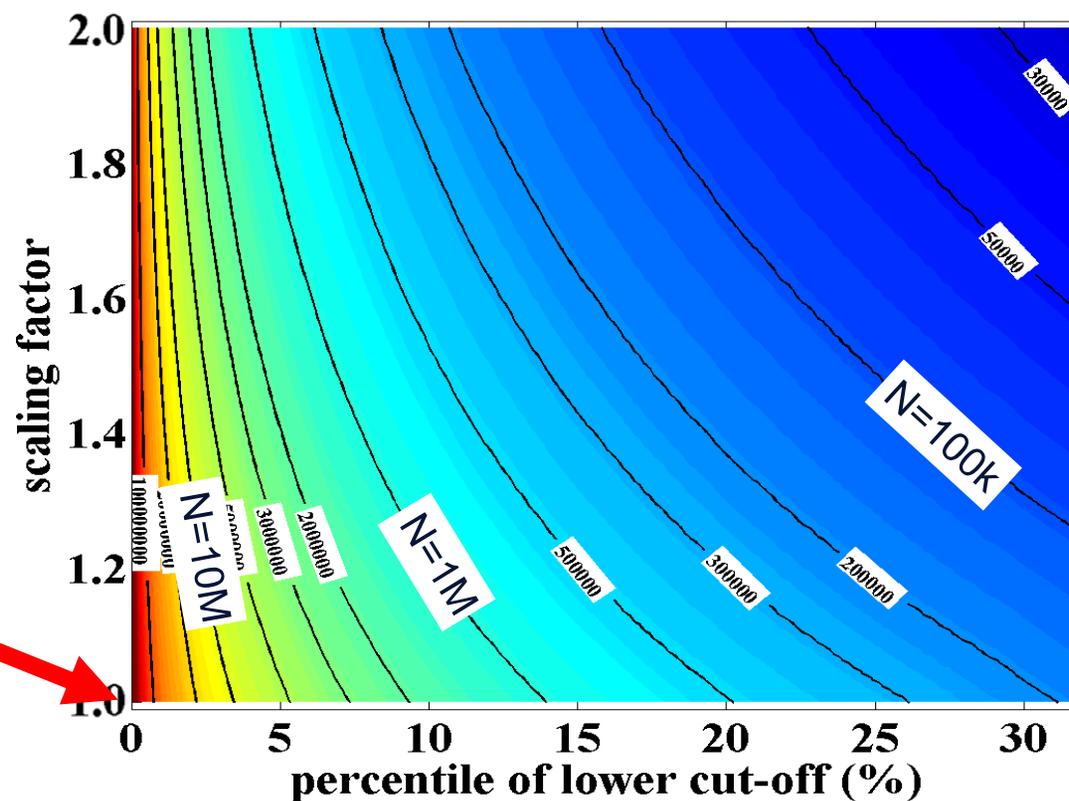


- Volume of test chamber  $\sim 100 \text{ mm}^3$  – about the size of a pencil eraser
  - We should be able to model this volume of powder using DEM in a realistic way!
    - **No, it's too computationally intensive!**



# Estimate Number of Real Particles in SSSpinTester

## Polydisperse (Weibull) size distribution



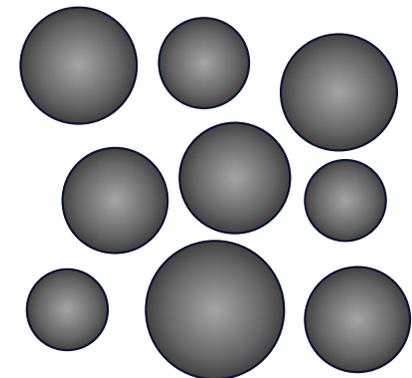
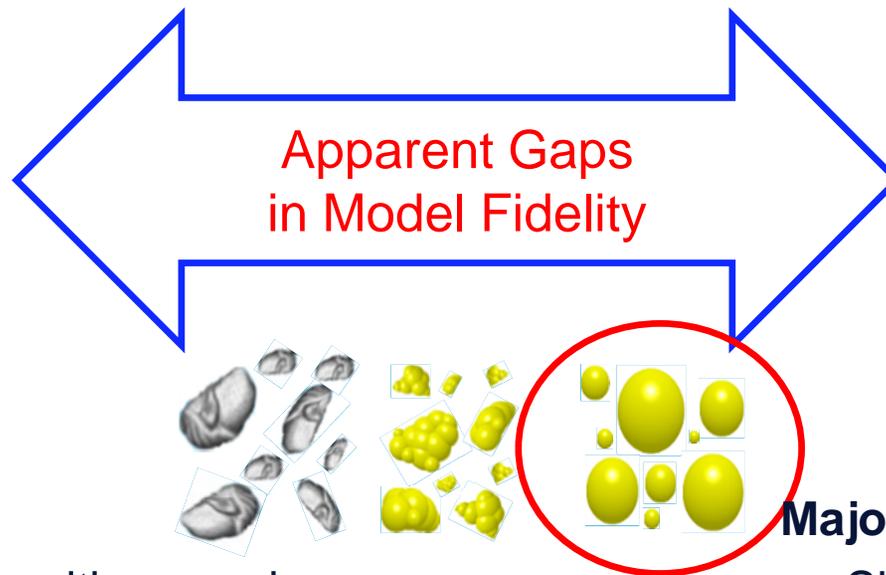
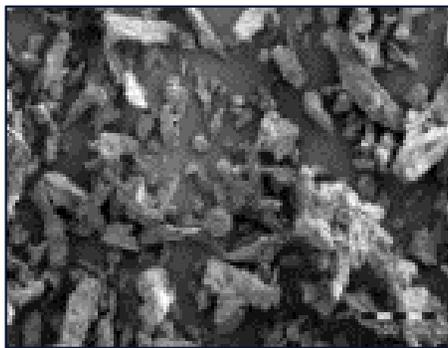
Full distribution,  
with no scaling of  
particle size  
requires  $N > 100$   
million particles

(a)

- Computational approaches:
  - Either scale up the particle size,
  - Or exclude the smaller particle sizes from the PSD – huge reduction in the total number of particles

# Application of DEM to Fine Powders

- DEM can be a useful tool to better understand the behavior of bulk solids
  - Explore process design space computationally
  - Guide process development with **actionable predictions**:
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## Majority of Powders

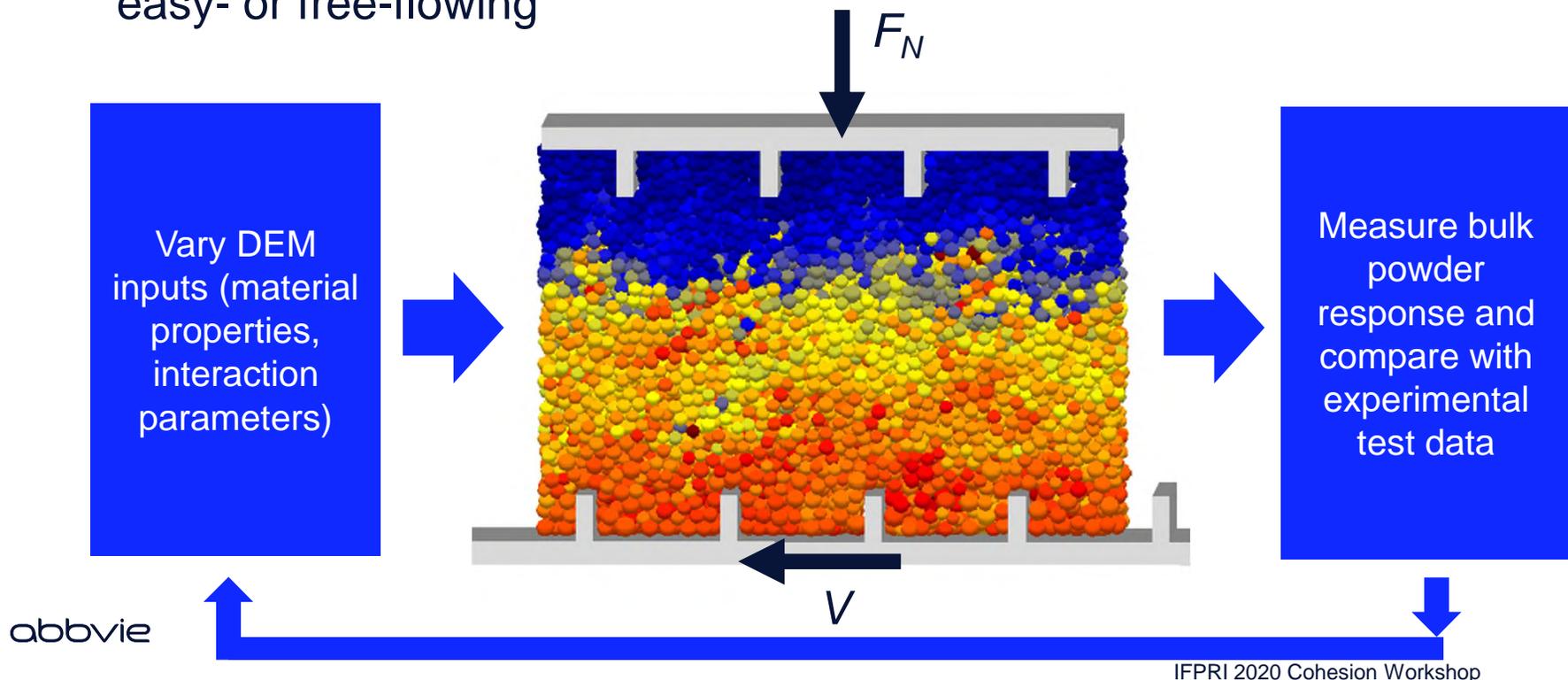
- Complex shapes, asperities, roughness
- Wide PSD (~1000-fold range)
- Anisotropic surface properties
- Heterogeneous composition

## Majority of DEM Models

- Simplified shapes
- Narrow PSD (~10-fold range)
- Simplified physical models

# DEM Material Model Calibration

- Model simplifications
  - Particle size distribution:  $d = 1.40 \pm 0.14$  mm, spherical shape, ...
- Model calibration based on shear cell test
  - Hertz-Mindlin contact model (non-cohesive)
  - Not expecting accurate predictions of particle-scale phenomena
  - Aim for reasonable predictions of bulk-scale kinematics for powders that are easy- or free-flowing

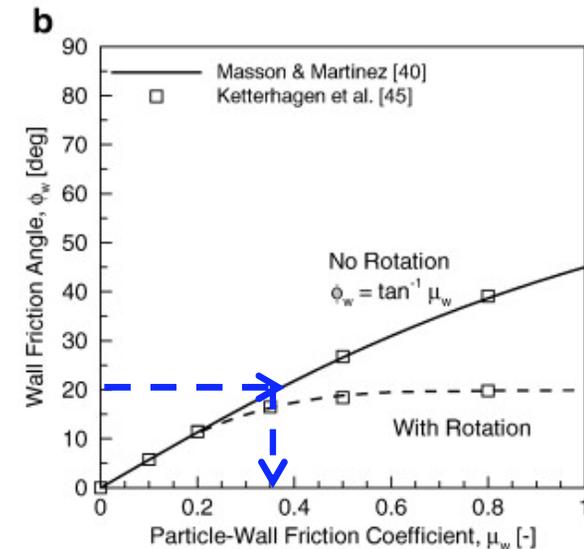
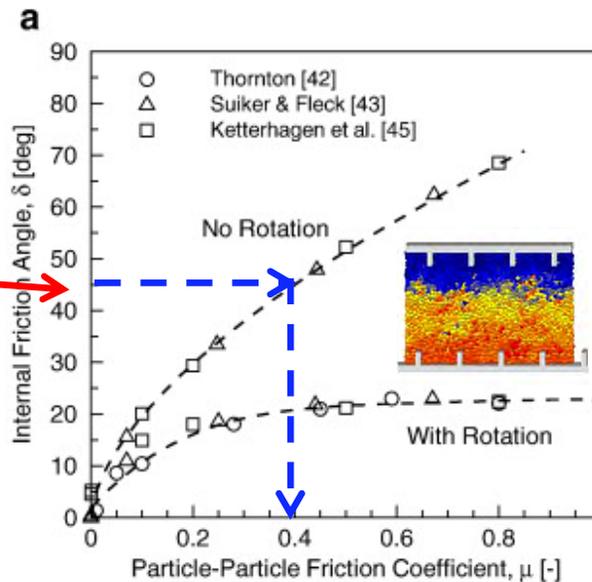
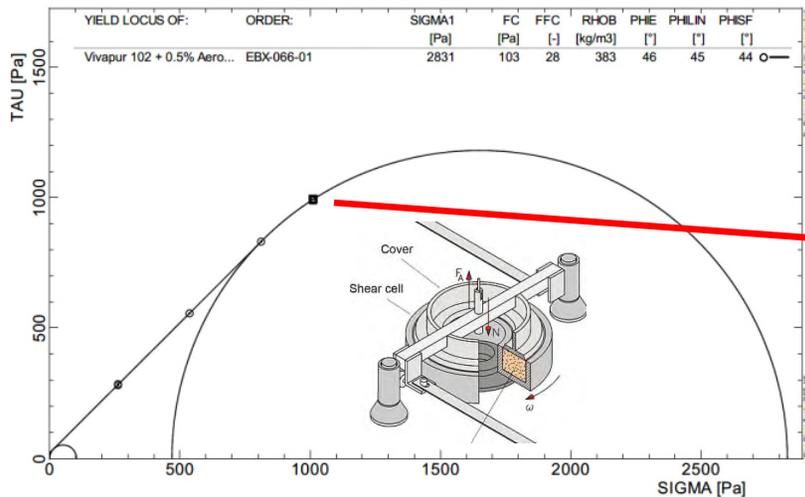


# Material Model Calibration

## Blend formulation

99.5 wt% microcrystalline cellulose (Vivapur®102; JRS Pharma, Germany)

0.5 wt% colloidal silica (Aerosil®200; Evonik, Germany)



## Experimental Ring Shear Test Results

### Powder friction

- $\tau_{\text{preshear}} = 990 \text{ Pa}$
- $\sigma_{\text{preshear}} = 1010 \text{ Pa}$
- $\delta \sim 44^\circ$

### Wall friction

- $\phi_w \sim 12\text{-}28^\circ$
- (Dependent on material pairs and normal stress)

## Calibrated DEM Contact Parameters

### Particle-Particle Contacts

- Coefficient of restitution = 0.3
  - Sliding friction = 0.39
  - Rolling friction = 0.0
- (no particle rotation)

### Particle-Wall Contacts

- Coefficient of restitution = 0.3
  - Sliding friction = 0.35
  - Rolling friction = 0.0
- (no particle rotation)

# Experimental Validation

## • Recent experimental work

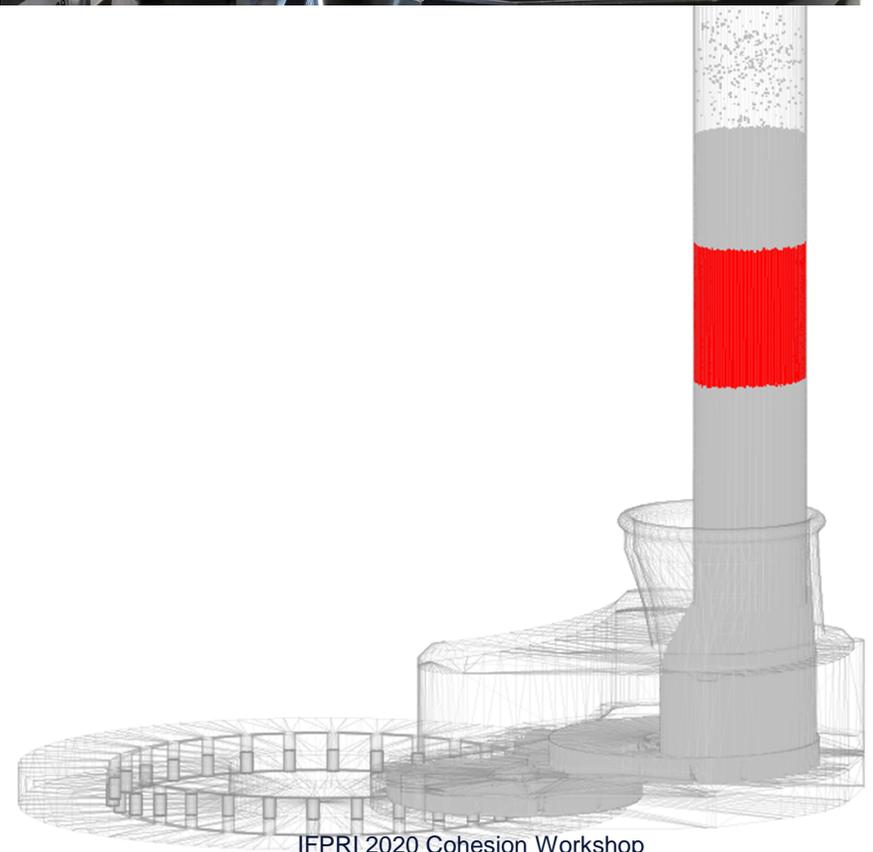
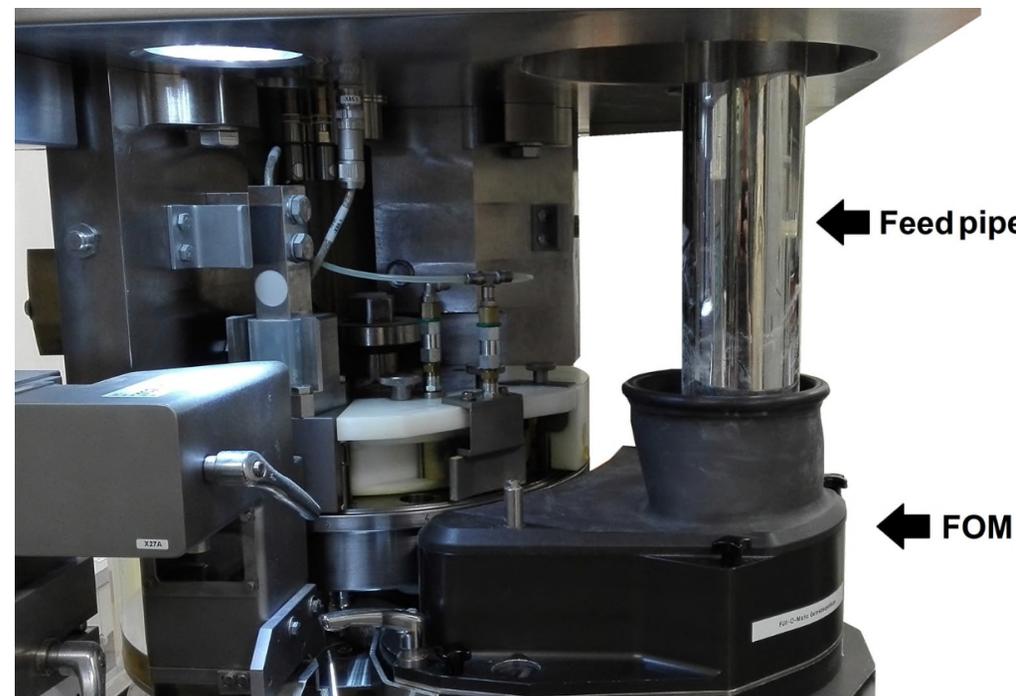
- Dülle, M., H. Özcoban, and C. S. Leopold. "Investigations on the residence time distribution of a three-chamber feed frame with special focus on its geometric and parametric setups." *Powder Technology* 331 (2018): 276-285.

## • Tablet Press

- Fette 102i commercial scale rotary tablet press
- Three chamber feed frame with three rotating paddle wheels
- 30 die stations, 8mm flat-faced tooling
- The usual hopper replaced with feed pipe for residence time experiments
- 12 mm filling cam, 11.5 mm fill depth

## • Materials

- 99.5 wt% microcrystalline cellulose (Vivapur®102; JRS Pharma, Germany)
- 0.5 wt% colloidal silica (Aerosil®200; Evonik, Germany)



# Model Validation

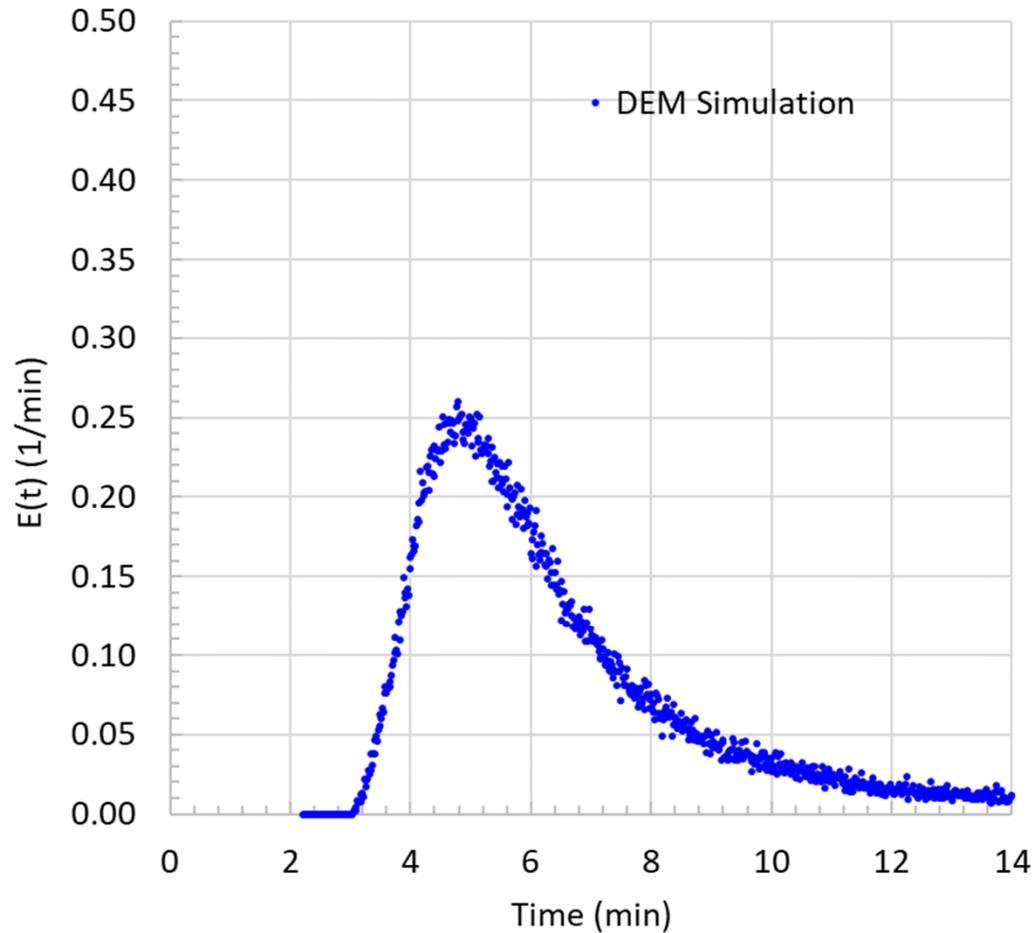
- Animation of tracer flow into and through feeder
- Feeder = 100 RPM
- Turret = 36 RPM



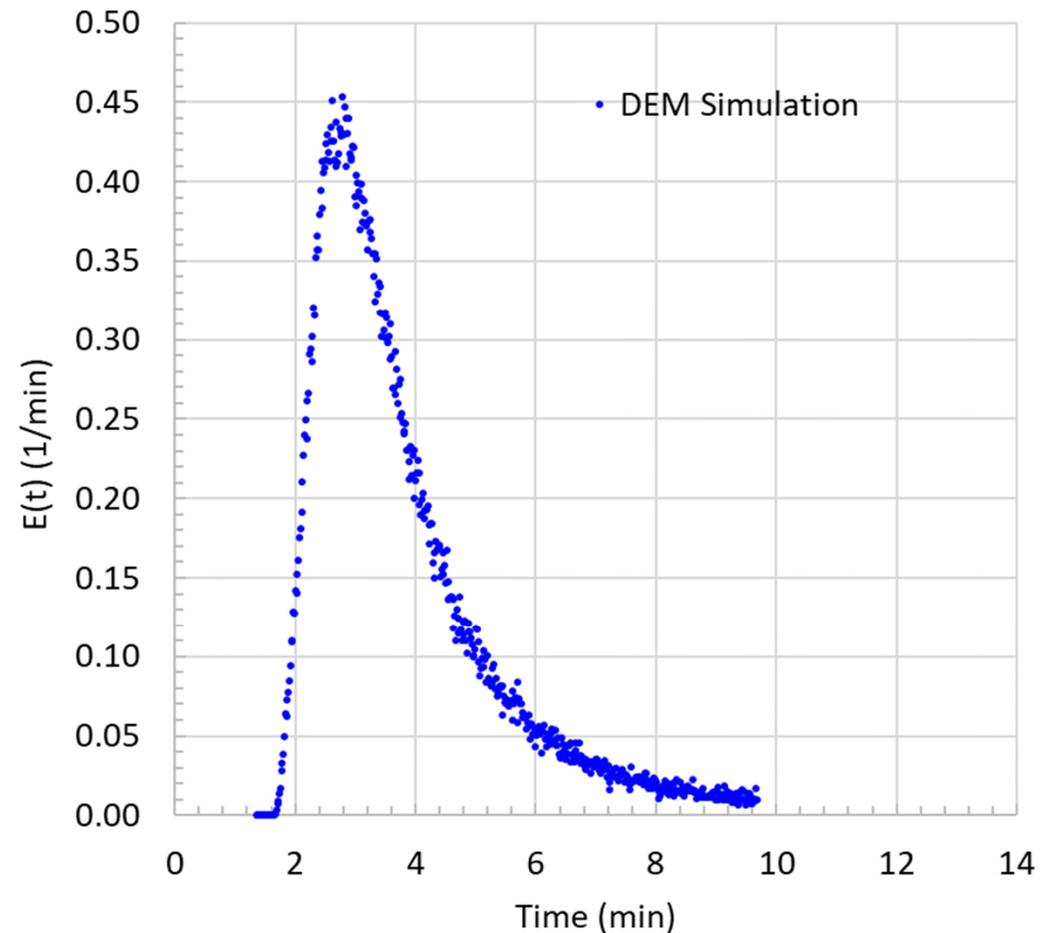
# Residence Time Distributions

- RTD extracted from DEM simulations
- Paddle wheel speed = 100 RPM

Turret speed = 20 RPM



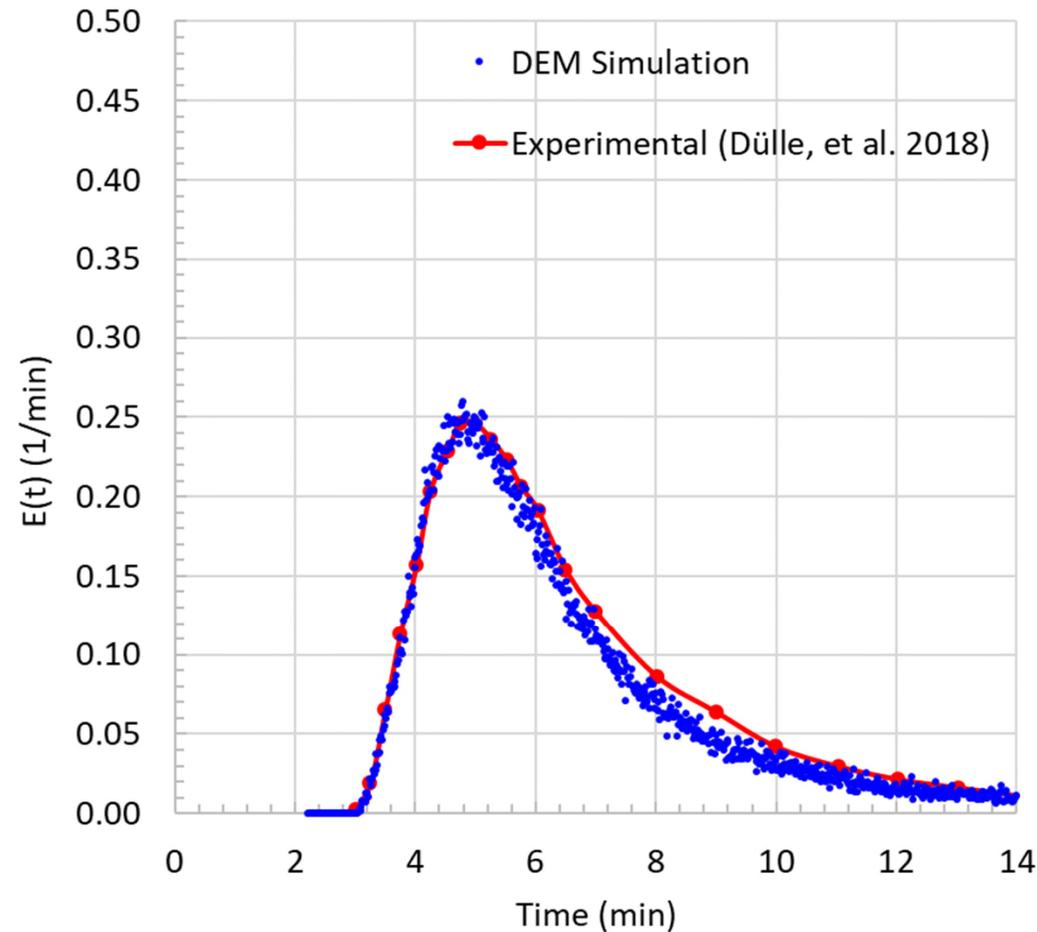
Turret speed = 36 RPM



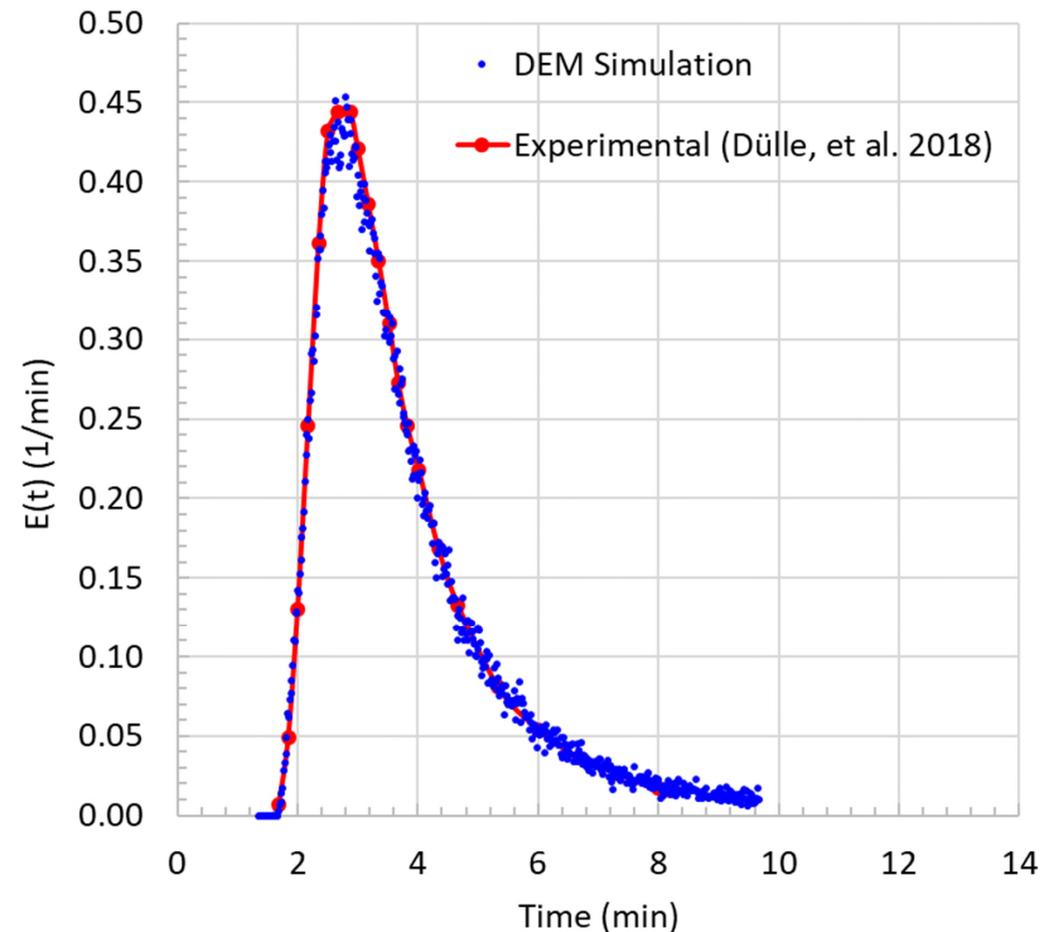
# Residence Time Distributions

- RTD from DEM simulations closely match experimental data of Dülle, et al. (2018)
- Good confidence simulations capture flow pattern for this powder blend

Turret speed = 20 RPM



Turret speed = 36 RPM



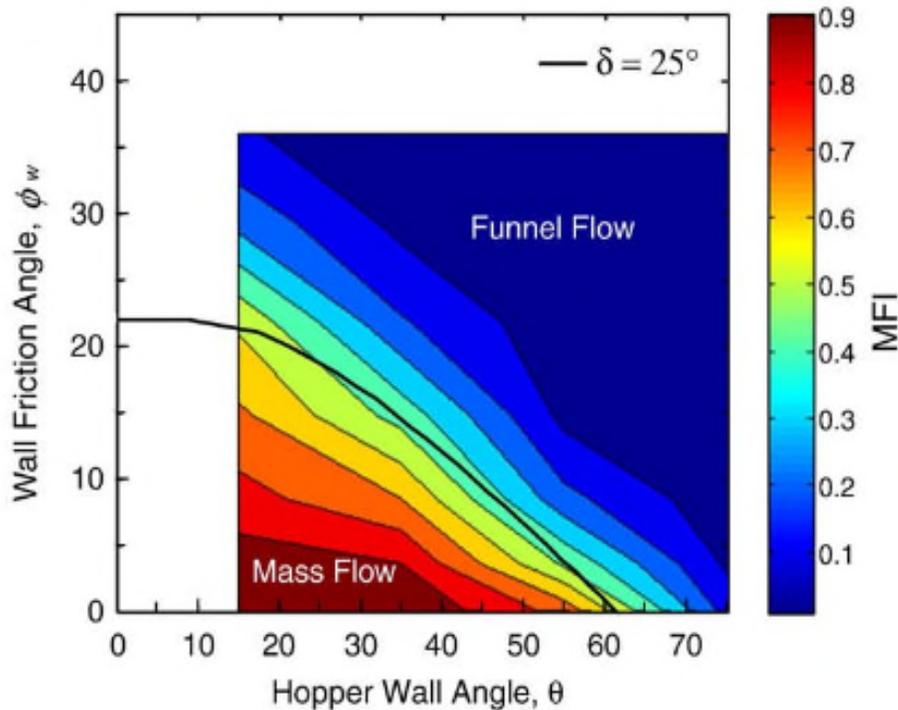
# Good Success in Other Systems

- Prediction of hopper discharge flow mode

- Mass flow limit

- Jenike theory: **black line**

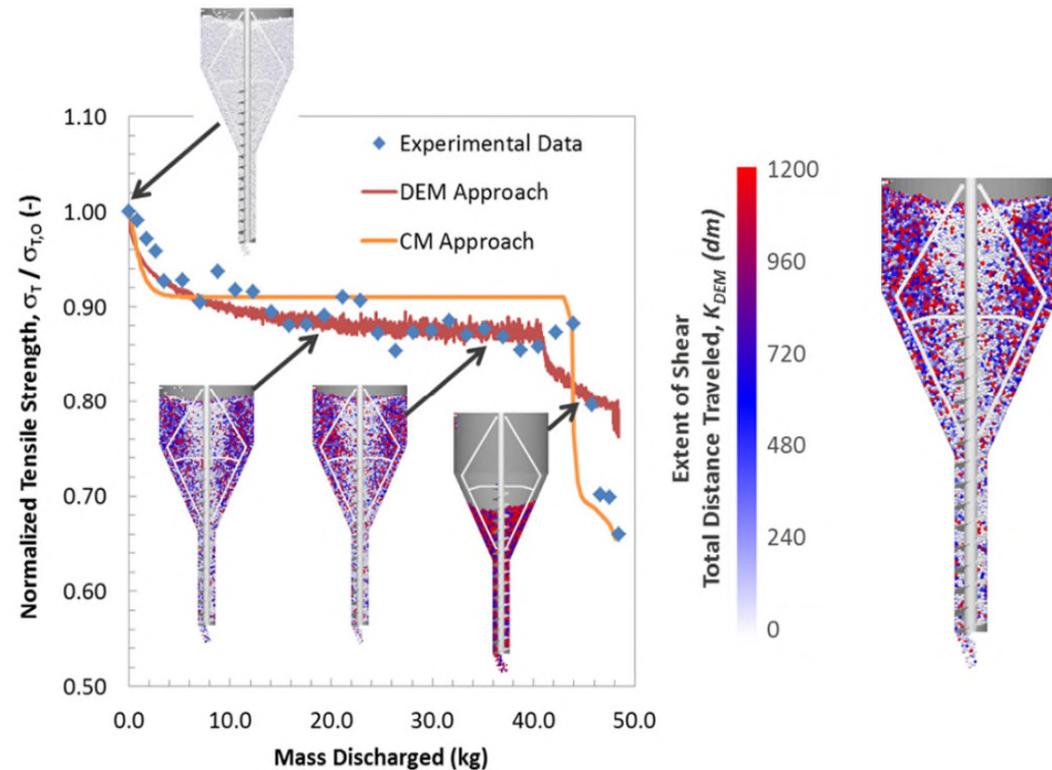
- DEM: **light blue contour**



Ketterhagen, W. R., Curtis, J. S., Wassgren, C. R., & Hancock, B. C. (2009). Powder Technology, 195(1), 1-10.

- Prediction of powder lubrication in an agitated feed hopper

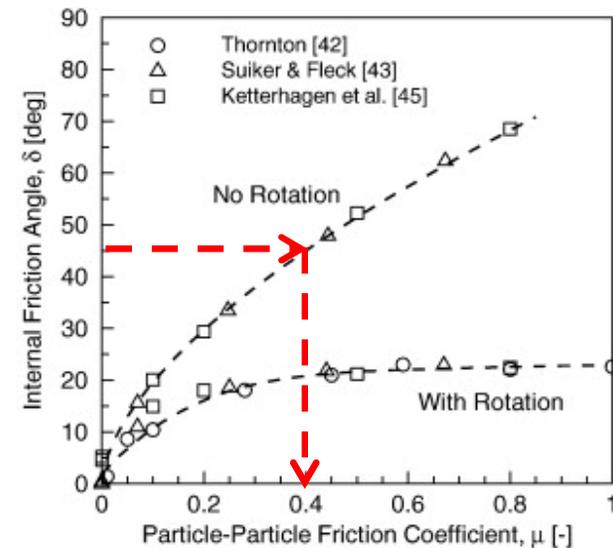
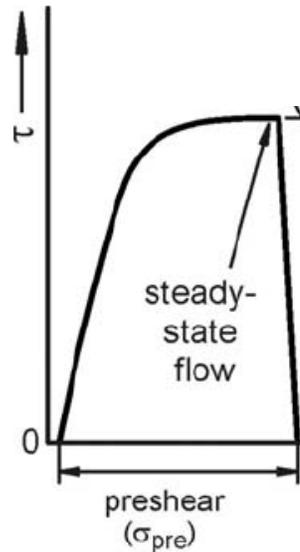
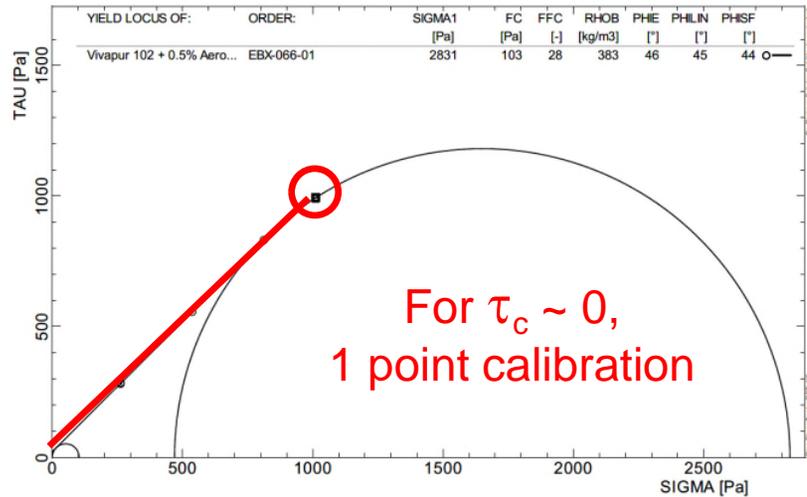
- Tensile strength decrease



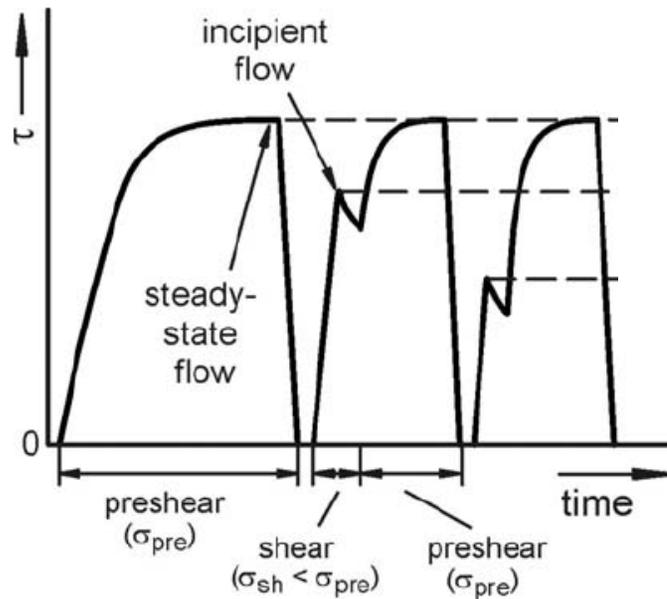
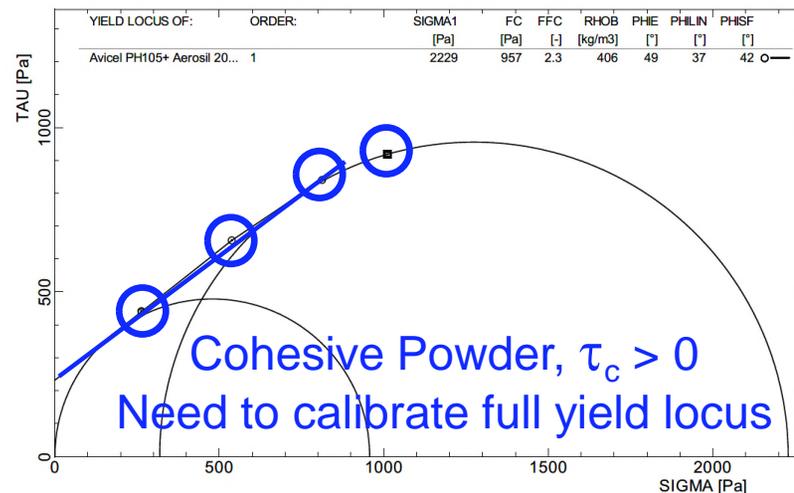
Ketterhagen, W. R., Mullarney, M. P., Kresevic, J., & Blackwood, D. (2018). Powder Technology, 335, 427-439.

# Material Model Calibration

- Free-flowing powder (FFC~15)



- Cohesive powder (FFC~2-3)



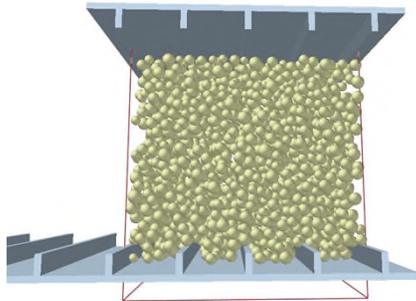
Add:

- Cohesive contact model,
- Additional model parameters introduced,
- Additional complexity

# Cohesive Material Model Calibration

- Wide ranging simulations via a cloud-based compute
  - 1280 parameter sets examined
- JKR cohesion model

- Schulze ring shear tester



- Freeman FT4 powder rheometer



## DEM Parameters

Friction coefficient	$\mu_{p-p}$	0.10, 0.17, 0.24, 0.31, 0.38, 0.45
	$\mu_{p-g}$	0.10, 0.25, 0.35, 0.45, 0.60
Restitution	$\epsilon_{p-p}$	0.2, 0.5, 0.8
	$\epsilon_{p-g}$	0.2, 0.5, 0.8
Surface energy	$\gamma_{p-p}$	0, 0.005, 0.05, 0.5 (J/m <sup>2</sup> )
	$\gamma_{p-g}$	0, 0.01, 0.1, 1 (J/m <sup>2</sup> )
Particle size	$d_p$	Normal dist.; $\mu = 2.0\text{mm}$ ; Min=1.4mm; Max =2.6mm; $\sigma = 0.20\text{mm}$
Particle shape		Non-rotating spheres
Density	$\rho$	1200 kg/m <sup>3</sup>
Poisson's ratio	$\nu$	0.25
Shear modulus	$G$	$2.4 \times 10^6 \text{ Pa}$

Varied

Fixed

# Summary of Experimental Materials

Experiments conducted for a wide range of materials, covering the range of anticipated materials that may be of interest for DEM simulations

## Excipients

- MCC Avicel
- Lactose
- Dicalcium Phosphate
- Sugar Spheres
- Klucel
- Sucrose
- Starch

## Actives

- Ibuprofen (IBU)
- Acetaminophen (APAP)

## Blends

Placebo Blend: 2:1 MCC 102:Lactose 316, 3% SSG, 1% MgSt

Placebo Blend at:

- K~300 dm
- K~2000 dm
- K~10,000 dm

Active Blend at K~100dm with:

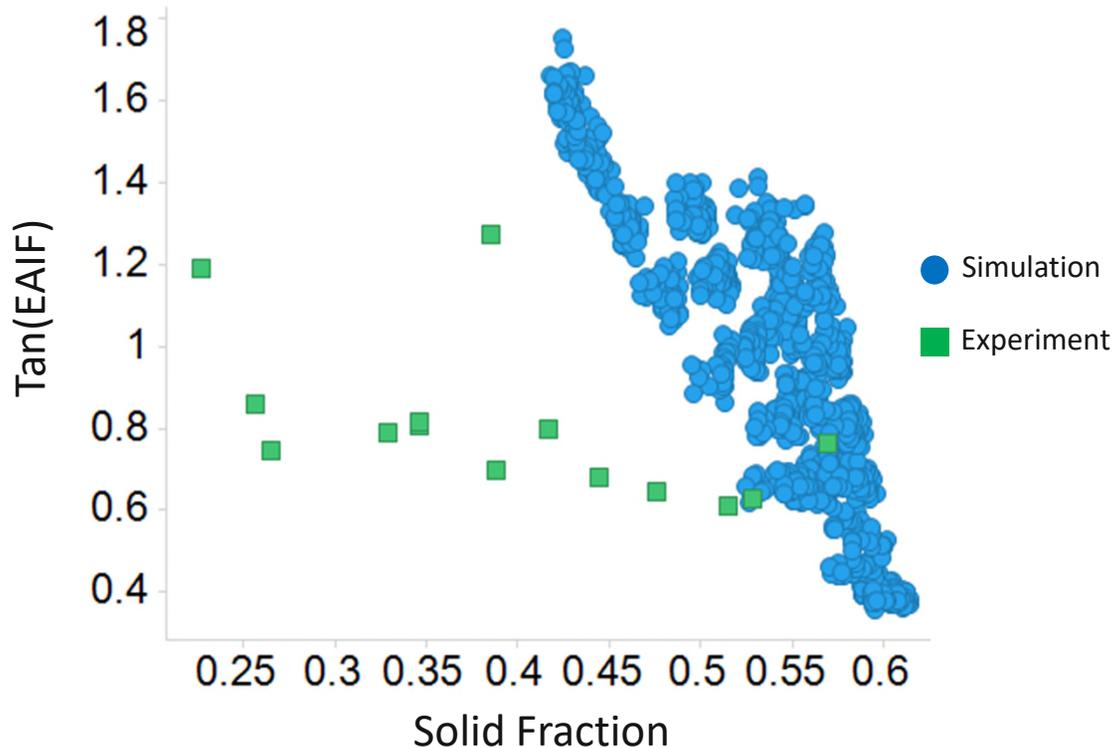
- 10% Acetaminophen (APAP)
- 20% Acetaminophen (APAP)
- 50% Acetaminophen (APAP)
- 10% Ibuprofen
- 20% Ibuprofen
- 50% Ibuprofen

Placebo Blend Wet Granules with:

- 10% H<sub>2</sub>O
- 20% H<sub>2</sub>O

# Comparison of Results

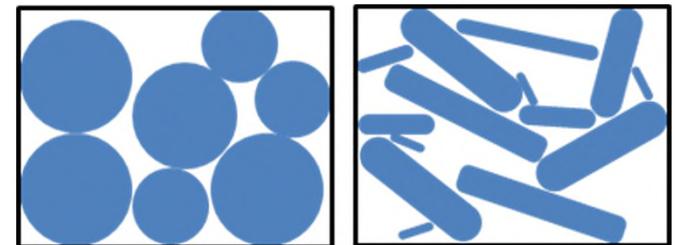
## Schulze Ring Shear Tester Results



- Simulation EAIF results encompass the range of pharma materials
- Simulation solid fraction values do not span the experimental range
  - Solid fraction is dependent on other parameters such as particle shape, size distribution, etc.

Can a sphere-based DEM model replicate the solid fraction of a cohesive powder?

Can any DEM model replicate the solid fraction of a cohesive powder under varying stress states?



Solid fraction is sensitive to the particle model (size and shape distributions)

# Summary (1/2)

- Motivation
  - Guide process development with actionable predictions
  - Use modeling to make the next decision more quickly, confidently, efficiently
- Value and Aspirations
  - Modeling must add value beyond what we already know
    - e.g. in a tablet press: more cohesive powders → greater die fill weight variability



- Differentiate among formulations with different cohesiveness
  - What is upper limit of drug content, before e.g. die fill weight variability is too large

## Summary (2/2)

- Needs and open questions
  - Opportunities to improve computational tractability (hardware, algorithms)?
    - Increase number of particles, PSD breadth, shape complexity
  - Are sufficient cohesive DEM contact models available?
    - JKR, Luding, Thornton, Edinburgh Elastic-Plastic-Adhesive, and more
  - Can a robust framework for calibration of cohesive contact models be developed?
    - How generalizable? Suitable across unit operations? Powder stress states? What are the best lab-scale, bulk calibration tests to use?
  - Can DEM adequately simulate the range of bulk densities of cohesive powders?
  - Further exploration of non-DEM approaches, e.g. FEM
    - Particle-scale calibration not required

# Disclosures

- Bill Ketterhagen is an employee of AbbVie and may own AbbVie stock. AbbVie sponsored and funded the study; contributed to the design; participated in the collection, analysis, and interpretation of data, and in writing, reviewing, and approval of the final presentation.

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