research
center
pharmaceutical
engineering

Combining Mechanistic Models and Experimentation to Drive Pharmaceutical Innovation

Massimo Bresciani

Research Center for Pharmaceutical Engineering

FFG Das Land Steiermark SFG

K1 Competence Center - Initiated by the Federal Ministry of Transport, Innovation and Technology (BMVIT). and the Federal Ministry of Science, Research and Economy (BMWFW) Funded by the Austrian Research Promotion Agency (FFG), Land Steiermark and the Styrian Business Promotion Agency (SFG).

TU Graz UNI GRAZ JOANNEUM RESEARCH

Do We Need Mechanistic Models?

"I can never satisfy myself until I can make a mechanical model of a thing. If I can make a mechanical model, I can understand it. As long as I cannot make a mechanical model all the way through I cannot understand."

- Lord Kelvin

From a speech Kelvin presented at Johns Hopkins University in Baltimore on 'Molecular Dynamics and the Wave Theory of Light' (1884)

How we Benefit from Models

- Mechanistic Understanding of a Process
  - Finding the CPPs
  - Sensitivity analysis
  - Guide for experimentation – risk reduction
- Scale-up and scale-down
  - Regime analysis
  - Scale-independence of design space
- Control
- Process optimization
- Scheduling

What are the Steps?

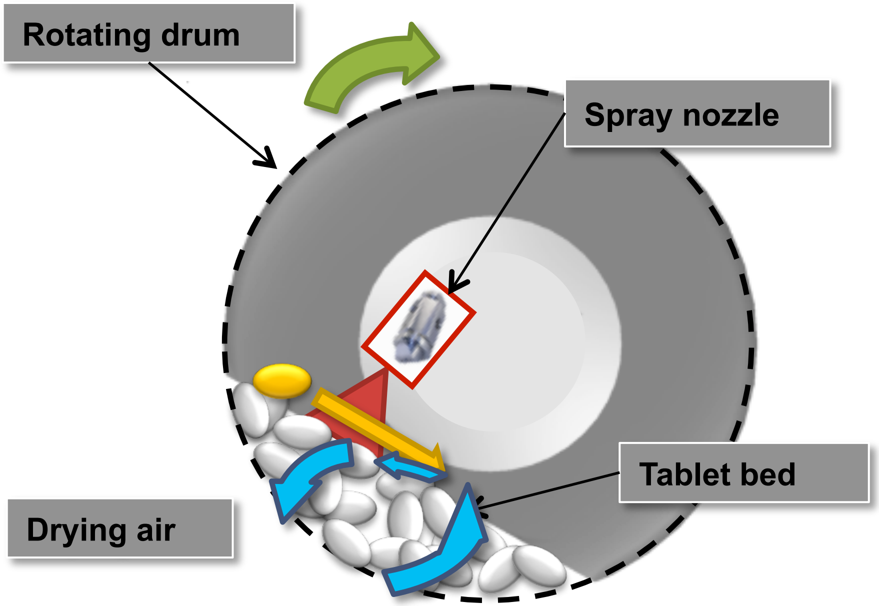
Critical steps model development:

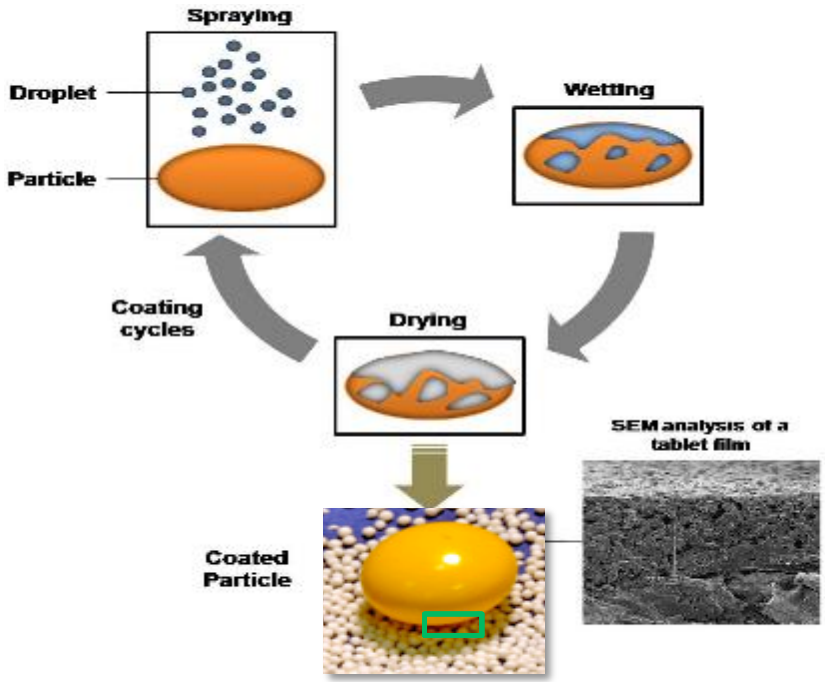
- Aim & structure (cause-effect)
- Model formulation
- Model validation
- Model reduction
- Model life cycle

A Few Examples

Coating/Fluid Beds/Control

Example 1- Tablet Coating





Goal

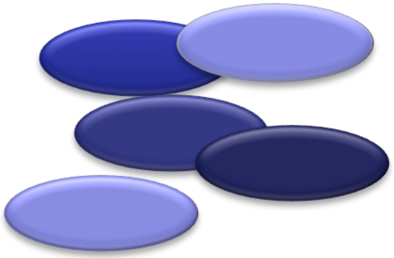
- Application of a thin film around the tablet core
- Mostly, aqueous coating is used, producing polymer-based films

Aim: Understanding the CQAs

- The central CQAs are coating **thickness** and **variability**:
  - *Intra*-tablet: coating thickness variation on one tablet
  - *Inter*-tablet: differences between the tablets

Intra-tablet

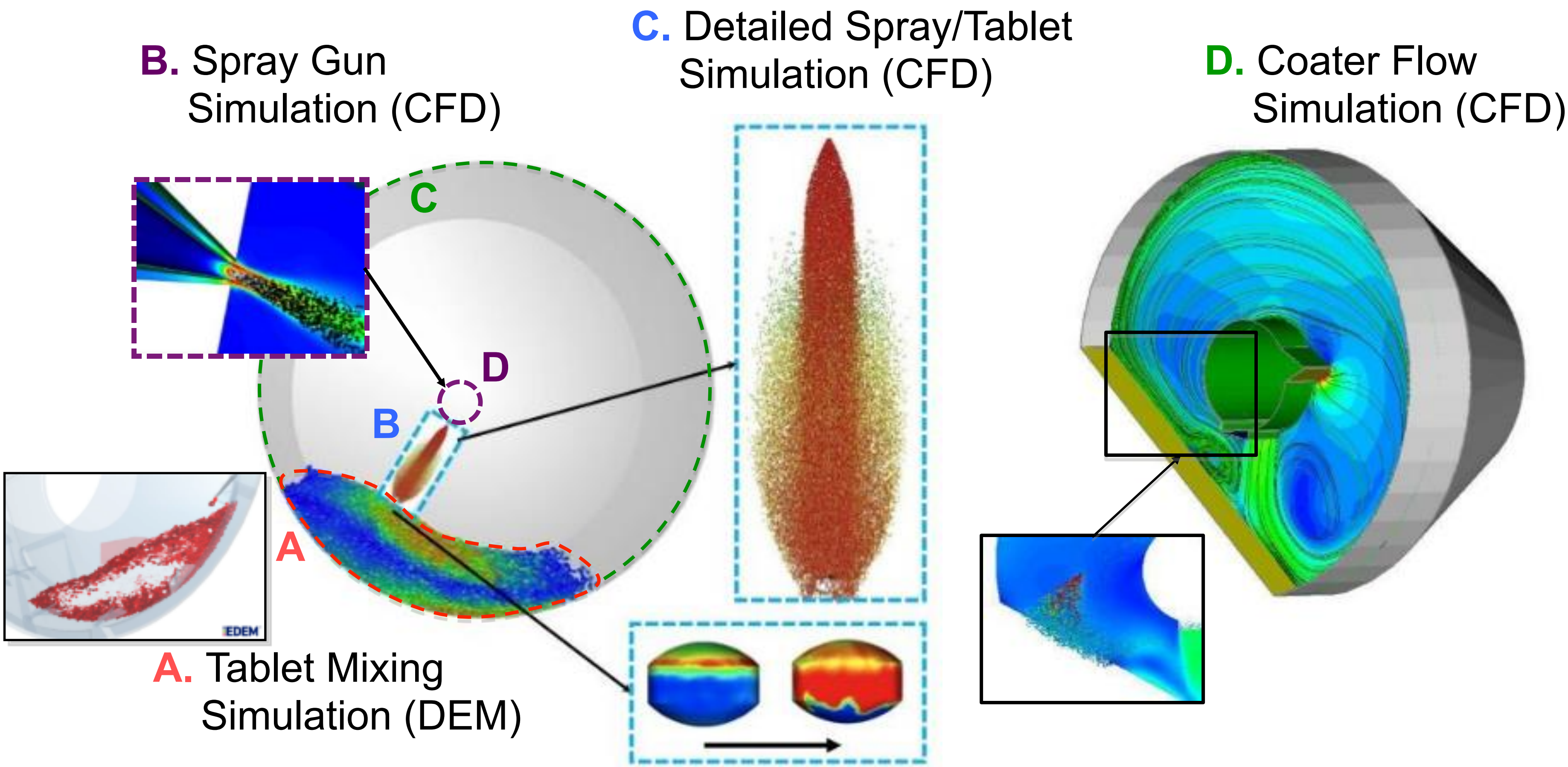
Inter-tablet



- Other CQAs are lack of
  - orange peeling
  - sticking / picking
  - bridging / filling etc.

Model Structure

- **Coating Effects**



Suzzi, D., Radl, S., Khinast, J.G., 2010. Local Analysis of the Tablet Coating Process: Impact of Operation Conditions on Film Quality. *Chem. Eng. Sci.*

Model Formulation: DEM Code

main equations solved in DEM

research center pharmaceutical engineering

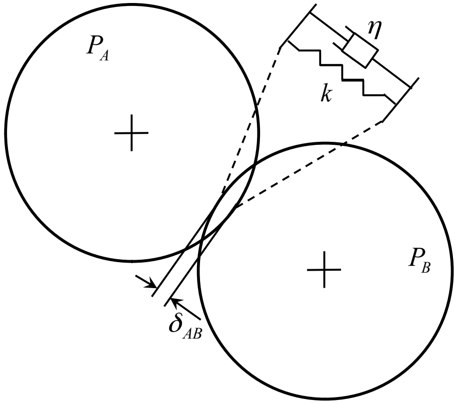
DEM – running on GPU

- Newton's second law for each particle (particle interacting forces)

$$m_p \frac{d\mathbf{u}_p}{dt} = \beta\left(\mathbf{u}_f - \mathbf{u}_p\right) + \sum_{N_p} \mathbf{F}_{p \to p} + \sum_{N_w} \mathbf{F}_{p \to w} + m_p \mathbf{g}$$

- Rotation of the particles, angular momentum

$$I_p \frac{d\boldsymbol{\omega}_p}{dt} = \sum_{N_p} \mathbf{M}_p$$



TU Graz UNI GRAZ JOANNEUM RESEARCH

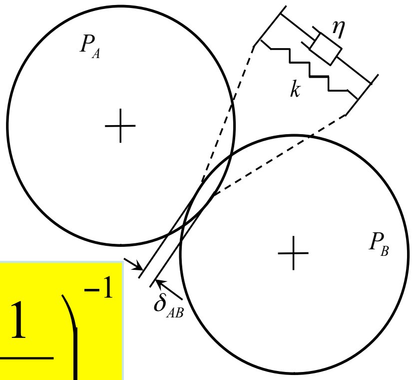
DEM Basics

how forces between particles/walls are calculated

- Normal particle-particle and particle-wall interactions

$$\mathbf{F}_{p_A \to p_B} = \left[k\delta_{AB} - \eta\left(\mathbf{u}_A - \mathbf{u}_B\right)\cdot\mathbf{n}\right]\cdot\mathbf{n}$$

$$\eta = -2\ln(e_{n,p\to p})\frac{\sqrt{m_{AB}k}}{\sqrt{\pi^2 + \left(\ln(e_{n,p\to p})\right)^2}}, \quad with \quad m_{AB} = \left(\frac{1}{m_A} + \frac{1}{m_B}\right)^{-1}$$



Normal forces and tangential component/ forces
Interaction forces

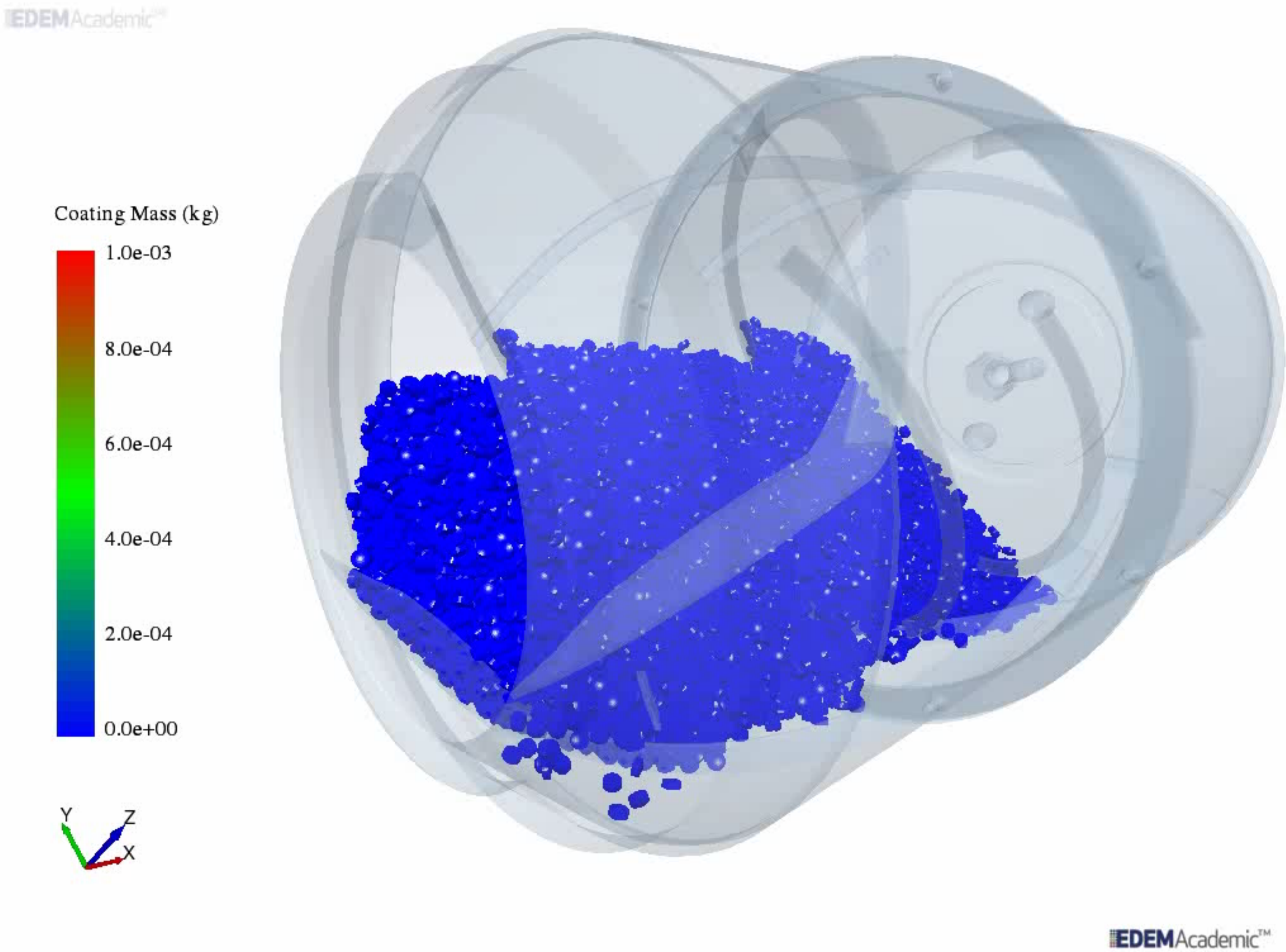
- Tangential component via Coulomb-type friction law

$$\mathbf{F}_{p_A \to p_B,t} = \begin{cases} -k_t\boldsymbol{\delta}_t - \eta_t\mathbf{u}_{AB,t} & if \quad \left|\mathbf{F}_{p_A \to p_B,t}\right| \le \left|\mathbf{F}_{p_A \to p_B,n}\right| \\ -\mu_{fr,p\to p}\left|\mathbf{F}_{p_A \to p_B,n}\right|\mathbf{t}_{AB} & if \quad \left|\mathbf{F}_{p_A \to p_B,t}\right| > \left|\mathbf{F}_{p_A \to p_B,n}\right| \end{cases}$$

$$\eta_t = -2\ln(e_{t,p\to p})\frac{\sqrt{\frac{2}{7}m_{AB}k_t}}{\sqrt{\pi^2 + \left(\ln(e_{t,p\to p})\right)^2}}$$

k - spring stiffness
η - damping parameter
subscript *t* referring to tangential component

Coater Simulation Including Spray



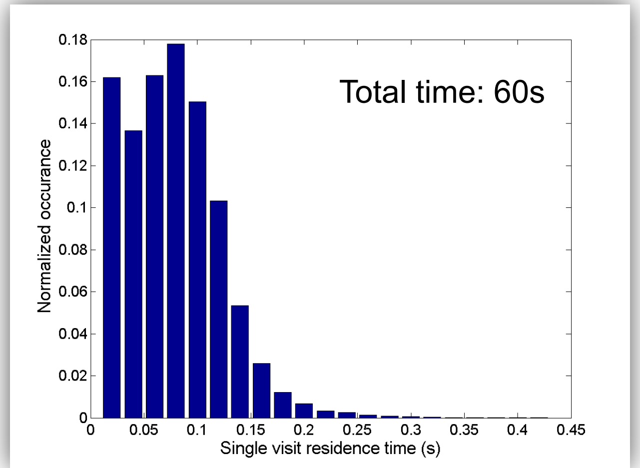
Simulation data

- 14272 convex tablets
- each tablet from 8 spheres
- 10-20 rpm
- Spray rate: 2.4 mio. drops/sec
- Elliptical spray zone

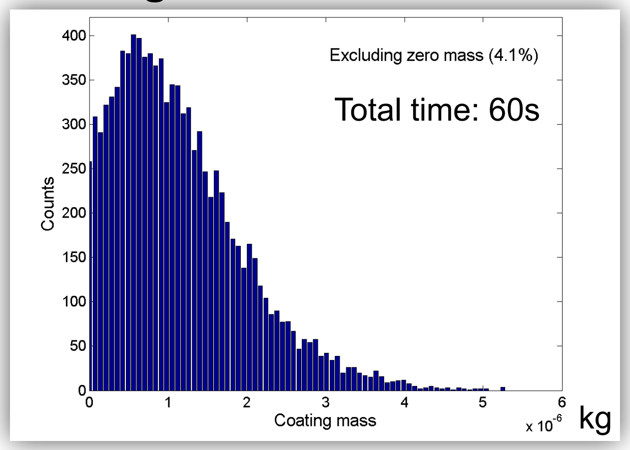
Results: Coating Distribution

examples of outcome of simulation

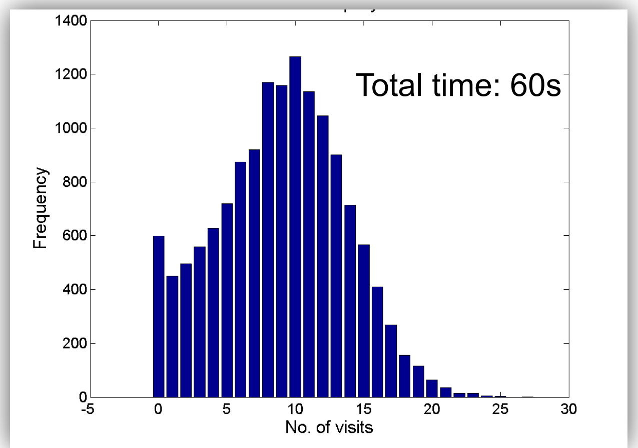
Single visit residence time



Coating mass distribution



Nr. of visits to the spray zone

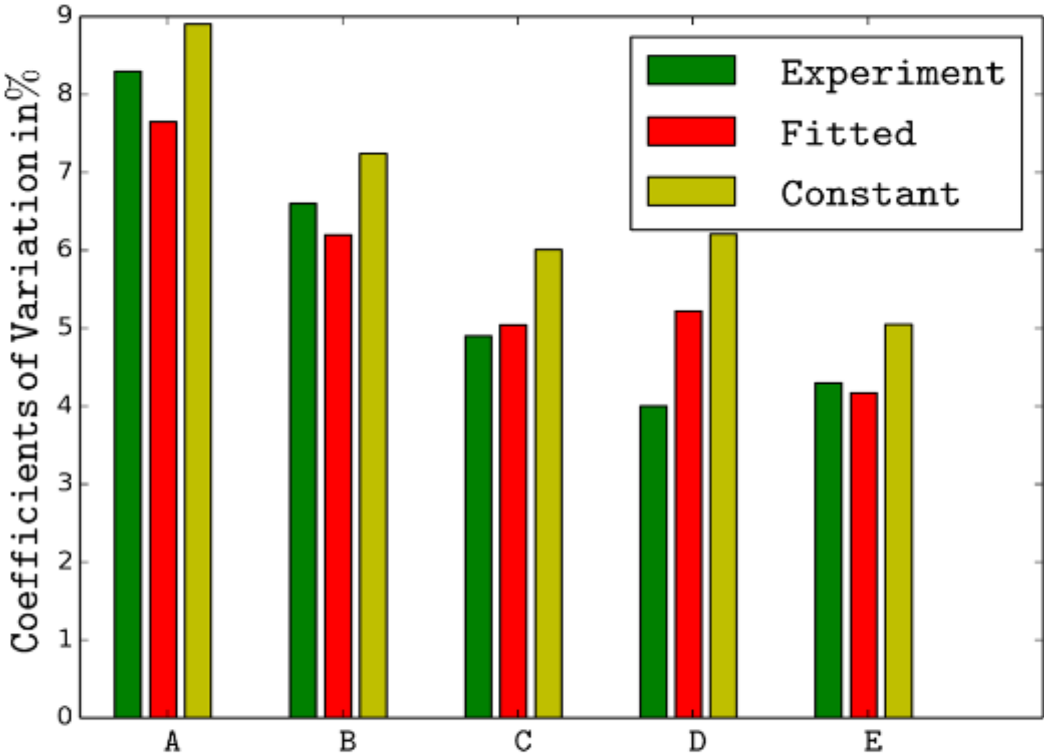


- **Different layers of information** are available
  - Single visit residence time
  - Nr. of visits to the spray zone
  - Coating mass distribution
- From the coating mass distribution, the **Relative Standard Deviation (RSD)** is calculated to show the coating uniformity

Just S., Toschkoff G., Funke A., Khinast, J.G.; Knop, K., Kleinebudde P. et al. (2013), Optimization of the inter-tablet coating uniformity for an active coating process at lab and pilot scale, *International Journal of Pharmaceutics*, Vol. 457(1),

Model Validation 1

research center pharmaceutical engineering



A: 260 kg 9 rpm 172 min
B: 240 kg 9 rpm 248 min
C: 250 kg 9 rpm 368 min
D: 250 kg 9 rpm 345 min
E: 250 kg 9 rpm 522 min

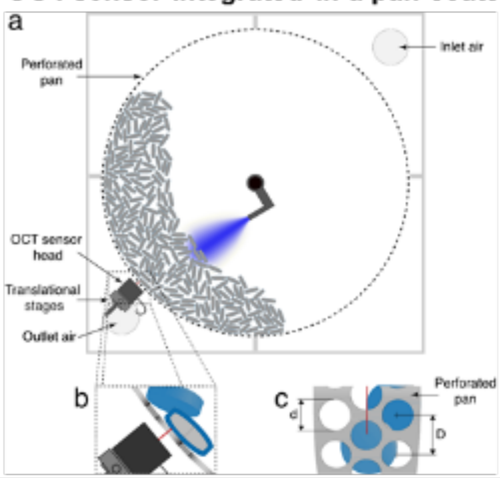
A,B,C etc variantions

- Experimental results (at Bayer) **match closely** the extrapolated results
- The calculated decay exponent matches the results very closely

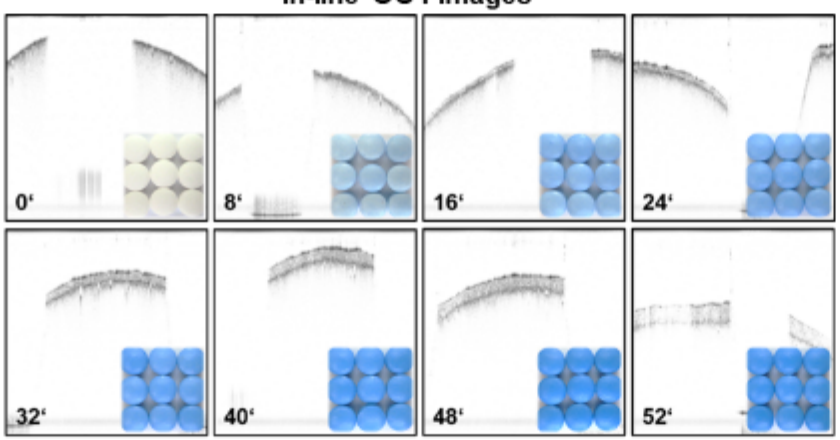
Boehling et al., Analysis of Large-Scale Tablet Coating: Modeling, Simulation and Experiments, Eur J Pharm Sci, 2015

Model Validation II: Comparison to Coherence Tomography (OCT)

OCT sensor integrated in a pan coater

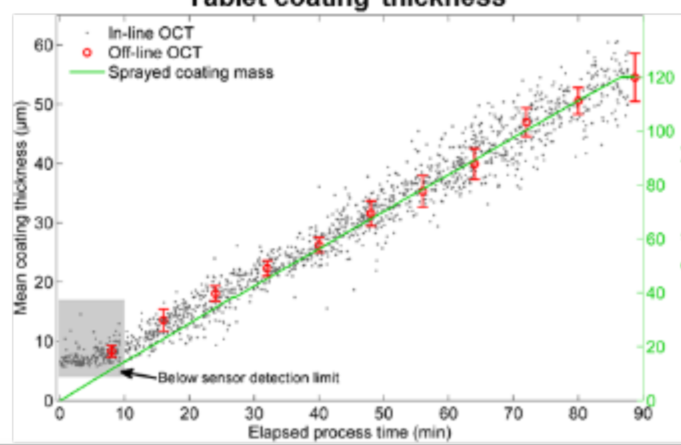


In-line OCT Images



- **Real-time monitoring:**
  - Mean coating thickness of a single particle
  - Inter-particle coating variability
  - Intra-particle coating variability
  - Roughness analysis (core and coating)

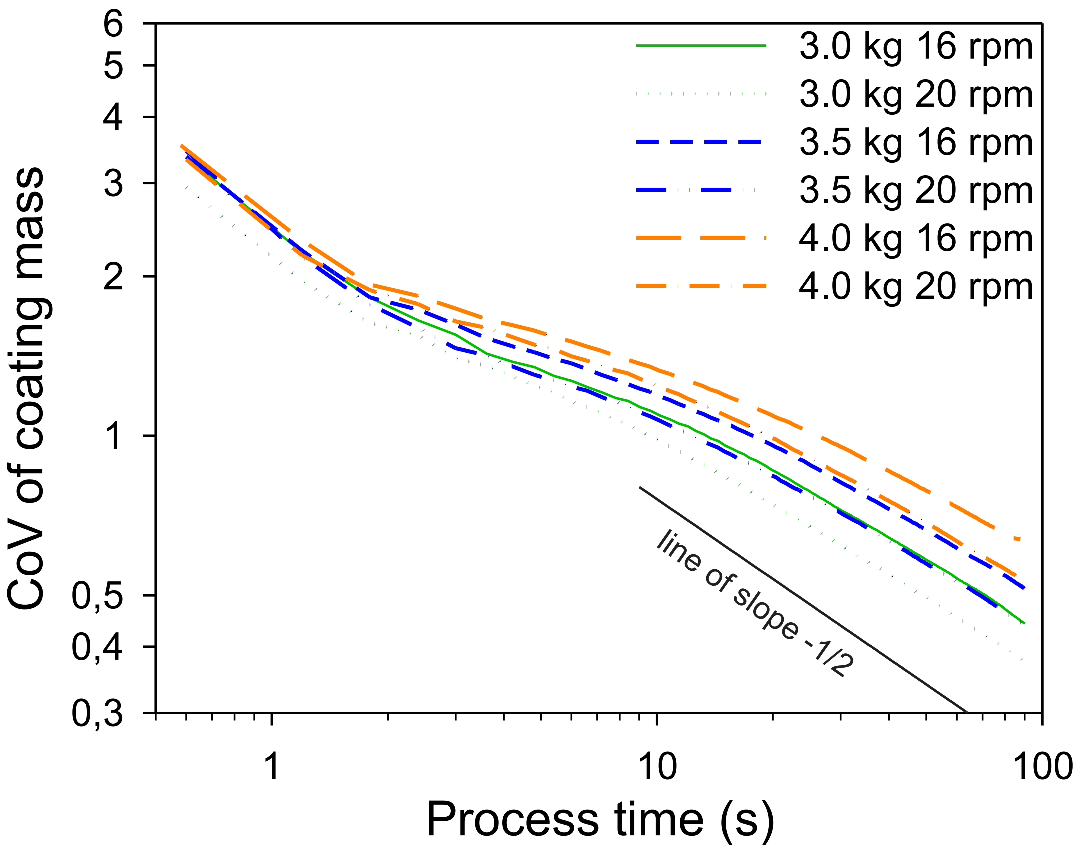
Tablet coating thickness



Markl D., Leitner M., Khinast J.G. et al. (2014), Optical coherence tomography as a novel tool for in-line monitoring of a pharmaceutical film-coating process, *European Journal of Pharmaceutical Sciences* 55,

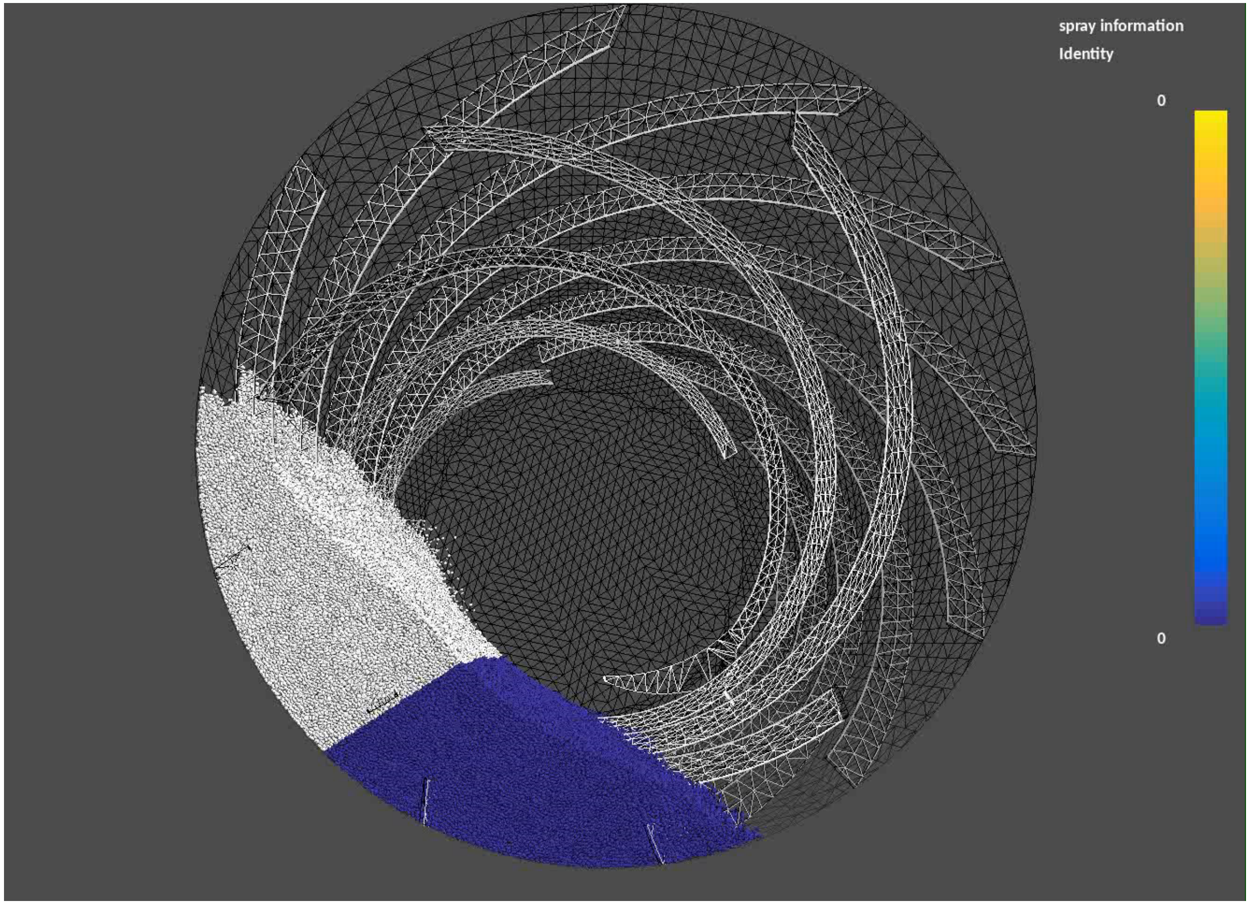
Model Reduction: Prediction of COV (Extrapolation)

Coefficient of Variation (COV) = RSD = Coating Variability



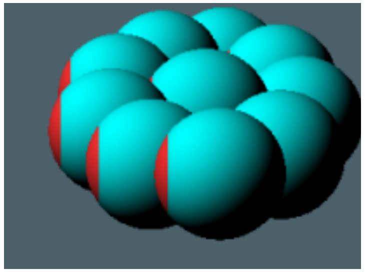
- Random mixing models predict a decrease inversely proportional to the square root of time (shown by the line of slope of -1/2)
- Here coating is slightly better
- Can be used to develop simplified model
- Simplified model predicts COV based on 90s of simulation

Life Cycle 1: GPU Multisphere Approach



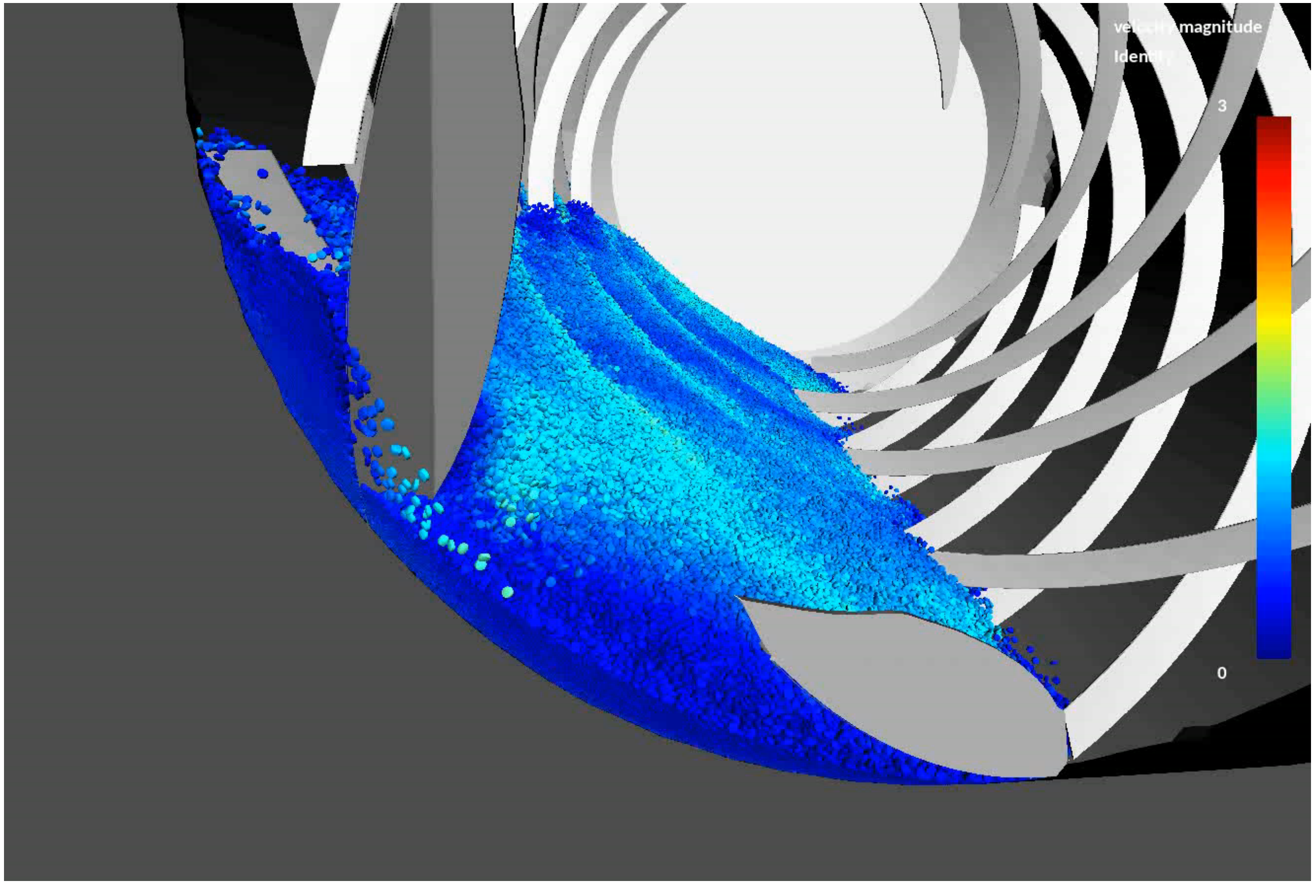
Included:

- 1.4 million tablets
- 8 spheres/tablet
- 400 kg total mass
- 5 fan-shaped sprays
- Convective heat
- Conductive heat
- Spray cooling



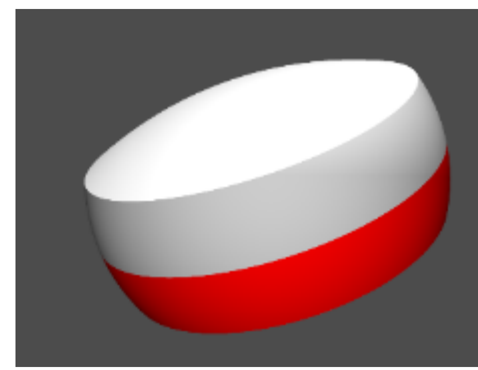
P. Boehling · G. Toschkoff · K. Knop · P. Kleinebudde · S. Just · A. Funke · H. Rehbaum · J.G. Khinast, Analysis of large-scale tablet coating: Modeling, simulation and experiments, Eur. J Pharm Sci (2015)

Life Cycle 2: True-Shape DEM



Included:

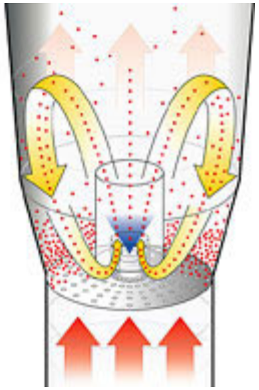
- 1.8 Mio TS objects
- 500 kg total mass
- 5 fan-shaped sprays
- Convective heat
- Conductive heat
- Spray cooling



C. Radeke, P. Böhling and J.G. Khinast, manuscript in preparation, 2016

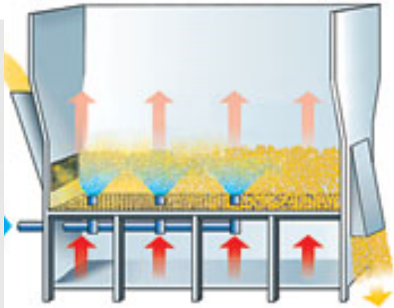
Example 2: Fluidized Beds

- Fluidized beds in the pharmaceutical industry are mainly used for **drying, agglomeration, pelletization and coating**
- In other industries:
  - Catalytic reactions (e.g., cracking, CFB).
  - Non-catalytic reactions (e.g., gasification, combustion)
  - Adsorption-desorption
- Aim: Understanding, scale-up, optimization, control



Glatt Wurster Coater

GEA Consigma



Glatt Continuous FB

Structure/Formulation: CFD-DEM

research center pharmaceutical engineering

- Theoretical Background

CFD code	DEM code
CPU	GPU

CFD code – CPU

Gas flow

$$\frac{\partial}{\partial t}(\varepsilon_f \rho_f) + \nabla \cdot (\varepsilon_f \rho_f \mathbf{u}_f) = 0$$

$$\frac{\partial}{\partial t}(\varepsilon_f \rho_f \mathbf{u}_f) + \nabla \cdot (\varepsilon_f \rho_f \mathbf{u}_f \mathbf{u}_f) = -\varepsilon_f \nabla p - \nabla \cdot (\varepsilon_f \tau_f) + \varepsilon_f \rho_f \mathbf{g} - \mathbf{S}_\mathbf{p}$$

$\mathbf{S}_\mathbf{p} \rightarrow$ *Drag force source term*

- Solves Navier-Stokes equations in a multiphase setup
- Turbulence modeling via the k-ζ-f model
- Code is Fire (AVL)
- Coupling via drag force

DEM code – GPU

Particle motion

$$m_p \frac{d\mathbf{u}_p}{dt} = \beta \frac{V_p}{\varepsilon_p}(\mathbf{u}_f - \mathbf{u}_p) + m_p \mathbf{g} + \sum_{N_p} \mathbf{F}_{p \rightarrow p} + \sum_{N_p} \mathbf{F}_{p \rightarrow w}$$

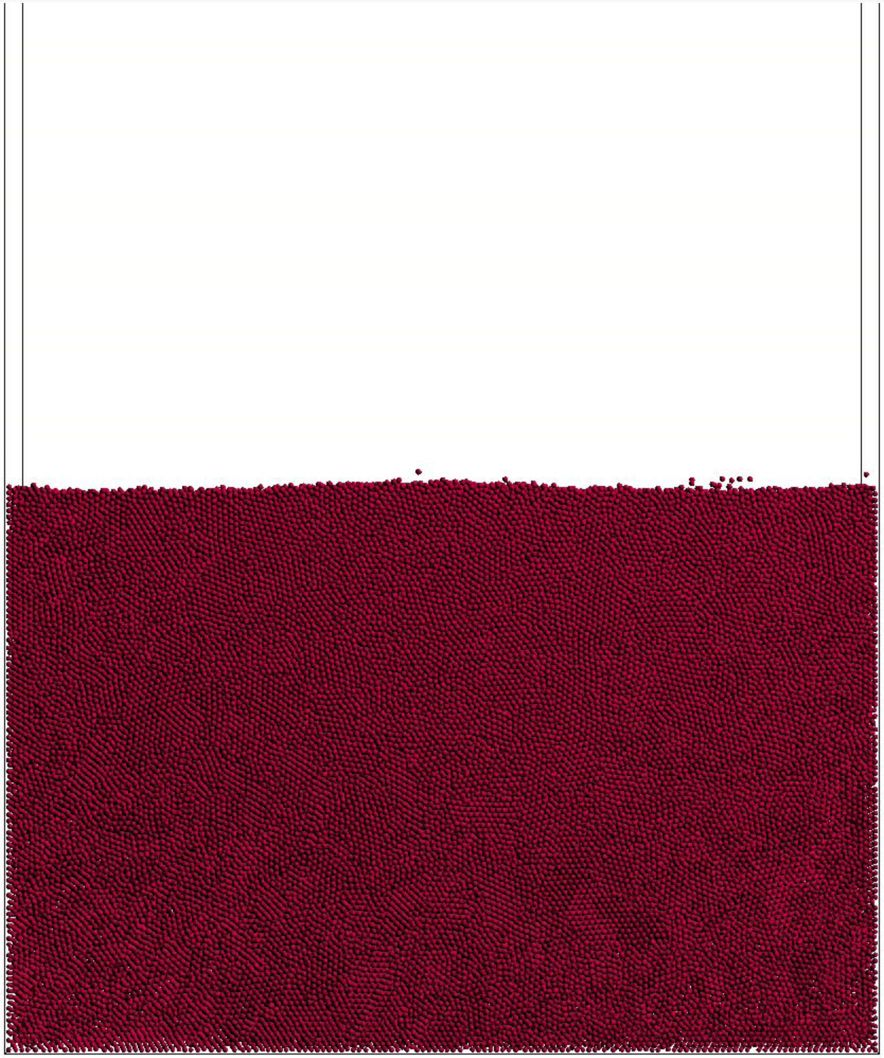
$$I_p \frac{d\boldsymbol{\omega}_p}{dt} = \sum_{N_p} \mathbf{M}_p$$

- Spring-dashpot model (Hertz-Mindlin)
- Coulomb-friction (slider) is included
- Particle rotation may be turned off
- Coupling via drag force

Refs: Kuipers, Heinrich, Sundaresan, Li, Khinast and others.

TU Graz UNI GRAZ JOANNEUM RESEARCH

Example: Triple-spouted Bed

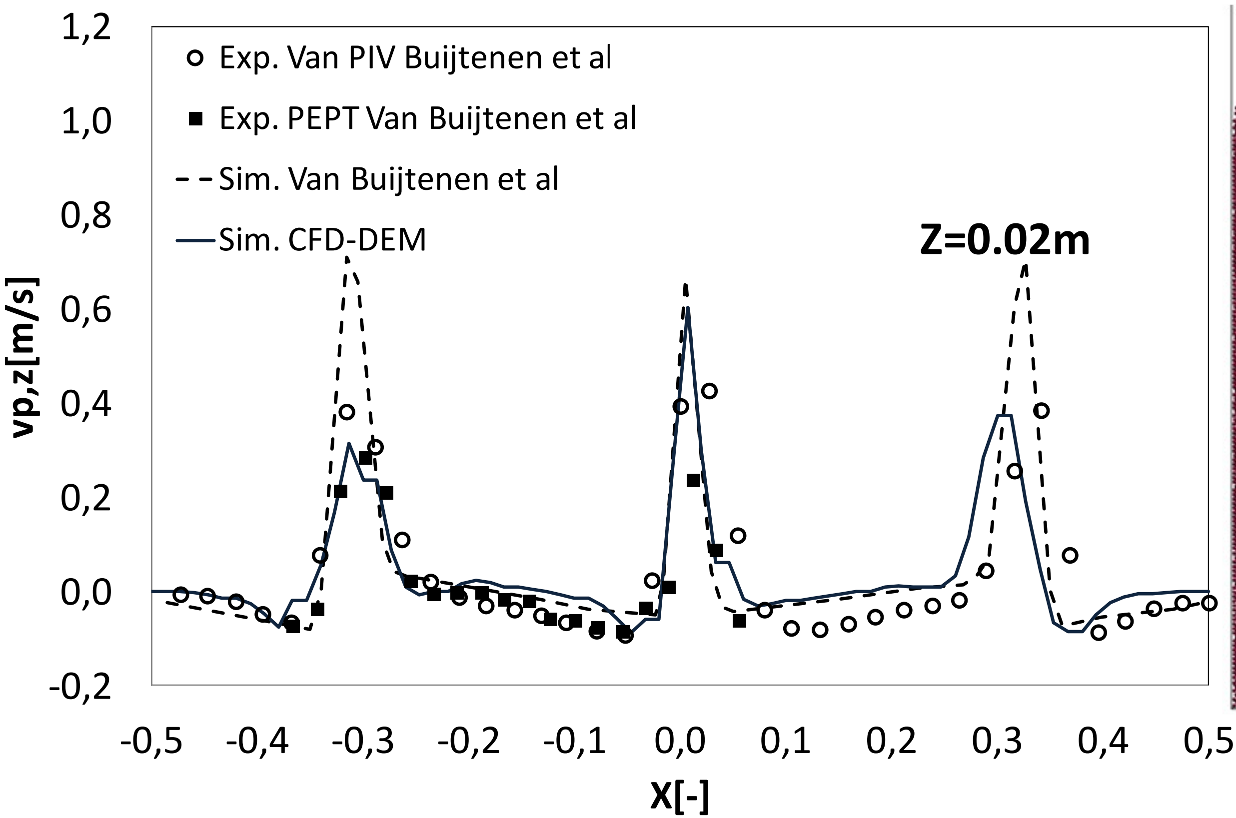


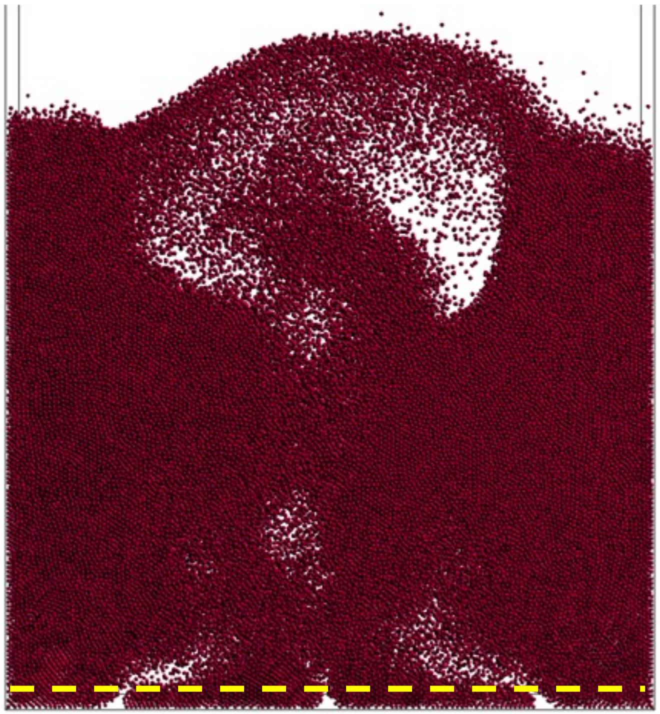
n_p = 100,000
d_p= 3mm

Reference: Jajcevic D., C. Radeke and J.G. Khinast, Large-scale simulation of fluidized beds, Chem. Eng. Sci (2013)

Results and Validation

- Validation – Triple Spout Fluidized Bed



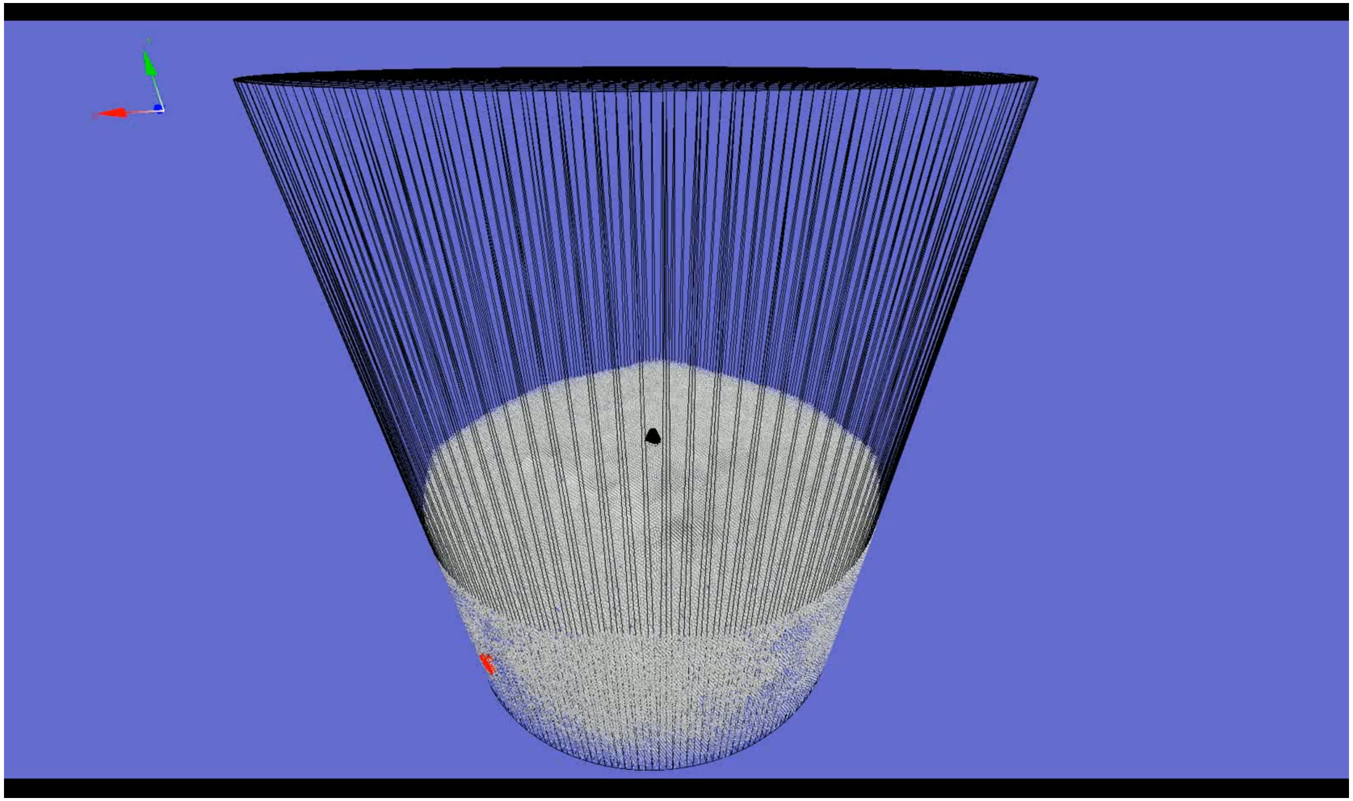


Vertical particle velocity over the yellow line

Ref: "Numerical and experimental study on multiple-spout fluidized beds", Van Buijtenen et al., 2011

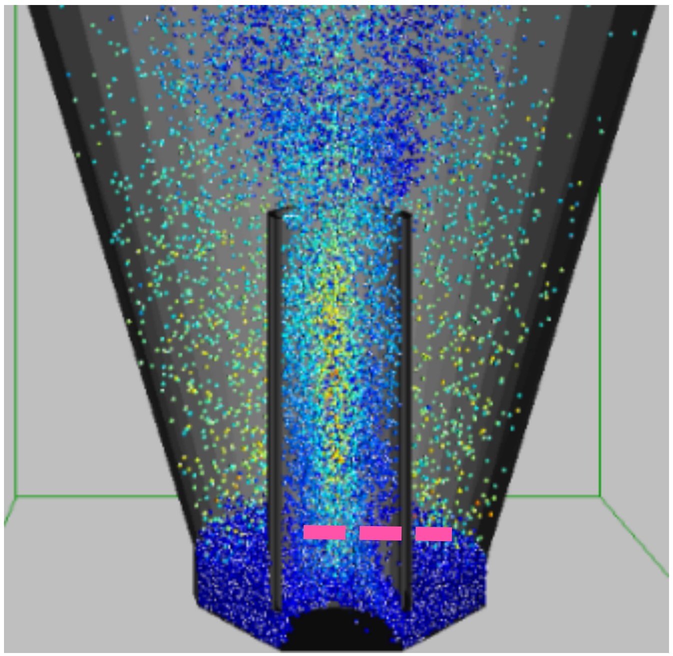
Application: Fluidized Bed

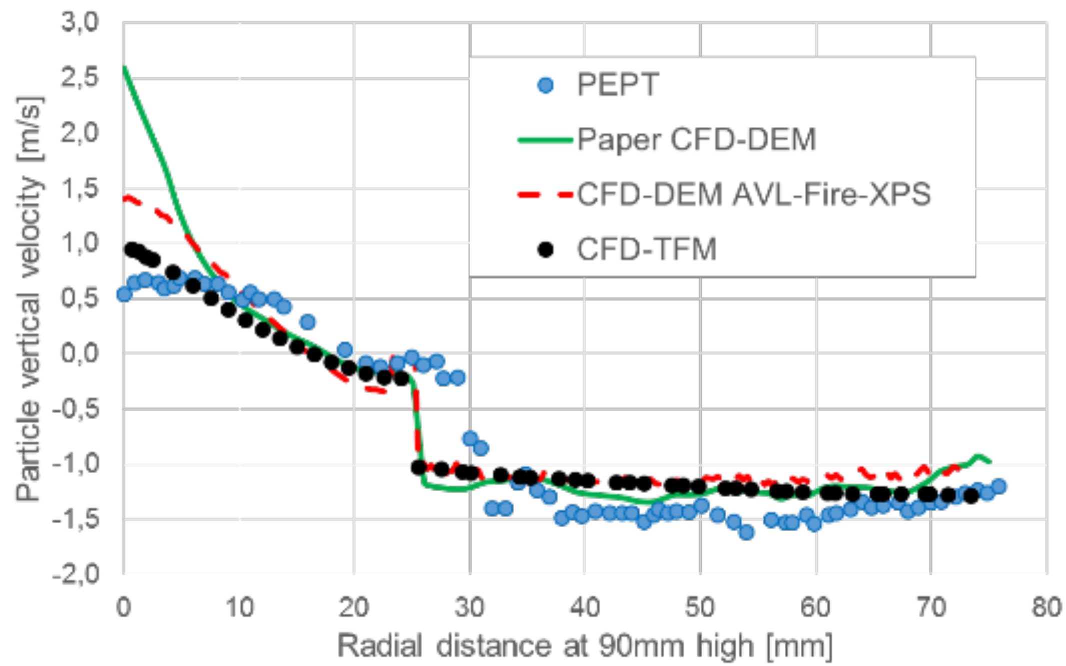
- Fluidized bed system with two spray nozzles



n_p = 7 million
d_p = 1.6 mm
ρ = 600 kg/m³
Air flow: 1020 Nm³/h

Life Cycle: New Model based on CFD-TFM vs. CFD-DEM





Li et al., “Residence time distributions of different size particles in the spray zone of a Wurster fluid bed studied using DEM-CFD”
Zadravec M., Jajcevic D. and J.G. Khinast, manuscript in preparation

Example 3: Control

Level 1 – Input Output
Considers the total Input/Outputs. The CQAs that are visible at the I/O level are the CQA's of the final product.

Level 2 – Intermediate
Considers the interactions between the unit operations.

Level 3 – Process Unit
Represents the process at the most detailed level. Separate considerations for every involved unit.

Types of Controls

- **Open system:**
  - No active controls but may trigger external action
  - Needs clear rules of engagement with the process. (e.g., separation of non-conforming material and/or operator adjustment).

- **Feed back:**
  - Output information is used to automatically trigger upstream action

- **Feed forward**:
  - Input/output information used to automatically trigger control action
  - Need knowledge of process dynamics (i.e., a model) to automatically adjust process in order to compensate for the event. (e.g., run the press differently, if detected granule density is high).
  - MPC is advanced form of feed-forward control and is most suitable

Types of Models

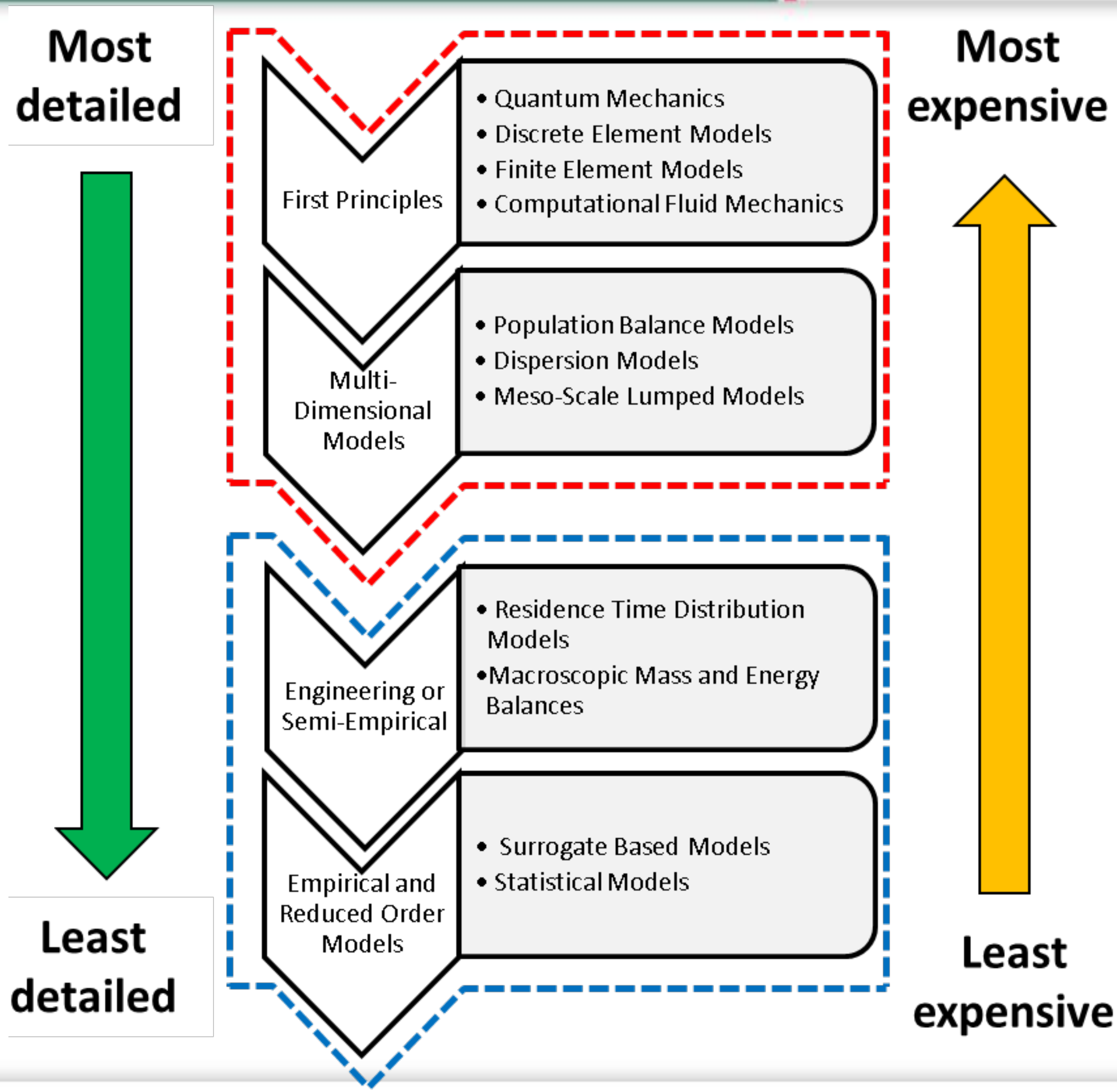


Figure courtesy Ierapetritou group at Rutgers University

Model Simplification

research
center
pharmaceutical
engineering

First principles

XPS

(granular & fluidized systems)

SPH

(extruders, melts, mixing)

PowCom

(tableting, compaction)

Model simplification

Fast control models

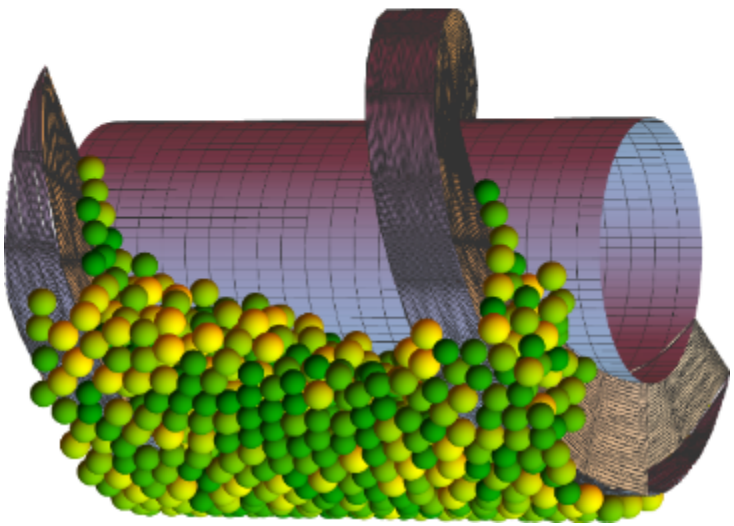
- Fluid bed granulator
- Fluid bed dryer
- Fluid bed coater
- GEA coater
- Drum coaters
- Hot-melt extruder
- Wet extruder
- Tableting
- Blenders/hoppers/feeders

gSOLIDS

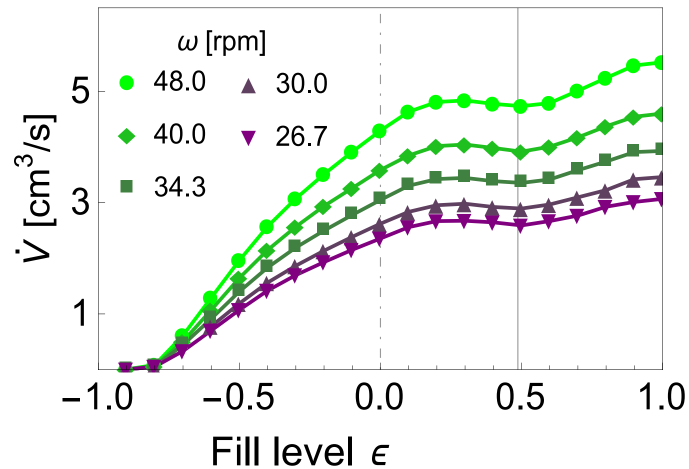
DEM Model of a Screw Conveyer for Powder Feeding/Mixing

research center pharmaceutical engineering

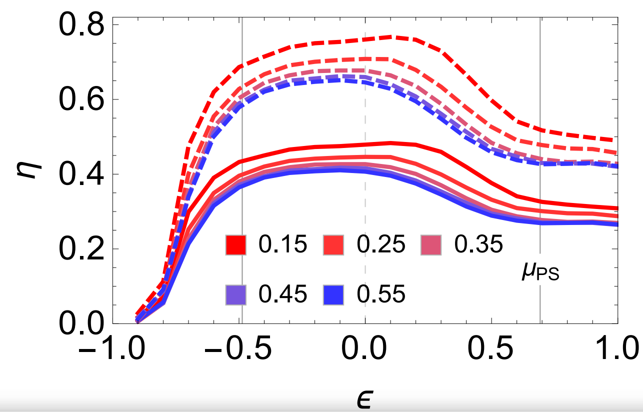
DEM simulation of powder transport in screw



Throughput:



Feeding Efficiency:



Orefice L. and J.G. Khinast, submitted to Chem. Eng. Sci. (2016)

TU Graz UNI GRAZ JOANNEUM RESEARCH

RTD Model of a Screw Conveyer for Powder Feeding/Mixing

research center pharmaceutical engineering

Model: Fokker-Planck Equation (FPE):

$$\frac{\partial C}{\partial \theta} + \frac{\partial C}{\partial \xi} = \frac{1}{Pe} \frac{\partial^2 C}{\partial \xi^2}$$

Solution:

$$C(\xi,\theta) = \frac{C_0 Pe^{1/2}}{(4\pi\theta)^{1/2}} e^{-Pe(\xi-\theta)^2/4\theta}$$

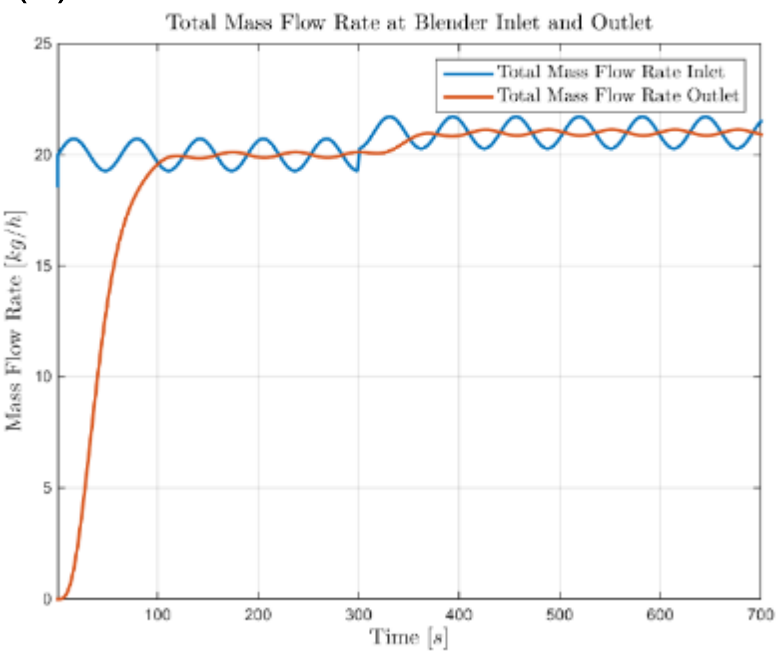
$$\theta = \frac{t - t_0}{\tau}, \quad \xi = z/l$$

θ and ξ are dimensionless time and space

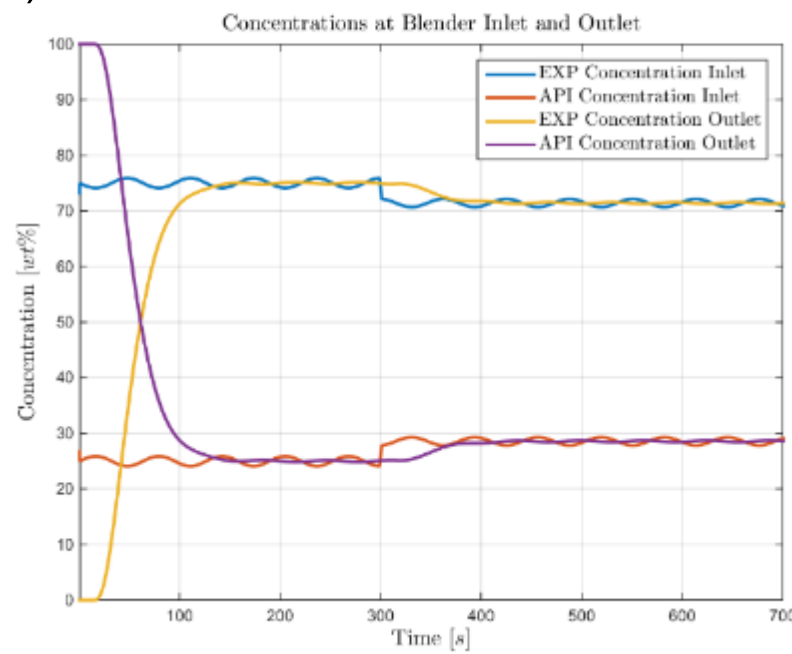
- Describes mixing and transport of material. Pe is a function of blender geometry and rotation speed, material properties and powder velocity.
- Approximation with transfer function.
- *Pe* is determined via experiments or DEM

Impact of Feeder Fluctuations

(a)



(b)



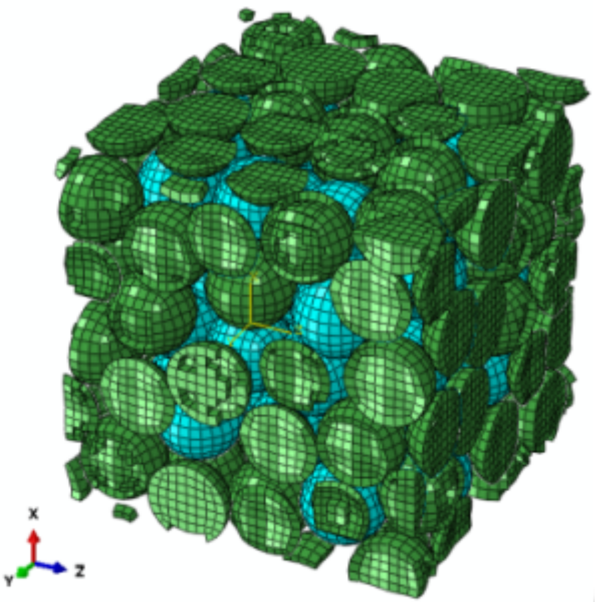
(a) Total mass flow rate at blender inet and outlet. (b) inlet and outlet concentrations of API (lower lines) and EXC (upper lines) are shown.

Kruisz J, Sacher S.. and J.G. Khinast, to be submitted 2016

Compaction: Multi-particle FE-Model (finite element model)

- Use a Representative Volume Element (RVE) to minimize computational costs
- Use periodic boundary conditions to avoid boundary effects

3D periodic box of meshed particles

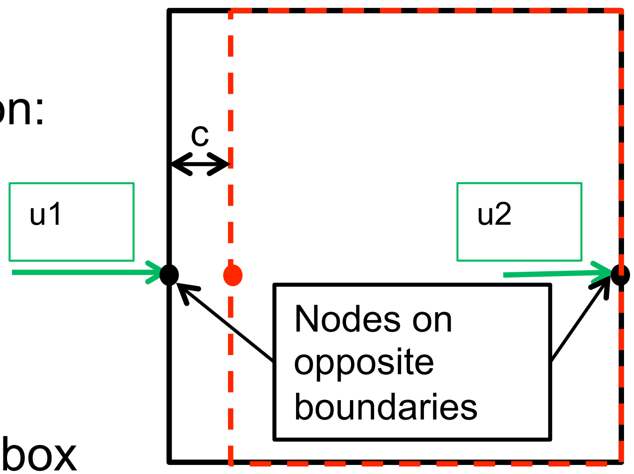


Constraint equation:

u2-u1=c

u…displacements
c…deformation of box

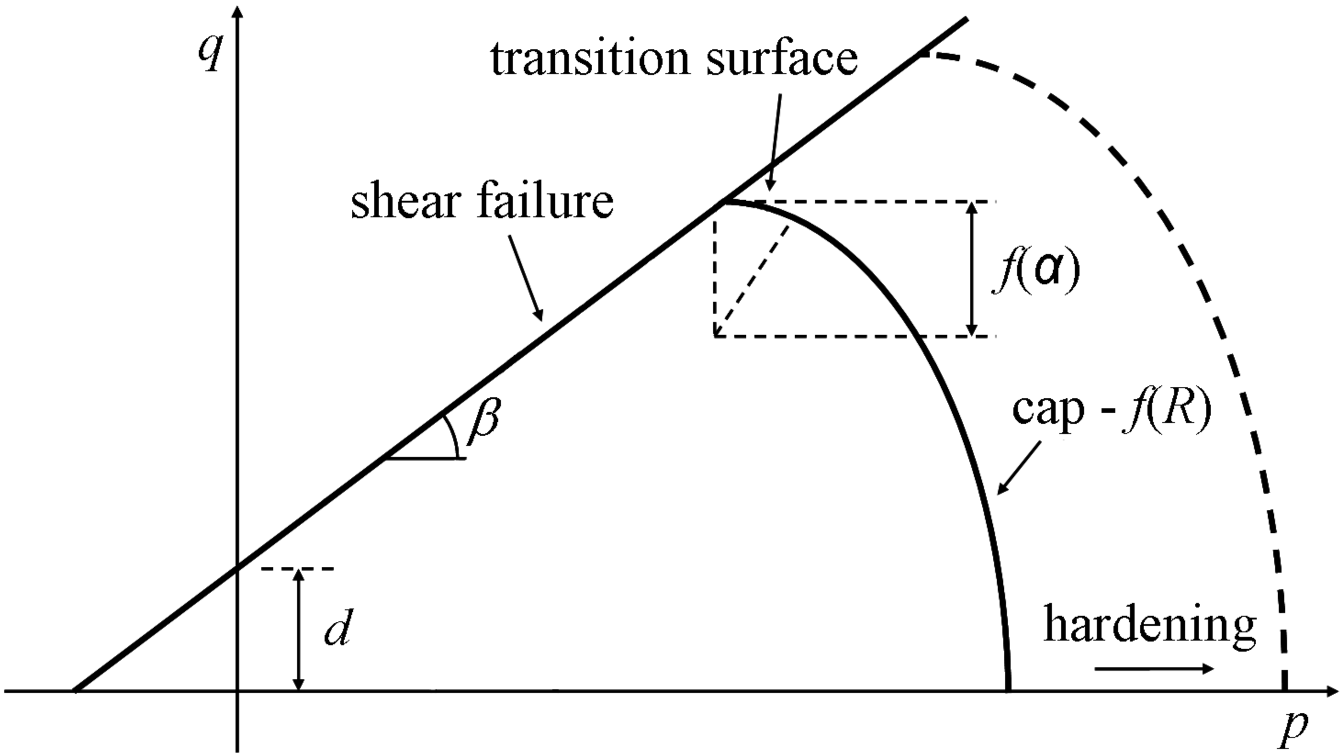
2D periodic box



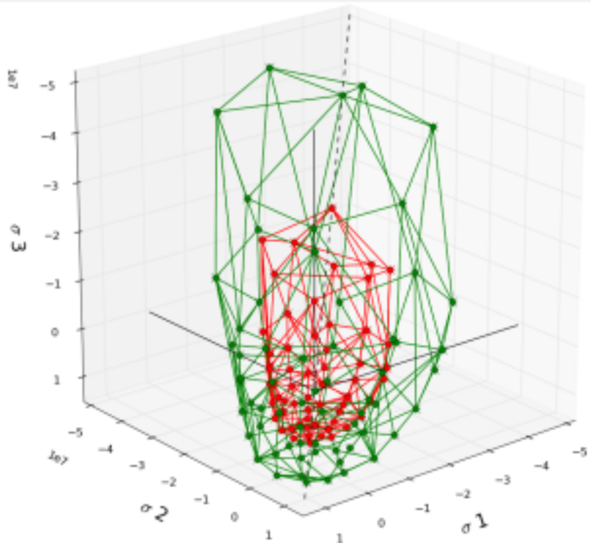
Loidolt P., M. Ulz and J.G. Khinast, to be submitted 2016

Compaction: Drucker-Prager Cap Model

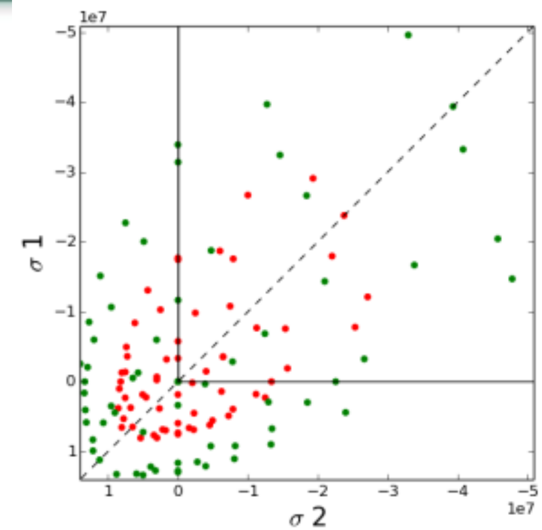
- Determined from experiments

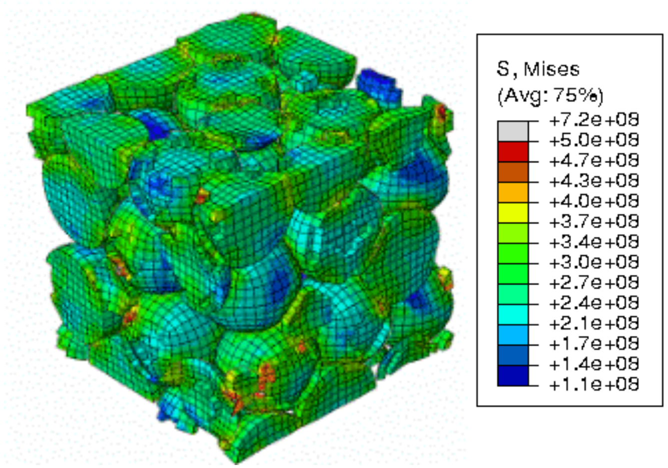


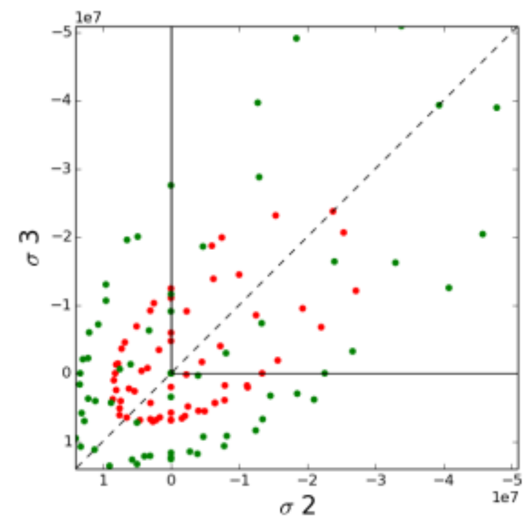
Yield Surfaces for Isostatic Compaction



- Porosity 0.25
- Porosity 0.15



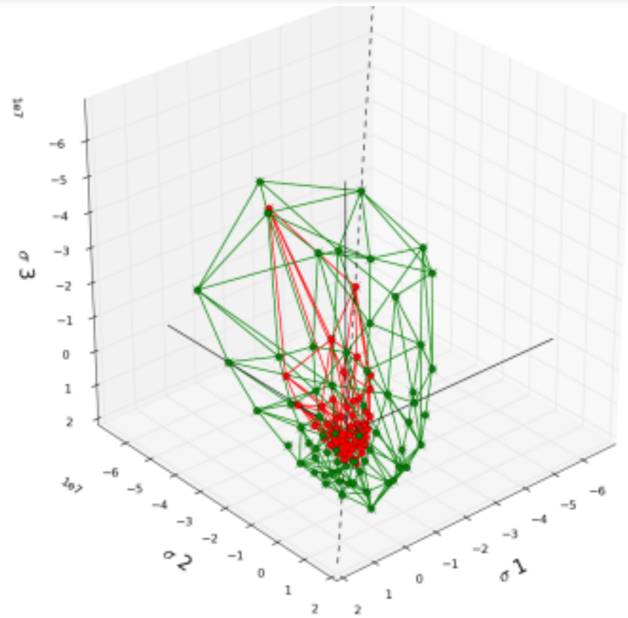




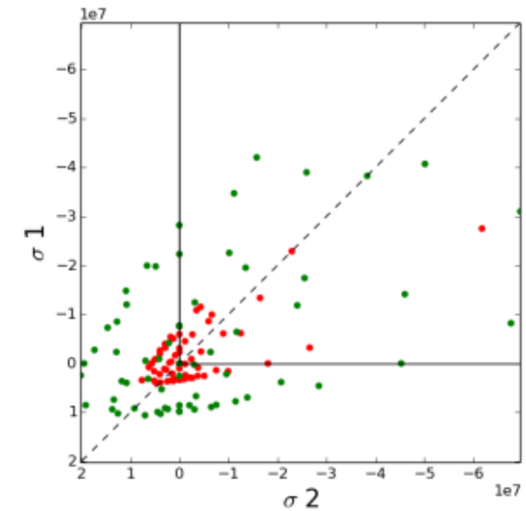
Loidolt P., M. Ulz and J.G. Khinast, to be submitted 2016

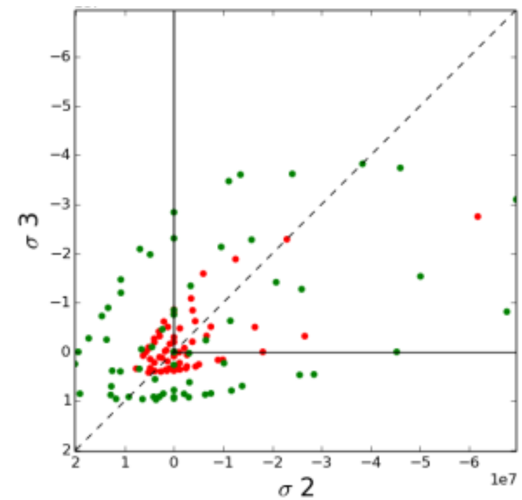
Yield Surfaces for Closed-Die Compaction

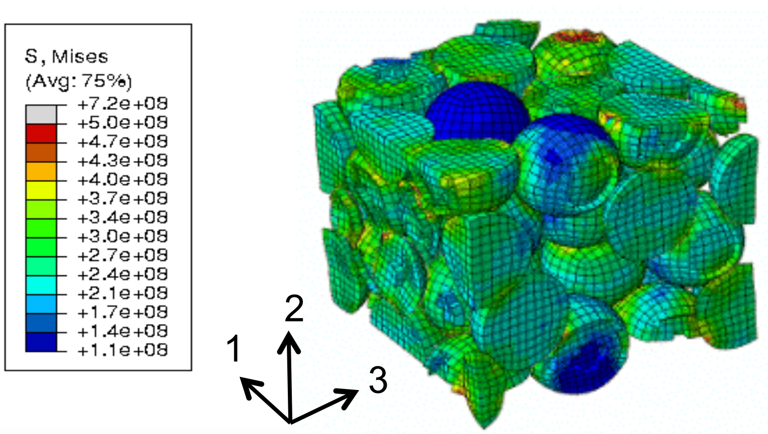
research
center
pharmaceutical
engineering



- Porosity 0.25
- Porosity 0.15

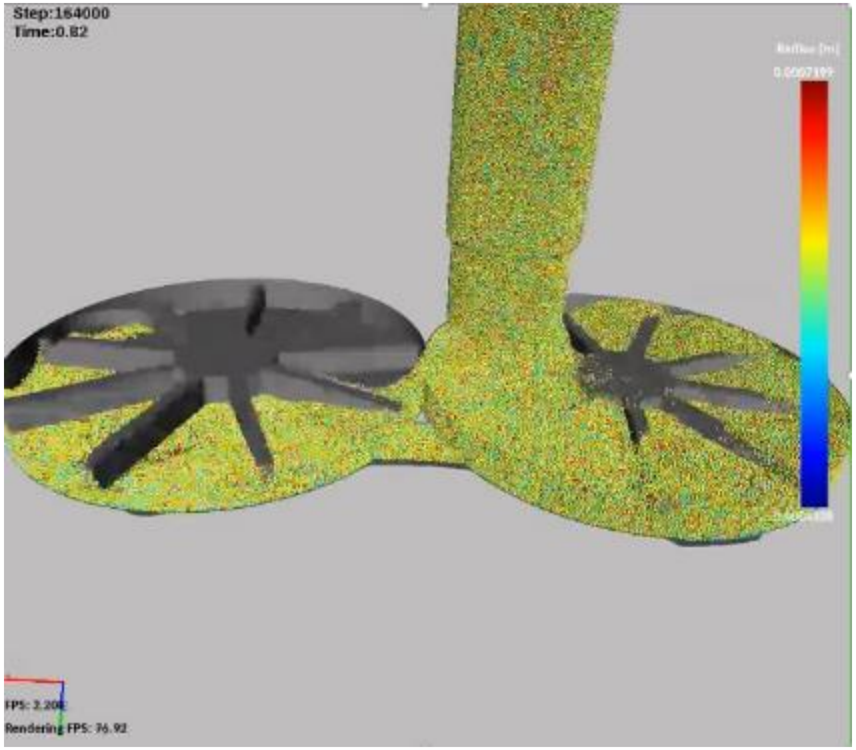


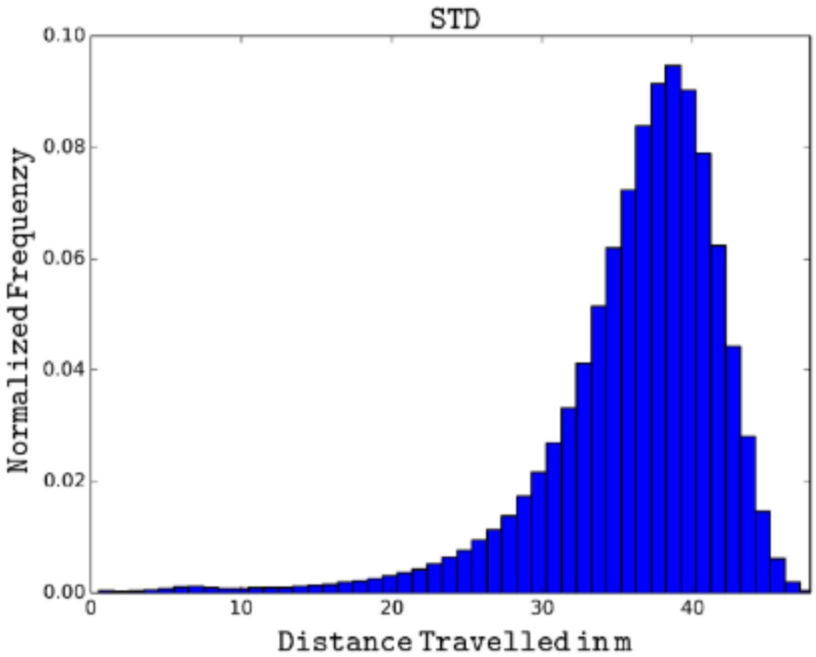




Feed Frame Analysis

CFD/DEM

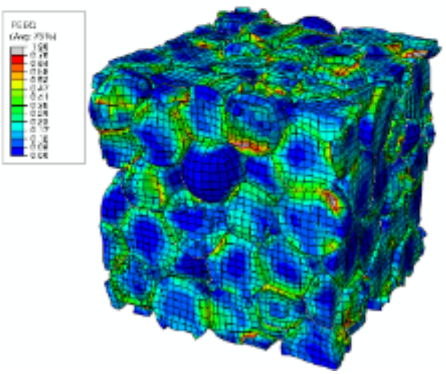


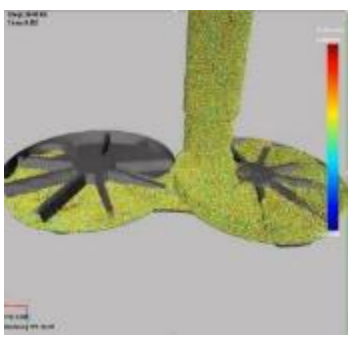


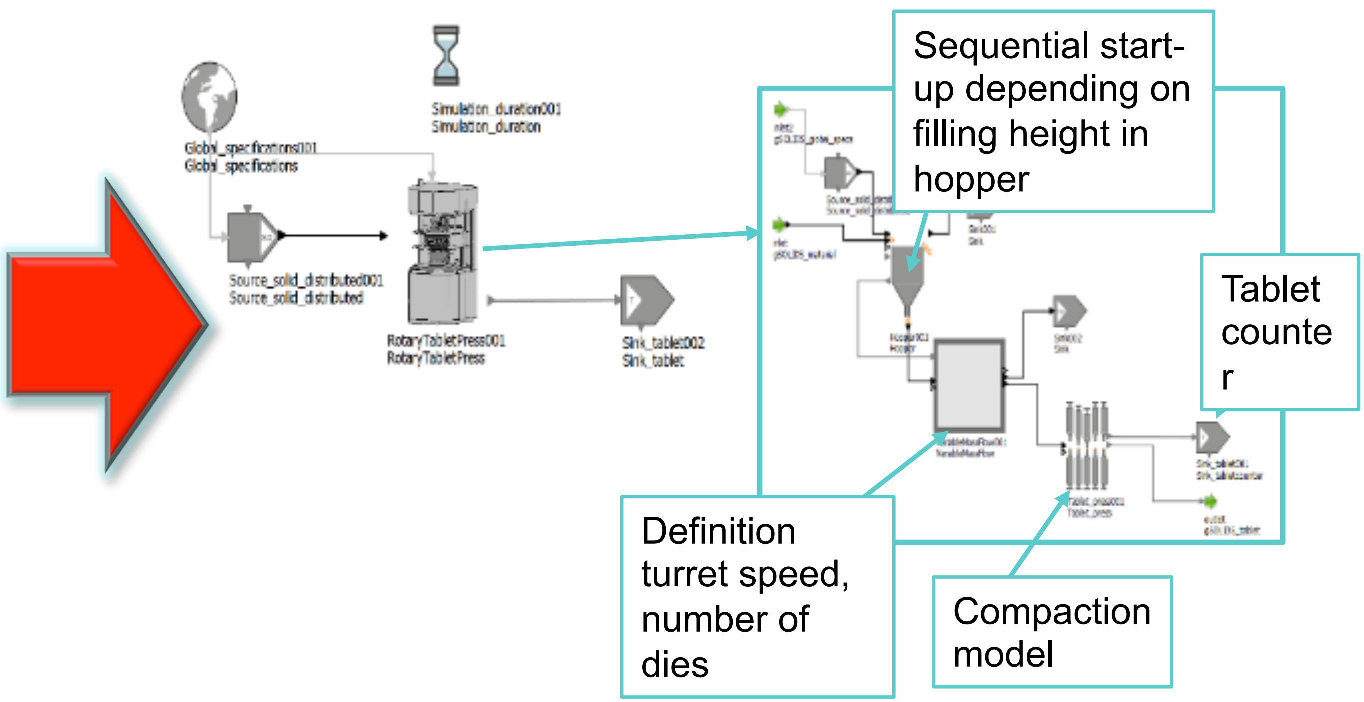
Rotary Tablet Press Model

Detailed Model (PowCom)

gsolids rotary tablet press model







Acknowledgement

Academic:

- Prof. Peter Kleinebudde
- Prof. Thomas DeBeer
- Prof. Jukka Rantanen
- Prof. Jarkko Ketolainen
- Prof. Fernando Muzzio
- Prof. Ben Glasser
- Prof. Eva Roblegg
- Prof. Sven Stegemann (Capsugel)

Students and PostDocs

- Dr. Stephan Laske (RCPE)
- Dr. Stephan Sacher (RCPE
- Dr. Andreas Eitzlmayr (TU Graz, Austria)
- Dr. Gerold Koscher (RCPE)
- Ramona Baumgartner (RCPE)
- Massimo Bresciani (RCPE, Austria)
- Dr. Andreas Witschnigg (RCPE, Austria)
- Dr. Eva Faulhammer (RCPE, Austria)
- Dr. Marcos LLusa (RCPE, Austria)
- Luca Orefice, Josip Matic, Julia Kruisz (TU Graz, Austria)

Contact

Prof. Dr. Johannes G. Khinast
Director – Science
e-mail: khinast@tugraz.at
phone: +43/316/873/30400

Dr. Thomas K. Klein
Director – Finance and Legal
e-mail: thomas.klein@rcpe.at
phone: +43/316/873/30900

Massimo Bresciani
Director - BD & Sci Ops
e-mail: massimo.bresciani@rcpe.at
phone: +43/316/873/30915

Inffeldgasse 13, A-8010 Graz, Austria

Science and commercial combined offerings

- **PSE and RCPE** announce that we will be setting up a **Centre of Excellence ("CoE")** aimed at bringing combined model-based analytical technology and **services** to the **pharmaceuticals industry** and more in general to **life science** field of application

- **PSE-RCPE CoE** will be started **1st July 2016**, offering advanced simulation science and tools:
  - **Fit-for-purpose models** that combine **detailed mechanistic models** at **multiple length scales**
  - **Targeted and integrated experimentation** to reduce time and cost
  - Combination and integration of **most advanced modelling tools available** from PSE and RCPE
  - **Model-based workflows** that help you design robust products and processes rapidly and effectively
  - Combined and **integrated capacity** and **expertise**
  - **Integrated commercialization** stream