Virtual Formulation Laboratory

for prediction and optimisation of manufacturability of advanced solids based formulations

C. Sinka (PI), R. Davidchack, M. Ghadiri, X. Jia, M. Bradley, R. Berry, J. Heng

Future Formulation meeting organised by
Formulation Science and Technology group (FSTG) of the Royal Society of Chemistry
24 May 2017 Durham University

Academic Collaborators

- Csaba Sinka and Ruslan Davidchack

  University of Leicester

- Mojtaba Ghadiri and Xiaodong Jia

  University of Leeds

- Mike Bradley and Rob Berry

  University of Greenwich

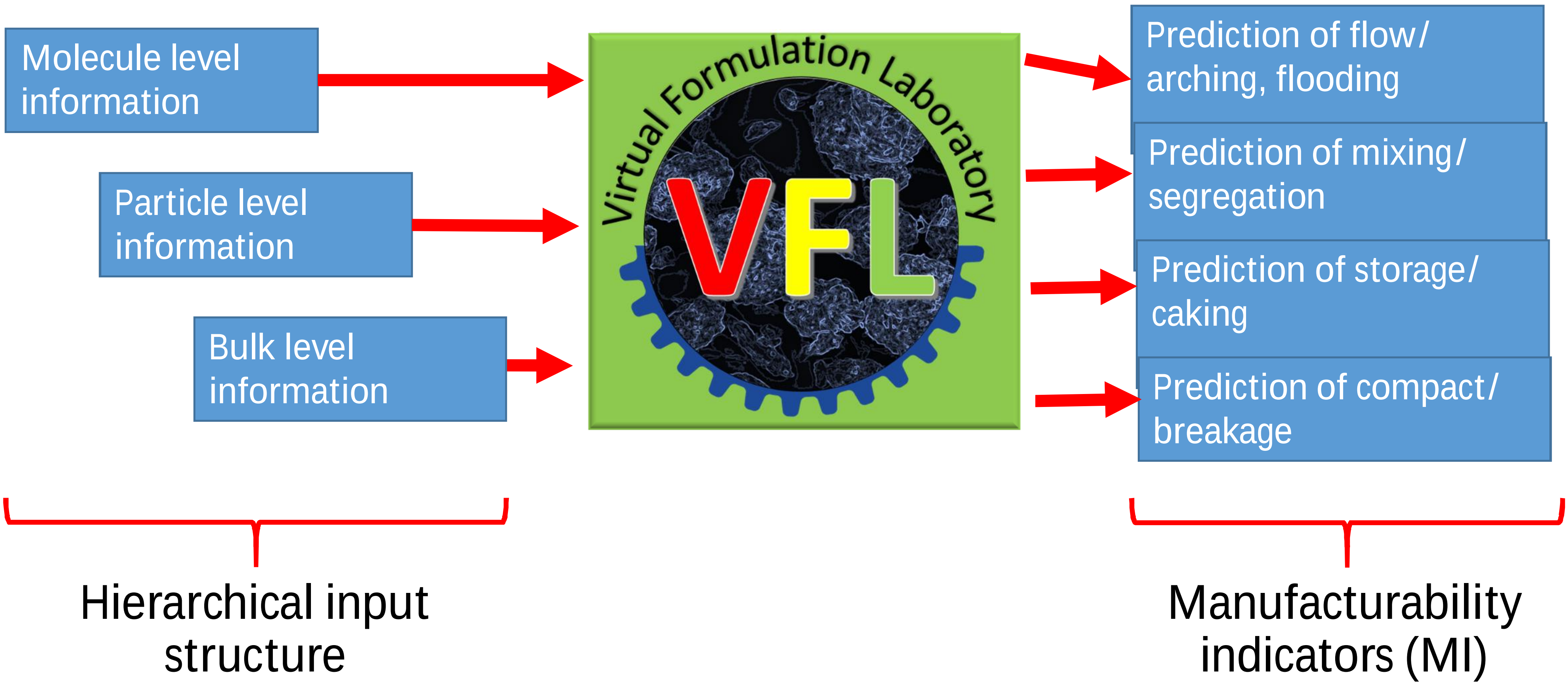
- Jerry Heng

  Imperial College

Industrial Partners

- Centre for Process Innovation (CPI)
- Procter & Gamble
- GlaxoSmithKline
- AstraZeneca
- Nestle
- KP Snacks
- Brookfield
- Britest
- Process Systems Enterprise (PSE)
- Griffiths Food
- Freeman Technology
- DEM Solutions

VFL: 4 Processes/ 4 Problems



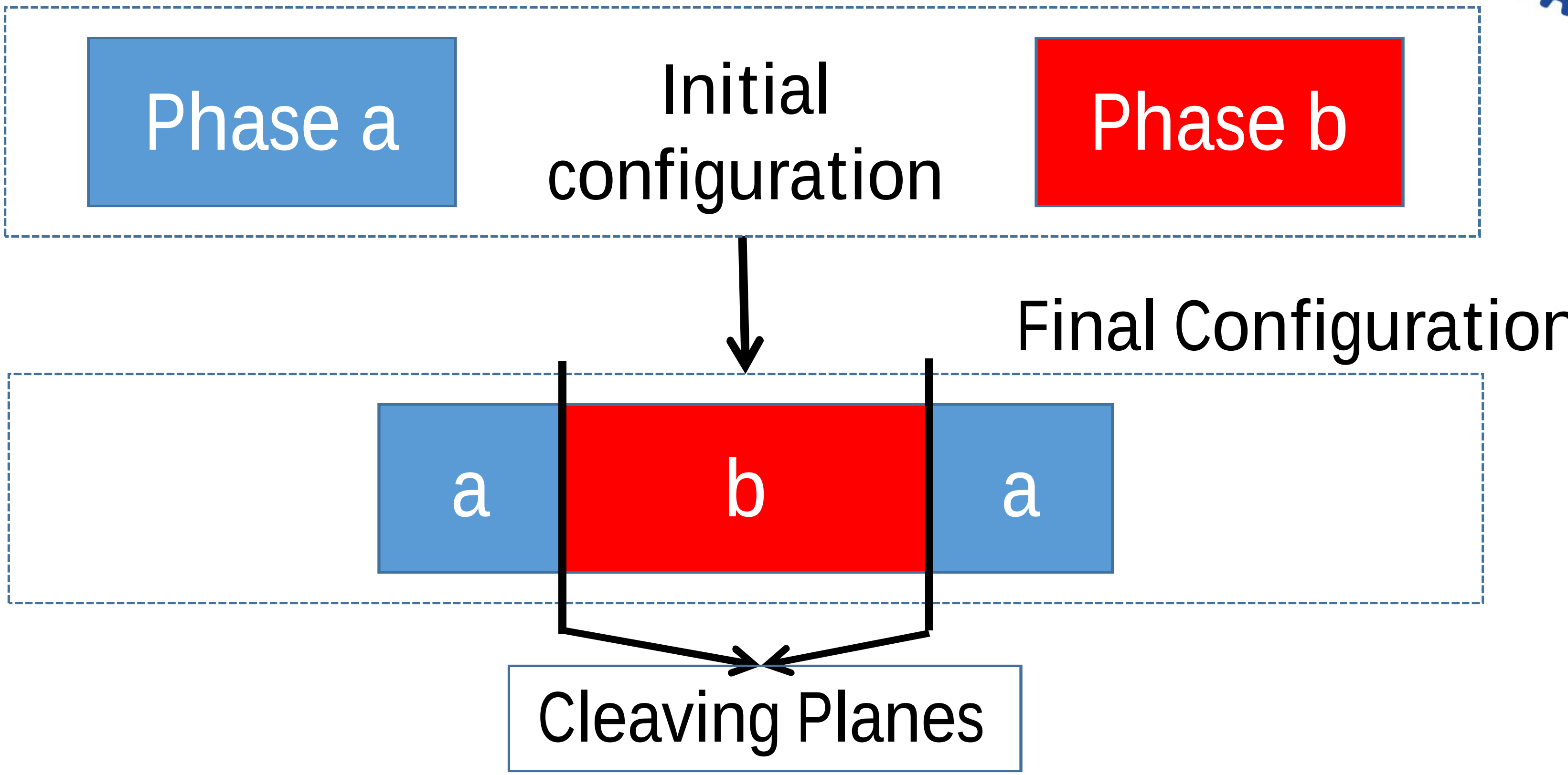
Surface Free Energy Predictions

Dr Nicodemo Di Pasquale and Prof. Ruslan Davidchack

- Prediction of Adhesive Interactions by Molecular dynamics (MD)

- Cleaving Method
  - Extension to heterogeneous surfaces
  - Effect of crystal orientation

Cleaving Method



Surface Free Energy is the reversible work required to create a unit area of the interface between two phases (one of the phases could be vacuum)

Current MD simulation objectives

- Implement the cleaving method in LAMMPS
- Selection of model materials
- Comparison of results from MD simulation with FD-IGC experimental work at ICL

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Surface Energy Characterisation using Inverse Gas Chromatography (FD-IGC)

Dr Vikram Karde and Dr Jerry Heng

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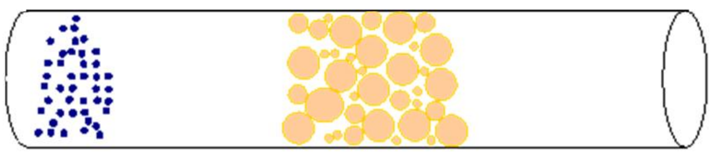
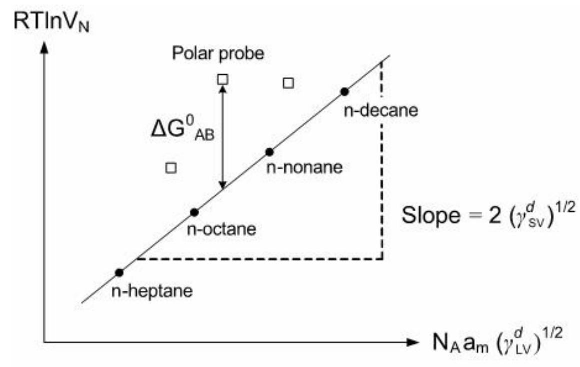
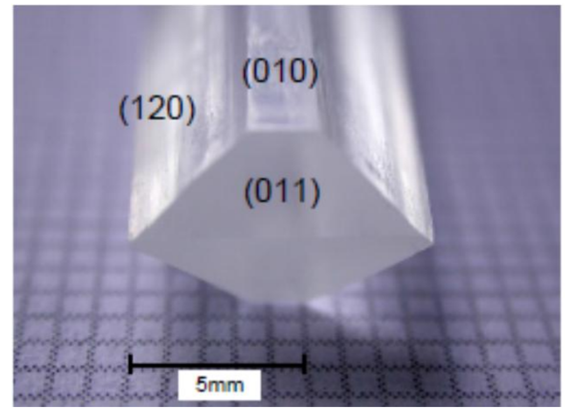
Surface energy determination using IGC

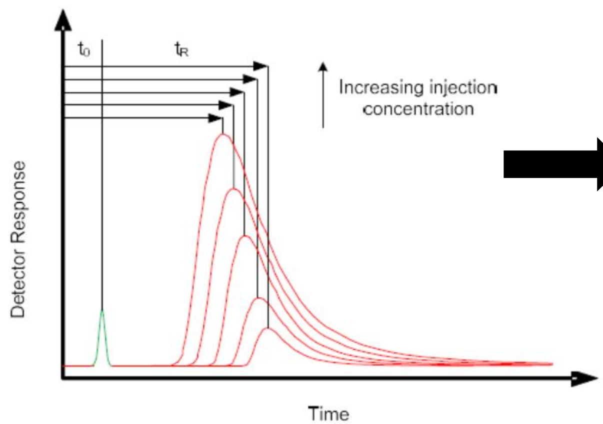


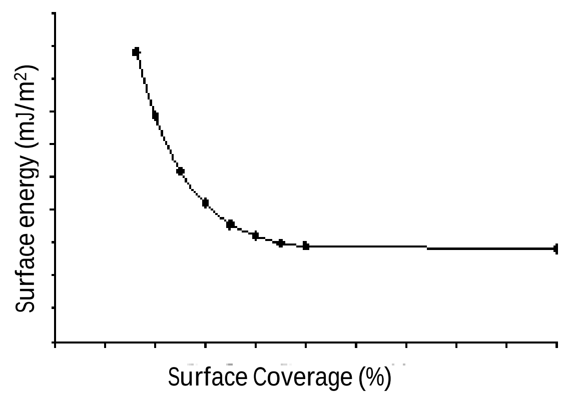


Anisotropy in crystalline solids (Heterogeneous surfaces)



Surface energy heterogeneity using Finite Dilution IGC (FD-IGC)



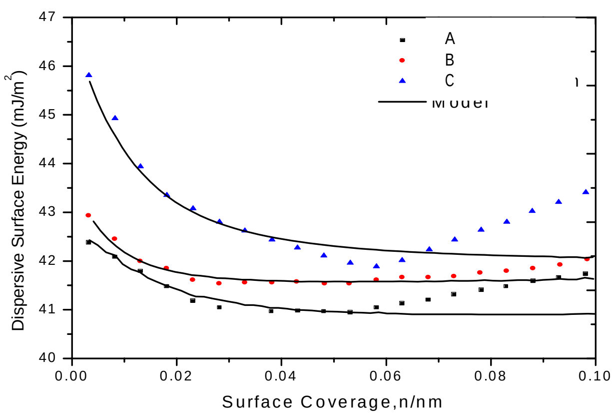


Surface energy heterogeneity profile

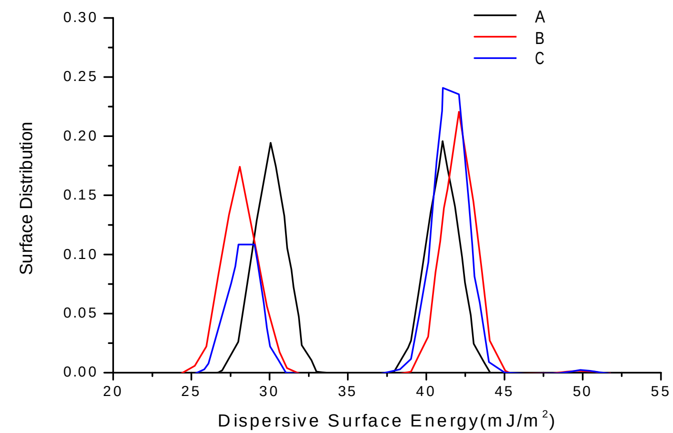
Facet specific surface energy using Contact angle

Surface Energy Distribution

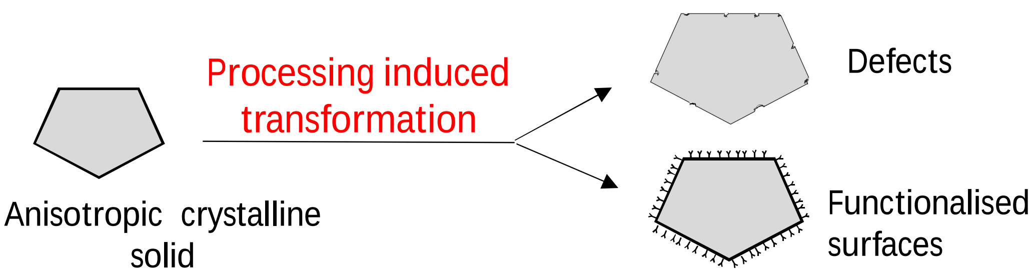
De-convolution of surface energy heterogeneity for the prediction of energy site distributions

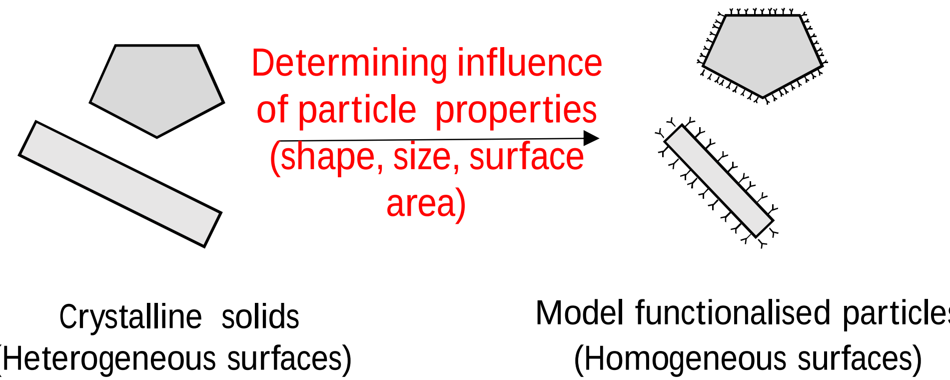


Surface energy heterogeneity profiles



Predicted energy site distribution





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Flowability, Mixing, Segregation

Dr Mehrdad Pasha, Dr Xiaodong Jia and Prof. Mojtaba Ghadiri

Parameters

Surface Adhesion

Binary Mixture

- *Spherical*
- *Same size*
- *Same plasticity*
- *Same density*
- *Adhesion by salinization two extreme levels*

Particle Size

Binary Mixture

- *Spherical*
- *None-adhesive*
- *Same density*
- *Same plasticity*
- *Two extreme size*

Density

Binary Mixture

- *Spherical*
- *None-adhesive*
- *Same plasticity*
- *Same size*
- *Two extreme densities*

Particle Shape

Binary Mixture

- *Same size & density*
- *Preferably non-adhesive*
- *Preferably same plasticity*
- *Two extreme particle shapes*

Plasticity

Binary Mixture

- *Spherical*
- *Same size*
- *None-adhesive*
- *Preferably same density*
- *Two extreme level of plasticity*

Processes

Segregation

- *Elutriation Segregation in a 2D box*
- *Segregation in FT4*

Flowability

- *Effect of strain rate on shear for the above systems*
- *Effect of various material properties on flowability*

Mixing

- *Investigation of effect of various material properties on mixing of formulated powders*
- *Effect of air in mixing*

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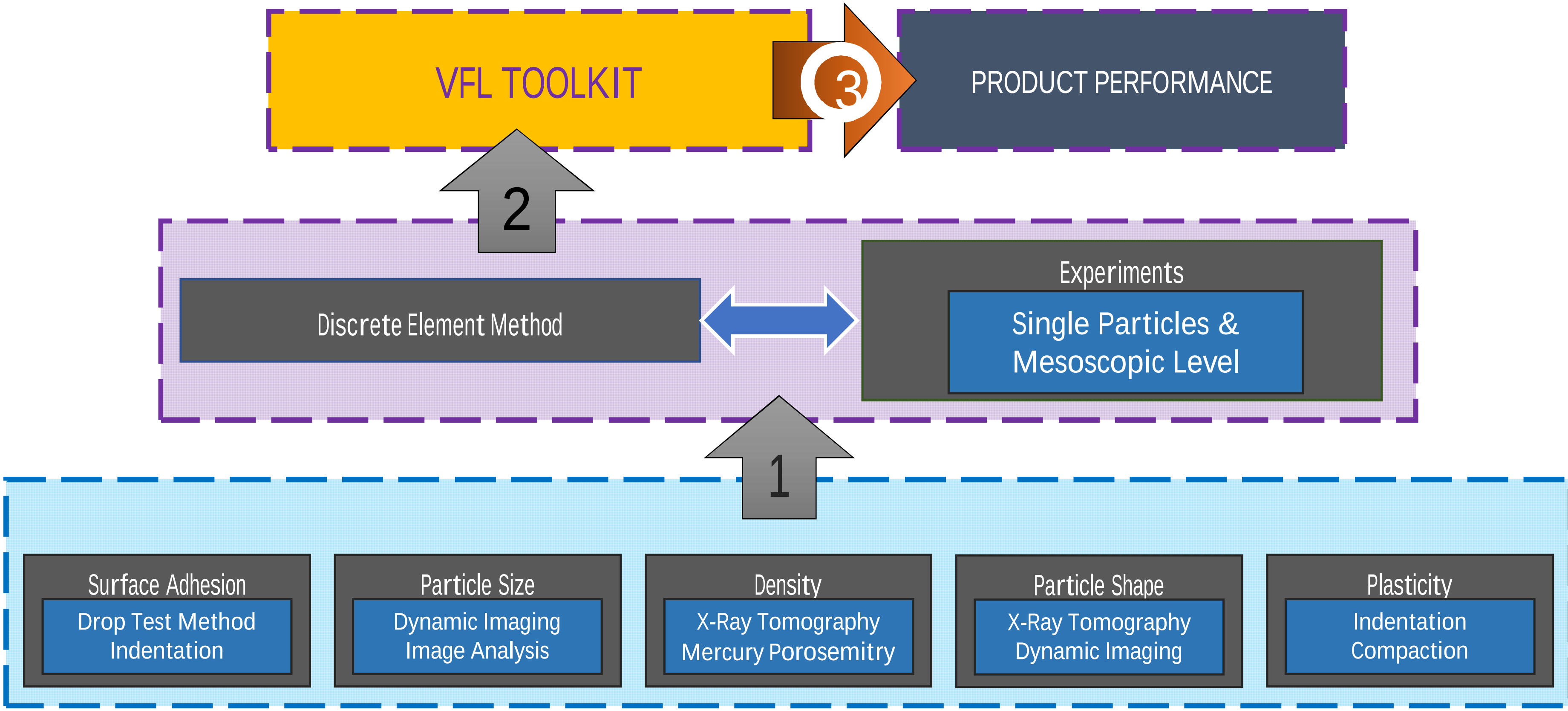
Flowability, Mixing, Segregation



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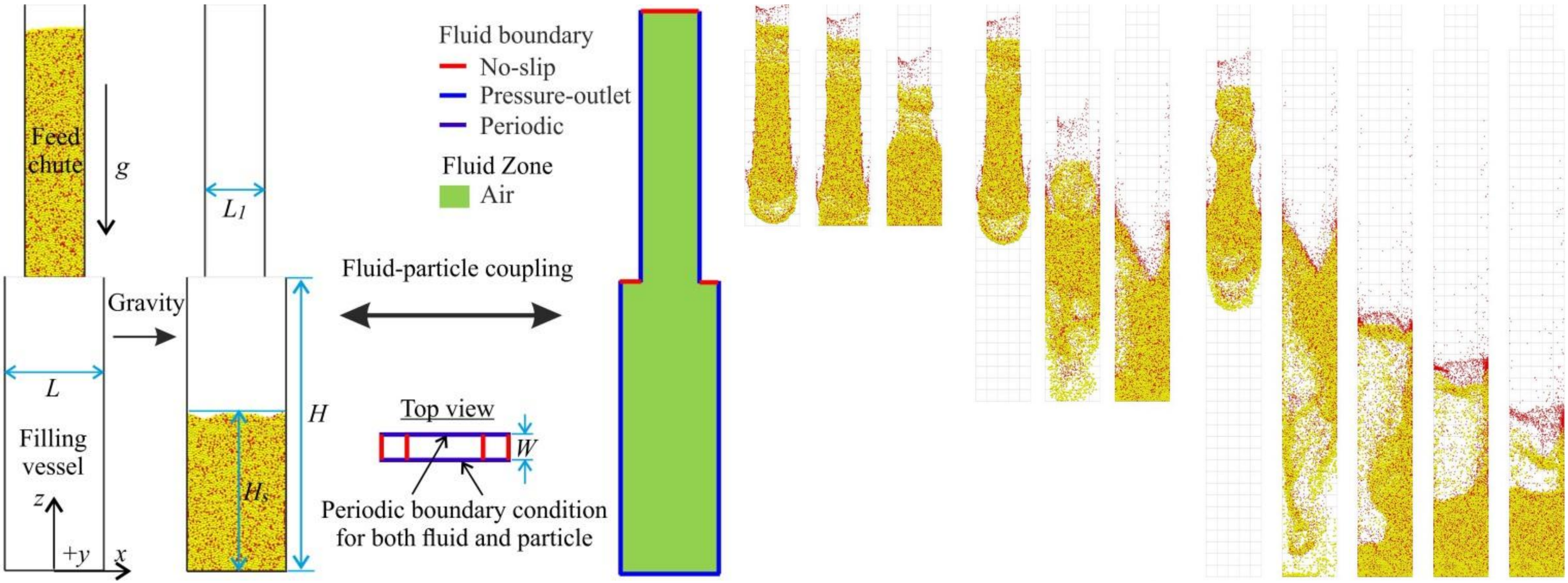
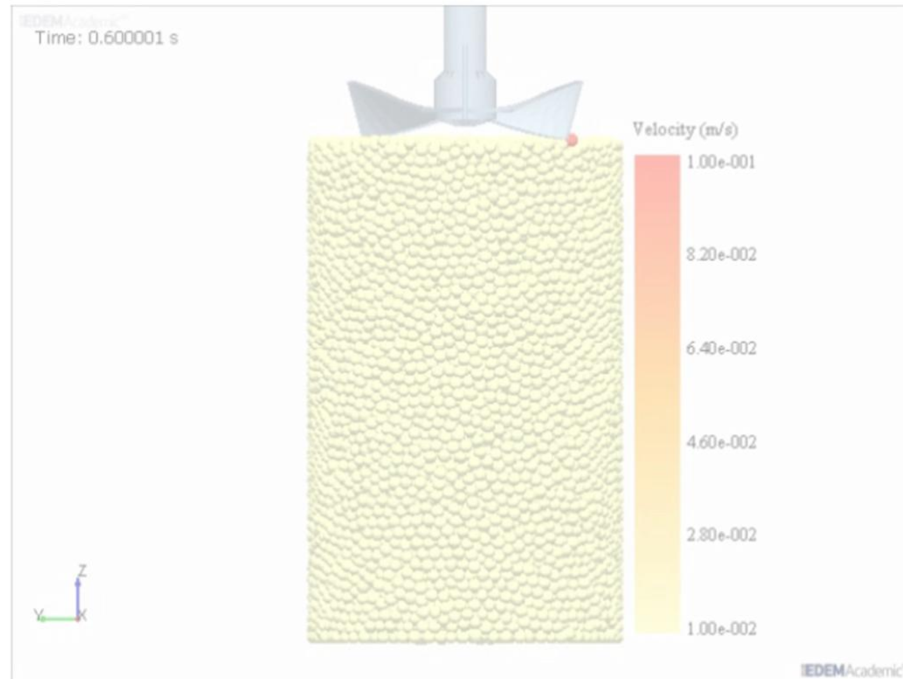
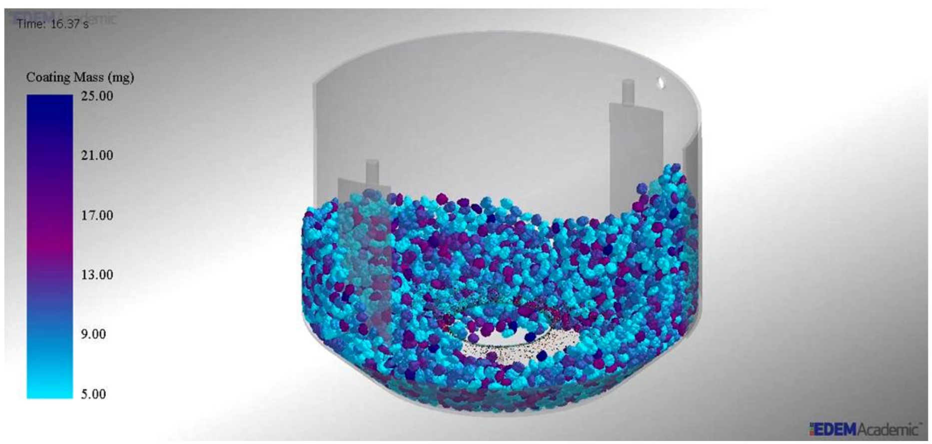
Elutriation Segregation



Flowability, Mixing and Segregation





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Modelling Powder Compaction

Dr Ben Edmans and Dr Csaba Sinka

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Constitutive Model
State variables

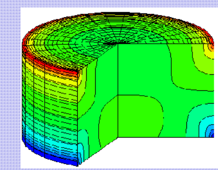
Friction
Dependencies

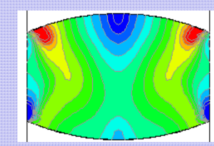
Geometry
Tablet image

Loading schedule
Sequence of punch motion

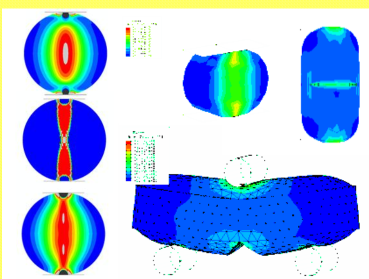
Initial conditions
Die fill

Tablet compaction modeling
FEA - ABAQUS
Solving equations:
- Equilibrium
- Compatibility
- Constitutive

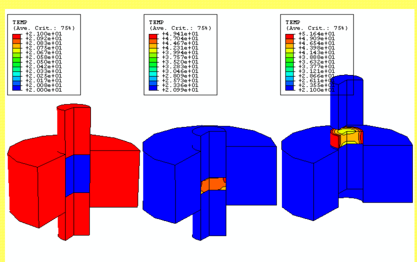




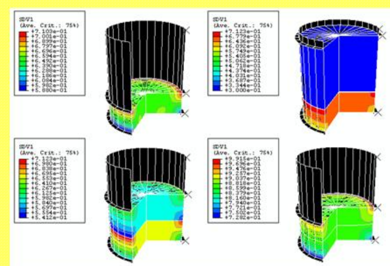
Tablet strength



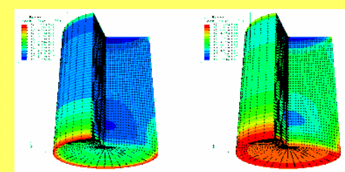
Temperature



Bilayer tablets



Tool design



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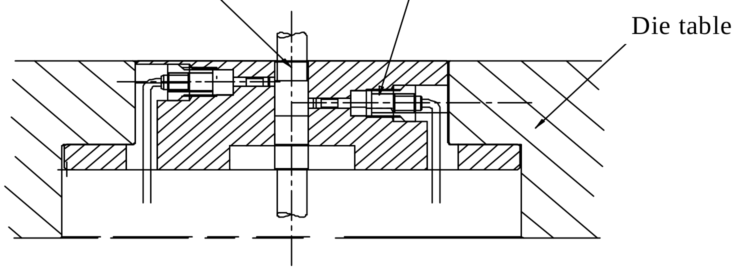
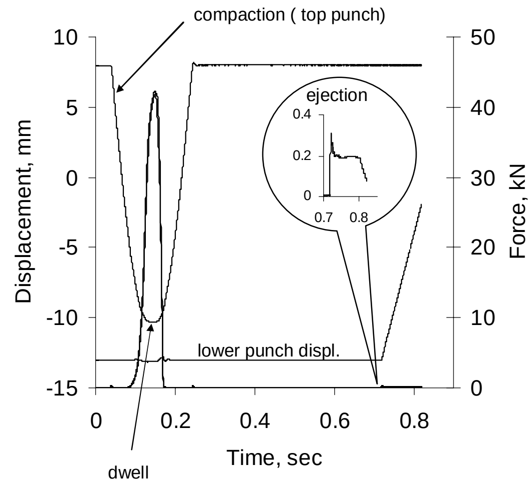
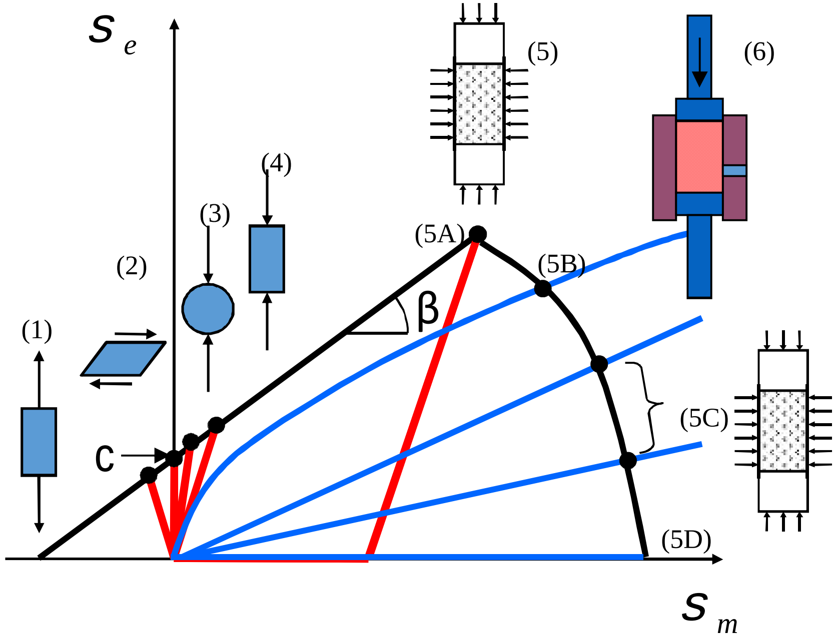
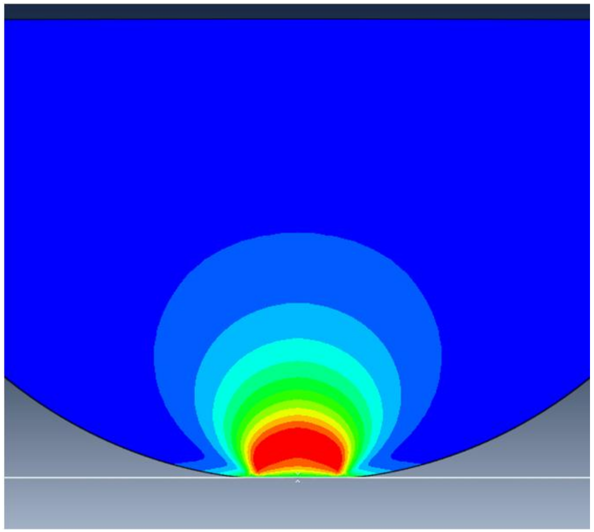
Compaction characterisation



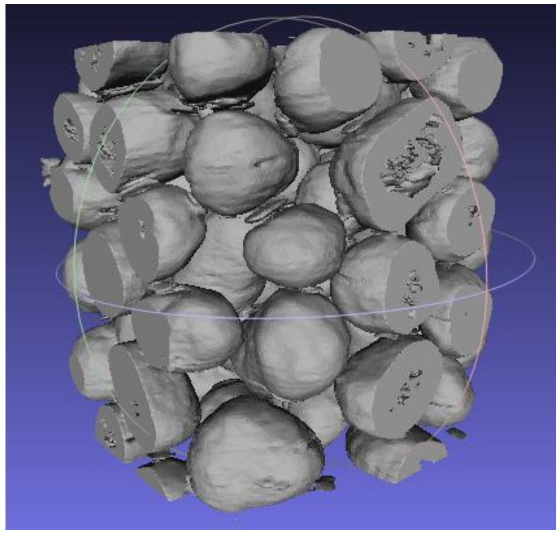




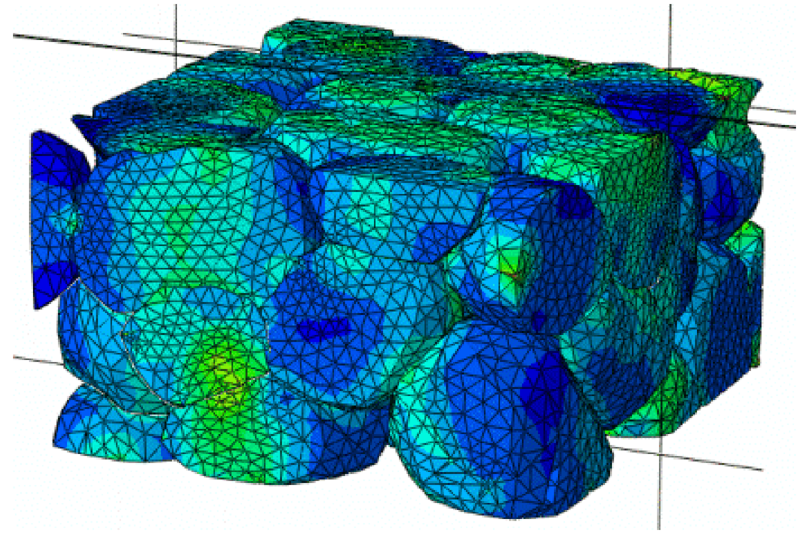
Finite Element Analysis of Particle Interactions



Contact stress between particles



X-ray CT particle assembly



Numerical constitutive law

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Particle and Bulk Scale Measurements

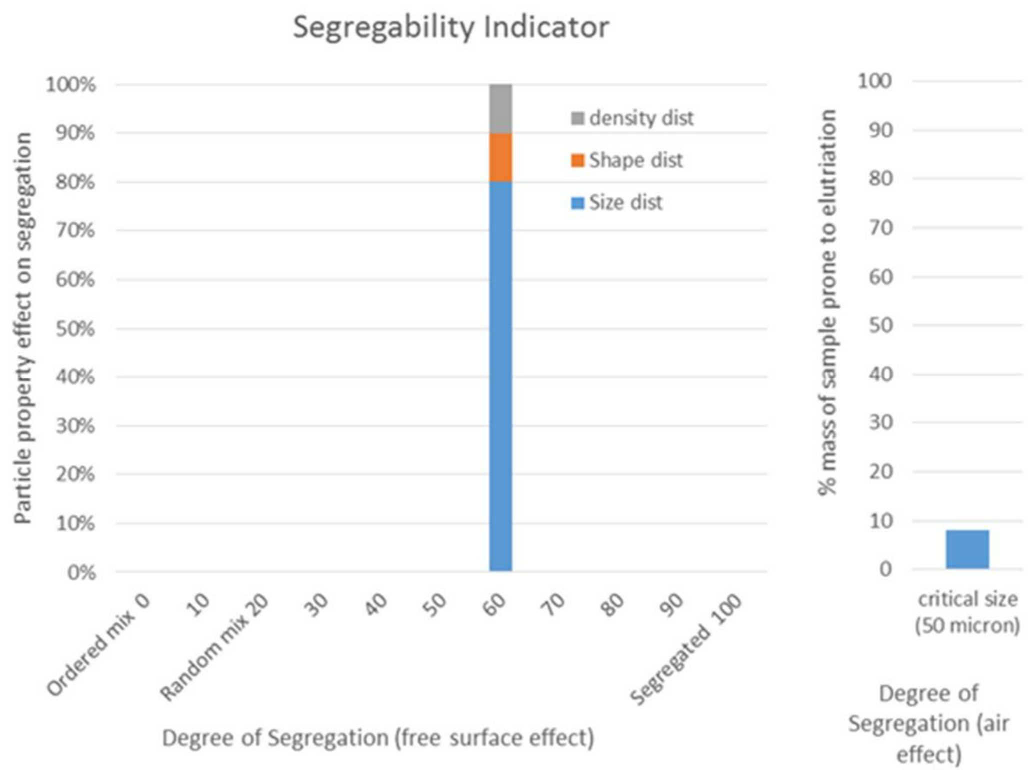
Dr Pablo Garcia Trinanes, Dr Rob Berry and Prof. Michael Bradley

- Particle size and shape measurement
  - G3 morphologi – shape/ size
  - Air-swept sieve – size
  - Pycnometer – material density
- Bulk flow properties
  - Brookfield (PFT) - freeman for high stress tests? – flow function, friction, bulk density (voidage)
  - Uniaxial compaction test – for high stress tests
- Segregation properties
  - Free surface (rolling segregation) for coarse particles > approx. 100 mm
  - Air induced (elutriation) for separation of fines (sub 50 mm) from wider distribution
- Caking properties
  - Capability for measuring cake strengths driven by:
    - moisture migration, chemical reaction or plastic flow mechanisms in storage

Segregability Indicator

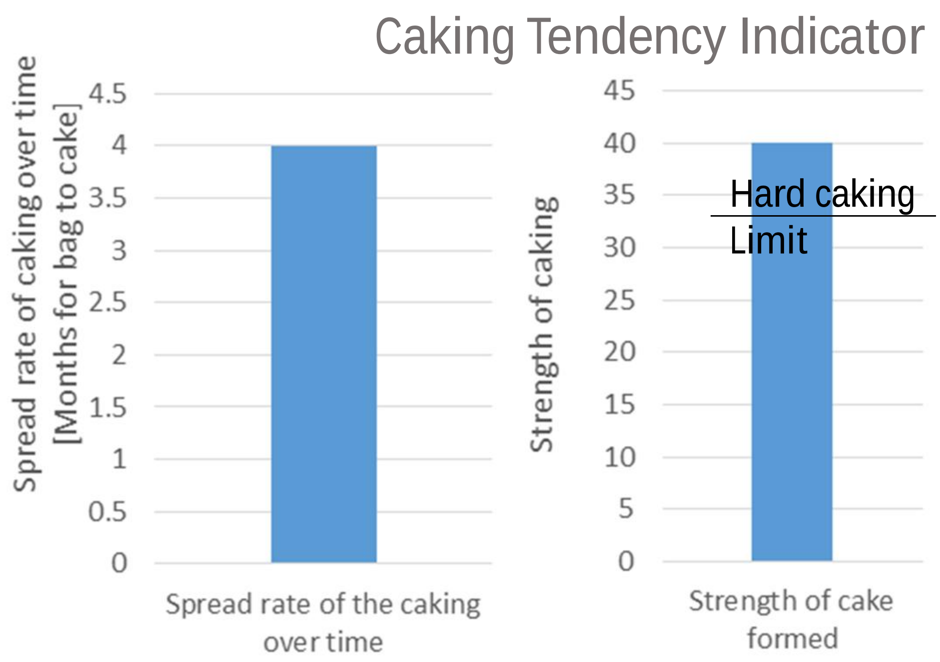
- Focus on characterising materials propensity to:
  - free surface segregation when discharged to form a heap (silo loading etc.)
  - Elutriate when dropped at high velocity into a confined space (into a silo, chute)

- Quantify degree of segregation (from top to bottom of slope) based on a scale from blended (20) to perfectly segregated (100)
- Define limiting particle size below which air effects dominate and the % product weight below this size



Caking Tendency Indicator

- Unwanted caking in manufacturing processes not considered:
  - time periods short,
  - issues solvable through environmental control and mass flow equipment
- Focus, caking in long term storage/transport as little can be done to minimise the variations in environmental conditions experienced over time:
  - spread rate of caking (time for bag to set e.g. 25 kg sack, bulk bag)
  - strength of caking soft (will break up on mesh when bag opened) or hard making material un-processable



Leveraging Other Local Programmes

- CHARIOT (David York and P&G):

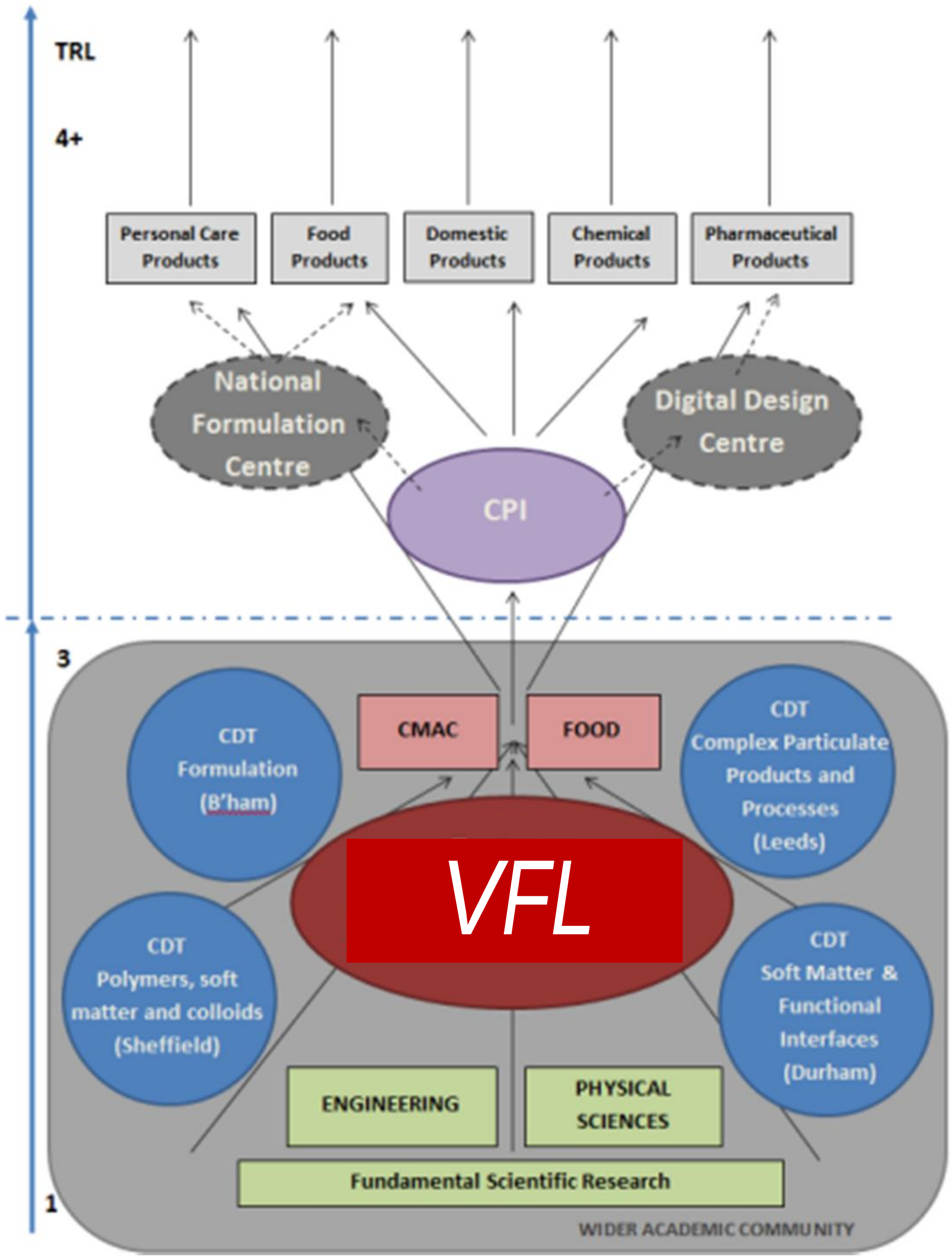
WP1	WP2	WP3	WP4	WP5	WP5s	WP6	WP6s	WP7
Milling	Spray dried Structure	Micro-waves	Coating / Twin Screw Mixer	Segregation	At line quality (spectral) Sensor development	Coating/ Mix Drum	Acoustic sensor development	Open access facility

- ADDoPT (Kevin Roberts and 8 Industrial Partners):

Whole spectrum of pharmaceutical manufacturing

- TIPOW & MAPP (Andrew Bayly and Future Manufacturing)

Powder flow in Additive Manufacturing



Interactions and Networking with National Programmes

Concluding remarks

Virtual Formulation Laboratory

VFL

- develop the science base for understanding of particle surfaces, structures and bulk behaviour to address physical, chemical and mechanical properties and behaviour during processing and storage
- develop formulation science to link molecule to manufacturability (through experimental characterisation and numerical modelling)
- establish methodologies to formulate new materials through developing functional relationships, considering the limits and uncertainties
- Develop a software tool for prediction and optimisation of manufacturability and stability of advanced solids-based formulations