# Virtual Formulation Laboratory for prediction and optimisation of manufacturability of advanced solids based formulations


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PDRAs: B.D. Edmans, N. Di Pasquale, M. Pasha, H. Salehi, V. Karde, V. Garg (PhD student)

Future formulation 4
University of Edinburgh (online meeting)
23 June 2020

RSC INTEREST GROUP FORMULATION SCIENCE & TECHNOLOGY

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# Virtual Formulation Lab Team

| Academic partners | PDRAs and visitors |
|---|---|
| Prof. Csaba Sinka (PI) – Leicester<br>Prof. Ruslan Davidchack | Dr. Ben Edmans<br>Dr. Nicodemo Di Pasquale |
| Prof. Mojtaba Ghadiri – Leeds<br>Dr. Xiaodong Jia | Dr. Mehrdad Pasha<br>Dr. Koichiro Ogata (visiting scholar)<br>Dr. Sadegh Nadimi (Leeds U.)<br>Dr. Wenguang Nan (visiting scholar) |
| Prof. Mike Bradley – Greenwich<br>Dr. Rob Berry (RIP)<br>John Cummins | Dr. Hamid Salehi<br>Vivek Garg (PhD student)<br>Dr. John Cummins (Greenwich U.) |
| Dr. Jerry Heng – Imperial College | Dr. Vikram Karde<br>Izabela Phillips (PhD student) |

| Industrial partners |
|---|
| CPI, NFC |
| P&G |
| GlaxoSmithKline |
| AstraZeneca |
| Nestle |
| KP Snacks |
| Brookfield |
| Britest |
| PSE |
| Griffiths Food |
| Freeman Technology |
| Chemours |
| EDEM |
| Johnson Matthew |
| Abbvie |

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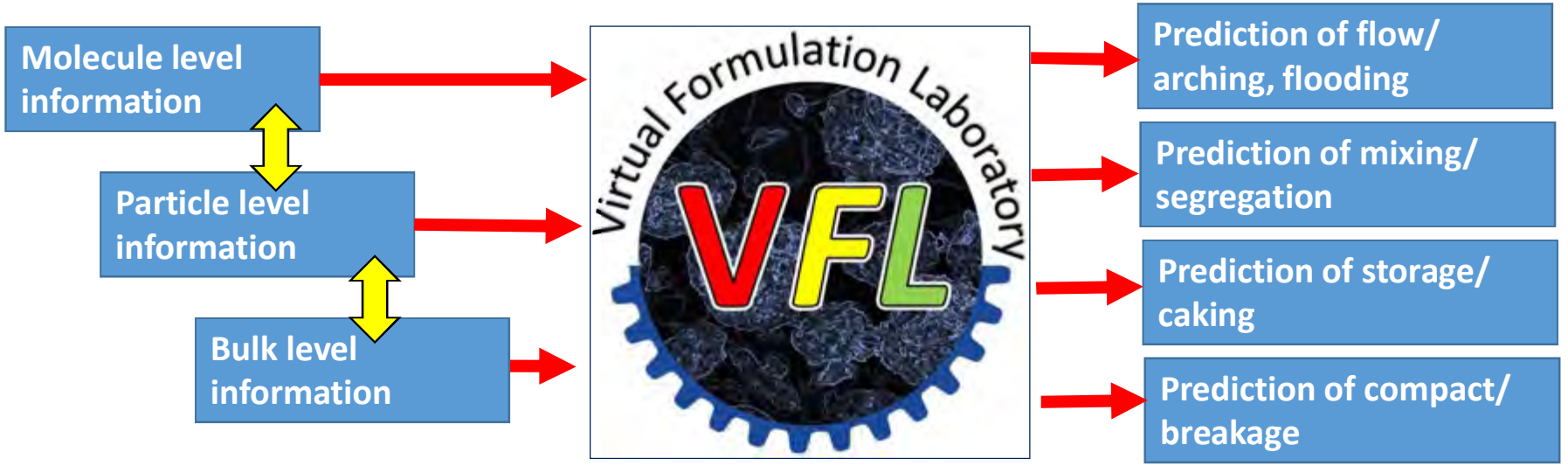
# Virtual Formulation Laboratory for prediction and optimisation of manufacturability of advanced solids based formulations




Hierarchical input structure

EPSRC
Engineering and Physical Sciences Research Council

Manufacturability indicators (MI)

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# VFL work programmes

- Predicting bulk properties from particle properties
- Predicting particle properties from molecular structure
- Characterisation of adhesive interactions and surface energy of functionalised particles
- VFL toolkit development

# VFL approach to powder surface energy (I)

Vikram Karde and Jerry Heng

Imperial College London

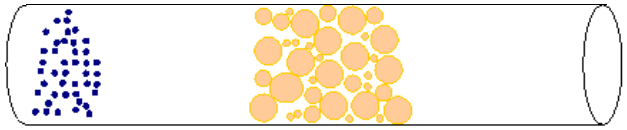


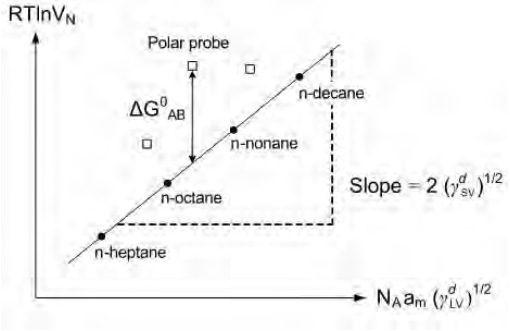


Imperial College London

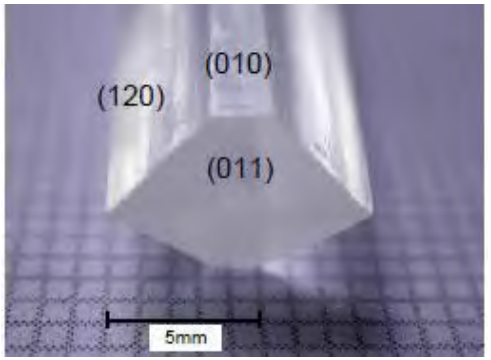
# Surface Energy Characterisation using Inverse Gas Chromatography (FD-IGC)

**Surface energy determination using IGC**

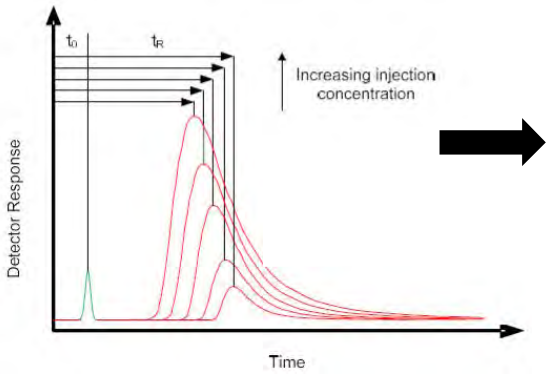


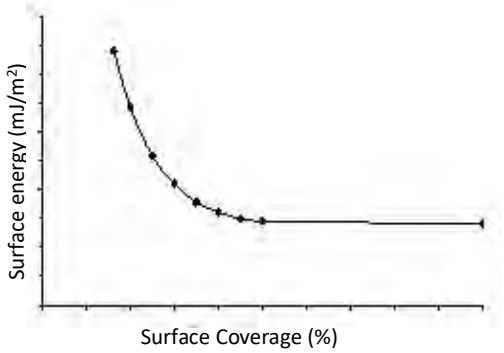




**Anisotropy in crystalline solids**
(Heterogeneous surfaces)

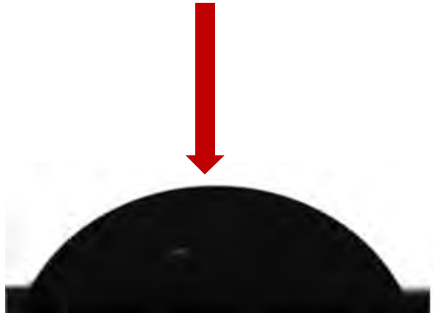



**Surface energy heterogeneity using Finite Dilution IGC (FD-IGC)**




Surface energy heterogeneity profile



**Facet specific surface energy using Contact angle**

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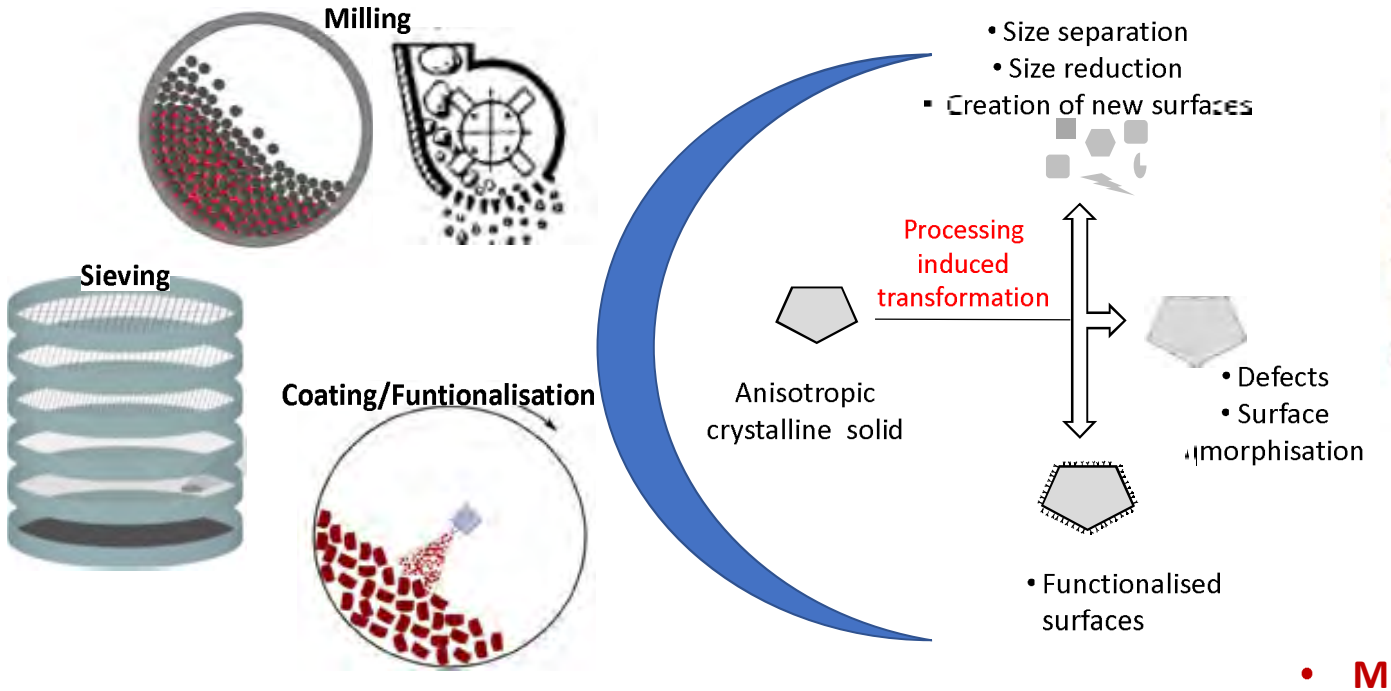
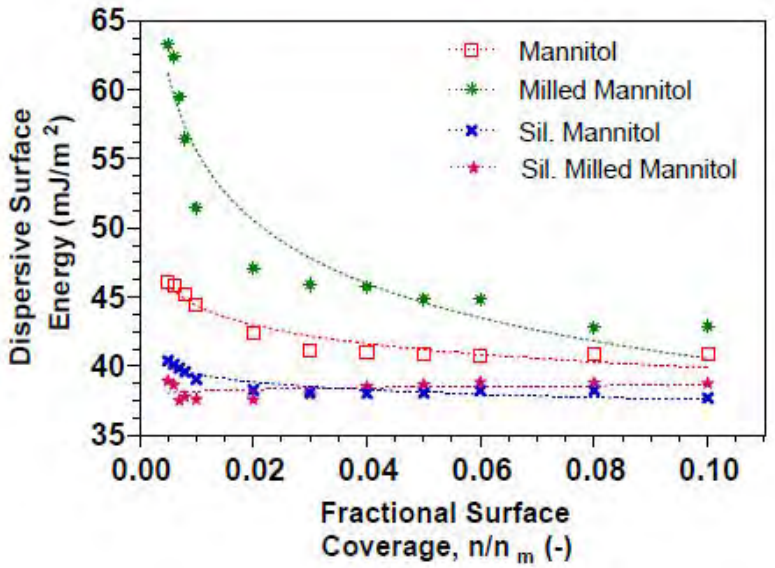
# Processing and Surface Energy




- **Milling induced surface damage led to high heterogeneity surface**
- **Functionalisation creates energetically homogeneous surfaces**

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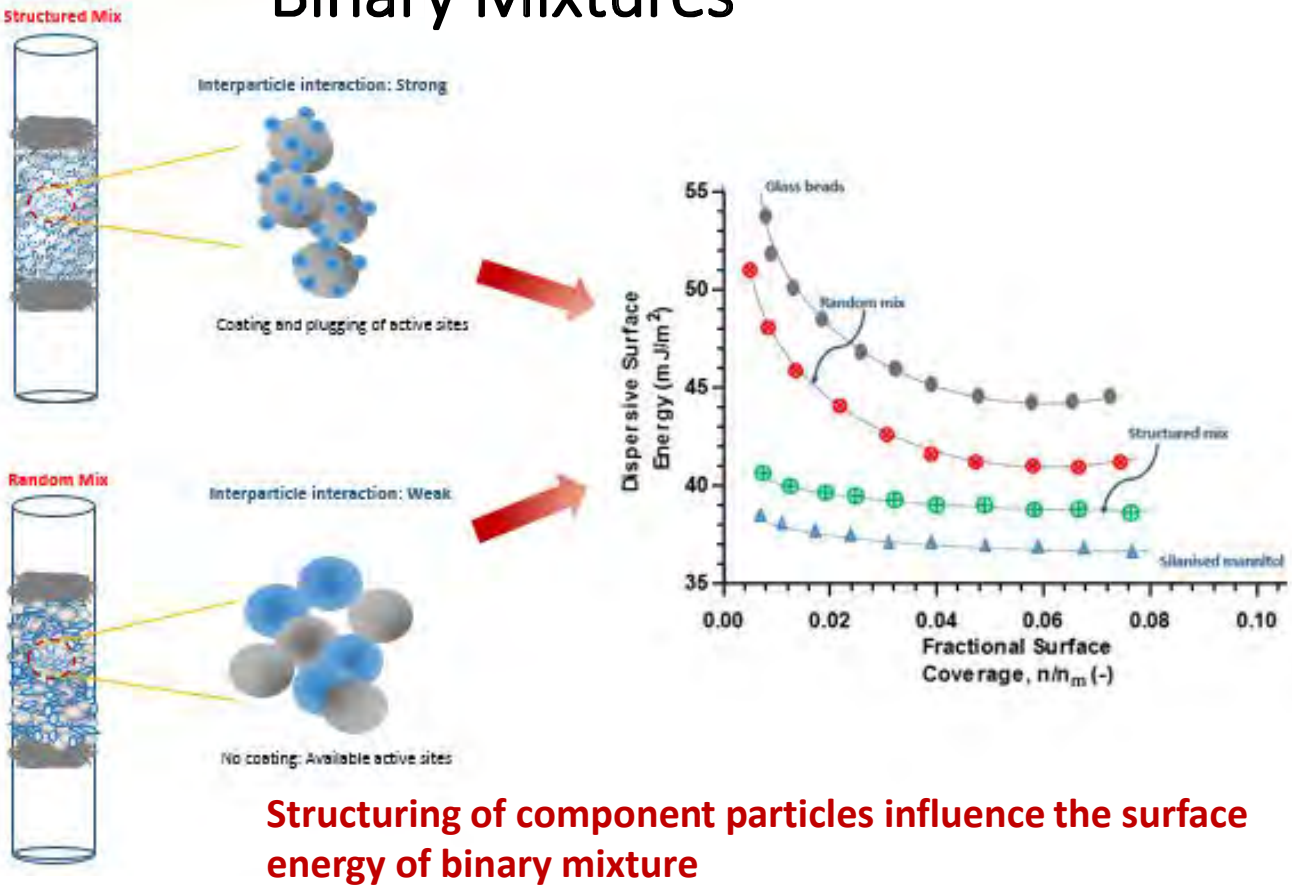
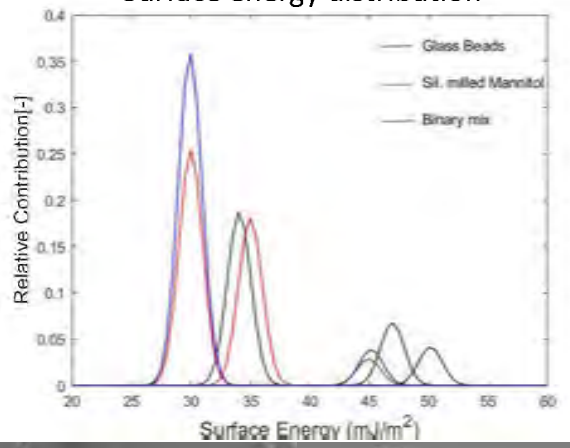
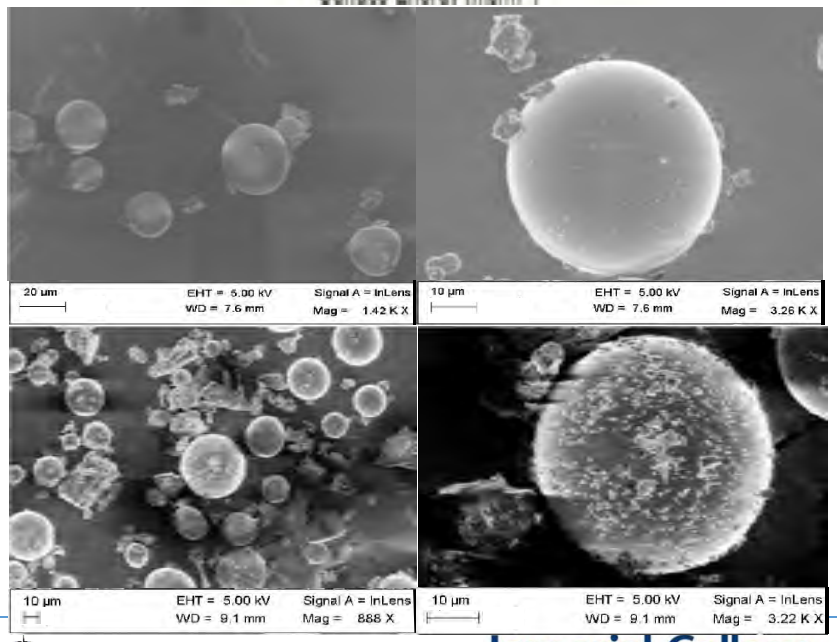
# Interparticle Structuring and Surface Energetics of Binary Mixtures




Surface energy distribution




**Structuring of component particles influence the surface energy of binary mixture**

Karde et al.,(2020) Influence of interparticle structuring on the surface energetics of a binary powder system. *Int. J. Pharm.* **581**, 119295

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# VFL approach to surface energy (II)

Nicodemo Di Pasquale and Ruslan Davidchack

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## Shuttleworth Equation (1950)

Surface Stress tensor $f_{ij}^{SS}$, Surface Free Energy $\gamma$, strain tensor $u_{ij}$

$$f_{ij}^{SE} \equiv \gamma\delta_{ij} + \frac{\partial\gamma}{\partial u_{ij}} = f_{ij}^{SS}, \quad i,j = x,y$$

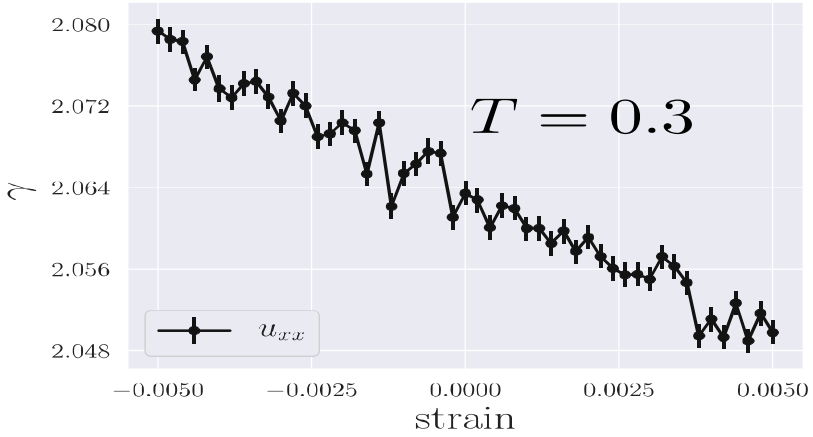
- $\frac{\partial\gamma}{\partial u_{ij}}$ can be positive or negative
- $\gamma$ always positive
- $f_{ij}$ can be positive or negative

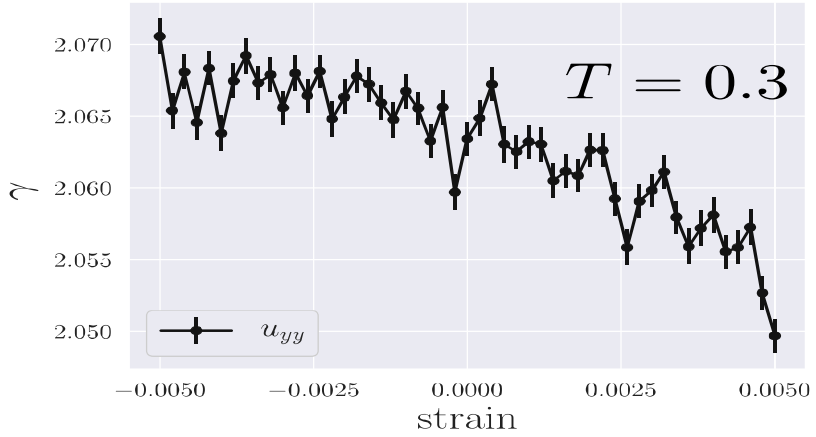
## Verification for LJ crystal at finite temperature with cleaving

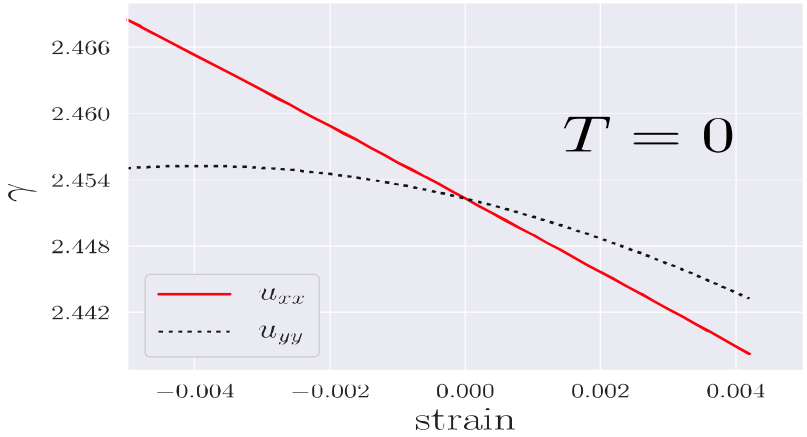
| $T = 0.3$ | $\gamma$ | $\frac{\partial\gamma}{\partial u_{ii}}$ | $f_{ii}^{SS}$ | $f_{ii}^{SE}$ |
|---|---|---|---|---|
| $u_{xx}$ | $2.063(2)$ | $-2.87(6)$ | $-0.783(8)$ | $-0.81(6)$ |
| $u_{yy}$ | $2.063(2)$ | $-1.38(6)$ | $0.69(2)$ | $0.68(6)$ |

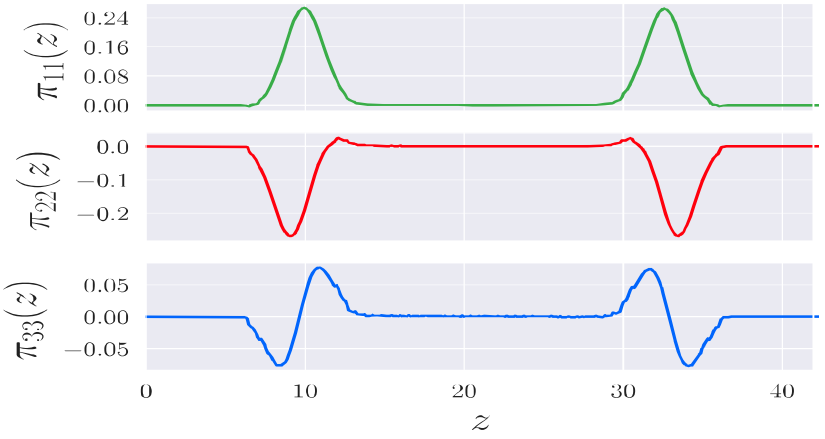
(Reduced LJ units, fcc(110))

# LJ system: fcc(110)



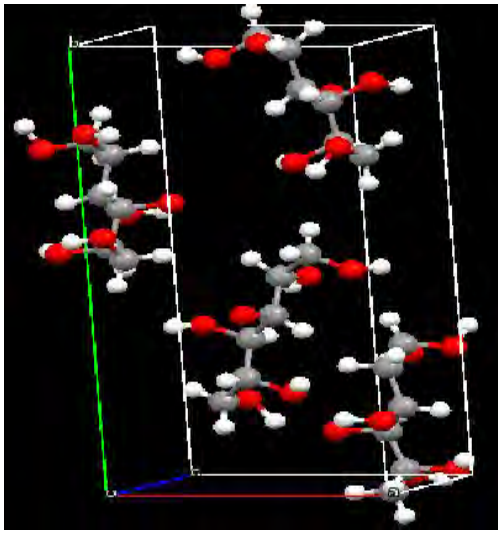




Results in reduced LJ units

# Surface Free Energy organic crystals: Mannitol

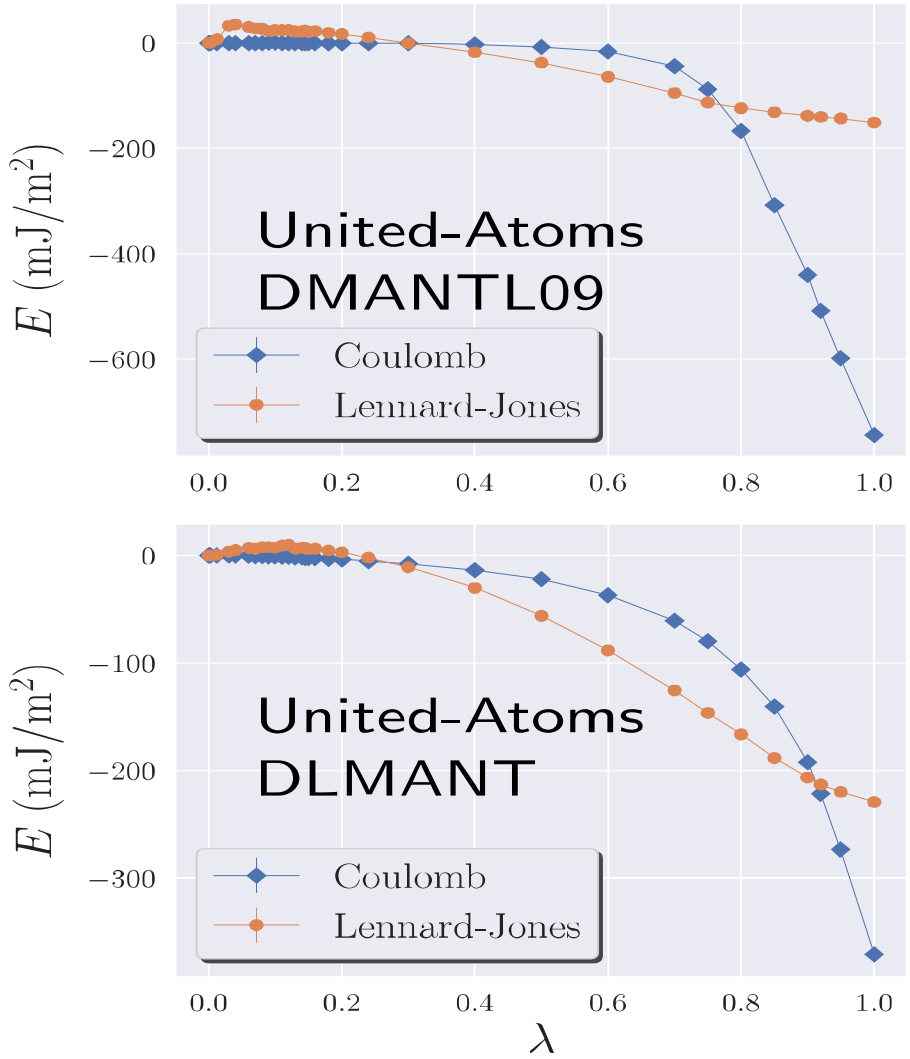
The cleaving methodology is applied to molecular crystals

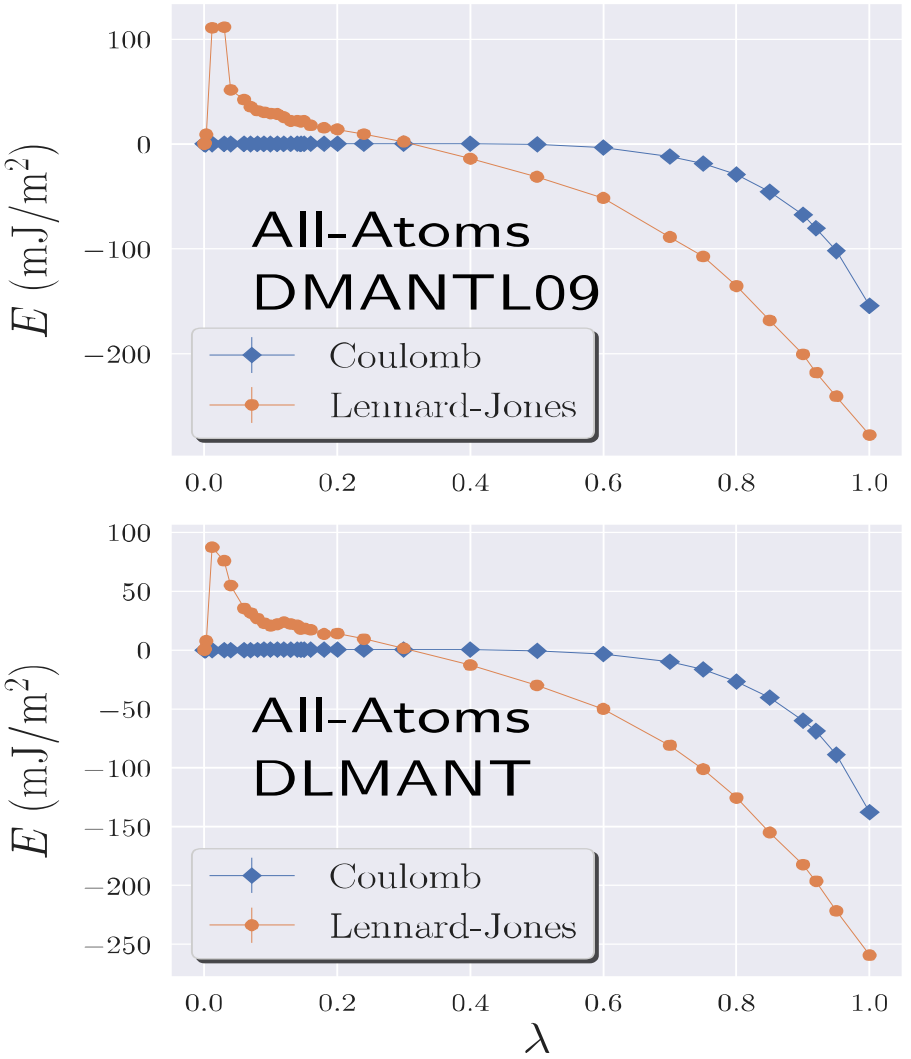


- Different orientations considered: (001), (010), (100), (011),(120)
- Different Experimental lattice parameters (**a**, **b**, **c**) considered: DLMANT, DMANTL09
- GROMOS Force-field (FF)
  - United-atoms
  - All-atoms

**Qualitative** agreement with experiments (most stable orientation) but SFE shows **significative differences** for different FFs and crystal structures considered

# Cleaving: Mannitol (surface perpendicular to $b$ axis)



| Model | Structure | orientation | Total | Lennard-Jones Component | Coulomb Component |
|---|---|---|---|---|---|
| ATB | dm | (100) | 178 | 52 | 126 |
| ATB | dm | (010) | 141 | 79 | 62 |
| ATB | dm | (001) | 264 | 2 | 262 |
| GROMOS | dm | (100) | 80 | 60 | 20 |
| GROMOS | dm | (010) | 70 | 54 | 16 |
| GROMOS | dm | (001) | 92 | 69 | 23 |
| ATB | dm09 | (001) | 179 | 41 | 139 |
| ATB | dm09 | (100) | 161 | 35 | 126 |
| ATB | dm09 | (010) | 155 | 50 | 105 |
| ATB | dm09 | (120) | 139 | 36 | 104 |
| ATB | dm09 | (011) | 139 | 36 | 104 |
| GROMOS | dm09 | (001) | 92 | 70 | 22 |
| GROMOS | dm09 | (100) | 92 | 70 | 21 |
| GROMOS | dm09 | (010) | 75 | 57 | 18 |
| GROMOS | dm09 | (120) | 69 | 52 | 17 |
| GROMOS | dm09 | (011) | 70 | 53 | 17 |

Results in $mJ/m^2$, dm=DLMANT, dm09=DMANTL09, error $\approx 1$ $mJ/m^2$ in all cases

# VFL approach to compaction

Ben Edmans and Csaba Sinka

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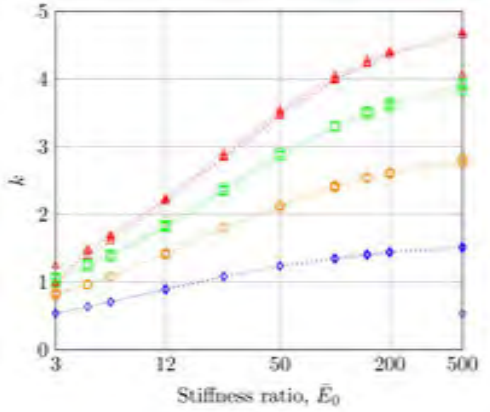
# Contact laws for compressible particles

- Contact laws can link particle to bulk behaviour but remain under-developed for compressible particles
- Generic compressible plasticity model proposed
- FE simulations used to investigate influence (right) of material parameters on linear-exponential contact law
- Particle internal zone development mapped (below)

$$\bar{F}_{model}(\bar{\delta}) = \begin{cases} k\bar{\delta}, & \bar{\delta} \leq \bar{\delta}_t \\ k\bar{\delta}_t \exp(a(\bar{\delta} - \bar{\delta}_t)), & \bar{\delta}_t < \bar{\delta} \leq \bar{\delta}_{max} \end{cases}$$




Edmans B.D. and Sinka I.C. 2019. Numerical derivation of a normal contact law for compressible plastic particles. *Mechanics of Materials*. https://doi.org/10.1016/j.mechmat.2019.103297

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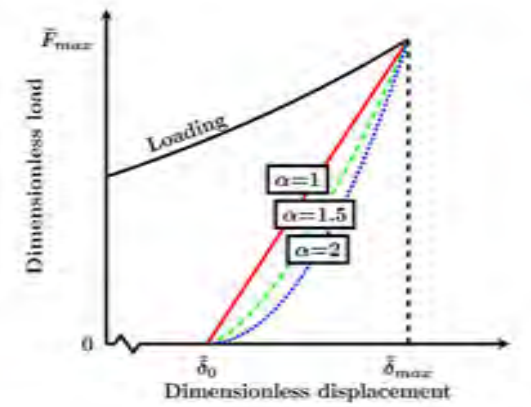
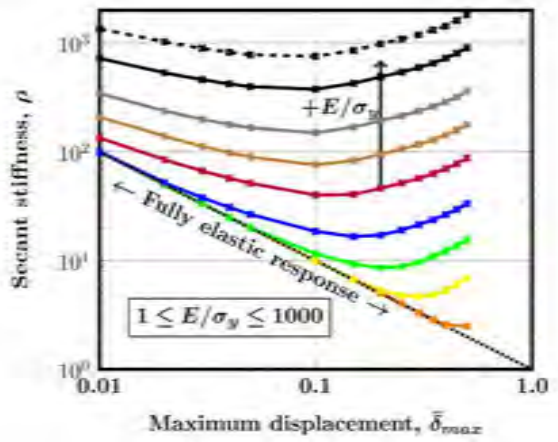
# Particle unloading response

- Accurately representing unloading response is important for DEM at high deformations.
- Stiffness (ρ) and nonlinearity (α) of unloading load-displacement curves at large displacements investigated
- 560 FE simulations (binary contacts, elastic perfectly-plastic material model) established dependence of α and ρ on displacement and material parameters

$$\rho(\bar{E},\ \nu,\ \bar{\delta}_{max}) \approx \frac{1}{\bar{\delta}_{max}} + \phi\bar{E}\left(\gamma_1\bar{\delta}_{max} + \gamma_2\bar{\delta}_{max}^{-\gamma_3} + \gamma_4\nu\right)$$




Edmans B.D. and Sinka I.C. Unloading of elastoplastic spheres from large deformations. *Powder Technology*. Accepted for publication

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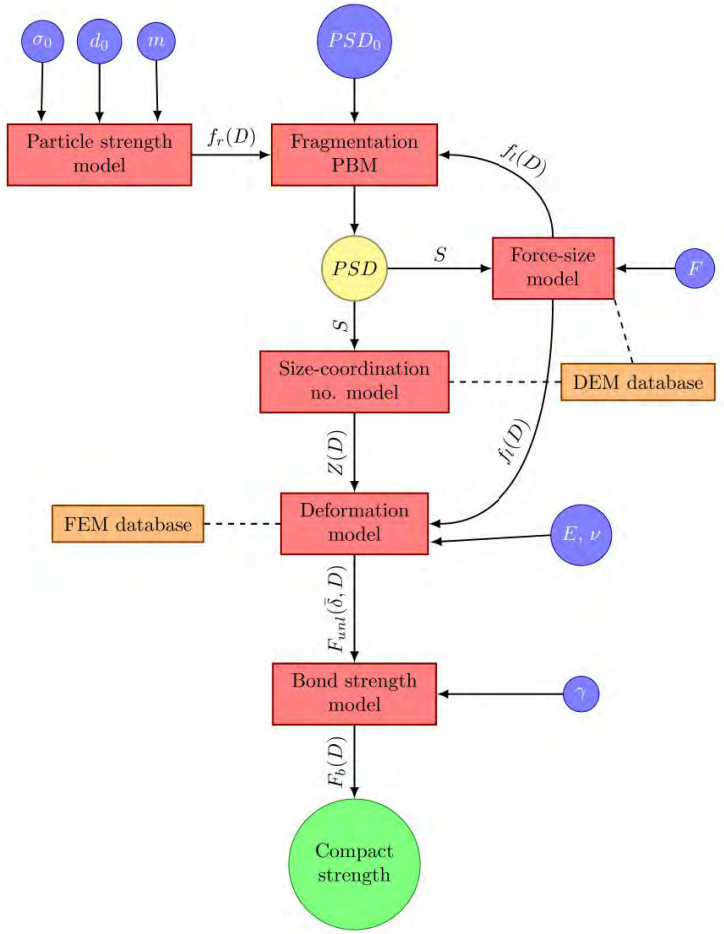
# Compact strength prediction

- Goal: predicting strength of compacts from particle/surface properties
- Three main components
  - Fragmentation Population Balance Model
  - FE deformation database for interpolation
  - Adhesion model
- Effective adhesion force function found by calibration
- Key features
  - Modular
  - Represents key compaction mechanisms
  - Component models well supported



# VFL approach to powder flow

Hamid Salehi, Mike Bradley and Vivek Garg

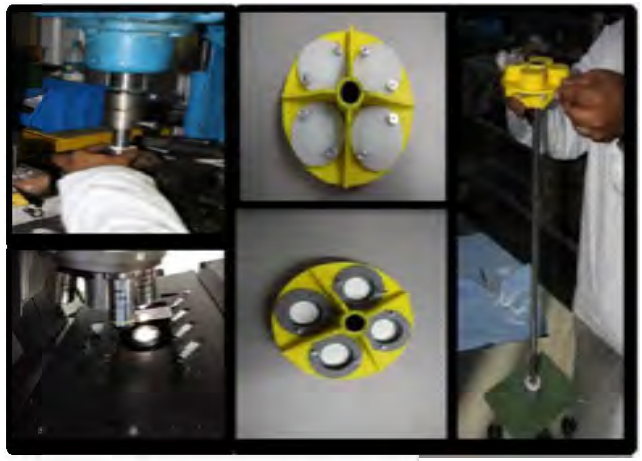


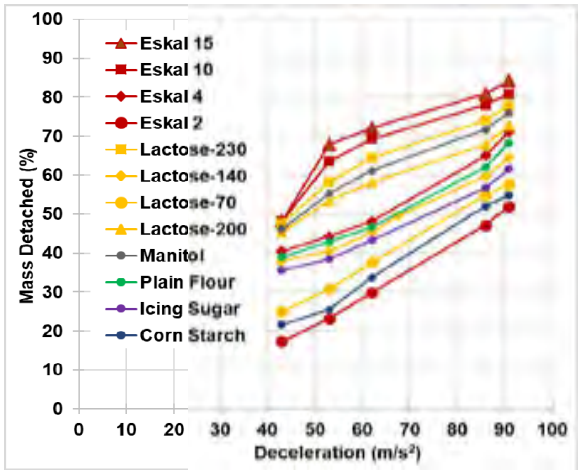


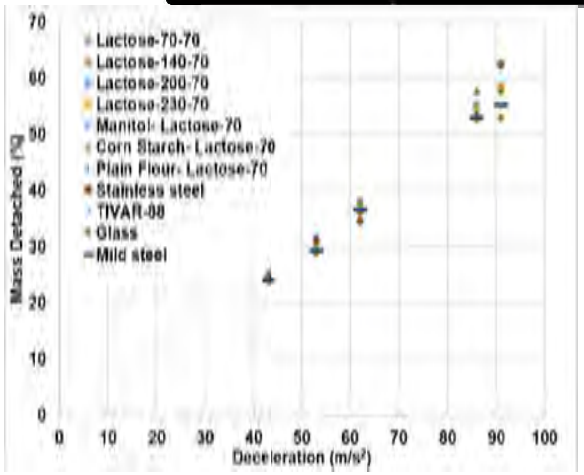

UNIVERSITY of GREENWICH
The Wolfson Centre for Bulk Solids Handling Technology

# 1. Flow in Quasi-static Conditions

- A new technique developed/modified to determine the **inter-particle forces** of the cohesive powders using a few particles.
- From a few grams at an early stage of formulation, a user can predict whether a bulk of this material will be easy or hard to process.
- An empirical model developed for predicting the flow function from Bond Number/ Adhesion forces.

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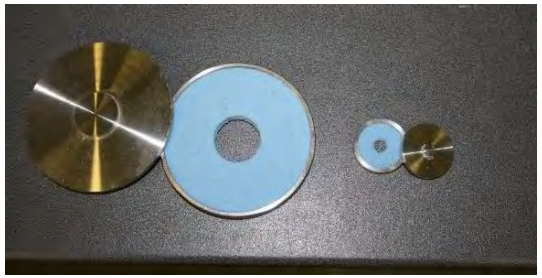
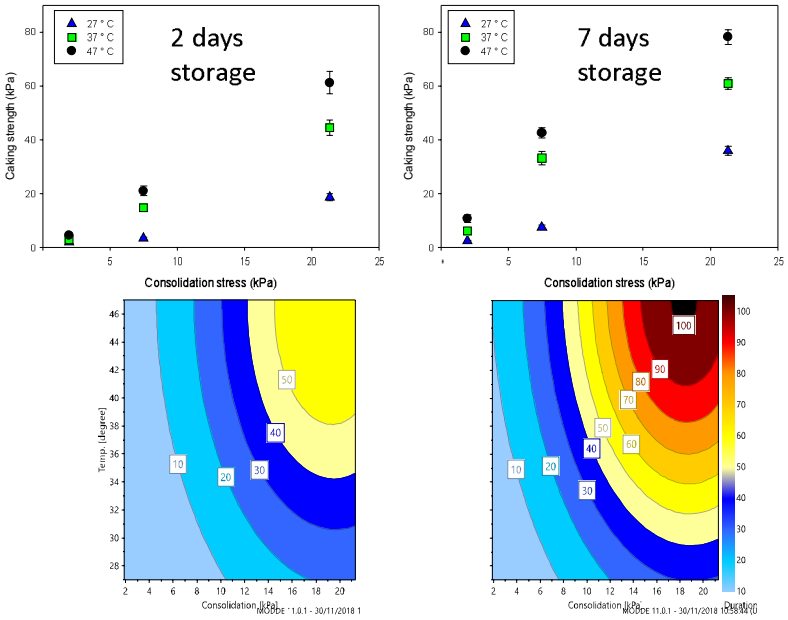
# 2. Plastic Flow Caking



Aim: measuring cake strengths driven by plastic flow mechanisms in storage.

This outperformed the conventional uniaxial unconfined failure caking tester due to the defined location of the failure plane to maximise repeatability, the necessity for a lower quantity of powder, maximised exposed surface and lower wall friction as well as production costs.




A statistical model has been successfully developed to study the effect of each variable on the cake strength.

*Salehi et al. Development and application of a novel cake strength tester, Doi: 10.1016/j.powtec.2019.03.024*

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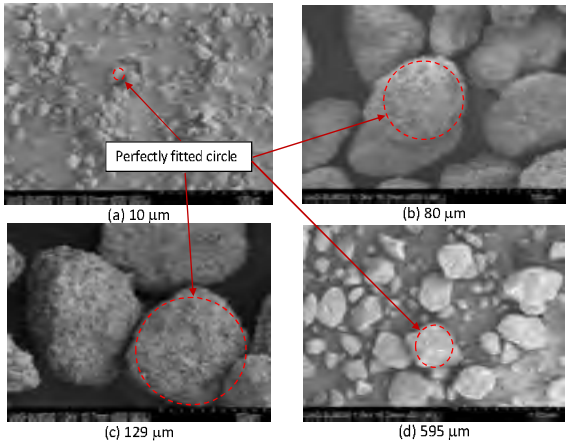
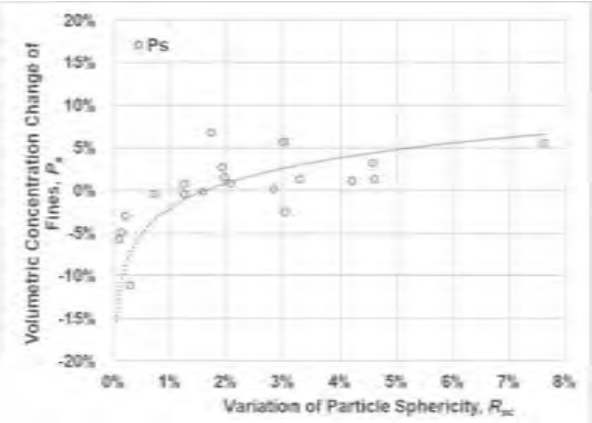
# 3. Segregation

Predicting materials propensity to free surface segregation when discharged to form a heap.

- Measure degree of segregation (from top to bottom of slope) by using a scale from perfectly blended (20) to segregated sample (100) based bulk cohesion and particle sphericity.

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# VFL approach to powder flow

Mehrdad Pasha, Xiaodong Jia and Mojtaba Ghadiri






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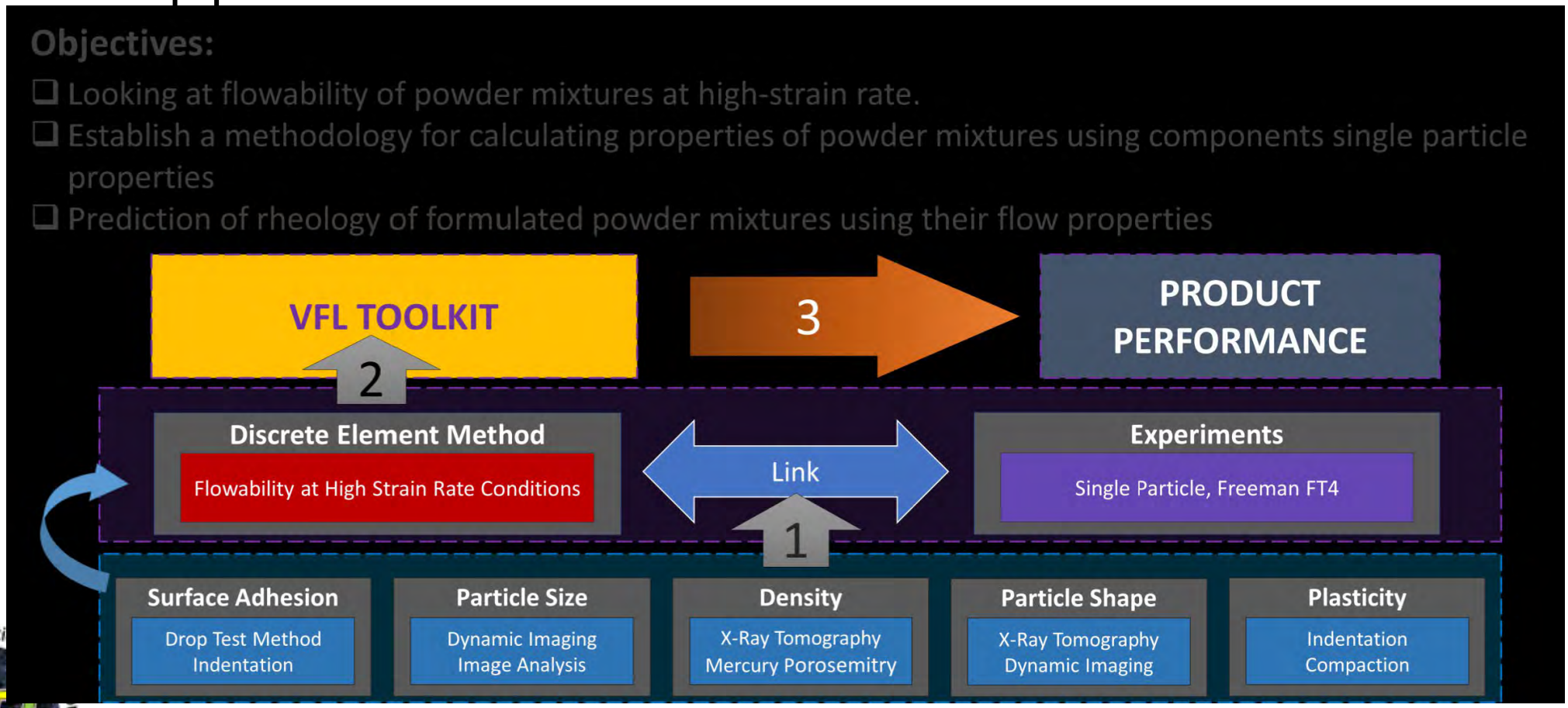
# Our Approach

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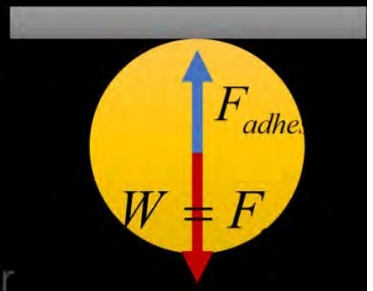
# Powder Mixture Bond Number

**Bond Number** is the ratio between the force of adhesion and gravitation force:

*'The larger the value of Bond Number, the more cohesive the powder is.'*




Since powder mixtures consist of several components having different values of granular Bond Number, an averaged value must be calculated.

**Mixture Bond Number** can be calculated by averaging the bond number of individual components and introducing a weighting factor (calculated based of fractional surface area of individual components

| Arithmetic Weighted Mean | Harmonic Weighted Mean | Geometric Weighted Mean | General Equations |
|---|---|---|---|
| $Bo_{mix} = \sum_{i=1}^{n}\sum_{j=1}^{n} Bo_{ij} \times w_{ij}$ | $Bo_{mix,har} = \left(\sum_{i=1}^{n}\sum_{j=1}^{n} \frac{w_{ij}}{Bo_{ij}}\right)^{-1}$ | $Bo_{mix,geo} = \prod_{i=1}^{n}\prod_{j=1}^{n} Bo_{ij}^{\,w_{ij}}$ | Bond Number: $Bo_{g,ij} = \frac{F_{ad,ij}}{W_{ij}}$ <br> Weighting Factor: $w_{ij} = f_{SA,i} f_{SA,j}$ <br> Average Weight: $W_{ij} = \frac{2W_i W_j}{W_i + W_j}$ |

**Note:** in our study, we are considering individual interactions in the mixture. For example, a binary system has four interactions (AA,AB,BA,BB)

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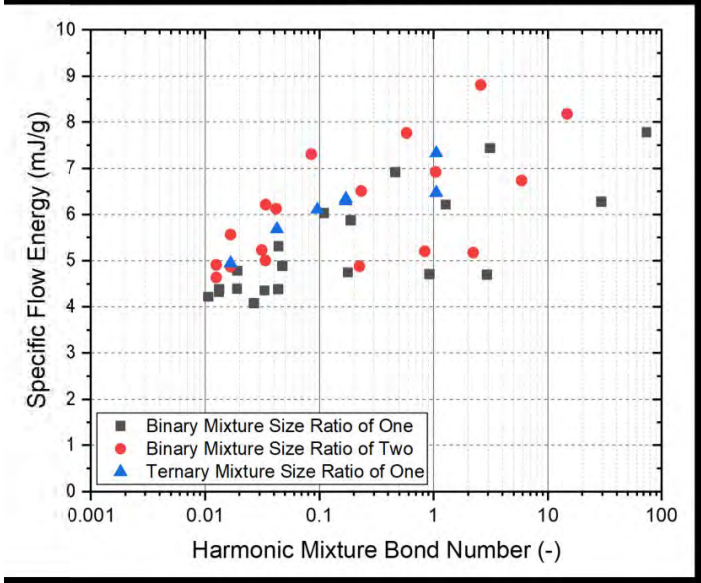
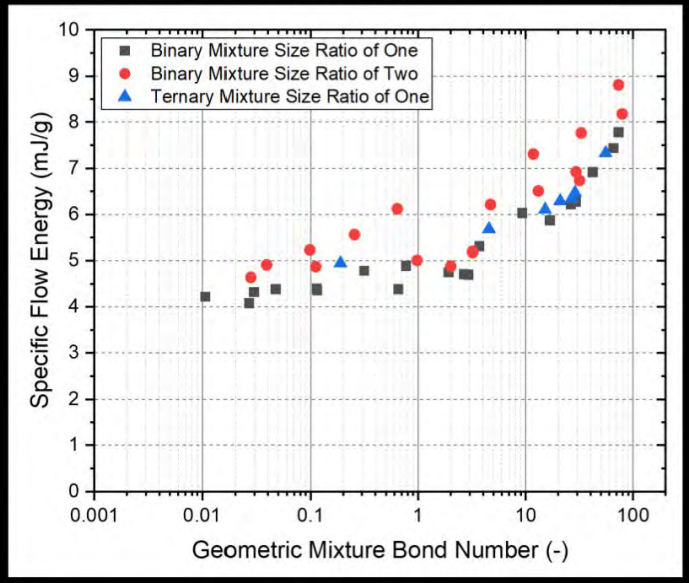
# Powder Mixture Bond Number

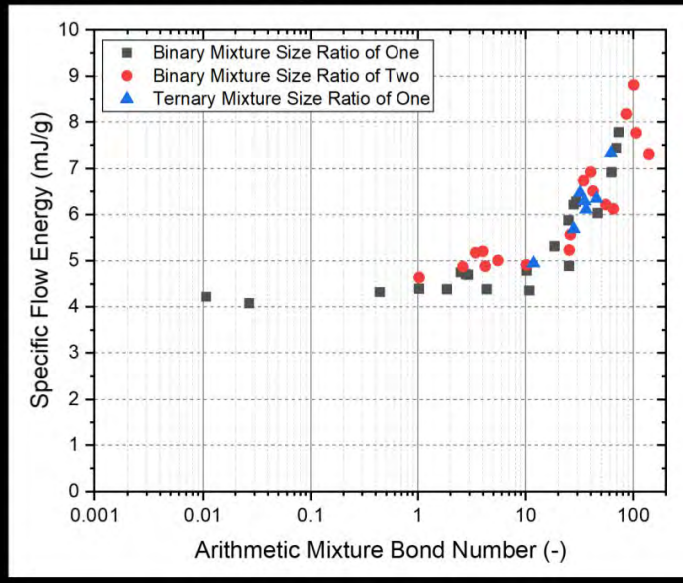
## Harmonic Mixture Bond Number




## Geometric Mixture Bond Number




## Arithmetic Mixture Bond Number




- A clear trend is observed when using geometric and arithmetic bond numbers.
- A good unification of the data can only be achieved with arithmetic mixture bond number
- Specific flow energy only starts rising when $Bo_{mix,arth} > 10$

Pasha, M., Hekiem, N.L., Jia, X. and Ghadiri, M., 2020. Prediction of flowability of cohesive powder mixtures at high strain rate conditions by discrete element method. *Powder Technology*.

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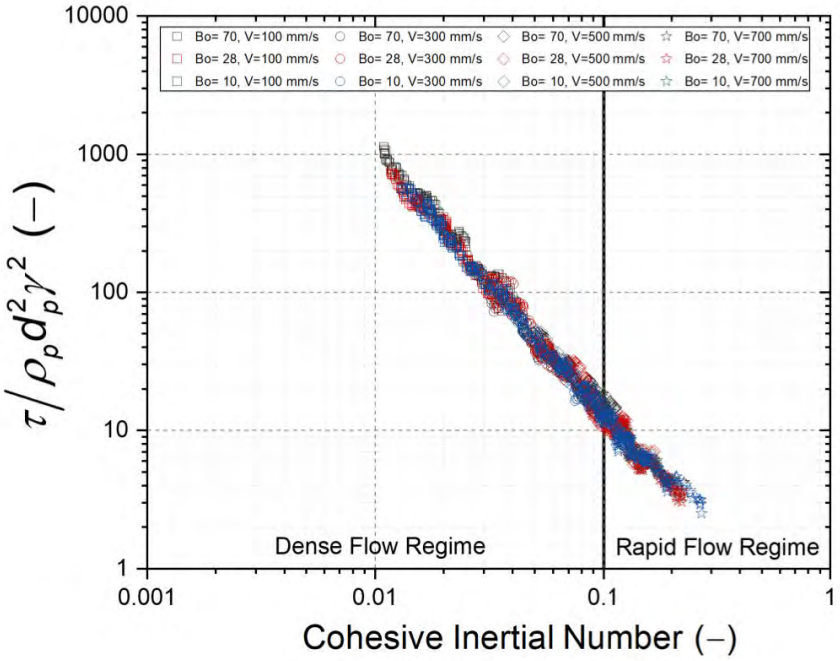
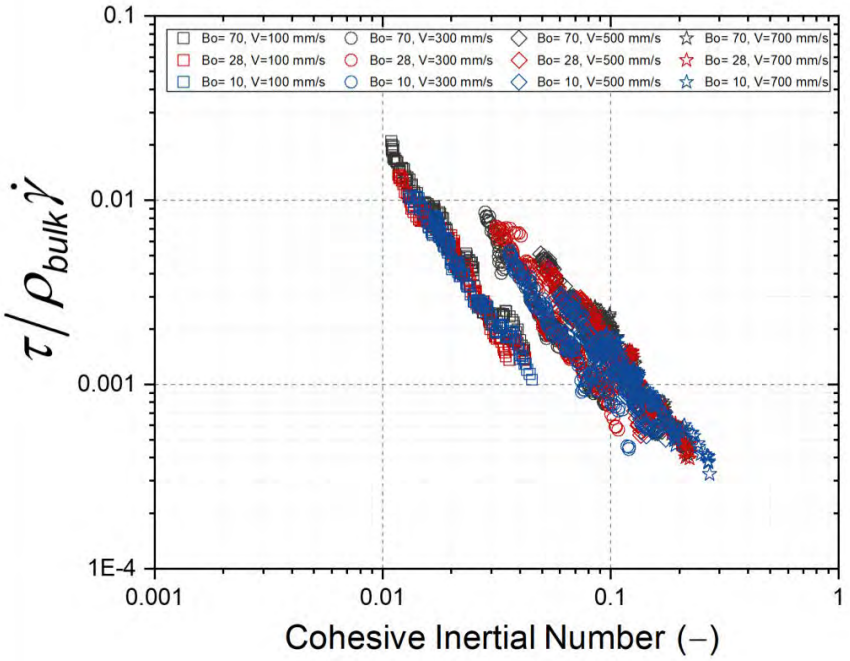
# Rheology of Powder Mixtures

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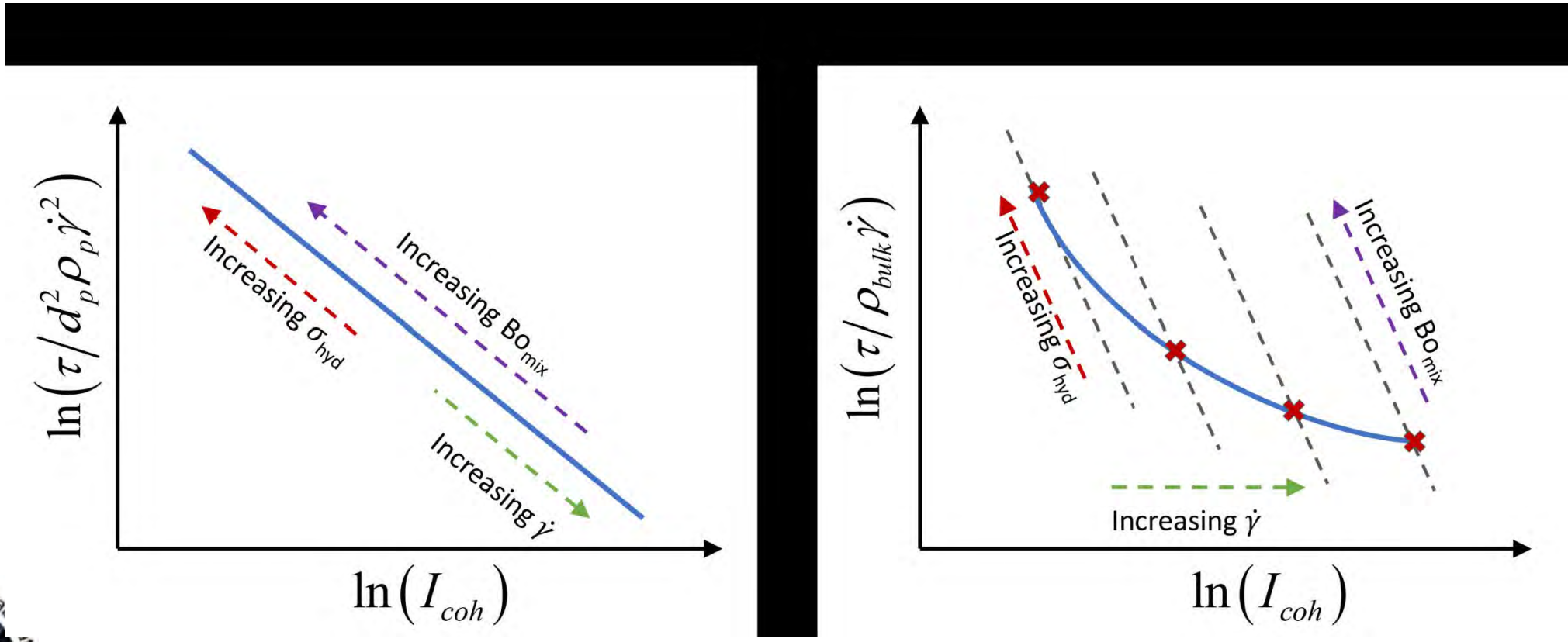
# Rheology of Powder Mixtures

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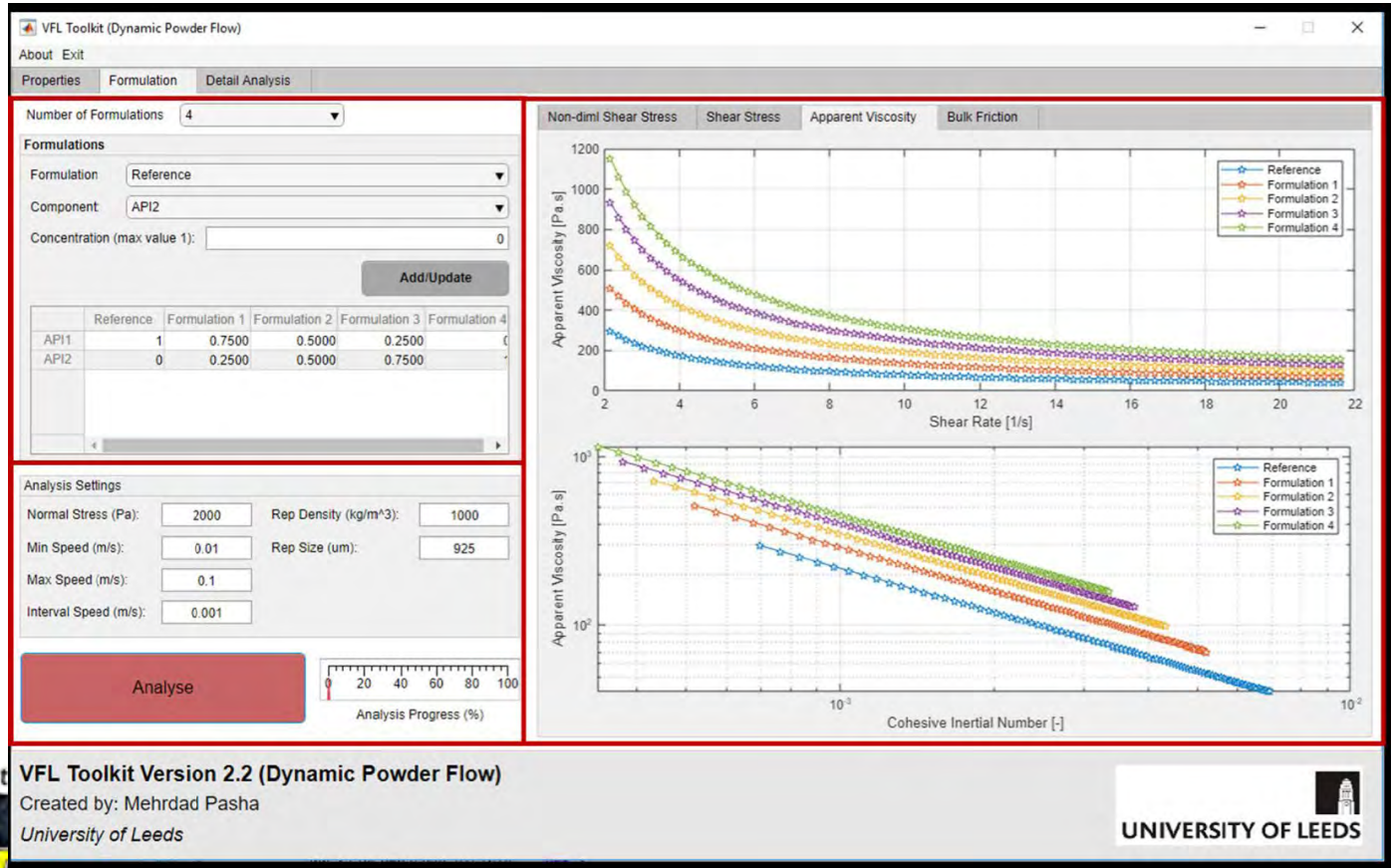
# Rheology of Powder Mixtures

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# Concluding remarks


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


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"Virtual Formulation Laboratory
for prediction and optimisation of
manufacturability
of advanced solids based formulations"