ADVANCED DIGITAL DESIGN OF PHARMACEUTICAL THERAPEUTICS

UNIVERSITY OF LEEDS

UNIVERSITY OF CAMBRIDGE

Powder Flow Issues in ADDoPT

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[1]University of Leeds and [2]University of Cambridge

ADDoPT: A UK Government-Industry-Academia collaboration

Part-funded under the Advanced

Manufacturing Supply Chain Initiative (AMSCI*)

Department for Business Innovation & Skills

*A BIS initiative delivered by Finance Birmingham and Birmingham City Council

Instigated by the Medicines Manufacturing Industry Partnership (MMIP)

Digital Design – An Integrated Pathway from Molecules to Crystals to Medicines

Define a system for top-down, knowledge-driven Digital Design and Control for drug products and their manufacturing processes

Bring together the range of ***predictive models***

Product and Process Design

Upstream

Materials properties

Surface chemistry

Release profiles

Manufacturing classification

Particle attributes

Processing rules

Quality systems

Formulation

Product Performance

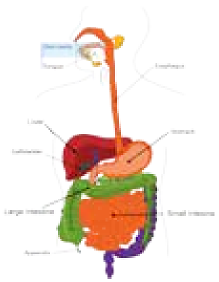
Downstream

Primary Manufacturing - Secondary Manufacturing

Active Ingredient (API)

Crystallisation
Filtration
Washing
Drying

Milling
Blending
Compaction
Coating



Processes

Products

Performance

Design and control of optimised development & manufacturing processes through data analysis and first principle models

Two-Pronged Approach in Cohesive Powder Flow Analysis

- **Cambridge:** Quasi-static characterisation and role of material properties by DEM Modelling of Ring Shear Test for powder flowability (Chunlei Pei and James Elliott)
- **Leeds:** Powder characterisation under dynamic conditions

Schulze Ring Shear Test

RST-XS (standard)

Volume: ~ 30 ml

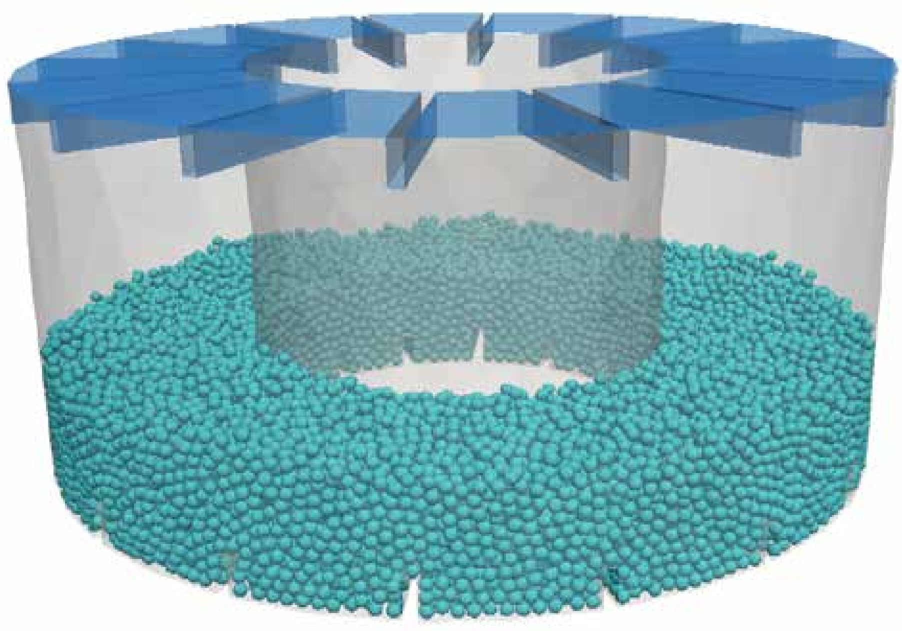
Cross-sectional (annular) area: 24.23 cm^2

Outer radius: 32 mm; inner radius: 16 mm

16 bars (3 mm in height) at top and bottom*

Rotational speed

- 7.5 mm/min; 0.05 rpm (half of the max.)
- 0.5 rpm (modelling)

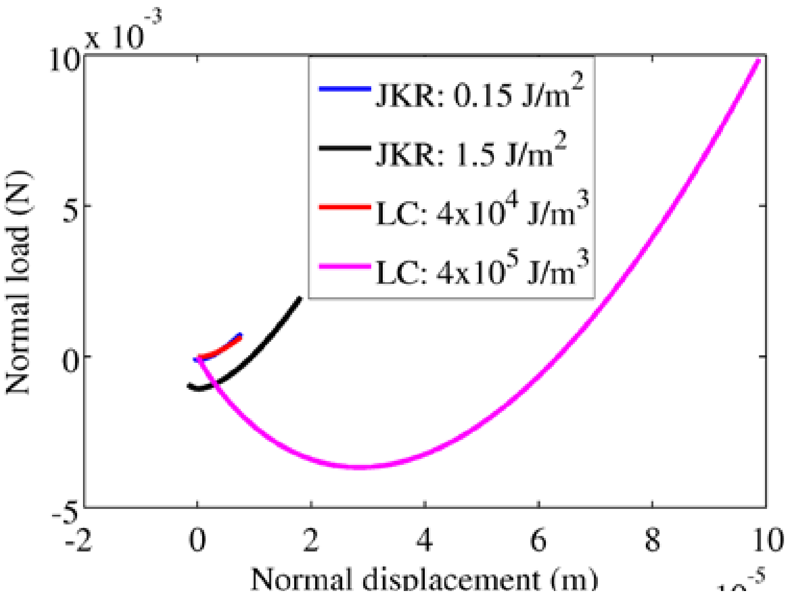


DEM model for ring shear test

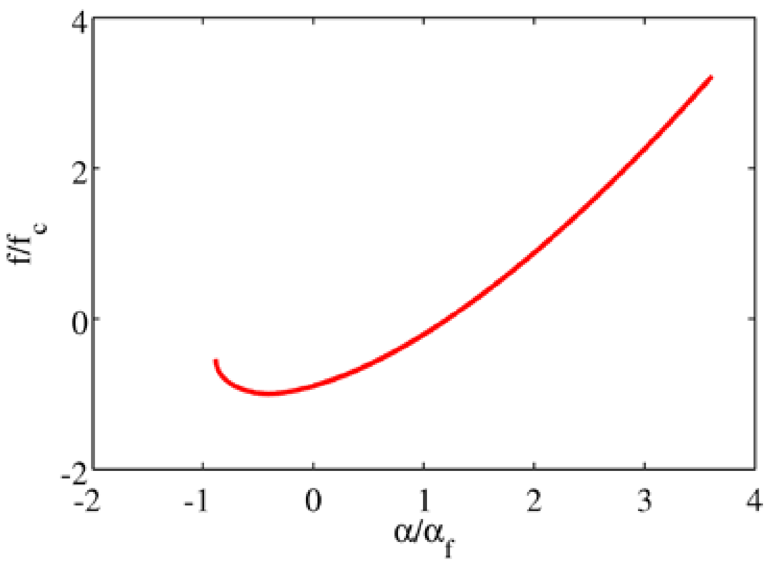
- Linear cohesion vs JKR
- Flow function (ff_c)
- Particle shape
- Rescaling

Cohesion Model in DEM

- Linear cohesion (LC) model
  - Cohesive energy density (J/m^3)
  - Proportional to the contact area
  - Without the work of adhesion

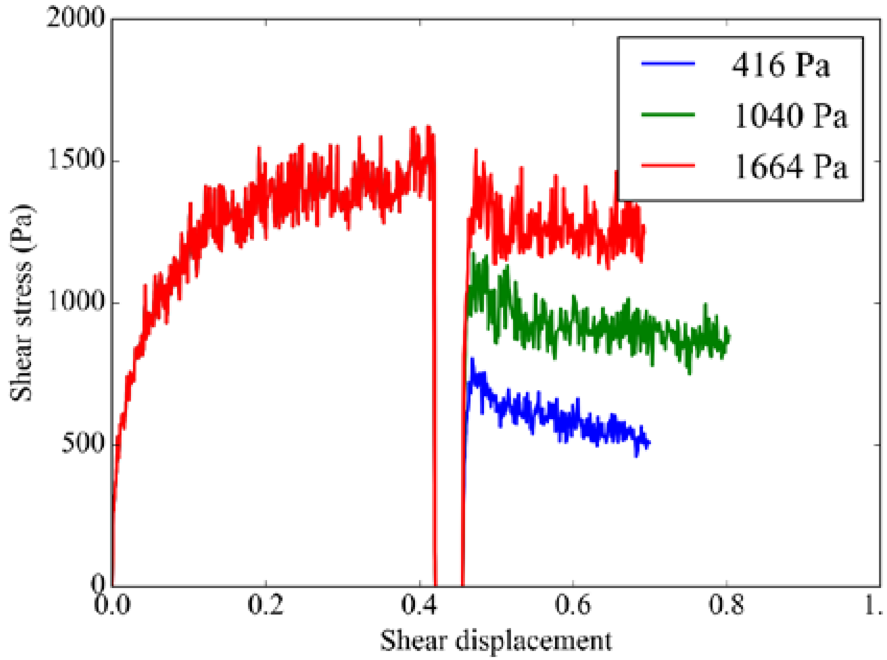


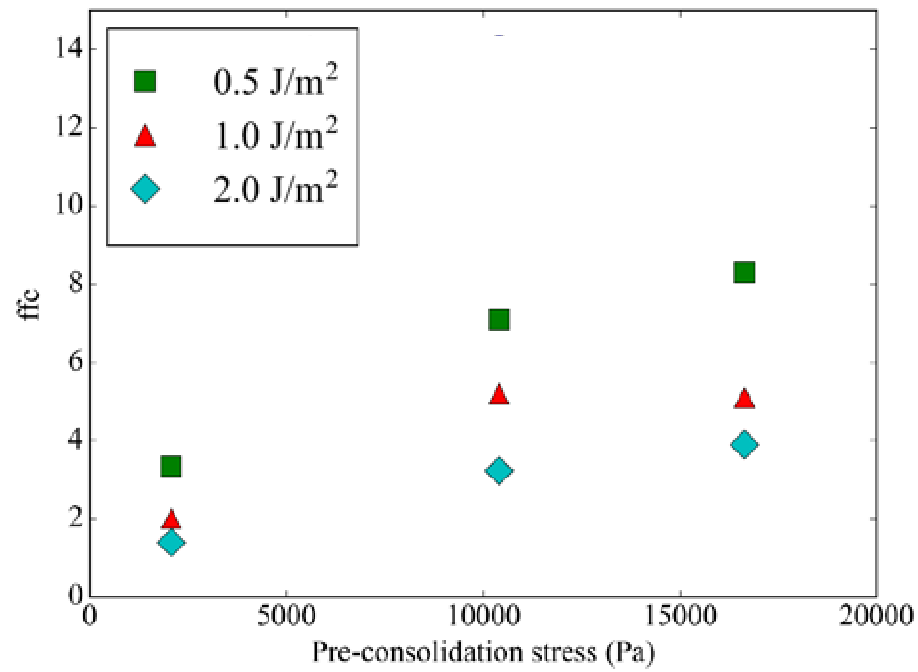
- JKR model
  - Surface energy (J/m^2)
  - Work of adhesion



Flow Function from DEM

Normal stress at pre-shear: 2081 Pa

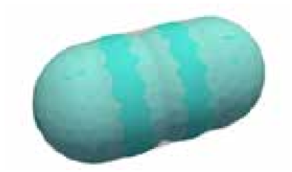




Particle Shape

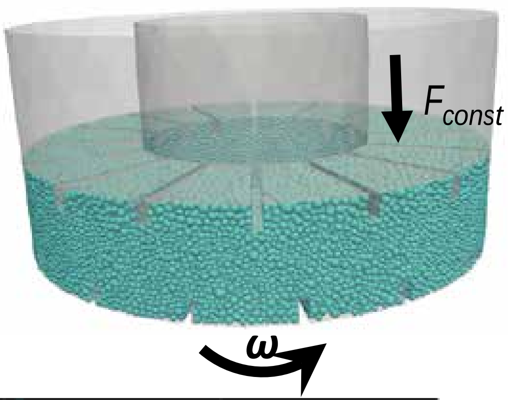
- Spherical vs Elongated
  - Equivalent volume diameter
  - JKR cohesion ongoing

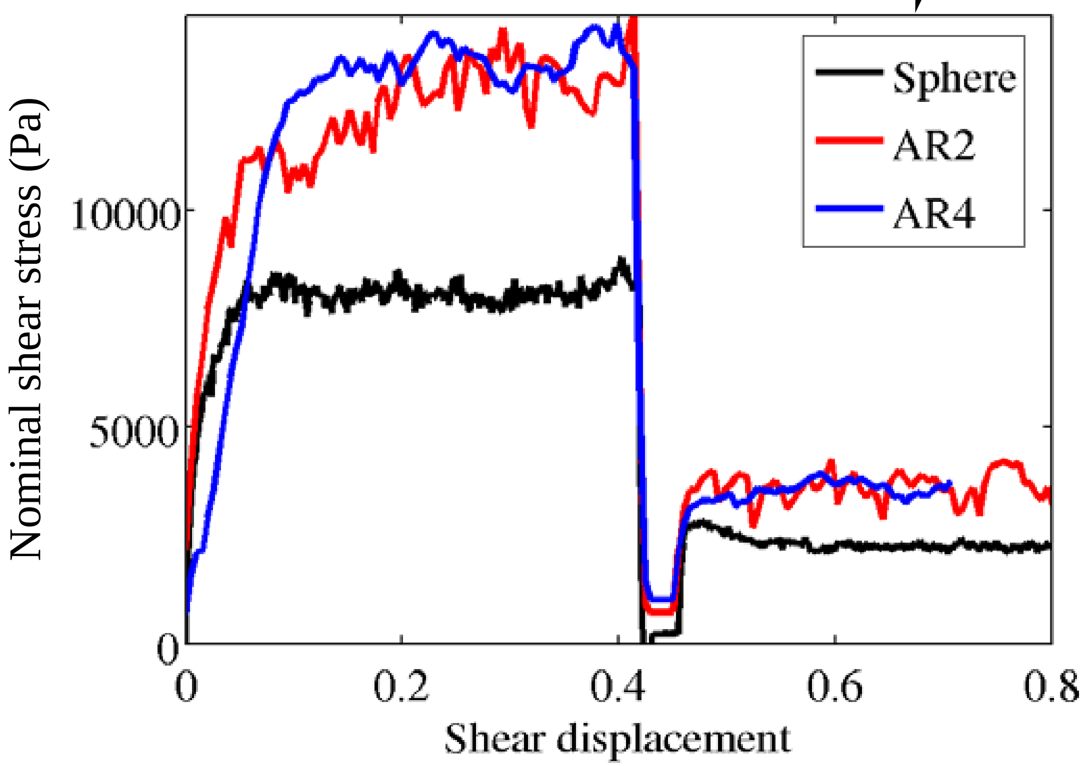
Sphere



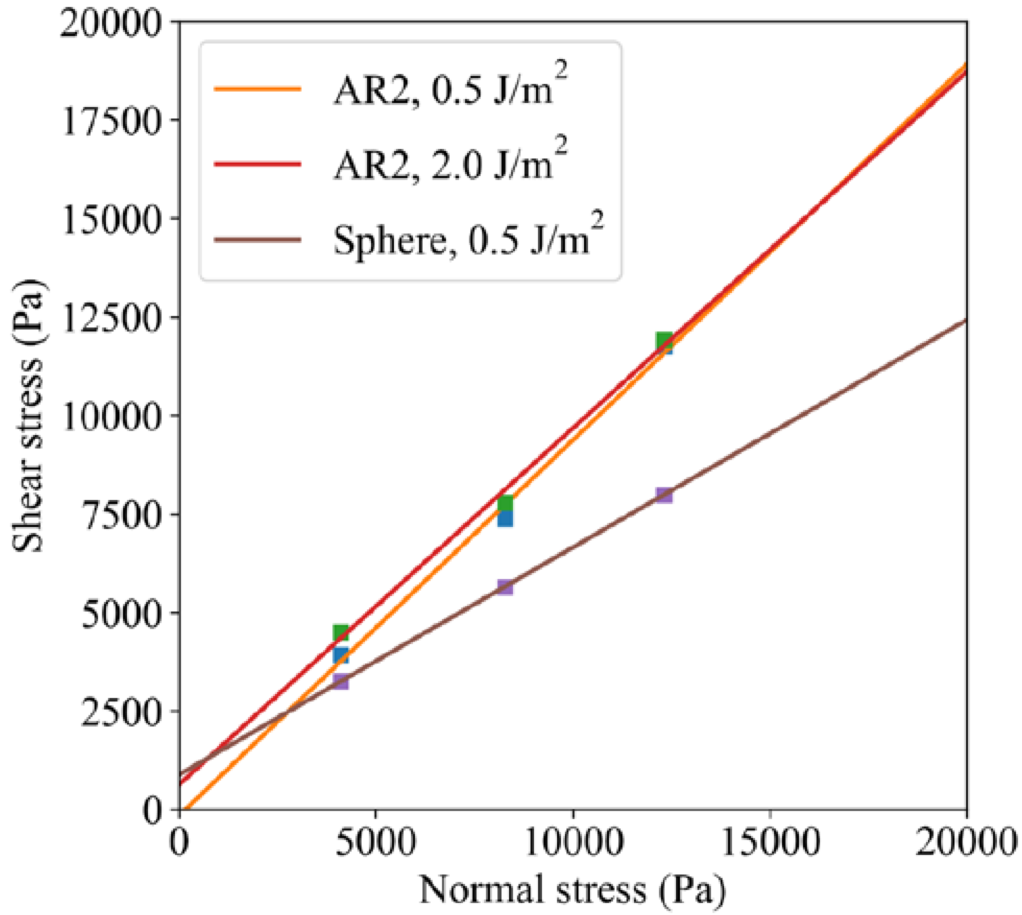
Aspect ratio = 2

Aspect ratio = 4



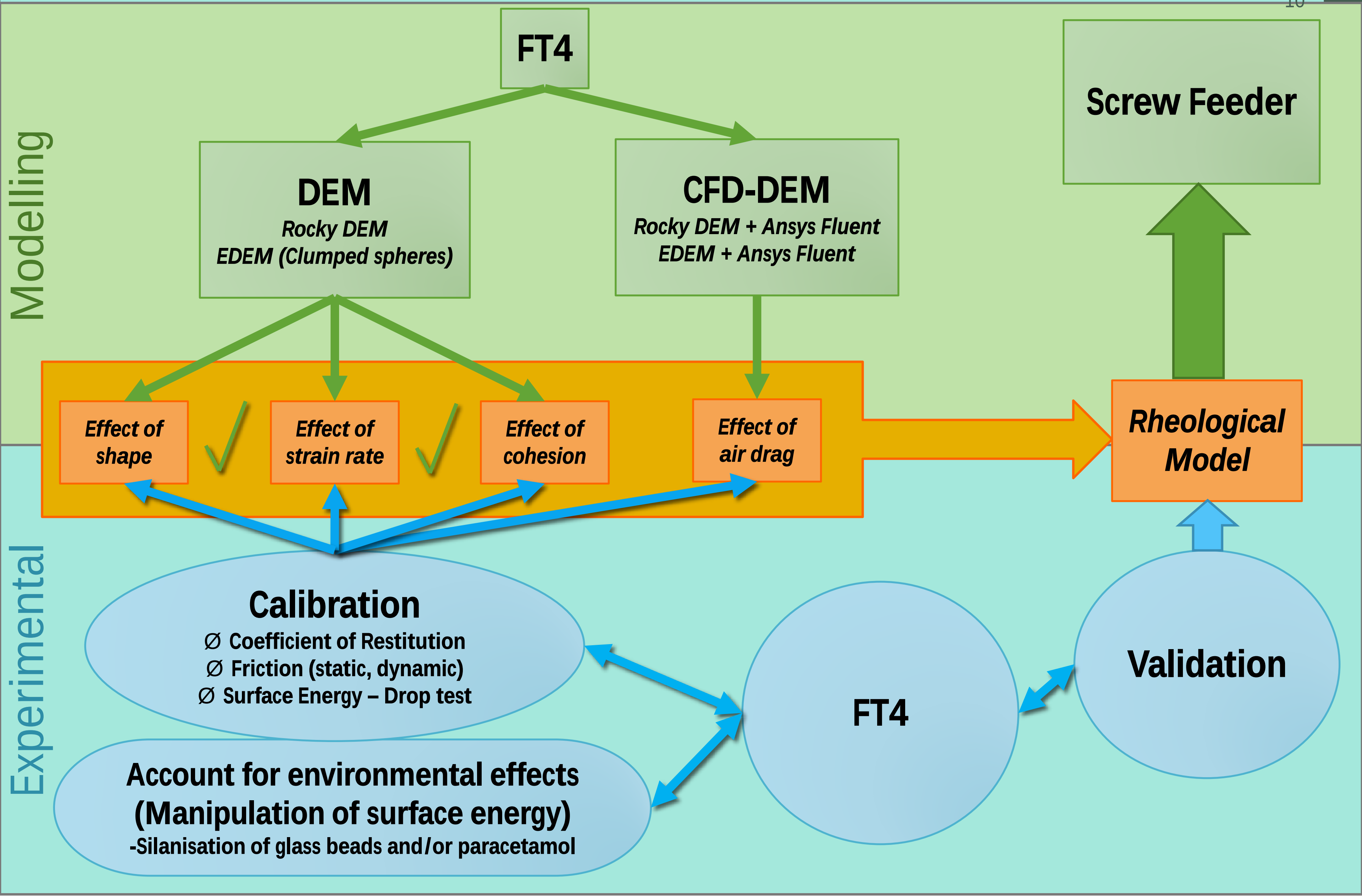


The Influence of Particle Shape and Adhesion



The particle shape plays a role in the angle of friction of failure which also varies the intercept on the axis of shear stress.

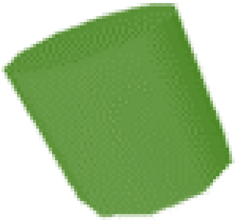
Work Outline: Dynamic Regime



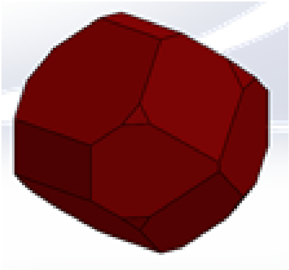
Rocky DEM (ESSS)

- Deltahedron (faces=16, corners=10):

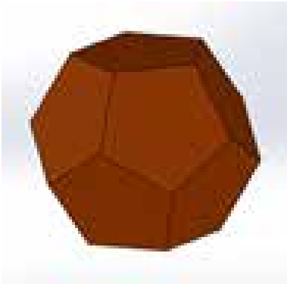
- Faceted cylinder (faces=12, corners=20):



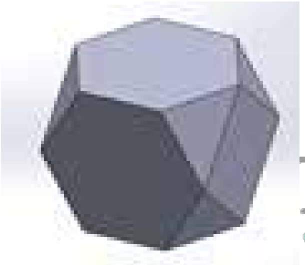
- Actual paracetamol shape (faces=25, corners=44):



- Dodecahedron (faces=12, corners=20):

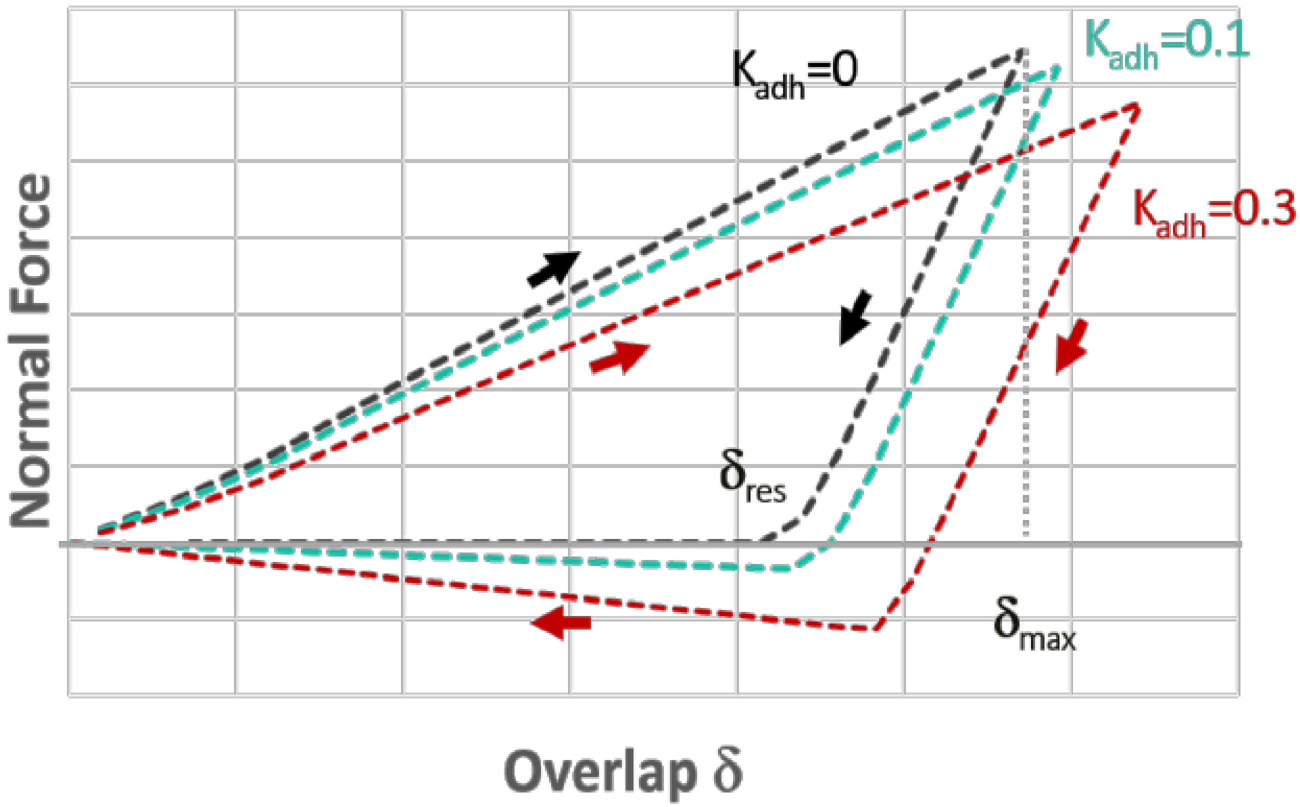


- Truncated polyhedron (faces=14, corners=16):



Rocky DEM (ESSS) Contact model

- Contact deformation: Linear spring hysteresis model
  - k_{nl}
  - k_{nu}
  - μ

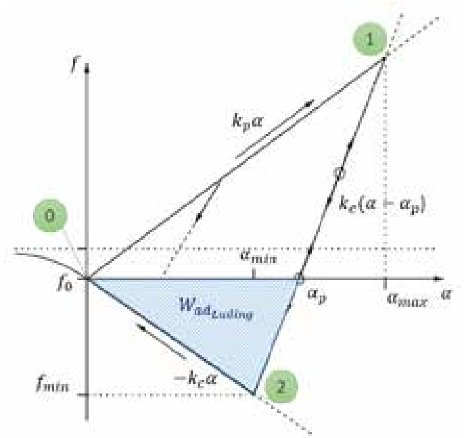


- Adhesion model
  - Luding's model[1]
  - k_{adh}

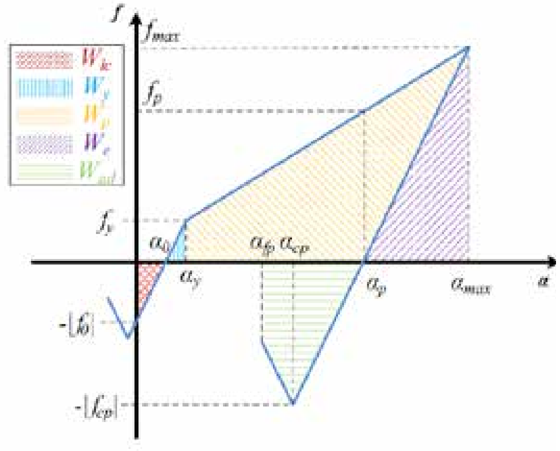
[1]Luding, S. (2008), *Granular matter*, 10, 235-246.

Surface Energy vs Adhesive Stiffness

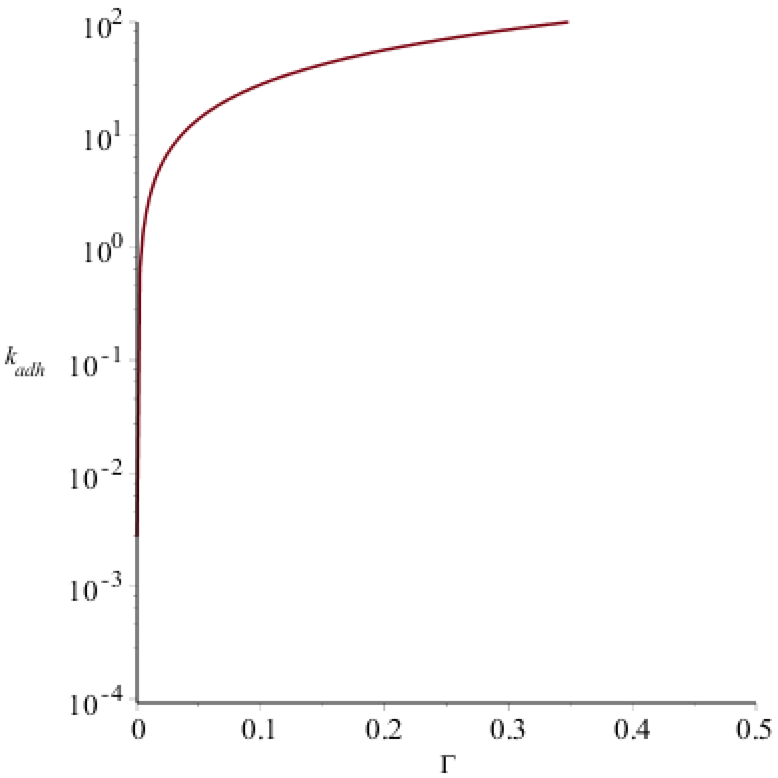
Comparison in terms of work of adhesion based on parameters by Thornton & Ning[2]



Luding[1]



Pasha et al.[3]



$$\left|W_{ad_{Pasha}}\right| = \left|W_{ad_{Luding}}\right|$$

[2]Ning, Z. (1995). Elasto-Plastic Impact of Fine Particles and Fragmentation of Small Agglomerates. *PhD Thesis*. Aston University

[3]Pasha, M. et al. (2014), *Granular matter*, 16, 151-162

Faceted vs Rounded Particles

Parameters used in the simulations

Material Property	Particles	Geometry
Density (kg/m^3)	2450	7800
Young's Modulus (GPa)	0.1	100

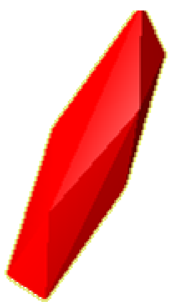
Interaction Property	Particles-particles	Particle-geometry
Restitution coefficient (no cohesion)	0.8	0.8
Restitution coefficient (with cohesion)	0.4	0.4
Sliding friction coefficient	0.3	0.1
Rolling friction coefficient	0.01	0.01

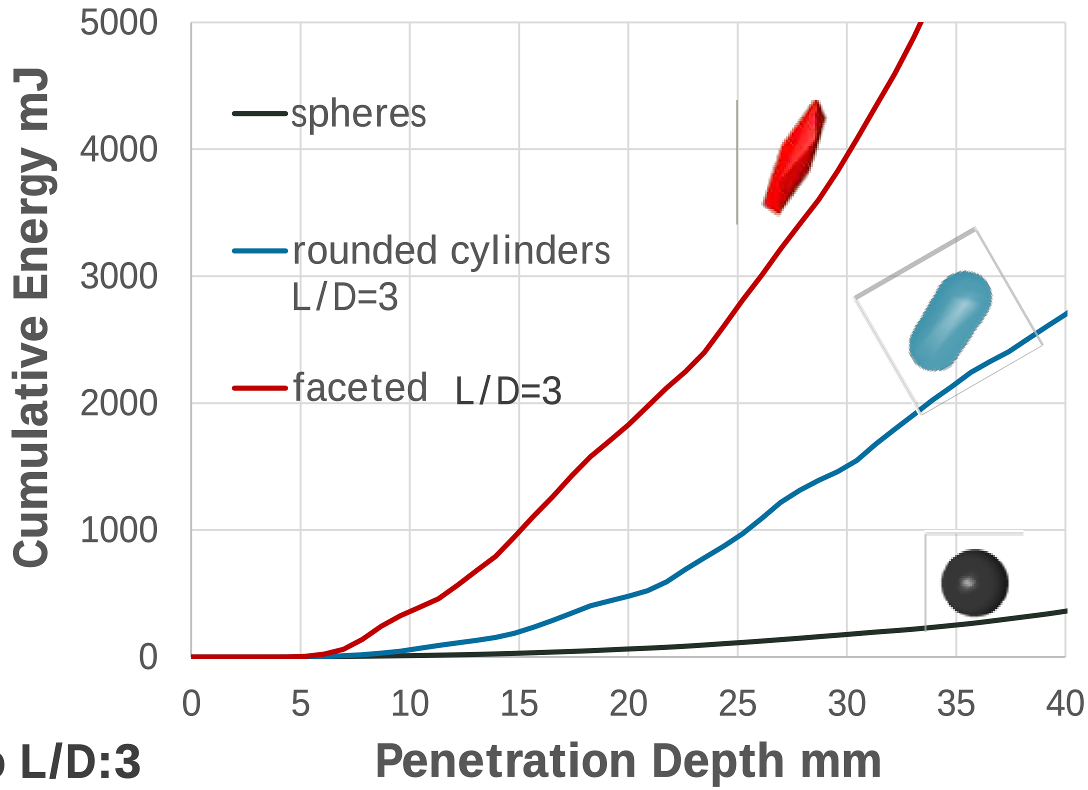
ADDOPT

Faceted vs Rounded Particles

2 mm mean volume diameter

Faceted

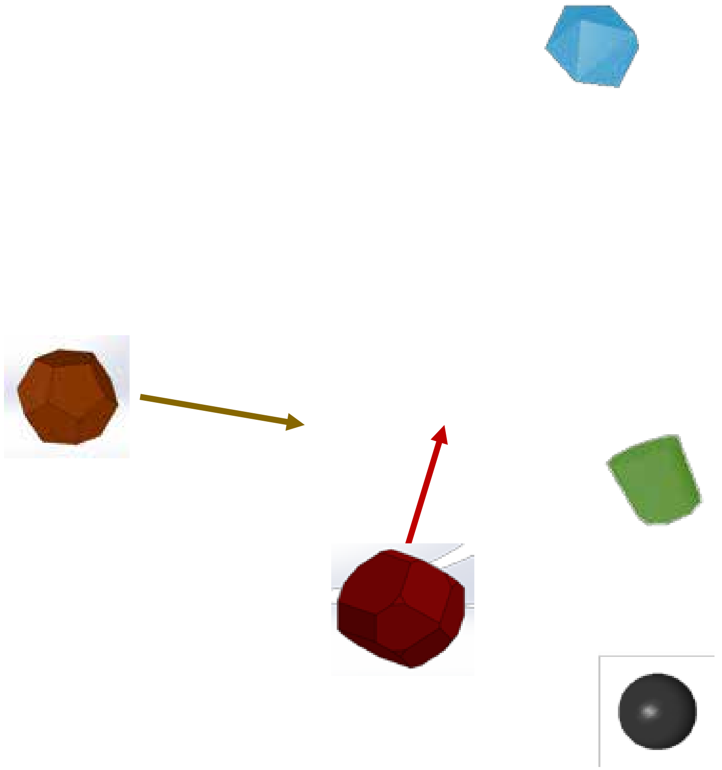




Aspect Ratio L/D:3
# of faces:16
# of corners:10

ADDOPT

Shape Effect: Flow Energy Comparison at 100 mm s^{-1} and 5° Helix Angle



2 mm mean volume diameter

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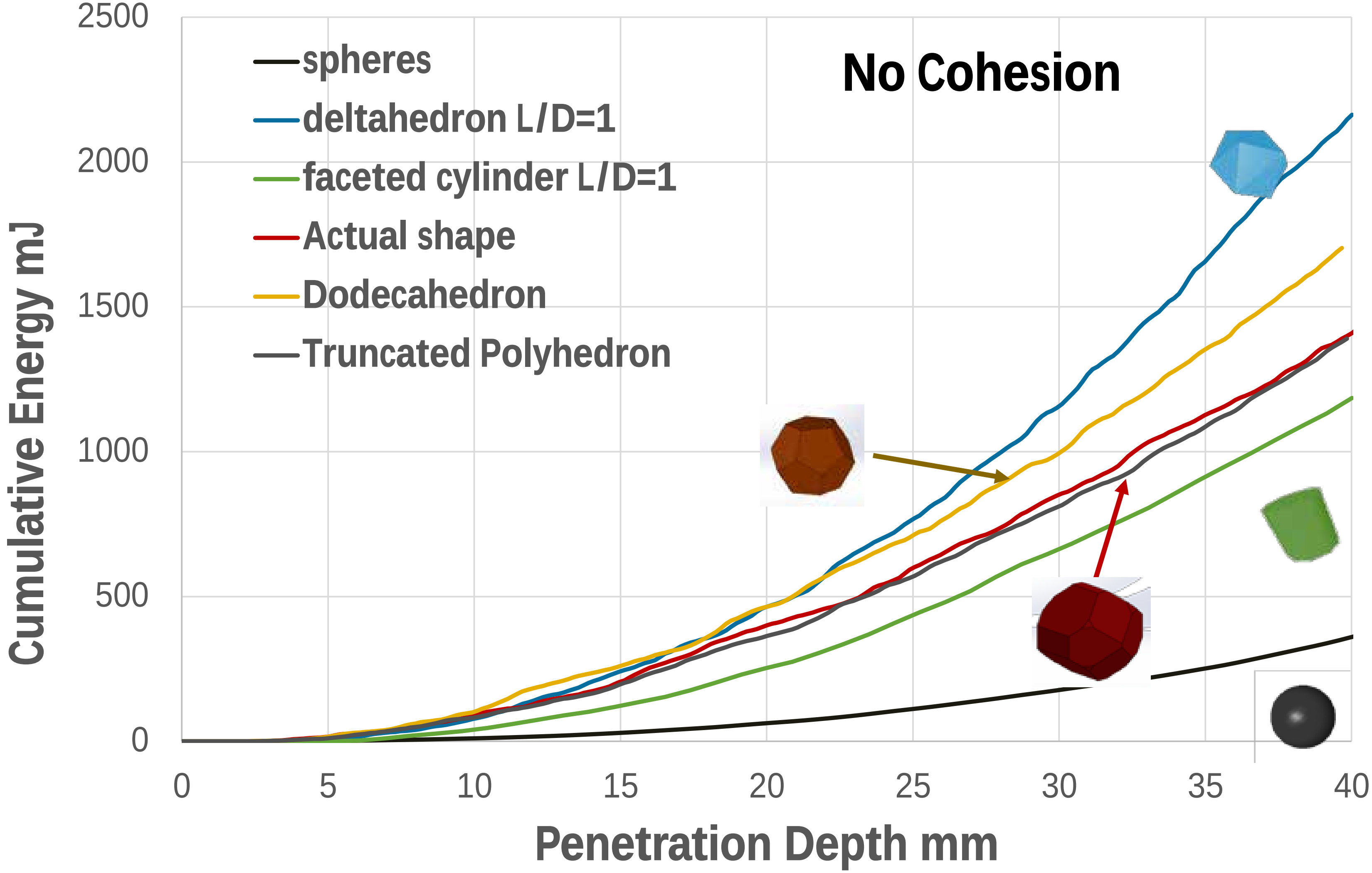
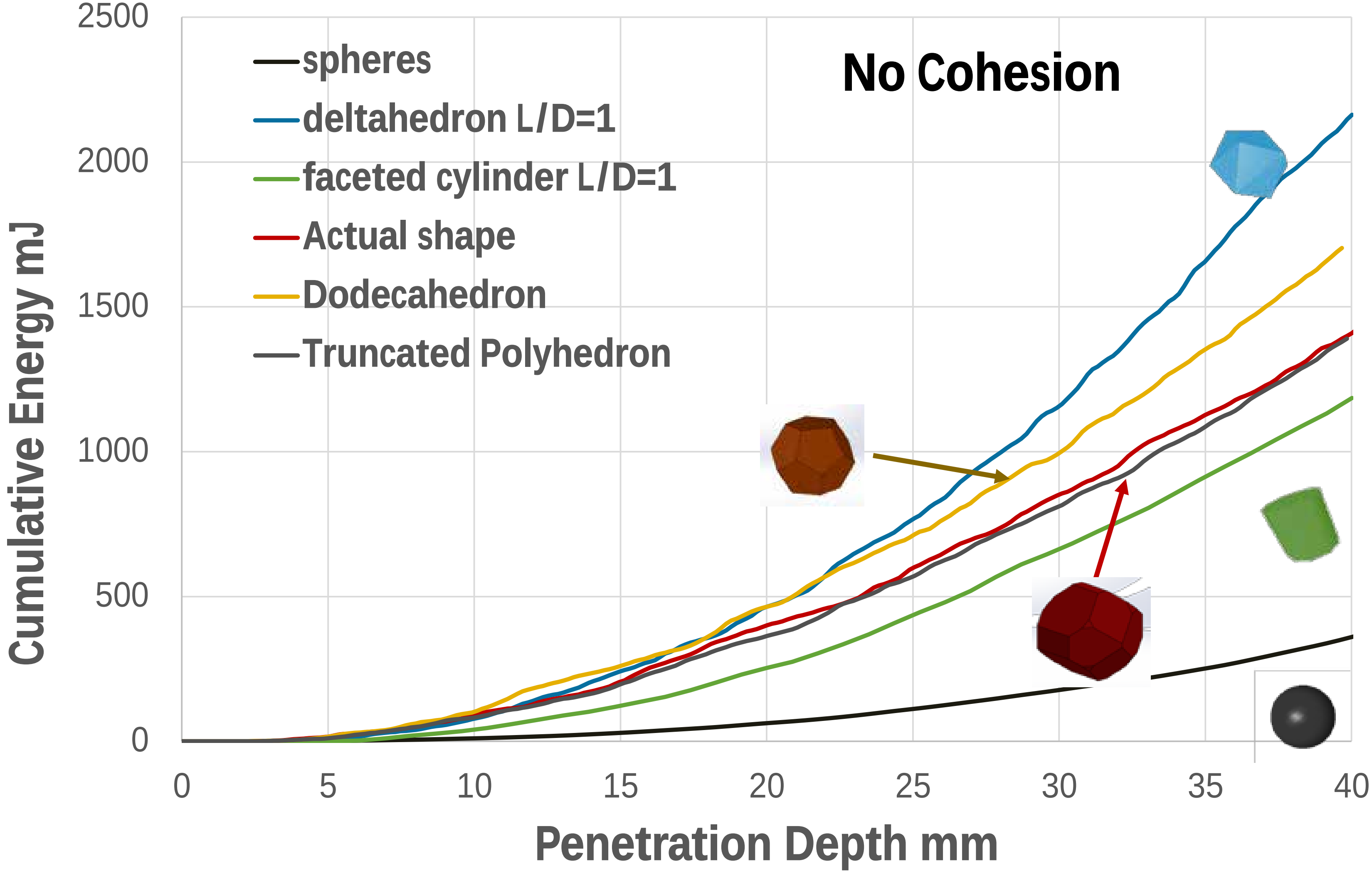


2 mm mean volume diameter

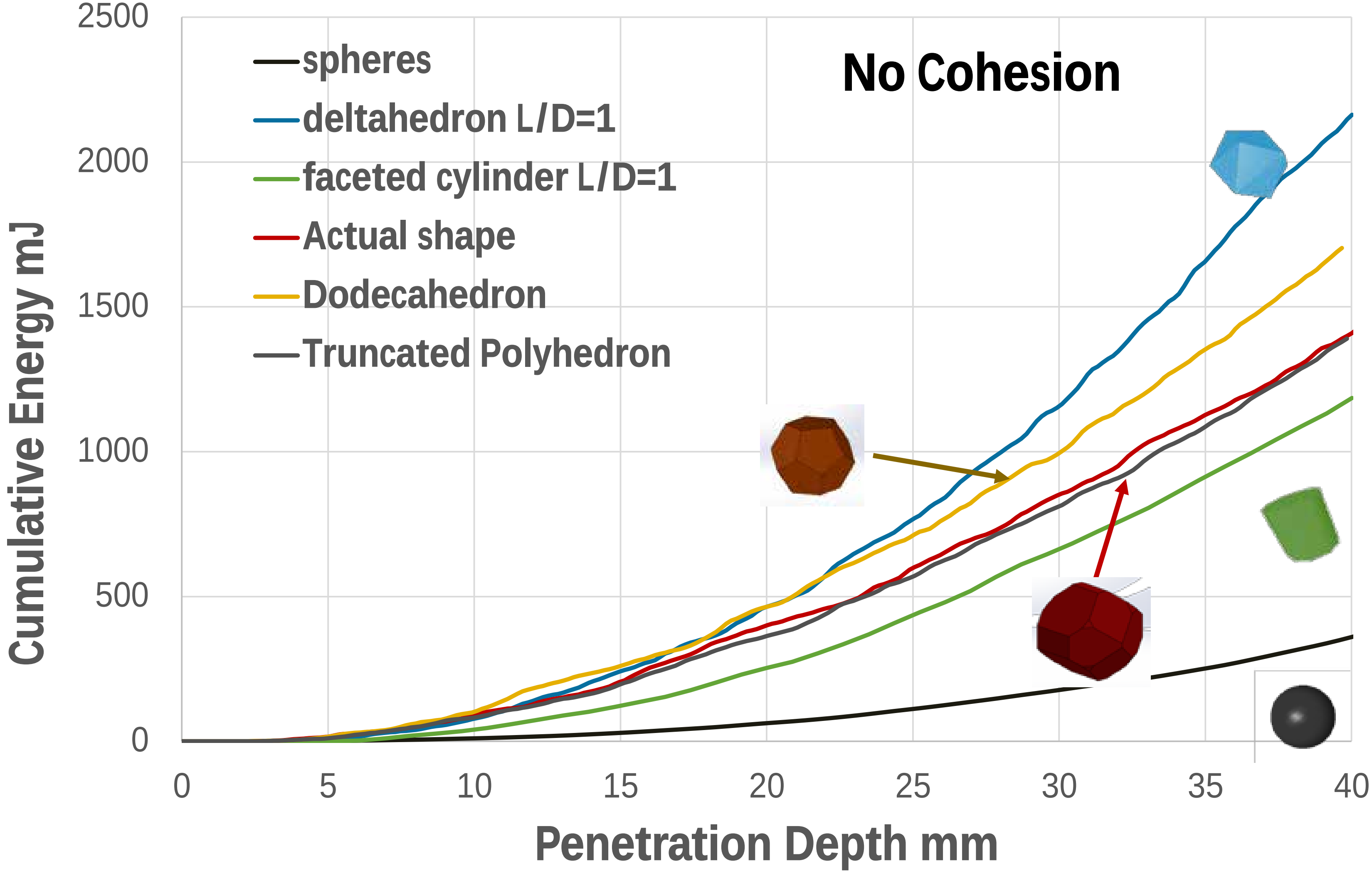
ADDOPT

Shape Effect: Flow Energy Comparison at 100 mm s^{-1} and 5° Helix Angle



2 mm mean volume diameter

Shape Effect: Flow Energy Comparison at 100 mm s^{-1} and 5° Helix Angle



2 mm mean volume diameter

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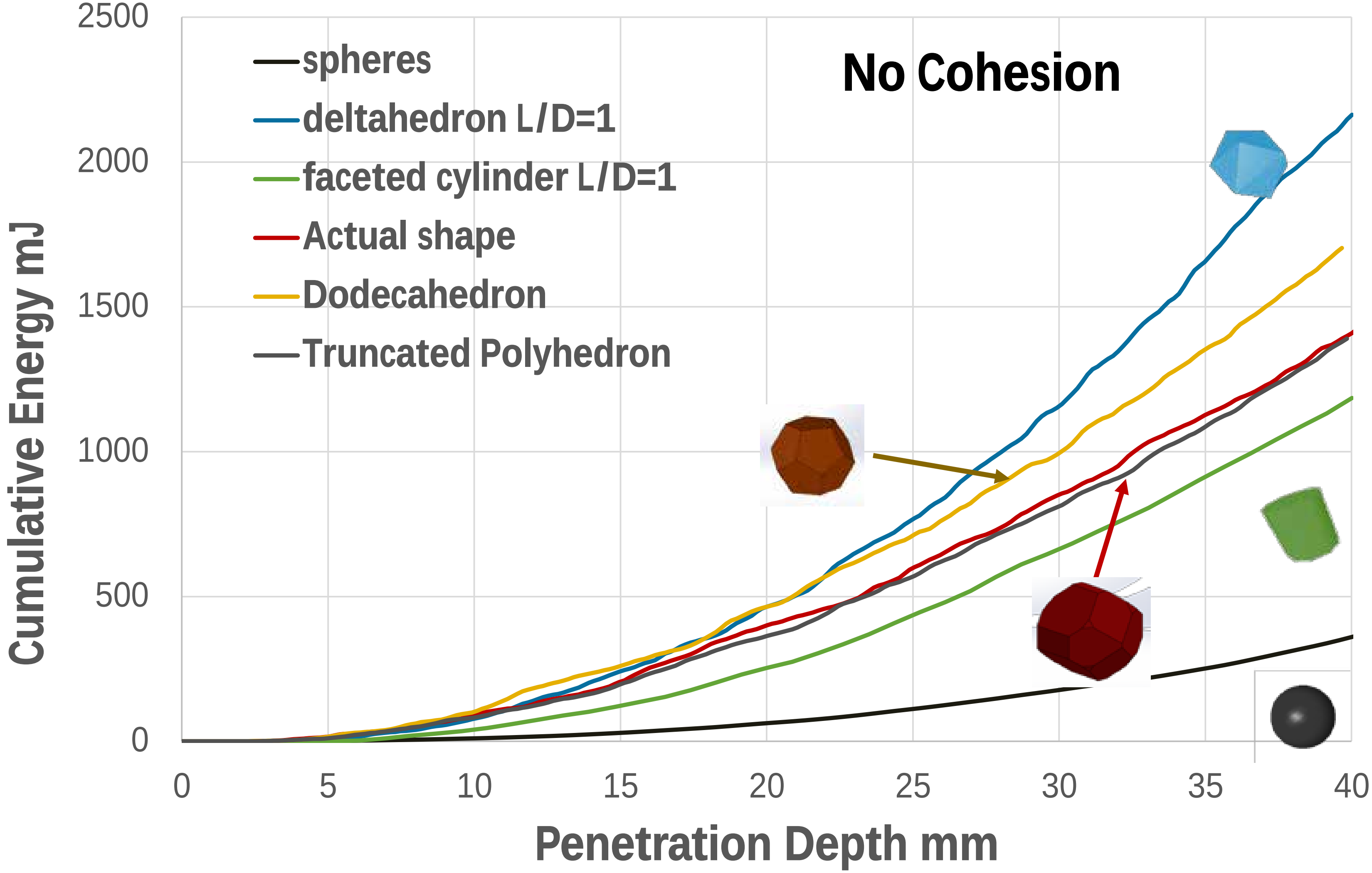

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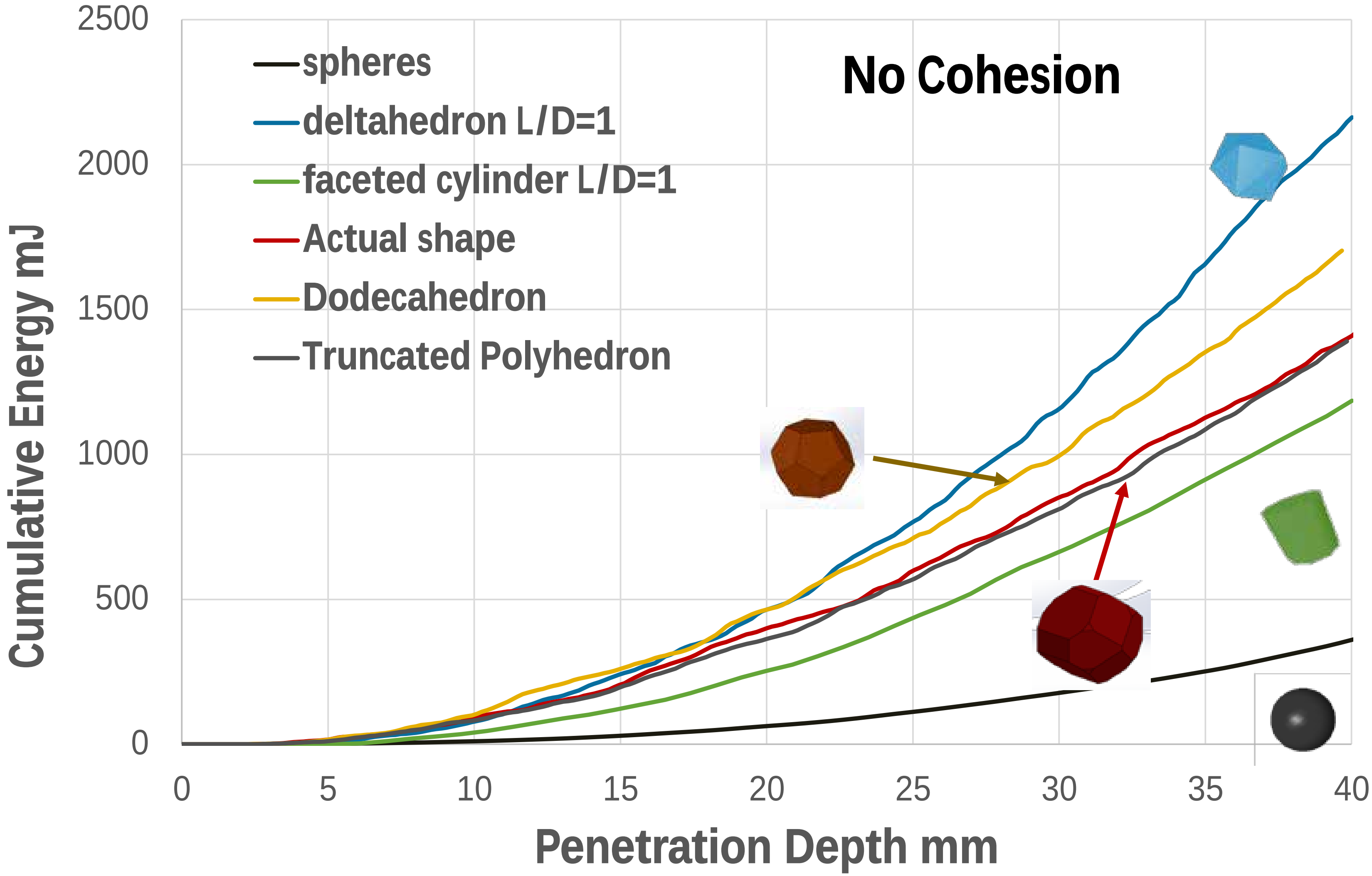
ADDOPT

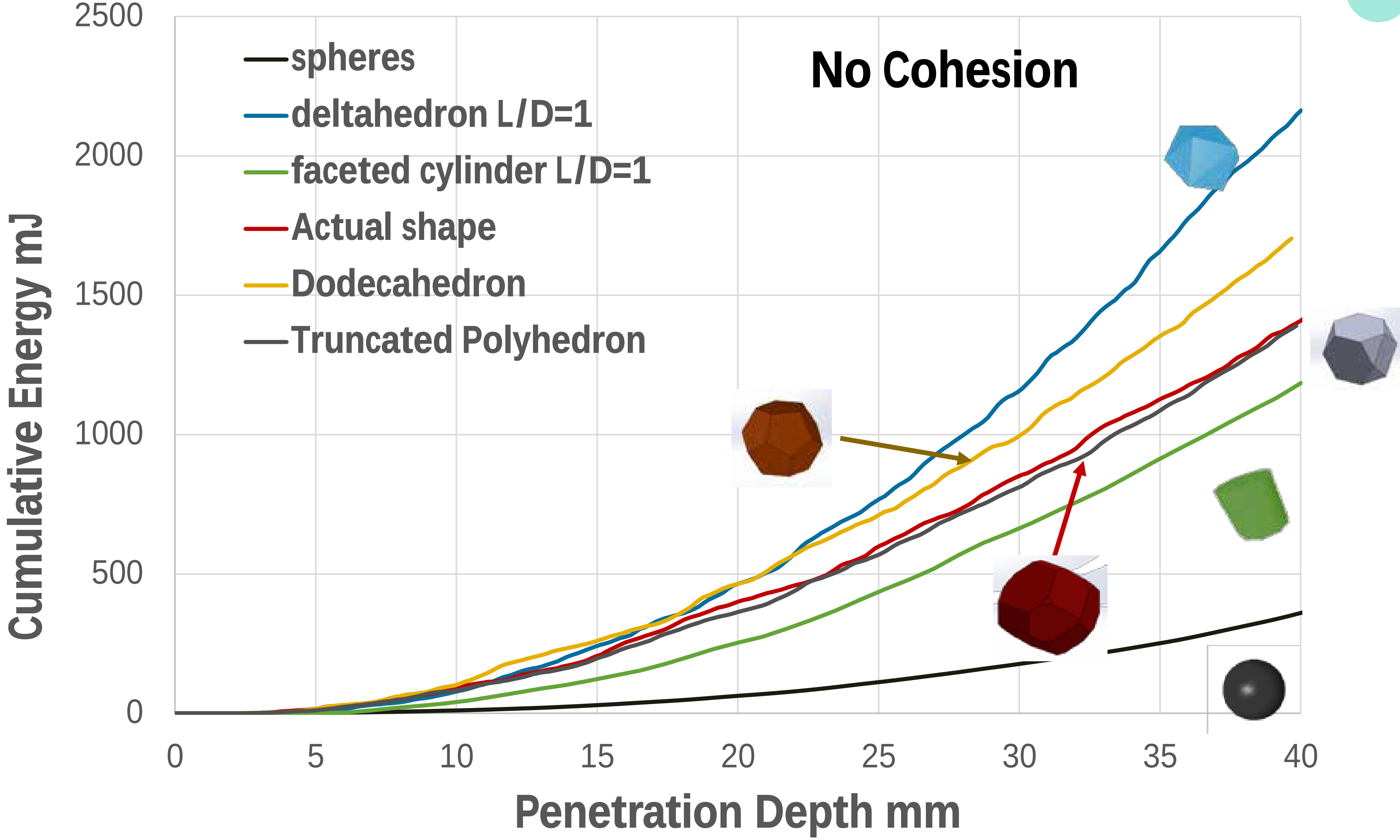
Shape Effect: Flow Energy Comparison at 100 mm s^{-1} and 5° Helix Angle



2 mm mean volume diameter

ADDOPT

Shape Effect: Flow Energy Comparison at 100 mm s^{-1} and 5° Helix Angle



2 mm mean volume diameter

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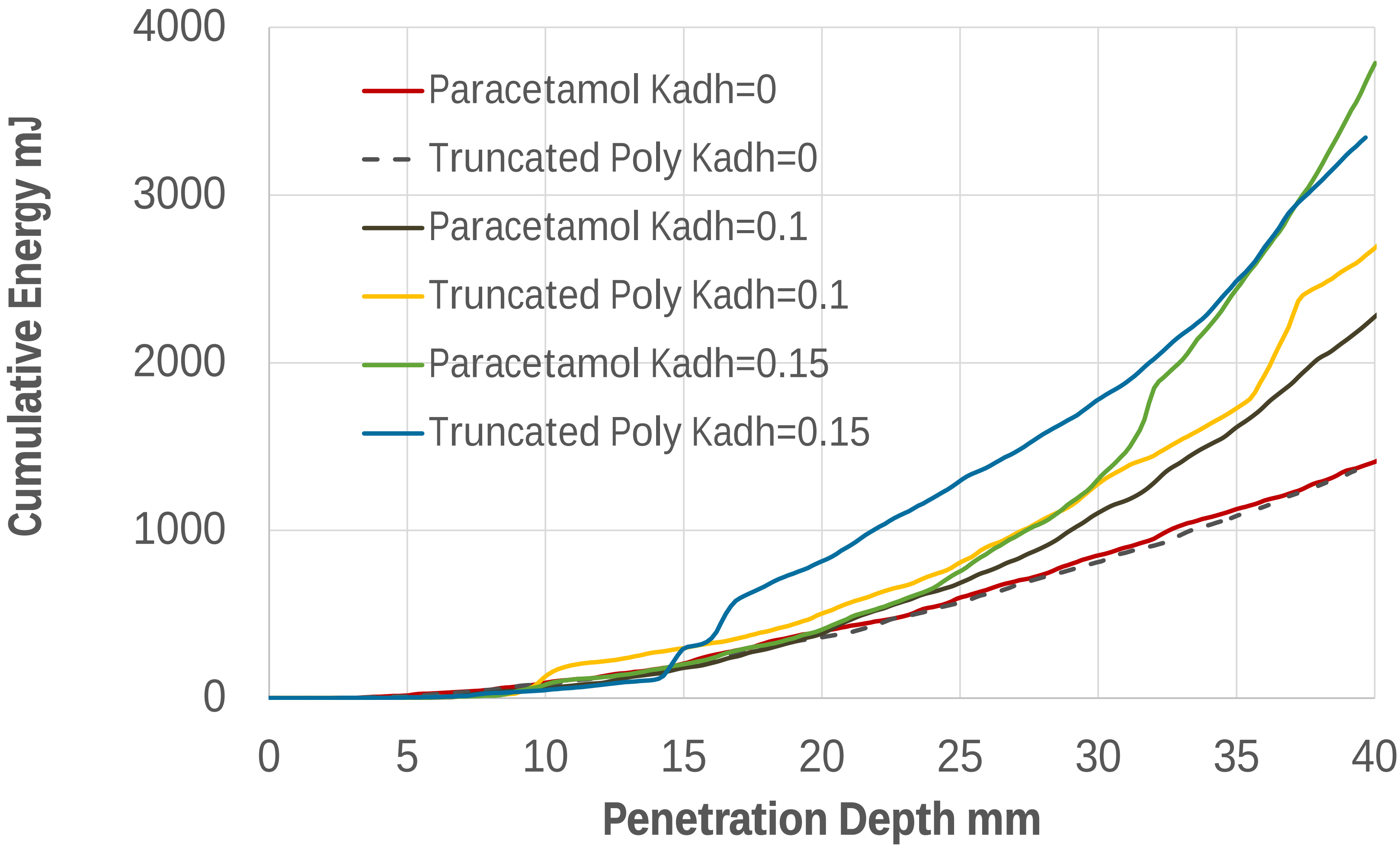
Energy Comparison at 100 mm s^{-1} and 5° Helix Angle



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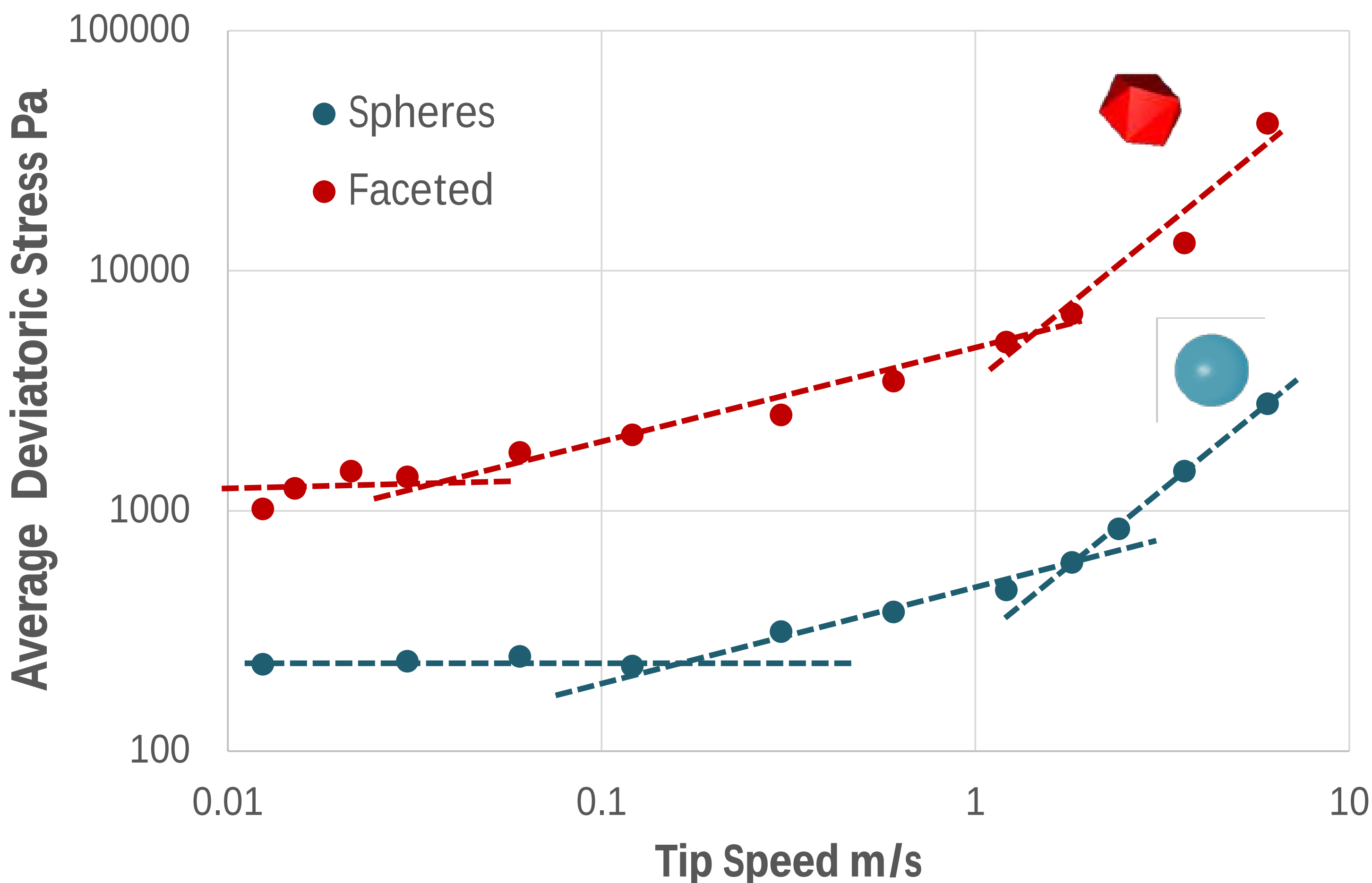
Regime Transition: Effect of Shape

2 mm mean volume diameter, no cohesion



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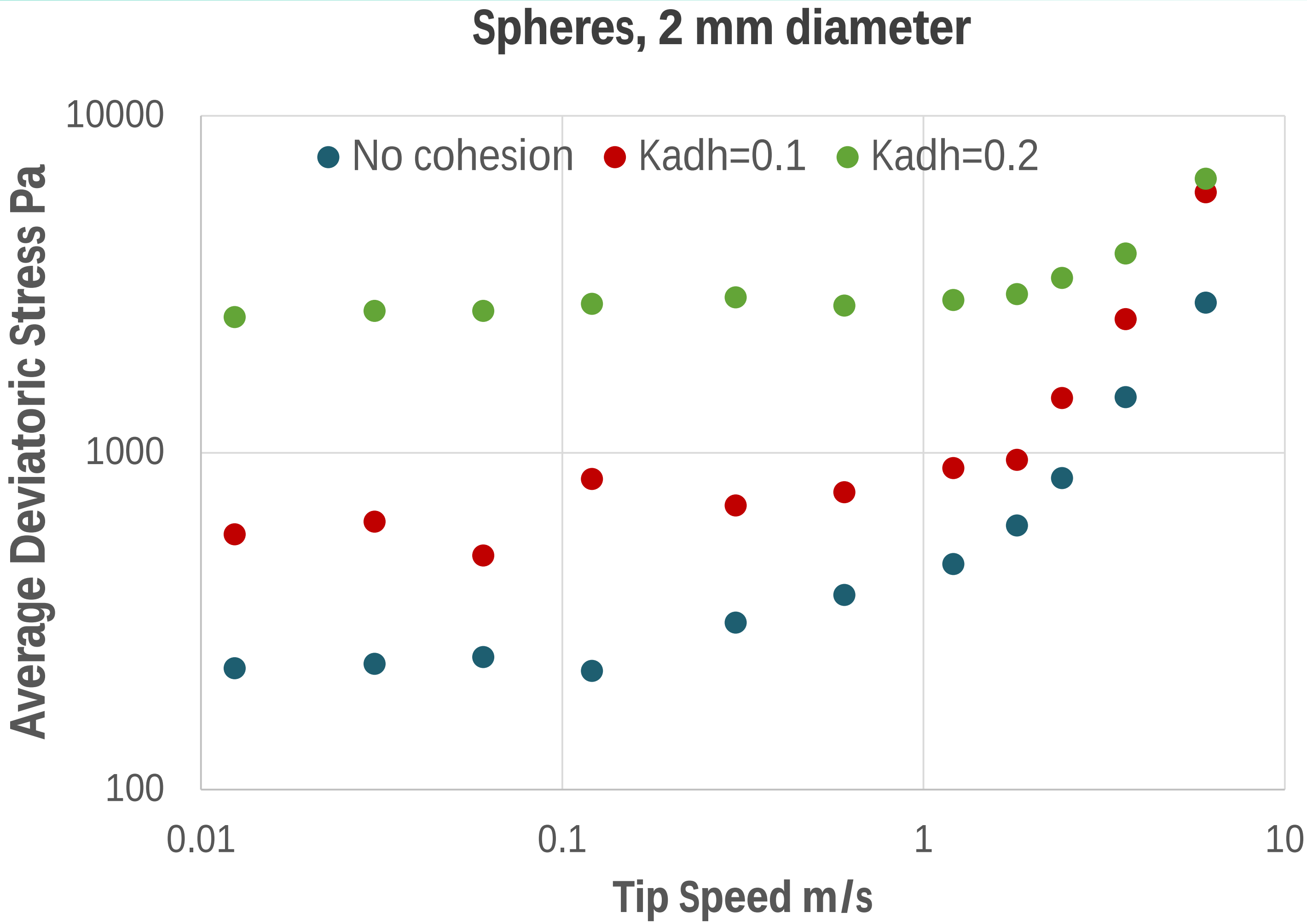
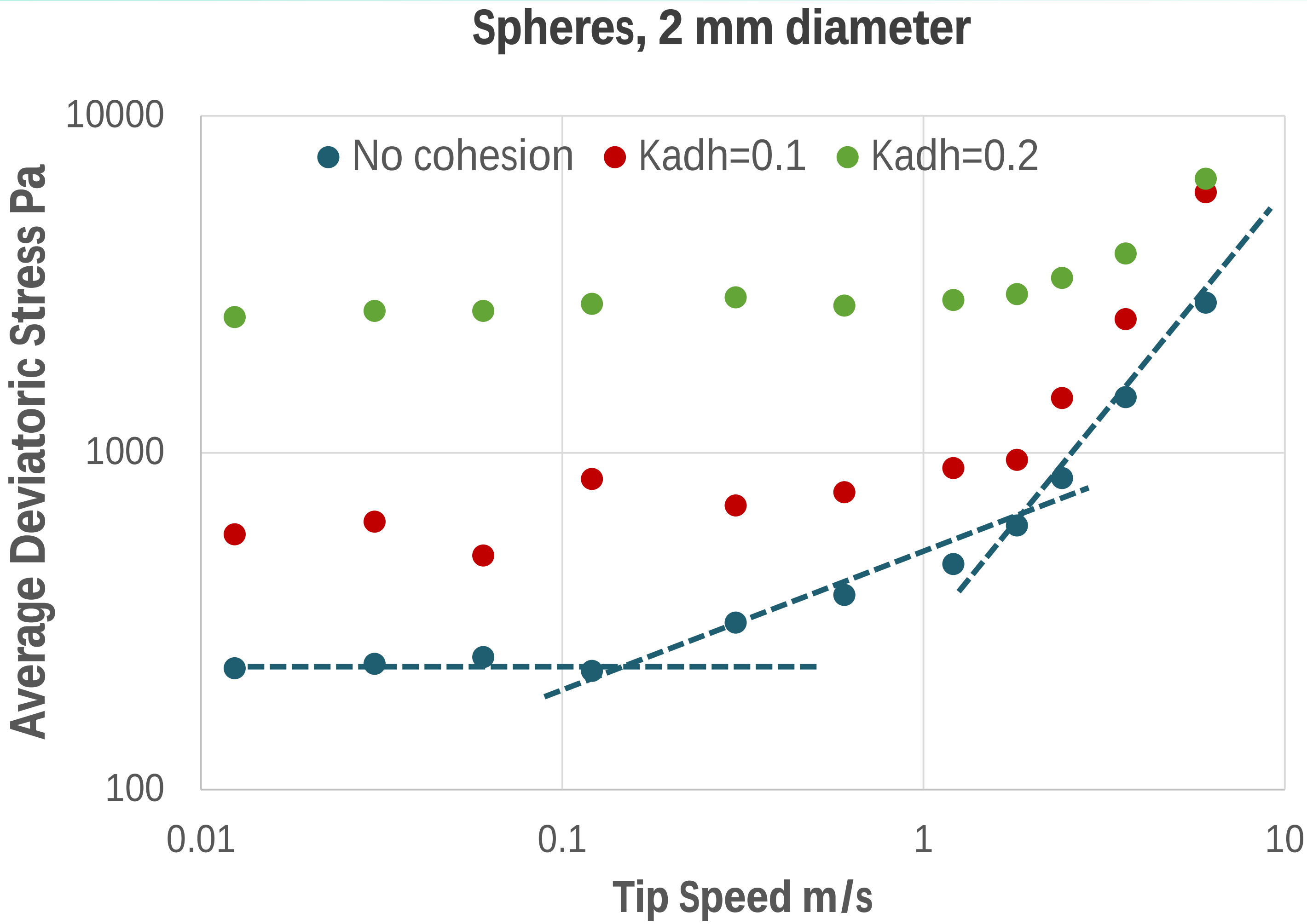
Regime Transition: Effect of Cohesion

Spheres, 2 mm diameter

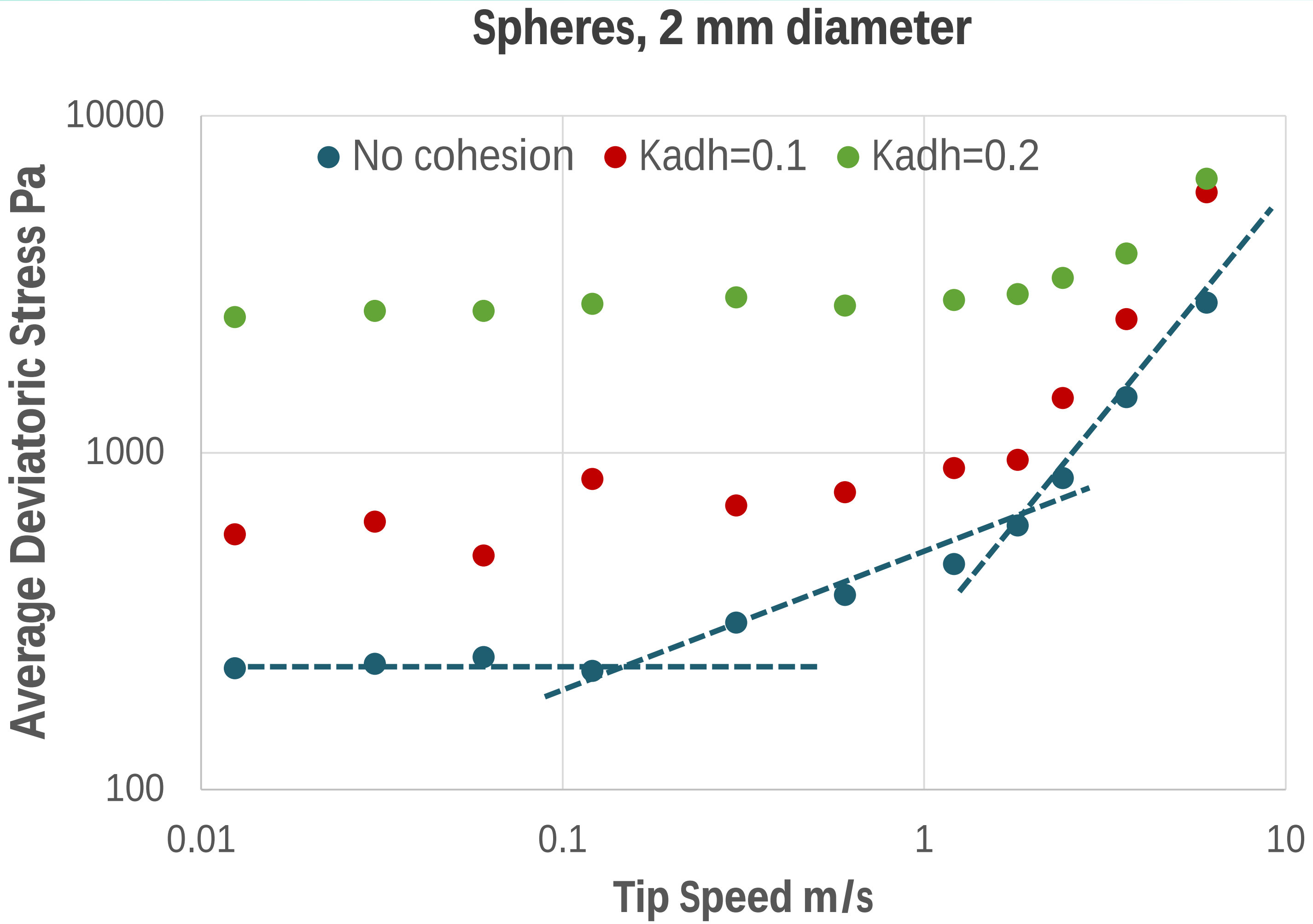
Regime Transition: Effect of Cohesion



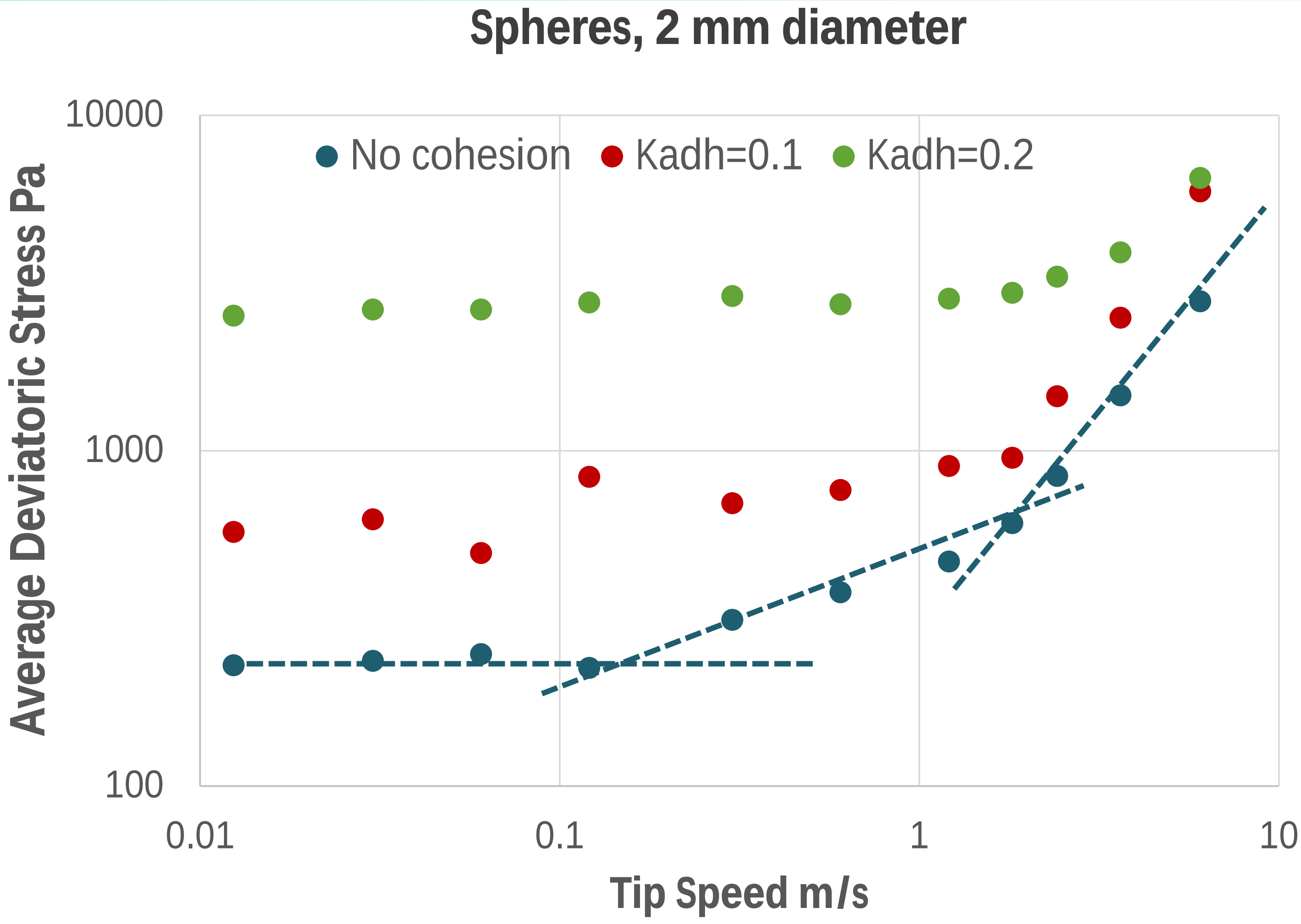
Regime Transition: Effect of Cohesion



Regime Transition: Effect of Cohesion

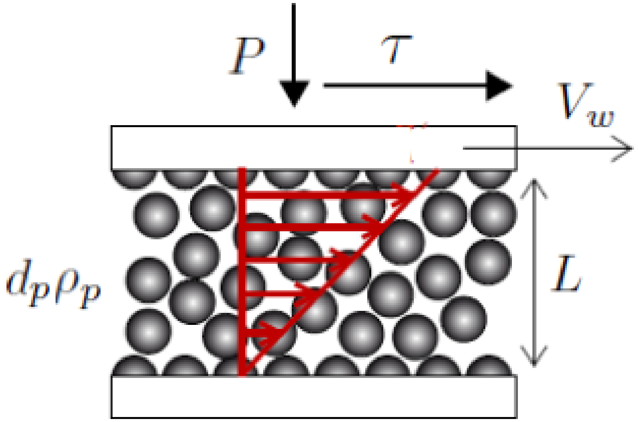


Regime Transition: Effect of Cohesion



Inertial Number

Local Rheology



$$\gamma = V_w / L$$

The process is described by a single dimensionless number

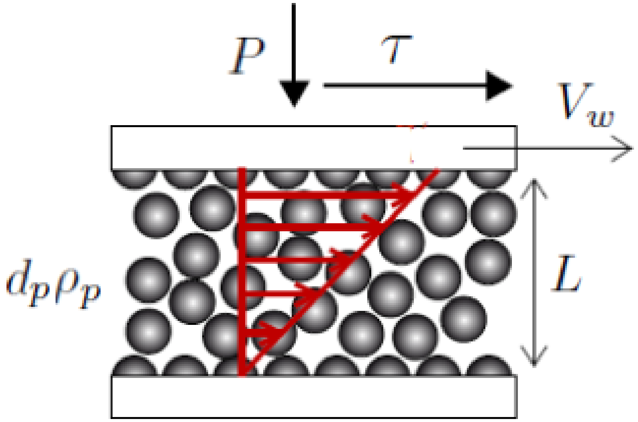
$$\text{Inertial number, I} = d_p \gamma \sqrt{\frac{\rho_p}{P}}$$

- special case: $\gamma(d_p/g)^{0.5}$, assuming that P equals to $\rho_p d_p g$
- ratio between the inertial timescale $d_p/(P/\rho_p)^{0.5}$ and macroscopic deformation timescale $(1/\gamma)$.

ADDOPT

Inertial Number

Local Rheology



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Constitutive law: $\tau = \mu(I) P$ — $\mu(I)$ is the bulk friction coefficient

ADDOPT

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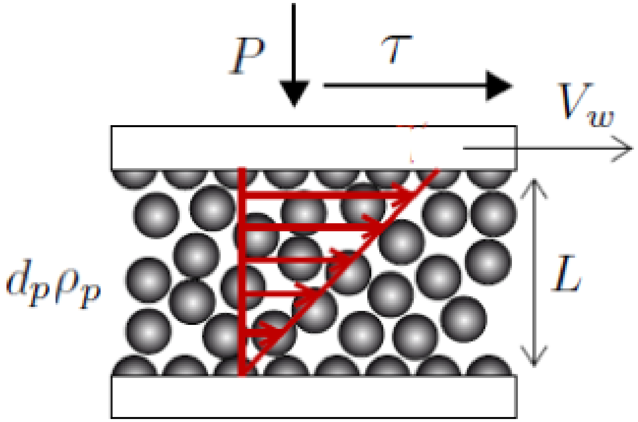

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3D Generalisation[1]

Stress Tensor

$$\sigma_{ij} = -P\delta_{ij} + \tau_{ij} \qquad \tau_{ij} = \eta_{eff}(I)\frac{\partial u_j}{\partial x_i}$$

Effective viscosity

$$\eta_{eff} = \frac{\mu(I)P}{|\gamma|}$$

[1] P. Jop, Y. Forterre, O. Pouliquen, A constitutive law for dense granular flows, Nature 441 (2006), 727-30.

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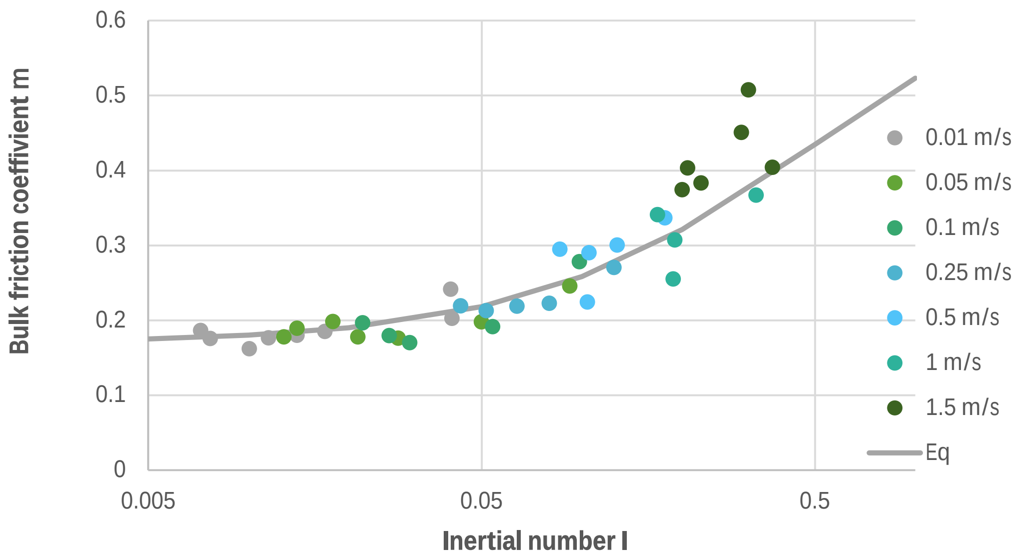
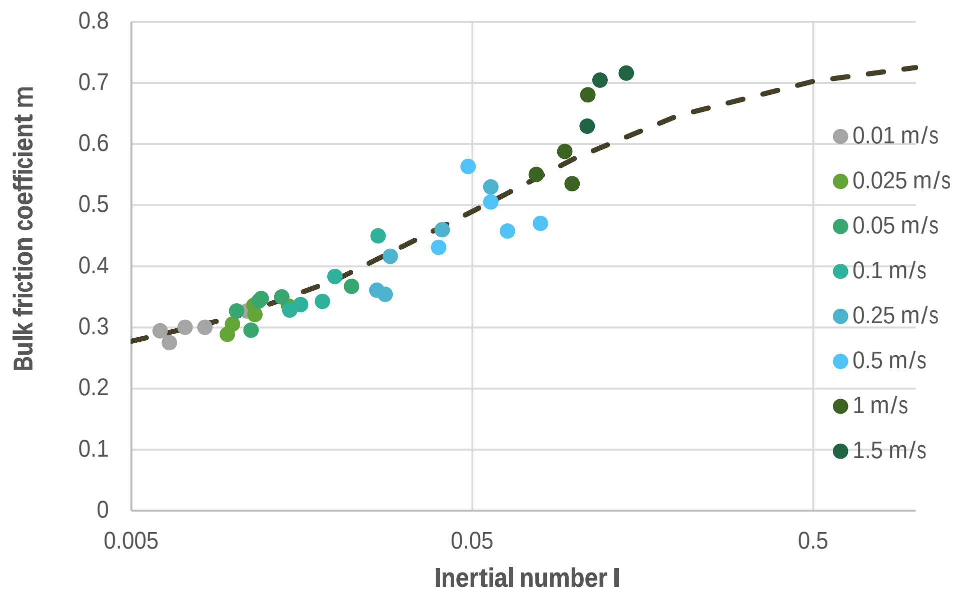
Bulk Friction Coefficient



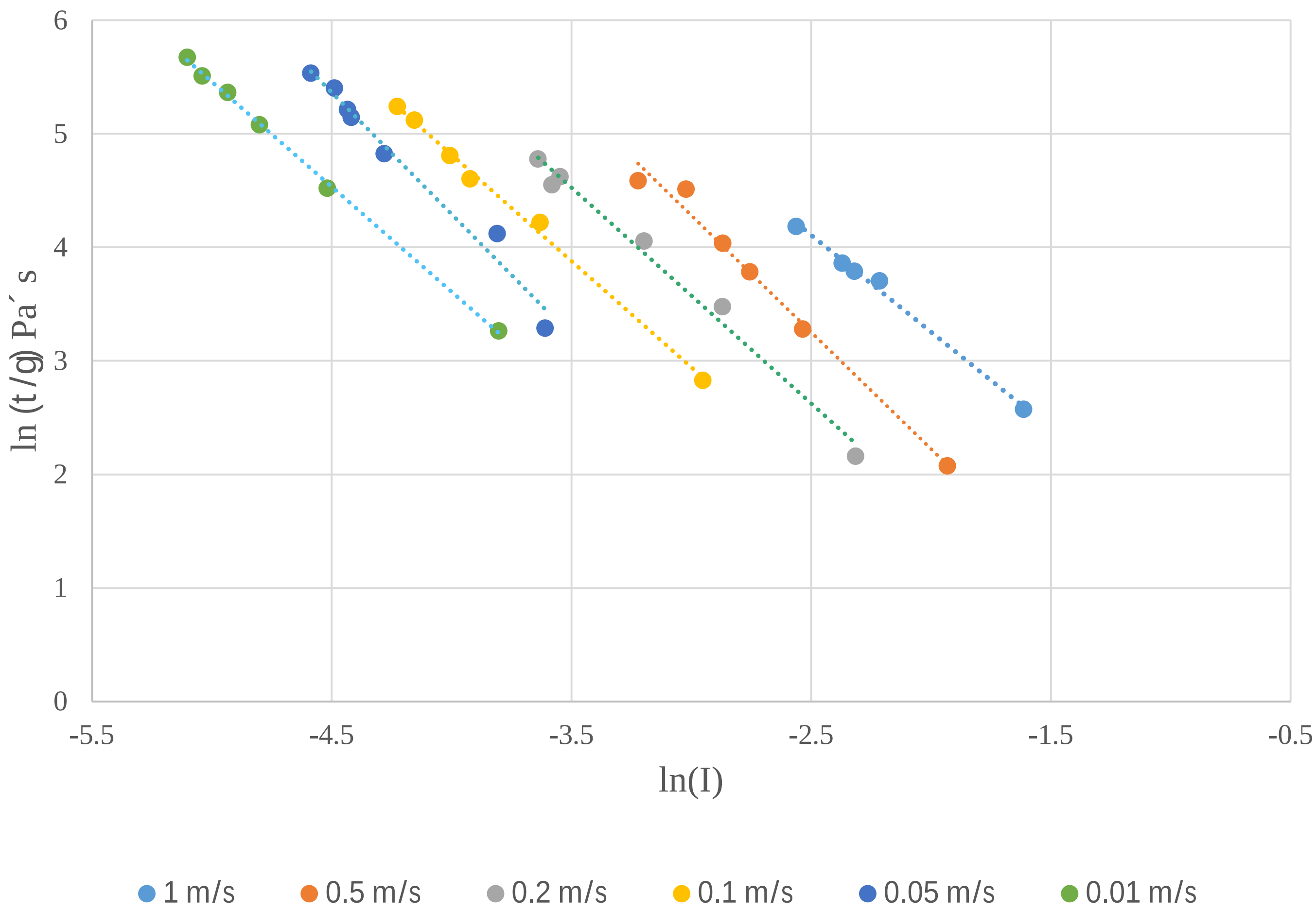
non-cohesive spheres

$$\mu = \frac{\tau}{p} = \mu_1 + \frac{\mu_2 - \mu_1}{I_0/I + 1}$$



non-cohesive deltahedra

Apparent Viscosity for Non-Cohesive Deltahedra



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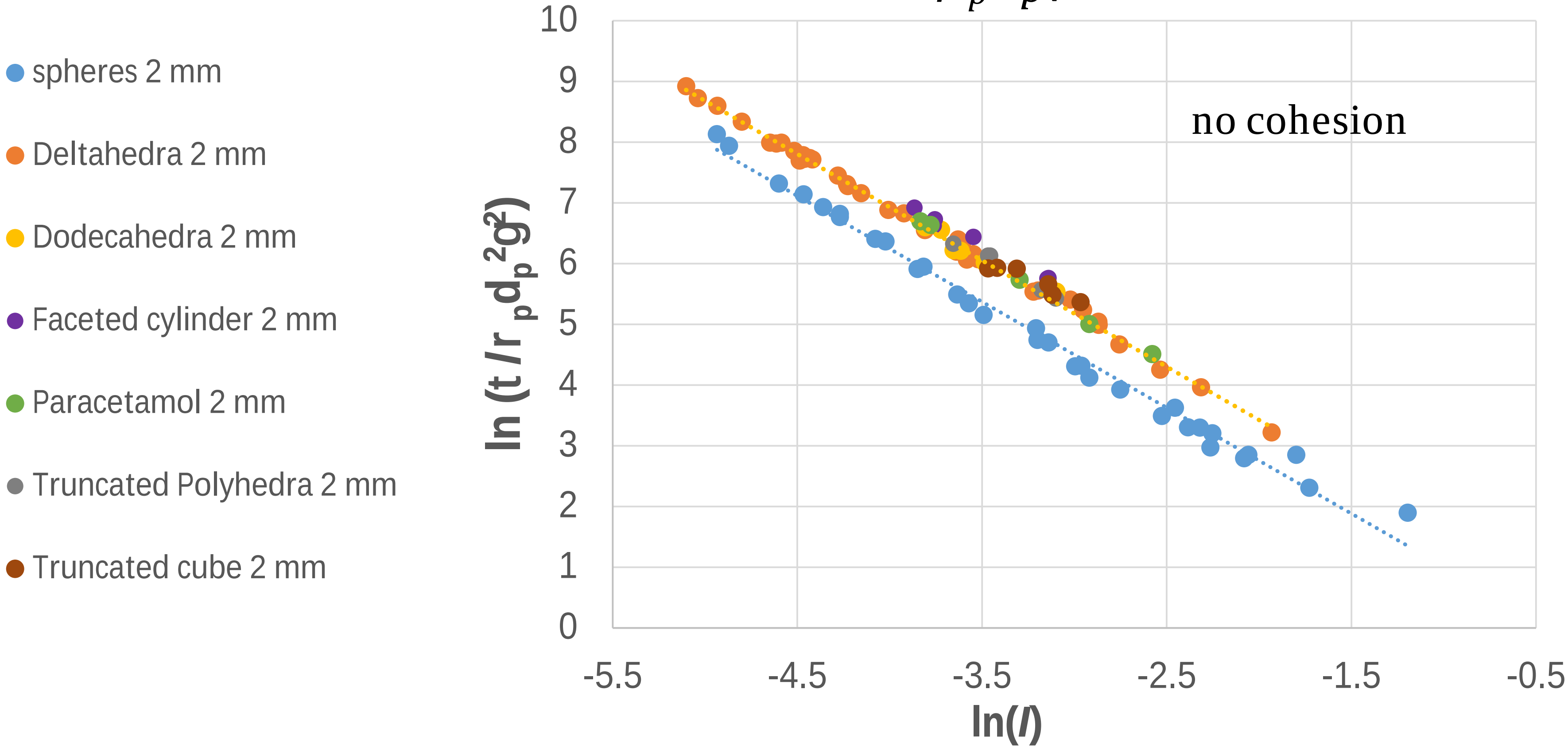
Faceted Particles

$$\frac{\tau}{\rho_p d_p^2 \gamma^2} = f(I)$$



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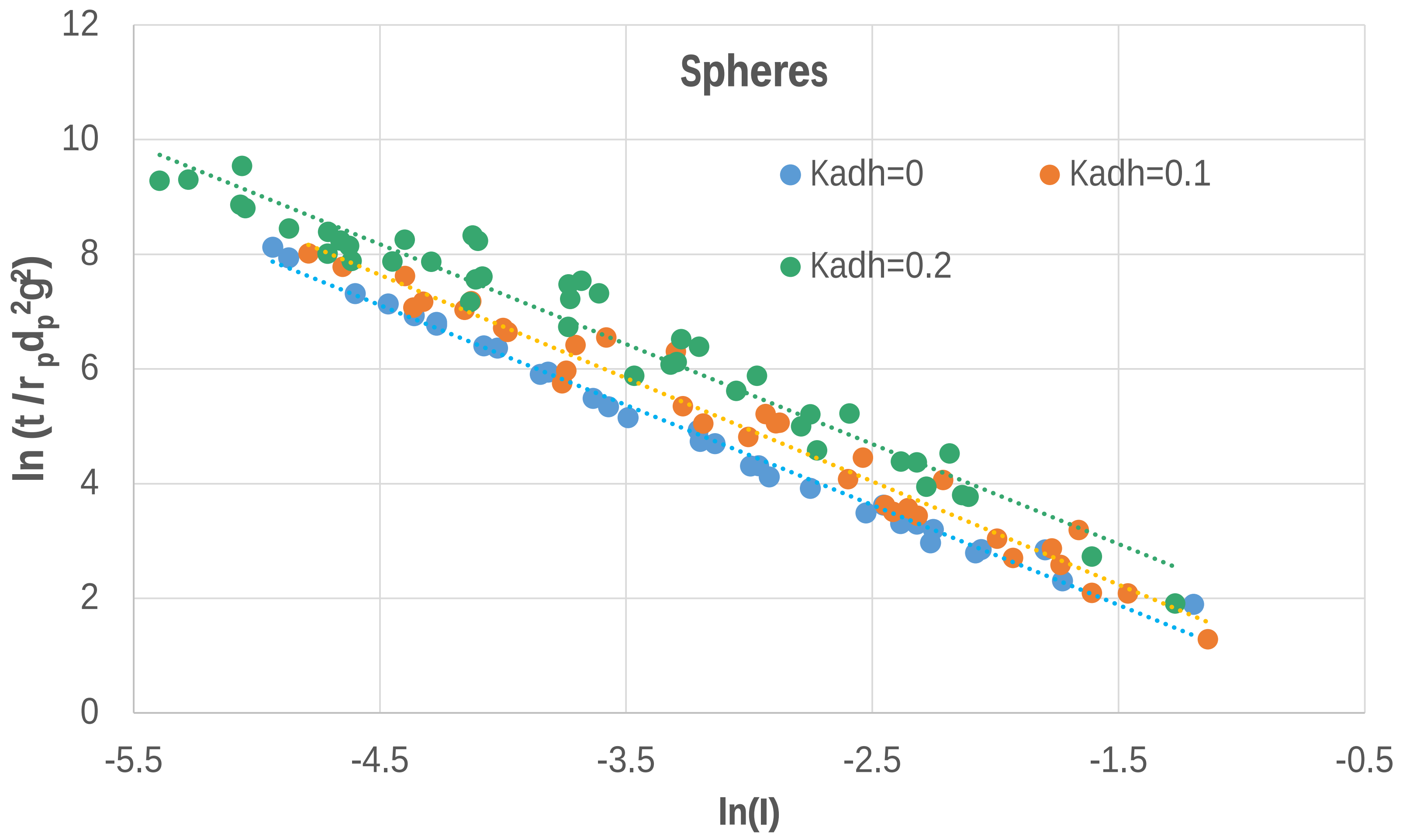
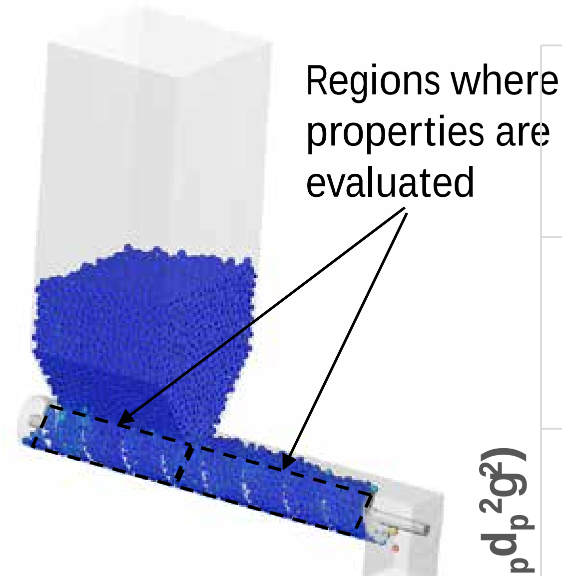
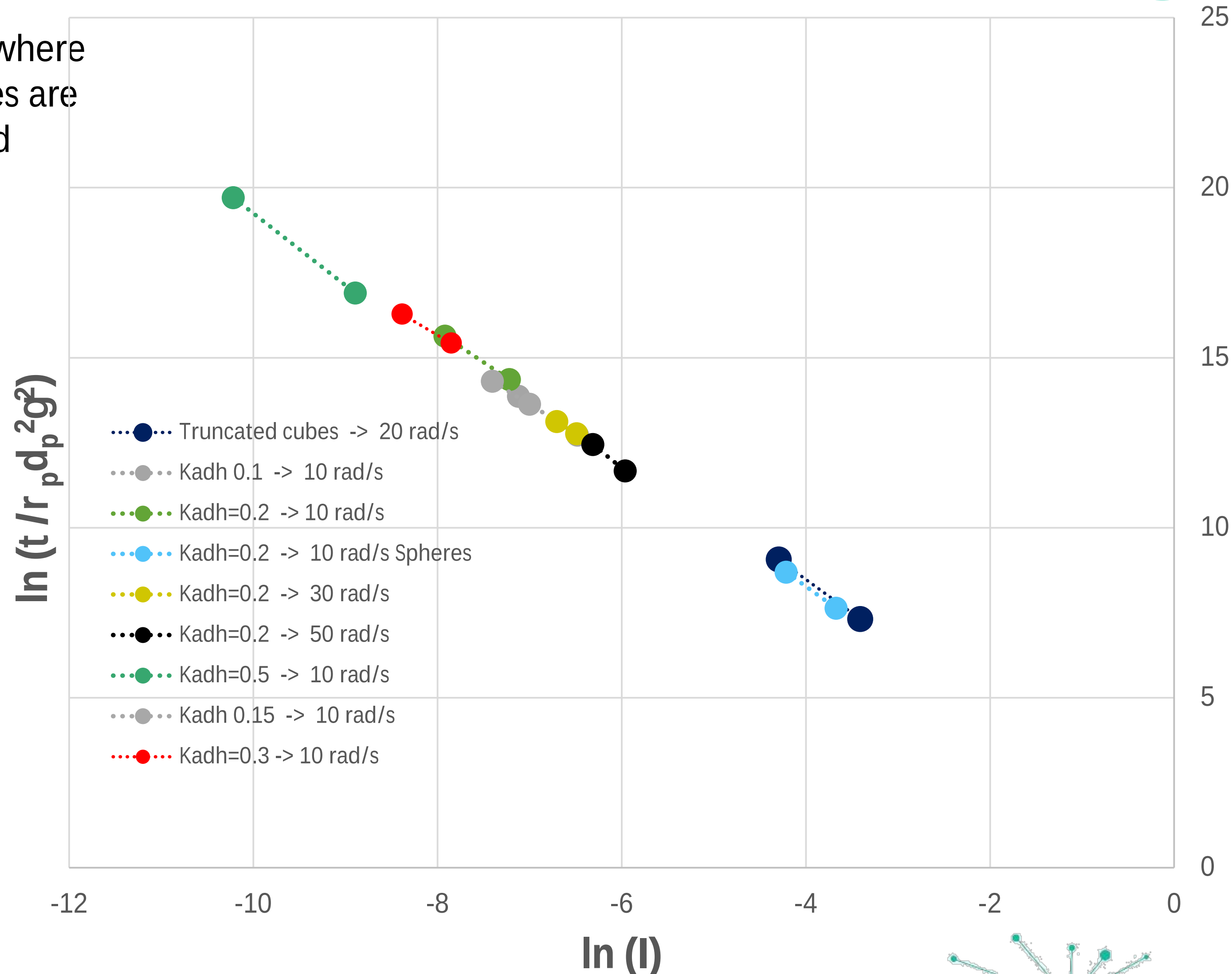
Different Cohesion Levels



Screw Feeder vs FT4

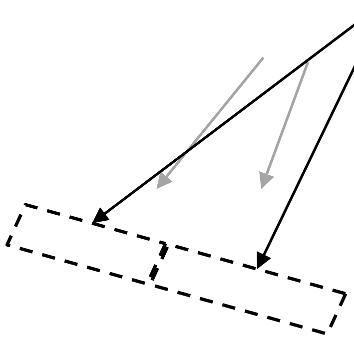


Rotational velocity:
2, 5, 10 and 20 rad/s



Screw Feeder vs FT4

Regions where properties are evaluated



Rotational velocity:
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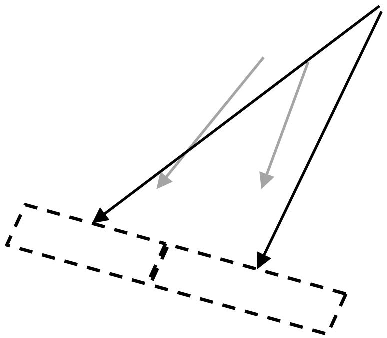
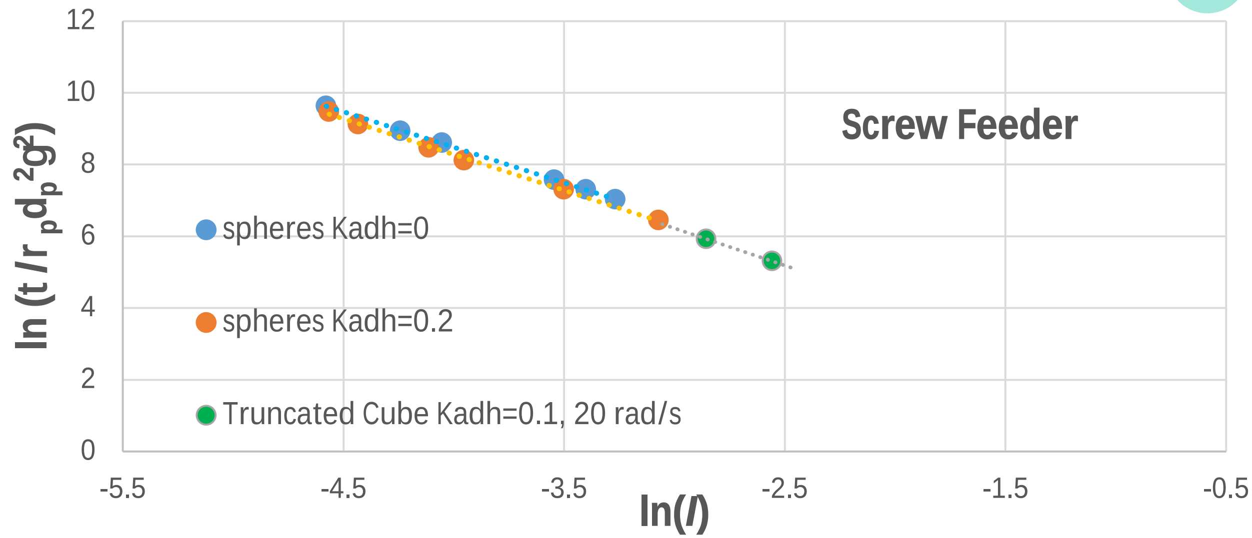
The powder rheology in screw feeders and FT4 are similar

Both systems – dimensionless shear stress = f(I)

Screw Feeder vs FT4

Regions where properties are evaluated





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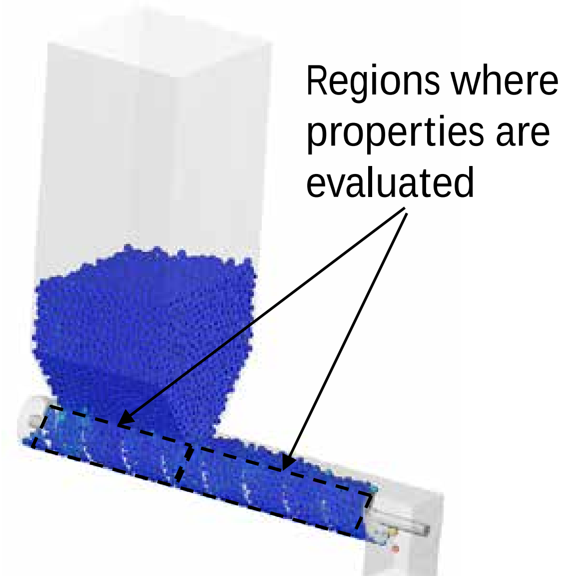
Screw Feeder vs FT4



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2, 5, 10 and 20 rad/s

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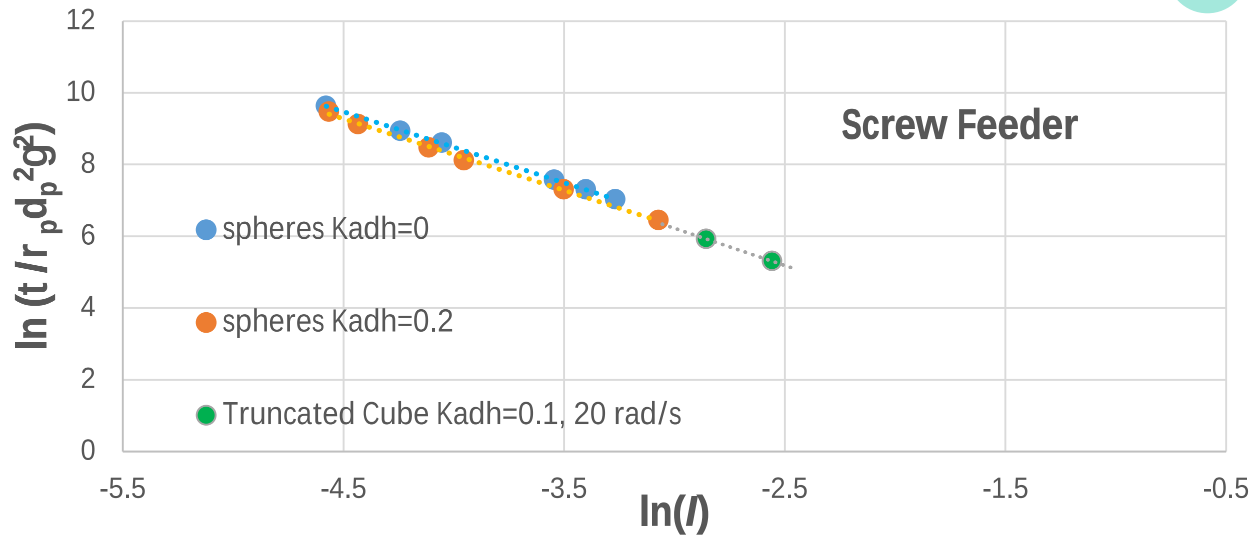
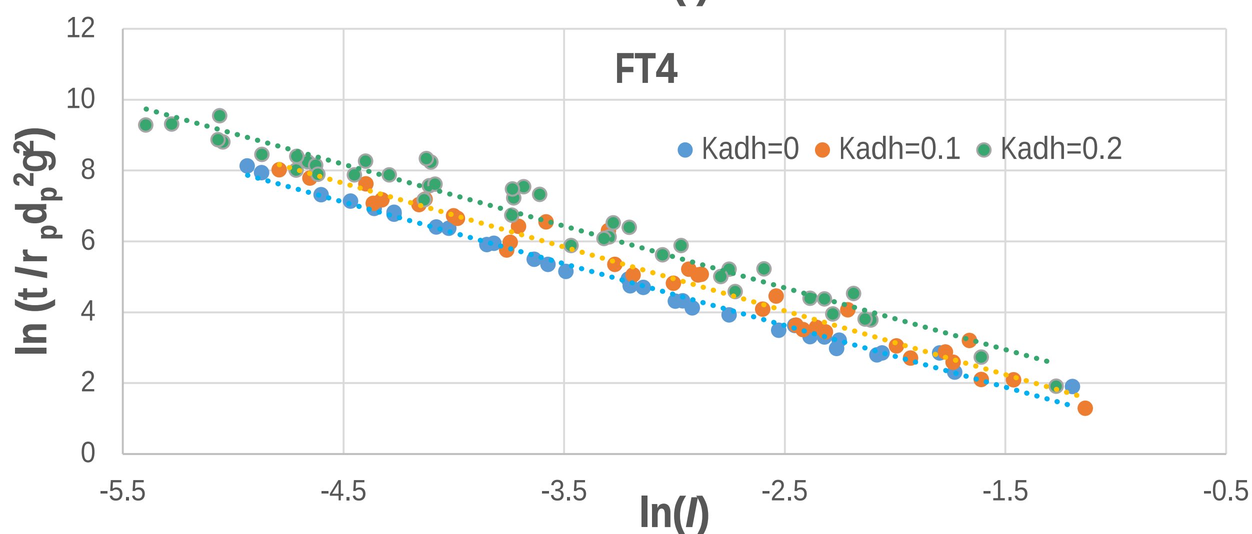
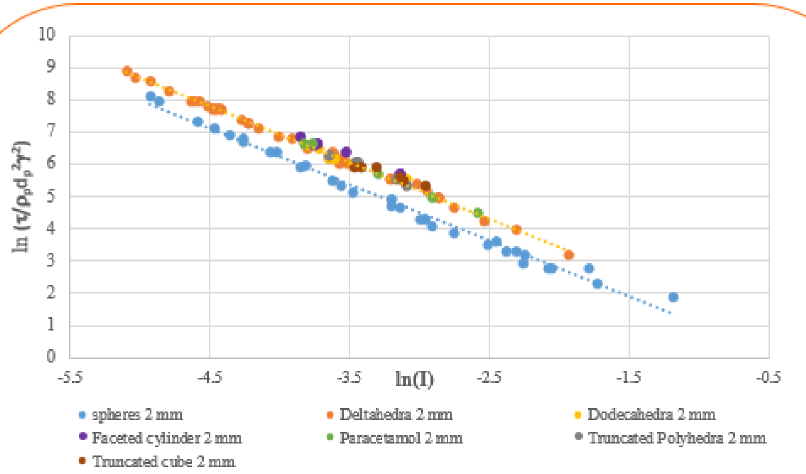




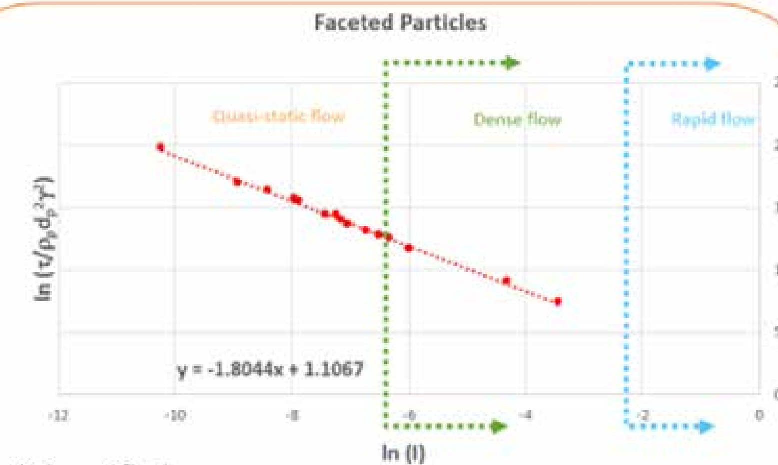
Rheological models



Constitutive laws for powder flow valid in the intermediate flow regime

$$\frac{\tau}{\rho_p d_p^2 \gamma^2} = 0.481 I^{-1.743}$$

$$\frac{\tau}{\rho_p d_p^2 \gamma^2} = 0.918 I^{-1.754}$$



Possible unified rheology for faceted particles in the screw feeder and different cohesion levels – Linear equation

$$\frac{\tau}{\rho_p d_p^2 \gamma^2} = 3.024\, I^{-1.8044}$$

Conclusions

- Quasi-static and dynamic shear deformation of cohesive large particles have been simulated and the incipient yield and dynamic bulk friction and 'effective' shear viscosity are predicted.
- Particle shape influences the angle of friction in bulk failure of particles
- The presence of vertices in faceted shapes strongly influences the resistance to shear deformation
- Approximating real crystal shapes by truncated polyhedron shapes provides a close match in flow energy and shear deformation behaviour between the two shapes
- Shear stress normalised by the inertial stress is unified for faceted shapes with and without cohesion when expressed in terms of the inertial number
- The same pattern of unification prevails for the conditions in screw feeders
- Experimental validation is ongoing

ADDOPT

Thank you for your attention