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Application of Peridynamics to Predict Pharmaceutical Tablet Robustness

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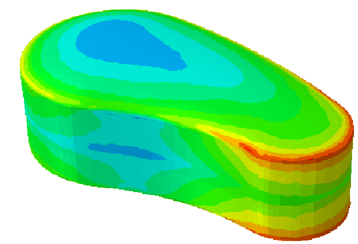
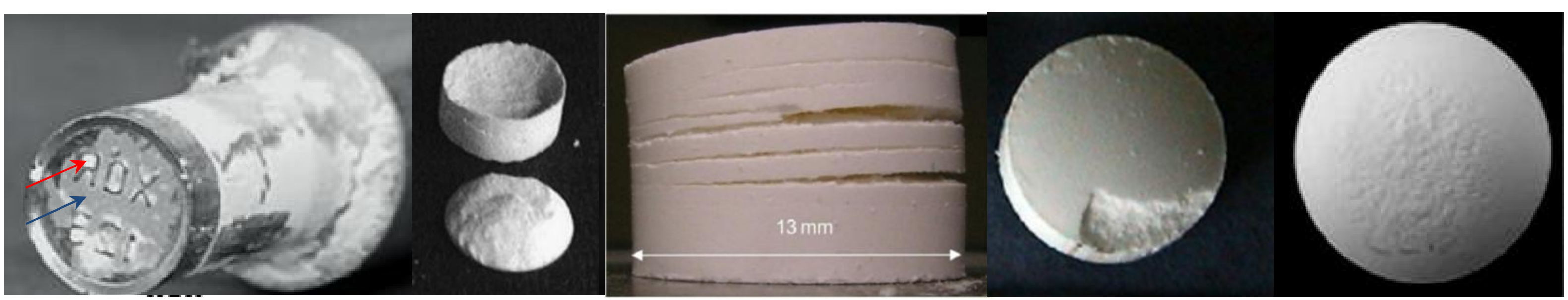
Introduction

- Tablets are a common oral solid dosage form
- Much is understood about the powder compaction process
  - Decades of manufacturing experience
  - Lab-based tools (e.g. compaction simulators)
  - Computational tools (e.g. FEM simulation)
- Despite the extensive experience with compaction, some issues are still observed in development and commercial tableting operations



Picking (Red) / Sticking (Blue) | **Capping** | **Lamination** | **Chipping** | **Erosion**



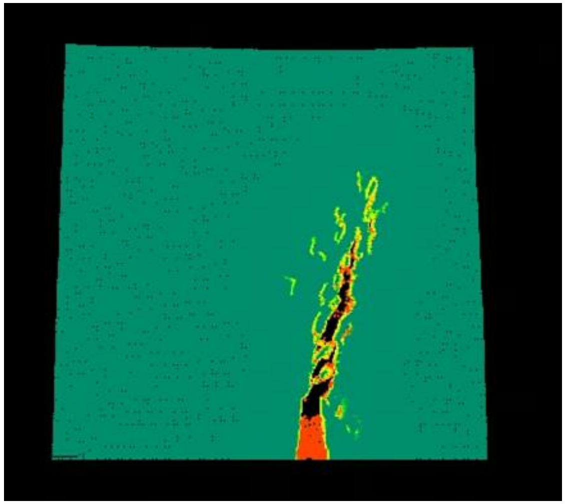
Simmons and Gierer, (2011) | Wu et al., (2007) | Anuar and Briscoe, (2010) | Wu et al., (2007) | Sinka et al., (2004)

Objectives

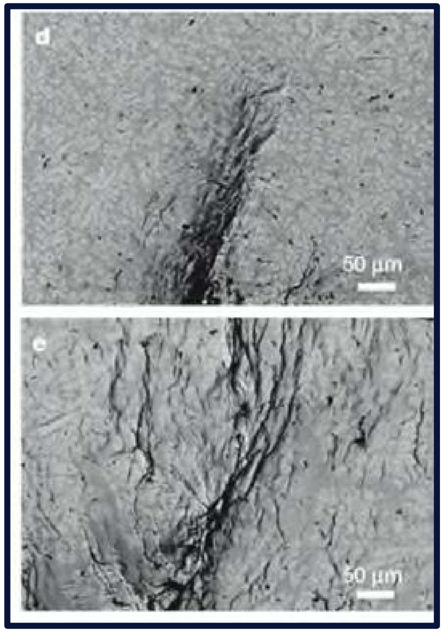
- Develop a peridynamics-based simulation approach to predict tablet robustness and fracture
  - Focus on unloading and ejection stages of the compaction process
- Predict tablet robustness (modes of tablet breakage) for
  - varying process conditions,
  - tooling geometries, and
  - material properties (as characterized by Drucker-Prager Cap model)
- Objectives aim to improve predictive capabilities for tablet failure, provide insight into breakage modes, and guide improvements to formulation/process.

Background – What is Peridynamics?

- A generalization of the standard theory of solid mechanics that allows fracture within its basic equations
  - Seamlessly models the transition from continuous deformation to fracture.



Peridynamic simulation

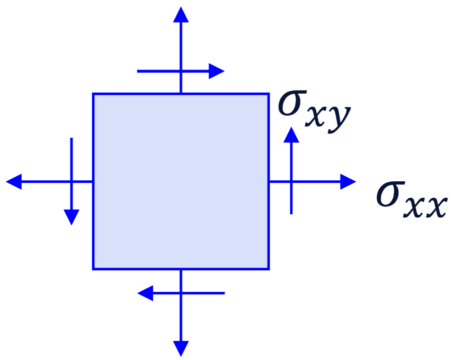


Metallic glass crack tip
Images: Hofmann et al, 2008

First paper on peridynamics: Silling SA. Reformulation of elasticity theory for discontinuities and long-range forces. *Journal of the Mechanics and Physics of Solids*. 2000 Jan 1;48(1):175-209.
Reference book: Madenci E, Oterkus E. *Peridynamic theory and its applications* 2014. Springer, New York, NY.

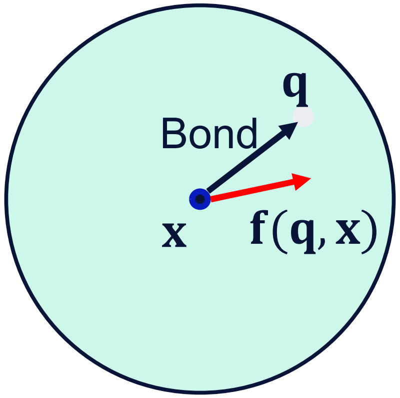
Background – Peridynamic Approach

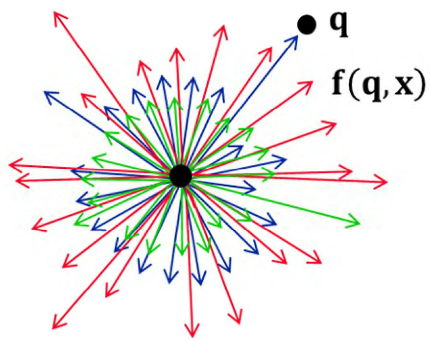
- The standard partial differential equations don't allow discontinuous such as cracks.
- Integral equations can be applied directly on discontinuities.



$$\frac{\partial \sigma_{xx}}{\partial x} + \frac{\partial \sigma_{xy}}{\partial y} + b_x = 0$$
$$\frac{\partial \sigma_{yx}}{\partial x} + \frac{\partial \sigma_{yy}}{\partial y} + b_y = 0$$

PDEs of standard solid mechanics





Peridynamic integral equation

$$\int_{\mathcal{H}} \mathbf{f}(\mathbf{q}, \mathbf{x}) d\mathbf{q} + \mathbf{b}(\mathbf{x}) = 0$$

- The material point $\mathbf{x}$ interacts directly with neighbors $\mathbf{q}$ within its horizon (cutoff distance).
- The bond between $\mathbf{x}$ and $\mathbf{q}$ has a bond force density $\mathbf{f}(\mathbf{q},\mathbf{x})$ (force/volume2).
- $\mathbf{b}(\mathbf{x})$ is the external body force density.
- $\mathcal{H}$ is the family of $\mathbf{x}$ (material points within the horizon).
- The integral sums up all these forces acting on $\mathbf{x}$.

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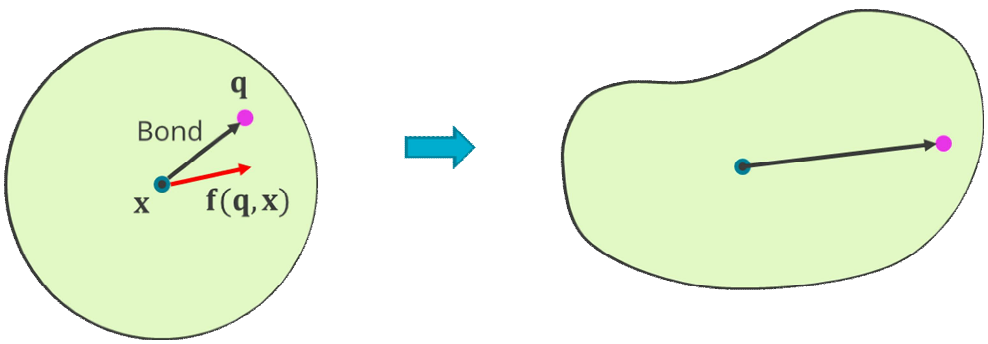
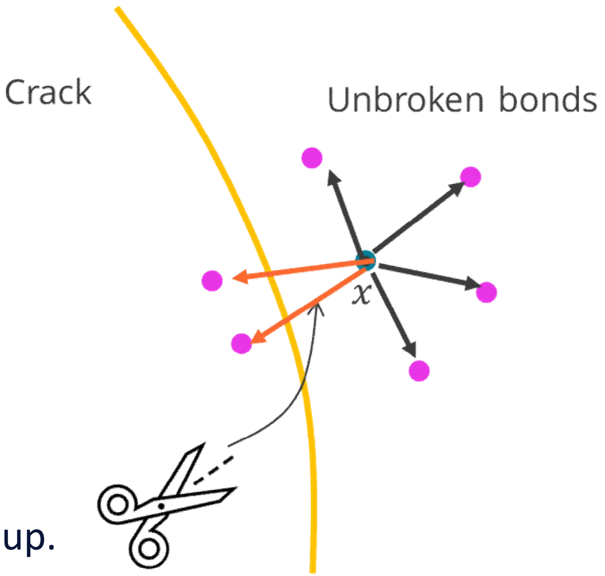
Background – Peridynamic Material Model

- The material model determines $\mathbf{f}(\mathbf{q},\mathbf{x})$ for every $\mathbf{q}$ in $\mathcal{H}$, for every possible deformation of $\mathcal{H}$.
- Any material model from the standard theory can be used.

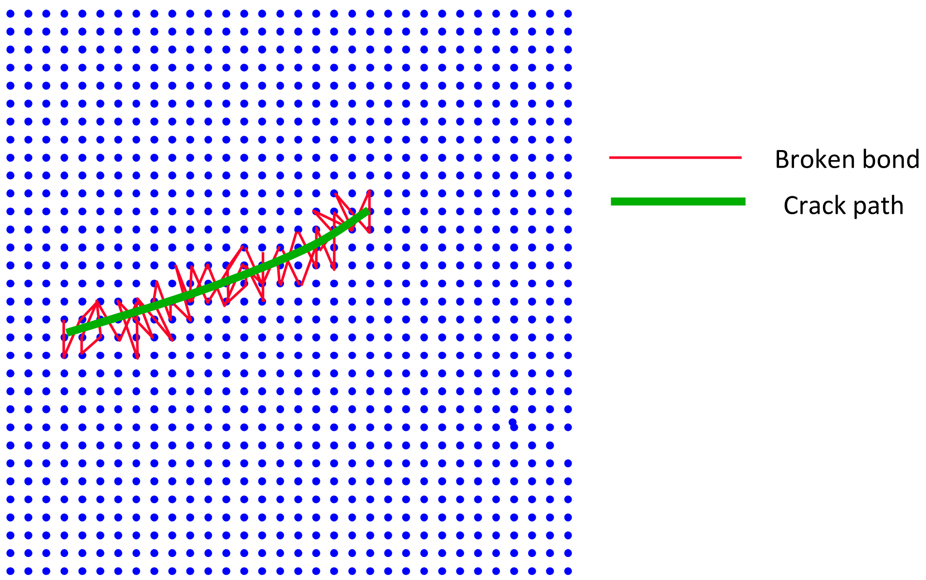


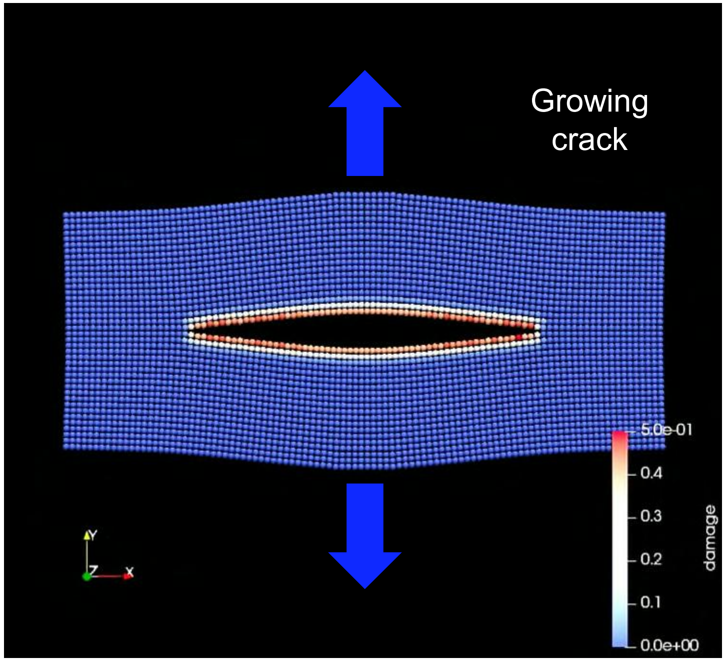


- Bonds can break irreversibly.
- After breakage, a bond cannot carry any tensile load.
- The criterion for bond breakage can be anything you can dream up.
- The simplest criterion is ***critical bond strain***.
  - This criterion is used in the tablet simulations described later, but with dependence of the critical strain on pressure and solid volume fraction.

Autonomous Crack Growth

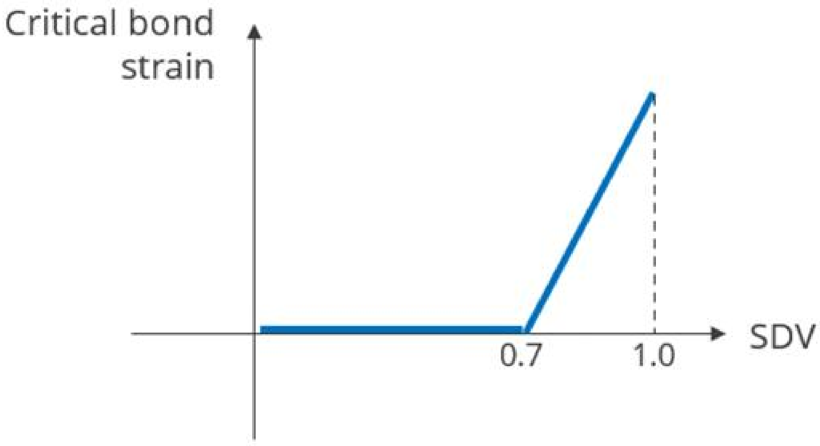
- Bonds break whenever they feel like it.
- When a bond breaks, it becomes more likely that a neighboring bond will also break.



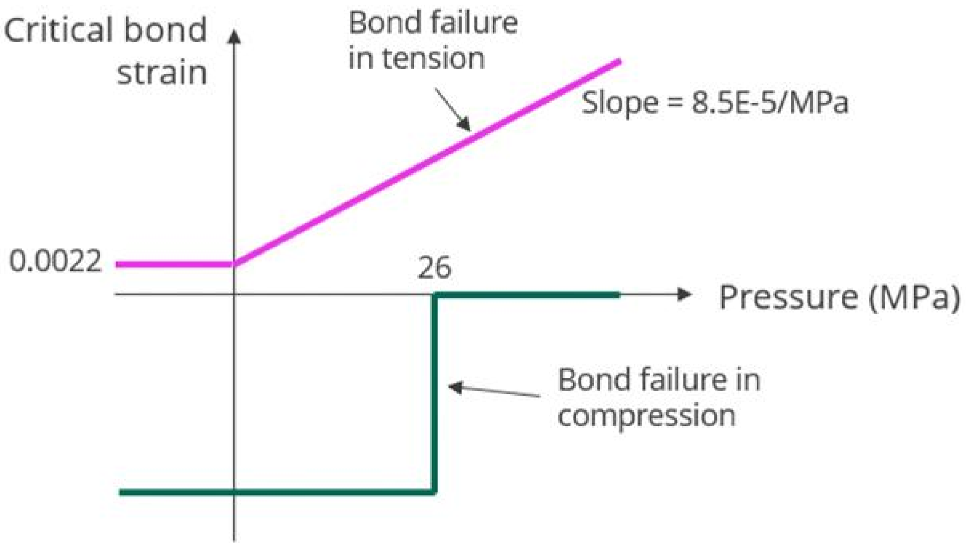


Peridynamic Material Model for Tablet Breakage

- Bond force is linear in strain until failure.
- Bonds fail when their strain ϵ exceeds a critical strain ϵ_c.
- The critical strain depends on:
  - Hydrostatic pressure P.
  - Solid volume fraction (SDV).
- Parameters are calibrated from diametral compression & axial compression tests.



Bond failure dependence on solid volume fraction



Bond failure dependence on pressure

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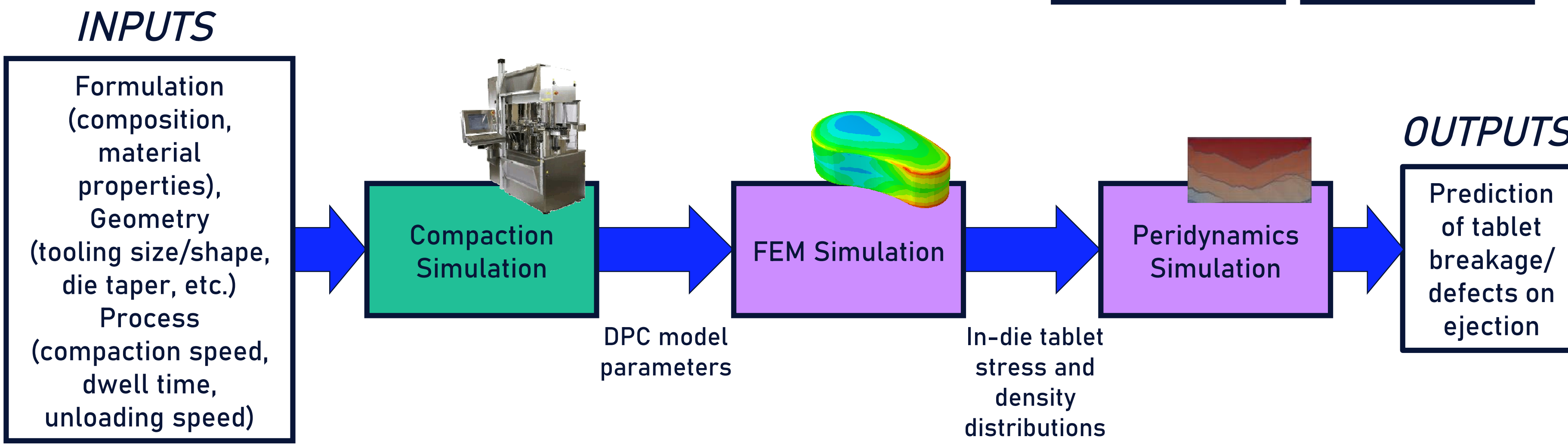
Future Workflow Envisioned

Lab-based Experiments

Computational

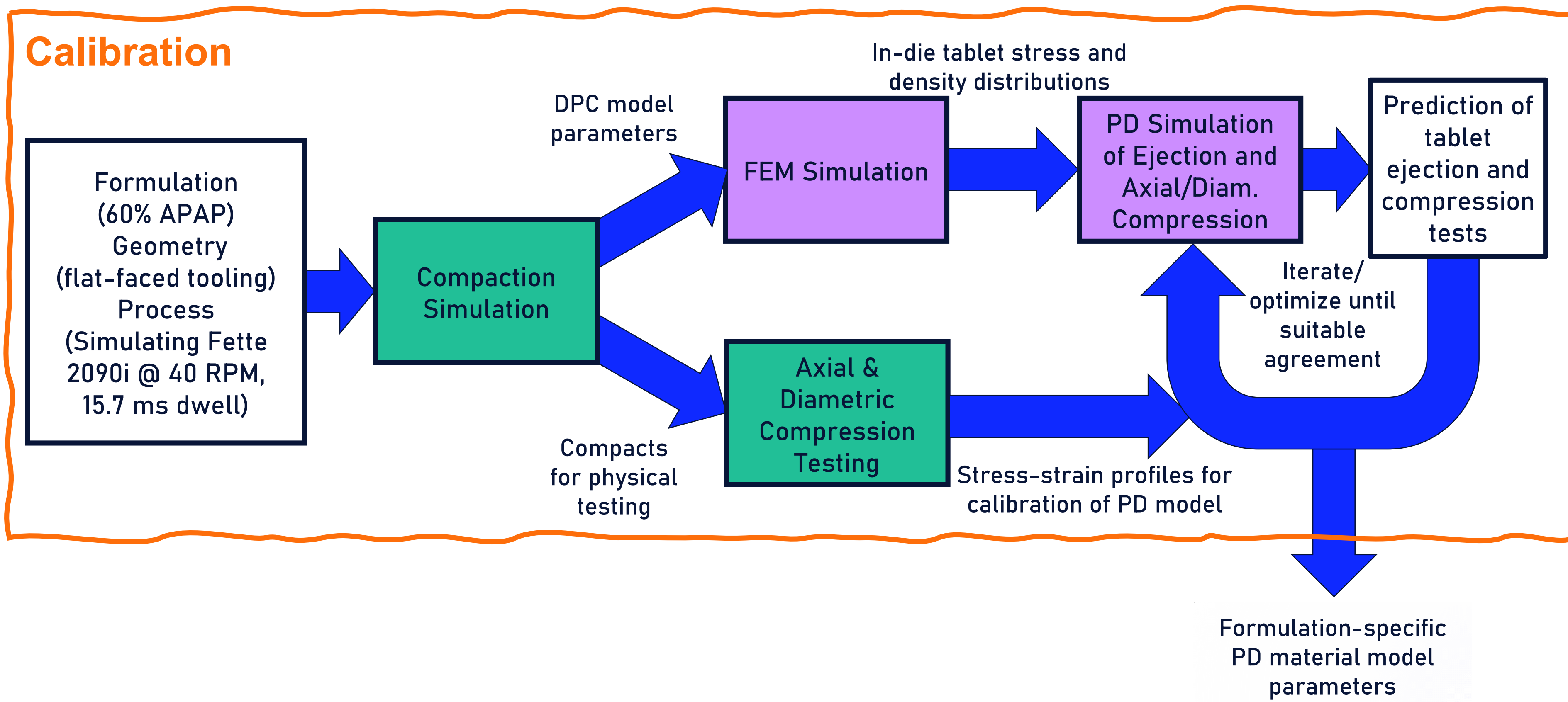


- Material-sparing, predictive approach to guide tablet development
- More responsive troubleshooting of compaction issues
    - The performance of each tooling iteration can be assessed *in silico*

Workflow for Model Development

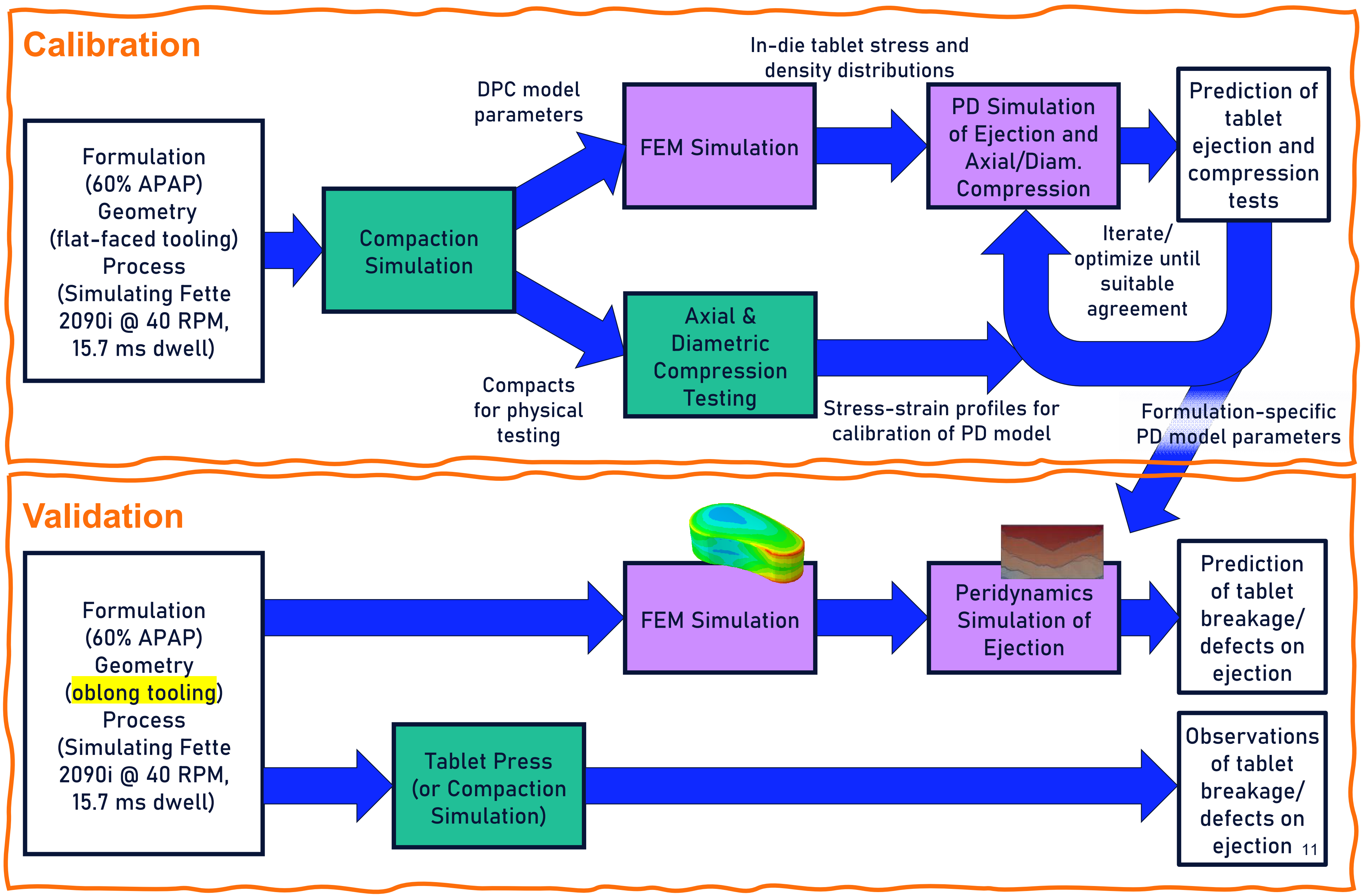
Lab-based Experiments

Computational



Workflow for Model Development

Lab-based Experiments
Computational



Calibration Inputs

- Formulation
  - 60% Acetaminophen (APAP)
  - 39% Avicel PH102 (MCC)
  - 1% Silicon Dioxide MP5
- Geometry
  - 10 *mm* diameter flat-faced tooling
  - Straight wall die
- Process Conditions – Compacts for Axial Compression Testing
  - Fill weights: ~300 mg
  - Compaction pressures: ~200 MPa
  - Thickness: ~3.50 mm (fixed)
- Process Conditions – Compacts for Diametric Compression Testing
  - Fill weights: ~750 mg
  - Compaction pressures: ~230 MPa
  - Thickness: ~7.7 mm (fixed)

Formulation (composition, material properties), Geometry (tooling size/shape, die taper, etc.) Process (compaction speed, dwell time, unloading speed)

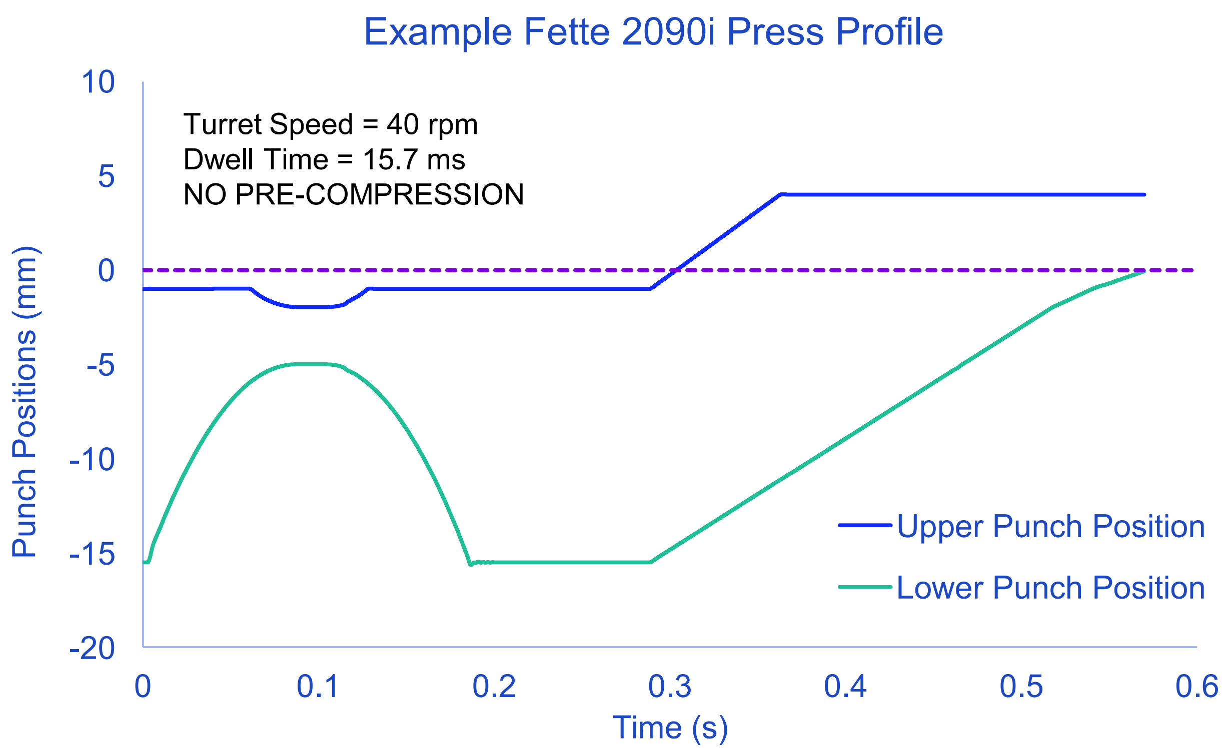
Resulting Solid Fractions (axial compression compacts):

In-die (SDV):	0.97
Out-of-die:	0.86

Resulting Solid Fractions (diametric compression compacts):

In-die (SDV):	0.97
Out-of-die:	0.89

Compaction Simulation



- Fette 2090i tablet press was simulated using a Huxley-Bertram compaction simulator
- All tablets produced in this study used a similar press profile with only changes in main compression gaps – turret speed and dwell time were the same for all tablets produced

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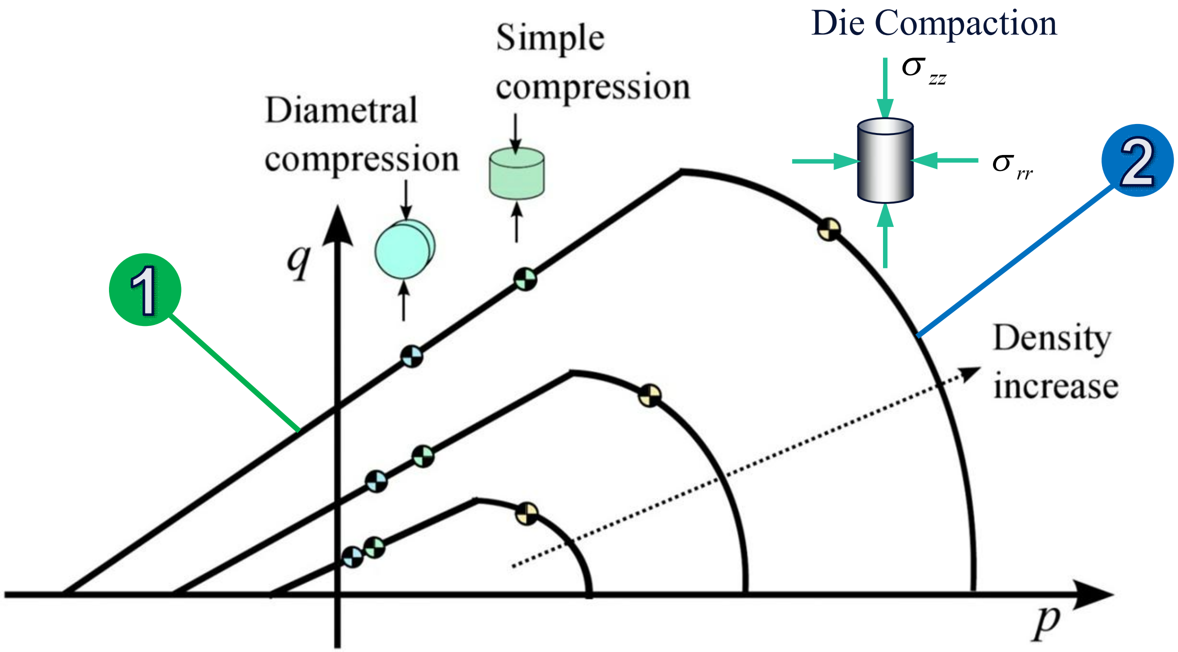
Compaction Simulation for DPC Model Calibration



- Describes the limit to elastic deformation
- One curve per relative density (denser=stronger)
- Calibrated easily by press simulator experiments

1 **Diametral and Simple Compression Strength Tests**

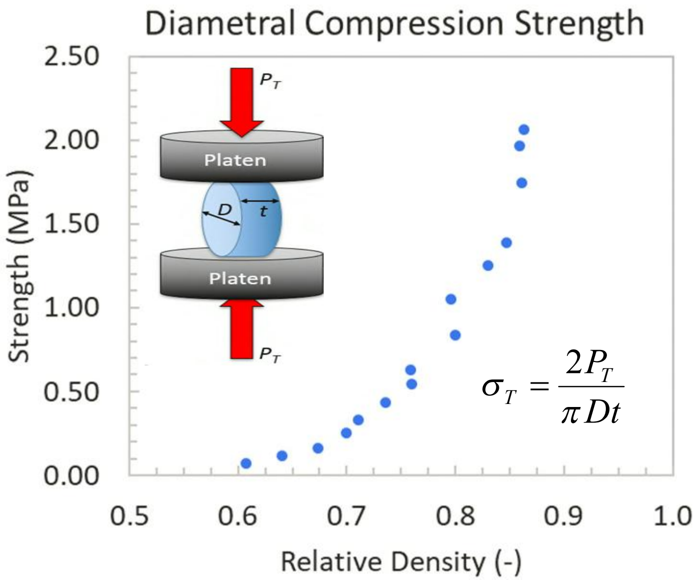
❖ Two tests per density level

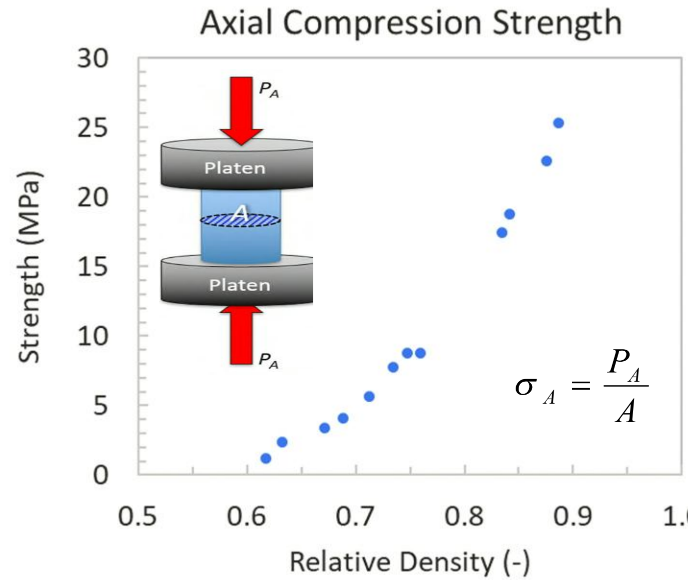
2 **Fully Instrumented Die Compaction Experiments**

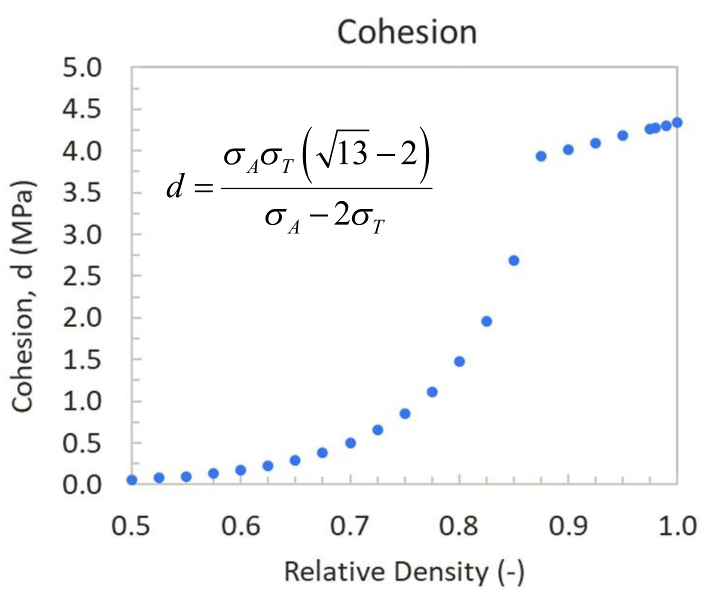
❖ Only one experiment required for all densities

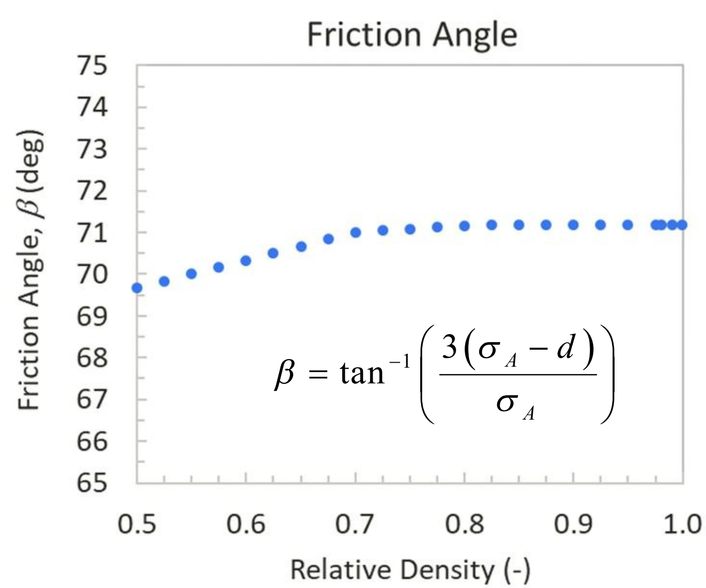
Compaction Simulation – DPC Shear Failure Surface Calibration

- Following Cunningham, et al., (2004) and Han, et al., (2008)



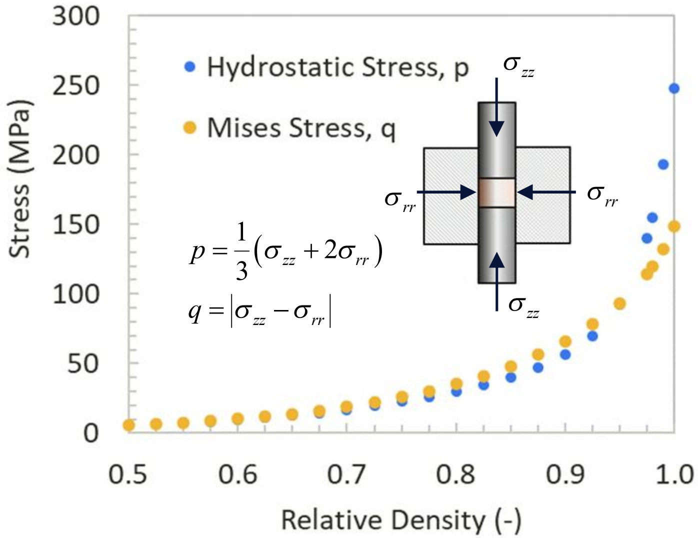


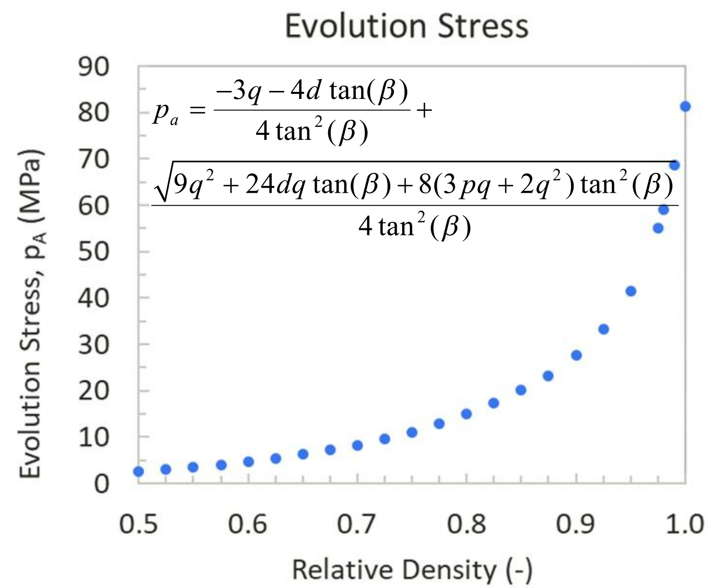


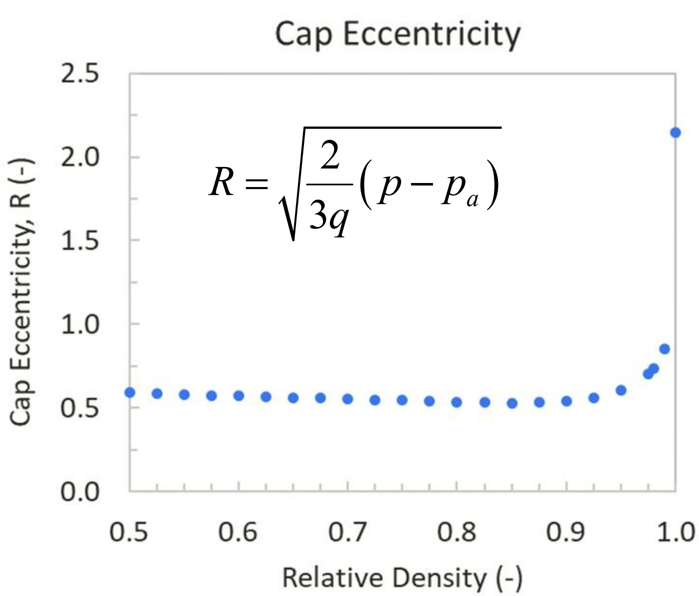


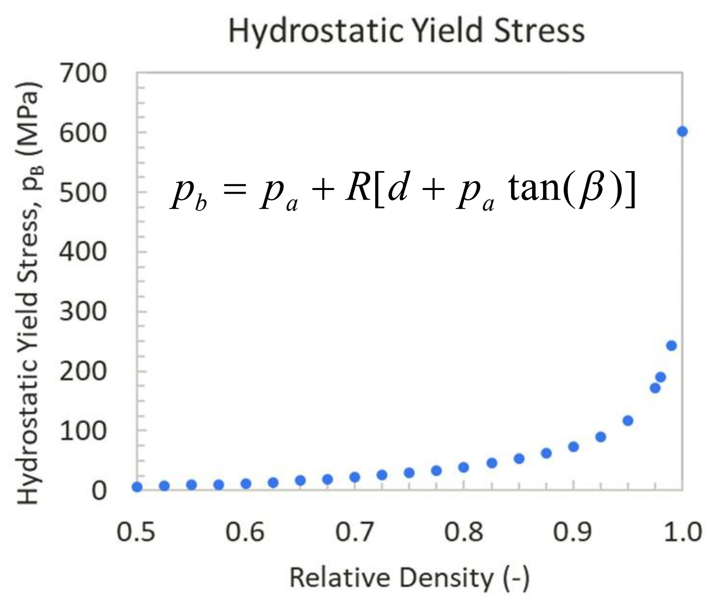
Compaction Simulation – DPC Cap Surface Calibration

- Following Cunningham, et al., (2004) and Han, et al., (2008)



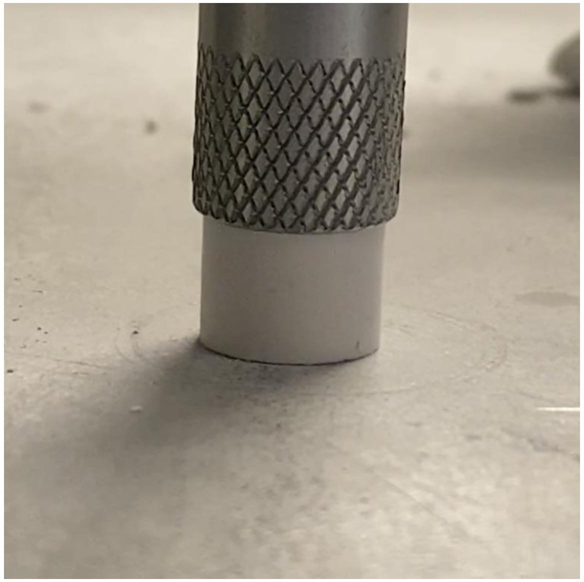


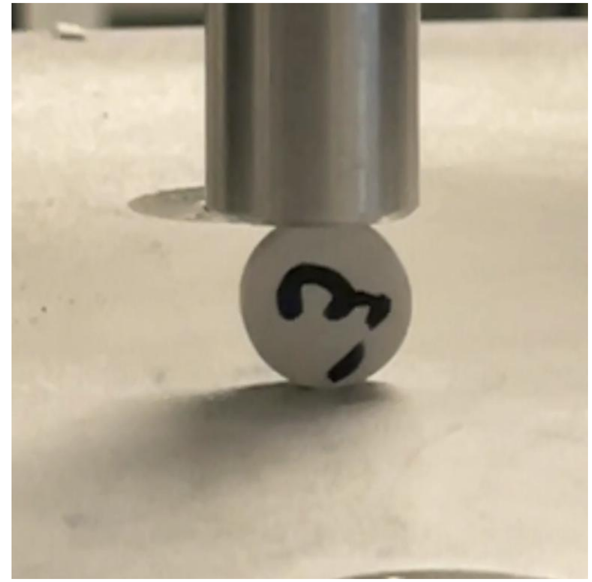




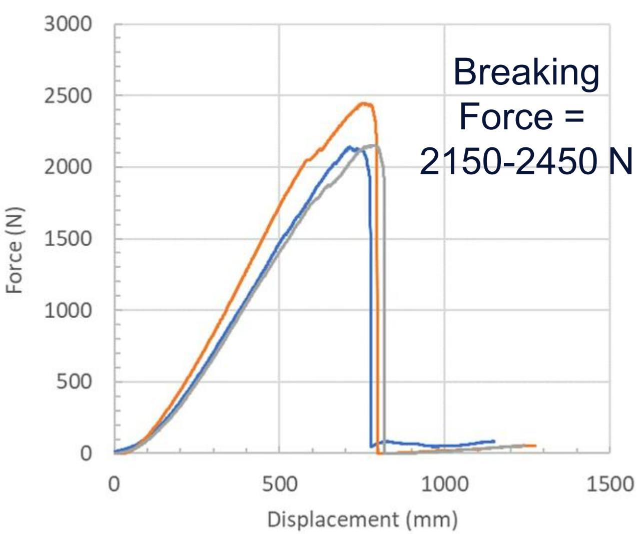
Calibration Experiments

Axial & Diametric Compression Testing

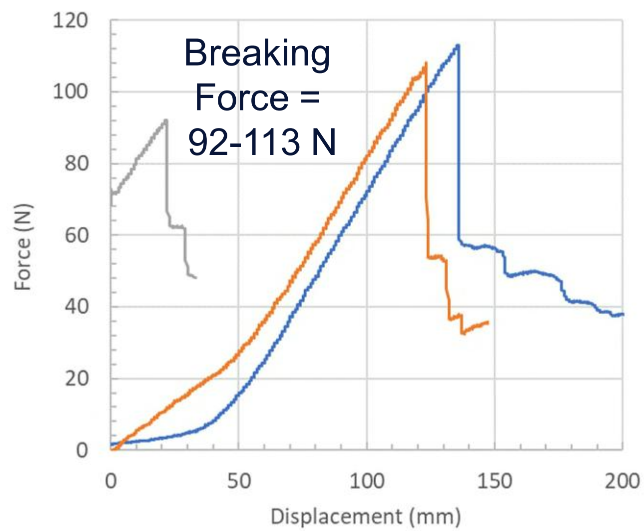




Axial Compression

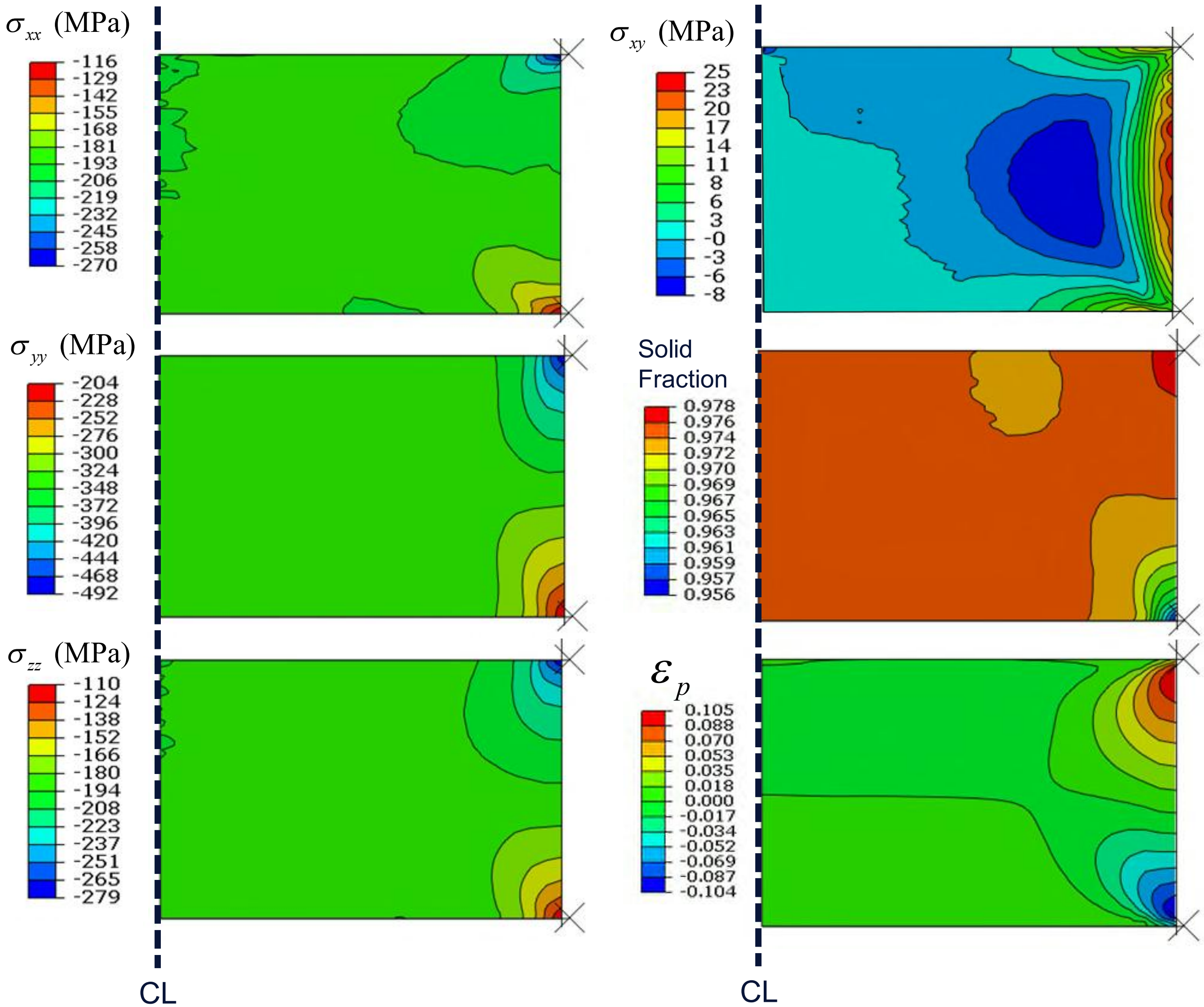


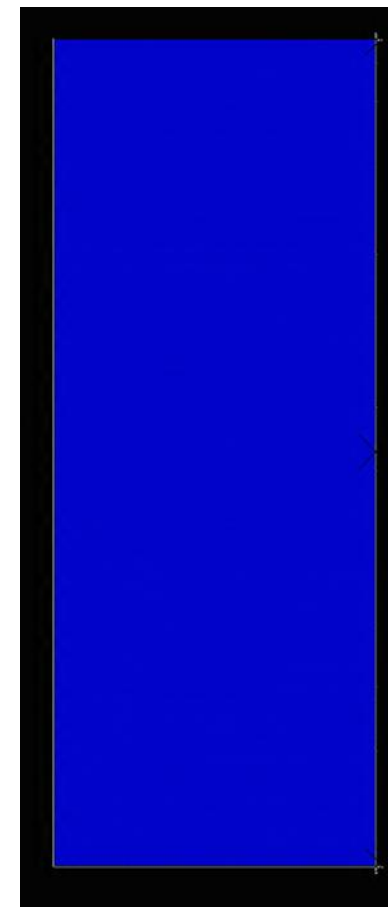
Diametric Compression



FEM Simulation

- FEM simulations of powder compression
- The final compressed, in-die state becomes the input to the peridynamics simulation





Peridynamics Simulation – Overview

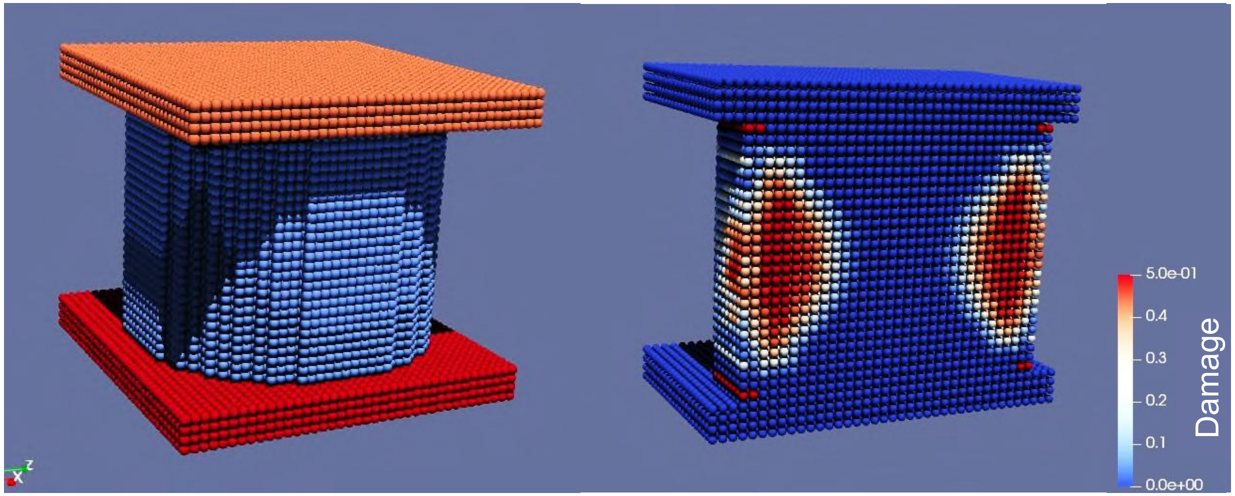
PD Simulation of Ejection and Axial/Diam. Compression

- Inputs for PD simulation
  - DPC material model parameters from compaction simulation
  - In-die tablet stress and solid fraction distribution from FEM
  - Compression conditions as desired
- PD simulates same process as used in the experiments:
  - (1) Ejection of tablet from die
  - (2) Axial or diametric compression test

Peridynamics Simulation – Axial Compression

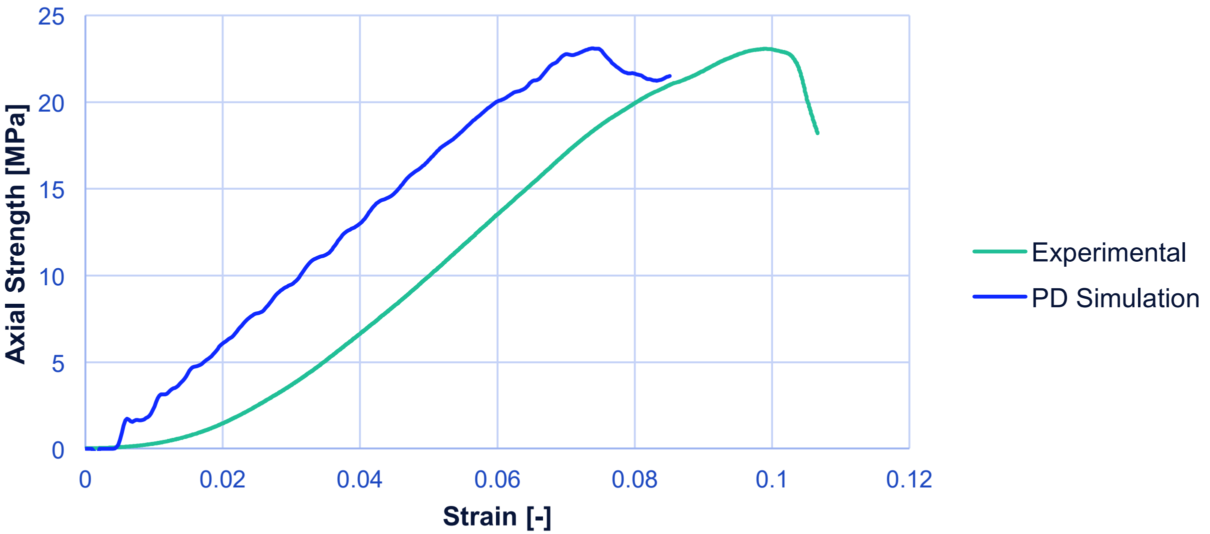
PD Simulation of Ejection and Axial/Diam. Compression

- Simulated mechanical testing (SDV ≈ 0.97)



Initial State

Start of failure



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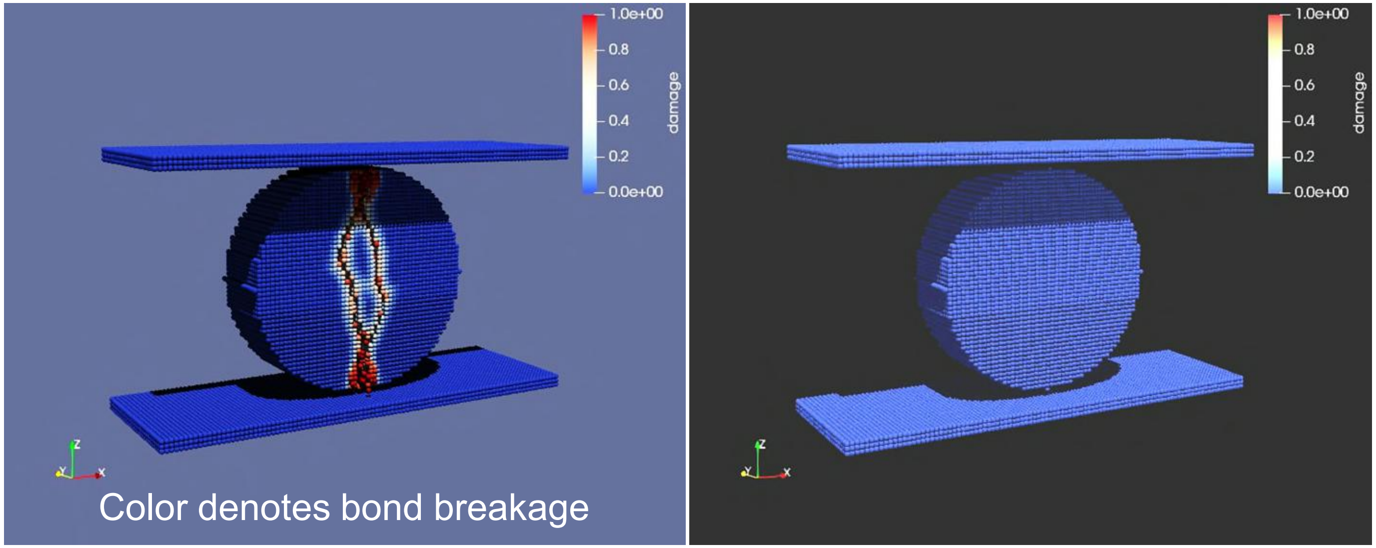
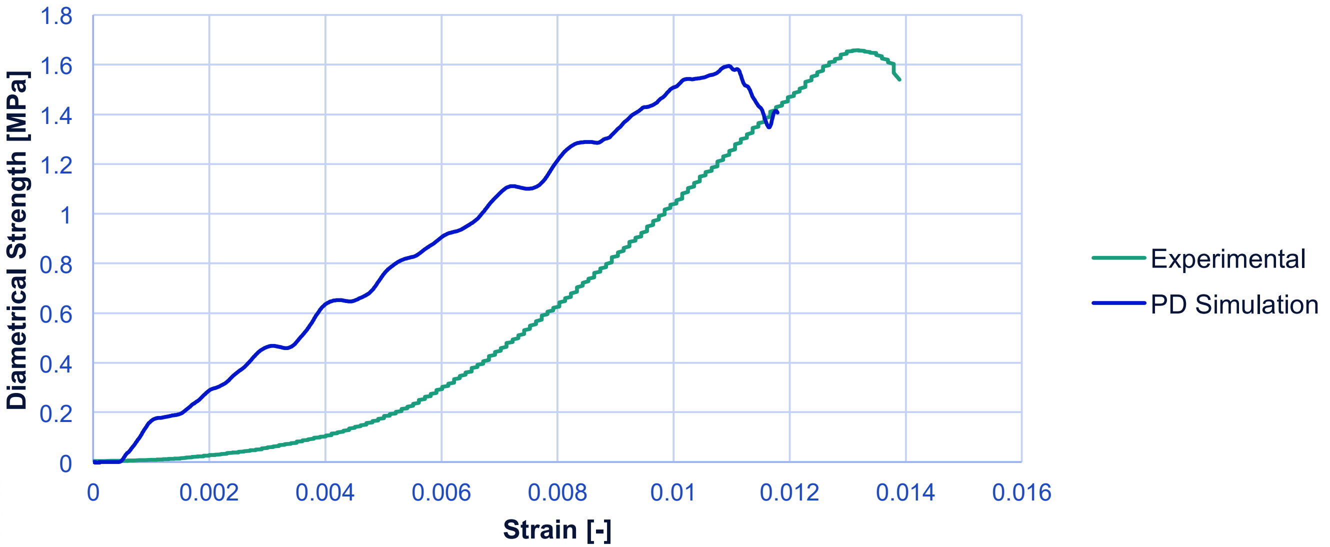
Peridynamics Simulation – Diametric Compression

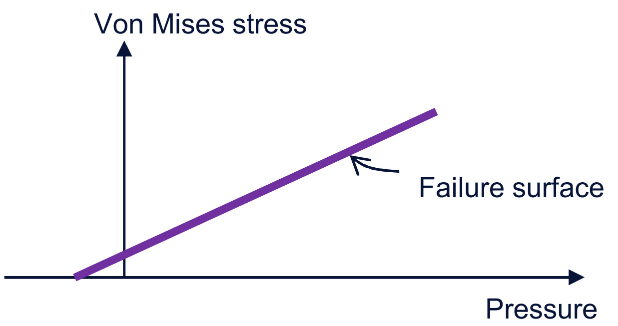
PD Simulation of Ejection and Axial/Diam. Compression

- Simulated mechanical testing (SDV ≈ 0.97)



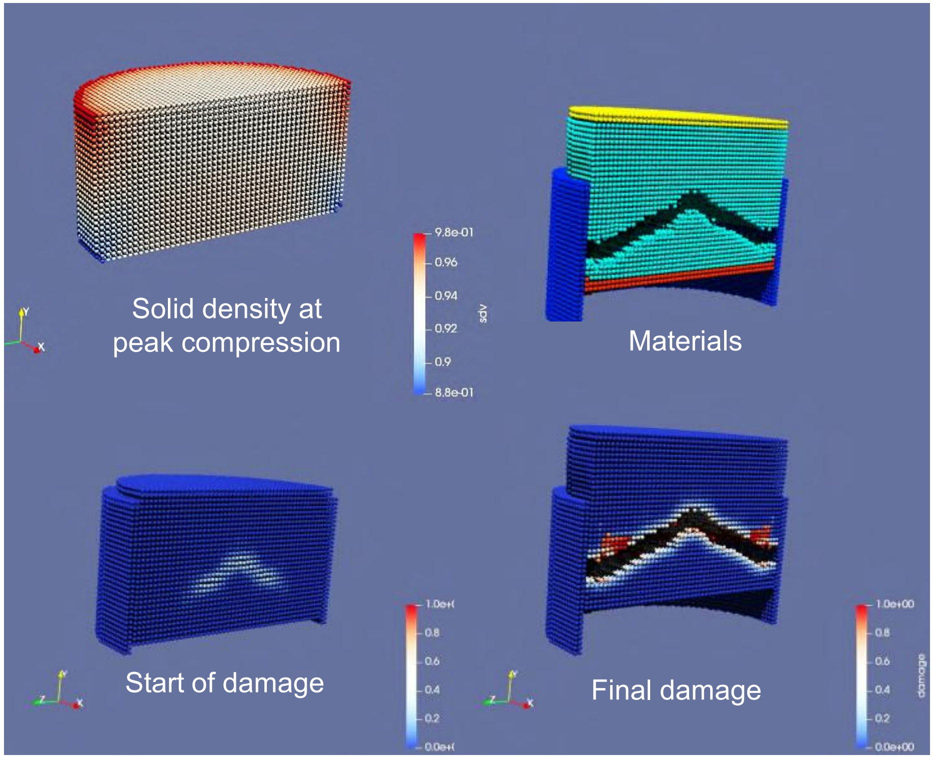


Drucker-Prager failure model during ejection



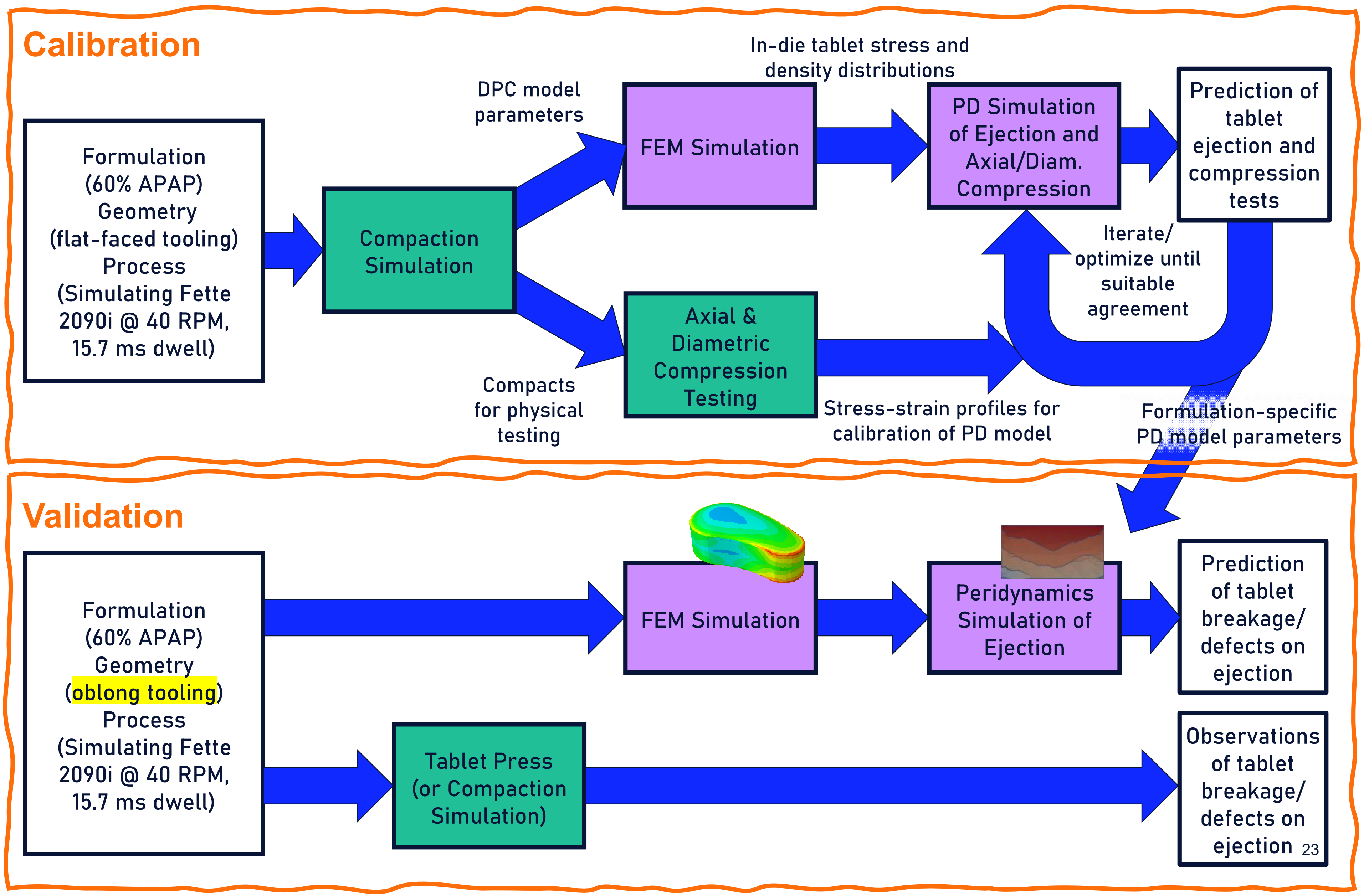
Tablet “capping” failure
Image: merlin-pc.com

Ejection of a pharmaceutical tablet from a rotary press



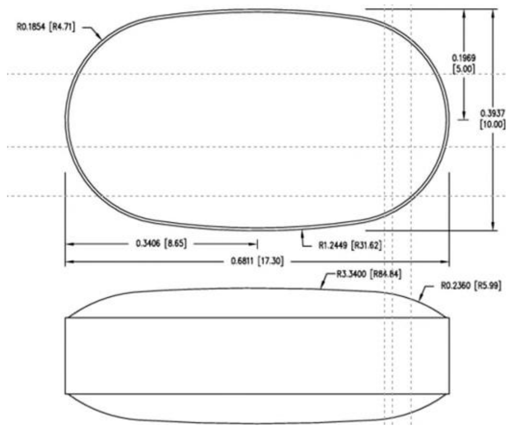
Workflow for Model Development

Lab-based Experiments | Computational



Validation Inputs

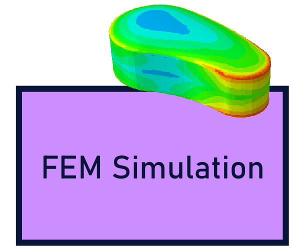
- Formulation [same as before]
  - 60% Acetaminophen (APAP)
  - 39% Avicel PH102 (MCC)
  - 1% Silicon Dioxide MP5
- Geometry [different tablet shape]
  - 10 *mm* x 17.3 *mm* oblong tooling
  - Straight wall die
- Process Conditions [different]
  - Fill weight: ~900 mg
  - Compaction pressure: ~200 MPa
  - Thickness: ~6.5 mm

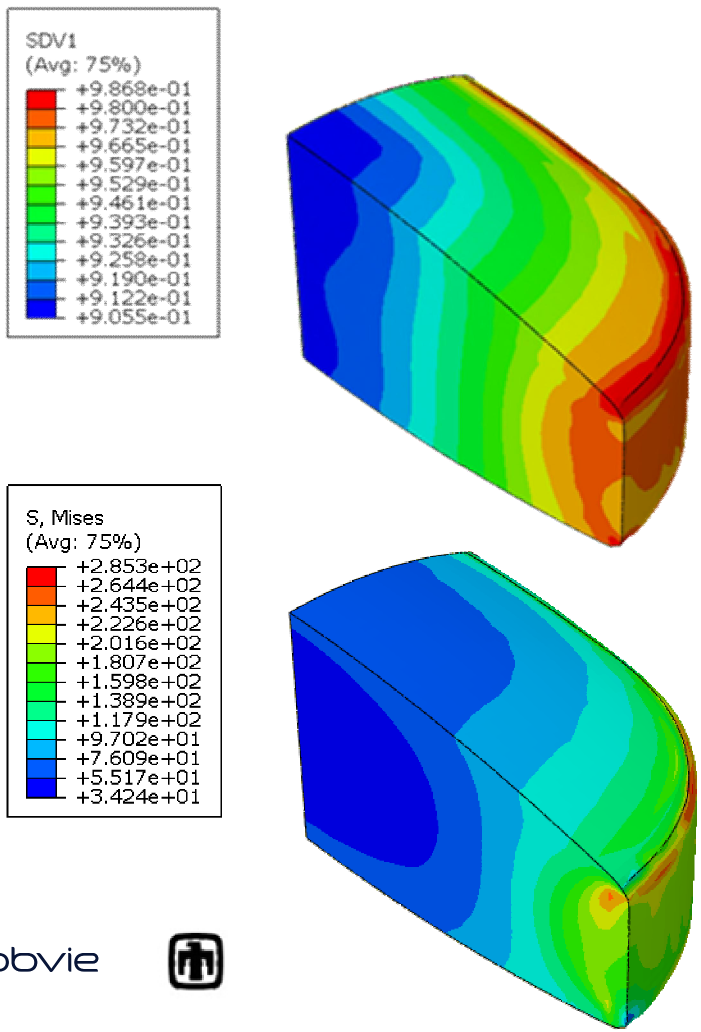


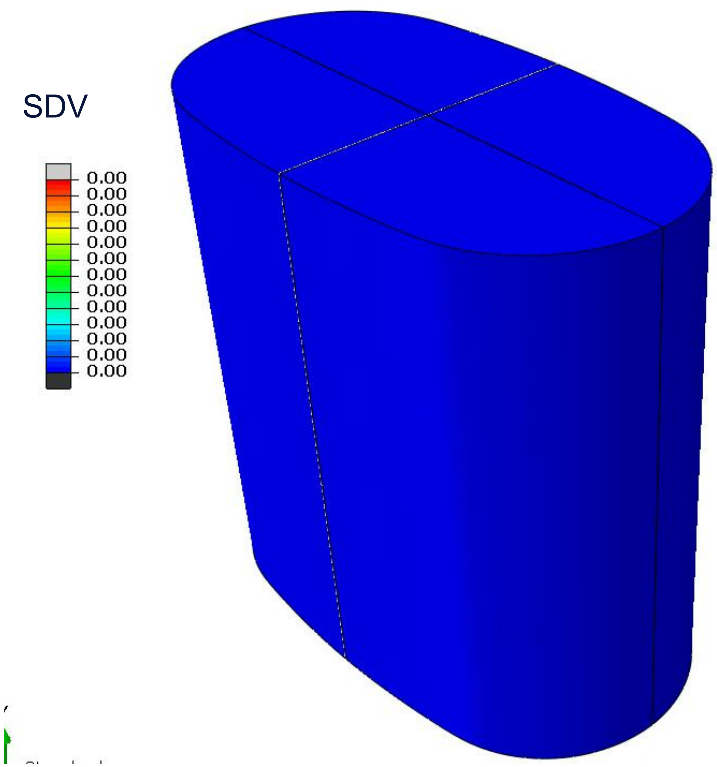
Formulation (60% APAP)
Geometry (oblong tooling)
Process (baseline compaction conditions)

FEM Simulation

- FEM simulations of the compaction (only) of the oblong tablet
- DPC material model parameters as before

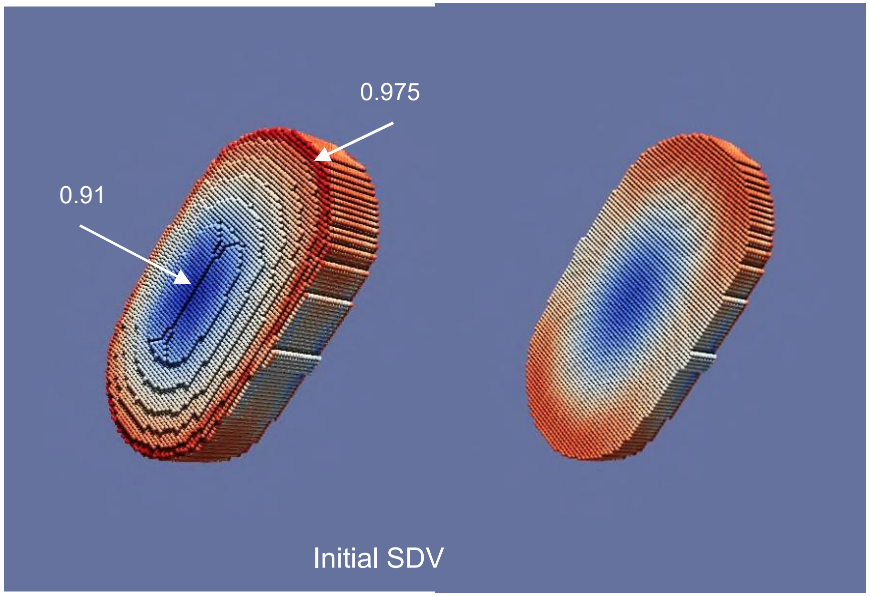


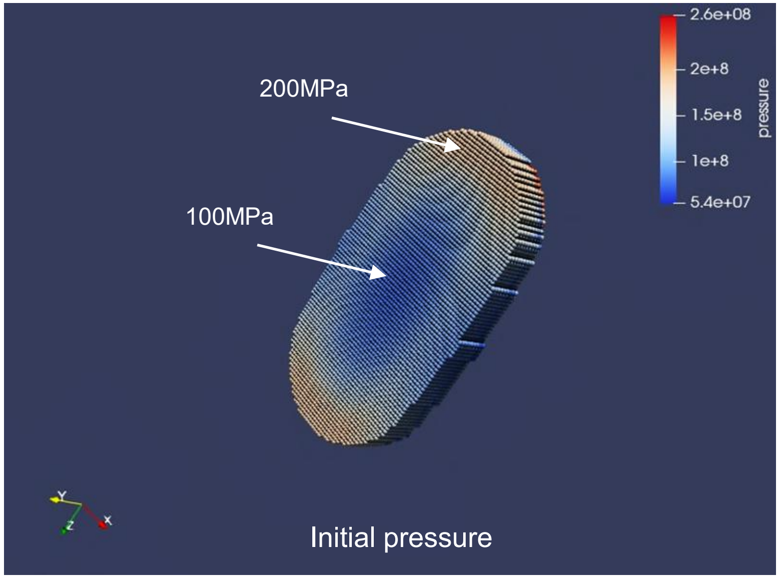


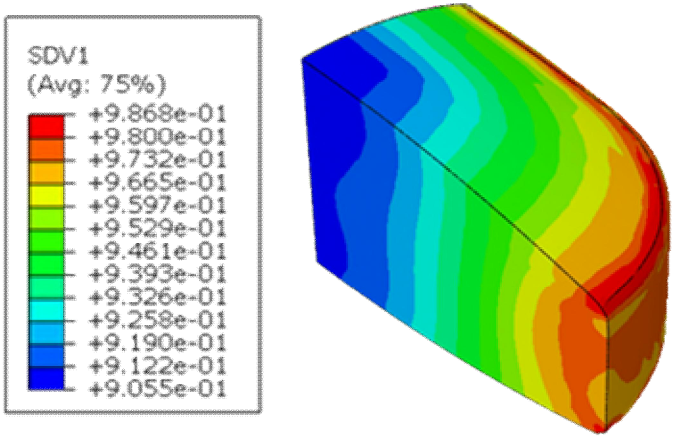


Peridynamics Simulation of Ejection

Peridynamics Simulation of Ejection





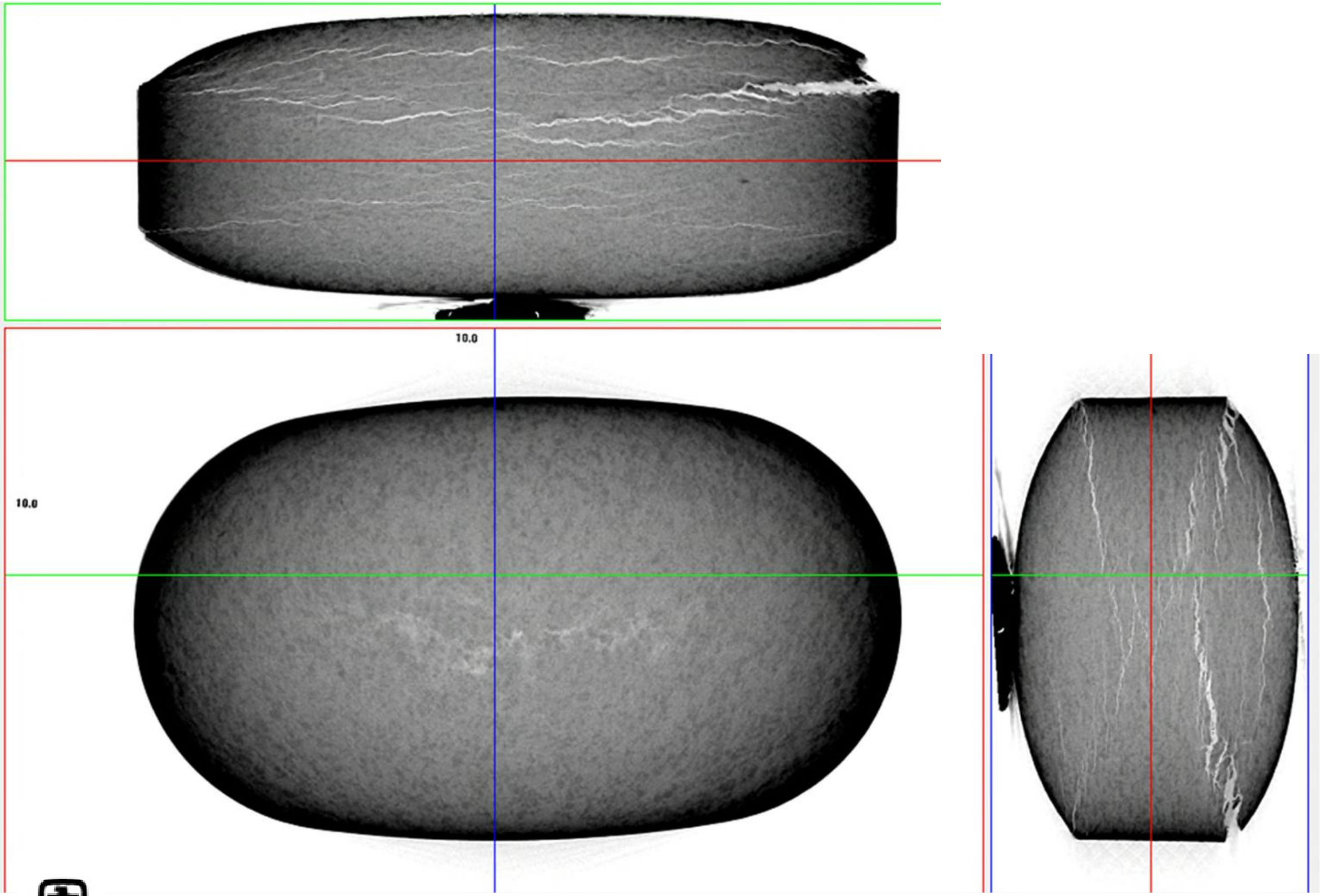


- The PD simulation of ejection is initialized from an Abaqus simulation of compression.
- The initial pressure and solid fraction vary significantly with position.

Experimental Observations – Oblong Tablet

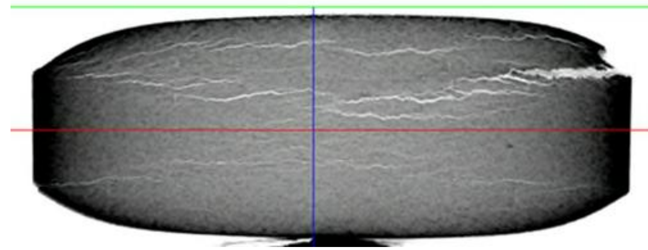
Tablet Press (or Compaction Simulation)

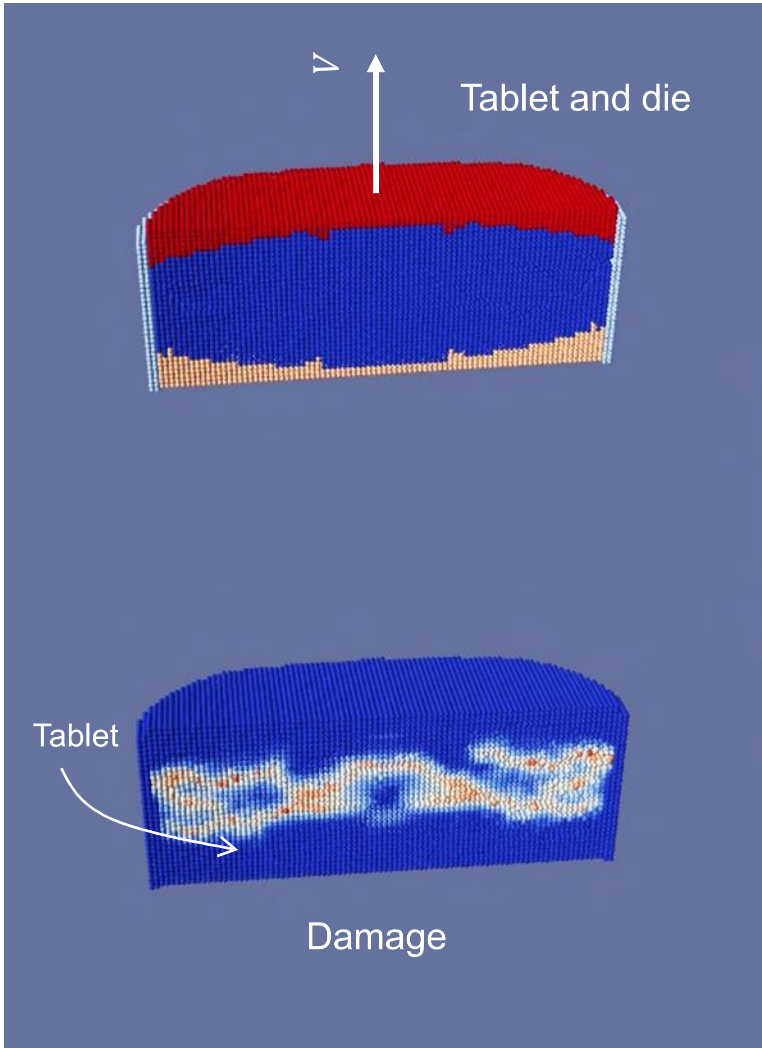
- Post-ejection μCT
- Significant damage occurs during ejection

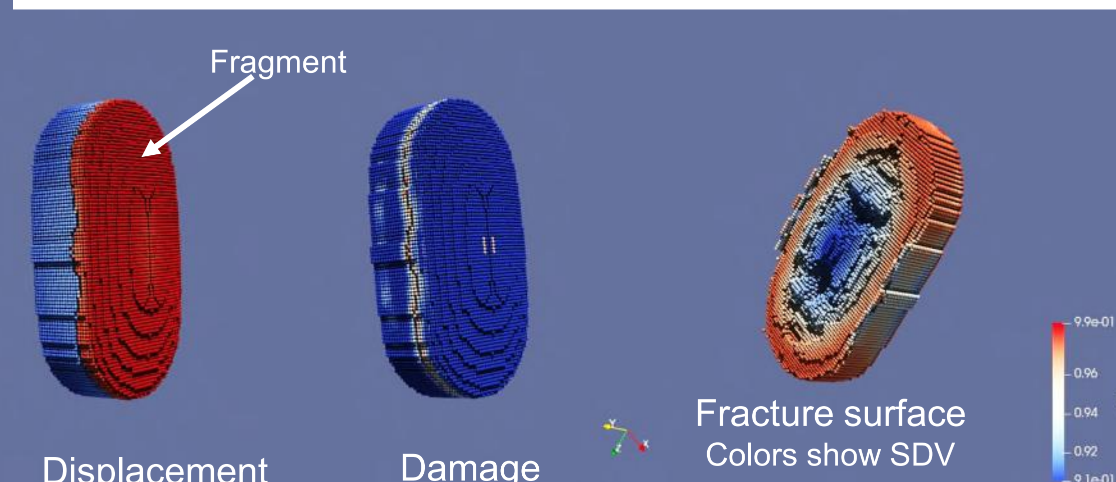


Peridynamics Simulation Prediction of Ejection

Peridynamics Simulation of Ejection





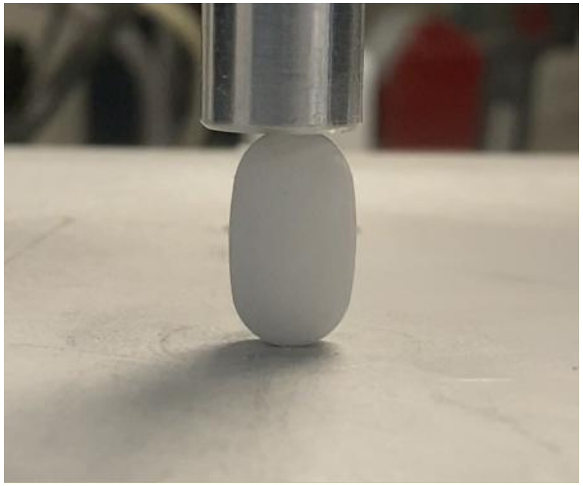


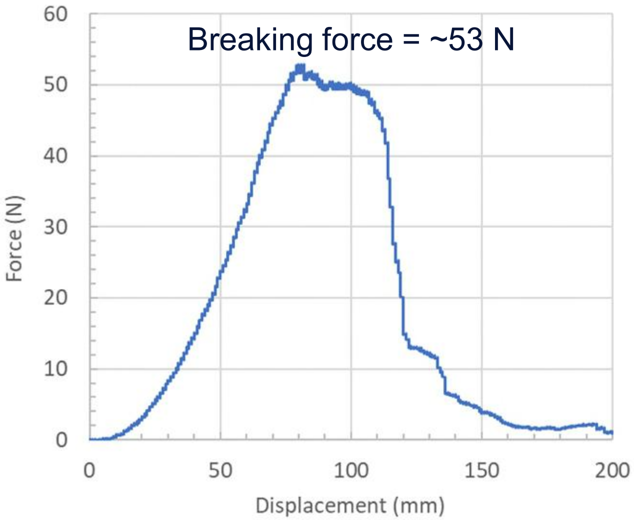
- For this tablet, the ejection simulation predicts a complete fracture and additional internal damage.
- Drucker-Prager condition is used as a nucleation condition for damage.
- Fracture surface is rough.

Experimental Observations – Oblong Tablet

Tablet Press (or Compaction Simulation)

- Mechanical Testing





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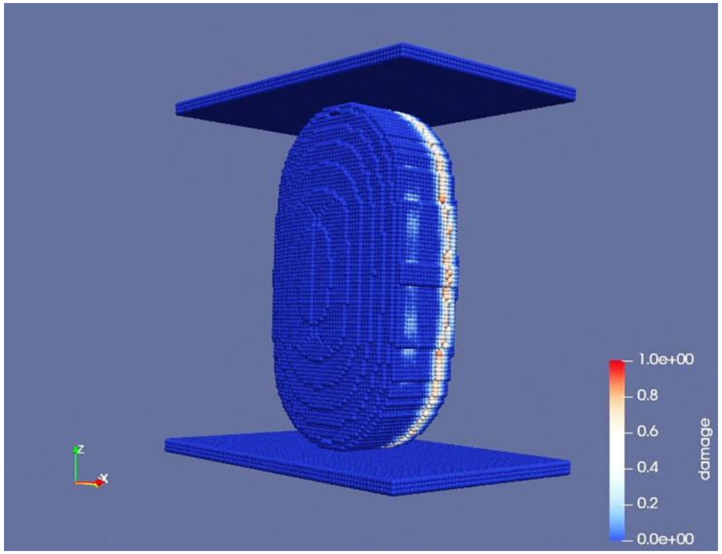
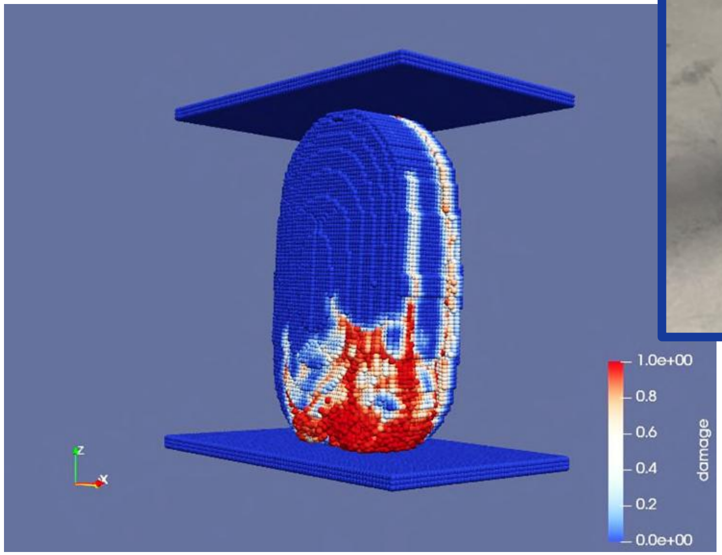
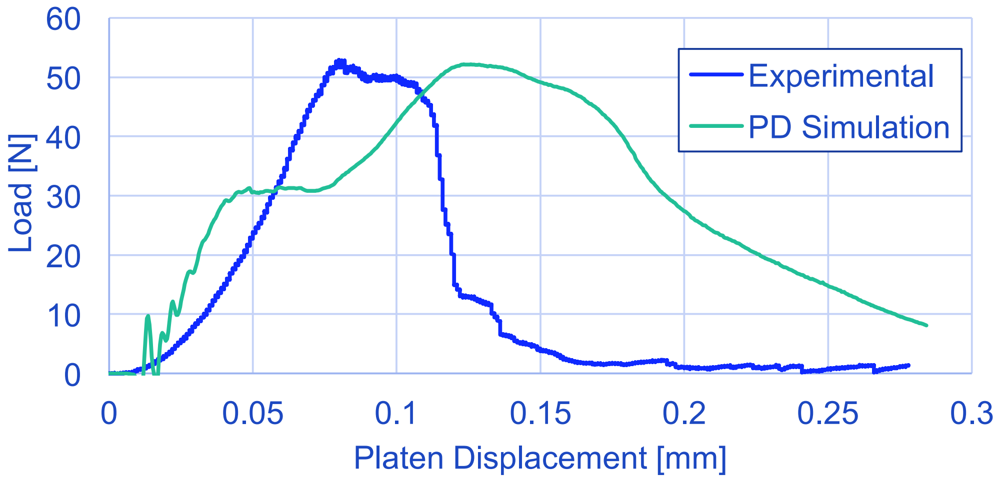
Mechanical Testing Peridynamics Simulation Prediction



Start of diametral compression
Colors show damage



Post-failure
Colors show damage

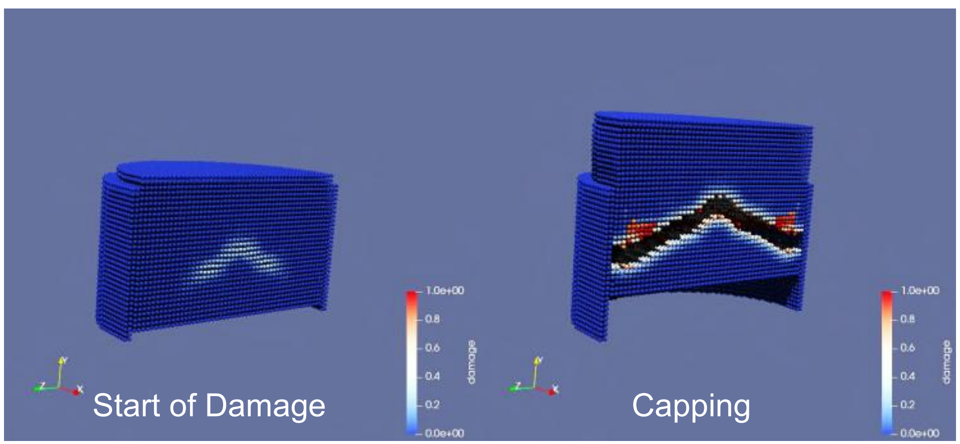


- The post-ejection tablet model, including damage, is then subjected to compression.
- Failure load is ~52 N.

Summary & Future Work

- The use of peridynamics for prediction of tablet breakage looks promising
  - Material-sparing, predictive approach to guide tablet development and troubleshooting
- Presented a general workflow for calibration and validation
  - Quantitative agreement on breaking force
  - Qualitative agreement on damage / breakage pattern
  - Working on refinements for improved predictions

Peridynamics prediction of tablet capping



Good agreement with experimental observations of Wu et al. (2008).

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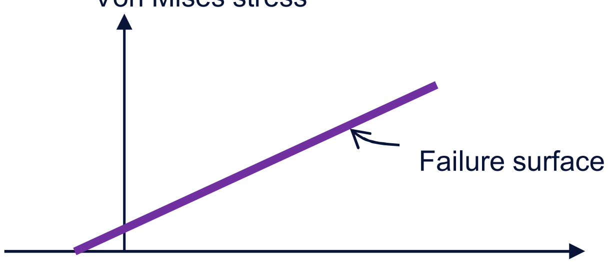
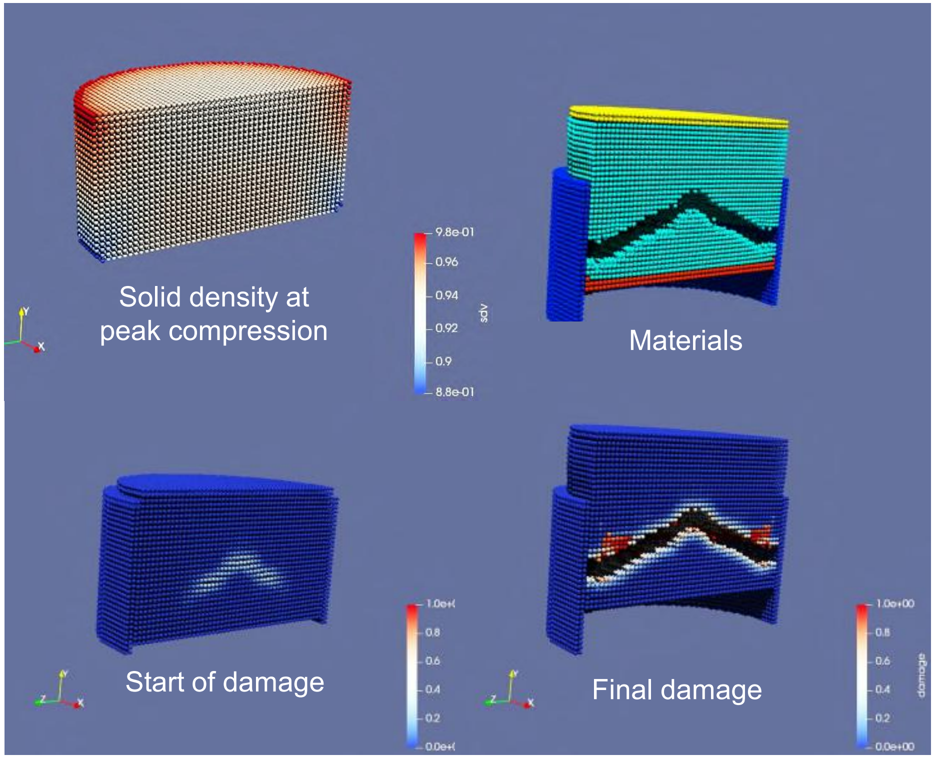
Drucker-Prager failure model during ejection



Tablet “capping” failure
Image: merlin-pc.com

Ejection of a pharmaceutical tablet from a rotary press



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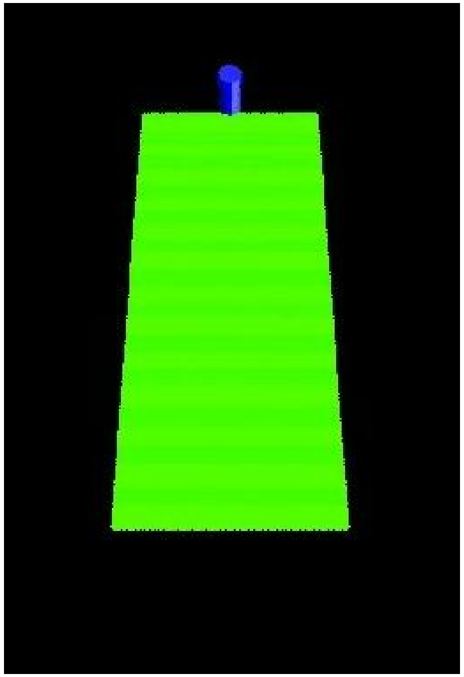
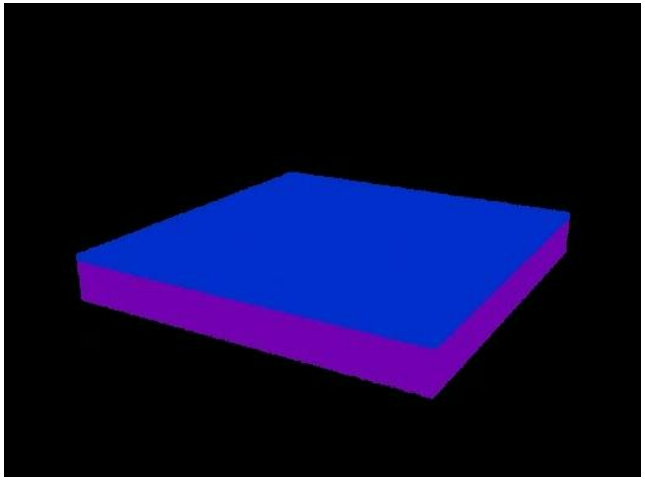
Fun applications

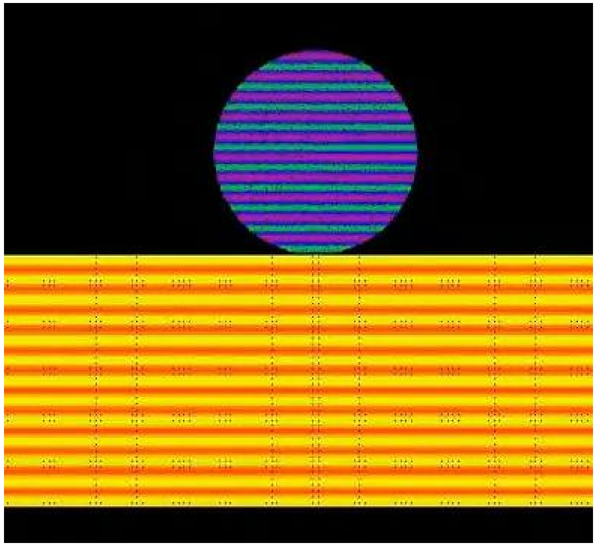
VIDEOS



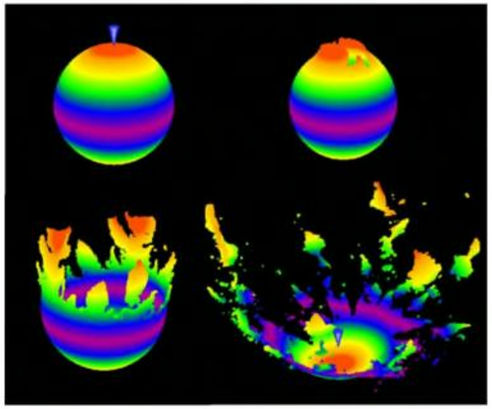
Unstable crack path in a polyethylene membrane



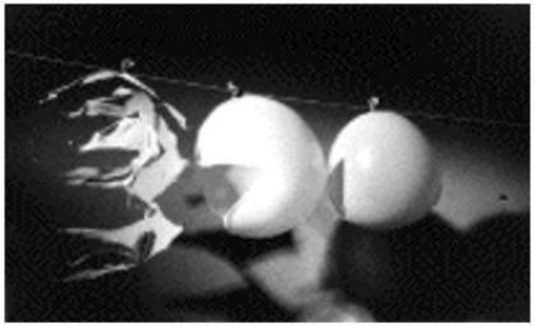
Peeling of tape



Grinding
(includes friction in short-range forces)



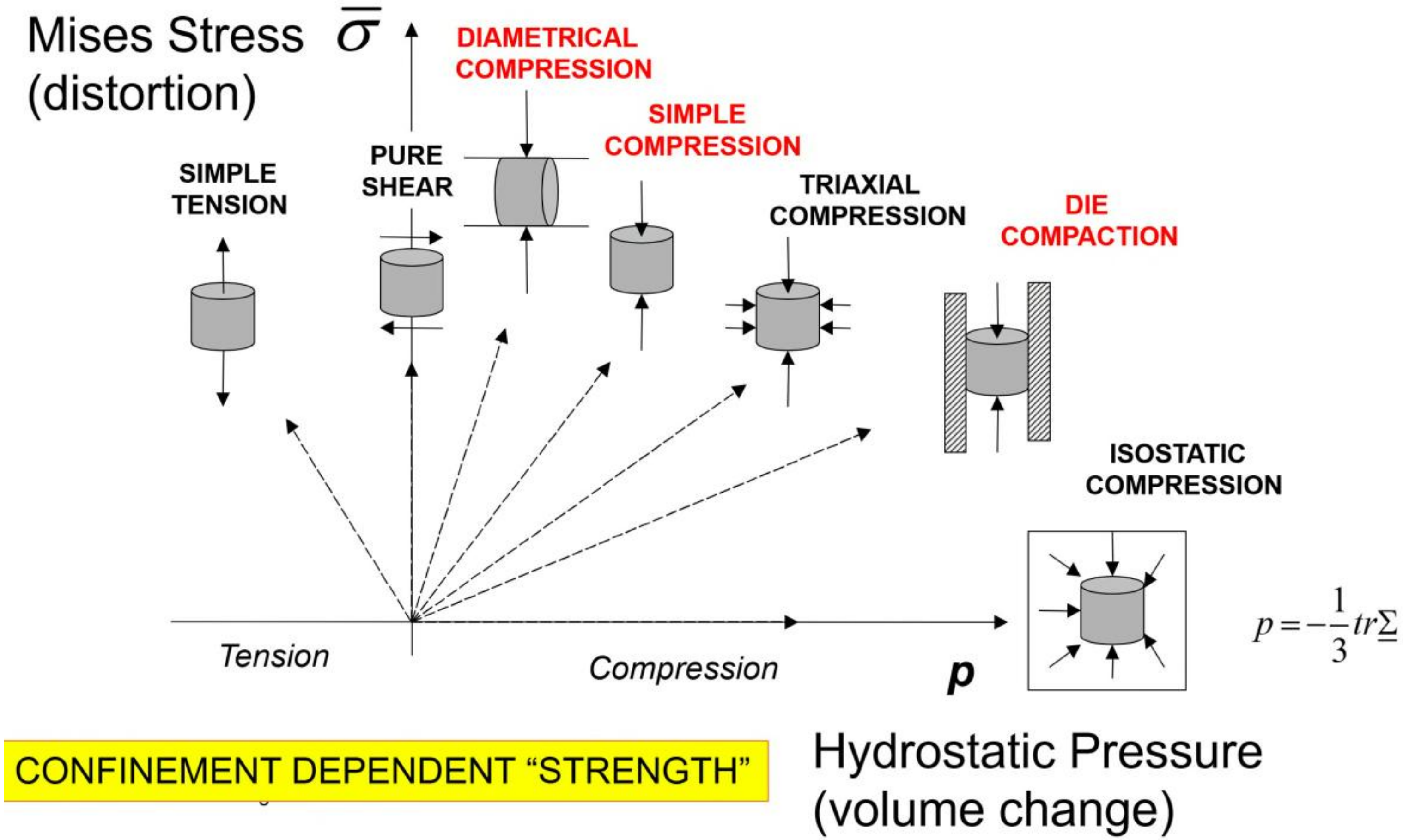
EMU model of a balloon penetrated by a fragment



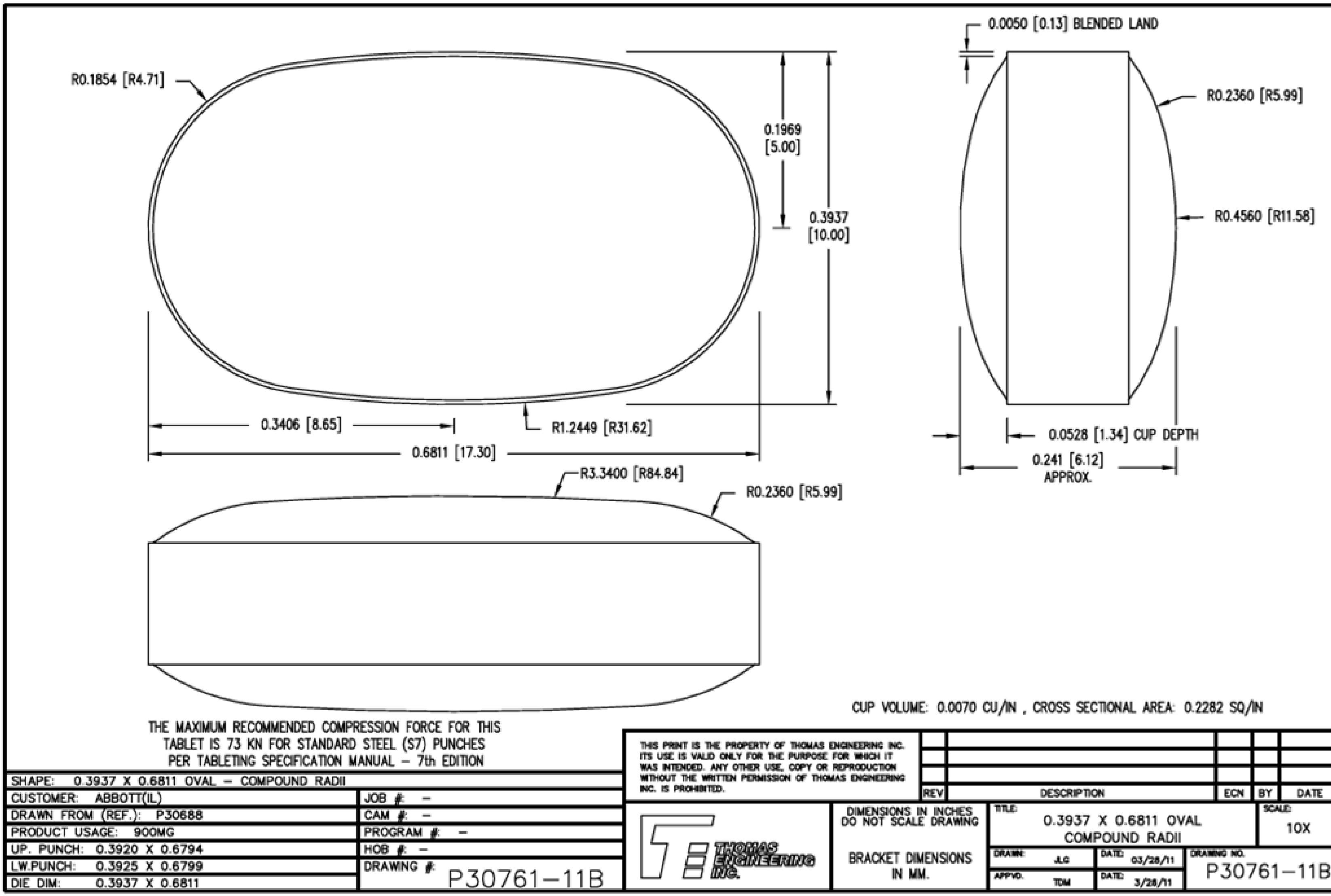
Early high speed photograph by Harold Edgerton (MIT collection)
http://mit.edu/6.933/www/Fall2000/edgerton/edgerton.ppt

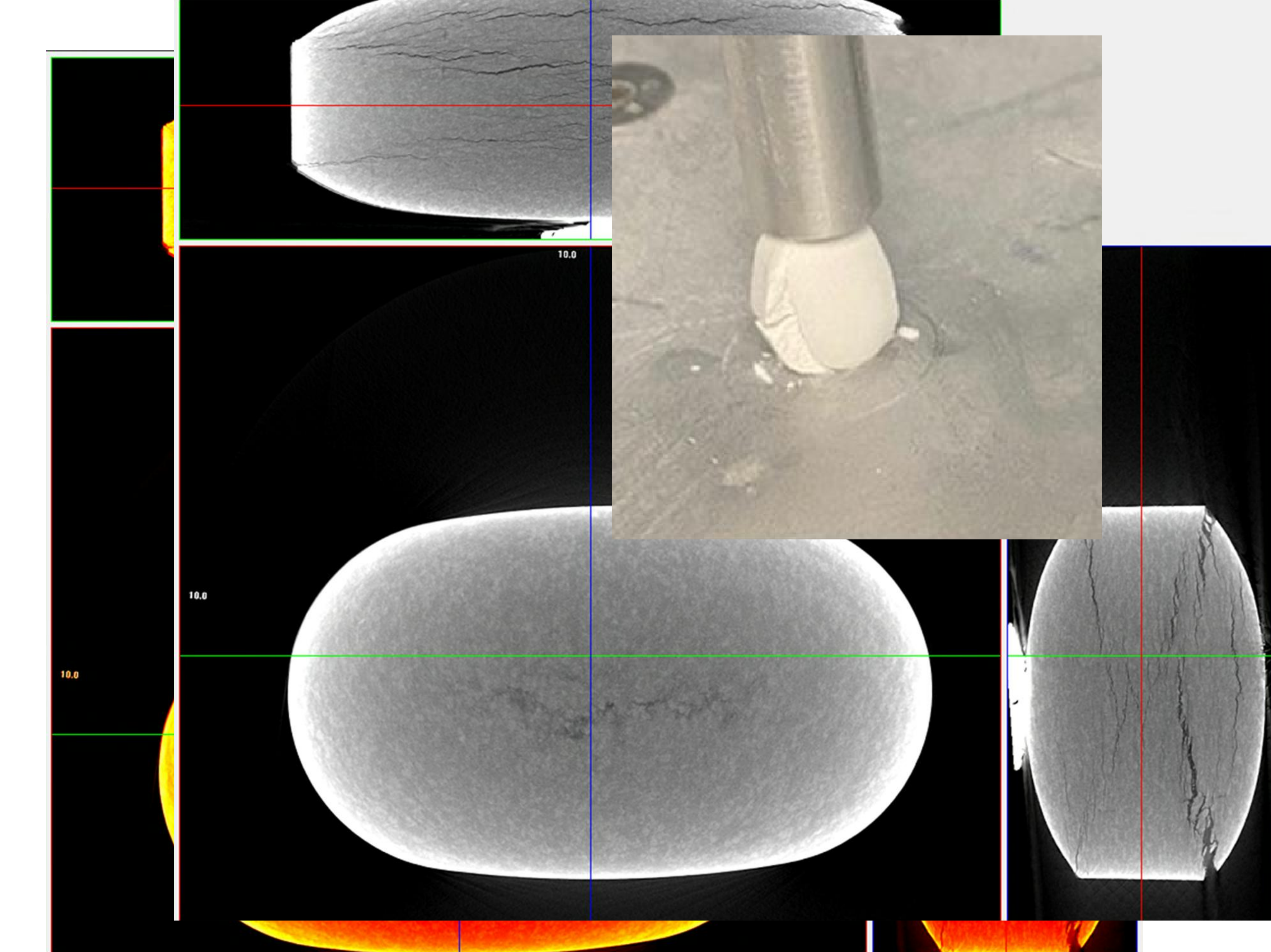
Mechanics Models for Powders in terms of *Continuum Mechanics*

Pressure Dependence of Mechanical Response



Tablet Geometry

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