A PAT Example: Tablet Coating

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Outline

- Literature review
- Discrete element modeling
- Tablet forces
- Inter-tablet variability
- Intra-tablet variability
- Conclusions and future work

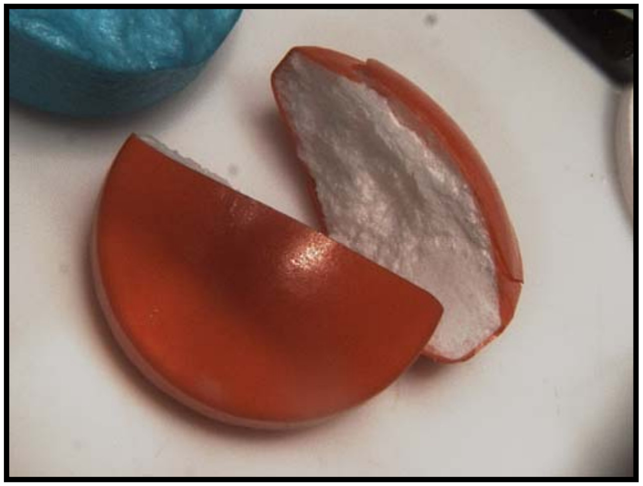
Process Analytical Technology

- "A system for **designing**, **analyzing**, and **controlling** manufacturing through timely **measurements** (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality."
- "The ability to **predict** reflects a high degree of **process understanding**."

Source: FDA, ***Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*** (Sep. 2004).

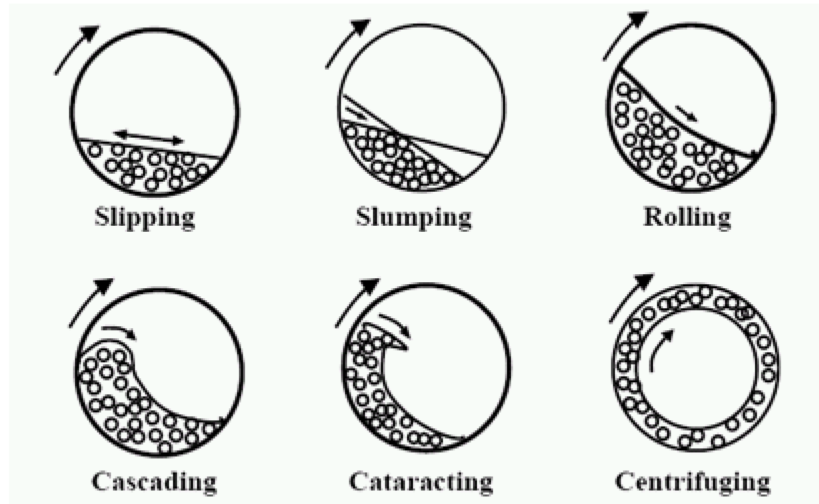
Why coat tablets?

- Product appearance and ID
- Increase swallowability / patient compliance
- Provide a barrier from environment
  - core stability (heat, light, moisture)
  - mask taste and odor
- Increase strength and fracture resistance
- Alter drug release from core (functional)
- Separate reactive drug compounds

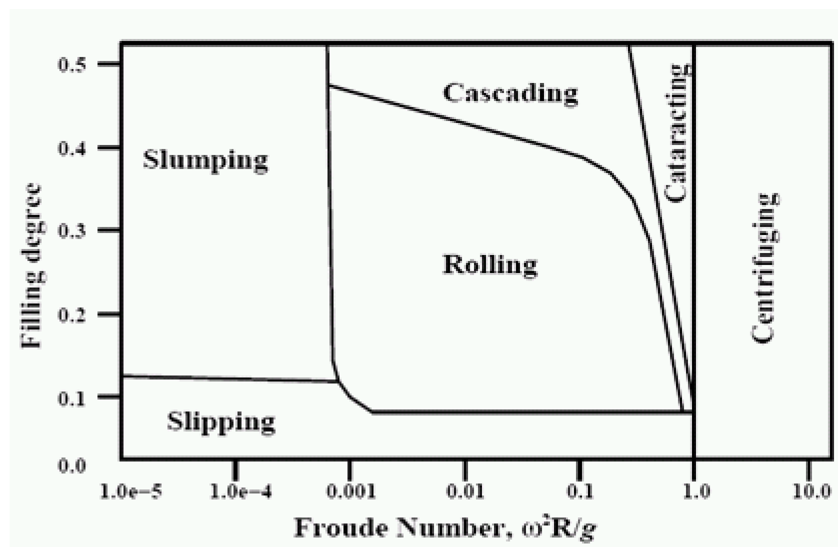


Some Previous Work

- Rotating horizontal drum dynamics (Rutgers, 1965; Henein *et al*., 1983; Mellmann, 2001)

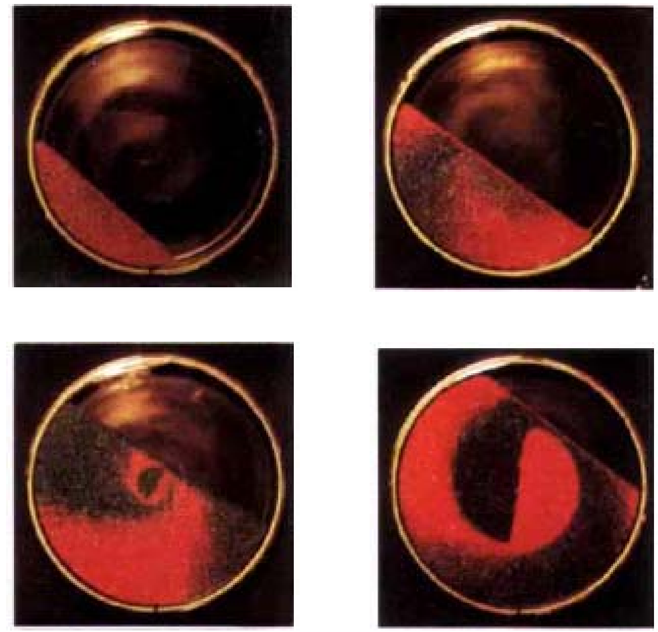


$$\mathrm{Fr} = \underbrace{\frac{\omega^2 R^2}{gR}}_{=\sim \frac{KE}{PE}} = \frac{\omega^2 R}{g}$$



Some Previous Work…

- Mixing and segregation in rotating horizontal drums (Metcalfe *et al*., 1995; Ottino and Khakar, 1995)



Some Previous Work…

- Tablet exposure and circulation times (Prater *et al*., 1980[1]; Leaver *et al*., 1985[2]; Yamane *et al*., 1995[3]; Sandadi *et al*., 2004[4]; Denis *et al*., 2003[5])
  - avg. surface exposure time per pass and std. dev. ↓ as drum speed and fill level ↑
  - circulation period ↓ as drum speed ↑ and fill level ↓
  - circulation period independent of fill level[5]

- Inter-tablet variability (Leaver *et al*., 1985[1]; Rege *et al*., 2002[2]; Tobiska and Kleinebudde, 2003[3]; Chang and Leonzio, 1995[4])
  - due to uneven circulation times
  - variability ↓ as drum speed ↑ and fill level ↓
  - variability not a function of drum speed[4]
  - variability ↓ as coating time ↑

Some Previous Work…

- Intra-tablet variability (Wilson and Crossman, 1997[1]; Sandadi *et al*., 2004[2])
  - variability ↓ as tablet sphericity ↑
  - variability ↓ as drum rotation speed ↑
- Mixing elements (Leaver *et al*., 1985[1]; Sandadi *et al*., 2004[2]; Skultety *et al*., 1988[3]; Smith *et al*., 2003[4])
  - baffles ⇒ surface exposure and circulation times ↓ ⇒ inter-tablet variability ↓
  - baffles eliminate “dead zones”
  - in some cases, baffles do not significantly affect variability[2,3]

Some Previous Work…

- Spray aspects (Tobiska and Kleinebudde, 2003[1]; Rege *et al*., 2002[2]; Twitchell *et al*., 1995[3])
  - atomizing pressures $\uparrow \Rightarrow$ droplet sizes $\downarrow \Rightarrow$ intra-tablet variability $\downarrow$, coating efficiency $\downarrow$[1]
  - atomizing pressures $\uparrow \Rightarrow$ inter-tablet variability $\uparrow$ and non-uniform and elliptical spray patterns[2]
  - exhaust fan speed, inlet air flow, and temperature do not significantly affect inter-tablet variability[2]
  - exhaust fan speed $\uparrow \Rightarrow$ coating efficiency $\downarrow$
  - temperature $\uparrow \Rightarrow$ coating efficiency $\downarrow$[3]

State of Knowledge

- Important parameters identified
- Primarily qualitative trends – few quantitative models
  - some conflicting data
  - some variables may be related
  - experimental data is specific to system and operating parameters
  - not clear how to scale or extrapolate data to different conditions
- Only one computational model (Yamane *et al*., 1995)

Modeling Particulate Systems

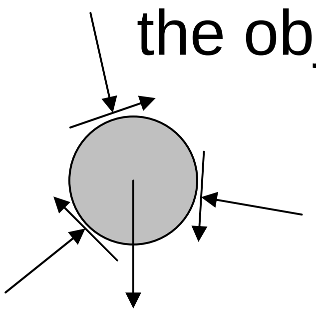
- Continuum Modeling
  - Computational Fluid Dynamics (CFD):
    - processing gases and liquids, fluidized beds, sprays, pneumatic transport
  - Finite Element Modeling (FEM):
    - tablet strength, roller compaction
  - [Population Balance Modeling (PBM)]:
    - granulation and milling

- Discrete (Element) Modeling
  - Model the dynamics of discrete objects
  - Four common approaches:
    - cellular automata
    - Monte Carlo methods
    - hard-particle approach
    - soft-particle approach

Soft-Particle
Discrete Element Modeling

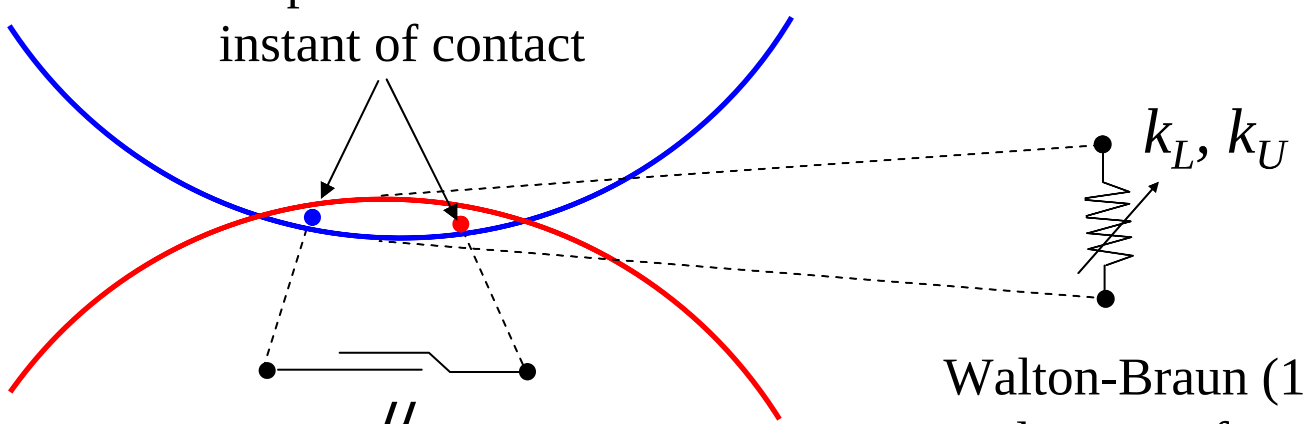
Newton's 2nd Law: The rate at which an object's momentum changes (= mass * acceleration, if the object's mass isn't changing) is equal to the net force acting on the object.

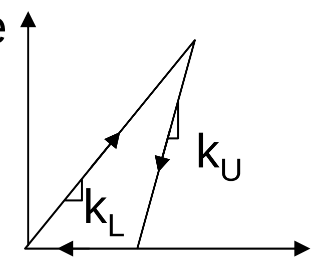
$$\mathbf{F} = m\mathbf{a}$$



$$\frac{d\mathbf{v}}{dt} = \mathbf{a} \quad \text{and} \quad \frac{d\mathbf{x}}{dt} = \mathbf{v}$$

Soft-Particle DEM…





Soft-Particle DEM…

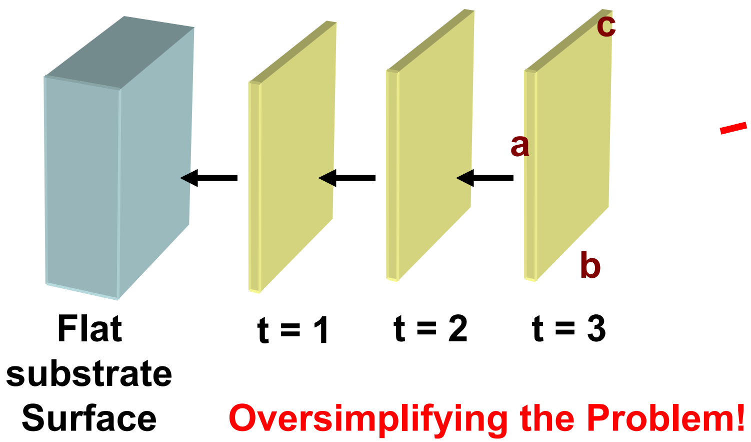
- With soft-particle DEM we know at each instant in time:
  - all particle positions, orientations, and translational and rotational velocities
  - the normal and tangential components of the contact forces acting on each particle and the locations of these forces on a particle's surface
- We can also specify individual particle and contact parameters, e.g.:
  - size, density, and shape distributions
  - contact friction coefficients and/or stiffnesses

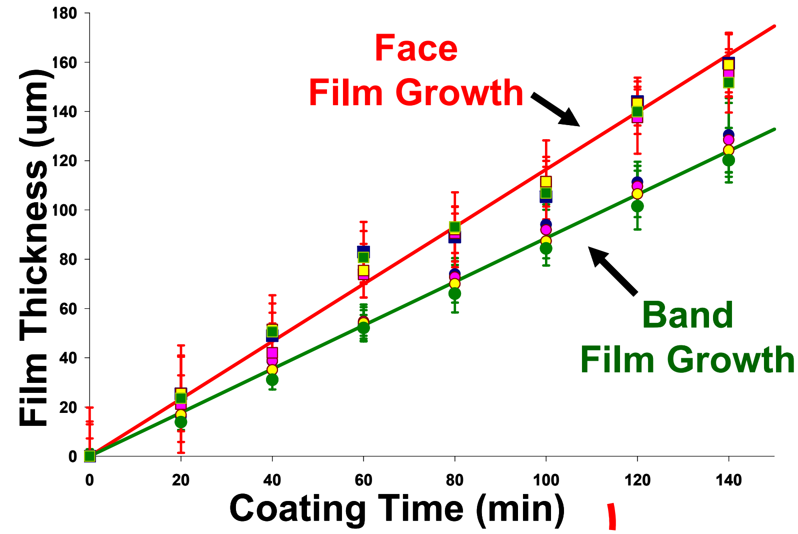
Tablet Coating in a Horizontal Pan

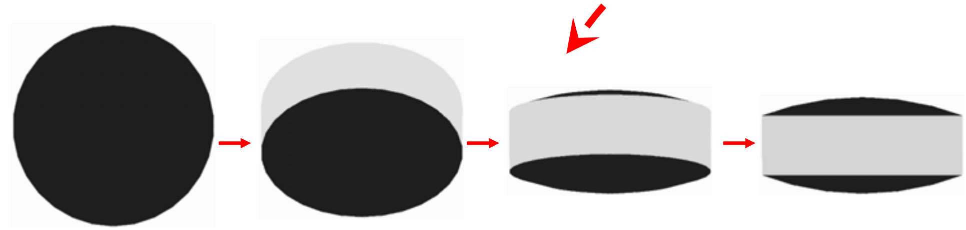
- Sponsored by CAMP
  - The Consortium for the Advancement of Manufacturing of Pharmaceuticals
  - A non-profit consortium of pharmaceutical companies that conducts research focused on decreasing new product time-to-patient, increasing quality, and lowering product costs by enhancing pharmaceutical manufacturing performance.

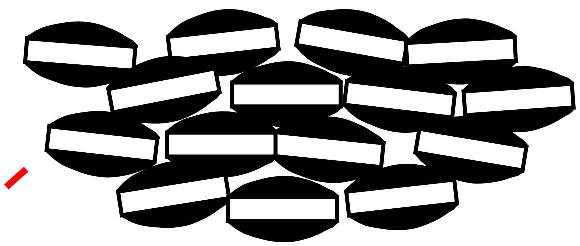
- People working on the project:
  - Ph.D. students: Arjun Kalbag (ME), Sumana Penumetcha (IPPH), José Pérez-Ramos (IPPH, GSK)
  - M.S. students: Alexis Déchelette (ME), Vince Hoon (CS), Ariel Muliadi (ME)
  - Faculty: Dr. Ken Morris (IPPH), Dr. Paul Sojka (ME), Dr. Carl Wassgren (ME)
  - Technical Champions: Keith Hill (GSK), Dr. Shawn Whitfield (GSK)

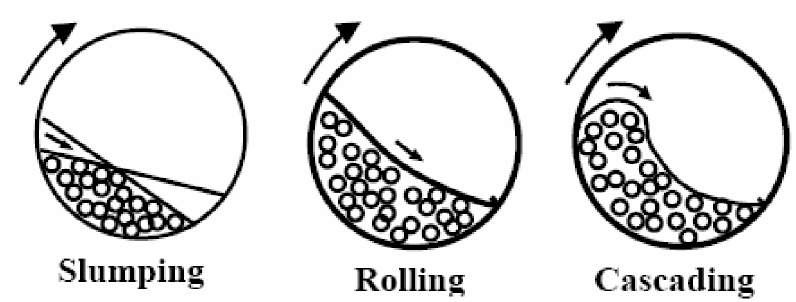
Predicting Film Growth on a Tablet Surface

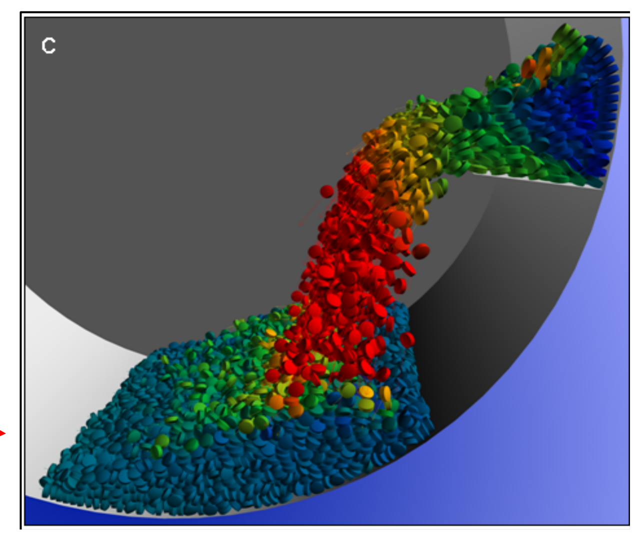








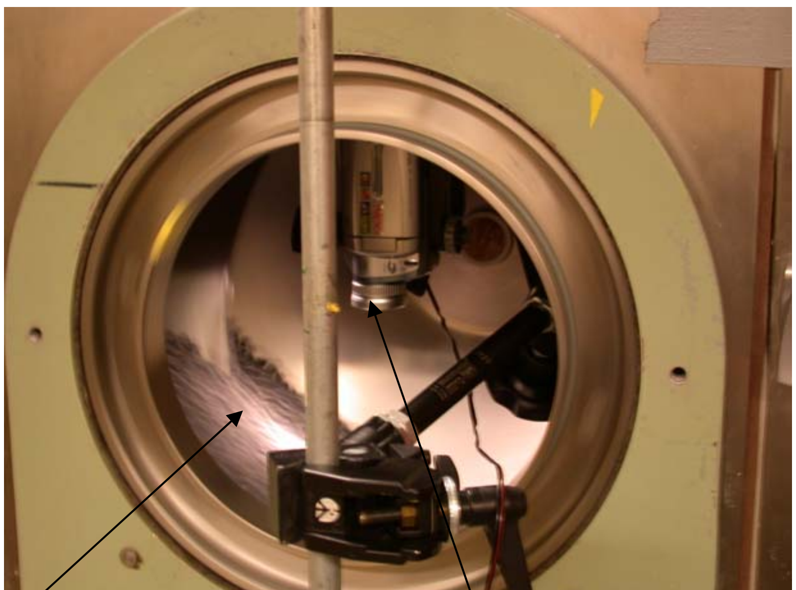


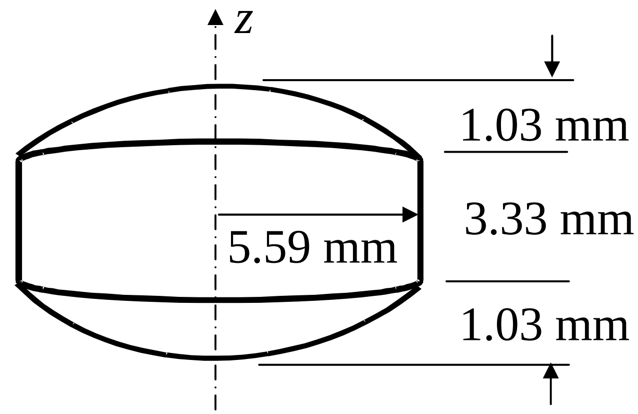


Slide source: Jose Perez, Purdue University

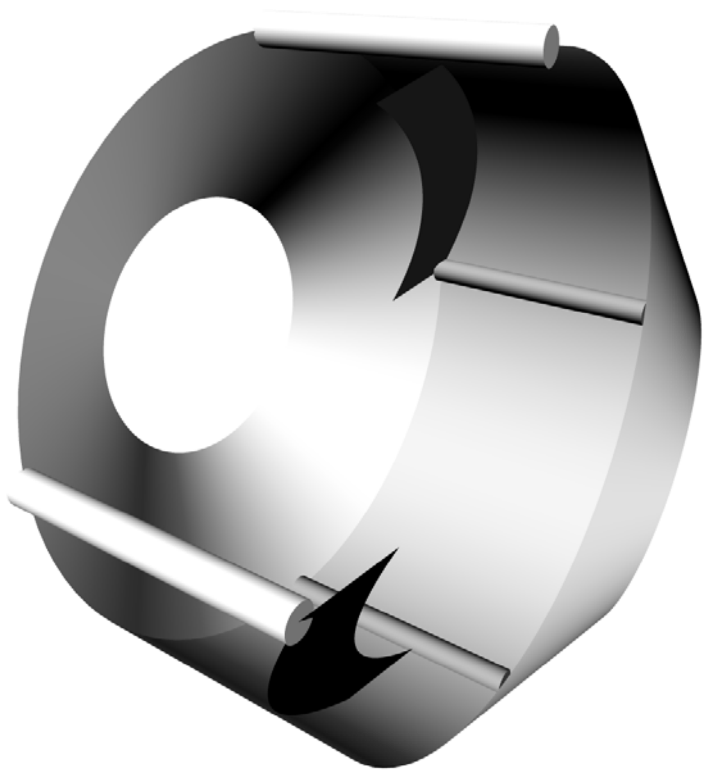
Tablet Coating Experiment

- Thomas Eng. Accela-Cota 24 in. diameter coating pan
- Four slip bars and two baffles
- Experiments use ~7 kg load (~15% fill level in drum) of bi-convex tablets





Tablet Coating Simulations



- The simulated pan has the same dimensions as the experimental pan.

- Most of the current simulations use spherical particles with the same volume as the biconvex tablets used in the experiments. (d = 4.7 mm)

- The range of drum speeds and fill loads used in the simulations are the same as in the experiments.

Tablet Coating Simulations…

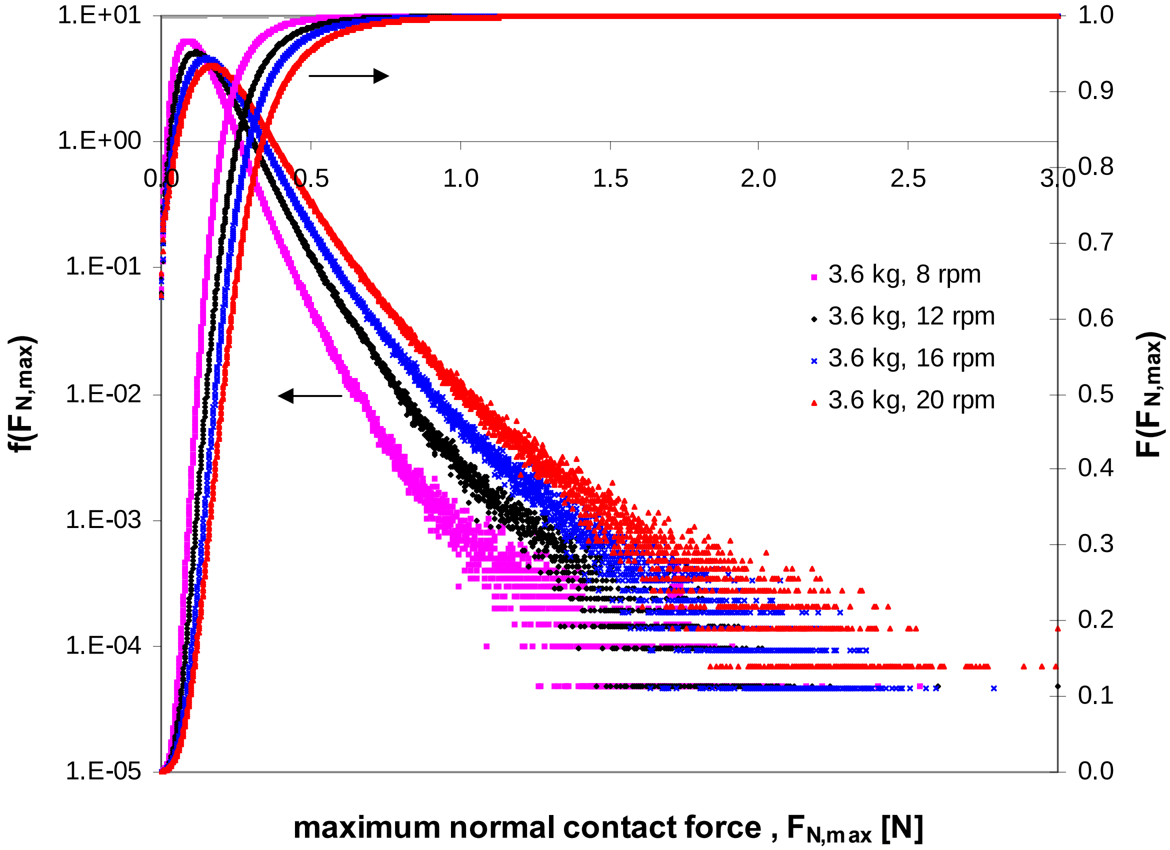
- Simulation conditions:
  - 5.4 kg load (11,250 tablets) at 12 rpm with and without baffles

- A simulation movie showing:
  - tablets colored based on their translational speed:
    - red $\Rightarrow$ largest speed
    - blue $\Rightarrow$ smallest speed
  - slip bar vortices.

Data visualization using ParticleVis (Vince Hoon, Purdue University)

Contact Force Measurements

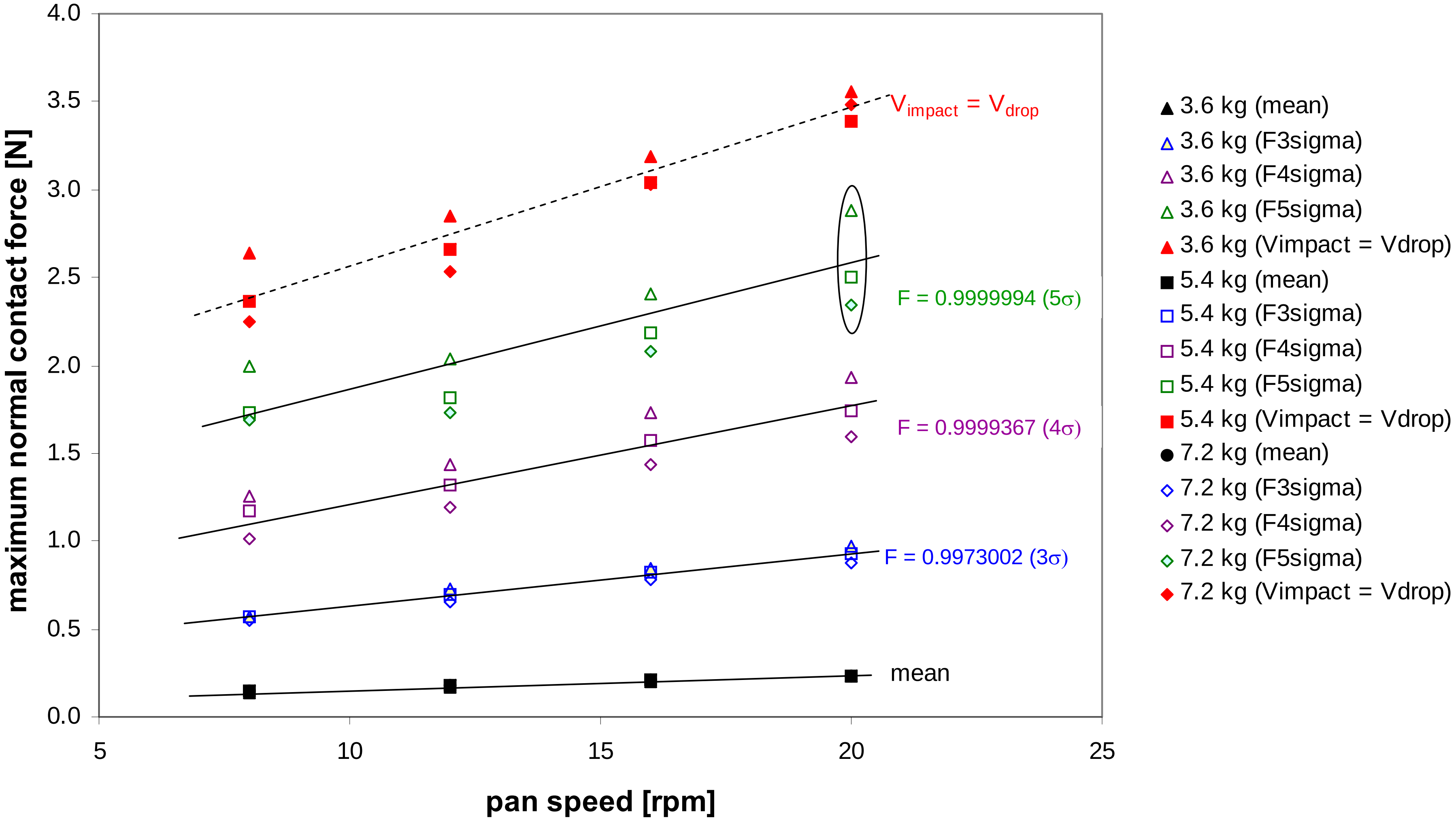
Measurements of the **max normal force** for each tablet are made every 1/60th sec over a period of ~57 sec (depends upon pan speed).



fraction of measurements with a max normal force between ($F_{N,max}$) and ($F_{N,max}+dF_{N,max}$) = $f(F_{N,max})dF_{N,max}$

fraction of measurements with a max normal force less than $F_{N,max}$ = F($F_{N,max}$) = $\int_0^{F_{N,\max}} f\left(F_{N,\max}\right) dF_{N,\max}$

Contact Force Measurements…



- **max contact forces increases linearly with pan speed**
- **range of max contact forces decreases linearly with pan load**
- **largest forces due to particles falling from slip bars**

Contact Force Measurements…

- Simulation conditions: 7.2 kg load (15,000 tablets) at 12 rpm
- A simulation movie showing tablets colored based on the value of the maximum normal force acting on the tablet (white is large, black is small).
- A movie for the same simulation but only highlighting contacts having a maximum normal force greater than the F = 0.9973 (3σ) value highlighted.

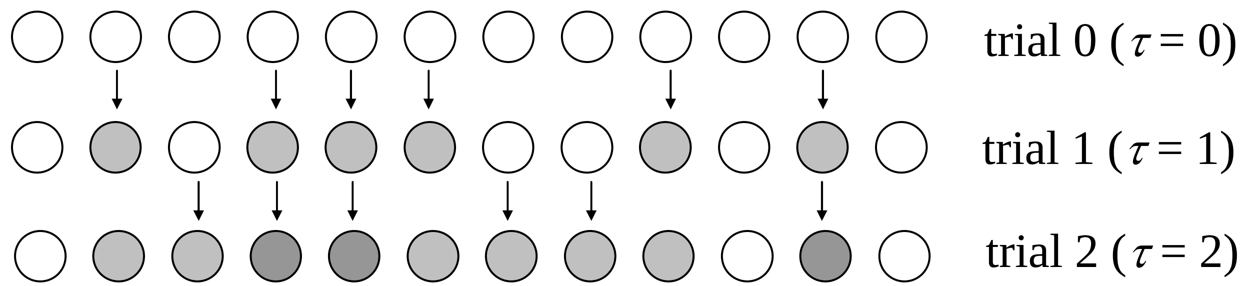
Data visualization using ParticleVis (Vince Hoon, Purdue University)

Inter-Tablet Coating Variability

An analytical "random coating" inter-tablet variability model:

Consider N tablets, all initially with no coating mass. After one "trial," give a random selection of n tablets an additional coating mass of Δm.

e.g., $N = 12$, $n = 6$



Now determine the average coating mass, the standard deviation of the coating mass, and the coefficient of variation of the coating mass.

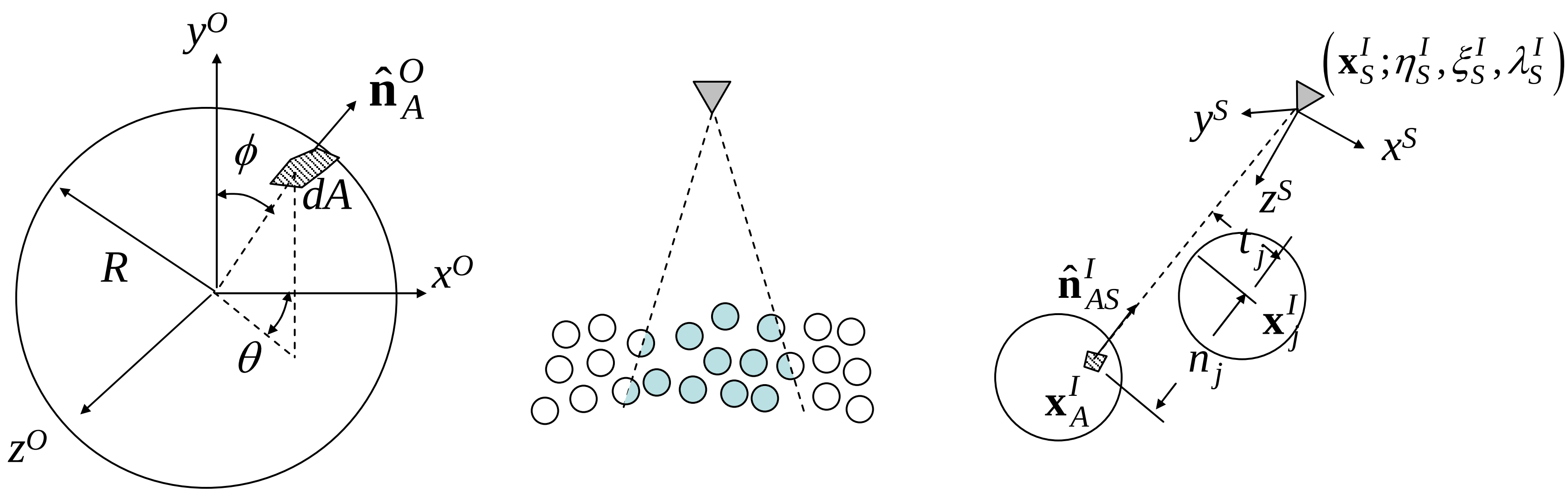
$$\bar{m}(\tau) = \frac{1}{N}\sum_{i=1}^{i=N} m_i(\tau) \qquad \sigma(\tau) = \sqrt{\frac{1}{N}\sum_{i=1}^{i=N}\left[m_i(\tau) - \bar{m}(\tau)\right]^2} \qquad CoV(\tau) = \frac{\sigma(\tau)}{\bar{m}(\tau)}$$

$$\Rightarrow \boxed{CoV(\tau) = \sqrt{\frac{1}{\tau}\left(\frac{1}{n/N} - 1\right)}}$$

Inter-tablet coating variability in a random coating process decreases with 1/(# coating trials)$^{1/2}$. Also ~proportional to 1/(coating fraction)$^{1/2}$.

Tablet Coating Algorithm

1. Discretize each tablet's surface into a collection of "panels."
2. Determine if the panel is within the spray cone.
3. Determine if the panel can "see" the spray.
4. Determine the mass accumulated on the panel.



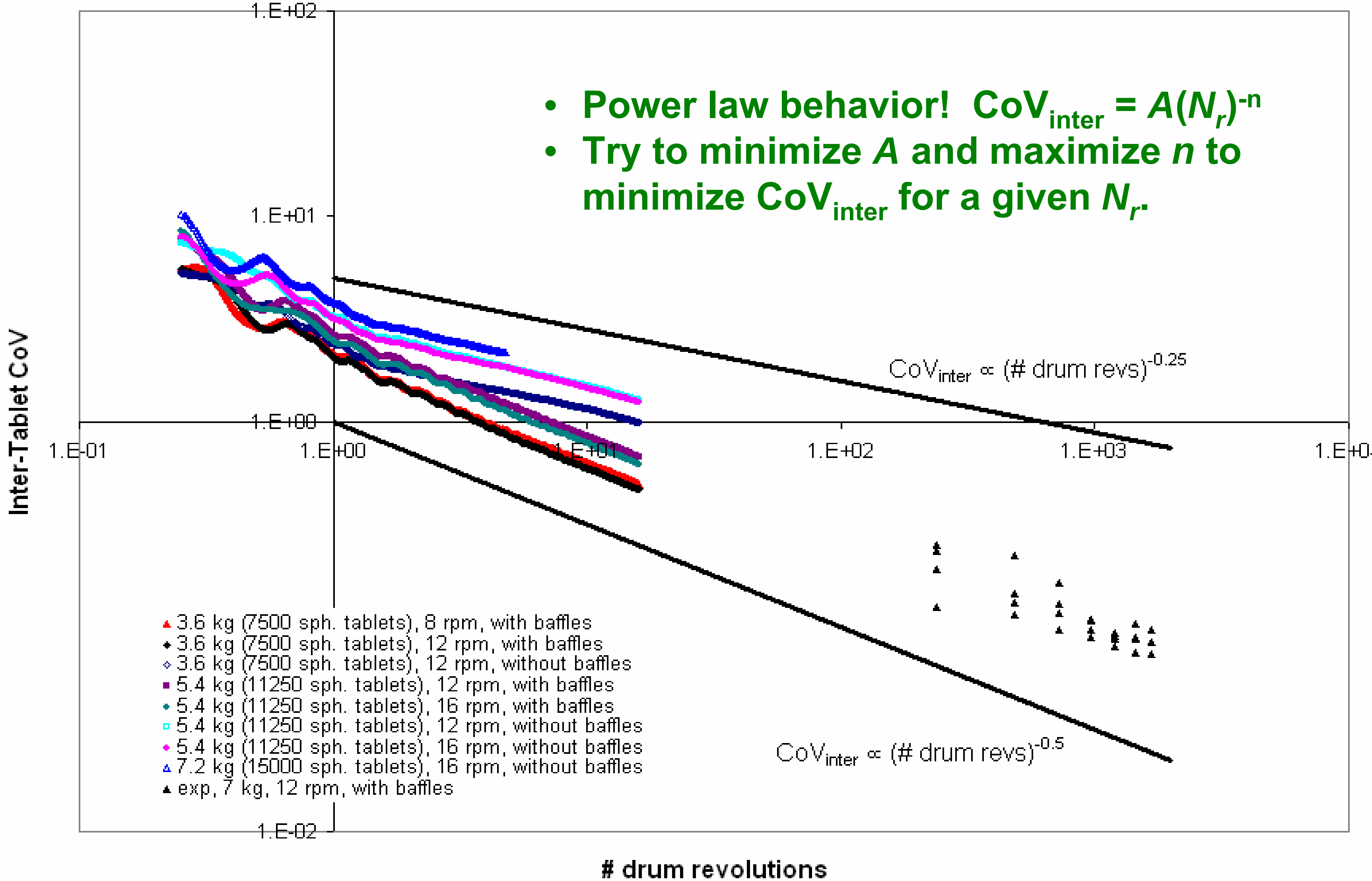
Tablet Coating Algorithm…

- Simulation conditions:
  - 5.4 kg load (11,250 tablets) at 12 rpm with and without baffles

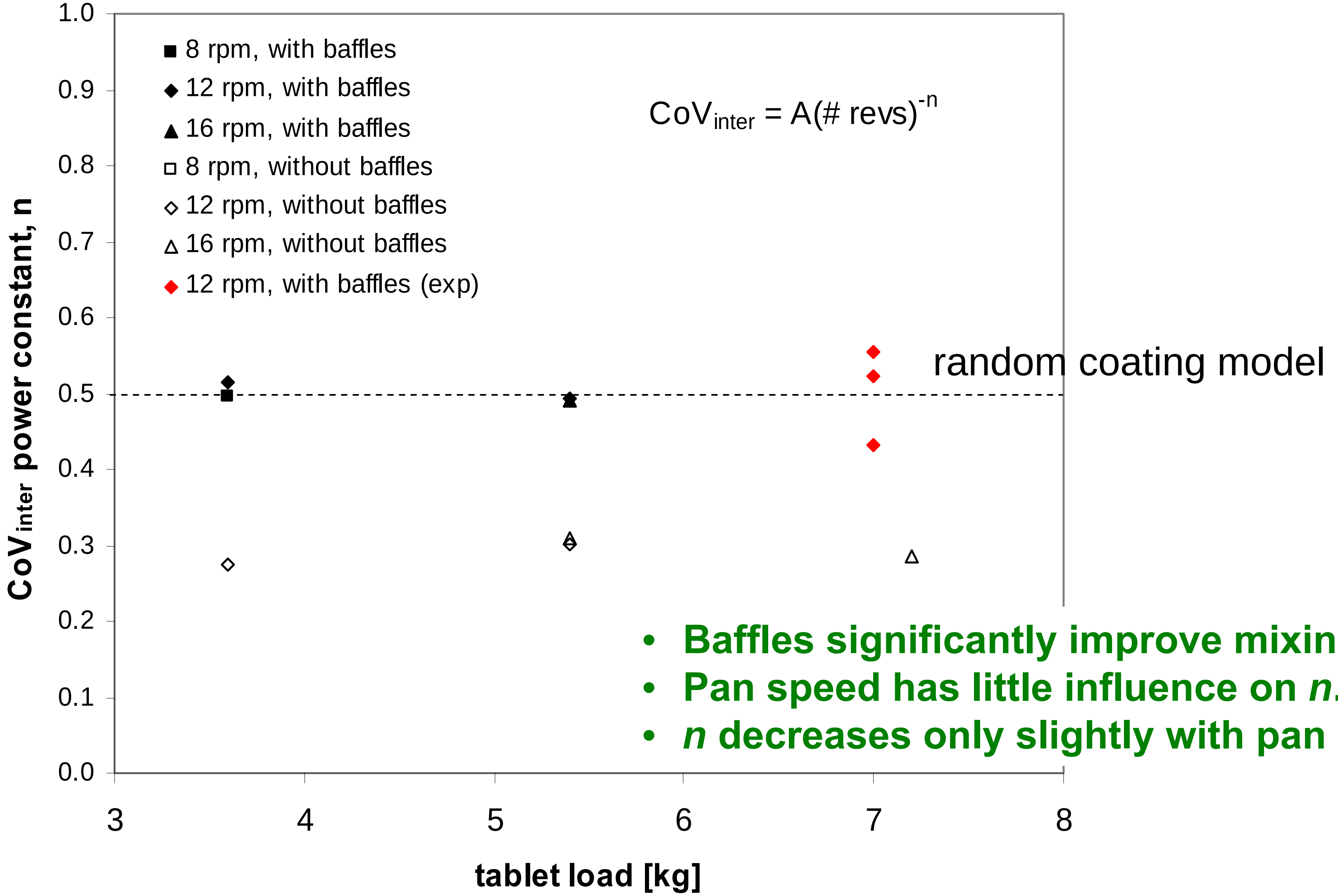
- A simulation movie showing:
  - tablets accumulate coating mass as they pass through the spray cone
    - purple $\Rightarrow$ no coating mass
    - brighter colors $\Rightarrow$ increased coating mass

Data visualization using ParticleVis (Vince Hoon, Purdue University)

Inter-Tablet Coating Variability

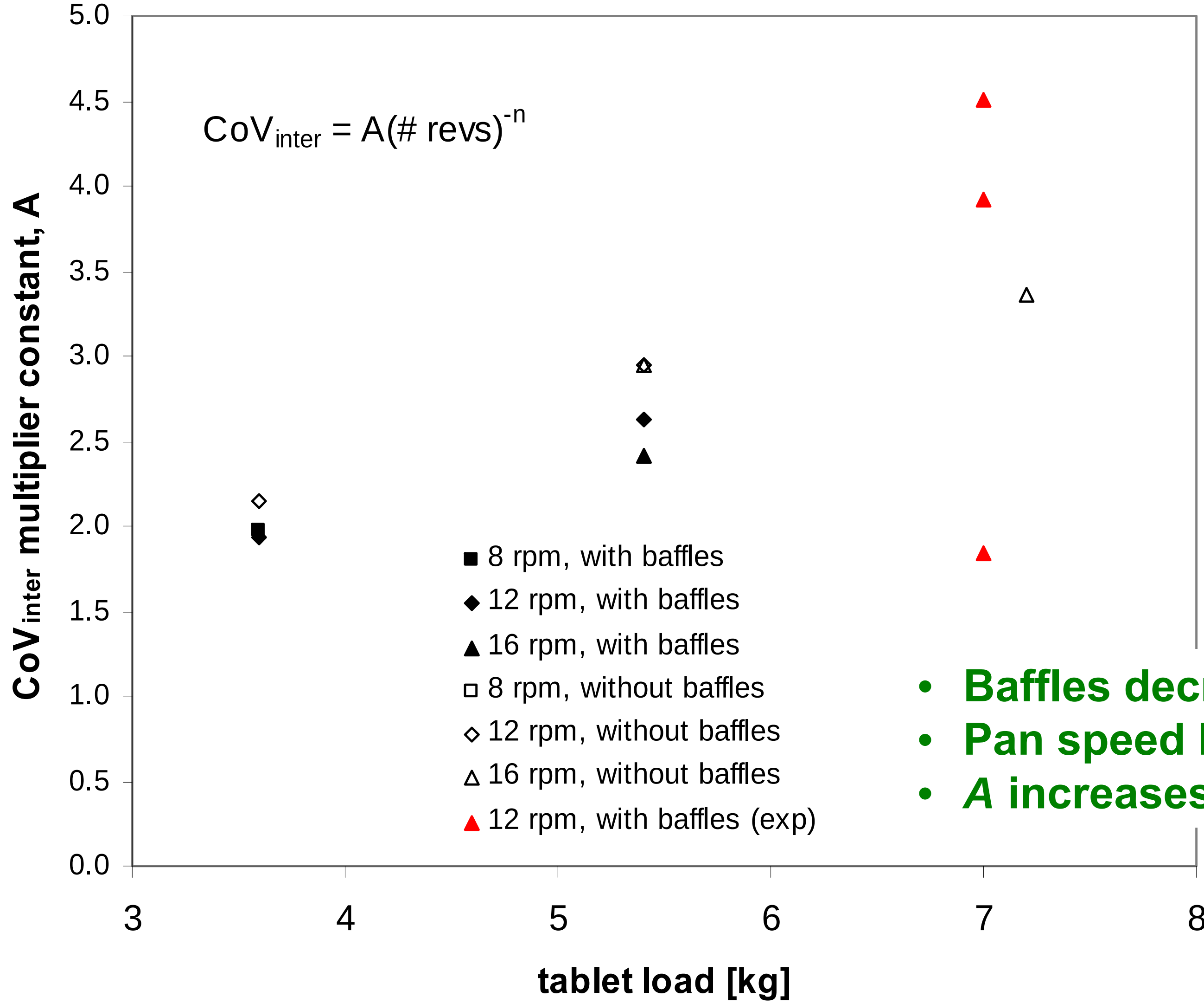


Inter-Tablet Coating Variability…



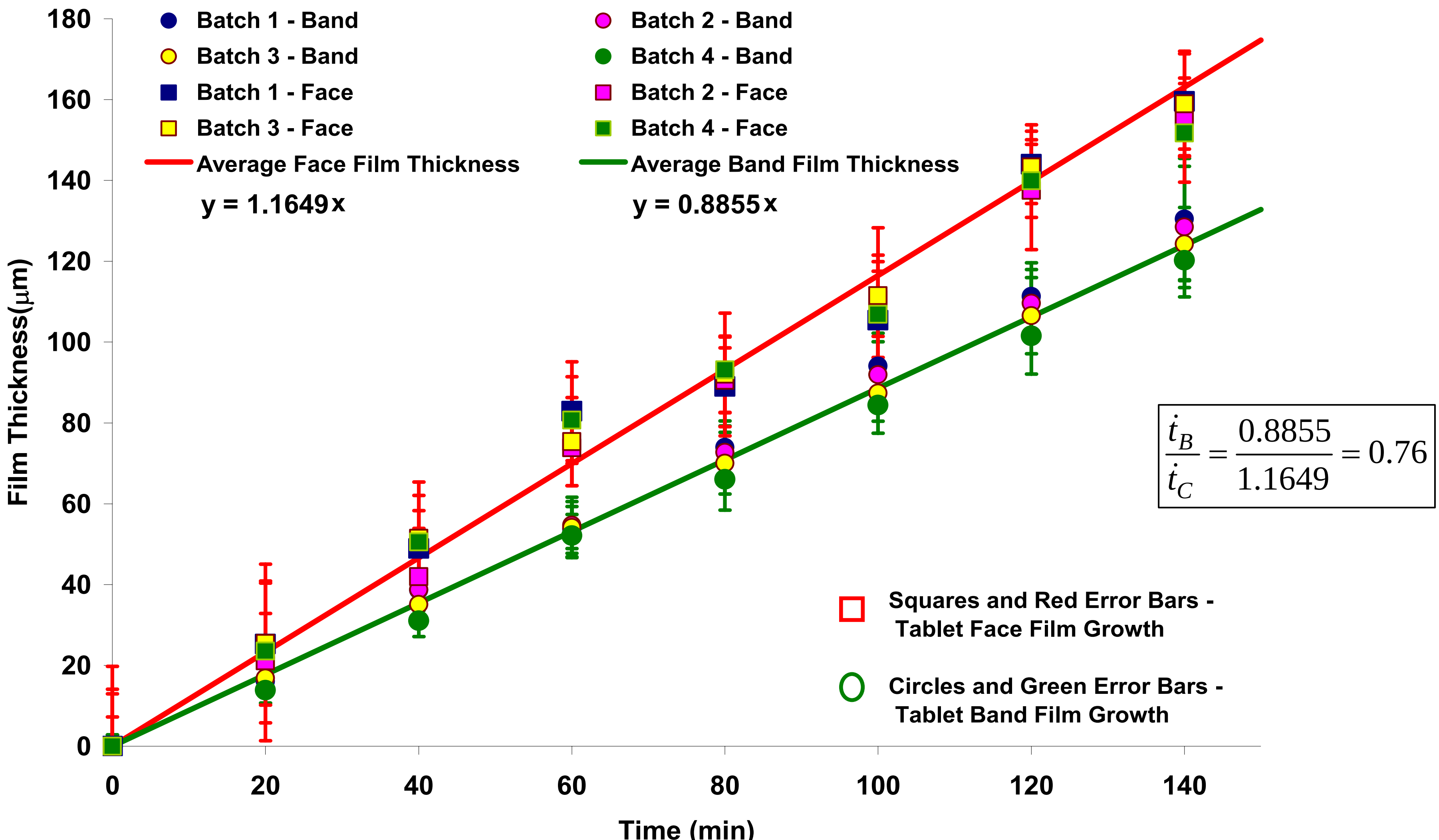
- **Baffles significantly improve mixing.**
- **Pan speed has little influence on *n*.**
- ***n* decreases only slightly with pan load.**

Inter-Tablet Coating Variability…



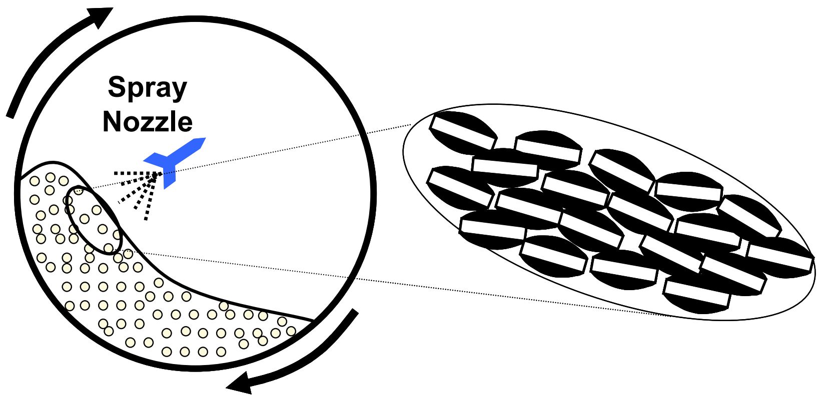
- **Baffles decrease *A*.**
- **Pan speed has little influence on *A*.**
- ***A* increases linearly with pan load.**

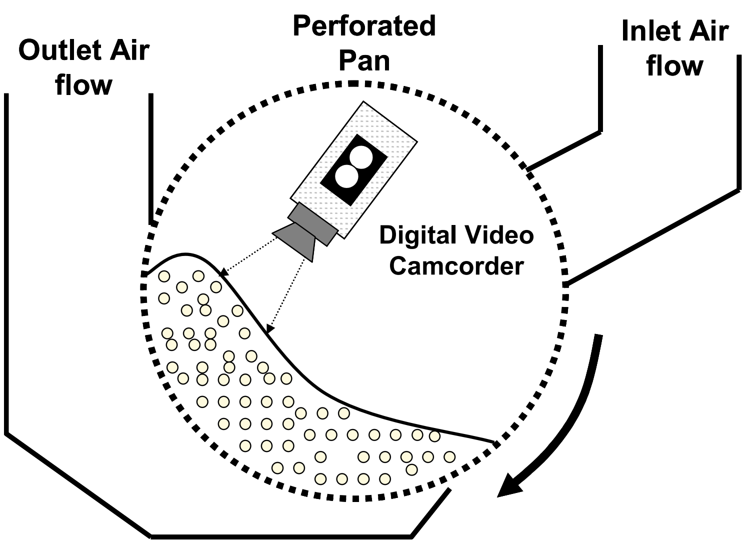
Intra-Tablet Coating Variability

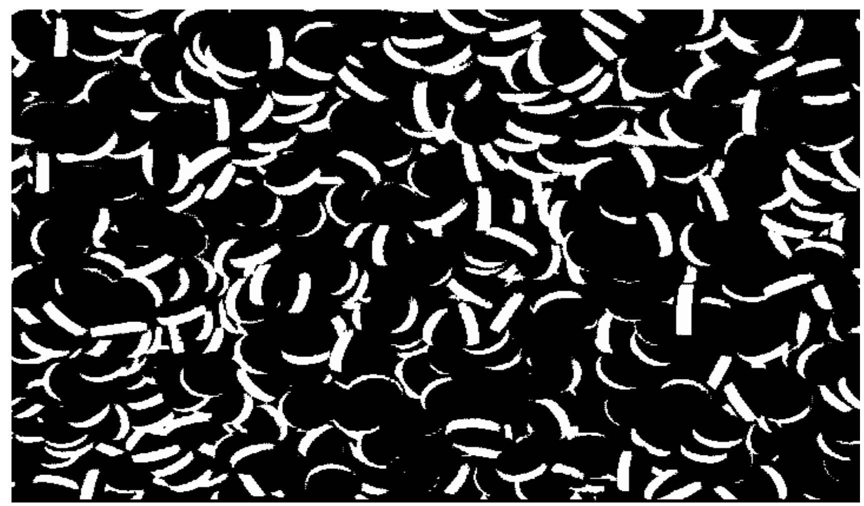


Experimental data provided by: Jose Perez, Purdue University

Intra-Tablet Coating Variability…







Intra-Tablet Coating Variability…

- Define the preferred orientation index, σ:

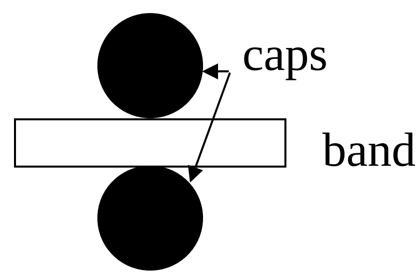
$$\sigma \equiv \frac{B/C\big|_{\text{measured}}}{B/C\big|_{\text{ideal}}}$$

$\sigma < 1 \Rightarrow$ more cap than desired
$\sigma = 1 \Rightarrow$ ideal
$\sigma > 1 \Rightarrow$ more band than desired

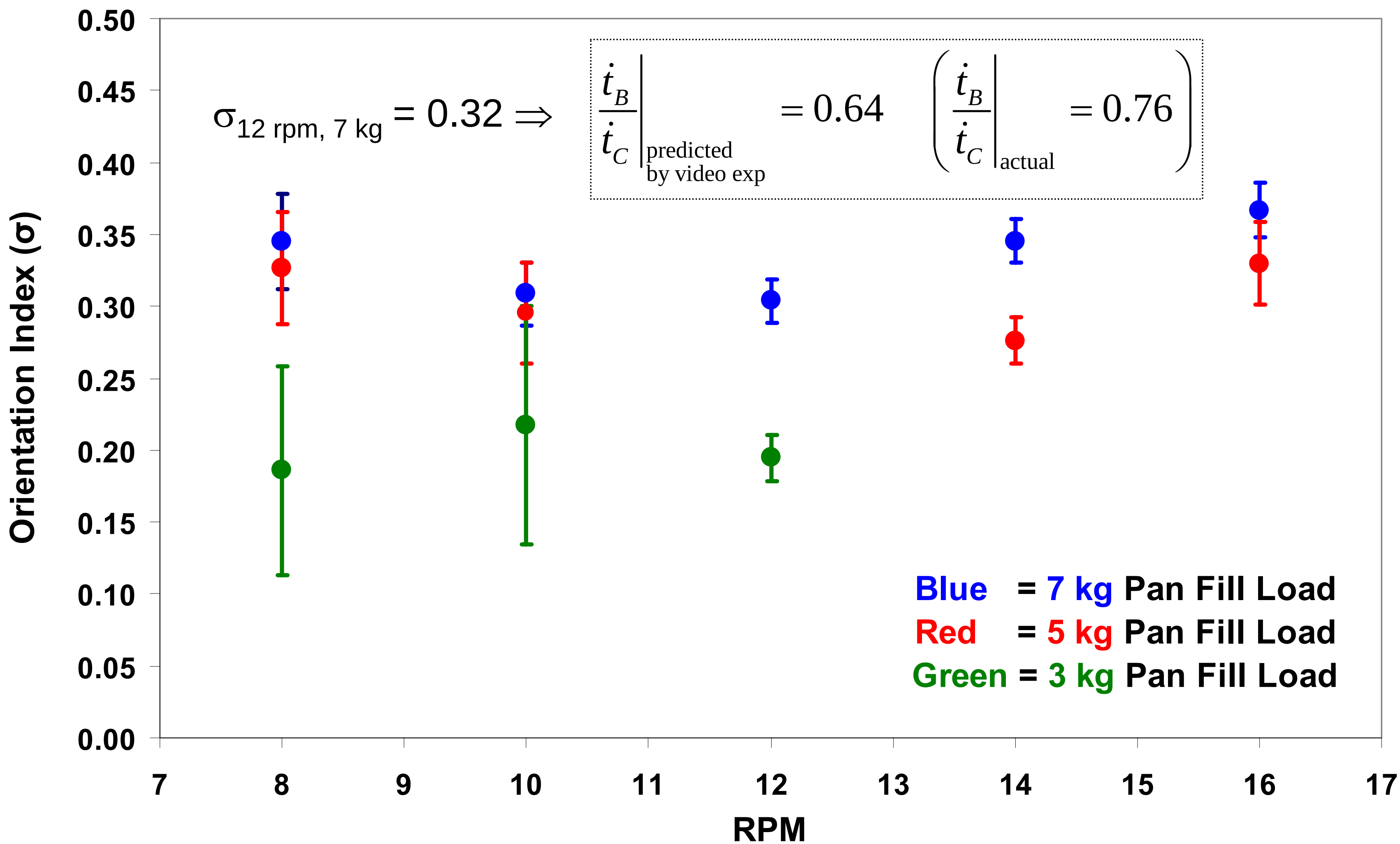
$$\frac{\dot{t}_B}{\dot{t}_C} = 2\sigma$$

where *B*/*C* is the ratio of the projected band-to-cap surface area.

- For the current tablets: $B/C\big|_{\text{ideal}} = 0.58$



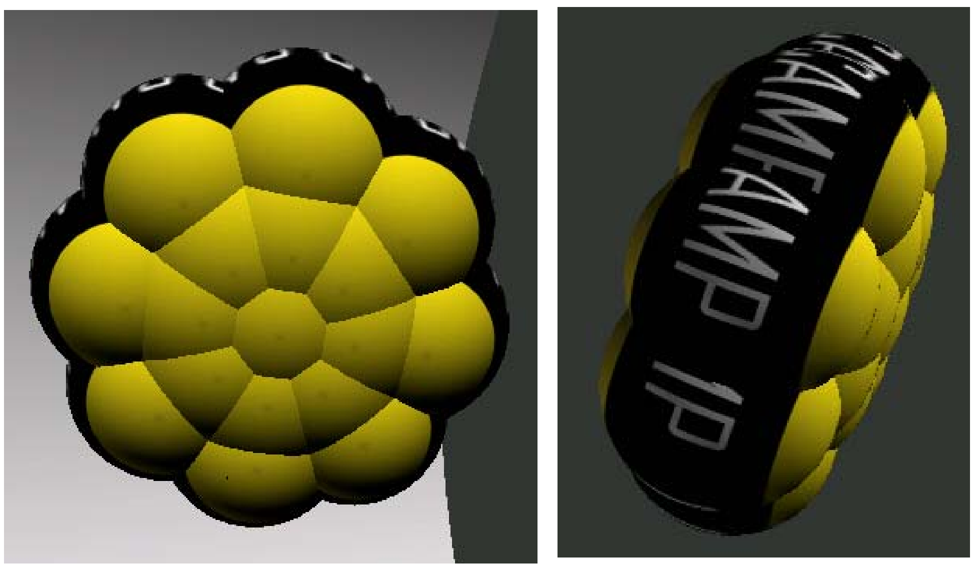
Intra-Tablet Coating Variability…



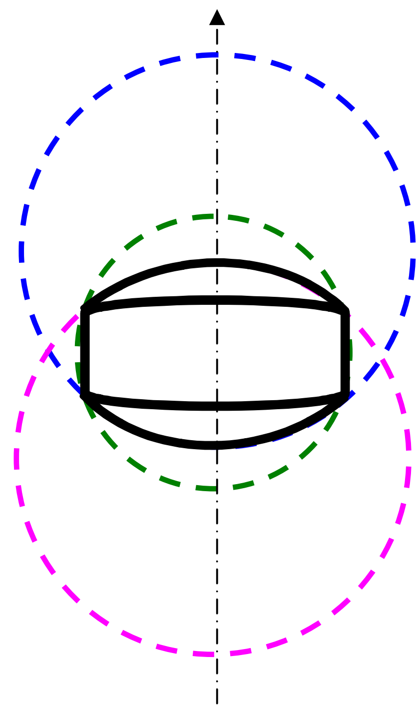
Experimental data provided by: Jose Perez, Purdue University

Bi-Convex Tablet Simulations

Glued Spheres Model



Intersecting Glued Spheres Model



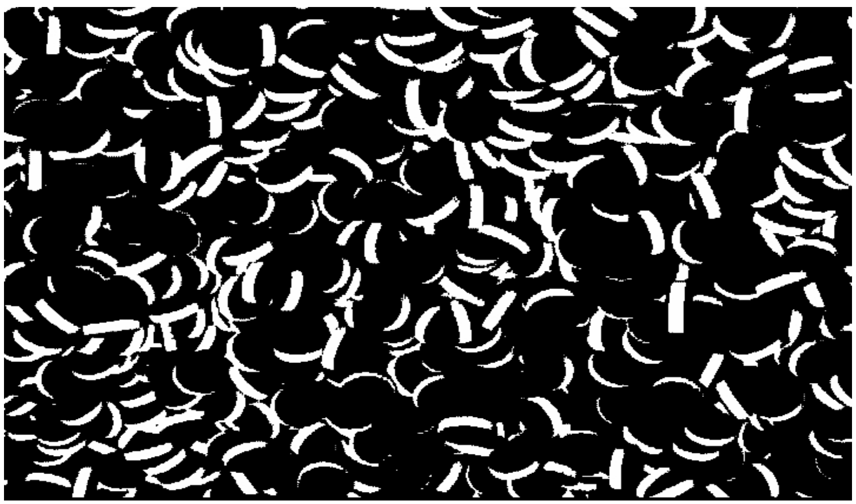
Intersecting glued spheres model: Song *et al*. (2004)

Bi-Convex Tablet Simulations…

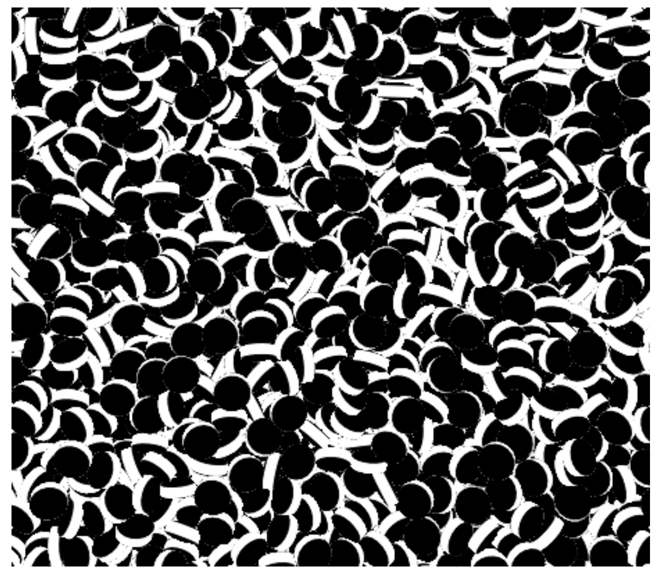
- Simulation conditions:
  - 7.2 kg load (15,000 tablets) at 20 rpm with modified baffles
  - glued sphere model with 17 spheres/tablet

Data visualization using ParticleVis (Vince Hoon, Purdue University)

Projected Area Comparison



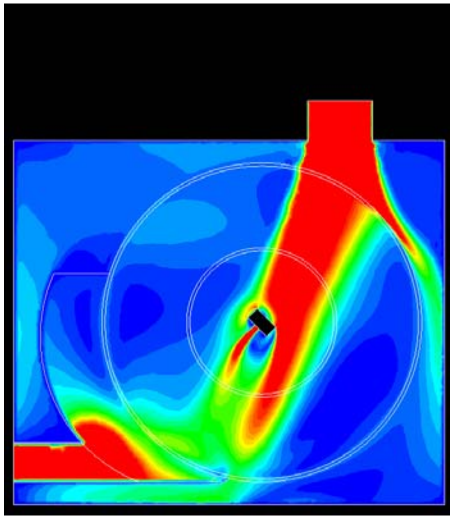
experiment

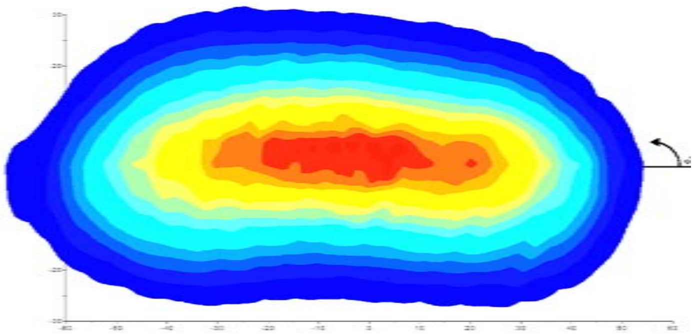


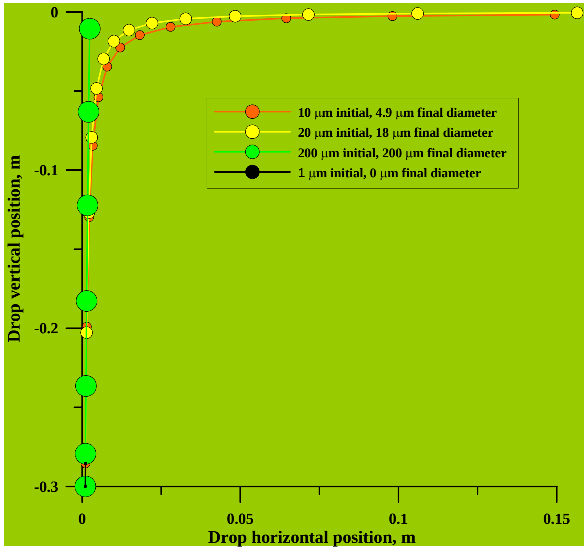
simulation

Additional Tablet Coating Work at Purdue

- Spray dynamics (Prof. Paul Sojka – sojka@purdue.edu)
  - computational fluid dynamics (CFD) studies of the spray and drying air
  - experimental measurements of spray drop size, velocity, number flux, and patternation
  - models of drop trajectories and size including evaporation

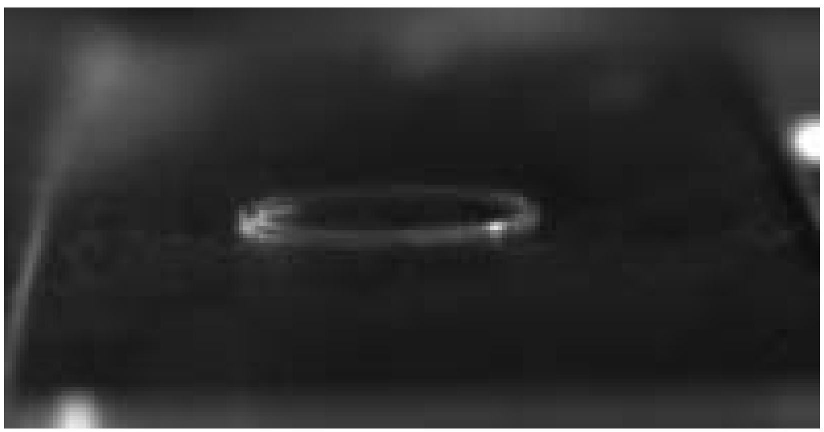




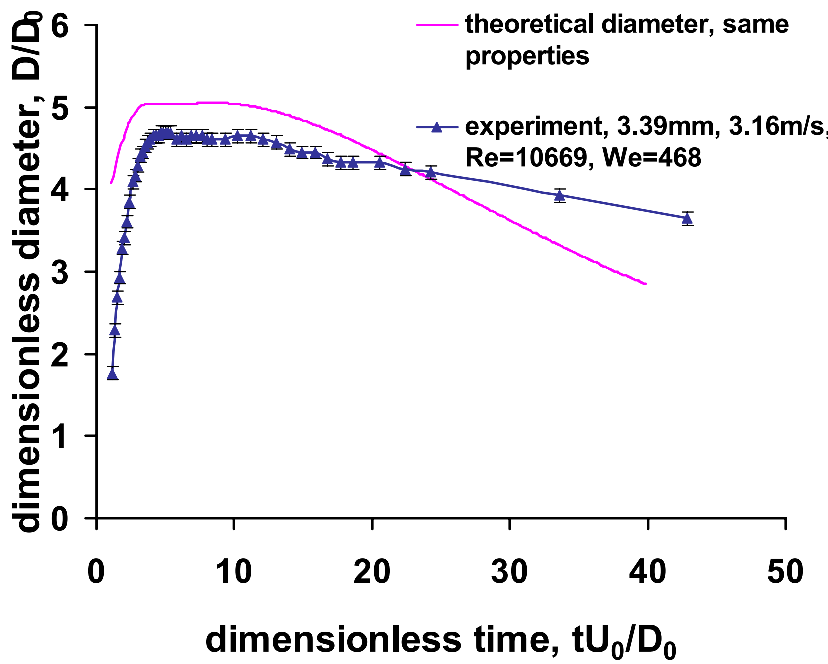


Additional Tablet Coating Work at Purdue

- Drop impact and spreading (Profs. Sojka and Wassgren)
  - analytical and experimental measurements of drop impact and spreading dynamics
  - Newtonian and non-Newtonian liquids

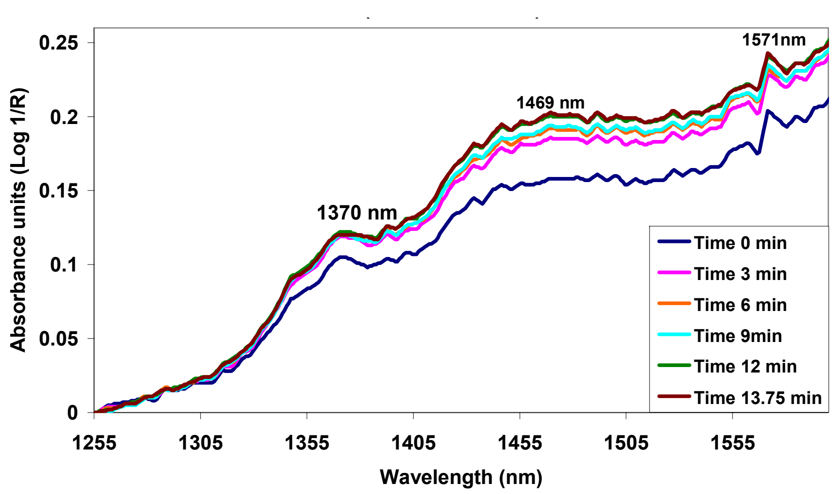


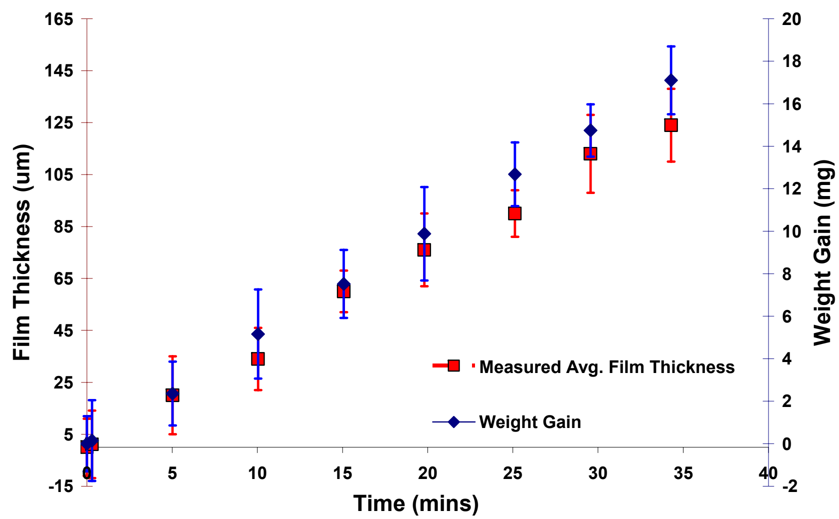
10% HPMC spreading drop



Additional Tablet Coating Work at Purdue

- NIR sensors applied to tablet coating (Prof. Morris – morriskr@purdue.edu)





Conclusions

- Analyses, computations, and experiments can all contribute process **understanding**
  - empirical curve fits alone are not sufficient
- The discrete element method (DEM) has proven to be a useful computational tool for modeling pharmaceutical systems
  - especially useful for design
  - need to develop simplified relations for real-time control

Questions?