

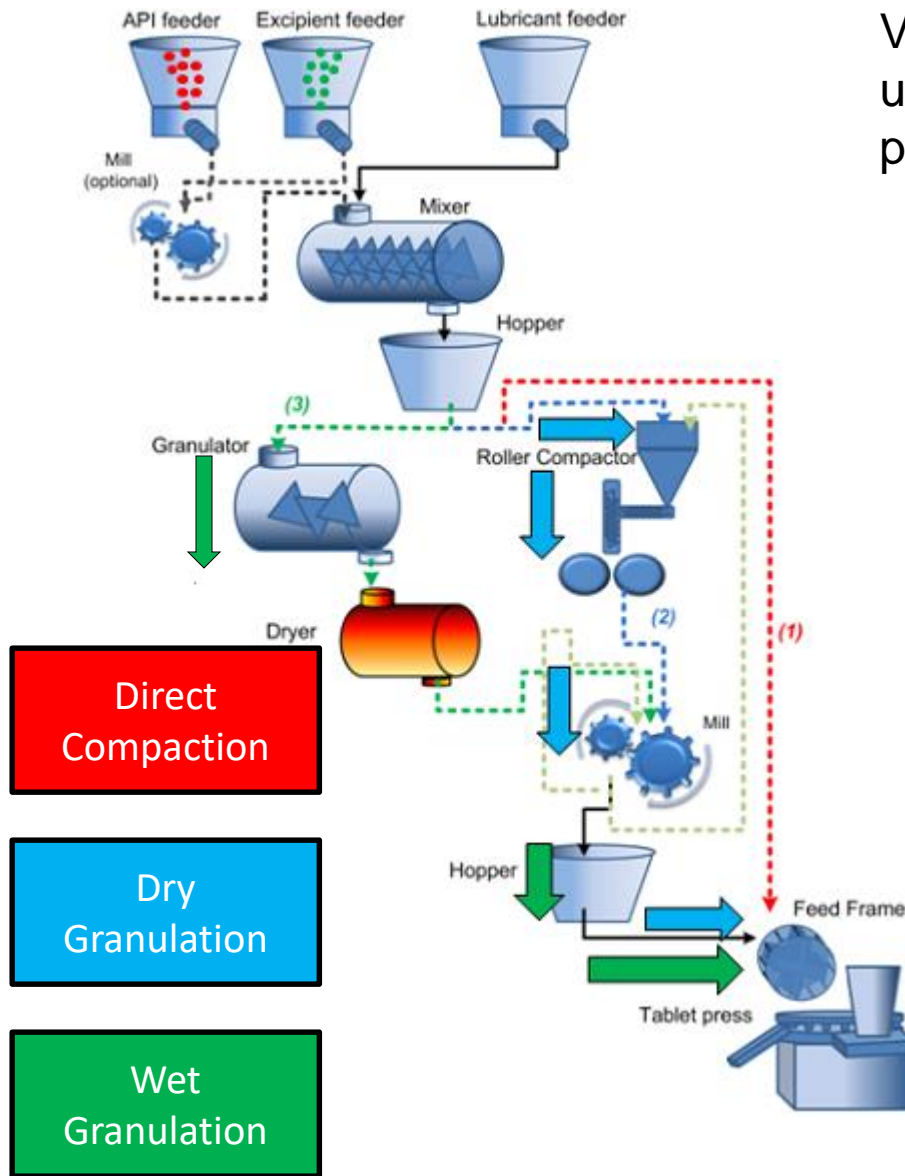
# Hybrid modeling approaches for pharmaceutical unit operations

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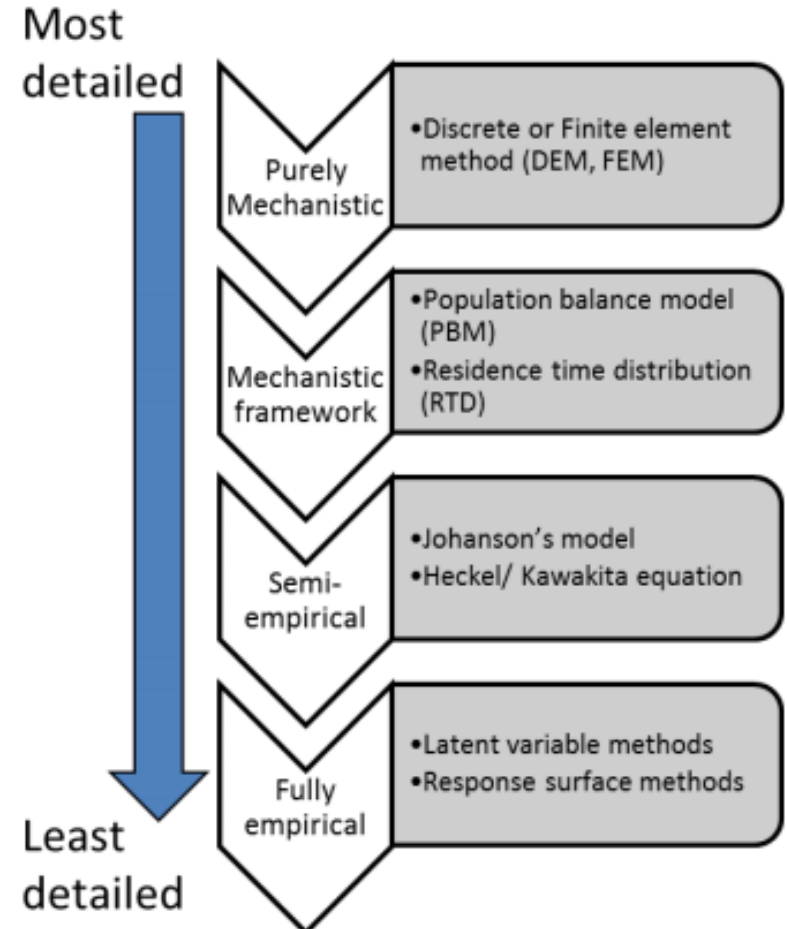
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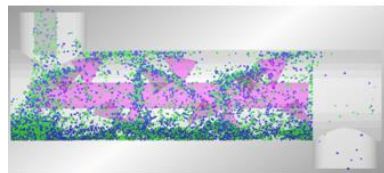
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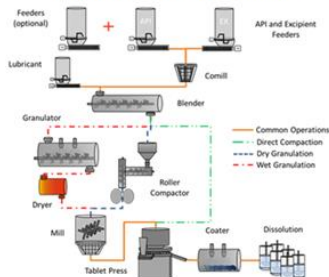
Variety of modeling techniques have been used addressing influence of particle level phenomenon on bulk behavior



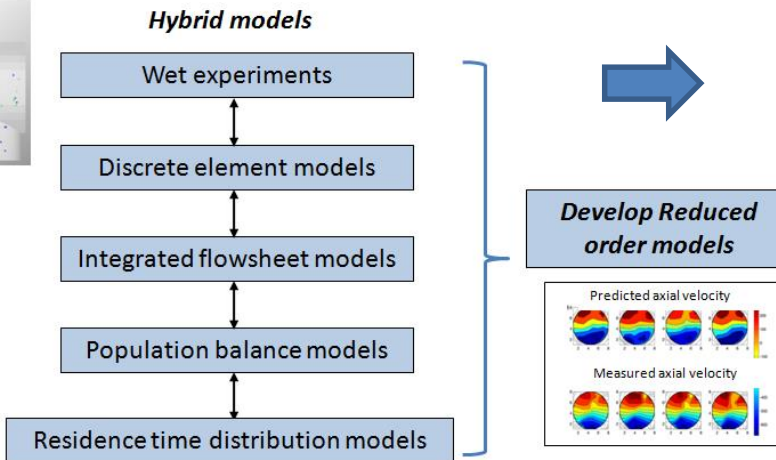
- Develop hybrid/reduced order models for understanding and evaluating pharmaceutical unit operations performance
- **Motivation:**
  - Reduce computational expense from using high dimensional models such as Discrete element model, Population balance model, Integrated flowsheet models etc.
  - Utilize capabilities of different modeling techniques and explore hybrid approach for increased efficiency and accuracy



DEM for continuous mixer



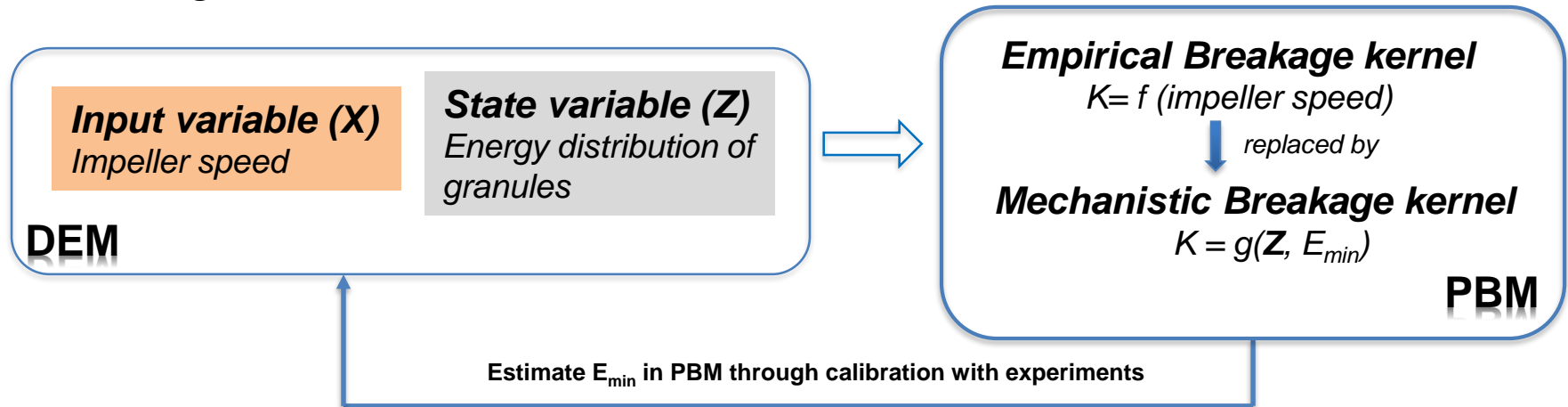
Integrated flowsheet model



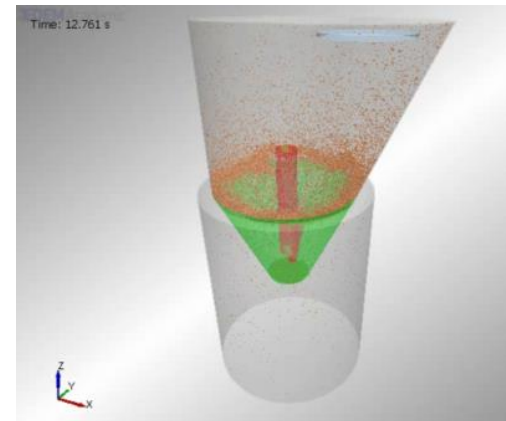
- Principal component analysis  
If  $X_{N \times K}$  is data matrix then  
 $T_{N \times A}^{NEW} = X_{N \times K} P_{K \times A}^{NEW}$   
 $A$  : Reduced dimension ( $< K$ )
- Partial least squares regression  
 $X = TP' + E$  ;  $T = XW^*$   
 $Y = TC' + F = XB + F$   
Scores:  $T, U$   
Weights:  $W^*, C$
- Kriging, Radial basis functions, Artificial neural networks, HDMR are some other Reduced order modeling techniques

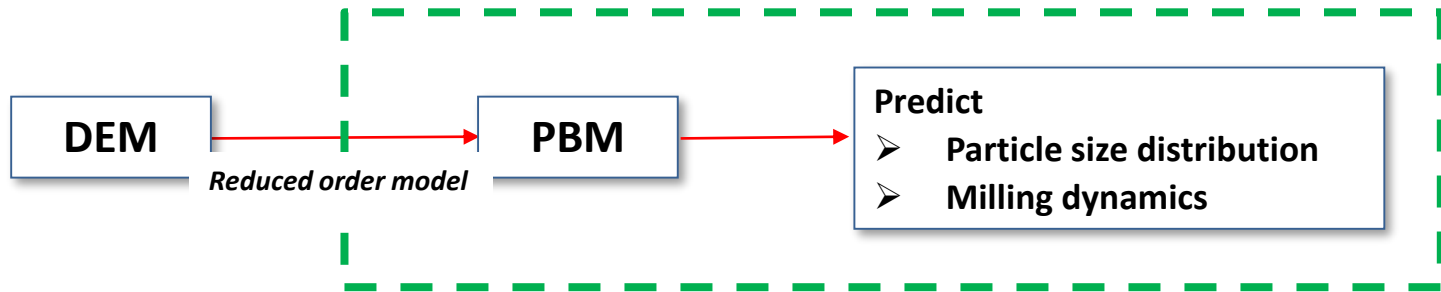
Various projects involved are in the following slides....

Binary breakage of particles in comill due to impact of impeller was modeled in DEM. Energy distribution data from DEM is used as input to PBM to incorporate a mechanistic understanding to the model.

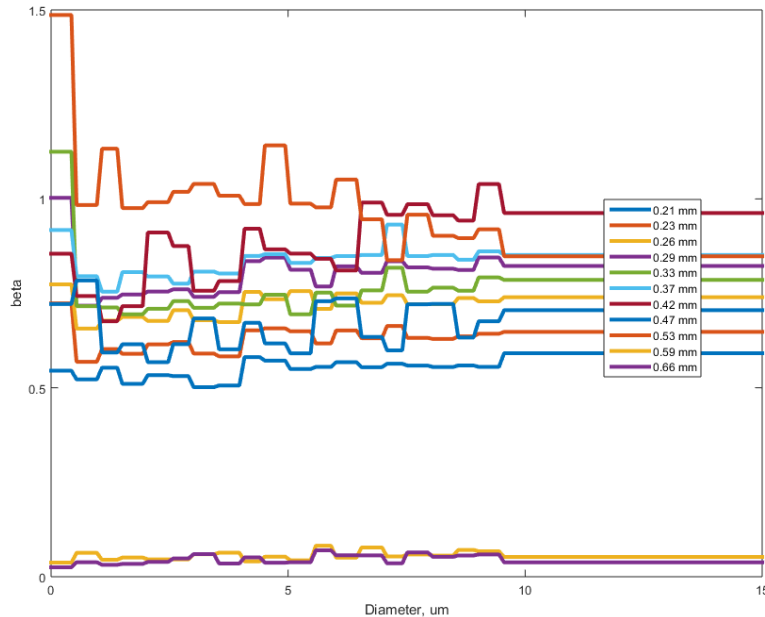


- Breakage of granules in DEM occurs when energy > **Threshold energy** ( $E_{min}$ )
- A **PBM-DEM coupling** algorithm is used to
  - predict milled product particle size distribution
  - estimate Threshold energy, which is a material property
  - provide a means to **effectively calibrate** the model with experiments
  - capture advantage of PBM which is computationally **less expensive**





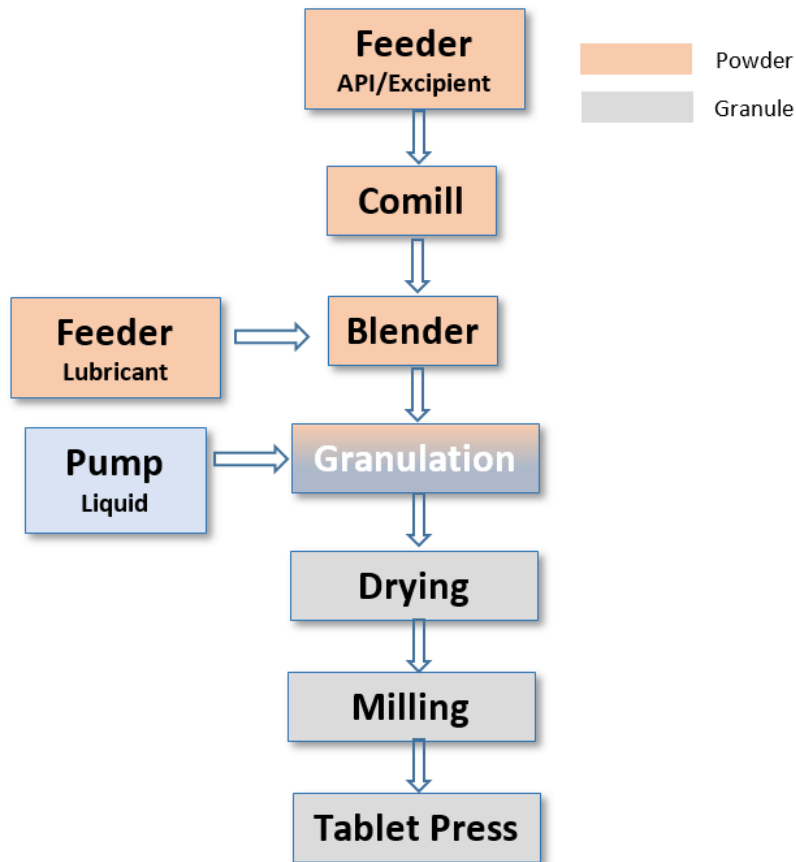
*Breakage kernel values from mechanistic information for various particle sizes*



Efficient integration into a flowsheet model for continuous line

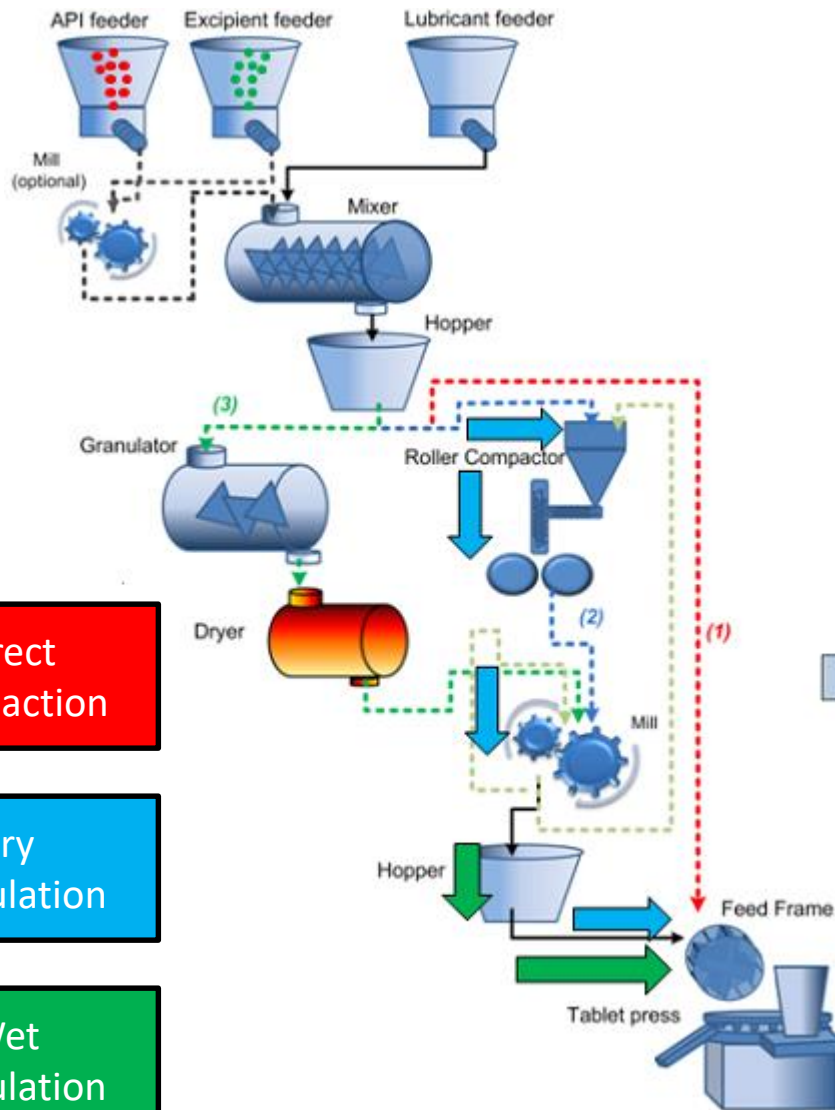
- DEM Simulations run at various flow rates and impeller speeds
- Collect mechanistic information as such as energy distribution, collision frequency for various particle sizes at various times
- Use this mechanistic information in a kernel via developing reduced order model to efficiently represent the data in PBM; And predict mechanistic values at new flow rates and impeller speeds

## Integration of various units in a wet granulation manufacturing route into a flowsheet model



- To model and predict effects of disturbances from various sources
- Efficiently perform sensitivity analyses to understand effect of various operating parameters on product quality
- To identify feasibility regions for making on-spec material
- To predict and track the path of off-spec material

Thank you!



Direct  
Compaction

Dry  
Granulation

Wet  
Granulation

