



# **Mechanistic Modelling Approach to Continuous Granulation Process in Pharmaceutical Industries**

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UGent



# Ashish Kumar

2007,  
Bachelors and Masters in Bioengineering  
from India

Worked 2-yrs for a mAb production unit  
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2009,  
Moved to Netherlands...

TU Delft for Professional doctorate in  
engineering

Worked for Sanquin Plasma product and  
Crucell-J&J as process engineer.

Moved to Belgium....

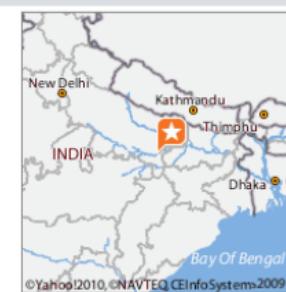
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## Varanasi, India

[travel.yahoo.com](#)

Tue Apr 10 2:56 pm (IST) | Sunny, 99°F ☀

The great Hindu city of VARANASI, also known as Banaras or Benares, stretches along the crescent of the River Ganges, its waterfront dominated by stone ghats where pilgrims and residents come for their daily ritual ablutions. Known to the devout as Kashi, the Luminous – the City of Light, founded by ... [more](#)



## Varanasi - Wikipedia, the free encyclopedia

[History](#) | [Geography and climate](#) | [Economy](#) | [Administration and politics](#)

Varanasi (Sanskrit: वाराणसी Vārāṇasī, Hindustani pronunciation: [vəːrəɳəsɪ] ), also commonly known as Banaras or Benaras (Banāras ...

[en.wikipedia.org/wiki/Varanasi](#) - [Cached](#)

[More results from en.wikipedia.org »](#)

## Official Website Of Varanasi District

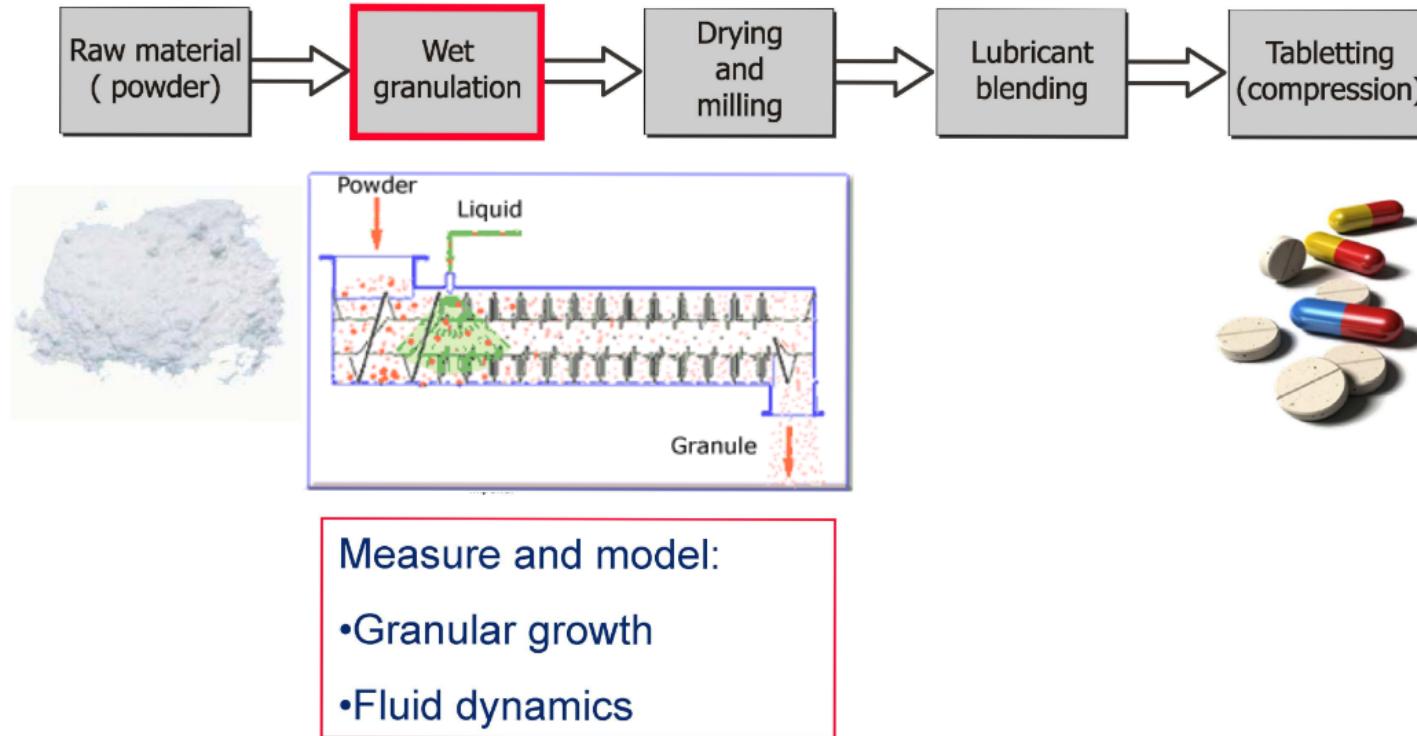
District government site, with historical, tourist and administrative information on the city and its surrounds.

[varanasi.nic.in](#) - [Cached](#)

# Outline

- Scope
  - Equipment
  - Process
- Develop mechanistic models
  - Knowledge on current state of art
  - Basic model formulation
  - Way forward

# Scope: High Shear Wet Granulation



# Scope: Equipment

a

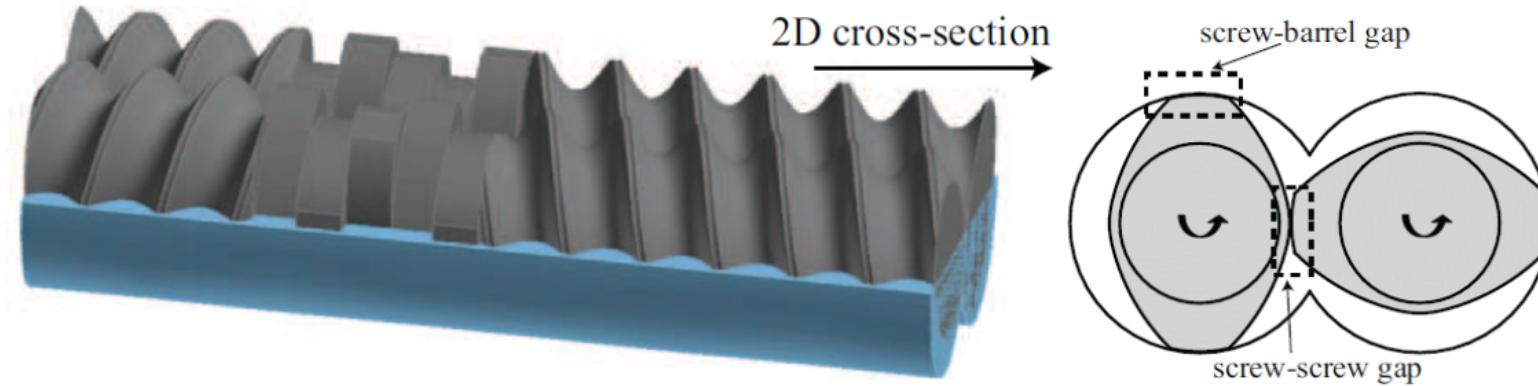


b



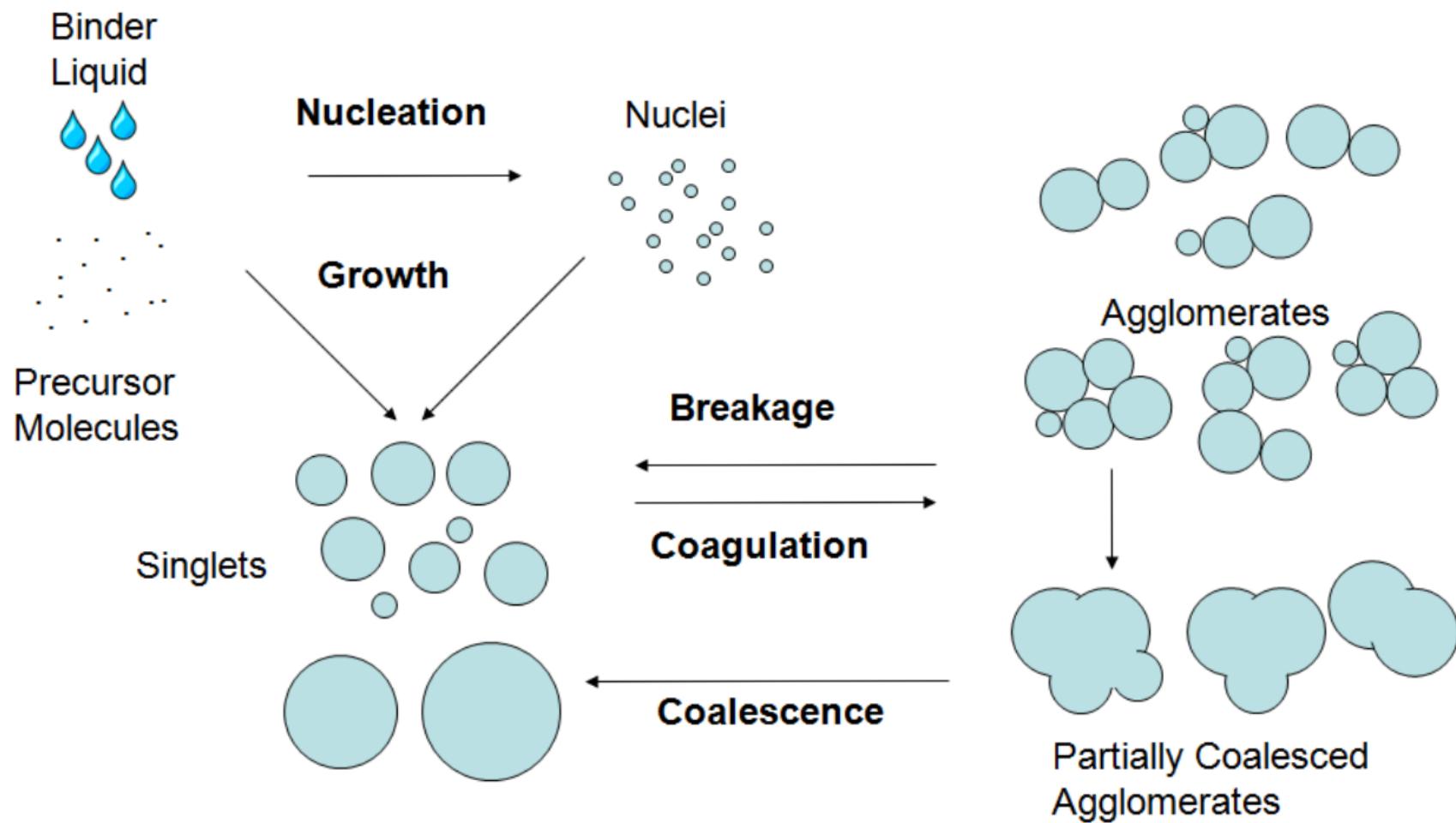
Ref: Real-time assessment of critical quality attributes of a continuous granulation process (Fonteyne et.al)  
(doi:10.3109/10837450.2011.627869)

# Scope: Equipment Twin Screw Granulator- Simplified

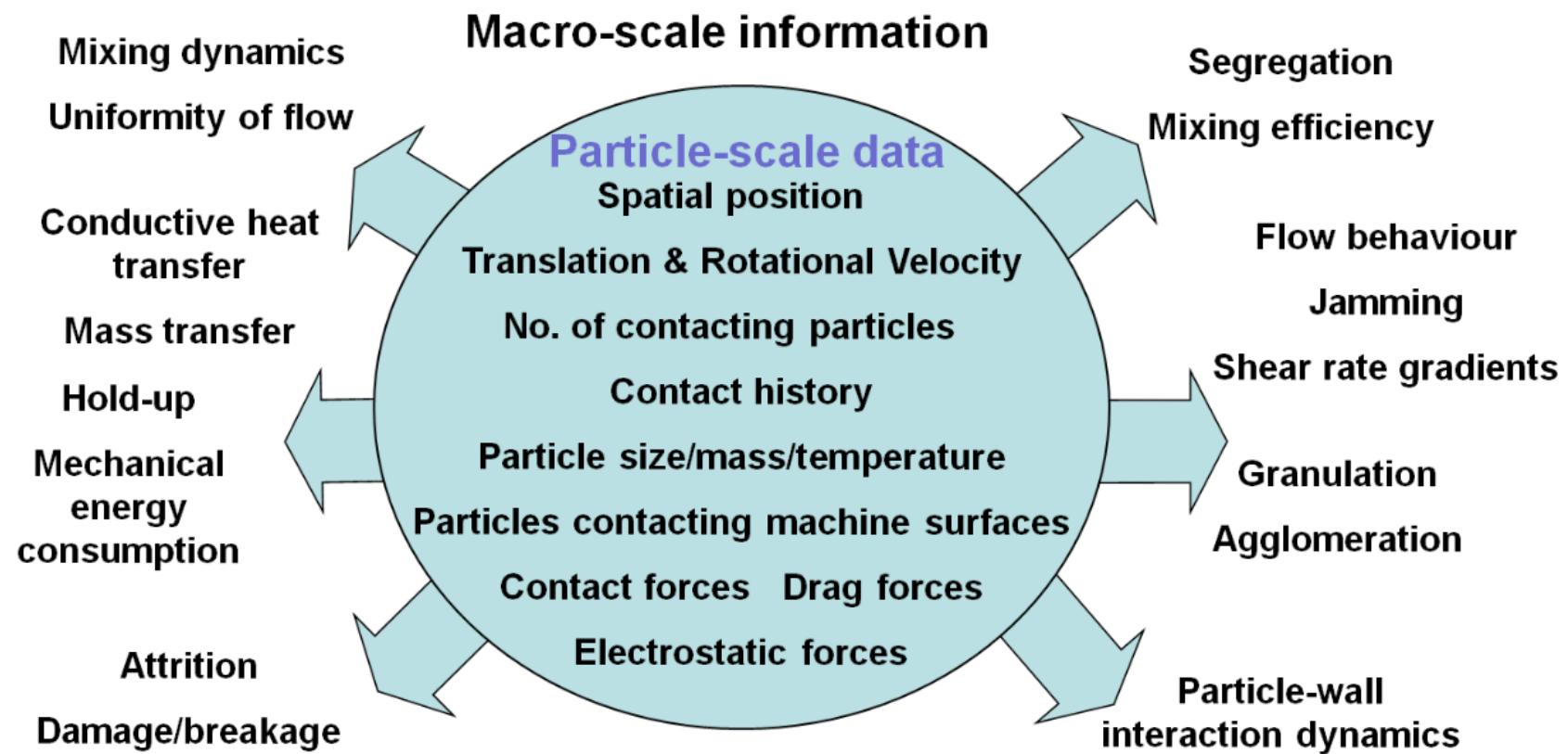


# Scope: Process

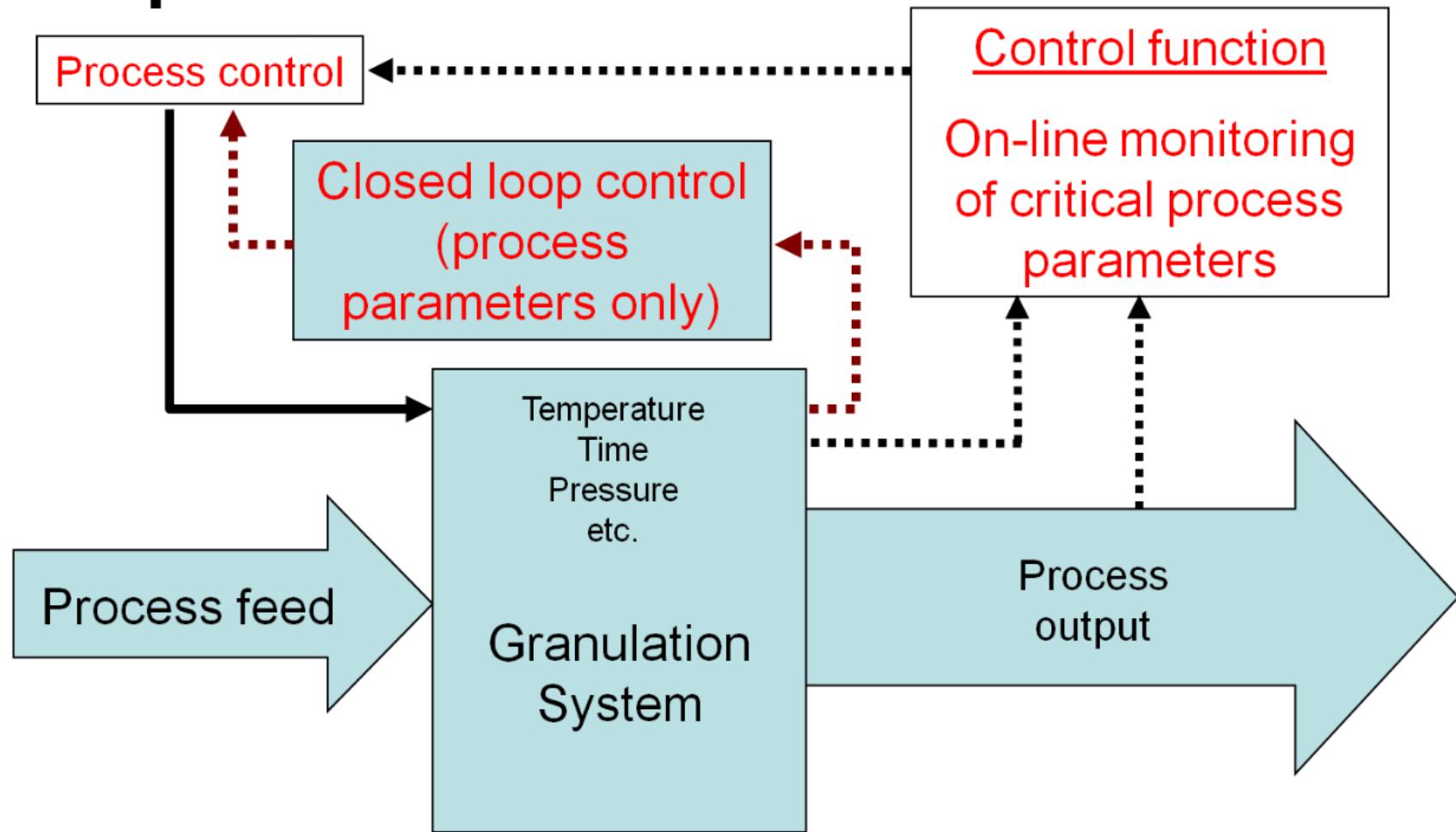
## Particle Formation, Growth & Transformation



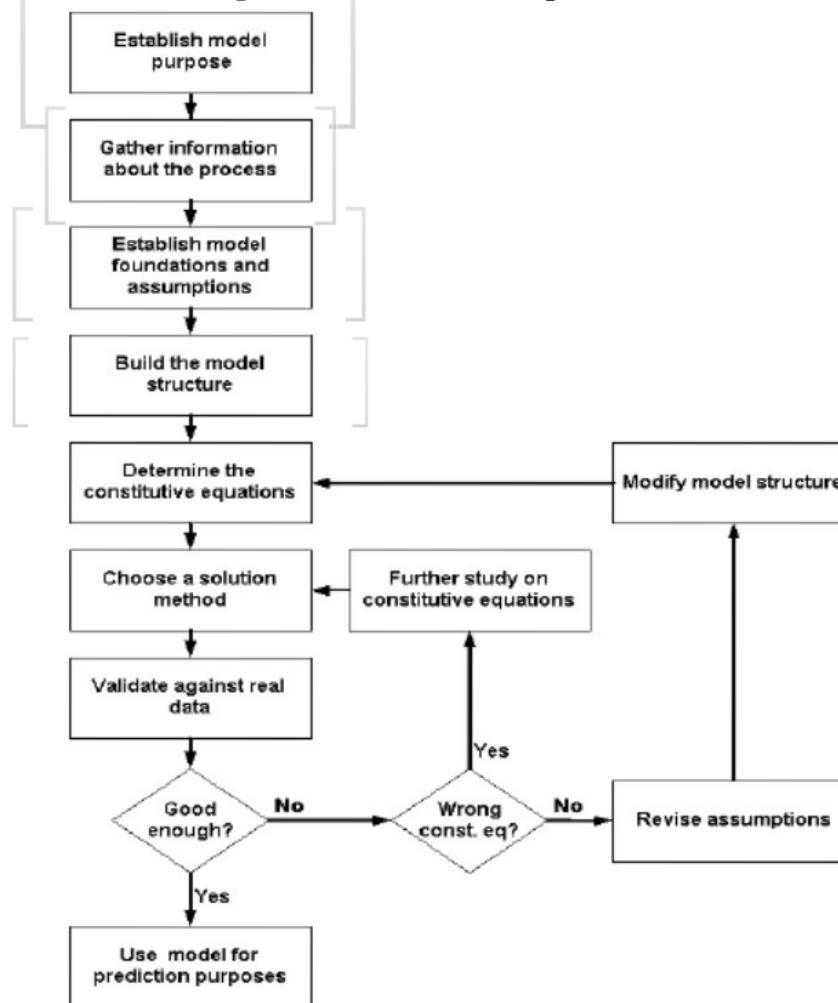
# Scope: Process: Multi-scale computational tool



# Scope: Desired Outcome



# A systematic way to develop mechanistic models



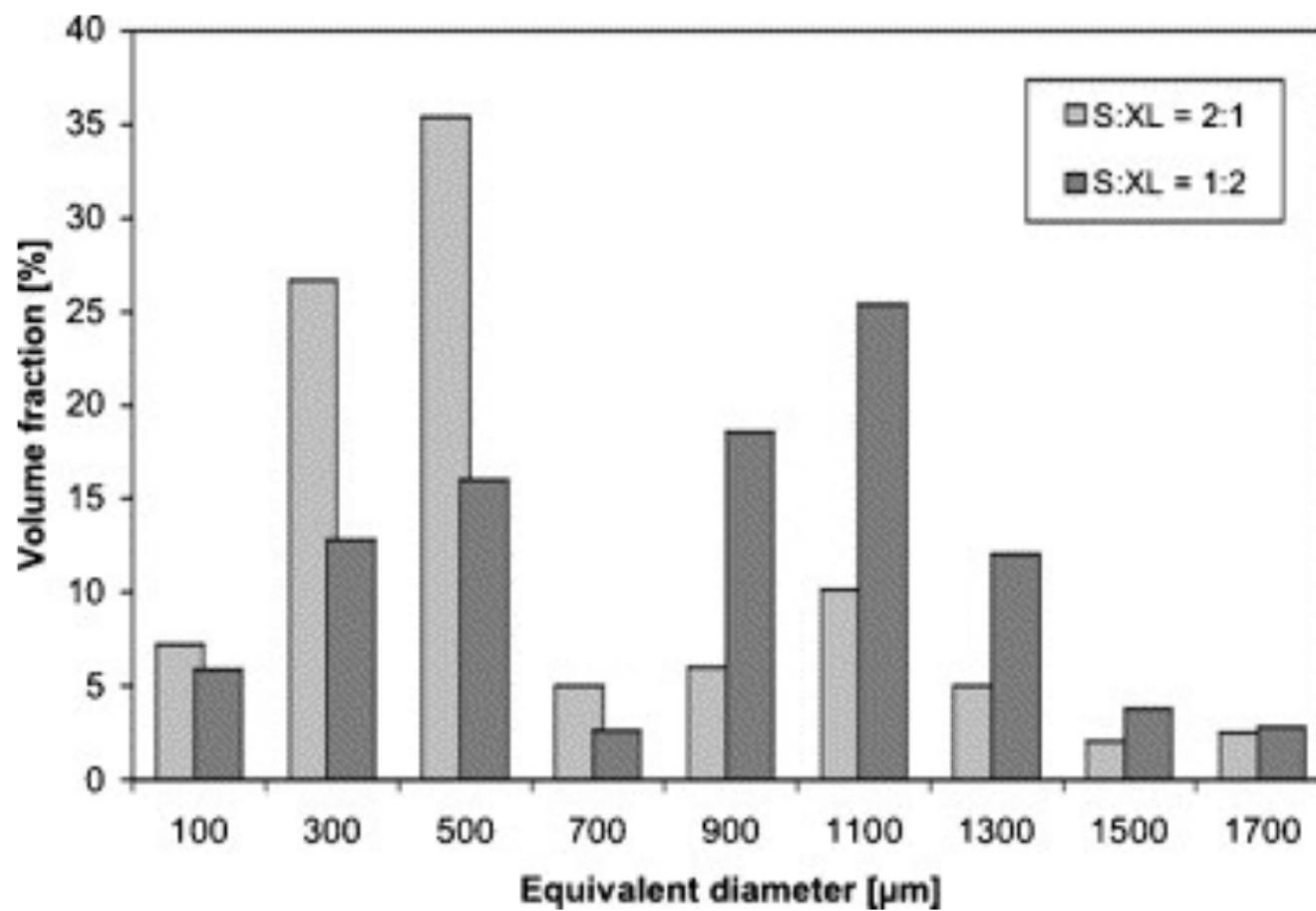
# **matic way to**

**Establish model  
purpose**



**Gather information  
about the process**

# Bimodal Granulation Size Distribution



# Representative graph: Not from data of current project

**PURPOSE**



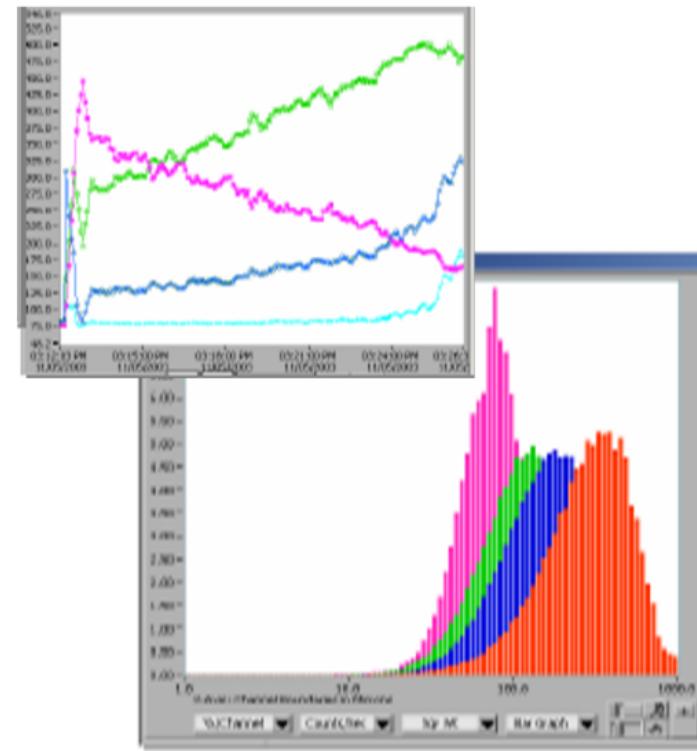
**Gather information  
about the process**



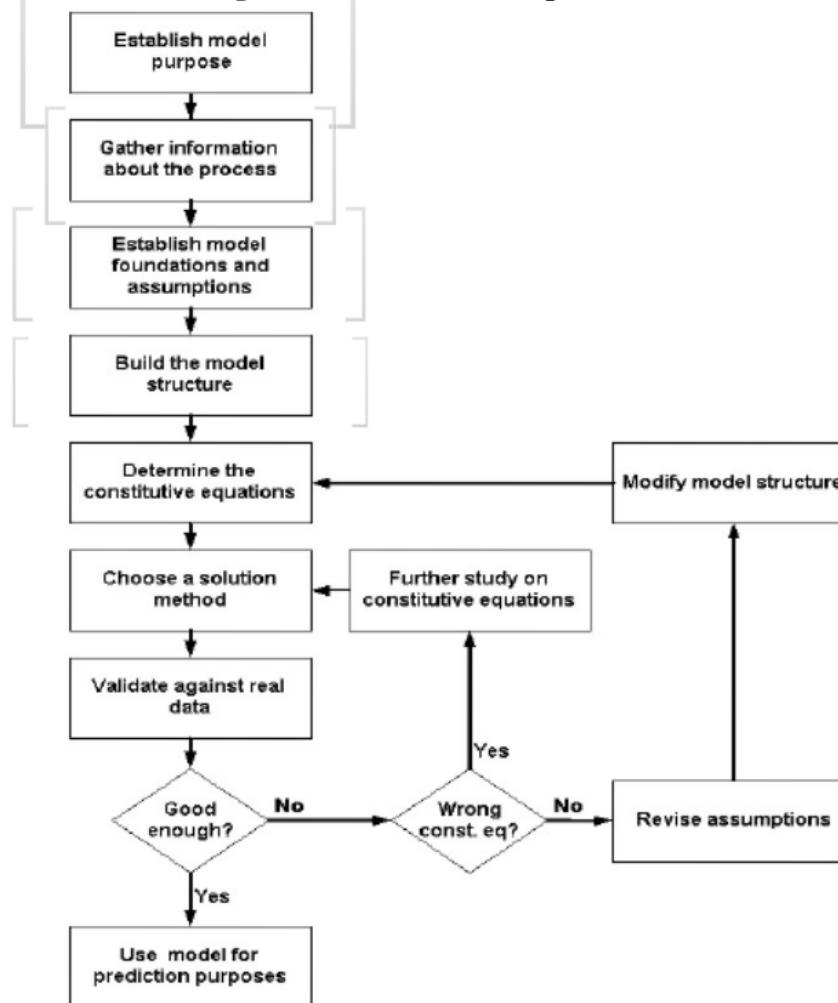
**Establish model  
foundations and**

# Measuring: Granulation Size Distribution

- Sieve
  - Vibrating spring
- Image Analysis
  - Camsizer
  - Pharma vision, Bead Check
  - Image Eye
- Optical
  - Light scattering, Malvern/Sympatec
  - Lasentec FBRM and PVM
  - Malvern Parsum
- Indirect
  - NIR, Ultra Sound, Impeller torque
  - Surface photo correlation



# A systematic way to develop mechanistic models



# Modeling: Granulation Size Distribution

## Handbook of Pharmaceutical Technology Technology

21

### Granulation Process Modeling

I. T. Cameron and F. Y. Wang

Particle and Systems Design Centre, School of Engineering,  
The University of Queensland, Queensland, Australia

#### 1. MODELING OF GRANULATION SYSTEMS

In this section, we introduce the background to granulation modeling by posing the question, "Why model?" and a further one, "How are models used in granulation systems technology?" The following sections seek to answer these questions and demonstrate the benefits that can be derived from appropriate granulation process modeling.

##### 1.1. Motivation for Modeling

There are many motivations for modeling granulation systems that are common to all process-related modeling. This is an area, that has grown enormously over the last 50 years. Michaels (32) has pointed out that despite the change of particle technology from an underfunded and widely scattered research enterprise to a thriving globally recognized engineering discipline over the past 25 years, design and analysis of industrial particulate processes remain rooted in empiricism. Without exception, granulation processes, like most solid-handling operations, continue to be one of the least understood and hence inefficient in the process industries. Thus, granulation remained more of "an art than a science" until a decade ago, as stated by Litster (24). Granulation operations were performed by employing popular practice rather than through systematic scientifically-based strategies. The ineffectiveness of this approach led researchers on a quest to represent the dynamic or steady-state characteristics of systems through a deeper understanding of the relevant phenomena of the physico-chemical phenomena being studied. Likewise in granulation systems, there has been a growing interest in the building of models and their deployment to address a range of applications.

##### 1.1.1. Benefits

The benefits from the use of modeling include:

- An increased understanding of the governing mechanisms through endeavoring to represent them in the model description.

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## Handbook of Powder Granulation

### CHAPTER 24 Population Balance Modelling of Granulation

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# Publications from research groups:



**Research Center Pharmaceutical Engineering GmbH, Graz, Austria**  
Project coordination, process engineering, PAT, QbD, pilot plant



**G.L. Pharma GmbH, Lannach, Austria**  
Pharmaceutical company; future user of the production platform



**Coperion GmbH, Stuttgart, Germany**  
Extrusion technology: know how & hardware supplier



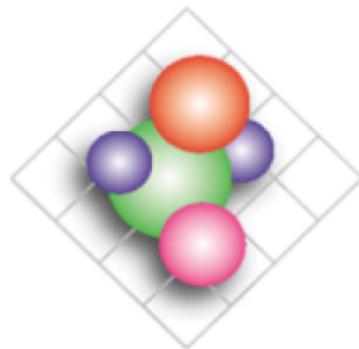
**Automatik Plastics Machinery GmbH, Grossostheim, Germany**  
Granulation technology: know how & hardware supplier



**Institute for Process and Particle Engineering,  
Graz University of Technology, Graz, Austria**  
Process engineering



**Institute for Pharmaceutical Sciences, University of Graz, Austria**  
Formulation development



Dr. Agba Salman  
Dr. Gavin Reynolds  
Mr. Amol Nilpawar  
Mr. Hong Sing Tan



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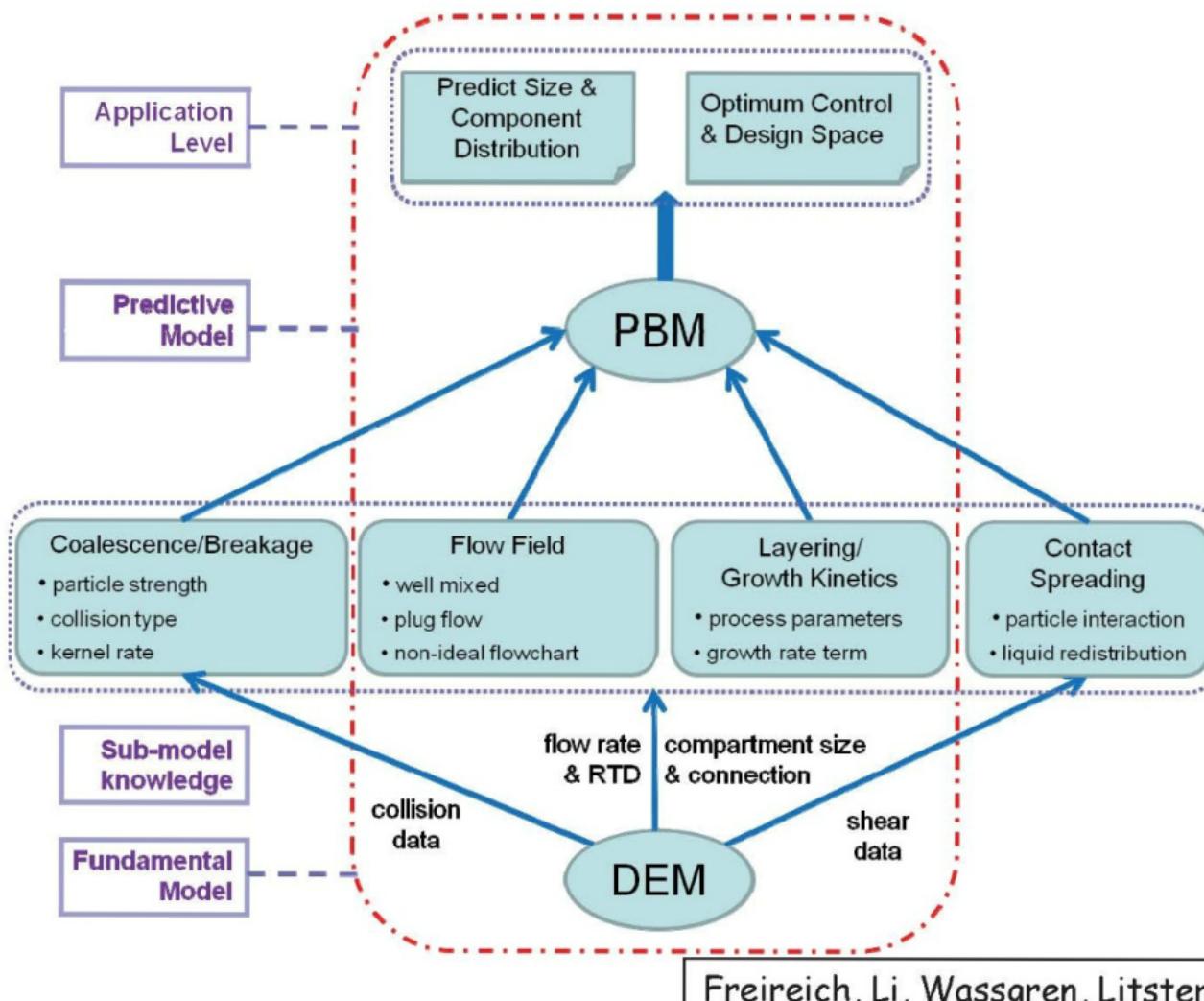
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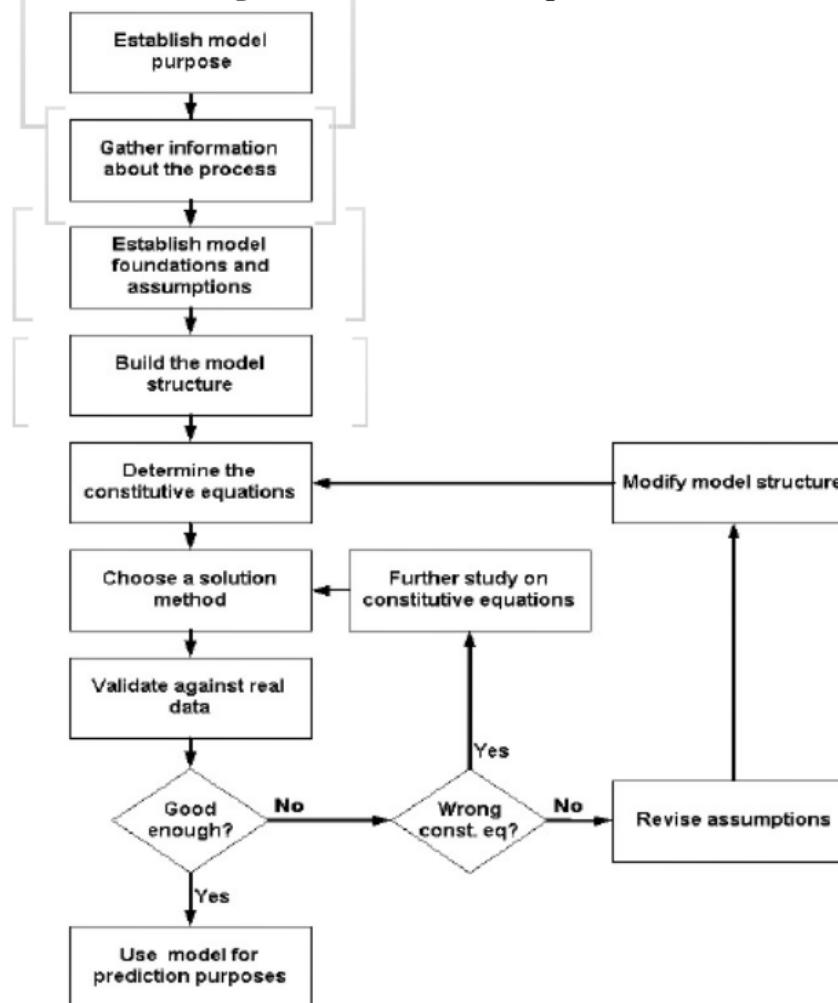
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UNIVERSITY OF PUERTO RICO AT MAYAGÜEZ

# Example: Combined PBM and DEM based approach for granulation



# A systematic way to develop mechanistic models



# Describing granules and its distribution

- 2 internal co-ordinates
  - particle mass  $\zeta_1$
  - liquid mass  $\zeta_2$
- Two dimensional population density function  $\psi$
- The number of particles in the neighbourhood  $(\zeta_1, \zeta_2)$  is



$$d\psi = f(\zeta_1, \zeta_2) d\zeta_1 d\zeta_2$$

# Population Balance

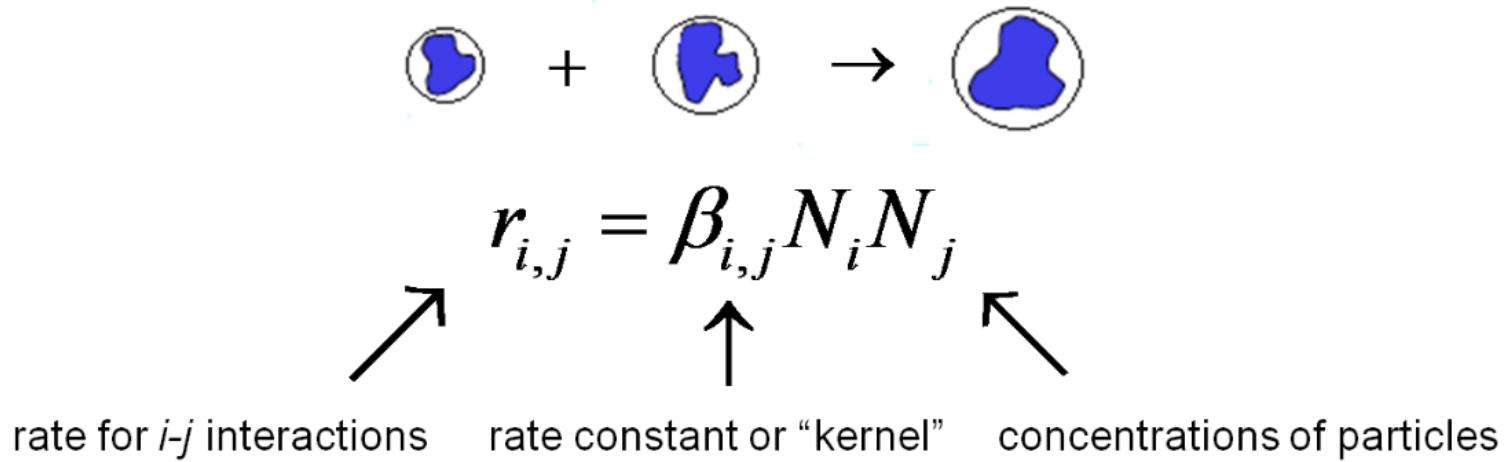
$$\underbrace{\frac{1}{V} \frac{\partial (V\psi)}{\partial t}}_{\text{Accumulation}} = \underbrace{\sum_j \frac{q_j \psi_j}{V}}_{\text{Inflow} - \text{Outflow}} + B - D - \underbrace{\sum_{i=1}^m \frac{\partial (v_i \psi)}{\partial \zeta_i}}_{\text{Generation} - \text{Disappearance}},$$

$$B = \frac{(\text{birth of entities})}{\left( \frac{\text{unit}}{\text{time}} \right) \left( \frac{\text{unit}}{\text{volume}} \right) \left( \frac{\text{unit}}{\text{property}} \right)}$$
$$D = \frac{(\text{death of entities})}{\left( \frac{\text{unit}}{\text{time}} \right) \left( \frac{\text{unit}}{\text{volume}} \right) \left( \frac{\text{unit}}{\text{property}} \right)}.$$

$\psi(t, \zeta_1, \zeta_2, \dots, \zeta_m)$  is the multidimensional population density distribution

(Hulbert & Katz 1964) and (Randolph 1964)

## Mechanism aggregation only



Aggregation rate = Collision rate  $\times$  Efficiency

$$\beta_{i,j} = \beta_0 \times \psi$$

$$\psi = \begin{cases} 1 & \text{if } St \leq St^* \\ 0 & \text{if } St \geq St^* \end{cases}$$

## Solution methods: Partial list of techniques

- Similarity Solutions
  - Laplace Transforms
- }
- If analytical method works use it!
- 
- Discrete Methods
  - Sectional Methods
  - Monte Carlo Methods
- }
- to get distribution detail right,  
but...  
it is a 1-D problem, and  
it is a stand-alone model
- 
- Moment Methods
- }
- If an approximate distribution will do, or  
if the distribution is multivariate, or  
if the model will be embedded in a larger  
model (typical of process simulation)

## **Software tools:**

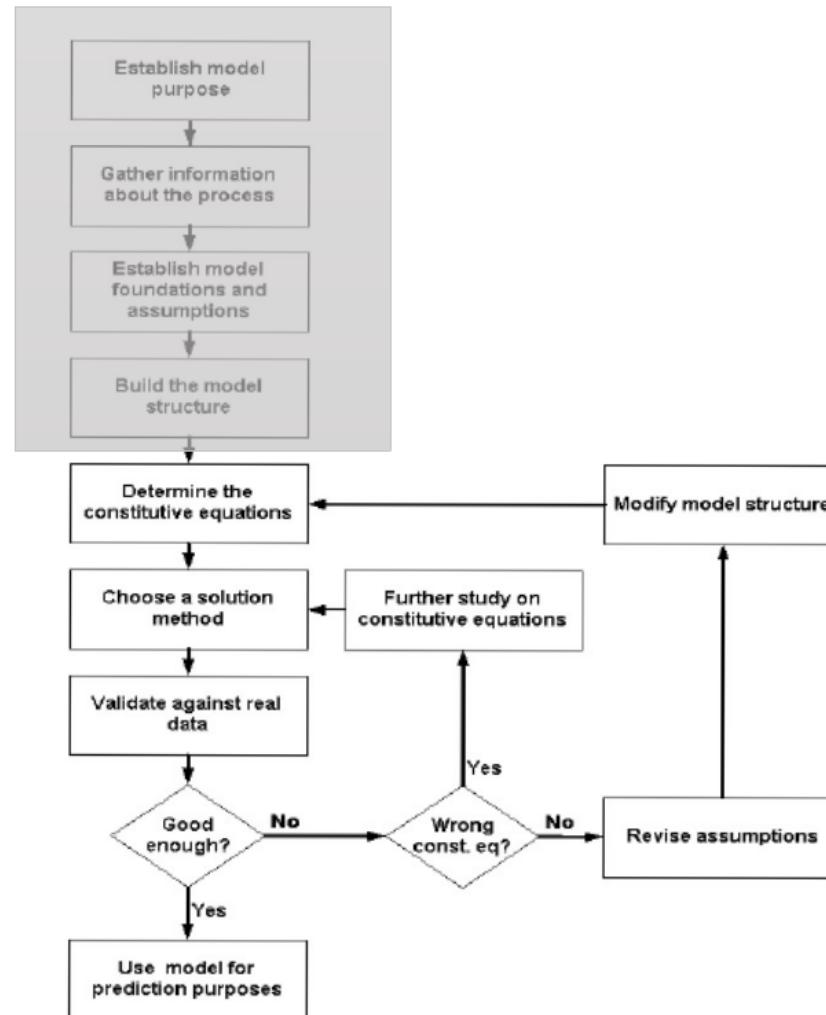
Purdue University, United States: C++, Matlab  
(Jim Lister, Wassgren CR)

Chalmers University of Technology, Sweden: Matlab/Fluent  
(Anders Rasmuson)

KU Leuven, Belgium: C++/Python  
(Bert Tijskens)

Research center pharmaceutical engineering GmbH, Austria:  
OpenFOAM

# The way forward



# Thank You!

