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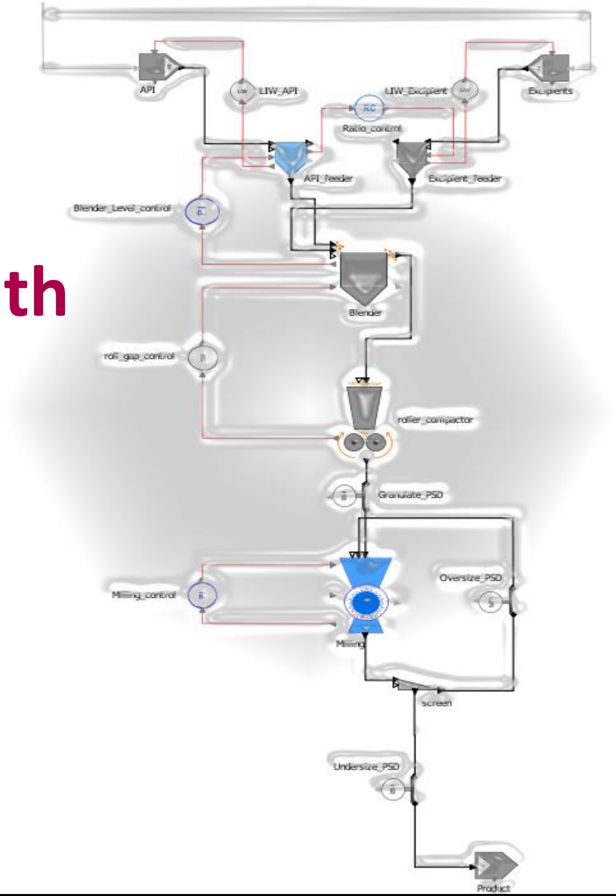
Intelligent Decision Support and Control Technologies for Continuous Manufacturing and Crystallisation of Pharmaceuticals and Fine Chemicals (ICT-CMAC)

WP4:Plant-wide Modelling and Control



A Population Balance-based Dynamic Impact Milling Model with an Enhanced Single Particle Breakage Kernel

Qinglin Su, Zoltan K. Nagy, Chris D. Rielly
Loughborough University

@PSE Advanced Process Modelling Forum, London, 22-23 April, 2015

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Content

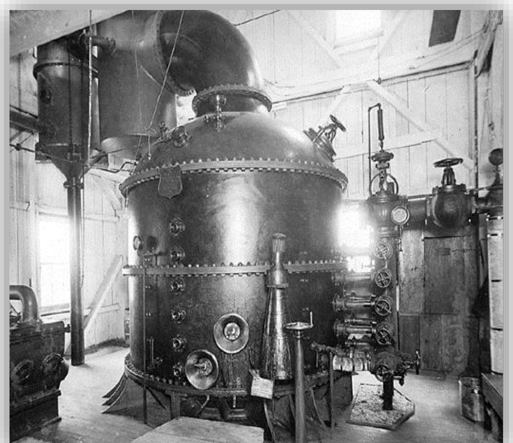
- Introduction
- Single particle breakage model
- Dynamic modelling of impact milling
- Results and discussion
- Conclusions and future work

Introduction

- The pharmaceutical and fine chemical industrials have used **batch** crystallisation as a trusted method of isolating and purifying high value active pharmaceutical ingredients (APIs).

‘Industrial’ scale in the 18th century

20th century process industrial scale



Modern day industrial batch crystalliser

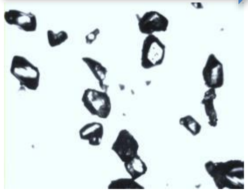
[1] http://www.wopc.co.uk/otc/production.html
[2] http://www.lib.lsu.edu/special/exhibits/e-exhibits/sugar/contents.html
[3] http://www.dcsc.tudelft.nl/Research/Current/matrix-58-oifmzengro-1372158498-9dfb.html

Key problems with batch processing

- Batch-to-batch variability in product attributes and qualities
- Difficulties in scaling up of batch processing
- Relatively low processing and energy efficiencies; labour and cost intensive
- Quality-by-testing rather than quality-by-design (QbD)

Formulation

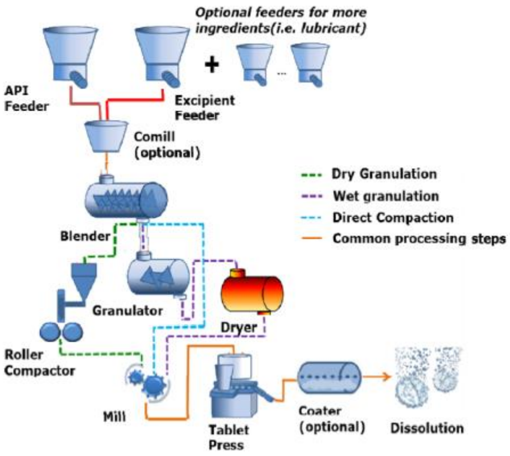
Batch *n*



Batch *n*+1

Batch-to-batch variability

Filtration and solid processing

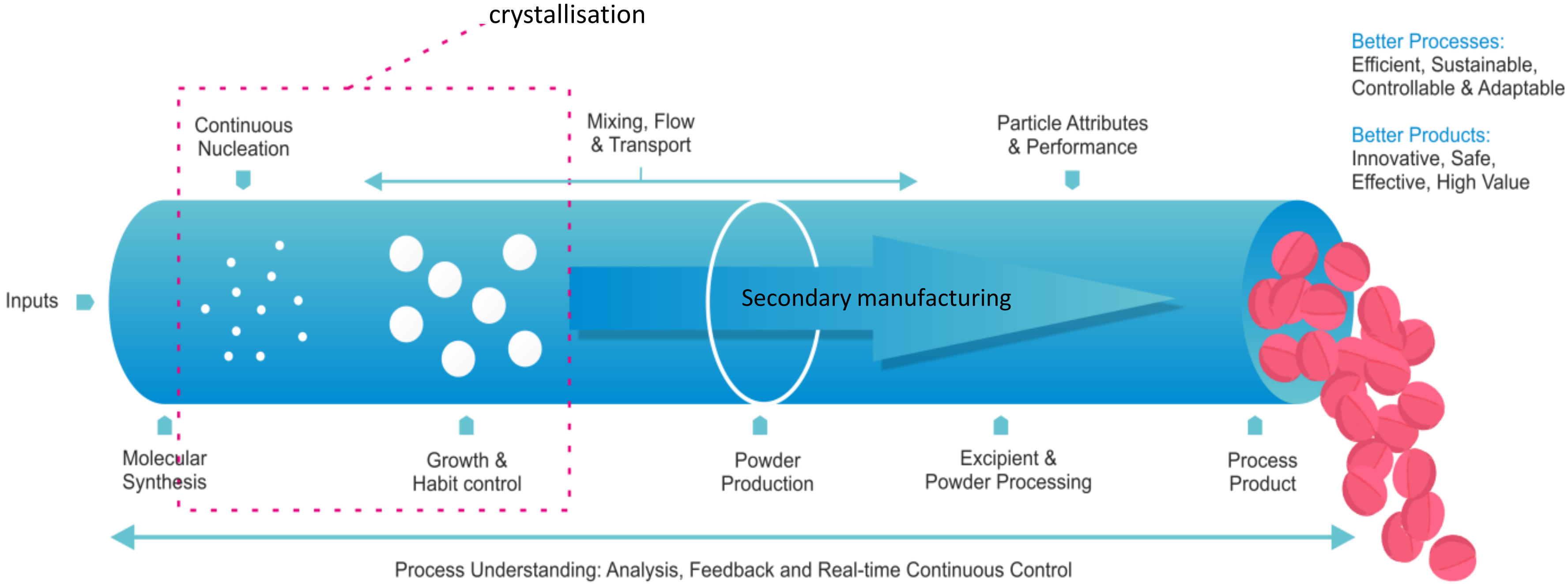


Inconsistent final drug quality and performance

[1] Rogers AJ, Hashemi A, Ierapetritou MG. *Process*. 2013;1:67-127.

Vision: Continuous manufacturing and crystallisation (CMAC)

- Continuous steady-state operation for intensive production
- Compact and consistent production with lower manufacturing cost



"Continuous processing holds the potential to make better, more uniform/consistent products, whilst simplifying production, saving energy, resources and cost."

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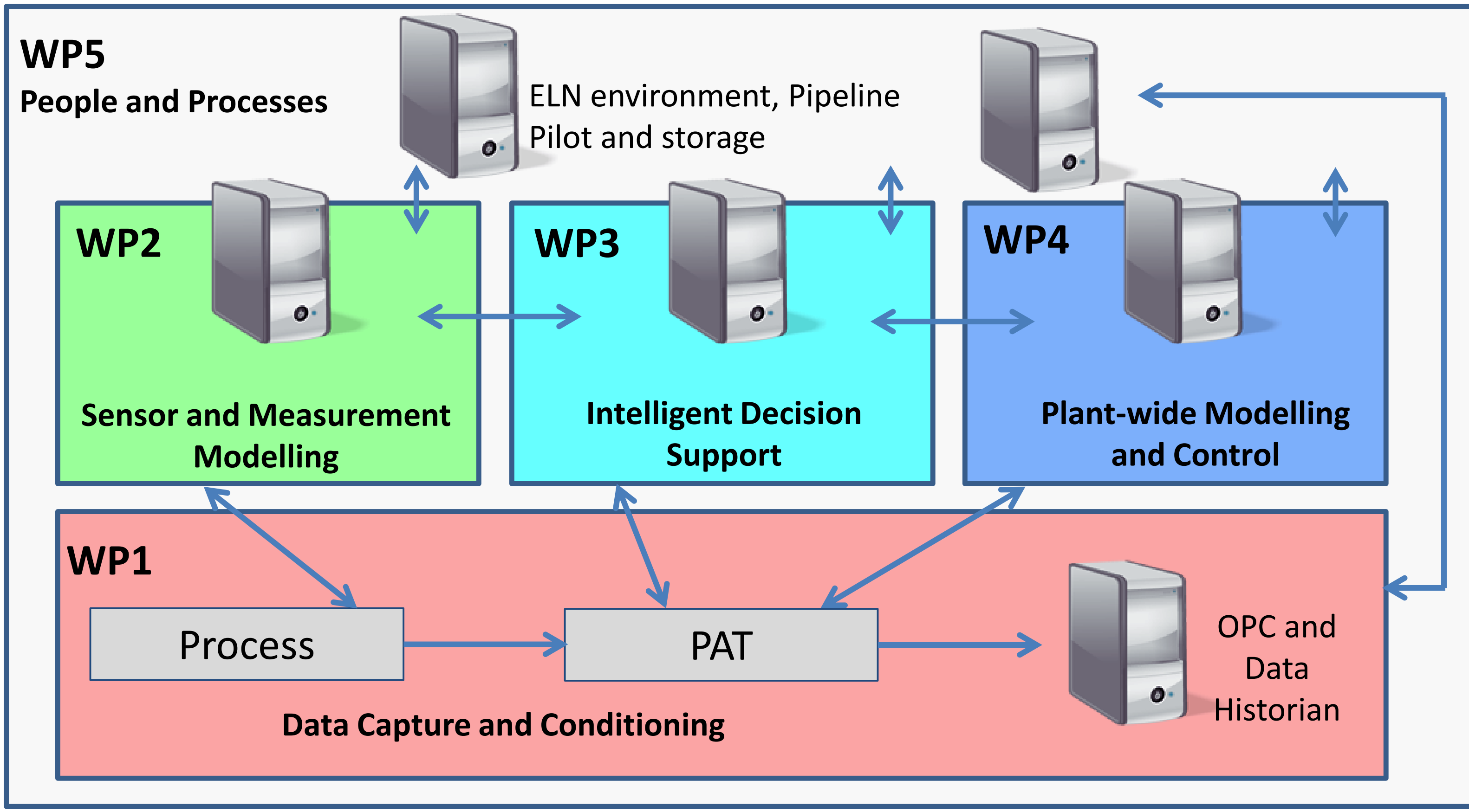
Intelligent decision support and control technology (ICT)



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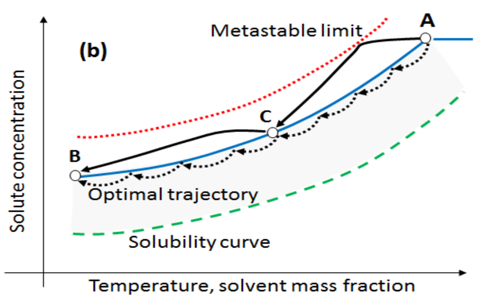
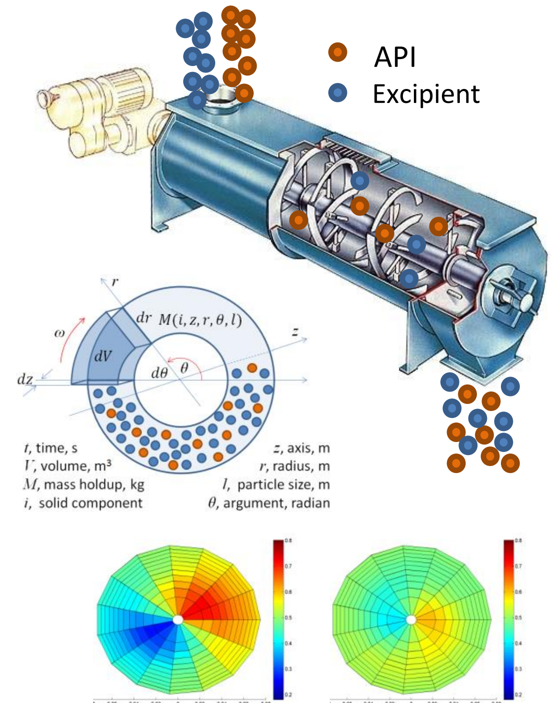
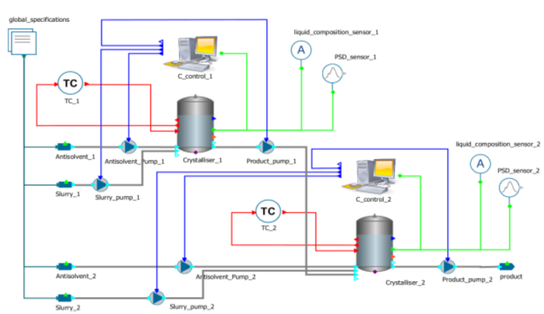
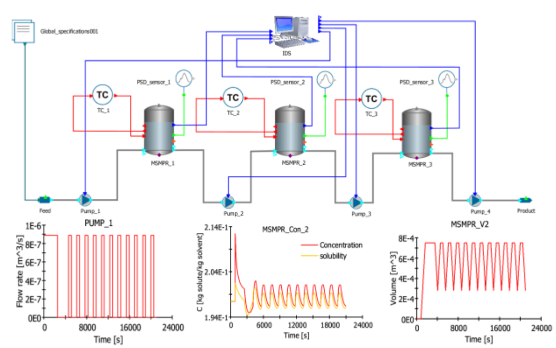
Previous implementation of gCRYSTAL & gSOLIDS

- Modelling and control of continuous anti-solvent crystallisation process
- Model development of a plug-flow crystalliser
- Process modelling and design of periodic flow crystallisation process
- Simulation of a 3D continuous mixing blender









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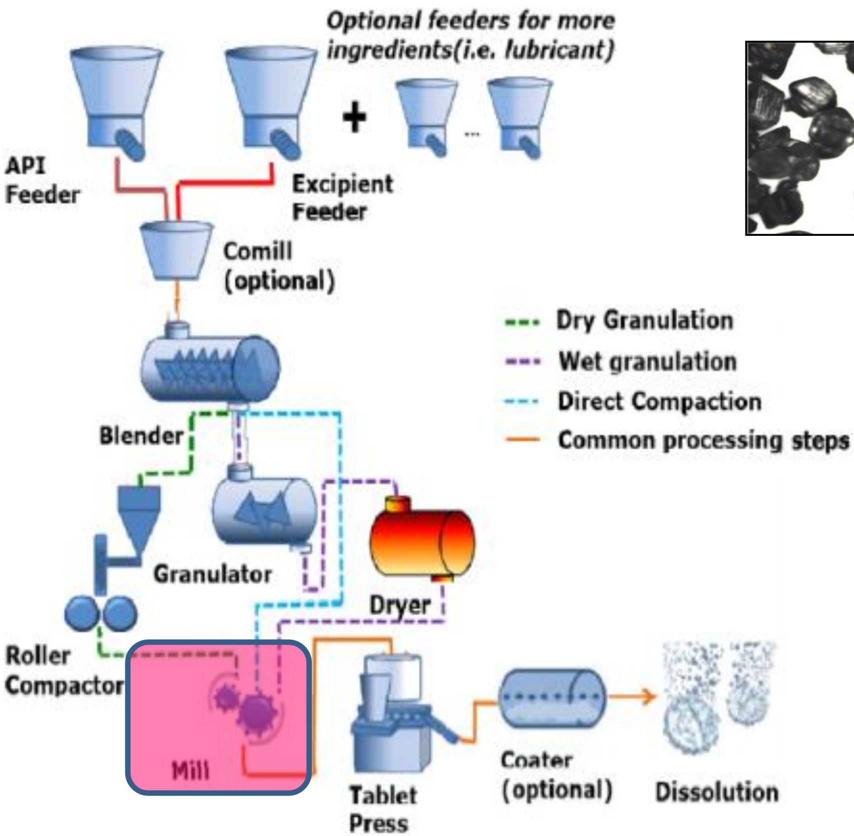
Milling in pharmaceutical industries



[1] Rogers AJ, Hashemi A, Ierapetritou MG. *Process*. 2013;1:67-127.

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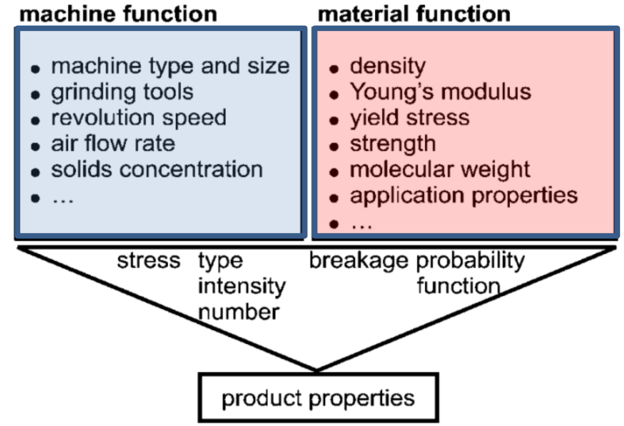
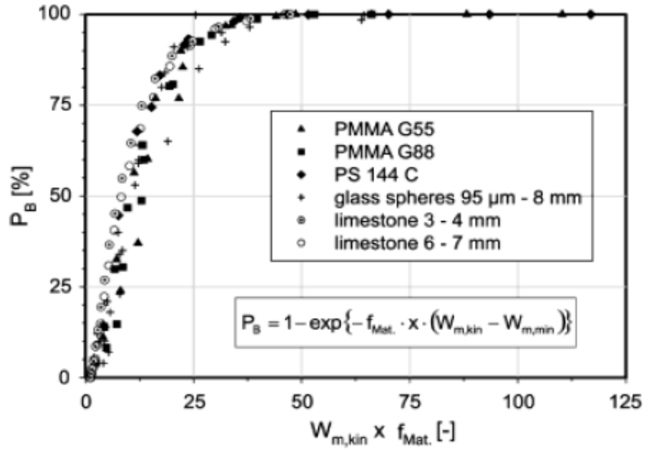
Single particle breakage model

Peukert and Vogel (2001) first reported the separation of two material parameters from the machine and operating parameters.

Breakage probability P_B
denotes the fraction of particles of size w which is broken after k stressing events.



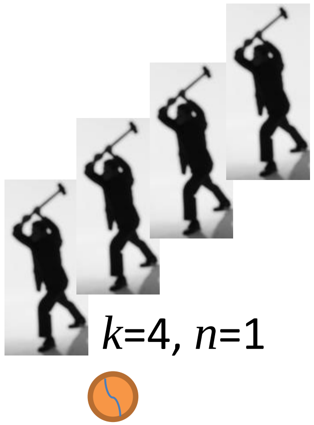
$$P_B = 1 - exp\left(-f_{Mat.} wk\left(W_{m,kin} - W_{m,min}\right)\right)$$



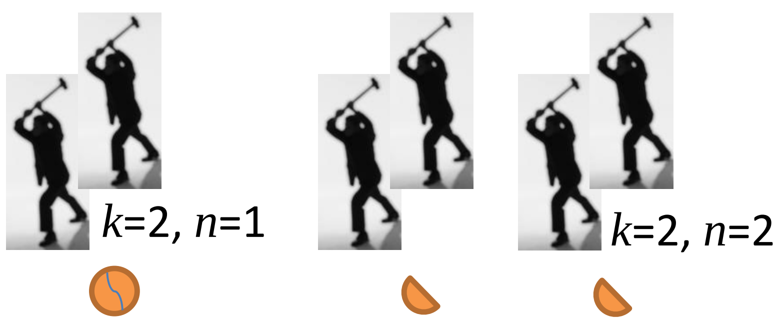
- $f_{Mat.}$: mass-based material strength parameter, kg/Jm
- w : particle size, m
- k : number of successive impacts, dimensionless
- $W_{m,kin}$: mass specific impact energy, J/kg
- $W_{m,min}$: mass specific threshold energy, J/kg

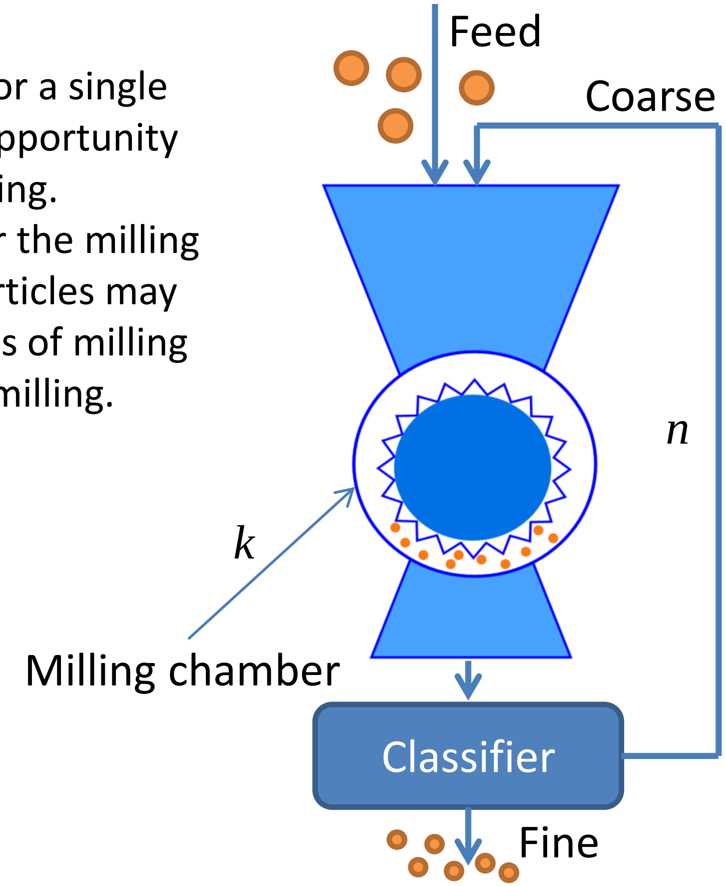
[1] Peukert W, Vogel L. Chemical Engineering and Technology. 2001;24(9):945-950.

Number of successive stressing k & Number of passage of milling chamber n



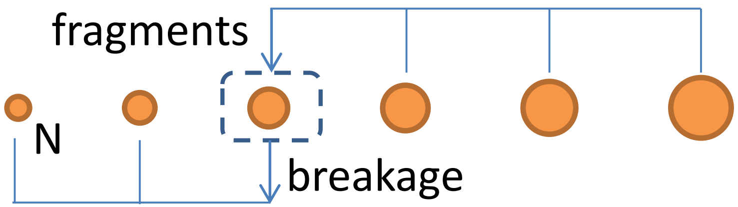
- Within the milling chamber for a single passage, particles have the opportunity to receive k successive stressing.
- If the classifier is assumed for the milling chamber, then the coarse particles may need several pseudo passages of milling chamber to finally leave the milling.





[1] Vogel L, Peukert W. Chemical Engineering Science. 2005;60:5164-5176.

Population balance model based on stressing event



$$m(n) = \prod_{l=1}^{n} \boldsymbol{Z}_l \times m(0)$$

The comminution matrix

$$\boldsymbol{Z}_l = \begin{bmatrix} 1-P_{B,1} & 0 & \cdots & 0 & 0 \\ b_{21}P_{B,1} & 1-P_{B,2} & & 0 & 0 \\ \vdots & & \ddots & \vdots & \\ b_{N1}P_{B,1} & b_{N2}P_{B,2} & \cdots & & 1 \end{bmatrix}$$

$$b_{i,j} = B_{i-1,j} - B_{i,j}$$

denotes the fraction of fragments breaking from class j into the size band i

Breakage probability P_B

Denotes the fraction of particles of size w which is broken after a certain stressing event.

$$P_B = 1 - exp\left(-f_{Mat.}wk\left(W_{m,kin} - W_{m,min}\right)\right)$$

Breakage function B

The size distribution of the fragments, not taking into account the amount of undestroyed particles.

$$B_{M,p}(w,v) = \left(\frac{w}{v}\right)^q \frac{1}{2}\left(1 + tanh\left(\frac{w-w'}{w'}\right)\right)$$

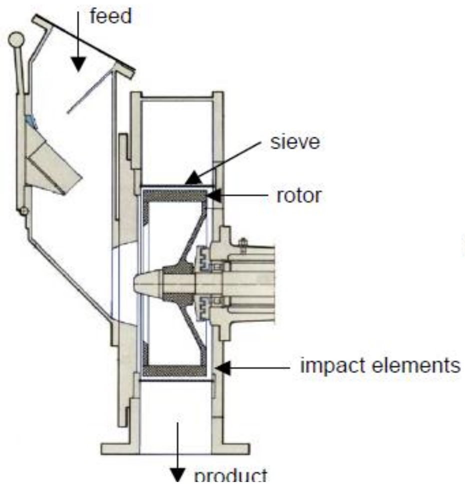
- w : fragmental particle size, m
- v : the size of the mother particle, m
- w' : fragment size for additional fading, m
- q : power law exponent, dimensionless

[1] Vogel L, Peukert W. Chemical Engineering Science. 2005;60:5164-5176.

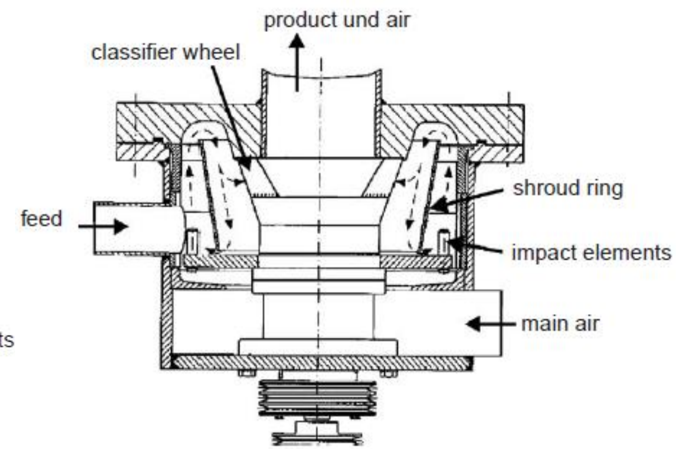
[2] Vogel L, Peukert W. Particle & Particle Systems Characterization. 2002;19(3):149-157.

Applications of PBM based on stressing event

- A mean value of k successive impacts should be assumed, usually k = 1;
- A free tuneable parameter n used for the simulation;
- All the particles receive the same k successive impacts at the same time;
- The model is based on the number of stressing event rather on the time;
- Good for process design but not suitable for dynamic process simulation.



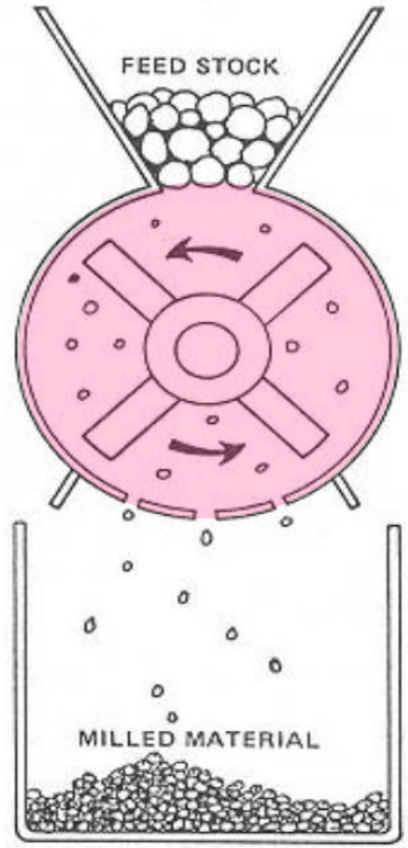
Sieve hammer mill UTL



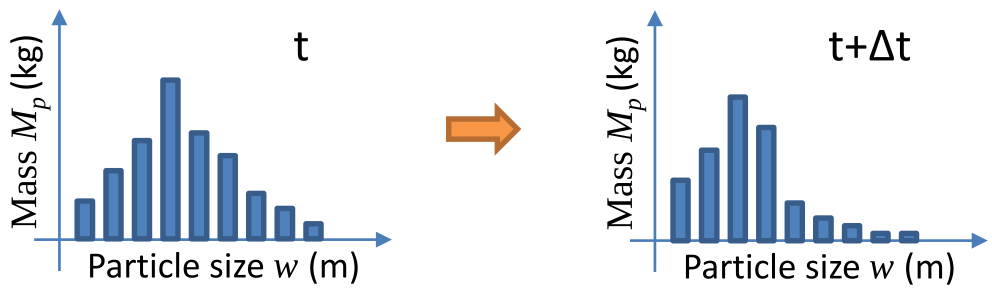
Air classifier mill ACM

[1] Vogel L, Peukert W. Particle & Particle Systems Characterization. 2002;19(3):149-157.
[2] Vogel L, Peukert W. Mineral Processing (Aufbereitungs Technik). 2002;43(08):19-30.
[3] Vogel L, Peukert W. Powder Technology. 2003;129:101-110.
[4] Vogel L, Peukert W. International Journal of Mineral Processing. 2004;74S:S329-S338.
[5] Peukert W, Vogel L. Chemical Engineering and Technology. 2001;24(9):945-950.
[6] Vogel L, Peukert W. Chemical Engineering Science. 2005;60:5164-5176.

Dynamic modelling of impact milling



Objectives:
- Only consider the population balance in the milling chamber
- Focus on process responses to changes in feeding and operation
- Describing breakage rate based on the stressing events



Assumptions:
- Hammer milling occurs in a dilute phase, effects of particle and particle interactions on the milling are negligible.
- When Δt is small, then within this Δt, fragments from the broken particles are not stressed again.

[1] http://3.bp.blogspot.com/-5HxewGIbk0s/UavnEqfu76I/AAAAAAAAAIQ/ePNX_wQcO64/s1600/ball+mill.PNG

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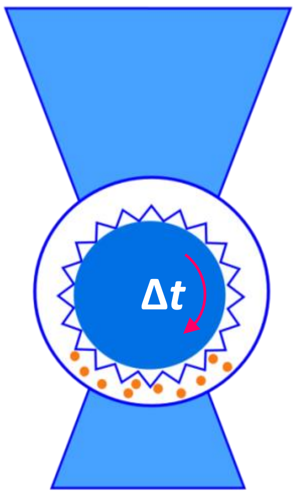
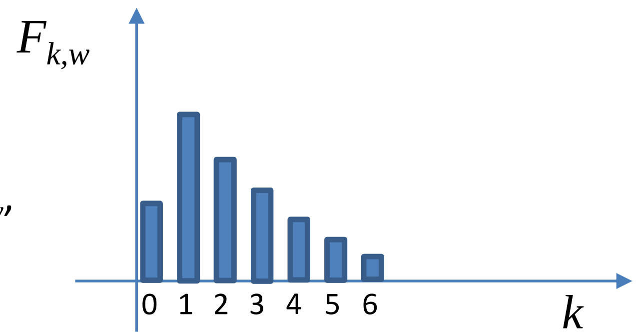
Continuous breakage using Vogel and Peukert model



- Run the milling for a finite time of Δt,
- Within this Δt, denote the fraction of particles of size w (m_w) that have received kth successive impacts as $\Delta m_{k,w}$, where k=0,1,2,…,
- When Δt goes infinity, then

$$F_{k,w} = \lim_{\Delta t \to 0} \left(\frac{\Delta m_{k,w}}{\Delta t m_w} \right)$$



Histogram distribution of $F_{k,w}$ vs. k

$F_{k,w}$: impact rate constant for particles of size w receiving the kth successive impacts, or physically the fraction of particles of size w receiving the kth successive impacts per unit of time, s^{-1}.

The breakage rate

$$S_M(w,t) = \sum_{k=0}^{k=\infty} F_{k,w} P_B(k,w)$$

$$P_B = 1 - exp\left(-f_{Mat.} wk\left(W_{m,kin} - W_{m,min}\right)\right)$$

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Population balance model using Vogel and Peukert model

Population balance equation based on a mass basis

$$\frac{\partial M_p(w,t)}{\partial t} = \int_w^{w_{max}} \underbrace{S_M(v,t) b_{M,p}(w,v) M_p(v,t) dv}_{\text{Birth term}} - \underbrace{S_M(w,t) M_p(w,t)}_{\text{Death term}} + \underbrace{\sum_{i=1}^{N} M_i(w,t)}_{\text{Flow term}}$$

Birth term: larger particles of size v ($v>w$) break into smaller fragments with size w, viz., entering the size class of w.

Death term: particles of size w break into smaller fragments, viz., leaving the size class of w.

Flow term: particles of size w flow in or out, viz., entering or leaving the size class of w.

The breakage probability

$$S_M(w,t) = \sum_{k=0}^{k=\infty} F_{k,w} P_B(k,w)$$

$$P_B = 1 - exp\left(-f_{Mat.} wk\left(W_{m,kin} - W_{m,min}\right)\right)$$

The breakage function

$$b_{M,p}(w,v) = \frac{\partial B_{M,p}(w,v)}{\partial v} \qquad B_{M,p}(w,v) = \left(\frac{w}{v}\right)^q \frac{1}{2}\left(1 + tanh\left(\frac{w - w'}{w'}\right)\right)$$

$$q = \mathrm{c}v + d$$

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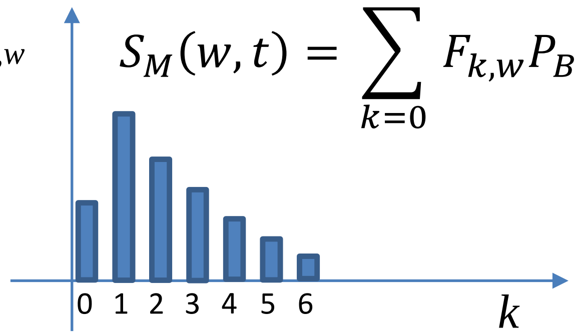
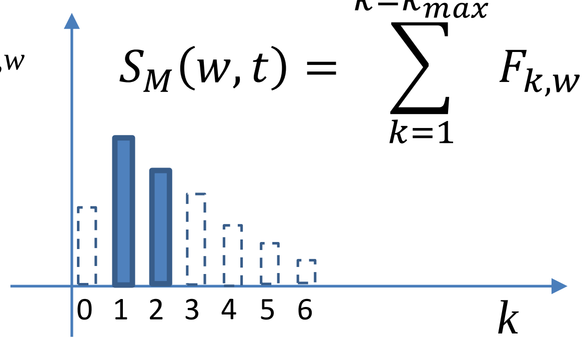
A simplified population balance model

$$S_M(w,t) = \sum_{k=0}^{k=\infty} F_{k,w} P_B(k,w)$$



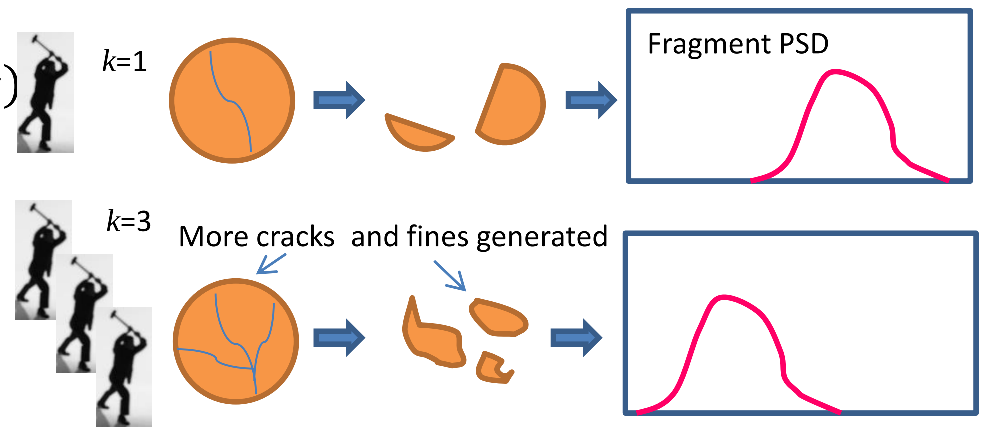
Histogram distribution of $F_{k,w}$ vs. k

$$S_M(w,t) = \sum_{k=1}^{k=k_{max}} F_{k,w}\, P_B(k,w)$$

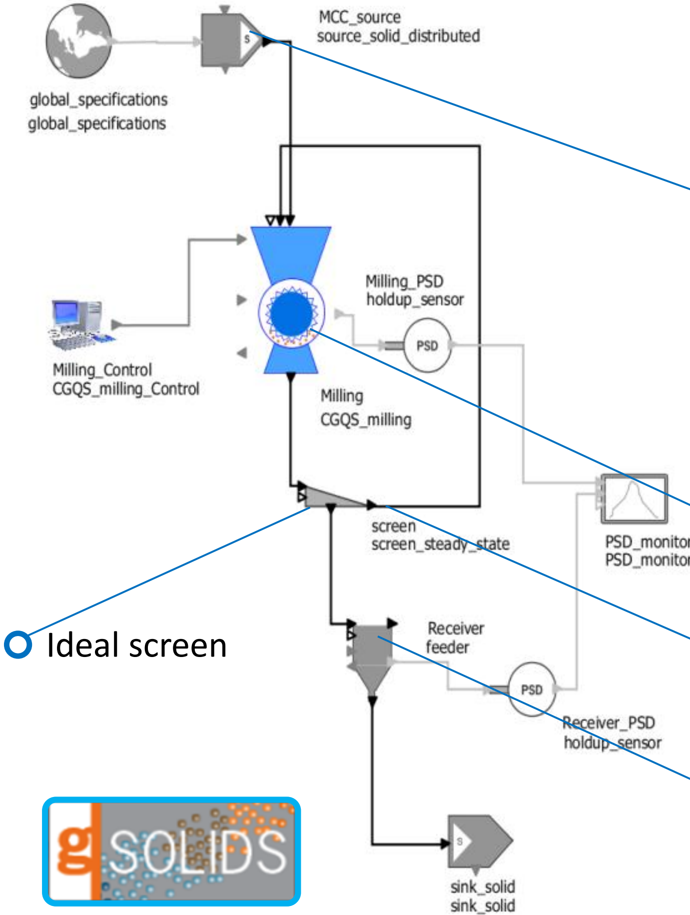


Histogram distribution of $F_{k,w}$ vs. k

- A maximum number of impacts, k_{max}, value can be assumed when the breakage probability reaches a high value after these impacts.
- $F_{k,w}$ changes with machine operating conditions, and can be attributed to be as machine properties.

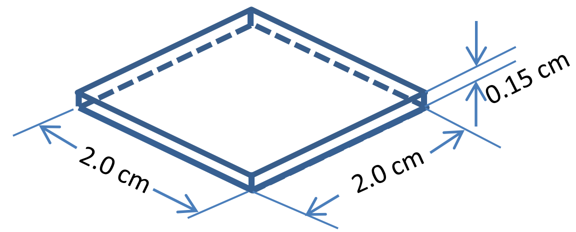


Results and discussion



A batch screen milling model in gSOLIDS

- Microcrystalline cellulose ribbon dimension



- Batch milling of a Frewitt hammer milling
- Oversize particles are totally recycled
- Total down size particles are weighted
- Ideal screen

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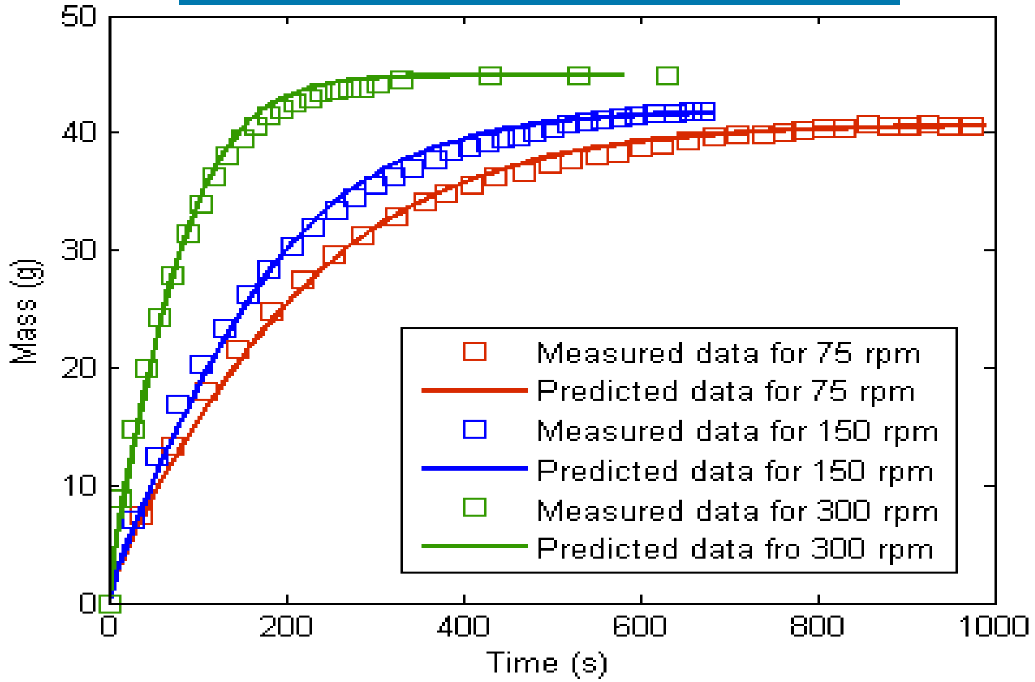
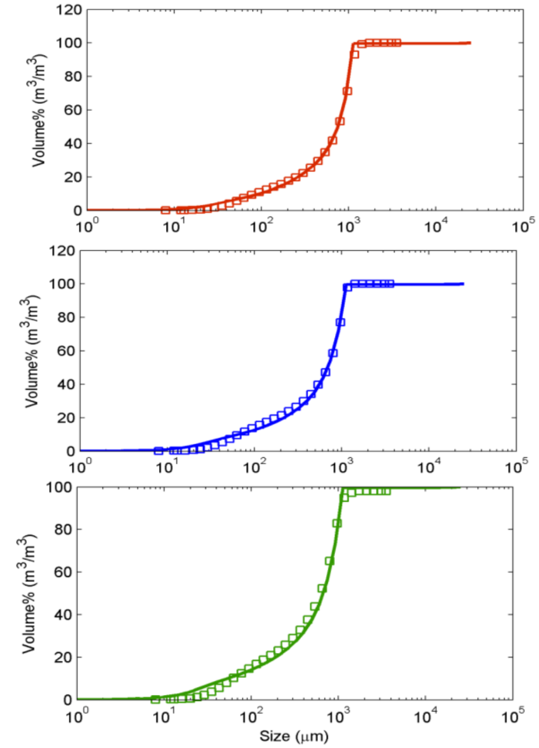
Parameter Estimation using Batch Impact Milling

- Impact events of k = 1, 2, 3 were considered each with distinct breakage probability and breakage function
- The impact rate constants $F_{k,w}$ were found to be decreasing with increased rotation speed

Mass of fine particles leaving the milling



PSD of final products



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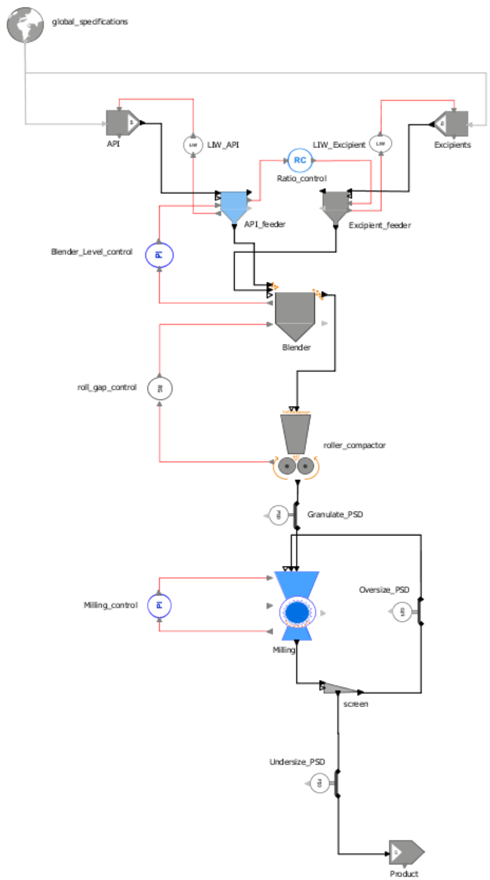
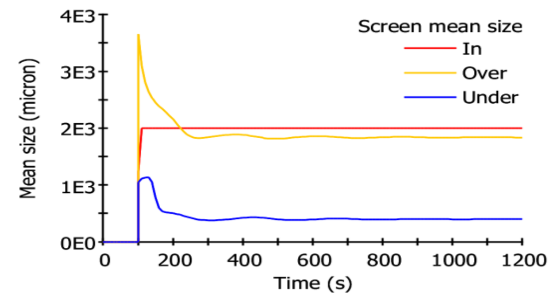
Process Control of Continuous Dry Granulation

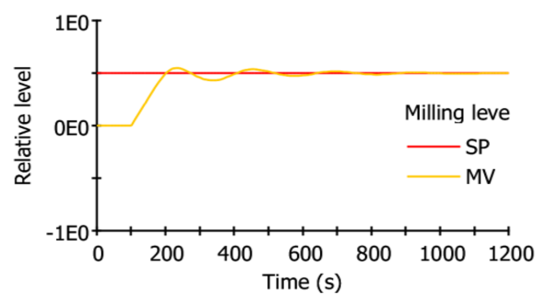


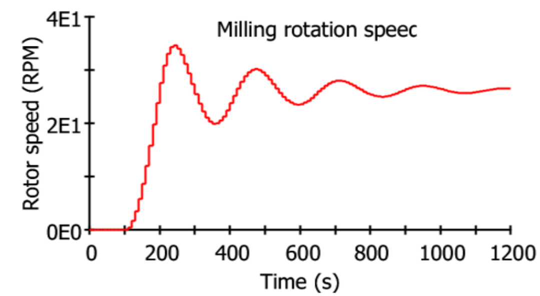
- A flowsheet model for a continuous dry granulation process, considering feeder, blender, roller compaction and dry milling, was developed in gSOLIDS 3.1 according to Gavi and Reynolds (2014).
- A series of customised *digital* Ratio and Proportional and Integral (PI) controllers have been implemented to control the process from start-up to the steady-state operation.

Mean particle sizes of fine particles crossing screen



Milling level was controlled using rotor rotation speed





[1] Gavi E, Reynolds GK. System model of a tablet manufacturing process. *Computers and Chemical Engineering*. 2014;71:130-140.

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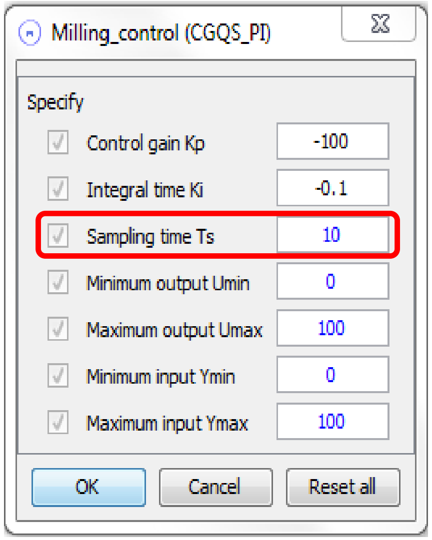
Process control configuration

PI controller within the “*Processes*” file in gSOLIDS.




```
REASSIGN
   WITHIN Flowsheet DO

      WITHIN Blender_Level_control DO
         U_k := OLD(Control_Output.signal); # Previous control output;

      Y_mv_k := OLD(Control_Input.signal);  # Previous control input;

         E_k := OLD(Y_sp_k) - OLD(Control_Input.signal); # Current control error
        dE_k := OLD(Y_sp_k) - OLD(Control_Input.signal) - OLD(E_k); # difference in the control error
     END # Blender_Level_control

     WITHIN Milling_control DO
         U_k := OLD(Control_Output.signal); # Previous control output;

      Y_mv_k := OLD(Control_Input.signal);  # Previous control input;

         E_k := OLD(Y_sp_k) - OLD(Control_Input.signal); # Current control error
        dE_k := OLD(Y_sp_k) - OLD(Control_Input.signal) - OLD(E_k); # difference in the control error
     END

  END # Flowsheet
END # REASSIGN
```

Conclusions and future work

- An improved approach of incorporating the single particle breakage model of Vogel and Peukert (2005) into a rigorous population balance model has been developed.
- By considering the distributed impact events and their effect on fragment particle size distributions, the bimodal particle size distribution of final particles can be obtained without the use of complex breakage functions.

- Dependence of the impact rate constants $F_{k,w}$ on the milling rotation speed needs more investigation effort from both experimental and modelling work.
- An integrated model for screen milling in the model library is expected for convenient drag & drop flowsheeting in gSOLIDS platform.
- Pilot plant data for pharmaceutical continuous secondary manufacturing process are important to validate the flowsheet model and to propose efficient and robust process control strategies to industrial scale processes.

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