UNIVERSITEIT GENT

Linking granulation performance with residence time & liquid distributions in twin-screw granulation

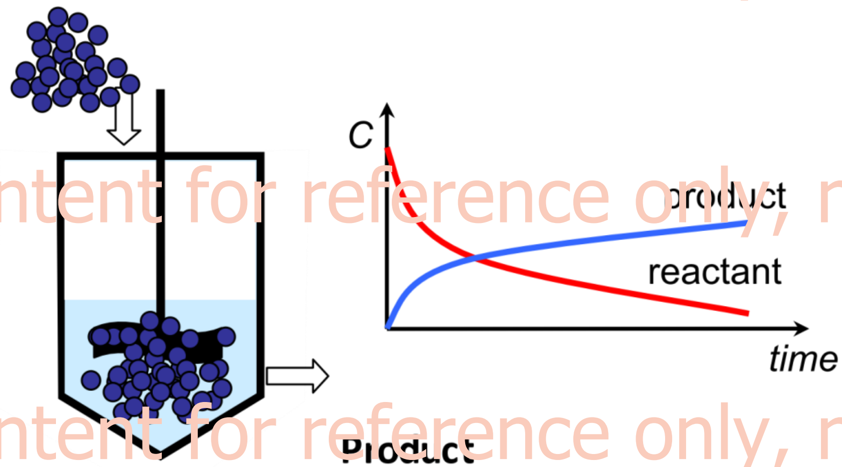
Ashish Kumar

7th pan-European Science Conference on QbD and PAT Sciences

LP PAT BIOMATH

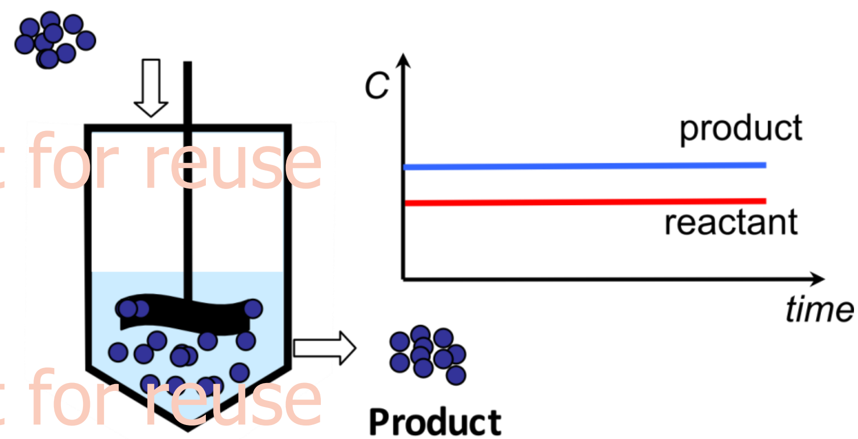
Continuous manufacturing is better

Batch



- ✗ No feed and effluent
- ✗ Concentration is time variant
- ✗ High variability

Continuous



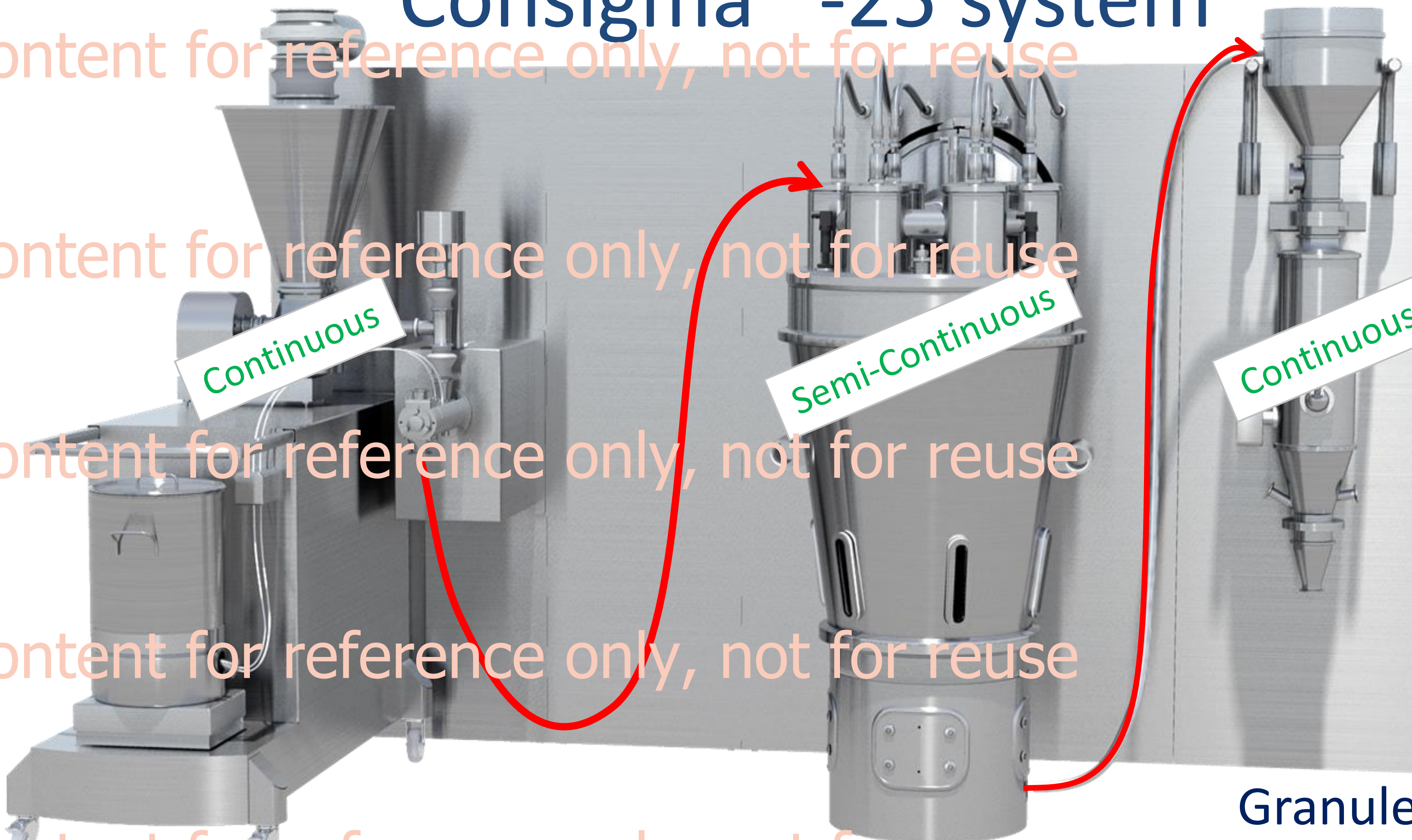
- ✓ Constant feed and effluent
- ✓ Concentration are constant
- ✓ Low variability

But in pharma processing switch is not easy either…

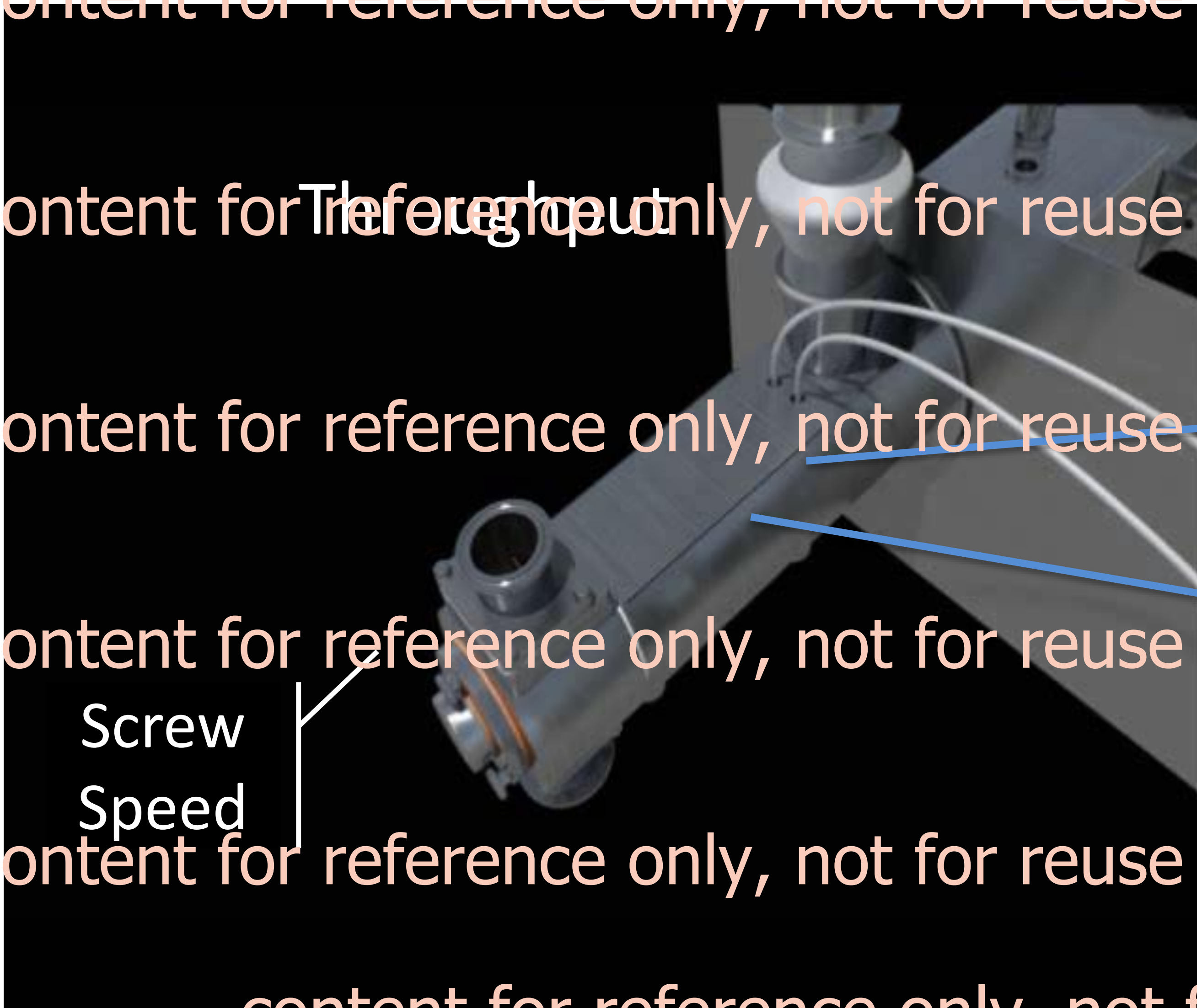
- ✓ Process control is easy
- ✗ Rigorous control required

robust understanding of the processes is needed

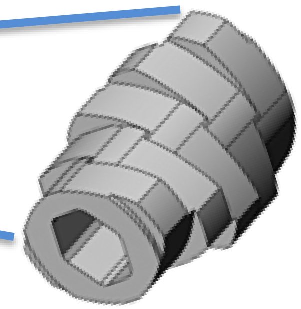
Continuous manufacturing line
Consigma™-25 system



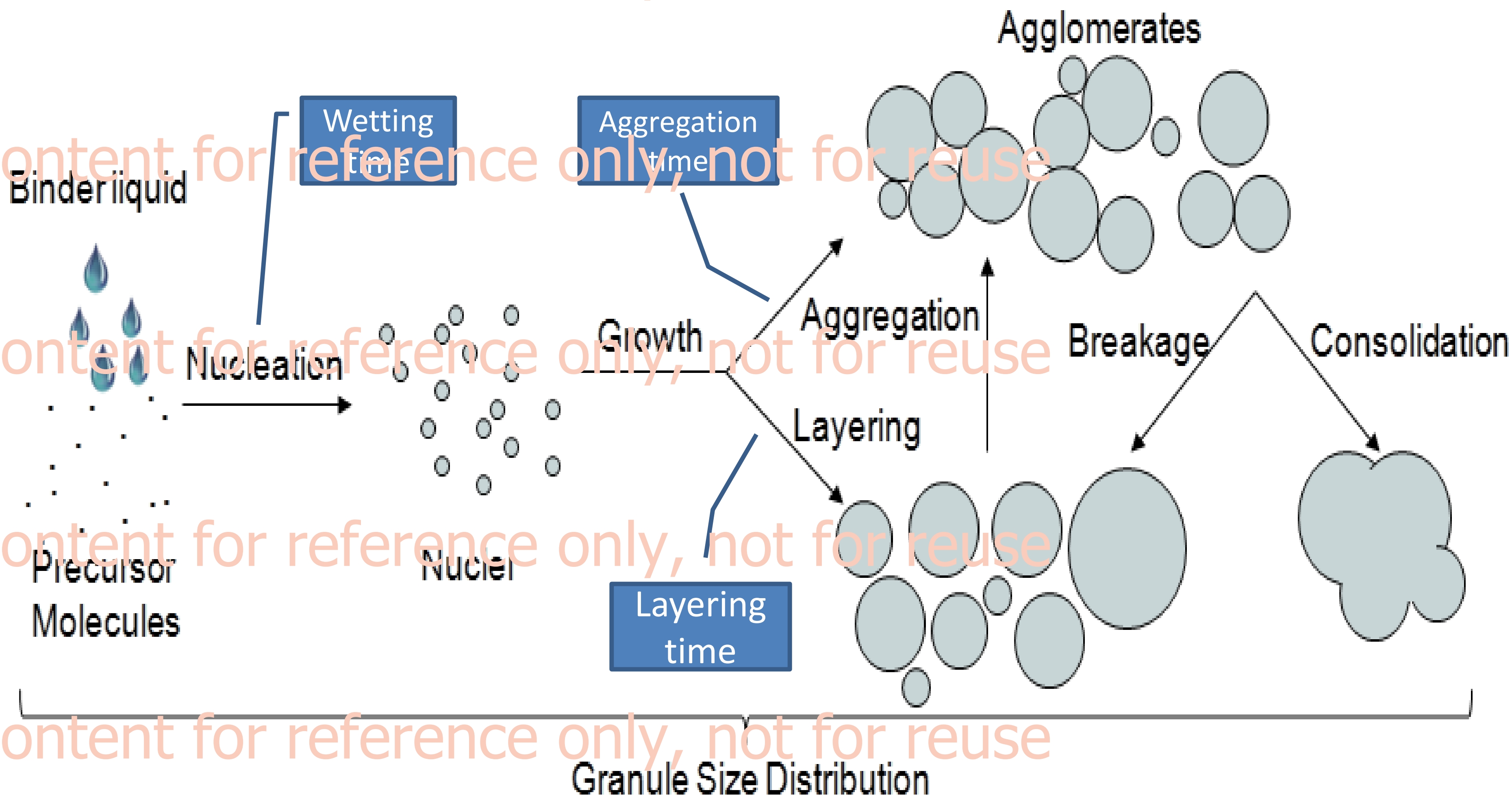
Design of granulator screw, screw speed, material feed rate control granulation



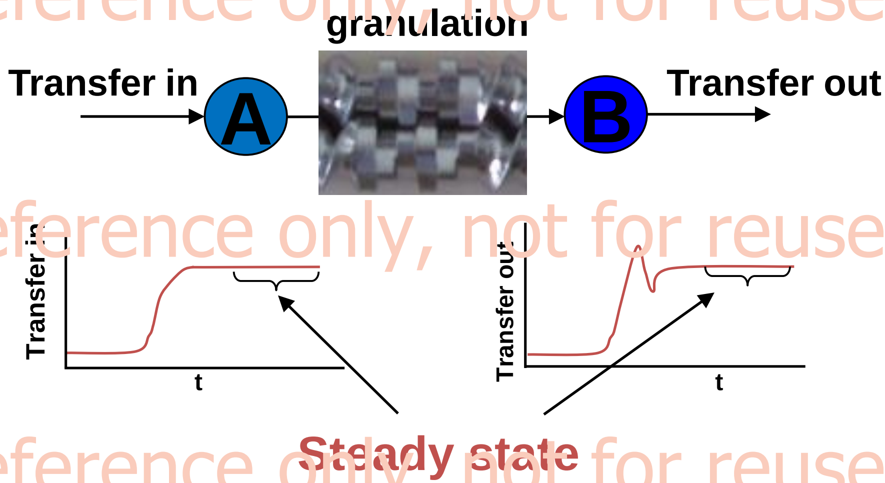
Kneading discs at certain stagger angle



High Shear Wet Granulation involves different rate processes



At appropriate conditions, granulation is in steady state



$$\textit{transfer in} \approx \text{constant} \approx \textit{transfer out}$$

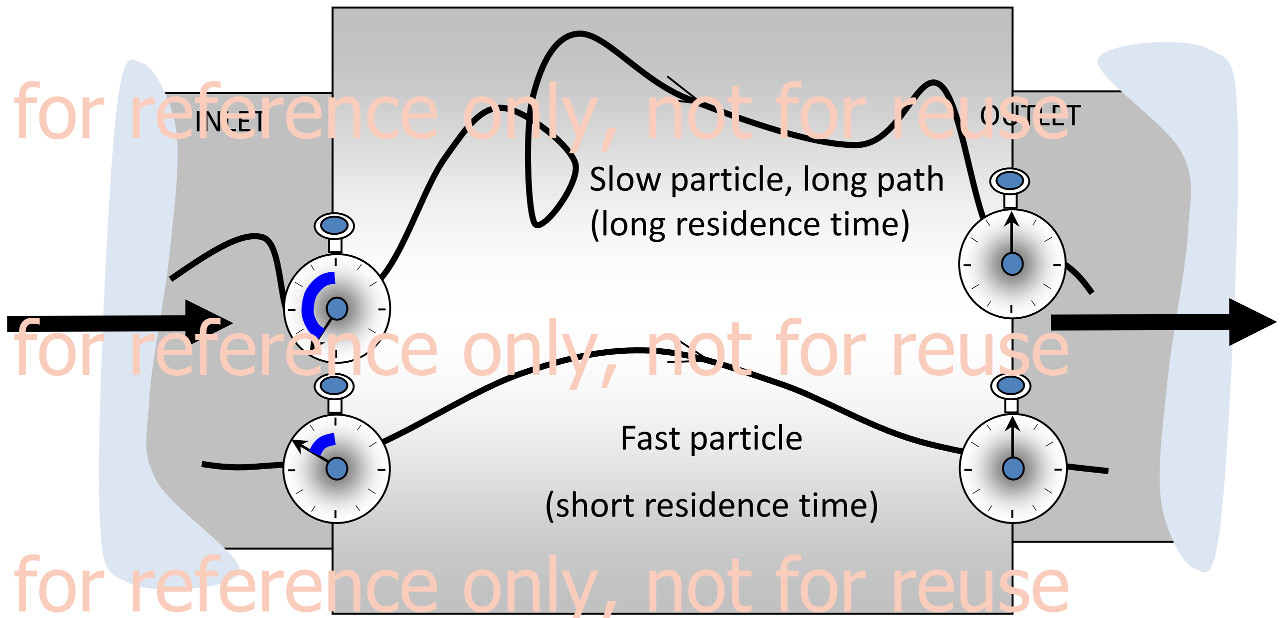
$$\frac{d[P_m]}{dt} \approx 0 \approx \frac{d[G_m]}{dt}$$

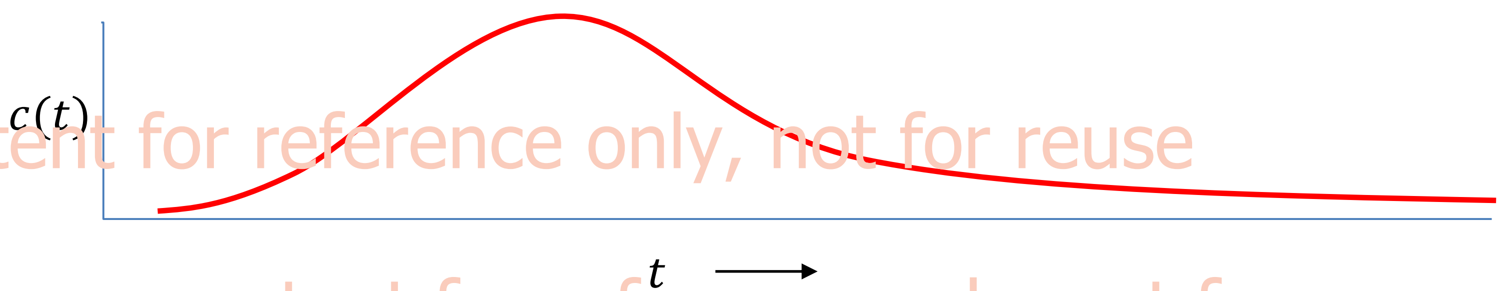
Two key implications

1. Fluxes are roughly constant (Dynamics are transient)
2. Same amount of time is to complete all sub-processes

Having many time-scales is challenging

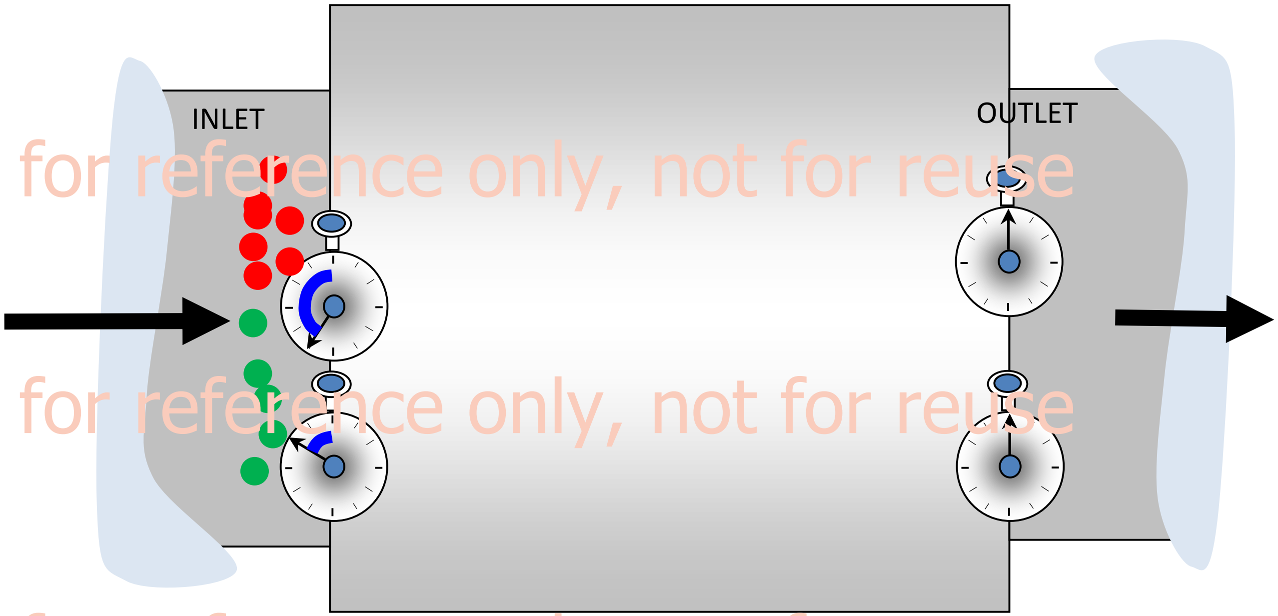
Residence time-scale





Having many time-scales is challenging

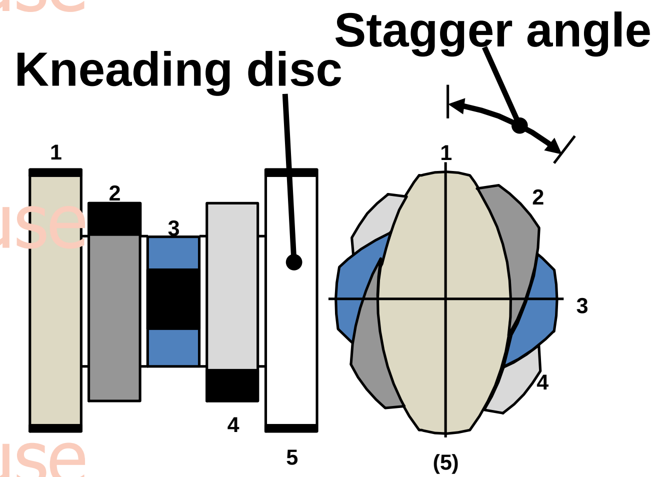
Mixing time scale



Residence time and moisture distributions effect on the granulation performance

Screw Configuration

- Number of kneading discs (4, 6, 2x6)
- Stagger angle (30°, 60°, 120°)



Process parameters

- Material throughput (10-25 kg/h)
- Screw speed (500-900 rpm)
- Liquid-to-solid ratio (6-8%)

spike

Fines < 150 µm	Yield fraction > 150 to <1400 µm	Oversized > 1400 µm

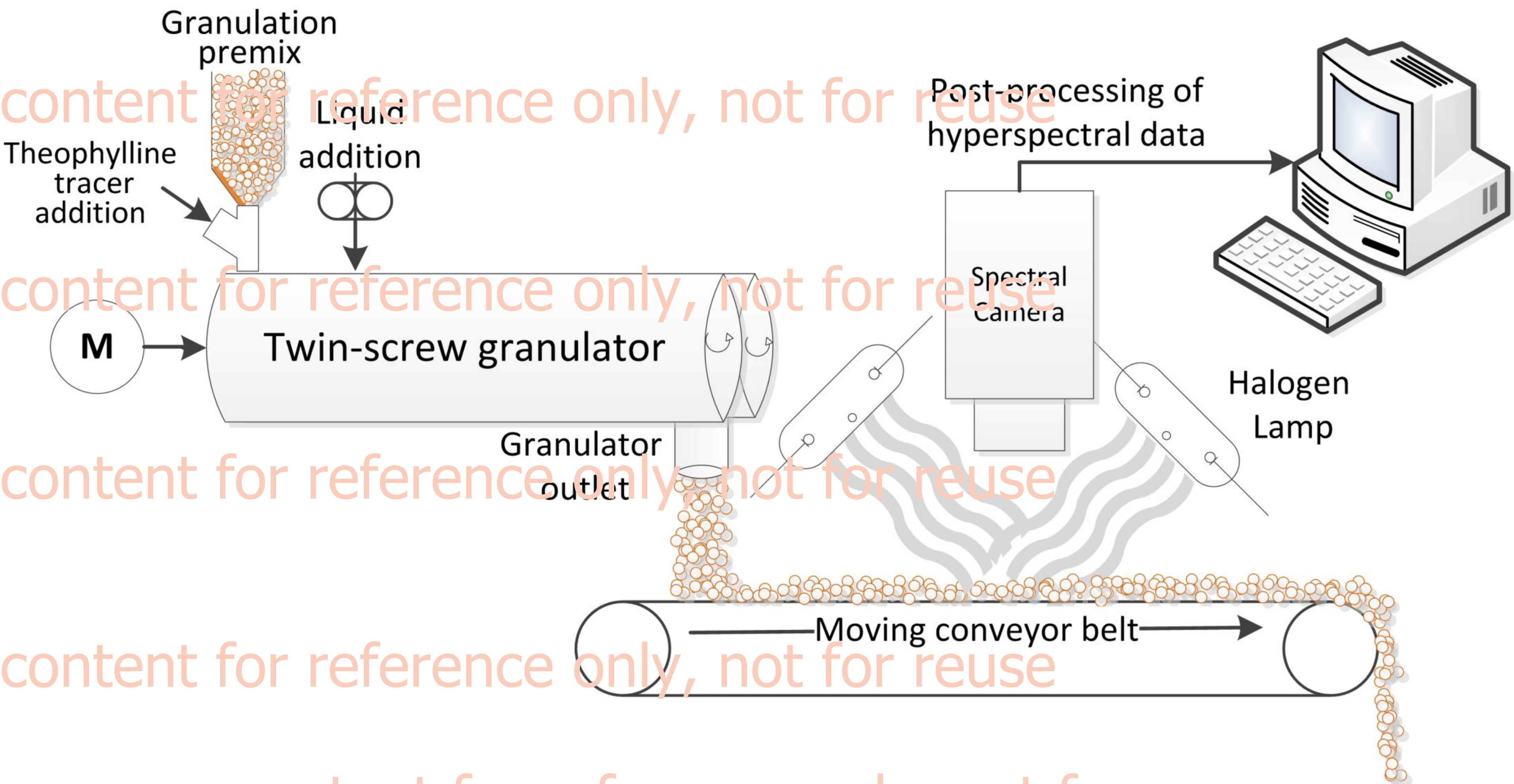
Analysis of distributions in twin-screw granulation

Measurement by distributions

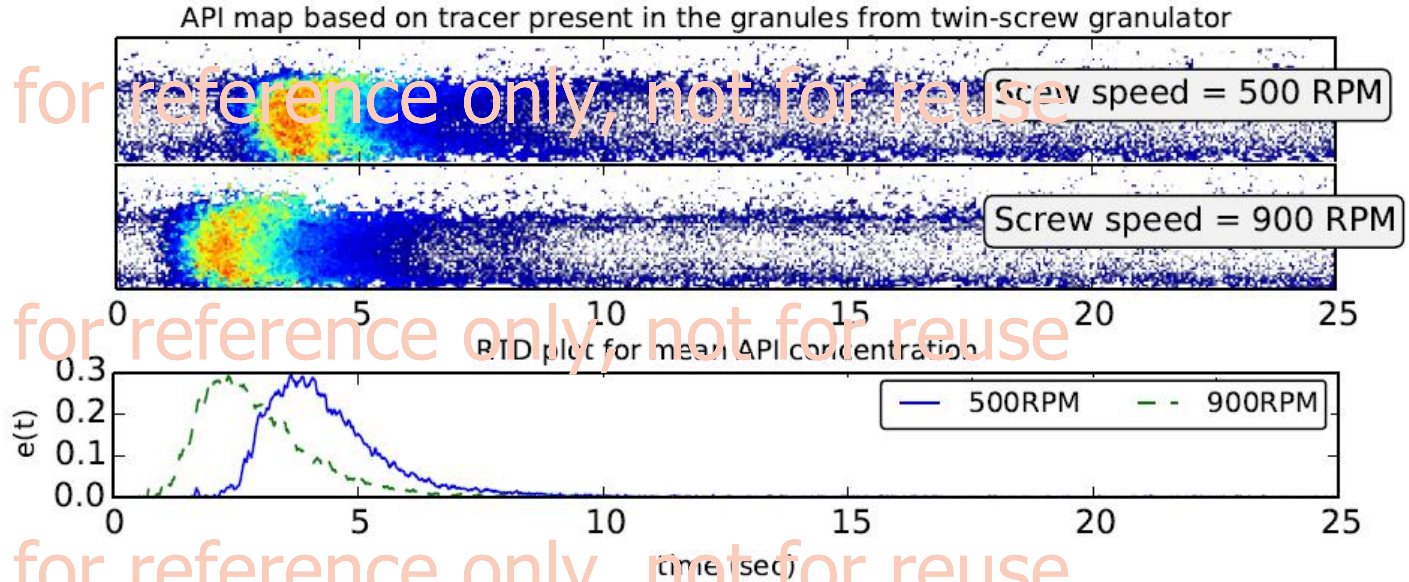
Results

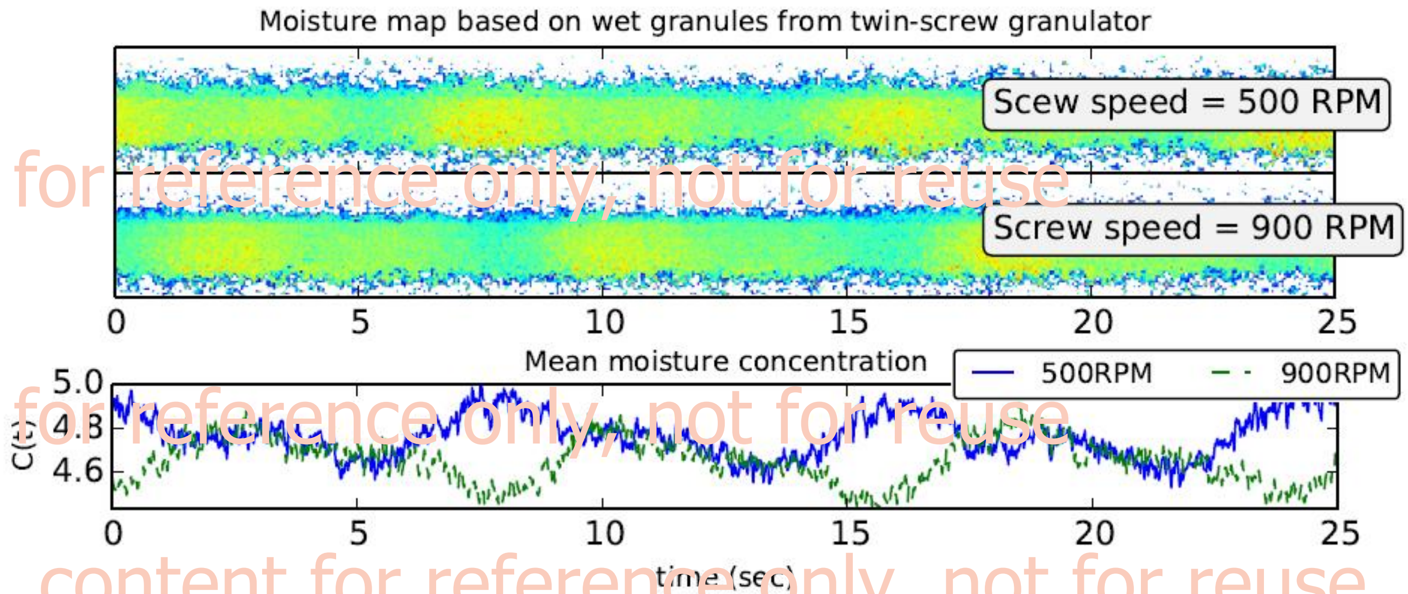
Summary

Tracer concentration in granules measured by NIR chemical imaging

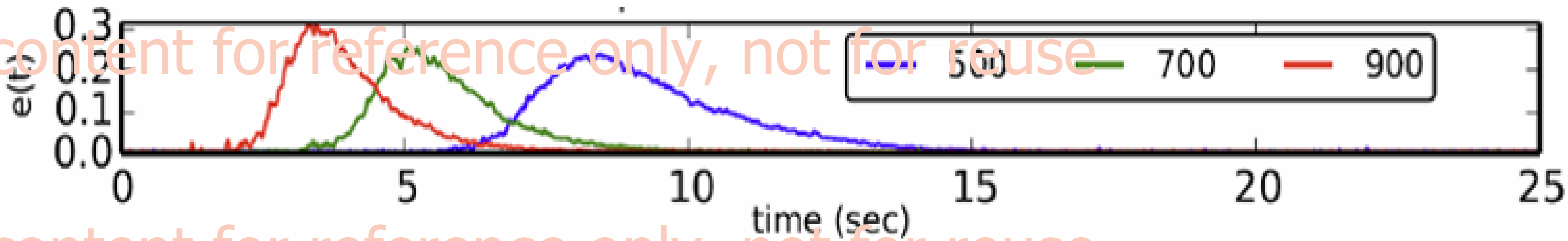


Tracer maps used to measure distributions





Qualitative assessment of the RTD profiles



$$\tau = \frac{\int_0^\infty t \cdot e(t)dt}{\int_0^\infty e(t)dt}$$

Mean residence time , τ
(a measure of the mean of the distribution)

$$\sigma^2 = \frac{\int_0^\infty (t-\tau)^2 \cdot e(t)dt}{\int_0^\infty e(t)dt}$$

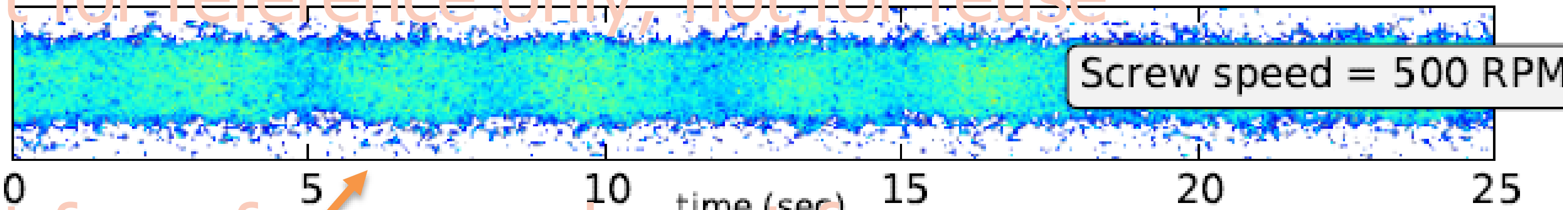
Variance, σ^2
(width of the distribution)

$$Pe = \frac{UL}{D}$$

Péclet Number, Pe

$$\left(\frac{\text{Rate of axial transport by convection}}{\text{Rate of axial transport by dispersion}}\right)$$

Qualitative assessment of the moisture maps

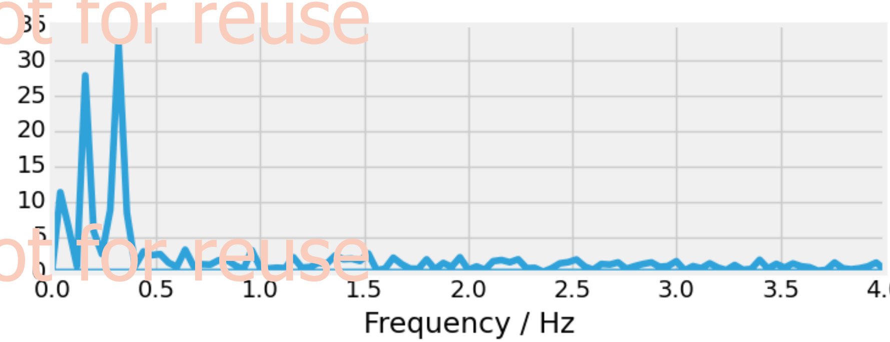


Shannon Entropy based Mixing Index

$$H(X) = \sum_{j=1}^{n} P(X)\log_{200}(1/P(X_j))$$

$$MI = \frac{1}{\log_{200}(n)} \sum_{j=1}^{n} P(X_j)\log_{200} P(X_j)$$

FFT to obtain Frequency and amplitude



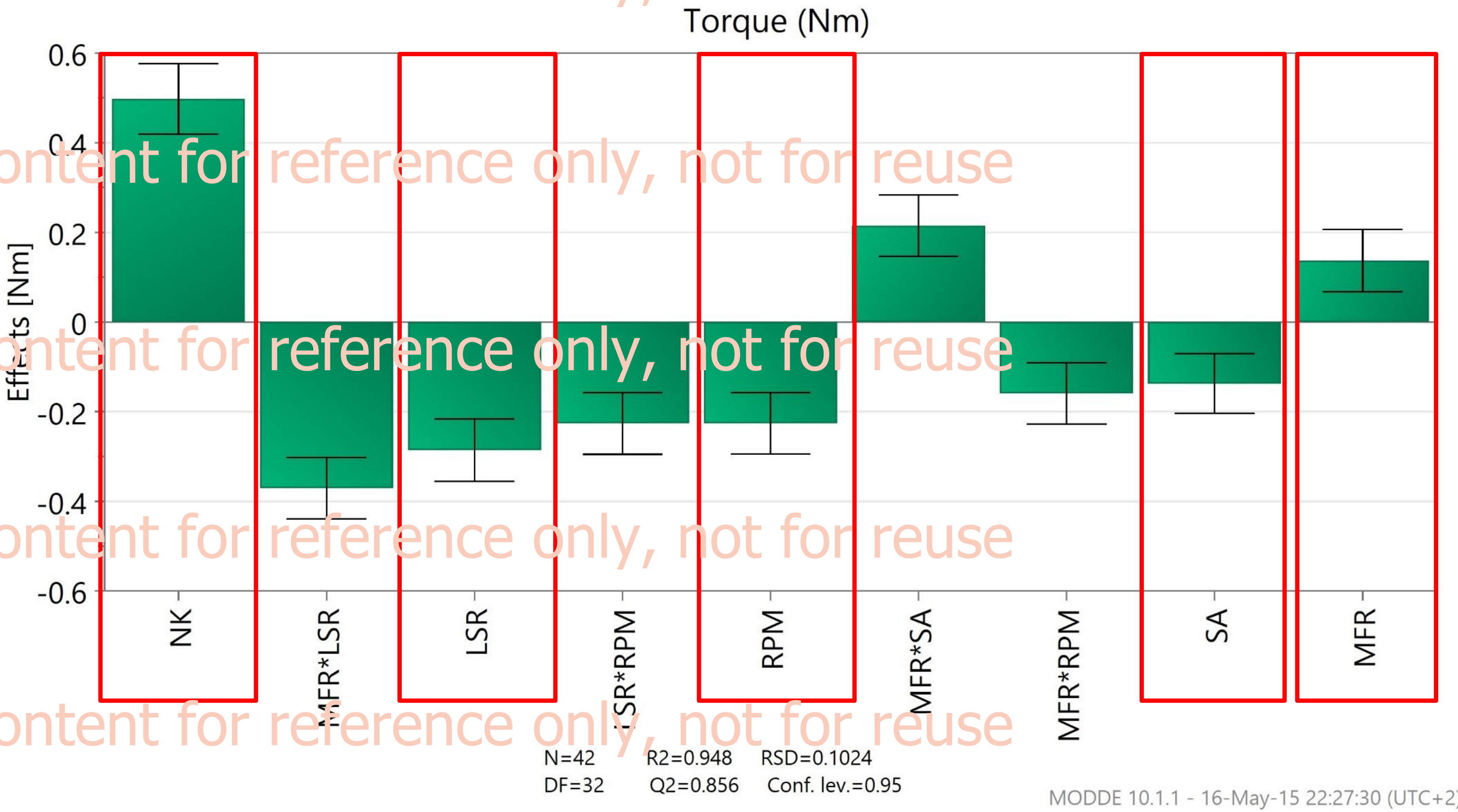
Analysis of distributions in twin-screw granulation

RTD Measurement by Chemical Imaging

Results

Summary

Experimental domain was effective in causing variations



Size fraction change is response of change in residence time and mixing

Factors	Size fractions				Axial mixing		Solid-liquid mixing		
	Fines	Yield	Oversized	Res. time	Variance	Péclet No.	Mixing Index	freq. Var.	Amp. Var.
Screw speed	↑	↑	↓	↓	↑	↓	↓	↑	↑
Throughput	0	↓	↑	0	0	0	↓	↑	↓
L/S ratio	↓	↑	↑	0	0	0	0	0	↓
kneading discs	↓	0	↑	↑	↓	↑	↑	↓	0
Stagger angle	↑	↓	↓	0	0	↑	↑	0	↑

Increase in L/S and no. of kneading led to improved liquid distribution, hence less fines

Factors	Fines	Yield	Oversized	Res. time	Variance	Péclet No.	Mixing Index	freq. Var.	Amp. Var.
	Size fractions			Axial mixing			Solid-liquid mixing		
Screw speed									
Throughput									
L/S ratio	↓	↑	↑	0	0	0	0	0	↓
kneading discs	↓	0	↑	↑	↓	↑	↑	↓	0
Stagger angle									

Increase in screw speed caused low residence time and mixing so more fine

Factors	Size fractions				Axial mixing		Solid-liquid mixing		
	Fines	Yield	Oversized	Res. time	Variance	Péclet No.	Mixing Index	freq. Var.	Amp. Var.
Screw speed	↑	↑	↓	↓	↑	↓	↓	↑	↑
Throughput									
L/S ratio									
kneading discs									
Stagger angle	↑	↓	↓	0	0	↑	↑	0	↑

↑ axial mixing by ↑ screw speed & ↑ liquid distribution at ↑ L/S lead to more yield

Factors	Fines	Yield	Oversized	Res. time	Variance	Péclet No.	Mixing Index	freq. Var.	Amp. Var.
	Size fractions				Axial mixing		Solid-liquid mixing		
Screw speed	↑	↑	↓	↓	↑	↓	↓	↑	↑
Throughput									
L/S ratio	↓	↑	↑	0	0	0	0	0	↓
kneading discs									
Stagger angle									

Increase in screw speed caused low residence time and mixing so less yield

Factors	Fines	Yield	Oversized	Res. time	Variance	Péclet No.	Mixing Index	freq. Var.	Amp. Var.
	Size fractions				Axial mixing		Solid-liquid mixing		
Screw speed									
Throughput	0	↓	↑	0	0	0	↓	↑	↓
L/S ratio									
kneading discs									
Stagger angle	↑	↓	↓	0	0	↑	↑	0	↑

Increase in axial-mixing and low residence time lead to less oversized

	Size fractions				Axial mixing		Solid-liquid mixing		
Factors	Fines	Yield	Oversized	Res. time	Variance	Péclet No.	Mixing Index	freq. Var.	Amp. Var.
Screw speed	↑	↑	↓	↓	↑	↓	↓	↑	↑
Throughput									
L/S ratio									
kneading discs									
Stagger angle	↑	↓	↓	0	0	↑	↑	0	↑

Reducing amount of oversized is difficult

more oversized

Factors	Fines	Yield	Oversized	Res. time	Variance	Péclet No.	Mixing Index	freq. Var.	Amp. Var.
	Size fractions				Axial mixing		Solid-liquid mixing		
Screw speed									
Throughput	0	↓	↑	0	0	0	↓	↑	↓
L/S ratio	↓	↑	↑	0	0	0	0	0	↓
kneading discs	↓	0	↑	↑	↓	↑	↑	↓	0
Stagger angle									

Analysis of distributions in twin-screw granulation

RTD Measurement by Chemical Imaging

Results

Summary

Combined results showed that..

..a balance between material throughput and screw speed is required for high yield.

..material throughput and number of kneading discs dictate solid-liquid mixing.

..non-conventional screw elements with modified geometries should be explored for improvement in solid-liquid mixing.

Perspectives

In further study we will investigate material properties influence on the RTD + mixing and granulation yield.

Utilise the mixing and residence time information for mechanistic modeling of the TSG.

Prof. Thomas De Beer
Prof. Ingmar Nopens
Prof. Krist V. Gernaey

Valérie Vanhoorne
Dr. Jurgen Vercruysse

Maunu Toiviainen
Dr. Mikko Juuti

Maija Alakarjula
Prof. Jarkko Ketolainen

UNIVERSITEIT GENT

DTU

UNIVERSITY OF EASTERN FINLAND

UNIVERSITEIT GENT

LP PAT

Laboratory of Pharmaceutical Process Analytical Technology

BIOMATH

Model-based analysis and optimization of bioprocesses

Ashish.Kumar@UGent.be