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Investigation of twin screw granulation: integrating experimental and computational approaches

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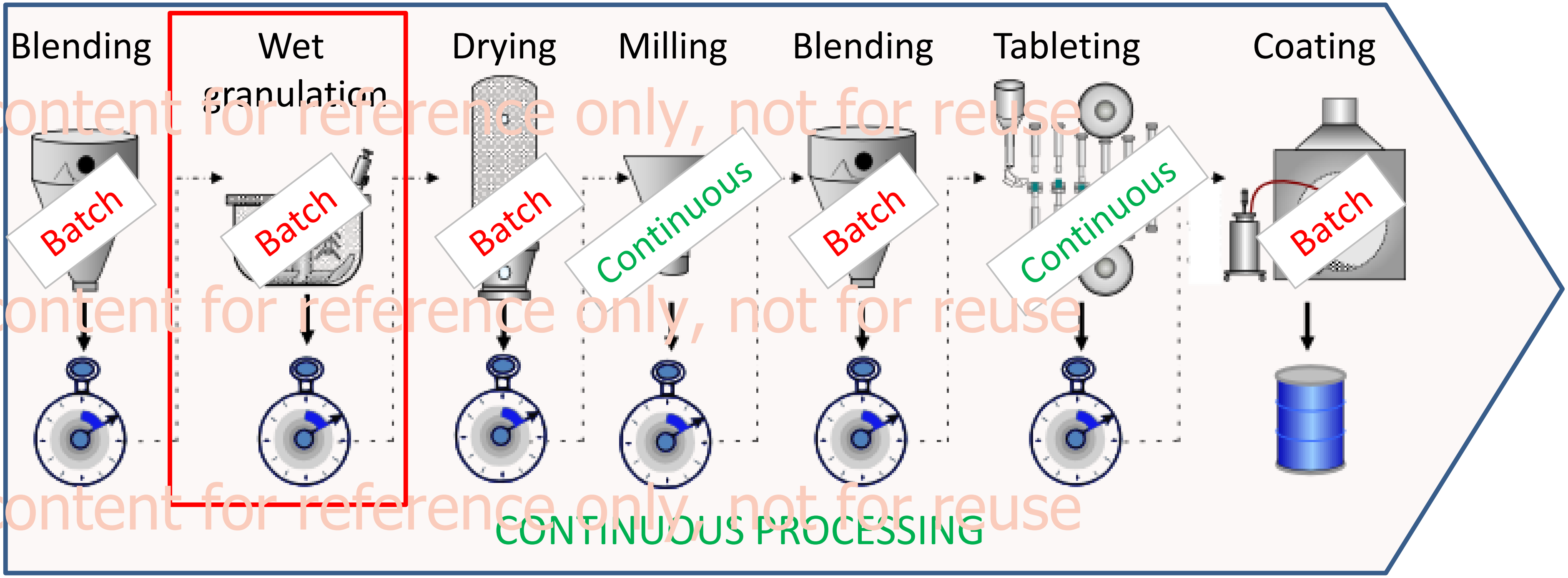
IFPAC® Annual Meeting 2015

Session: QbD – Applications and Tools

LABORATORY OF PHARMACEUTICAL PROCESS ANALYTICAL TECHNOLOGY

FACULTY OF PHARMACEUTICAL SCIENCES

Current solid-dosage manufacturing is slow and expensive

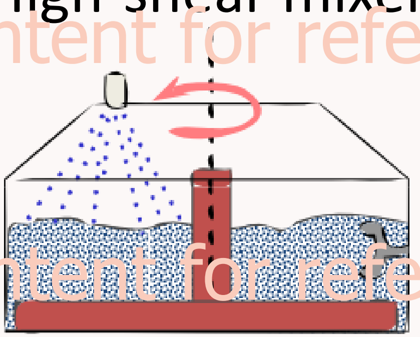

Blending
Wet granulation
Drying
Milling
Blending
Tableting
Coating
Batch
Batch
Batch
Continuous
Batch
Continuous
Batch
CONTINUOUS PROCESSING

Product collected after each unit operation

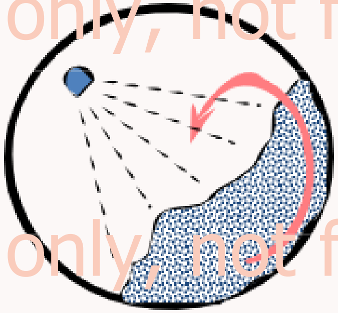
Actual processing time = days to weeks

Traditional to new granulation method

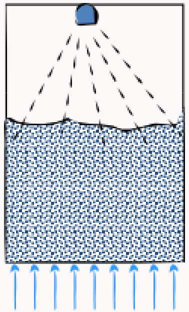
High-shear mixer



Drum



Fluidised-bed

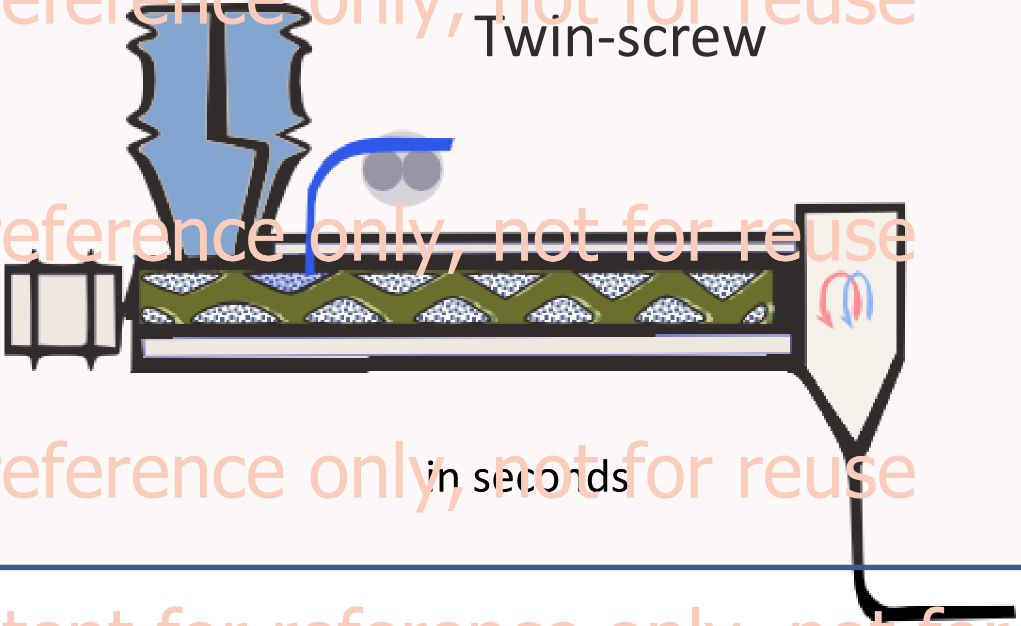


From minutes to hours

Batch

Continuous

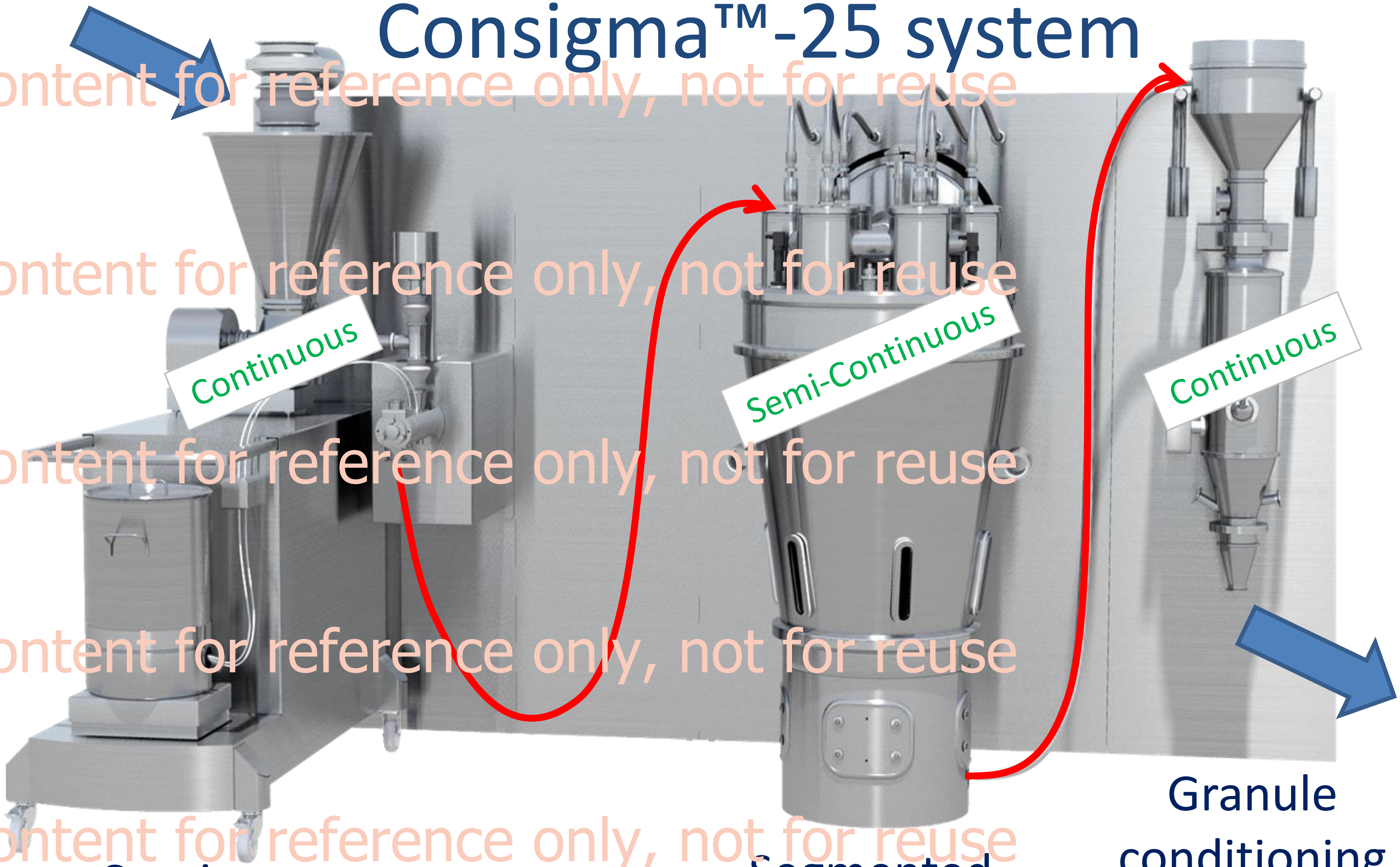
Twin-screw



in seconds

Continuous manufacturing line

Consigma™-25 system


Continuous
Semi-Continuous
Continuous

Continuous

twin-screw granulator

Segmented

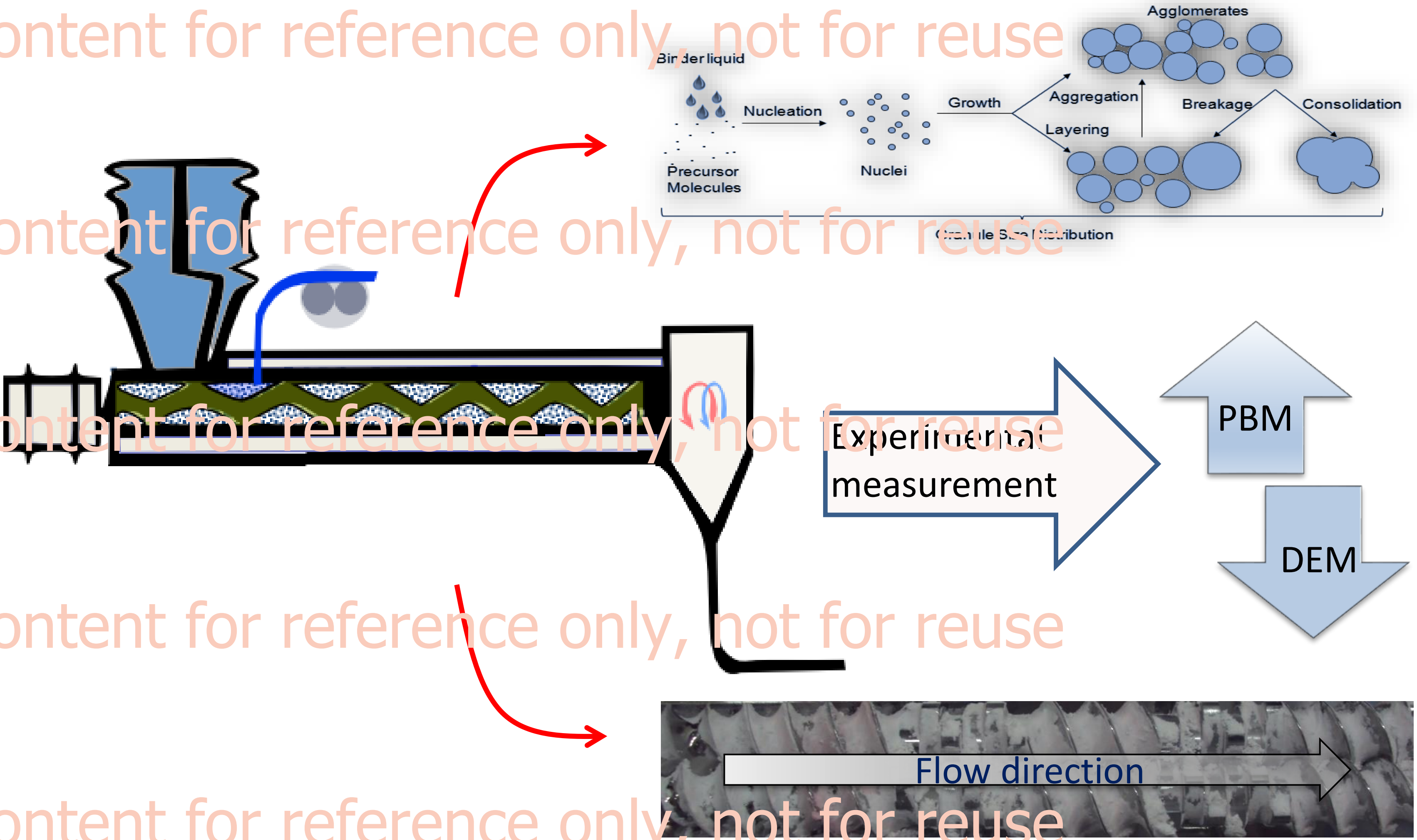
Fluid bed dryer

Granule

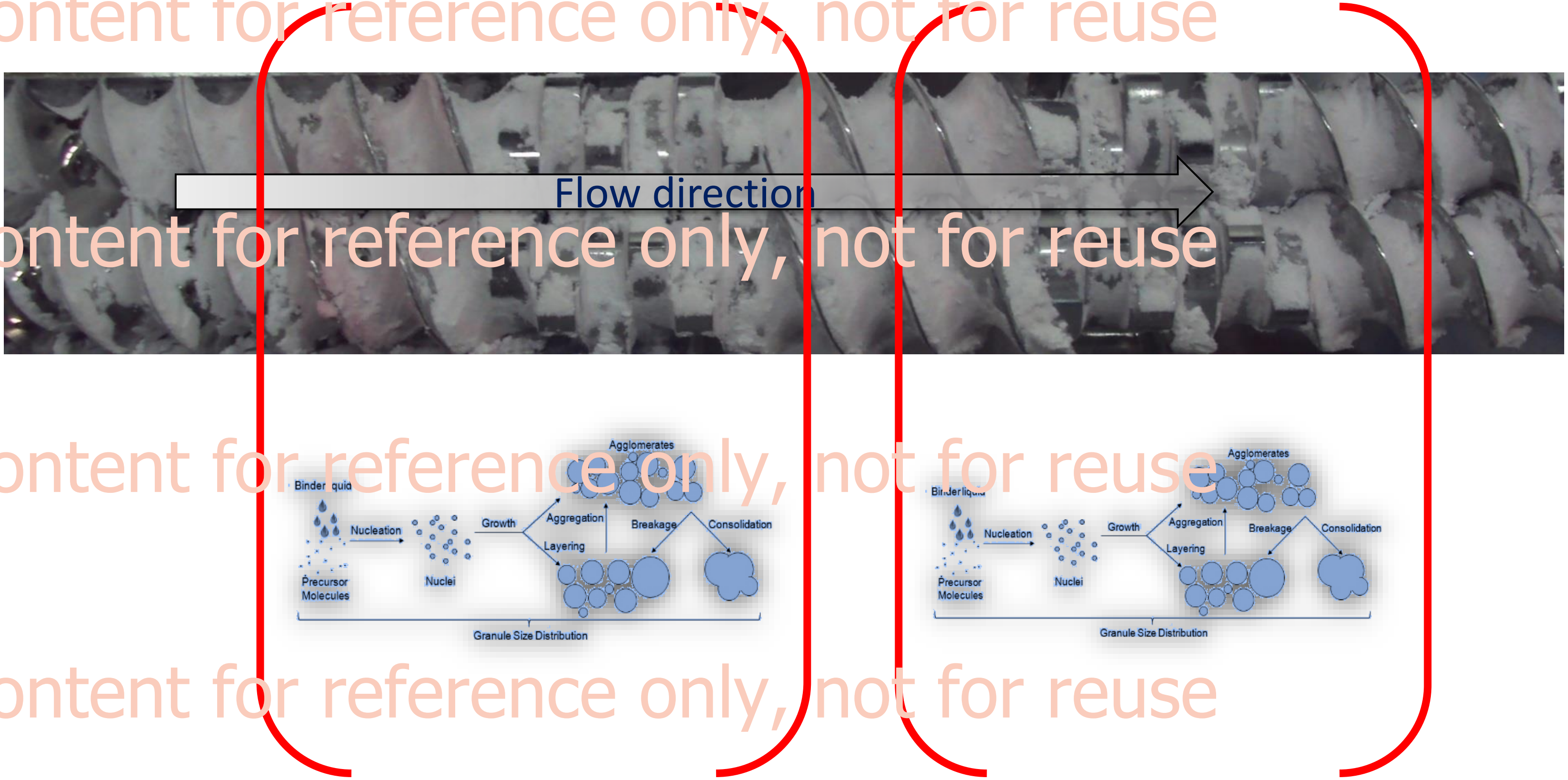
conditioning

module

Both geometry and process conditions drive constitutive mechanisms


Agglomerates
Binder liquid
Nucleation
Precursor Molecules
Nuclei
Growth
Aggregation
Layering
Breakage
Consolidation
Granule Size Distribution
Experimental measurement
PBM
DEM
Flow direction

Understanding the role of screw design


Flow direction
Binder liquid
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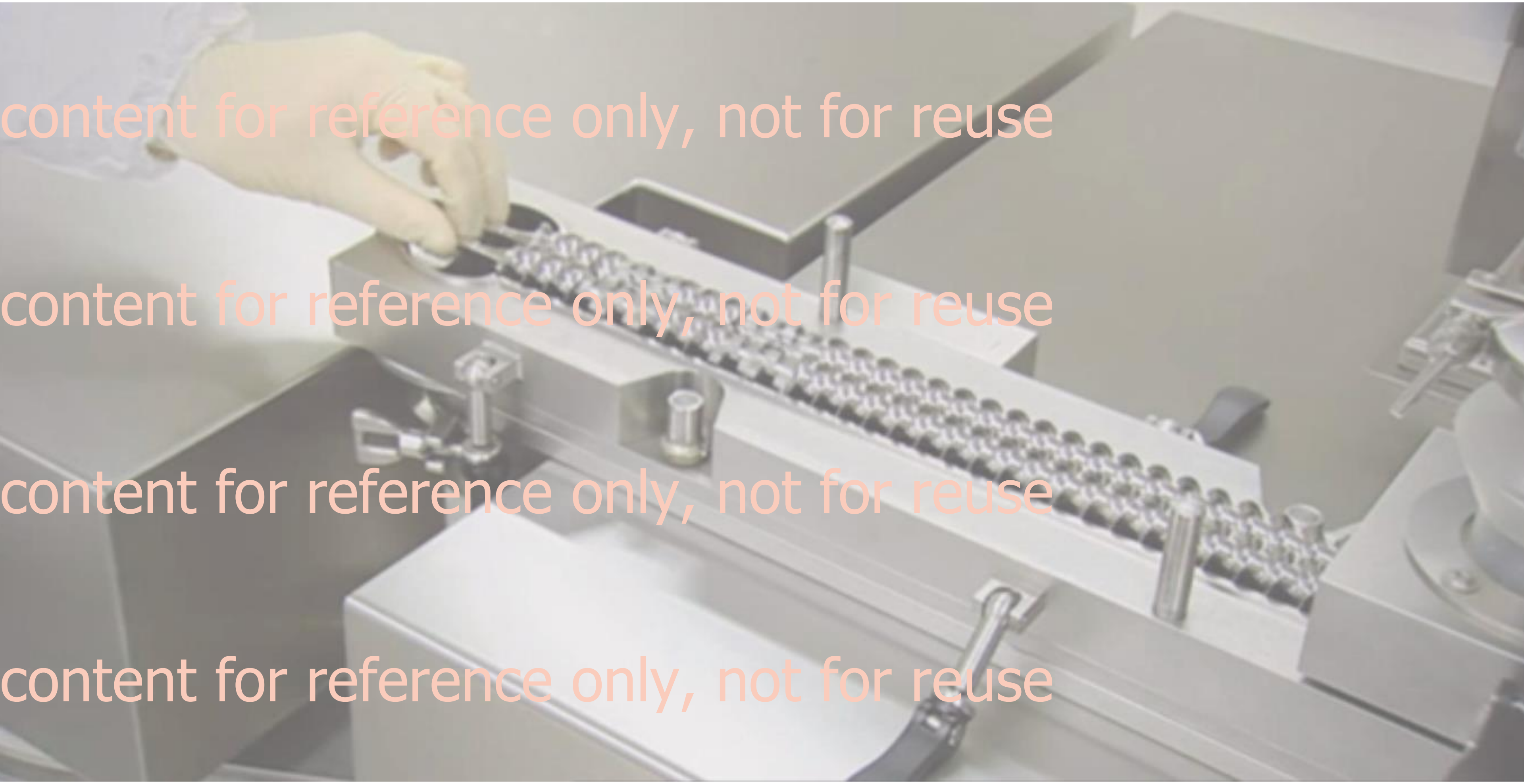
Binder liquid
Nucleation
Precursor Molecules
Nuclei
Growth
Aggregation
Layering
Agglomerates
Breakage
Consolidation
Granule Size Distribution

Consigma™-1 system

(GEA pharma systems, Collette)

Open barrel of a twin screw granulator

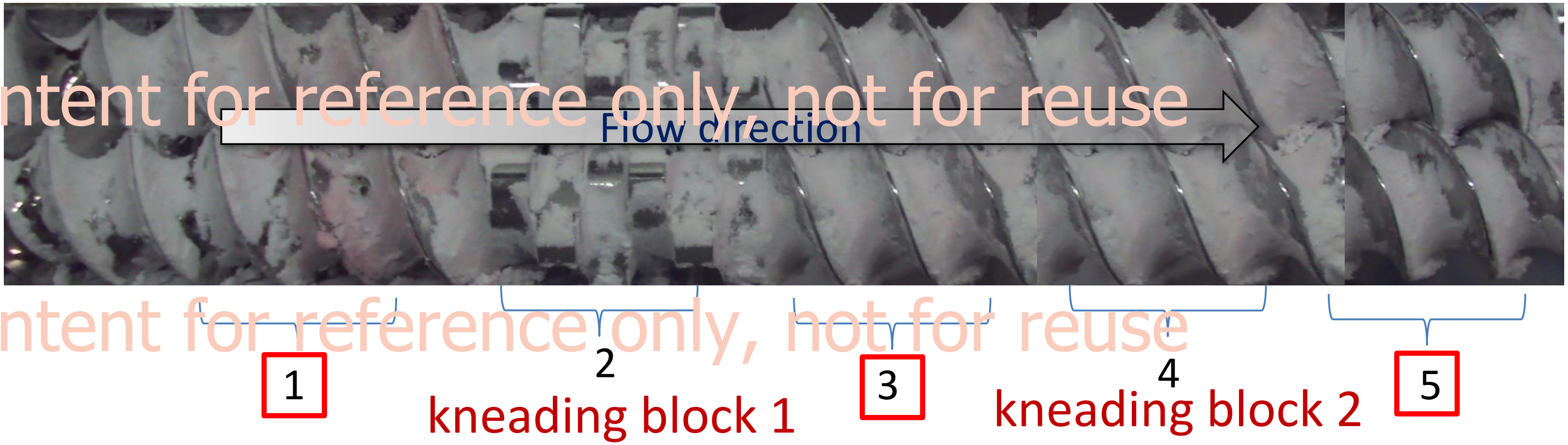


Consigma™- 1 experiments

Granulated Lactose monohydrate with distilled water

Factors:

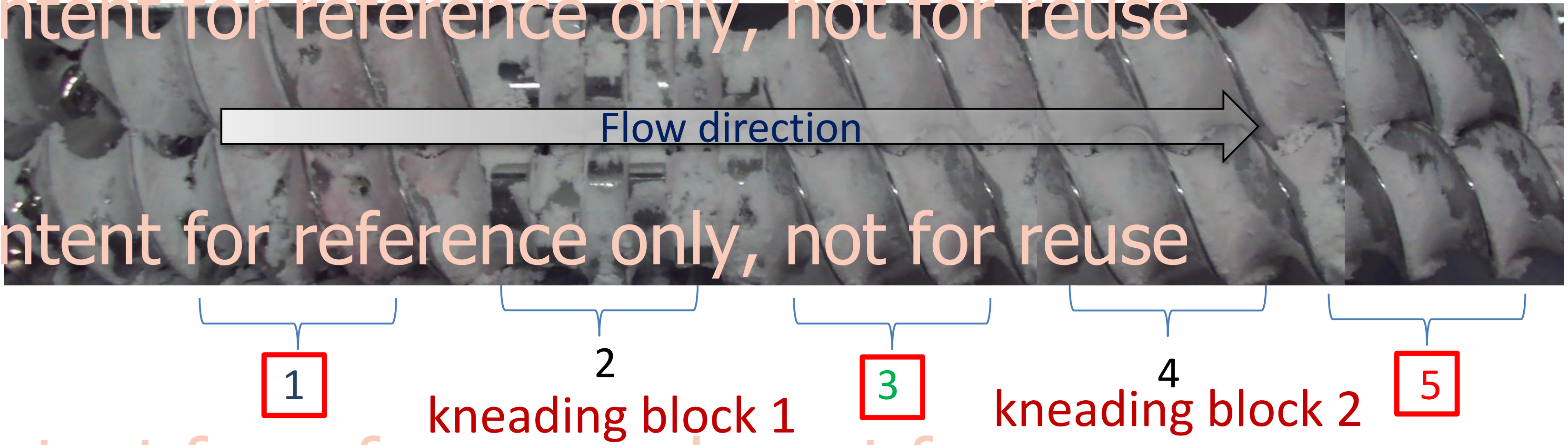
Parameters	Low	High
Throughput	10 Kg/h	25 Kg/h
Liquid-solid ratio	4.58 %	6.52%
Screw speed	500 RPM	900 RPM


Flow direction
1
2
kneading block 1
3
4
kneading block 2
5

Responses:

Particle characterization by Dynamic Image Analysis
(Location 1, 3, 5)

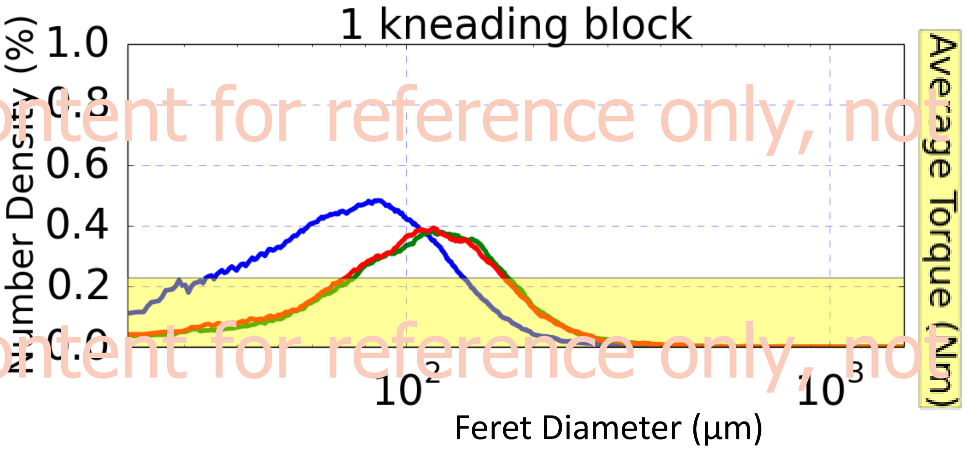
Consigma™- 1 experiments


Flow direction
1
2
kneading block 1
3
4
kneading block 2
5

Throughput **High**

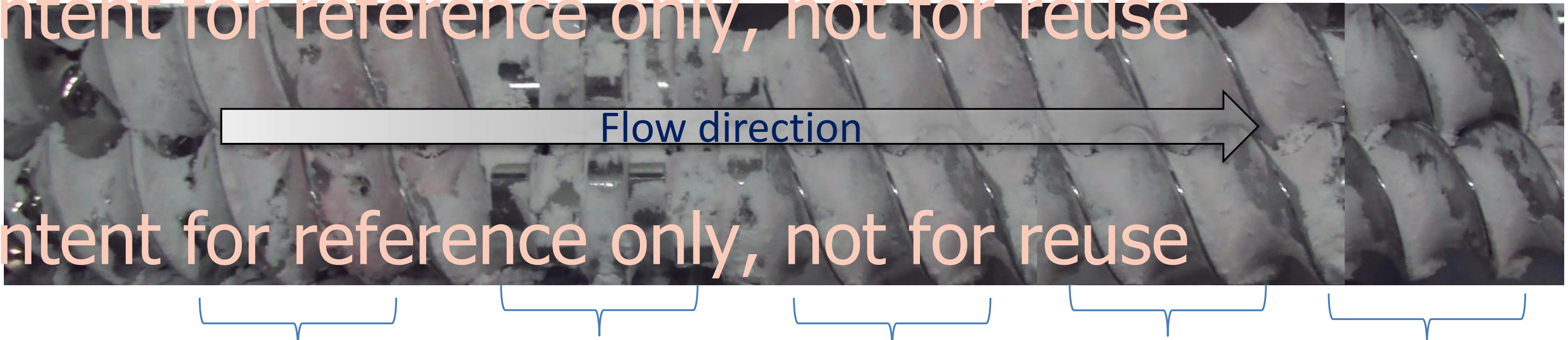
Liquid-solid ratio **High**

Screw speed **Low**



For details see: Kumar, et al. "Experimental investigation of granule size and shape dynamics in twin-screw granulation." *I J Pharma* 475.1 (2014): 485-495.

Consigma™- 1 experiments



1

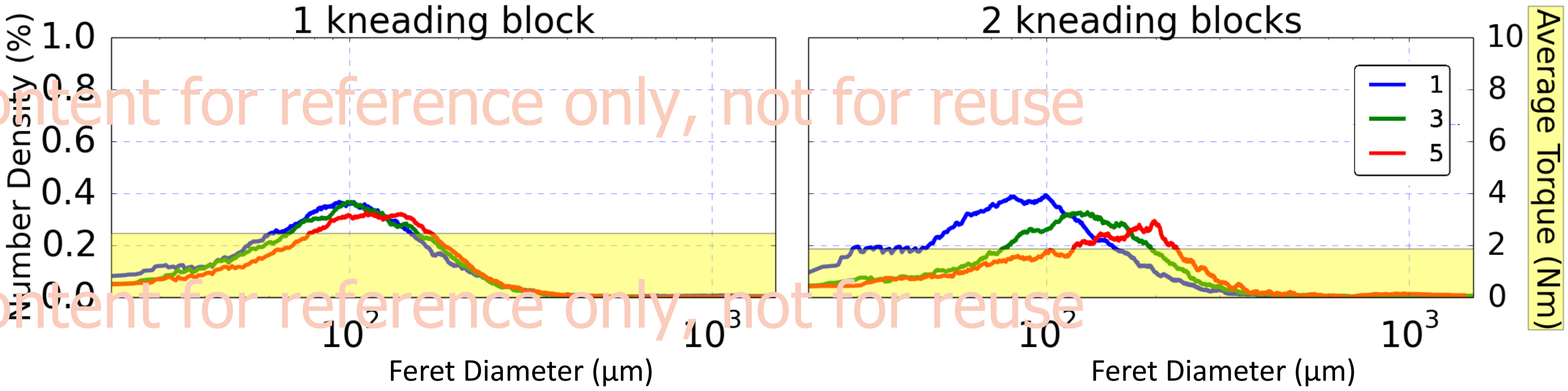
2
kneading block 1

3

4
kneading block 2

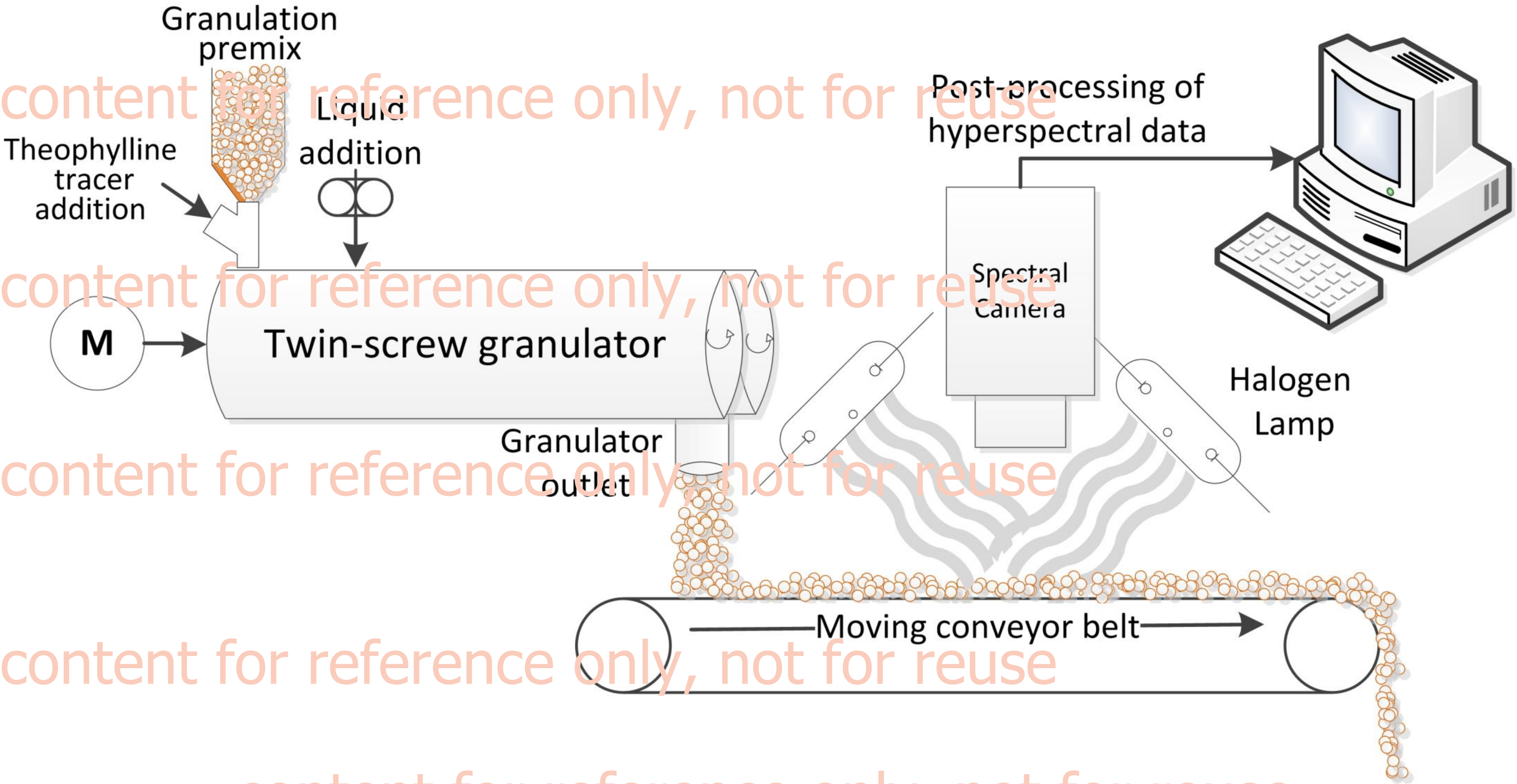
5

Throughput **High** | Liquid-solid ratio **High** | Screw speed **High**

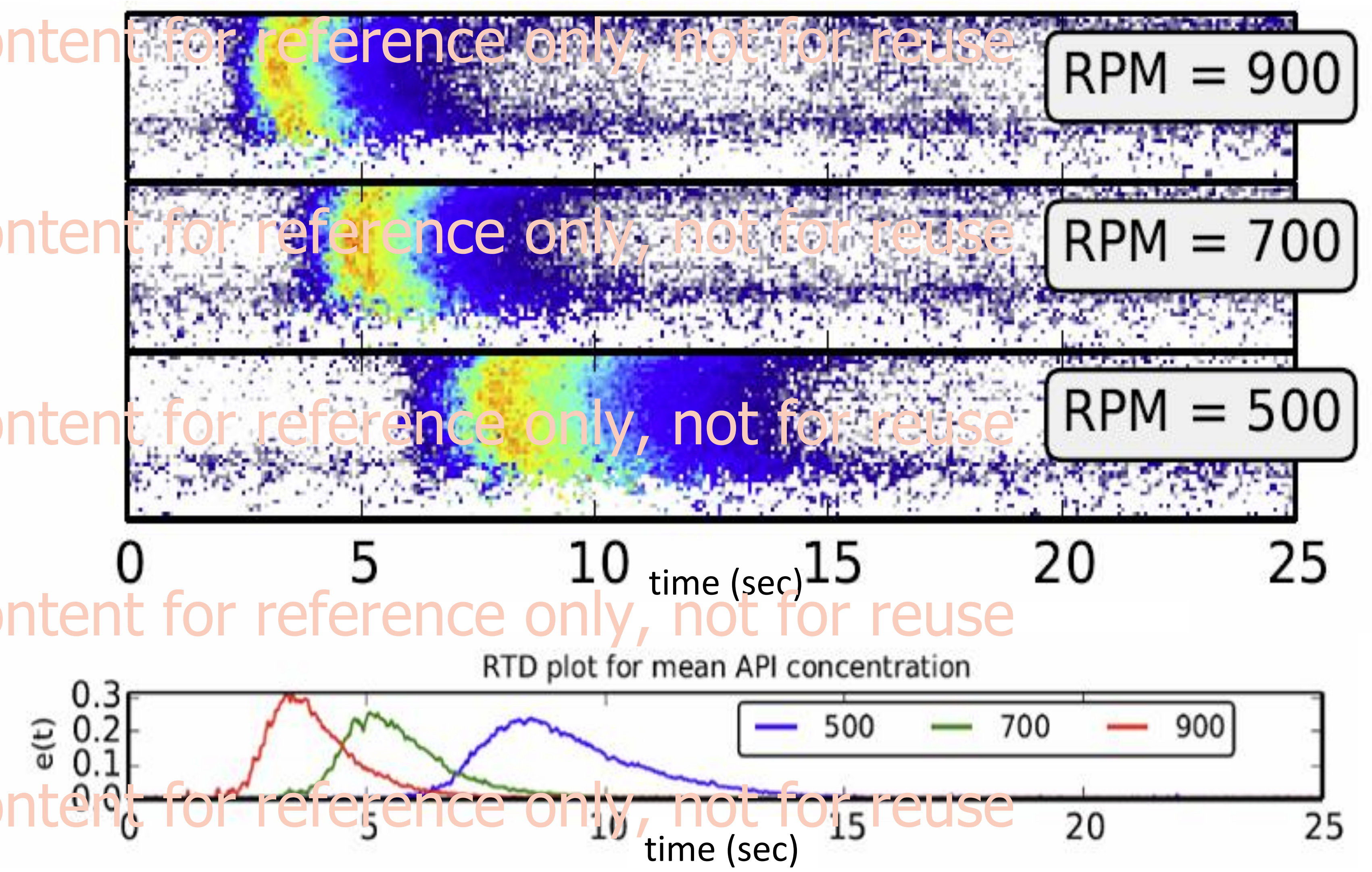


For details see: Kumar, et al. "Experimental investigation of granule size and shape dynamics in twin-screw granulation." *I J Pharma* 475.1 (2014): 485-495.

Tracer concentration in granules produced was measured using NIR chemical imaging

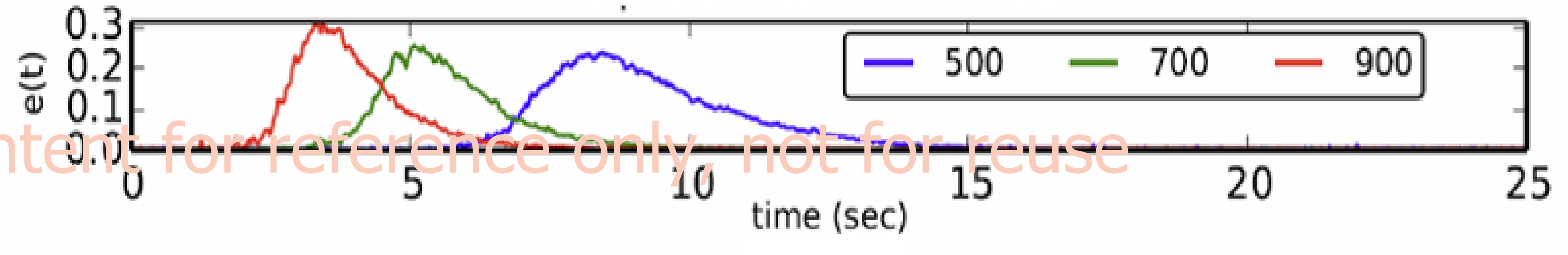

Granulation premix
Liquid addition
Theophylline tracer addition
M
Twin-screw granulator
Granulator outlet
Post-processing of hyperspectral data
Spectral Camera
Halogen Lamp
Moving conveyor belt

API Map was used to measure RTD



For details see: Kumar, et al. "Mixing and transport during pharmaceutical twin-screw wet granulation: Experimental analysis via chemical imaging." *E J Pharma. Biopharma.* 87.2 (2014): 279-289.

Measure of the mean of the distribution



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

Mean residence time, τ

For details on results visit my presentation in Imaging Session of IPFAC 2015 on :
"Mixing and transport during pharmaceutical twin-screw wet granulation: Experimental analysis via chemical imaging"
or
Read: Kumar, et al. *E J Pharma. Biopharma.* 87.2 (2014): 279-289.

Population balance models can track granule attributes

$$\frac{\partial n(t,x)}{\partial t} = \frac{Q_{in}}{\tilde{V}} n_{in}(x) - \frac{Q_{out}}{\tilde{V}} n_{out}(x)$$

GSD balance

Aggregation term

$$+\frac{1}{2}\int_0^x \underbrace{\beta(t,x-\varepsilon,\varepsilon)}_{\text{aggregation rate}} n(t,x-\varepsilon)\,n(t,\varepsilon)\,d\varepsilon$$

$$-n(t,x)\int_0^\infty \underbrace{\beta(t,x,\varepsilon)}_{\text{aggregation rate}} n(t,\varepsilon)\,d\varepsilon$$

Breakage term

$$+\int_0^\infty \underbrace{b(x,\varepsilon)}_{\text{breakage fun.}} \underbrace{S(\varepsilon)}_{\text{selection rate}} n(t,\varepsilon)\,d\varepsilon$$

$$\underbrace{-S(x)}_{\text{selection rate}} n(t,x)$$

Semi-empirical kernels

Aggregation Kernel

$$\beta(x, y) = \beta_0$$

(Constant kernel)

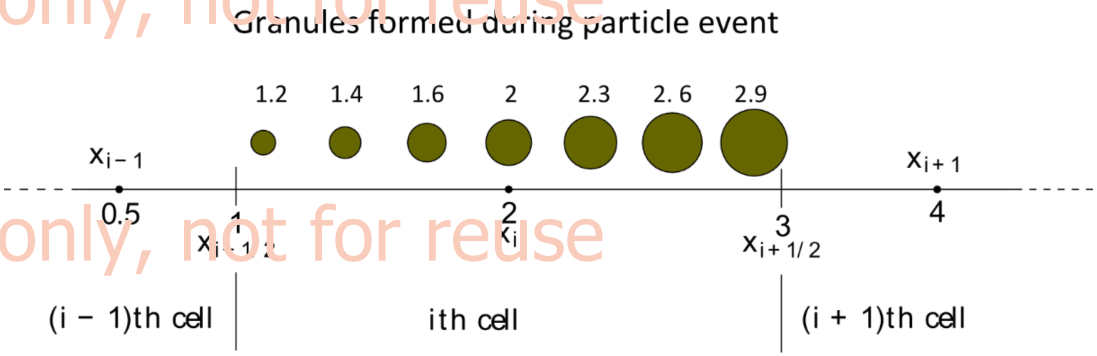
Breakage Kernel

$$S(y) = S_0 (y)^{\mu}$$

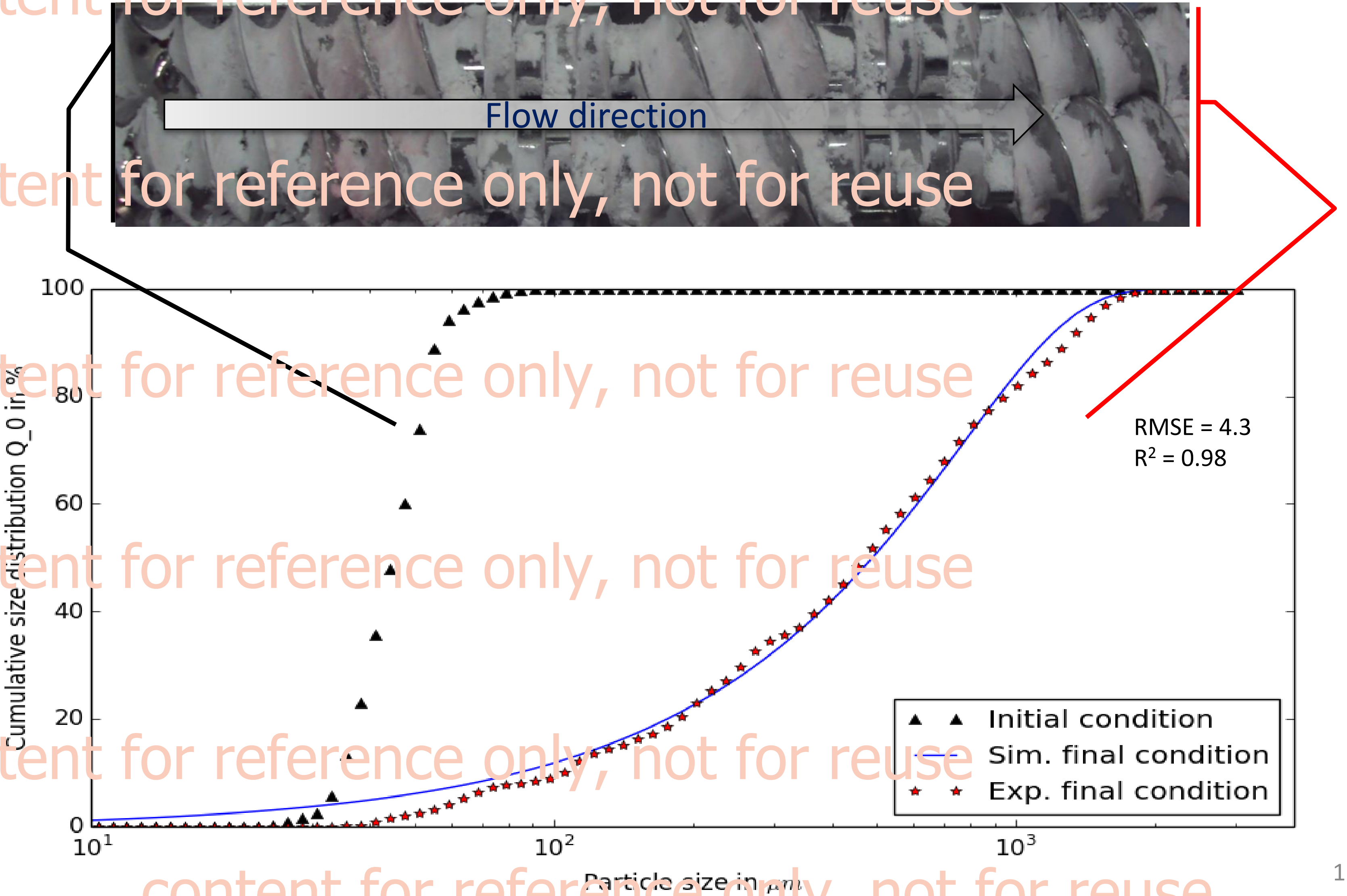
$$b(x, y) = \frac{\dfrac{\phi\gamma x^{\gamma-1}}{y^{\gamma}} + \dfrac{(1-\phi)\alpha x^{\alpha-1}}{y^{\alpha}}}{\dfrac{\phi\gamma}{\gamma+1} + \dfrac{(1-\phi)\alpha}{\alpha+1}}$$

(Austin, 2002)

Cell-average technique


Granules formed during particle event
1.2
1.4
1.6
2
2.3
2. 6
2.9
x_{i-1}
x_{i+1}
0.5
1
$x_{i-1/2}$
2
x_i
3
$x_{i+1/2}$
4
(i − 1)th cell
ith cell
(i + 1)th cell

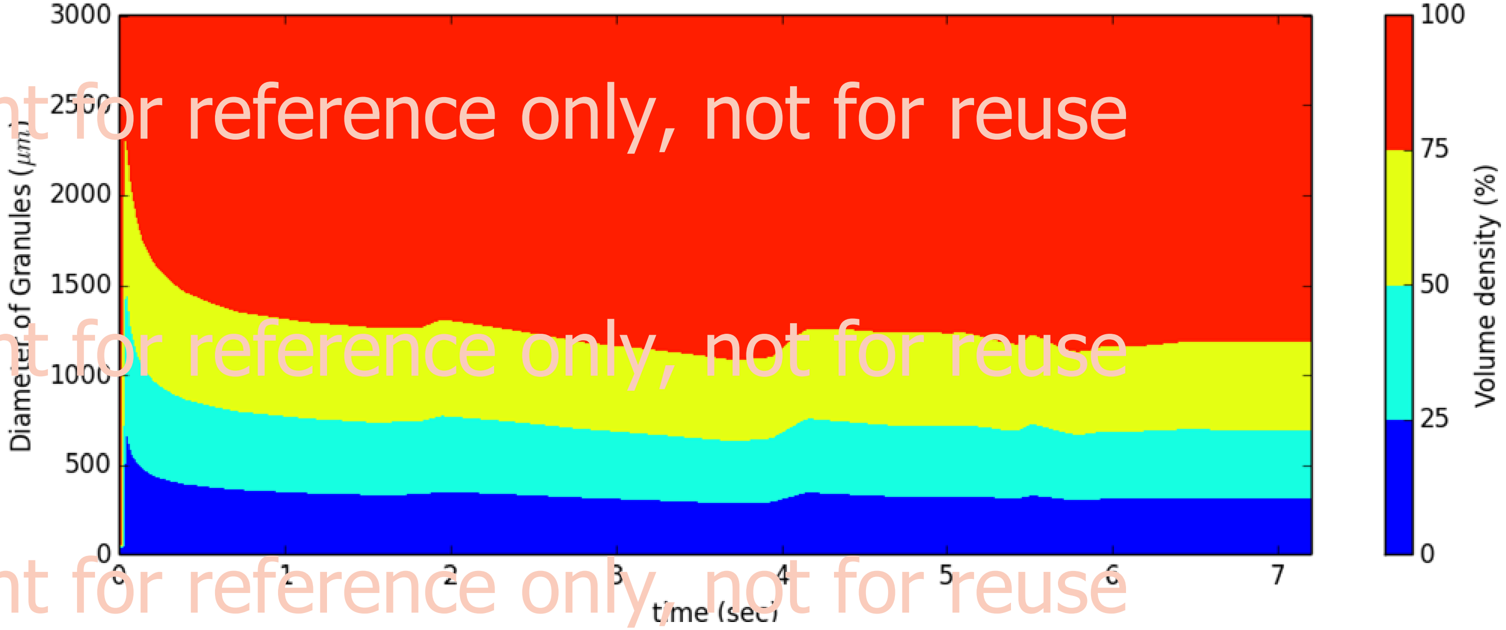
Experimental and simulated data have a good agreement



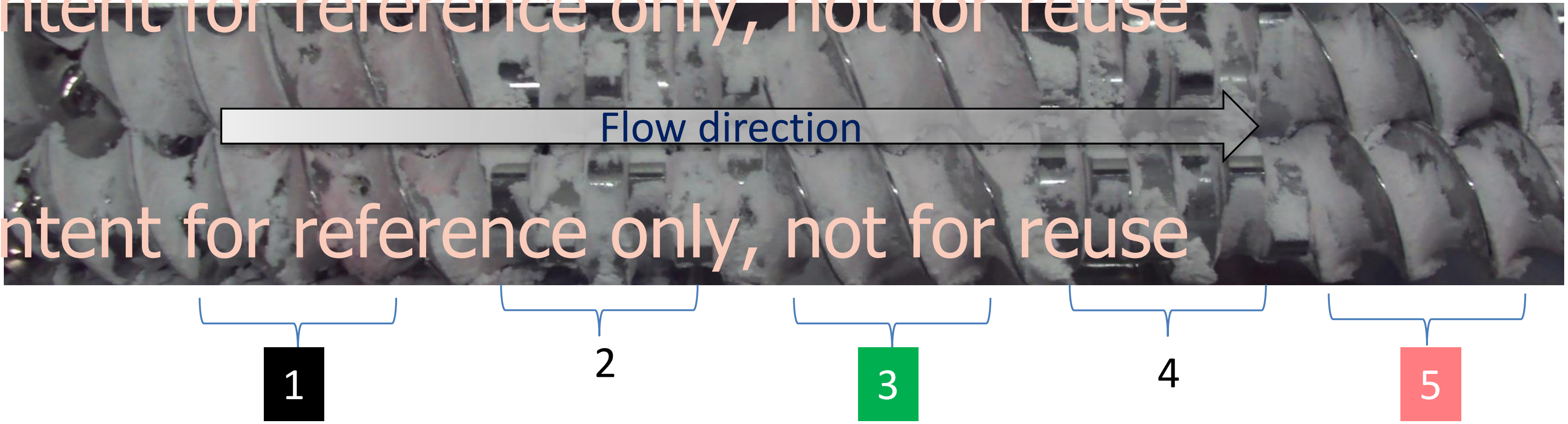
RMSE = 4.3
R^2 = 0.98

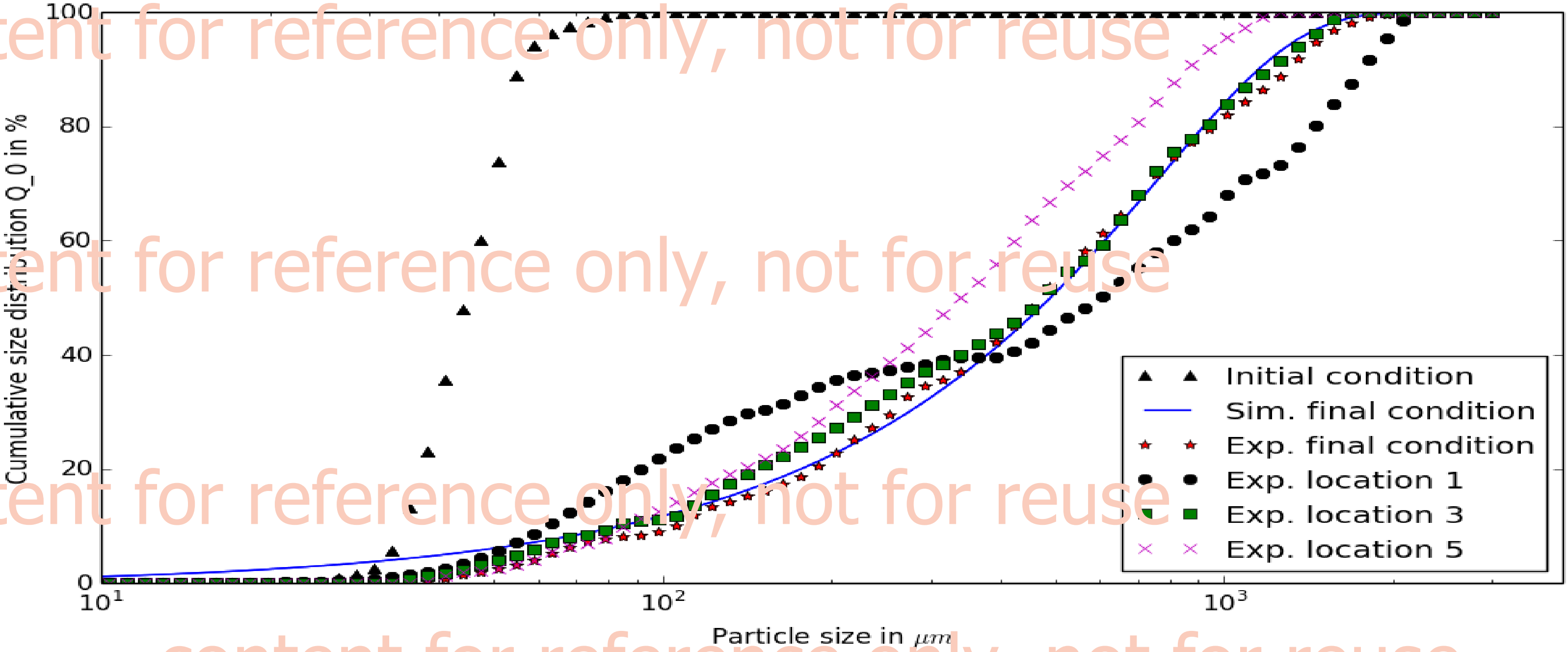
Particle population dynamics during granulation

Flow direction

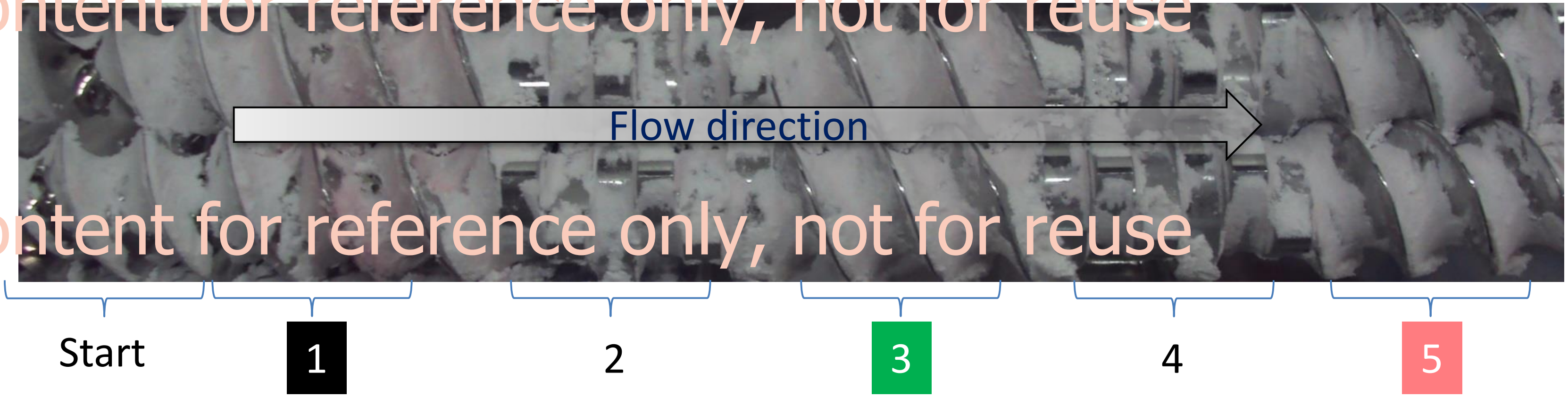


including effect of granulator design on granule size distribution

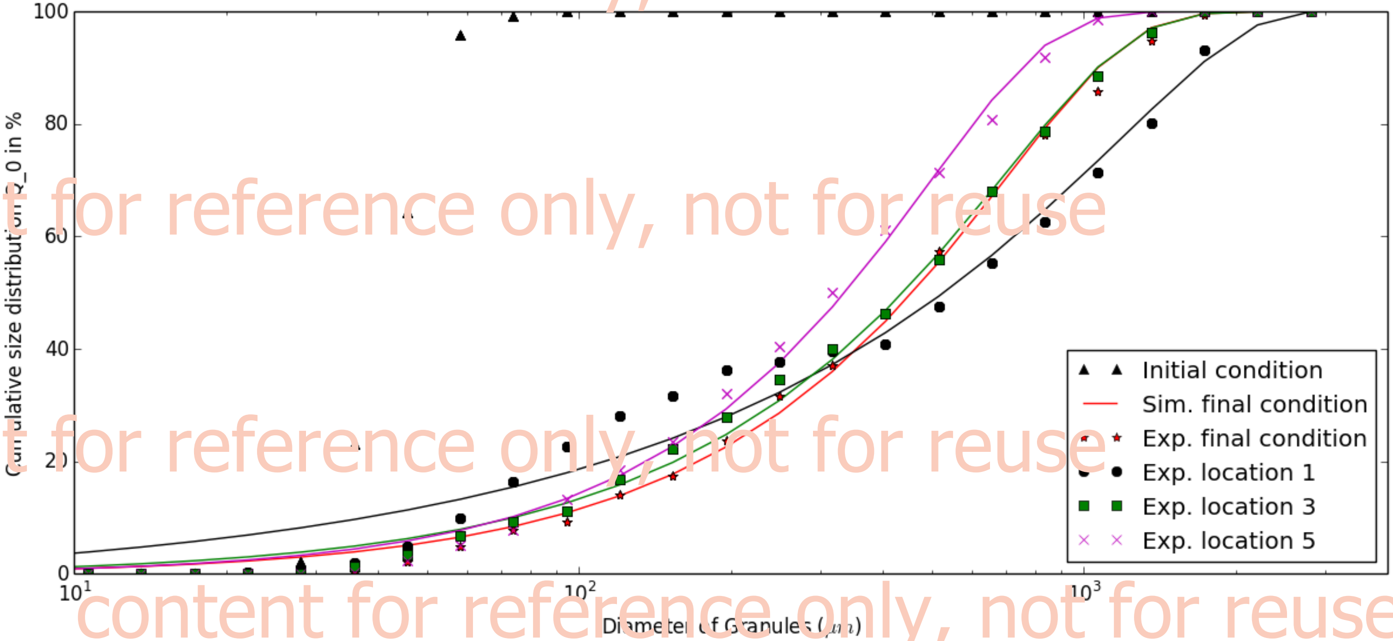

Flow direction
1
2
3
4
5



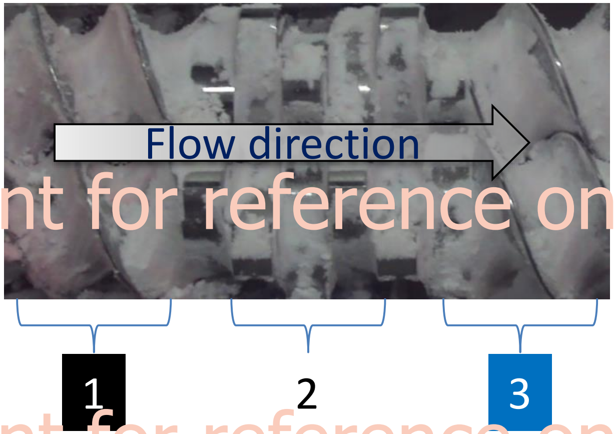
Including effect of granulator design on granule size distribution


Flow direction
Start
1
2
3
4
5

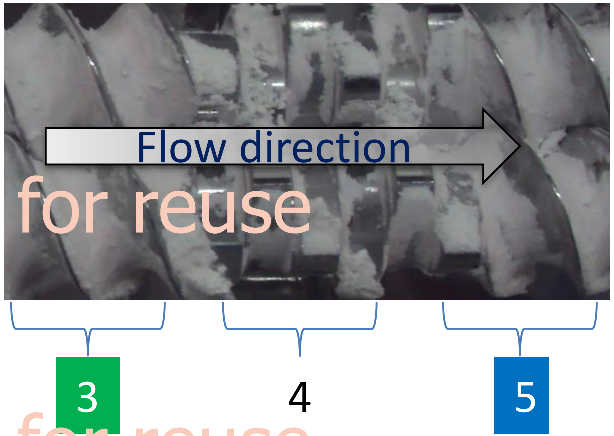
RMSE	16.25	2.72	2.14



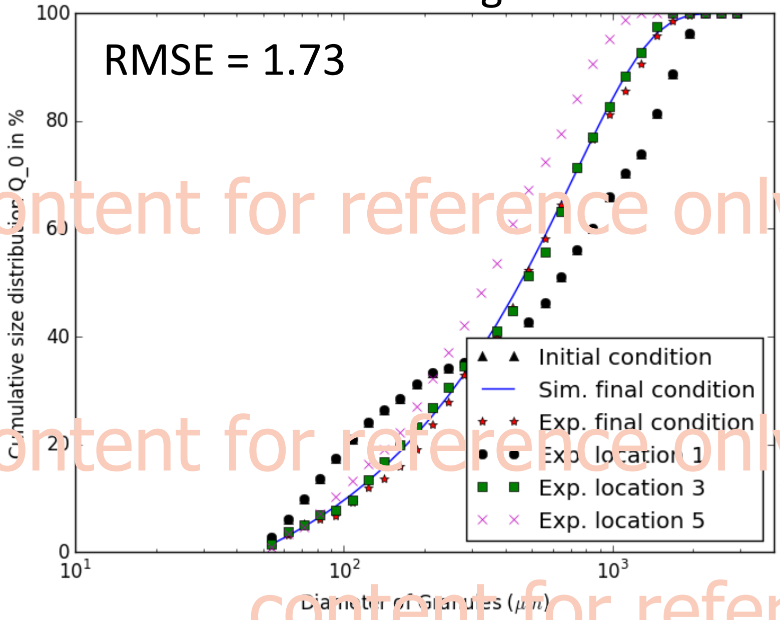
Including effect of granulator design on granule size distribution

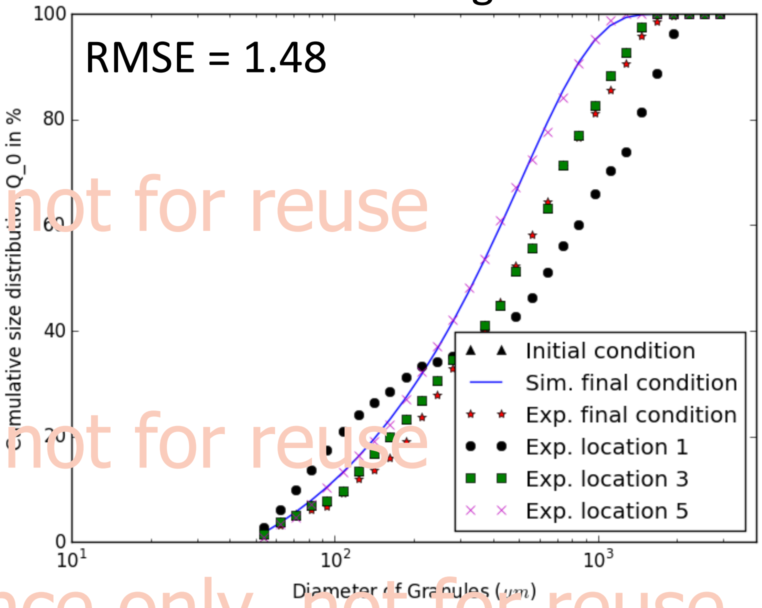

Flow direction
1
2
3

1st kneading block


Flow direction
3
4
5

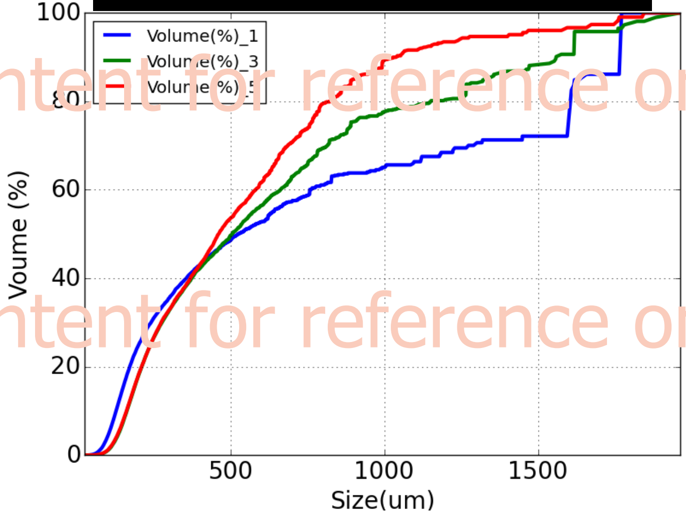
2nd kneading block



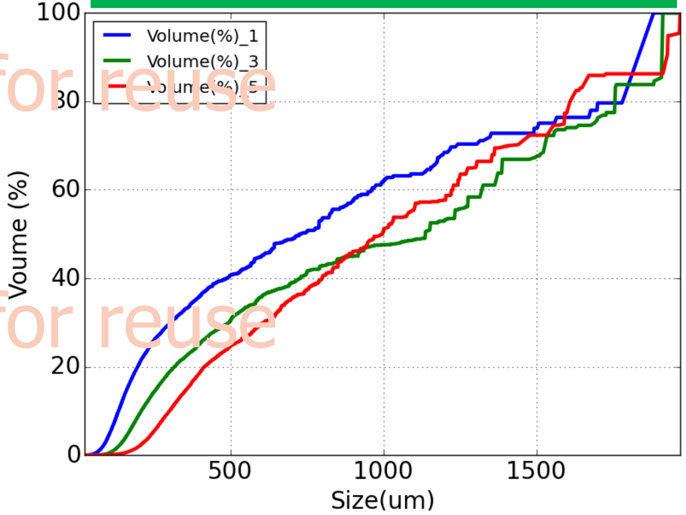


Throughput High | **Liquid-solid ratio High** | **Screw speed Low**

1 mixing zone



2 mixing zones



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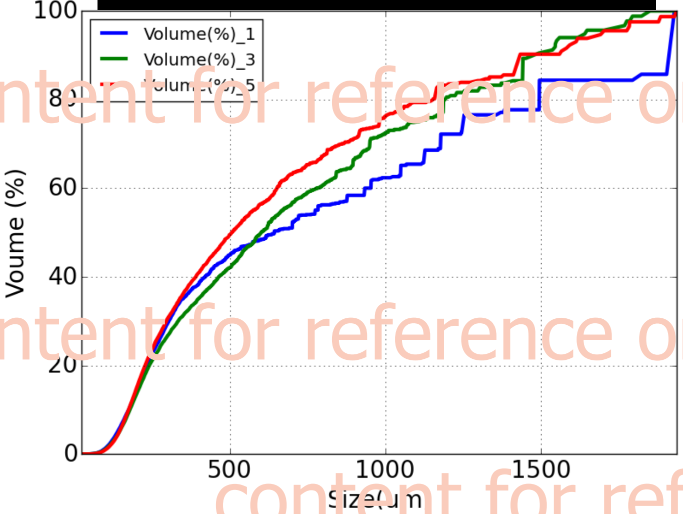
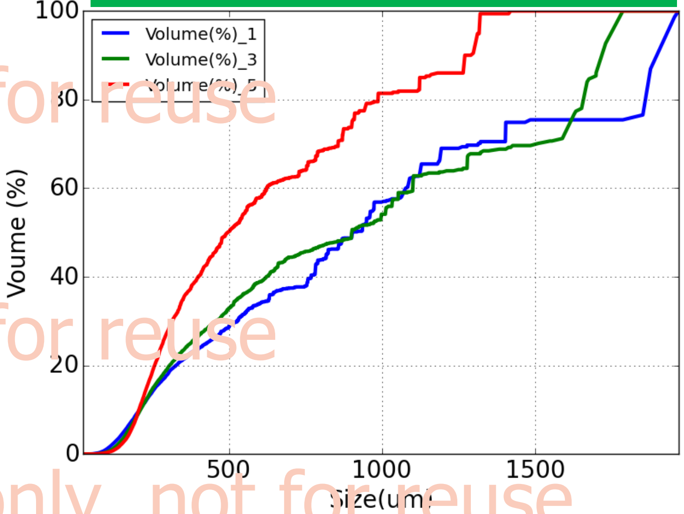
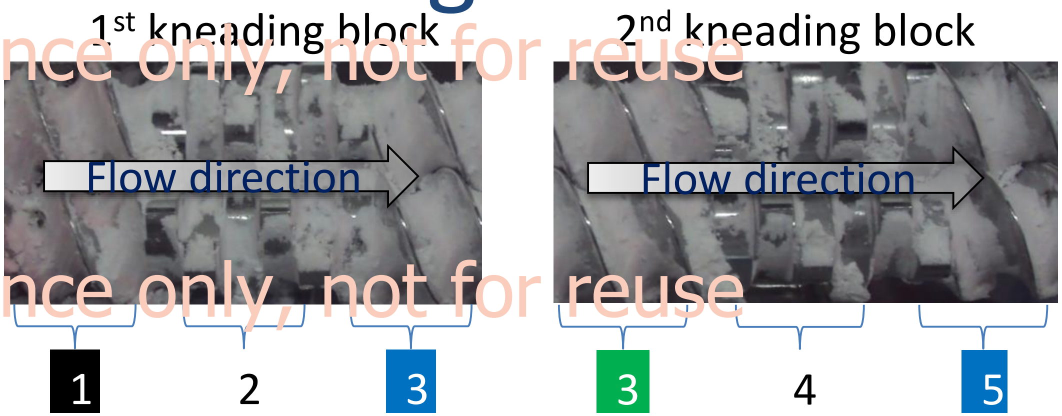


2 mixing zones

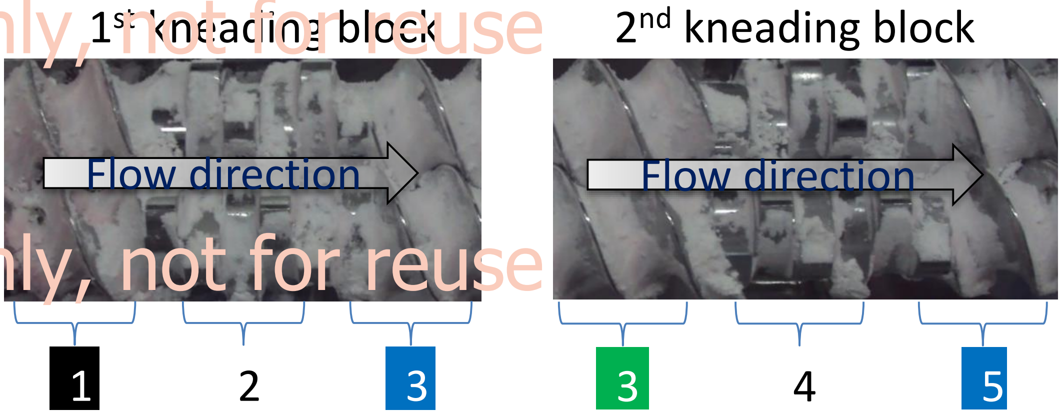


Investigating effect of screw speed and screw configuration


1st kneading block
2nd kneading block
Flow direction
Flow direction
1
2
3
3
4
5

High throughput, high L/S

	Low Screw Speed				High Screw Speed			
	1 mixing zone		2 mixing zones		1 mixing zone		2 mixing zones	
Zone	1-3	3-5	1-3	3-5	1-3	3-5	1-3	3-5
RMSE	2.424	2.317	2.716	3.929	1.153	3.366	8.176	3.772
R^2	0.989	0.987	0.984	0.983	0.989	0.983	0.97	0.982


1st kneading block
2nd kneading block
Flow direction
Flow direction
1
2
3
3
4
5

High throughput, high L/S

	Low Screw Speed				High Screw Speed			
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Zone	1-3	3-5	1-3	3-5	1-3	3-5	1-3	3-5
RMSE	2.424	2.317	2.716	3.929	1.153	3.366	8.176	3.772
R^2	0.989	0.987	0.984	0.983	0.989	0.983	0.97	0.982
β_0	1.05E-03	3.12E-01	3.11E-03	1.20E-02	2.36E-04	2.95E-01	8.97E-02	2.44E-01
S_0	0.030	3.304	0.023	0.062	0.051	1.180	0.030	3.340
α	6.01E-02	1.65E-07	1.47E-05	5.09E-04	1.86E-04	1.14E-06	1.39E-03	6.37E-07
γ	0.52	0.42	3.69	0.63	0.83	0.31	0.26	0.48
ϕ	0.97	0.72	0.93	0.98	0.41	0.53	1.00	0.48

Throughput **High**

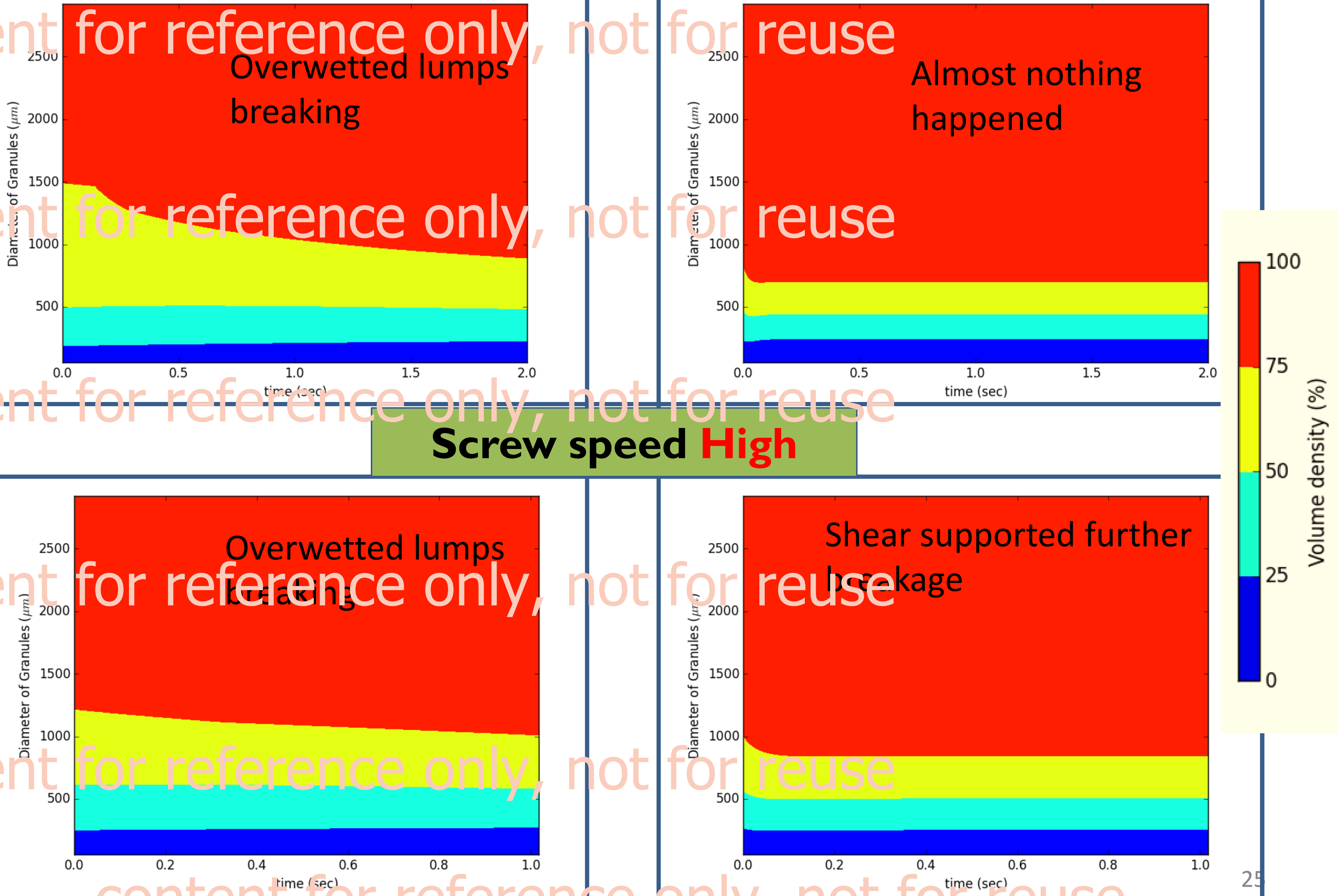
Liquid-solid ratio **High**

Screw speed Low

Location 1-3

Location 3-5

1 mixing zone



Overwetted lumps breaking

Almost nothing happened

Screw speed High

Overwetted lumps breaking

Shear supported further breakage

Throughput High

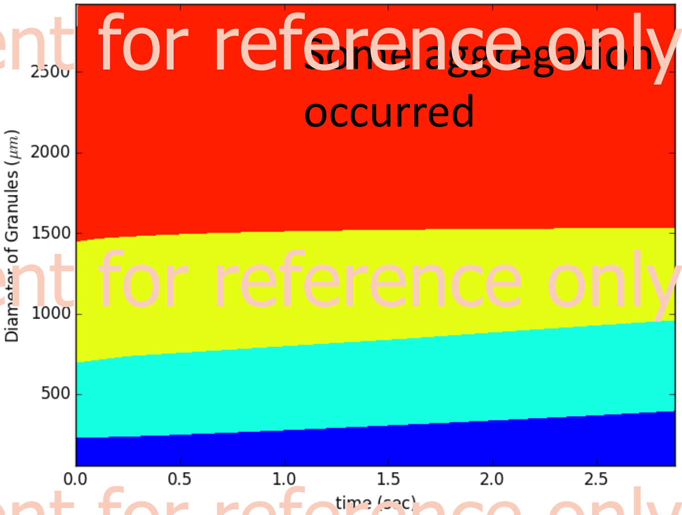
Liquid-solid ratio High

2 mixing zones

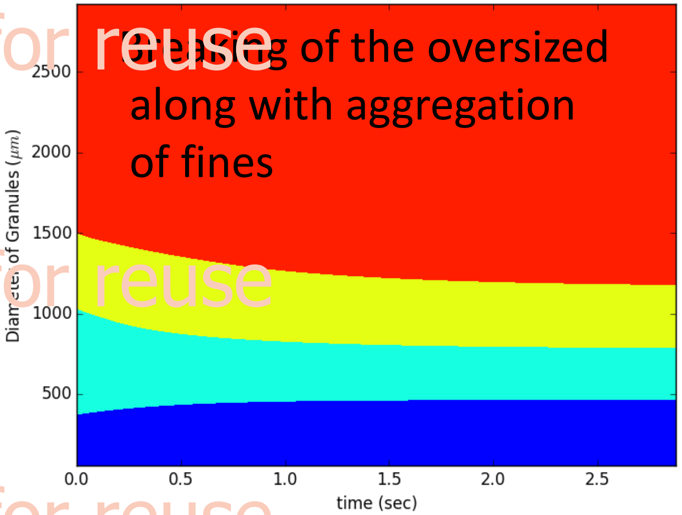
Screw speed Low

Location 1-3

Location 3-5

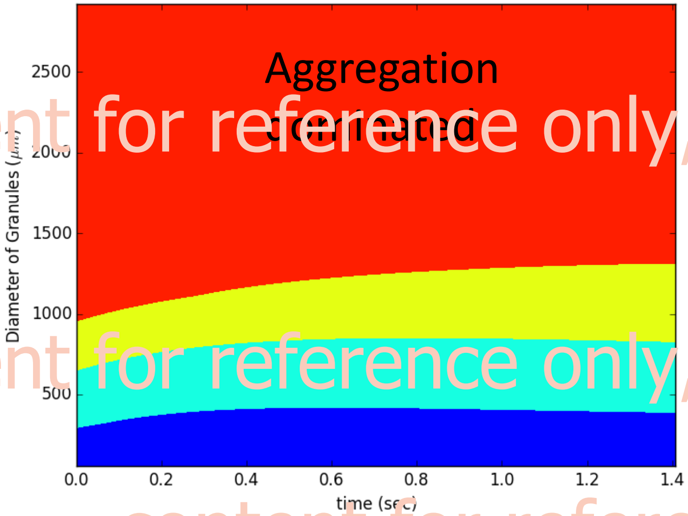


Some aggregation occurred

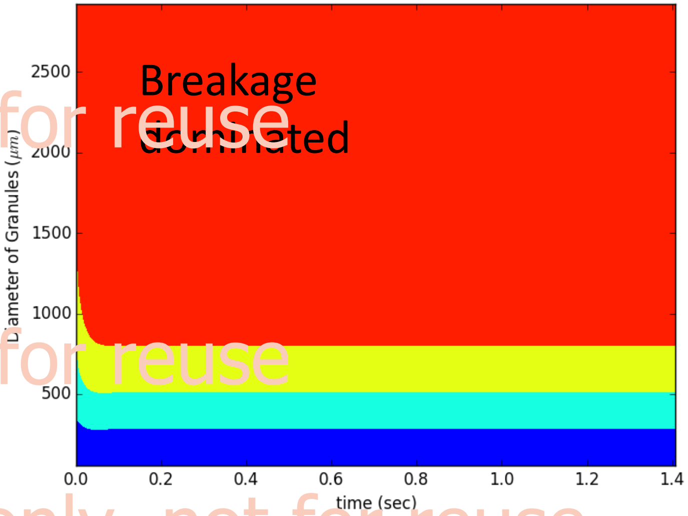


Breaking of the oversized along with aggregation of fines

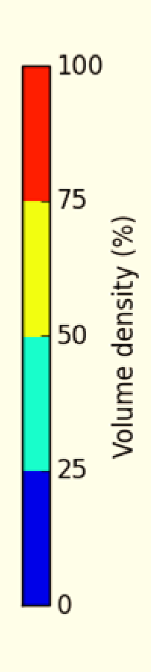
Screw speed High



Aggregation dominated



Breakage dominated



Conclusions

Along with experimental study, an improved insight can be obtained by model-based analysis.

Wetting kinetics requires a separate explanation in the twin-screw granulation modelling.

Aggregation and breakage are most dominant phenomena in the twin-screw granulation.

Particle population dynamics and screw geometry effect can be better understood by compartmental PBM, and can ultimately be used for predictive modelling of twin-screw granulation.

Acknowledgements

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DTU

VTT

GEA

Thomas.DeBeer@UGent.be

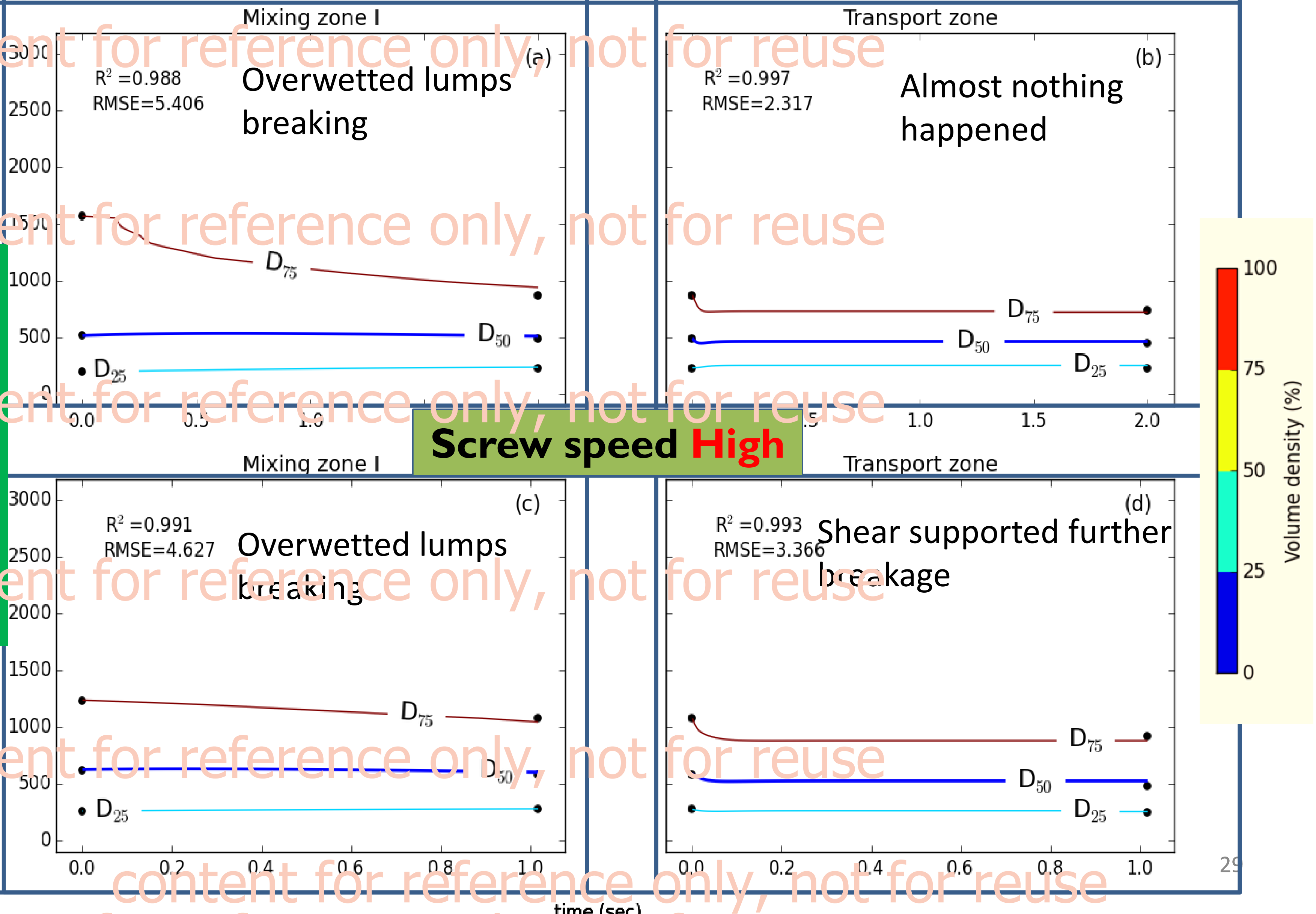
Throughput High | **Liquid-solid ratio High**

Screw speed Low

Location 1-3

Location 3-5

1 mixing zone



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Almost nothing happened

Screw speed High

Overwetted lumps breaking

Shear supported further breakage

Throughput **High**

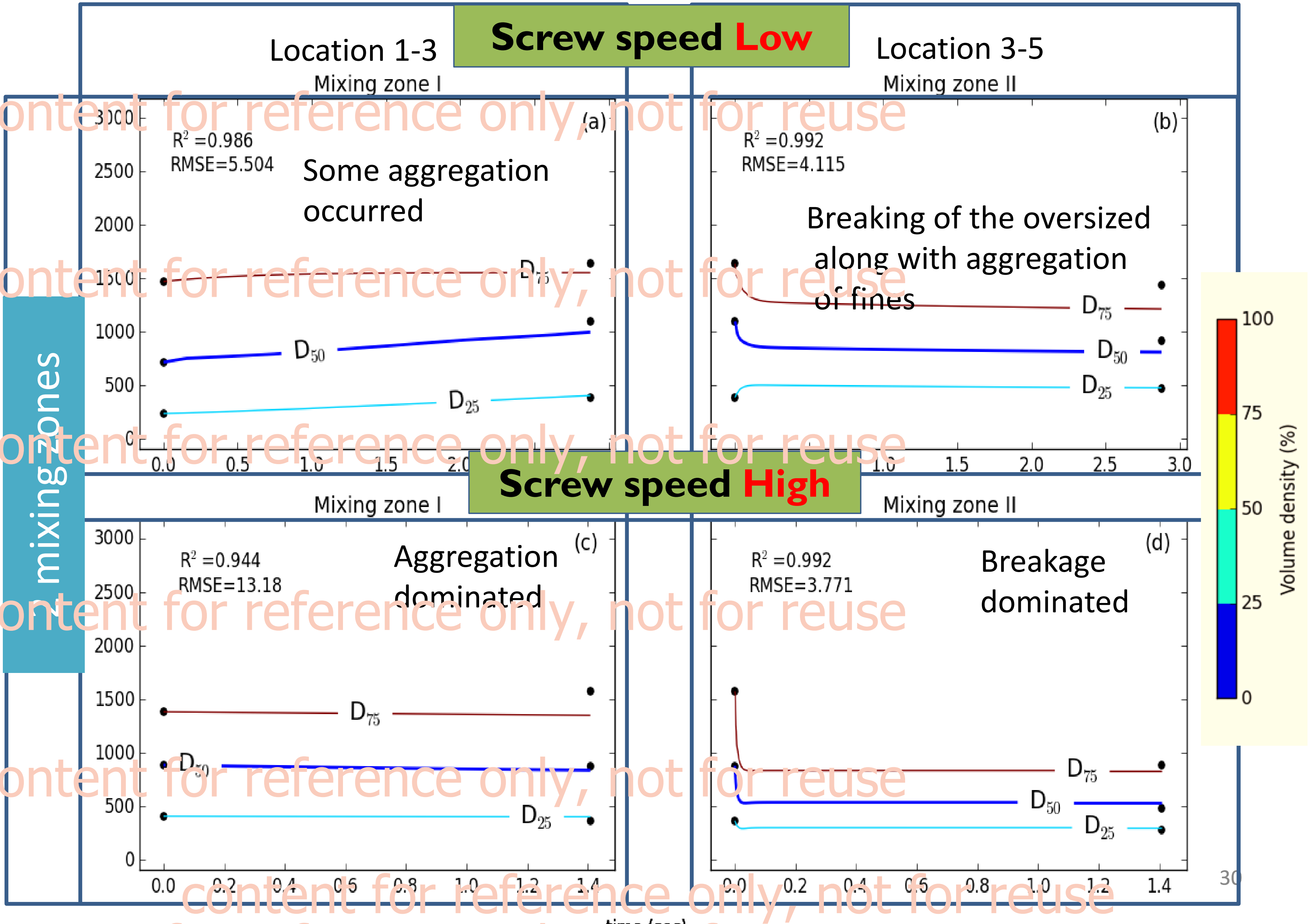
Liquid-solid ratio **High**

Screw speed Low

Location 1-3

Location 3-5

2 mixing zones



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Screw speed High

Aggregation dominated

Breakage dominated