Analysis of a twin-screw granulation process using a combined experimental and computational approach

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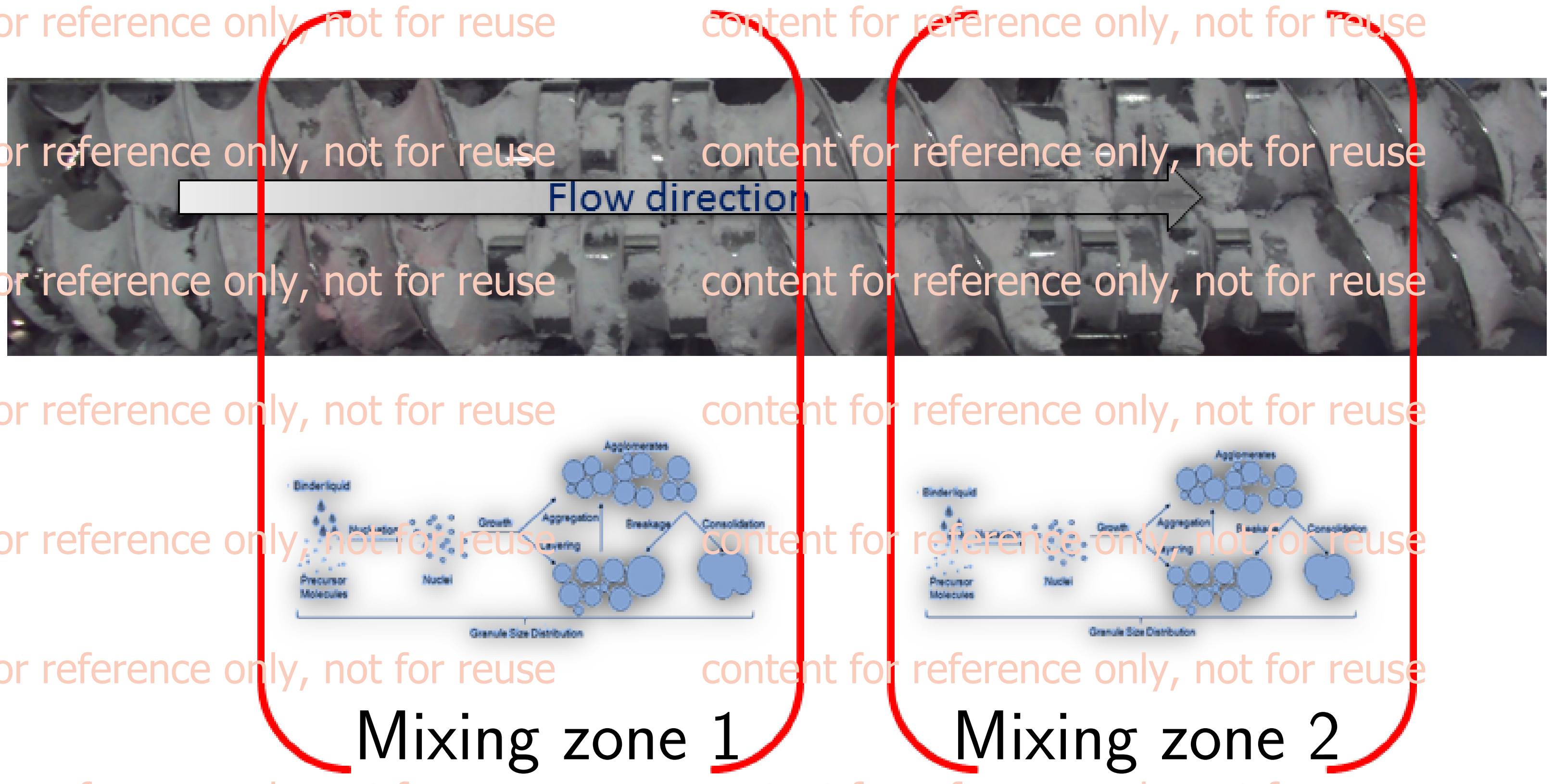
Introduction

- **Continuous wet granulation** using twin-screw granulators (TSG) is an important unit operation in future continuous manufacturing of pharmaceutical solid dosage forms.
- Several process and equipment settings govern the extent of different **rate processes such as aggregation and breakage** involved in granulation.
- However, little is in fact known about how these variables affect the evolution and kinetics of granule formation.
- **Combination of theoretical development and experimental validation** of a population balance modelling framework can bridge this gap to track the particle evolution during twin-screw granulation.

Twin-screw wet granulation

- Granulation time is short (in the order of seconds).
- At appropriate time scales and conditions, granulation is in steady state.



Mixing zone 1

Mixing zone 2

- Mixing zones in the TSG were assumed as well-mixed compartments.

PBM to track particle size evolution

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

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

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

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

Kernels and solution method

Aggregation Kernel

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

(Constant kernel)

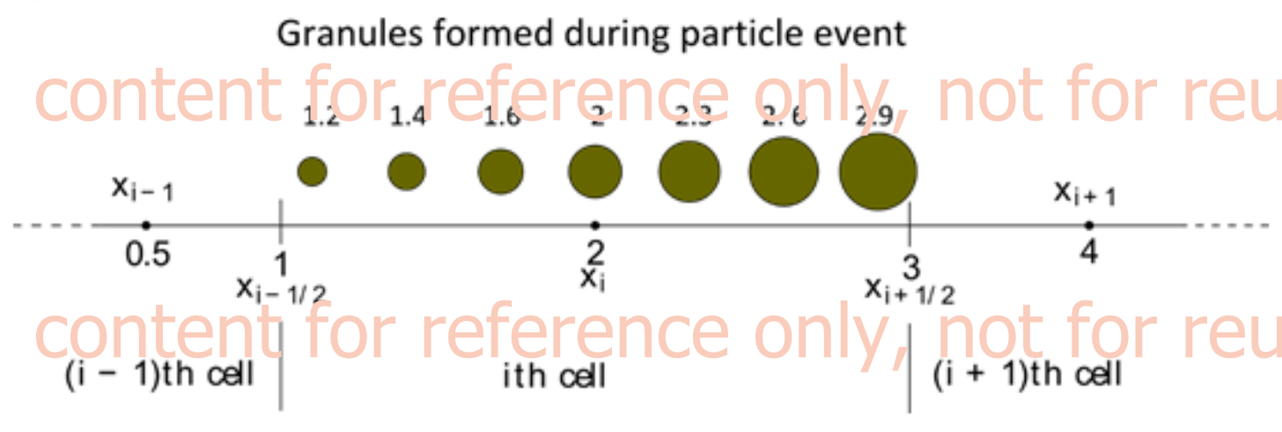
Breakage Kernel

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

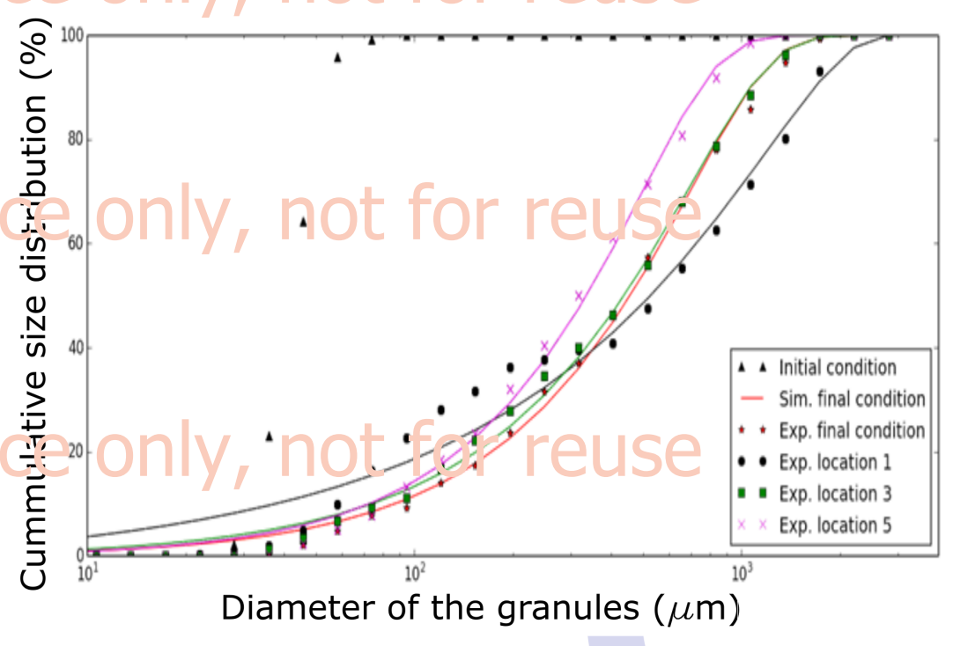
$$b(x,y) = \frac{\frac{\phi\gamma x^{\gamma-1}}{y^{\gamma}} + \frac{(1-\phi)\alpha x^{\alpha-1}}{y^{\alpha}}}{\frac{\phi\gamma}{\gamma+1} + \frac{(1-\phi)\alpha}{\alpha+1}}$$

(Austin, 2002)

Cell-average technique

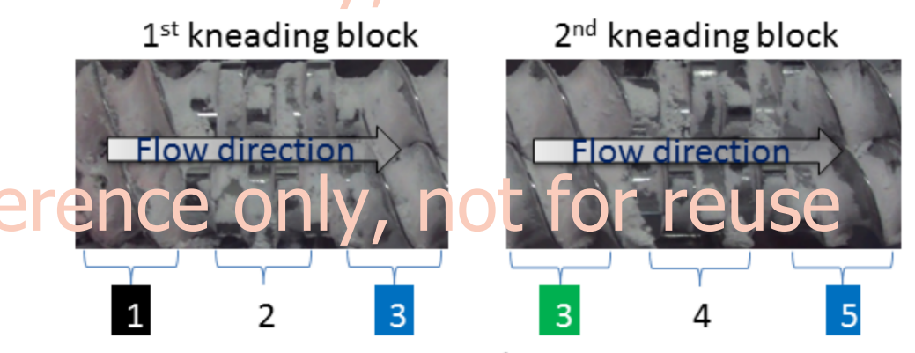


Parameter estimation



Paramter sets were derived by minimising the root mean square error (RMSE) via Monte Carlo Simulations

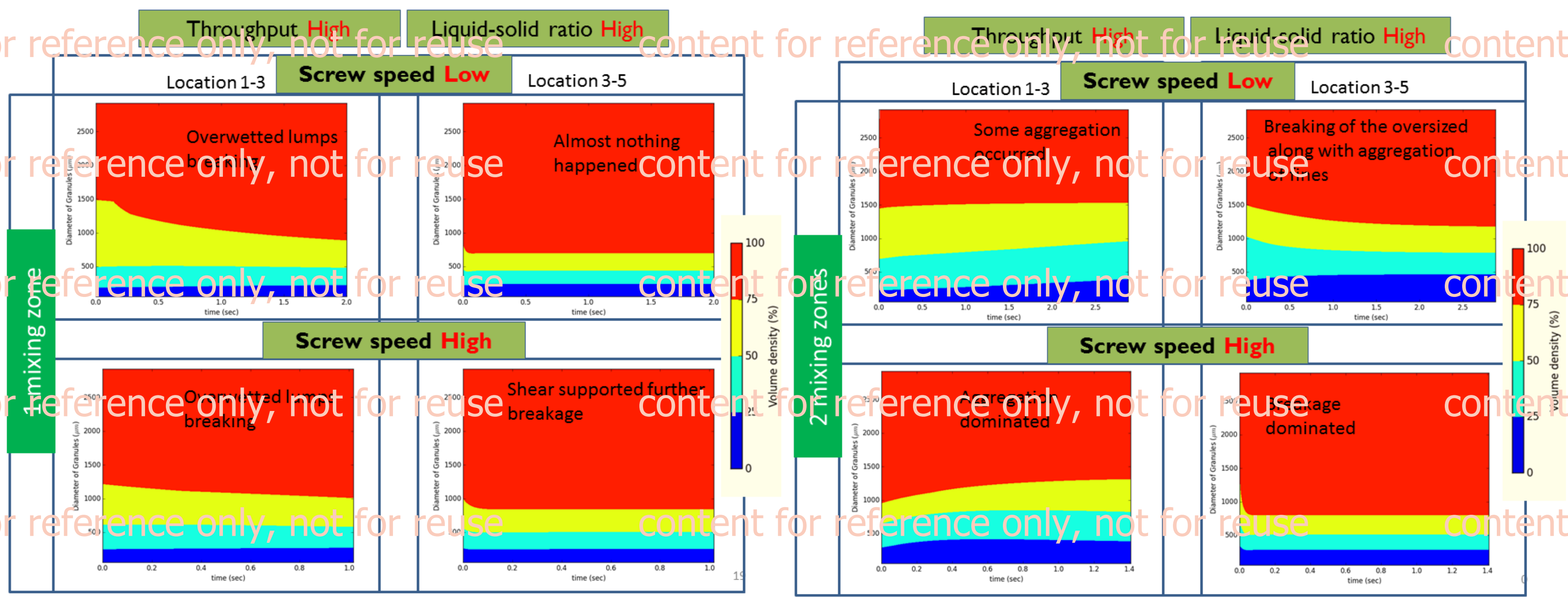
$$\mathrm{RMSE} = \sqrt{\frac{\sum_{i=1}^{n}(y_{\exp} - y_{\mathrm{sim}})^2}{n}}$$



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
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	5.01E-02	1.55E-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

Data postprocessing results



Take home message

By choosing appropriate process conditions regime separation can be achieved in TSG, allowing for improved design and operation of the continuous granulation process.

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