Mechanistic modeling of modular co-rotating twin-screw extruders

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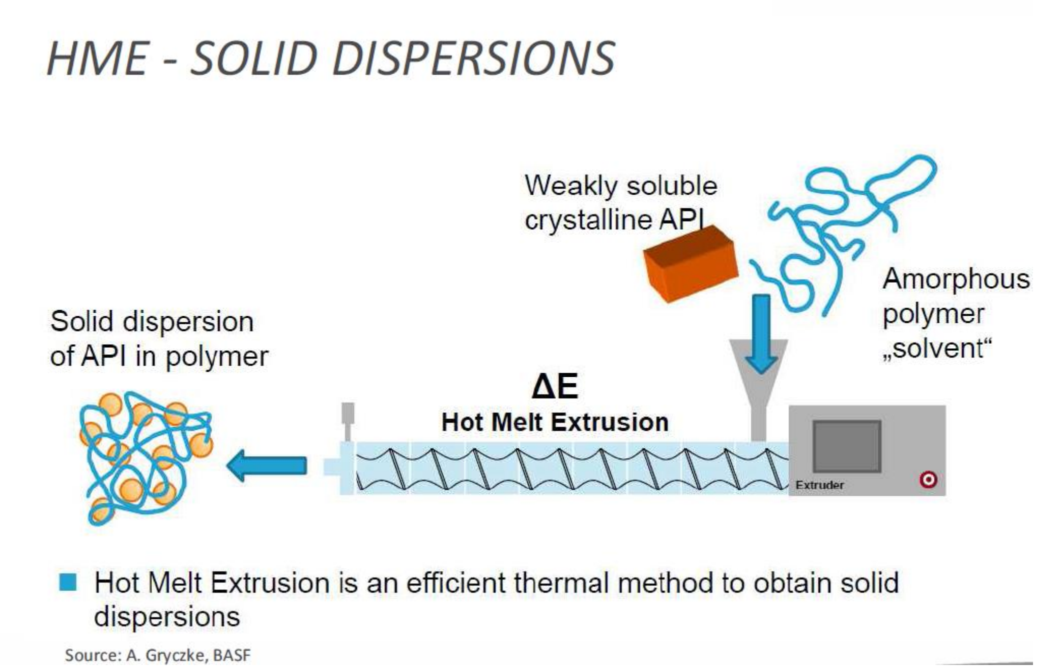
Outline

1. Introduction of Hot Melt Extrusion (HME) process
2. Aim and strategy of HME model application
3. Mechanistic model development and calibration
4. Model application / case study
5. Summary & discussion

Introduction to Hot Melt Extrusion

A solid solution of DS in polymers to increase the bioavailibility of poorly soluble DS

- HME gives a less porous particle with increased stability of granules compared to spray drying
- Eliminates water/solvent solutions
- Relatively short processing
- Continuous process



Aim and strategy of HME model application

Develop a mechanistic model that would increase process understanding and support / de-risk scale-up or equipment transfer, based on several process conditions:

1. Residence time distribution (RTD)
2. Specific mechanical energy (SME) input
3. Melt temperature profile

Perform risk analysis at the higher scale based on:

1. Fill level
2. Pressure
3. Max melt temperature

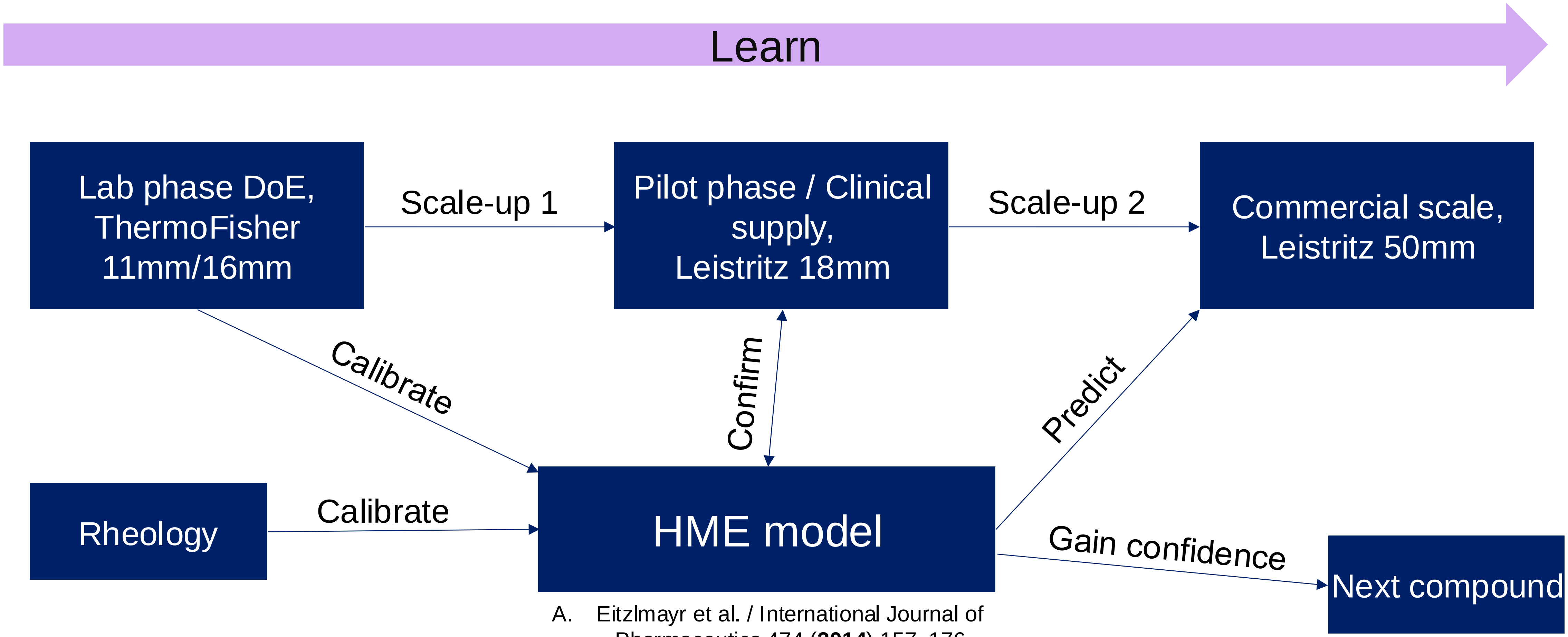
ThermoFisher Pharma 16 mm

10x

Scaleup

Leistritz 50 mm

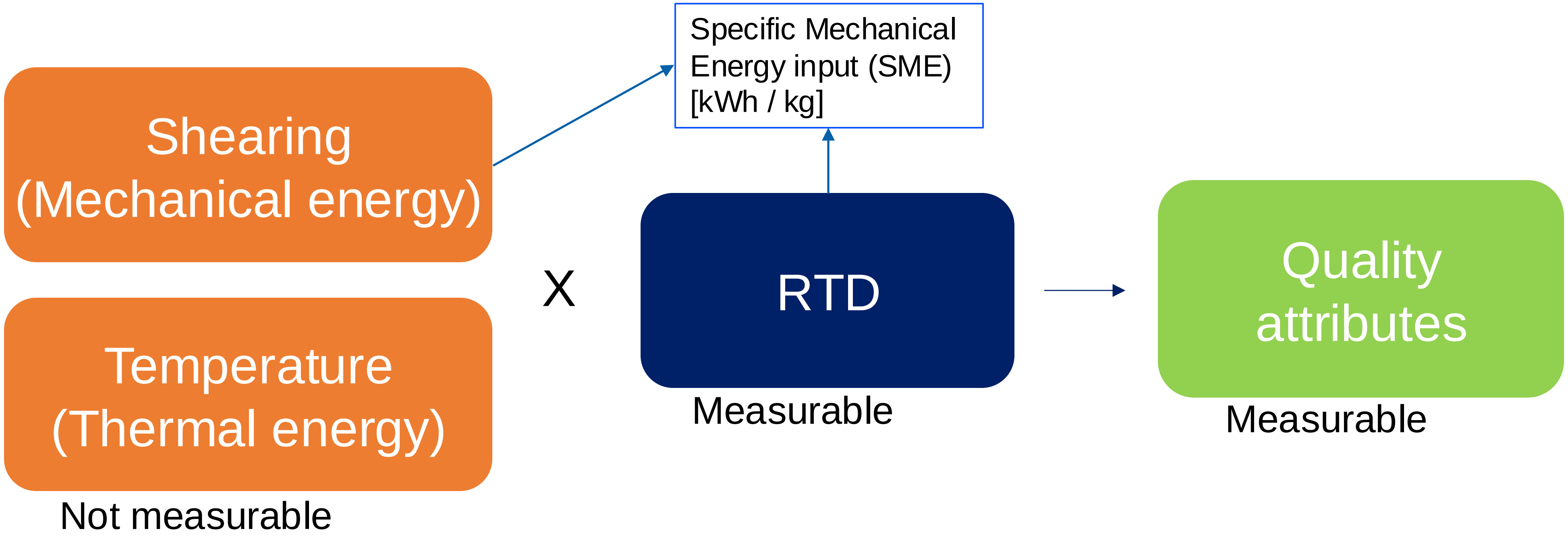
Aim and strategy of HME model application



A. Eitzlmayr et al. / International Journal of Pharmaceutics 474 (**2014**) 157–176 (RCPE Graz)

Why is Residence Time Distribution important?

What does the material experience when traveling through the extruder?



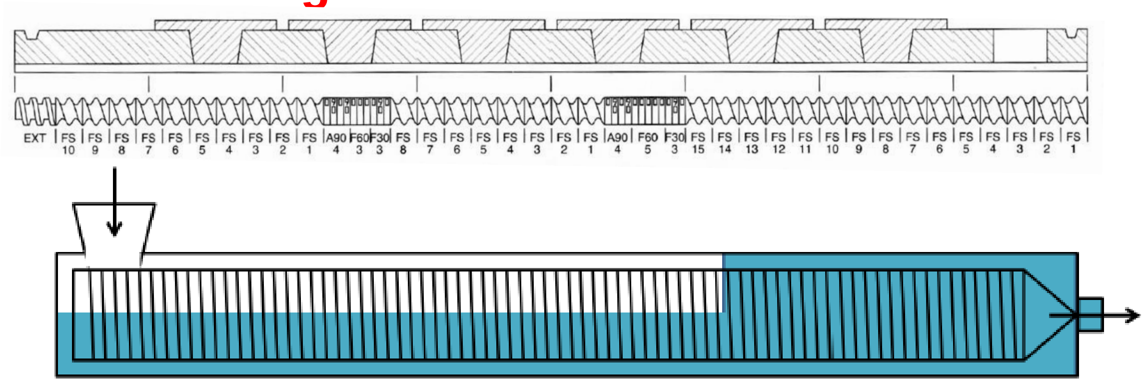
Assumption: Process conditions (Melt T, SME, RTD) define the product’s QAs regardless of scale and equipment.

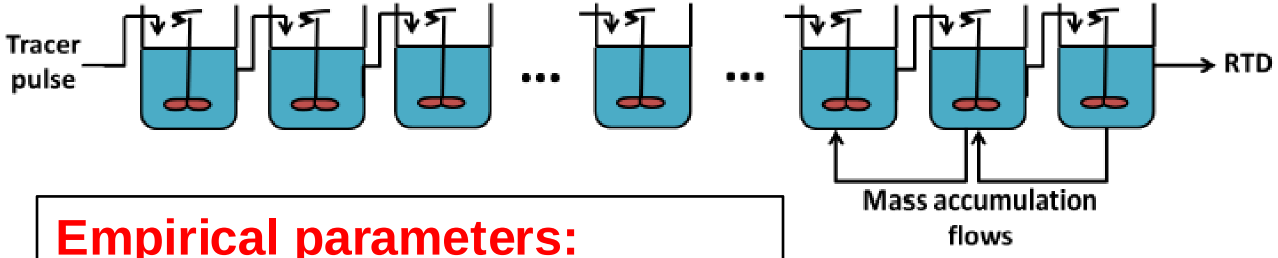
Stationary 1D model: Inputs and outputs

Operational parameters:
Mass flow
Screw speed
Temperature zones (setpoints)

Material parameters:
Viscosity (rheology)
Density
Heat capacity (DSC)
Thermal conductivity

Screw configuration:





Axial distributions:
Average melt T
Maximum melt T
Fill level
Pressure
Heat flow

Measurable outputs:
Torque
Die pressure
Residence time distribution (RTD)

Empirical parameters:
- Conveying parameter, A1
- Pressure parameter, A2
- Shear parameter, A3
- Axial dispersion coefficient
- Heat transfer coefficient

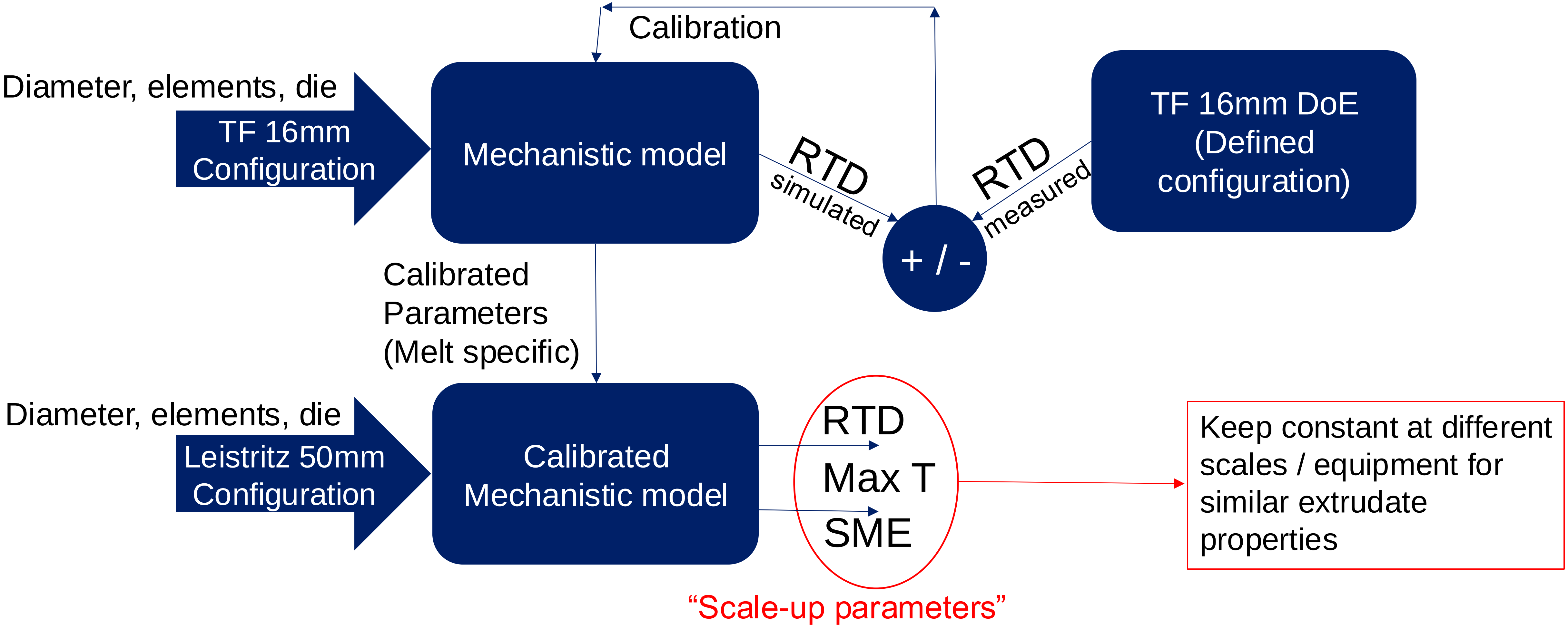
Literature →

← Experiments

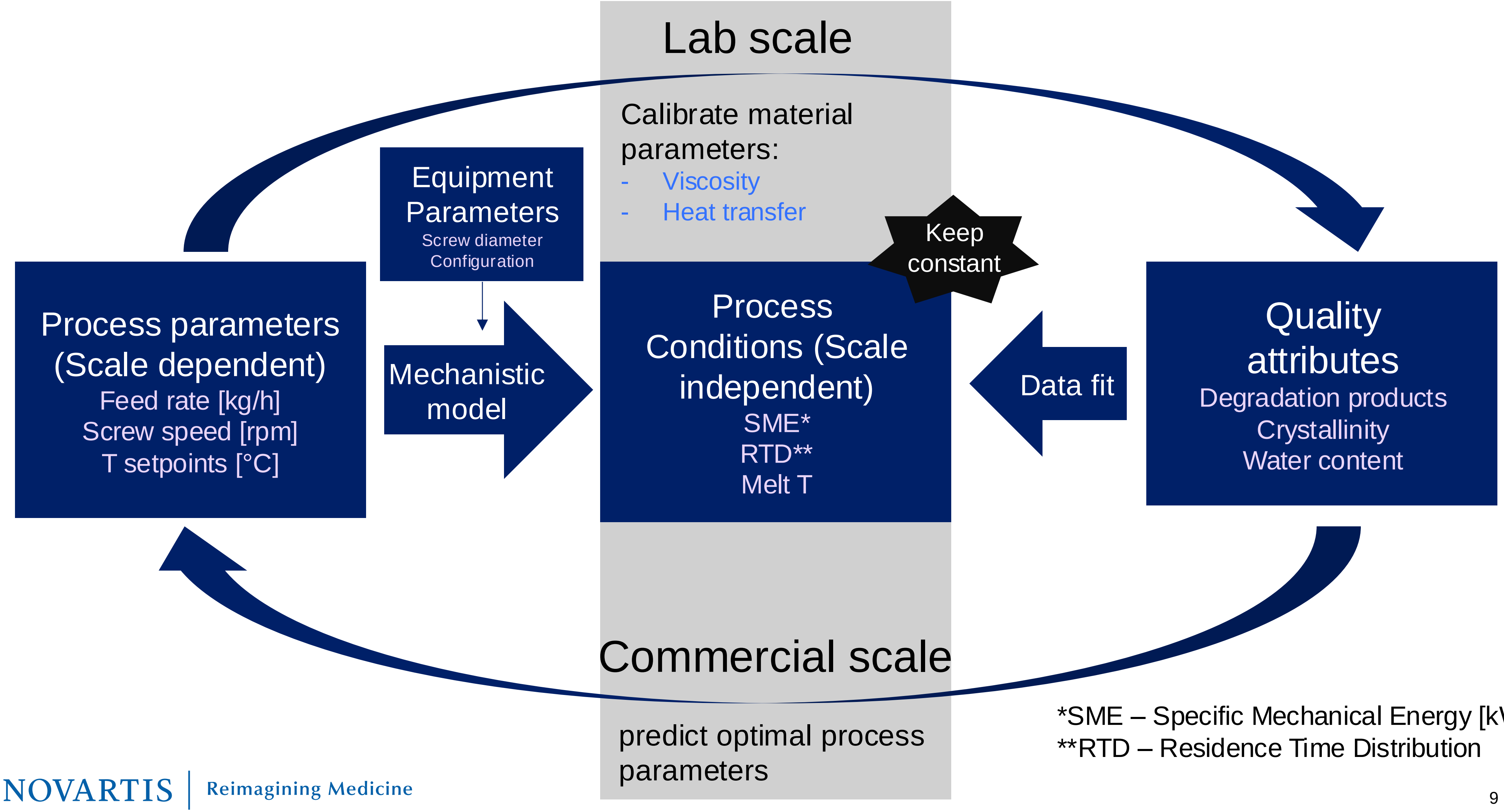
← CFD / DEM Simulations

A. Eitzlmayr et al. / International Journal of Pharmaceutics 474 (**2014**) 157–176

Streamlined approach for calibration



Hybrid process modeling workflow



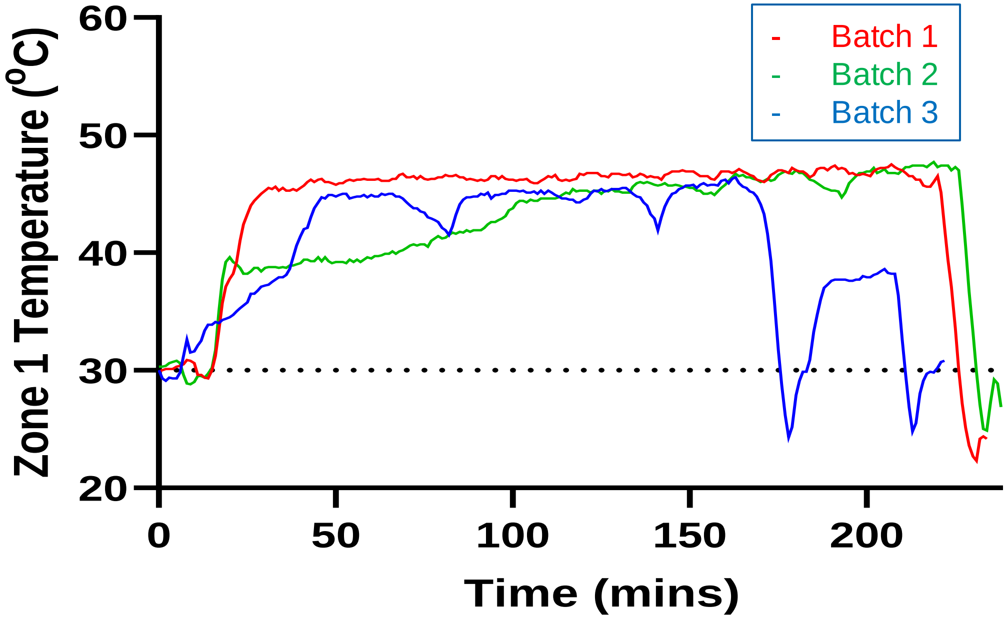
*SME – Specific Mechanical Energy [kWh/kg]
**RTD – Residence Time Distribution

Model application / case study

The problem:
Feeding zone is clogging, lumps are forming, temperature of zone 1 is rising.

Question of Interest (QoI): Is the feeding port overfilled?

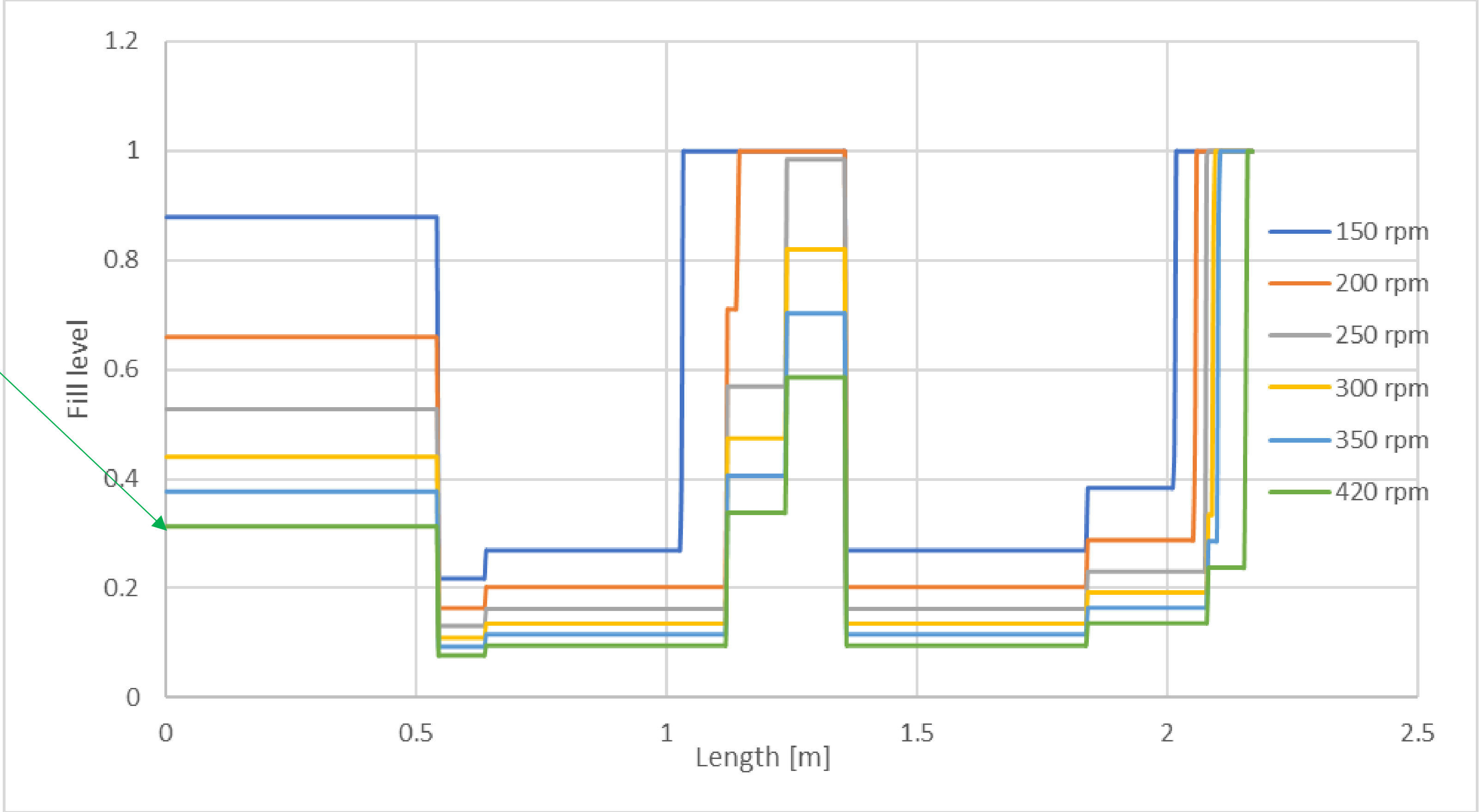
Context of Use (CoU): Use the calibrated 1D HME model to simulate fill level in the extruder.



Understanding status QUO

Is our extruder feeding port (zone 1) overfilling at applied process parameters? No!

Feed [kg/h]	Speed [rpm]	Avg Fill	Zone1 fill level
60	150	59%	88%
60	200	44%	66%
60	250	36%	53%
60	300	30%	44%
60	350	26%	38%
60	420	20%	31%



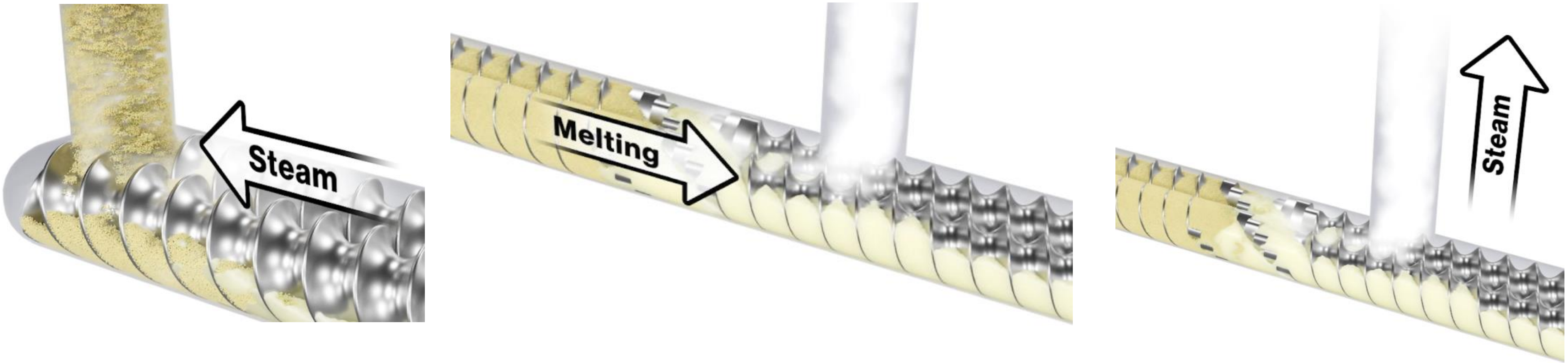
Conveying powder | Conveying melt | Kneading | Conveying melt | Die

Optimizing the process parameter settings

The problem:
Feeding zone is clogging, lumps are forming, temperature of zone 1 is rising.

Question of Interest (QoI): How to reduce generation of steam and/or redirect it towards venting ports?

Context of Use (CoU): Use the calibrated 1D HME model to simulate fill level and Specific Mechanical Energy (SME) input. Use the model to predict process parameters that will reduce SME and consequently translate the melting point downstream to redirect the steam while keeping the fill level at sufficient (not to high) level.



Optimizing the process parameter settings

Feeding zone fill level map (keep as high as possible):

Feed rate (kg/h)

Screw speed (rpm)	30	40	50	60	70	80	90	100	110	120	130	140
40	1	1	1	1	1	1	1	1	1	1	1	1
60	0.699041	0.932054	1	1	1	1	1	1	1	1	1	1
80	0.52428	0.699041	0.873801	1	1	1	1	1	1	1	1	1
100	0.419424	[illegible]	0.699041	0.838849	0.978657	1	1	1	1	1	1	1
120	0.34952	[illegible]	[illegible]	0.699041	0.815547	0.932054	1	1	1	1	1	1
140	[illegible]	0.399452	[illegible]	[illegible]	0.699041	0.798904	0.898767	0.998629	1	1	1	1
160	0.26214	0.34952	0.4369	[illegible]	[illegible]	0.699041	0.786421	0.873801	0.961181	1	1	1
180	0.233014	0.310685	0.388356	0.466027	[illegible]	[illegible]	0.699041	0.776712	0.854383	0.932054	1	1
200	0.209712	0.279616	0.34952	0.419424	0.489328	[illegible]	[illegible]	0.699041	0.768945	0.838849	0.908753	0.978657
220	0.190647	0.254197	0.317746	0.381295	0.444844	0.508393	[illegible]	[illegible]	0.699041	0.76259	0.826139	0.889688
240	0.17476	0.233014	0.291267	0.34952	0.407774	0.466027	0.52428	[illegible]	[illegible]	0.699041	0.757294	0.815547
260	[illegible]	0.215089	0.268862	0.322634	0.376406	0.430179	0.483951	0.537724	0.591496	0.645268	0.699041	0.752813
280	[illegible]	[illegible]	[illegible]	0.299589	0.34952	0.399452	[illegible]	0.499315	0.549246	0.599178	0.649109	0.699041
300	0.139808	0.186411	[illegible]	[illegible]	[illegible]	0.372822	0.419424	[illegible]	0.51263	0.559233	0.605835	0.652438
320	[illegible]	[illegible]	0.21845	[illegible]	[illegible]	0.34952	0.39321	0.4369	[illegible]	0.52428	0.567971	0.611661
340	[illegible]	[illegible]	0.2056	0.24672	0.28784	0.32896	0.37008	0.4112	0.45232	[illegible]	0.53456	0.575681
360	0.116507	0.155342	0.194178	0.233014	0.271849	0.310685	0.34952	0.388356	0.427192	0.466027	0.504863	0.543698
380	0.110375	0.147166	0.183958	0.22075	0.257541	0.294333	0.331125	0.367916	0.404708	0.441499	0.478291	0.515083
400	0.104856	0.139808	0.17476	0.209712	0.244664	0.279616	0.314568	0.34952	0.384472	0.419424	0.454376	0.489328

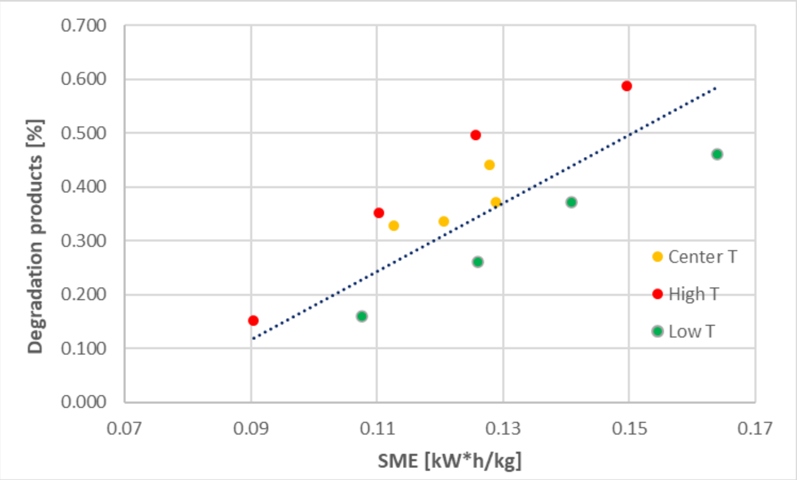
Overfilling

Good processability window

Too high energy input

Model output: Prediction map for zone 1 (feeding zone) fill levels

SME relation to degradation products (keep as low as possible):



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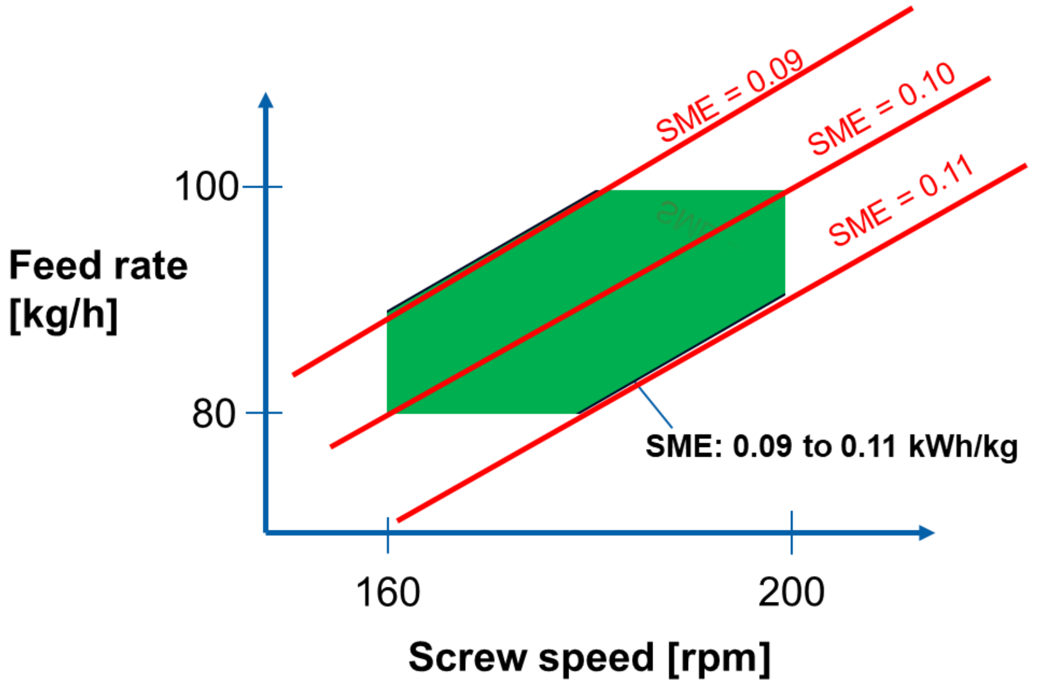
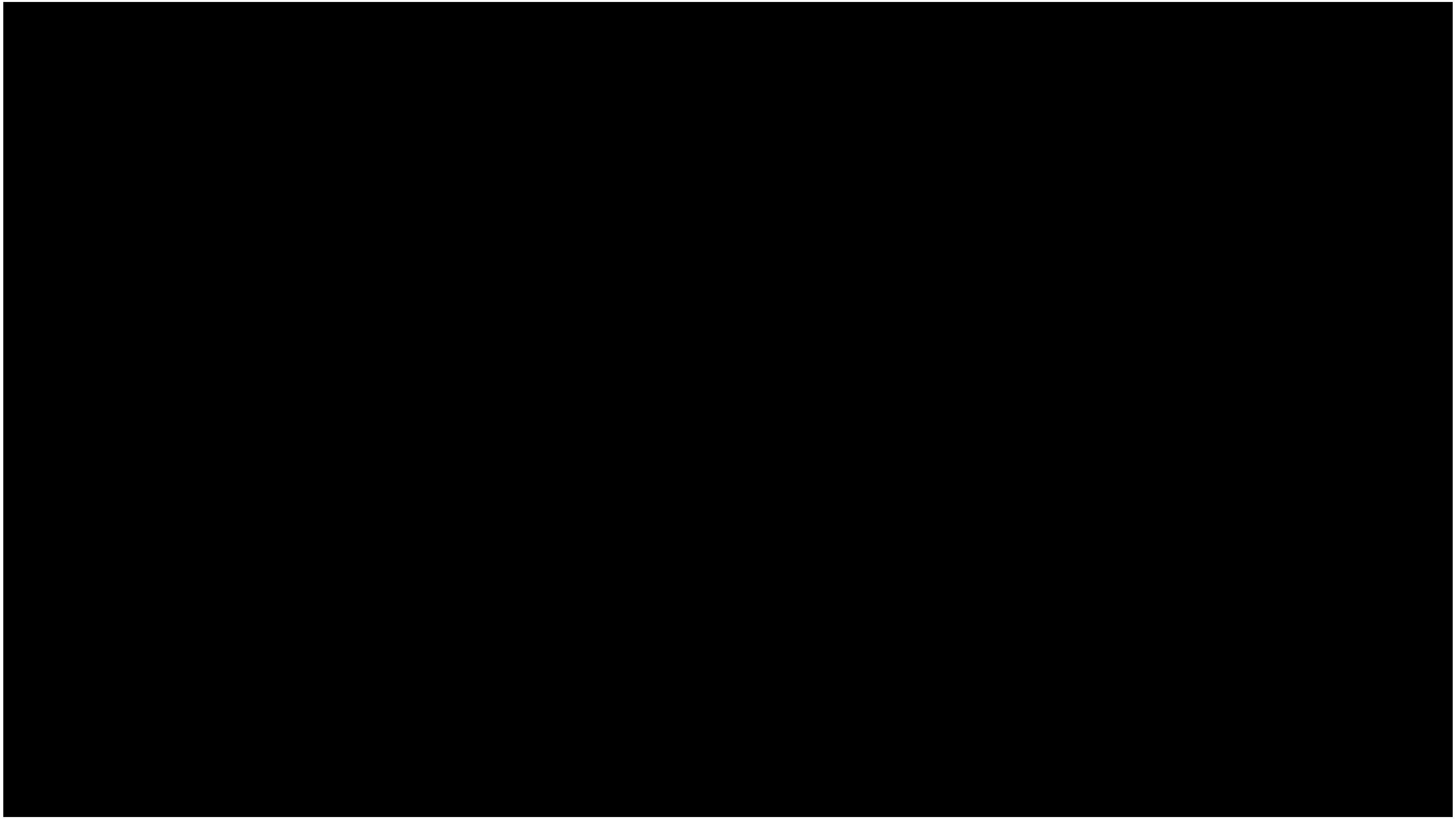
Optimizing the process parameter settings



Conclusion:

The process is robust between 80 and 100 kg/h of feedrate, 160 and 200 rpm of screw speed, **as long as the SME value remains between 0.09 and 0.11.**

Limit type	Feed rate	Screw speed	Calculated SME
Low feed	80	182	0.11
High speed	88	200	0.11
Low speed	91	160	0.09
High feed	100	175	0.09



Summary

1. HME process can be well described with a tanks-in-series mechanistic model

2. Model requires calibration with off-line measurements (Rheology) and lab scale experiments, which may be integrated in the standard DoE.

3. The Mechanistic model can be used in development for different purposes:
    - Gaining additional knowledge (unboxing the black box)
    - In-silico experiments
    - Process scale-ups
    - Process scale-downs (reduce need to experiment at large scale)
    - Increasing process robustness
    - Process parameters optimization
    - Troubleshooting

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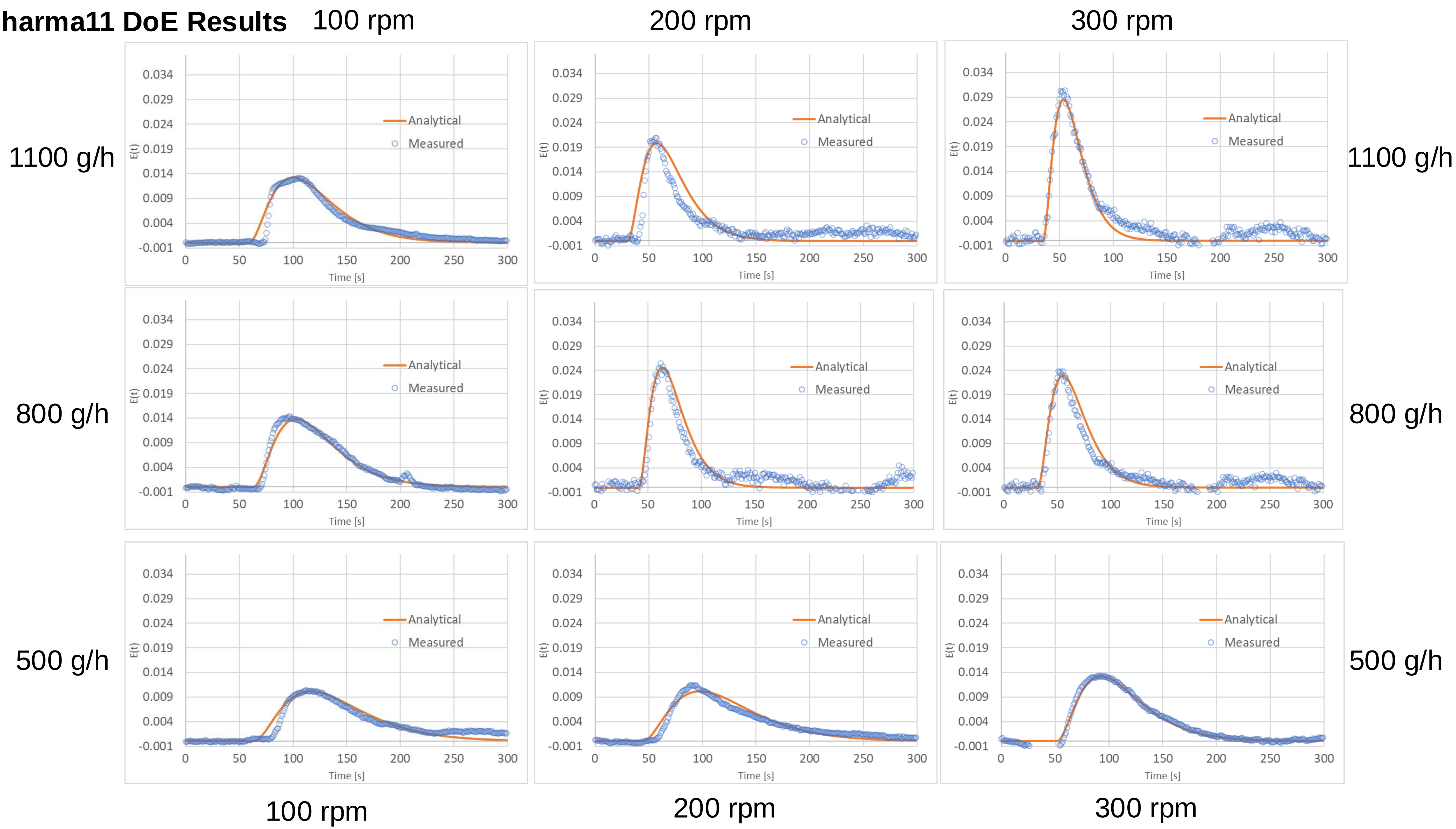
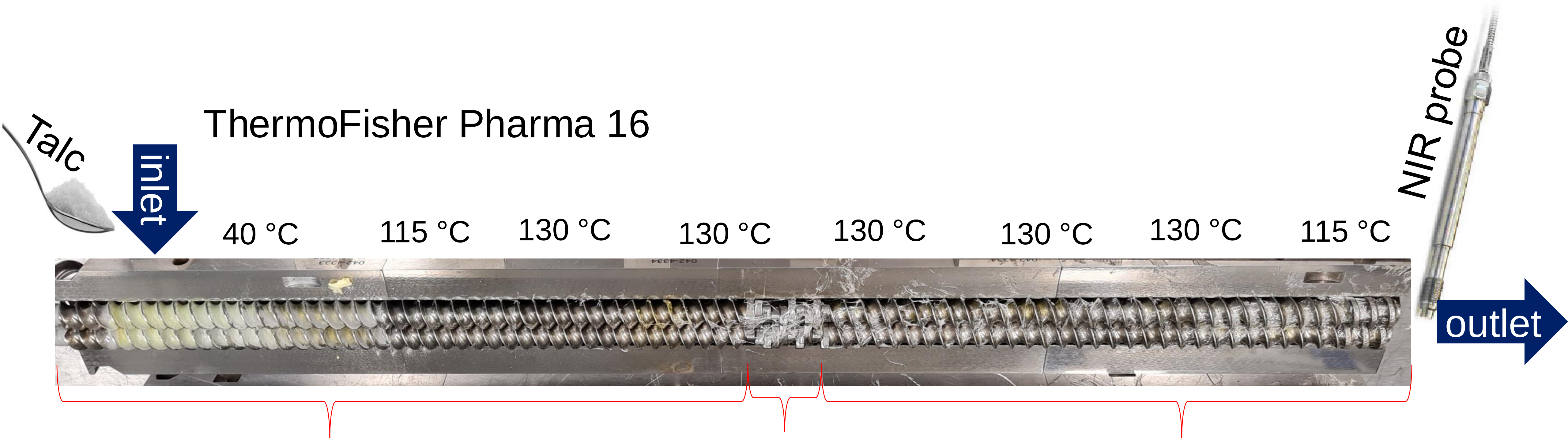
Thank you

Backup slides

Pharma11 DoE Results



Experimental details – Extruder configuration

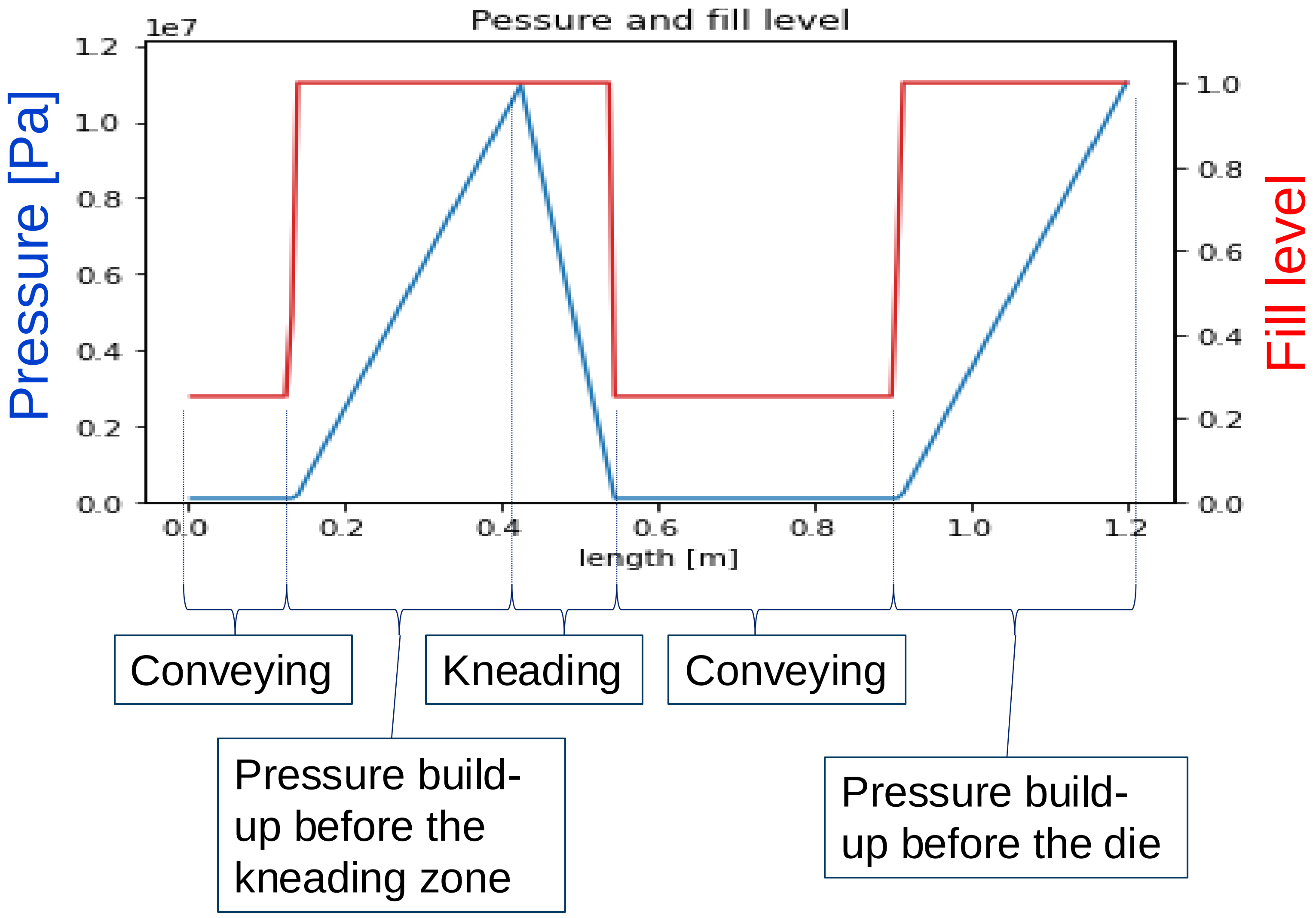


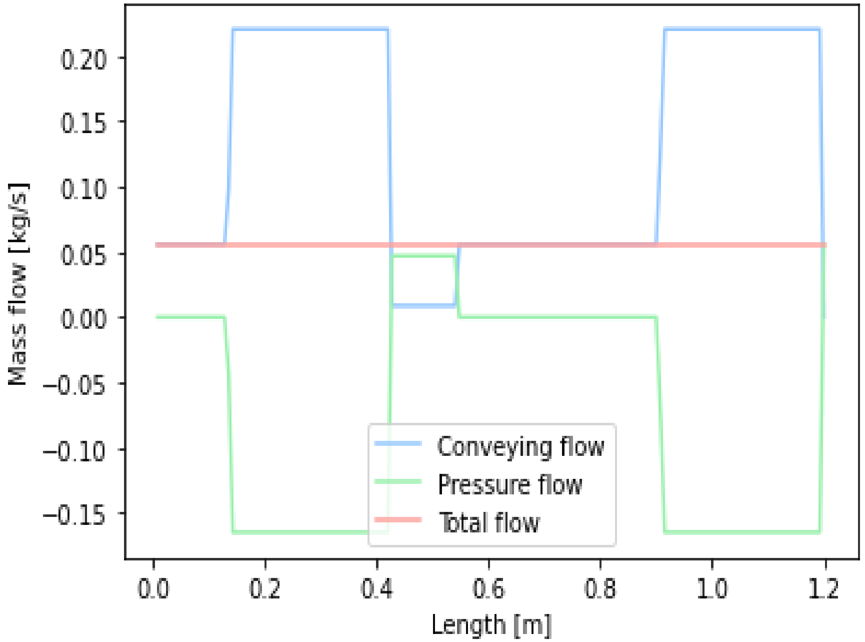
Conveying zone
21x FS

Kneeding zone
4x 30° + 6x 60°

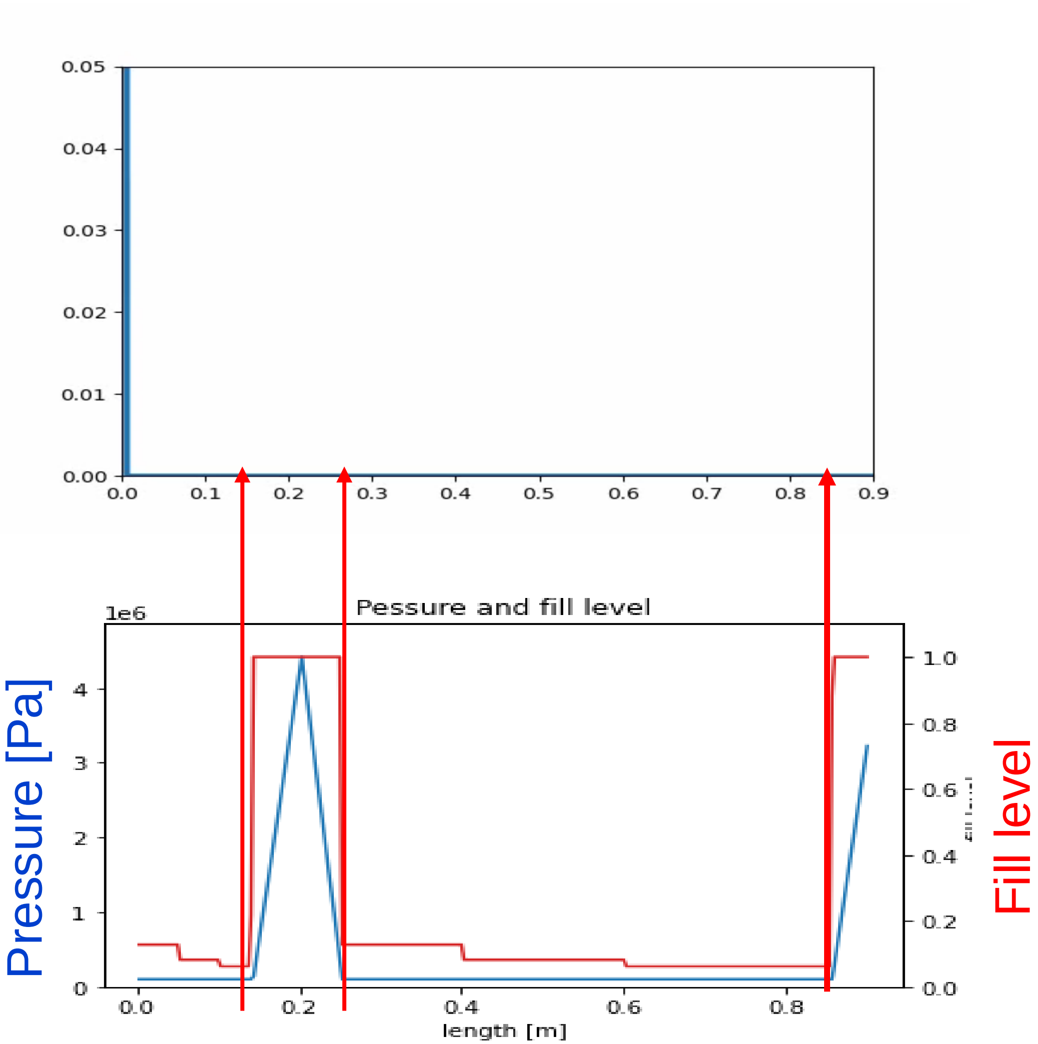
Conveying zone
15x FS

Model outputs: Mass flow and pressure



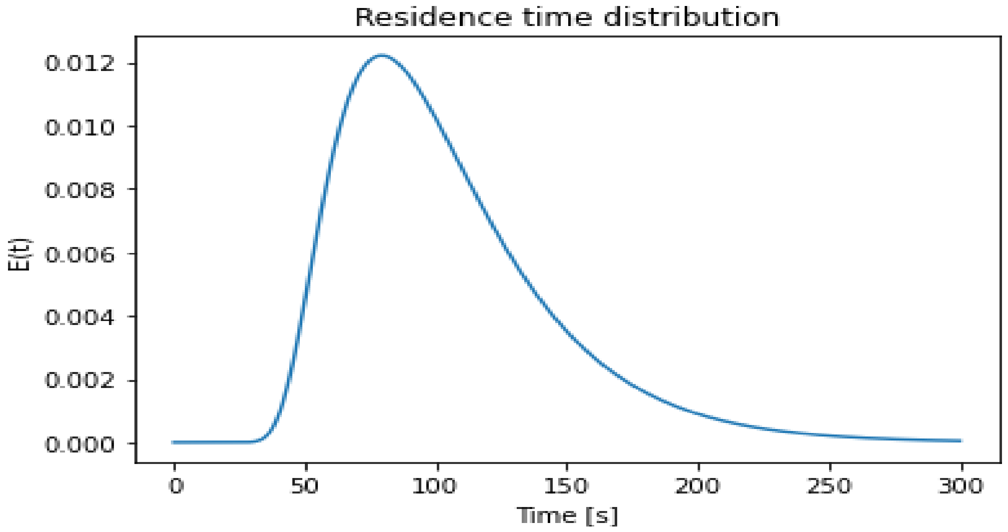


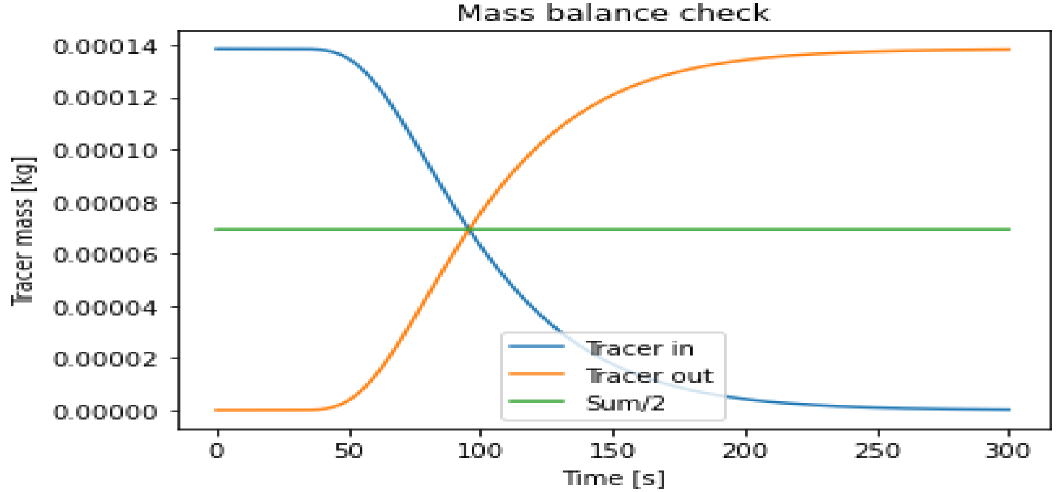
Model outputs: Residence time



Mixing zone

Pressure buildup (die)





Model details: Mass balance

For each discretization element solve species conservation:

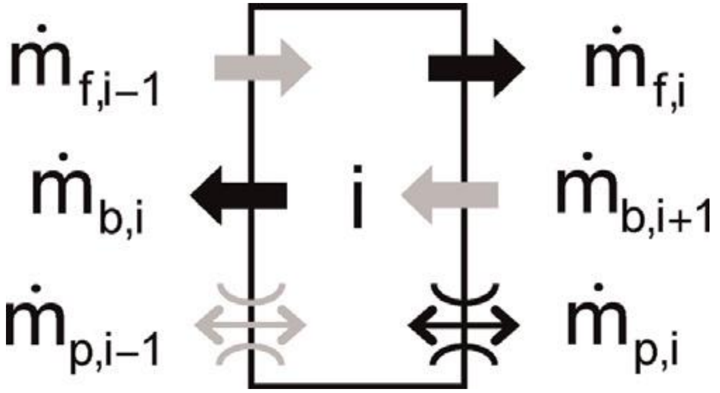
Accumulation in current element (i)

Inflow from previous element (i-1)

Inflow from next element (i+1)

Outflow from current element (i)

$$\frac{d}{dt}(\rho_i \times V_i \times f_i \times w_i) = \sum_{i-1\to i} \dot{m} \times w_{i-1} + \sum_{i+1\to i} \dot{m} \times w_{i+1} - \left(\sum_{i\to i-1}\dot{m} + \sum_{i\to i+1}\dot{m}\right)\times w_i$$



- Stationary solution for mass flow
- Pulse inlet condition for tracer
- Transient solution for tracer
- Explicit method (>10k time steps)
- Calculation time on laptop: 1-10 min

Model details: Energy balance

Accumulation in current element (i)

Inflow from previous element (i-1)

Inflow from next element (i+1)

$$\frac{d}{dt}\left(\rho_i \times V_i \times f_i \times c^m_{p,i} \times T^m_i\right) = \sum_{i-1 \to i} \dot{m} \times c^m_{p,i-1} \times T^m_{i-1} + \sum_{i+1 \to i} \dot{m} \times c^m_{p,i+1} \times T^m_{i+1} - \left(\sum_{i \to i-1} \dot{m} + \sum_{i \to i+1} \dot{m}\right) \times c^m_{p,i} \times T^m_i + \dot{Q}_{bm,i} + \dot{Q}_{sm,i} + \dot{Q}_{diss,i}$$

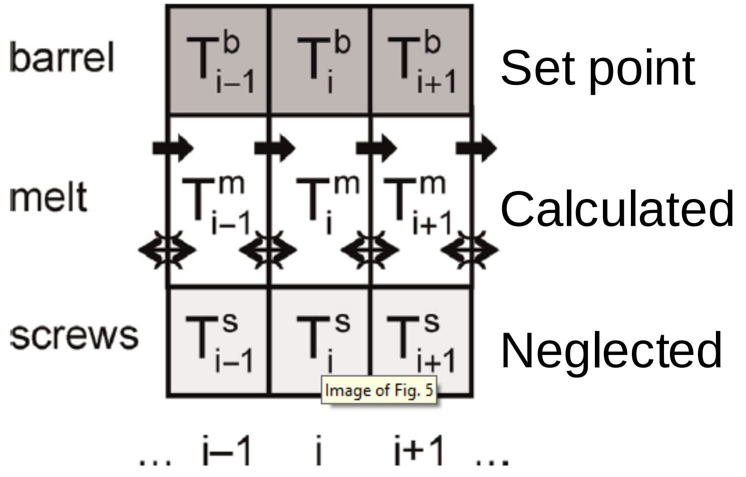
Outflow from current element (i)

Heat flux from barrel

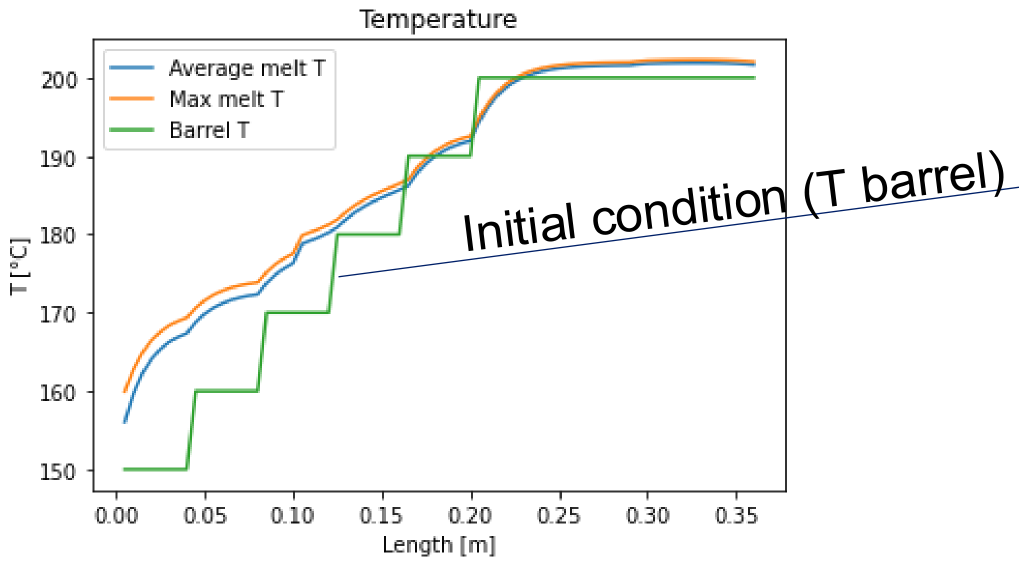
Energy dissipation from shearing

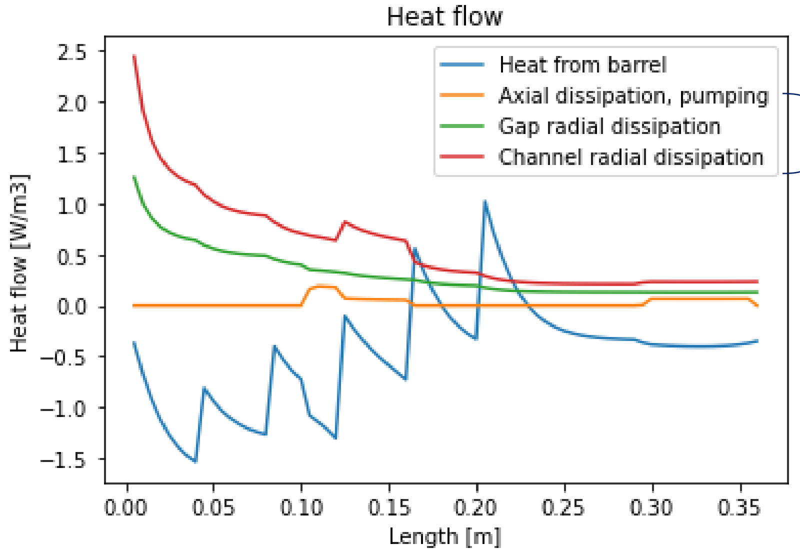
$$\dot{Q}_{bm,i} = \alpha_{b,i} \times A_{bm,i} \times \left(T^b_i - T^m_i\right)$$

- Stationary solution for mass flow
- Initial condition = Barrel temperature profile
- Transient solution for temperature
- Explicit method (>10k time steps)
- Calculation time on laptop: 1-10 min

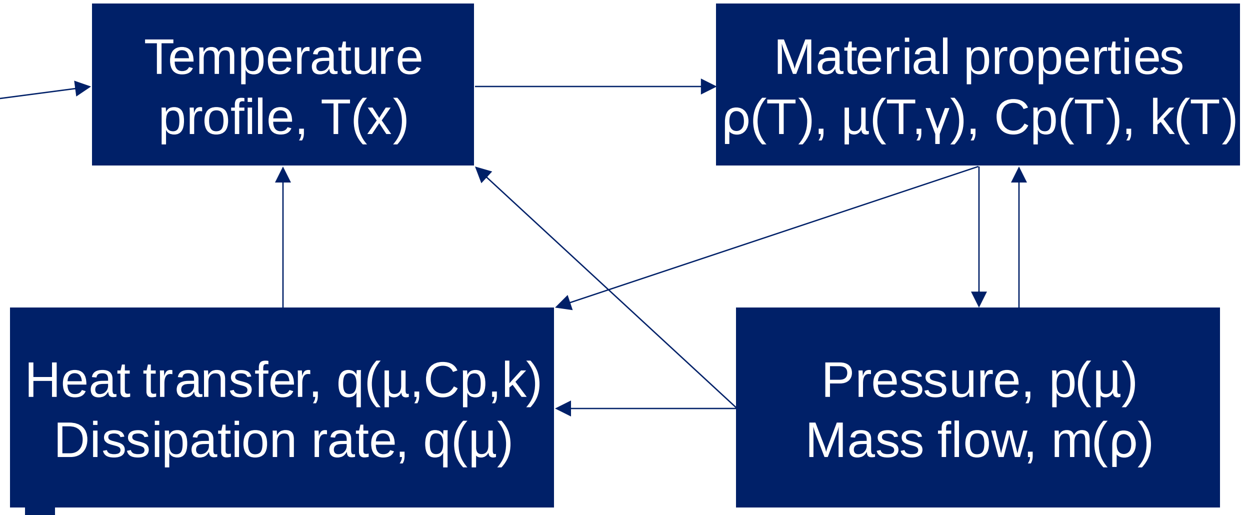


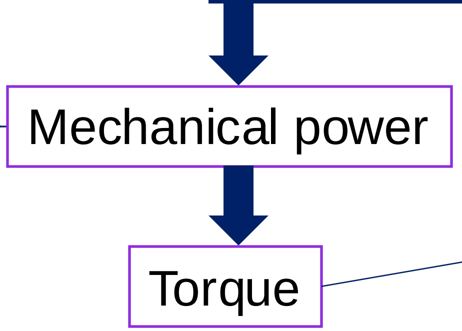
Model details: Iterations

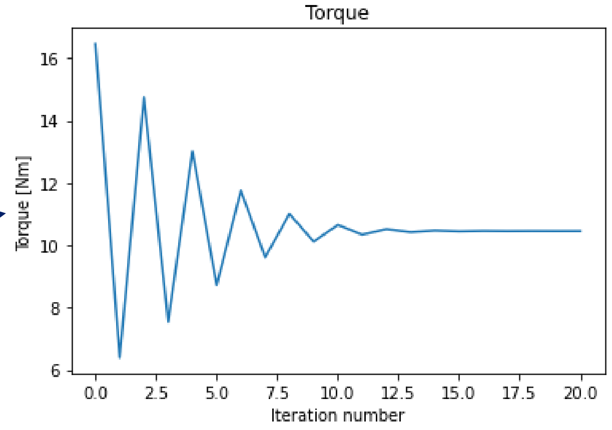




Iterative approach:







20 iterations
~ 30 min on laptop