

LABORATORY OF PHARMACEUTICAL PROCESS ANALYTICAL TECHNOLOGY

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FLWSHEET MODELING OF THE COMPRESSION STEP OF A CONTINUOUS WET GRANULATION PRODUCTION LINE

INTRODUCTION

Mathematical models of the unit operations match the QbD paradigm. **Flowsheet modelling** is a framework for gaining process and product knowledge by employing:

- Sensitivity analysis (risk assessment, CPP & CMA definition)
- State-of-Control determination (dynamic optimisation, minimize waste streams)
- Scenario analysis (interactions between unit operations and quality management)
- Soft sensors
- Controller designs
- Product timings (traceability and rejection strategy)

AIM: A flowsheet model, of the **compression step** from a **wet granulated** product, consisting of **4 submodels**. Implementable in an overall powder-to-tablet flowsheet.

① Residence time distribution (RTD) model → ② Die filling model → ③ Potency model → ④ Tablet Hardness model

RTD MODEL

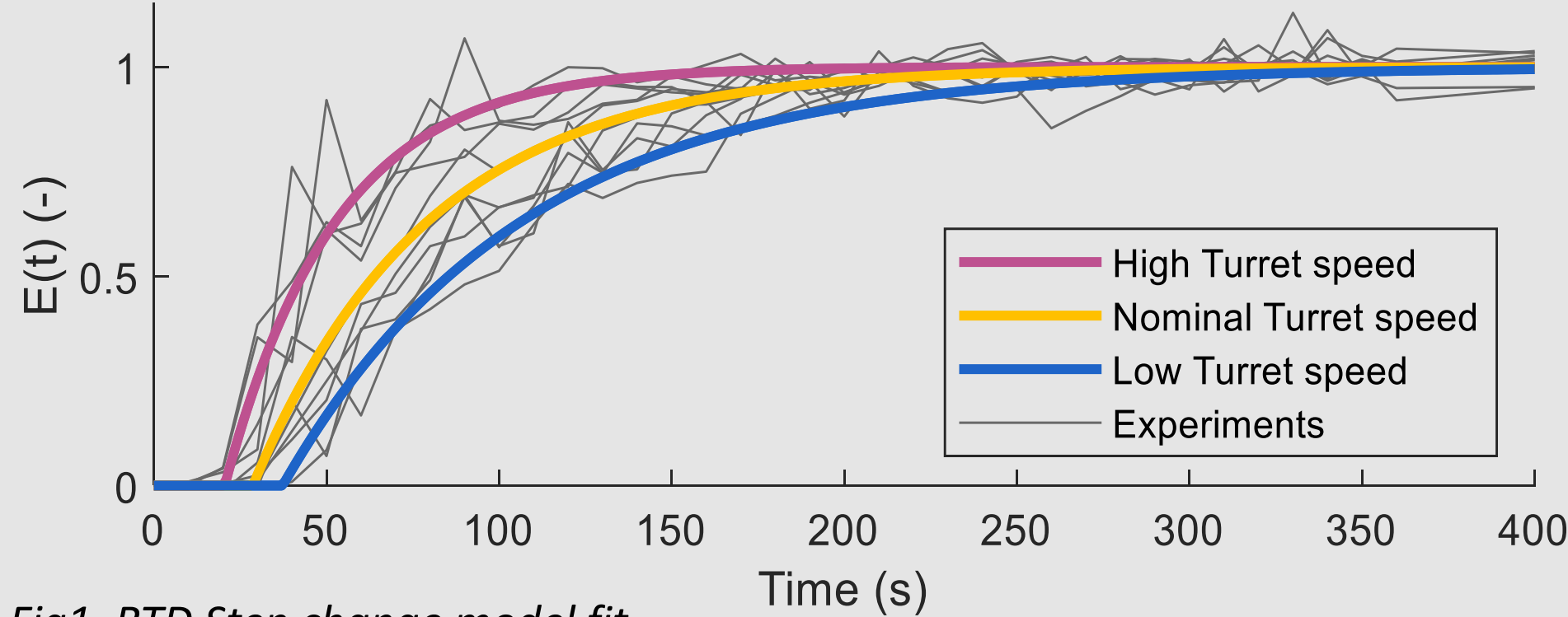
Powder dosing valve and feedframe

Methods:

- Step change of 5% NaSaccharin, determined with offline Raman spectroscopy of tablets.
- Design of experiments (DoE) with all critical process parameters (CPP) → multiple linear regression (MLR) of the model parameters.
- Continuous stirred tank model with plug flow ($t_p + t_{cstr}$).

Results:

- Spectroscopic PLS model with RSMEcv of 0,1726 %.
- Mean residence time between 50 and 110 s.
- t_p and t_{cstr} are dependent on the turret speed.



DIE FILLING & POTENCY MODEL

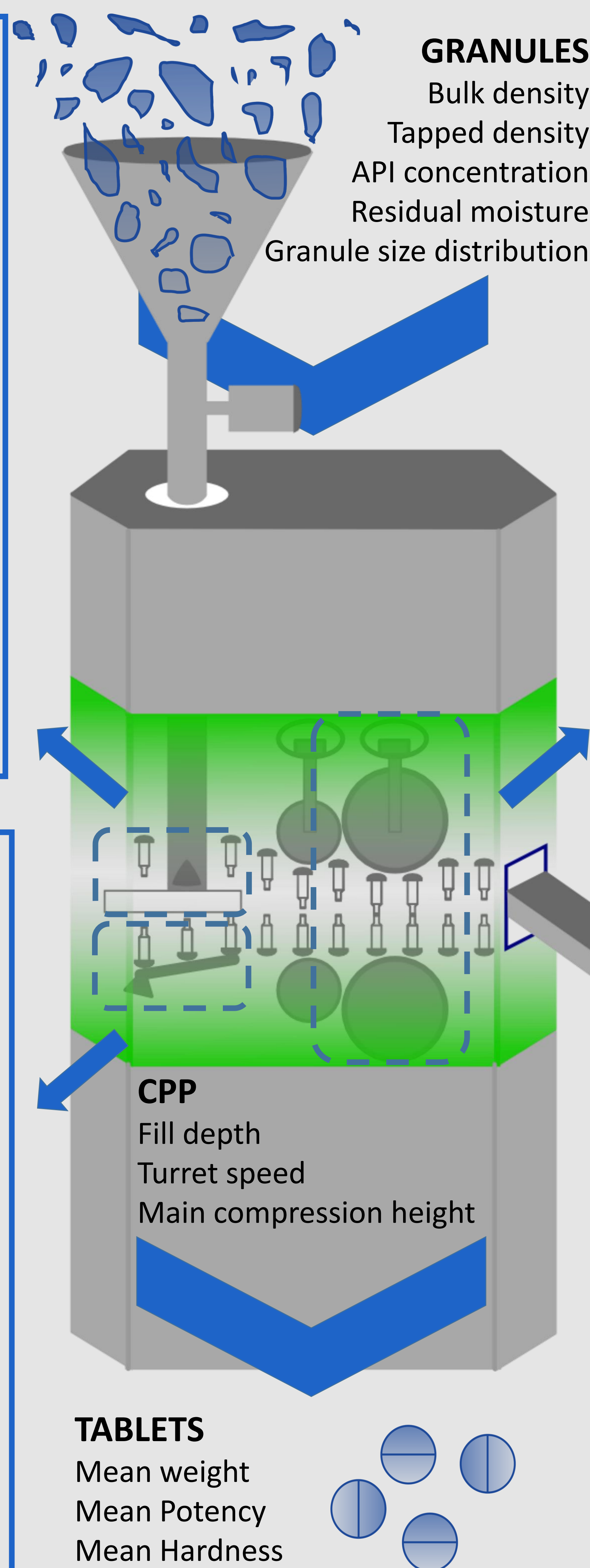
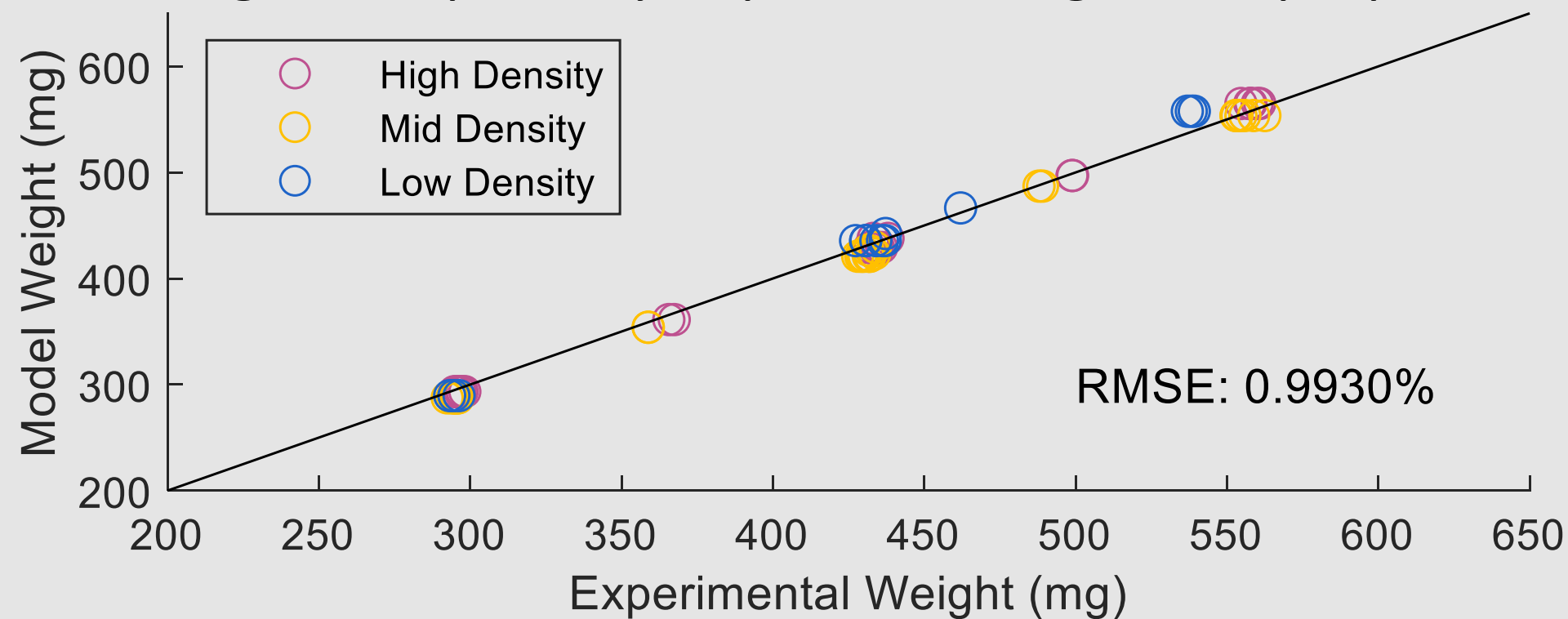
Die filling stage of a rotary press

Methods:

- Tablet volume from tooling dimensions and fill depth.
- Mean tablet weight determined by regression of granules with varying bulk and tapped density.
- Solid tablet volume prediction using true density.
- Potency estimated with the API granule concentration.

Results:

- 21.8th percentile between bulk and tapped indicative for granule density at filling position.
- First principle model with RMSE of 0.9930 %.
- Weight and potency dependent on granule properties.



TABLET HARDNESS MODEL

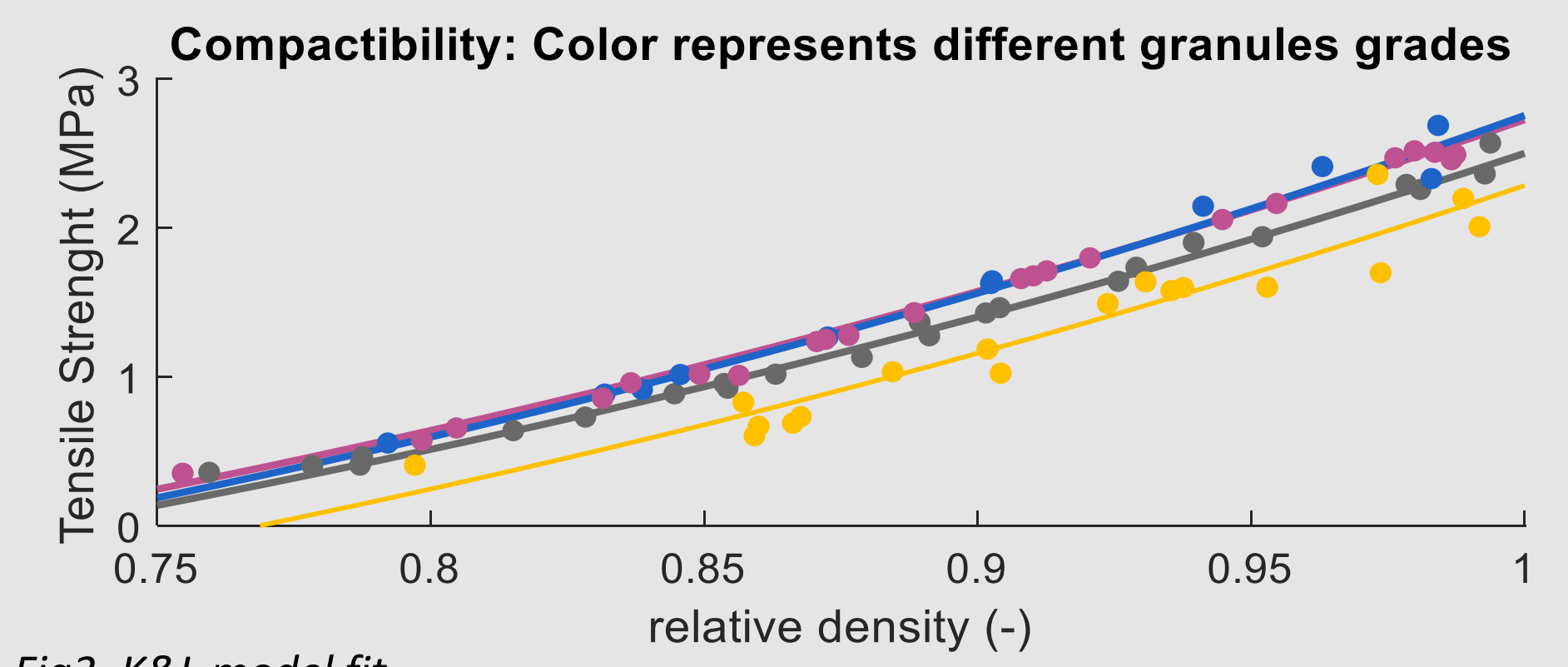
Compression stage of a rotary press

Methods:

- Compactibility estimation by regression of 90 different conditions with a *Kuentz and Leuenberger (K&L)* model.
 - Impact of granules with varying granule sizes (Span) and residual moisture (LoD) on tablet hardness.
- MLR model with LoD and Span for *K&L* parameters.

Results:

- Max tensile strength ~ LoD and Span
- Critical density ~ LoD
- *K&L* - MLR model has RMSEcv of 0.1447 MPa

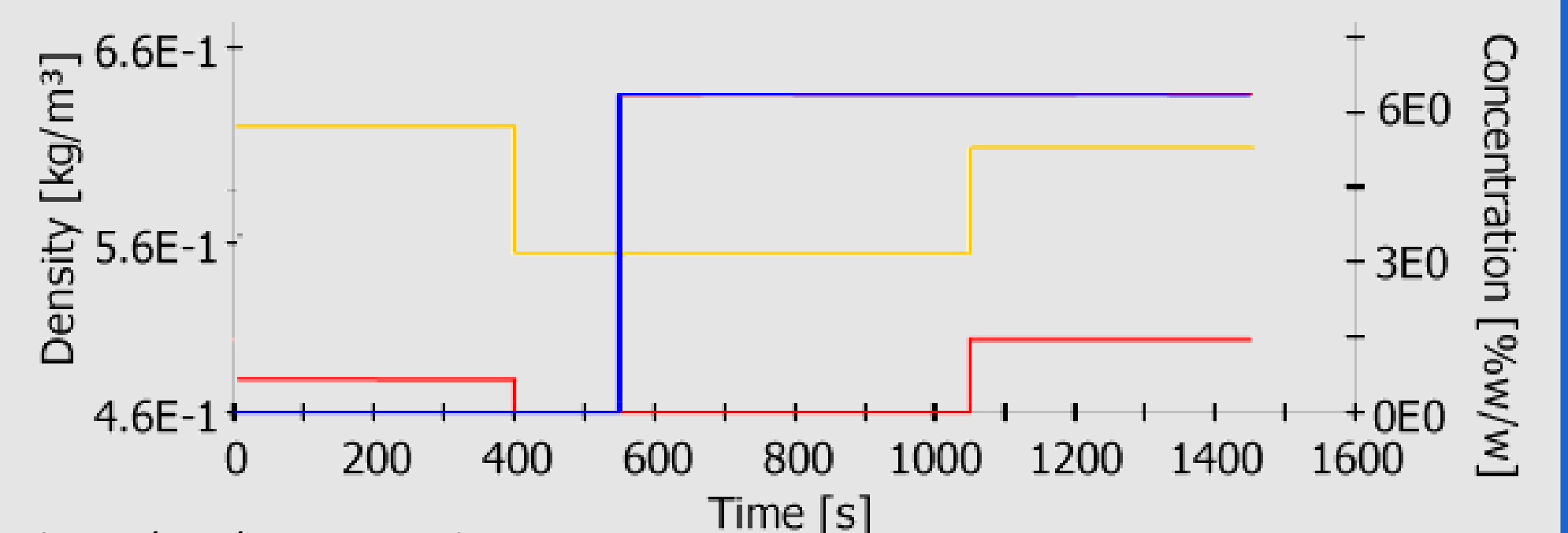


INTEGRATED MODEL

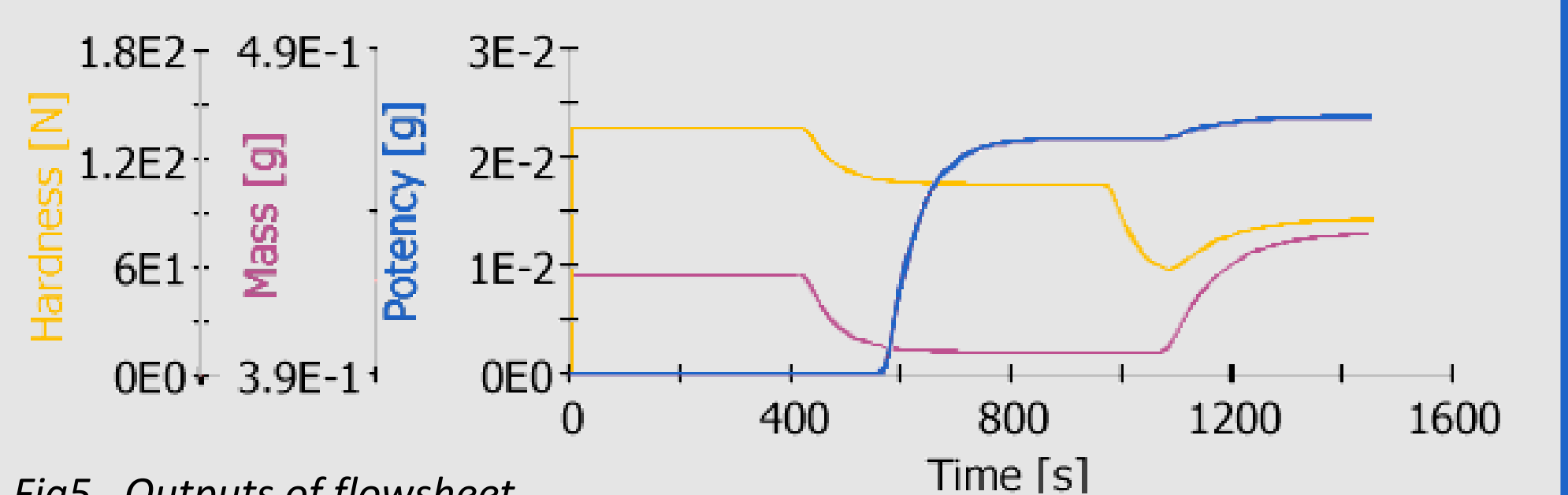
Flowsheet model of the rotary tablet press

Methods:

- All models integrated in gSOLIDS (PSE)
- Dynamic modelling of transient phases



Input changes: Bulk Density [y], Tapped Density [y], API Concentration [y2]



CONCLUSION & FUTURE APPLICATIONS

Conclusion

- Standalone flowsheet model of the compression step developed, integratable in a continuous powder-to-tablet line flowsheet (ConSigma-25, GEA pharma systems).
- Model capable of dynamically predicting tablet properties from varying CPP and critical material attributes (CMA).

Future applications

- Gather process insights and develop applications using the flowsheet.
- Decision support tool for regulatory process filing.

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