UNIVERSITEIT GENT

FACULTEIT FARMACEUTISCHE WETENSCHAPPEN

PAT for model based design, optimization, monitoring and control of continuous manufacturing

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Outline

Case study I: continuous tablet manufacturing via TSWG

- PAT for process understanding & process modeling
- PAT for process monitoring & control

Case study II: pharmaceutical suspension manufacturing

- Model based PAT implementation

Case study III: continuous freeze-drying

- PAT & model based design

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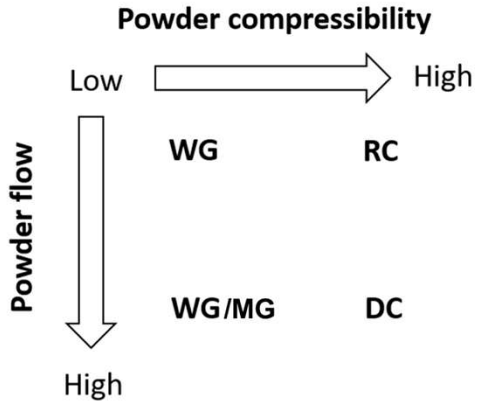
Case study 1 - TSG

Direct compression (DC) – roller compaction (RC) – wet granuation (WG)

- API solid state properties
- API solubility
- API load (dosage range)
- API flow properties (adhesion/cohesion)
- API compaction properties



Case study 1 - TSG

Modular screw configuration resulting in shear environment changes:

- **mixing**
- **various rate processes of wet granulation**

↳ **shaping final granule characteristic distribution (size, shape, moisture content, strength,...)**

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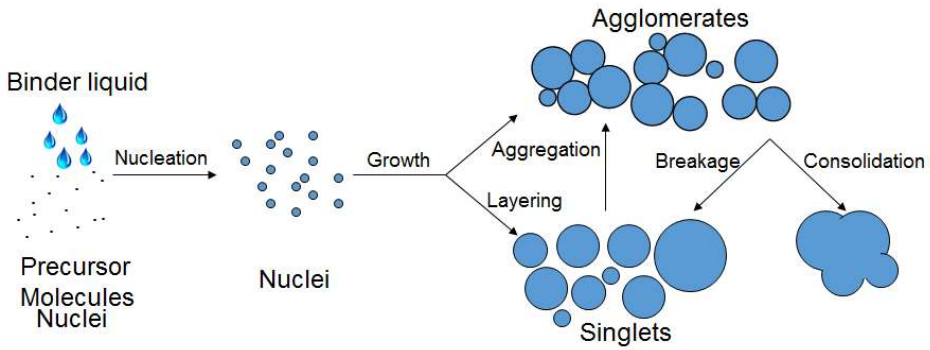
Case study 1 - TSG

- Process understanding is limited
- Mechanistic models:
  - Develop mechanistic understanding of the functional role of **individual** screw elements on different granulate CQA's
- Population Balance Modelling (PBM): Mechanistic description of particulate system undergoing size change mechanisms
- 1-dimensional PBM: Granule size distribution (GSD) during TSG
- Multi-dimensional PBM: tracking GSD in combination with granule CQA's (porosity, moisture distribution, etc.) of each size class

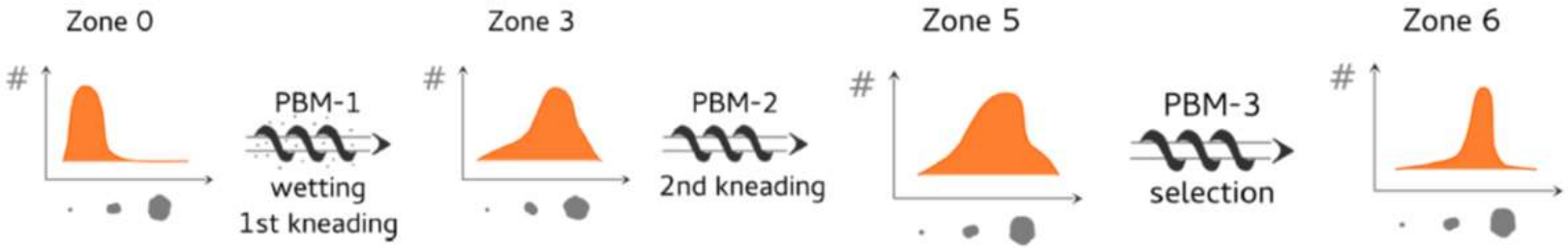


Case study 1 - TSG

- State-of-the-art modeling methodology: Experimental data only collected at granulator outlet
  - No experimental information about granule formation along length of granulator barrel
  - Difficult/impossible to calibrate PBM adequately

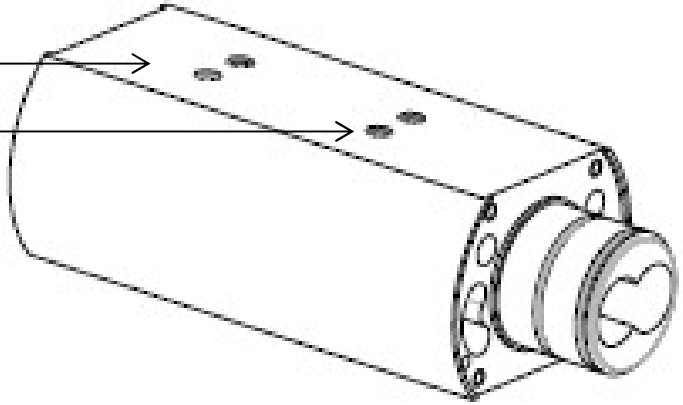
- Solution: **Compartmental "multi-dimensional" PBM**
  - Granulator considered as series of individual blocks/modules
  - Track particle size/porosity/moisture dynamics along length of granulator barrel

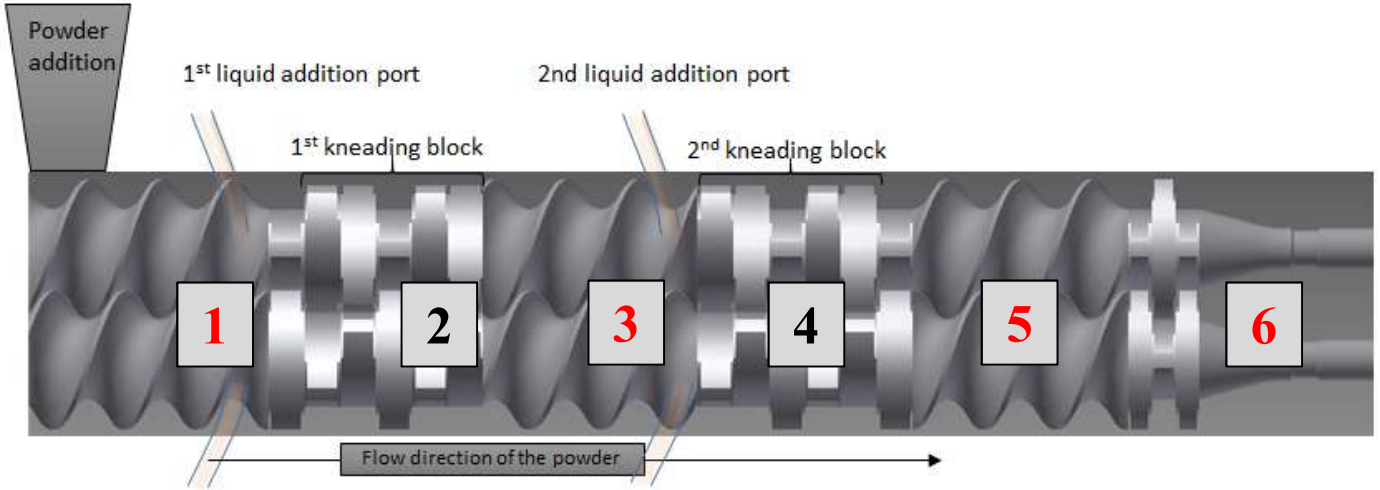
➡ **Role of individual blocks can be understood**



Case study 1 - TSG

1st liquid addition port
2nd liquid addition port





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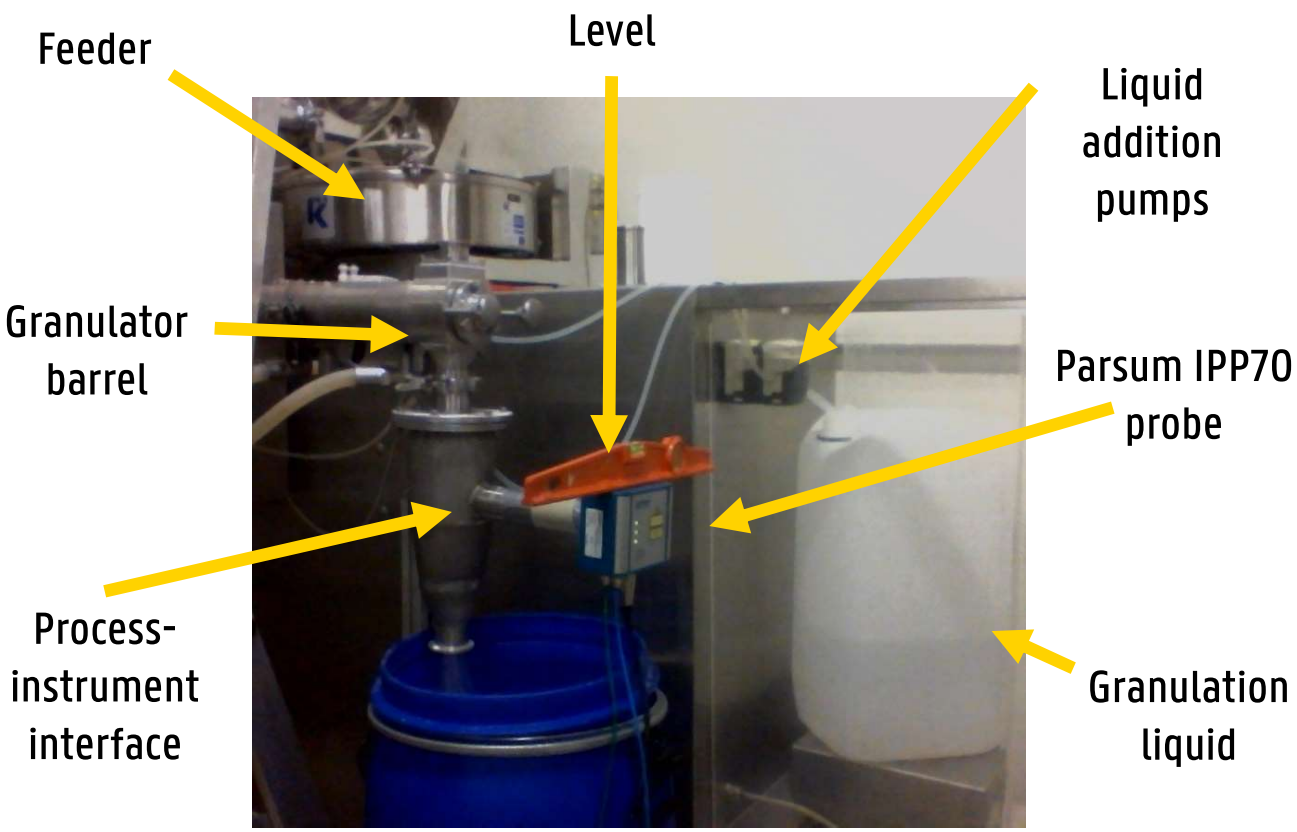
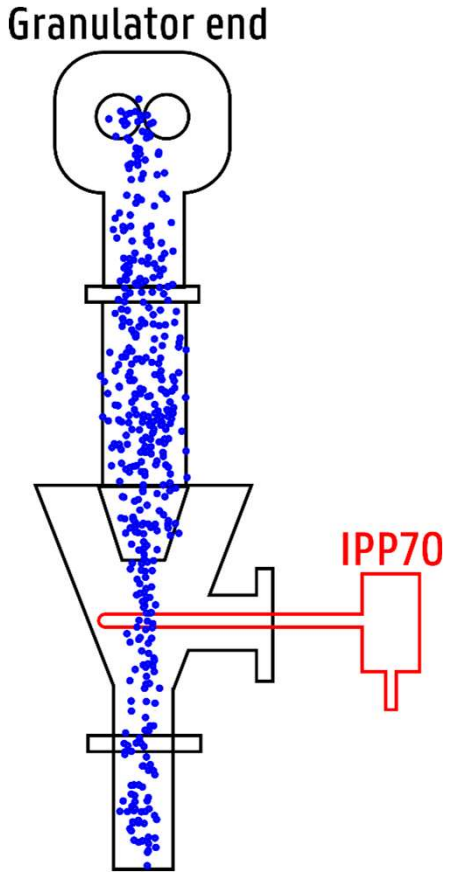
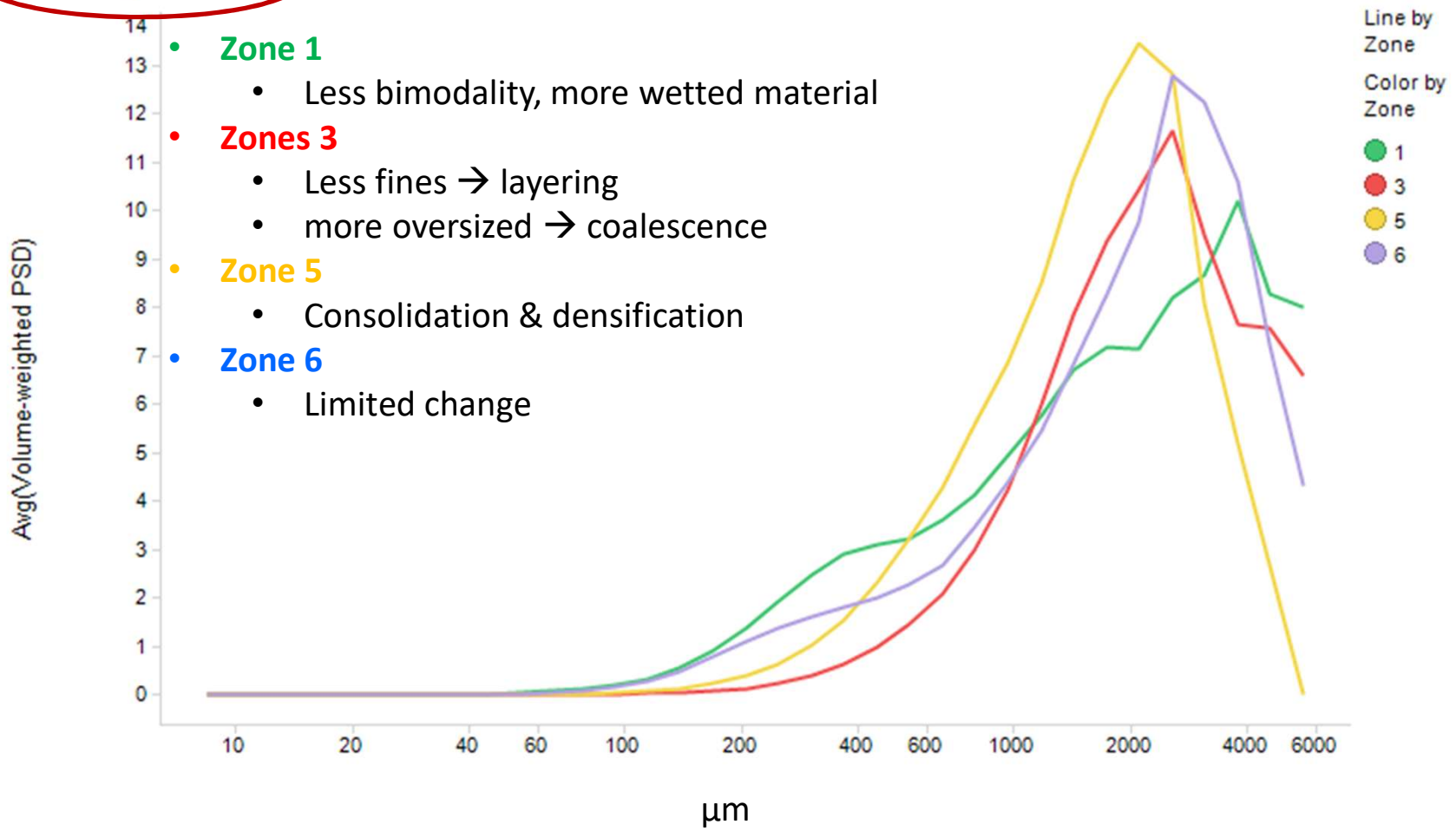




Case study 1 - TSG

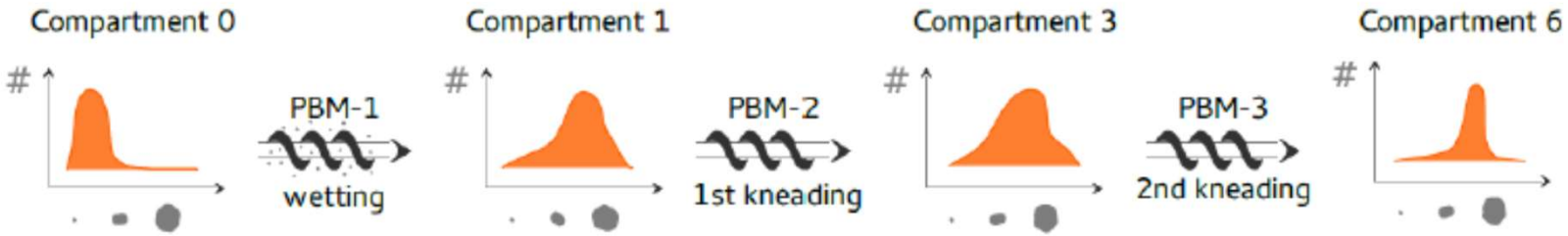
HCT - High L/S ratio

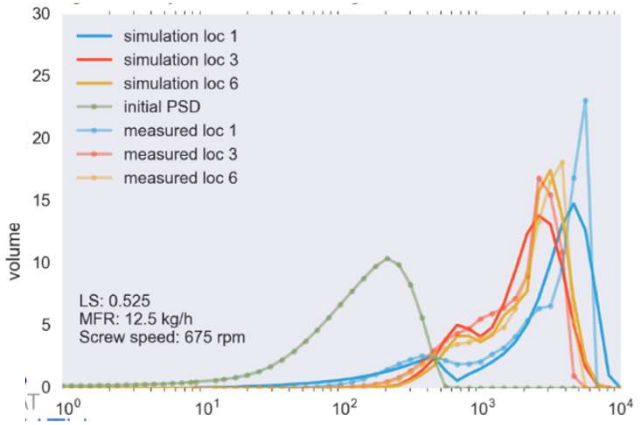
- **Zone 1**
  - Less bimodality, more wetted material
- **Zones 3**
  - Less fines → layering
  - more oversized → coalescence
- **Zone 5**
  - Consolidation & densification
- **Zone 6**
  - Limited change

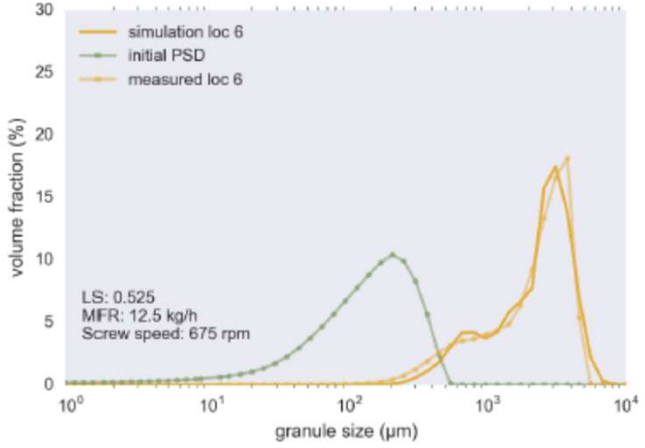


Case study 1 - TSG

- **New kernel** developed based on experimental observations, which can predict both mono-modal and multi-modal distributions
- Breakage not needed in **wetting zone** → bimodality caused by lack of aggregatation due to limited liquid (binder) availability







Case study 1 - TSG

Modeling conclusions:

- Reasonable fits for all zones
- Sound calibration based on **unique PAT data**; high predictive power
- Fast calculation: ideal for **scenario analysis**

Future perspectives:

- Development of **generic** twin-screw granulation model
- Upgrade PBM models allowing the prediction of other granule quality attributes (such as **porosity/density**) besides particle size
- Up-scaling/down-scaling

Through pre-competitive consortium: academia & industry

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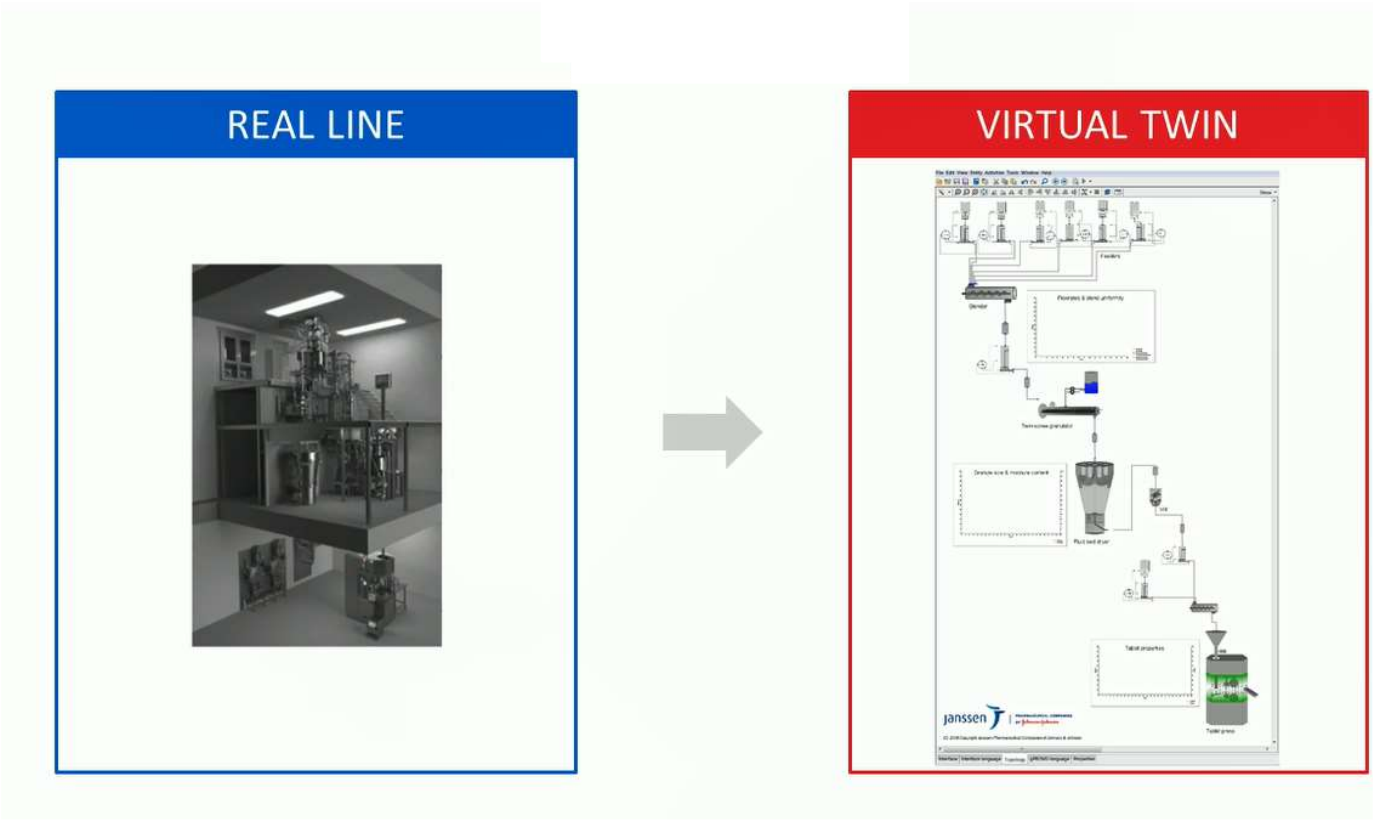
Case study 1 - TSG



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THE STATE UNIVERSITY OF NEW JERSEY

Case study 1 - TSG

SIMULATION

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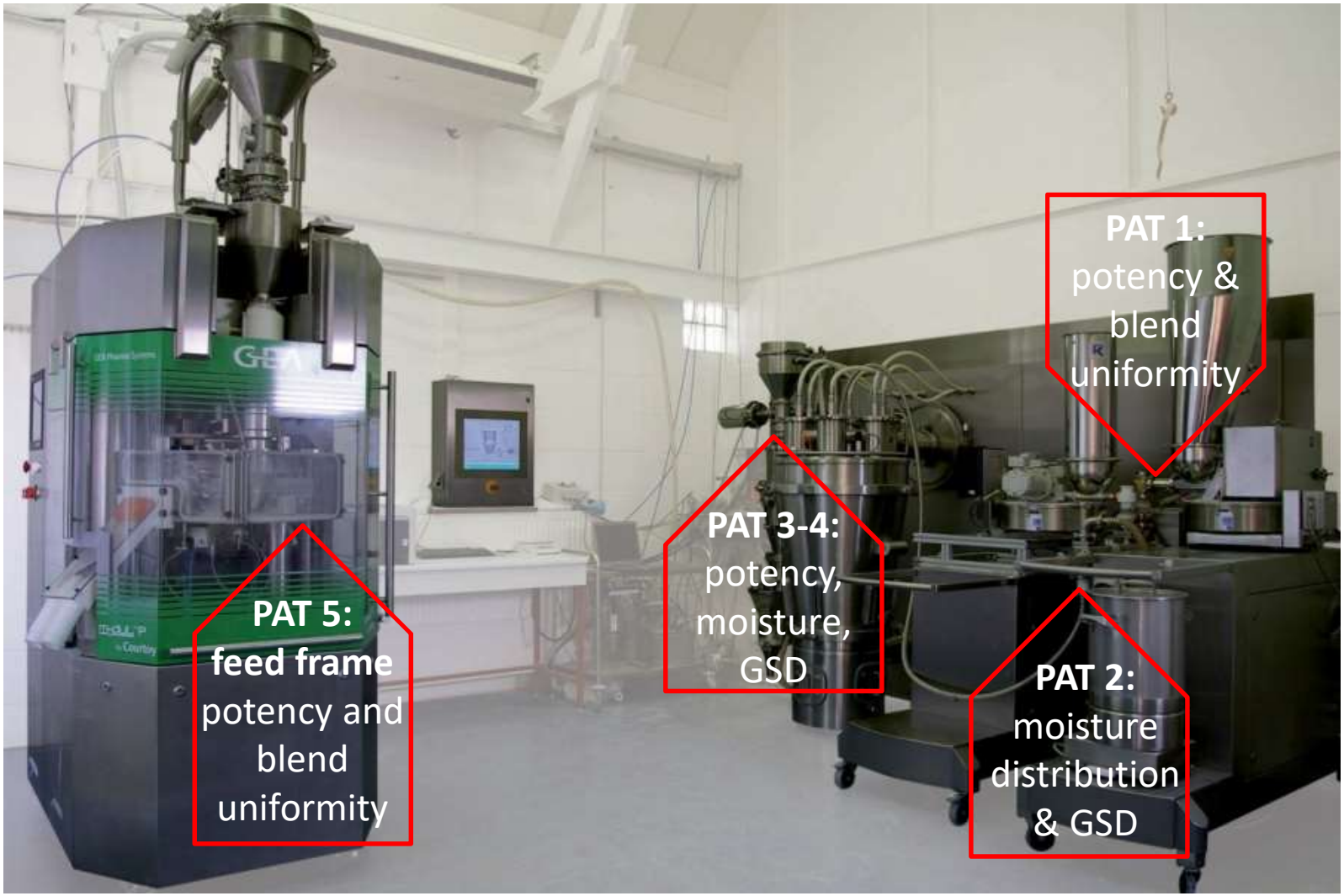

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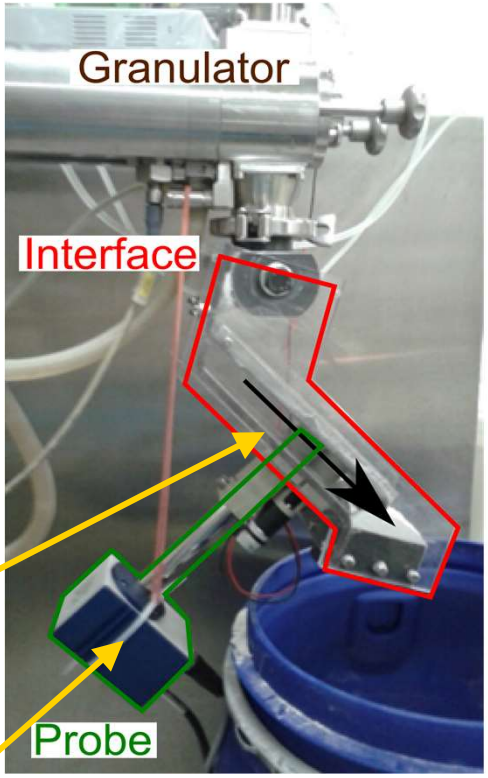
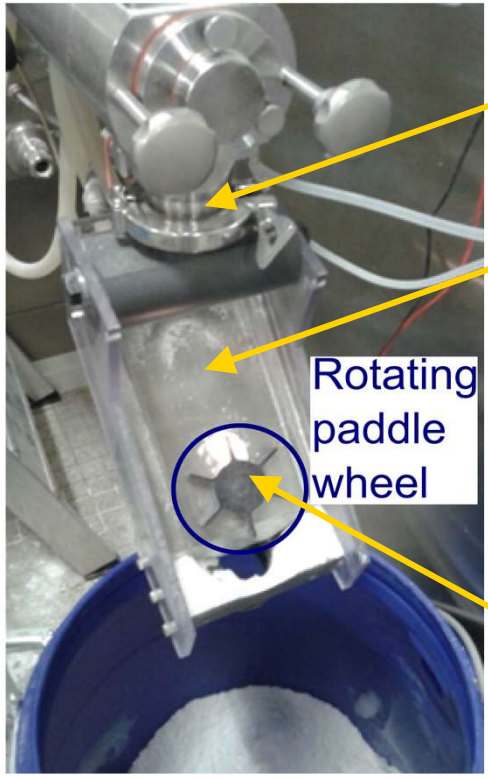
Case study 1 - TSG

Monitoring of L/S ratio





Heated probe tip

NIR instrument:
SentroPAT FO
(Reflectance)

Flange:
DIN 50

Heated slide:
5 W

Angular freq.
DC motor:
0.18 Hz

Vacuum proof in-line implementation possible

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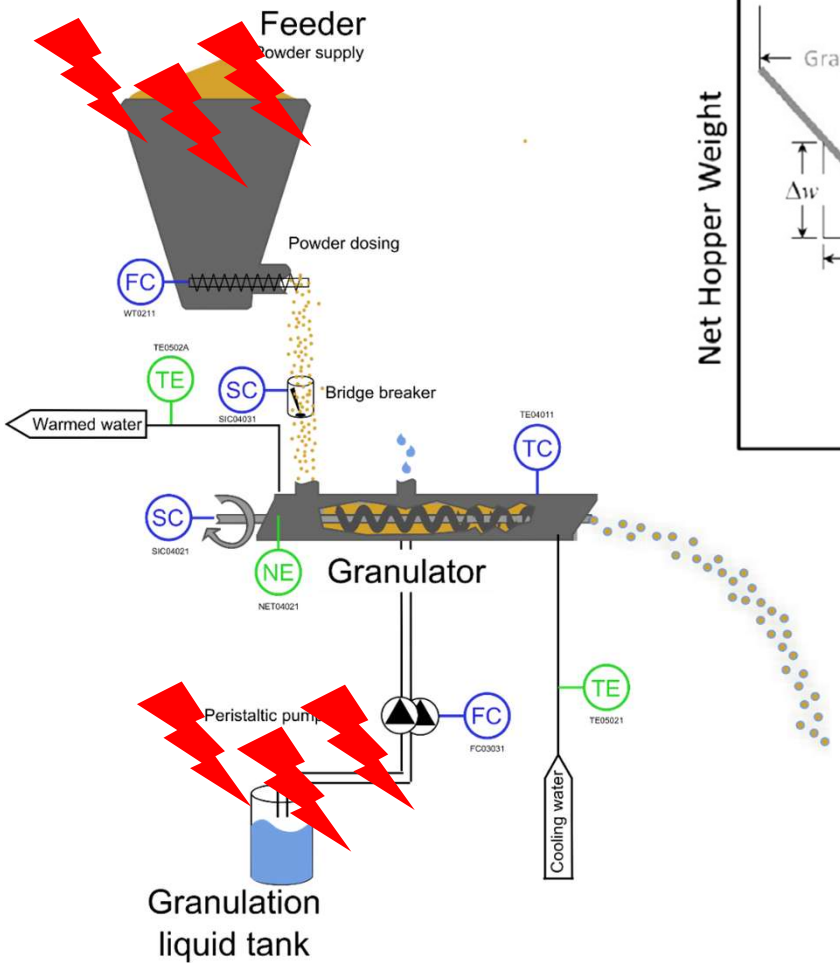

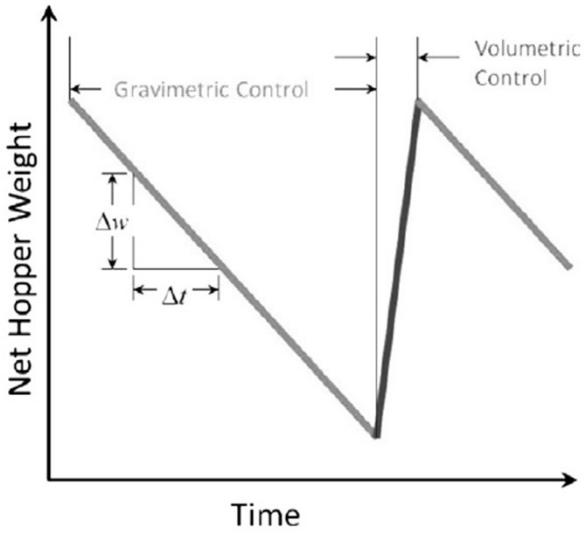

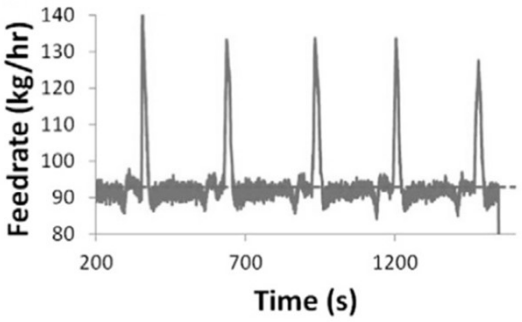

Normal operation

Extreme feedrate error

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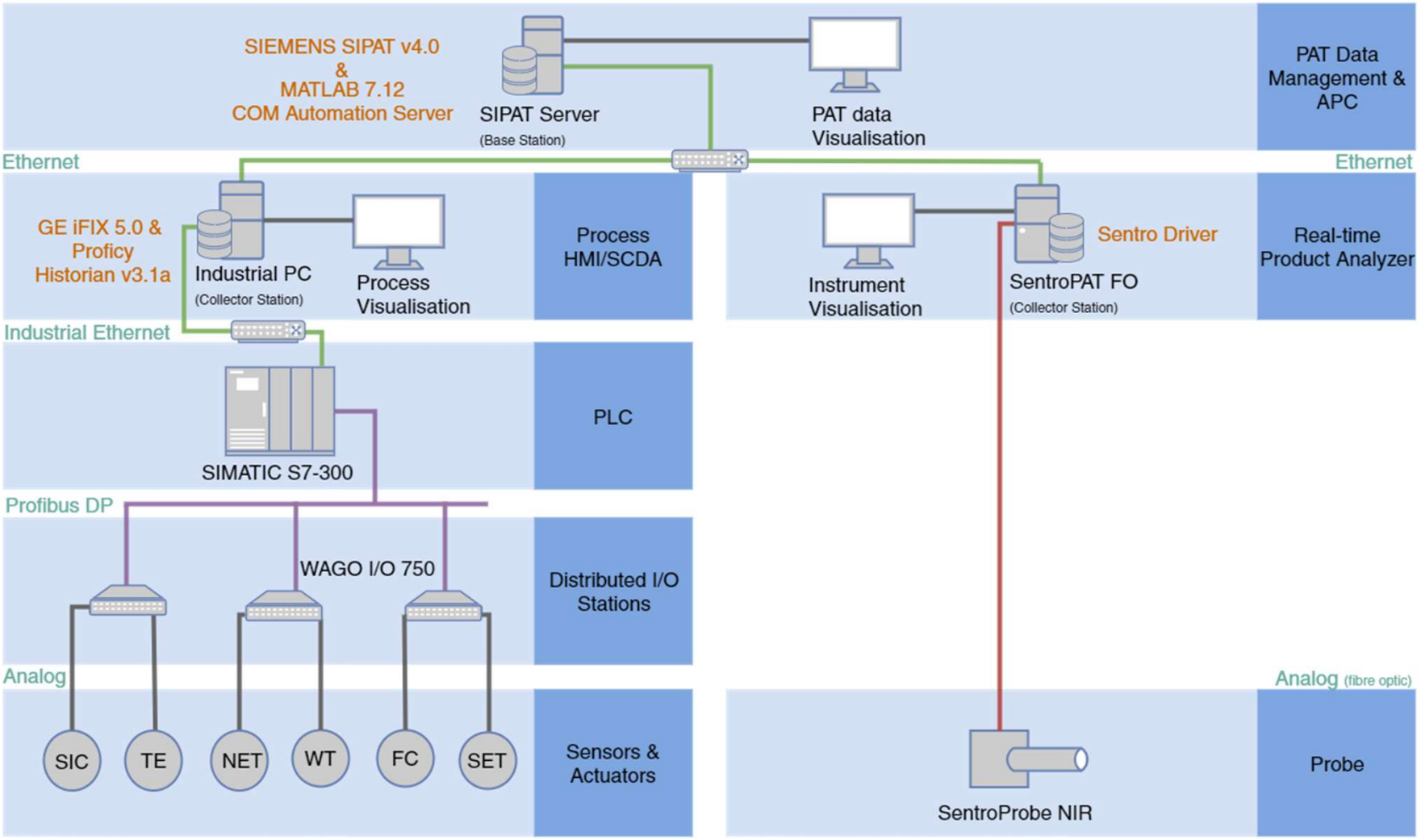
Case study 1 - TSG



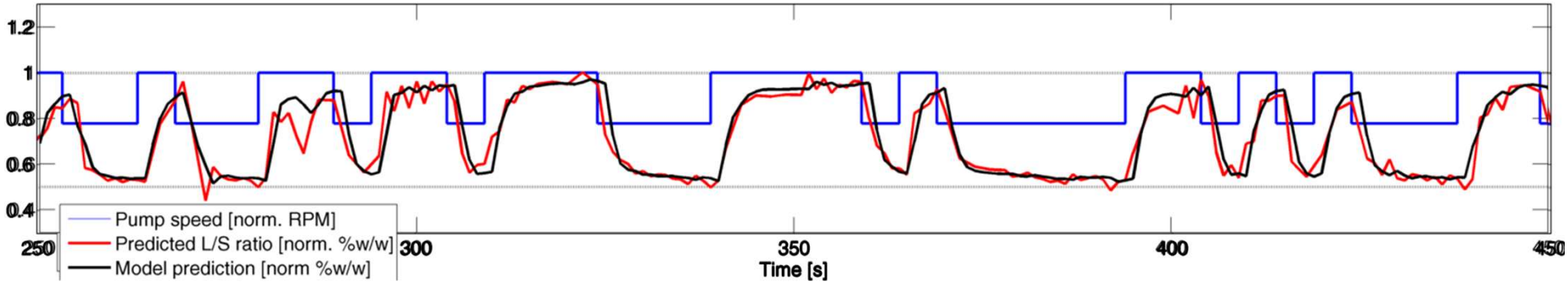
Case study 1 - TSG

"The only way to learn something about a system is to disturb it and then observe it." Kevin Dunn

» Dynamic process excitation

Manipulated variable: Liquid addition pump speed

Response variable: Granule L/S ratio



» Control relevant model:

$$G(s) = \frac{0.1557s + 0.2253}{s + 0.4687} e^{-3s}$$

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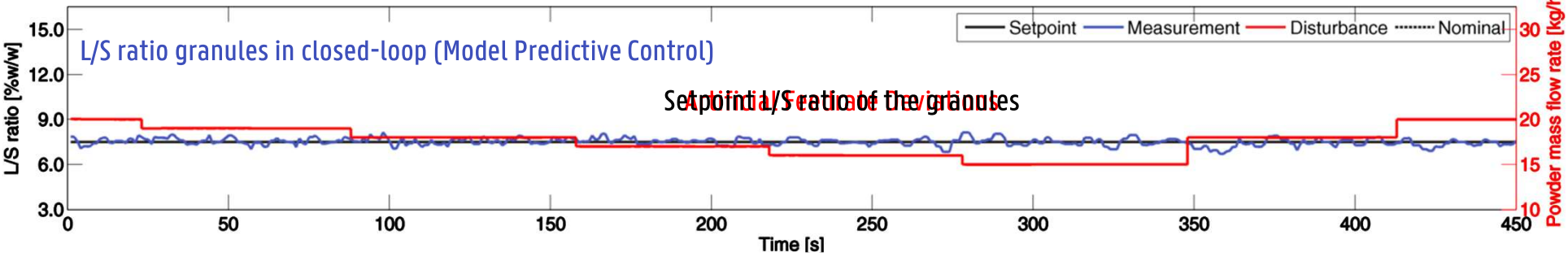
Case study 1 - TSG

OUTPUT from the process



Nominal pump speed (no deviations)

Continuous Direct Compression

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Continuous Direct Compression

RAW MATERIAL PROPERTY DATABASE

Material selection

- Excipients: WG + DC filler + Disint. + Binder + Glid. + Lubric.
- APIs: Micronized + fine to dense + granular

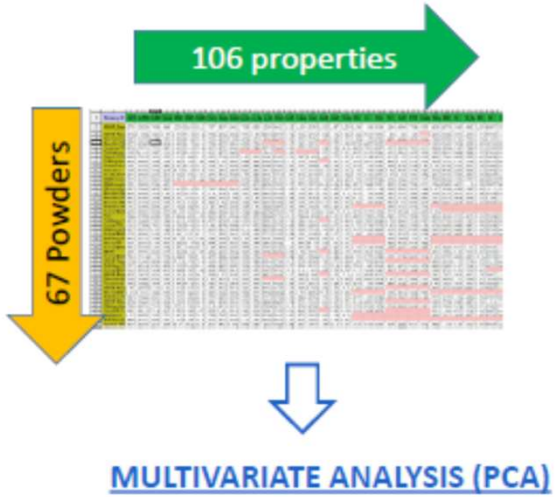
⇒ **Aim to span wide property range such that model cover properties of new materials**

Particle properties

- Particle size distribution
- Particle shape quantification
- Surface area

Bulk properties

- Bulk, tapped and true density
- Compressibility
- Electrostatic charge
- Moisture content, sorption and desorption
- Permeability and fluidization
- Powder flow: (Dynamic) angle of repose, Flow energy, Flow through an orifice, Ring shear testing Wall friction



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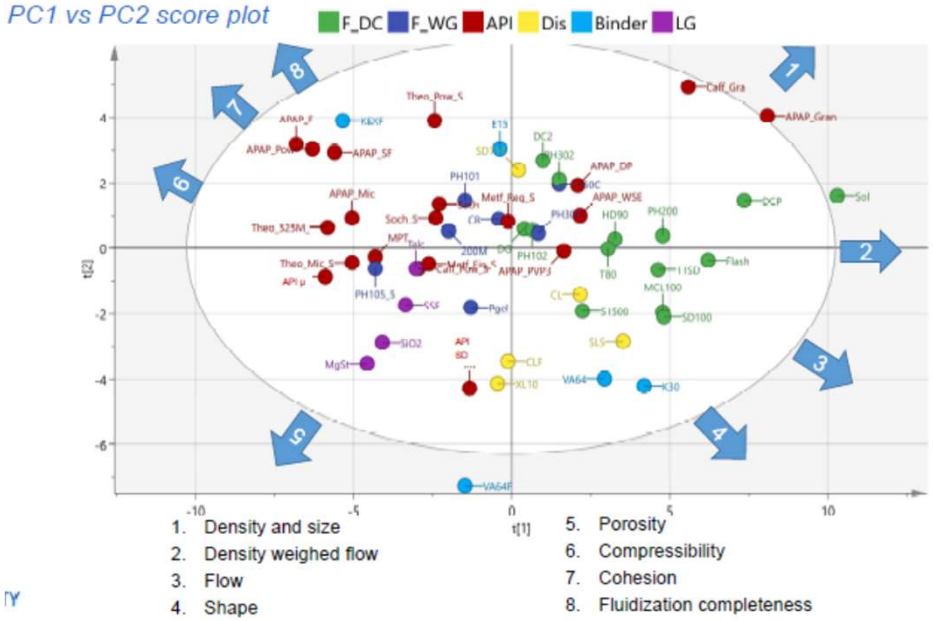

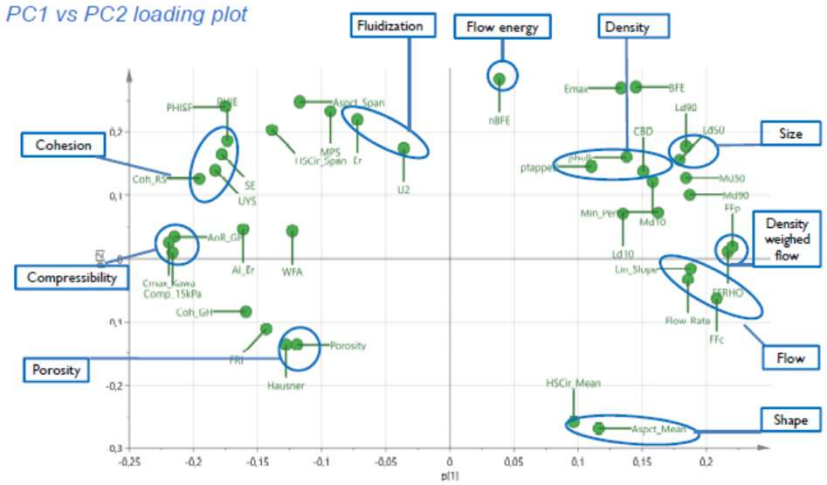

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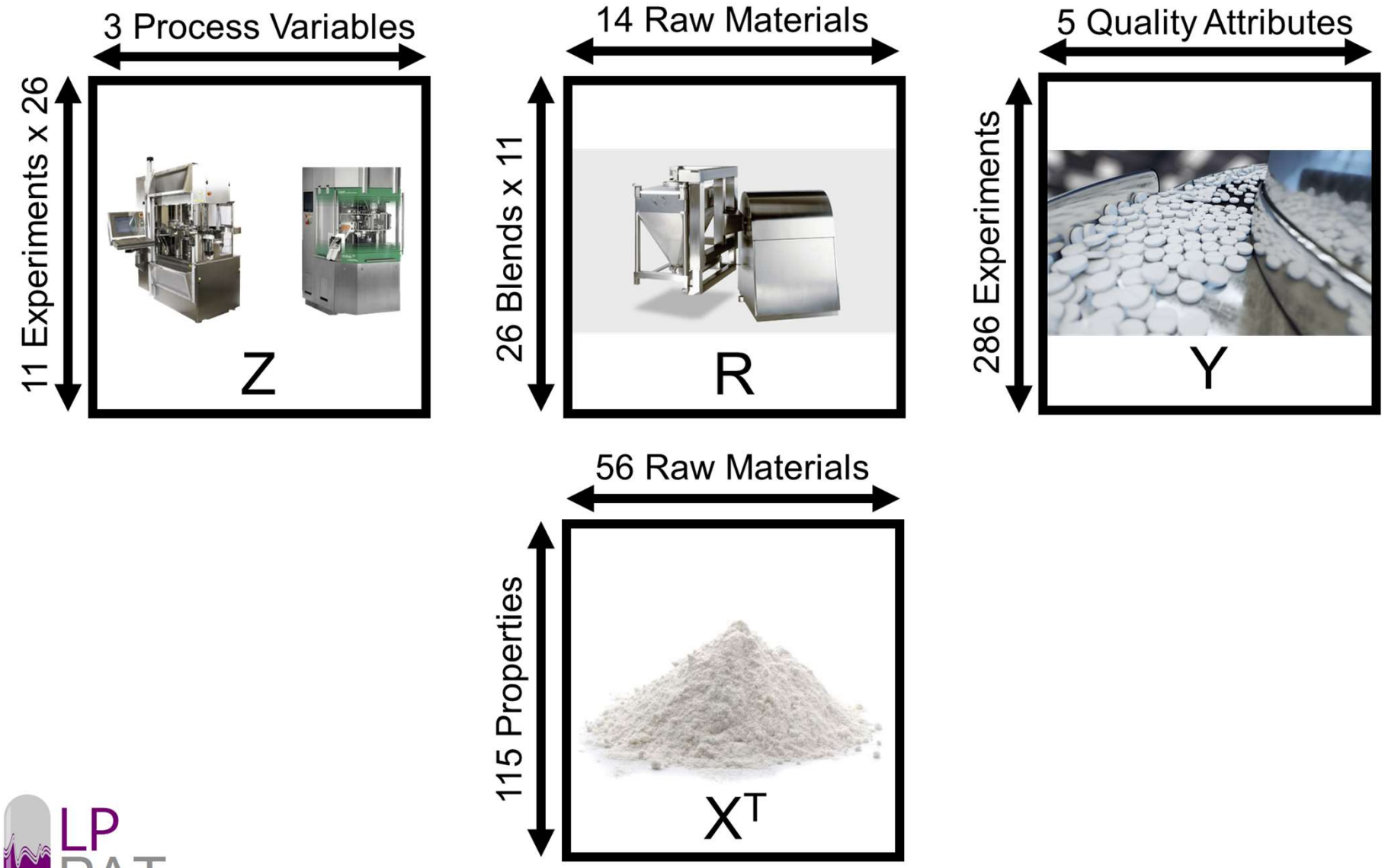

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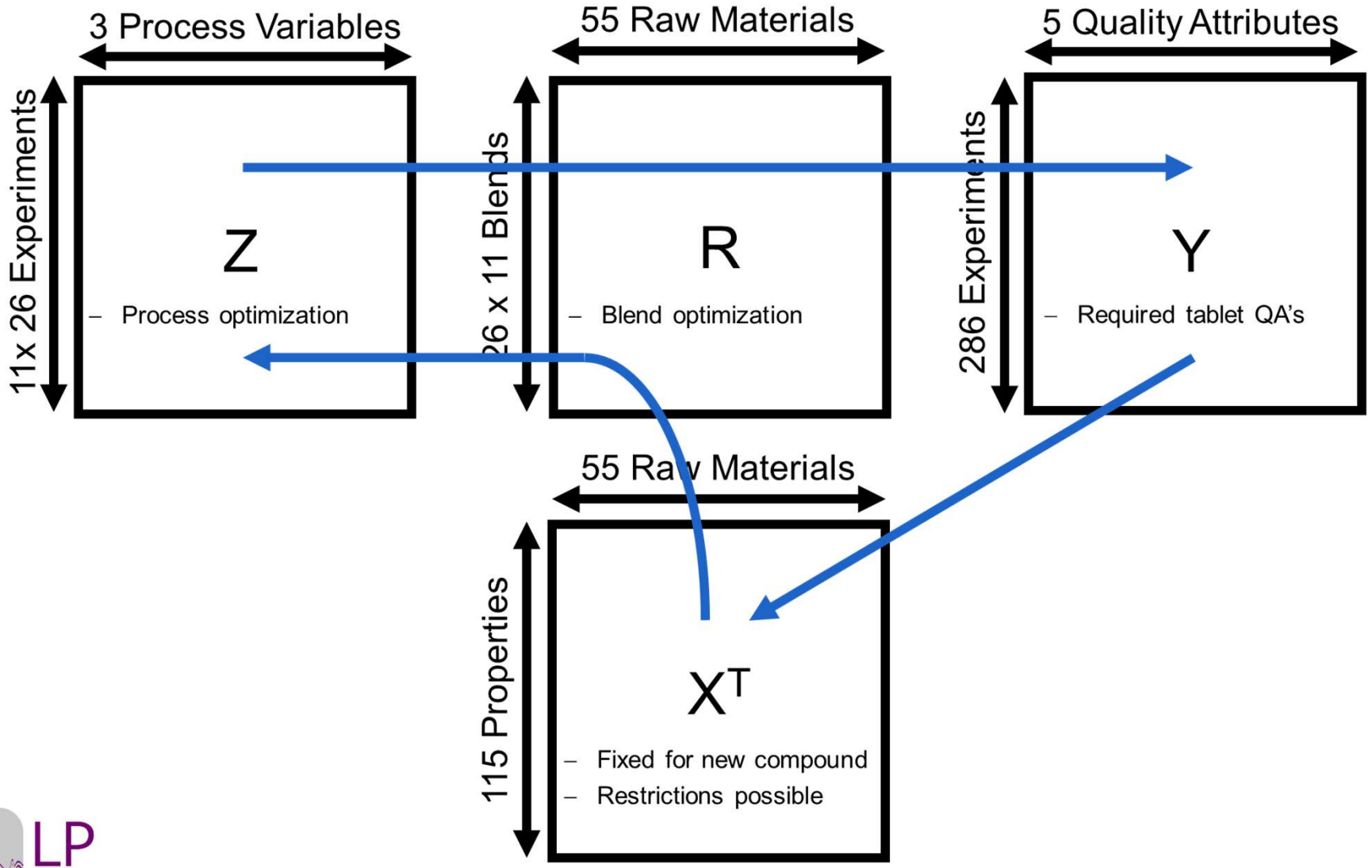
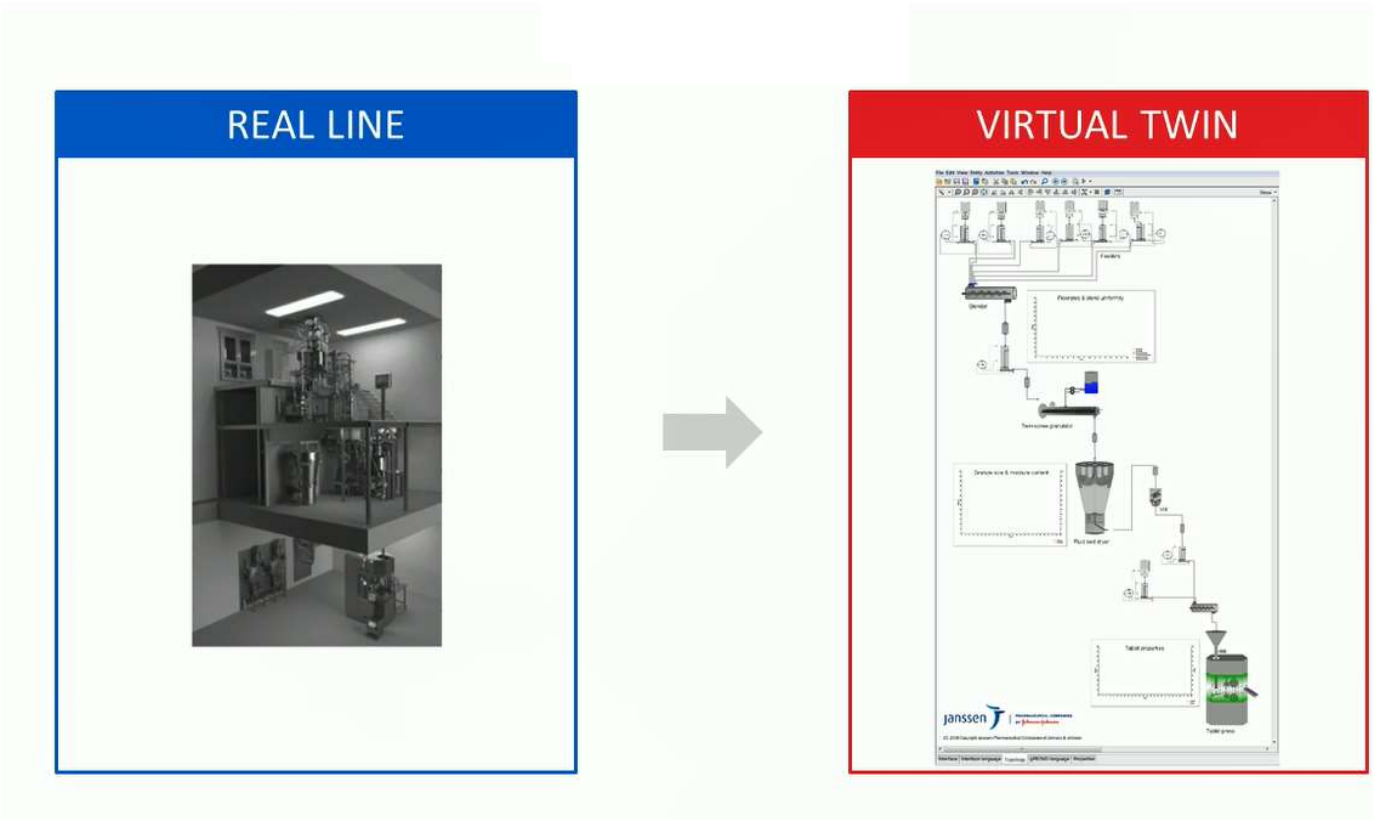


Virtual Twin



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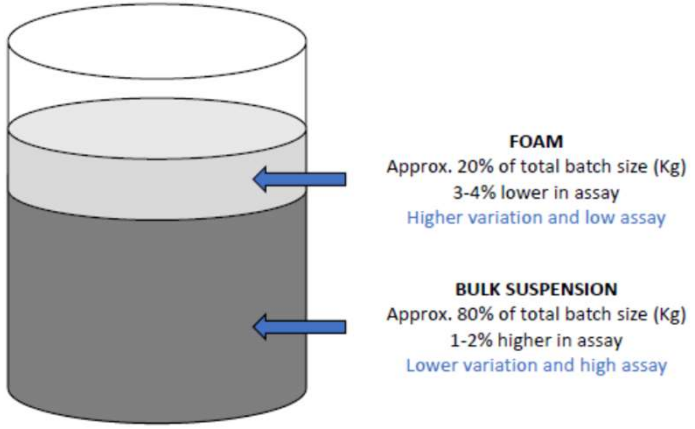
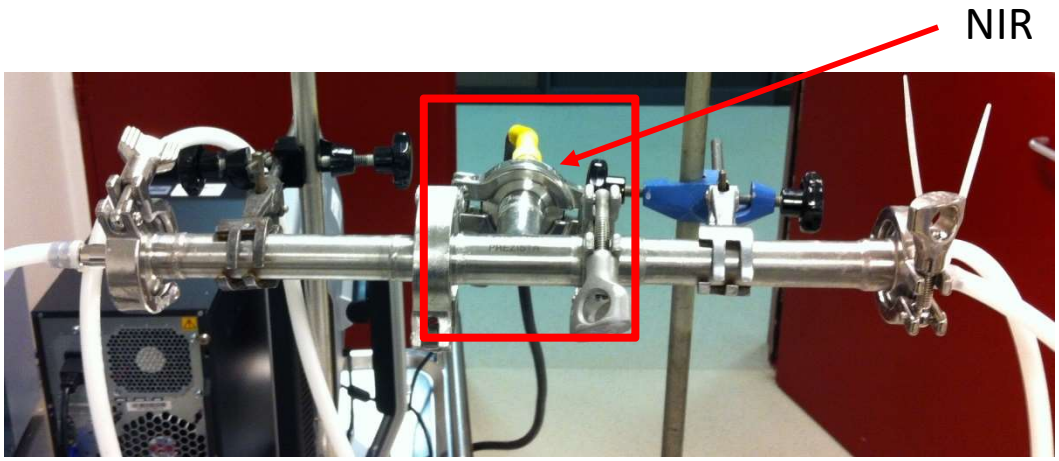
Model based PAT implementation

CFD model based NIR spectroscopy implementation for in-line assay monitoring of a pharmaceutical suspension

- High dose (100 mg/mL) suspension
- Manufactured at full scale
  - 150 L compounding vessel
  - One-pan process
  - Gradually discharged to a bottle filling system
    - Peristaltic flow





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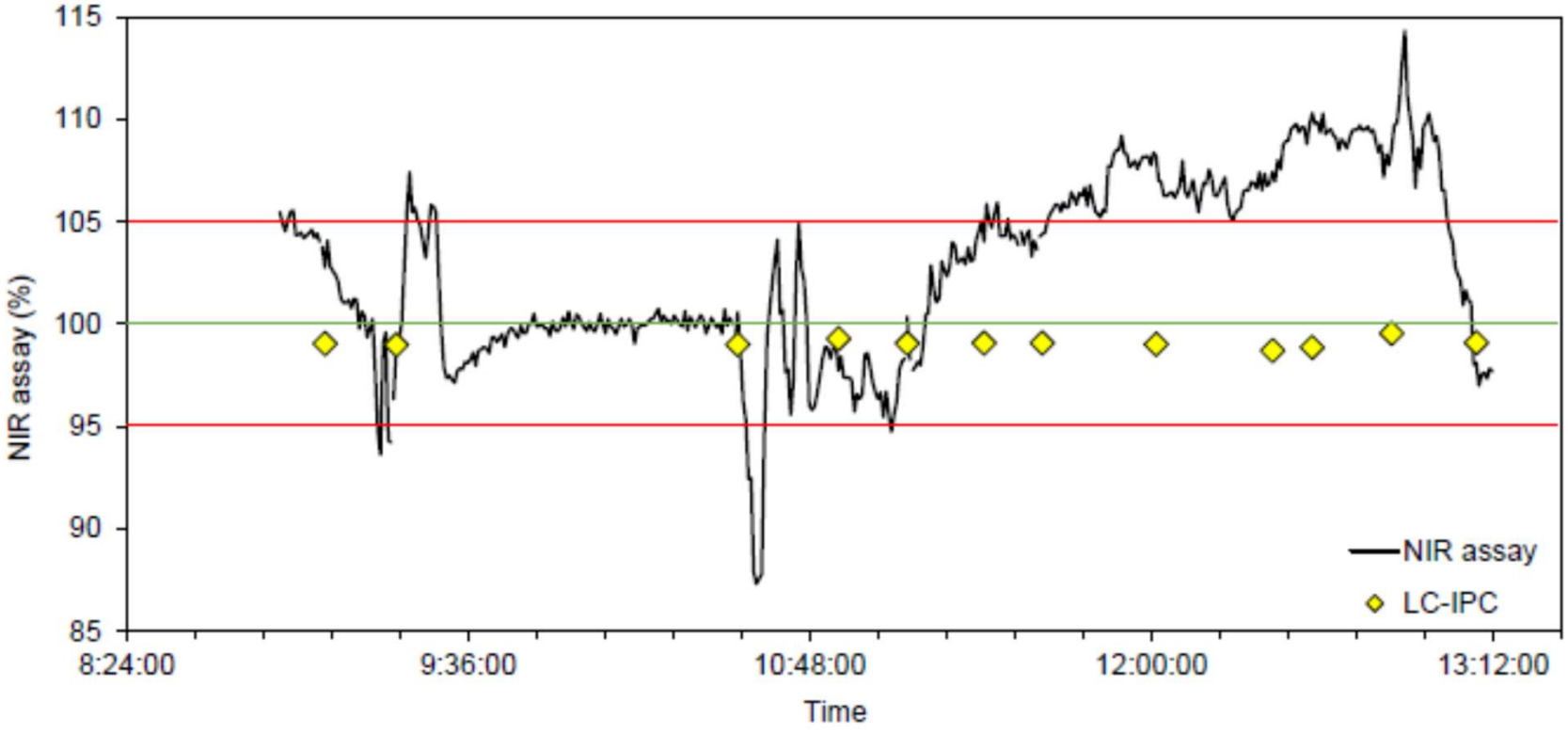

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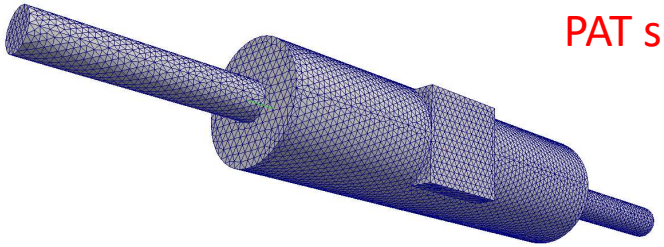
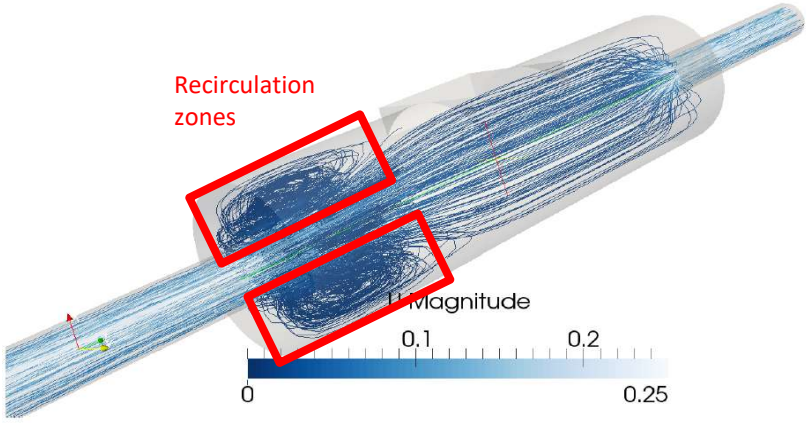
Model based PAT implementation

CFD model based NIR spectroscopy implementation for in-line assay monitoring of a pharmaceutical suspension

- Recirculation zone at entrance T-piece
- **Flow not yet fully stabilised into laminar flow profile at NIR sensor location**
- **Solution:** extend T-piece to ensure fully developed laminar paraboloidal flow profile
  - Hydrodynamic entry length $L_{h,laminar} = 0.05 \times Re \times D \times c$
    - Re = Reynolds number [-]
    - D = diameter circular tube [m]
    - c = safety factor [-]



PAT sensor



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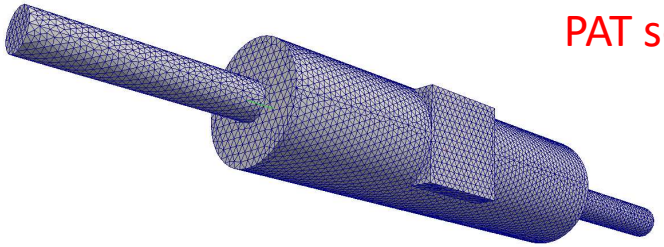
- Solution: extend T-piece to ensure fully developed laminar paraboloidal flow profile
  - Hydrodynamic entry length $L_{h,laminar} = 0.05 \times Re \times D \times c$ **= 0.1643 m = 16.43 cm**
    - Re = Reynolds number **= 43.8**
    - D = diameter circular tube **= 0.025 m**
    - c = safety factor **= 3**



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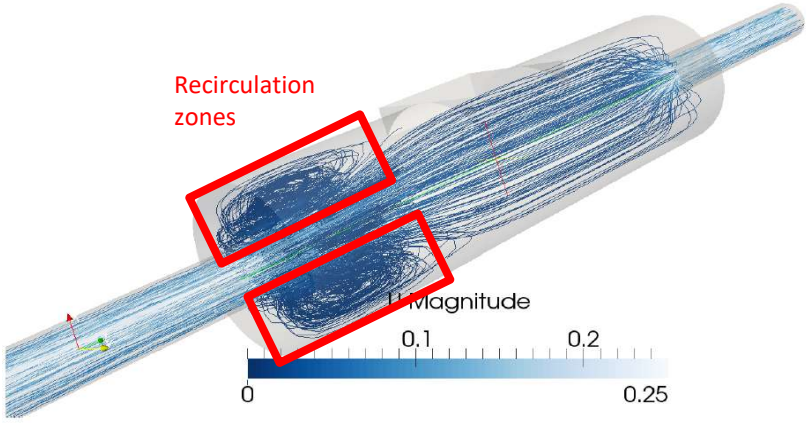

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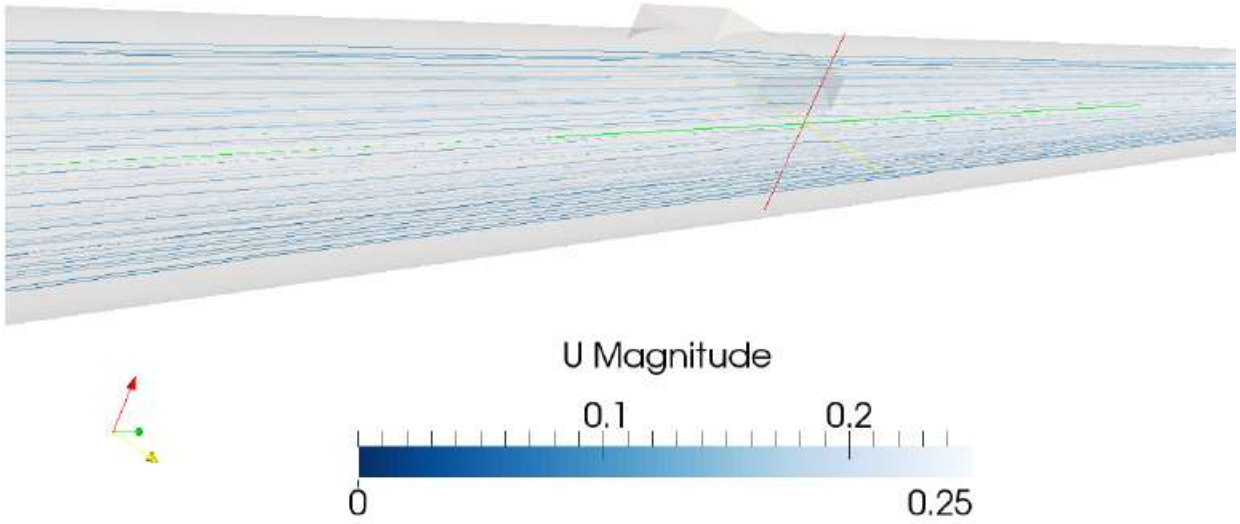

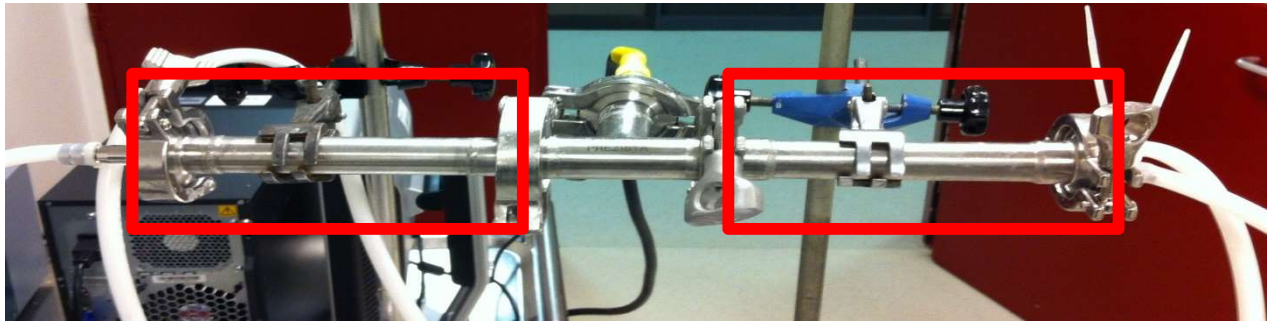

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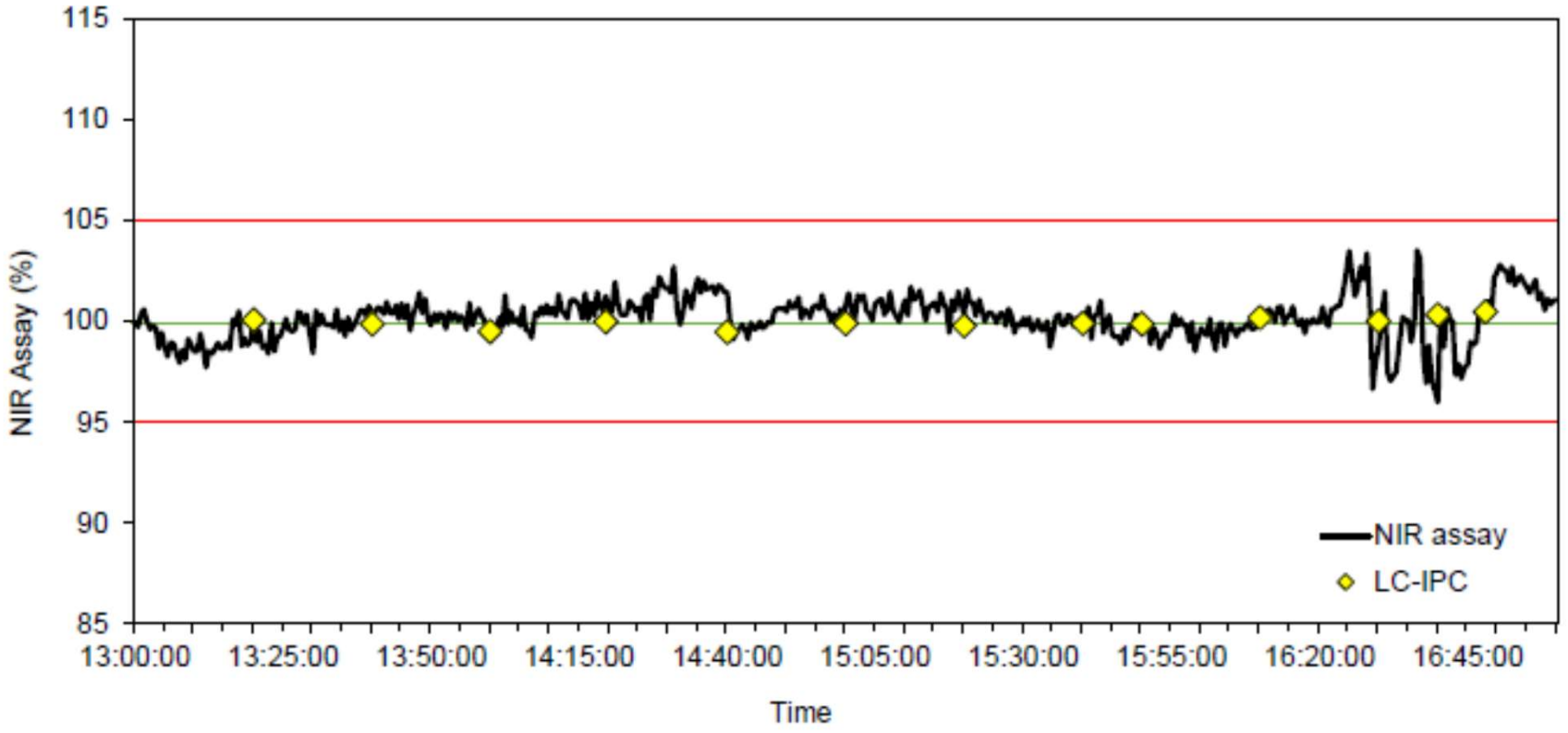

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Case study 3 – Continuous Freeze-Drying

- **large molecules** considered key driver of growth in pharma industry
- over 300 FDA and EMA approved biopharmaceutical products
- **± 50%** freeze-dried
- freeze-drying **preferred way of stabilizing** biopharmaceutical drug products

Antibodies


Enzymes
Hormones


Antibiotics


Dry Drops


Body Tissue

Vitamins
Bacteria

Vaccines
Cytostatics


Fast Melting
Tablets

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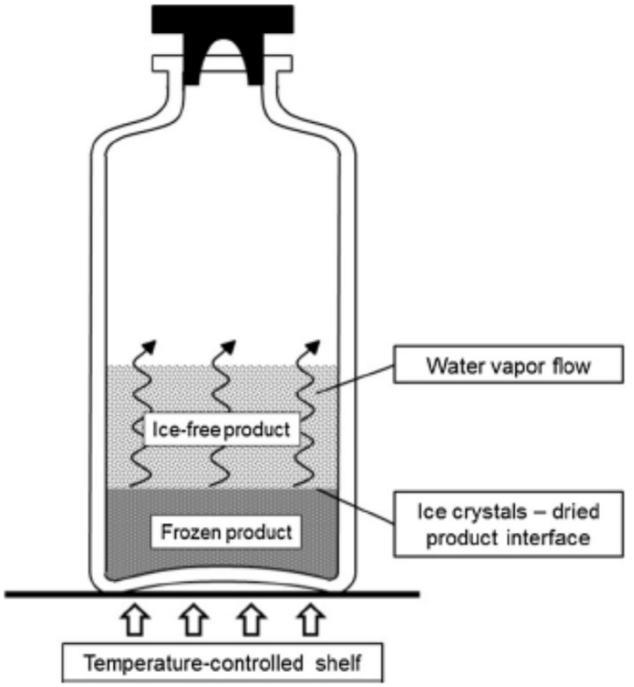
Pharmaceutical Batch Freeze Drying



low temperature drying process to convert solutions of (**heat-) labile** materials into solids having **sufficient stability**

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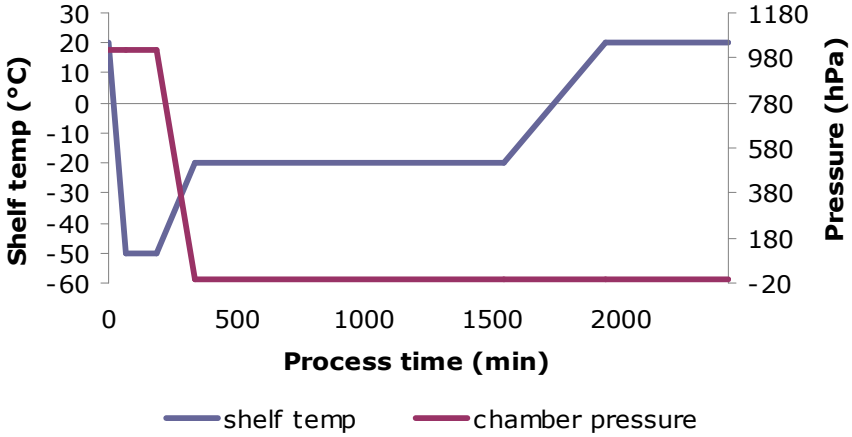
Pharmaceutical Batch Freeze Drying

Lab scale freeze-dryer

1. **Drying chamber**
   - vials to be freeze-dried on shelves
   - shelf temperature is controlled
   - chamber pressure is controlled

2. **Condensor**

only 2 process settings



CQA's freeze-dried product:

(i) API state and stability
(ii) residual moisture content
(iii) freeze-dried product cake structure
(iv) reconstitution time

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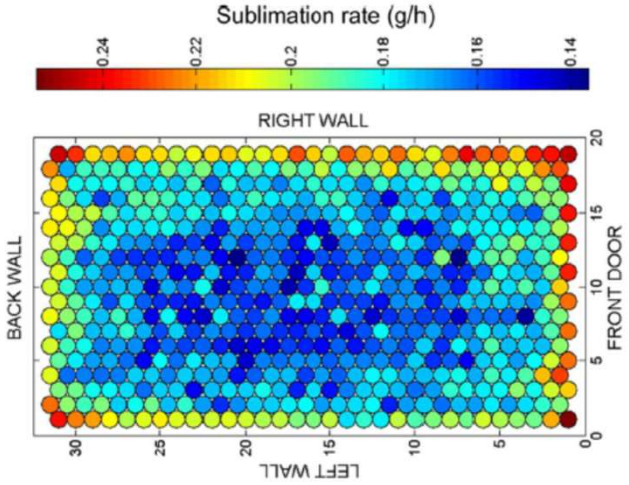
Pharmaceutical Batch Freeze Drying

1. **High production cost**
   - large equipment with high operational, maintenance and energy costs
   - high standards of cleanliness and sterility
2. **Time-consuming** (> 7 days)
3. **Up-scaling → re-optimisition and validation**
4. **Impaired quality**
   - **freezing** step is **uncontrolled**
   - **unefficient & uneven heat transfer**
     ⇒ variability in sublimation rate
     ⇒ vial-to-vial **product variability** (in conflict with FDA/EMA guidelines)
   - **no monitoring and control at vial level**
5. **No flexibility**
   - batch freeze-dryer validated for fixed amount of vials
   - time gap between upstream processing and start of freeze-drying too long
   - handling equipment before and after freeze-drying continuous



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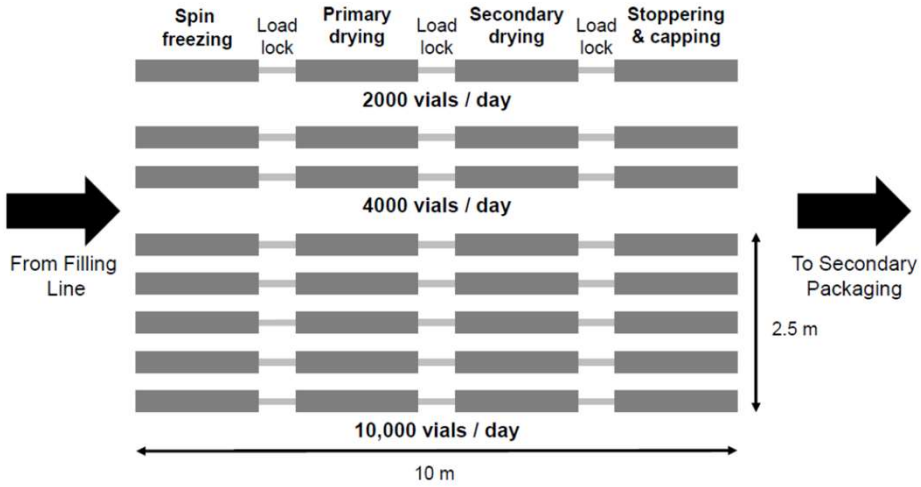
Aim & concept

To develop & validate a continuous and controlled freeze-drying technology for unit doses

- **Spin-freezing** to create **thin layer** + **large surface area**
- Separate **process modules**, separated by **load-locks**
- Extensive implementation of **PAT** tools to assure process control
- Scale-up through multiplication



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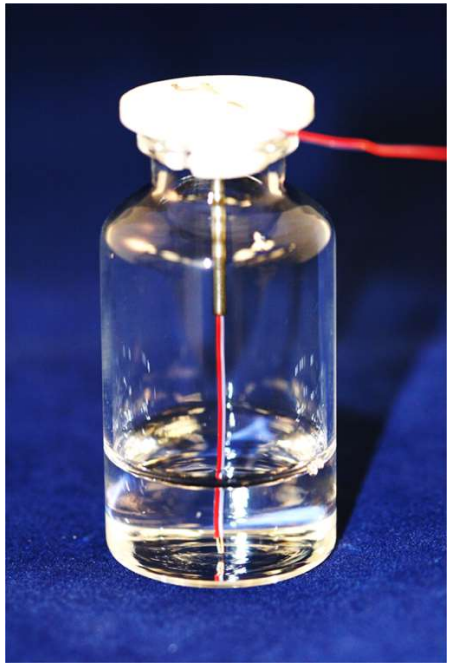
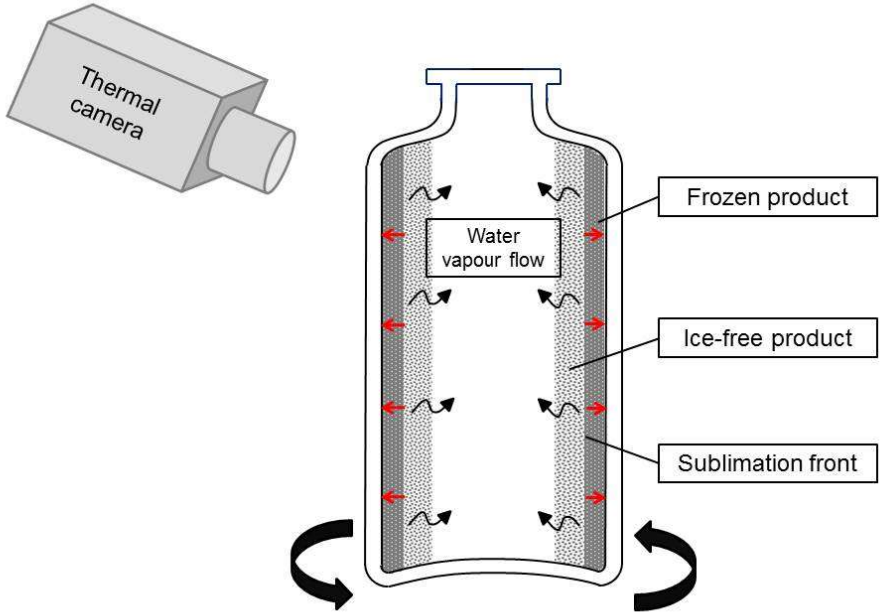
Opportunity

Sublimation front moves from inside the vial towards PAT tool





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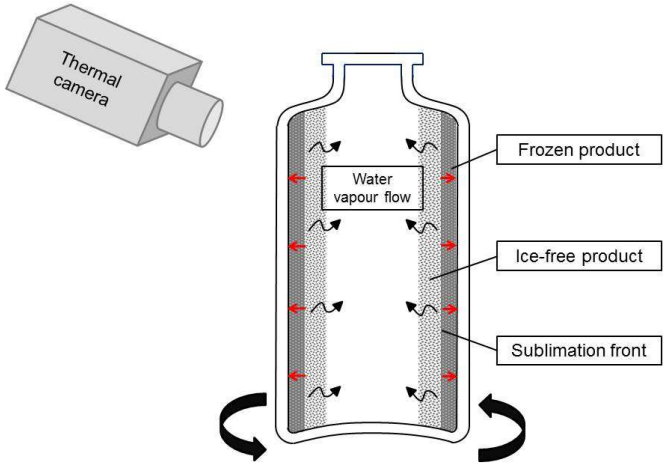
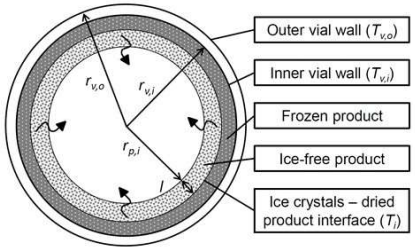
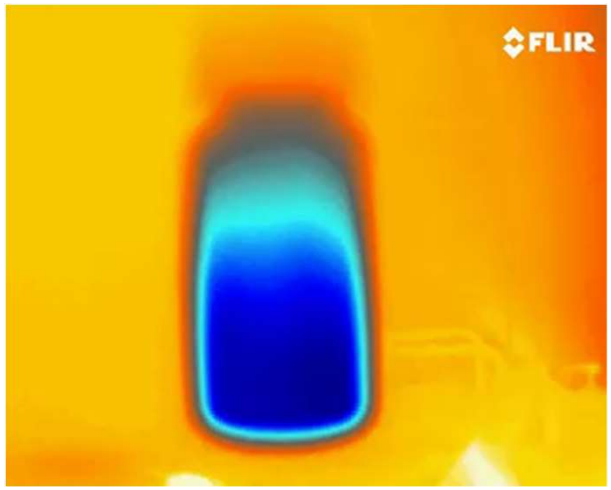
Thermal imaging

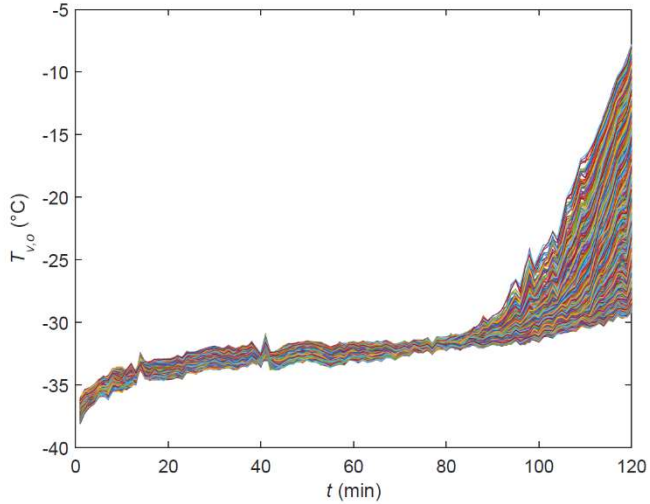




$$P_{tot} = 2\pi k_{glass} h \frac{(T_{v,o} - T_{v,i})}{\ln(\frac{r_{v,i}}{r_{v,o}})}$$

Temperature gradient over <u>glass wall</u> and <u>ice layer</u> can be calculated: 0,5°C





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Single Vial Continuous Freeze-Dryer

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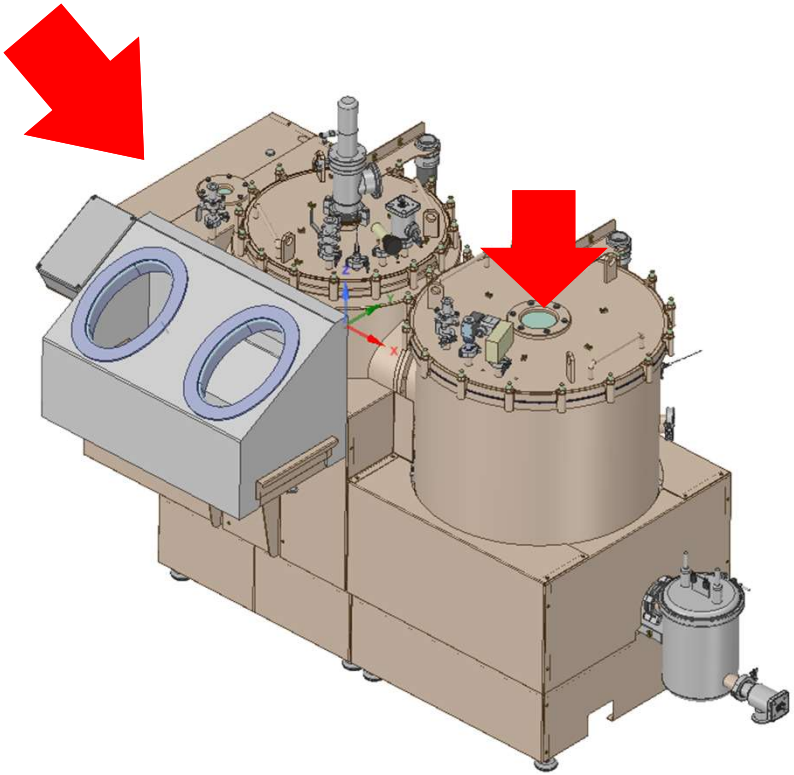
Engineering Prototype



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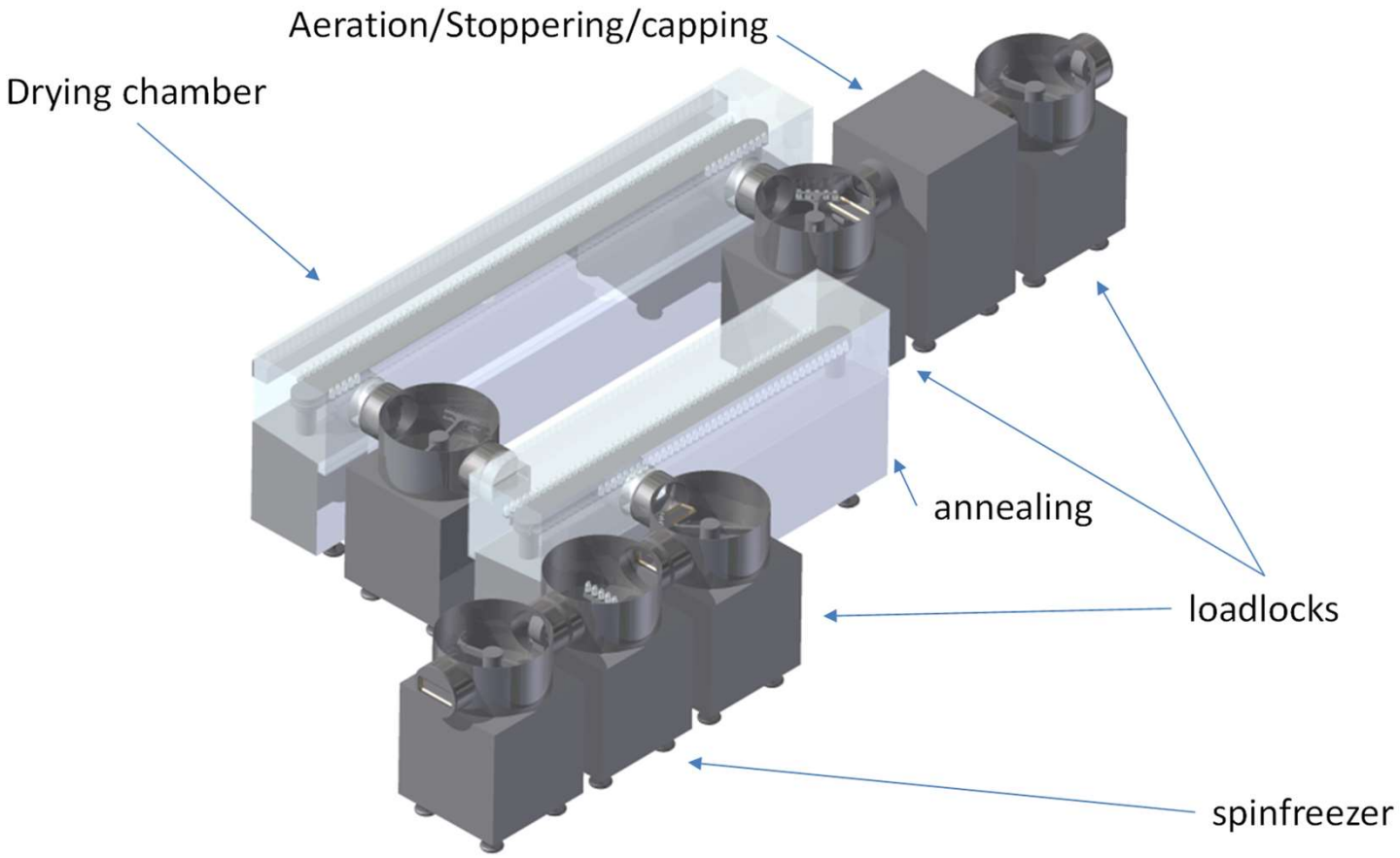
Prototype – GMP



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Outline

Case study I: continuous tablet manufacturing via TSWG

- PAT for process understanding & process modeling
- PAT for process monitoring & control

Case study II: pharmaceutical suspension manufacturing

- Model based PAT implementation

Case study III: continuous freeze-drying

- Model based design of innovative pharmaceutical manufacturing processes

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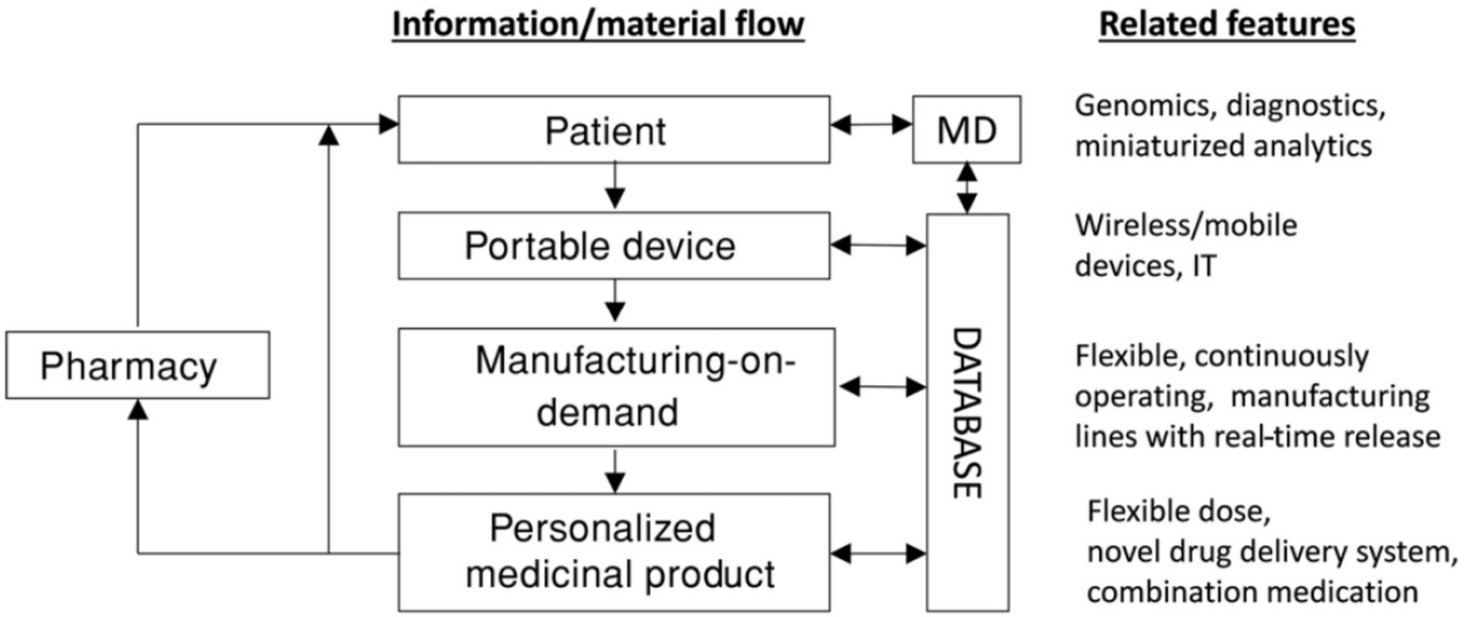
General Conclusions

- Manufacturing innovation crucial for future healthcare system



- Towards **model-based design** of flexible manufacturing equipment

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Questions?