A systematic computer aided framework for design and analysis of PAT systems

Krist V. Gernaey, Ravendra Singh and Rafiqul Gani

Department of Chemical and Biochemical Engineering
Technical University of Denmark
Lyngby
Denmark
Outline

- Introduction
- Model-based framework (objectives, main idea, ...)
- Methodology for design/analysis of PAT systems
- Knowledge-base, model-library, step-by-step description of algorithm
- Software and case study
- Conclusions and future perspectives
Outline

• Introduction

• Model-based framework (objectives, main idea, ....)

• Methodology for design/analysis of PAT systems

• Knowledge-base, model-library, step-by step description of algorithm

• Software and case study

• Conclusions and future perspectives
Process Analytical Technology

• Objective? Product quality assurance in real-time ("real time release")

• How to achieve this?
  – Process-product monitoring
  – Process control

• How to identify the PAT system?
  – Exploit available process knowledge, i.e. understand the product-process properties to configure the PAT system (select the methods & tools to be used)
Outline

• Introduction

• **Model-based framework (objectives, main idea, ....)**
  
  • Methodology for design/analysis of PAT systems
  
  • Knowledge-base, model-library, step-by step description of algorithm
  
  • Software and case study
  
  • Conclusions and future perspectives
PAT system design
PAT system design

Design of a process monitoring and analysis system for a PAT process involves:

- Selection of critical process variables
- Selection and location of suitable measurement methods
- Selection of suitable actuators
- Implementation of a control system

• **In this work:** Collected data is supplemented with generated data from models to quickly design and/or analyze (configure) a PAT system – what to measure, what to analyze, which equipment to use, ....?

• **Inherent assumption:**
  - Implementing models – mechanistic models – is an excellent way to archive and later on exploit process knowledge in a structured way!

  Sin et al. (2008), Biotechnology and Bioengineering, 101, 153-171.
  Sin et al. (2009), Biotechnology Progress, 25, 1043-1053.
  Gernaey et al. (2009), Biotechnology Journal, 4, 593-598.
Outline

• Introduction

• Model-based framework (objectives, main idea, ....)

• **Methodology for design/analysis of PAT systems**

  • Knowledge-base, model-library, step-by-step description of algorithm

  • Software and case study

  • Conclusions and future perspectives
Systematic design framework, overview

- **Product Quality Specifications**
- **Process Specifications**
- **Problem definition**

**Design algorithm**

- **Knowledge base**
  - Literature
  - Industrial survey

**Model library**

**ICAS-MoT Modelling Tool**

**Proposed process monitoring and analysis system (PAT system)**

**Final process monitoring and analysis system (PAT system)**

**Predefined product quality**

**Validation**

1. Does the process performance comply with the process specifications?
   - Yes
   - No

Outline

• Introduction

• Model-based framework (objectives, main idea, ....)

• Methodology for design/analysis of PAT systems

• **Knowledge-base, model-library, step-by step description of algorithm**

• Software and case study

• Conclusions and future perspectives
Structure of the knowledge base 1 – Process knowledge

Structure of the knowledge base  
2 – Knowledge on measurement methods & tools

(doi:10.1016/j.compchemeng.2009.06.021)

DTU Chemical Engineering  
Department of Chemical and Biochemical Engineering
Knowledge base in numbers (May 2009)

Pharmaceutical processes (e.g. Tablet manufacturing)
Bio processes (e.g. Fermentation)
Food production processes (e.g. Cheese & butter manufacturing)
Other general processes (e.g. Crystallization)

No. of variables stored in the knowledge base = 210
No. of monitoring techniques stored in the knowledge base = 230
No. of monitoring tools stored in knowledge base = 346
No. of specifications of each monitoring tool = 11
No. of literature & industrial references = 232
Flow diagram design methodology

1. product property specifications
2. Process specifications

Problem definition

3. Process analysis

Supporting Tools
- Knowledge base
- Model library

4. Sensitivity analysis

5. Interdependency analysis

Model library

6. Performance analysis of monitoring tools

Knowledge base

7. Proposed process monitoring and analysis system (PAT system)

Not accepted

8. Validation

Acceptable

9. Final process monitoring and analysis system (PAT system)
Outline

• Introduction

• Model-based framework (objectives, main idea, ....)

• Methodology for design/analysis of PAT systems

• Knowledge-base, model-library, step-by step description of algorithm

• **Software and case study**

• Conclusions and future perspectives
Software implementation of the design framework: ICAS-PAT

New problems

General supporting tools (protected)
- Knowledge base
- Model library

Problem specifications (input)
- General interface

Search engine
- Add

User specific supporting tools
- Knowledge base
- Model library

Case specific problems

Problem specific supporting tools (can be edited/replaced by user)
- Problem specific knowledge/data
- Problem specific models

Search engine
- Add

Product quality and process specifications (input)

Search engine
- Add

Problem specific interface

Designed PAT system (output)
ICAS-PAT: Software overview

- Design of process monitoring and analysis systems (PAT systems)
  - Load knowledge base
  - Select process
  - Select process points
  - Create problem specific knowledge base
  - Load model library
  - Raw material storage
  - Mixing tank
  - Milling machine
  - Granulator
  - Tablet press

- Open solved example
  - Pharmaceutical: Tablet n

- Find applications of monitoring tools
  - Retrieve the knowledge/data

- Specific problems
  - Problem specific interface
### Additional features of the software: Find applications of monitoring techniques

#### Results

<table>
<thead>
<tr>
<th>Monitoring technique</th>
<th>Monitoring tool</th>
<th>Monitoring variable</th>
<th>Process point</th>
<th>Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIR</td>
<td>AvaSpec-NIR256-1.7</td>
<td>Content uniformity</td>
<td>Tablet storage</td>
<td>Pharmaceutical, Tablet manufacturing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homogeneity</td>
<td>Fermentor</td>
<td>Fermentation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homogeneity</td>
<td>Mixing tank</td>
<td>Fermentation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homogeneity</td>
<td>Mixing tank</td>
<td>Pharmaceutical, Tablet manufacturing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homogeneity</td>
<td>Crystalizer</td>
<td>Crystalization</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homogeneity</td>
<td>Mixing tank</td>
<td>Insulin production</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homogeneity</td>
<td>Fermentor</td>
<td>Insulin production</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homogeneity</td>
<td>Blender</td>
<td>Insulin production</td>
</tr>
<tr>
<td></td>
<td>AvaSpec-NIR256-2.2</td>
<td>Content uniformity</td>
<td>Tablet storage</td>
<td>Pharmaceutical, Tablet manufacturing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homogeneity</td>
<td>Fermentor</td>
<td>Fermentation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homogeneity</td>
<td>Mixing tank</td>
<td>Fermentation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homogeneity</td>
<td>Mixing tank</td>
<td>Pharmaceutical, Tablet manufacturing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homogeneity</td>
<td>Crystalizer</td>
<td>Crystalization</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homogeneity</td>
<td>Mixing tank</td>
<td>Insulin production</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homogeneity</td>
<td>Fermentor</td>
<td>Insulin production</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homogeneity</td>
<td>Blender</td>
<td>Insulin production</td>
</tr>
<tr>
<td></td>
<td>AvaSpec-NIR256-2.5</td>
<td>Content uniformity</td>
<td>Tablet storage</td>
<td>Pharmaceutical, Tablet manufacturing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homogeneity</td>
<td>Fermentor</td>
<td>Fermentation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homogeneity</td>
<td>Mixing tank</td>
<td>Fermentation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homogeneity</td>
<td>Mixing tank</td>
<td>Pharmaceutical, Tablet manufacturing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homogeneity</td>
<td>Crystalizer</td>
<td>Crystalization</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homogeneity</td>
<td>Mixing tank</td>
<td>Insulin production</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homogeneity</td>
<td>Fermentor</td>
<td>Insulin production</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Homogeneity</td>
<td>Blender</td>
<td>Insulin production</td>
</tr>
<tr>
<td></td>
<td>KUT270 Desktop C</td>
<td>Centrifuge</td>
<td>Insulin production</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sludge solid composition (centrifuge and p)</td>
<td>Centrifuge</td>
<td>Insulin production</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Centrifuge composition (liquid/waste)</td>
<td>Centrifuge</td>
<td>Insulin production</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sludge solid composition (centrifuge and p)</td>
<td>Centrifuge</td>
<td>Cheese &amp; butter manufacturing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Centrifuge composition (liquid)</td>
<td>Centrifuge</td>
<td>Cheese &amp; butter manufacturing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sludge solid composition (centrifuge and p)</td>
<td>Centrifuge</td>
<td>Cheese &amp; butter manufacturing</td>
</tr>
<tr>
<td></td>
<td>KUT5500 NIR Online C</td>
<td>Centrifuge</td>
<td>Insulin production</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sludge solid composition (centrifuge and p)</td>
<td>Centrifuge</td>
<td>Cheese &amp; butter manufacturing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Centrifuge composition (liquid/waste)</td>
<td>Centrifuge</td>
<td>Pharmaceutical, Tablet manufacturing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sludge solid composition (centrifuge and p)</td>
<td>Centrifuge</td>
<td>Cheese &amp; butter manufacturing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Centrifuge composition (liquid)</td>
<td>Centrifuge</td>
<td>Cheese &amp; butter manufacturing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sludge solid composition (centrifuge and p)</td>
<td>Centrifuge</td>
<td>Cheese &amp; butter manufacturing</td>
</tr>
<tr>
<td></td>
<td>uniSPEC-4000</td>
<td>Casein protein</td>
<td>Milk storage tank</td>
<td>Cheese &amp; butter manufacturing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Casein protein</td>
<td>Peletouzer &amp; cooling system</td>
<td>Cheese &amp; butter manufacturing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Casein protein</td>
<td>Cheese vat</td>
<td>Cheese &amp; butter manufacturing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fat</td>
<td>Milk storage tank</td>
<td>Cheese &amp; butter manufacturing</td>
</tr>
</tbody>
</table>
Application to tablet manufacturing

Tablet manufacturing case study


• Detailed simulation models provided in appendix to the manuscript!
  – Share knowledge / experience
  – Benchmarking!
Provide product quality specifications

1. Product quality specifications
2. Process specifications
3. Process analysis
4. Sensitivity analysis
5. Interdependency analysis
6. Performance analysis of monitoring tools
7. Proposed process monitoring & analysis system
8. Validation
9. Final process monitoring & analysis system

Design of process monitoring and analysis systems (PAT systems) [Open solved example] [Find applications of monitoring tools] [Retrieve the knowledge/data]

Write the number of products: 1

1. Product name: Tablet

**1. Specifications of Tablet** | **Value** | **Unit**
---|---|---
Weight | 5.0E-04 | Kg/tablet
Water content | 5.0E-03 | % w/w
Coating | 1.0E-05 | Kg/tablet
Coating thickness | 1.0E-04 | m
Hardness | 145 | Mpa
Solubility in water (at 20 °C) | 14 | Kg/m³
Volume | 5.0E-07 | Kg/m³
Tablet thickness | 4.0E-03 | m

**Qualitative specifications**

| Shape | Cylindrical |
| Color | White |
| Odor | Pleasant |
| Taste | Sweet |
| Content | Uniform |

Provided by user
Provide the process specifications

1. Product quality specifications
2. Process specifications
3. Process analysis
4. Sensitivity analysis
5. Interdependency analysis
6. Performance analysis of monitoring tools
7. Proposed process monitoring & analysis system
8. Validation
9. Final process monitoring & analysis system

Select the process (Type, if not in the list): Pharmaceutical; Tablet manufacture

Write the No. of equipments used: 6
Select equipments (Type, if not in the list): Tablet coater

Write the No. of raw materials used: 9
Raw material list:
- USP (United States Pharmacopeia) Water
- Sucrose
- API
- Stabilizer
- Excipient
- Mannitol
- Flavoring
- OpaDry
- Hot-USP-Water

Equipment list:
- Mixing tank
- Milling machine
- Granulator
- Tablet press
- Storage tank
- Tablet coater

Provided by user
# Process analysis

## Mixing tank

<table>
<thead>
<tr>
<th>Process variables in Mixing tank</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Unit</th>
<th>Process variables in Milling machine</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Unit</th>
<th>Process variables in Granulator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stirrer speed</td>
<td>0</td>
<td>36000</td>
<td>rpm</td>
<td>Particle size</td>
<td>1.10E-09</td>
<td>1.20E-09</td>
<td>m</td>
<td>Granule size</td>
</tr>
<tr>
<td>Stiring duration</td>
<td>0</td>
<td>3</td>
<td>hour</td>
<td>Milling duration</td>
<td>0</td>
<td>3</td>
<td>g</td>
<td>Bed temperature</td>
</tr>
<tr>
<td>Homogeneity</td>
<td>0.95</td>
<td>1</td>
<td>Fract</td>
<td>Rotational speed</td>
<td>0</td>
<td>36000</td>
<td>rpm</td>
<td>Fluidization air flow rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Solid fraction in feed</td>
<td>0.66</td>
<td>1</td>
<td>Kg</td>
<td>Fluidization air flow rate</td>
</tr>
</tbody>
</table>

**TOTAL NO. OF SELECTED VARIABLES = 3**

**TOTAL NO. OF SELECTED VARIABLES = 6**

## Milling machine

<table>
<thead>
<tr>
<th>Process variables in Milling machine</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Unit</th>
<th>Process variables in Granulator</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>g</td>
<td>Granule size</td>
</tr>
</tbody>
</table>

## Granulator

- Atomizing air flow rate
- True density
- Bulk density
- Tap density
- Dissolution
- Porosity

**TOTAL NO. OF SELECTED VARIABLES = 5**

## Tablet press

<table>
<thead>
<tr>
<th>Process variables in Tablet press</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Unit</th>
<th>Process variables in Storage tank</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Unit</th>
<th>Process variables in Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>0.000436</td>
<td>0.000522</td>
<td>Kg</td>
<td>Level</td>
<td>95</td>
<td>100</td>
<td>%</td>
<td>Inlet air flow rate</td>
</tr>
<tr>
<td>Thickness</td>
<td>0.00395</td>
<td>0.00402</td>
<td>m</td>
<td>Temperature</td>
<td>10</td>
<td>15</td>
<td>°C</td>
<td>Inlet air temperature</td>
</tr>
<tr>
<td>Shape</td>
<td>4.50E-07</td>
<td>5.50E-07</td>
<td>m³</td>
<td>Inlet air humidity</td>
<td></td>
<td></td>
<td></td>
<td>Inlet air humidity</td>
</tr>
<tr>
<td>Pre-compression force</td>
<td>500</td>
<td>600</td>
<td>N</td>
<td>Outlet air flow rate</td>
<td></td>
<td></td>
<td></td>
<td>Outlet air flow rate</td>
</tr>
<tr>
<td>Main compression force</td>
<td>16000</td>
<td>17000</td>
<td>N</td>
<td>Outlet air temperature</td>
<td></td>
<td></td>
<td></td>
<td>Outlet air temperature</td>
</tr>
<tr>
<td>Press speed</td>
<td>1500</td>
<td>2100</td>
<td>m³/h</td>
<td>Outlet air humidity</td>
<td></td>
<td></td>
<td></td>
<td>Outlet air humidity</td>
</tr>
<tr>
<td>Dwell time</td>
<td>1.75E-03</td>
<td>1.79E-03</td>
<td>hr</td>
<td>Pan air temperature</td>
<td></td>
<td></td>
<td></td>
<td>Pan air temperature</td>
</tr>
<tr>
<td>Feed volume</td>
<td>9.52E-07</td>
<td>9.88E-07</td>
<td>m³</td>
<td>Negative air pressure (psig)</td>
<td></td>
<td></td>
<td></td>
<td>Negative air pressure (psig)</td>
</tr>
</tbody>
</table>

**TOTAL NO. OF SELECTED VARIABLES = 9**

## Storage tank

- Rotating speed of the pan
- Temperature of coating liquid
- Flow rate of coating liquid
- Spraying air pressure
- Spraying air temperature
- Surface roughness

**TOTAL NO. OF SELECTED VARIABLES = 5**

## Tablet coater

- Outlet air flow rate
- Outlet air temperature
- Outlet air humidity
- Pan air temperature
- Negative air pressure (psig)
- Rotating speed of the pan
- Temperature of coating liquid
- Flow rate of coating liquid
- Spraying air pressure
- Spraying air temperature
- Surface roughness

**TOTAL NO. OF SELECTED VARIABLES = 9**
Sensitivity analysis

**Result section**

**HO is a critical variable**
Interdependency analysis

5.1. Select a process point
Mixing tank

5.2. Select critical process variables

5.2.1. Select a critical process variable

5.2.2. List the actuator candidates

Critical Process Points/Critical Process Variables/Actuator Candidates

Mixing tank

Milling machine

Granulator

Perturbation Setup

<table>
<thead>
<tr>
<th>Lower</th>
<th>Upper</th>
<th>Step</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>15</td>
<td>3</td>
</tr>
</tbody>
</table>

5.3.1. Performed interdependency analysis

5.3.2. Select critical variable

5.3.3. Result

% Change in actuators

Mixing time
Stirrer speed

% Change in control variable absolute

Mixing time
Stirrer speed

Retrieved from knowledge base
Example of actuator selection: Moisture content in the granulation process

Result section for interdependency analysis
Performance analysis of monitoring tools

- Critical process points: Mixing tank, Milling machine
- Critical process variables: Homogeneity, Particle size
- Monitoring techniques: NIR, UV-Visible
- Performance criteria: Accuracy, Precision, Lower operating limit

Retrieved from knowledge base
# Proposed process monitoring and analysis system (PAT system)

<table>
<thead>
<tr>
<th>Critical process points</th>
<th>Critical process variables</th>
<th>Actuators</th>
<th>Monitoring techniques</th>
<th>Monitoring tools</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixing tank</td>
<td>Homogeneity</td>
<td>Mixing time</td>
<td>NIR</td>
<td>AnaSpec-NIR256-1.7</td>
</tr>
<tr>
<td>Milling machine</td>
<td>Particle size</td>
<td>Milling duration</td>
<td>FBRM</td>
<td>FBRM® C35</td>
</tr>
<tr>
<td>Granulator</td>
<td>Granule size</td>
<td>Granulation time</td>
<td>FBRM</td>
<td>FBRM® C35</td>
</tr>
<tr>
<td>Granulator</td>
<td>Moisture content</td>
<td>Binder flow rate</td>
<td>NIR</td>
<td>AnaSpec-NIR256-1.7</td>
</tr>
<tr>
<td>Granulator</td>
<td>Bed temperature</td>
<td>Fluidisation air temperature</td>
<td>Thermocouple</td>
<td>WZ-08541-28</td>
</tr>
<tr>
<td>Granulator</td>
<td>Fluidisation air temperature</td>
<td>Cooling/heating fluid flow rate</td>
<td>Thermocouple</td>
<td>WZ-08541-28</td>
</tr>
<tr>
<td>Granulator</td>
<td>Atomizing air flow rate</td>
<td>Valve pressure</td>
<td>Rotameters</td>
<td>PITE - Rotameter</td>
</tr>
<tr>
<td>Granulator</td>
<td>Dissolution</td>
<td>Binder flow rate</td>
<td>UV Analysis</td>
<td>F20-UV</td>
</tr>
<tr>
<td>Granulator</td>
<td>Porosity</td>
<td>Binder flow rate</td>
<td>Hg Porosimetry</td>
<td>PoreMaster 60</td>
</tr>
<tr>
<td>Tablet press</td>
<td>Weight</td>
<td>Feed volume</td>
<td>Strain Gauge</td>
<td>BSC - Strain Gauge - SS-027</td>
</tr>
<tr>
<td>Tablet press</td>
<td>Hardness</td>
<td>Tablet thickness</td>
<td>Strain Gauge</td>
<td>BSC - Strain Gauge - SS-027</td>
</tr>
<tr>
<td>Tablet press</td>
<td>Pre-compression force</td>
<td>Feed volume</td>
<td>Strain Gauge</td>
<td>BSC - Strain Gauge - SS-027</td>
</tr>
<tr>
<td>Tablet press</td>
<td>Main compression force</td>
<td>Tablet thickness</td>
<td>Strain Gauge</td>
<td>BSC - Strain Gauge - SS-027</td>
</tr>
<tr>
<td>Tablet press</td>
<td>Dwell time</td>
<td>Press speed</td>
<td>Timer</td>
<td>Timer</td>
</tr>
<tr>
<td>Tablet storage</td>
<td>Temperature</td>
<td>Heat transfer rate</td>
<td>Thermocouple</td>
<td>WZ-08541-28</td>
</tr>
<tr>
<td>Tablet coater</td>
<td>Film thickness (coating)</td>
<td>Inflow rate of coating materials</td>
<td>F20-UV</td>
<td>F20-UV</td>
</tr>
<tr>
<td>Tablet coater</td>
<td>Inlet air temperature</td>
<td>Cooling/heating fluid flow rate</td>
<td>Thermocouple</td>
<td>WZ-08541-28</td>
</tr>
<tr>
<td>Tablet coater</td>
<td>Pan air temperature</td>
<td>Inlet air temperature</td>
<td>Thermocouple</td>
<td>WZ-08541-29</td>
</tr>
<tr>
<td>Tablet coater</td>
<td>Temperature of coating liquid</td>
<td>Cooling/heating fluid flow rate</td>
<td>Thermocouple</td>
<td>WZ-08541-30</td>
</tr>
<tr>
<td>Tablet coater</td>
<td>Spraying air temperature</td>
<td>Cooling/heating fluid flow rate</td>
<td>Thermocouple</td>
<td>WZ-08541-30</td>
</tr>
</tbody>
</table>

**DTU Chemical Engineering**

Department of Chemical and Biochemical Engineering
PAT system design validation

1. Product quality specifications
2. Process specifications
3. Process analysis
4. Sensitivity analysis
5. Interdependency analysis
6. Performance analysis of monitoring tools
7. Proposed process monitoring & analysis system
8. Validation
9. Final process monitoring & analysis system

8.1. Select a process point
8.2. Select the control variable
8.3. Select the actuator
8.4. Solve the closed loop mode
8.5. Load simulation result

8.6. Select variable
8.7. Operational limit of selected variable

8.8. Select the control parameters
Proportional (Kc) Integral (Ki) Differential (Kd) On-off

K_switch

8.9. Analyze the selected variable

Homogeneity

Particle size

Homogeneity

Particle size

Achieved profile
Lower limit
Upper limit
Set points

Achieved profile
Lower limit
Upper limit
Set points
# Final process monitoring & analysis system

<table>
<thead>
<tr>
<th>Critical process points</th>
<th>Critical process variables</th>
<th>Actuators</th>
<th>Monitoring techniques</th>
<th>Monitoring tools</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixing tank</td>
<td>Homogeneity</td>
<td>Mixing time</td>
<td>NIR</td>
<td>AmSpec-NIR256-1.7</td>
</tr>
<tr>
<td>Milling machine</td>
<td>Particle size</td>
<td>Milling duration</td>
<td>FBRM</td>
<td>FBRM950-C05</td>
</tr>
<tr>
<td>Granulator</td>
<td>Granule size</td>
<td>Granulation time</td>
<td>FBRM</td>
<td>FBRM950-C05</td>
</tr>
<tr>
<td>Granulator</td>
<td>Moisture content</td>
<td>Binder flow rate</td>
<td>NIR</td>
<td>AmSpec-NIR256-1.7</td>
</tr>
<tr>
<td>Granulator</td>
<td>Bed temperature</td>
<td>Fluidisation air flow rate</td>
<td>Thermocouple</td>
<td>W2-00541-23</td>
</tr>
<tr>
<td>Tablet press</td>
<td>Weight</td>
<td>Feed volume</td>
<td>Strain Gauge [147]</td>
<td>BSC- Strain Gauge - SS-027</td>
</tr>
<tr>
<td>Tablet press</td>
<td>Hardness</td>
<td>Tablet thickness</td>
<td>Strain Gauge [147]</td>
<td>BSC- Strain Gauge - SS-027</td>
</tr>
<tr>
<td>Tablet storage</td>
<td>Temperature</td>
<td>Cooling/heating fluid flow rate</td>
<td>Thermocouple</td>
<td>W2-00541-23</td>
</tr>
<tr>
<td>Tablet coater</td>
<td>Film thickness (coating)</td>
<td>Inflow rate of coating materials</td>
<td>F20-UV</td>
<td>F20-UV</td>
</tr>
<tr>
<td>Tablet coater</td>
<td>Pan air temperature</td>
<td>Inlet air temperature</td>
<td>Thermocouple</td>
<td>W2-00541-29</td>
</tr>
<tr>
<td>Tablet coater</td>
<td>Temperature of coating liquid</td>
<td>Cooling/heating fluid flow rate</td>
<td>Thermocouple</td>
<td>W2-00541-30</td>
</tr>
<tr>
<td>Tablet coater</td>
<td>Spraying air temperature</td>
<td>Cooling/heating fluid flow rate</td>
<td>Thermocouple</td>
<td>W2-00541-30</td>
</tr>
</tbody>
</table>
Final process monitoring & analysis system (PAT system): one feasible alternative

**Granulation**
- NIR: Near Infrared; UV: Ultraviolet; FBRM: Focussed Beam reflective measurement; HO: Homogeneity; $F_{pre}$: Pre-compression force; $F_{main}$: Main compression force; $R$: Response time; T90: Time for 90% response; c: Controller; [ ]: Reference no. in knowledge base

**DTU Chemical Engineering**
Department of Chemical and Biochemical Engineering

8th World Congress of Chemical Engineering
Montreal, Quebec, Canada 23-27 August 2009
Outline

• Introduction

• Model-based framework (objectives, main idea, ....)

• Methodology for design/analysis of PAT systems

• Knowledge-base, model-library, step-by-step description of algorithm

• Software and case study

• Conclusions and future perspectives
Conclusions

• A framework and methodology for the design of process monitoring and analysis systems (PAT systems) have been developed (Singh et al. (2009). Computers and Chemical Engineering, 33, 22-42)

• The framework has been implemented in a software (ICAS-PAT) (Singh, et al. (2009). Computers and Chemical Engineering (in press), doi:10.1016/j.compchemeng.2009.06.021)

• Supporting tools (knowledge base & model library) have been developed and populated with data

• Application of ICAS-PAT: demonstrated through the tablet manufacturing process case study
  – Fermentation process
  – Cheese manufacturing process
  – Crystallization
Future perspectives

- Extend number of applications
  - Extend knowledge base

- Test framework on practical case studies
  - Lab-scale: obvious limitations
  - Pilot-plant?
  - Industrial case study

- Extend methodology w.r.t. selection of controllers
  - More advanced control

- Combine framework with multi-scale modelling
  - Crystallization
Acknowledgement

The financial support of the Technical University of Denmark for the PhD project of Ravendra Singh is acknowledged.

Note!

The PhD thesis of Ravendra Singh (draft) should be completed this week. Final version available in a couple of months.

Contact: Prof. Rafiqul Gani (rag@kt.dtu.dk)