Process Systems Engineering in Pharmaceutical Development & Manufacture

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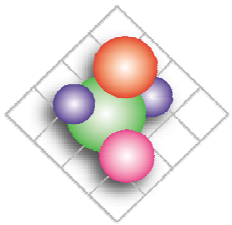
In Sympathy with Tom Edgar's 65th Birthday



NSF ERC
***FOR* STRUCTURED ORGANIC**
PARTICULATE SYSTEMS

10AIChE®
Annual Meeting, Salt Lake City, UT

PURDUE
UNIVERSITY

Outline

- Pharmaceutical Industry
  - Economics
  - Regulatory changes
- PSE Opportunity areas
  - Product/process design

    NIPTE case study
  - Process Operations

    ERC SOPS
- Summary

ims Total Unaudited and Audited Global Pharmaceutical Market By Region

	2009			2008	2004-2009	2010	2009-2014
	Mkt Size *US$bn	Mkt Size **Const. US$	% Growth **Const. US$	% Growth **Const US$	CAGR % **Const US$	Forecast % Growth **Const US$	CAGR % **Const US$
Total unaudited and audited global market							
	$ 808.3	$ 837.3	7.0%	5.5%	6.7%	4 - 6%	5 - 8%

Total unaudited and audited global market by region							
North America	$ 322.1	$ 323.8	5.5%	1.9%	5.2%	3 - 5%	3 - 6%
Europe	$ 247.6	$ 263.9	4.8%	7.0%	6.6%	3 - 5%	3 - 6%
Asia/Africa/ Australia	$ 102.6	$ 106.6	15.9%	15.0%	13.9%	13 - 15%	12 - 15%
Japan	$ 90.3	$ 95.0	7.6%	2.1%	3.9%	0 - 2%	2 - 5%
Latin America	$ 45.8	$ 47.9	10.6%	12.7%	10.9%	10 - 12%	12 - 15%

$800+ Billion/y Global Business!

North America	**39.80%**
Europe	**30.60%**
Asia, Africa, Australia	**12.70%**
Japan	**11.20%**
Latin America	**5.70%**

Source: IMS Health Market Prognosis, March 2010

New Drug Development Costs

Annual Pharma Sector R&D ~$60 Billion

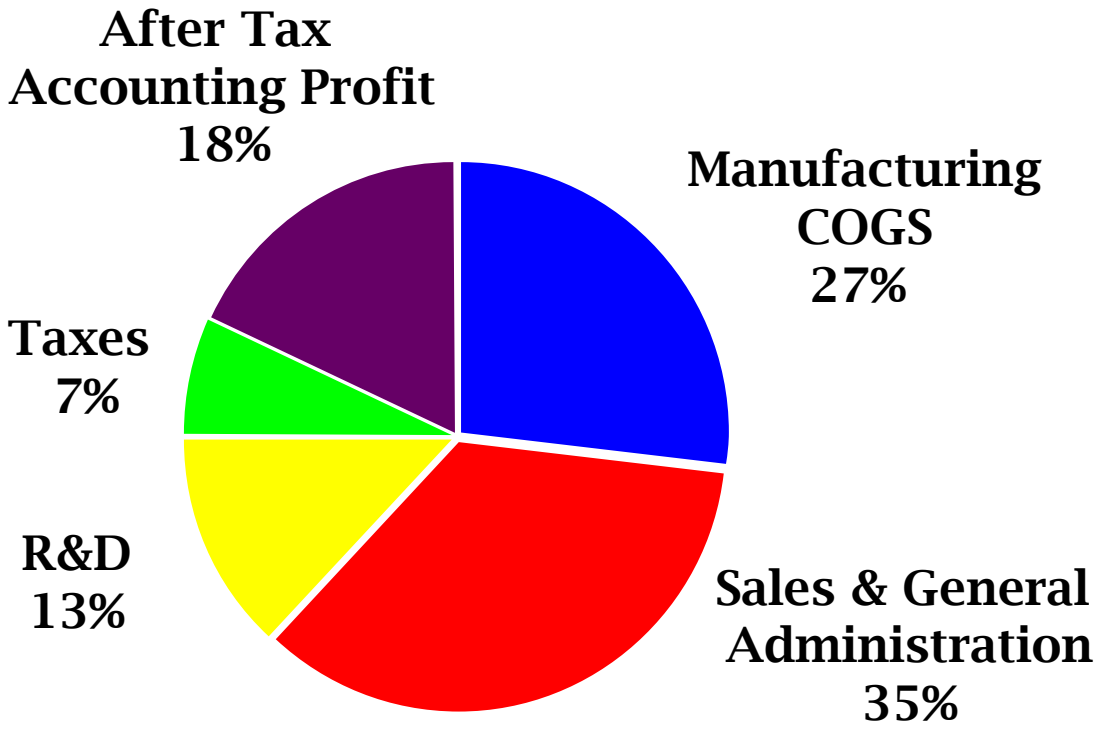
Total Cost of New Drug $0.8 Billion to $2 Billion

Cost Component Distribution	
Discovery	20- 25%
Safety & Toxicology	15–20%
Product Development API process design Product formulation & process design Clinical supply	30–35%
Clinical Trials (Phase I-III)	35-40%

*Suresh & Babu, J Pharm Innov, **3**, 175-187 (2008)*

Cost of Pharmaceuticals

Disposition of sales revenue of 8 largest research-based pharmaceutical manufacturers



U.S. pharmaceutical expenditures in 2009 ~ $320 B

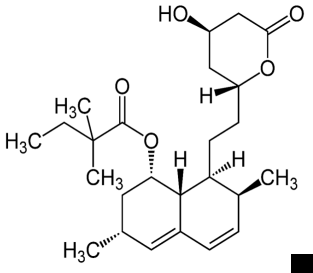
(*IMS Health and PMPRB Annual Report, 2010*)

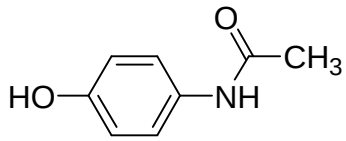
COGS (U.S) = ~ $90 B

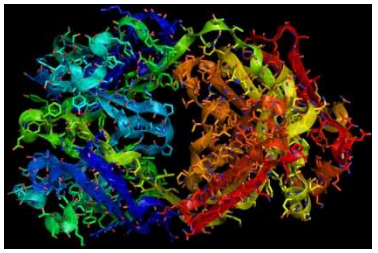
U.E. Reinhardt, Health Affairs, Page 136, September/October 2001

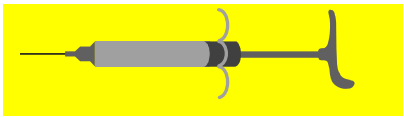
Pharmaceutical Development & Manufacturing Domains

- Active ingredient production
  - Small molecule synthesis
    - Organic chemical synthesis
  - Large molecule synthesis (bioprocesses)
    - Production via microorganisms or mammalian cells
- Drug Product Manufacture
  - Tablets, capsules, aerosols, inhalables, topicals, injectables
    - Solids processing steps
    - Sterile operations
    - Suspensions/emulsions
- Generally batch oriented processes

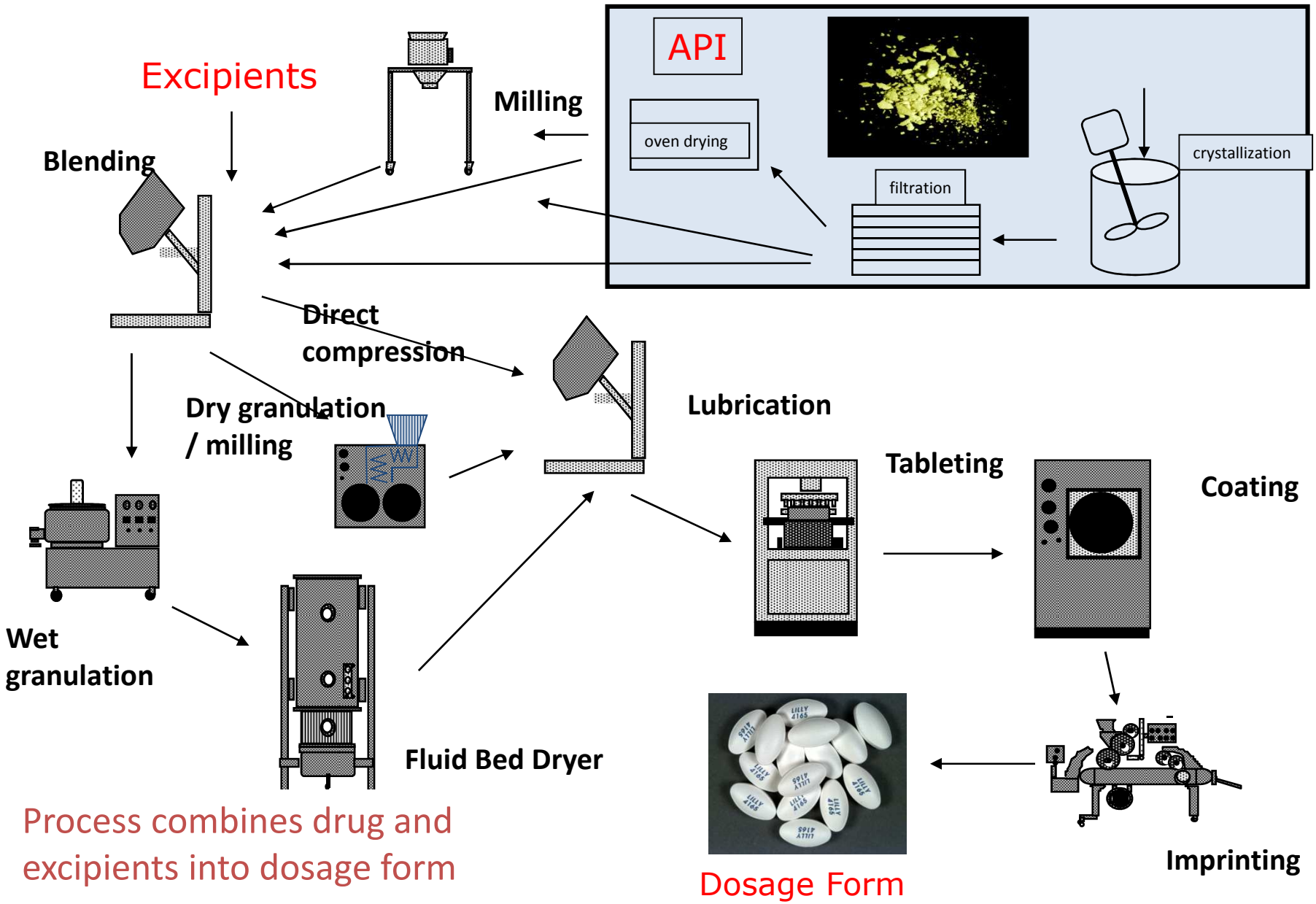








Solid Oral Drug Product Manufacture



Changes in Regulatory Approach

- **Traditional Approach**: Tightly Regulated Product & Process Design & Manufacture
  - FDA approval requires documentation of product critical attributes & specification of manufacturing details (recipe)
  - Formulation & recipe are rigidly maintained during manufacture
  - Changes in formulation, recipe and even equipment types require FDA approval
  - Quality is assured by final product testing prior to batch release
- **New Proposed Approach**: Quality by Design
  - Developer documents Design Space for new product
  - Changes within design space require no prior approval
  - QbD using on-line process measurement of Critical Quality Attributes of intermediate & final materials allow real time release of product batches

PSE Opportunity Areas

- Product & Process Design
  - API process synthesis
  - Product formulation & process design
  - Design space methodology
- Process Operations
  - Real Time Process Management
    - Integrated Batch Operations
    - Continuous processing
- Enterprise –wide Decisions problems
  - Product Development Pipeline Management

    (Varma et al CACE 2008; Zapata et al CACE 2008)
  - Clinical Trials Supply Chain Management (496a)
  - Commercial Product Supply Chain Management

    (Lainez et al , CACE 2009,2010)

Design Space

The established range of process parameters that has been demonstrated to provide assurance of quality….

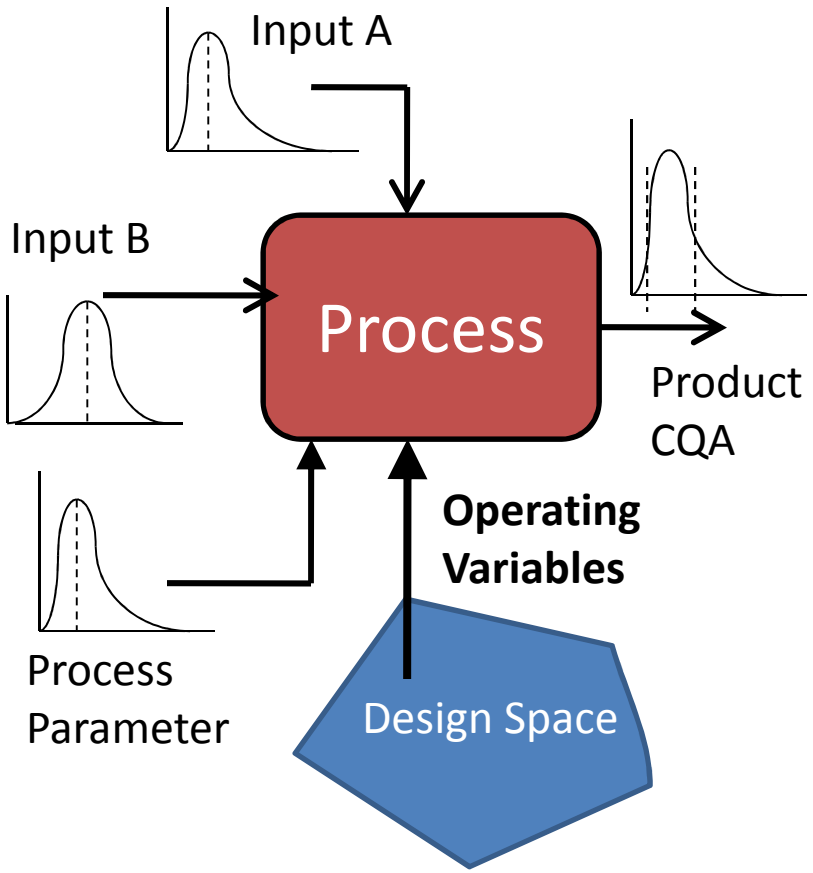
Quantitative definition

For selected set of equipment design parameters

- Probability distributions of feed material properties
- Probability distributions of internal process variables
- Required probability of meeting product critical quality attributes

Design space:

Multidimensional region defined by ranges of operating variables containing all variable adjustments necessary to achieve desired probability of meeting product CQA

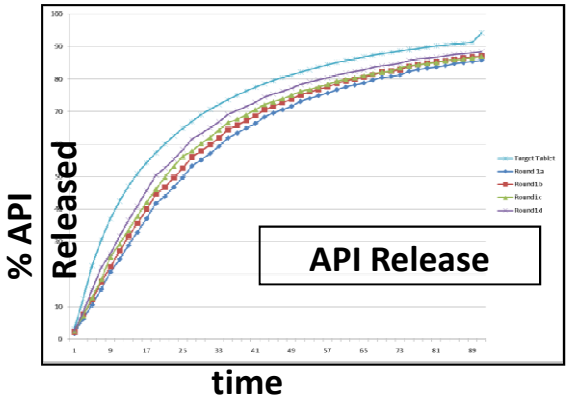


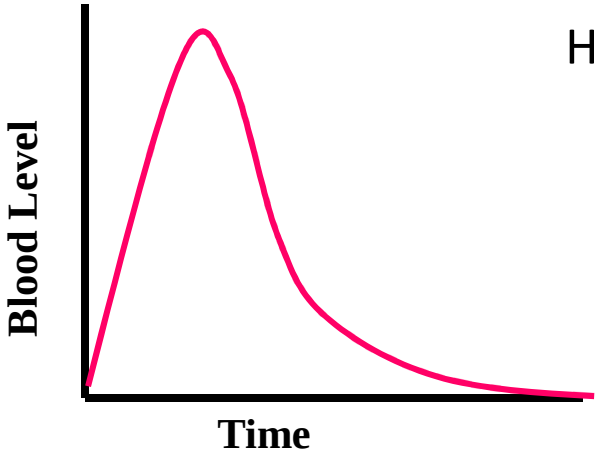
Design Challenges

- Predictive models of unit operations
- Understanding of physical and chemical changes: desired & undesired
  - E.g., Formation of degradents, polymorphs
- Process Analytical Technology
  - On-line sensing (composition, particle size distributions, powder properties)
  - Control strategies (control system design, expected range of manipulated variables)
- Quantification of uncertainties
- Quantification of risk of product failure to meet CQA for specific design space

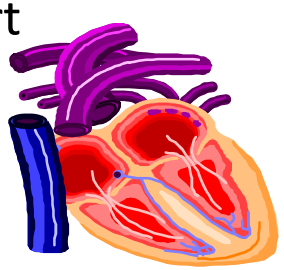
See Topical Conference I: *Comprehensive Quality by Design in Pharmaceutical Development & Manufacture*

Drug Product & Process Design
Impact on Product Performance





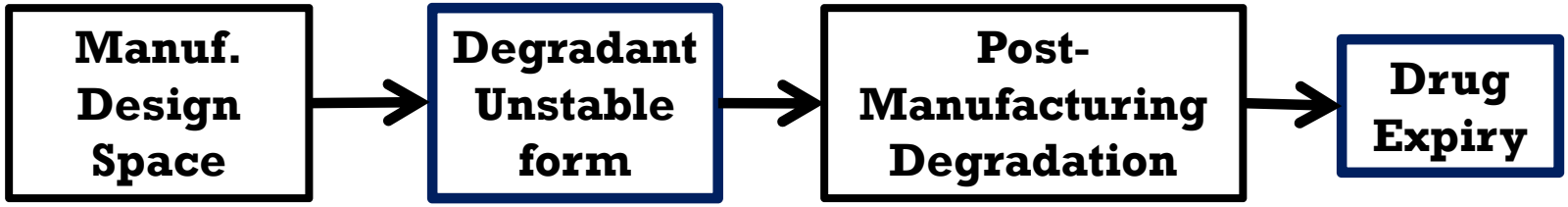
Heart

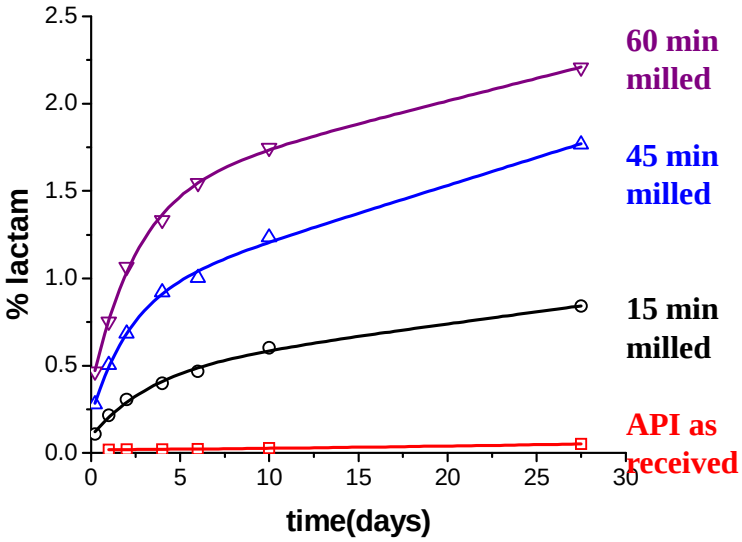


Pharmacologic Effect

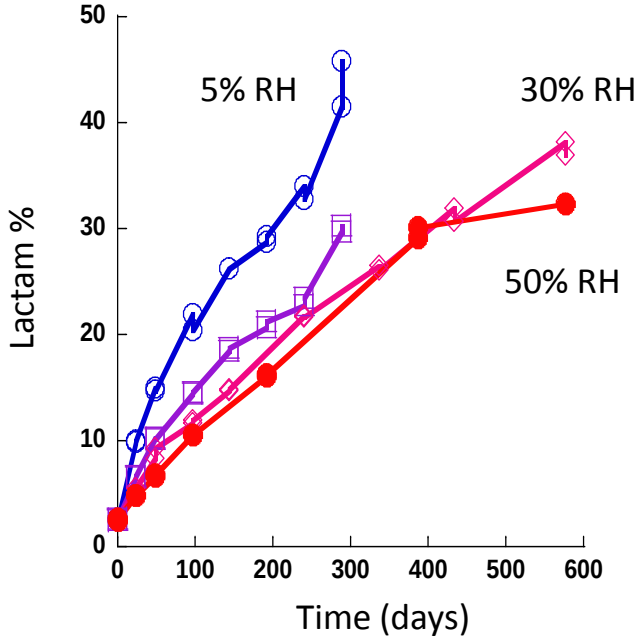
Disintegration Dissolution	Drug in Circulation	Drug in Tissues
Particle size distr	Particle size distribution	Permeability
Disintegrants	Permeability	Dosage level
Solubility	Solubility	Metabolism
Coating	Coating	Excretion
Tablet hardness	Dosage level	Stability
Tablet porosity	API form (salt, hydrate)	

Impact of Product Stability on Manufacturing Design Space





Degradent formation depends on processing stresses



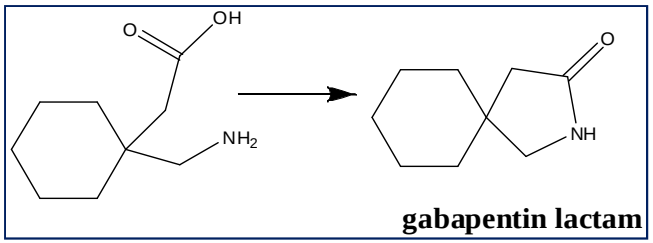
Degradent level depends on stress history & storage conditions

NIPTE The National Institute for Pharmaceutical Technology and Education

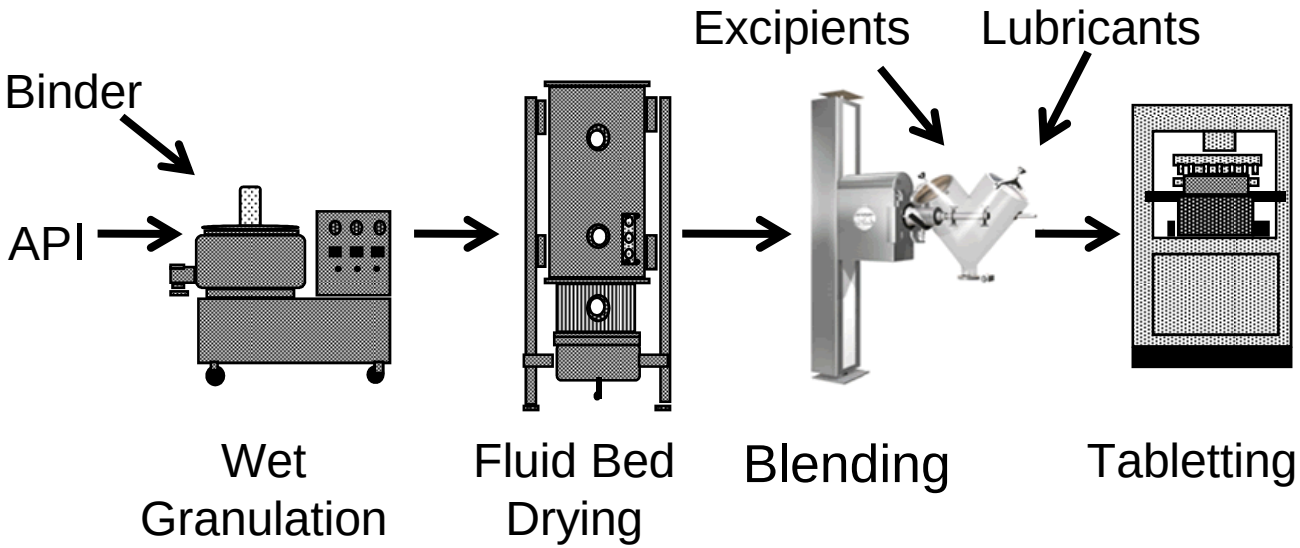
Improving quality and lowering costs of pharmaceuticals

June 2011 FDA/NIPTE workshop

QbD Case study: Gabapentin



API subject to degradation
High dosage formulation (70%): HPC, MCC, Crospovidone, Mg Stearate



+ PAT (on-line Sensing)

Goal: Demonstrate Approach to Model-based Design Space Development under scale-up and stability constraints

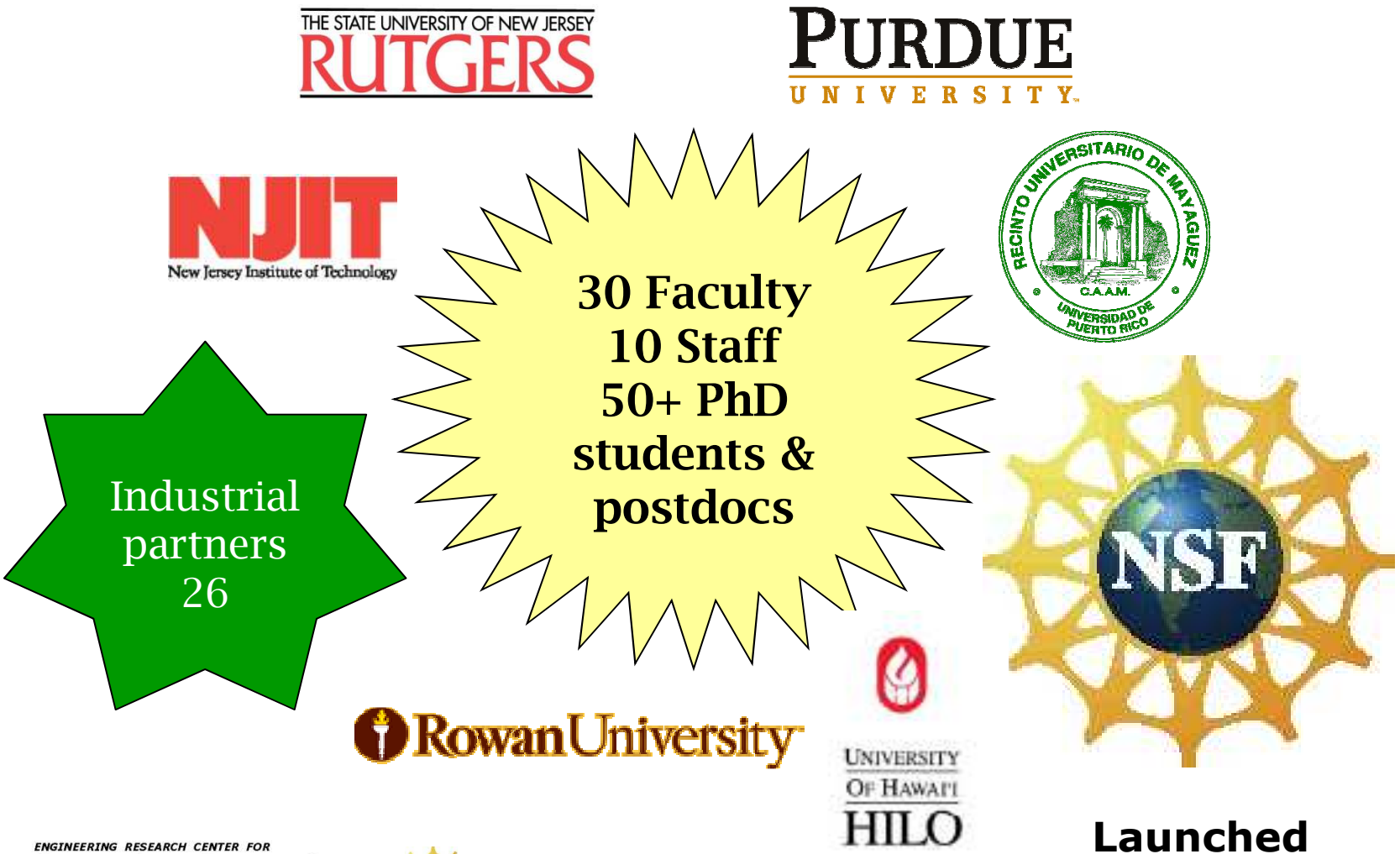
Outline

- Pharmaceutical Industry
  - Economics
  - Regulatory changes
- PSE Opportunity areas
  - Product/process design

    NIPTE case study
  - ***Process Operations***

    ERC SOPS
- Summary

NSF ERC for Structured Organic Particulate Systems

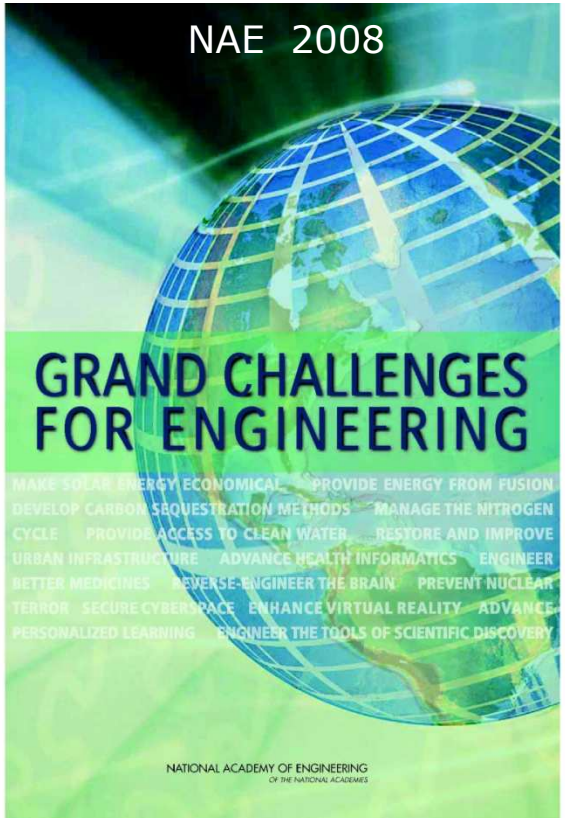


Launched July 2006

ENGINEERING RESEARCH CENTER FOR
STRUCTURED ORGANIC PARTICULATE SYSTEMS
RUTGERS UNIVERSITY
PURDUE UNIVERSITY
NEW JERSEY INSTITUTE OF TECHNOLOGY
UNIVERSITY OF PUERTO RICO AT MAYAGÜEZ

C-SOPS Objectives

- Develop scientific foundation for optimal design of structured organic composite products for pharmaceutical, nutraceutical & agrochemical industries
- Develop science and engineering methods for designing, scaling, optimizing and controlling relevant manufacturing processes.
- Demonstrate developed fundamentals on novel test beds.
- Establish effective educational and technology transfer vehicles.



Engineer better medicines !

Personalized medicine

Thrust D: Integrated Systems Science

Model predictive design and operation of integrated particulate processes

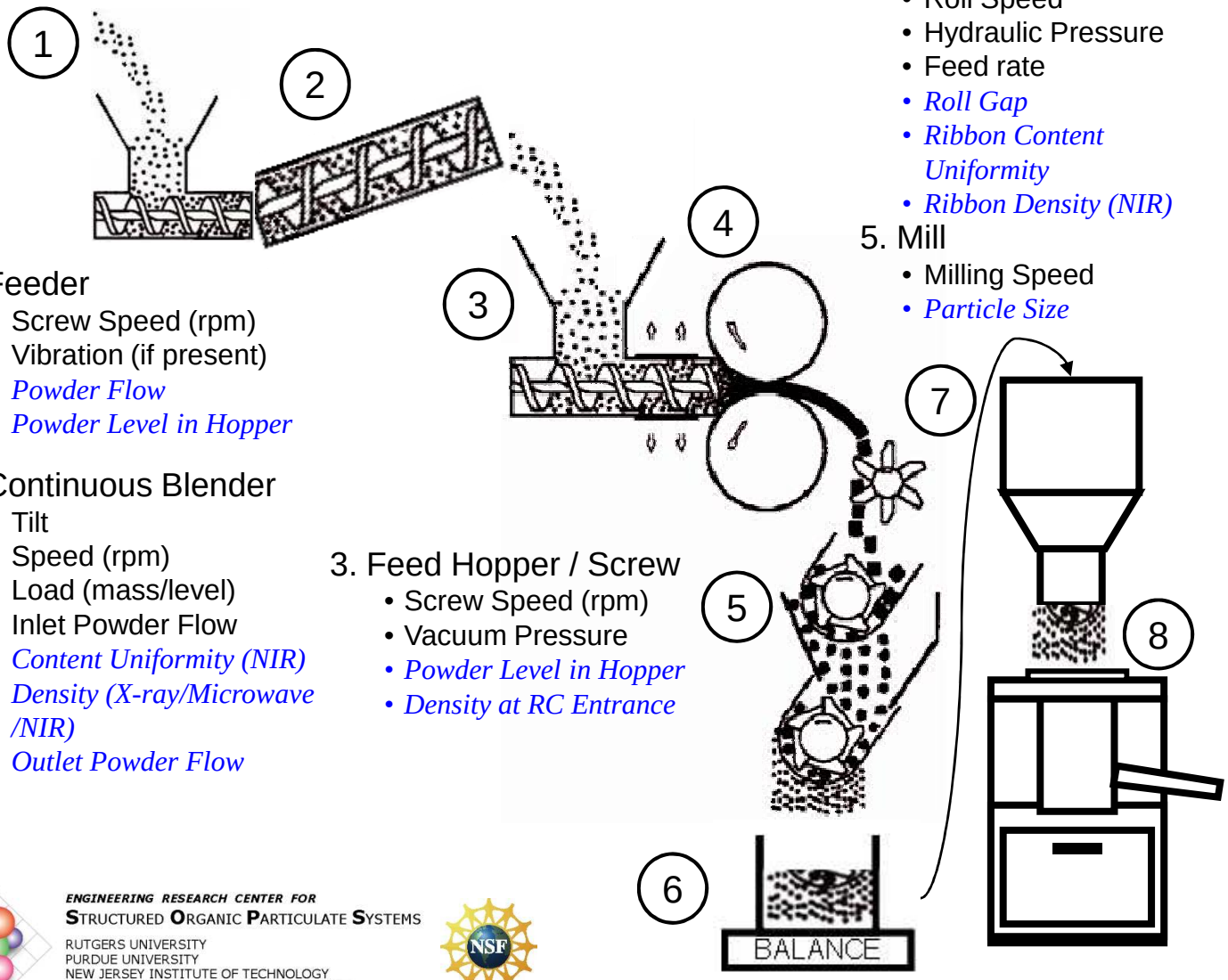
Thrust Leader: Venkat Venkatasubramanian (PU)

	Thrust D projects
D-1	Sensing Methodologies
D-2	Hardware and Software Integration
D-3	Ontological Informatics Infrastructure
D-4	Real-time Process Management
D-5	Integrated Design and Optimization

Demonstration on Test Beds

Data, Information, Models

Continuous Granulation Line



1. Feeder
   - Screw Speed (rpm)
   - Vibration (if present)
   - *Powder Flow*
   - *Powder Level in Hopper*

2. Continuous Blender
   - Tilt
   - Speed (rpm)
   - Load (mass/level)
   - Inlet Powder Flow
   - *Content Uniformity (NIR)*
   - *Density (X-ray/Microwave /NIR)*
   - *Outlet Powder Flow*

3. Feed Hopper / Screw
   - Screw Speed (rpm)
   - Vacuum Pressure
   - *Powder Level in Hopper*
   - *Density at RC Entrance*

4. Roll Compactor
   - Roll Speed
   - Hydraulic Pressure
   - Feed rate
   - *Roll Gap*
   - *Ribbon Content Uniformity*
   - *Ribbon Density (NIR)*

5. Mill
   - Milling Speed
   - *Particle Size*

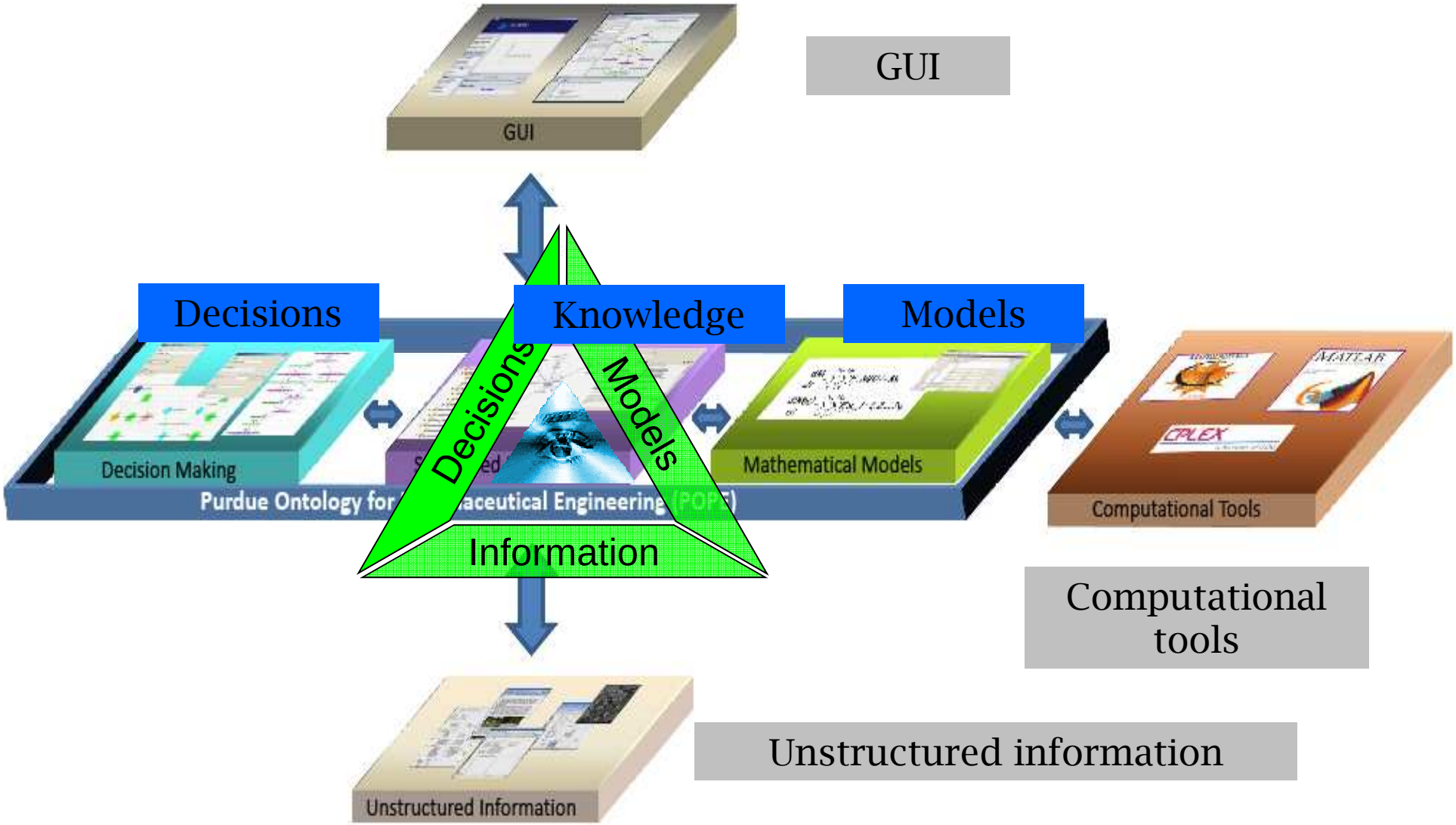
6. Transfer Receptacle
   - *Monitor mass over time*

7. Pneumatic Transfer

8. Tablet Press
   - Fill weight
   - Pressure
   - RPM
   - Feed Frame RPM
   - Feed Frame Blade Speed
   - Punch Distance
   - Inlet Powder Flow
   - *Content Uniformity*
   - *Density (NIR)*
   - *Tablet Weight*
   - *Tablet Density*
   - *Feed Frame Outlet Flow*
   - *Powder Density*
   - *Powder Segregation*

9. Tablets
   - *Weight*
   - *Tensile strength*
   - *Density*

Information Ontology Architecture

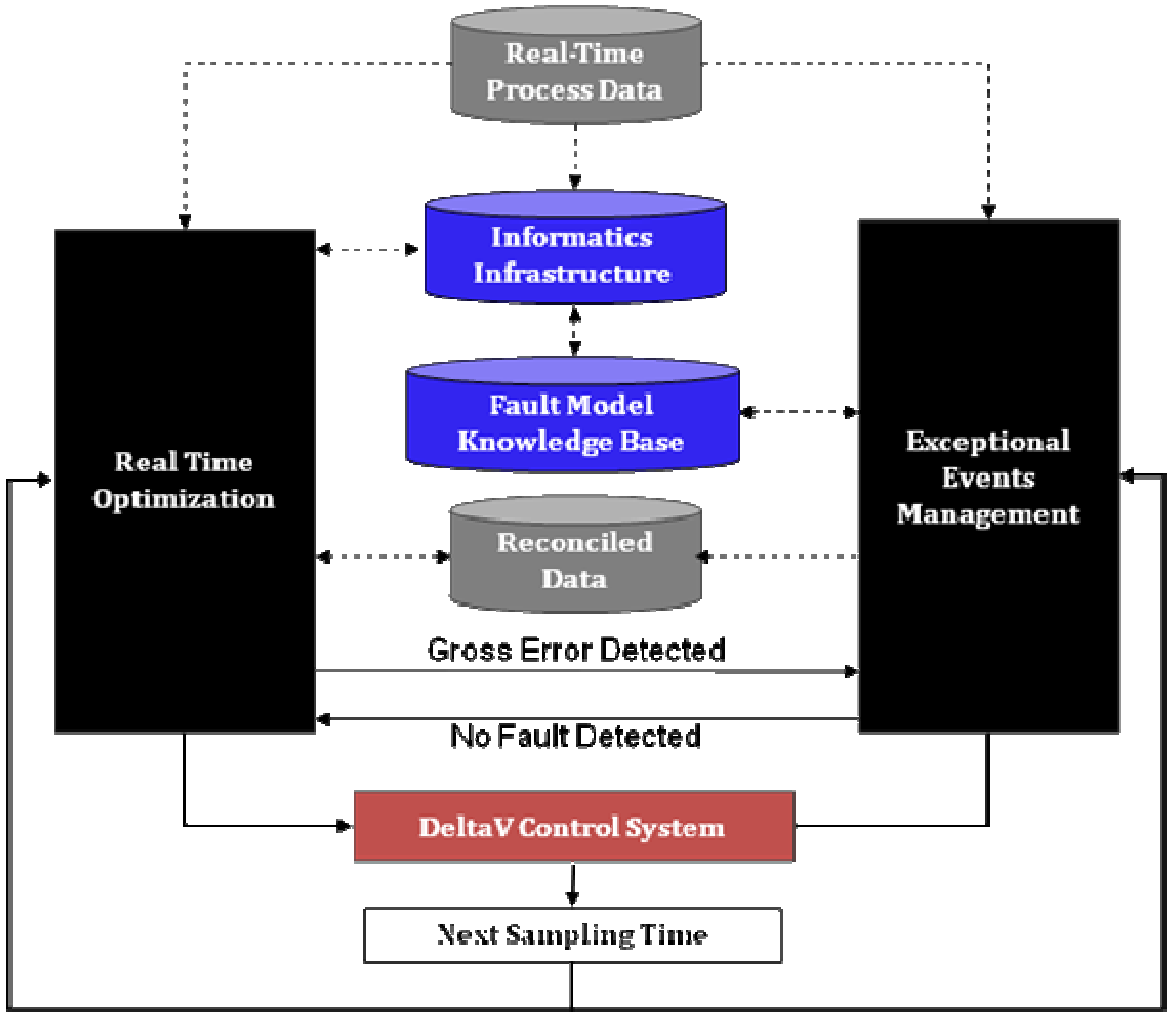


Computational tools

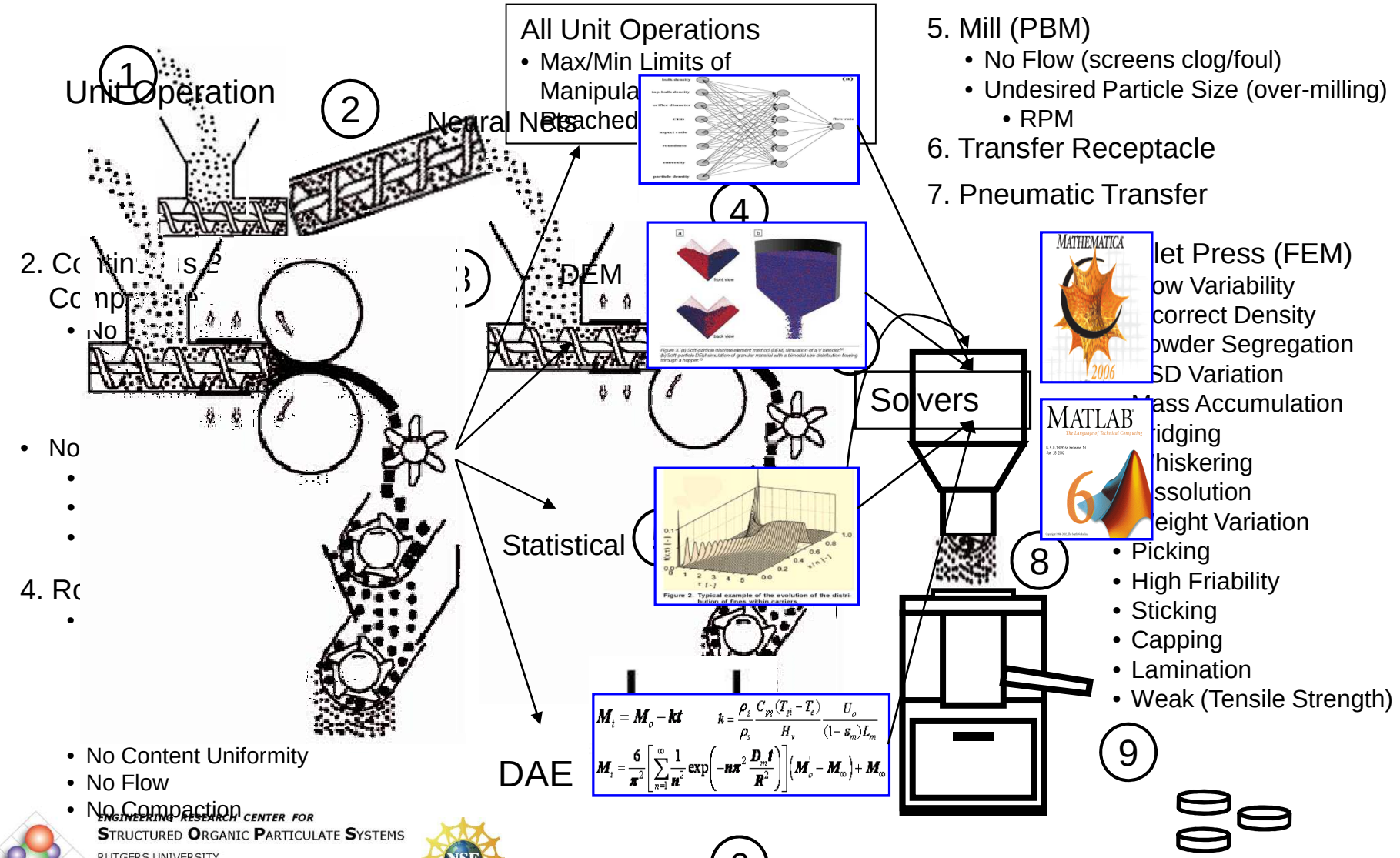
Unstructured information

Venkatasubramanian AICHE J 2009

Real Time Process Management

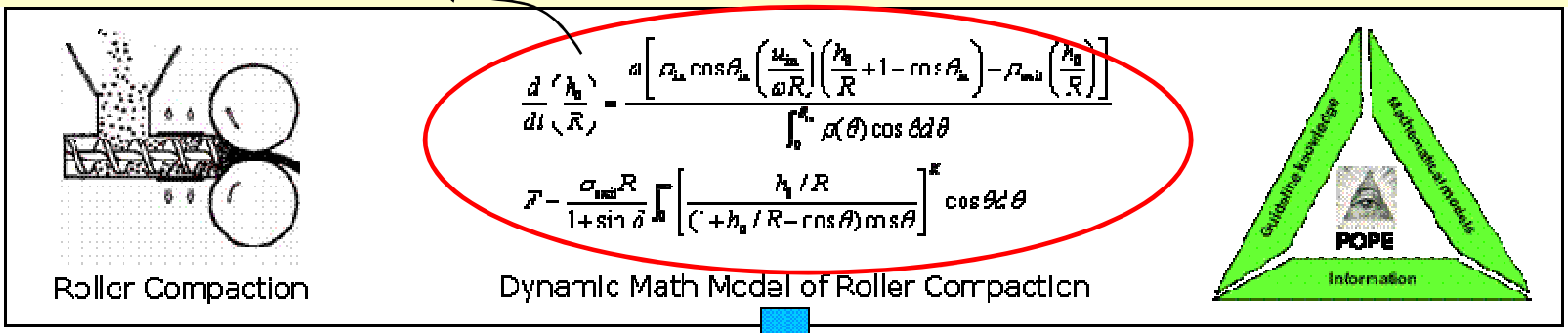


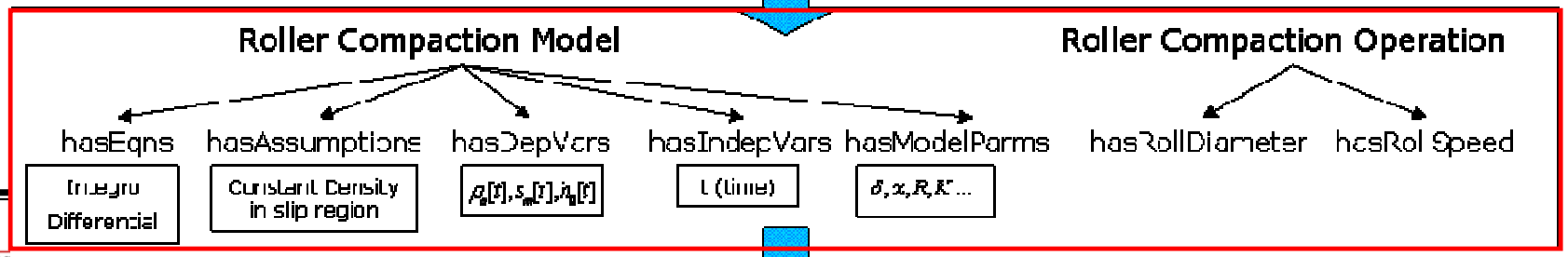
Process Faults & Disturbances



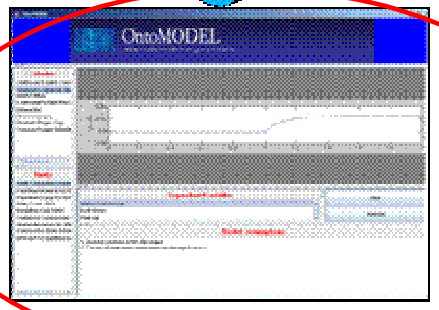
Roller Compaction Model Management in POPE

Johanson's rolling model with time variation of roll gap included





Model and Operation Ontology

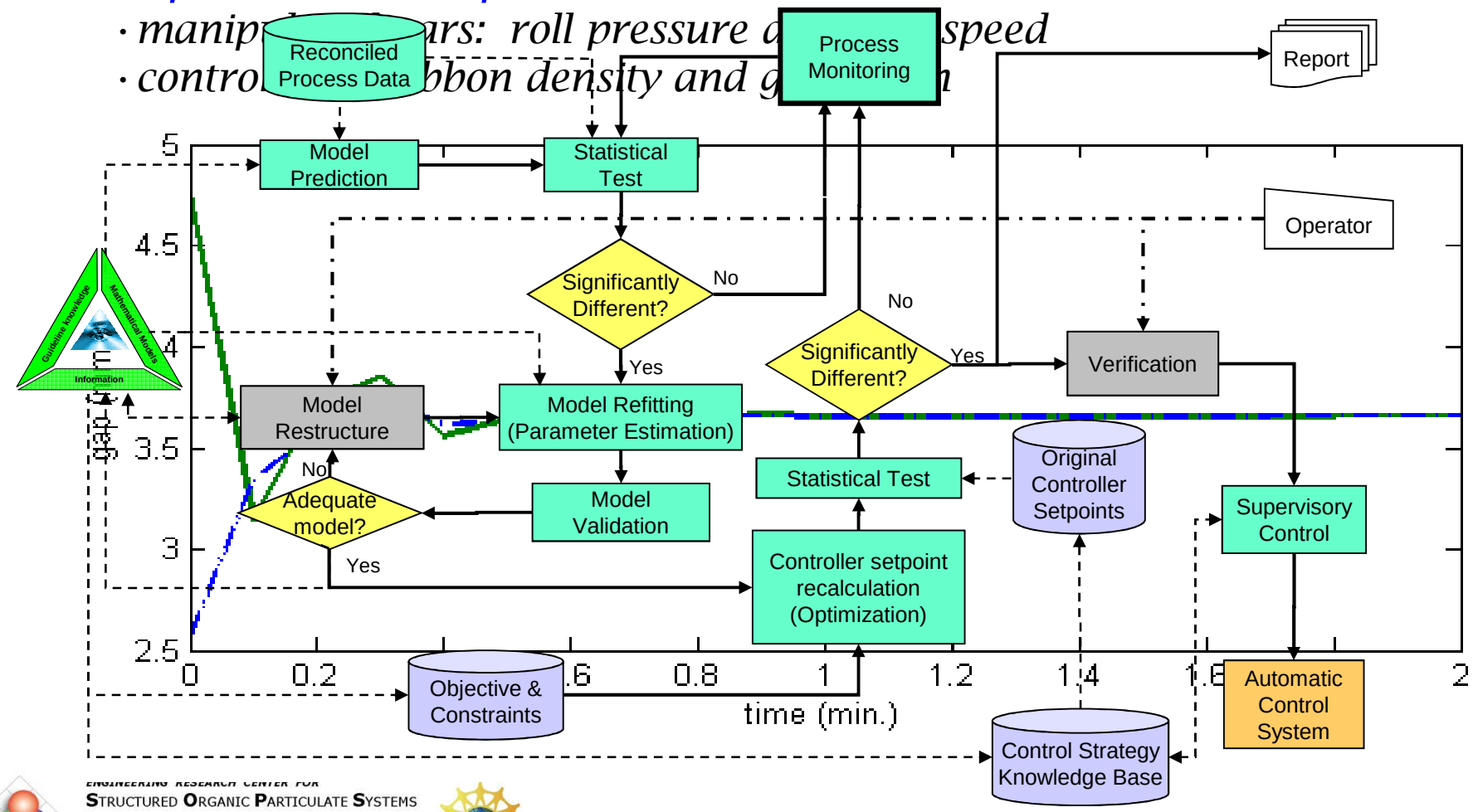


Interface

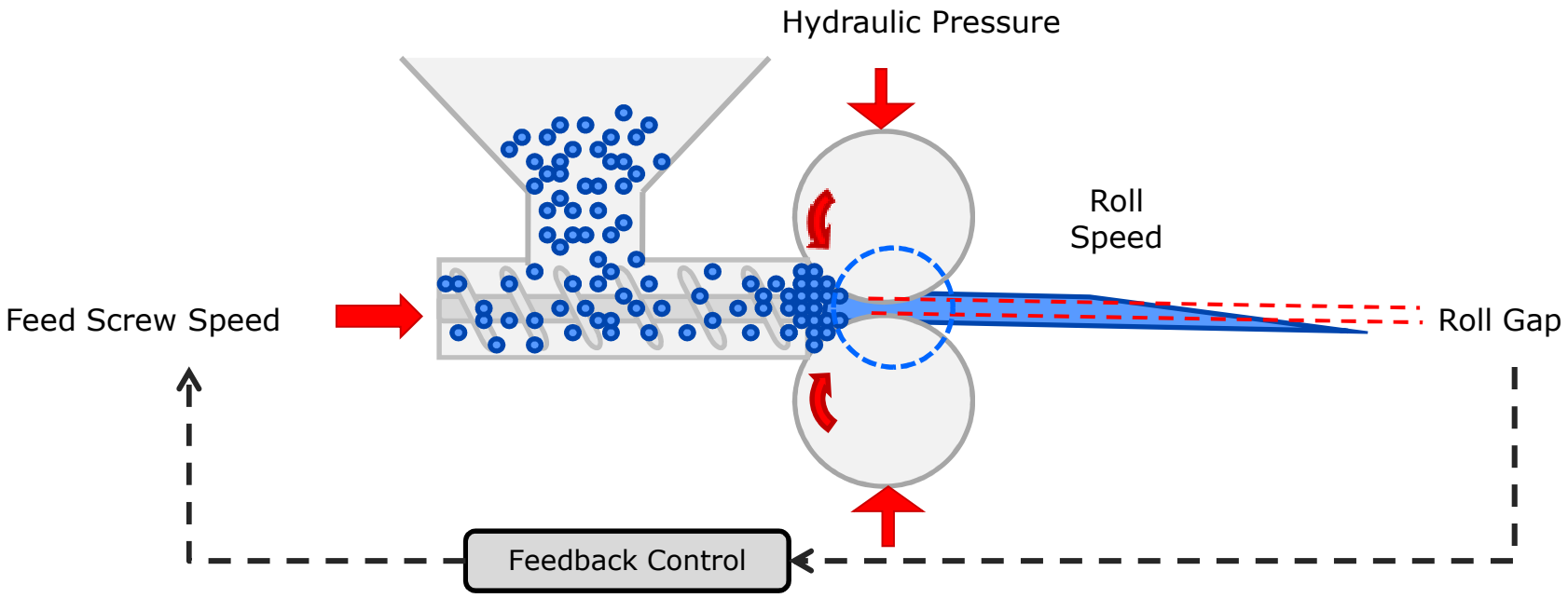
JAVA Engine and GUI

Model Predictive Control

- *MPC Architecture for Test Bed 1*
- *MPC for Roller Compactor*
  - *manip[illegible]ars: roll pressure d[illegible]speed*
  - *contro[illegible]bbon density and g[illegible]n*



EEM: Alexanderwerk Roller Compactor



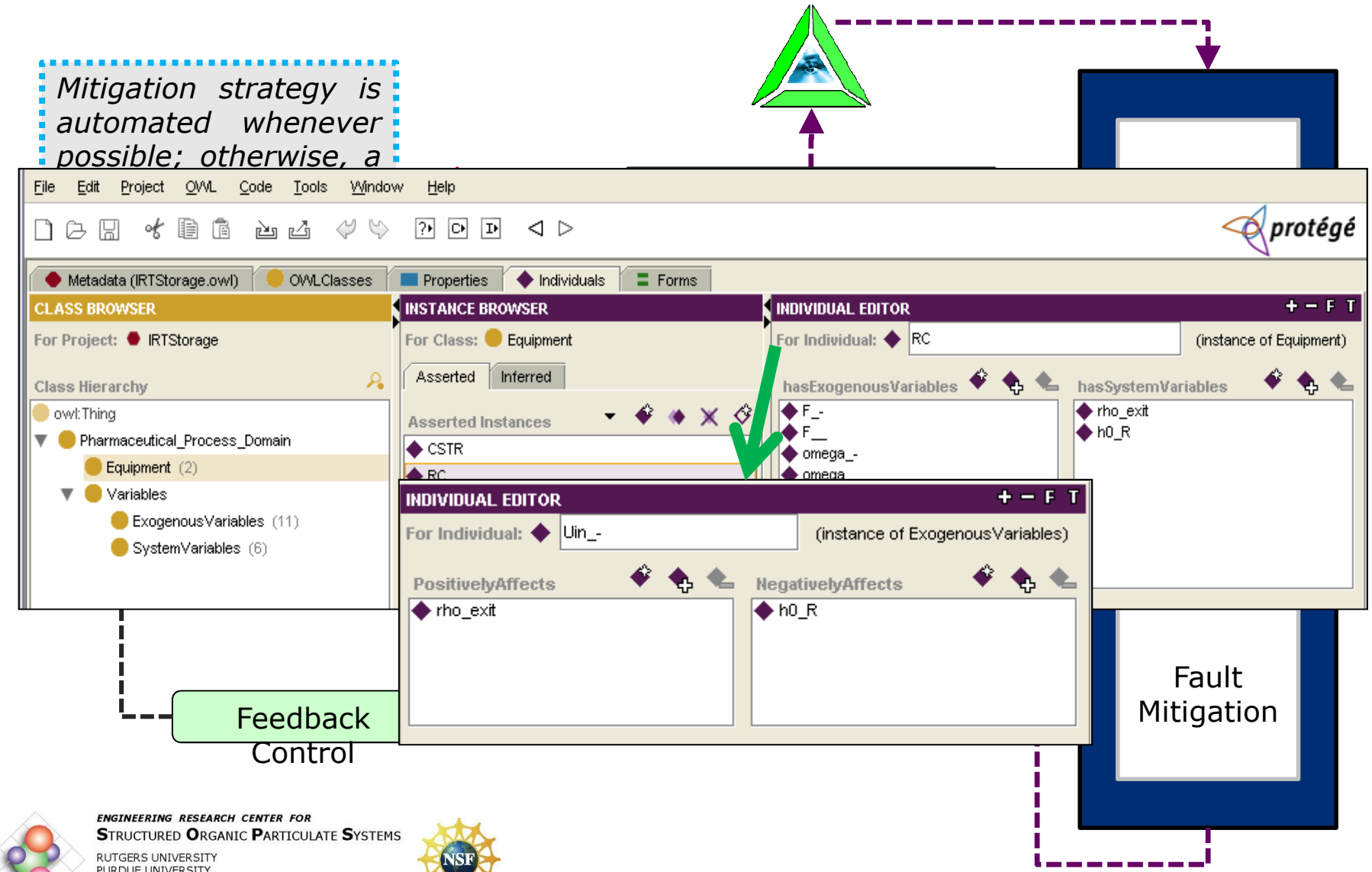
Event: *No powder entering roll region*

Causes: *No powder in hopper*

Blockage in hopper

Jam in nip region

Exceptional Events Management

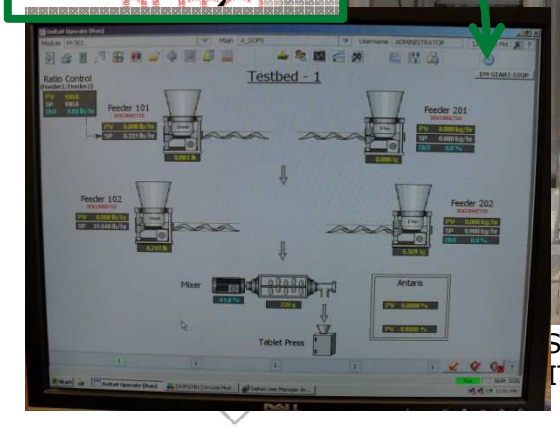


Feeders

Blender

Tablet Press

Multi-point NIR



Delta V Control System

Optical Tablet thickness Measurement

AIChE 2010 Mtg Presentations

- **383e,** Giridhar et at, “Facilitating Continuous Production in the Pharma Industry with Real-Time Process Management and Ontological Informatics”
- **444b**, Hamdan et al,” Exceptional Events Management for Continuous Pharmaceutical Manufacturing: Feeder, Blender, & Roller Compactor in Series”
- **456b**, Lainez et al,” A Cyber-Infrastructure for Research Collaboration and Knowledge Sharing in the Pharmaceutical Domain: The pharmaHUB “
- **456d**, Joglekar et al,” TOPS: Ontological Informatics in Pharmaceutical Manufacturing “
- **596b**, Giridhar et al,” Continuous Production in Pharmaceutical Manufacturing: The Informatics View “
- **697f,** Luque et al, “Modelling and Informatics Challenges IN Film-BASED Drug Formulations and Manufacture”
- **444a,** Kyonov et al, “QbD of Continuous Pharmaceutical Tablet Manufacturing” (Rutgers)
- Several more ……

Summary

- Changes in business environment have opened exiting opportunities for development and application of PSE methodology.
- Product /process design challenges: linking input material properties & manufacturing conditions to both product shelf life & therapeutic performance
- Key process operations challenges: predicting & optimizing performance of particulate and/or heterogeneous multicomponent systems
- Risk management is critical: opportunity for exploitation of quantitative Bayesian based estimation and analysis methods