Research collaboration and knowledge sharing in the pharmaceutical domain

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HUB BUB 2011

PURDUE UNIVERSITY

Outline

1. pharmaHUB mission
2. Background
3. Sample of available tools
   - Cyber-enabled product development
   - Excipients knowledge base
   - Powder flow database
   - Die-fill
   - Dissolution
4. Sample of available courses
5. Final remarks

PharmaHUB mission

- Resource for collaboration and sharing:
  - Science and engineering research on innovations in pharmaceutical manufacturing
  - Information, knowledge, modeling & decision support tools for drug product & process design
  - Educational materials & experiences for education and training of pharmaceutical engineers & scientists
- Sharing of R&D and educational output of national projects
  - NSF ERC Structured Organic Particulate Systems
  - National Institute for Pharmaceutical Technology & Education (FDA support)

pharmaHUB background

- NSF EVO seed project: Oct 2007-09
  - Build prototype based on partnership with HUBzero team
  - Share with ERC CSOP & NIPTE community
  - Build community

Total Users	% US	% Asia	% Europe	% Other
13,253	20	48	21	11

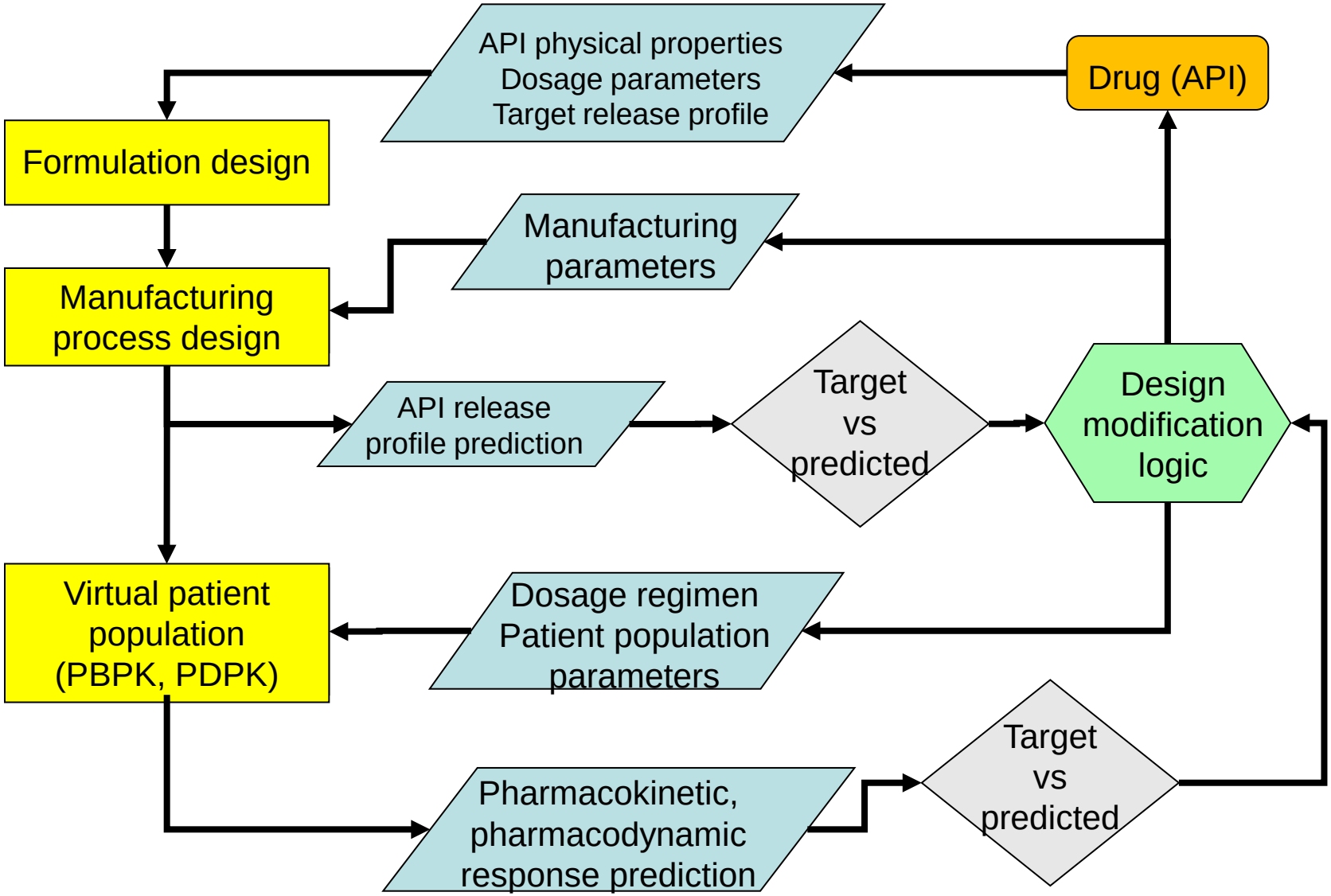
Organizations	% Edu	% Ind	% Gov	% Other
1,061	88	8	4	0

  - Develop design & plan for “production” version
- NSF CDI Type II grant: Oct 2009-2013
  - Implement “production” version with expanded content
  - Address complete product development cycle
  - Implement additional Hub functionalities , e.g., work flow

Cyber-enabled Product Development

- Expansion of HUB functionalities
  - Work flow execution & management
  - Improved data visualization
- Unit operations library expansion
  - E.g.,tableting, roller compaction, blending
- Product performance simulations
  - 2D and 3D Tablet Dissolution simulation
- Virtual patient population
  - Bayesian approach to Pharmacokinetic & Pharmacodynamic models
  - Case studies involving 5 models drugs

Cyber-enabled product development framework



Excipients Knowledge Base

- Establish an information system used to maintain values of fundamental pharmaceutical excipient material properties, and which contains models, best practices, and methods for using this data in the systematic design of pharmaceutical products and processes.

Pharmaceutical Excipients

- Non-pharmacologically active portion of the dosage form
  - used in virtually all drug products.
  - various functional purposes depending on formulation and manufacturing
- Chemical and physical properties are critical to manufacturing, stability, and performance of drug products
- Often derived from natural products, synthetically modified natural products, or completely synthetic
  - available from a multitude of sources
  - properties may vary from lot-to-lot, vendor-to-vendor, and even within a lot
  - property variations are often result in production problems and product failures

Different Grades from Different Manufacturers

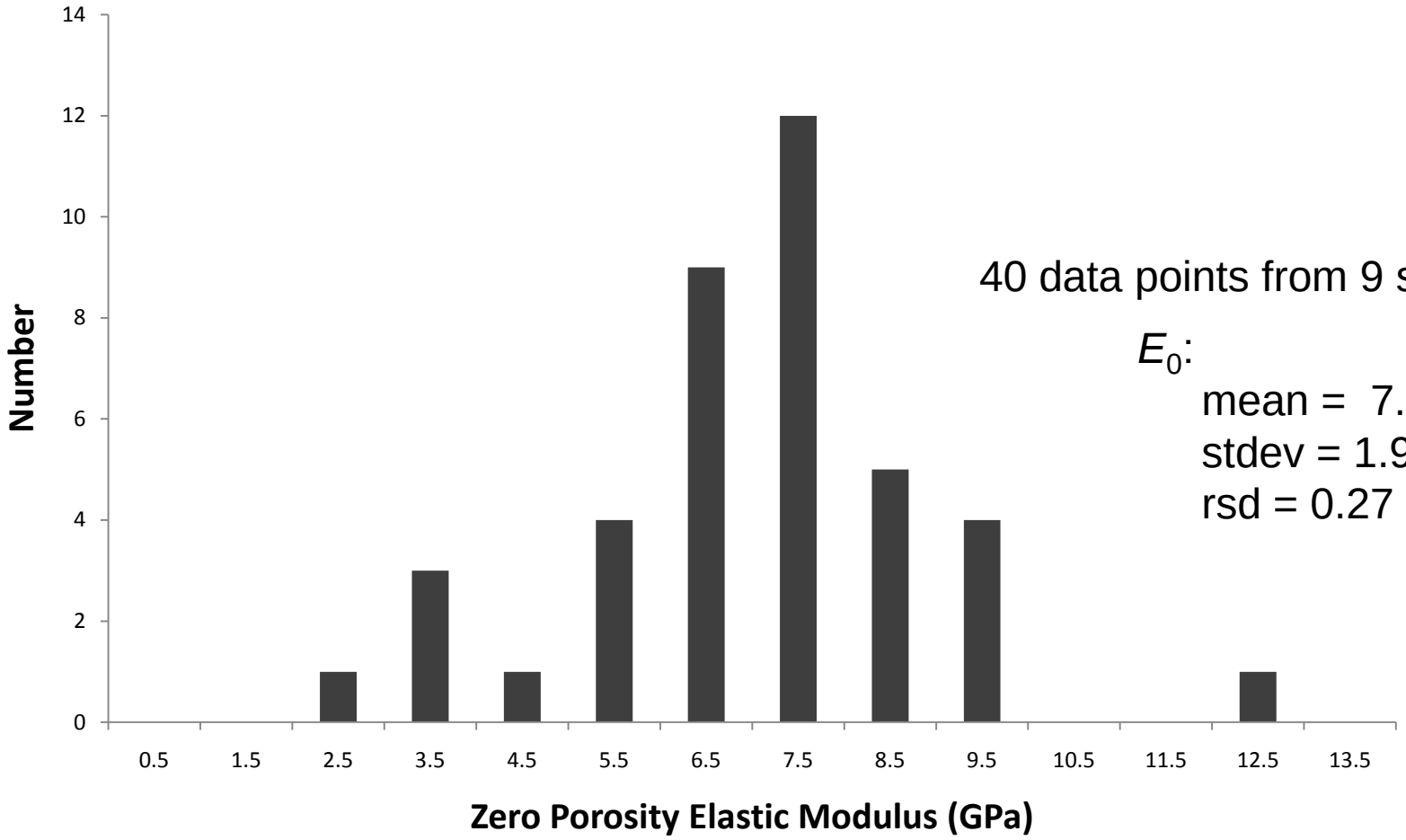
FMC = FMC BIOPOLYMERS

JRS = J Rettenmaier & Söhne GmbH and Co.KG

AKC = Asahi Kasei Corporation

Manufactures	Grades	Particle Size, µm	Moisture, %	Loose Bulk Density, g/cc
FMC	Avicel PH101	50	3.0-5.0	0.26-0.31
JRS	Vivapur 101	65	--	0.26-0.31
	Emcocel 50M			0.25-0.37
AKC	PH-101	50	2.0-6.0	0.22
	UF-711			0.21
	KG-802			0.12
	KG-1000			0.29
FMC	Avicel PH-102	100	3.0-5.0	0.28-0.33
JRS	Vivapur 102	100	--	0.28-0.33
	Emcocel 90M			0.25-0.37
AKC	PH-102	90	2.0-6.0	0.30

Property Variation



40 data points from 9 sources

E_0:

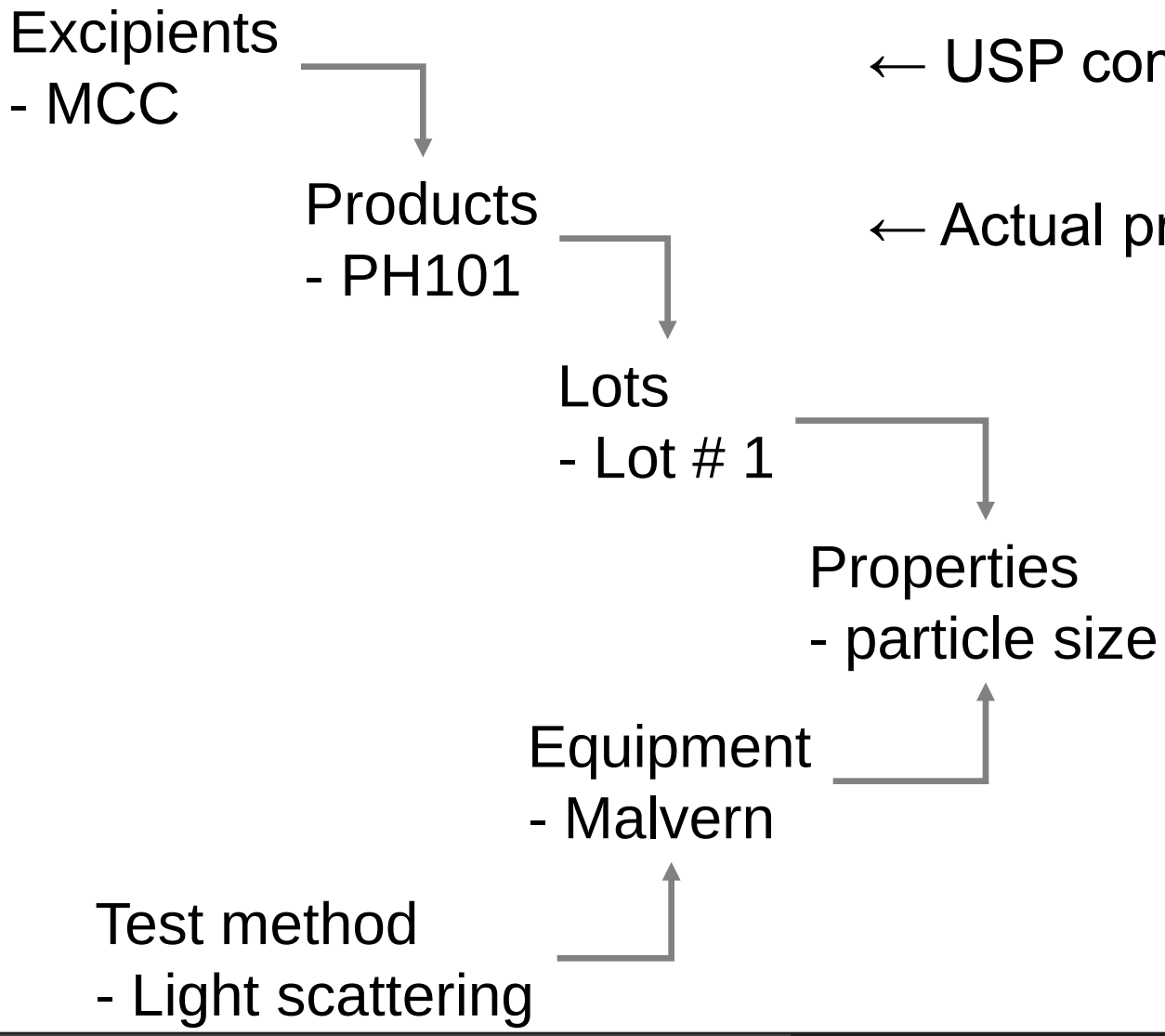
mean = 7.1 GPa

stdev = 1.9 GPa

rsd = 0.27

Variation due to natural variation, testing method, other? Need standardized, trustworthy source of data.

Database Structure



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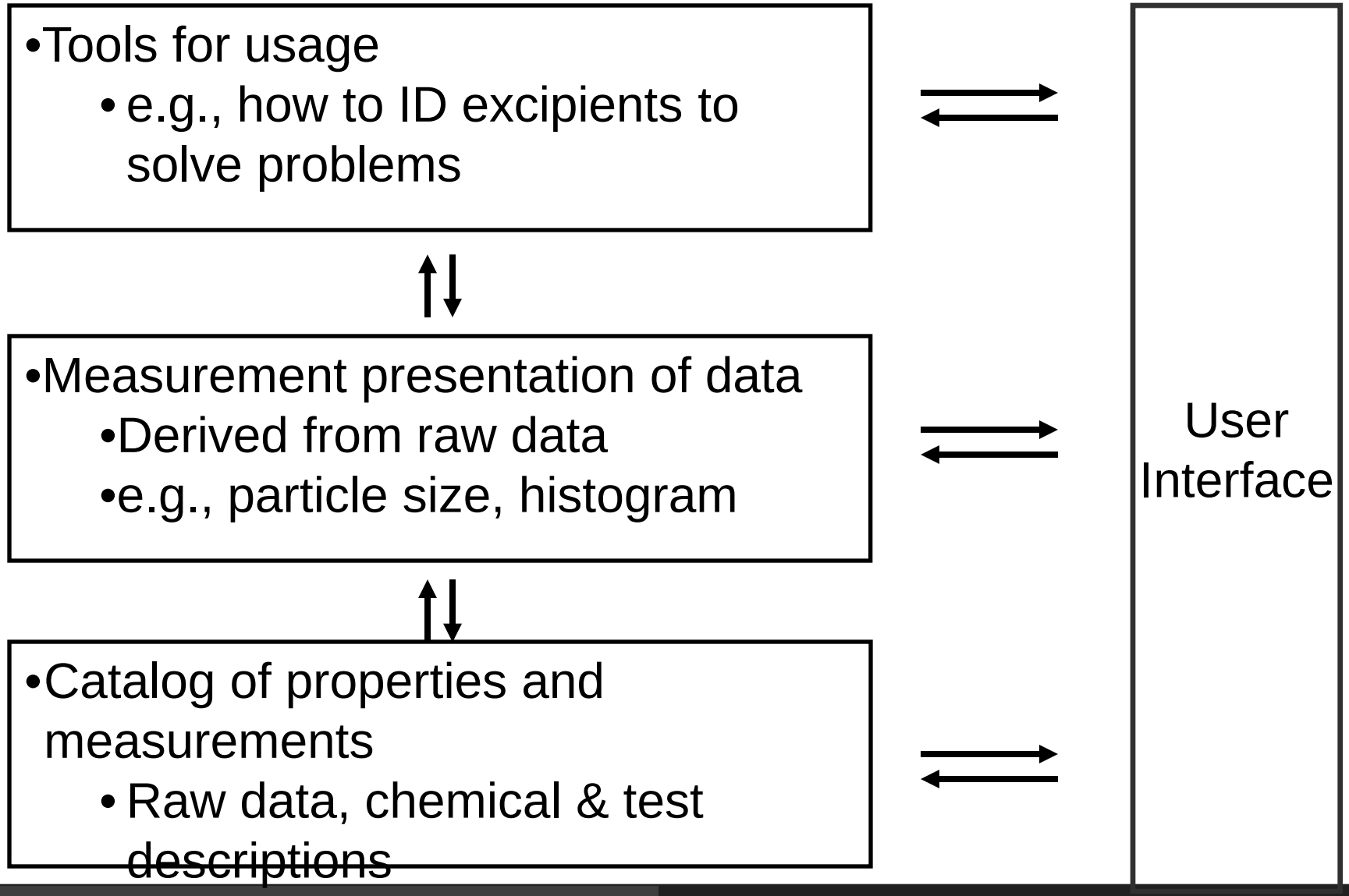
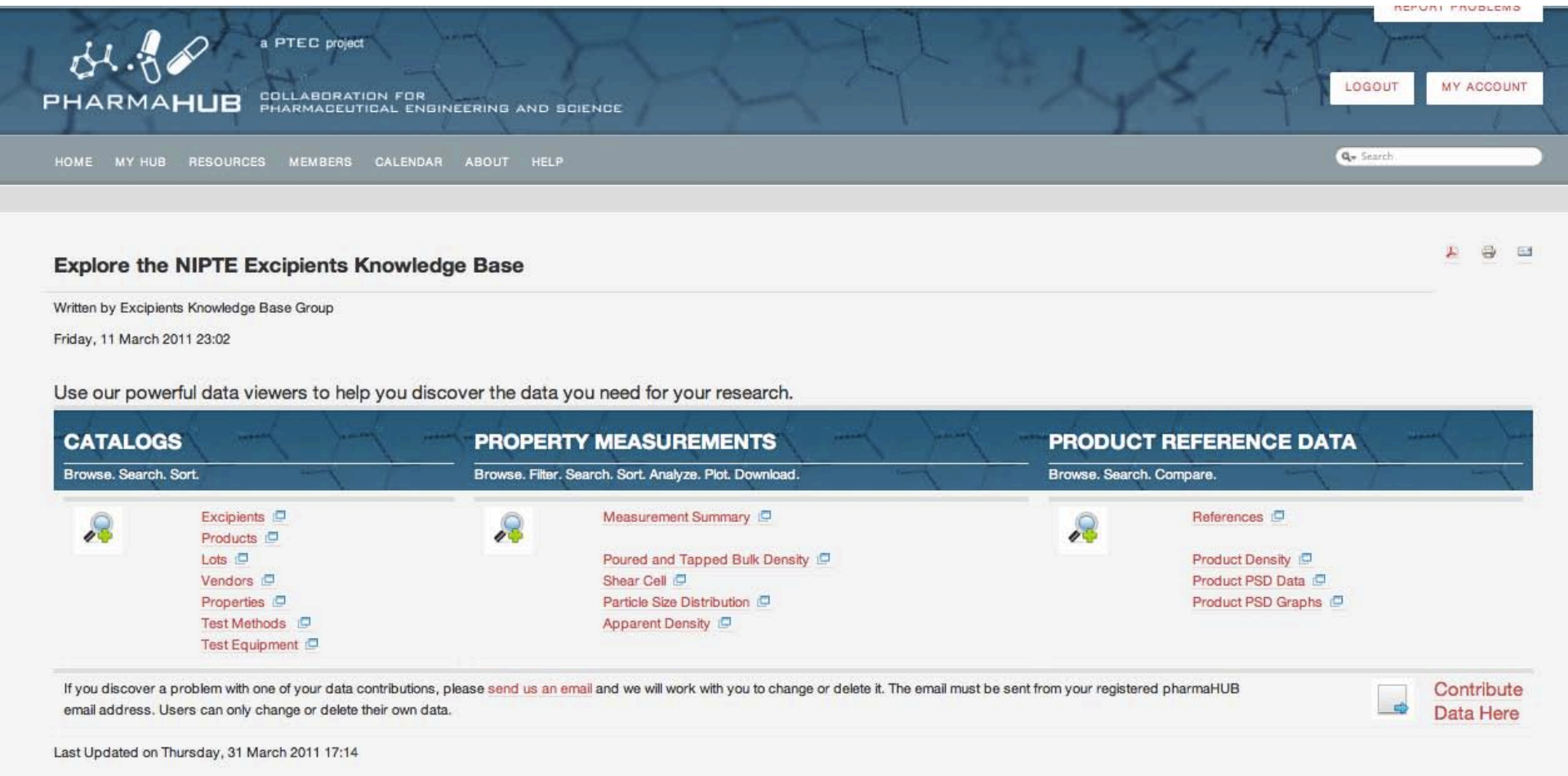


Portal


a PTEC project
PHARMAHUB
COLLABORATION FOR PHARMACEUTICAL ENGINEERING AND SCIENCE
LOGOUT
MY ACCOUNT
HOME
MY HUB
RESOURCES
MEMBERS
CALENDAR
ABOUT
HELP
Search
Explore the NIPTE Excipients Knowledge Base
Written by Excipients Knowledge Base Group
Friday, 11 March 2011 23:02
Use our powerful data viewers to help you discover the data you need for your research.
CATALOGS
Browse. Search. Sort.
Excipients
Products
Lots
Vendors
Properties
Test Methods
Test Equipment
PROPERTY MEASUREMENTS
Browse. Filter. Search. Sort. Analyze. Plot. Download.
Measurement Summary
Poured and Tapped Bulk Density
Shear Cell
Particle Size Distribution
Apparent Density
PRODUCT REFERENCE DATA
Browse. Search. Compare.
References
Product Density
Product PSD Data
Product PSD Graphs
If you discover a problem with one of your data contributions, please send us an email and we will work with you to change or delete it. The email must be sent from your registered pharmaHUB email address. Users can only change or delete their own data.
Contribute Data Here
Last Updated on Thursday, 31 March 2011 17:14

Property Retrieval

ze Distribution Measurements | Return to Excipients Knowledge Base

First Previous 1 2 Next Last

ct	Lot Number	Frequency Distribution	Cumulative Distribution	Distribution Type	x10 [µm]	x50 [µm]	x90 [µm]	Sauter Mean Diameter [µm]	Mass Mean Diameter [µm]	Span	Humidi [%]
H101	P109821003	View Graph	View Graph	Volume/Mass	22.957	57.438	123.273	42.341	66.612	1.747	2
H101	P109821003	View Graph	View Graph	Volume/Mass	23.112	57.569	123.135	42.487	66.721	1.737	2
H101	P109821003	View Graph	View Graph	Volume/Mass	22.642	56.770	120.918	41.865	65.507	1.731	2
H102	P208819026	View Graph	View Graph	Volume/Mass	35.461	108.262	229.404	69.949	122.161	1.791	2
H101	P109821003	View Graph	View Graph	Volume/Mass	28.689	61.278	126.846	52.091	70.670	1.602	1
H101	P109821003	View Graph	View Graph	Volume/Mass	20.755	59.404	133.793	31.554	70.052	1.903	1
H200	PN08819580	View Graph	View Graph	Volume/Mass	99.677	233.393	413.478	147.600	245.765	1.345	1
H200	PN08819580	View Graph	View Graph	Volume/Mass	102.405	237.208	416.197	147.456	248.860	1.323	1
H200	PN08819580	View Graph	View Graph	Volume/Mass	104.102	239.506	418.085	149.118	250.761	1.311	1
H102	P208819026	View Graph	View Graph	Volume/Mass	37.201	113.122	236.603	73.344	126.895	1.763	2
	Lot Number	Frequency Distr	Cumulative Dist	Distribution Ty	x10 [µm]	x50 [µm]	x90 [µm]	Sauter Mean Diame	Mass Mean Diame	Span	Humidity

Showing 1 to 10 of 18 entries

Property retrieval

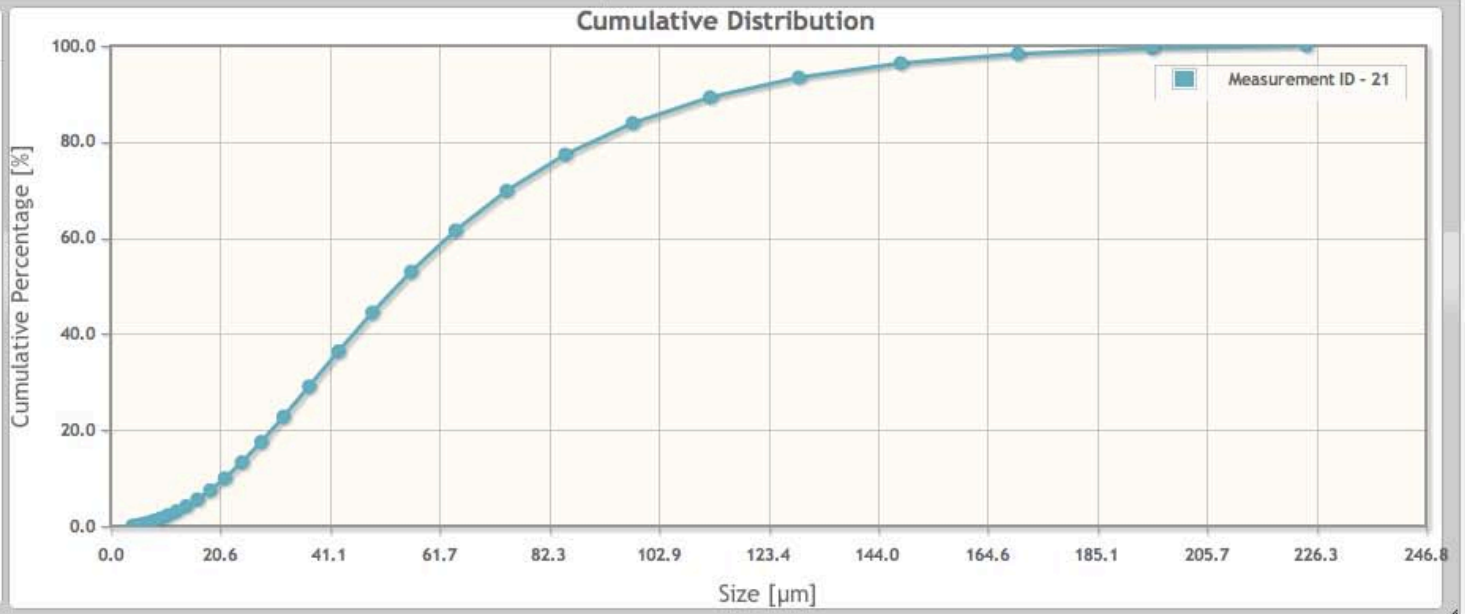
Charts | **Measurement Data PSD Graphs and Raw Data** | Return to Excipients Knowledge Base

Predefined Charts

Select a Chart:

Cumulative Distribution

View Chart



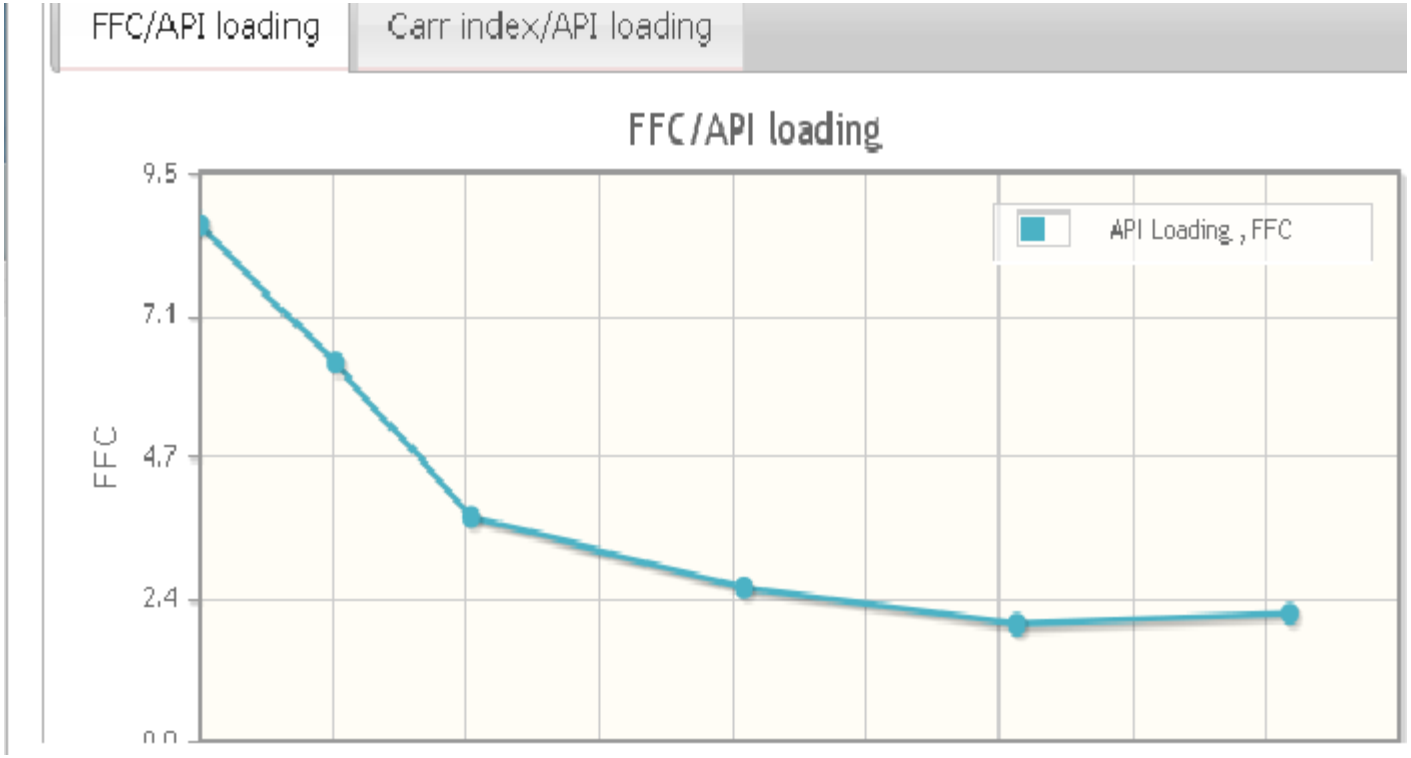
Show 10 entries

First Previous 1 2 3 Next Last

Search:

Meas. ID	Distribution Type	Particle Size Interval [µm]	Midpoint Of Size Interval [µm]	Volume / Mass Percentage [%]	Frequency [%/µm]	Cumulative [%]
21	Volume/Mass	3.802 - 4.365	4.084	0.040	0.071	0.040
21	Volume/Mass	4.365 - 5.012	4.688	0.090	0.139	0.130
21	Volume/Mass	5.012 - 5.754	5.383	0.140	0.189	0.270
21	Volume/Mass	5.754 - 6.607	6.181	0.210	0.246	0.480
21	Volume/Mass	6.607 - 7.586	7.097	0.280	0.286	0.760

Powder Flow Database

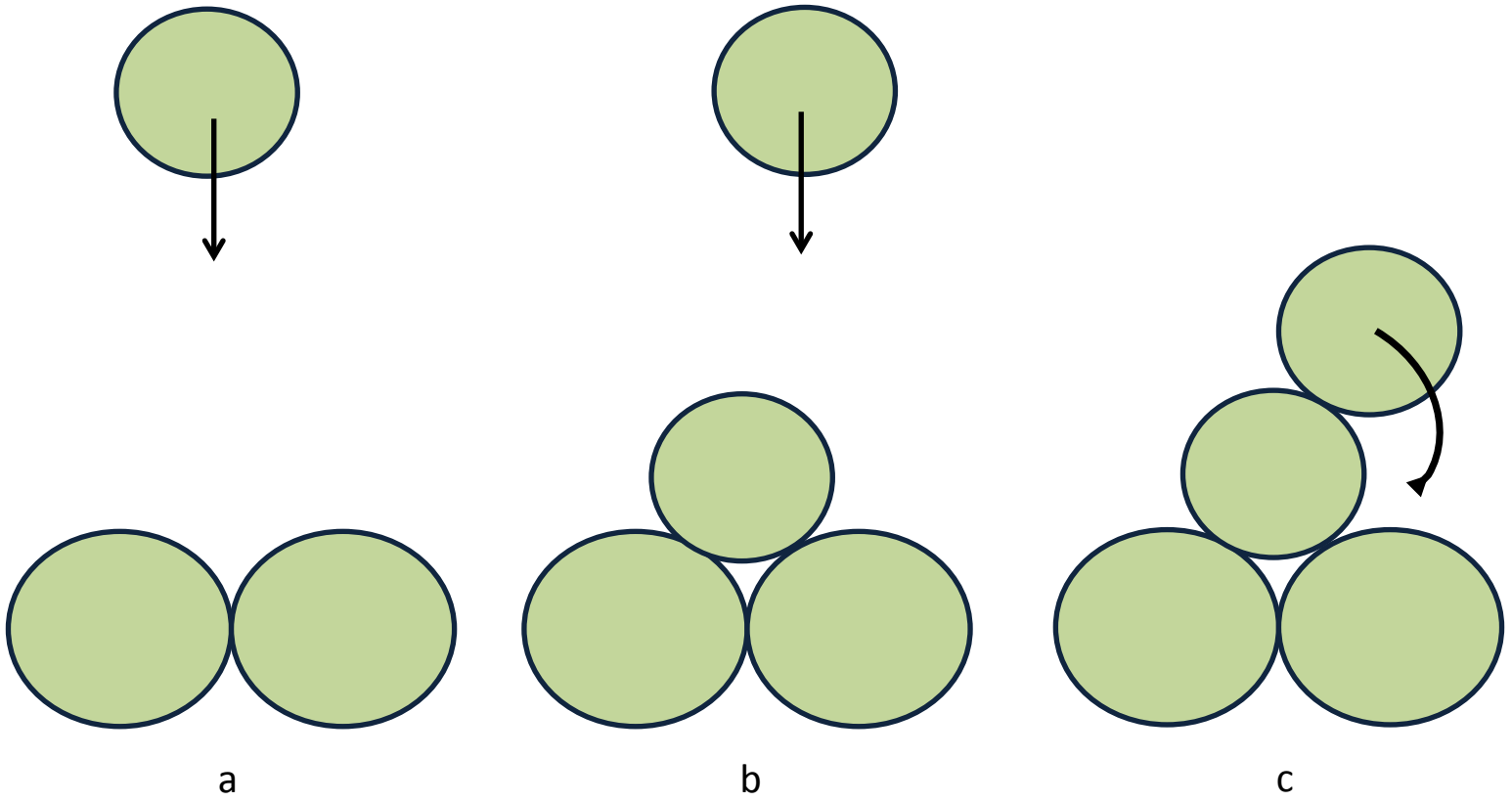


Die-filling

- Die-filling refers to the process of deposition of powder into the dies of a tablet press for subsequent compaction.
- Die-filling can affect tablet weight and, therefore, dosage form
- The quality of die-filling depends on the cohesiveness of the powder blend.
- Cohesive powders form meta-stable ring-like void structures
- The heterogeneous structure of the powder bed, resulting from pouring cohesive powders affects the process of compaction
- The mechanical properties of the compressed tablets will be affected by local low-density regions created during die-filling.

Ballistic deposition

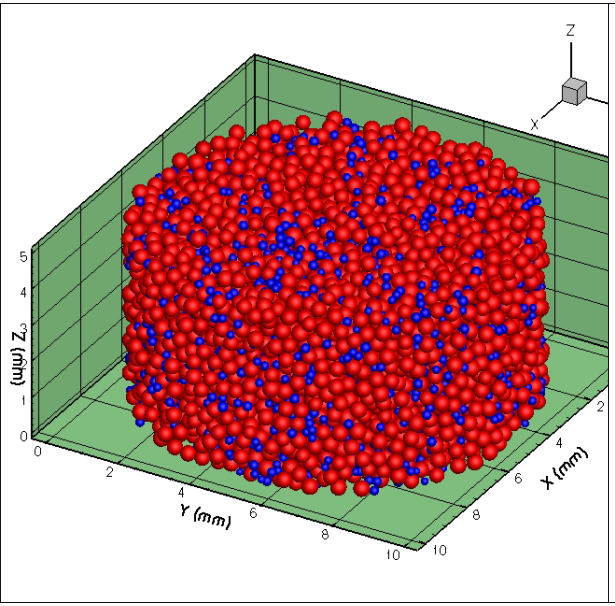
- Powder is deposited into the die one particle at a time.
- Once another particle is encountered the original particle starts rolling down until it reaches a stable configuration.
- Depending on the powder cohesiveness modeled, particle configurations are considered “stable” at different contact angles



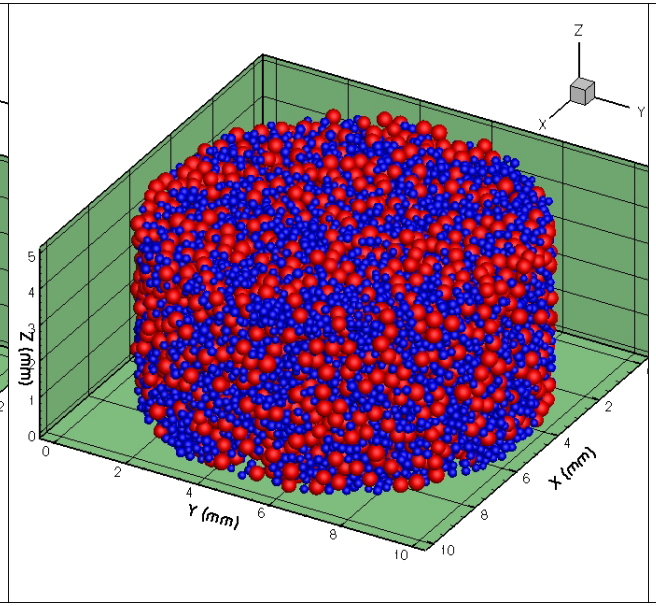
Powder Bed Generation

The ballistic deposition approach has been used to generate realistic powder beds consisting of multiple components with different size distributions.

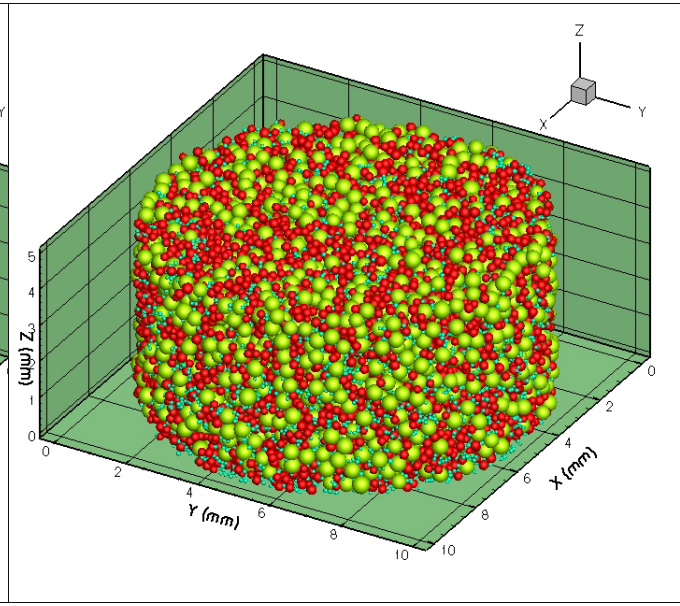
a 2D version of the model is implemented on PharmaHub.



2 components 9% active

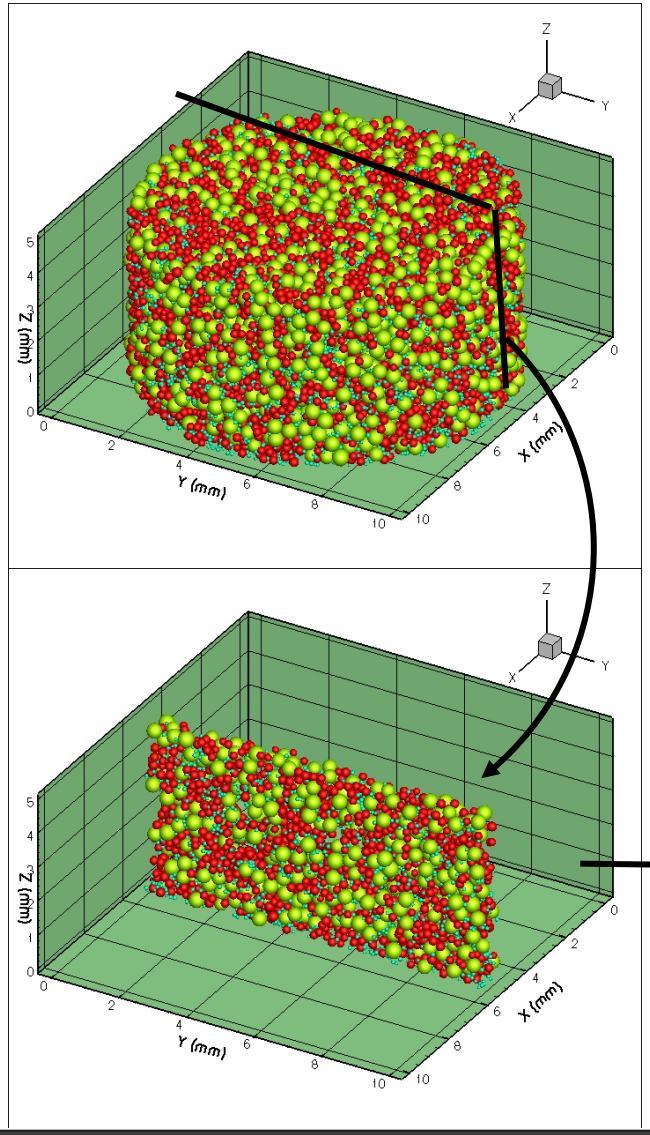


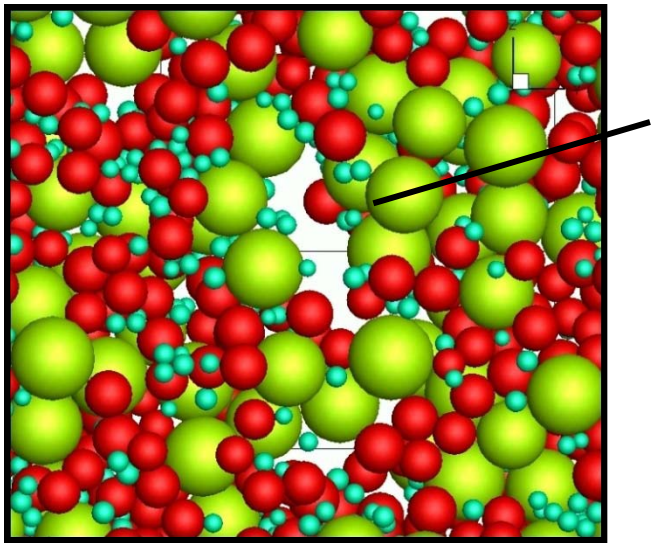
2 components 30% active



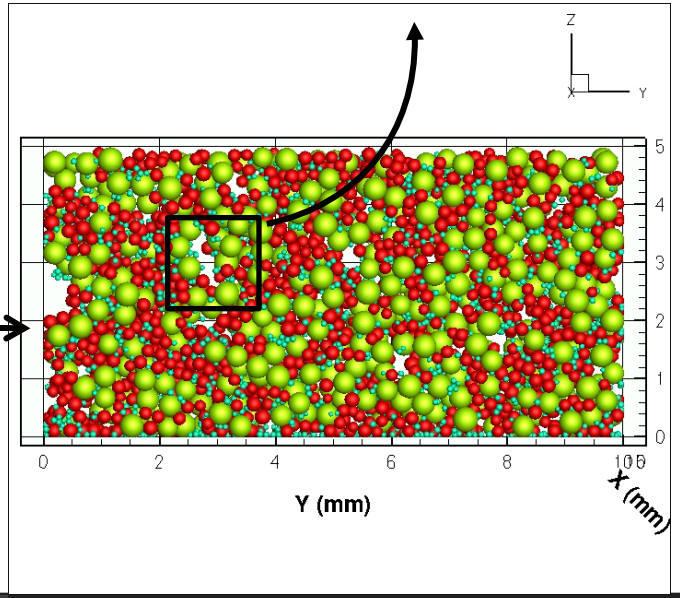
3 components 9% active, 2% additive

Powder Bed Structure





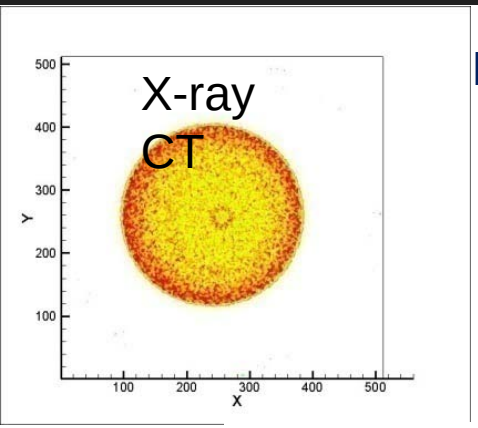
Void Structure



Dissolution

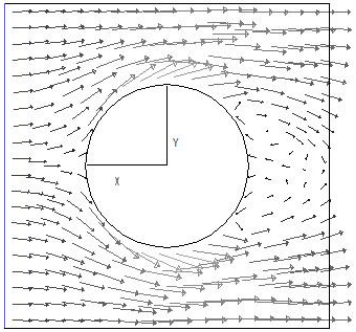
- To develop and test a design tool which is able to numerically model the dissolution of solid drug dosage forms.
- Users will be able to access tool via Pharmahub portal and after entering measurable properties of dosage, simulate dissolution
- Data from powder processing and environmental conditions are incorporated

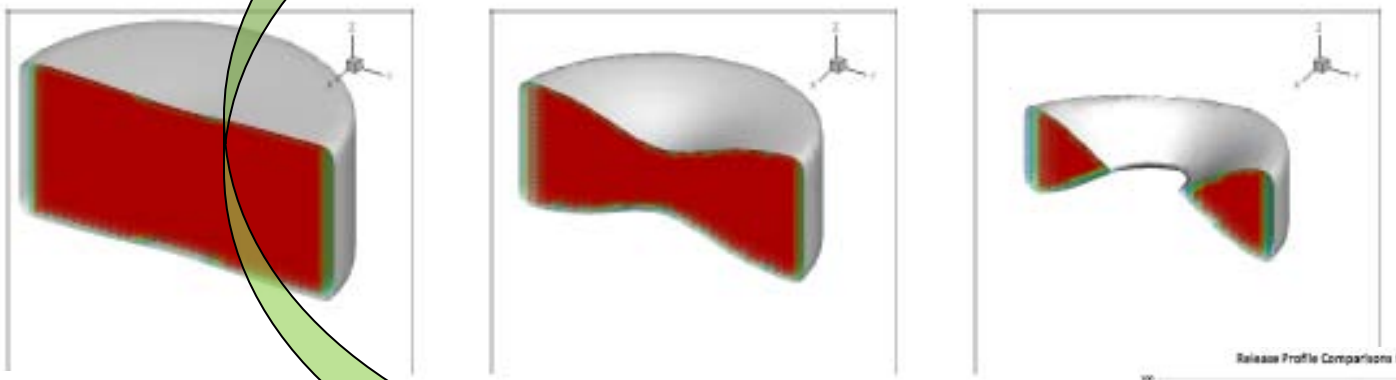
Process – Environment – Performance



Density variations in a tablet due to processing conditions (friction).
PROCESS

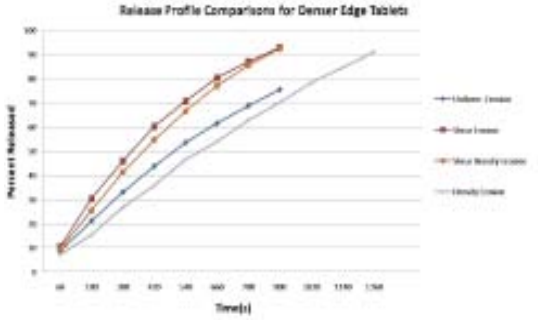
Flow around tablet (2-D approx.)
ENVIRONMENT





Simulation of erosion and dissolution considering the heterogeneous density distribution + Effects of FLOW

Drug Release profile
PERFORMANCE



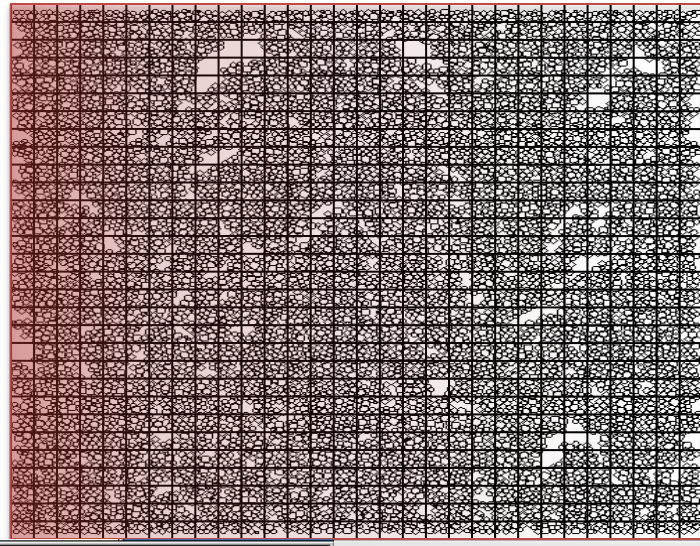
Physics Based Dissolution Engine

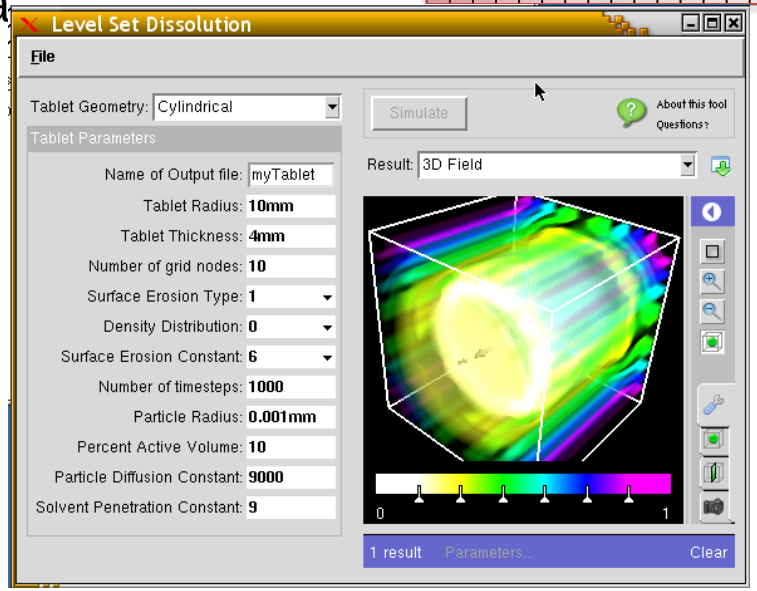
- The dissolution tool simulates multiple processes simultaneously
  - Track location of dosage/fluid interface and update BCs
  - Track progression of solvent absorption through excipient matrix
  - Calculate API dissolution at particle level considering surface to volume ratio and current surrounding solvent concentration
  - Model drug release as diffusion of drug solute out of excipient matrix

Tablet Model

- Tablet represented on Cartesian grid
  - Each cell is assigned:
    - Number and size of particles
    - Active particle dissolution coefficient
    - Solvent penetration coefficient
    - Distance to nearest tablet surface
- Values assigned as simple concentrations radii and representative coefficients
- Tablet/Bulk fluid interface handled via level set
  - Moving boundary conditions
  - Erosion type can be
    - Uniform
    - Density based
    - Fluid-Shear influenced

Simple depiction of solvent penetration over defined grid

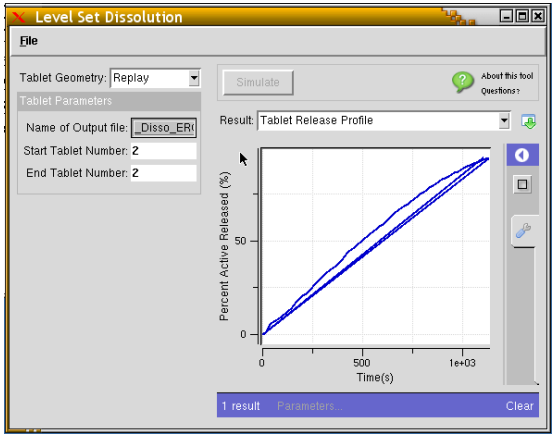




Pharmahub input gui for tablet dissolution

Internal Dissolution

- Solvent Penetration
  - Modeled using finite differencing method
    - Represented as cell based volume fraction of solvent
    - Influences rate of active particle diffusion
    - Incorporates moving tablet surface
- Particle Dissolution
  - Solved as diffusion of a sphere
    - Influenced by surrounding solvent and solute concentrations
    - Reduction in volume considered as release
- Solute Diffusion
  - Dissolved drug diffuses based on Fick's second law
    - Represents clearance of dissolved drug from tablet



$$\frac{\partial C_{active}}{\partial t} = \alpha_C (C_{active} - C_{solute})$$

$$\frac{\partial C}{\partial t} = \nabla . \alpha \nabla C$$

Sample of available tools (30)

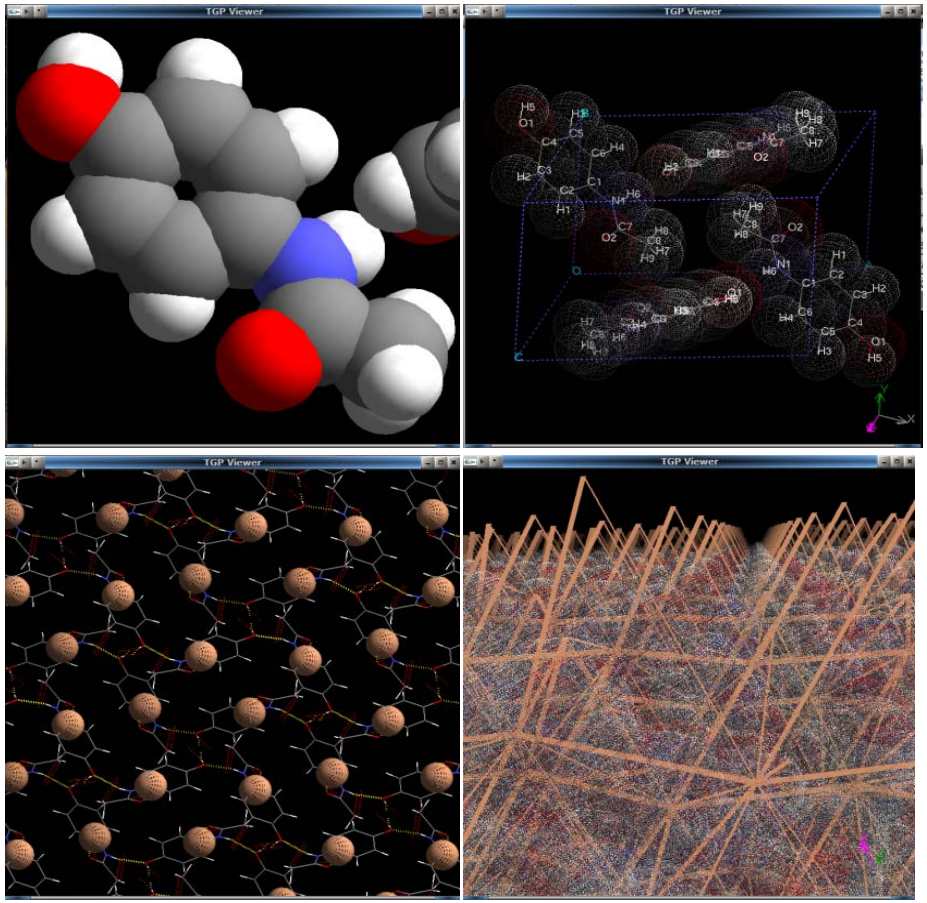
1. Visualization of molecular crystals
2. Particle-surface adhesion
3. Tablet dissolution model
4. Hopper flow discharge (Discrete Element Model)
5. Rotating drum (DEM)
6. High shear mixer (DEM)
7. Continuous particle blending (Compartment Model)
8. Roller compactor: steady state & dynamic models
9. Cake filtration model
10. Guideline ontology & SWOOP ontology browser
11. Multipurpose operation production planner (MOPP)
12. Lyophilization calculator

ViewStruct

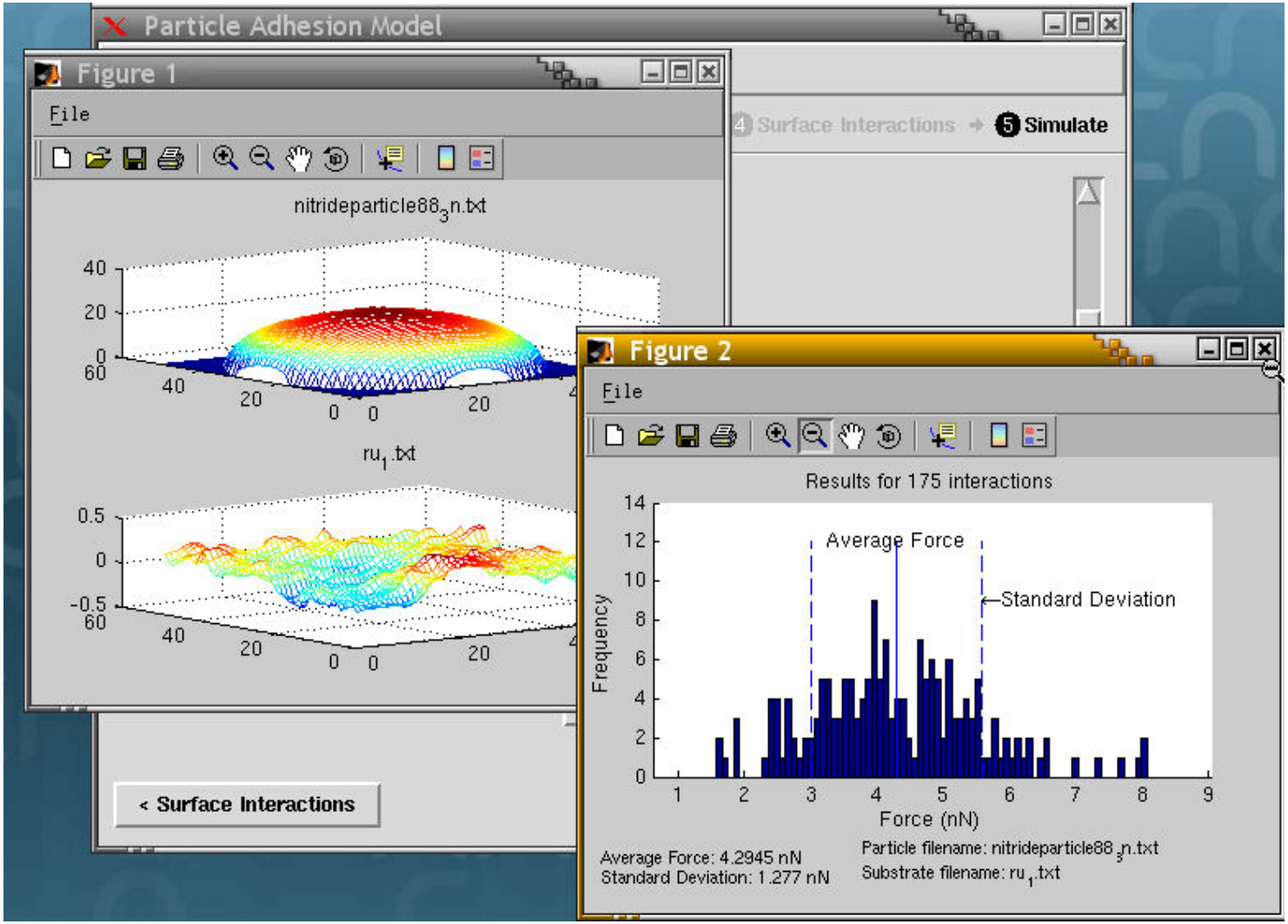
Visualization of crystal structures

S Boerrigter, IPPH

- Unit cells, labels
  - View range
- Representation Options
  - Wire frame
  - Covalent
  - Corey-Pauling-Koltun
  - Van der Waals
- Contacts and Interactions
  - Hydrogen bonds
- Crystal Graph
  - Growth Units
- View Options
  - Lighting, Perspective, Depth

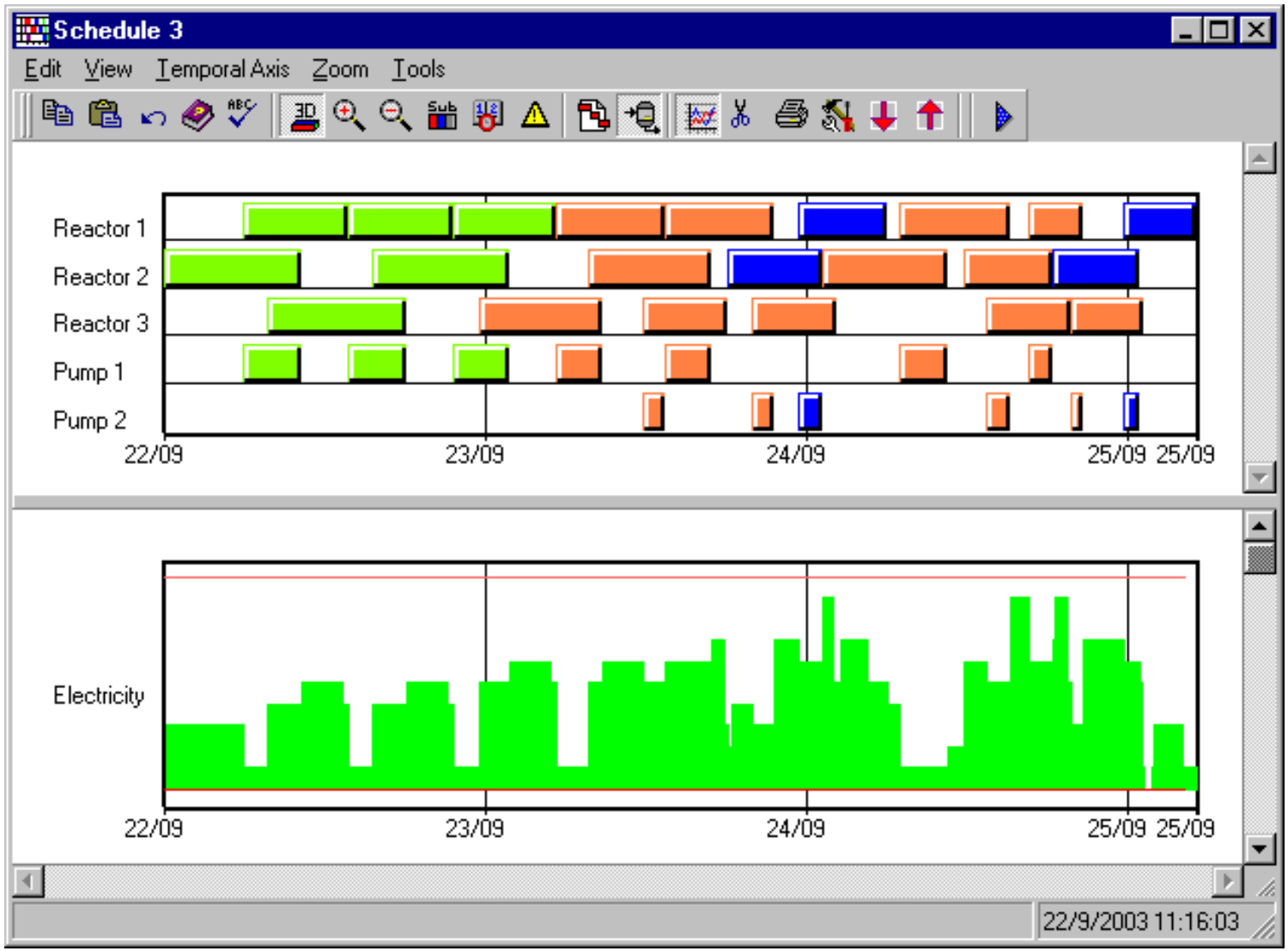


Particle adhesion simulation



MOPP

Equipment schedule and resource utilization



Sample of available courses (80)

1. Statistical model building and design of experiments
2. Computational methods for molecular crystals
3. Visualization of molecular crystals
4. Discrete element method (DEM)
5. Characterization of nanopharmaceutical materials
6. Colloids and surfactants
7. Liquid mixing fundamentals
8. Sterilization and disinfection
9. Mixing Equipment and Processes
10. API Process Unit Operations Development and Design
11. Pharmaceutical Bulk Drug Production
12. Application of ChE Principles to Drug Delivery
13. Particle and Flow Characterization
14. Introduction to Rheology of Complex Fluids
15. Pharmaceutical concepts into introductory ChE courses

MOPP

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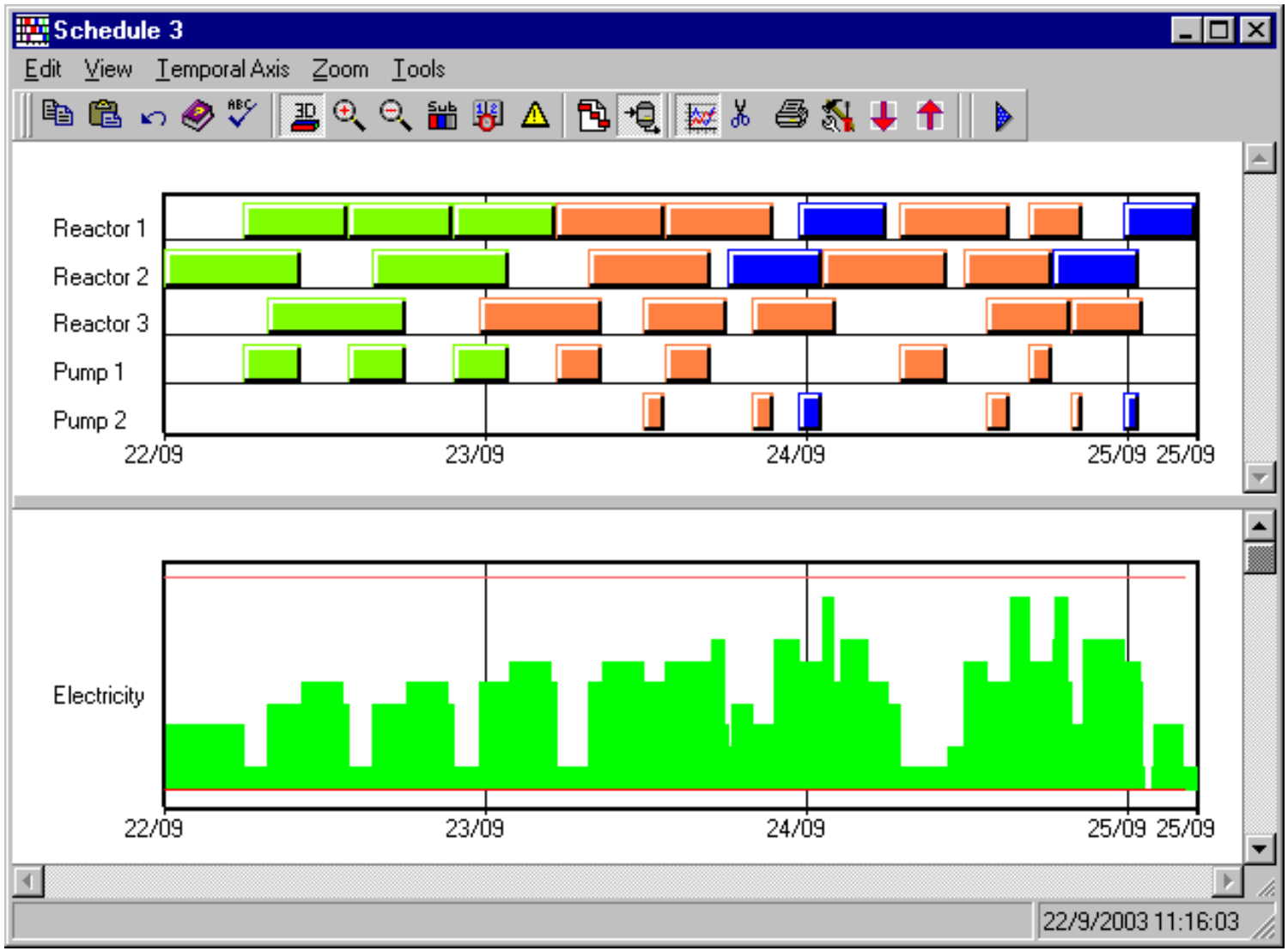

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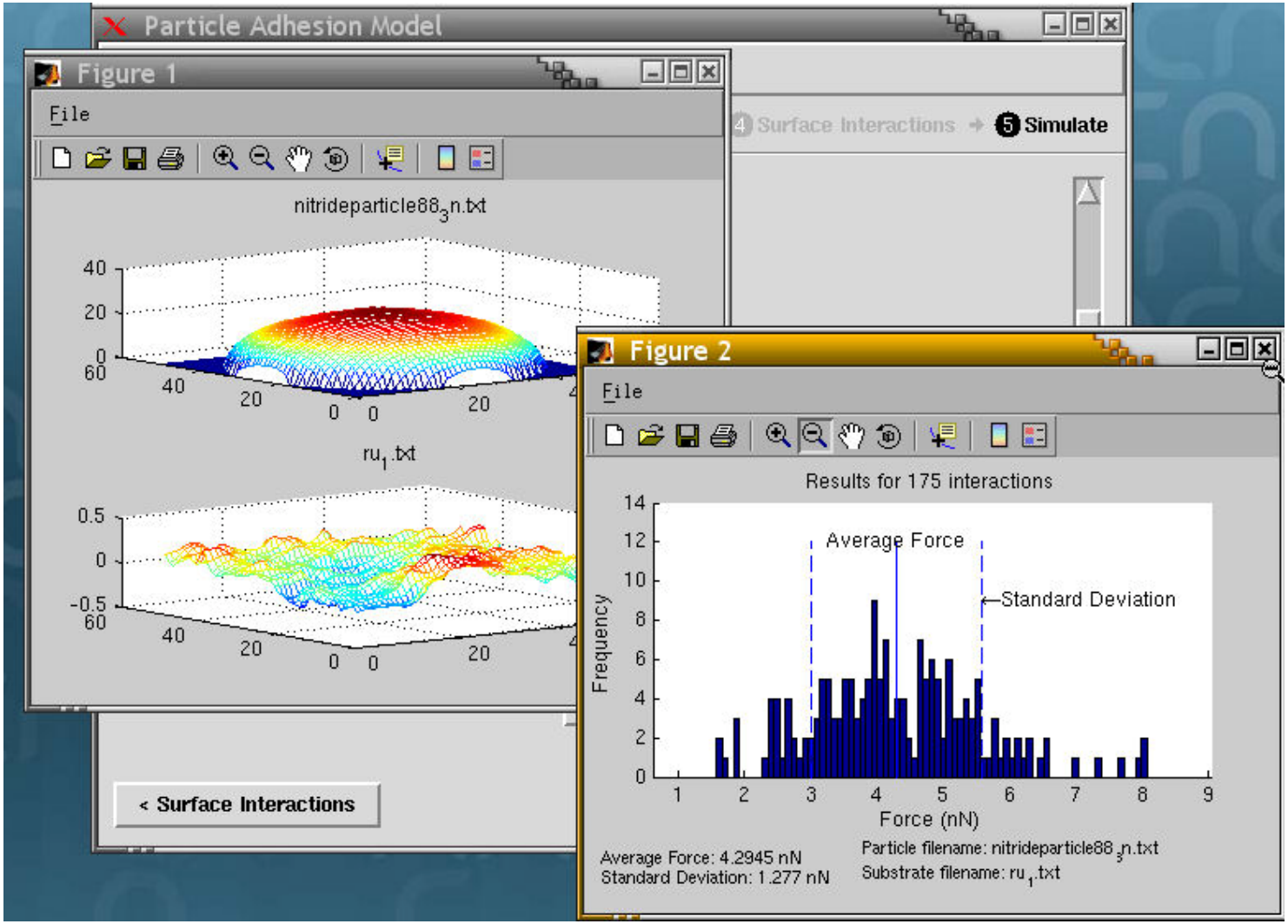

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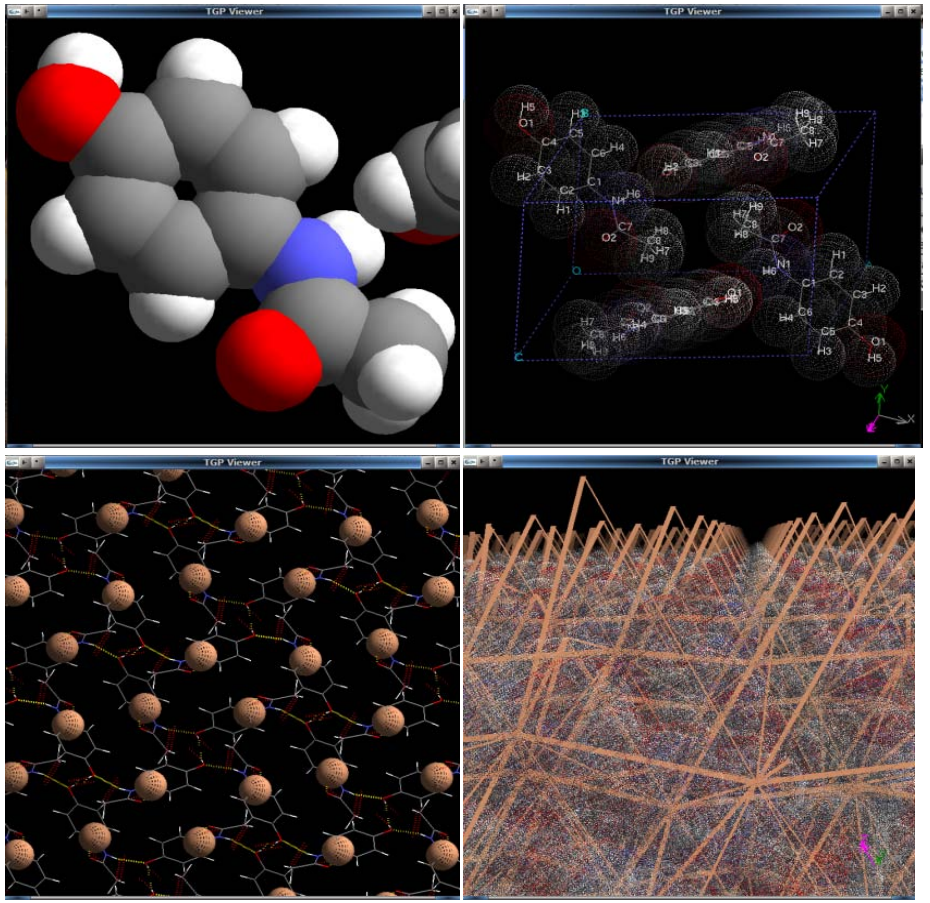

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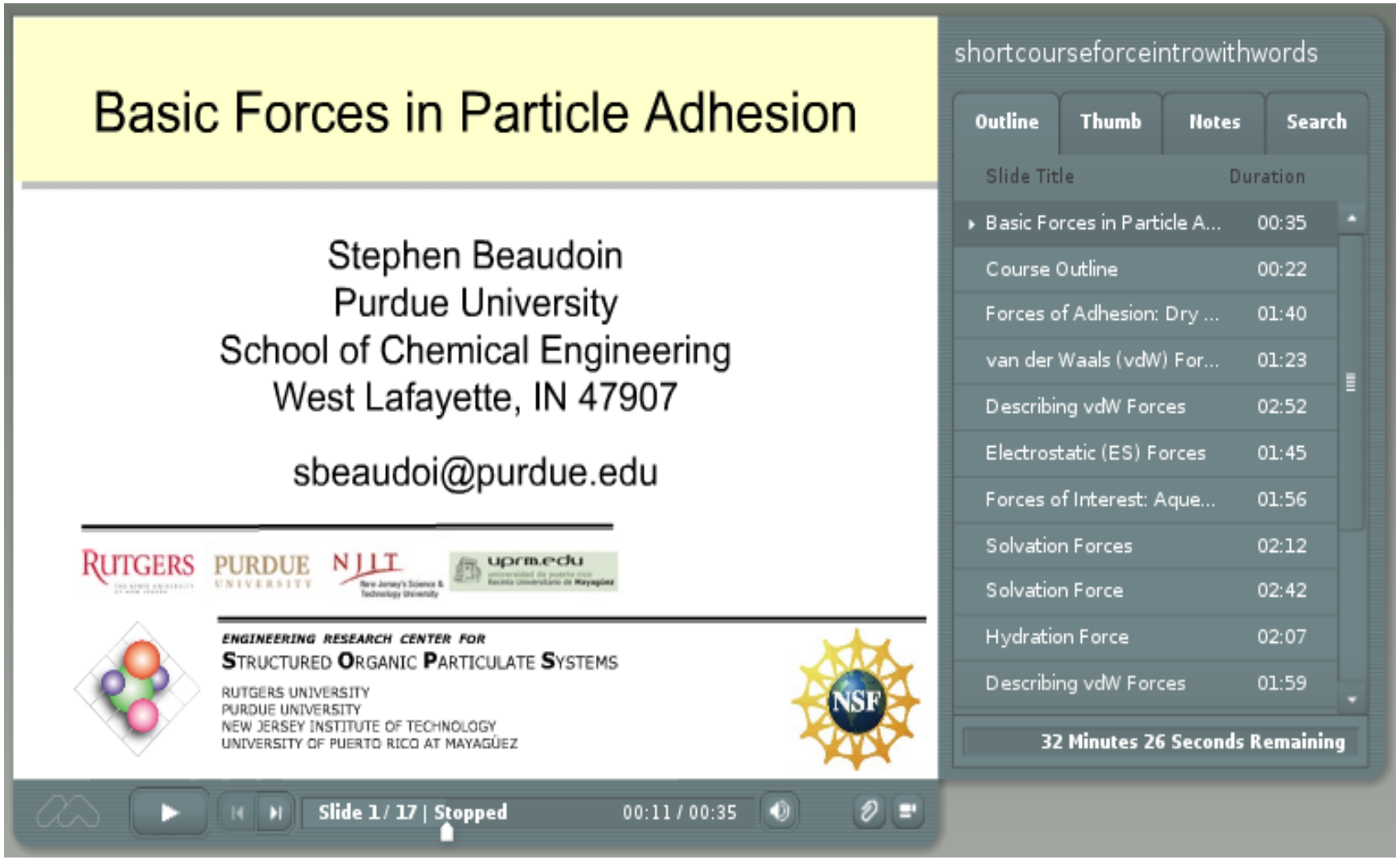
Online presentations



Final remarks

- HUBzero technology has been well received as a very flexible framework for both users & contributors
- NSF ERC program views HUB technology very favorably:
  - Important vehicle for making ERC work products accessible broadly (K-12, university, industry & FDA)
  - Workshop advertised across ERC programs
- Growing functional capabilities will enhance future value
  - Workflow management & workflow templates
    - Data management of successive utilizations of tools
  - Management of large numbers of repetitive runs (Markov Chain Monte Carlo)
  - Enhanced visualization capabilities
  - Data handling capabilities

Thanks for your attention!