Global System Analysis of Interconnected Flow Sheet Models for Drug Product Manufacturing to Performance

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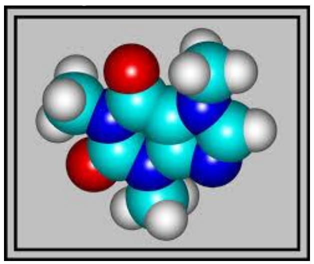
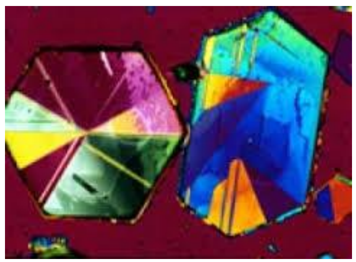
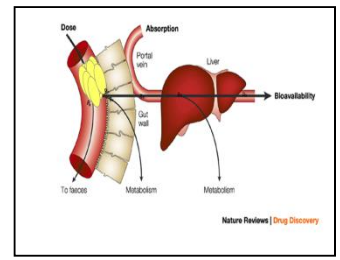
The Motivation for a Systems Based Approach to Pharmaceutical Development

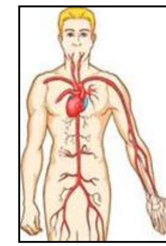
Research
Inventing the right molecule

Development
Creating the right product

Commercialization
Optimizing the operating margin





Advanced multi-scale modeling of all processes

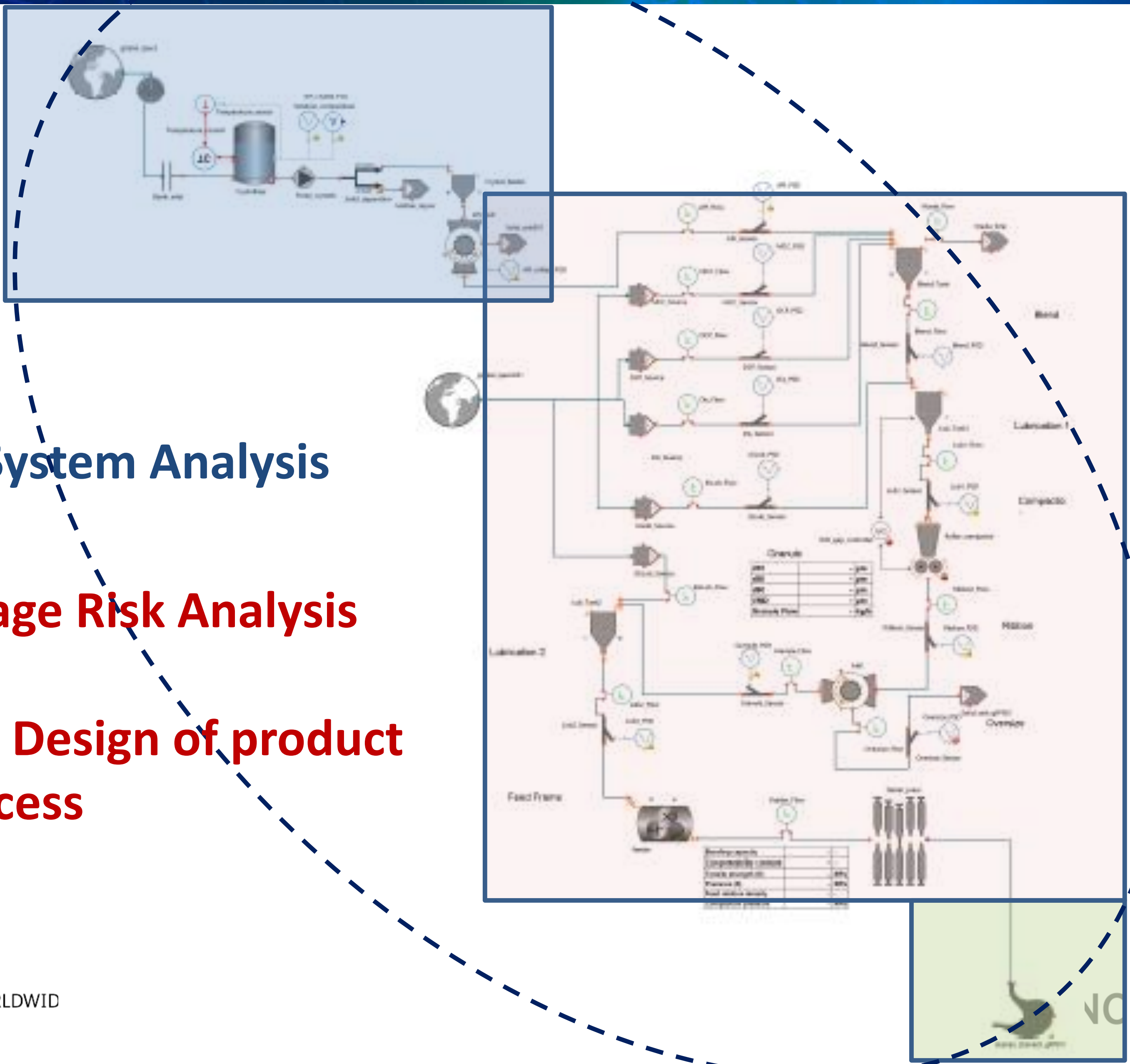
Systems Biology & System Pharmacology

Pharmaceutics — Transforming new chemical entity into medication

Biopharmaceutics — Relating properties of drugs and dosage to onset, duration & intensity of action

Molecular Design — Opportunity to influence molecular design

Long term Vision: Digital Design



Global System Analysis

Early Stage Risk Analysis

Optimal Design of product and process

Organization of the presentation

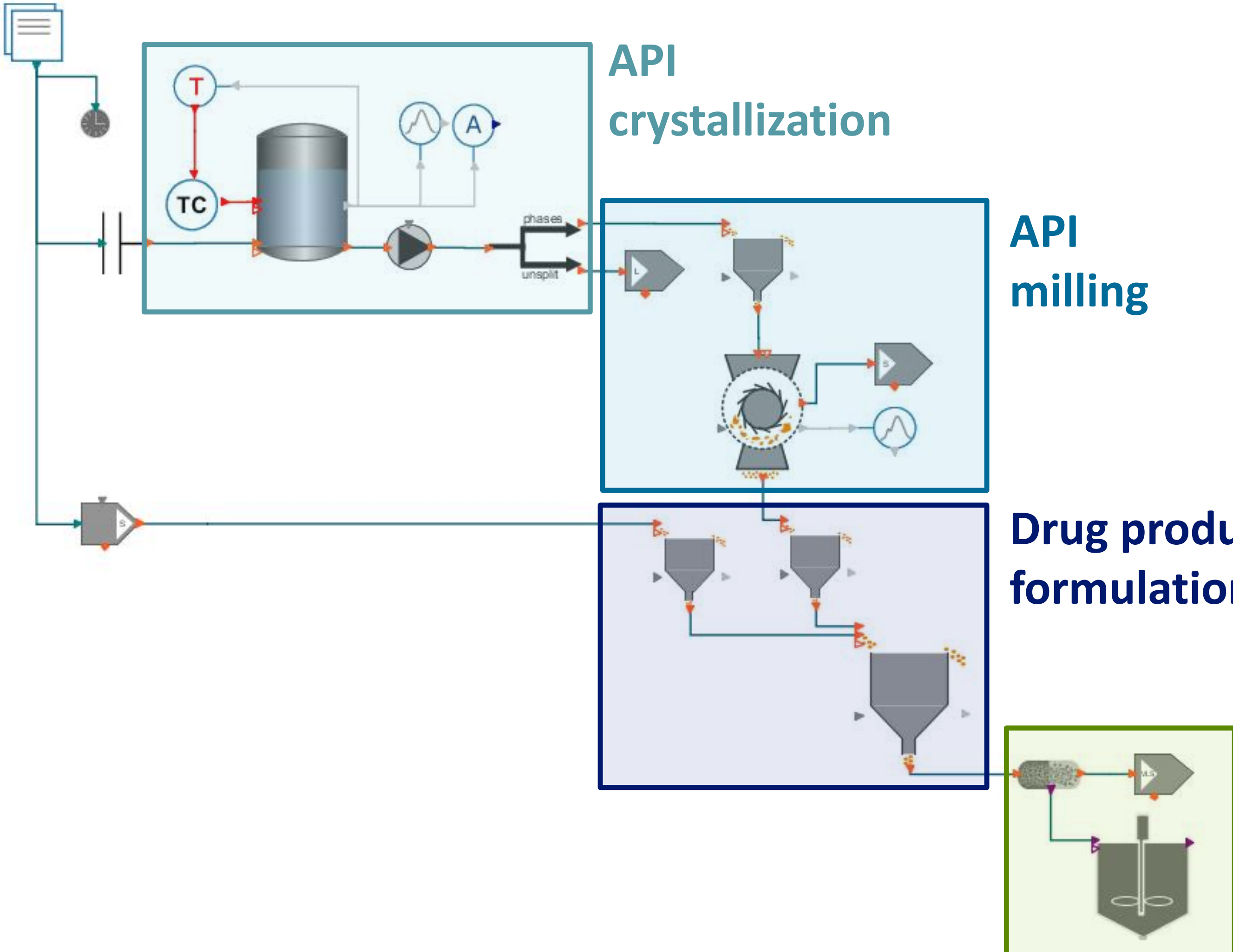
- Interconnected flowsheet model: Crystallization to Dissolution
  - Batch cooling crystallization model
  - Dry Milling Model
  - In vitro Dissolution Model

- Global System Analysis of individual unit operations

- Global System Analysis of Interconnected flowsheet model
  - First example of GSA applied to complex flowsheet
- Conclusion and Future Direction

Interconnected flowsheet

API crystallization → **API milling** → **Drug product formulation** → **Drug product performance**



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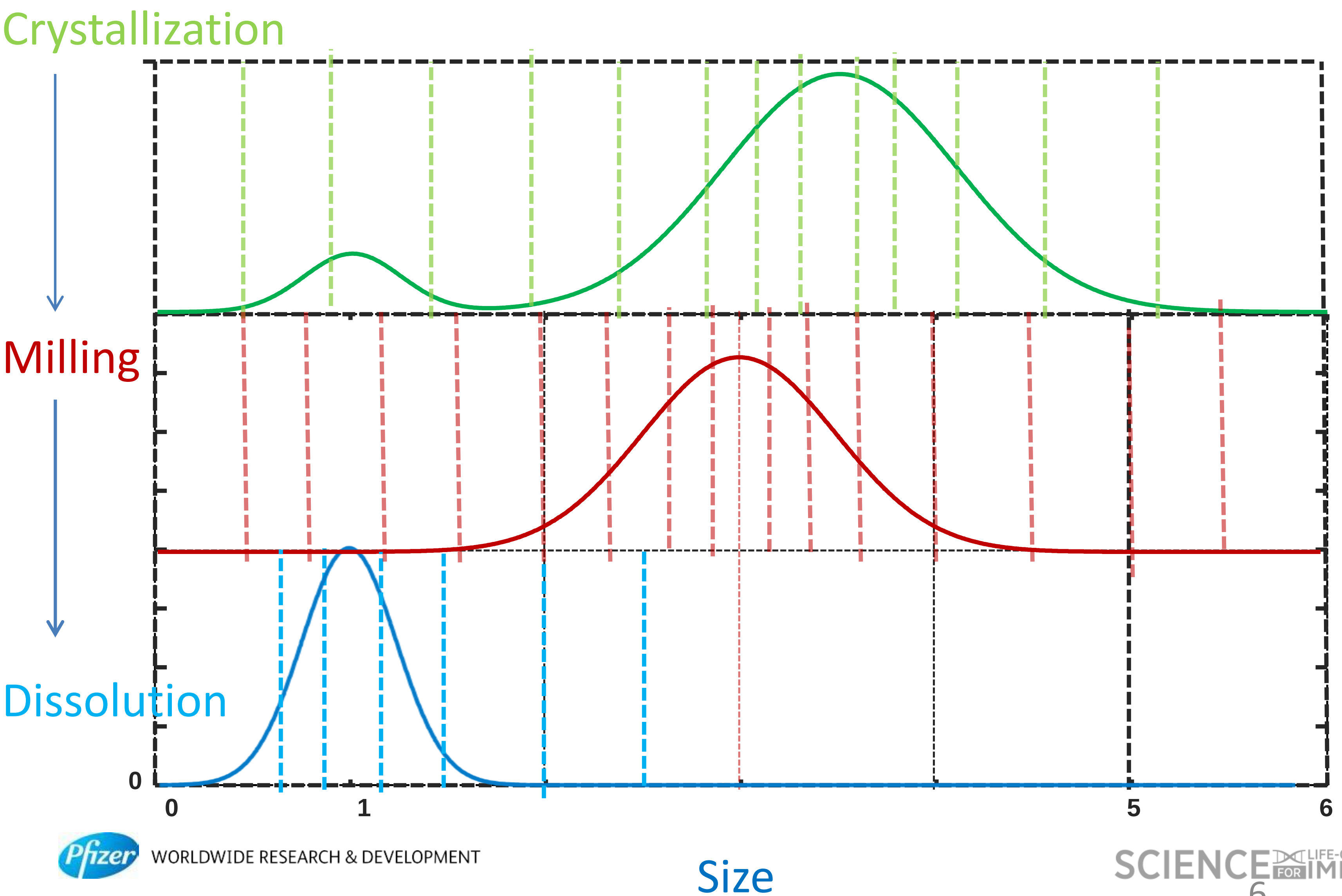
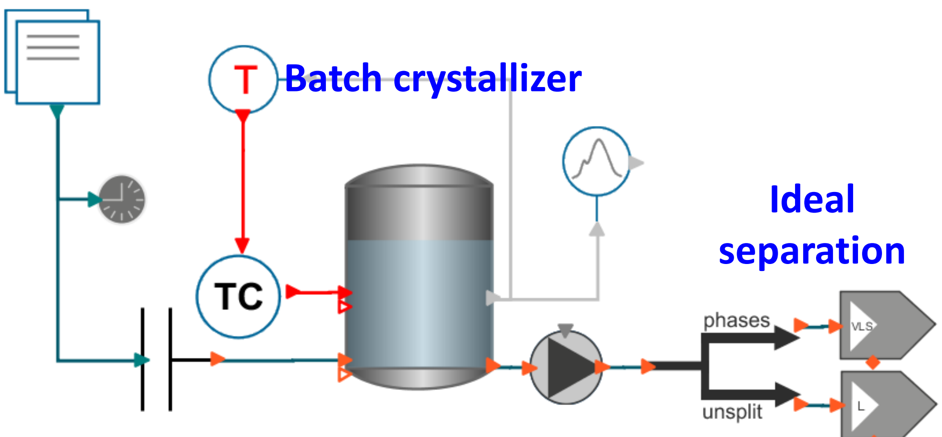
Interoperability of different models

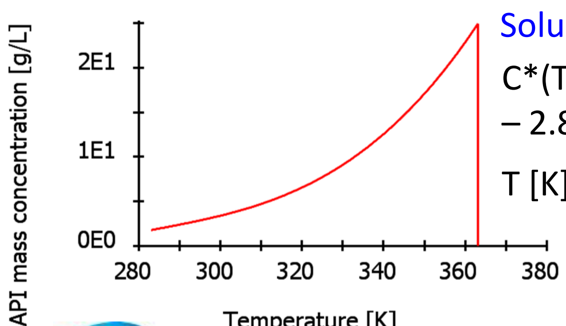


Crystallization Model

API crystallization



Growth and dissolution: *Classical two-step kinetics; Garside et al. (1990)*



Solubility curve

$C^*(T) = -797 + 8.27\,T - 2.88e^{-2}\,T^2 + 3.39e^{-5}\,T^3$

T [K], C* [g/L]

Batch recipe:
0h - 4h Cooling – piecewise linear ramp for T
Initial temperature (60-90°C)
Final temperature 10°C
4h - 6h Unload – Constant output flowrate

Input variables:
- Cooling profile: initial temperature (60-90°C)
- Impeller frequency (10-50 rpm)
- API concentration in solution (3-5 %w)
- Initial seed concentration (5-15 e^{-6} g/kg)
- Seed lognormal PSD: peak 15 µm; SD 5 µm

Physicochemical parameters:
- Nucleation rate (35 $m^{-3}s^{-1}$)
- Growth rate constant ($5e^{-6}$ m/s)
- Growth activation energy ($1.25e^{4}$ J/mol)
- API solubility function of T

Output variables:
- Crystal PSD

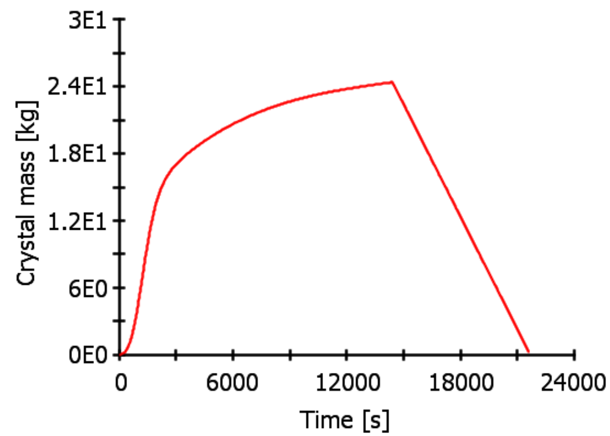
Results from single Crystallization Simulation

API crystallization

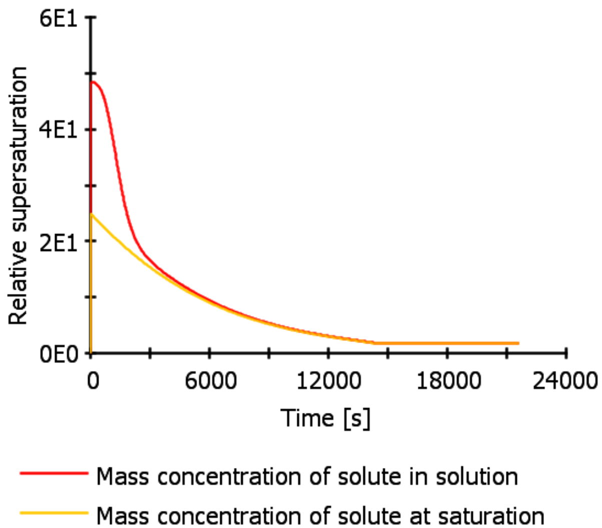
Scenario

- Cooling profile: initial temperature (90°C)
- Impeller frequency (25 rpm)
- API concentration in solution (5%w)
- Initial seed concentration (10 e^{-6} g/kg)

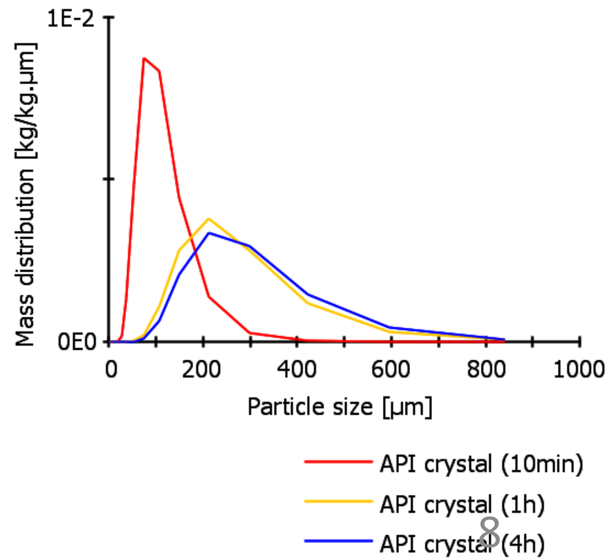
Solution and crystal mass in crystallizer



Solute concentration & solubility



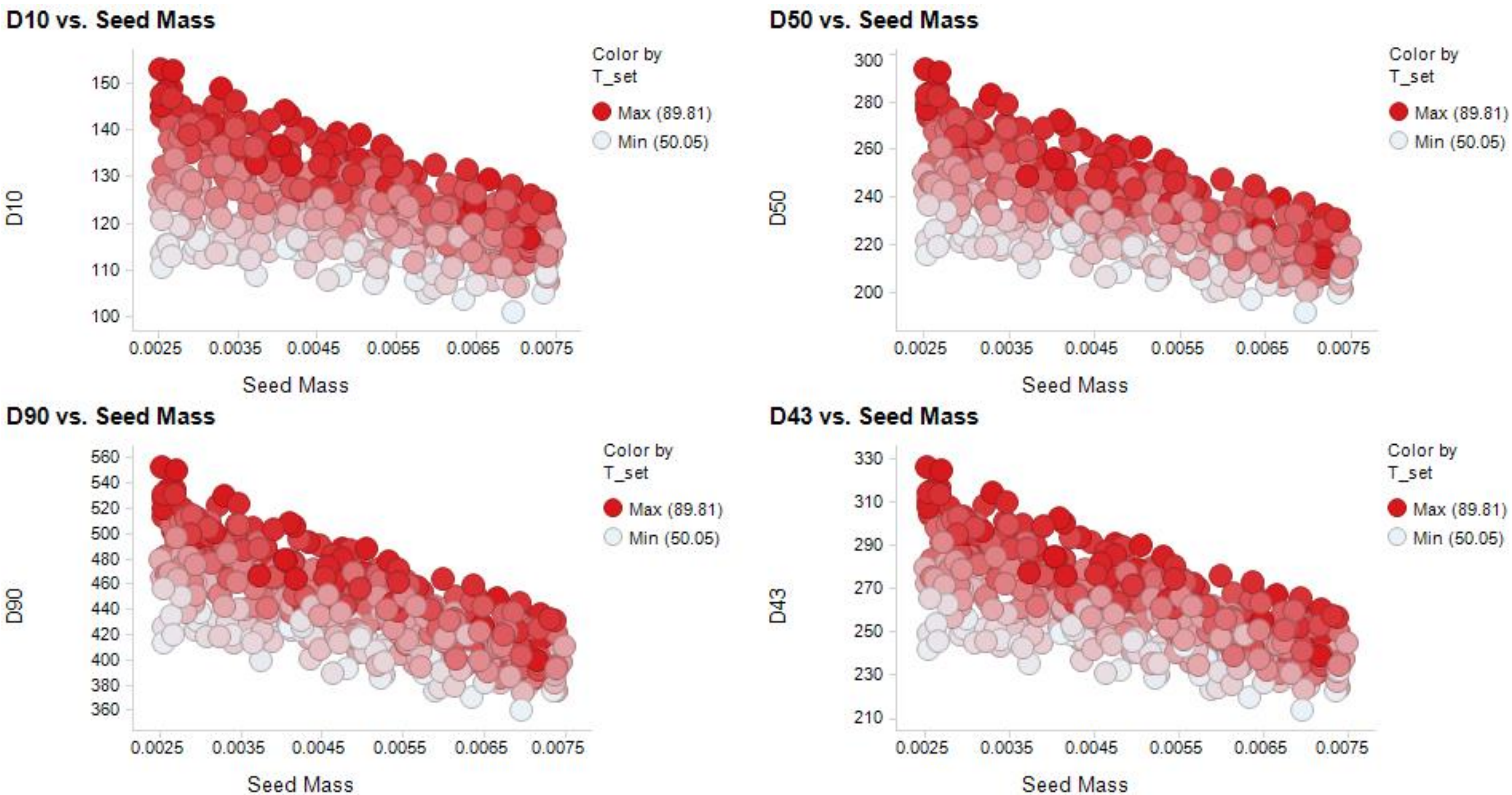
Cumulative particle size distribution



GSA Algorithm/Methodology

- Define the uncertainty distribution of model parameters and inputs
- Define a Monte Carlo simulations scheme
- Calculate the statistics (mean, variance and distributions) from the model output
- Calculate the Sobol indices using ANOVA decomposition
- Reduce the model keeping only dominant parameters for further analysis

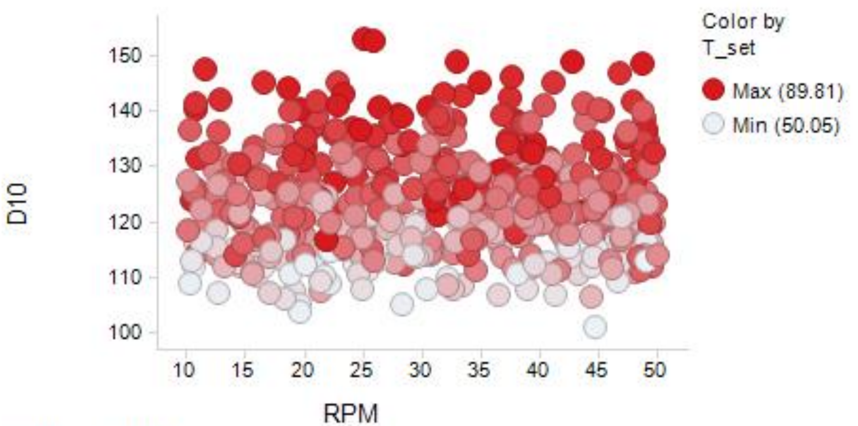
Effect of initial seed mass on Crystal PSD



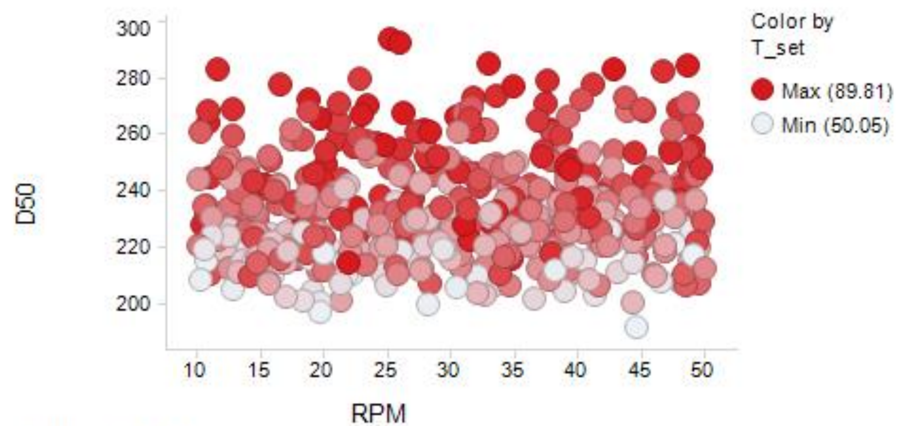
1000 -5000 simulations on 64 core machine

Effect of impeller RPM on Crystal PSD

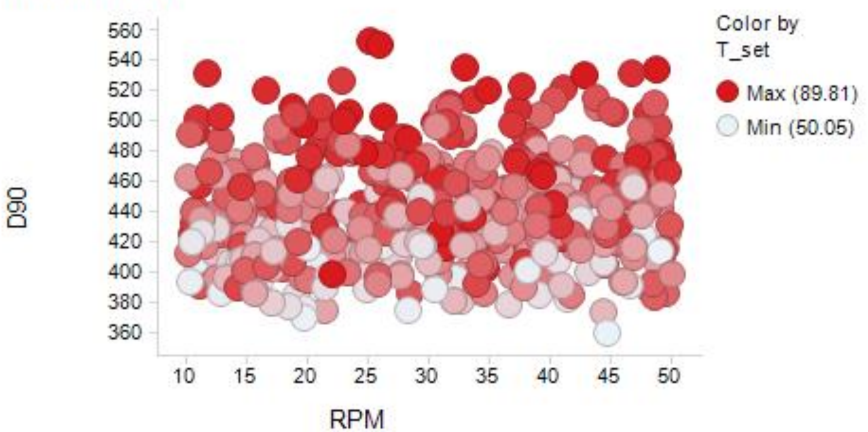
D10 vs. RPM



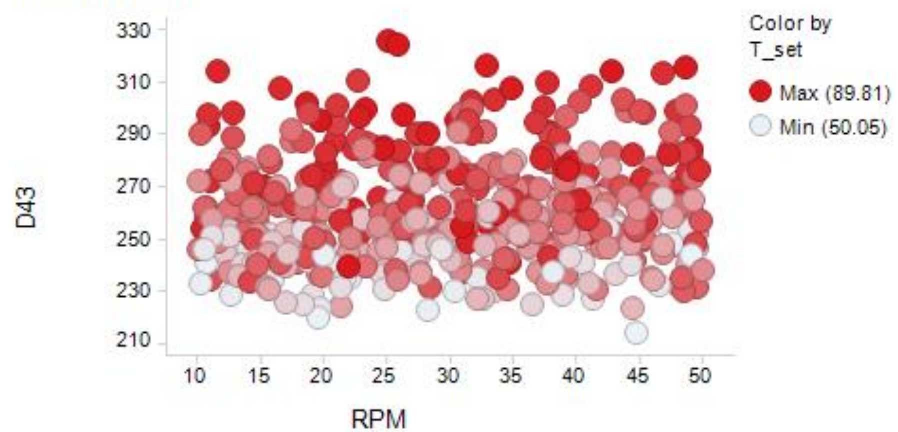
D50 vs. RPM



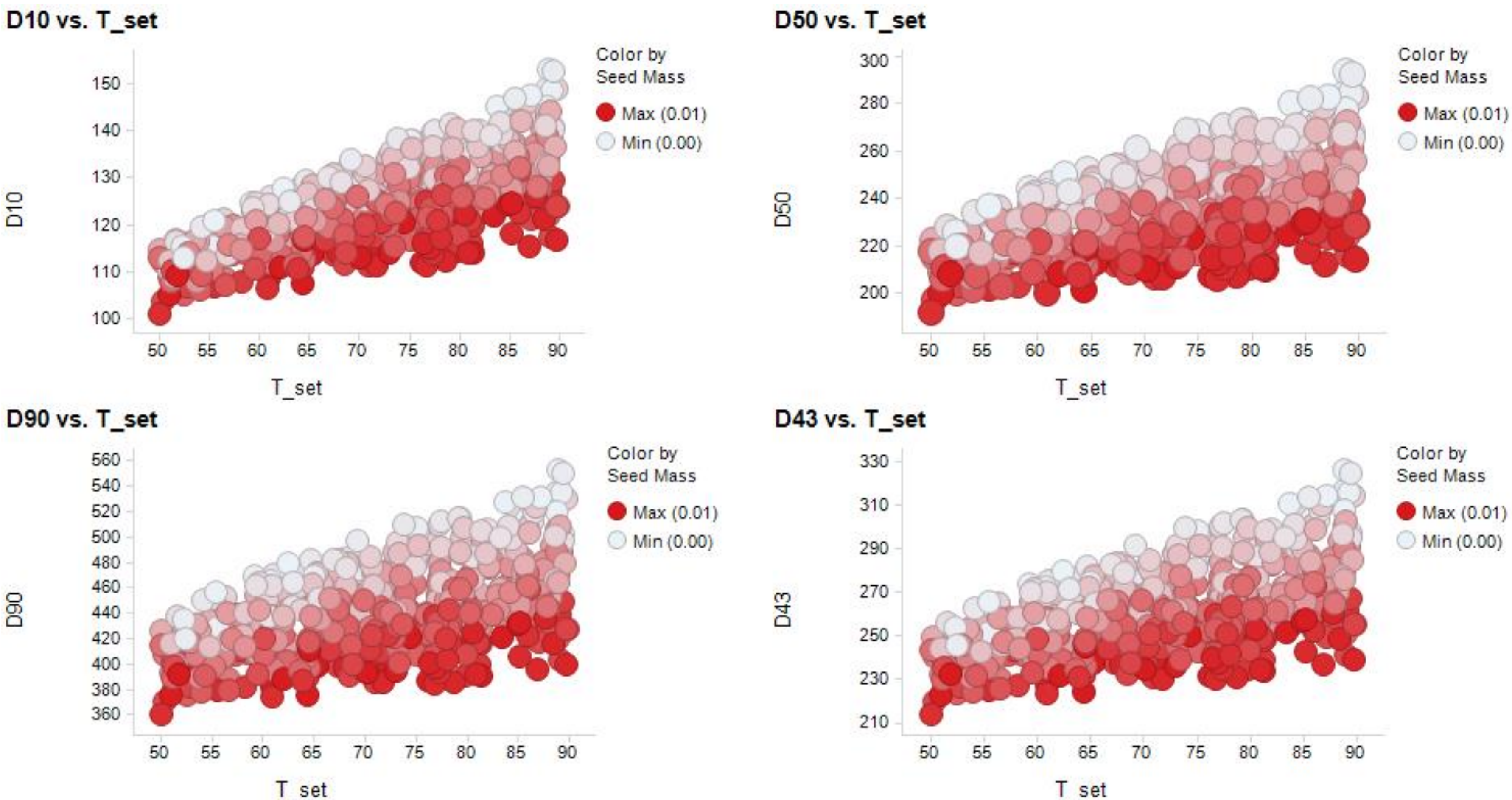
D90 vs. RPM



D43 vs. RPM

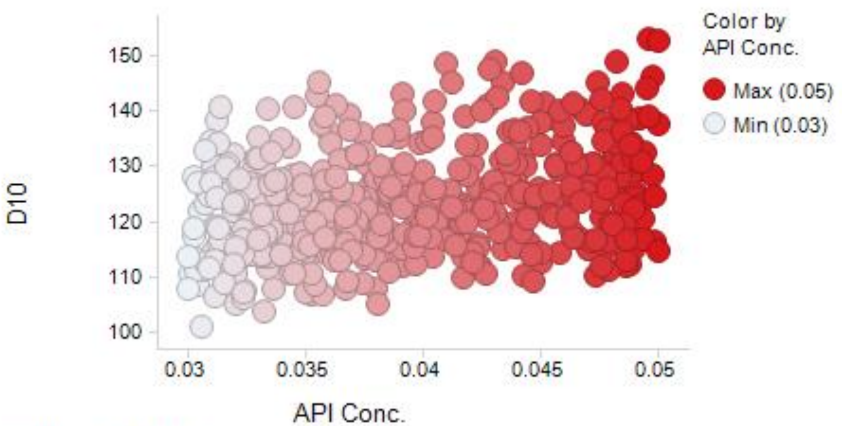


Effect of Initial Slurry Temperature on Crystal PSD

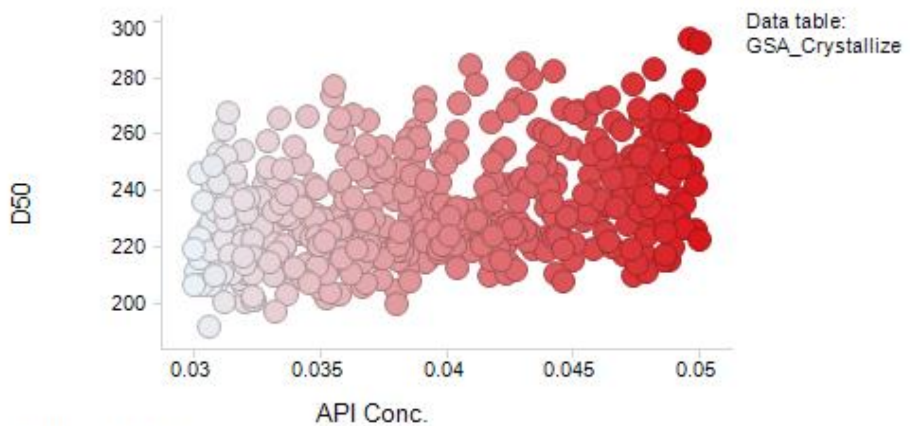


Effect of Initial API Concentration in Solution on Crystal PSD

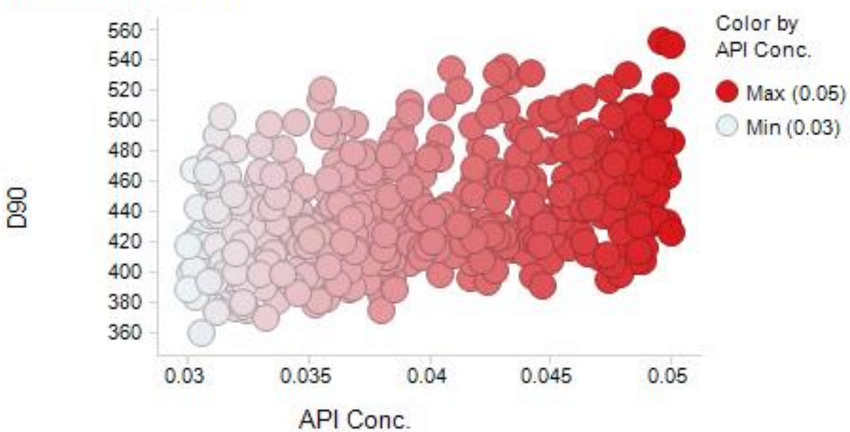
D10 vs. API Conc.



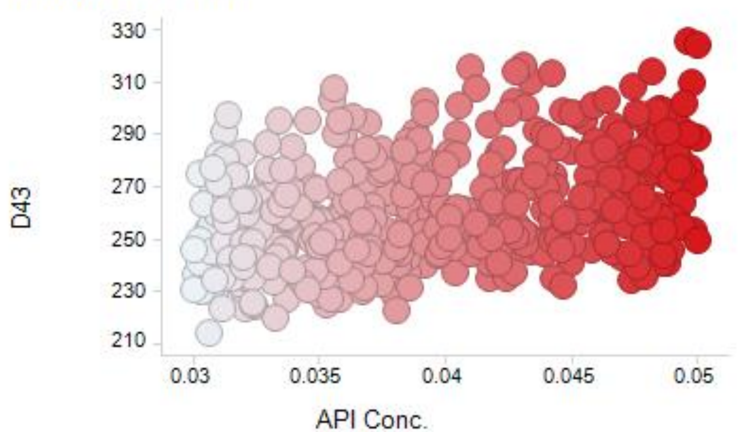
D50 vs. API Conc.



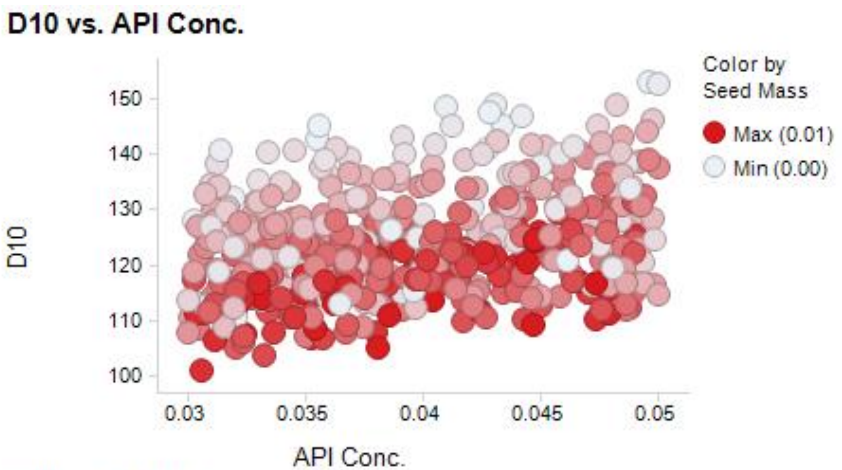
D90 vs. API Conc.

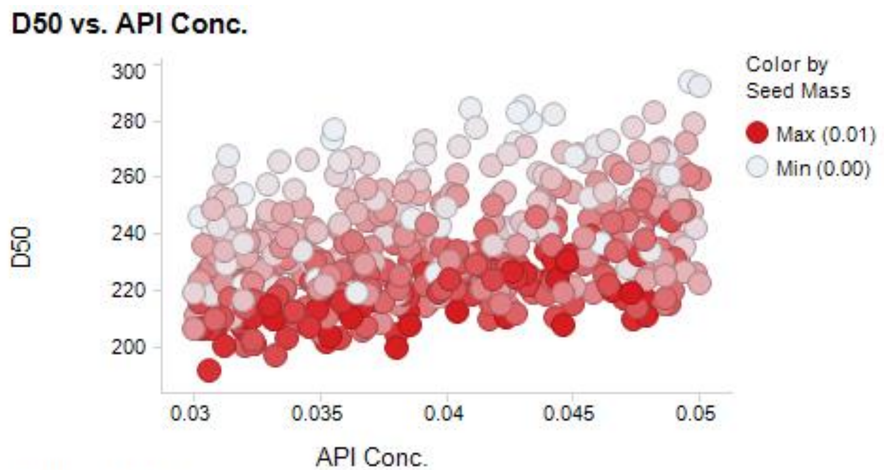


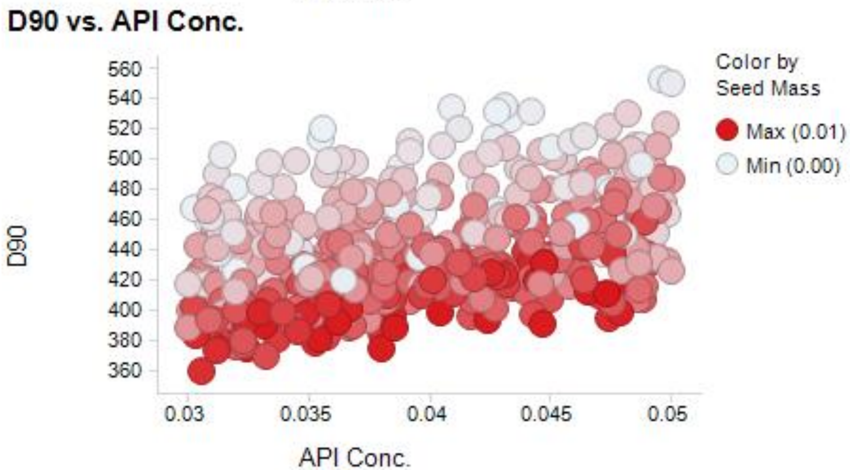
D43 vs. API Conc.

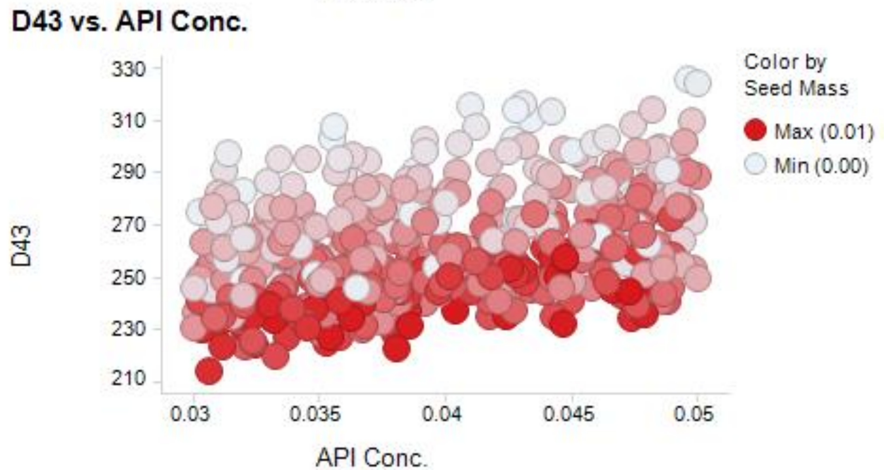


Effect of Initial API Concentration in Solution on Crystal PSD



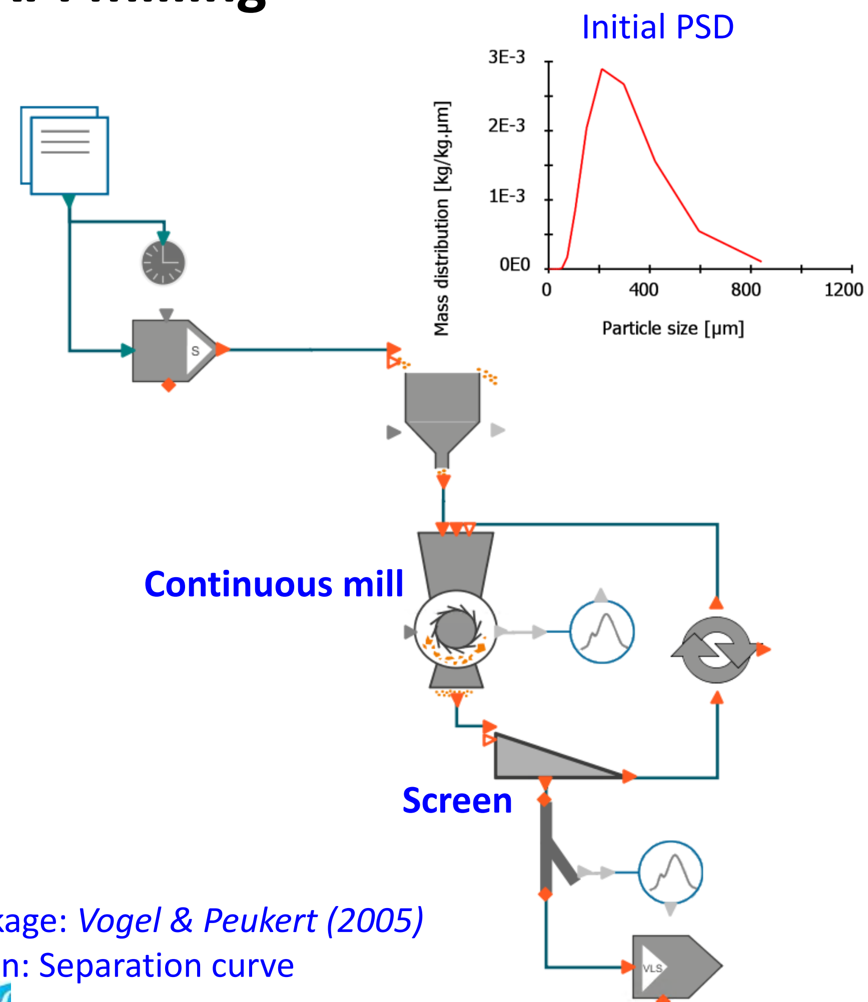






API Hammer Mill Model

API milling



Breakage: *Vogel & Peukert (2005)*
Screen: Separation curve

Processing conditions:
0h - 6h Constant operation
Flowrate 1.5 kg/h

Input variables:
- Crystal PSD (fixed from crystallizer)
- Impact energy (5,000-10,000 J/kg)
- No. impacts (1-10)
- Power law exponent (0.3-3)
- Screen aperture size (100-1,000 µm)

Physicochemical parameters:
- Material strength parameter (0.5 kg/Jm)
- Breakage rate constant (0.01 s^{-1})
- Product of threshold energy and particle size (0.25 Jm/kg)
- Range of non-ideal separation in screen (50 µm)

Output variables:
- Milled API PSD

Milling Breakage Parameters

Process parameters

k is the number of successive impacts or stressing events [-],

$W_{m,kin}$ is the mass specific impact energy to cause particle breakage [J/kg],

Material parameters

$W_{m,min}$ is the mass specific threshold energy that a particle can absorb without fracture [J/kg],

q is a kernel function to model breakage size distribution ($q<0$) [-],

x' is the fragment size from which on the additional fading of the power law becomes significant [m],

$f_{Mat.}$ characterises the particulate material resistance against fracture in impact comminution [kg/J/m],

$$B_{M,p}(x,y)=\left(\frac{y}{x}\right)^{q}\frac{1}{2}\left(1+\tanh\left(\frac{x-x'}{x'}\right)\right)$$

$$P_B(y)=1-\exp\left(-f_{Mat}\,y\,k\left(W_{m,kin}-W_{m,min}\right)\right)$$

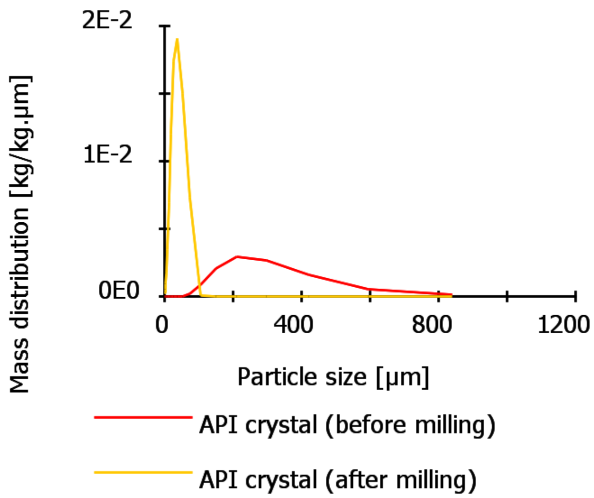
Results from single mill simulation

API milling

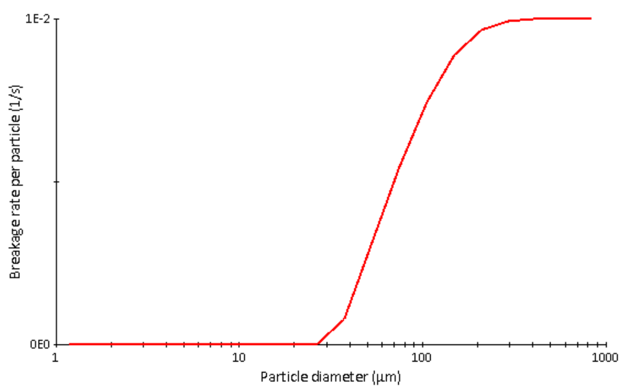
Scenario

- Impact energy (7,500 J/kg)
- No. impacts (5)
- Power law exponent (2)
- Screen aperture size (100 µm)

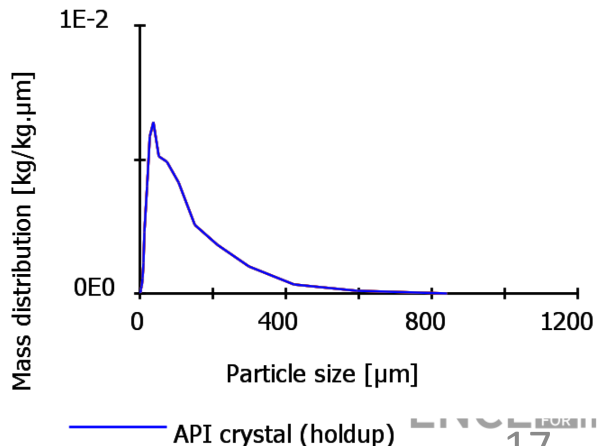
PSD before and after milling



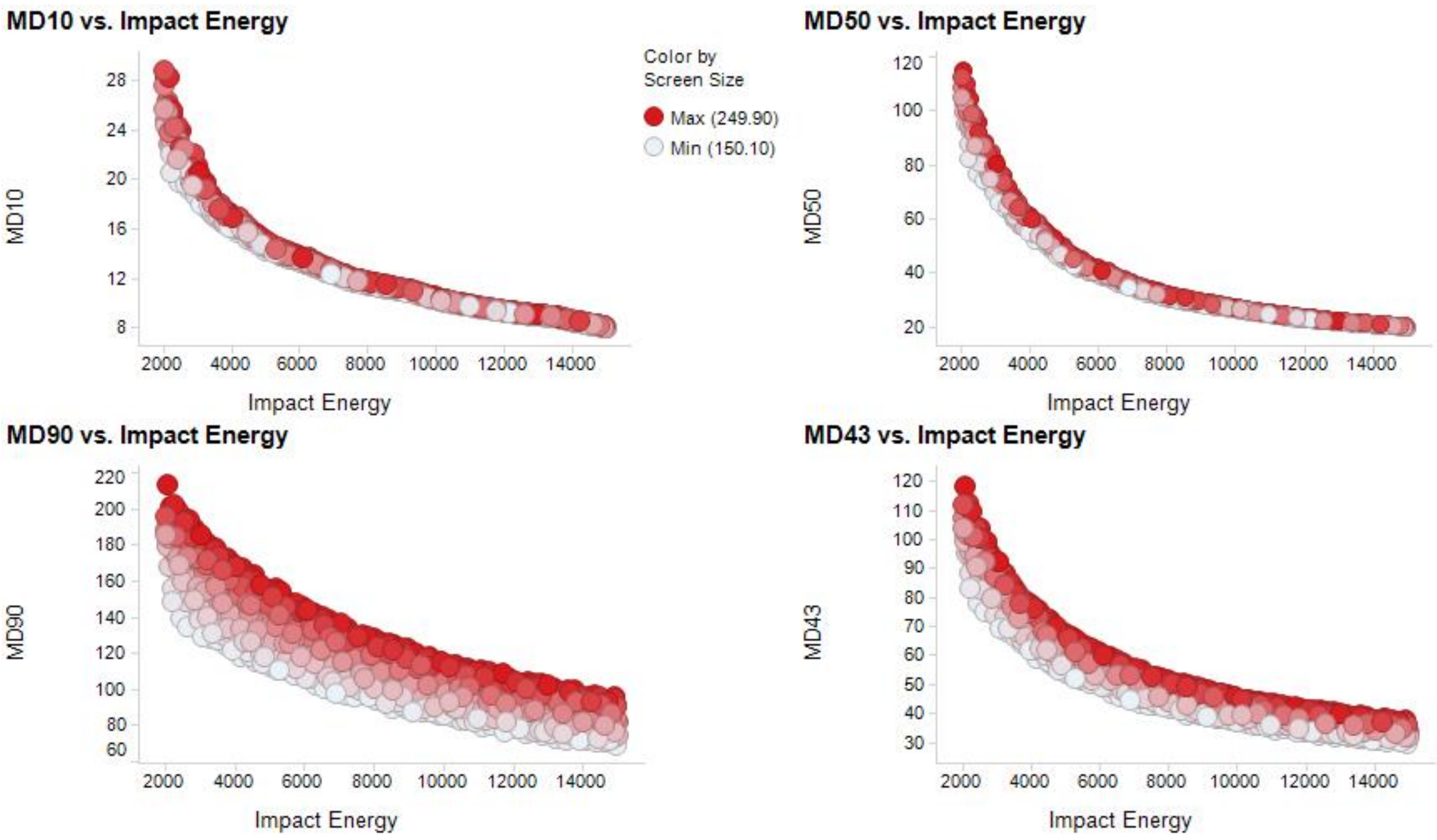
Breakage rate per particle size



PSD within the unit

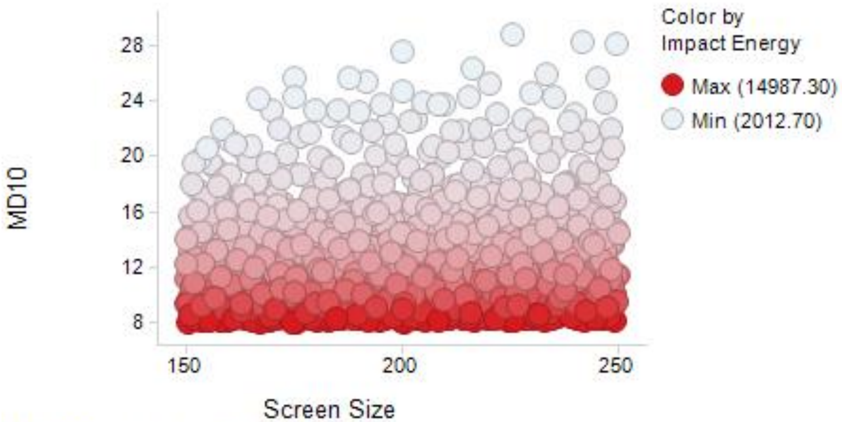


Effect of Impact Energy on the Milled PSD

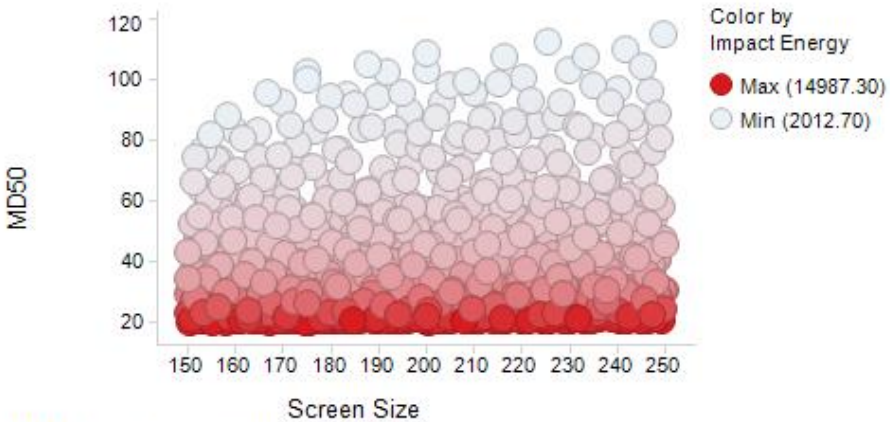


Impact of Screen Size on Milled PSD

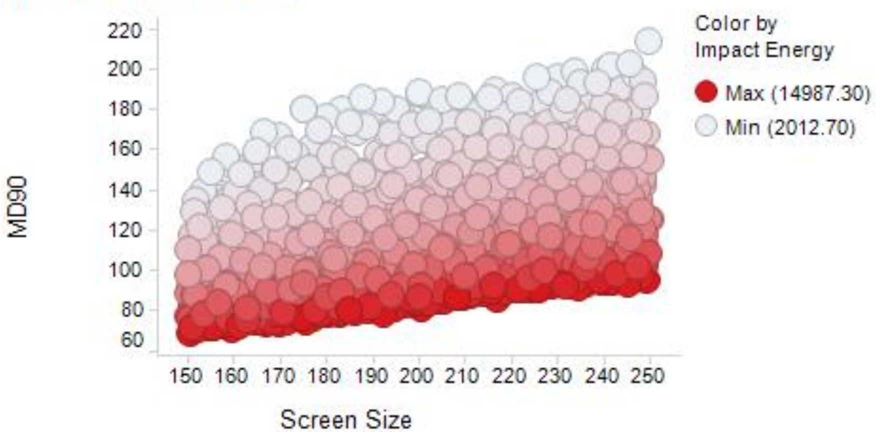
MD10 vs. Screen Size



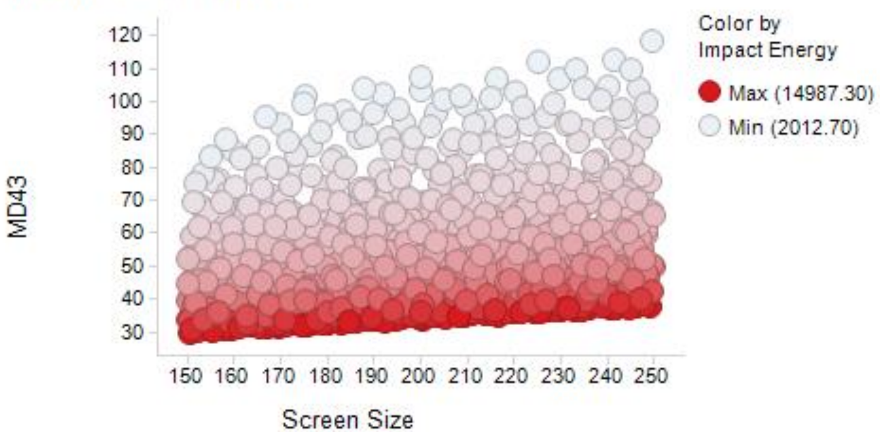
MD50 vs. Screen Size



MD90 vs. Screen Size

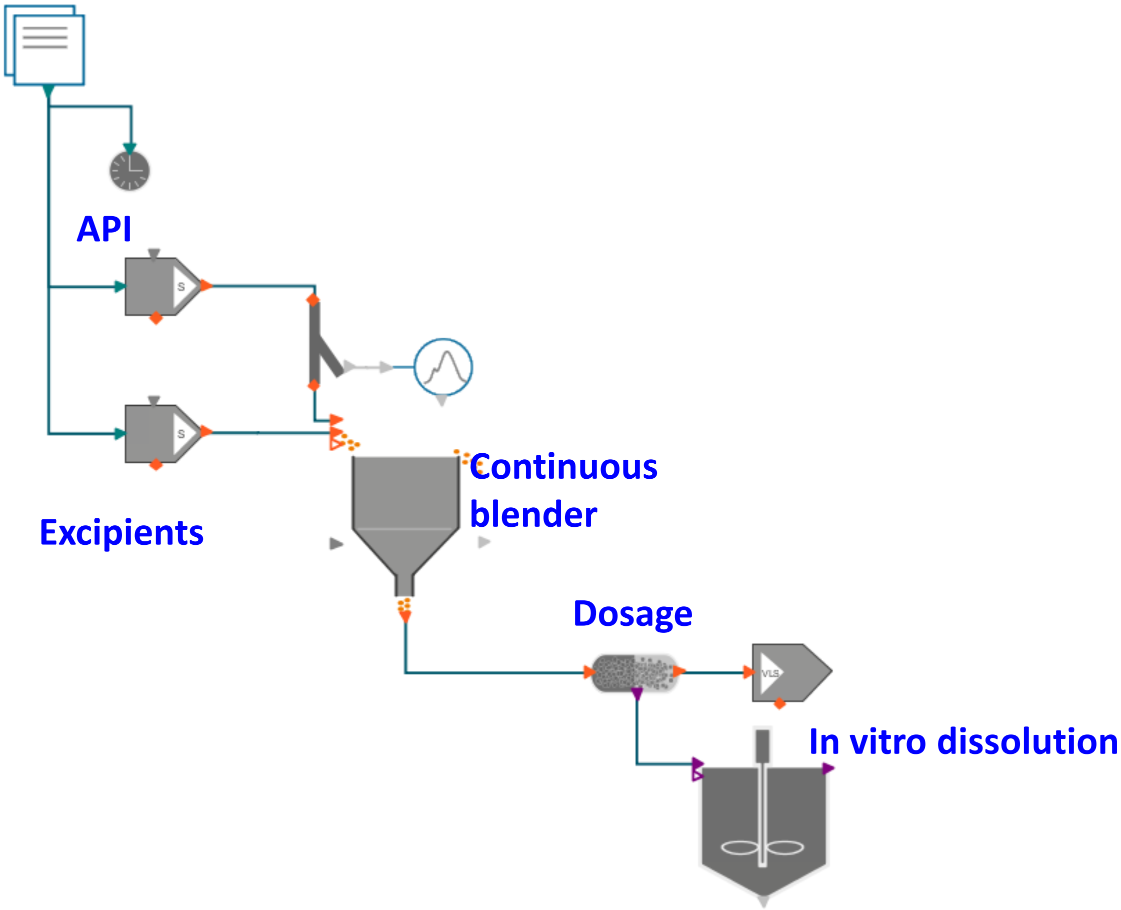


MD43 vs. Screen Size



In Vitro Dissolution Model

Drug product formulation and in vitro dissolution



Processing conditions:
- Media pH (4.5)
- Media volume (250 ml)

Input variables:
- API PSD (Lognormal with mean size)
- Drug load (10 %w)
- Dosage time (0 h)
- Tablet mass (100-500 mg)
- API diffusivity (50-500 $\mu m^2/s$)

Physicochemical parameters:
- API solubility (3.25 mg/L)
- Neutral compound

Output variables:
- API fraction dissolved
- API mass dissolved

Results from single dissolution simulation

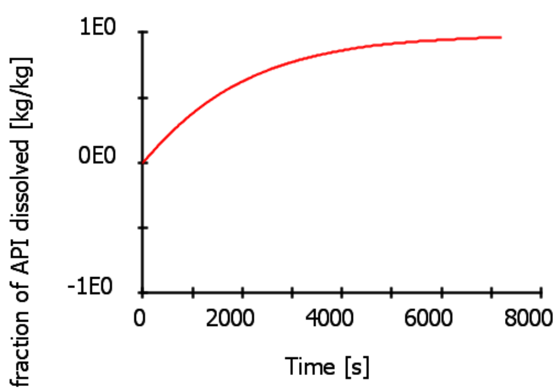
Drug product formulation and in vitro dissolution

Scenario

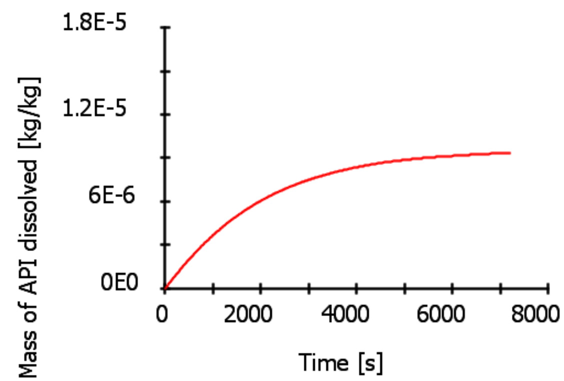
- API PSD (fixed from milling)
- Drug load (10 %w)
- Dosage time (0 h)
- Tablet mass (100 g)
- API diffusivity (500 µm^2/s)

API mass per dose = 10 mg
Fraction dissolved in 15 min = 0.346 mg/mg API in dose
Fraction dissolved in 2 h = 0.965 mg/mg API in dose

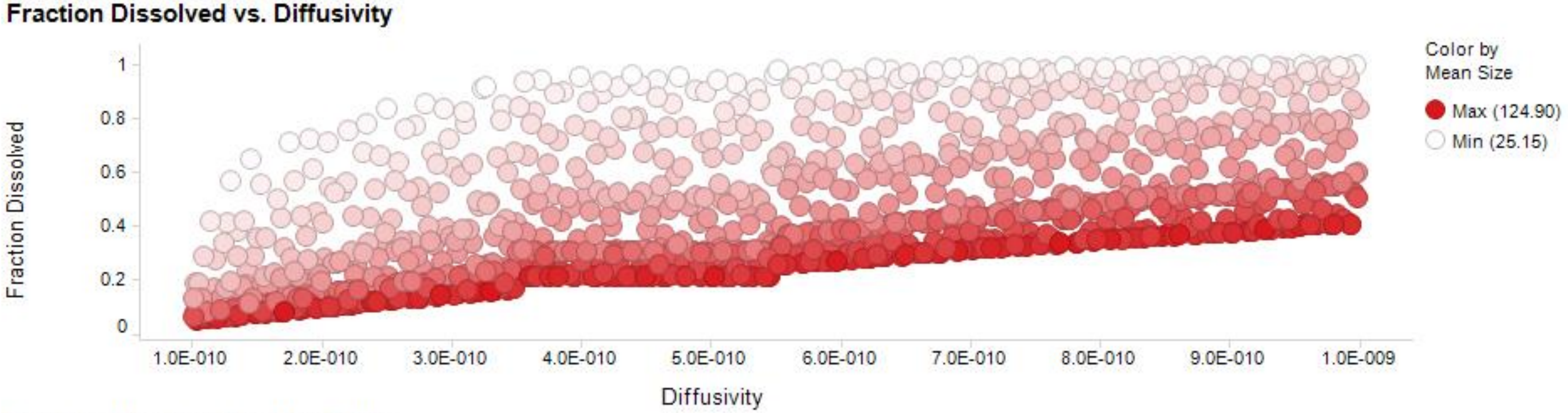
Fraction of total API dosed dissolved

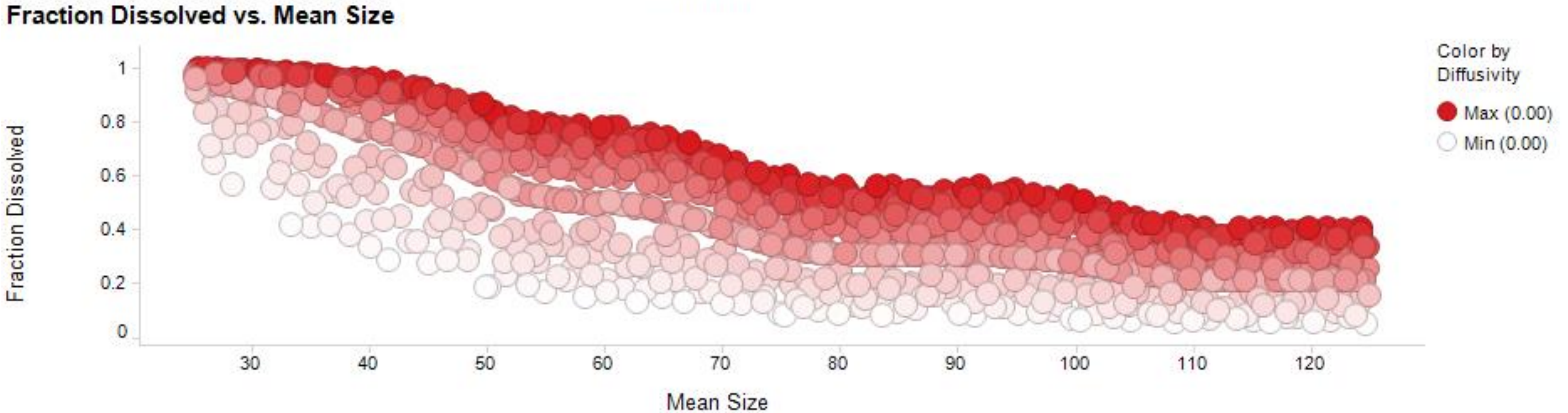


Mass of API dosed dissolved



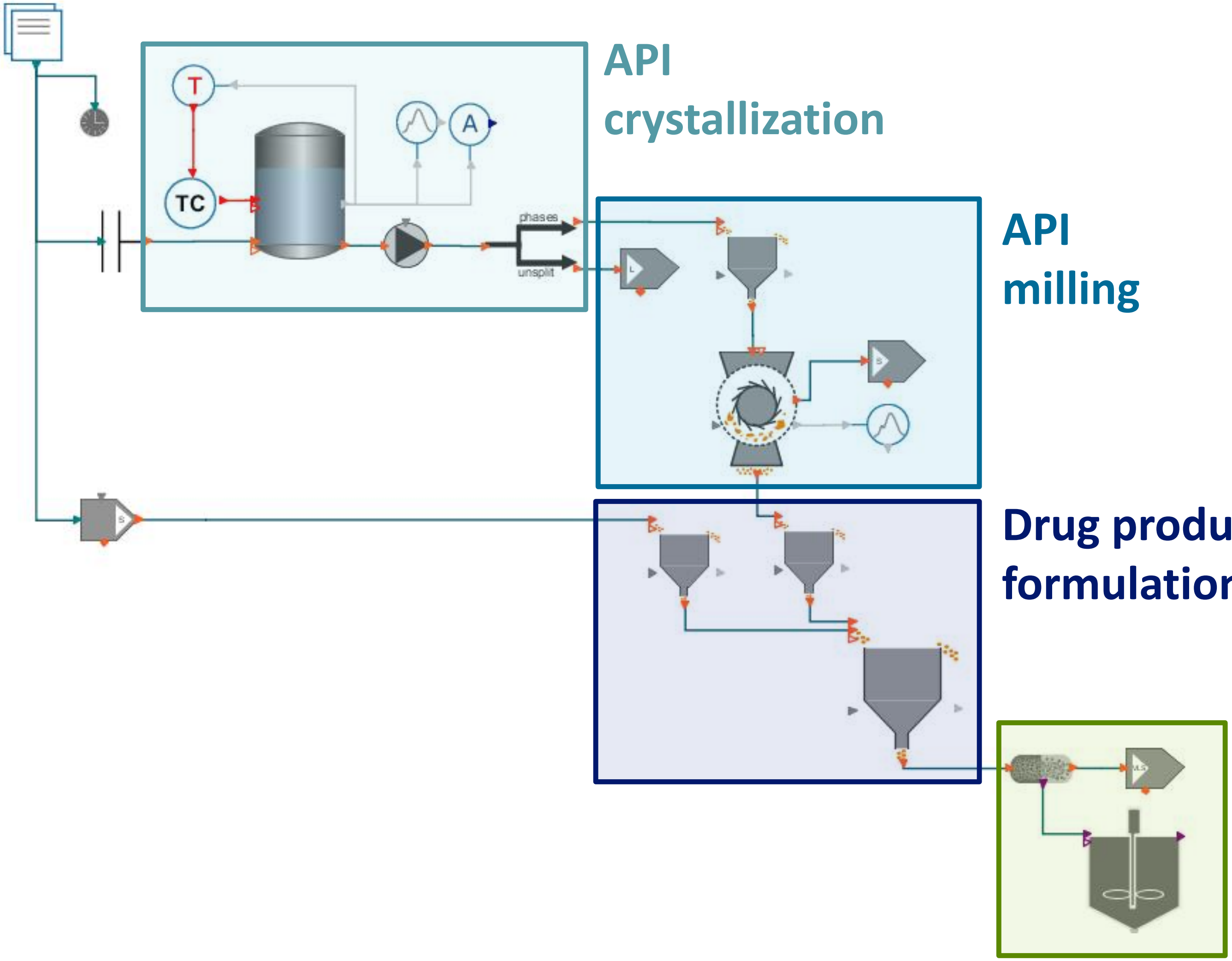
Dissolution_diff





Interconnected flowsheet

Interconnected drug manufacturing to performance



API crystallization

API milling

Drug product formulation

Drug product performance

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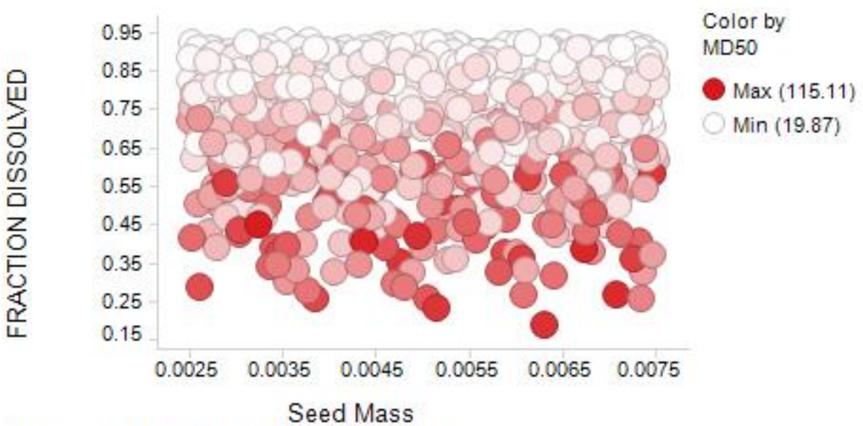
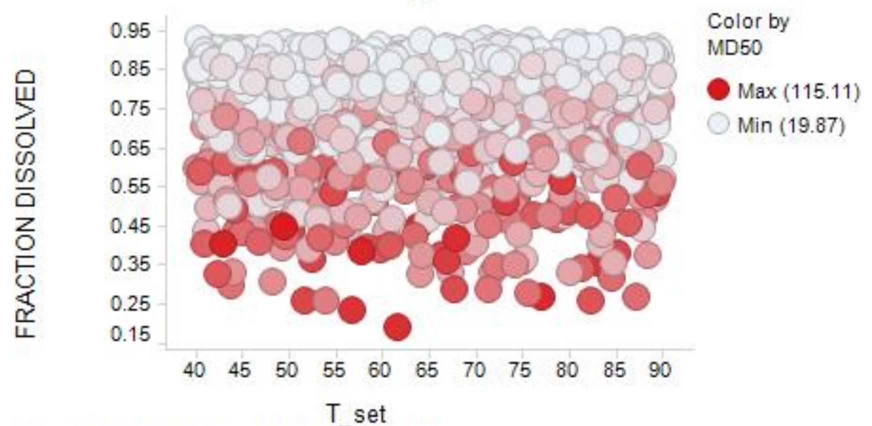
Effect of Crystallization Process on Fraction Dose Dissolved

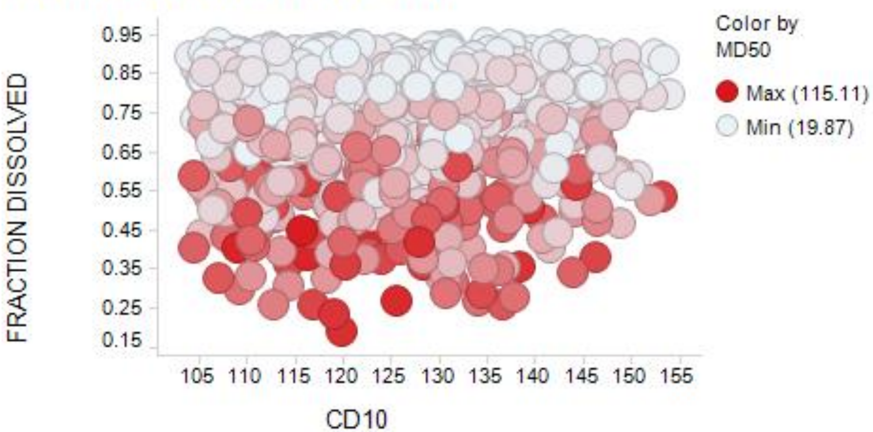
FRACTION DISSOLVED vs. Seed Mass



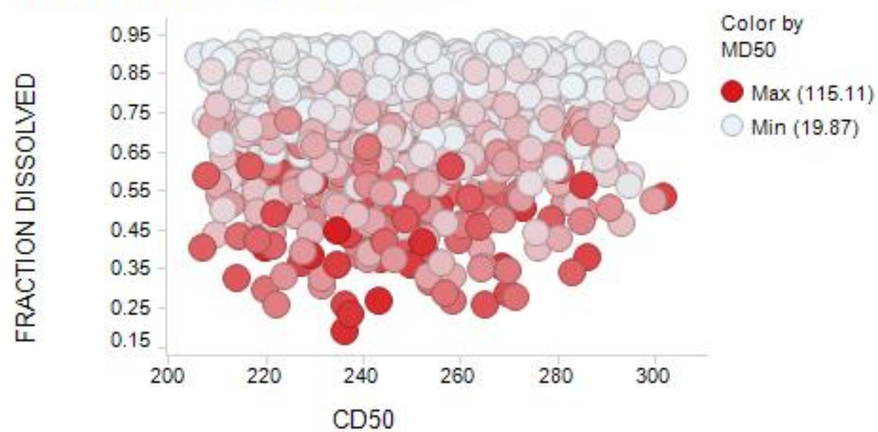
FRACTION DISSOLVED vs. T_set



FRACTION DISSOLVED vs. CD10

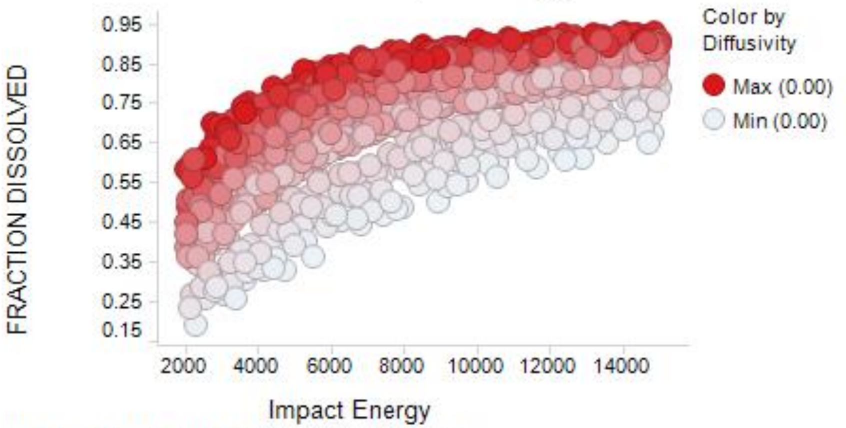


FRACTION DISSOLVED vs. CD50

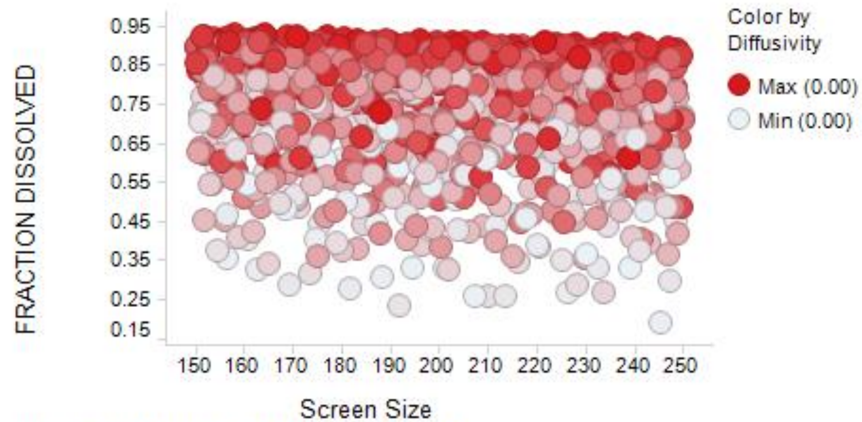


Effect of Milling Process on Fraction Dose Dissolved

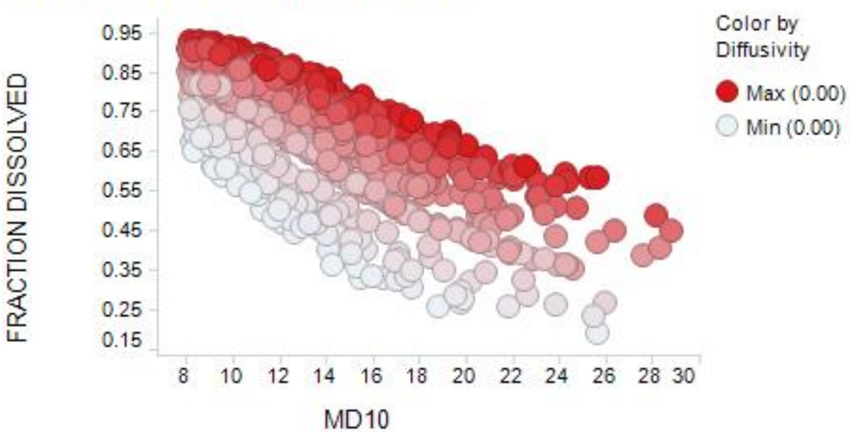
FRACTION DISSOLVED vs. Impact Energy



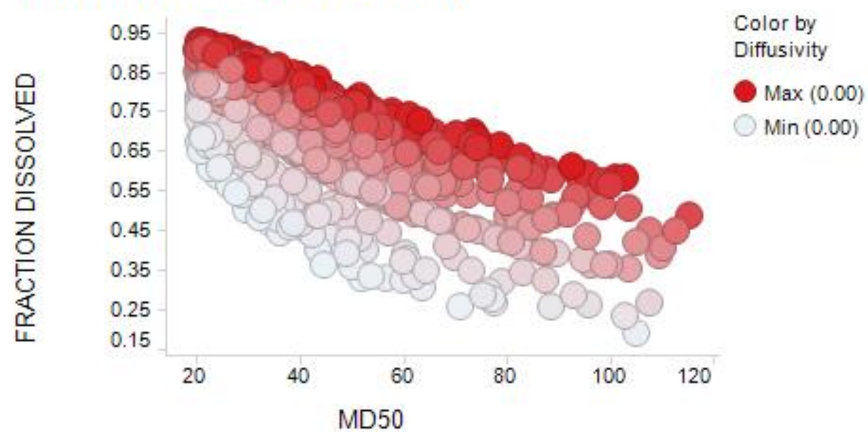
FRACTION DISSOLVED vs. Screen Size



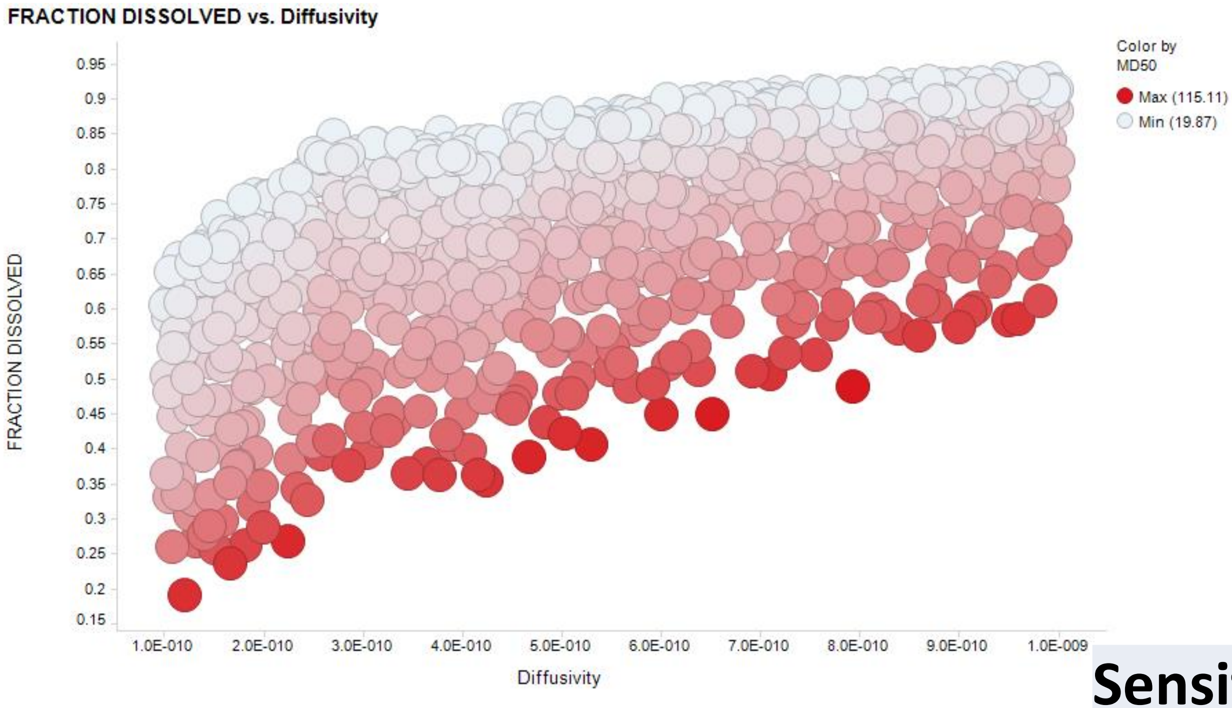
FRACTION DISSOLVED vs. MD10



FRACTION DISSOLVED vs. MD50



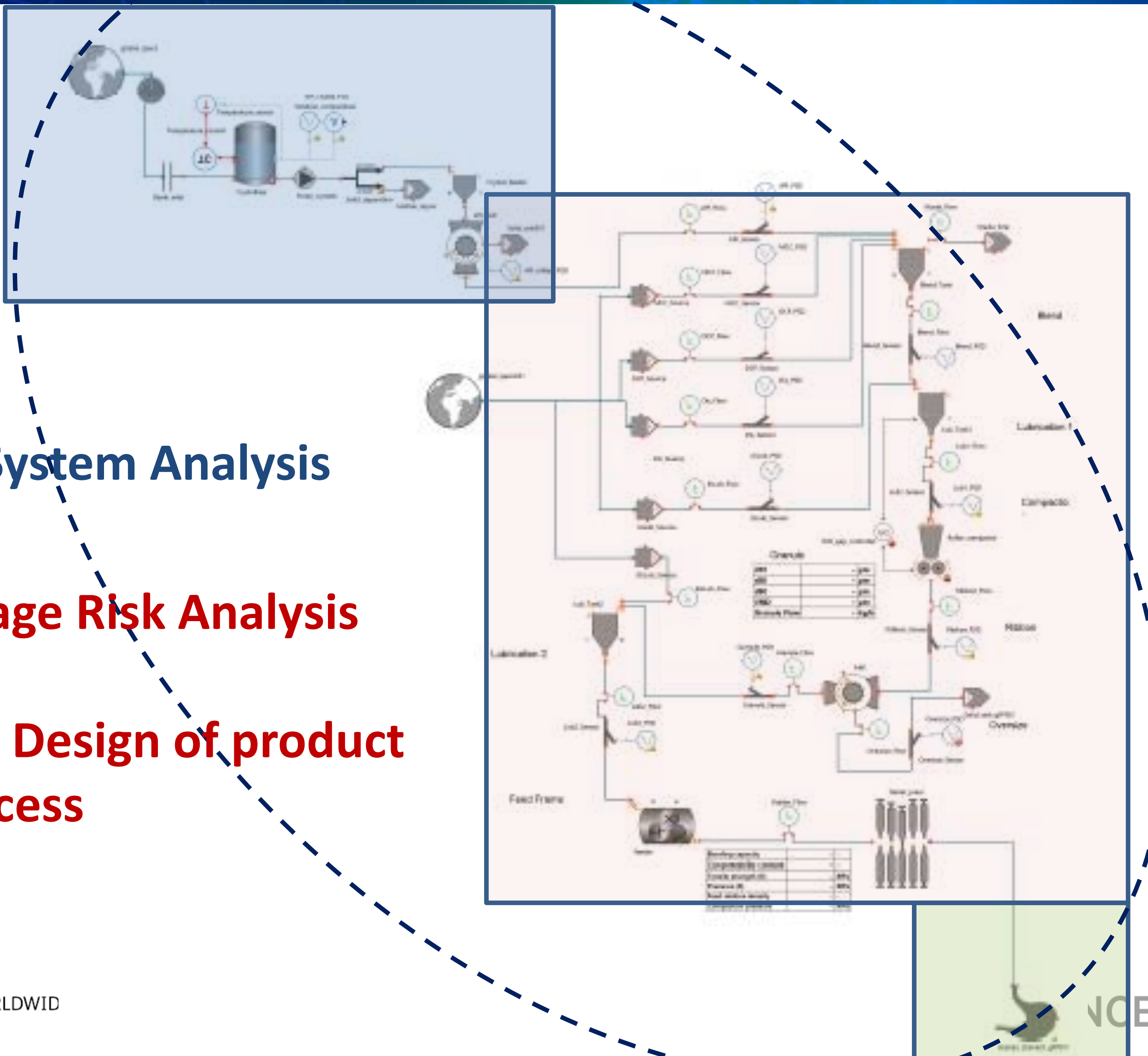
Effect of API Diffusivity on Fraction Dissolved



Sensitivity Indices

Parameters	First Order Effect	Total Effect
Impact Energy	0.58	0.62
Screen Size	0.01	0.01
Seed Mass	0.02	0.00
Tset	0.02	0.00
Diffusivity	0.37	0.41

Long term Vision: Digital Design



Global System Analysis

Early Stage Risk Analysis

Optimal Design of product and process

Conclusions

- Global System Analysis enables a comprehensive study of interconnected flowsheet models

- Seamless execution of large number of simulation (Virtual DOE) and aggregation of relevant output in a widows based “HPC environment” is a very powerful feature

- Extension to a Linux based HPC environment or Cloud computing infrastructure will be a very desirable feature

- Virtual DOE enables “stress testing of the model” leading to more rigorous verification and also exposing some shortcomings

- Sensitivity Analysis helps in dimensionality reduction

- Seamless, integrated *in silico* modeling from API and drug product manufacture to oral absorption will become part of work-flow

Acknowledgement

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