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THE ADVANCED PROCESS MODELLING COMPANY

Pharmaceutical Process & Product Development: What can Process Systems Engineering contribute?

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FIPSE

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Outline

1. Systems Engineering

2. Pharmaceutical Systems
   a. Drug substance manufacturing
   b. Drug product manufacturing
   c. Oral absorption & pharmacokinetics

3. Systems-based Pharmaceutics

4. Fundamental challenges & opportunities
   a. Materials properties & behaviour for Systems-based Pharmaceutics
   b. Design Space in pharmaceutical manufacturing

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1. Systems Engineering

(a short introduction for people in pharmaceutics)

Science and Engineering

H.A. Simon, "*The Sciences of the Artificial*" (1996, 3rd edition)

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- Science
  - aim: understanding of nature
  - examples: Physics, Chemistry, Biology/Biochemistry
- Engineering
  - aim: manipulation of nature to achieve specific objectives
  - examples:
    - Civil/Mechanical/Electrical/Chemical Engineering
    - Pharmacy
    - Medicine

Systems Engineering

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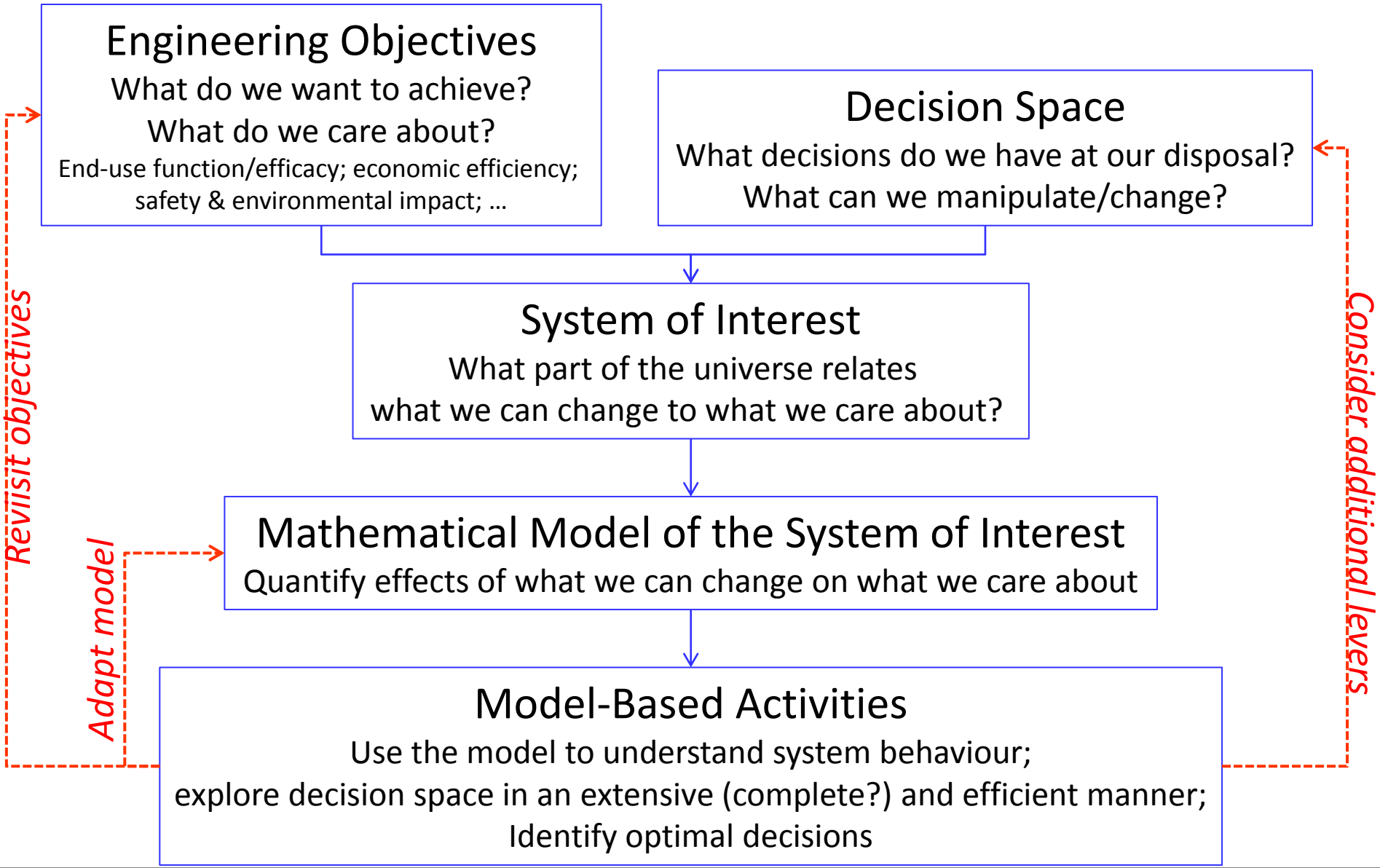
- *Systems*: complex entities comprising multiple interacting components
  - potentially complex components
  - potentially complex interactions
  - →complexity can arise both from the components themselves and from their interactions
- *Engineering* : focuses on achievement of specified objectives
- Distinguishing characteristics:
  - *Mathematical models* are used to capture scientific knowledge on component behaviour
    - not necessarily “first-principles” models
  - *Model integration*: from components to systems
  - *Model-based activities* use advanced mathematical techniques to extract value out of models

The Systems Engineering approach is a

Top-Down Approach



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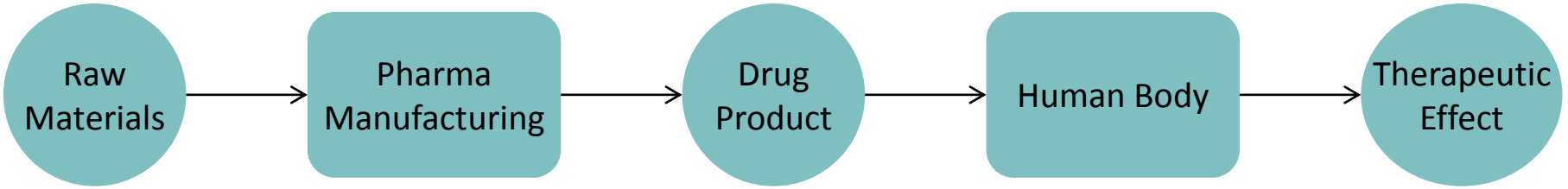
2. Pharmaceutical Systems

Key drivers in pharmaceutical industry



- External
  - end-use functionality & effectiveness
  - other product quality attributes (e.g. stability)

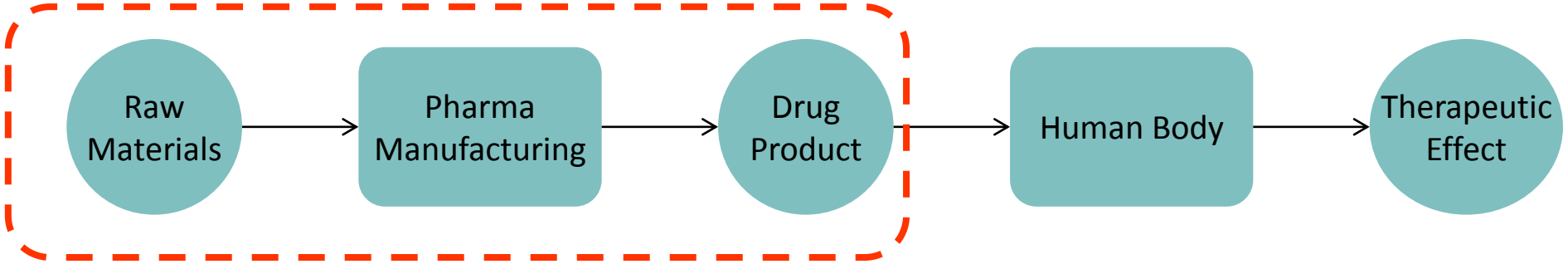
Regulation

ICH Q8 (3):
"Quality: The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity."

- Internal
  - R & D efficiency
  - time-to-market
  - efficiency of manufacturing
  - competitiveness & competition

Economic viability

Pharmaceutical systems – I



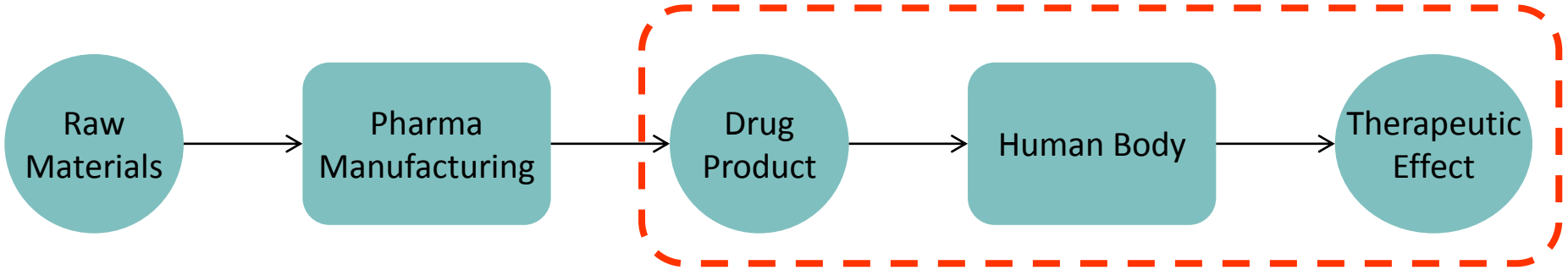
Step 1: Drug Substance manufacturing
Producing the active pharmaceutical ingredient (API)

- Reaction
- Distillation
- Crystallisation
- Agitated filter drier
- Centrifuge (horizontal; vertical)
- Single plate filter
- Drier (pan; tray/shelf))
- Milling (wet; dry)
- Sensors
- . . . . . .

Step 2: Drug Product manufacturing
Producing the drug delivery form (tablet, capsule etc.)

- Dry blending
- Continuous mixing/blending (PF/CST/other)
- Delumping (eliminate soft aggregates)
- Screw conveyor / feeder
- Granulation (fluid bed; high-shear wet)
- Drying (fluid bed; tray; spray)
- Roller compactor;
- Milling
- Fluid bed coating of particulates
- Hopper/storage: transfer to tablet press /capsule filling machine
- Encapsulation
- Compaction
- Coating of tablets
- . . . . . .

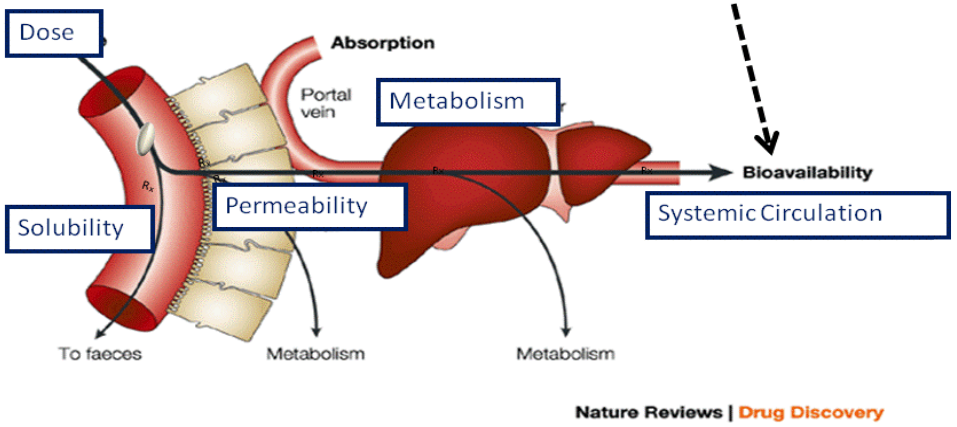
Pharmaceutical systems – II



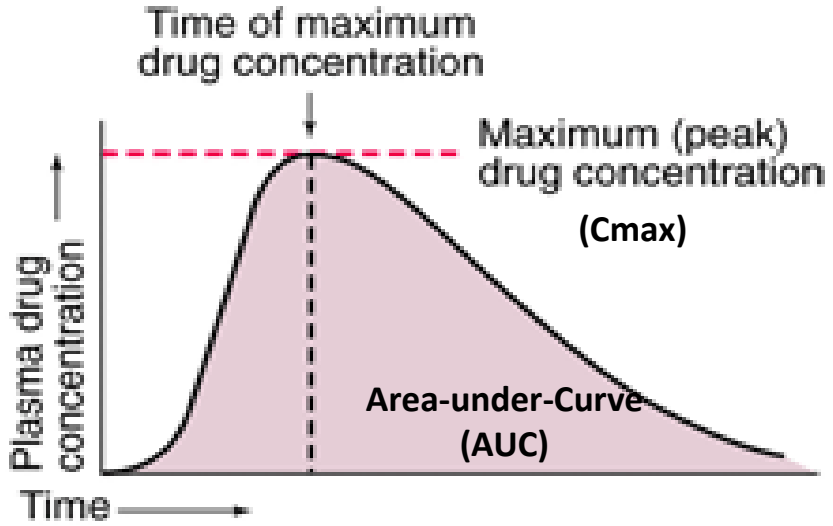
Step 3: Oral Absorption/Pharmacokinetics
Getting the drug into the systemic circulation

Step 4: Pharmacodynamics
Therapeutic effect on body

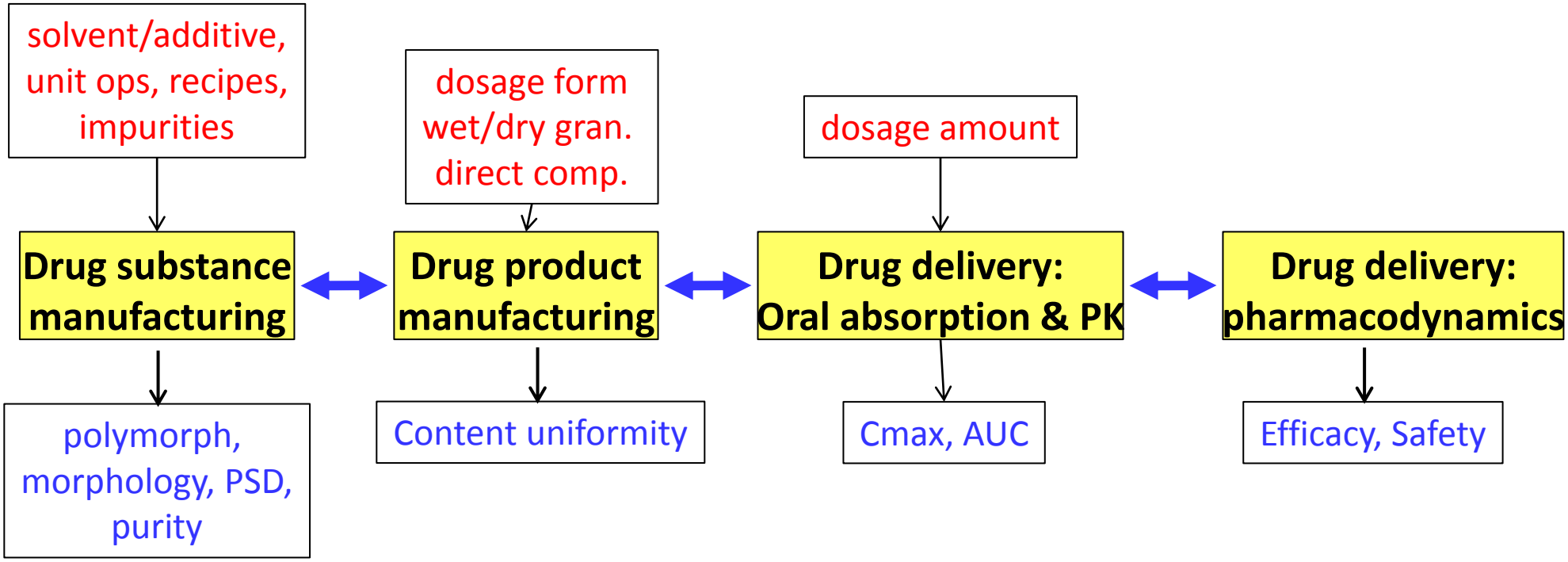
- Bioavailability: the extent to which the dose reaches systemic circulation



Nature Reviews | Drug Discovery



Decisions



Objectives/KPIs

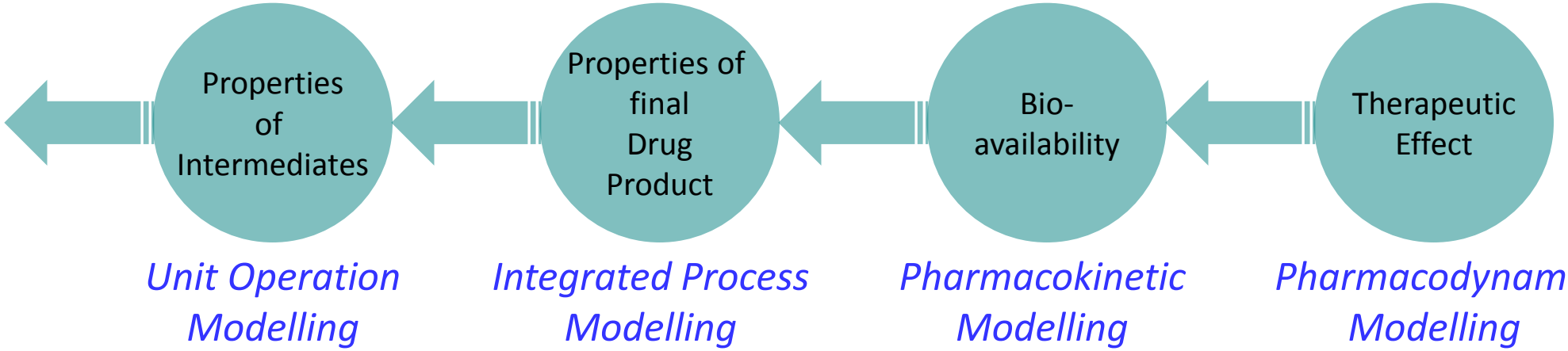
From real to surrogate objectives

- Many decisions & constraints; complex interactions

→ **Process Systems approach: effective/efficient exploration of decision space**

- **BUT…**
  - incomplete knowledge/understanding of parts of the system
  - inability to handle modelling complexity of entire system
  - organisational silos & barriers

→ **from real to surrogate objectives**



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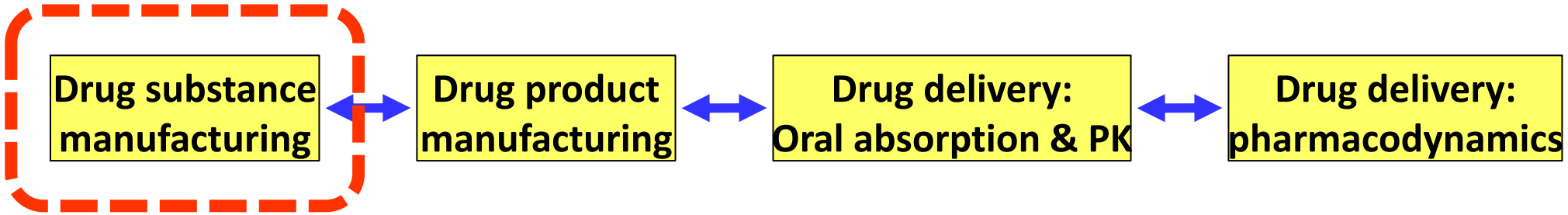
2a. Drug substance manufacturing



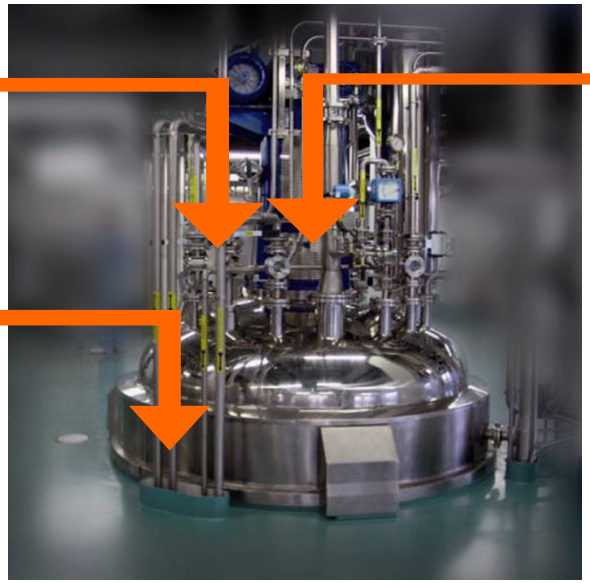
Drug substance manufacturing

- Closest to chemicals/fine chemicals sector, e.g. in terms of unit operations
  - reaction, distillation, crystallisation, filtration, drying…
- Key challenges for model-based engineering approach
  - complex molecules
  - complex chemistry
  - batch/semi-batch operations
  - (some) solids
  - mixing imperfections/scale-up
  - batch-to-continuous conversions

Drug substance manufacturing

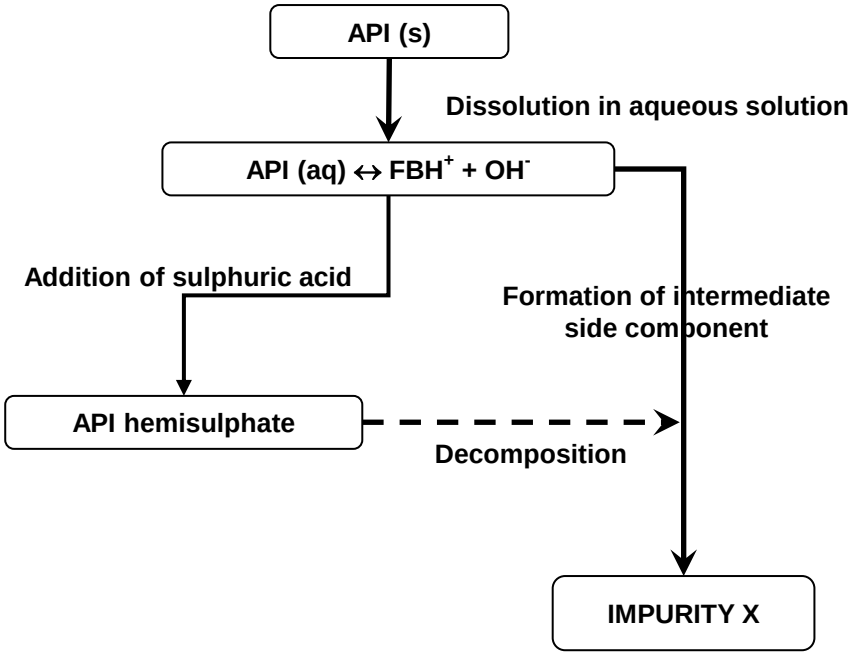
Reaction recipe optimisation & scale-up

Reagent, pH control addition profile?



Impeller speed/size / location ?

Heating/ cooling profile ?



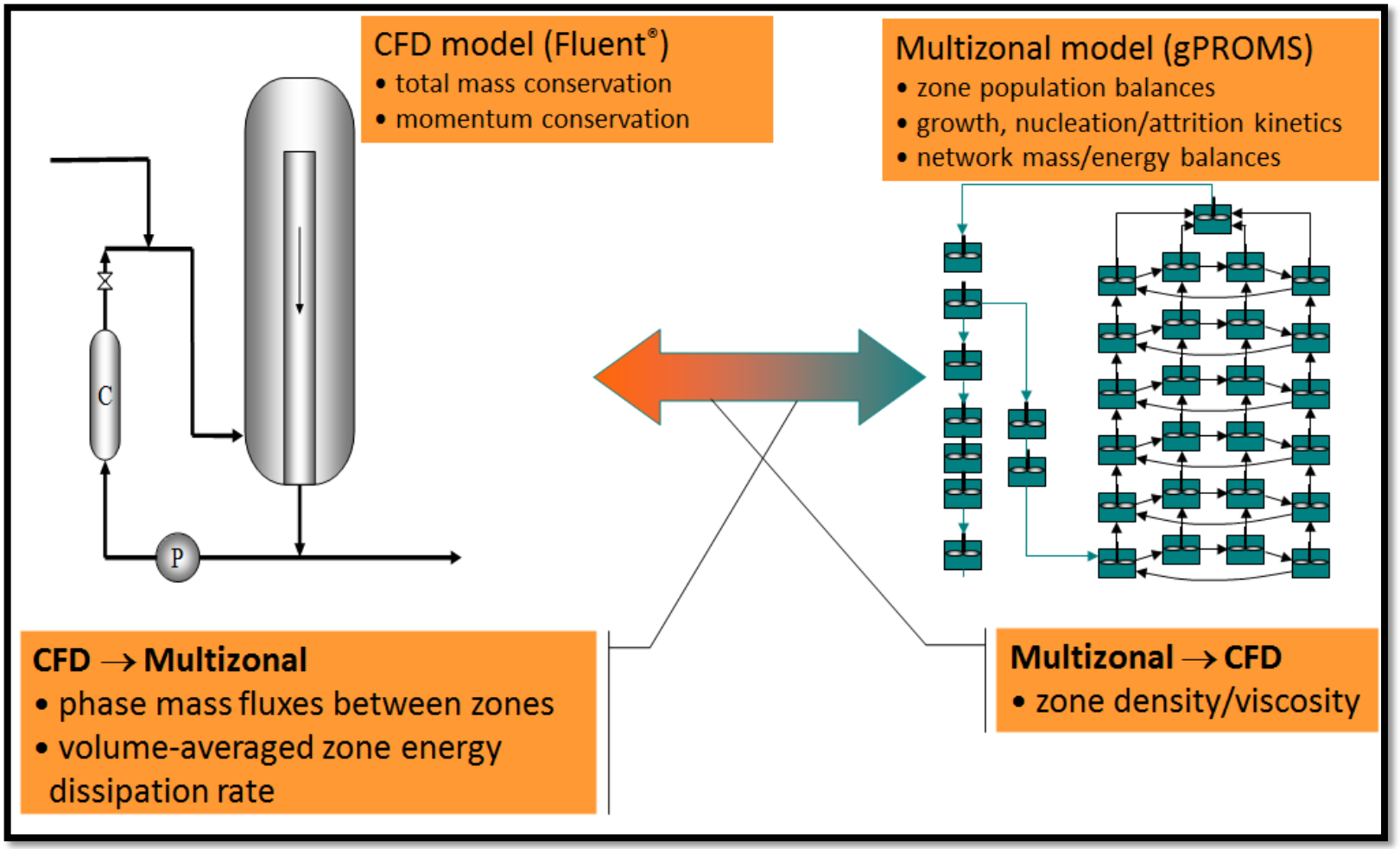
Key objective: minimise loss of batches due to unacceptable impurity levels (~€100k per batch)

Approach: mass-transfer limited dissolution of solid raw material*
kinetics of main & side- reactions*
hybrid multizonal/CFD modelling
dynamic optimisation of recipe

* Coupling with small-scale experiments

Hybrid multizonal/CFD equipment modelling

Agitated tank equipment



Bezzo, Macchietto & Pantelides,
***Comput. chem. Engng.* (2004), 28, 501-511; *AIChE J.* (2005), 28, 1169-1177**

Results

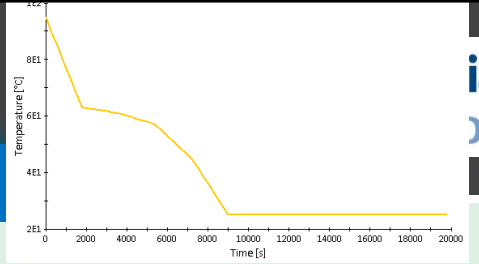
- Optimise addition profile to minimise impurity formation
- Eliminate mixing imperfections
- Keep reactor out of “danger region”
  - low pH, high temperature
- Optimal recipe validated experimentally

Crystallisation from solution

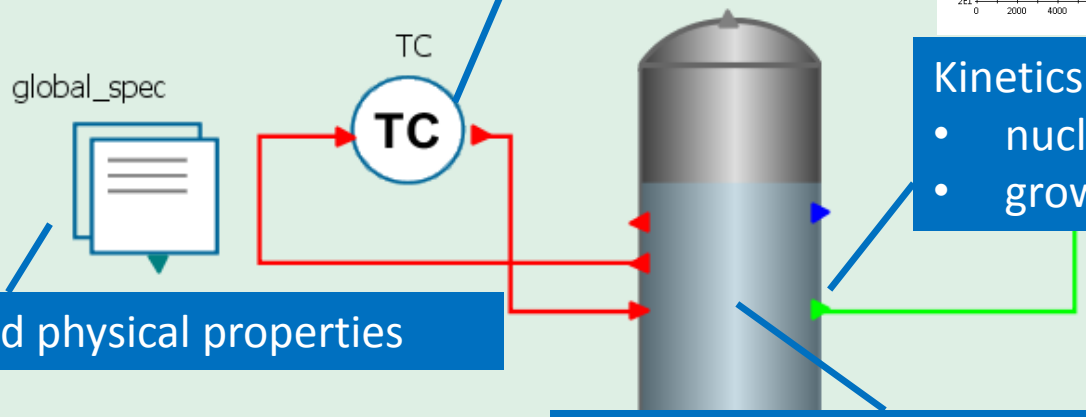
- Models based on 1-dimensional particle size distributions (PSD) are now routine from technological point of view
- Models incorporate all key phenomena
  - nucleation (primary + secondary)
  - growth
  - attrition
  - agglomeration
- Model-based engineering approach
  1. model identification based on experimental measurements
     - requires small number of batch experiments
  2. dynamic optimisation for recipe optimisation
  3. model-based scale-up

Drug substance manufacturing

Crystallisation from solution



Temperature Profile



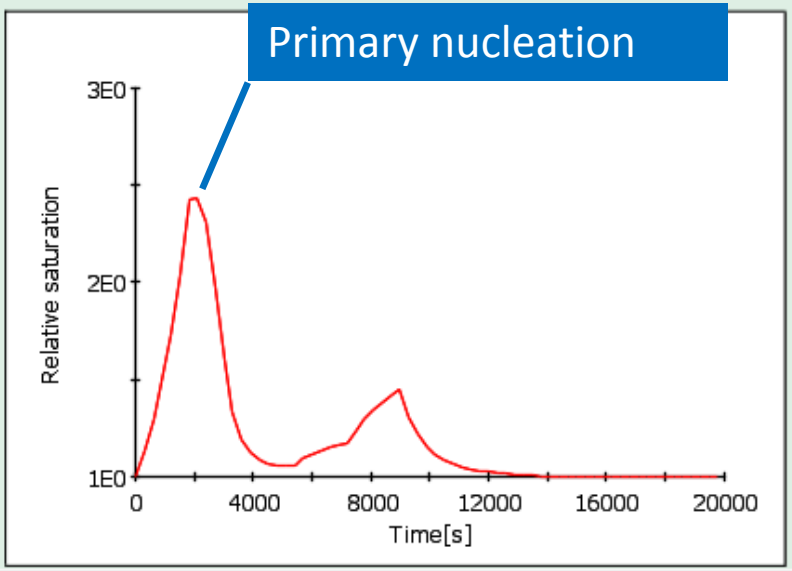
Kinetics of crystallisation

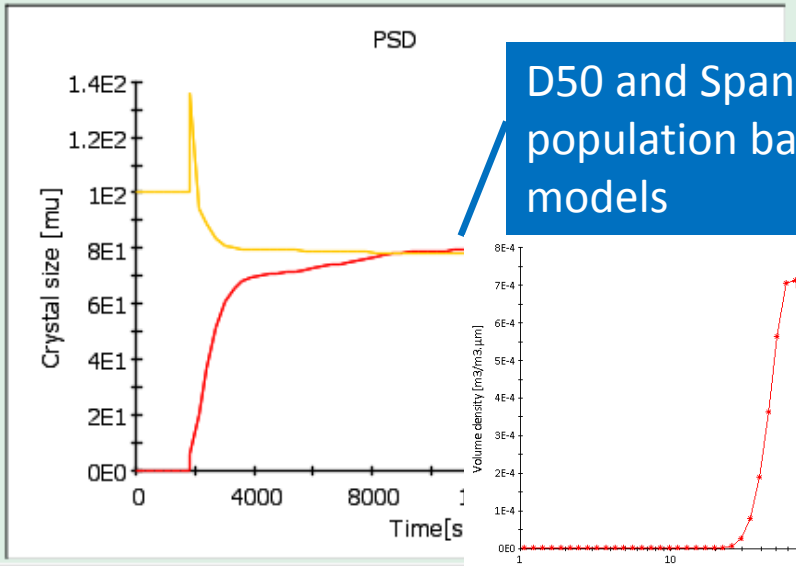
- nucleation (primary and secondary)
- growth

Solubility and physical properties

Equipment configuration (power input)
Initial conditions (temp, volume, comp)

Primary nucleation





D50 and Span using population balance models

Solution crystallisation case study – 1 (GSK/PSE*)

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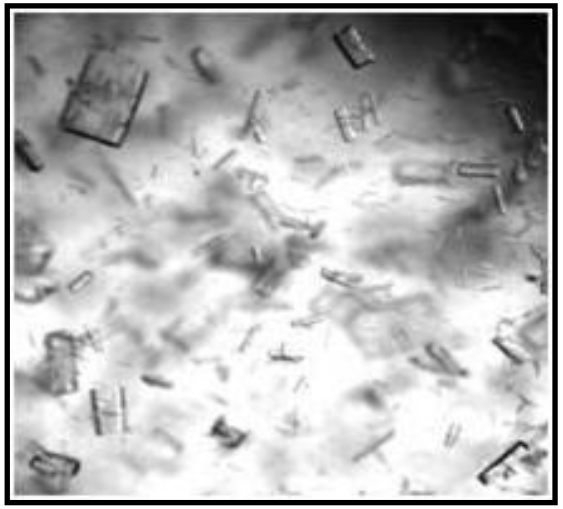
- Batch seeded cooling crystallisation of an API from an organic solvent
- Sampling strategy
  - solute concentration and PSD throughout the crystallisation
  - not standard sampling regime
- Data set of 8 experiments varying
  - agitation
  - supersaturation
  - seed PSD
  - T seeding
  - cooling rate

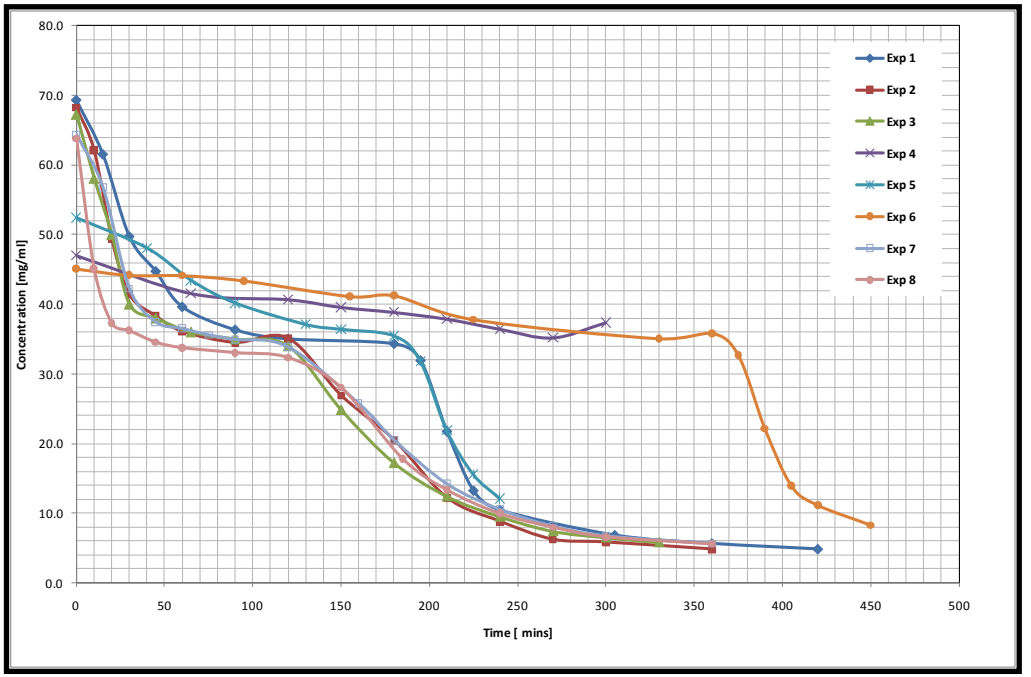
***Bermingham, Cocchini,**
"Model-Based Decision Support for Design and Operation of Pharmaceutical Crystallisation Processes: Efficient Workflows for Validation Against Experiments and Scale-up"
Paper #84c, AIChE Annual Meeting, Minneapolis, October 2011.

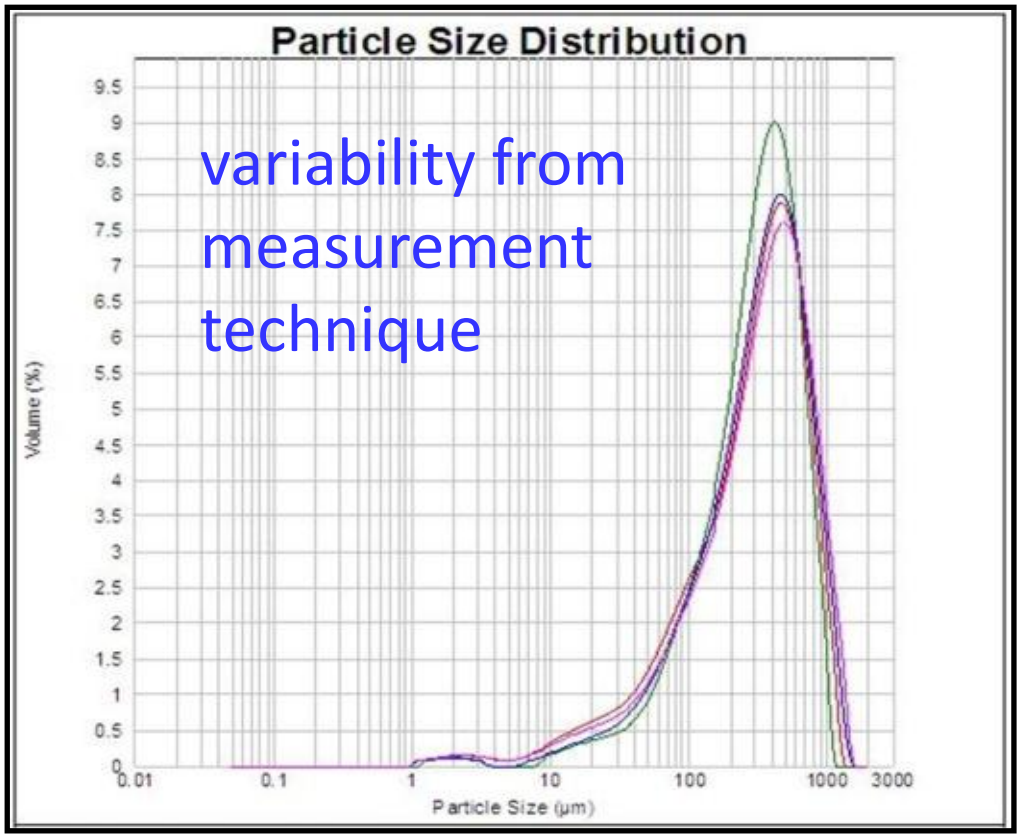


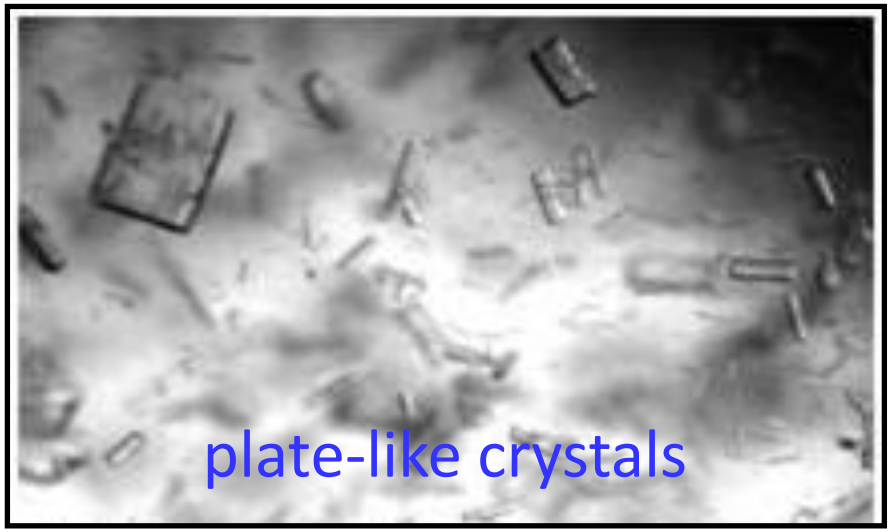
Exp		Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Run 7	Run 8
API	g/l	69.3	66.8	67.0	**47.0**	**52.4**	**45.7**	**64.4**	**63.8**
Seed Load	%	**0.7**	**0.5**	**0.4**	**0.5**	**0.5**	**0.7**	**0.5**	**0.4**
Stirrer speed RPM		216	**407**	217	220	217	**379**	**407**	217
Seeding Temp	degC	70	70	70	70	70	70	70	70
Holding time	hrs	**3.0**	**2.0**	**2.0**	**6.0**	**3.0**	**6.0**	**2.0**	**2.0**
Final Temp	degC	5	5	5	5	5	5	5	5
Cooling time	hrs	1	3	3	no cooling	1	1	3	3
Rate of cooling	deg/min	**1.08**	0.36	0.36	na	**1.08**	**1.08**	**0.36**	**0.36**
Holding at final temp	hrs	14	14	14	0	14	14	14	14
Total exp time	hrs	18.0	19.0	19.0	6.0	18.0	21.0	19.0	19.0

Experimental data

- Solute concentration (HPLC)
- PSD (laser diffraction)
- Morphology (microscopy)







Dominant mechanisms and hypothesis

- Process designed to induce high level of nucleation following seeding

- Dendritic breeding/ activated surface nucleation
  - nucleation as a result of dendritic growth on surface of seed crystals
  - mainly occurring at high supersaturation, typically post seeding.

- Throughout the process
  - **growth** of seed crystals and the nuclei
  - attrition (contact nucleation)
  - **breakage** (evidence of breakage observed at low supersaturation)

Key physical phenomena

- Dendritic breeding

  Mersmann et. al, Chem. Eng. Sci. 57 (2002) 4267 – 4275

  - $B_s = k_s \frac{D_{AB}}{d_m^4} \exp\left(-\pi \frac{[K ln(C_c/C^*)]^2}{\upsilon \ln s_a}\right)$; $J_{db} = B_s A_T$

- Growth

  - mass transfer

    $$G(L) = k_d(L)\left[\frac{C_{bulk} - C_{int}(L)}{\rho_{crys}}\right] \qquad D_{AB} = \alpha \frac{kT}{\pi\eta \frac{d_m}{2}}$$

    $$k_d \quad L \quad = \frac{D_{AB}}{L}\left[2 + 0.8\left(\frac{\bar{\varepsilon} L^4}{\upsilon_L^3}\right)^{1/5}\left(\frac{\upsilon_L}{D_{AB}}\right)^{1/3}\right]$$

  - surface integration

    $$G(L) = k_g \exp\left(\frac{-E_{A,g}}{RT}\right)\left[\frac{C_{int}(L) - C_{sat}}{\rho_{crys}}\right]^g$$

- Breakage (taken from milling literature)

  Vogel & Peukert, Chem. Eng. Sci. 60 (2005) 5164 – 5176

Parameter estimation

Parameter	Initial Guess	Optimal Estimate
Width parameter RR distribution	3.00E+00	3.11E+00
Location parameter RR distribution	2.60E+02	2.33E+02
Dendritic breeding - K	4.14E-01	4.14E-01
Dendritic breeding - ln(ks)	-3.20E+01	-3.85E+01
Stokes-Einstein - alpha	1.00E+00	1.75E+00
Surface integration - kg	5.97E-05	1.00E-04
Surface integration - g	1.00E+00	1.25E+00
Surface integration - Ea,g	5.50E+03	2.85E+03
Breakage - k	2.00E+02	3.13E+02
Breakage - yprime	1.00E-04	4.22E-04

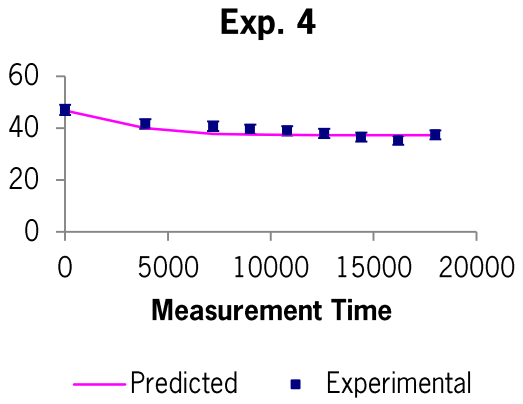
Dendritic breeding not active?!

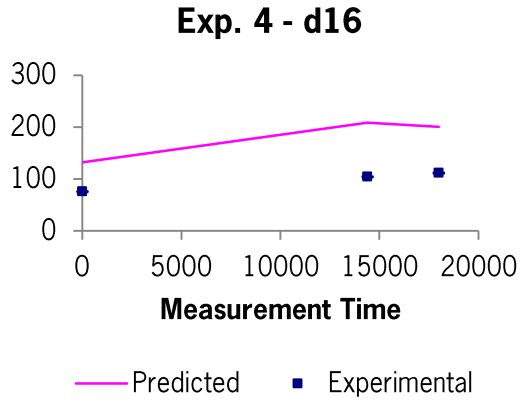
Increased mass transfer and surface integration to enable rapid depletion of supersaturation

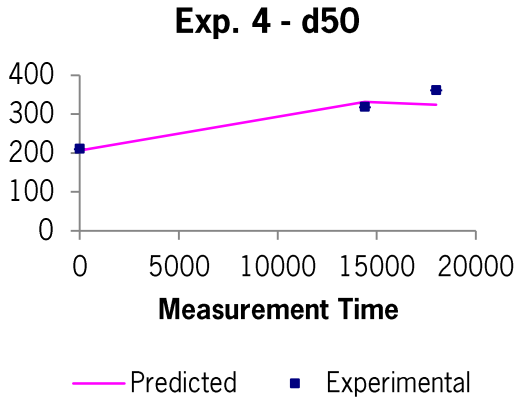
Significant breakage

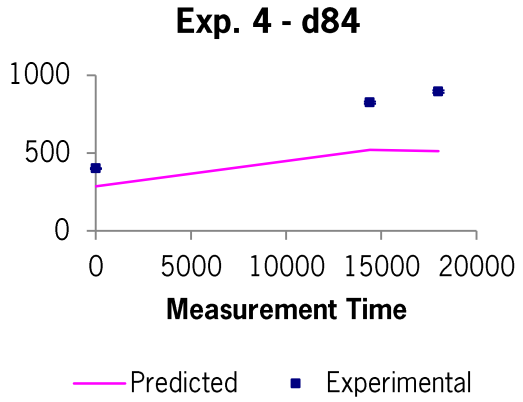
Testing of model predictions vs. experiment *not* included in parameter estimation

- Exp. 4: no cooling, desupersaturation only
- Good fit of solute concentration and d_{50}
- Model underestimates fines and coarse tail of PSD









Underestimation thought to be due to inherent error in laser diffraction measurement of PSD of non-spherical particles

Solution crystallisation case study – 2 (Pfizer/PSE*)

- Batch cooling crystallisation
  - no seeding
- Primary nucleation

$$J_{prim} = A_0 \exp\left(\frac{-16\pi\sigma^3 v_0^2}{3k^3T^3 \ln\ S^{\ 2}}\right)$$

- 2-step growth mechanism

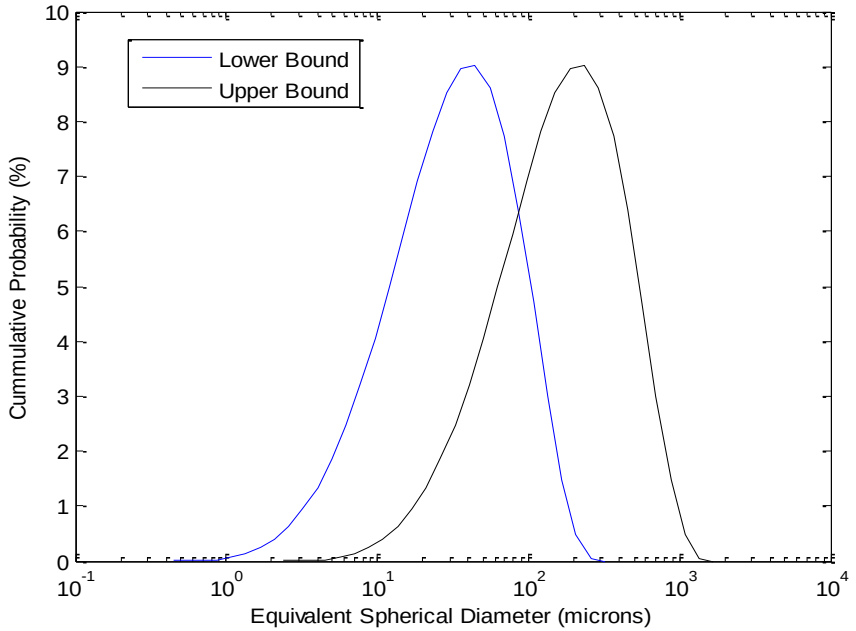
$$G(L) = k_d(L)\left[\frac{C_{bulk} - C_{int}(L)}{\rho_{crys}}\right]$$

$$= k_g \exp\left(\frac{-E_{A,g}}{RT}\right)\left[\frac{C_{int}(L) - C_{sat}}{\rho_{crys}}\right]^g$$

*Garcia-Muñoz, Yu, Pinto, Bermingham,
"A Model-Centric Solution to Link Content Uniformity Targets with API Particle Size Specifications and Process for a QbD Exercise"
Paper #202d, AIChE Annual Meeting, Minneapolis, October 2011.

Recipe optimisation

- Key focus: constraints on API particle size distribution
  - compliance with targets on Content Uniformity of tablets



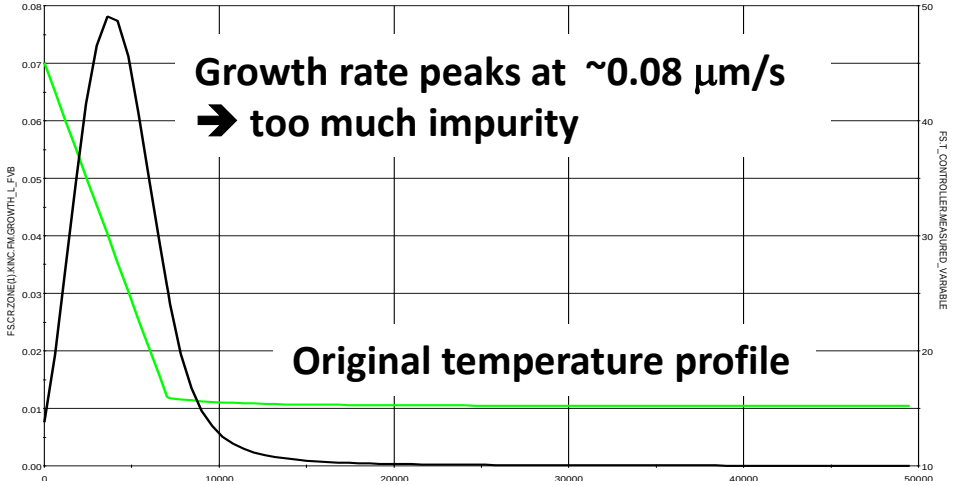
- **Objective**: minimise batch time
- **Control**: temperature ramp rate

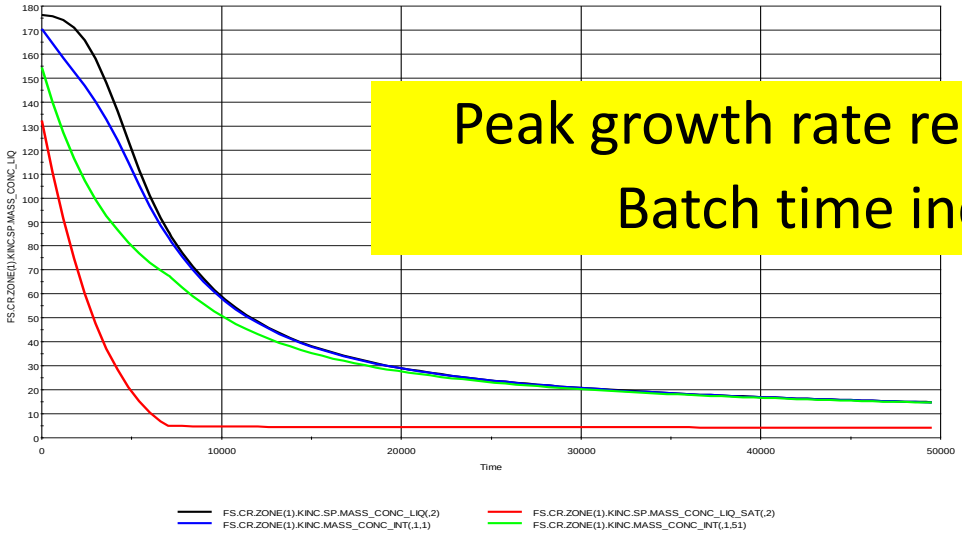
- **End-point constraints**
  - attain content uniformity targets
    - $d_{50,target}-1 < d_{50}\ [\mu m] < d_{50,target}+1$
    - $d_{90}/d_{10}\ [-] < d_{90}/d_{10},target$
  - ensure yield
    - $\sigma\ [-] = (c-c_{sat})/c_{sat} < 0.001$
  - stop crystallisation at end of batch
    - $T_{target}-0.1 < T\ [ºC] < T_{target}+0.1$
- **Path constraint**
  - ensure crystal purity: G [µm/s] < 0.01

Solution crystallisation case study – 2

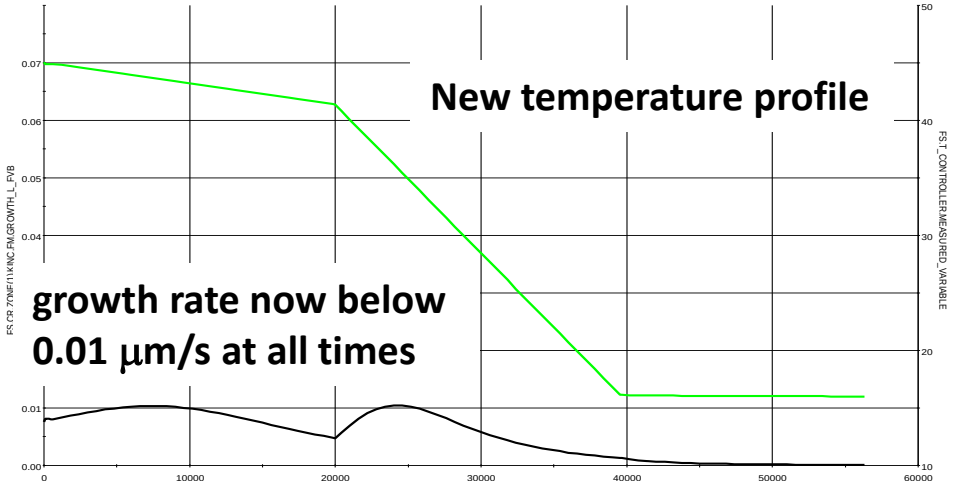
Results from a "similar" case study

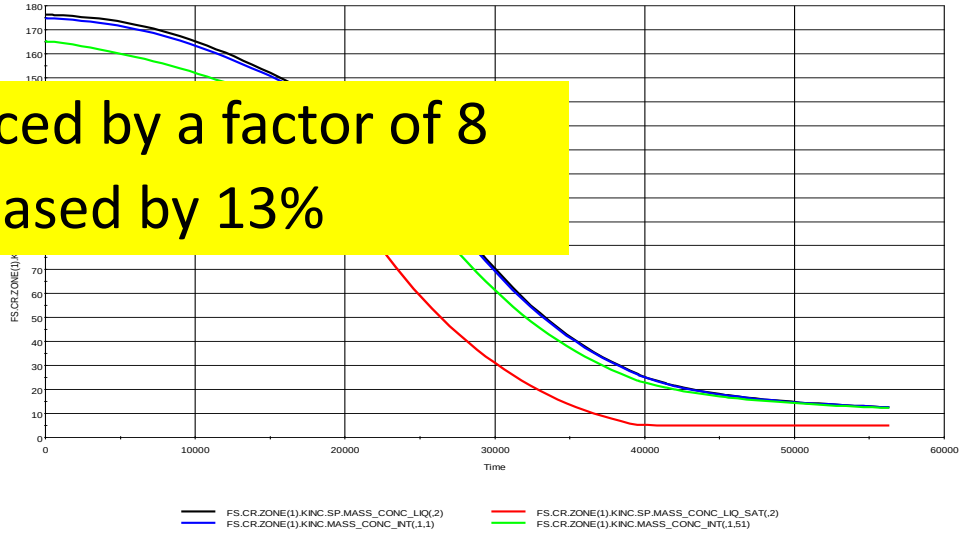
Original Recipe





Optimal Recipe





Peak growth rate reduced by a factor of 8

Batch time increased by 13%

Batch-to-continuous manufacturing

- Improved product quality control
  - stable continuously controlled operations
- Efficient manufacturing
  - lower capital cost
  - lower operational cost
  - smaller footprint
- Better handling of “difficult” products (e.g. metastable polymorphs, optical isomers)
  - ability to operate in narrow region

- **Batch or Continuous ?**

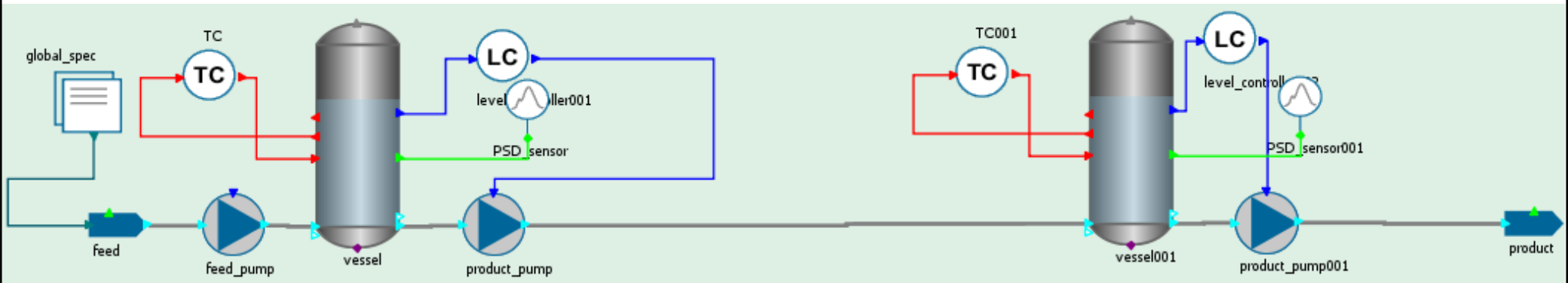
  Choice depends on…
  - difference in economics
  - material to be produced
  - scale of production
  - certainty of demand
  - in-house experience and the willingness to invest in non-standard practice / workflows

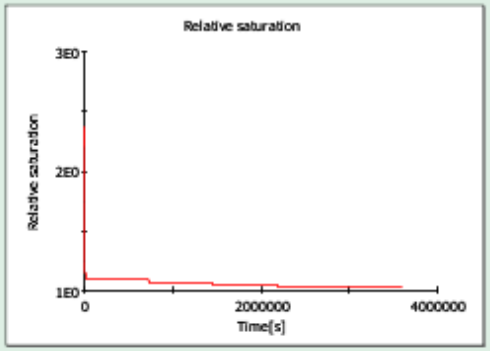
Require
quantitative assessment & comparison
of **optimised** alternatives

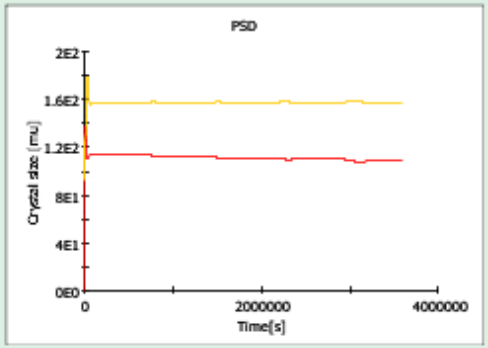
Crystallisation: from batch to continuous

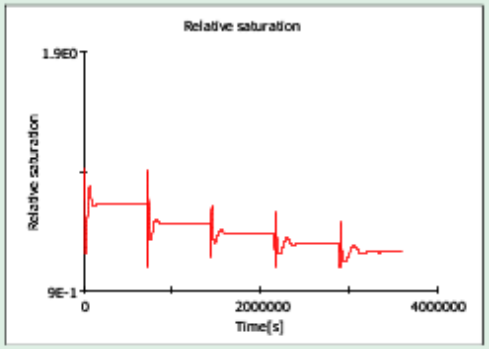
- Batch
  - Easy scale-up of recipe from lab to plant
  - Good traceability of off-spec product
  - Freedom to change recipe to ensure high yield / low material loss
  - Easy scale-down of production (reacting to demand)
  - Flexibility in equipment utilization (for other products)
  - Variability of product quality from batch to batch
  - Low plant availability / asset utilization
  - Storage and handling steps
  - Labour intensive
- Continuous
  - High plant availability
    - less maintenance / cleaning
  - Lower capital cost
  - Lower operating cost
    - including manpower and energy
  - Improved product quality control
  - Challenging and (usually) custom process design
  - Poor traceability of off-spec product
  - Complex startup, shutdown and emergency procedures
  - Minimum throughput (turndown) requires better demand planning
  - Energy and raw material cost of startup and shutdown

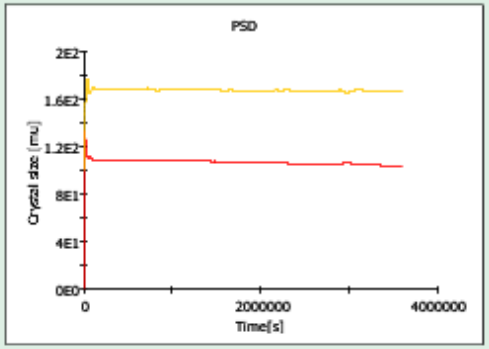
Multi-stage continuous cooling crystallisation



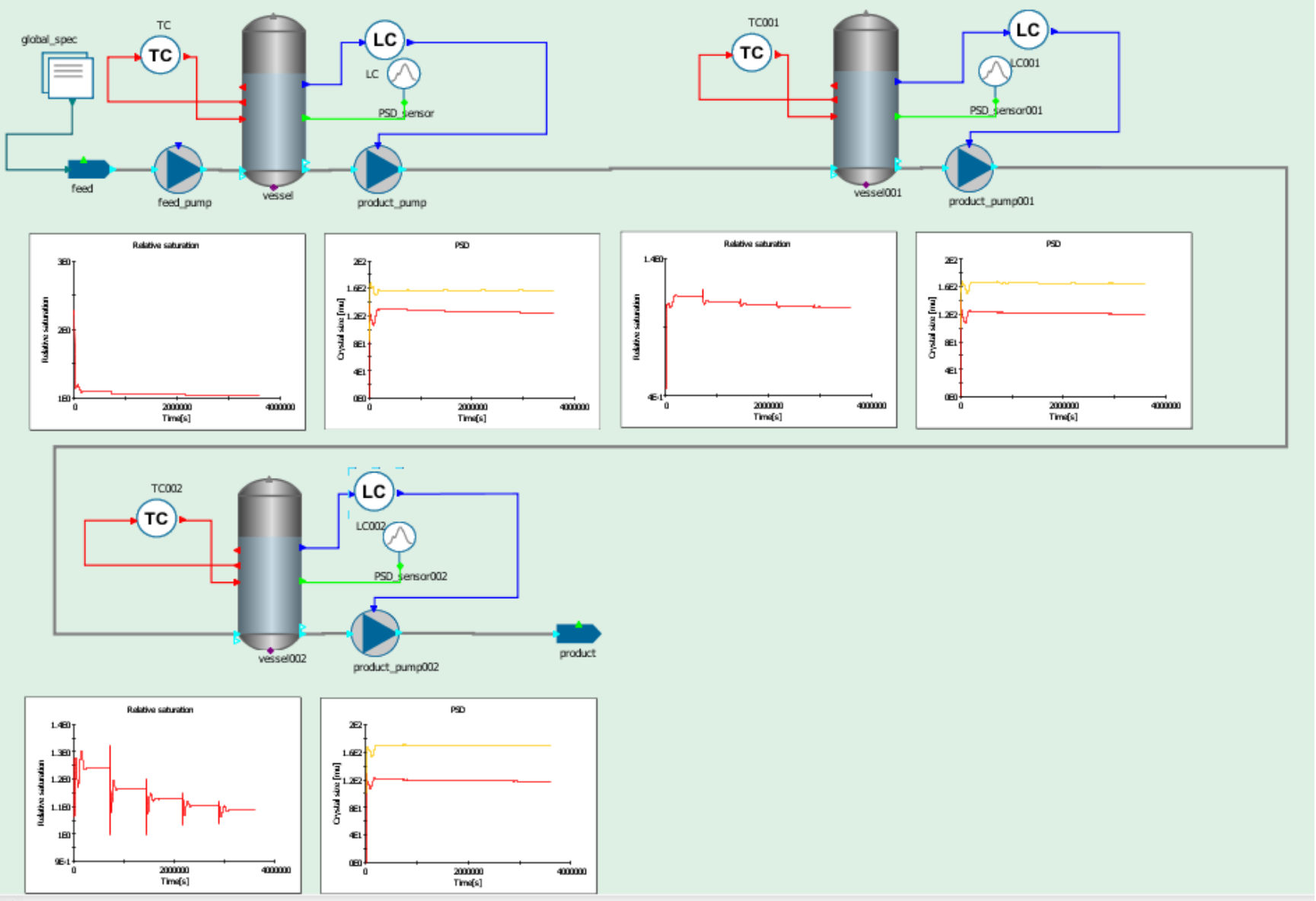




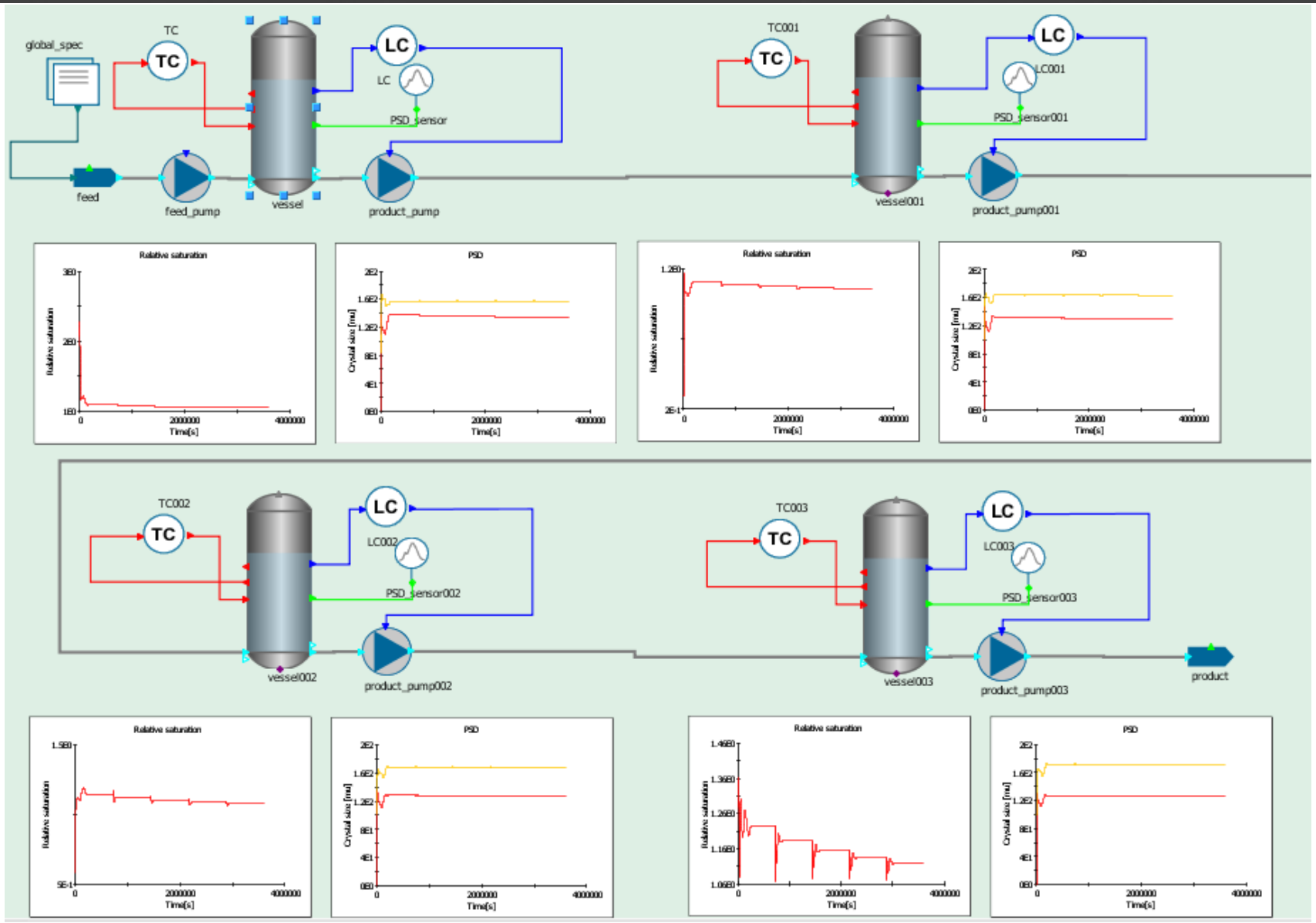




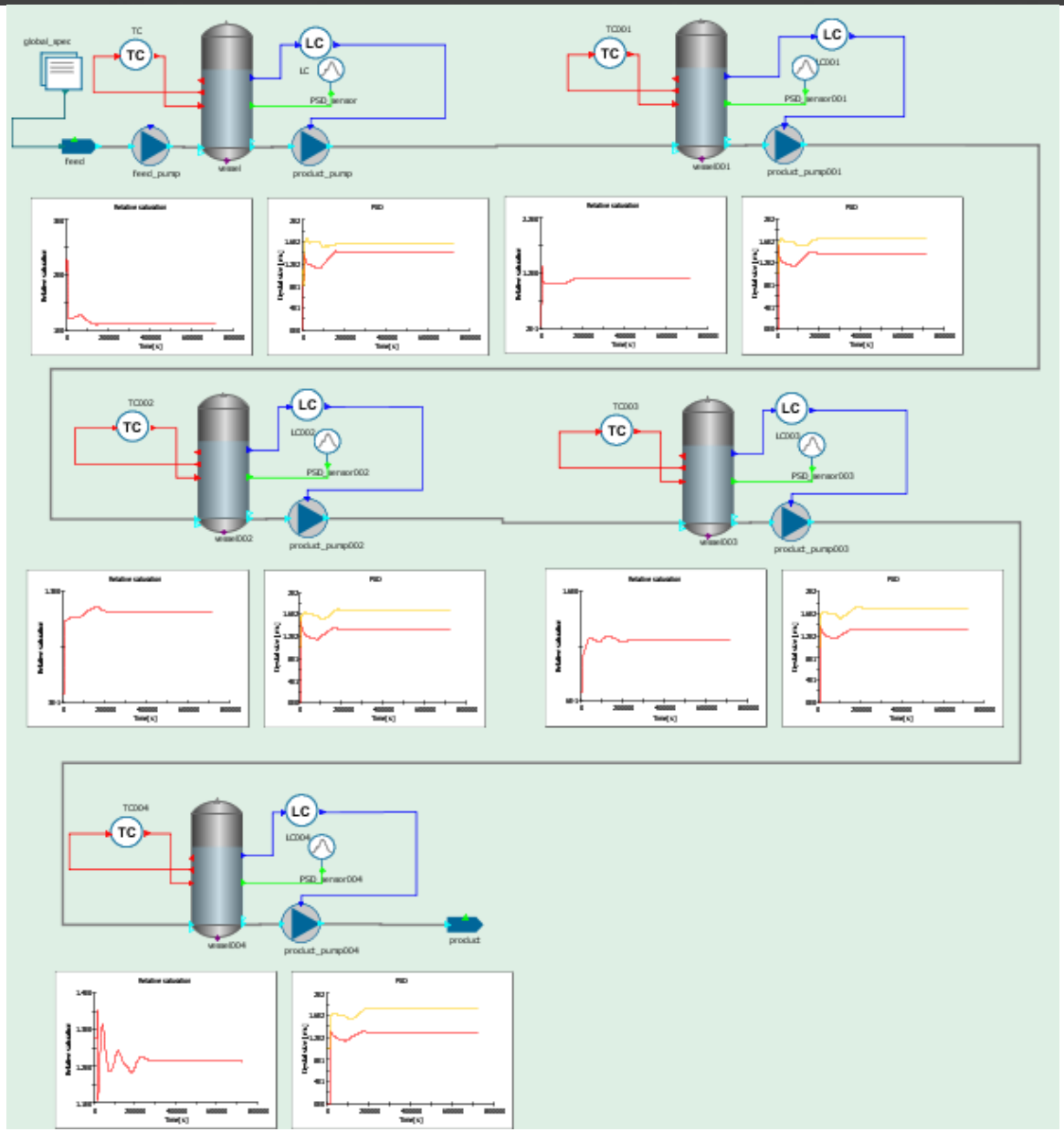
Multi-stage continuous cooling crystallisation



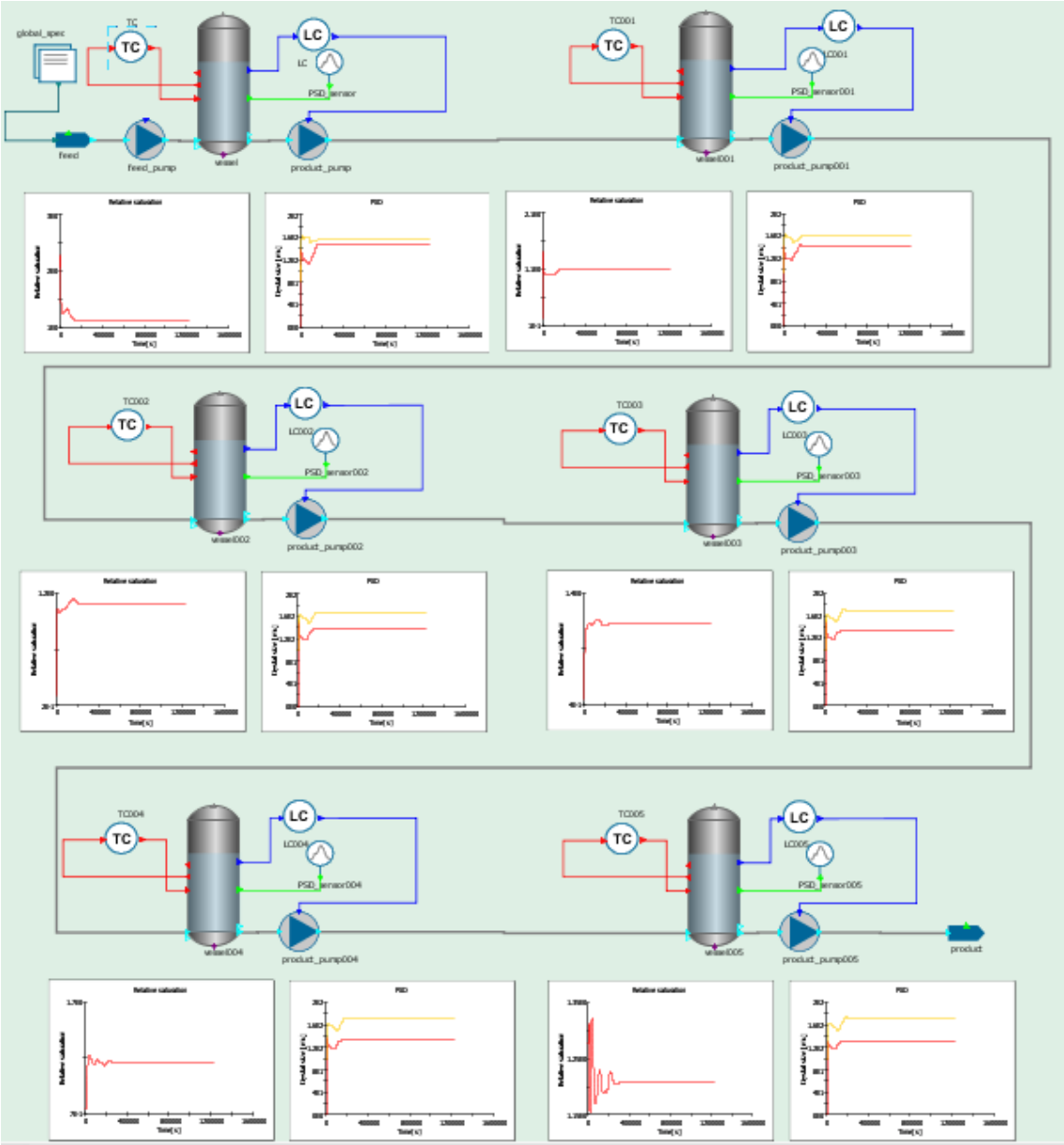
Multi-stage continuous cooling crystallisation



Multi-stage continuous cooling crystallisation



Multi-stage continuous cooling crystallisation



Multi-stage continuous cooling crystallisation

Not *quite* so simple

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Multi-stage continuous process

Total volume same as batch case, distributed equally among stages

Temperature range (95°C – 25°C) same as in batch case, distributed equally among stages

Flowrate = 90% of [batch size]/[batch time]

	Exit supersaturation	D50 (μm)	Span (%)
Batch	0	79.4	78.3
Continuous			
1-stage	0.303	75.5	157.7
2-stage	0.263	109.1	168.2
3-stage	0.239	120.8	170.6
4-stage	0.224	126.7	171.7
5-stage	0.214	129.9	172.2
6-stage	0.208	132.4	172.4

Diminishing improvement

Unacceptably high

Both D50 and Span increase with more stages

(and much higher compared to batch operation)

Multi-stage continuous cooling crystallisation

Not *quite* so simple

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	Exit supersaturation	D50 (μm)	Span (%)
Batch	0	79.4	78.3
Continuous			
6-stage (simple)	0.208	132.4	172.4
4-stage (simple)	0.224	126.7	171.7
4-stage (volumes: 10%, 20%, 30%, 40%)	0.152	124.1	175.5
4-stage (++ ΔT: 40%, 30%, 20%, 10%)	0.063	118.7	171.2
4-stage (++ flowrate reduced by 1/6)	0.052	119.2	170.1
4-stage (++ total volume increased by 50%)	0.034	119.4	168.1

Some improvement achieved

More formal optimisation approach required

Some conclusions

- Closest to chemicals/fine chemicals sector, e.g. in terms of unit operations
  - reaction, distillation, crystallisation, filtration, drying…
- Key challenges for model-based engineering approach
  - complex molecules
  - complex chemistry
  - batch/semi-batch operations
  - (some) solids
  - mixing imperfections/scale-up
  - batch-to-continuous conversions
- **…mostly within scope of existing technology?**

Potential pitfalls

1. **Bad choice of models**
2. **Insufficient/inappropriate coupling of models & experimentation**
3. **Lack of understanding/use of optimisation technology**

Failure to derive sufficient value from modelling investment ?

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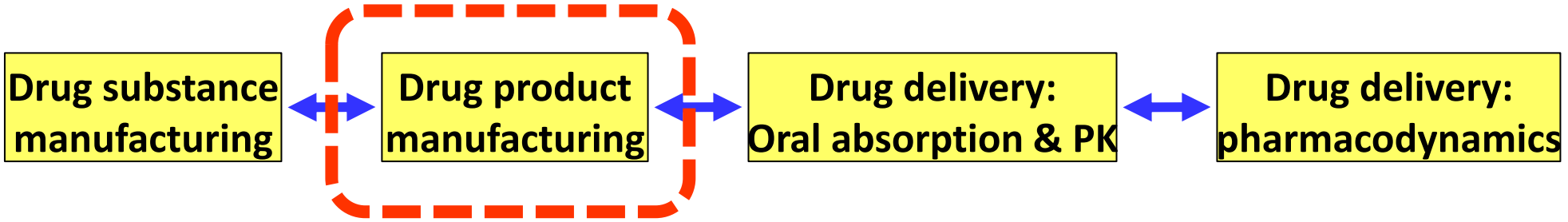
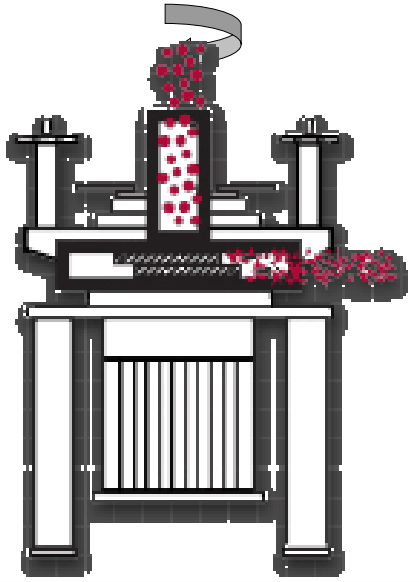
2b. Drug product manufacturing

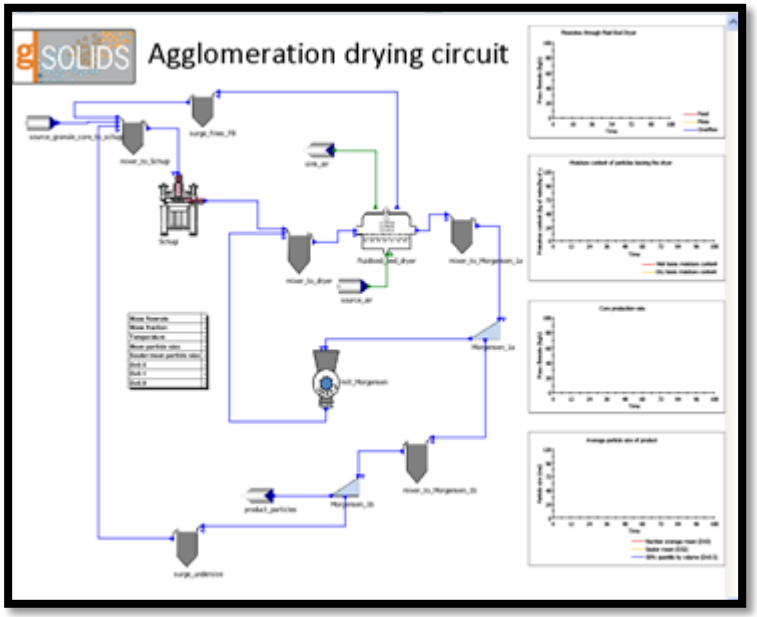


Drug product manufacturing

- Quite different to standard chemicals sector
  - mostly solids-based operations/transformations

- Dry blending
- Continuous mixing/blending (PF/CST/other)
- Delumping (eliminate soft aggregates)
- Screw conveyor / feeder
- Granulation (fluid bed; high-shear wet)
- Drying (fluid bed; tray; spray)
- Roller compactor;
- Milling
- Fluid bed coating of particulates
- Hopper/storage: transfer to tablet press /capsule filling machine
- Encapsulation
- Compaction
- Coating of tablets
- . . . . . .





- Key challenges
  - complex materials
    - multiple solids phases
    - particle size-dependent chemical composition
  - incomplete understanding of the physics
  - handling of solids-related aspects
    - population balances
      - potentially multi-dimensional
    - modelling of integrated processes
  - equipment scale-up

- Process Systems Engineering has limited potential for contributing to new fundamental science
- BUT it can provide a systematic, formal framework for
  - capturing all existing knowledge & understanding
    - first-principles *or* empirical
  - integrating knowledge across entire processes
  - deriving maximum value from existing knowledge
- It can also support new science by
  - identifying & prioritising needs
  - helping in assessing domain knowledge (e.g. model discrimination)

Modelling of integrated solids processes

Typical examples

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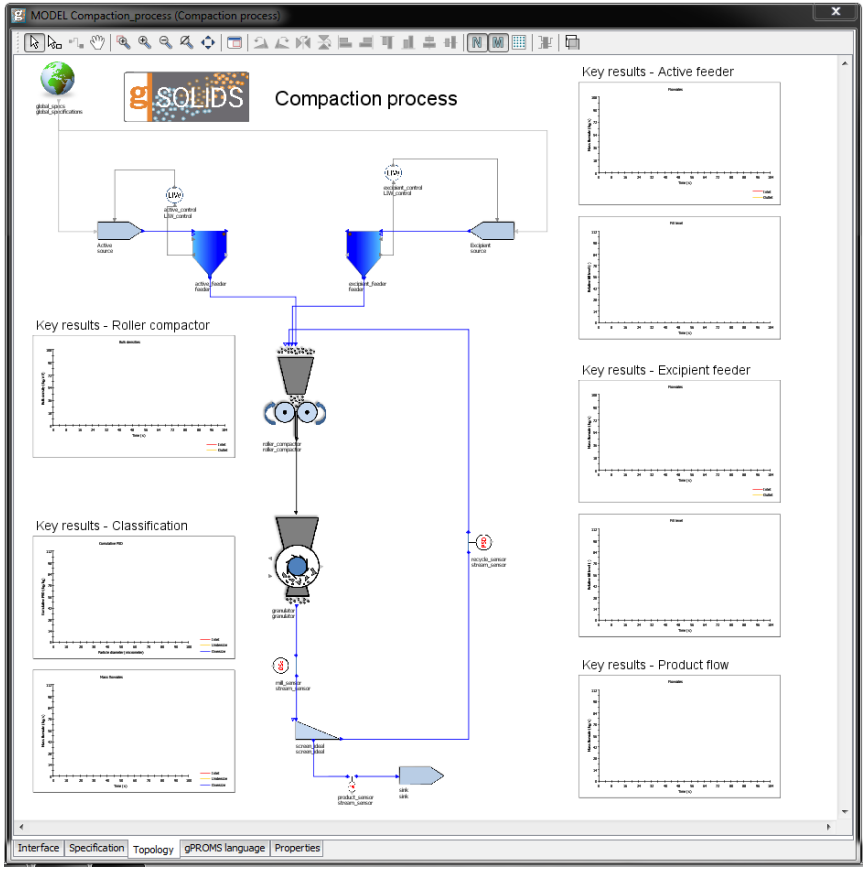
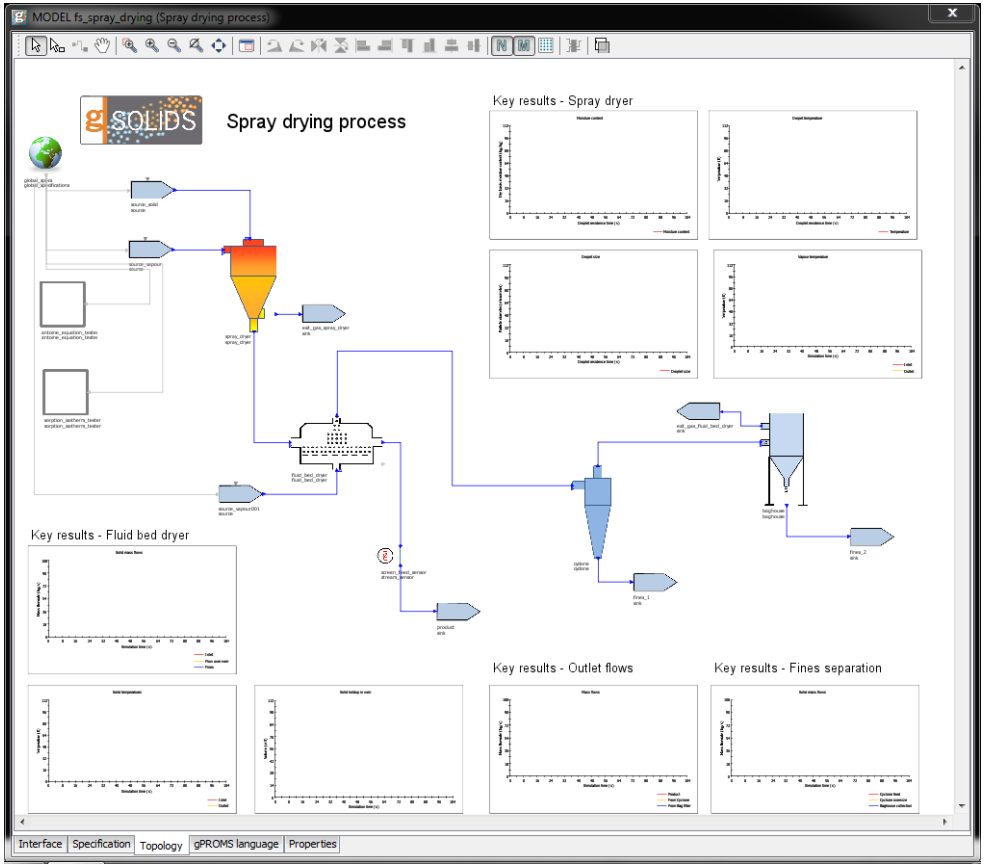
Compaction process



Spray drying process

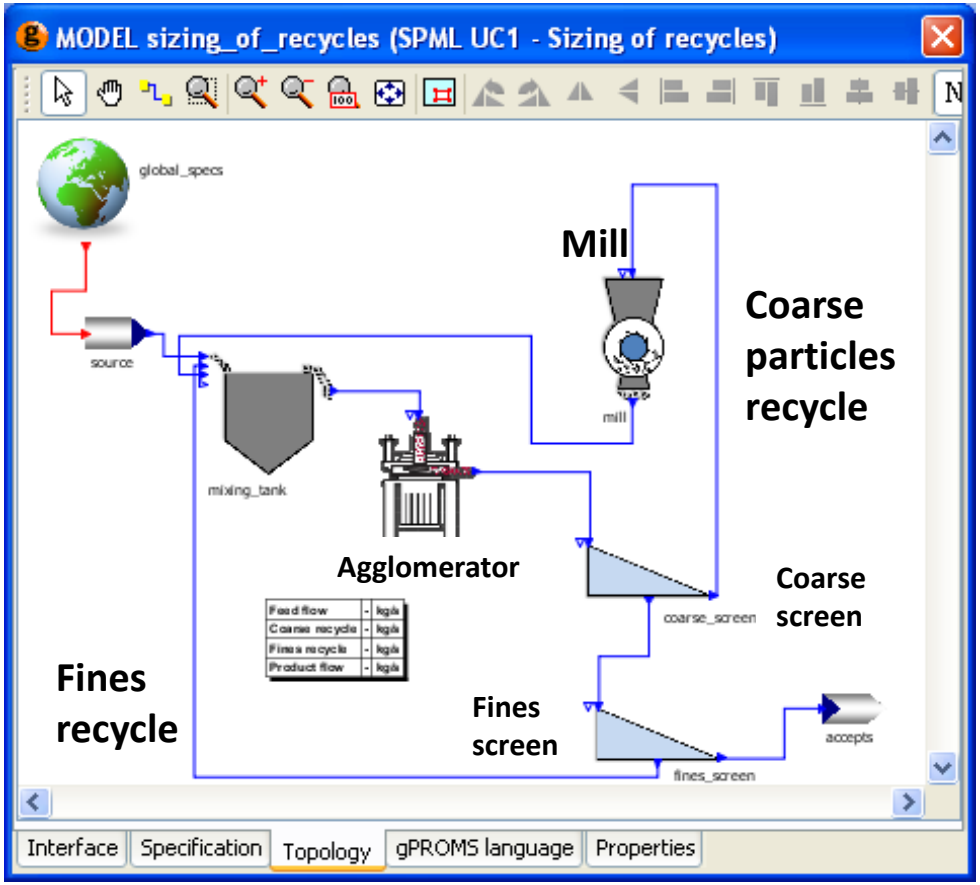


gSOLIDS

Agglomeration process optimisation

- Fine particles to be agglomerated
- Product particles to be within certain size range
- All other particles recycled
  - coarse ones crushed in a mill
- OPEX a strong function of recycles of fine & coarse particles

➔ need to balance OPEX and CAPEX (agglomerator, mill)



Agglomeration kernels

- Size-independent kernel
  - agglomeration rate independent of particle size
  - all events equally favoured

$$\beta = \beta_0\left(x, T, \omega, \ldots, t\right)$$

- Smoluchowski's shear kernel
  - large-large events favoured

$$\beta = \beta_0\left(x, T, \omega, \ldots, t\right)\left(L_1 + L_2\right)^3$$

- Equipartition of kinetic energy kernel (EKK)
  - large-small events favoured

$$\beta = \beta_0\left(x, T, \omega, \ldots, t\right)\left(L_1 + L_2\right)^2 \sqrt{\frac{1}{L_1^3} + \frac{1}{L_2^3}}$$

For a given range of operating conditions (temp, binder content etc.)

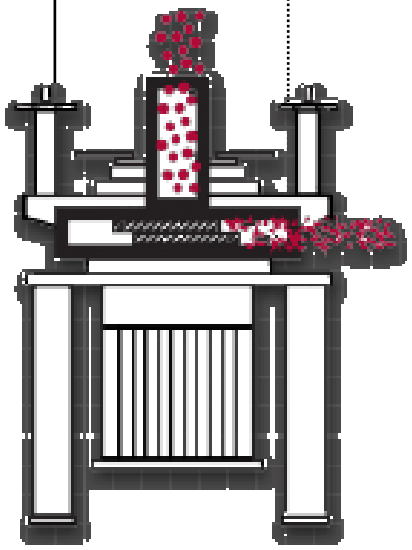
- **which agglomeration kernel best describes system?**
- **what are the values of the kernel parameter(s)?**

Agglomeration experiment #1

Fine powder, binder continually added during experiment

Quantiles measured every 20 minutes

Lab-scale fed-batch agglomerator



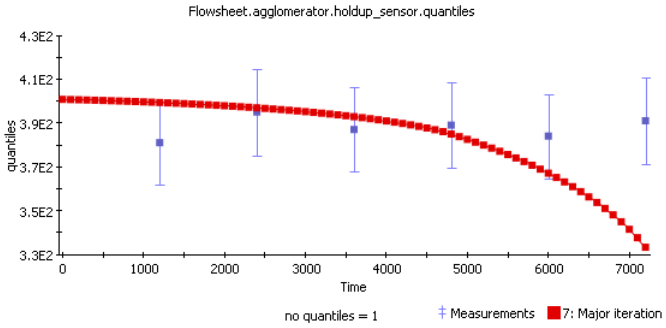
Unit initially contains coarse particles

Agglomeration model validation - Results after 1st experiment

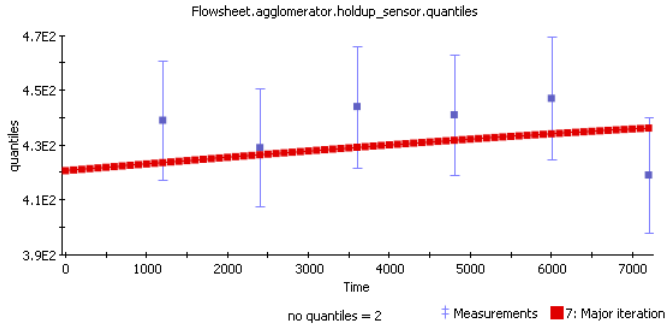
Size-independent kernel

95% confidence interval: ± 11%

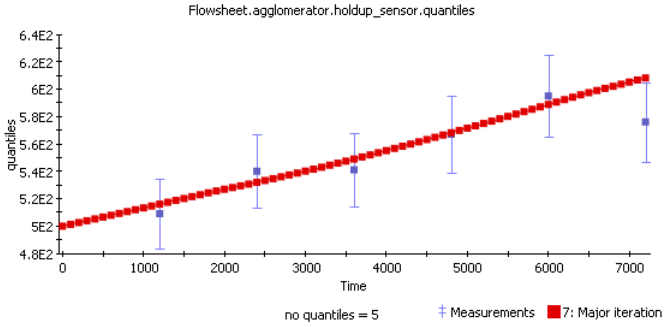
χ^2 Lack-of-Fit test: OK



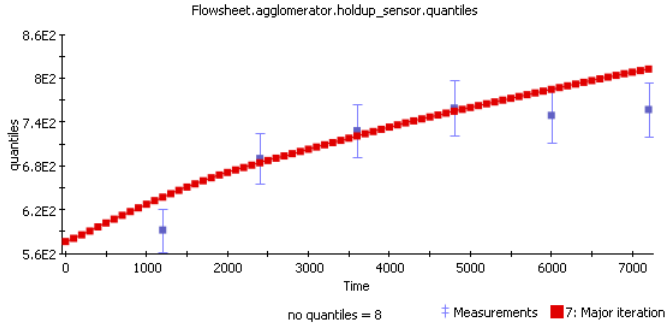
5% quantile - not so good



10% quantile - good fit



50% quantile - good fit



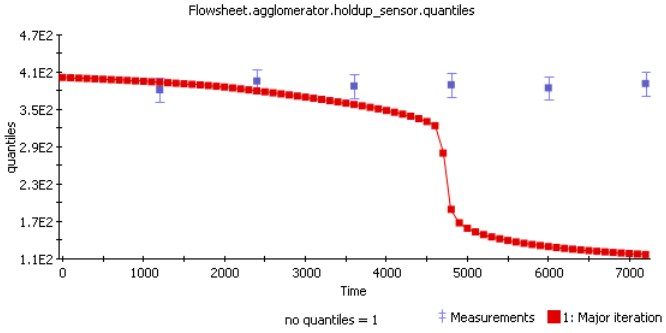
90% quantile - good fit

Agglomeration model validation - Results after 1st experiment

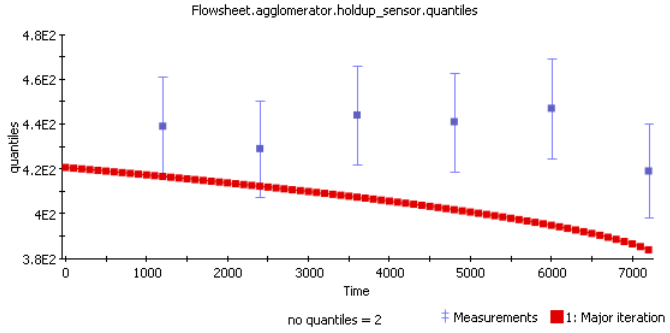
Smoluchowski shear kernel

95% confidence interval: v. large

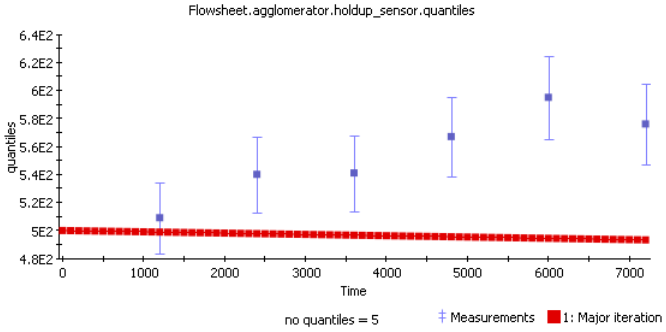
χ^2 Lack-of-Fit test: FAIL



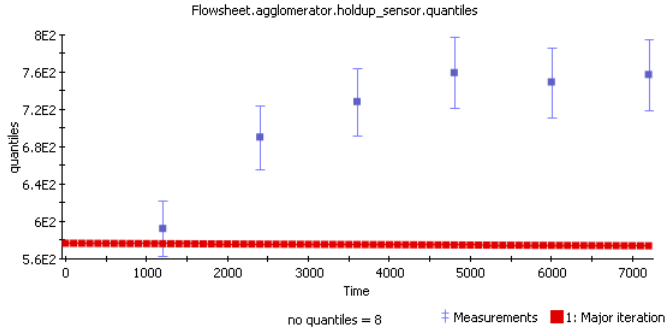
5% quantile - bad fit



10% quantile - not so good



50% quantile - not so good



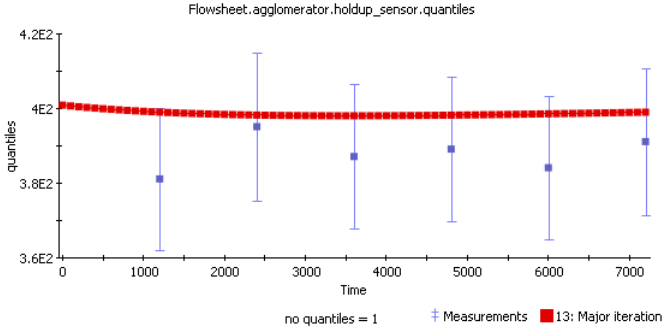
5% quantile - bad fit

Agglomeration model validation - Results after 1st experiment

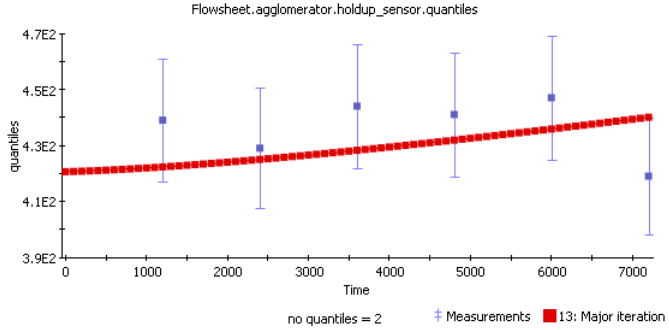
EKK kernel

95% confidence interval: ±13.5%

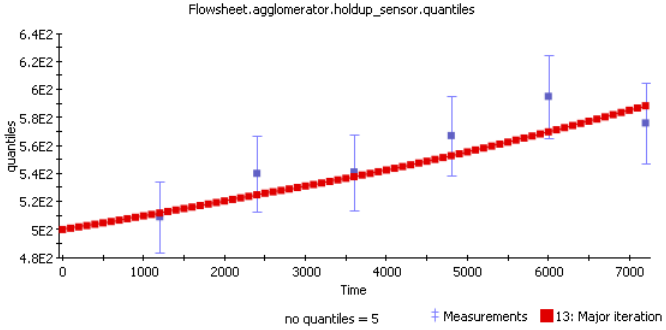
χ^2 Lack-of-Fit test: OK



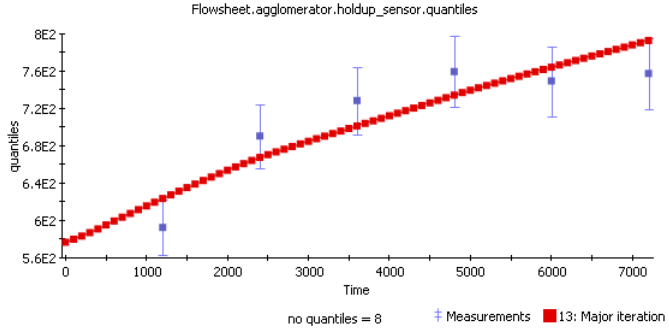
5% quantile - good fit



10% quantile - good fit



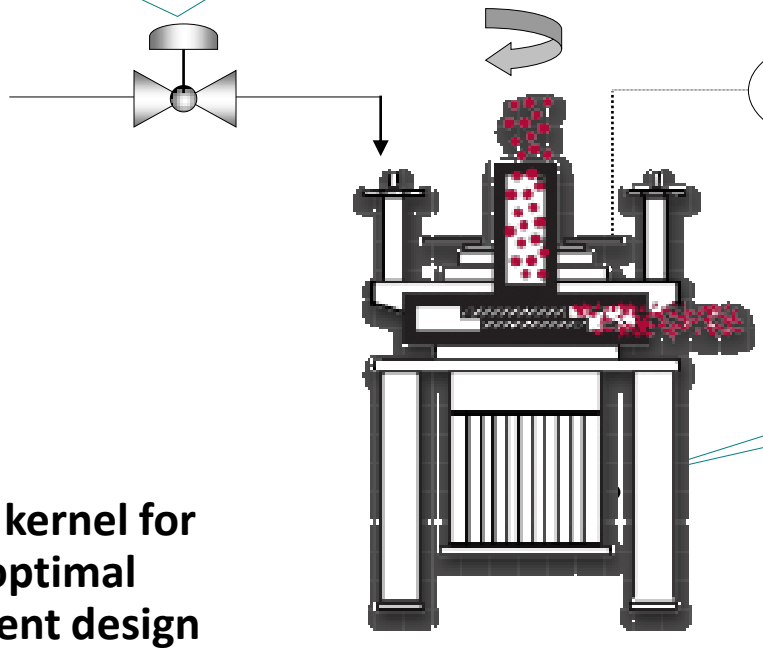
50% quantile - good fit



90% quantile - good fit

Designing the 2nd experiment

Feed rate of fine particles?
(constant throughout experiment)



y_1, y_2

Measurement times are fixed at 20 min intervals

Initial volume of coarse particles?

Use EKK kernel for solving optimal experiment design problem

Either kernel could be used in practice

Constraint

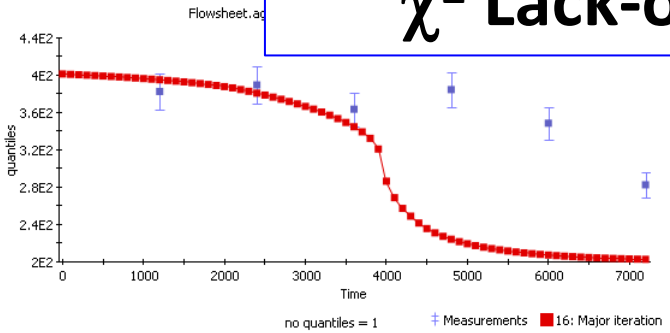
Volume of material within the tank should not exceed 95% of tank volume during experiment

Agglomeration model validation - Results after 2nd experiment

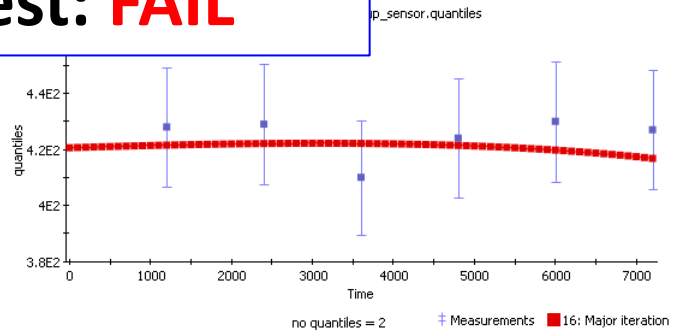
Size-independent kernel

95% confidence interval: ± 8%

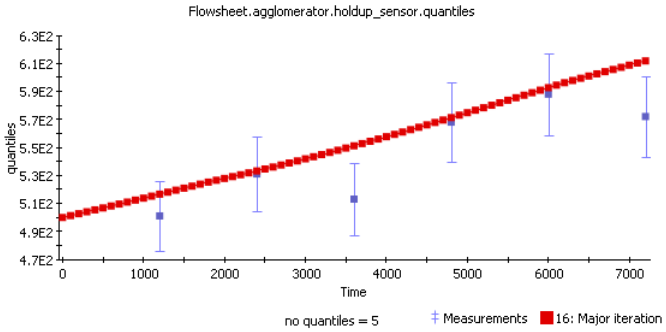
χ^2 Lack-of-Fit test: FAIL



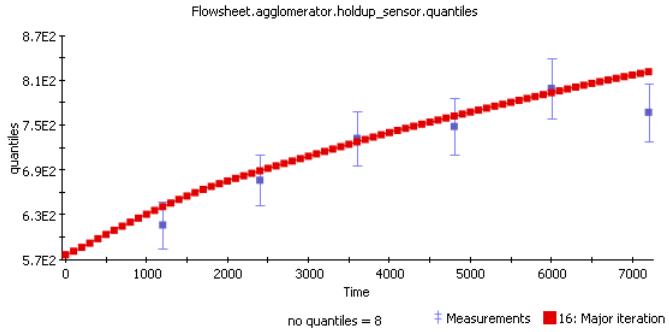
5% quantile - bad fit



10% quantile - good fit



50% quantile - good fit



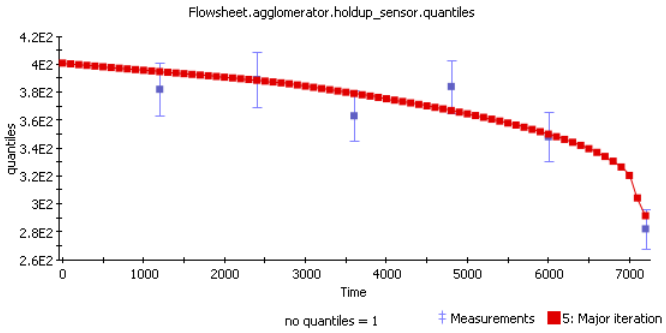
90% quantile - good fit

Agglomeration model validation - Results after 2nd experiment

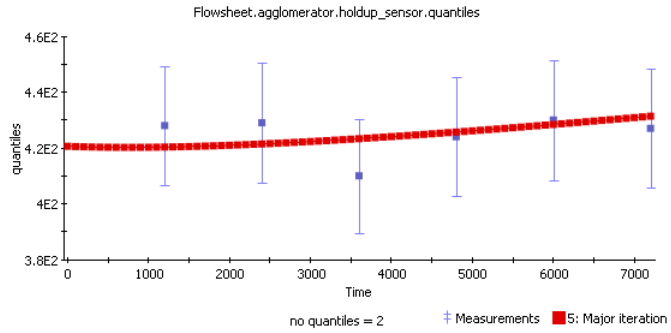
EKK kernel

95% confidence interval: ± 2%

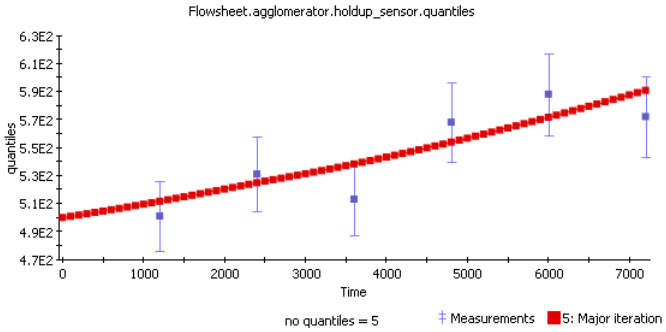
χ^2 Lack-of-Fit test: OK



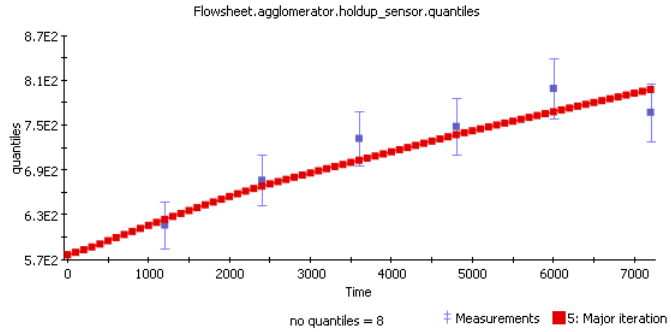
5% quantile - good fit



10% quantile - good fit



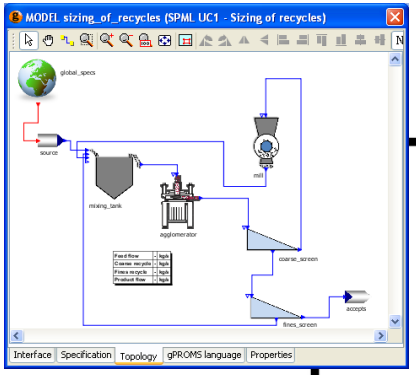
50% quantile - good fit



90% quantile - good fit

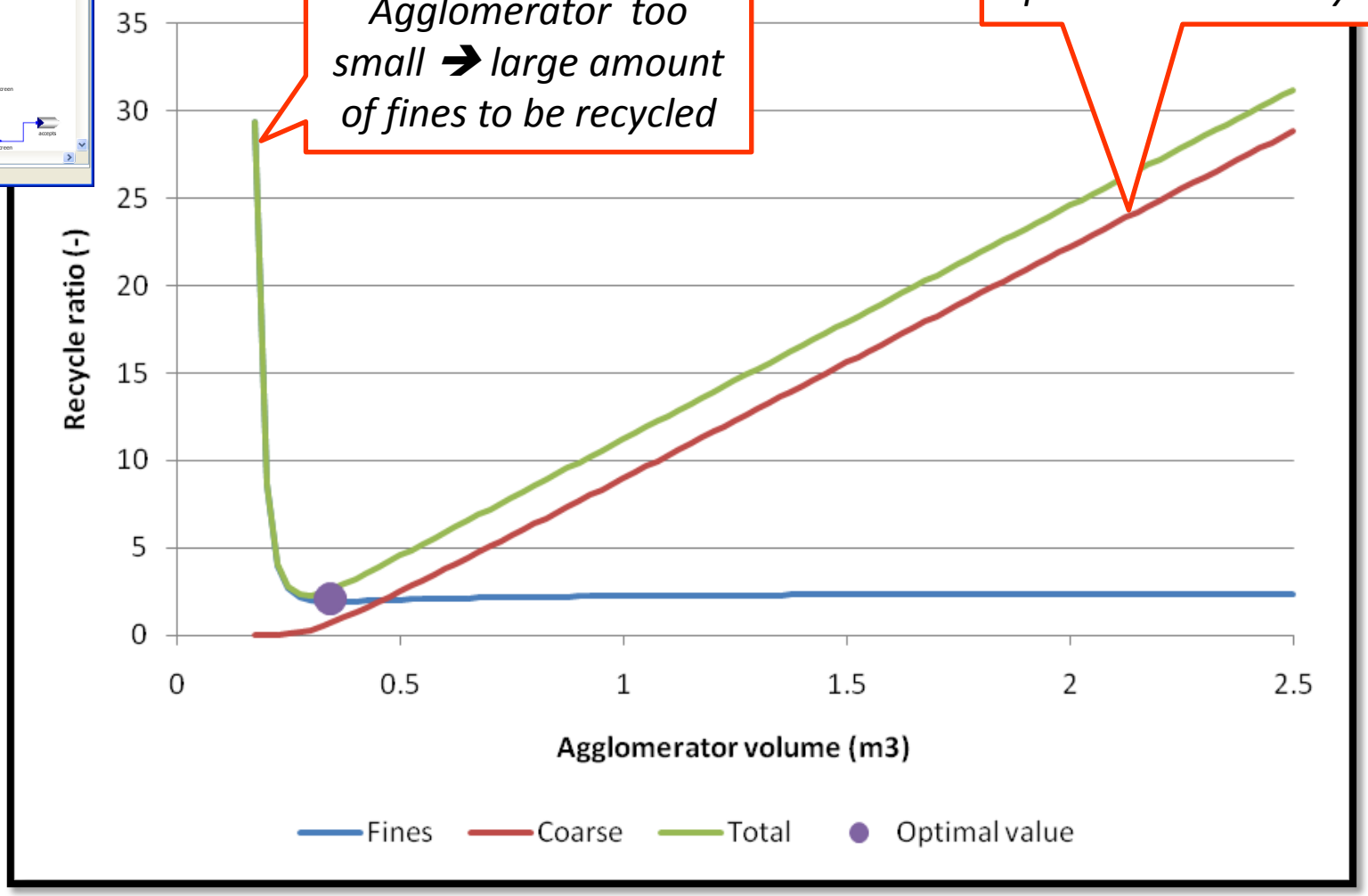
Drug product manufacturing – Example

Optimization of agglomerator capacity



Agglomerator too small ➔ large amount of fines to be recycled

Agglomerator too large ➔ too many coarse particles to be recycled



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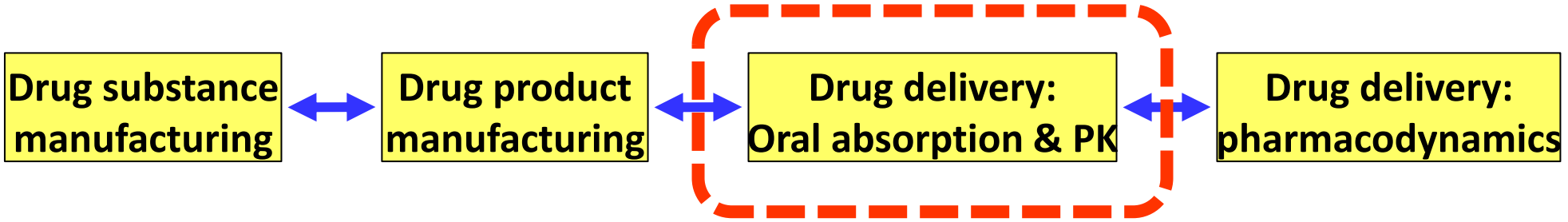
2c. Oral absorption & pharmacokinetics



Processing of oral dosage forms in body

An extremely simplified view

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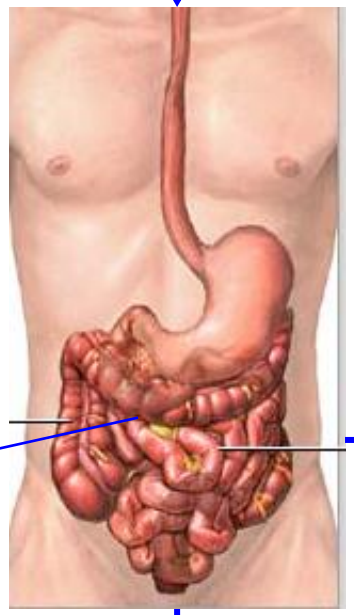
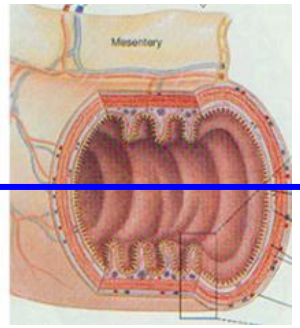
Dosage form
(tablets, capsules)



Dissolution in gastro-intestinal tract

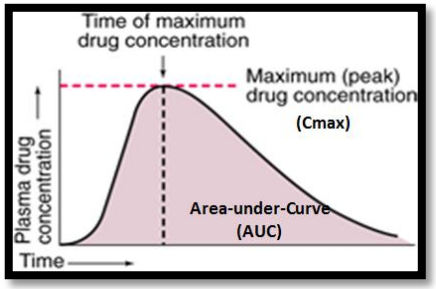
Excretion

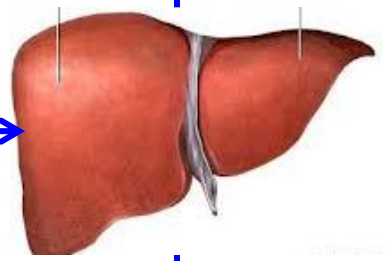


Absorption through intestine wall

Drug in systemic circulation

Bioavailability



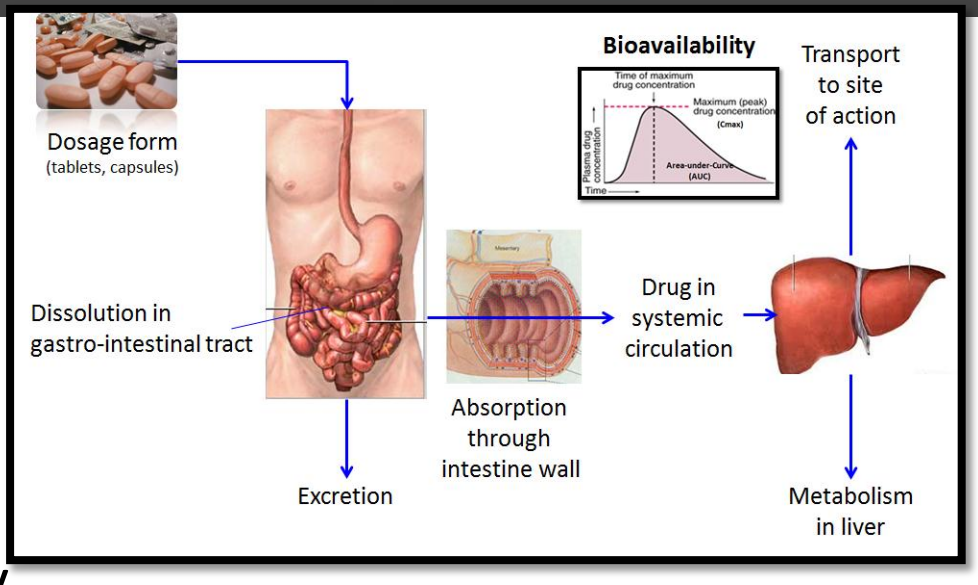


Transport to site of action

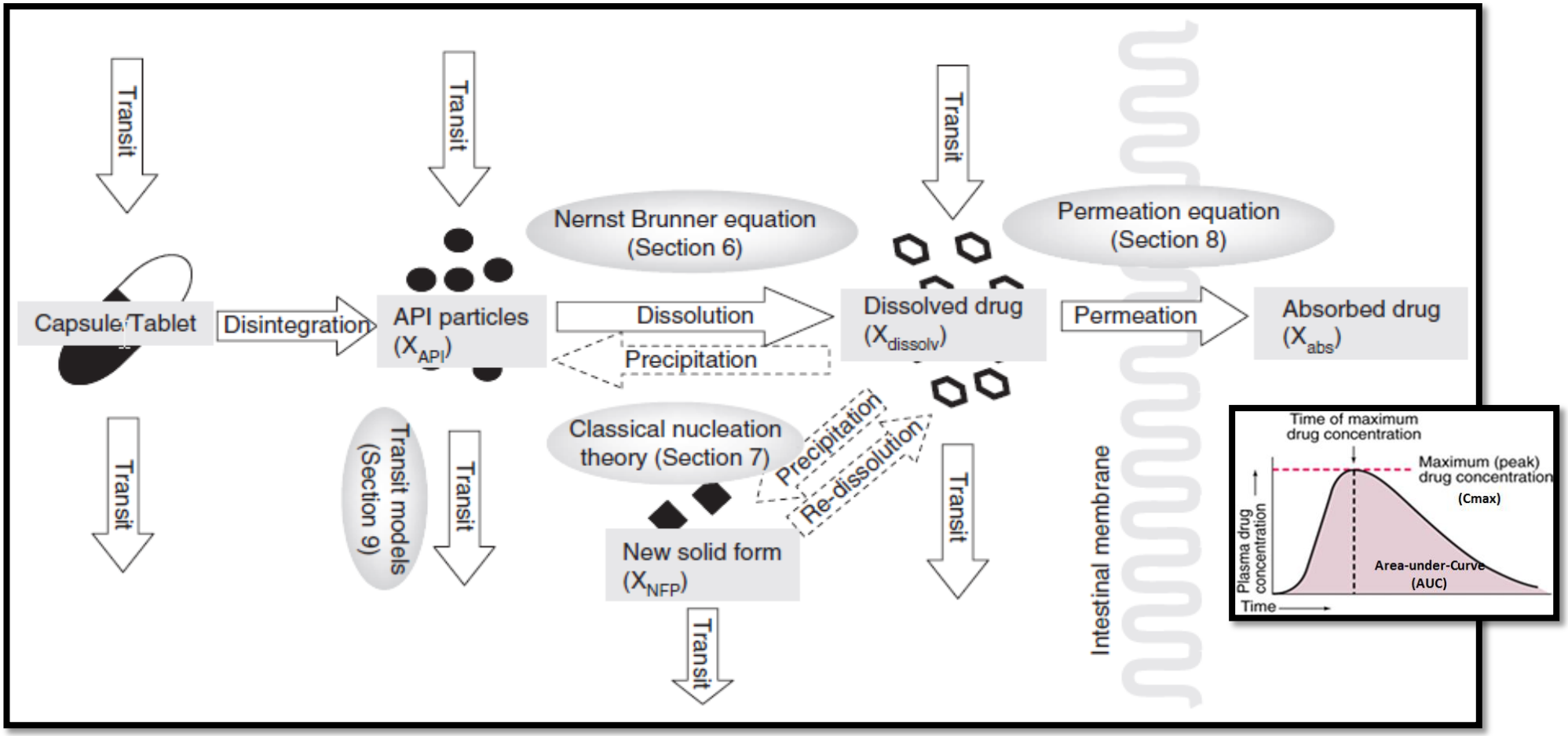
Metabolism in liver

Key factors influencing bioavailability

- Drug physical properties
  - solubility, hydrophobicity, pKa
  - dissolution rate
- Drug formulation
  - immediate vs. modified release (delayed, extended, sustained)
- Gastro-intestinal tract physiology
  - gastric emptying rate (GER)
  - fed vs. fasted state
- Metabolism
  - enzyme induction or inhibition by other drugs and foods
- Personal factors (age, disease state)
  - may affect both GI physiology and pharmacokinetics

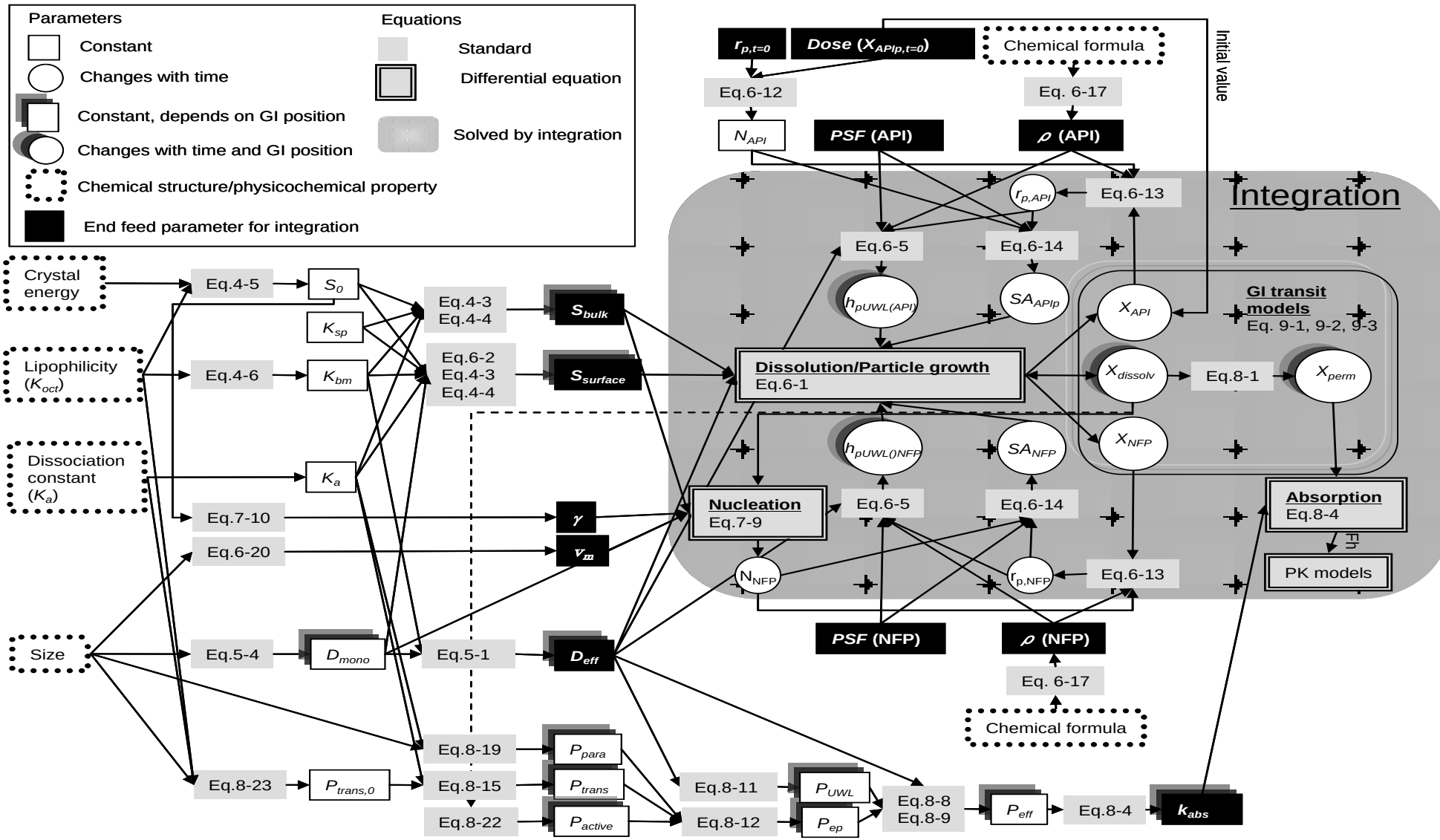


Modelling of oral absorption



K. Sugano, *Expert Opin. Drug Metab. Toxicol.* (2009) 5, 259-293.

Modelling of oral absorption



K. Sugano, *Expert Opin. Drug Metab. Toxicol.* (2009) 5, 259-293.

Modelling of oral absorption

- Increasingly detailed first-principles models are being developed to predict bioavailability …

- …and **are being used** by the pharmaceutical industry

- Both in-house and commercial tools
  - GastroPlus™ (Simulations Plus Inc.)
  - Simcyp™ (Certara Inc.)
  - PK-Sim® (Bayer Technology Services)
  - . . . . . .

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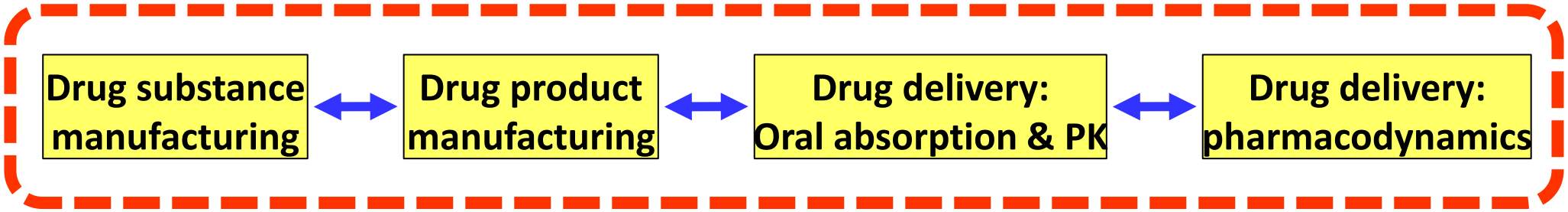
3. Systems-based Pharmaceutics



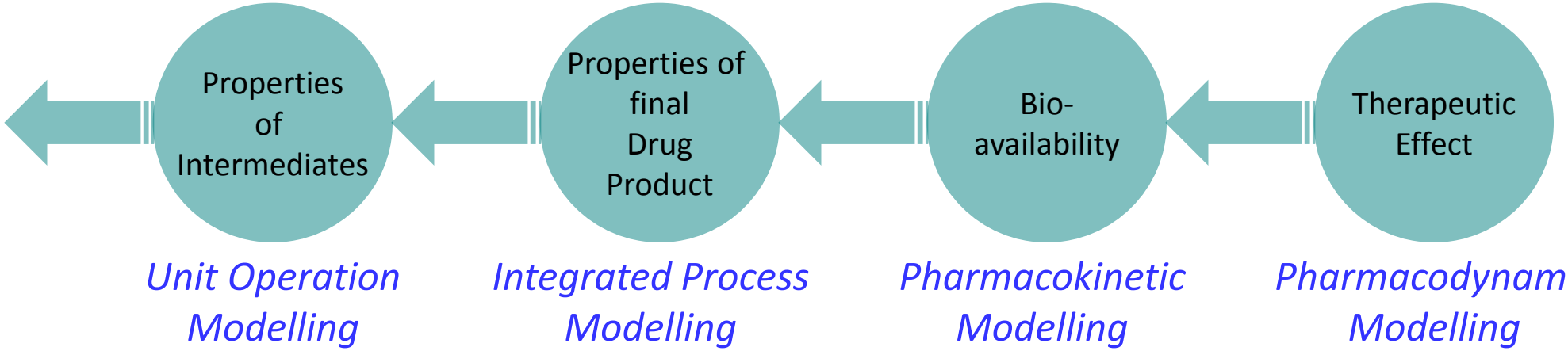
From real to surrogate objectives

- Many decisions & constraints; complex interactions

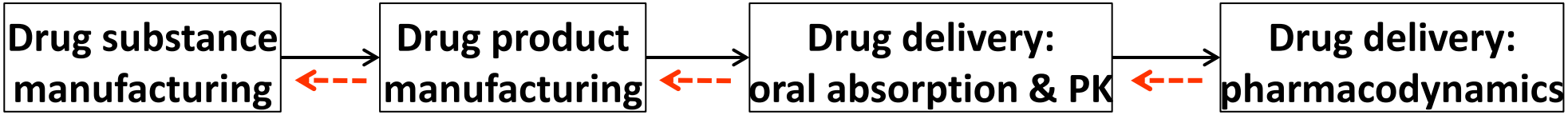
→ **Process Systems approach: effective/efficient exploration of decision space**

- **BUT…**
  - incomplete knowledge/understanding of parts of the system
  - inability to handle modelling complexity of entire system
  - organisational silos & barriers

→ **from real to surrogate objectives**

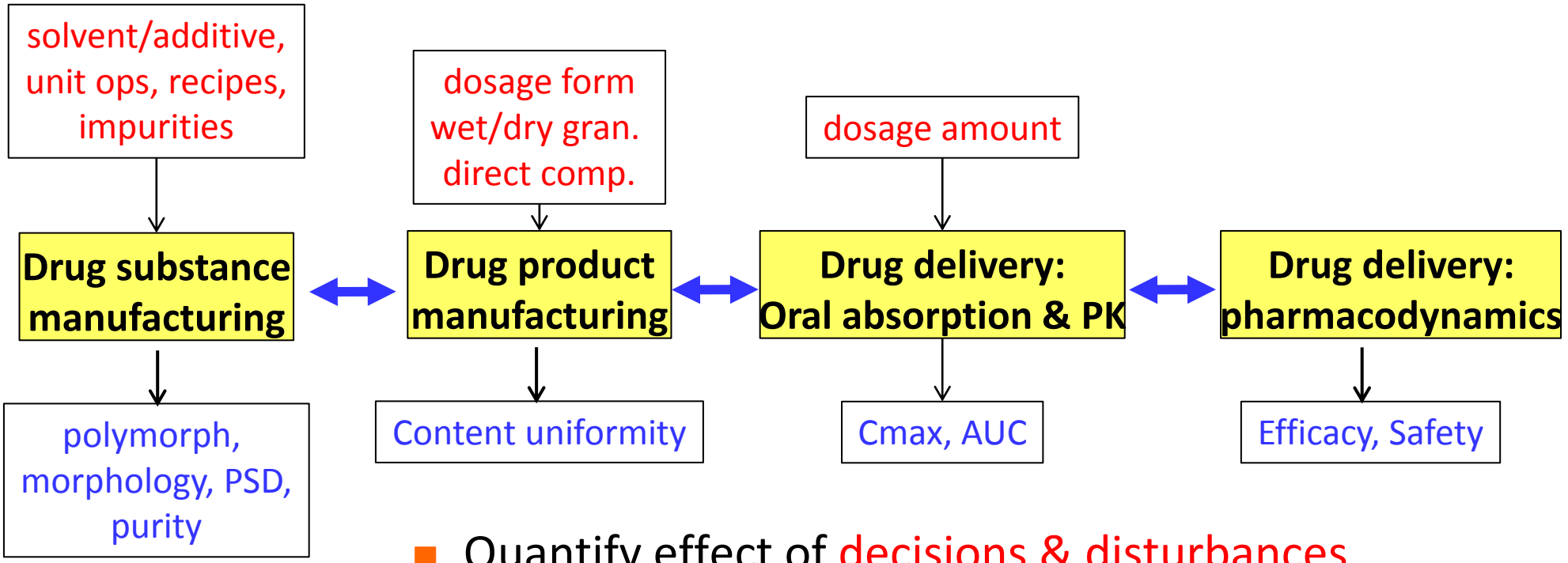


A price worth paying?



- Silo thinking
  - reflected in both tools and organisational structures
- Too many iterations …
  - between product design and manufacturing process design
  - between subsequent manufacturing steps
  - between bioavailability targets and drug product/process development
- … and other inefficiencies
  - no central repository of consistent knowledge
  - many, long learning curves

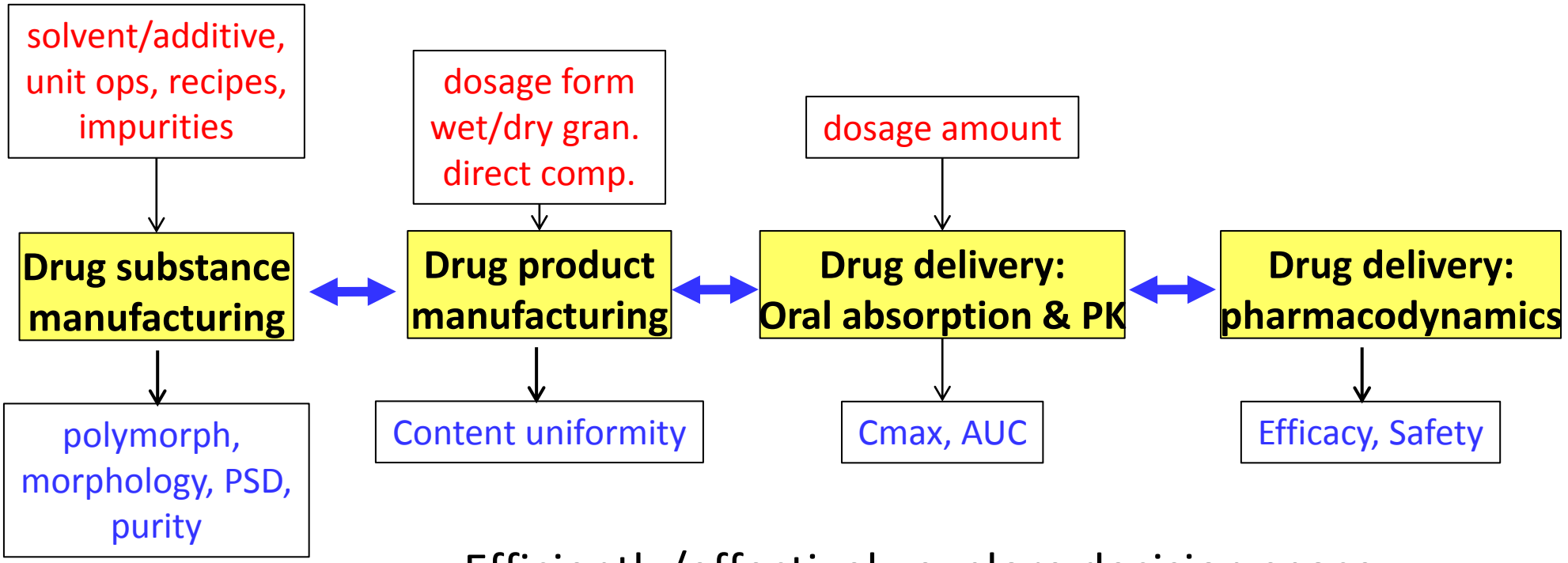
Systems-based Pharmaceutics – I



- Quantify effect of decisions & disturbances
  - uncertainty in process knowledge
  - common cause variability

  on Key Performance Indicators
  - Critical Quality Attributes
  - process economics, operability, safety
- **From surrogate objectives to true KPIs**

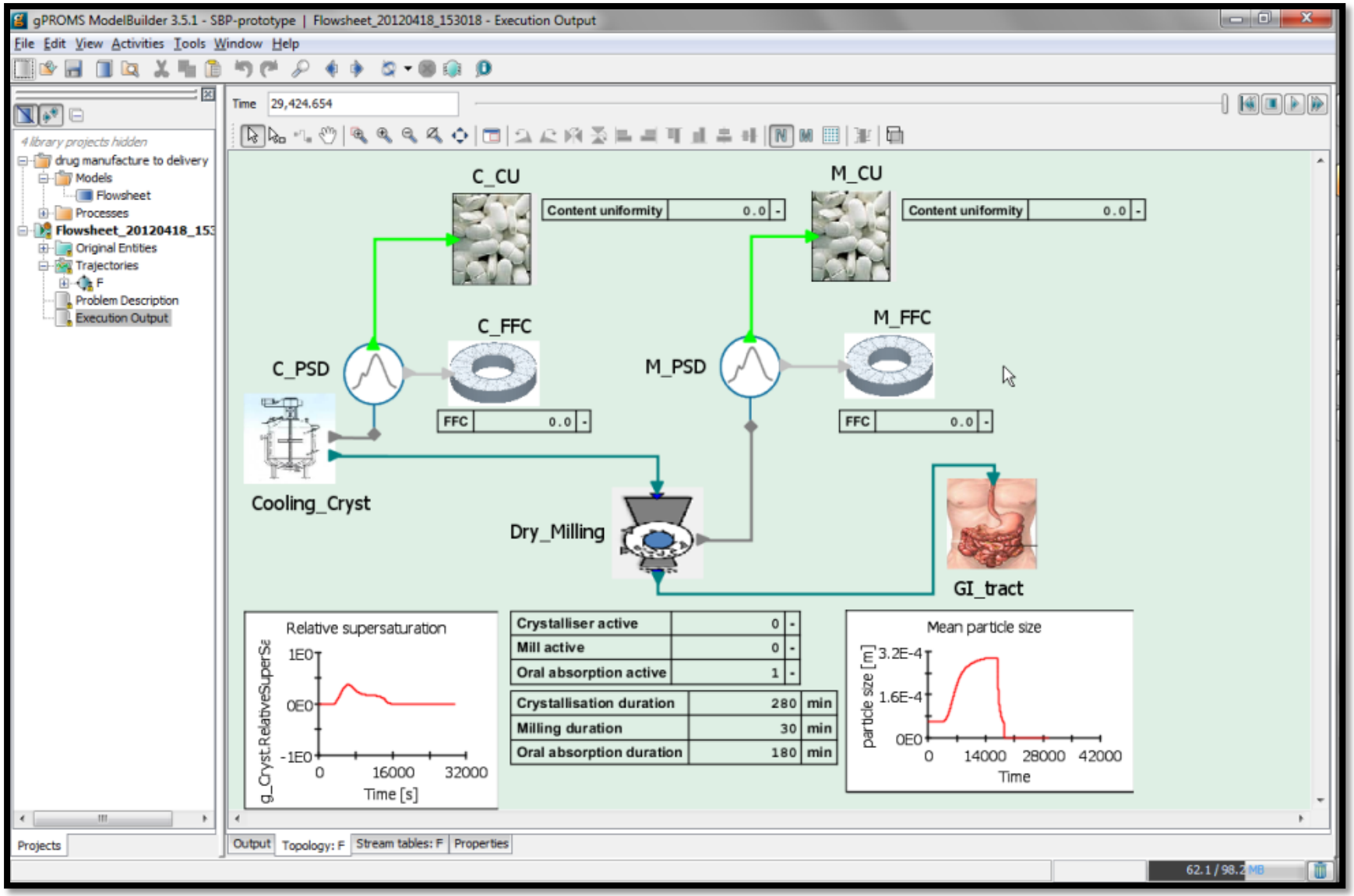
Systems-based Pharmaceutics – II



- Efficiently/effectively explore decision space
  - use advanced mathematics to reduce trial-and-error approaches
- Manage risk by quantifying impact of uncertainty
  - model uncertainties
  - external disturbances, e.g. excipient characteristics

Systems-based Pharmaceutics – III

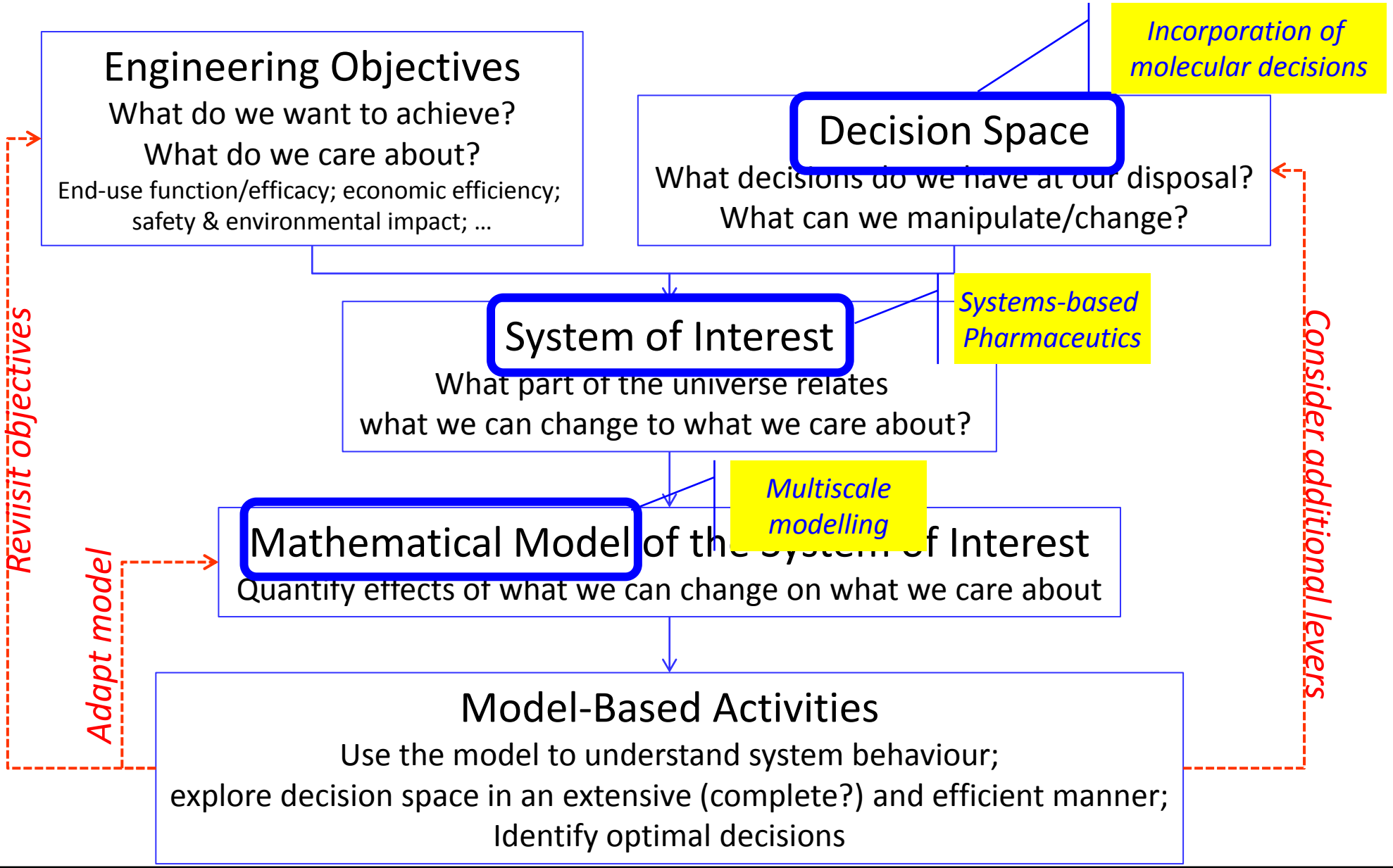
Illustrative example of integrated manufacturing/oral absorption modelling



4. Fundamental challenges & opportunities

The Systems Engineering approach is a

Top-Down Approach



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4a. Material properties & behaviour in SbP

Material properties & behaviour for SbP

(a partial view)

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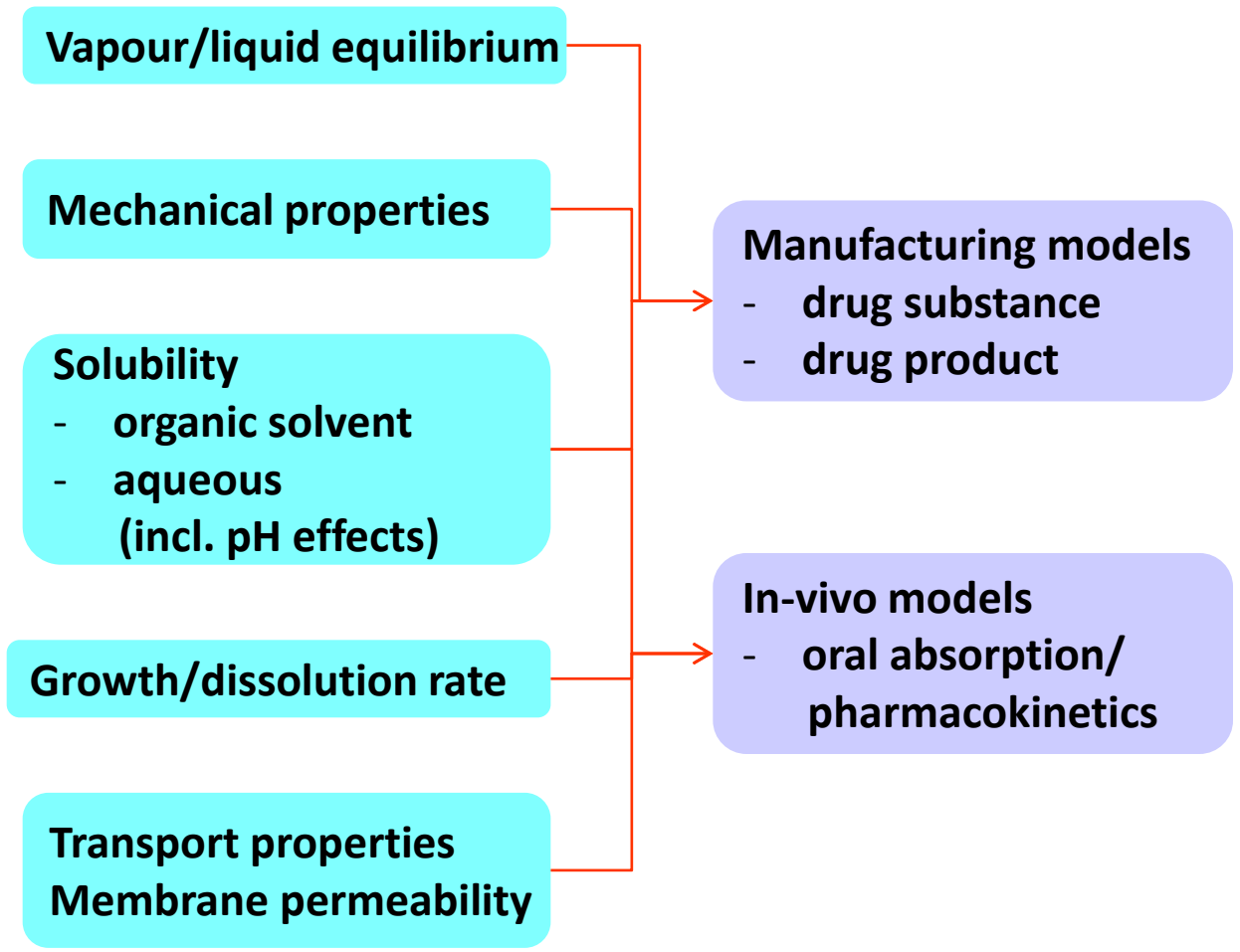
Needs

- increased accuracy of prediction
- reduced reliance on experimental data

➔ **Next-generation models (e.g. for crystallisation)**

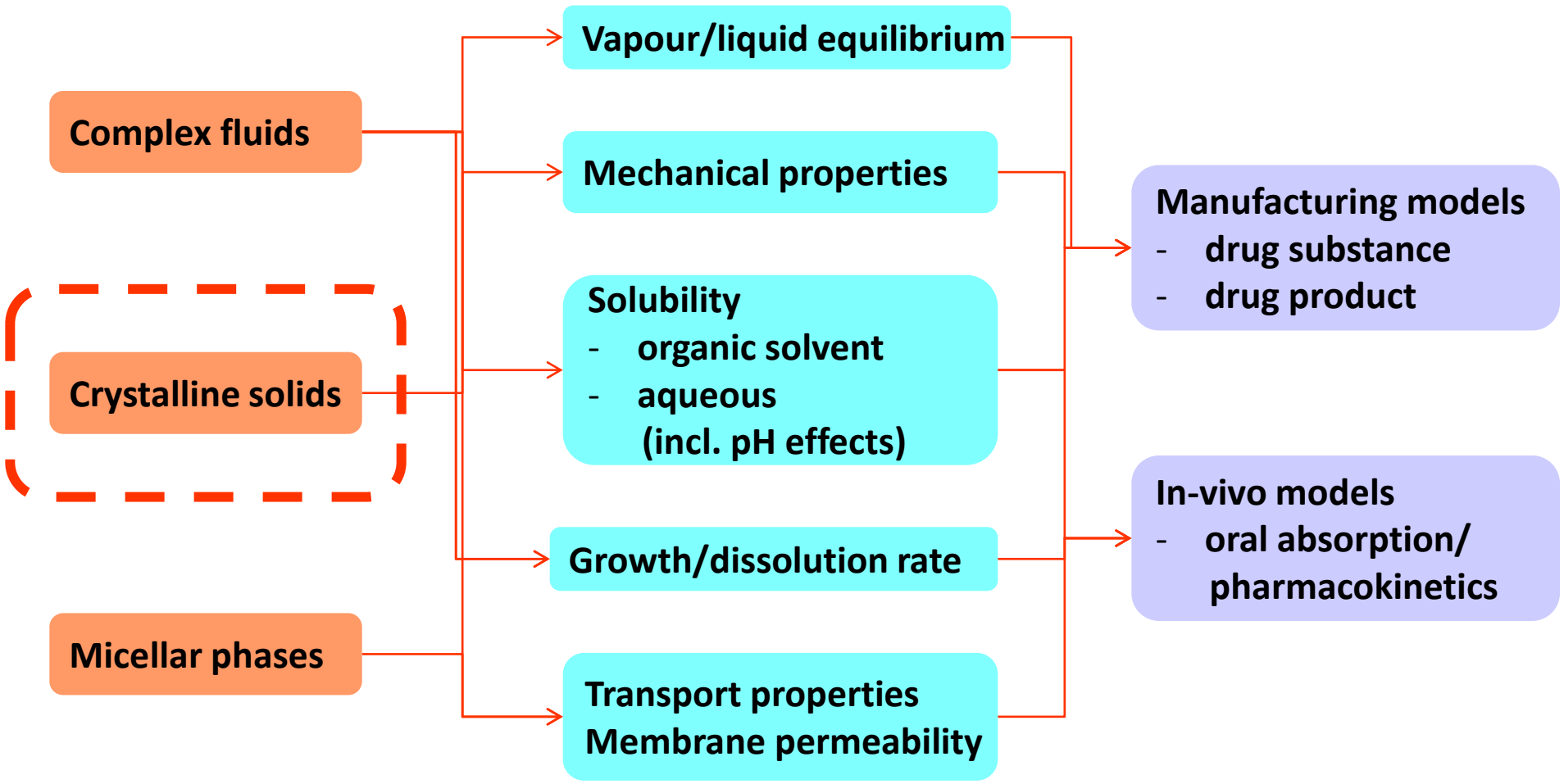
- prediction of behaviour of new materials
- molecular super-structure descriptions

➔ **Incorporation of molecular decisions in optimisation**



Material properties & behaviour for SbP

(a partial view)



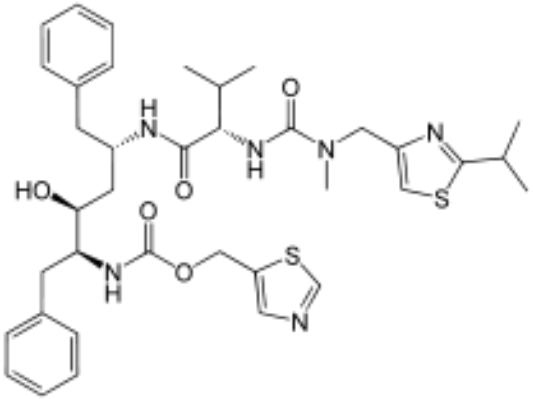
Crystalline solid phases

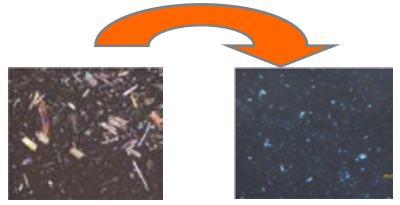
- Most pharmaceutical APIs are in crystalline form
- Polymorphism
  - same API molecule may appear in several crystalline forms (“polymorphs”) in nature
  - thermodynamically: one stable, others meta-stable
- Crystalline form determines physical properties affecting both manufacturing & bioavailability
  - solubility, dissolution rate
  - mechanical strength
- Polymorphism is key aspect of drug approval & patent protection

  ➔ important to identify **all** “stable” polymorphs

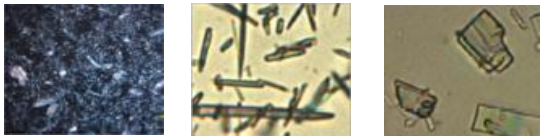
Ritonavir

(Norvir®- Abbott Labs)





Form I Form II



Form III Form IV Form V

Ab initio crystal structure prediction

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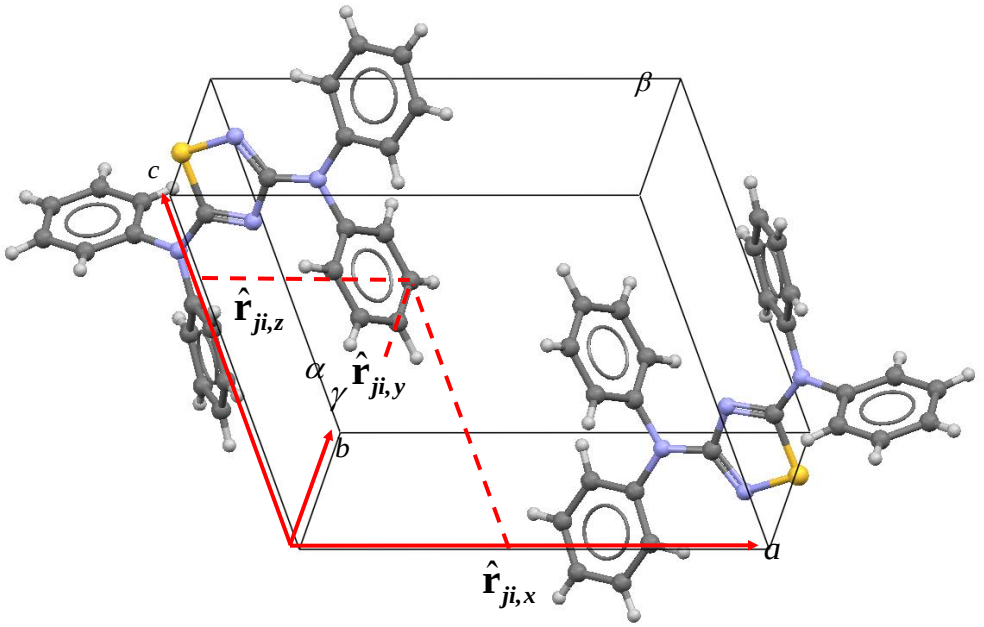
Unit cell is determined by:

- lattice lengths *a*, *b* and *c*
- lattice angles *α*, *β* and *γ*
- positions of all atoms

$\hat{\mathbf{r}}_{ji}, \quad i = 1,..,N, \quad j = 1,..,Z$



$$\min_{a,b,c,\alpha,\beta,\gamma,r_{ji}\,|\,(T,P)} G = U + PV - TS$$

Accurate evaluation via multiscale molecular/ quantum mechanical modelling

Kazantsev, Karamertzanis, Adjiman & Pantelides (2011)
J. Chem. Theory Comput. **7**, 1998-2016

All low-energy local minima via effective global search techniques

Karamertzanis & Pantelides (2004)
J. Comput. Chem. **26**, 304-323

$$\simeq U^{\text{intra}} + U^{\text{inter}}_{\text{electr}} + U^{\text{inter}}_{\text{disp/rep}} + PV$$

5th Blind Test for Crystal Structure Prediction

Cambridge Crystallographic Data Centre, 2010[1]

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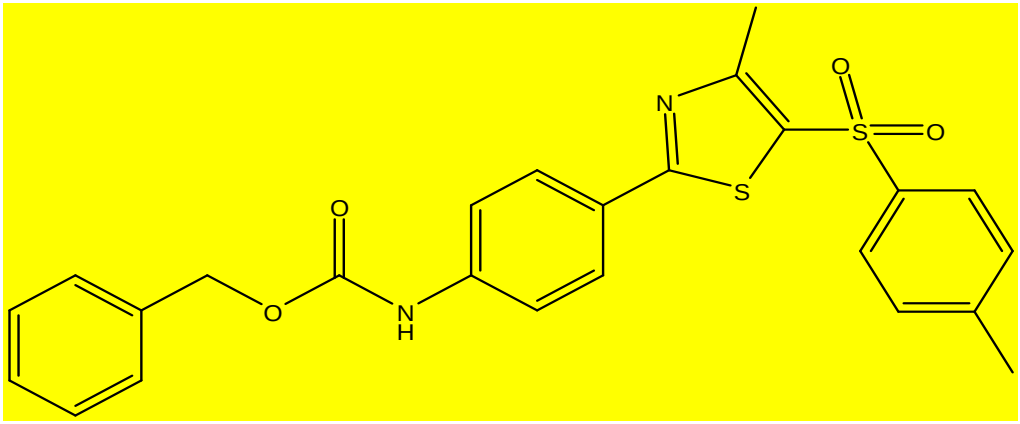

Molecule XX

benzyl-(4-(4-methyl-5-(p-tolylsulfonyl)-1,3-thiazol-2-yl)phenyl)carbamate

- Largest ever molecule considered under blind test conditions
- Entries by 14 research groups worldwide
- Two correct predictions[2] (Imperial College London, U. Cambridge)
  - Both using Crystal Predictor[3] for global search
  - Different methods for final refinement of the structures

1 Bradwell et al. (2011), *Acta Cryst. B* **67**, 535-551.

2 Kazantsev, Karamertzanis, Adjiman, Pantelides, Price , Galek, Day & Cruz-Cabeza (2011), *International Journal of Pharmaceuticals* **418**, 168-178.

3 Karamertzanis & Pantelides (2004), *J. Comput. Chem*. **26**, 304-323.

5th Blind Test: Molecule XX

Kazantsev, et al. (2011), *International Journal of Pharmaceuticals* **418**, 168-178.

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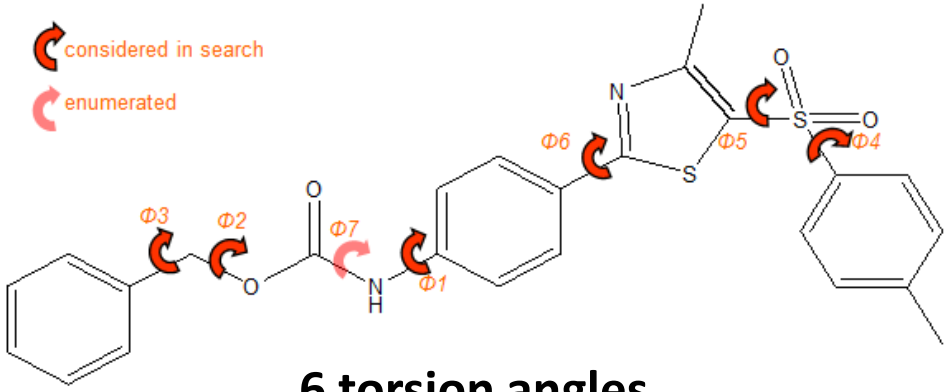
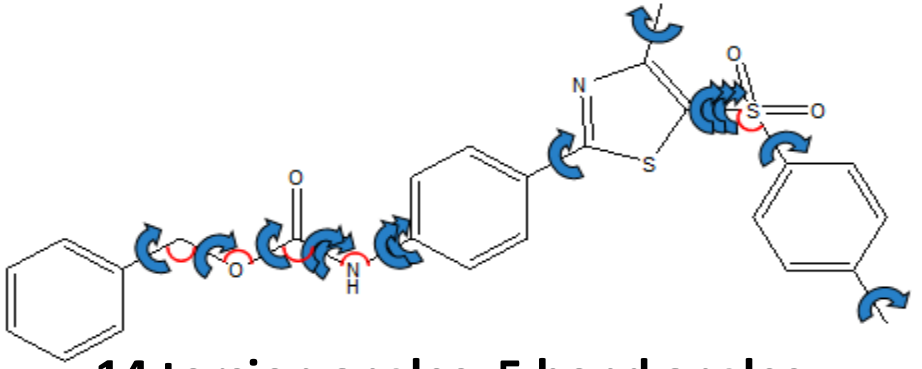
Stage I: Global search

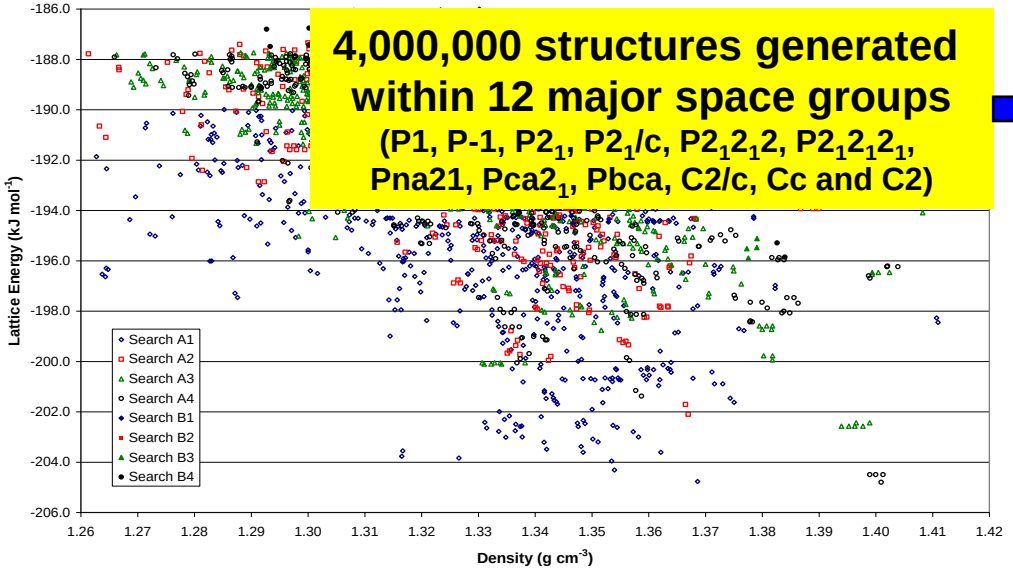


6 torsion angles

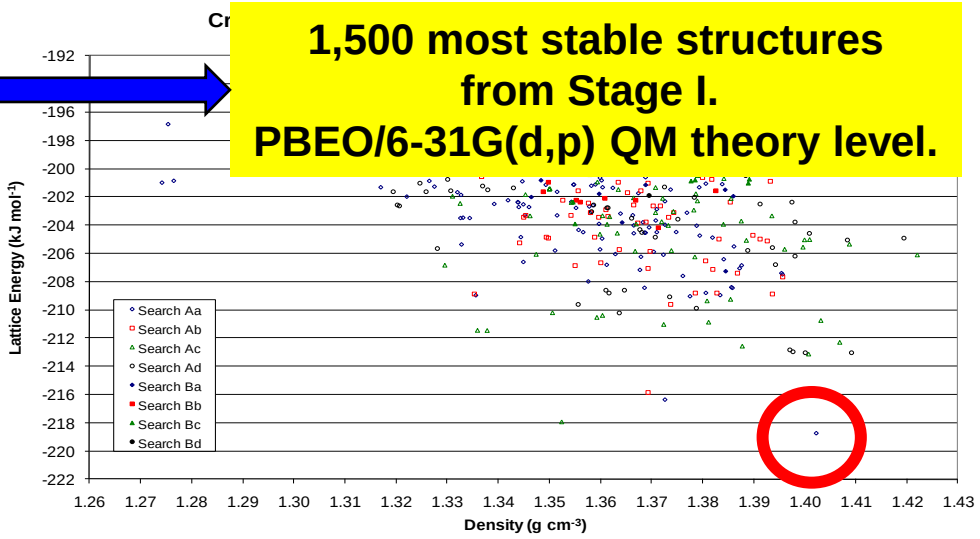
Stage II: Local refinement



14 torsion angles, 5 bond angles



4,000,000 structures generated within 12 major space groups
(P1, P-1, $P2_1$, $P2_1/c$, $P2_12_12$, $P2_12_12_1$, $Pna2_1$, $Pca2_1$, Pbca, C2/c, Cc and C2)



1,500 most stable structures from Stage I. PBEO/6-31G(d,p) QM theory level.

5th Blind Test: Molecule XX

Kazantsev, et al. (2011), *International Journal of Pharmaceuticals* **418**, 168-178.

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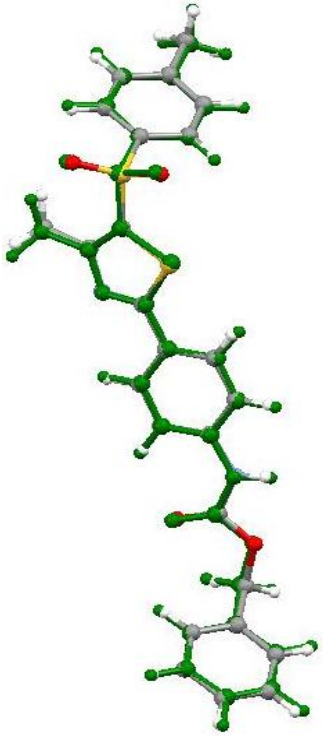
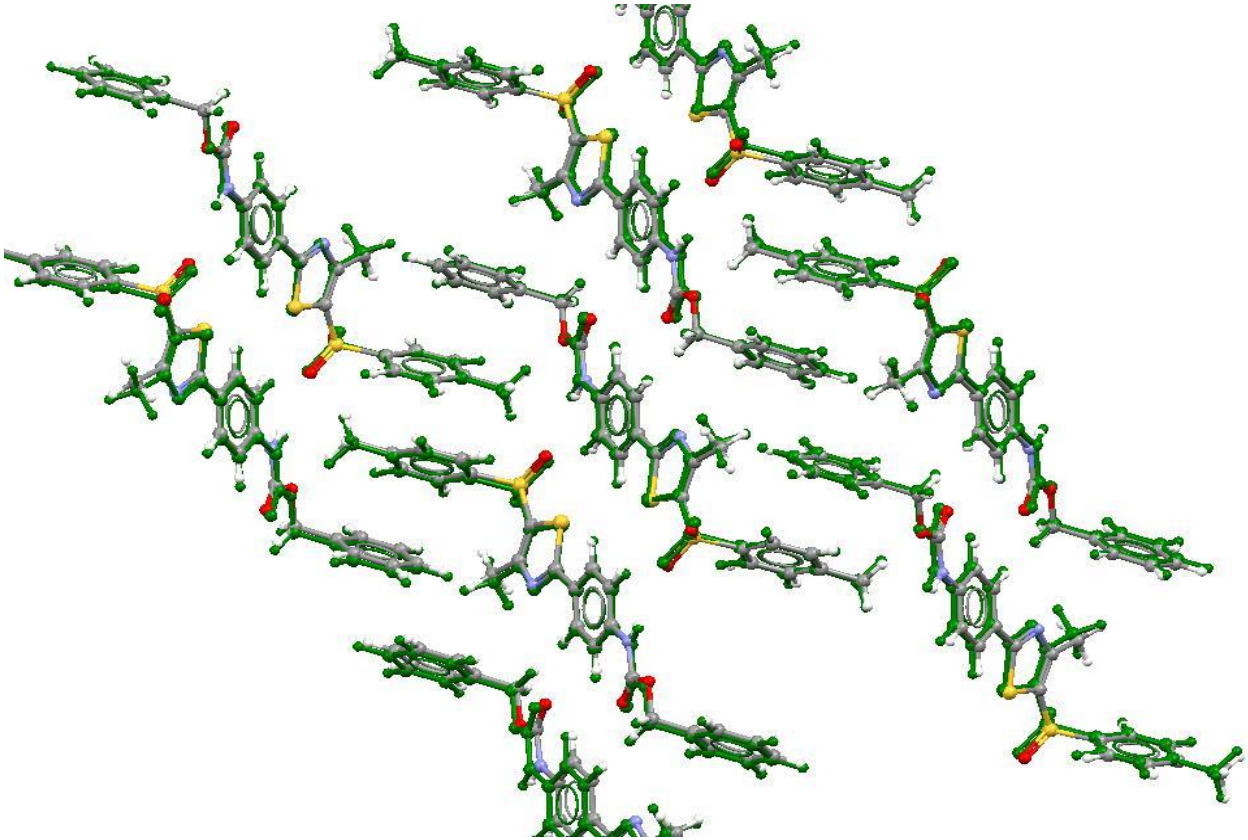
Overlays of experimental & predicted structures

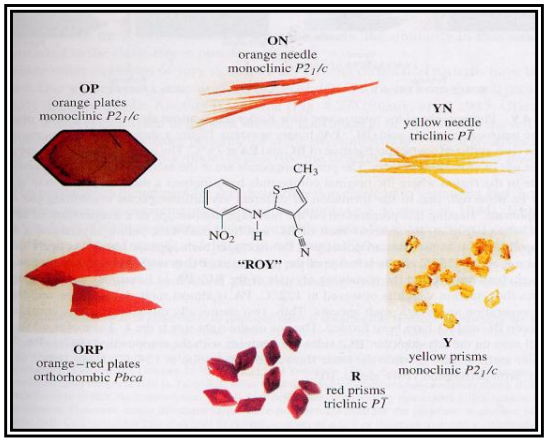




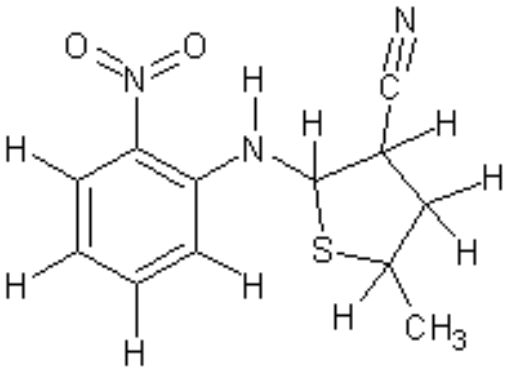
rms_1 = 0.099 Å

rms_{25} = 0.197 Å

Ab initio crystal structure prediction



L. Yu, *Acc. Chem. Res.* , 2010, 43, No. 9, 1257-1266

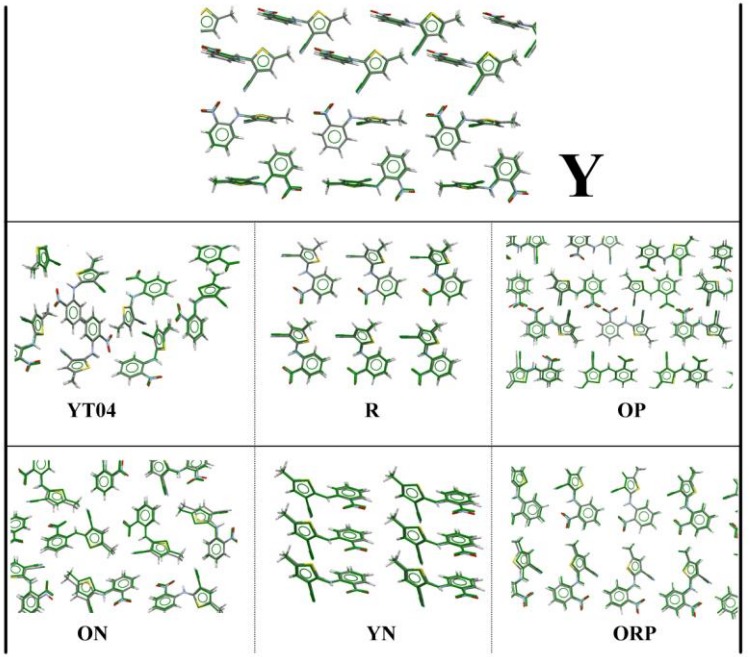


Vasileiadis, Kazantsev, Karamertzanis, Adjiman, Pantelides. *Acta Crystallographica B,* 2012, (accepted for publication)

Predicted vs. experimental structure overlays

Good agreement,

but stability order not yet quite right



Methodology also applicable to API salts & co-crystals (*but still rubbish for API hydrates*)

Karamertzanis, Kazantsev, Issa, Welch, Adjiman, Pantelides & Price (2009), *J. Chem. Theory Comput.* **5**, 1432-1448.

Kazantsev, Karamertzanis, Adjiman & Pantelides (2011), *J. Chem. Theory Comput*. **7**, 1998-2016.

Current research – addressing (some) gaps

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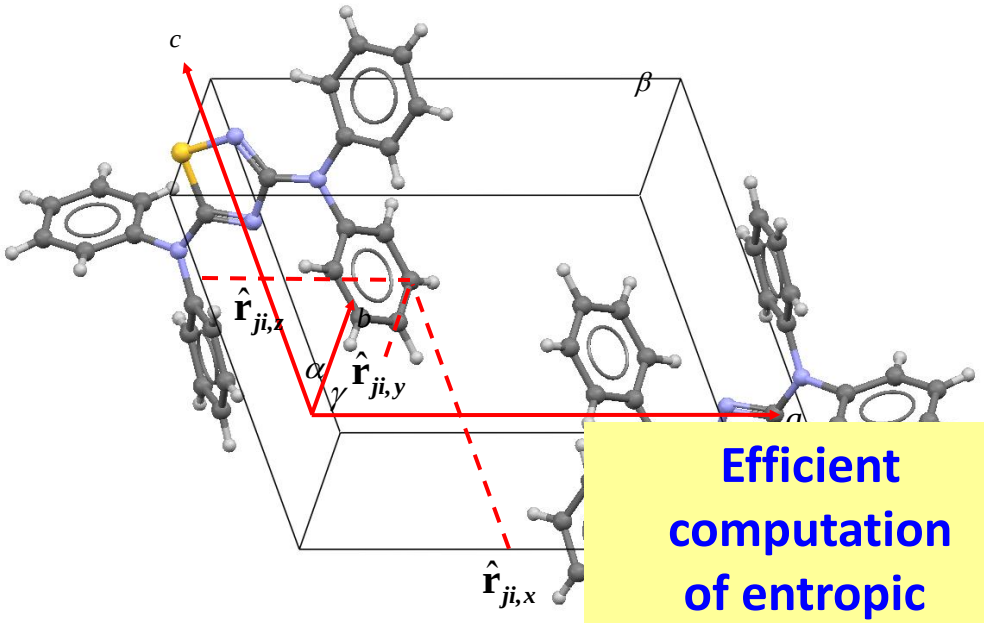
Unit cell is determined by:

- lattice lengths *a*, *b* and *c*
- lattice angles *α*, *β* and *γ*
- positions of all atoms

$\hat{\mathbf{r}}_{ji}, \quad i = 1,..,N, \quad j = 1,..,Z$



$$\min_{a,b,c,\alpha,\beta,\gamma,r_{ji}\,|\,(T,P)} G = U$$

$$= U^{\text{intra}} + U$$

$$= U^{\text{intra}} + U^{\text{inter}}_{\text{electr}} + U^{\text{inter}}_{\text{disp/rep}} + PV - TS$$

$$\simeq U^{\text{intra}} + U^{\text{inter}}_{\text{electr}} + U^{\text{inter}}_{\text{disp/rep}} + PV$$

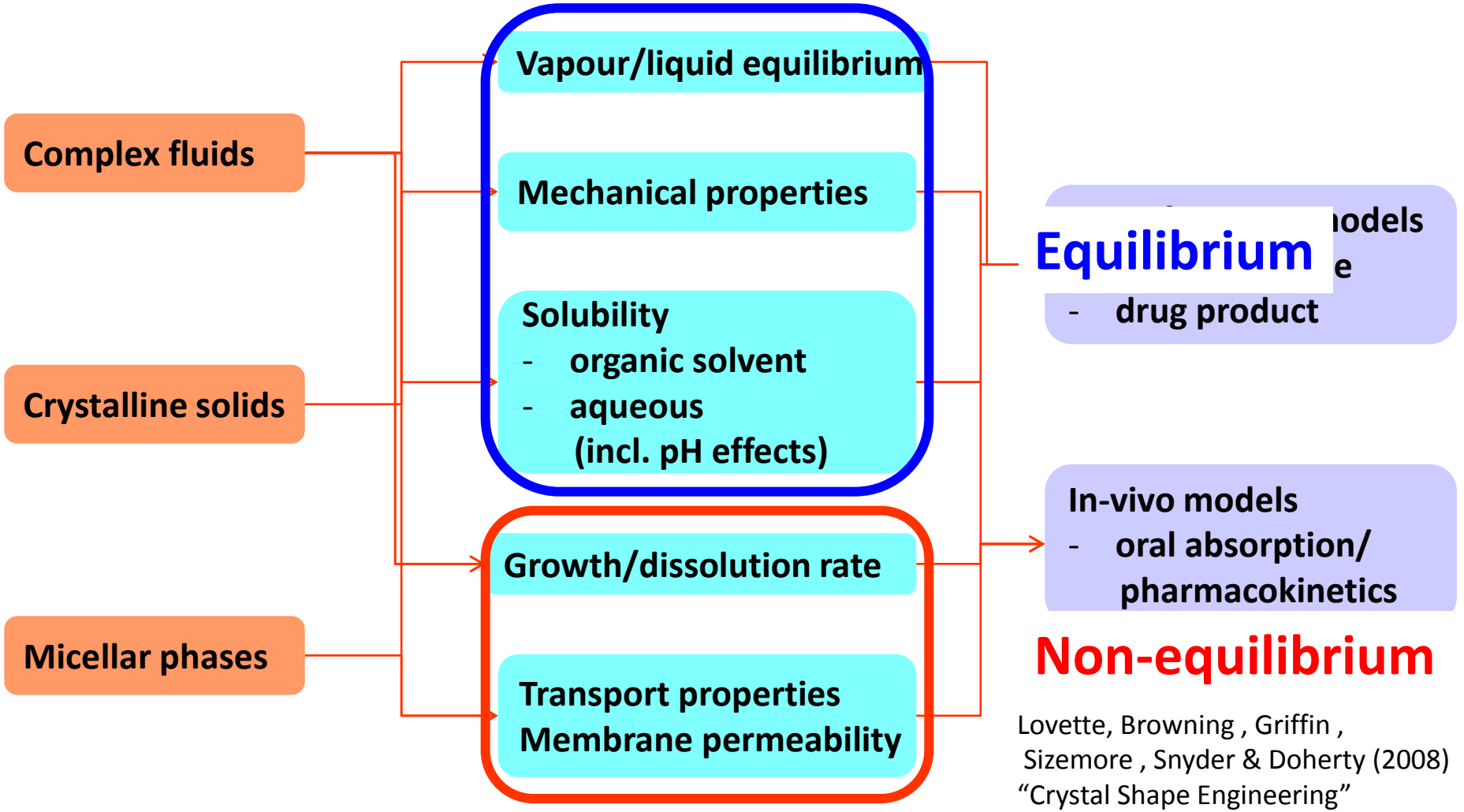
Accurate handling of dispersion/ repulsion

Efficient computation of entropic contributions

Vasileiadis, Karamertzanis, Adjiman & Pantelides AIChE Annual Meeting (Pittsburgh, Oct.2012)

Material properties & behaviour in SbP

(a partial view)



Lovette, Browning , Griffin , Sizemore , Snyder & Doherty (2008) "Crystal Shape Engineering" *Ind. Eng. Chem. Res.*, **47**, 9812–9833.

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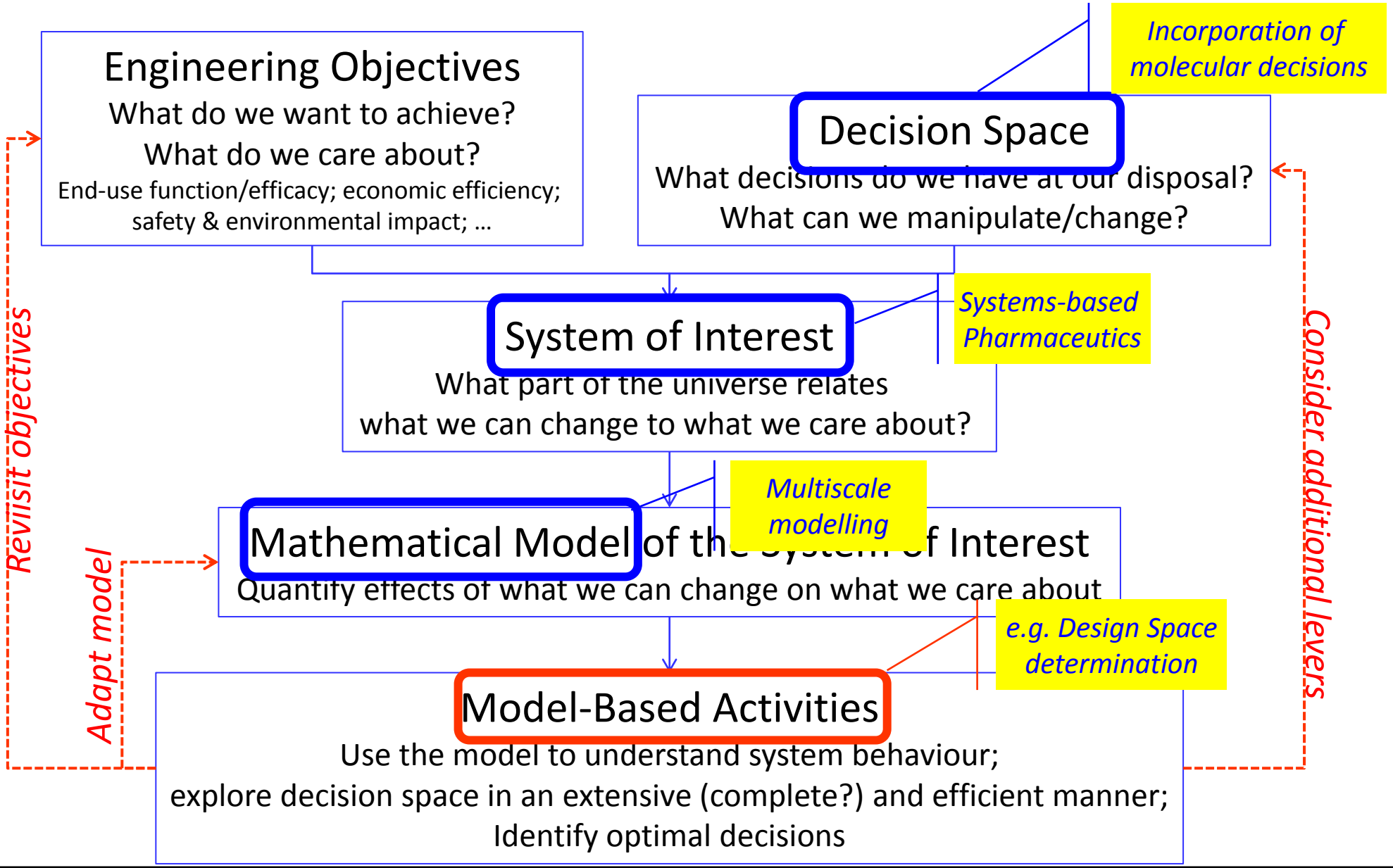
4b. Design Space in pharmaceutical manufacturing

The Systems Engineering approach is a

Top-Down Approach



Design Space

The multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality

International Conference for Harmonisation: Draft Guidance Q8 (Revision 1)

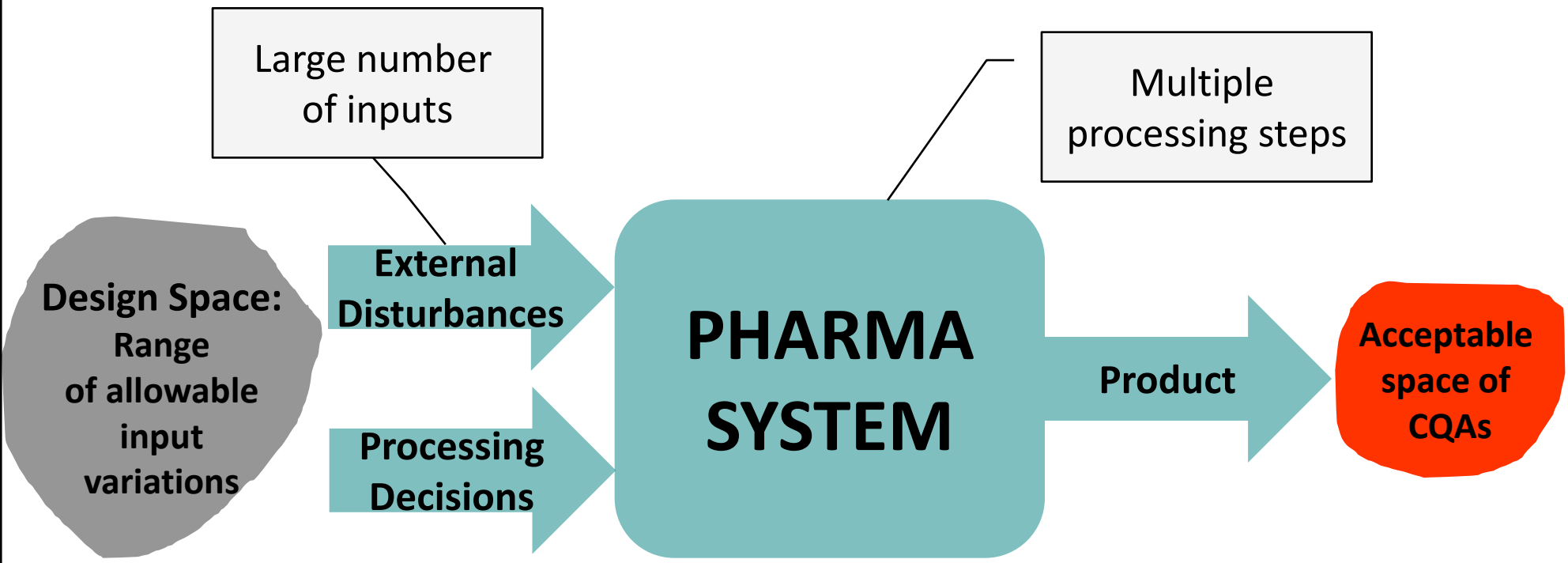
Regulatory flexibility:

Working within the Design Space is not considered to be a "change"

Design space is proposed by the applicant and is subject to regulatory assessment and approval

The case for

Model-based Design Space determination

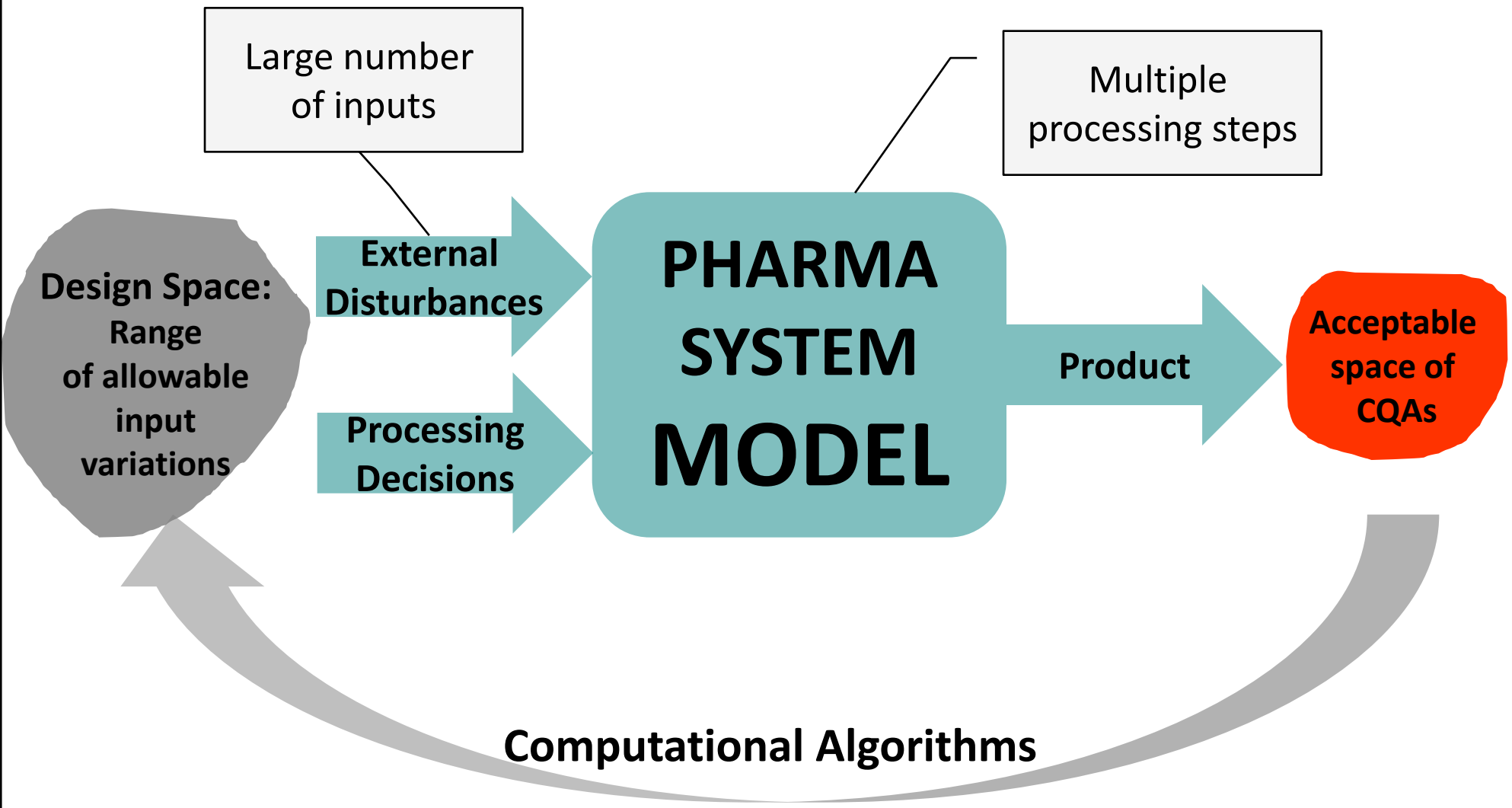


Impractical to determine Design Space experimentally

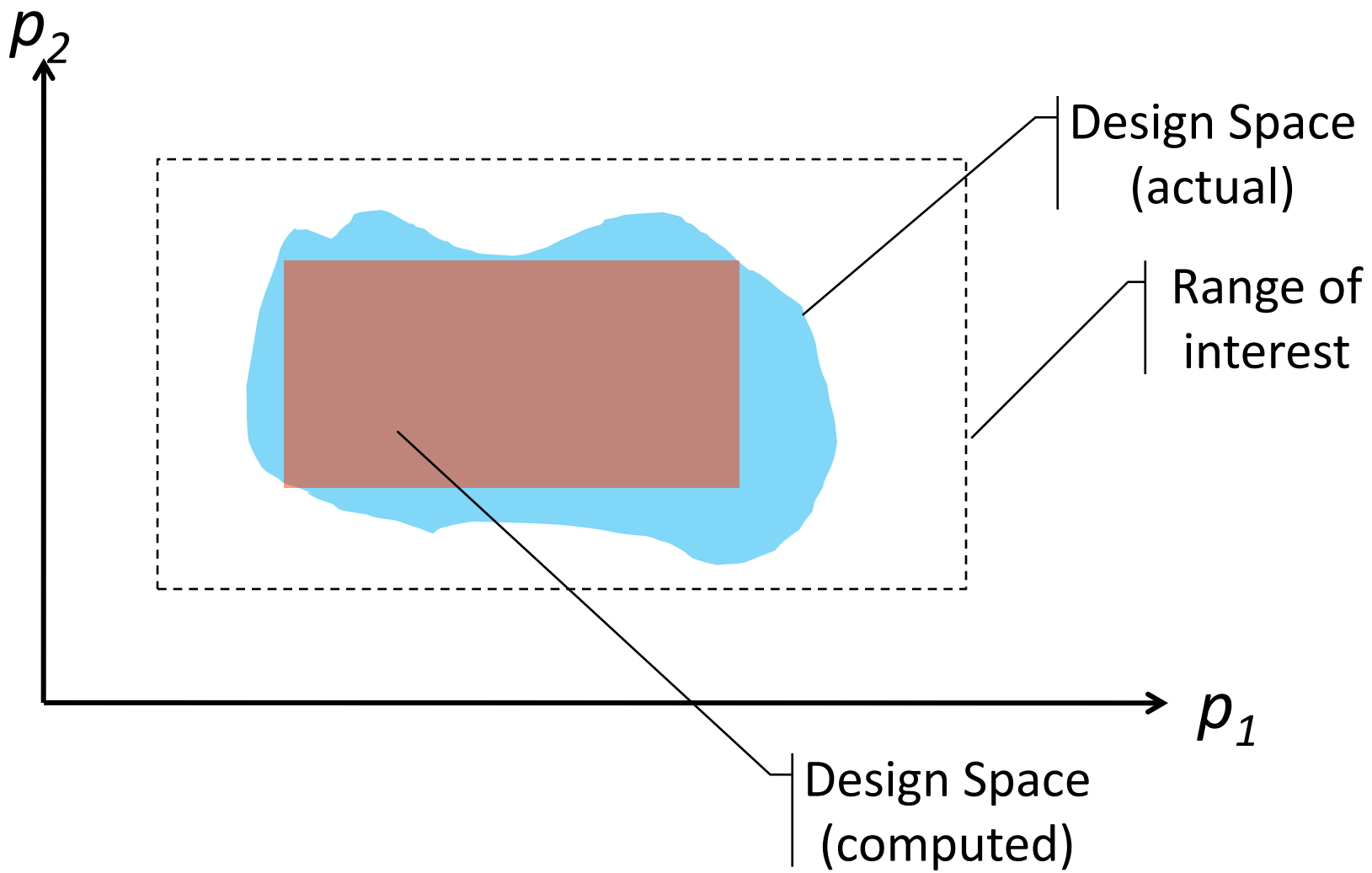
➔ **model-based approach**

The case for

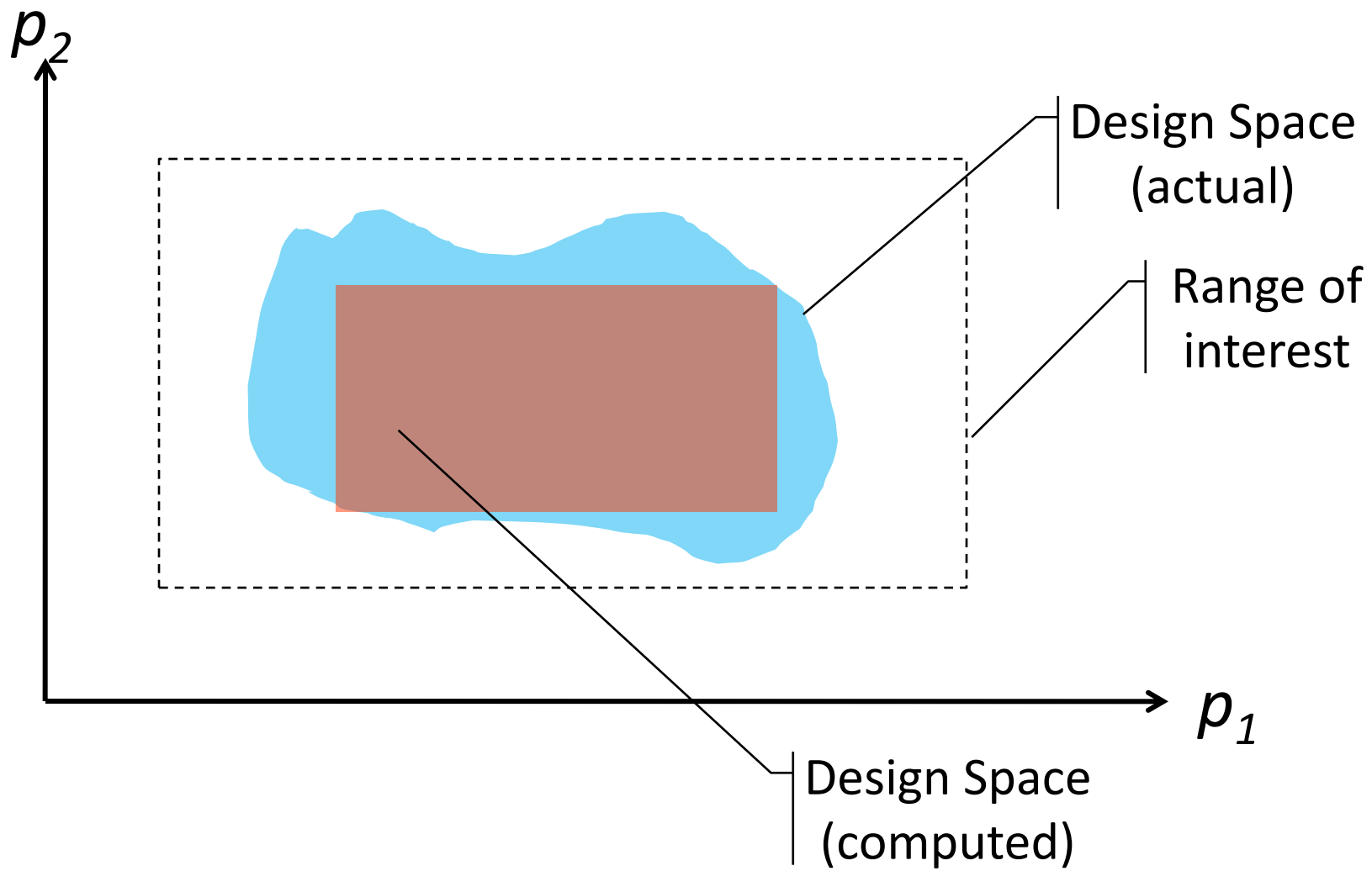
Model-based Design Space determination



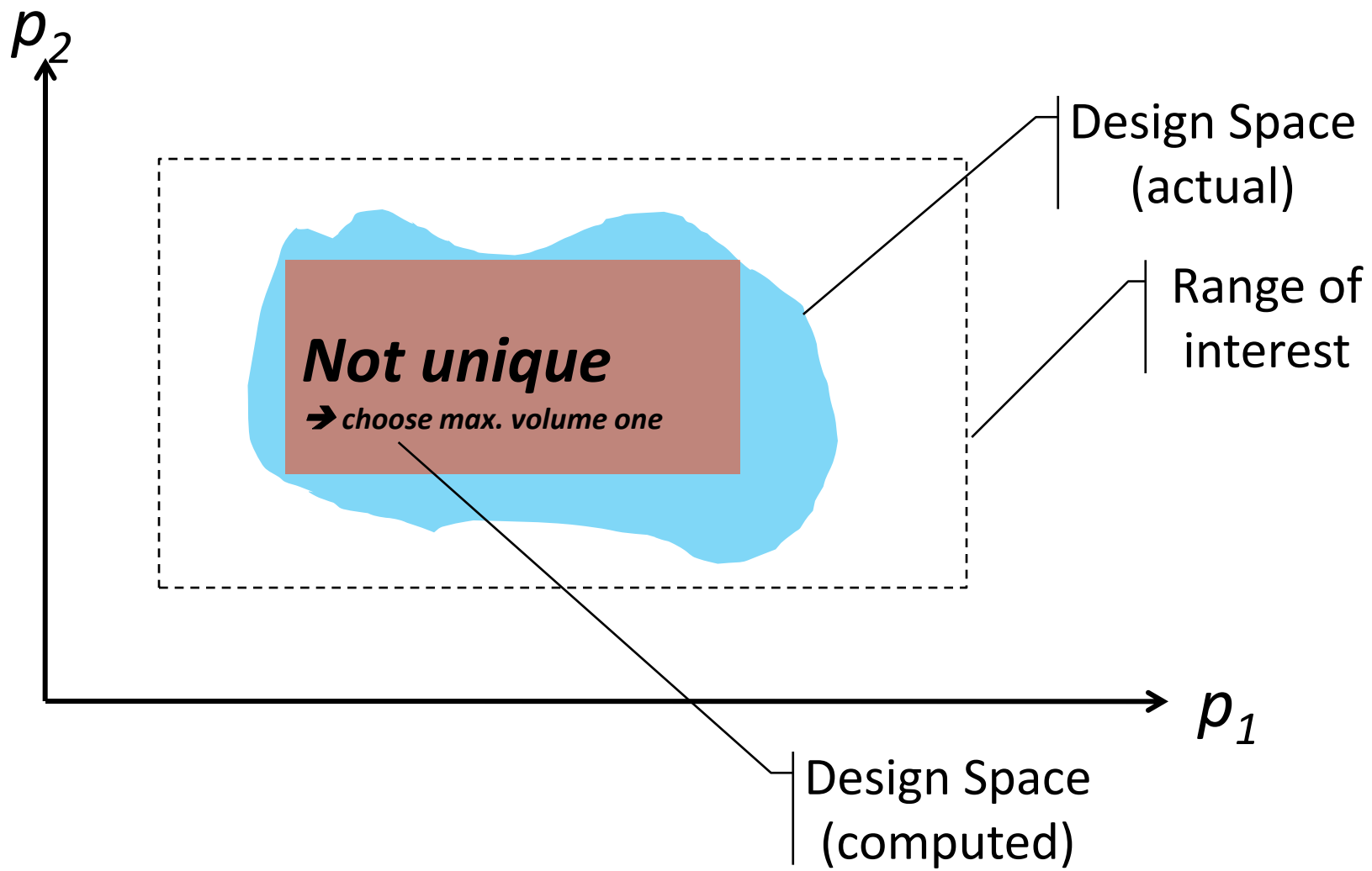
Design Space – a graphical perspective



Design Space – a graphical perspective



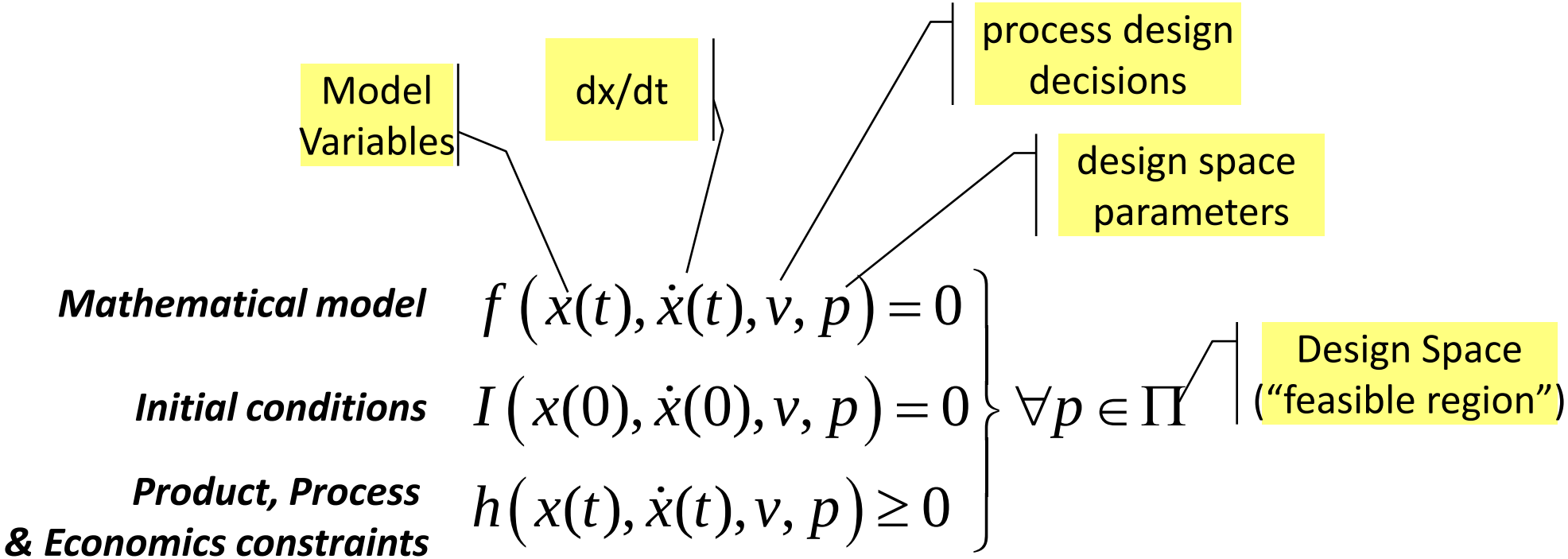
Design Space – a graphical perspective



Design Space
A process systems engineering perspective

- Quantification of "process flexibility" (i.e. size of Design Space)
  - a key concern of process systems research from mid-1980s to late 1990s
  - cf. Halemane & Grossmann, *AIChE J*, **29**, 425-433 (1983); Dimitriadis & Pistikopoulos, *Ind. Eng. Chem. Res.*, **34**, 4451-4462 (1995); Mohideen et al., *AIChE J.*, **42**, 2251-2272 (1996)

→ Decide on how to measure the size of the Design Space
  - … then design the process so as to maximise it



Design Space: a simple example

(paper #417f, 2009 Annual AIChE Meeting, Nashville, TN)

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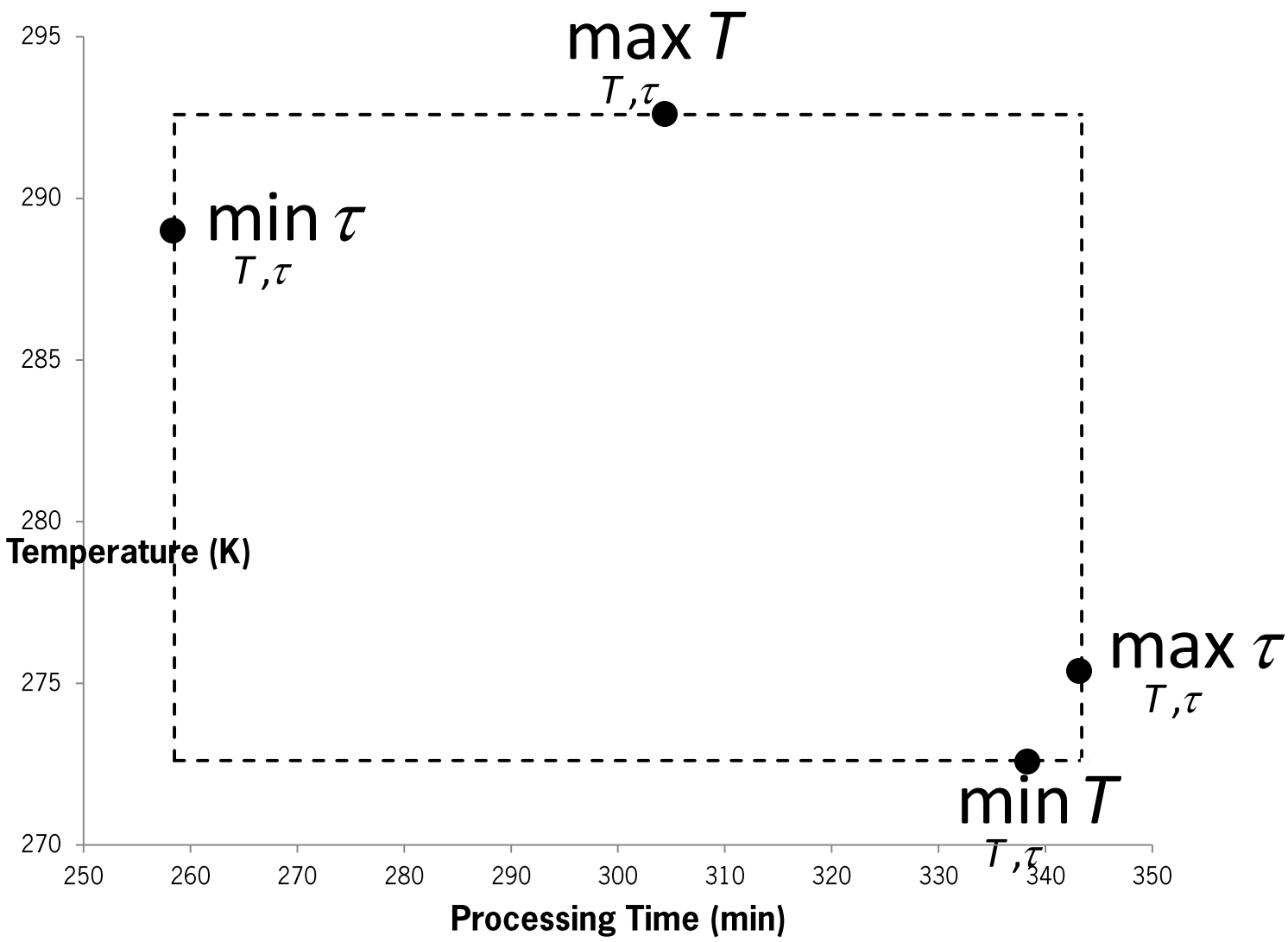
- Batch reactor $2A \rightarrow B \rightarrow C$
  - require at least 80% B in final product
- Process parameters
  - operating temperature, T
    - assumed constant over batch
  - processing time, τ
- Optimal nominal values
  - T = 287K
  - τ = 260 min

➔ economic benefit ~ $160/min

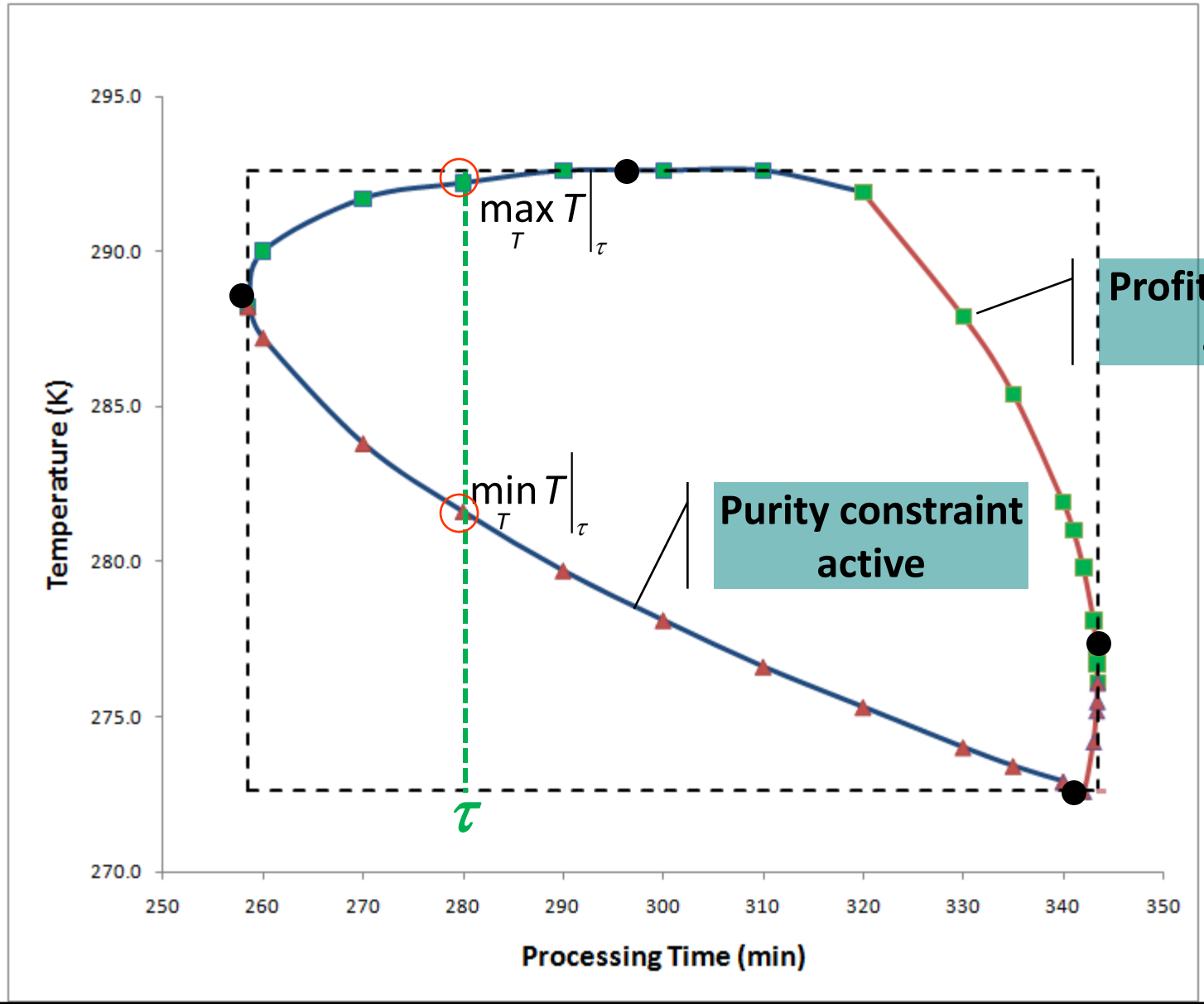
1. Design Space specifications

- Design Space in terms of process parameters T, τ
- Specifications
  - At least 80% of B in final product
  - Economic performance of at least $128/min
    - 80% of theoretical optimum of $160/min

2. Superscribing hyper-rectangle

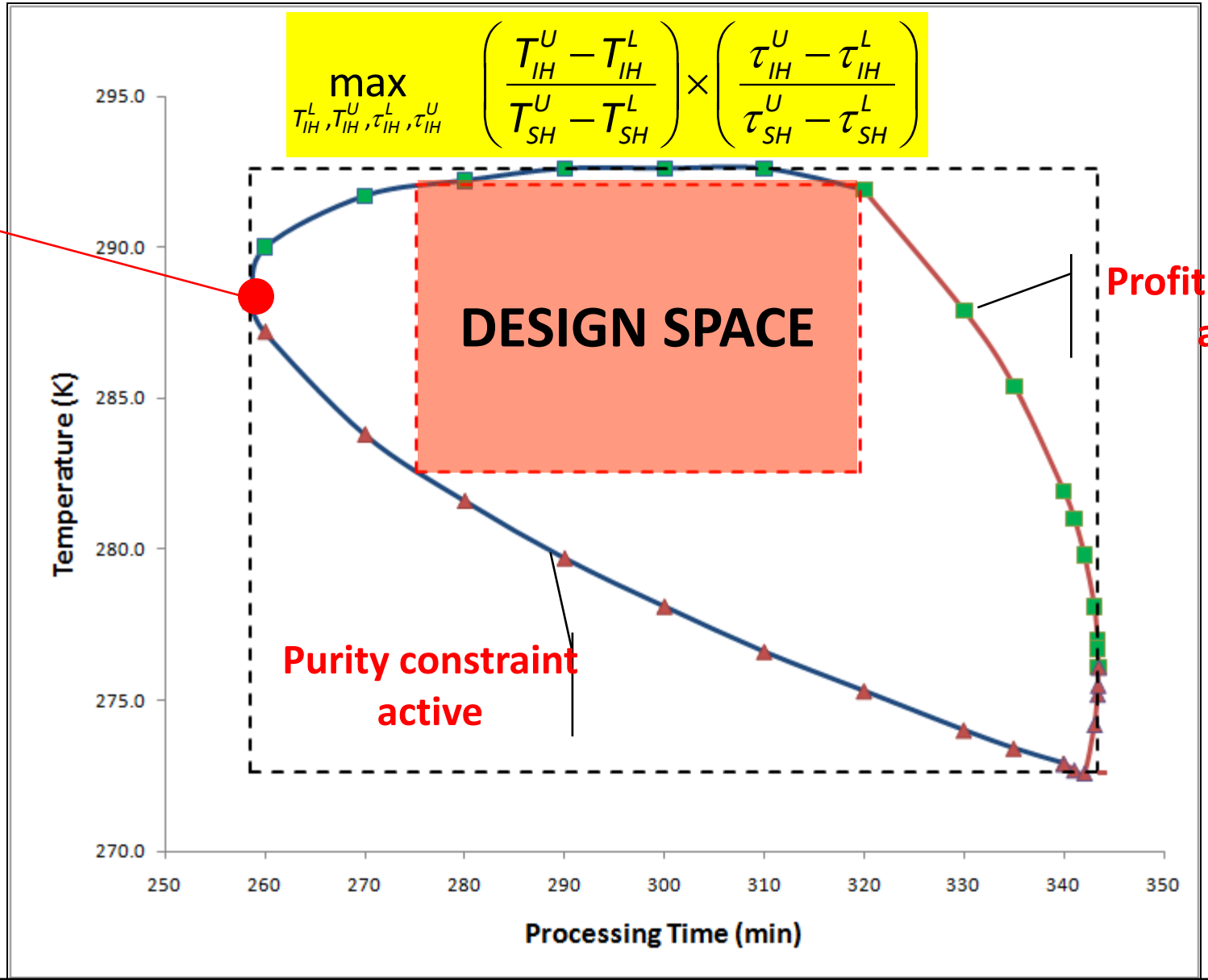


3. Feasible region determination



4. Inscribed max-volume hyper-rectangle

$$\max_{T_{IH}^L, T_{IH}^U, \tau_{IH}^L, \tau_{IH}^U} \left(\frac{T_{IH}^U - T_{IH}^L}{T_{SH}^U - T_{SH}^L} \right) \times \left(\frac{\tau_{IH}^U - \tau_{IH}^L}{\tau_{SH}^U - \tau_{SH}^L} \right)$$

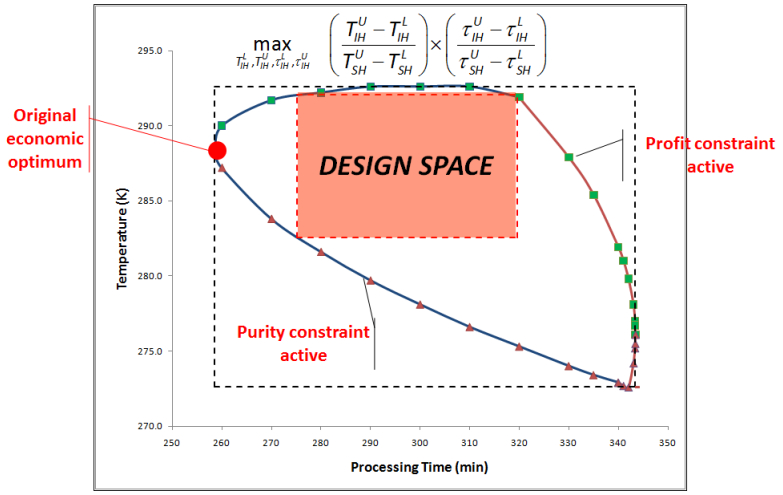


Design Space

- Any point in the region
  - $T \in [282.3\ K,\quad 292.1\ K\ ]$
  - $\tau \in [276.5\ min, 319.5\ min]$

  is guaranteed to deliver
  - a product with at least 80% B
  - an economic performance of at least \$128/min
- Algorithms exist for determining an inscribed hyper-rectangle directly for transient problems of large dimensionality

  (e.g. Samsatli, Sharif, Shah, Papageorgiou (2004), *AIChE J.*, **47**, 2277-2288)



BUT…

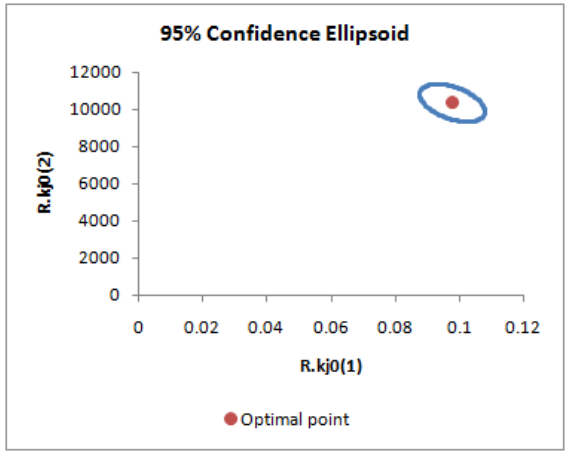
- For multidimensional problems, computed ranges for individual variables tend to be very narrow
- …and may exclude many feasible points of practical interest
- **Effects of model uncertainty?**

Simple example revisited

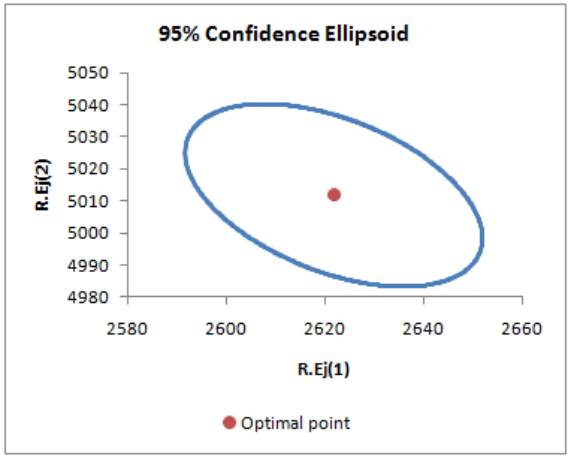
- Batch reactor 2A → B → C

- Kinetic rate constants $k_j^0 e^{-E_j/RT}, \quad j = 1,2$
- Kinetic parameters estimated from experimental data

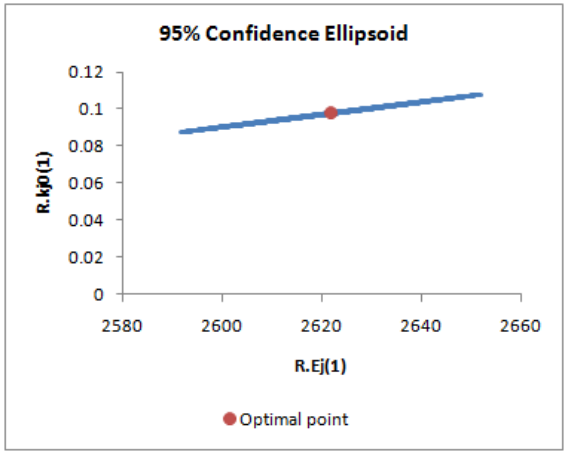
  → subject to uncertainty



Pre-exponential Arrhenius factors

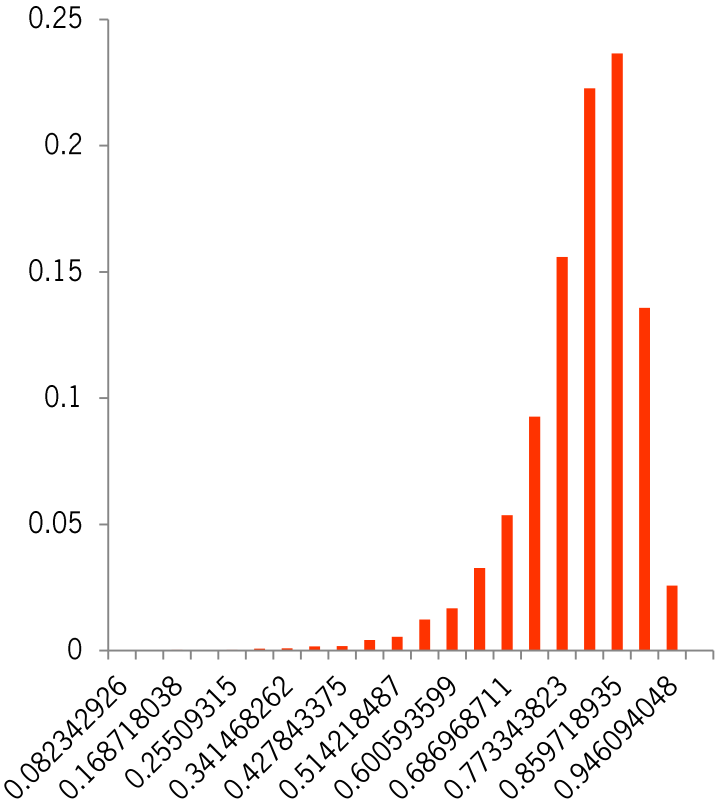


Activation energies

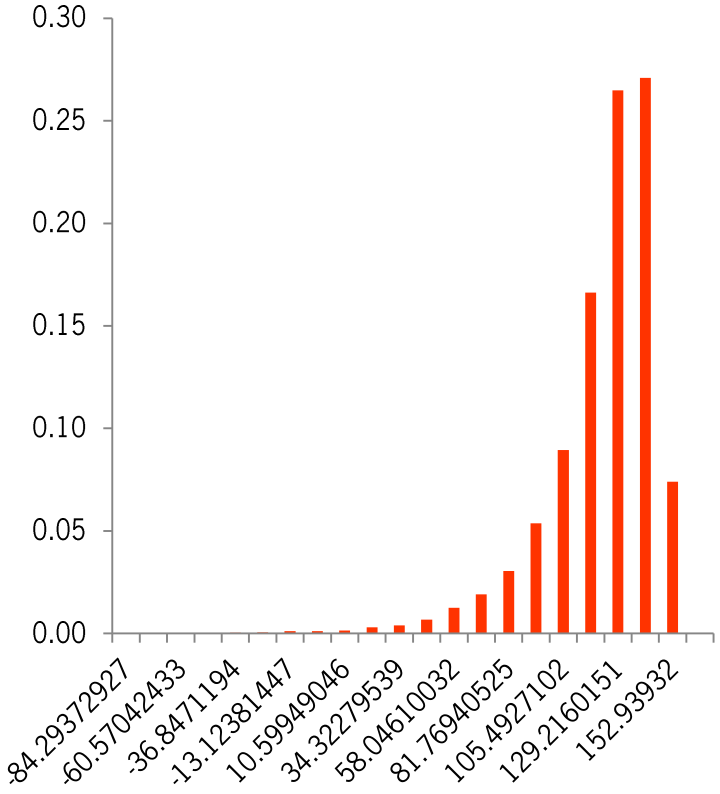


Pre-exponential Arrhenius factor vs. activation energy for 2A → B

Effect of kinetic parameter uncertainty on predicted process KPIs



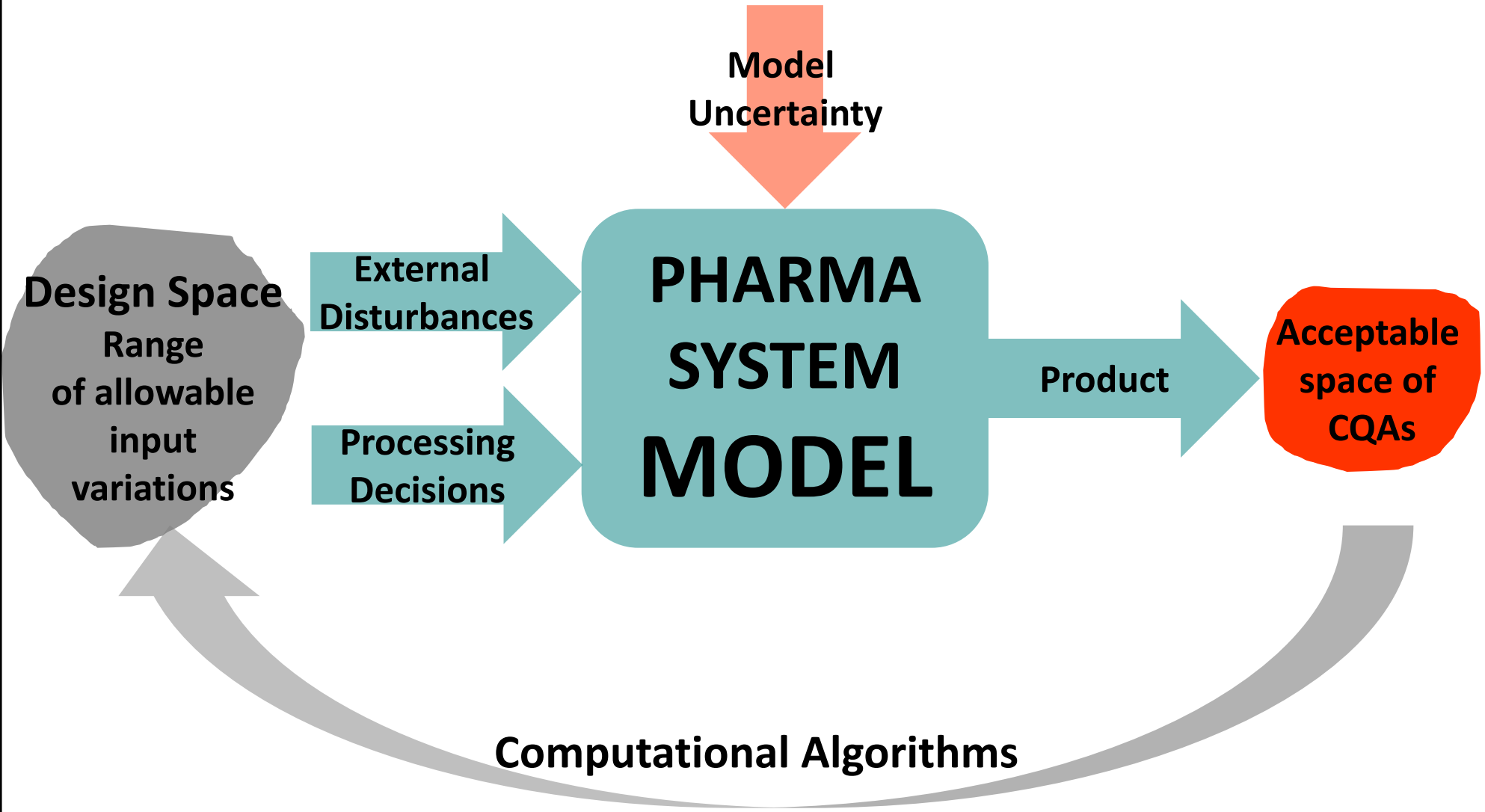
Product Purity



Economic Benefit ($/min)

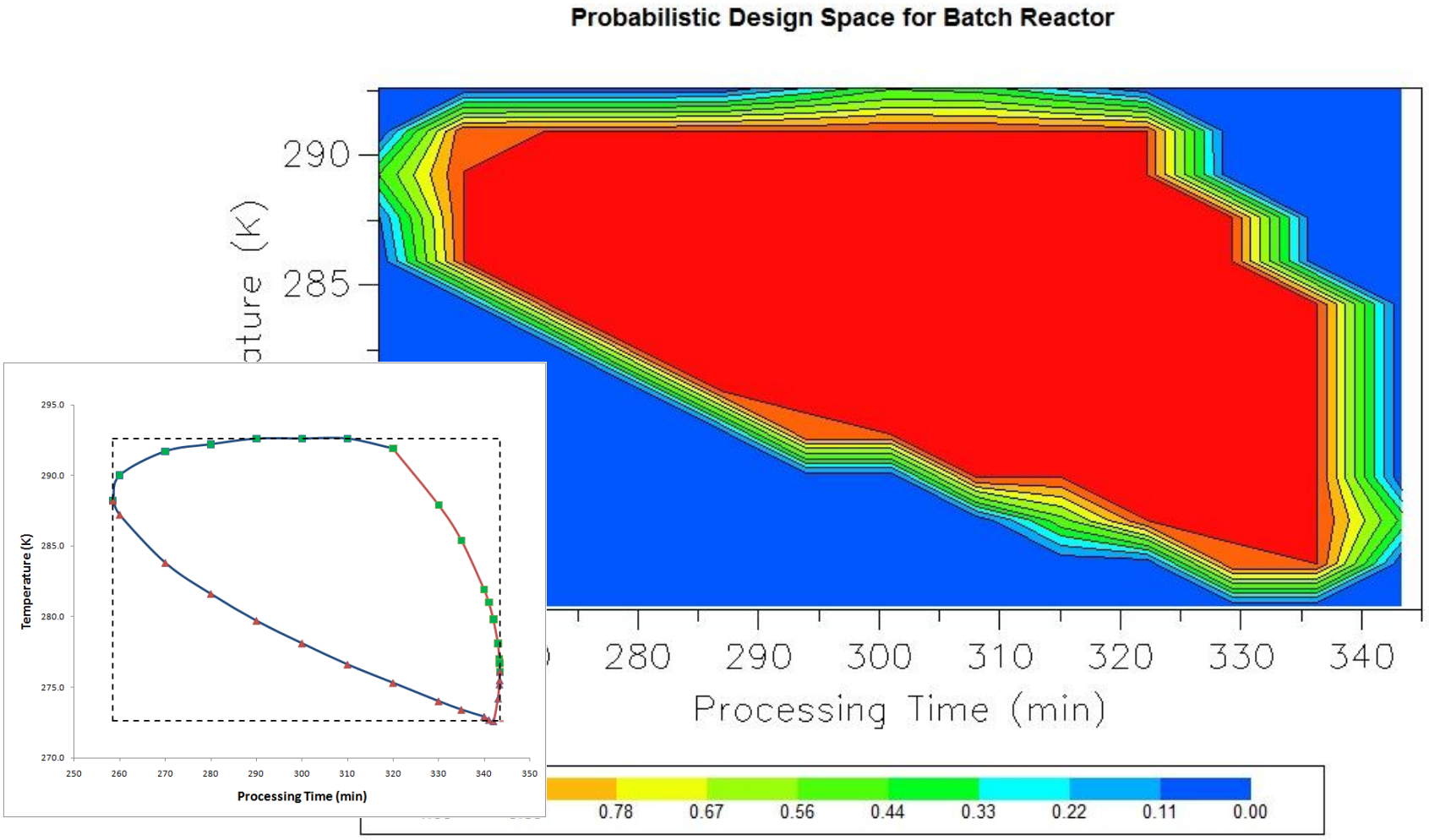
Computed at T=287K, τ = 340 min

Model-based Design Space determination



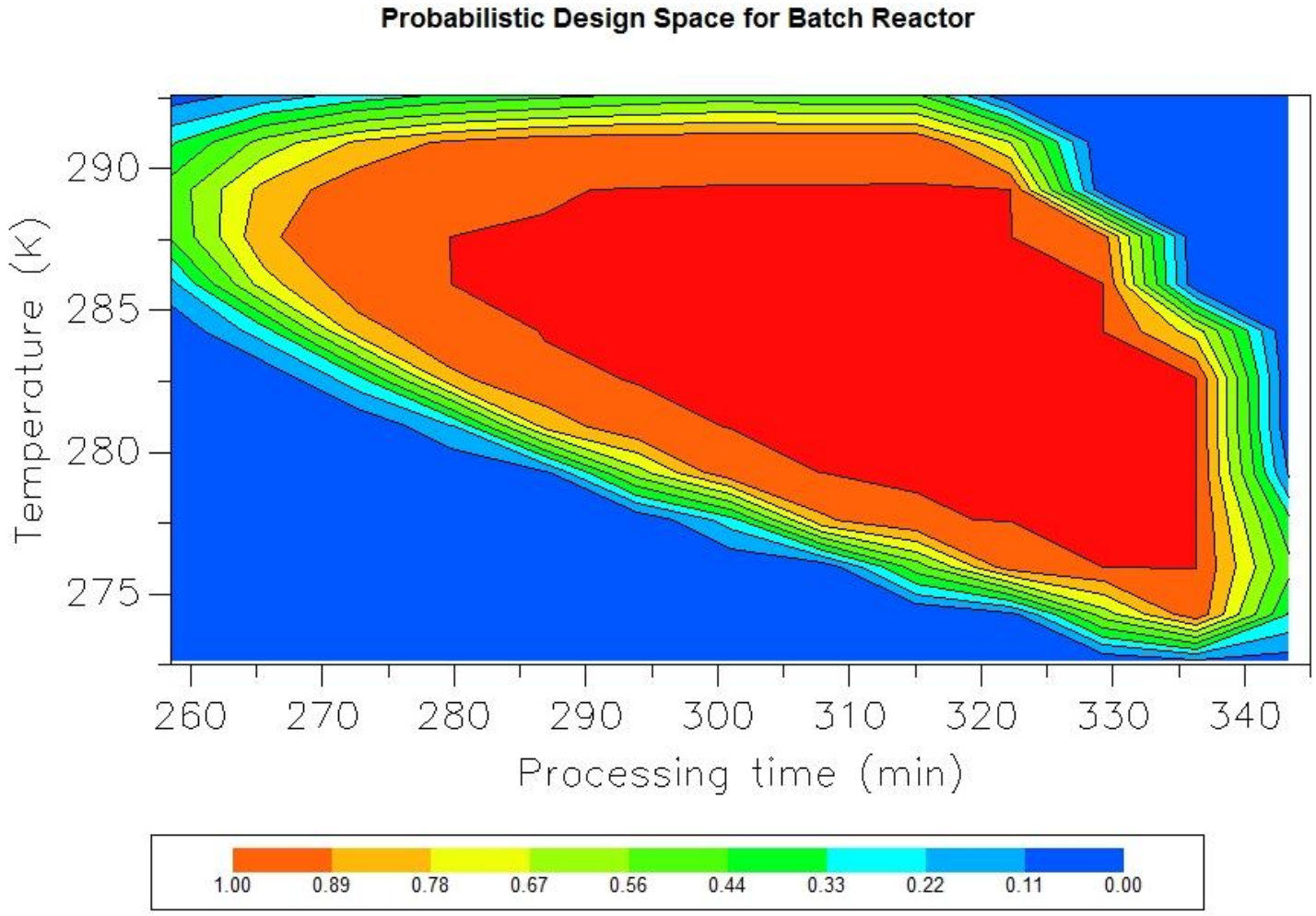
Effect of kinetic parameter uncertainty on design space

Independent Gaussian distributions, σ = 0.01%



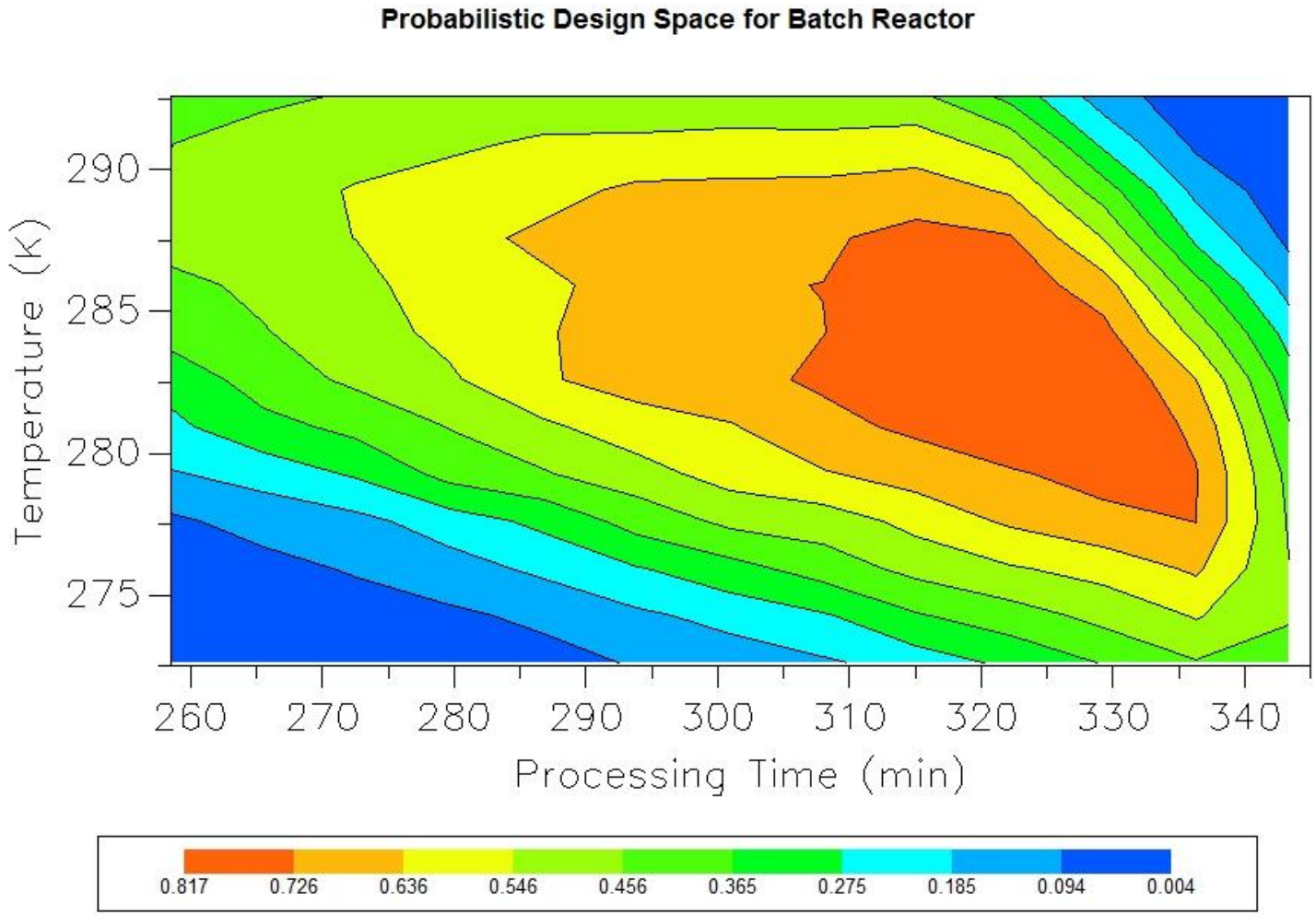
Effect of kinetic parameter uncertainty on design space

Independent Gaussian distributions, σ = 0.1%

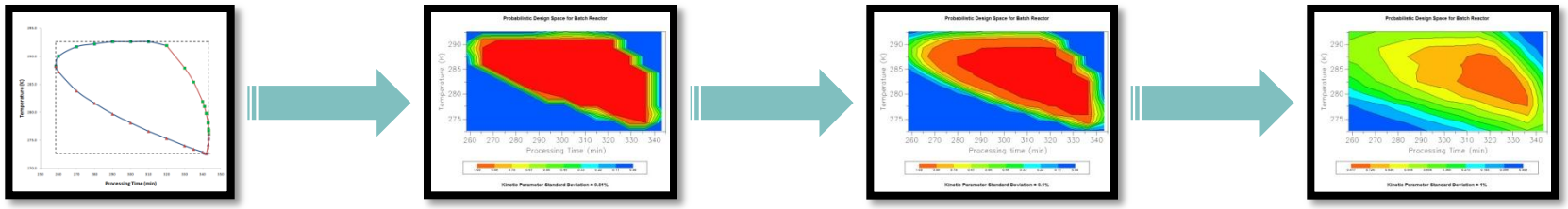


Effect of kinetic parameter uncertainty on design space

Independent Gaussian distributions, σ = 1%



Probabilistic Design Space



Deterministic DS ***σ = 0.01%*** ***σ = 0.1%*** ***σ = 1%***

- *Any* model-based techniques can determine only the ***probability*** of any set of inputs belonging to the Design Space

- Requires quantification of the model uncertainty
  - an integral part of formal **model validation/parameter estimation** procedures

Given a point *u* in the process input space…

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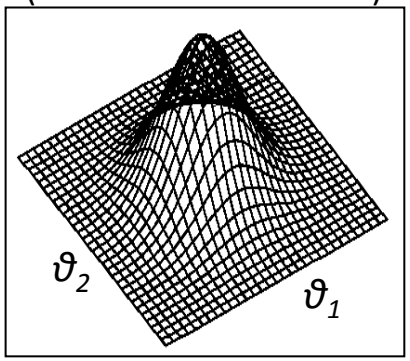
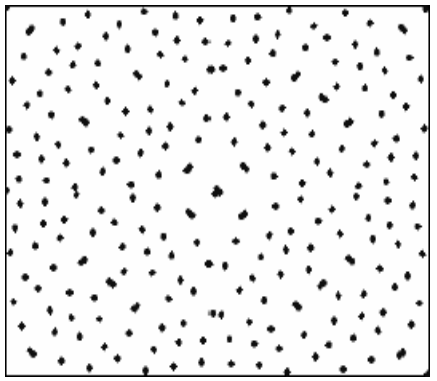
Probability distribution of model parameters
(from model validation)

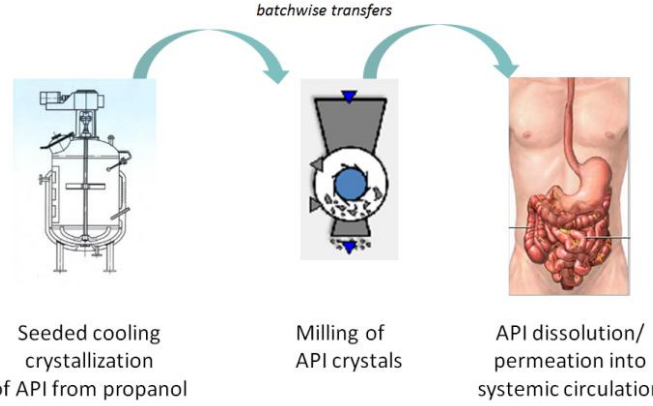


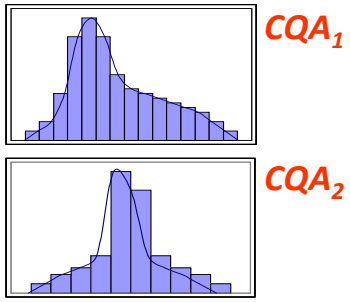
Sampling of parameter space
(low-discrepancy Sobol' sequences)



Probability of point *u* belonging to the Design Space

Model evaluation for given (u, θ) combination





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5. Concluding remarks

Concluding remarks

- Pharma: an industry in transition → challenges & opportunities
- Process Systems Engineering:
  integrating framework for existing & new scientific knowledge
- Concept of "risk" is central to regulatory framework
  → uncertainty quantification moves centre stage
- Modelling technology
  - probabilistic modelling → high-performance computing ?
  - interdisciplinary usage → user interfaces ?
  - formal validation of tools themselves ?

Thank you!