



How Modeling of Unit Operations can speed up Process Design and Validation?

BioProduction

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OUTLINE

- Introduction & Background
- Definitions
- Objectives during Biopharmaceutical Process Development
- Support of Process Modeling
- Mab case studies: Chromatography Capture & Polishing Step
 - Determination of Parameters
 - Process Modeling
 - ChromWorks™ Process Simulation
 - Process Simulation Results
- Conclusions & Perspectives

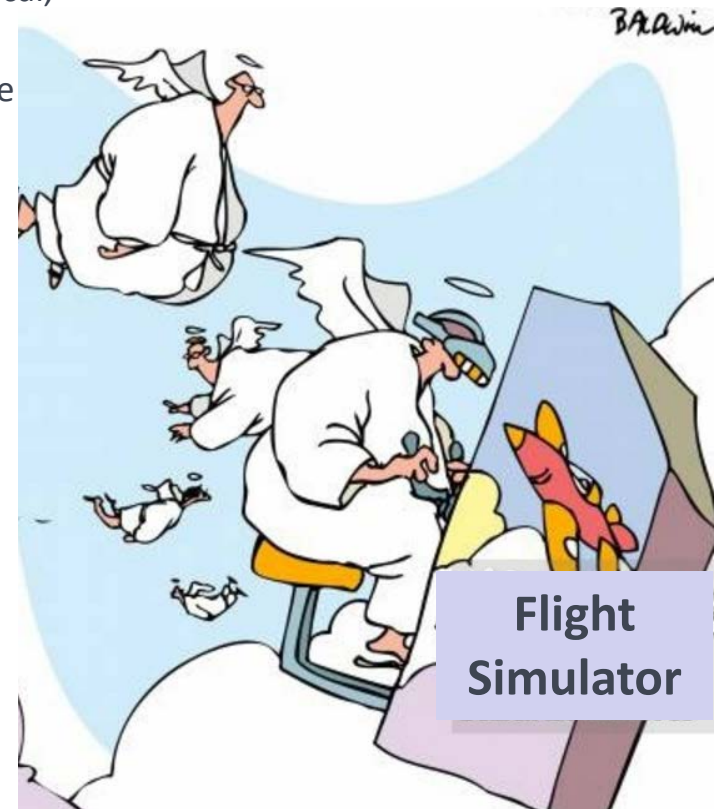
WHY MODELING AND SIMULATION ?

- Characterization and understanding of interactions (physical, chemical, biological, etc.)
- Speed-up development - time constants of the system are very large thus time-consuming – time to market constraint
- Cost of experiments is very high
- Limited amounts of materials available
- Inputs and outputs difficult/impossible to measure
- Easiness of testing extreme and variable inputs
- Experimental behavior might be affected by disturbances
- Experimentation might not be feasible

Industry Examples:

- Oil & Gas & Nuclear (Energy)
- Pharma & Medicine
- Aeronautics* & Automobile

* 800,000 simulation hours on the Cray Supercomputer replaced most physical prototypes in the design of the 2003 Boeing 787 Dreamliner.



MODELING & SIMULATION (M&S) IN THE PHARMA INDUSTRY SUPPORTED BY FDA

- **Process Validation**

Consists in evaluation of certain conditions and prediction of performance of the commercial process. These activities also provide information that can be used to M&S the commercial process. **Computer-based or virtual simulations of certain unit operations** or dynamics can provide process understanding and help avoid problems at commercial scale. Guidance for Industry Process Validation: General Principles and Practices ; 2011

- **PAT**

This benefit (knowledge base – scientific understanding) can be achieved through the use of multivariate mathematical approaches, such as statistical design of experiments, response surface methodologies, **process simulation and pattern recognition tools, in conjunction with knowledge management systems.**

Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance ; 2004

- **Use of M&S in drug development**

In November 2011, U.S. and EU regulators met with industry representatives to share ideas about **how best to use M&S in drug development.**

DEFINITIONS

- **Model**

A physical - chemical, mathematical, or other logical representation of a system, entity, phenomenon or process. Different stages: From Conceptual to Computerized
Deterministic (Reality) or Probabilistic

- **Verification**

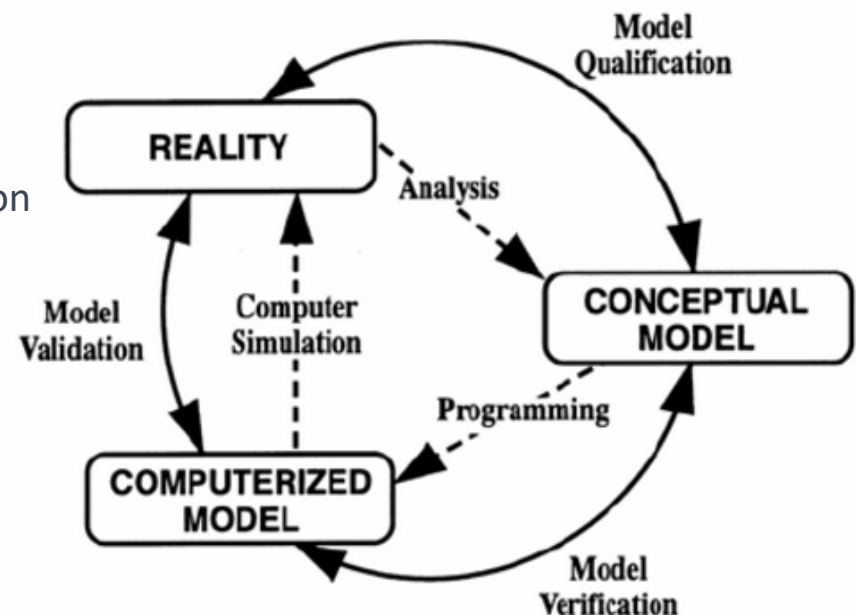
The process of determining that a model implementation and its associated data accurately represent the developer's conceptual description and specifications.

- **Simulation**

"Imitates a process by another one based on a chosen model". (Hartmann; 1996, 83).

- **Validation**

Confirmation that a model or simulation and its associated data accurately represent "Reality".



MODELING & SIMULATION

TYPICAL STEPS

1. Observations

- Data from experiments or literature

2. Hypothesis for Models

- Based on key physico-chemical parameters (e.g. adsorption isotherms, mass transfer, dispersion, etc.)

3. Selection & Confirmation of Models

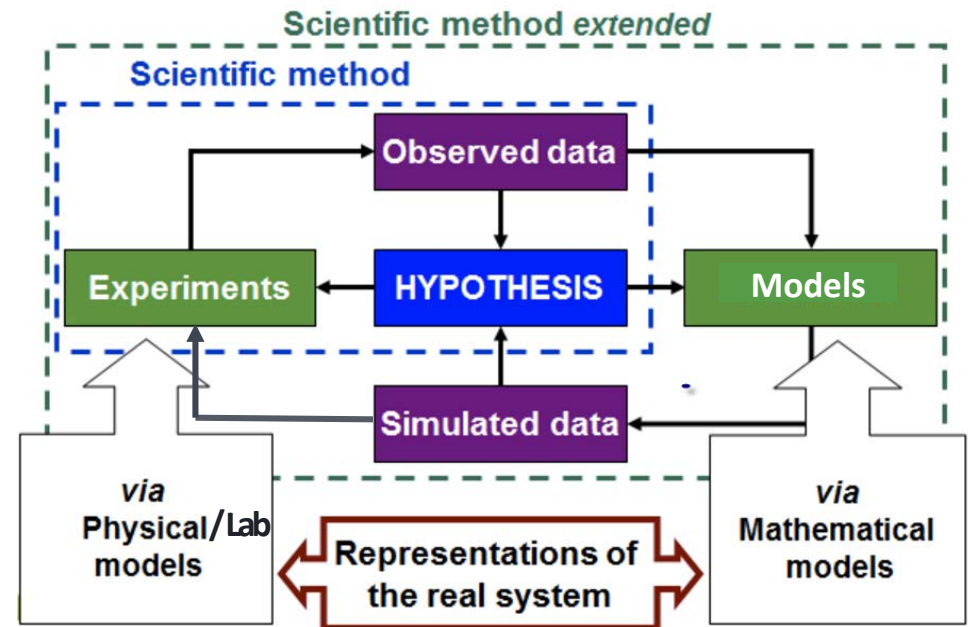
- Description of your system of choice

4. Simulate different Conditions

- Exploration of new conditions

5. Results

- Experimental confirmation of preselected conditions based on simulation results



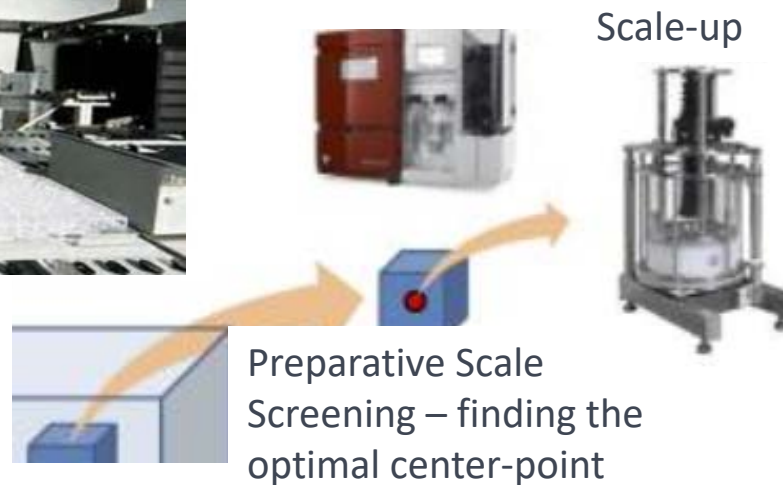
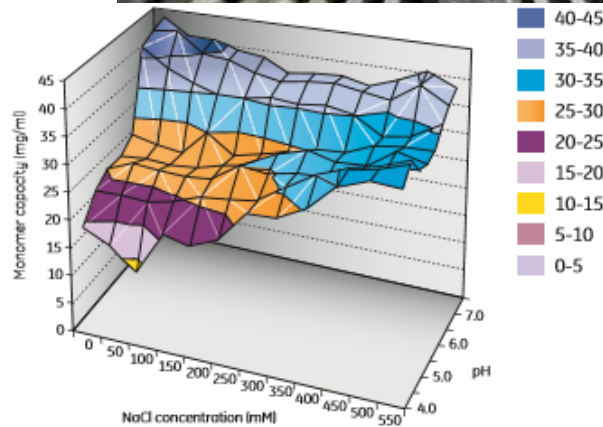
OBJECTIVES DURING BIOPHARMACEUTICAL PROCESS DEVELOPMENT

- Quality & Stability
 - Yield / Recovery
 - Productivity
 - Robustness
 - Costs
 - Development Duration
 - Easy Industrial Implementation (Scale, Production Setting, etc.)
- 

- Breakthrough Therapies
- Biosimilars
- New regulatory requests
- Current Development costs doubled
- Cost-pressure – Health Insurances
- Global market supply

CURRENT METHODOLOGIES OF PROCESS DEVELOPMENT – USING HTS

HTS in
microtiter
plates



MAB CASE STUDY – CAPTURE STEP USING THE M&S TOOL CHROMWORKS™

• How to start:

✓ Determination of the model parameters

- **Experimental set 1:** various Mab concentrations for the estimation of the Thermodynamic parameters
- **Experimental set 2:** various feed flow rates for the estimation of the Hydrodynamic and Kinetic parameters
- **Experimental set 3:** various pH for the elution

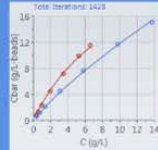
CASE STUDY – KINETIC PARAMETERS

ChromWorks

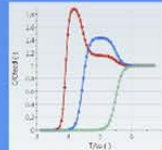
Adsorption isotherm
determination by BSTR



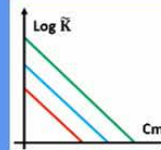
Adsorption isotherm
determination by ECP



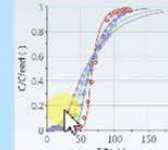
Adsorption isotherm
determination from BTC



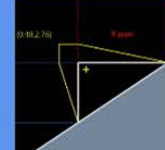
Modulated isotherm
parameter determination



Mass transfer
parameter determination



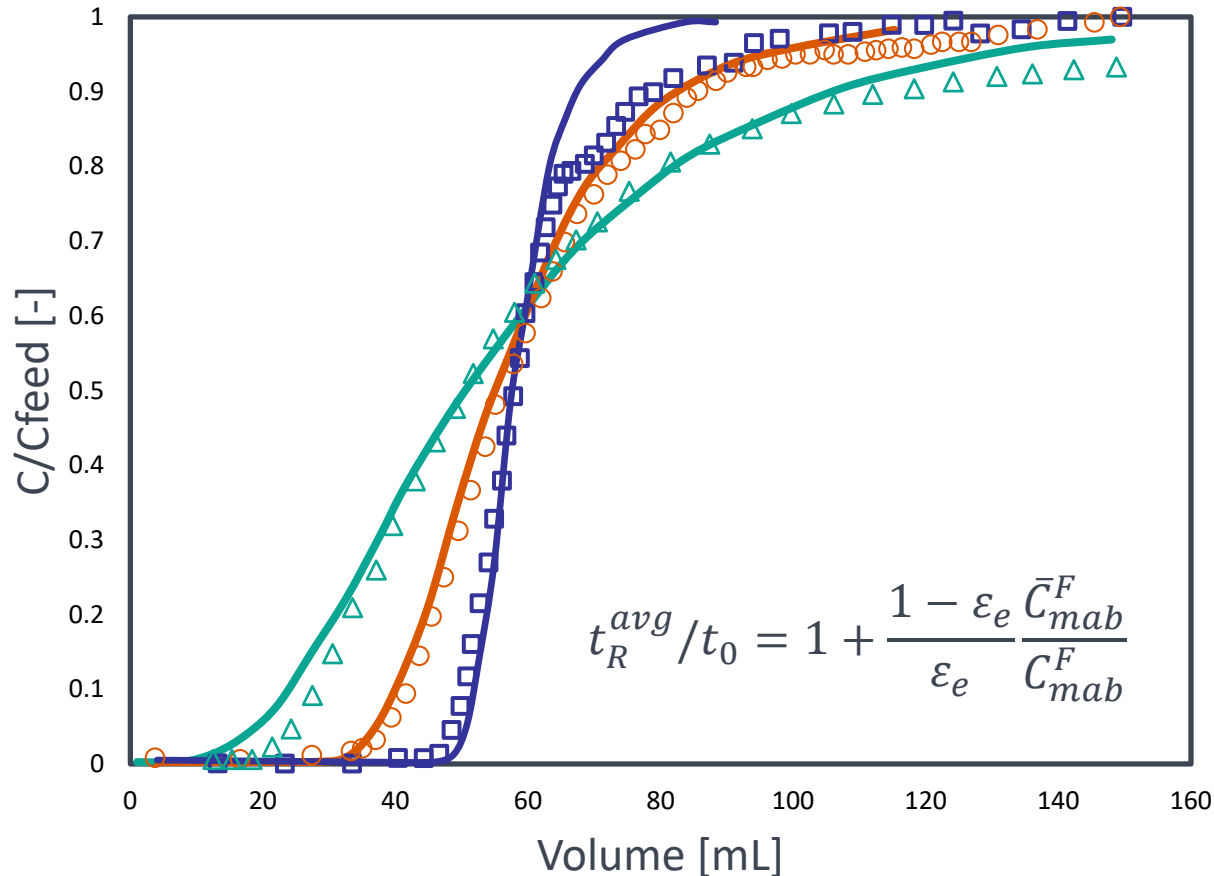
Triangle presentation



Properties library

C2H5O	443-51-4
C2H5O2	62-99-9
C2H5O4	62-99-9
C2H5O5	83-44-5
C2H5O6	107-22-1
Temperature Independent	
ID	Value Unit
MW	46.069 kg/kmol
BP	78.29 C
ACEN	0.643558 -
LVOL	0.0586198 m³/kmol

CASE STUDY - LAB DATA VS MODELING



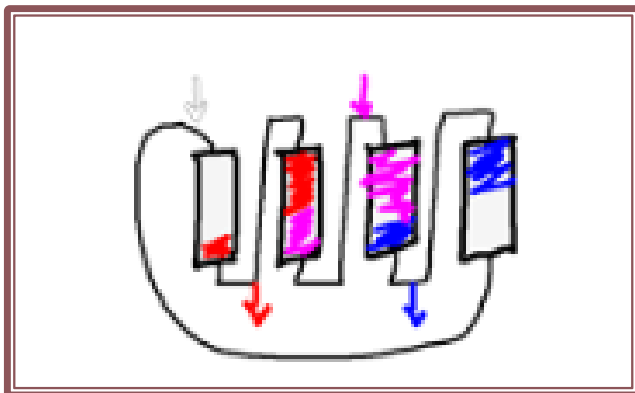
Fitted parameters:

- $\bar{N} = 85 \text{ g/L}$
- $\tilde{K} = 6.4 \text{ L/g}$
- $t_i = 14 \text{ min}$

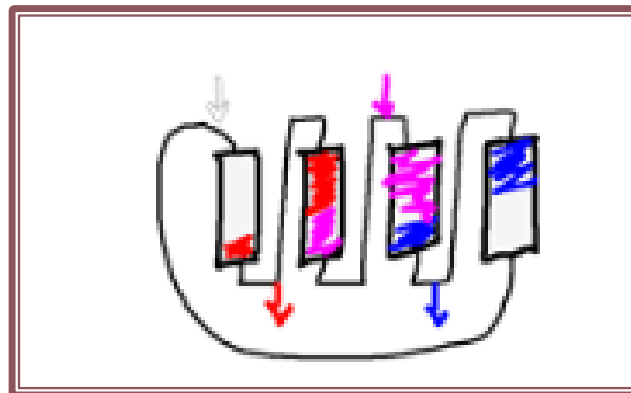
\bar{N} ... adsorption capacity of the chromatographic media (g/l)
 \tilde{K} ... adsorption constant
 t_i ... characteristic time for intra particle diffusion

CASE STUDY – MODELING A SINGLE COLUMN PROCESS

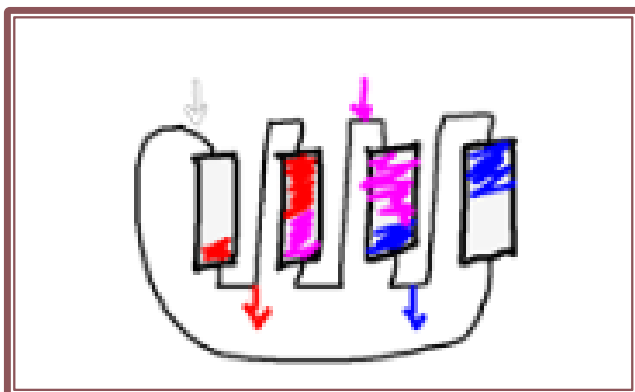
Load, Elution and Regeneration



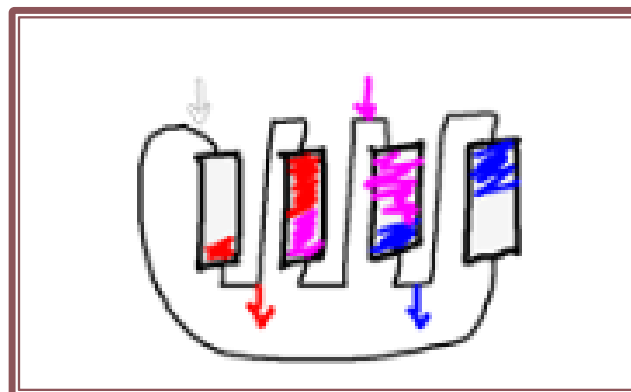
Effect of the feed concentration



Effect of the feed velocity



Effect of the elution pH



CASE STUDY – MODELING A SINGLE

CaptureSMB.smbxml - ChromWorks™ 2016 - Powered by YPSO-FACTO (Trial)

Home | Toolbox | Single Column | Standard MCC Systems | User Defined MCC | Process Example

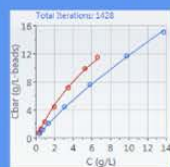
Toolbox

ChromWorks

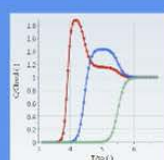
Adsorption isotherm
determination by BSTR



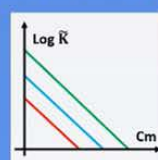
Adsorption isotherm
determination by ECP



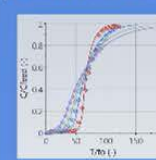
Adsorption isotherm
determination from BTC



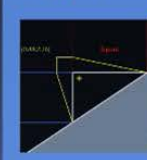
Modulated isotherm
parameter determination



Mass transfer
parameter determination



Triangle presentation

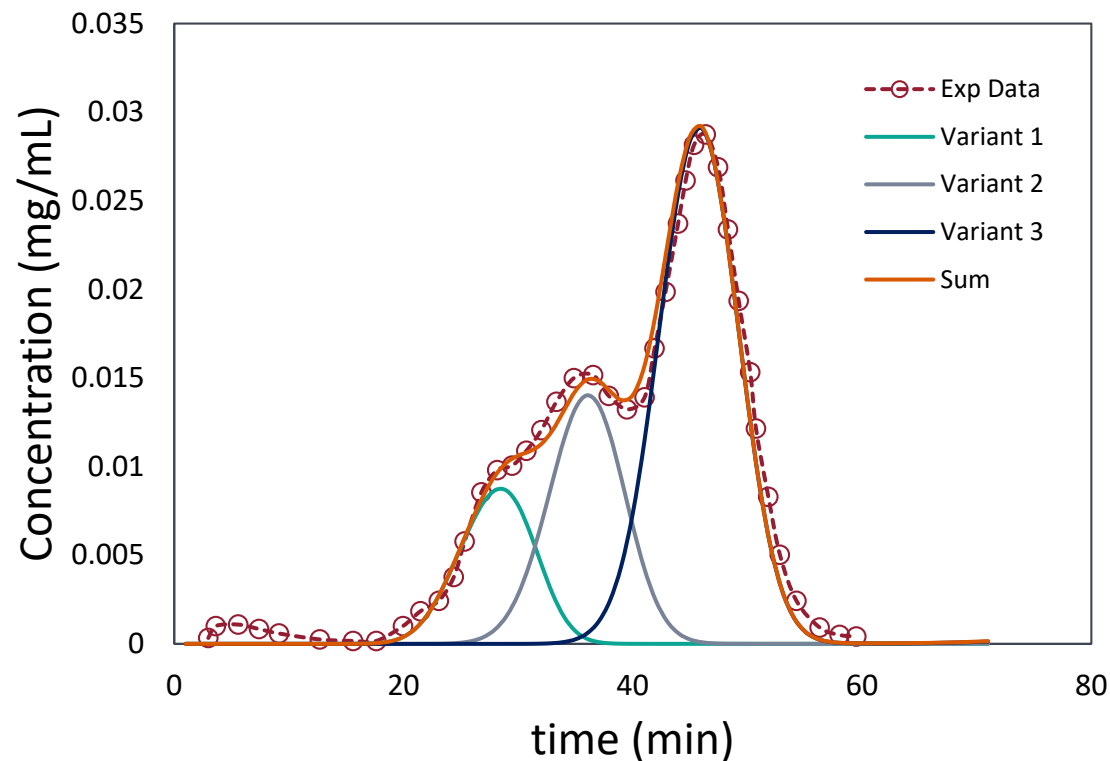


Properties library

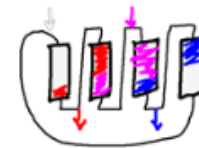
ID	Value	Unit
MIN	40.000	logarithm
BP	78.20	C
ACEN	0.042508	
LVOL	0.0506218	kg/mol

CASE STUDY MAB – POLISHING M&S USING CHROMWORKS™

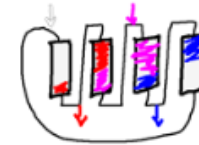
- Example Polishing: mAb charge variants



Single column process



Multi-column process with recycling



CASE STUDIES – SUMMARY OF RESULTS OF PROCESS SIMULATION CHROMWORKS™

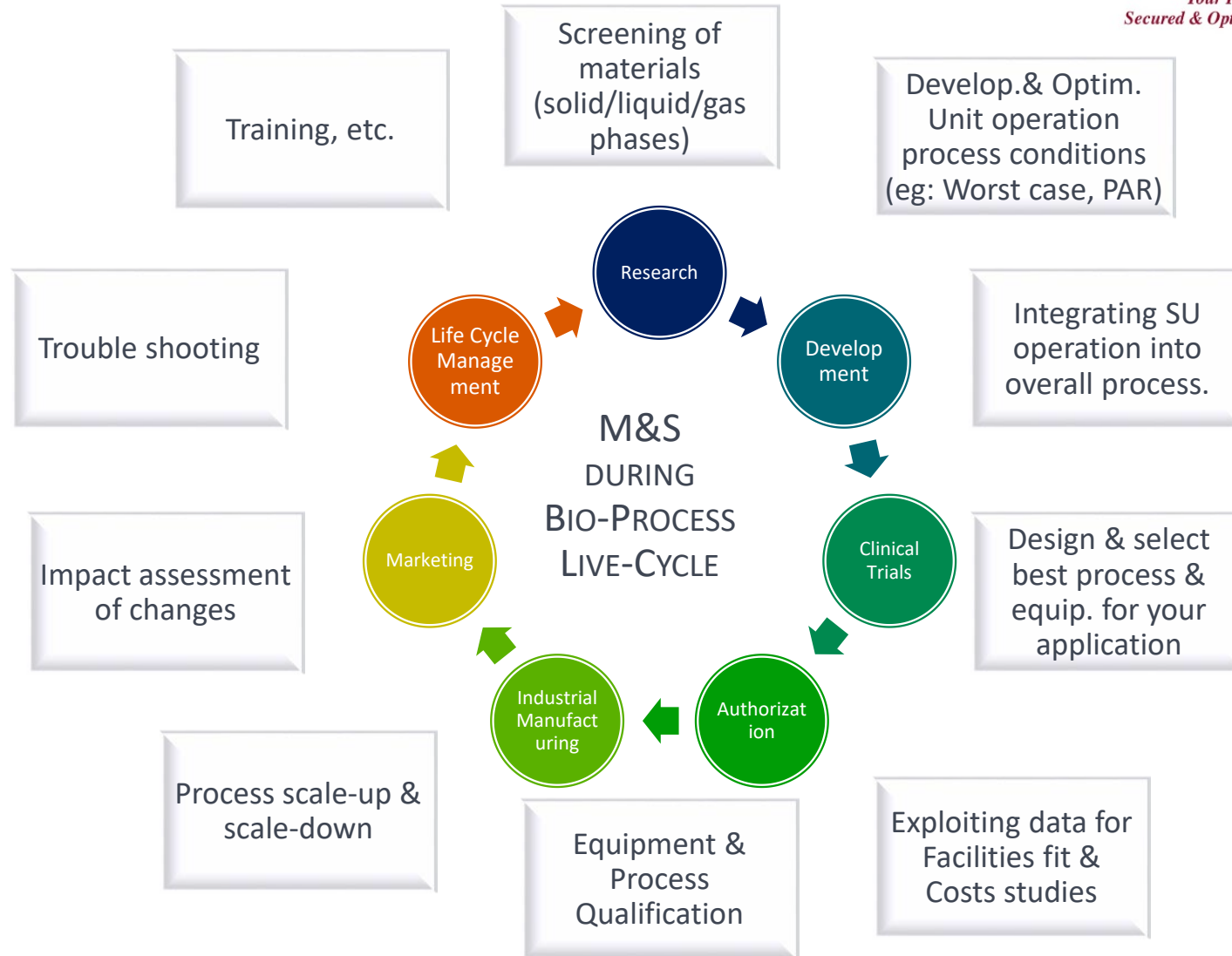
Experiments Various C^{Feed} Various Q^{Feed} Various pH	Process simulation	Simulate and reproduce exp. data	Results Productivity Yield Purity Solvent consumption	€
	Process understanding	Visualization of dynamic concentration profiles		
	Optimization	V_{inj} , Number of cycles, cleaning, elution and regeneration protocol		
	Process design	Change V_{inj} , L , D of flow rates		
	Robustness analysis	Quantify the variations of the process performance when C^{Feed} , Q^{Feed} and pH varies		
	Impact of column aging	Impact of decreasing binding capacity on the process		

➡ 10 lab experiments and simulation studies are typically necessary for such a study. Compared to classical development based on DoE the number of experiments can be tremendously reduced.

CONCLUSIONS

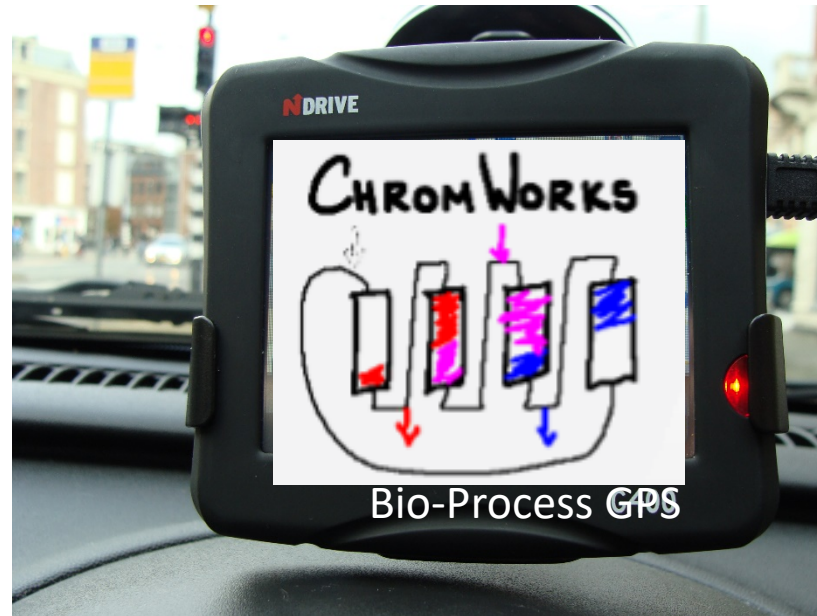
- M&S is established in many fields and industries
- More and more initiatives of the regulators together with the industry ask for M&S tools in the Pharma field
- ChromWorks is a universal and unique M&S tools, which can help to get in depth understanding of chromatographic separations, to optimize and design them
- The number of experiments using ChromWorks can be tremendously reduced, resulting in significantly shorter development times and costs - compared to classical development

PERSPECTIVES



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Jay Jun





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