Quality by Design

BERNT NILSSON[1], AND ARNE STABY[1,2]

[1] CHEMICAL ENGINEERING, LUND UNIVERSITY, SWEDEN
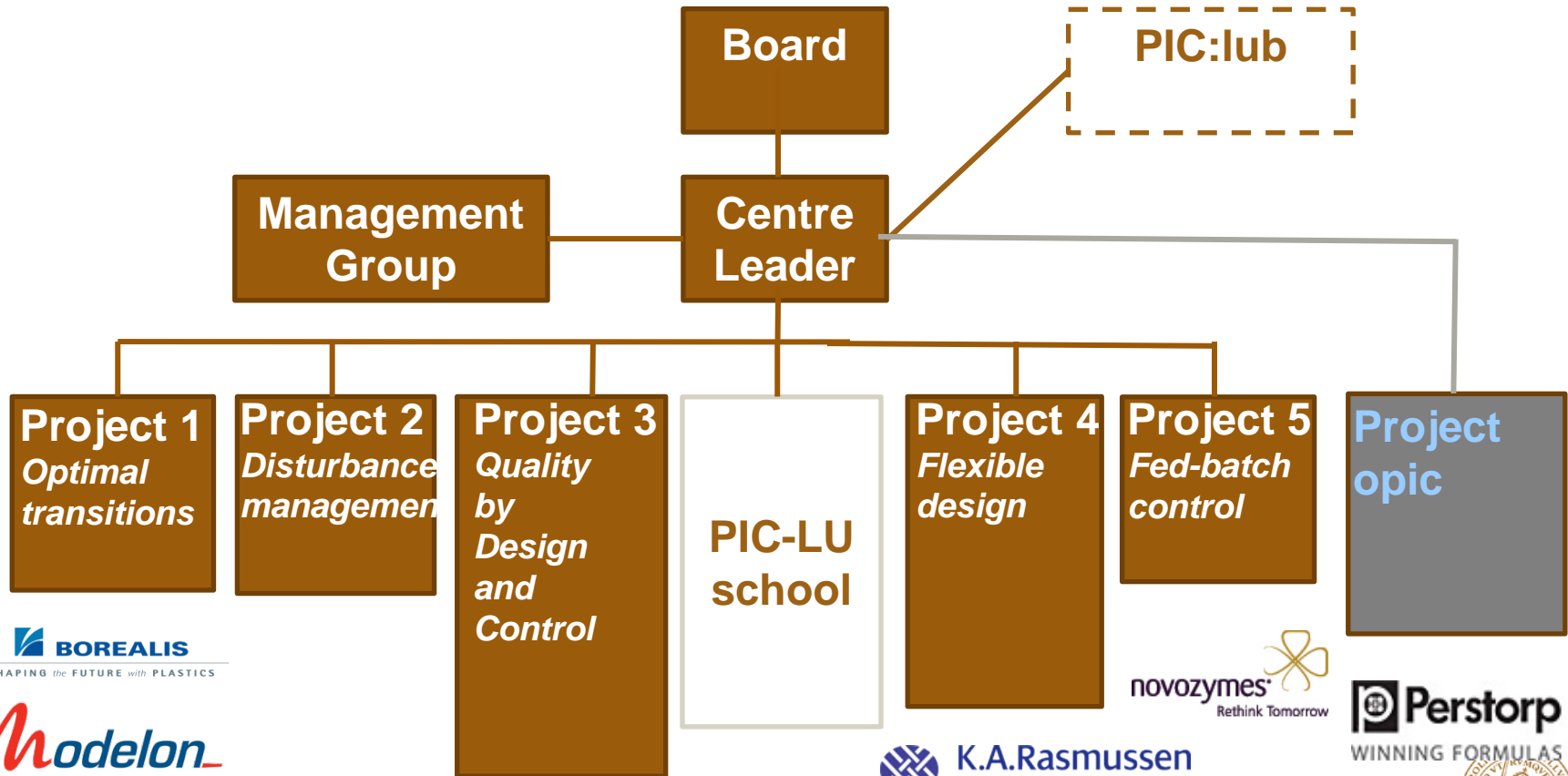**[2] NOVO NORDISK, GENTOFTE, DENMARK**

Innehåll

- PICLU projekt 3: *Quality by design and control*
- Biofarmaceuptisk industri och ***"Quality by Design"***
- Matematisk modellering vid Novo Nordisk
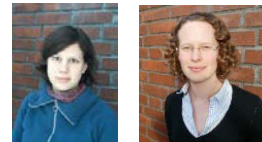 - Case story
- Samarbetet mellan LU och NN
- Results

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Organisation – PICLU etapp2

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Projekt 3 – Quality by Design and Control

A) Modellbaserad produktionsdesign

novo nordisk®
Pfizer

B) Modellering av proteinseparation

AMGEN®

novo nordisk®

C) Tekniköverföring
Verktyg, metodik & kurser

Pfizer novo nordisk® KNAUER
ASI - ADVANCED SCIENTIFIC INSTRUMENTS

Novo Nordisk at a glance

- More than 40,000 employees in 75 countries

- A world leader in diabetes care since 1923

- Leading position in:
  - Haemostasis management
  - Growth hormone therapy
  - Hormone replacement therapy

- Total net turnover (2013): ~84 billion DKK

- R&D spent (2013): ~12 billion DKK

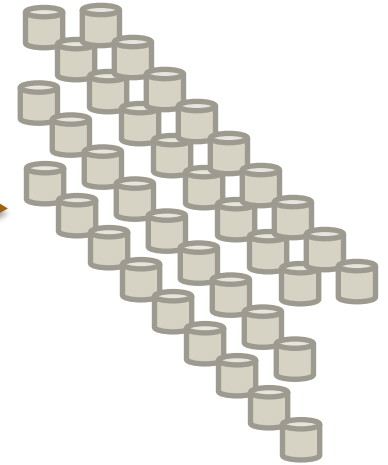- Committed to financial, environmental and social results

Biopharmaceutical production
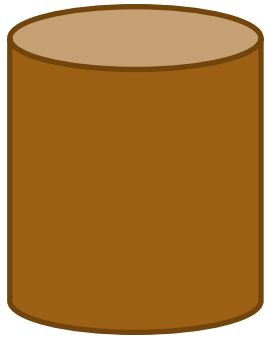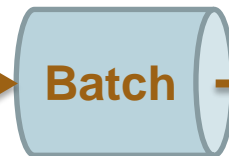

UPSTREAM

cultivation
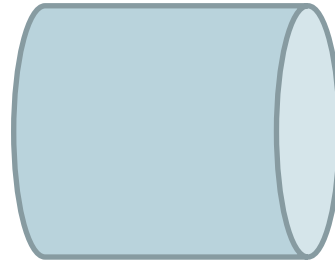
DOWNSTREAM

purification

FORMULATION

"packaging"

Regulatory Limitations

Batch

Manual work

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QbD Governance / Risk Assessment

Patient
"Voice of the customer"

- Product Profile
- Quality Target Product Profile

Product

- List of CQA's

Risk assessment

Process

- Process parameters
- Process model
- Design space

Requirements

Facility

- Control Strategy
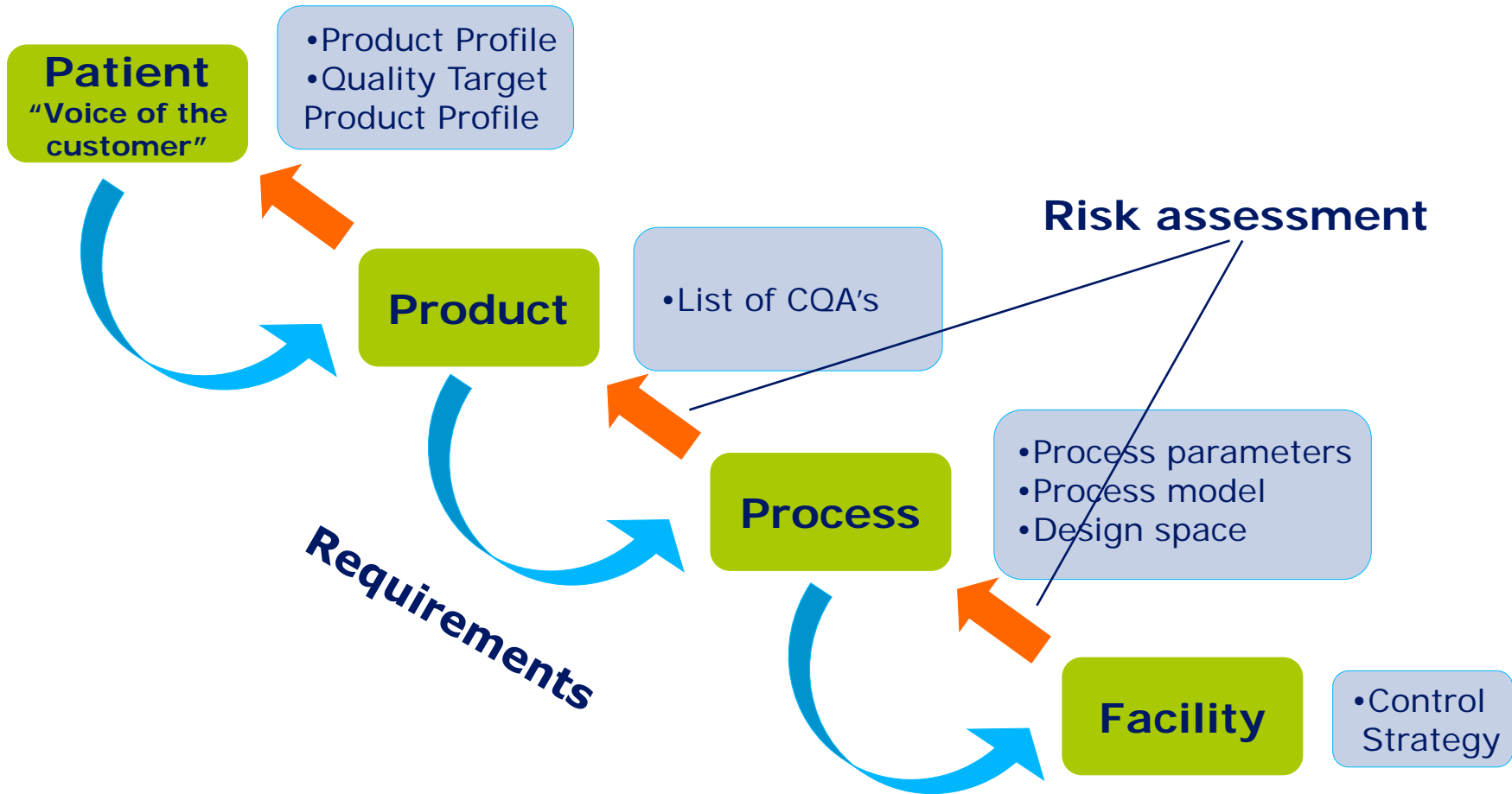
"Start with the end in mind"

Process Understanding

Extent of Knowledge (vertical axis arrow)

Pyramid levels from top to bottom:
- Mechanistic models
- Advanced statistical models / PCA etc.
- Simple statistical models / DoE
- OPAT (One parameter at a time)
- Preliminary experimentation
- Experience from other projects
- Theoretical knowledge

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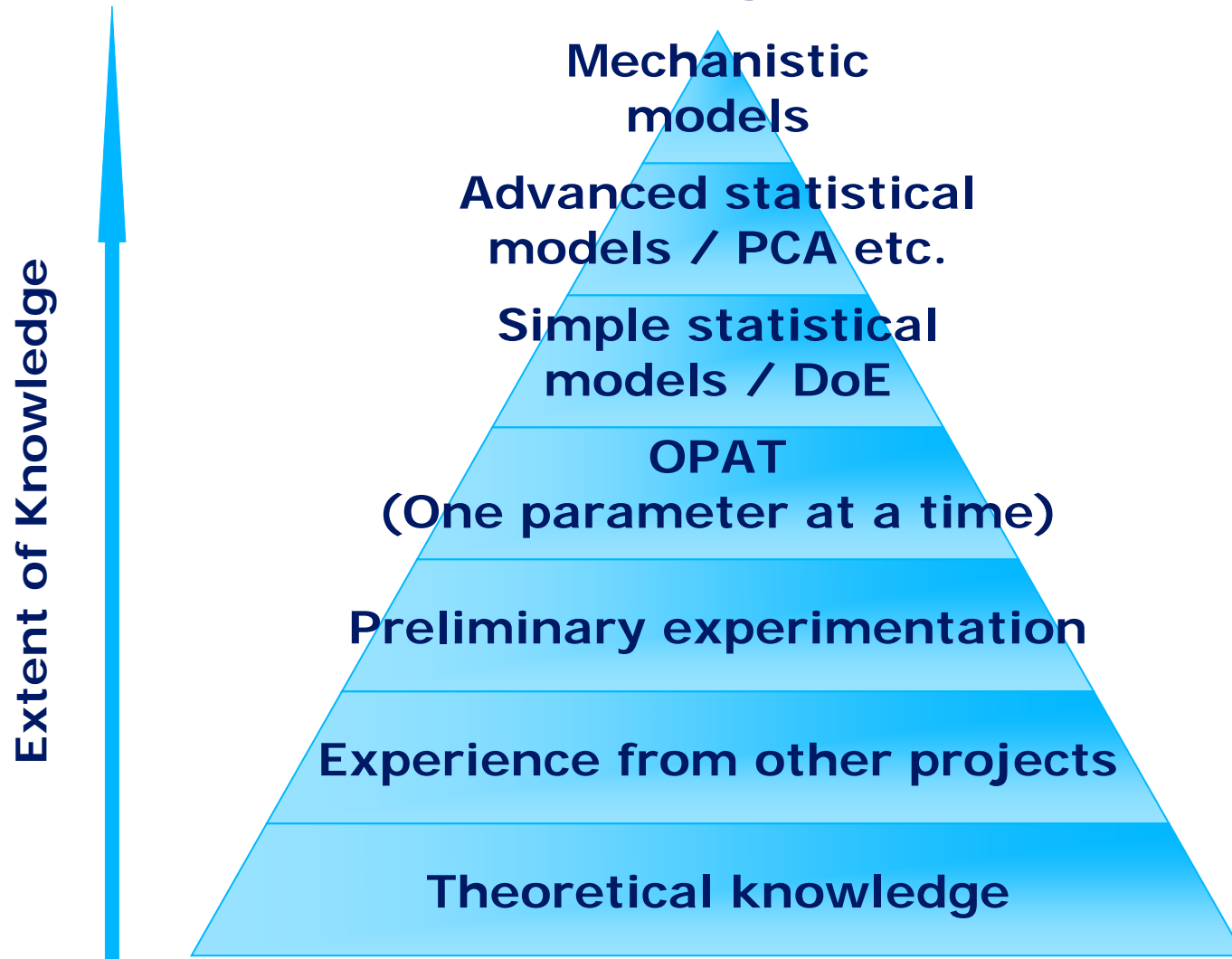
# Mathematical Modelling – Unit Operations

- Chromatography
    - Ion-Exchange (IEC) – mAbs, Haemostasis, insulin, GLP-1...
    - Size Exclusion (SEC) – Haemostasis
    - Hydrophobic (RP/HIC) - Insulin
    - Multi-Modal (MM) – Hæmostasis, Fab fragments...
    - Affinity (AC) – Haemostasis
    - Scaling – "All"
- Chemical Reactions/Modifications
    - PEG-modifications – Haemostasis
    - Acylations – Insulin, GLP-1
    - Enzymatic reactions etc. – Hæmostasis, hGH, Diabetes...
- Formulation
    - Stability – "All" (e.g. mAbs, Insulin...)
- Membrane Processes
    - Filtration and virus filtration – hGH, "Vira"...
- Other Opportunities
    - Centrifugation, Crystallisation, Precipitation, Freeze/Spray-Drying

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Mathematical Modeling - Use

- Process and analytical development
- Process optimisation
- Process validation/challenge and critical parameters
- Plant design
- Process control (PAT)
- Trouble shooting and deviation handling
- Process understanding and Design Space
- Scaling of chromatography

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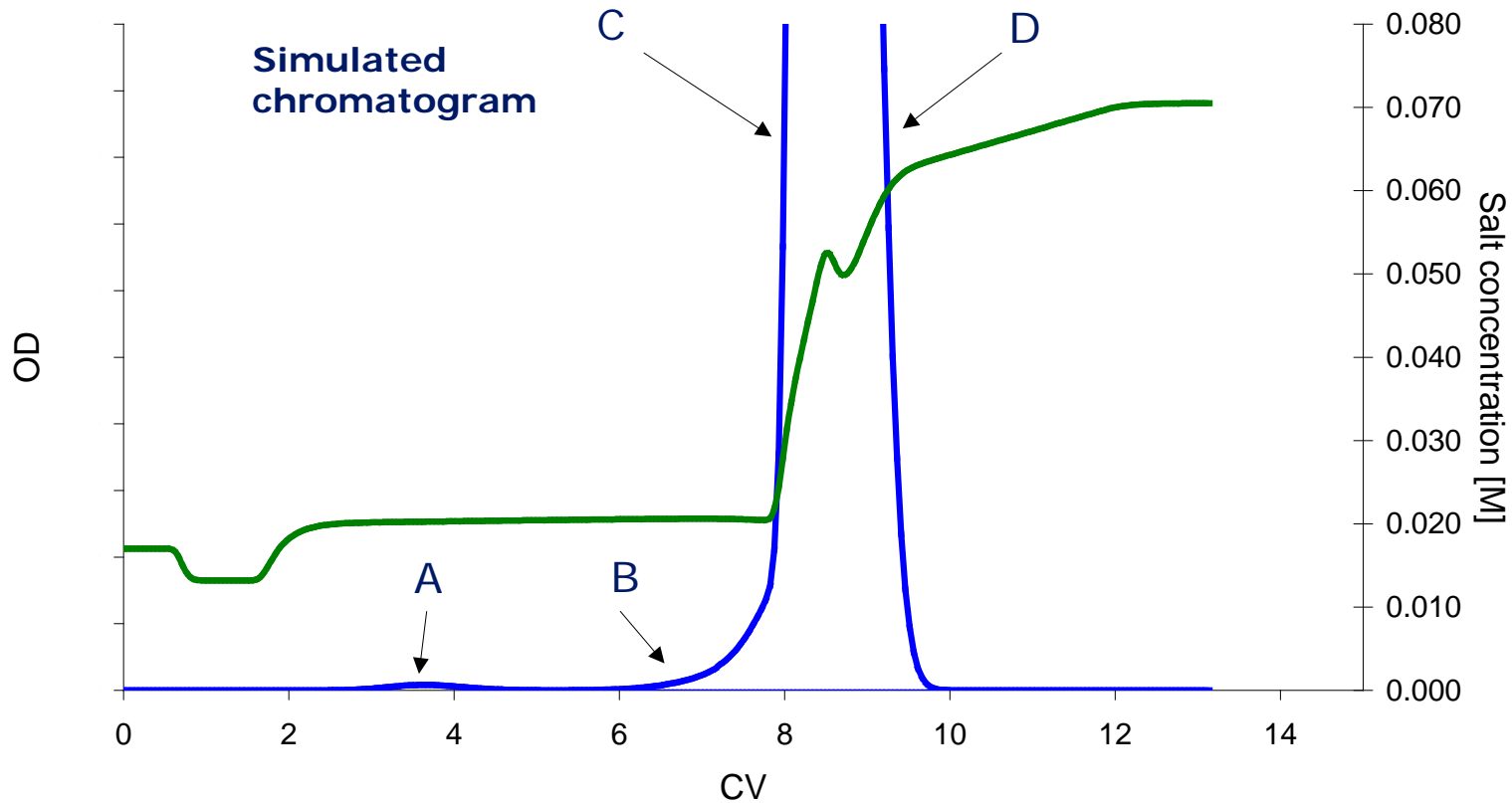# Case Story: IEC Process, Trouble shooting

Starting material: 81% C, 8% A, 2% B and 9% D
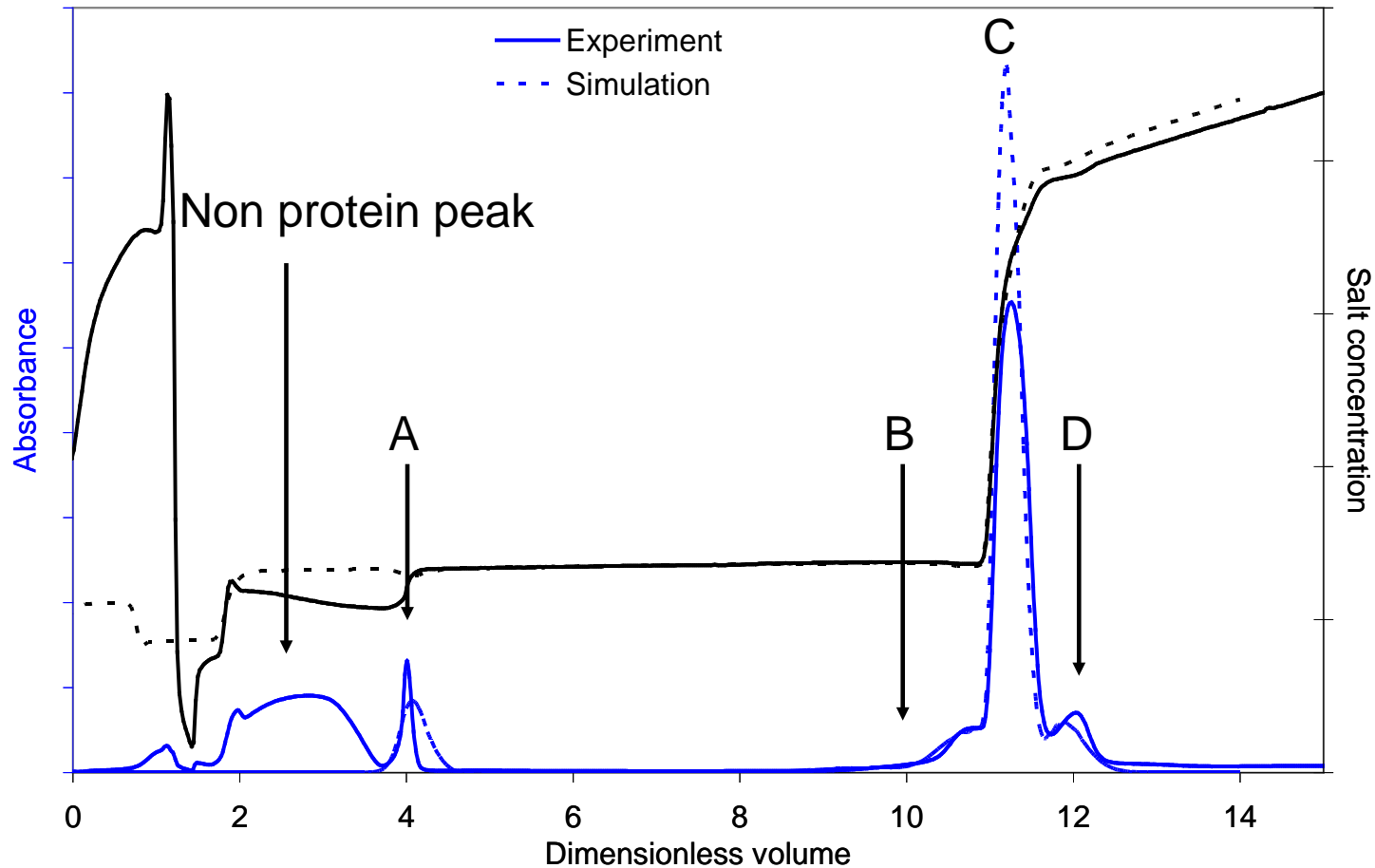
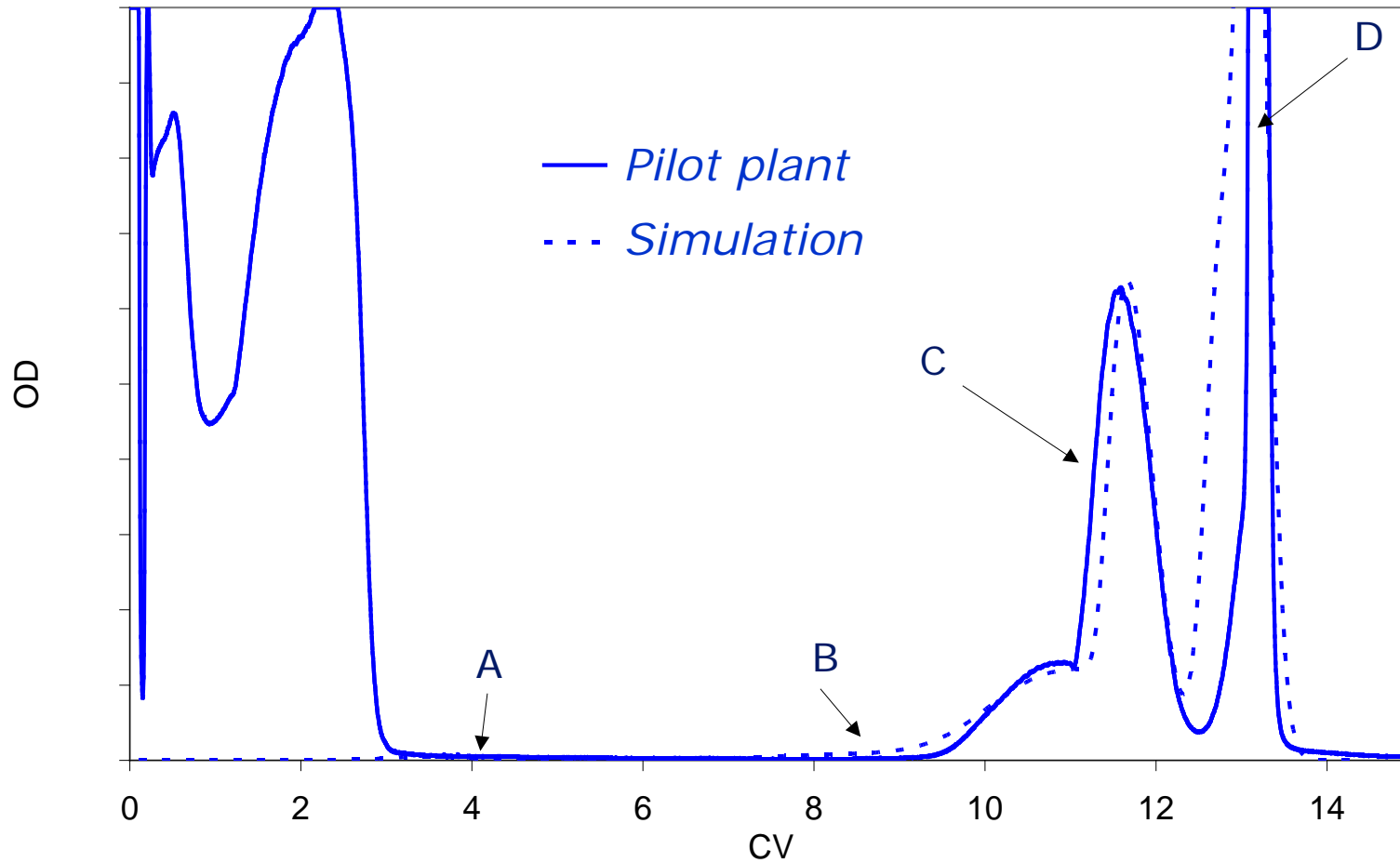*Simulation and standard process compared*

Case Story: Reaction on previous step went wrong:

Starting material: 39% C, 1% A, 1% B and 59% D

Standard method process A

Case Story: New in-silico process

Simulation and process compared

Case Story: Results

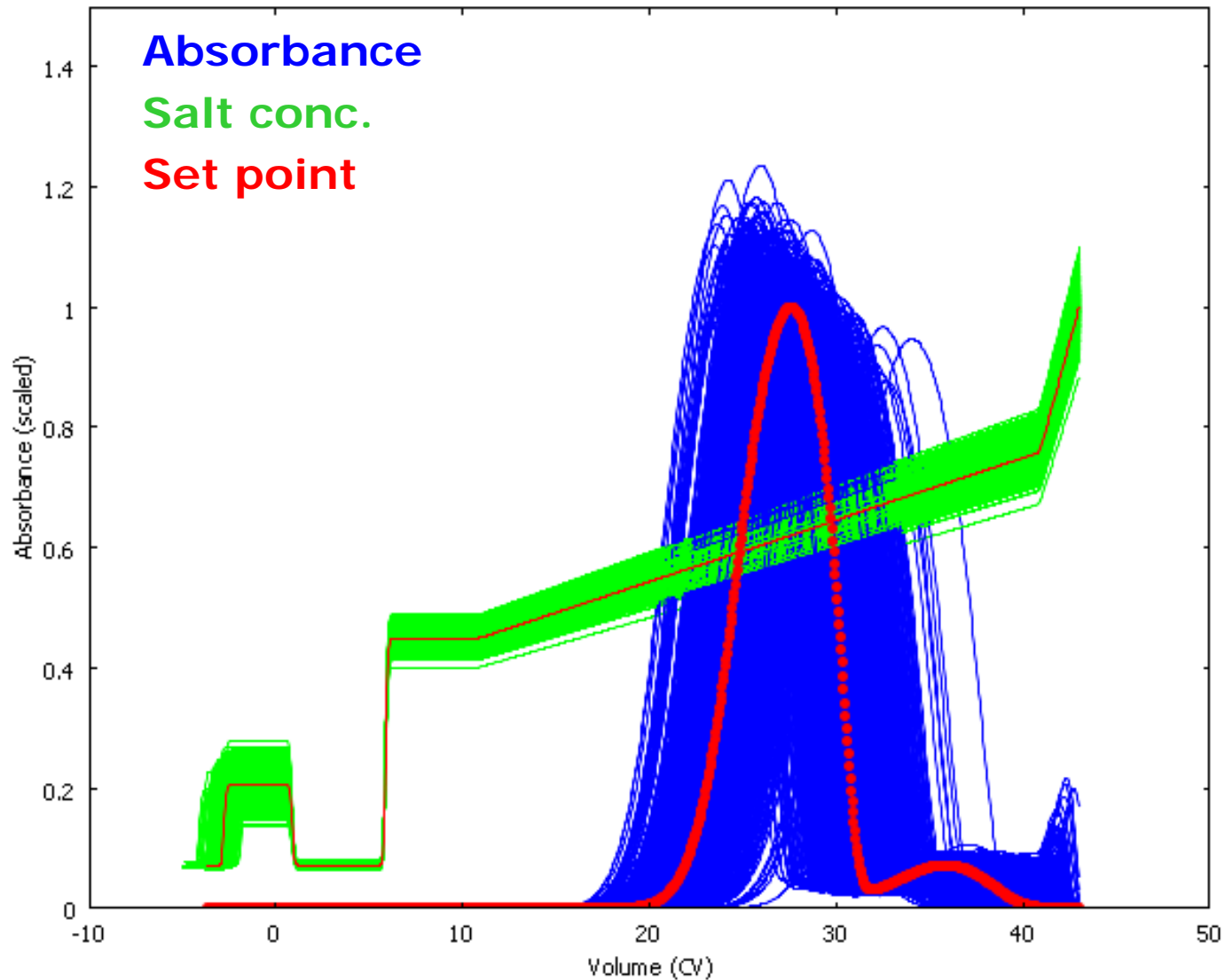| After last step	Purity [%]	D [%]	B [%]	Yield [%]	Other
Standard method*	96.9	0	1.04	75	2.06
Modified method	97.5	0	0.83	68**	1.67

Comparison between new and standard method
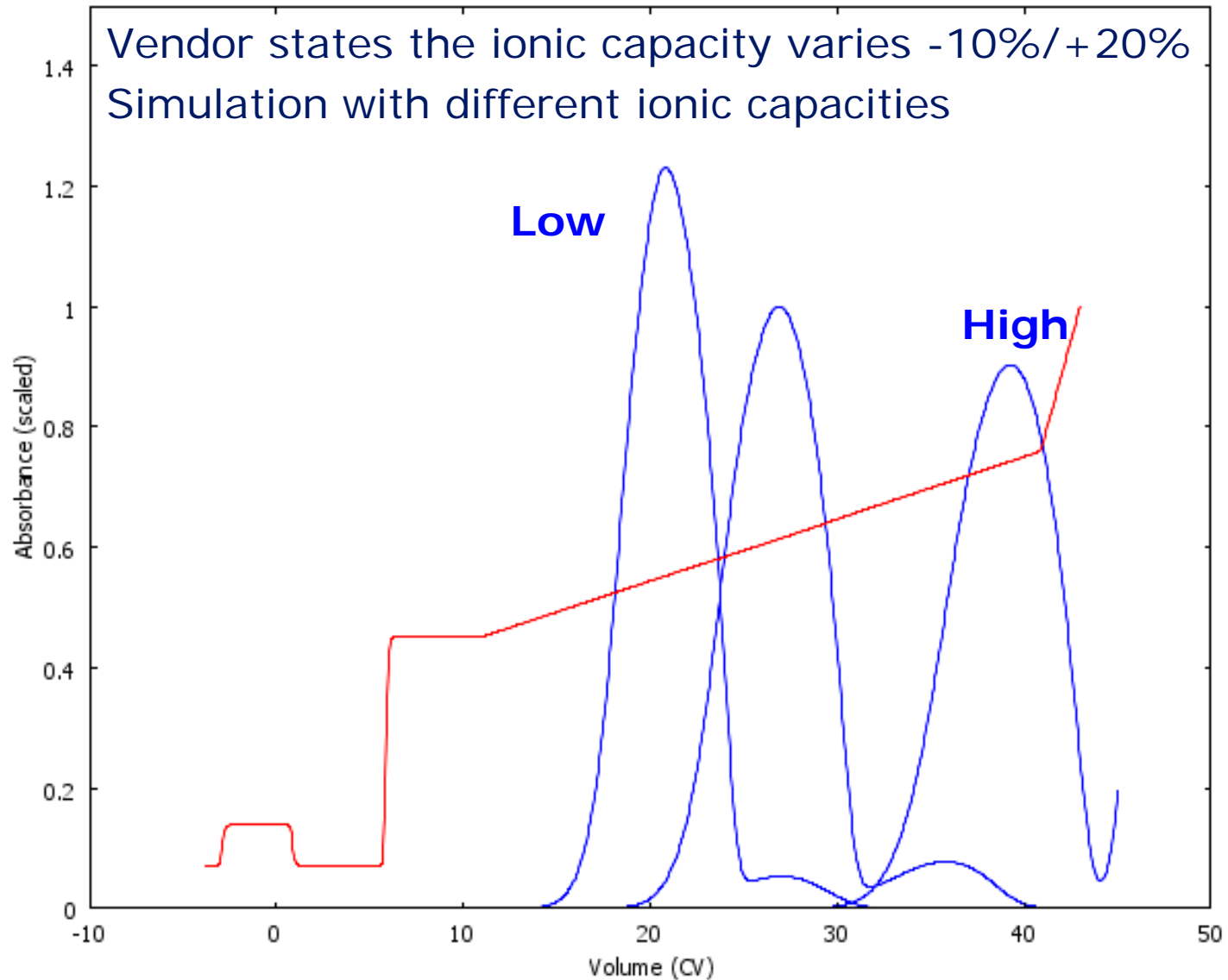
* Mean of all batches

** Loss due to low load (loading on total polypeptide concentration)

- More pure than normal
- Lower yield
- The batch was released

Other Applications: Simulated elution profile

Other Applications: Resin Properties

Vendor states the ionic capacity varies -10%/+20%
Simulation with different ionic capacities

Low

High

Absorbance (scaled)

Volume (CV)

Personer och delprojekt

| | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 |

- novo
- LU
- annan finansiär
- novo
- SSF
- AMGEN
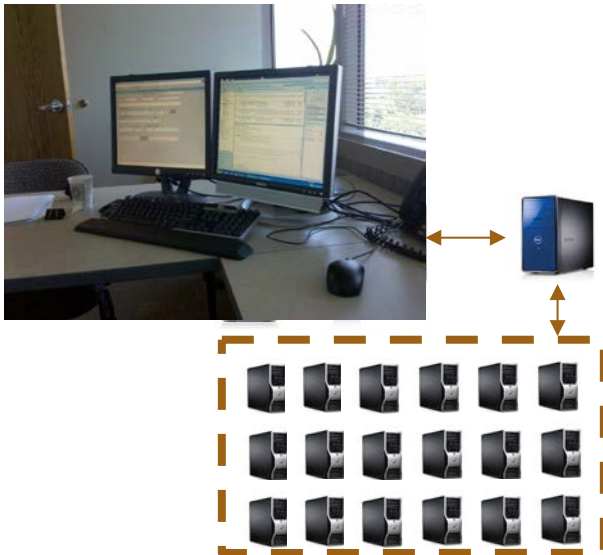- SSF
- novo — 2015
- SSF
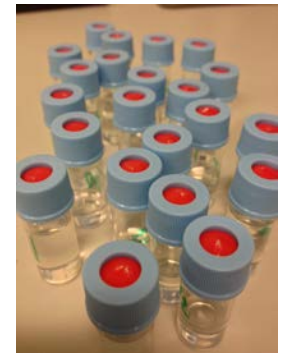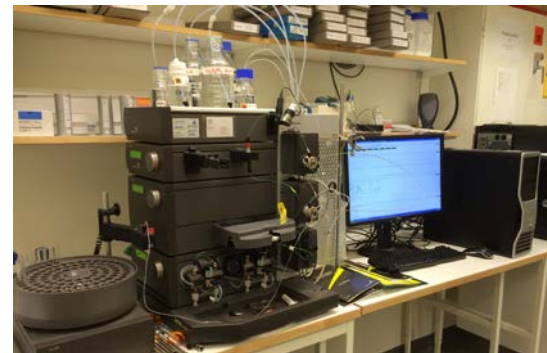- novo — 2016
- 2018 PiiA

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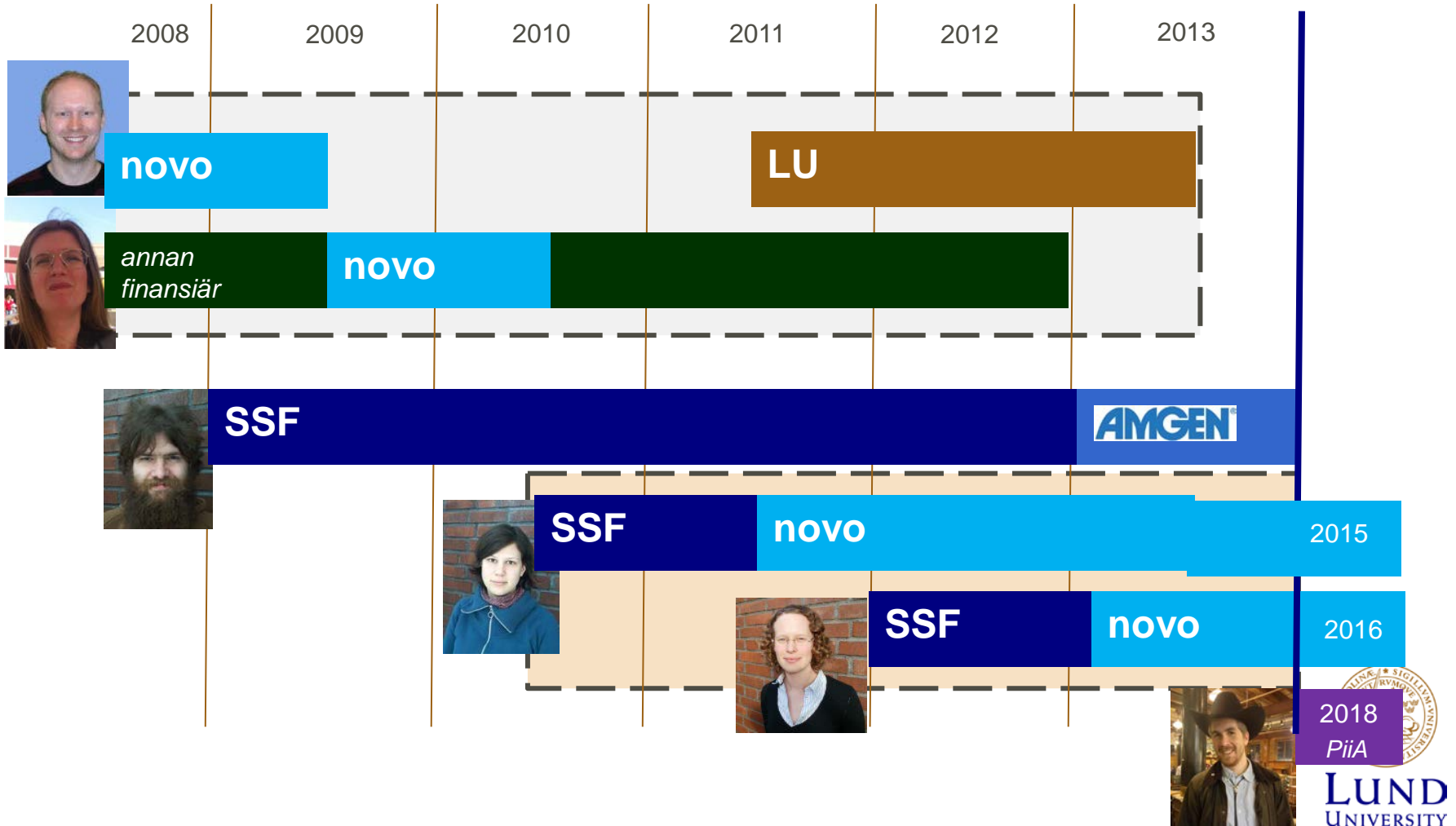
Samarbetsprojekt

- **Modellbaserad design**
  - Gemensam problemformulering
  - **Problemlösning, LU**
  - Tekniköverföring, NN

- **Modellering**
  - Gemensam problemformulering
  - **Experimentella studier, NN**
  - Modellering, LU

Doktorer och doktorander

- **Marcus Degerman**
  (PhD 2008-2009, postdoc 2011-2013)
  Design of robust preparative chromatography

- **Karin Westerberg** (2008-2012)
  Modeling of quality and safety in biopharmaceutical production process

- **Niklas Borg** (2008-2013)
  Modeling and calibration of preparative chromatography

- Frida Ojala (2010-2015)
  Modeling of protein aggregation

- Karolina Johansson (2011-2016)
  Modeling of hydrophobic interactions
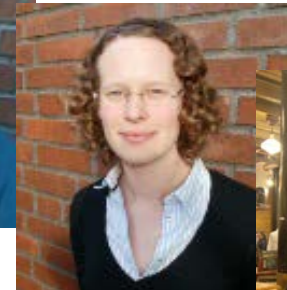
- *Anton Sellberg (2014-2018)*

Aktiva

Novo Nordisk
Softhouse

Amgen

HiQ

Examensarbeten inom projekt 3

1) **Niklas Borg** (2008), Fast model calibration…
2) Fredrik Nielsen (2009), Optimization of ion-exchange… **(Novo)**
3) **Niklas Andersson** (2009), Simulation of continuous chromatography…
4) Marcus Almqvist (2009), Modeling and calibration … using gProms
5) Mikael Edmundsson (2011), Metodik för modellkalibrering…
6) **Karolina Johansson** (2011), Flexible pooling… **(Pfizer)**
7) Alex Olsson (2012), Calibration and optimization… **(Novo)**
8) Peter Fransson (2012), Robust optimization…
9) Owais Sulehria (2012), Data to Knowledge…
10) Bruno Otero Garcia (2013), Optimization of two connected steps… **(Novo)**
11) **Anton Sellberg** (2013), Design space…
12) Emil Håkansson (2013), Simulated moving bed… **(ETH,Novartis)**
13) André Bugge (pågår), Optimization of integrated separation… **(Novo)**

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Publikationer – i tidskrifter

1. F. Ojala, M. Degerman, T. Budde Hansen, E. Broberg Hansen, B. Nilsson:
   Prediction of IgG1 aggregation in solution.
   Biotechnology journal, (Online April 24, 2014), 2014.
2. B. Otero, M. Degerman, T. Hansen, E. Hansen, B. Nilsson:
   Model-based design and integration of a two-step biopharmaceutical production process.
   Bioprocess and biosystems engineering, (Online March 2014), 2014.
3. N. Borg, K. Westerberg, N. Andersson, E. von Lieres, B. Nilsson:
   Effects of uncertainties in experimental conditions on the estimation of adsorption model parameters in preparative chromatography
   Computers & Chemical Engineering, 55 148-157, 2013.
4. K. Westerberg, E. Broberg-Hansen, L. Sejergaard, B. Nilsson:
   Model-based risk analysis of coupled process steps.
   Biotechnology and bioengineering, 110(9) 2462-2470, 2013.
5. K. Westerberg, E. Broberg Hansen, M. Degerman, T. Budde Hansen, B. Nilsson:
   Model-Based Process Challenge of an Industrial Ion-Exchange Chromatography Step
   Chemical Engineering & Technology, 35(1) 183-190, 2012.
6. K. Westerberg, N. Borg, N. Andersson, B. Nilsson:
   Supporting Design and Control of a Reversed-Phase Chromatography Step by Mechanistic Modeling
   Chemical Engineering & Technology, 35(1) 169-175, 2012.
7. K. Westerberg, M. Degerman, B. Nilsson:
   Pooling control in variable preparative chromatography processes.
   Bioprocess and biosystems engineering, 33 375-382, 2010.
8. M. Degerman, K. Westerberg, B. Nilsson:
   Determining Critical Process Parameters and Process Robustness in Preparative Chromatography - A Model-Based Approach
   Chemical Engineering & Technology, 32(6) 903-911, 2009.
9. M. Degerman, K. Westerberg, B. Nilsson:
   A Model-Based Approach to Determine the Design Space of Preparative Chromatography
   Chemical Engineering & Technology, 32(8) 1195-1202, 2009.
10. M. Degerman, N. Jakobsson, B. Nilsson:
    Designing robust preparative purification processes with high performance
    Chemical Engineering & Technology, 31(6) 875-882, 2008.
11. *+ två under review*
12. *+ ytterligare två manuskript*

4 (av 10) artiklar tillsammans med Novo Nordisk

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Sammanfattning

- Samarbetet mellan LU och Novo Nordisk

  – Gemensamma problemformuleringar

  – Mycket arbete av doktorander vid Novo Nordisk

  – Resultat "överförs" till Novo Nordisk.
    Novo fortsätter utvecklingen för "industrianpassning"

  – Gemensamma publikationer

  – Novo har haft möjligheten att sätt in resurser,
    egna och vid LU.

Projektet har karaktäriserats av
Långsiktig och ömsesidig kompetensutveckling

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