Accelerating

R&D

Rational High Throughput Screening in Chemical Applications

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Avantium Technologies

ChemSource 2005 Symposium High Throughput Experimentation
June 23 2005




Challenge in chemical and pharmaceutical process industry

Technical
- Increased selectivity of catalytic processes required
- Strong drive towards use of cheaper & greener feedstocks

Commercial
- Increased pressure on time to market

Financial
- Constant pressure on R&D budgets

Resources
- Decreasing number of available young chemists

Competition
- Increasing competition from China and India

⇒ Higher speed & efficiency of process and catalysis research required

Why High Throughput Experimentation

- Speed
  - Faster results
  - Speed to market
- Efficiency
  - More experimental results per $$ (man hours)
- Safety
  - Thanks to size

- Improved quality/ reproducibility
  - Robotic dispensing/ parallelization/ robotic sampling/ analysis
- More of the right experiments
  - Improved statistical analysis; QSPR
  - Automated evaluation (deconvolution, PCA)

Outline

- Introduction to- and approaches in high throughput technologies
- AVANTIUM approach
  - Technology
  - Life Sciences
  - Case studies

High Throughput: Work faster

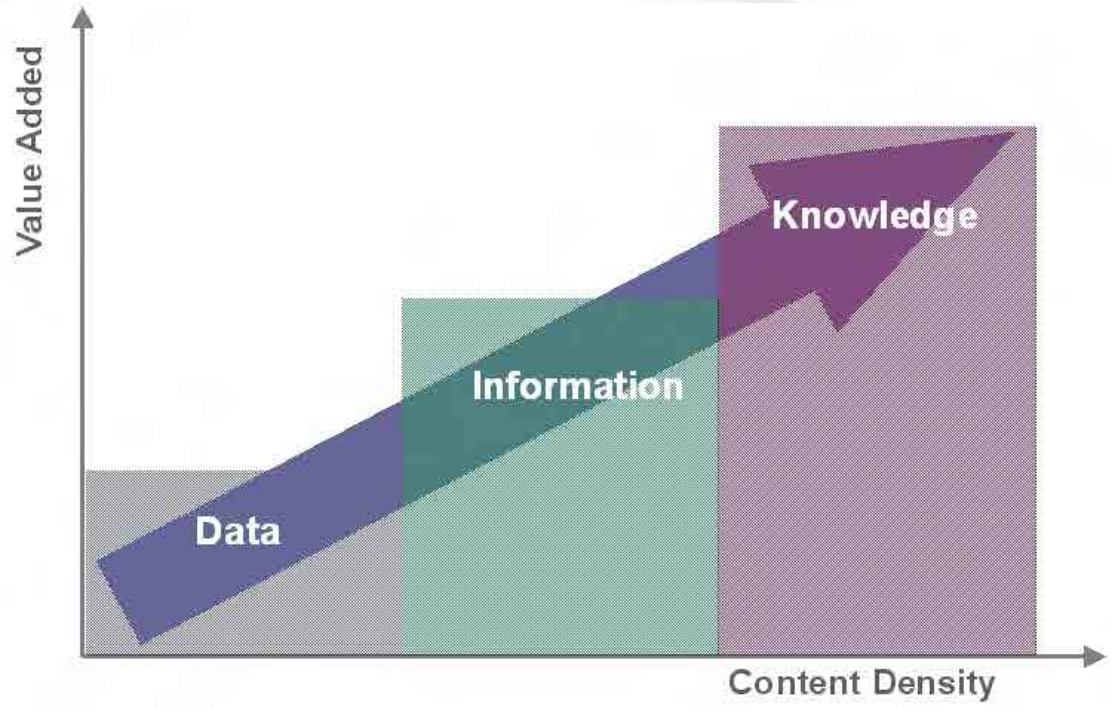
Optimize experimental workflows:

- Increase experimental throughput
- Increase the rate of data generation
  - Identify unit operations
  - Automate
  - Parallelize
  - Downscale

High Throughput: Work smarter

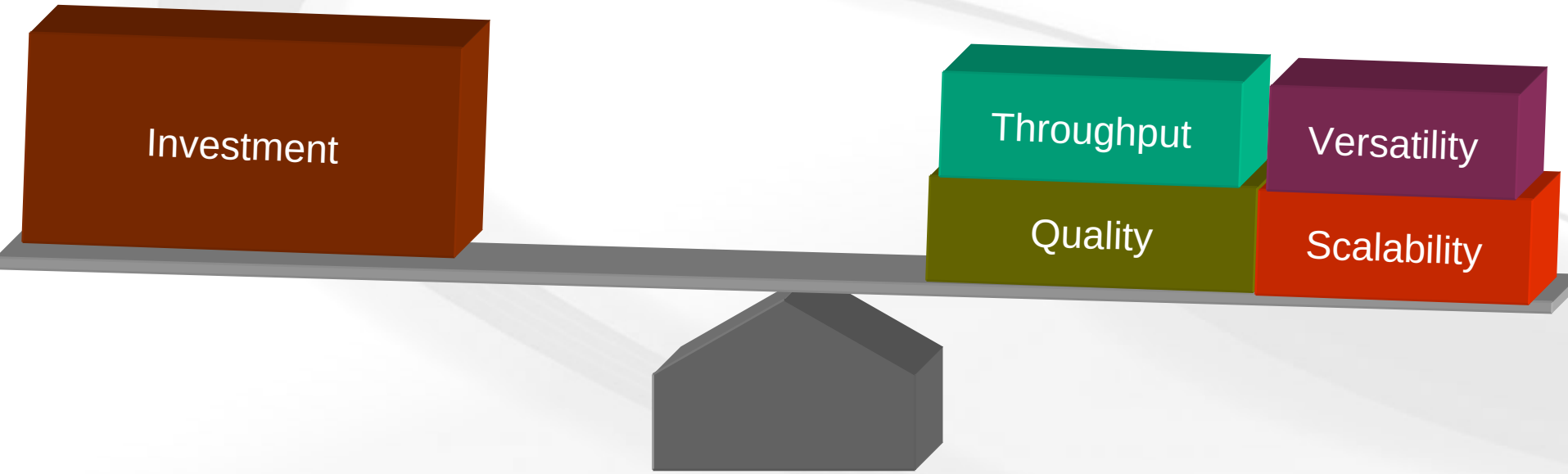
Use cheminformatics tools to focus experimentation:

- design knowledge-optimized experimental programs
- convert data into relevant knowledge
- reinvest knowledge in design of next set of experiments



Dilemma of high throughput technologies

- Directed vs. systematic
- Down scaled equipment vs non-traditional
- High quality data vs Quick-and-dirty
- Realistic conditions (Cat. Prep. And process) vs model feeds and conditions
- Optimization & Kinetic modeling vs lead finding



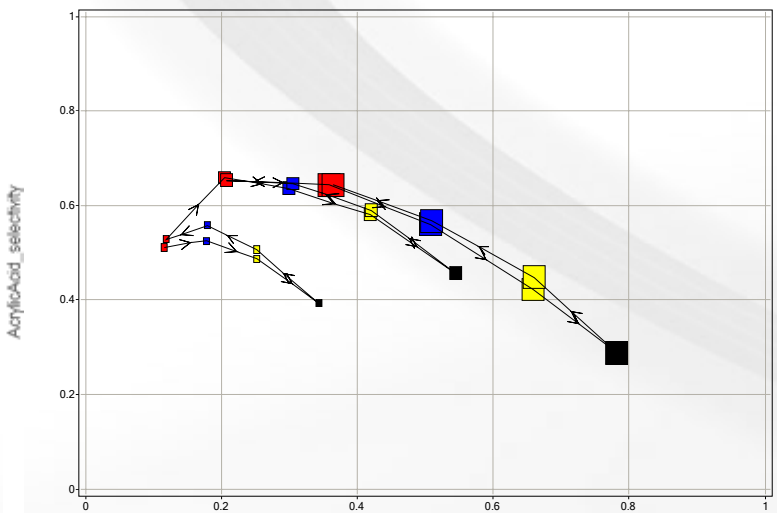
Avantium Approach & Focus

- High quality, moderately high numbers 10-100
- Screen, Test and Optimize under realistic conditions
  - Realistic feeds
  - Realistic process conditions
  - Realistic catalysts (3 dimensional pore structure)
- Multi variant experiments involving
    - Catalyst parameters
    - Process parameters
- Process optimization
- Improve experimental efficiency with modeling and simulation

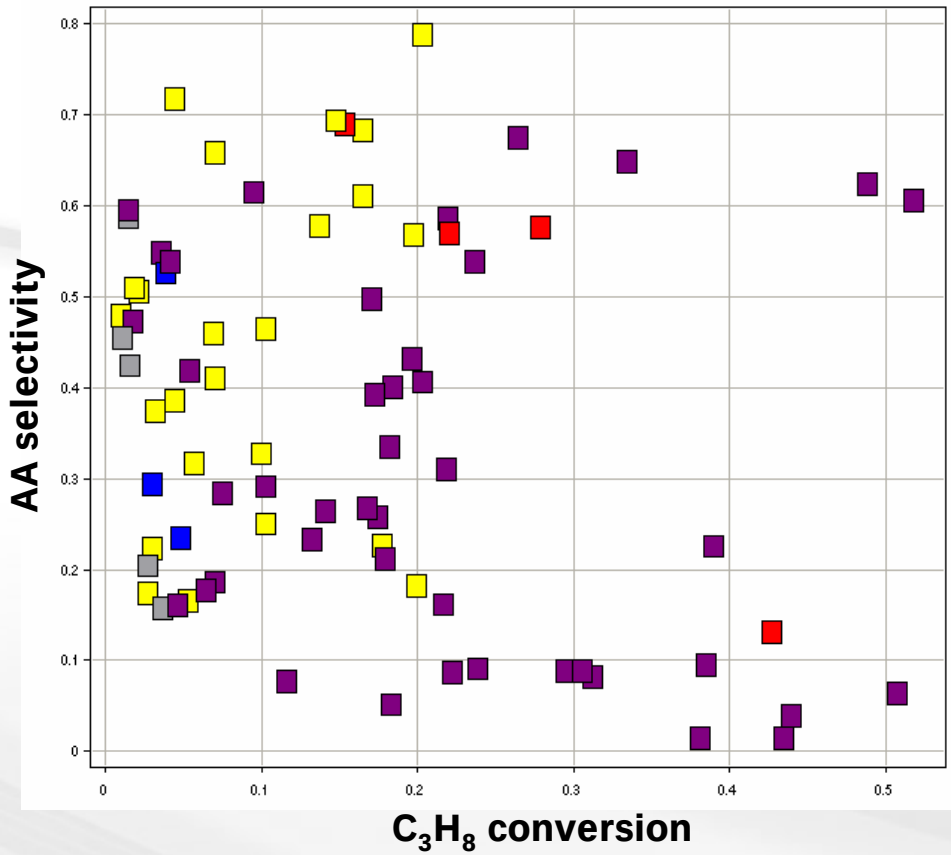
96 x $Mo_1V_{0.3}Te_{0.23}Nb_{0.12}O_x$

96 “reference” catalysts (same metal composition, different recipes)

screened at fixed process condition illustrate variation within single catalyst wrt performance



Propane conversion



Avantium Technologies

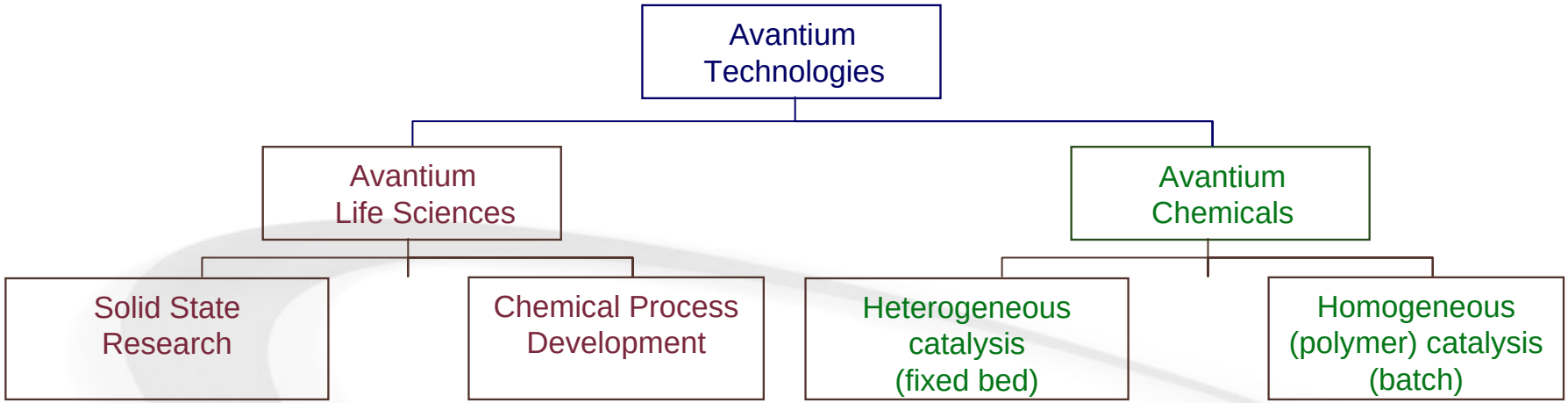
- Providing technology-based solutions to meet customers R&D objectives

- Access to advanced R&D technologies and skills on a contractual basis
  - Avantium infrastructure
    - Hardware platforms
    - Software suites (modelling, simulation, data processing, QSPR)
  - Custom solutions for application specific requirements
    - Hardware design, engineering, automation and build
  - Possible technology transfer to customer

Avantium **generates and extends IP for customers** on their products and processes.

Avantium Technologies

Independent R&D company founded 2/2000 in NL



Access to advanced R&D technologies and skills on a contractual basis

- Avantium infrastructure
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Avantium **generates and extends IP for customers**

Technology

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Application specific technology platforms

Batch Technology

12 functionally different platforms

> 750 autoclaves

Heterogeneous slurry/ Homogeneous/ Polymers/ Formulations **(incl. het. cat. prep.)**

Fixed Bed Techn.

>200 fixed bed reactors

Gas-phase

Vapour phase

Trickle phase

No single platform fits all applications

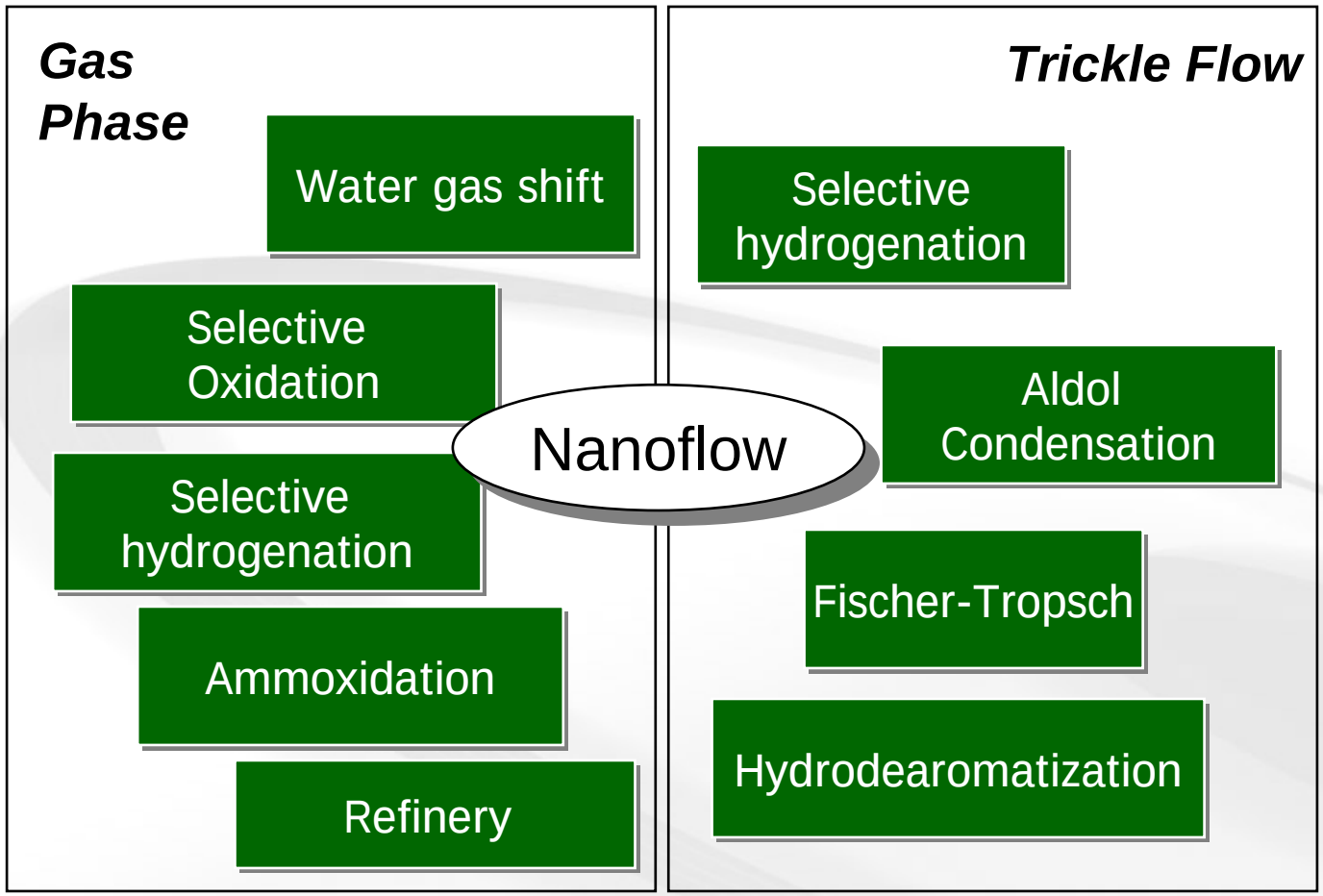

QUICK CATALYST SCREENING STATION
www.quick-catalyst-screen.com

Avantium Delft: Fully automated (polyolefin) cat. testing

Fixed Bed Testing Capabilities

Equiment	phase	T_{max} (°C)	p_{max} (bar)	GC analysis
1st generation	gas	450	1	on-line
2nd generation	gas/trickle	550	40	on-line
3rd generation	gas/trickle	550	100	on-/off-line
4th generation	liquid	300	100	on-/off-line

Proven Applications Fixed Bed



Avantium Life Sciences

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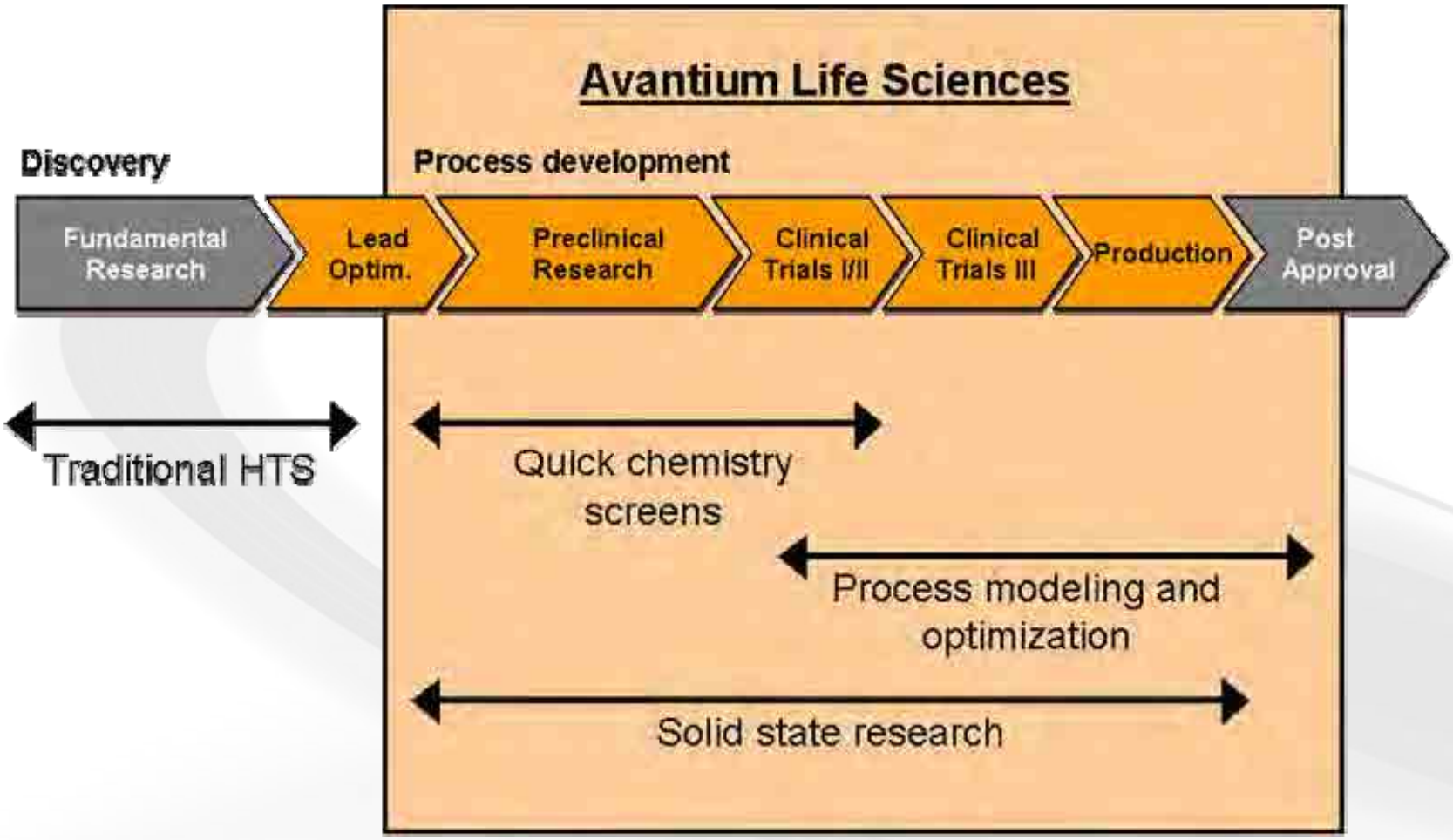
R&D services Avantium Life Sciences



Process Chemistry Services

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Avantium Rational Design

- Rational Design combines molecular modelling, multivariate statistical techniques and experimental design (DoE) to efficiently optimise complex products and processes.

- The aims of this technique are:
  - To avoid an intractable combinatorial explosion
  - To transform categorical variables into continuous variables
  - To systematically explore a wide experimental space
  - To build predictive QSPR models to pre-select promising catalysts / reactants / solvents

McKay, B.; Hoogenraad, M.; Damen, E.W.P.; Smith, A.A. *Current Opinion in Drug Discovery & Development* 2003, **6**:966-977.

Approach

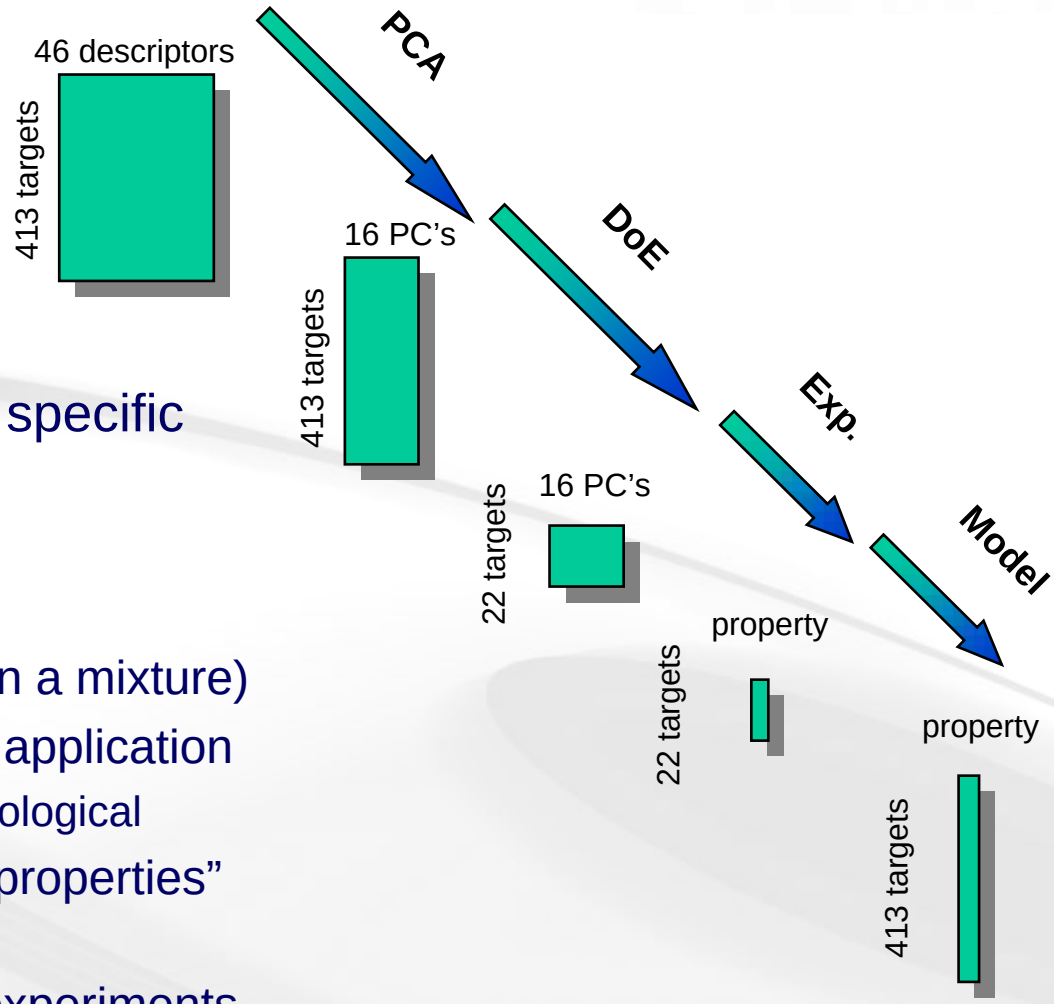
To predict responses of (catalytic) systems from empirical data

- (Catalytic) system is considered as a host phase:
  - Correlate structural diversity of a component with system responses
  - Ignore reaction mechanism
- Short computational times; quick answers:
  - Descriptor calculation
  - Principle component analysis
  - Modelling (PLS)
- Issues:
  - Limited data sets (Answer: HTS)
  - Consistency of the datasets (Answer: reproducible experiments: HTS)
  - Level of chemical knowledge in the models (Answer: expertise)

Descriptors – Transform categorical variables into numerical data

- Constitutional
  - Atom and group counts
- Topological
  - Use of the connection table representation of the chemical structure.
  - Employ methods drawn from mathematical graph theory.
- Geometrical
  - Calculated from 3D molecular models.
- Electronic
  - Calculated from semi-empirical or *ab-initio* calculations.
- Hybrid Representations
  - Encode the molecule's ability to interact with other compounds.
  - Encode the molecule's ability to form other species (e.g. complexes).
- Measured
  - Physicochemical (e.g. based on Spectroscopy or Thermodynamic)

Property Prediction
Typical example



Aim

- Develop predictive model for a specific component property

Scope:

- 413 targets (for a component in a mixture)
- 46 descriptors relevant for the application
  - Geometric, electronic and topological
- Wish to estimate the specific "properties" of 413 potential targets
- Perform minimum number of experiments

Rational Design Case Study

Stereoselective Oxazaborolidine reductions

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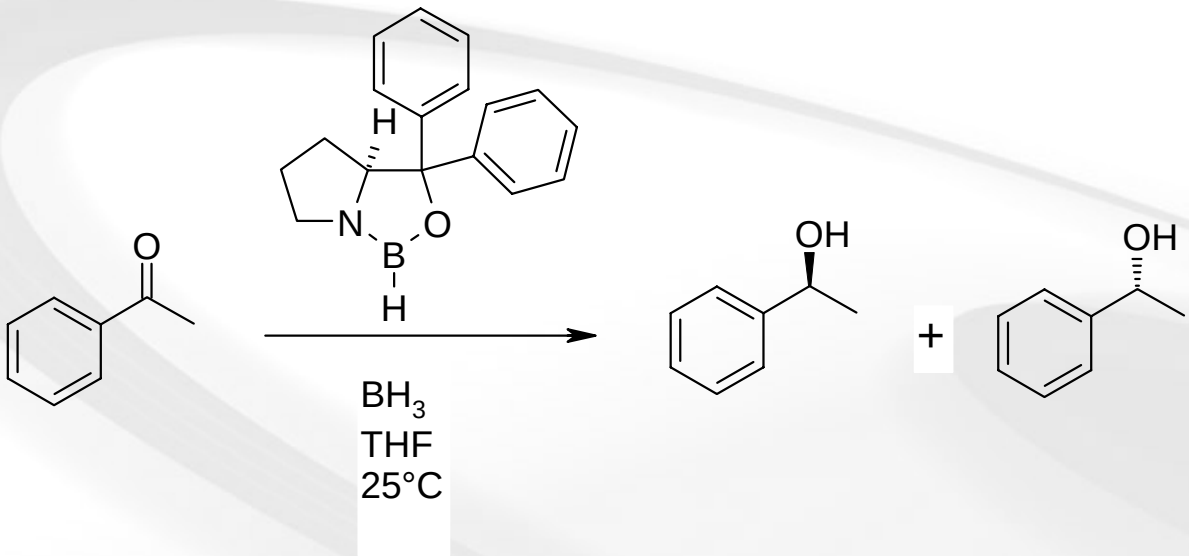
Hoogenraad, M.; Klaus, G.M.; Elders, N.; Hooijschuur, S.M.; McKay, B.; Smith, A.A.; Damen, E.W.P.

Tetrahedron Asymm. 15 (2004) 519 - 523

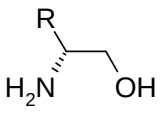
Chemistry

- Chiral oxazaborolidine mediated reduction of acetophenone

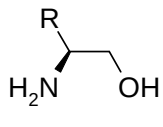


Chiral aminoalcohols and preformed oxazaborolidines

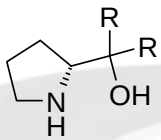
training set



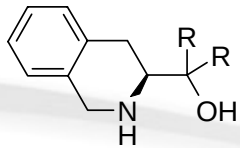
R = H (**1**)
R = iPr (**2**)
R = Ph (**3**)
R = CH_2Ph (**4**)



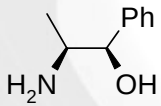
R = Me (**5**)
R = $CH_2CH(CH_3)_2$ (**6**)
R = tBu (**7**)
R = $CH(CH_3)CH_2CH_3$ (**8**)
R = CH_2OCH_2Ph (**9**)



R = H (**10**)
R = Ph (**11**)
R = 2-naphtyl (**12**)



R = H (**13**)
R = Ph (**14**)



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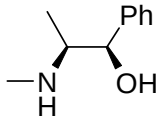

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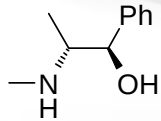

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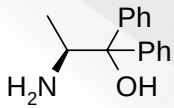

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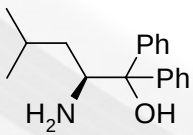

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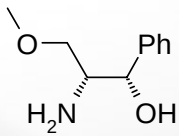

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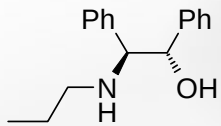

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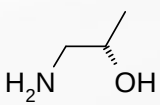

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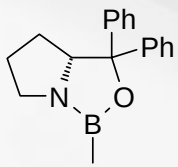

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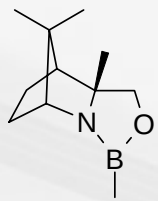

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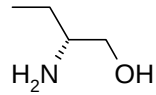
prediction set



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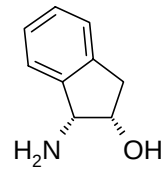

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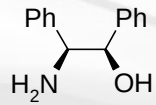

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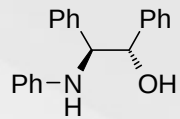

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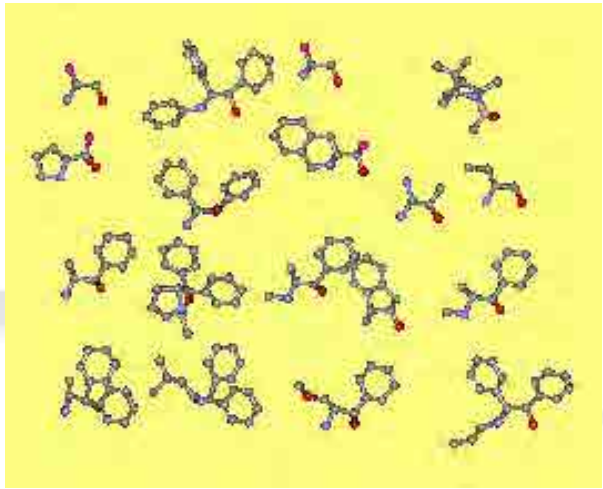
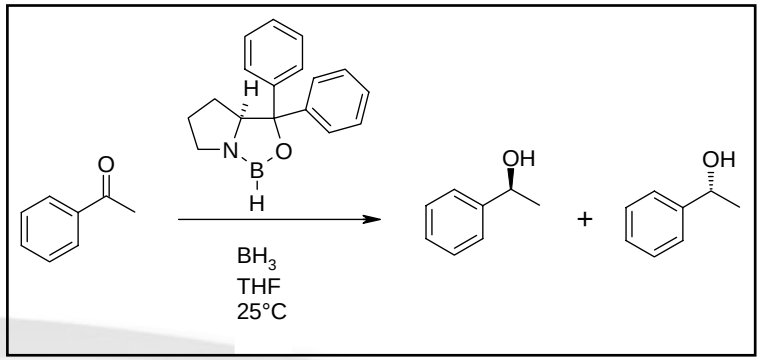
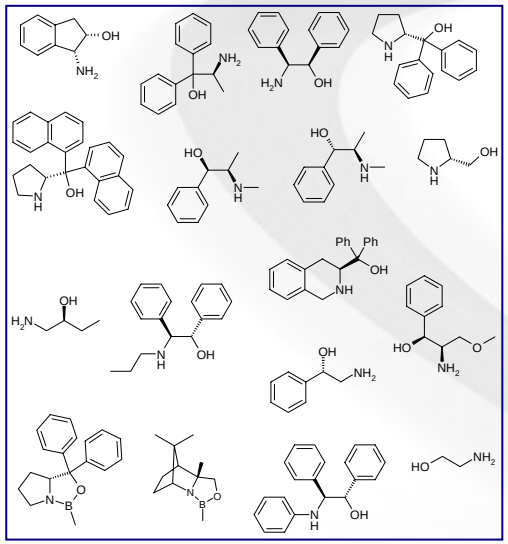
Descriptor calculation



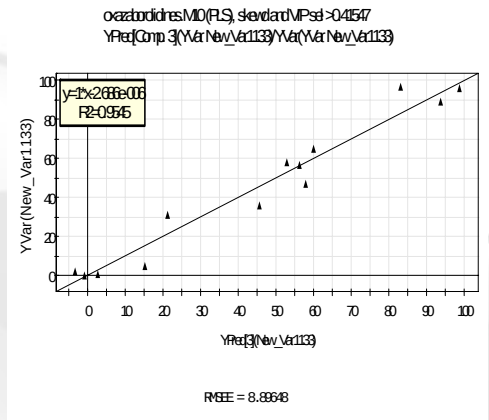
Compound	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	.....	Dxxx
oxaza 1	0.57	6.76	5.34	1.78	0.66	0.12	5.76	4.23	1.78	7.65	0.11	8.99	.....	2.22
oxaza 2	0.82	9.8	7.74	2.58	0.96	0.17	8.35	6.13	2.58	11.1	0.16	13	.....	3.22
oxaza 3	1.19	14.2	11.2	3.74	1.39	0.25	12.1	8.88	3.74	16.1	0.23	18.9	.....	4.66
oxaza 4	1.73	20.6	16.3	5.42	2.01	0.37	17.5	12.9	5.42	23.3	0.33	27.4	.....	6.76
.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
oxaza 28	2.52	29.8	23.6	7.85	2.91	0.53	25.4	18.7	7.85	33.7	0.49	39.7	.....	9.79

Reaction mechanism or TS modeling not considered





‘black box’



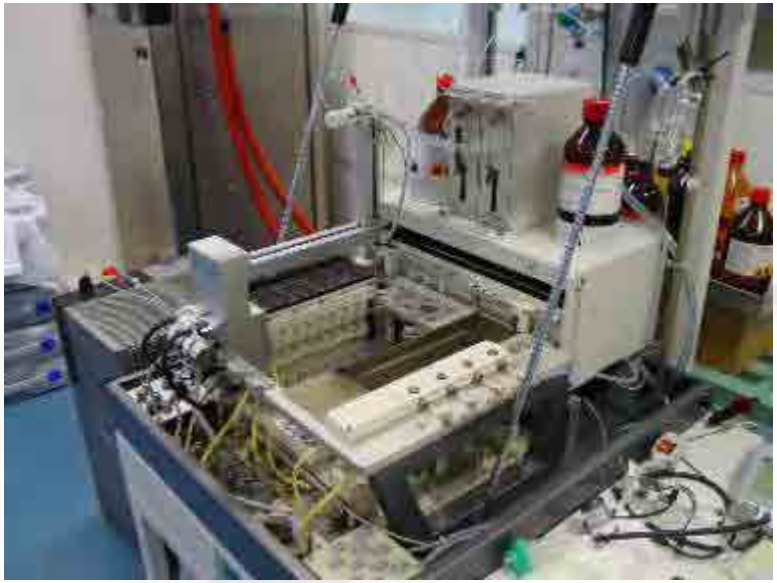
- Approach can provide insight in the reaction mechanism and may lead to new improved catalysts

Practical issues

- Requirements for modeling
  - Consistent datasets
  - Many replicates (preferably all reactions in triplicate)
  - Large datasets
  - Accurate substrate addition (very important for Corey reductions)
  - Valid analytical method
- Solution: automated workstations
- Analysis by chiral GC with internal standard

Automated workstation

- Chemspeed ASW2000



- Flexible and accurate feed rates
- Per run max. 80 reactors (13 mL)
- Accurate temperature control
- Inert conditions (also on stock solution rack and reservoir solvent)
- Automated quench and sampling

Results

- Complete conversion
- Satisfying mass balance
- Values of e.e. range from 0 - 97%
- Good reproducibility:

Entry	Compound name	Mass balance (%)	Conversion (%)	ee (%)
1	(R)-valinol	96.7	100	82
2	(R)-valinol	101.0	100	80
3	(R)-valinol	98.8	100	78
4	(R)-2-phenylglycinol	96.1	100	90
5	(R)-2-phenylglycinol	97.2	100	89
6	(R)-2-amino-3-Phenyl-1-Propanol	94.7	100	72
7	(R)-2-amino-3-Phenyl-1-Propanol	96.7	100	72
8	(R)-2-amino-3-Phenyl-1-Propanol	94.2	99	71
9	(R)-2-amino-3-Phenyl-1-Propanol	93.6	100	71
10	(R)-2-amino-3-Phenyl-1-Propanol	95.3	100	70
11	(S)-2-amino-1-propanol	94.7	100	56
12	(S)-2-amino-1-propanol	92.5	100	56
13	(S)-2-amino-1-propanol	96.4	100	54
14	(S)-leucinol	94.0	100	69
15	(S)-leucinol	93.9	100	68
16	(S)-leucinol	95.8	99	67
17	(S)-leucinol	96.0	100	66
18	(S)-tert-leucinol	97.6	100	90
19	(S)-tert-leucinol	97.4	100	89
20	(S)-isoleucinol	96.6	100	80
21	(S)-isoleucinol	96.2	100	79

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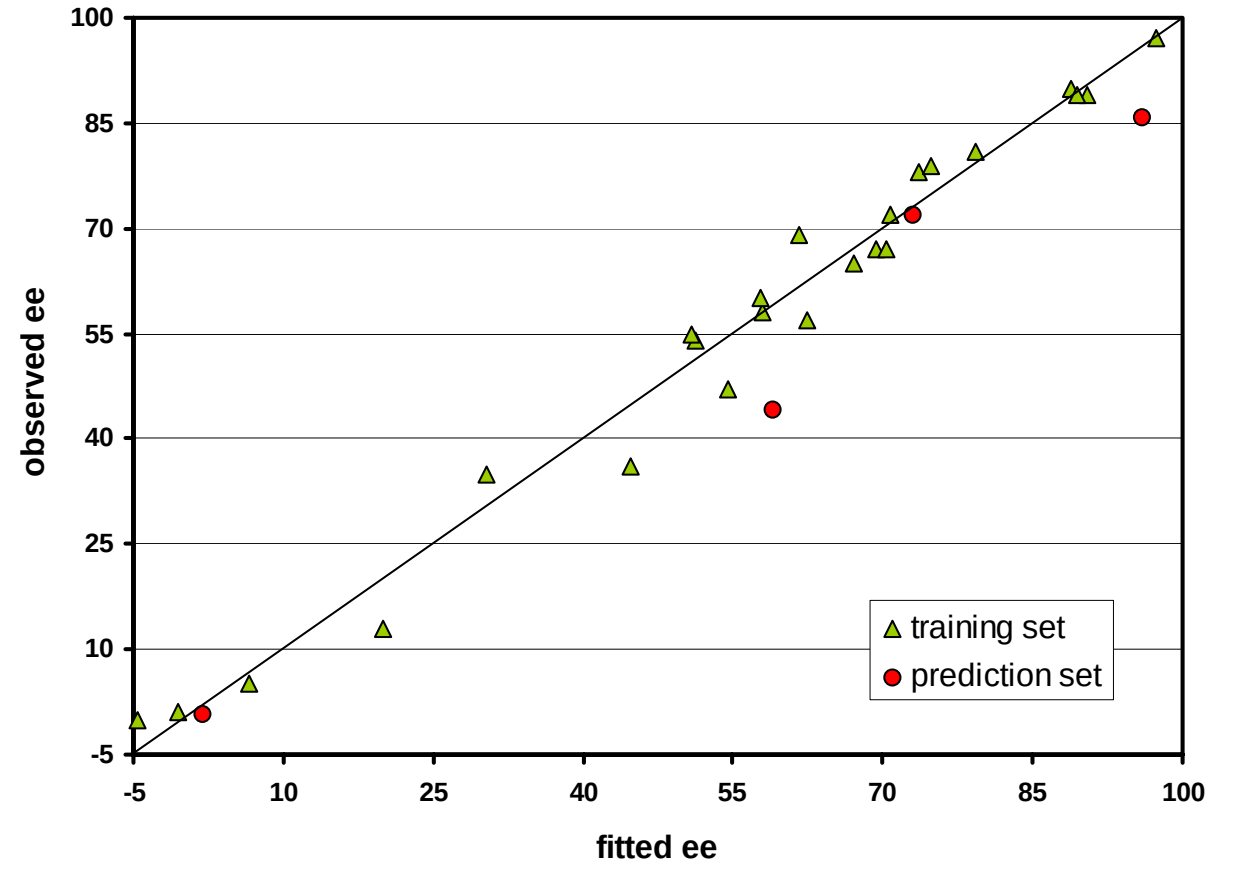
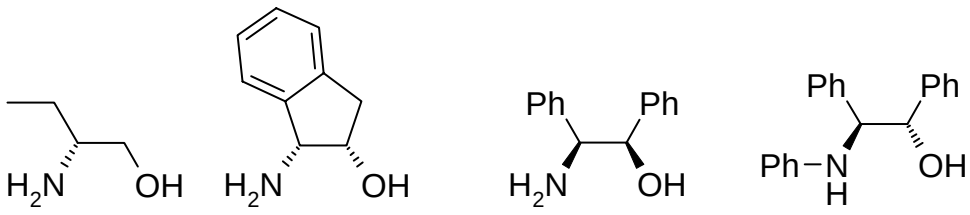
PLS model

- Partial least squares (PLS) model



- Predictive power (R^2) = 0.978; (Q^2) = 0.797

Results prediction



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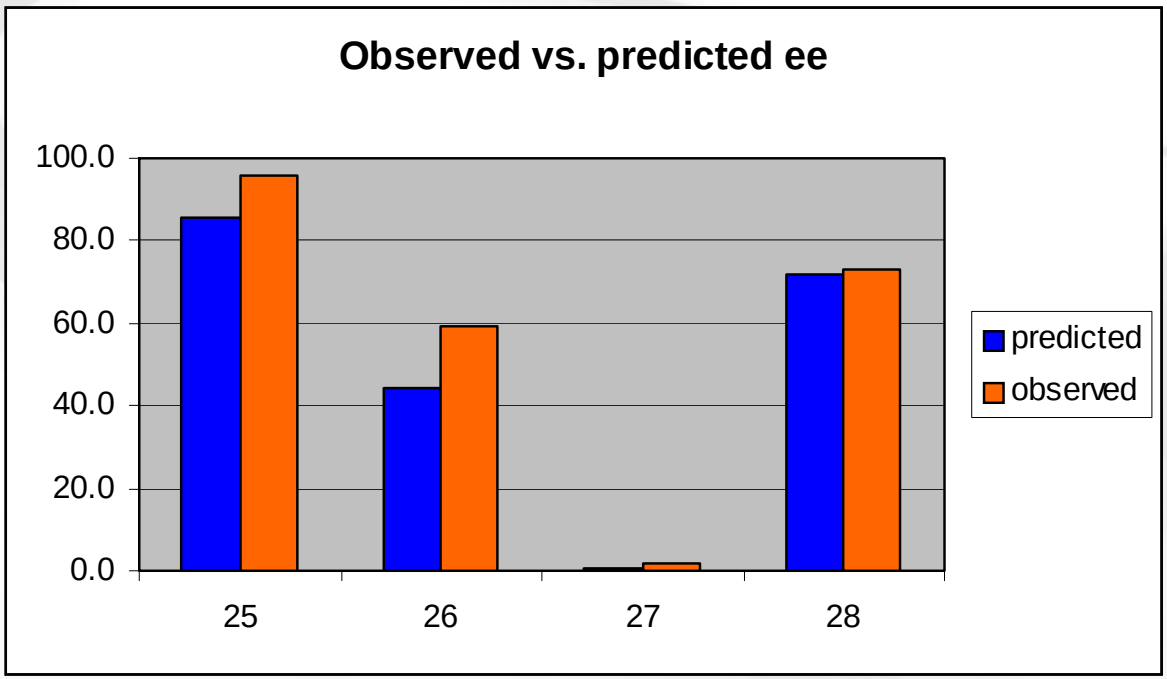
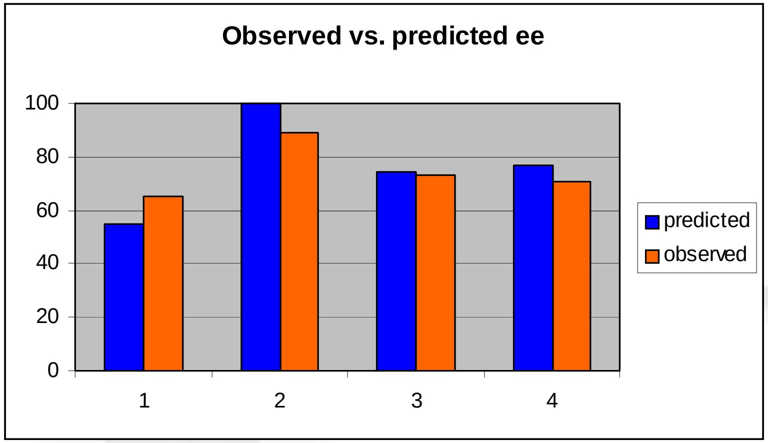
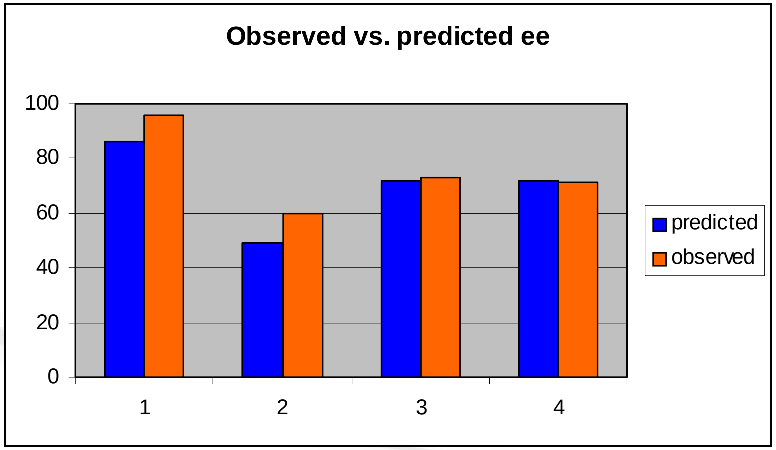
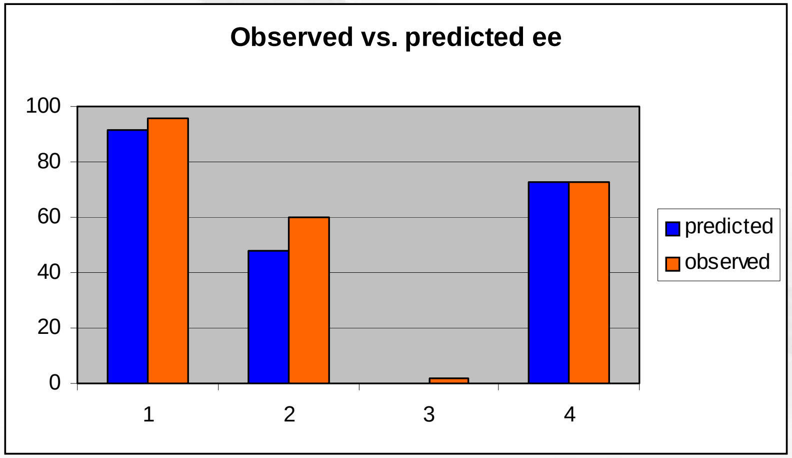
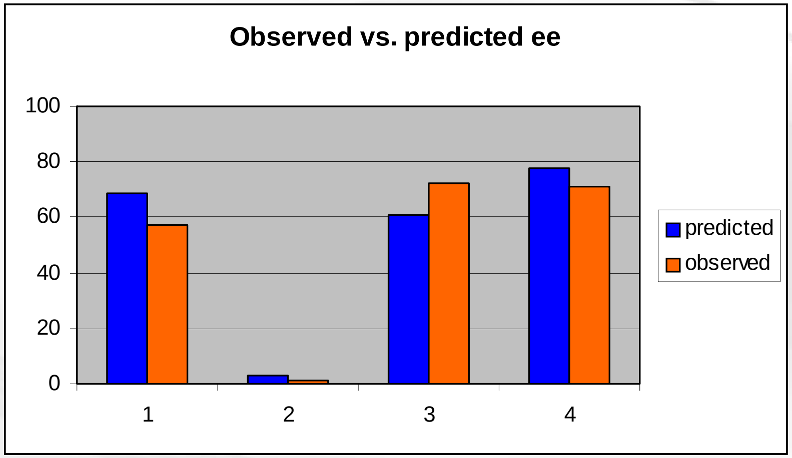


Other prediction sets





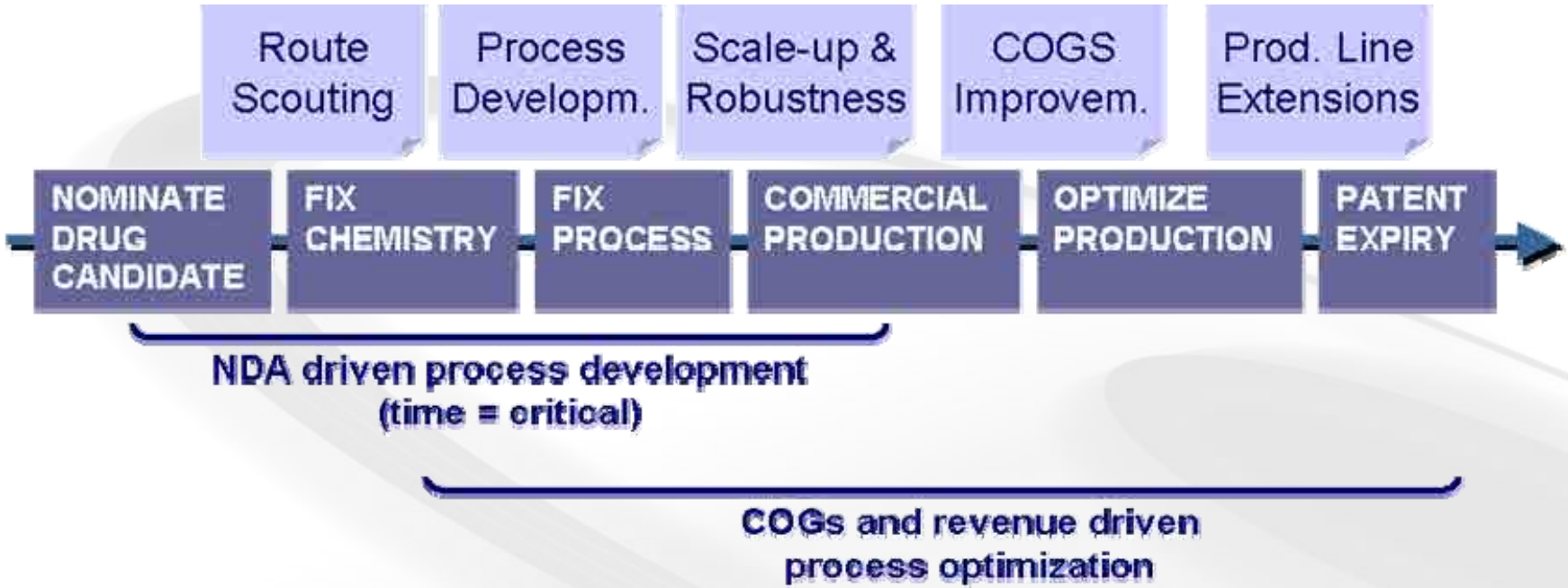




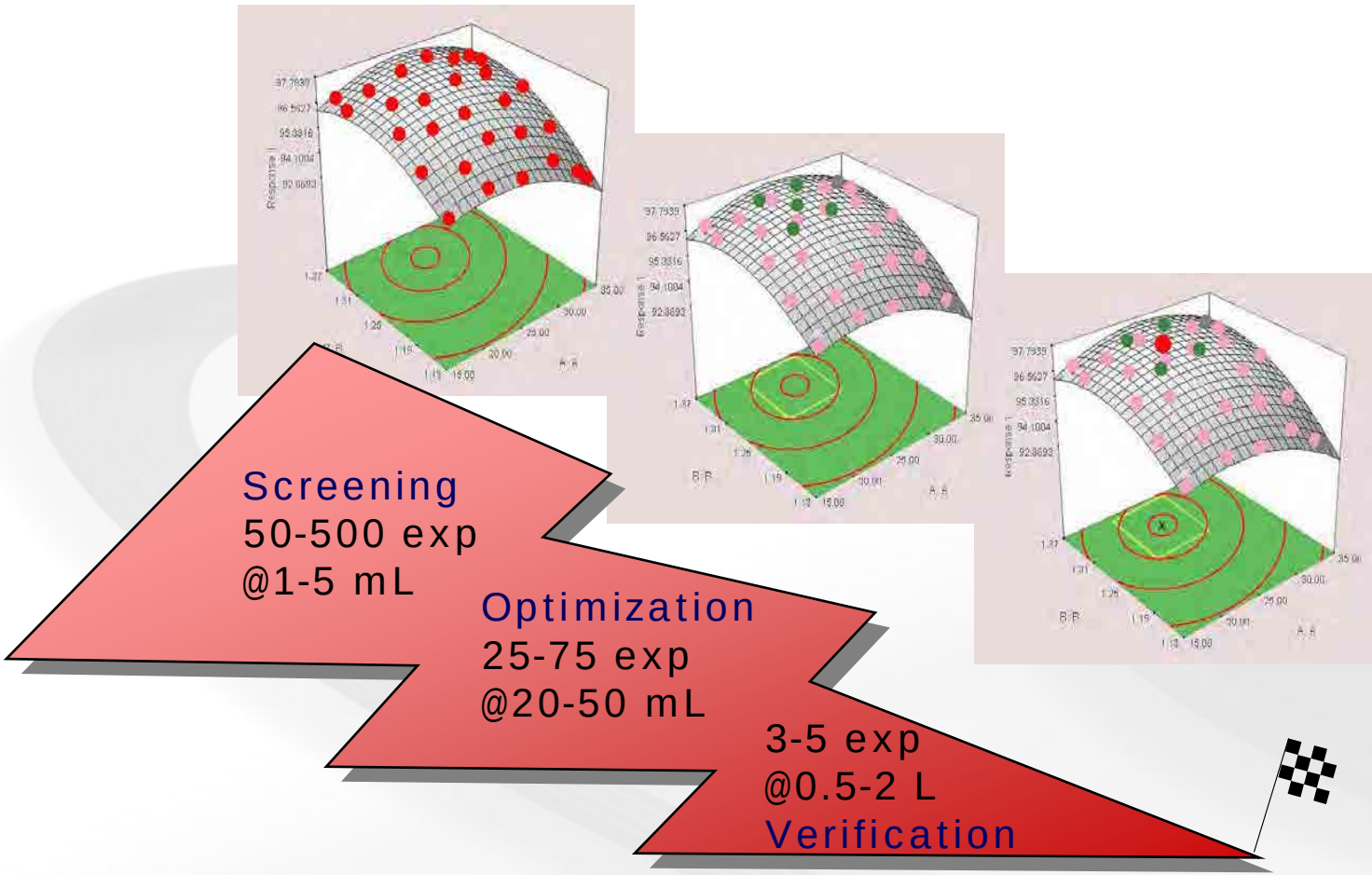
Performance

- Chemspeed provides excellent reproducibility and results are comparable with the literature
- A QSSR model was constructed successfully
- Moderate to good predictive power with multiple prediction and training sets
- FAST
- Next step: expanded model with variety of substrates

Process chemistry services



Process Optimization



Start to Finish in 2-3 months

Case Study
Process Optimization

FRAGMENT COUPLING: LAST STEP IN A MULTI-STEP SYNTHESIS

A-C=O + HN(R)-B → A=CH-NR-B

Reducing agent

Coupling agent

Reflux (water removal)

solvent

Starting point

- Process step has long cycle times and low yields
  - Reaction time >100 h
  - Yield 76%
  - Conversion 80%
- R&D at the customer's site:
  - Cycle time reduced to 40 h
  - Yield reduced to 73%
  - Conversion increased to 85%
  - Undesired impurity profile

The Objectives

- Reduce cycle time
- Minimize impurities
- Maximize yield

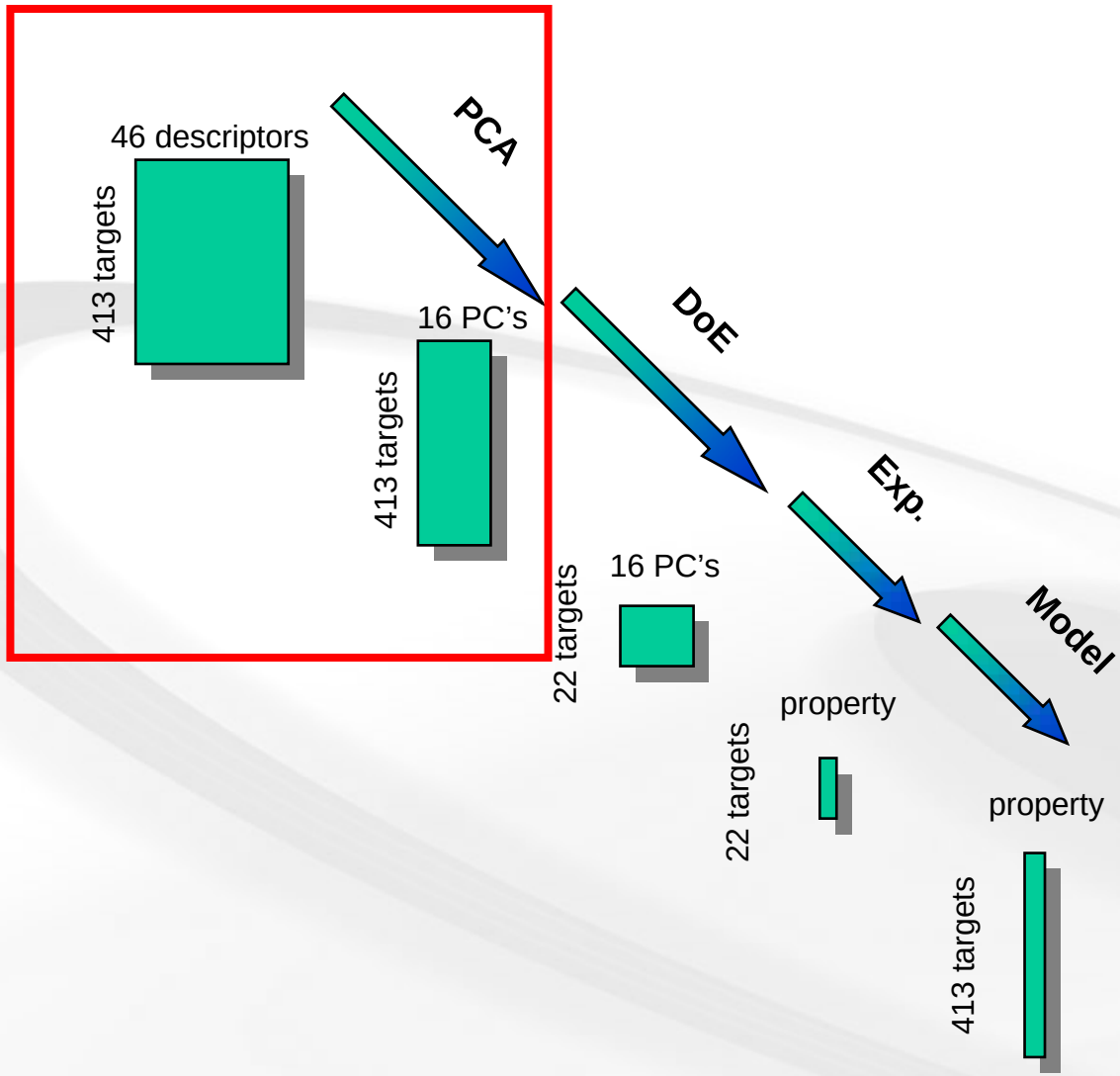
Project Scope

- Phase 1: Rational screening of solvents and coupling agents
- Phase 2: Optimize process parameters
- Phase 3: Best embodiment in RC-1, scale-up model in BatchCAD

Rational screening

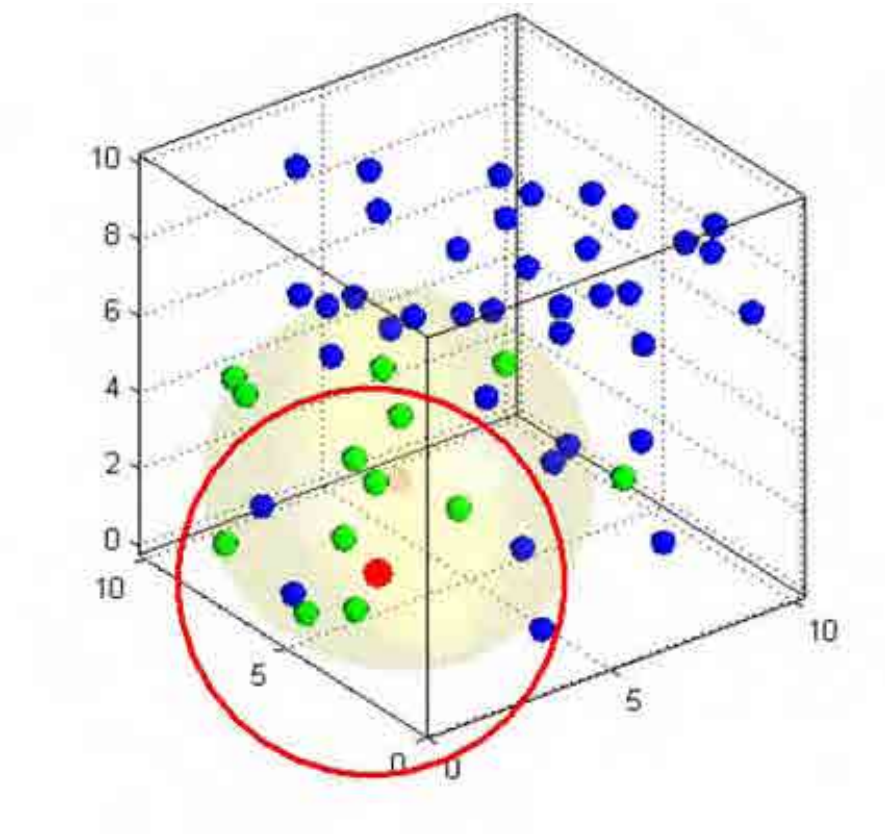
- How to select the solvents (=categorical variable)?
- How to select coupling agents ?
- How to ensure diversity?

PCA modeling



The rational HT screening approach

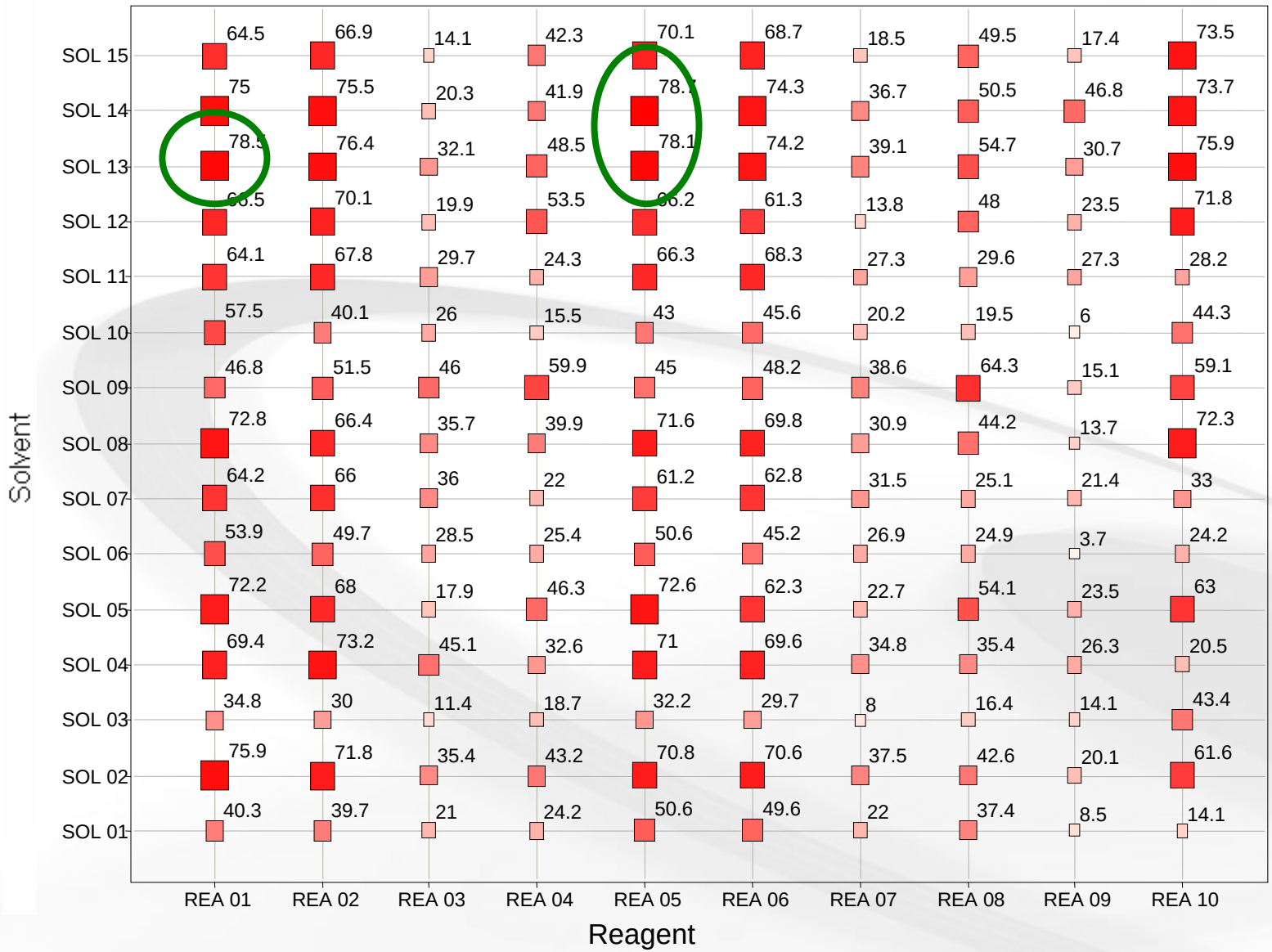
- Solvents represented as points in ‘property space’
- Selection of solvents that are close to “current-best”



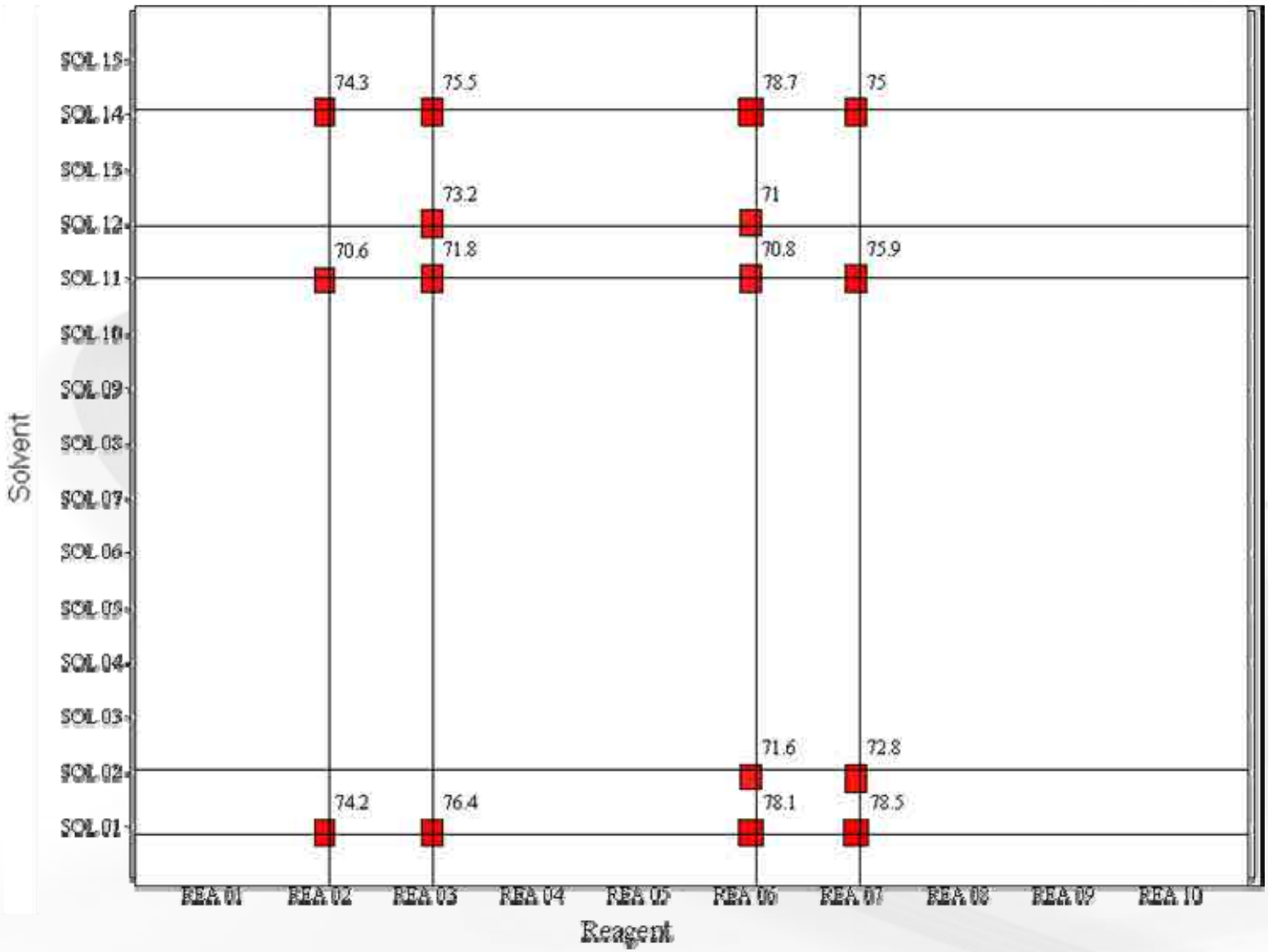
Rational Screening

- Experiments:
  - All combinations of 15 selected solvents and 10 coupling agents at 2 temperatures
  - Other conditions fixed based on current process conditions
  - 300 reactions within 2 weeks (including analysis)

Screening results T(1); 24 hrs (Yield)



Screening results T(2); 40 hrs (Y>70; Imp<10)



Conclusions Phase 1

Highlights:

- Yield improved to 78% with encouraging impurity profile (conversion of 84%)
- Co-solvent and reducing agent selected for optimization phase

Scope

- Phase 1: Rational screening of co-solvents / reducing agent

- Phase 2: Optimize process parameters

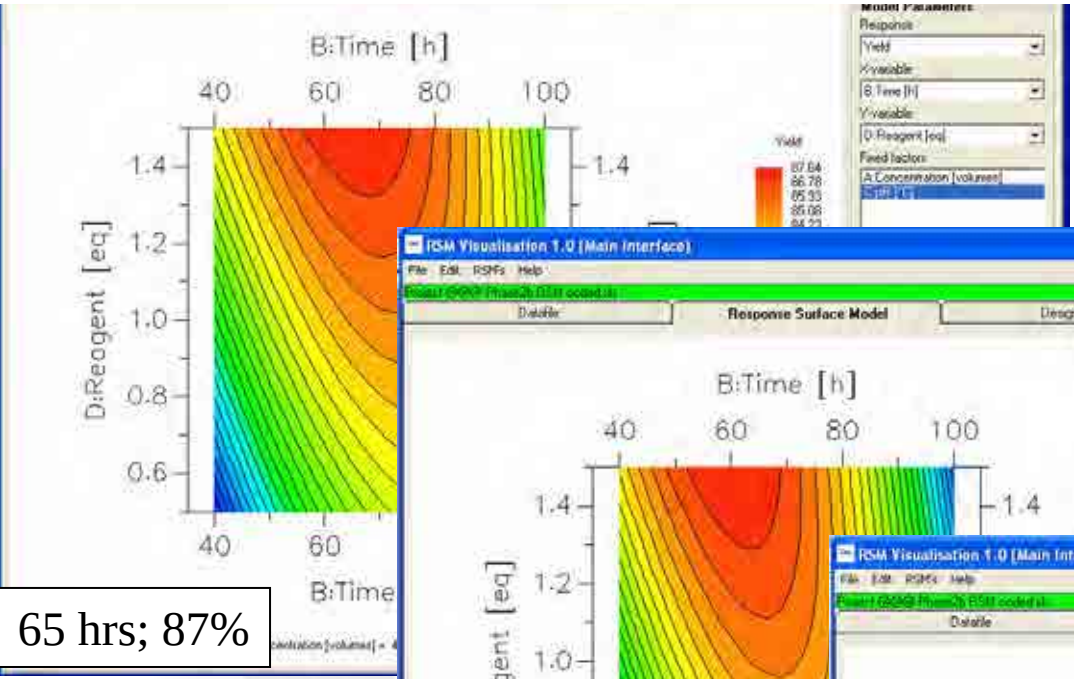
Response surface modeling

- Evaluate process parameters (main effects study)
  - Equivalents of coupling agent
  - Coupling agent addition rate
  - Reaction concentration
  - Stirring speed and method (mechanical vs. orbital shaking)
  - Reaction time
  - Temperature
  - pH
  - Ionic strength

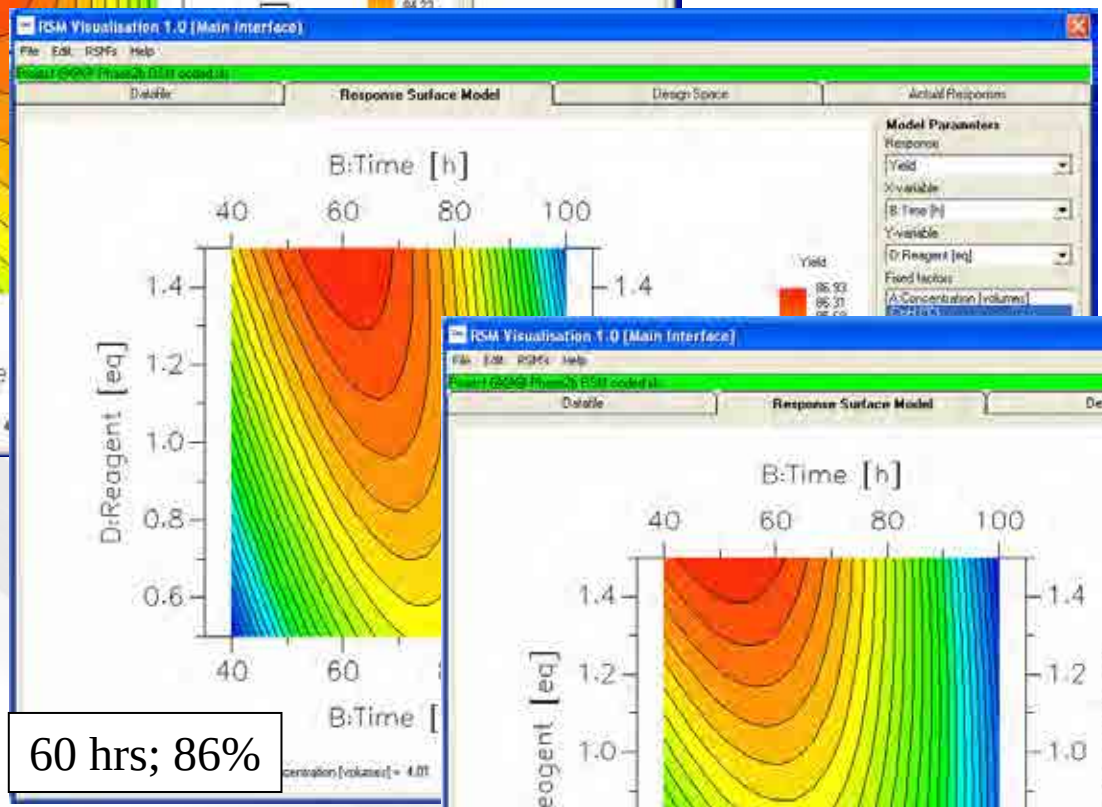
Response surface modeling

- Optimize significant process parameters and their interactions using statistical design of experiments (DoE)
  - Reaction concentration
  - Reaction time
  - Equivalents of coupling agent
  - pH
- I-optimal design (48 reactions including replicates) for selected solvent/coupling agent combination
- Results in a response surface model (RSM)

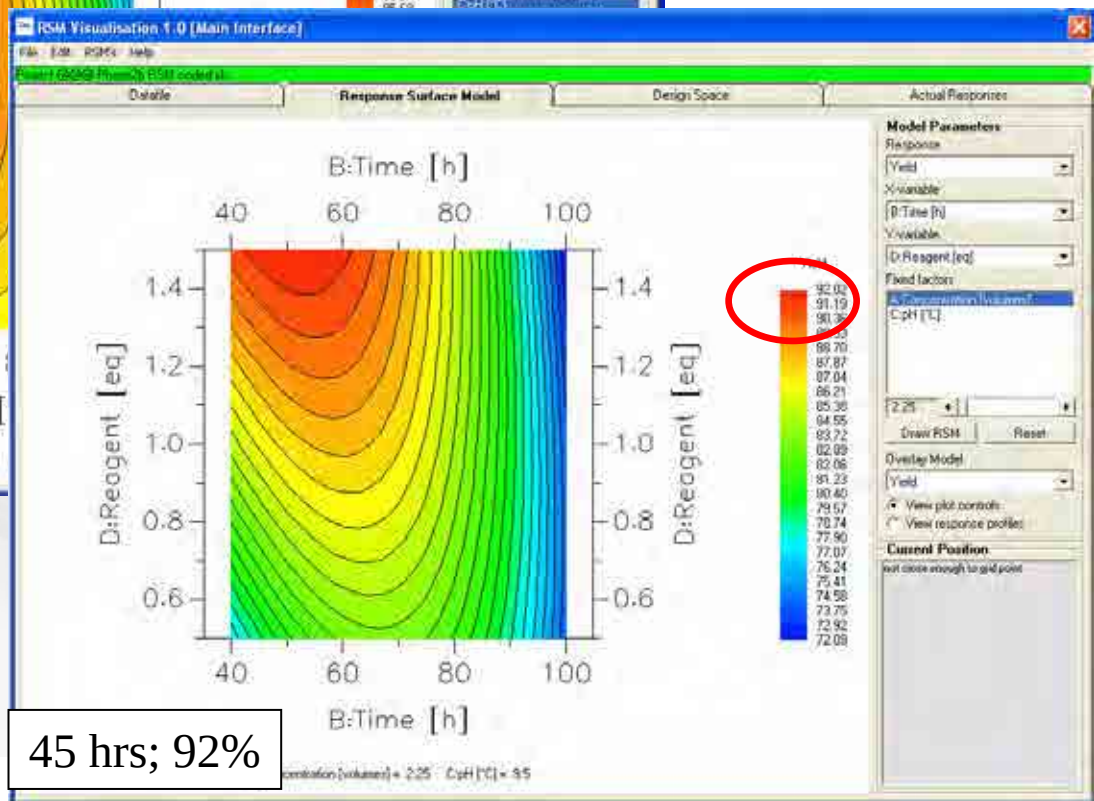
Response surface modeling



65 hrs; 87%



60 hrs; 86%



45 hrs; 92%

Conclusions Case study

- Optimal solvent/reagent combination and 4 main process conditions identified and explored
- Response Surface Model directed to process yield of 92% within process time of 50 hrs (instead of target 40 hrs)
- Potential yield improvement of >15% representing a COGS reduction of > $5 mio per annum
- Superior impurity profile
- Time frame: *<2 months*

Chemistries successfully performed

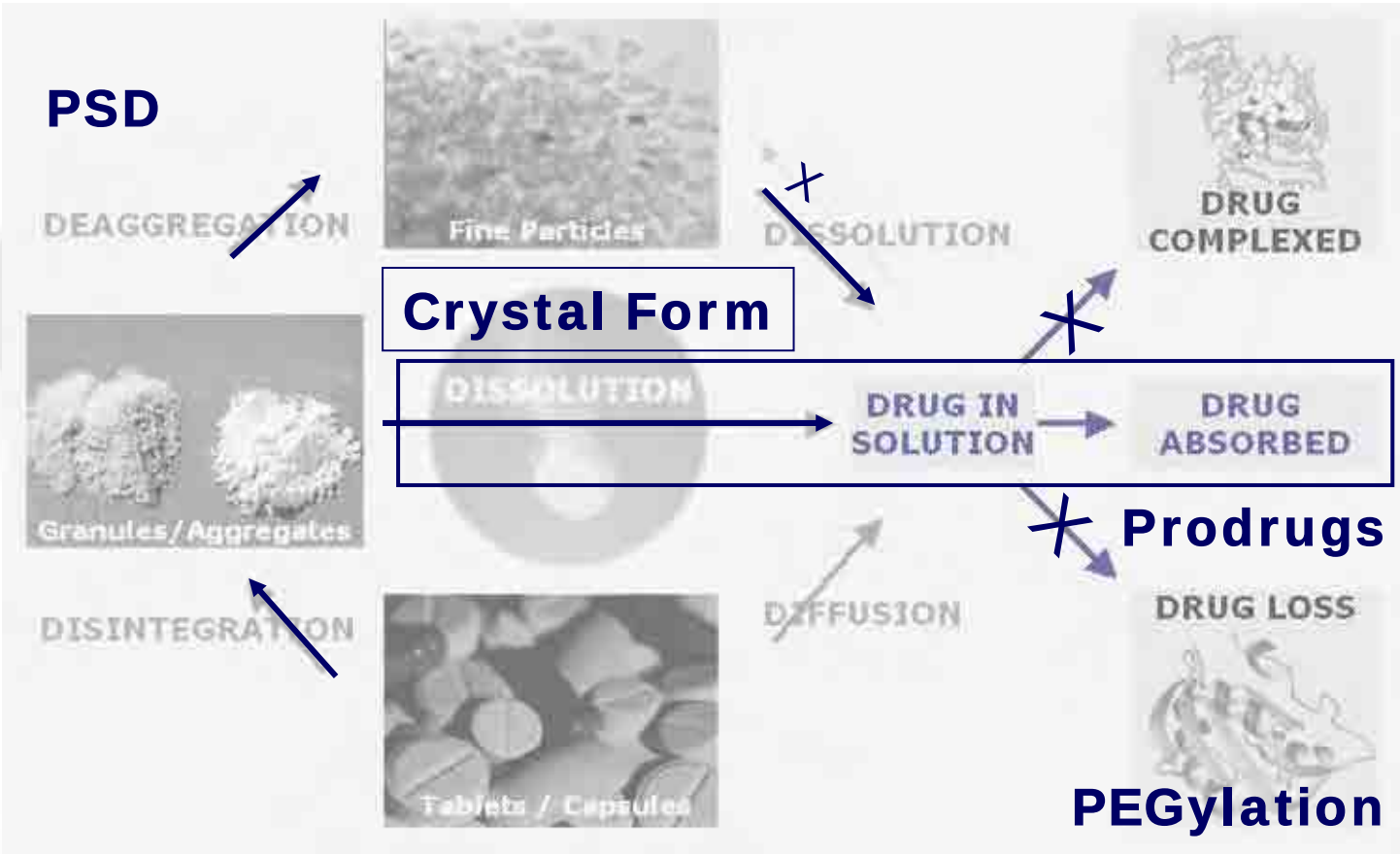
- Selective reductions
  - Nitro, oxime
  - Nitrile
  - Dehalogenation
  - Debenzylation
  - Alkene
- Amide reductions
- Reductive alkylation
- Alcohol oxidation (to acid)
- Alcohol oxidation (to aldehyde)
- Alcohol oxidation (to ketone)
- Enzymatic enantioselective hydrolytic resolution
- Enzymatic
- (Asymmetric) hydrogenation
- (Asymmetric) H-transfer reactions
- (Asymmetric) hydroformylation
- (Asymmetric) hydroamination
- Carbonylation reactions
- Suzuki couplings
- Hartwig / Buchwald aminations
- Metathesis reactions
- Oxazaborolidine mediated

Solid state
(polymorph screening & salt selection)
Services

Accelerating

R&D

Oral Drug Delivery Challenges



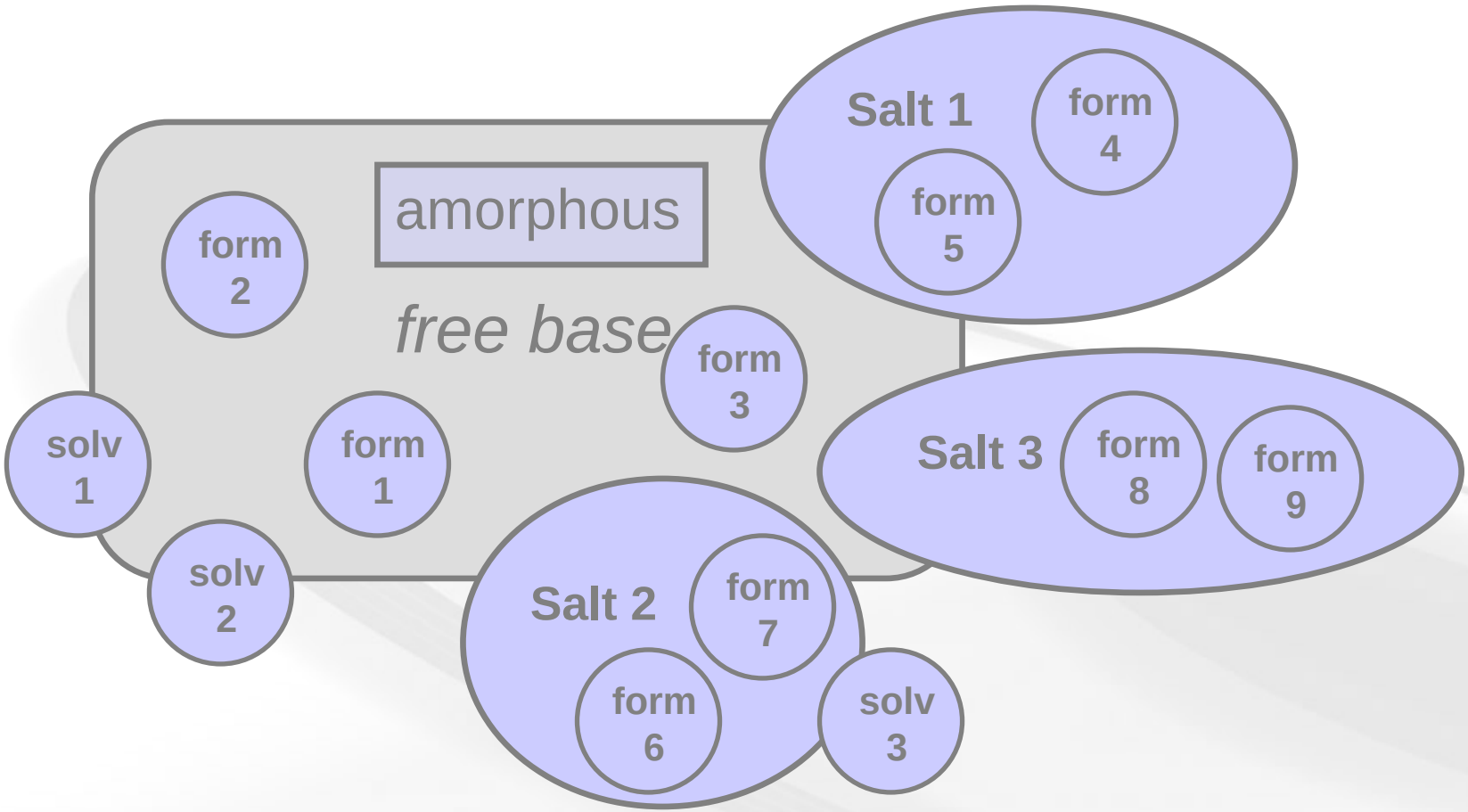
Adapt formulation to influence solubility and dissolution rate

- Amorphous / crystalline
- Polymorph
- Crystal size and shape
- Salt
- Co-crystal
- Pro-drug
- Use of Excipients

Solid Form Selection Criteria

- Crystallinity
- Chemical and physical stability
- Aqueous solubility
- Hygroscopicity
- Low toxicity
- Developability

Solid State Research



Which of these solid forms meets your selection criteria?

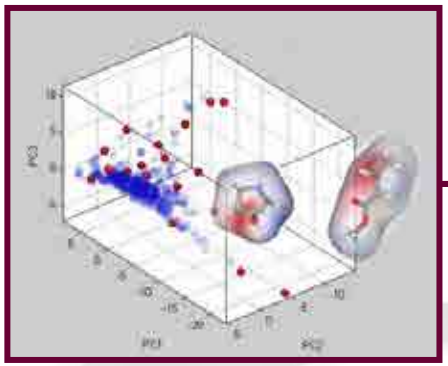
Crystallization

- Solvent
- Water content
- Anti-Solvent
- pH
- Agitation
- Seeding
- Concentration
- Temperature
- Cooling profile
- Time
- Material of Construction
- Impurities
- …

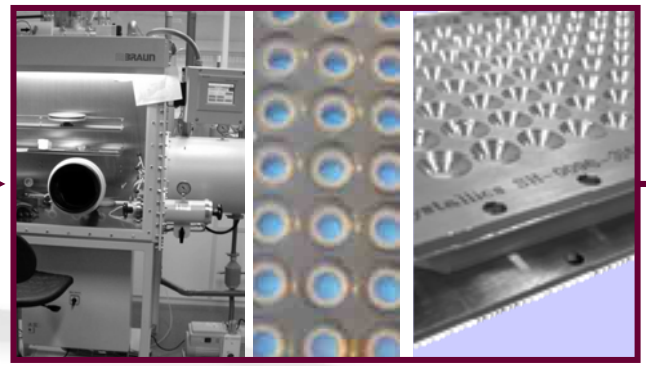
- Repetition of the Experiment
- Solution History
- Heterogeneous Nucleation / Seeding
- Scale
- …

Several categorical as well as continuous variables that may play a role in the process

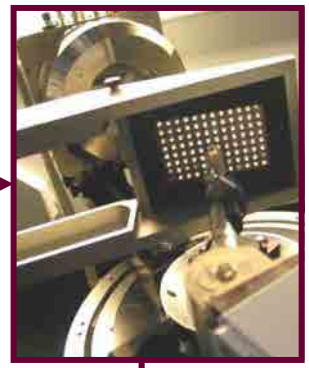
Rational HT Screening solid state workflow



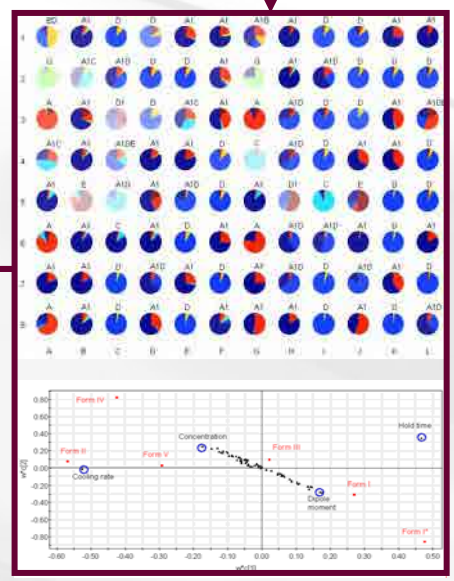
RATIONAL DESIGN



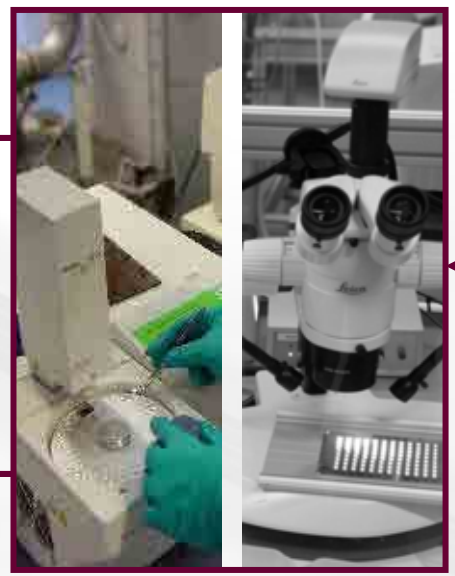
ISOLATED HT CRYSTALLIZATIONS



HT XRPD

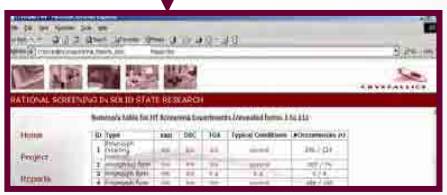


CHEMOMETRICS



CHARACTERIZATION

VALIDATION



e-REPORTING

Avantium Technologies - Summary

- Contract research services for high throughput process and solid-state chemistry
- Rational screening approach to ensure maximum knowledge return on R&D investments
- Access to unique infrastructure
- Immediate contribution to your innovation process
- Flexible business model with clear IP arrangement

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Accelerating

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