



Automating Synthesis through Flow Chemistry

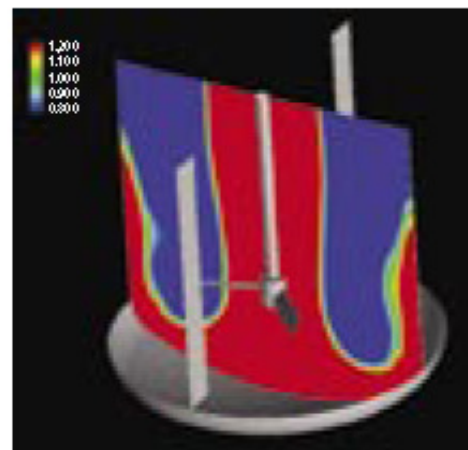
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Lab Automation 2008
Palm Springs, California
January 28th 2008

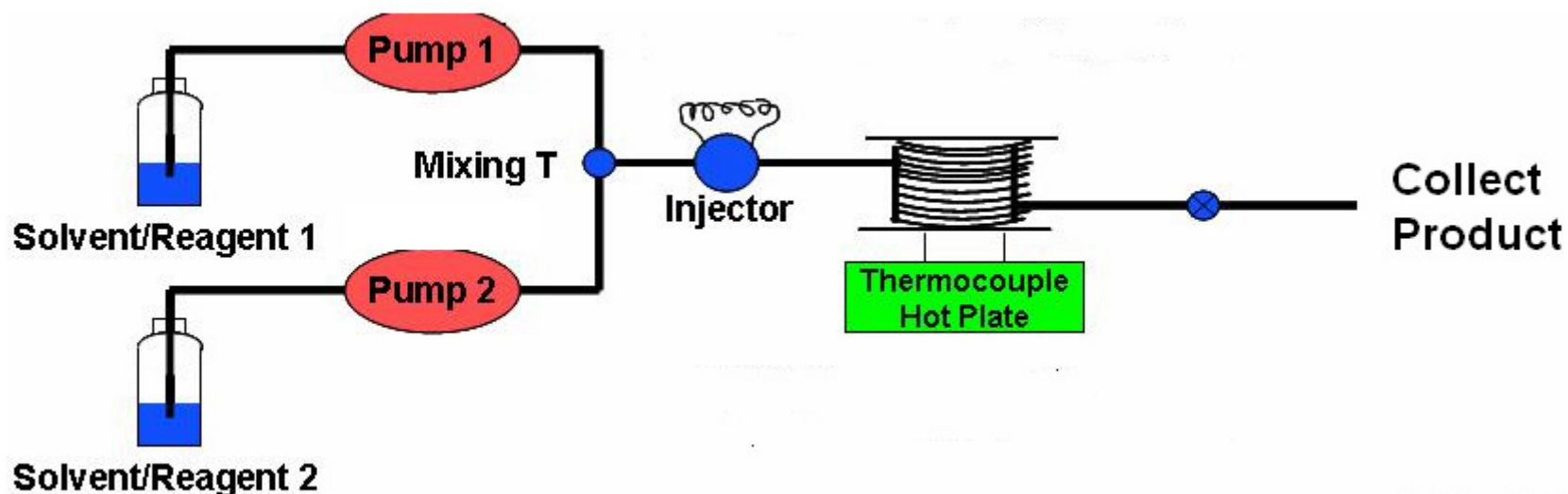


Batch vs. Flow

◆ Traditional Batch Chemistry



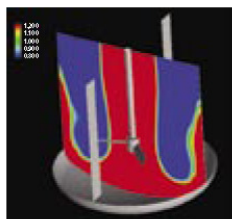
◆ Flow Chemistry - Chemistry run in a Flowing Stream





What are the Benefits of Flow?

◆ Excellent Mixing... Critical for Fast Reactions



Batch



Flow

 <chem>Nc1ccncn1</chem> + <chem>CC(C)(C)C(=O)N(Br)C(=O)N(Br)</chem> $\xrightarrow{\text{DMF / MeCN}}$ <chem>Nc1cc(Br)ncn1</chem> + <chem>Nc1c(Br)nc(Br)cn1</chem>		
Batch	60	40
Flow	99	1

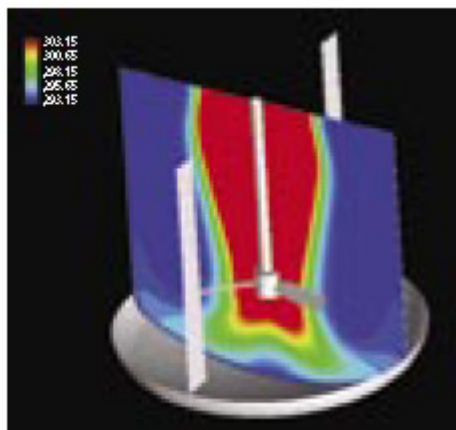


What are the Benefits of Flow?

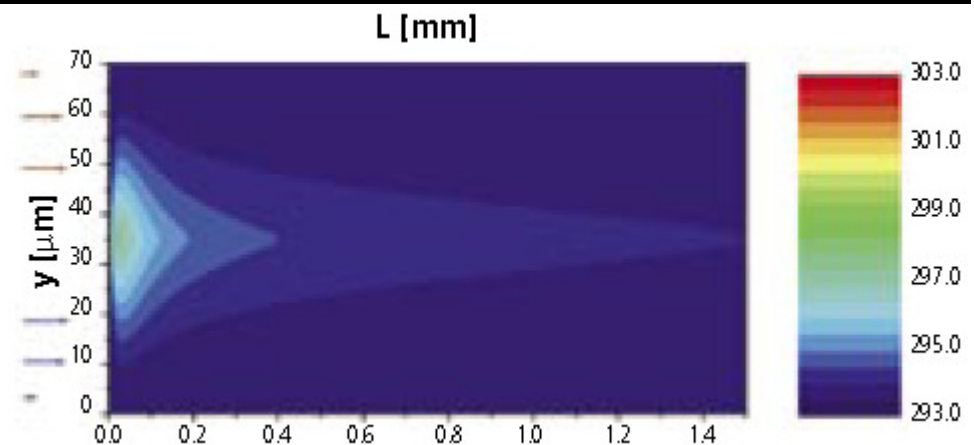
◆ Excellent Thermal Control

- High surface to volume area
- Heat loss figures under adiabatic conditions

Typical Flow Reactor	= $200\text{cm}^2\text{ cm}^{-3}$	10C=5 seconds
100ml Round Bottom Flask	= $1\text{cm}^2\text{ cm}^{-3}$	10C=2 minutes
1m ³ Plant Vessel	= $0.06\text{cm}^2\text{ cm}^{-3}$	10C=1 hours



Hot Spots

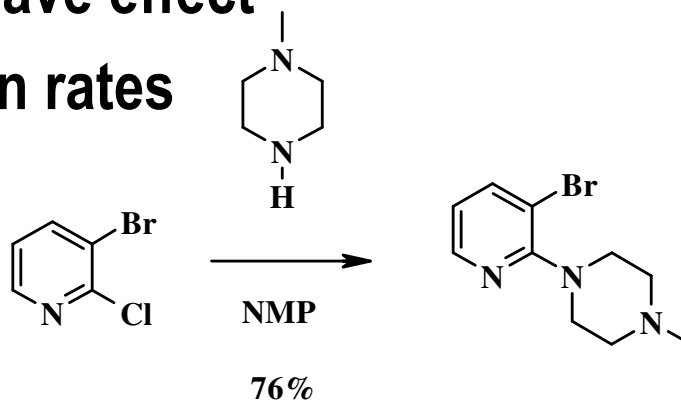


No Hot Spots



What are the Benefits of Flow?

- ◆ **Pressure Control**
- ◆ **Enables Suppression of Solvent Boiling Points**
 - Similar to microwave effect
 - Increased reaction rates

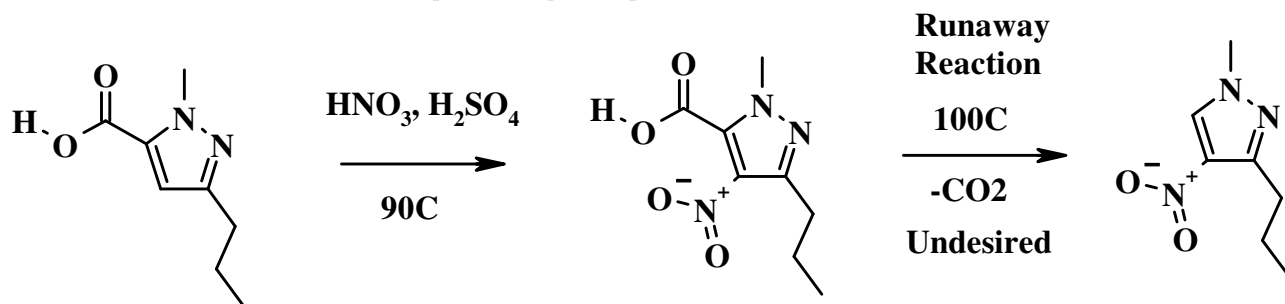


	Temperature	Conversion
Batch	200C	20%
Flow	260C	76%



What are the Benefits of Flow?

- ◆ **Tight Process Control**
- ◆ **Access to Forbidden Chemistries**
- ◆ **Sildenafil (Viagra) Nitration**



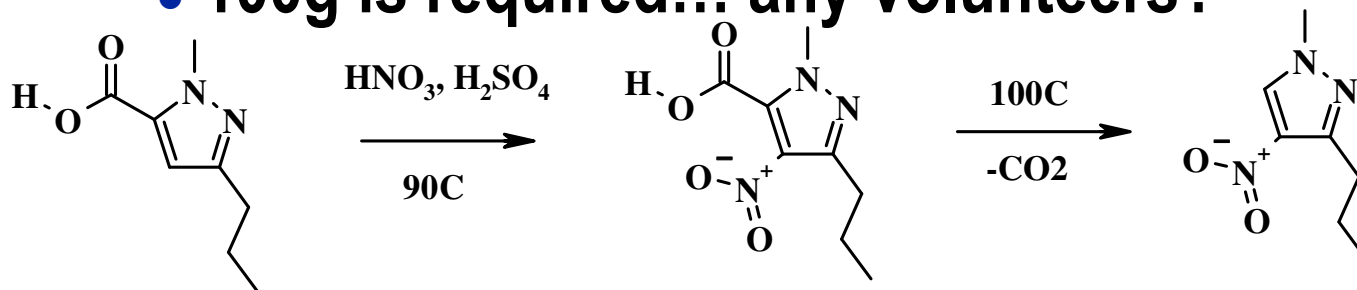
- ◆ **Extremely Exothermic Reactions** - Batch process must be run at 50C over 24hrs with v.slow c. HNO_3 addition. If exotherm exceeds $>100\text{C}$ reaction runs away and detonates
- ◆ Flow reaction can be run at 90C in 30min due to ability to dissipate exotherm safely



What are the Benefits of Flow?

◆ Scale-up considerations?... Minimized

- Flow throughputs are measured as a function of time
- 100g is required... any volunteers?

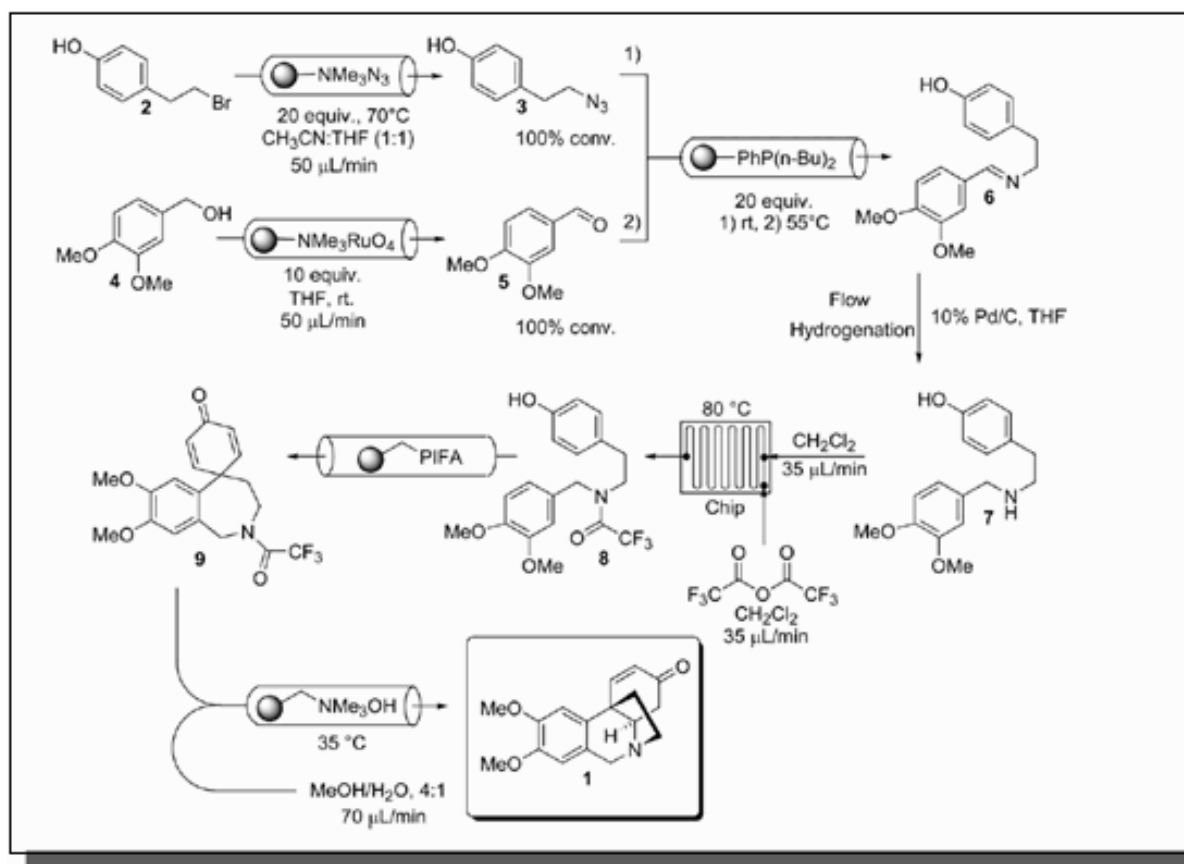


Scale	Active Chemistry	Reaction Temp/Time	Throughput in 24hr	Process Development
1000ml Batch	100g	50C / 24hr	=100g	YES!
1ml Flow Cell	0.1g	90C / 30 minutes	= 132g	Minimized



What are the Benefits of Flow?

- ◆ Potential to telescope multiple step processes...



Ley, et al. Chem Comm 2006 2566



Key Applications for Drug Discovery

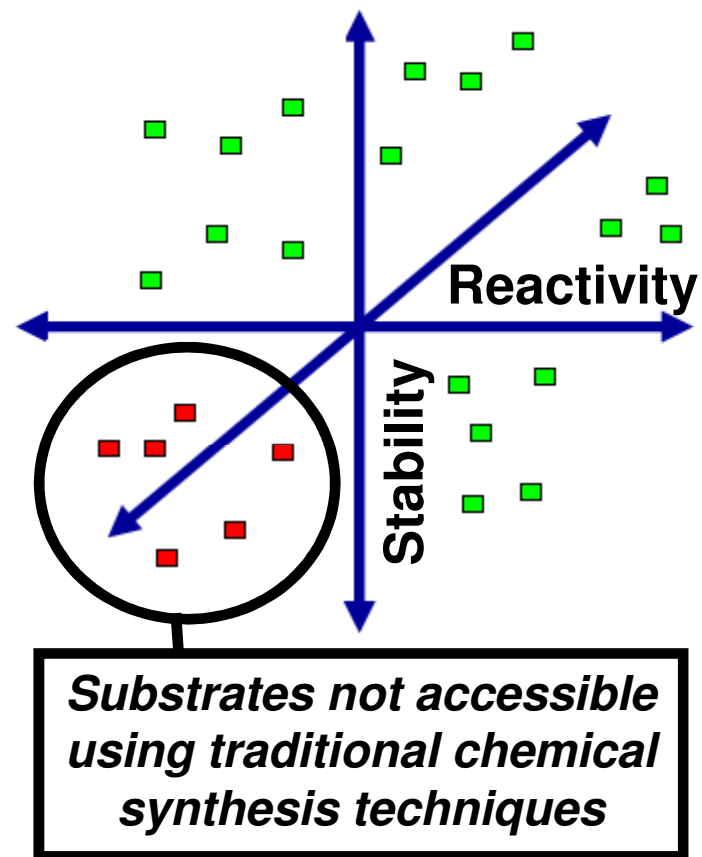
◆ Discovery - Expanding Chemical Space

- Forbidden Chemistries
- Extended Temperature Ranges
- Advantageous Kinetics

◆ Process - Enabling Discovery Chemistry

- High-energy chemistry (azides etc.)
- Microwave chemistry
- H3 Hydrogenations
- Flow Chemistry

◆ Early implementation of flow chemistry can significantly ease the transitions from Discovery to Process

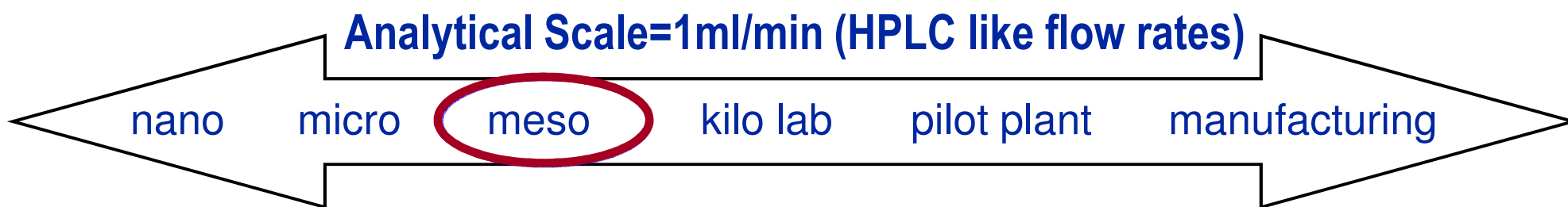




Flow Chemistry Limitations

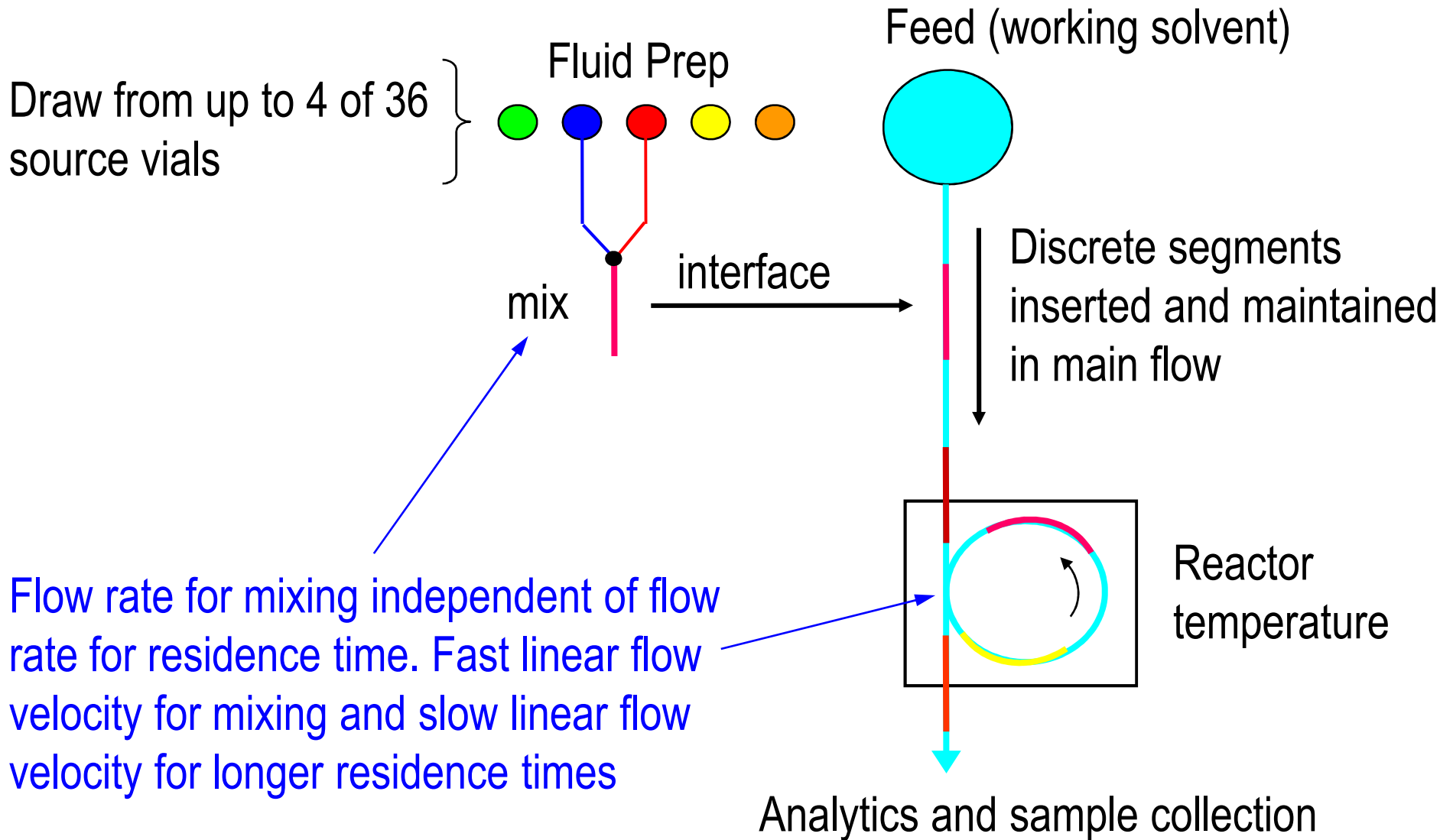
- ◆ Emerging Technology (at small scale)
- ◆ Suspensions
- ◆ Material Requirements
- ◆ Time Requirements

- ◆ Collaboration with Wyeth and an external partner





Conjure Schematic



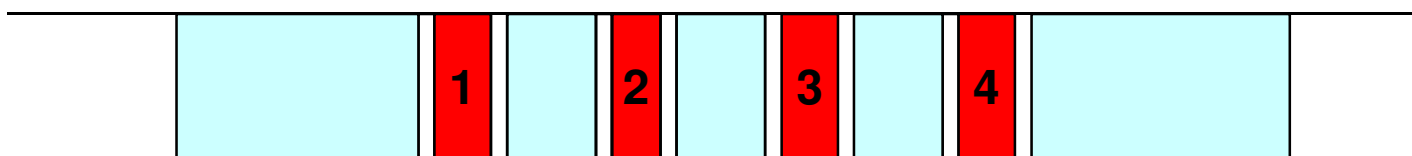


Conjure Square-Wave Reaction Segments

- ◆ Total Segment Size 150-500uL. Typically 300uL, 5mg Substrate

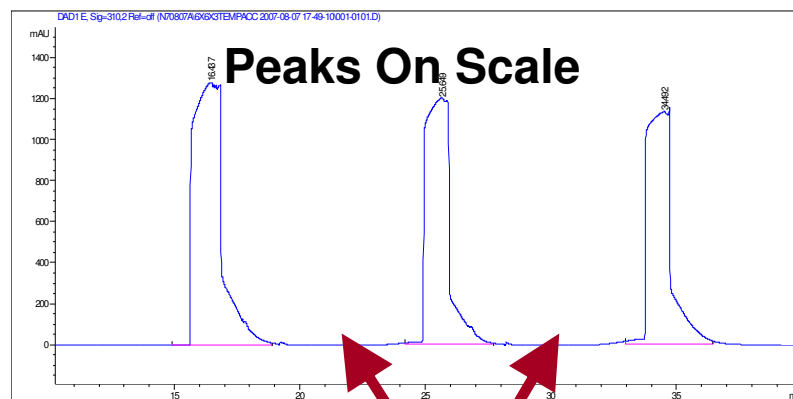


- ◆ Multiple Segments Active Within Reactor (up to 4)



Bubble or UV Detection

Each peak is a 5mg reaction
Exact Stoichiometry
Exact Reaction Time
Exact Temperature



No Dead Reckoning

- ◆ No contamination between reaction segments, key.



Conjure System Overview

◆ Prototype System Delivered 2Q 2007

◆ 0.75mm Diameter Throughout

◆ Feed Module

- 2 Feed Solvents
- Dual Head HPLC Pumps
- Inert Seals
- 2500psi Limit
- Solvent Degasser
- Flow Rate 0.001-2ml/min

◆ Fluid Prep Module

- 4 Channel Input
- 40-Vial Carousel
- 150-500uL Segments

◆ Reactor Module

- Hastelloy
- -30-300°C Range
- 2ml (or 5ml) Volume

◆ Conjure Analytical Interface

- Bubble Segment Detection
- UV Segment Analysis
- 1:1 -1:200 Dilution Potential

◆ Analysis Devices

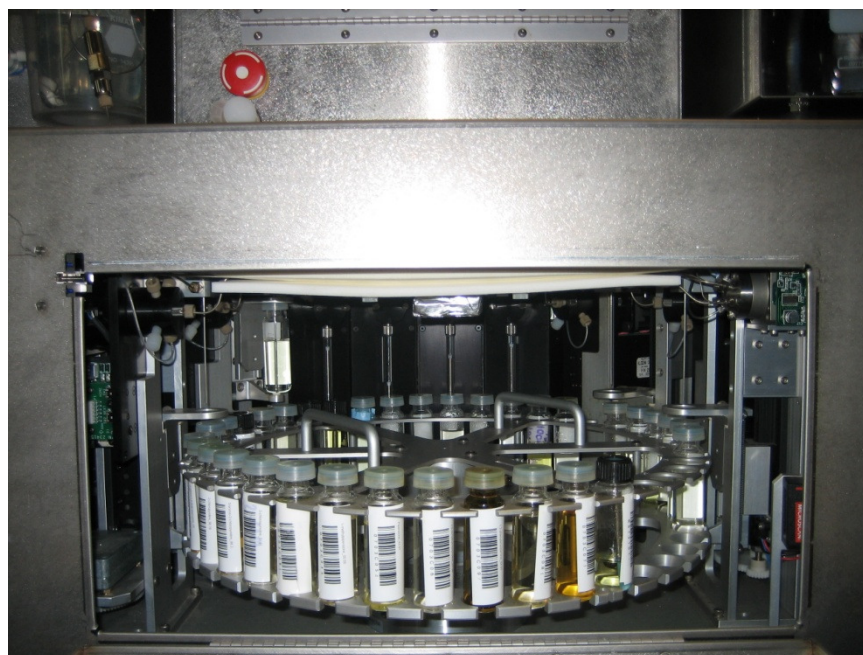
- HPLC/LC/MS/ELSD

◆ Fraction Collector

- UV/MS/AUX/Bubble Triggered



Conjure Hardware Video Overview

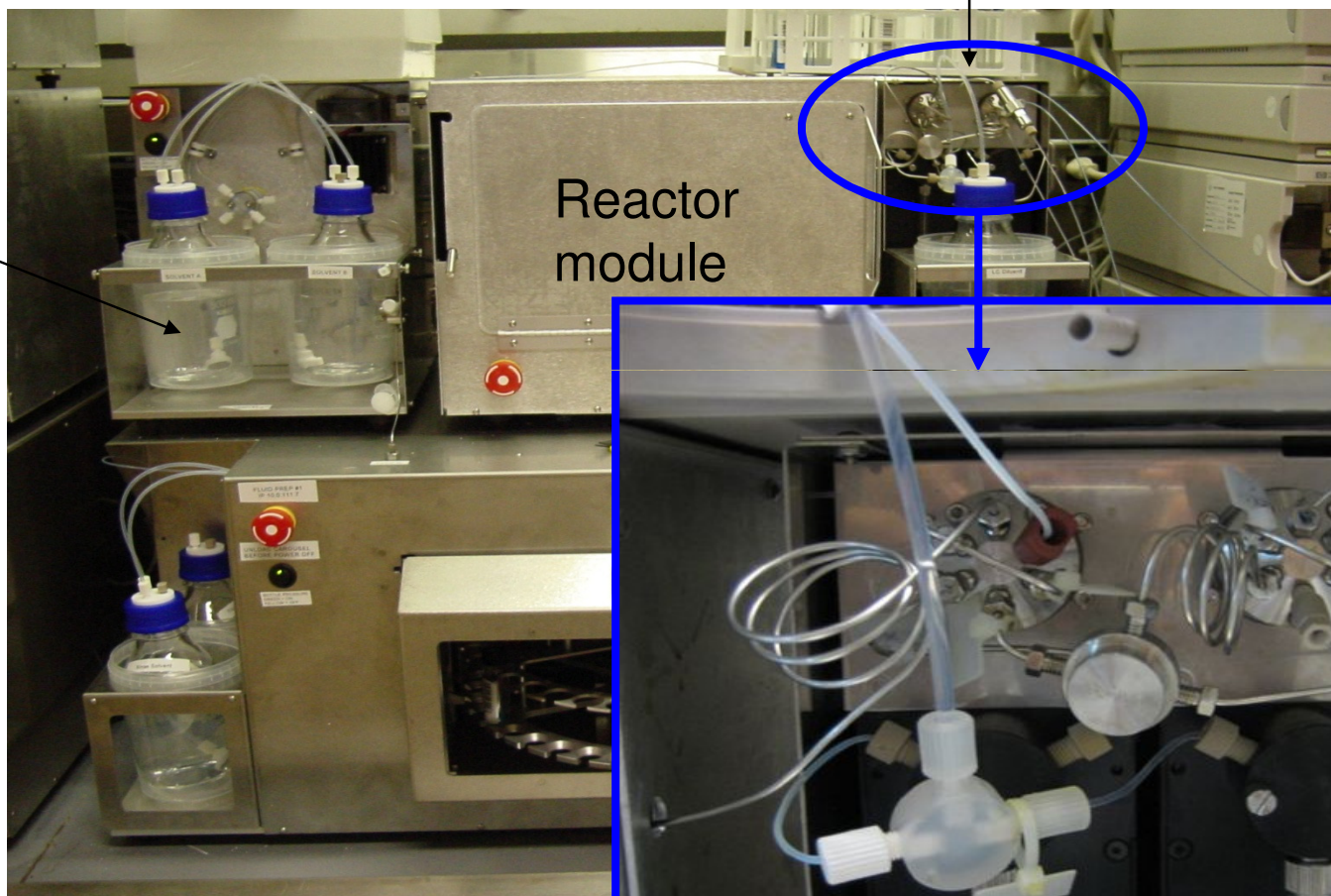




Heart-cut Sampling and Dilution

Sample dilutor module

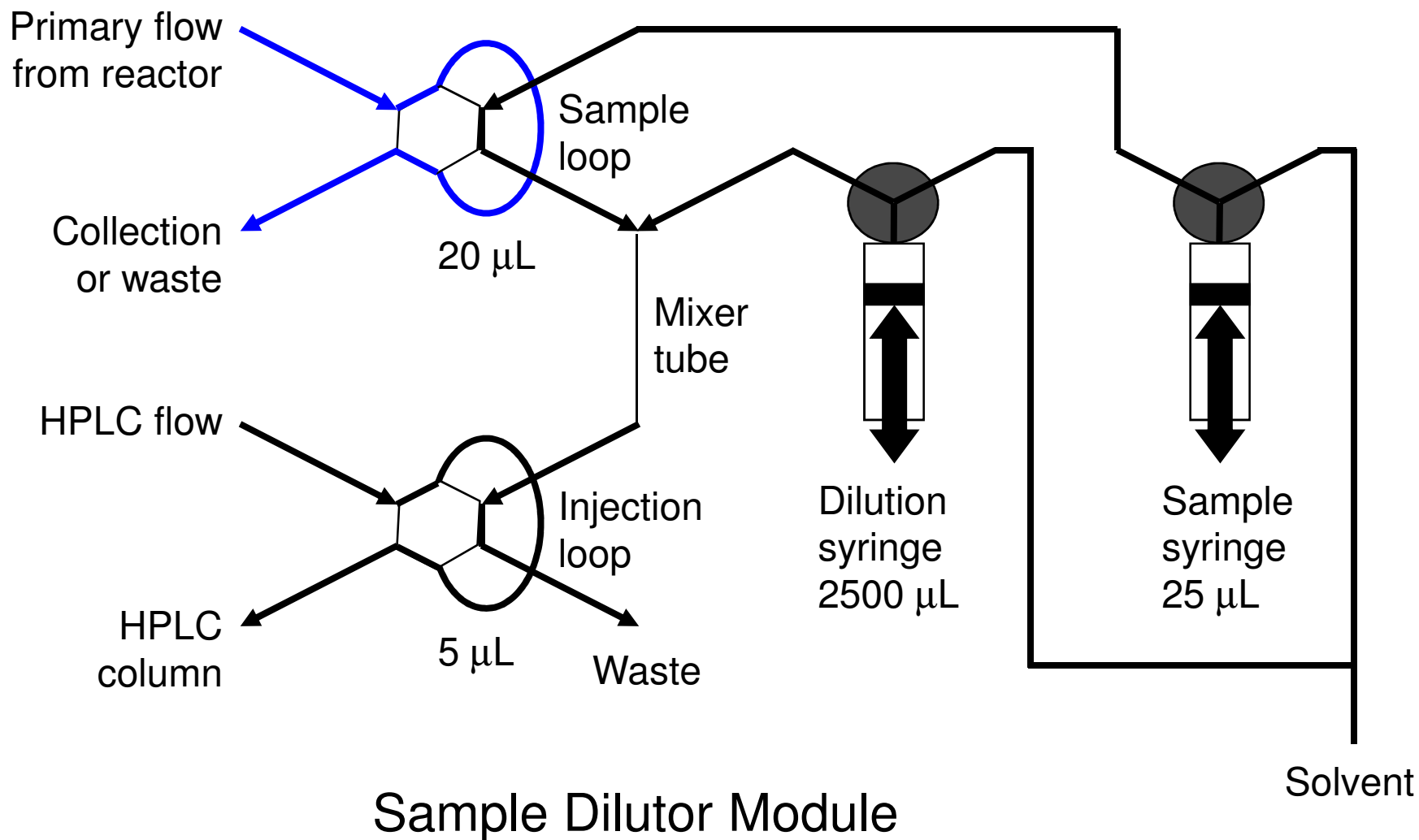
Feed module



Fluid

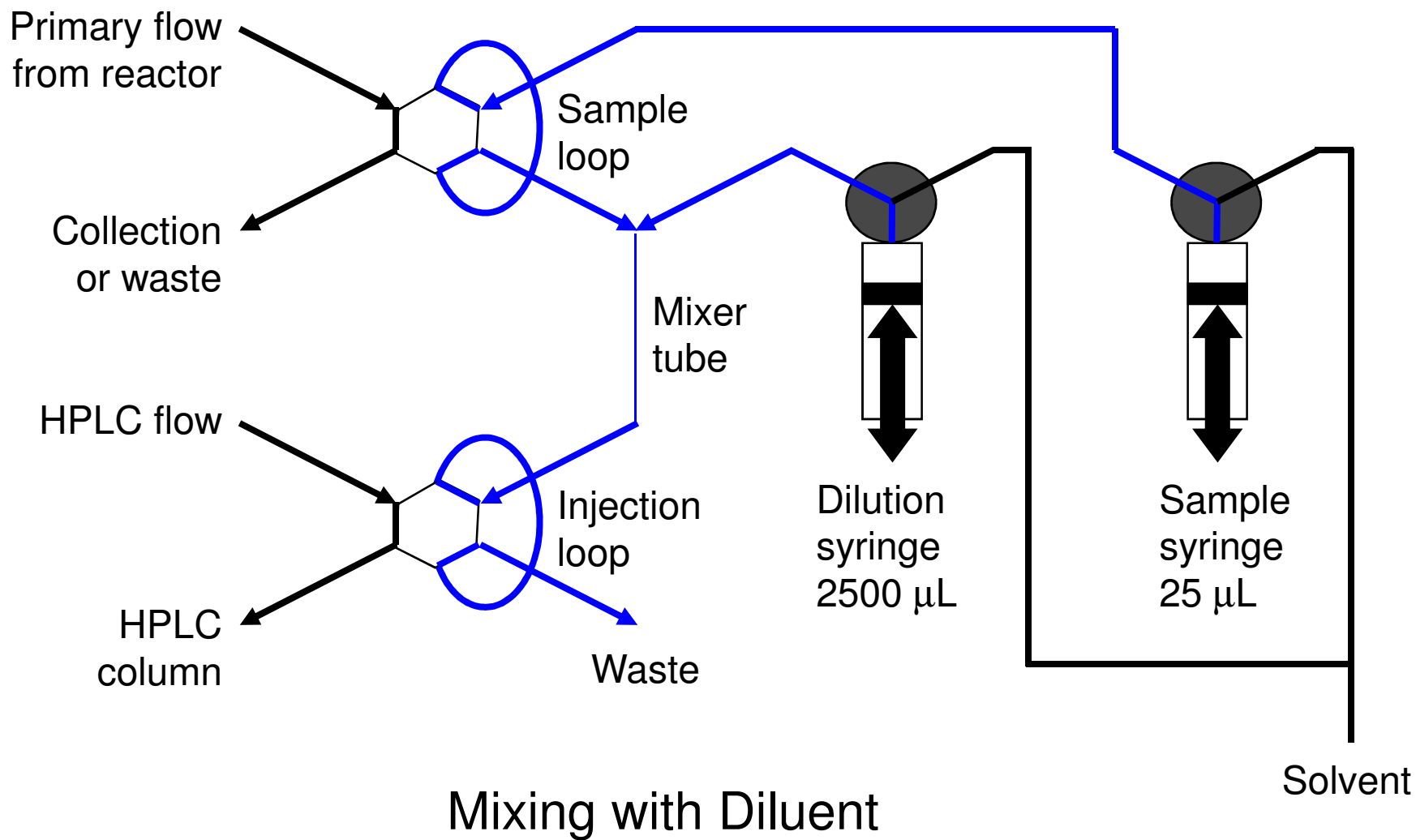


Sampling "Heart Cuts" from the Flowing Segments



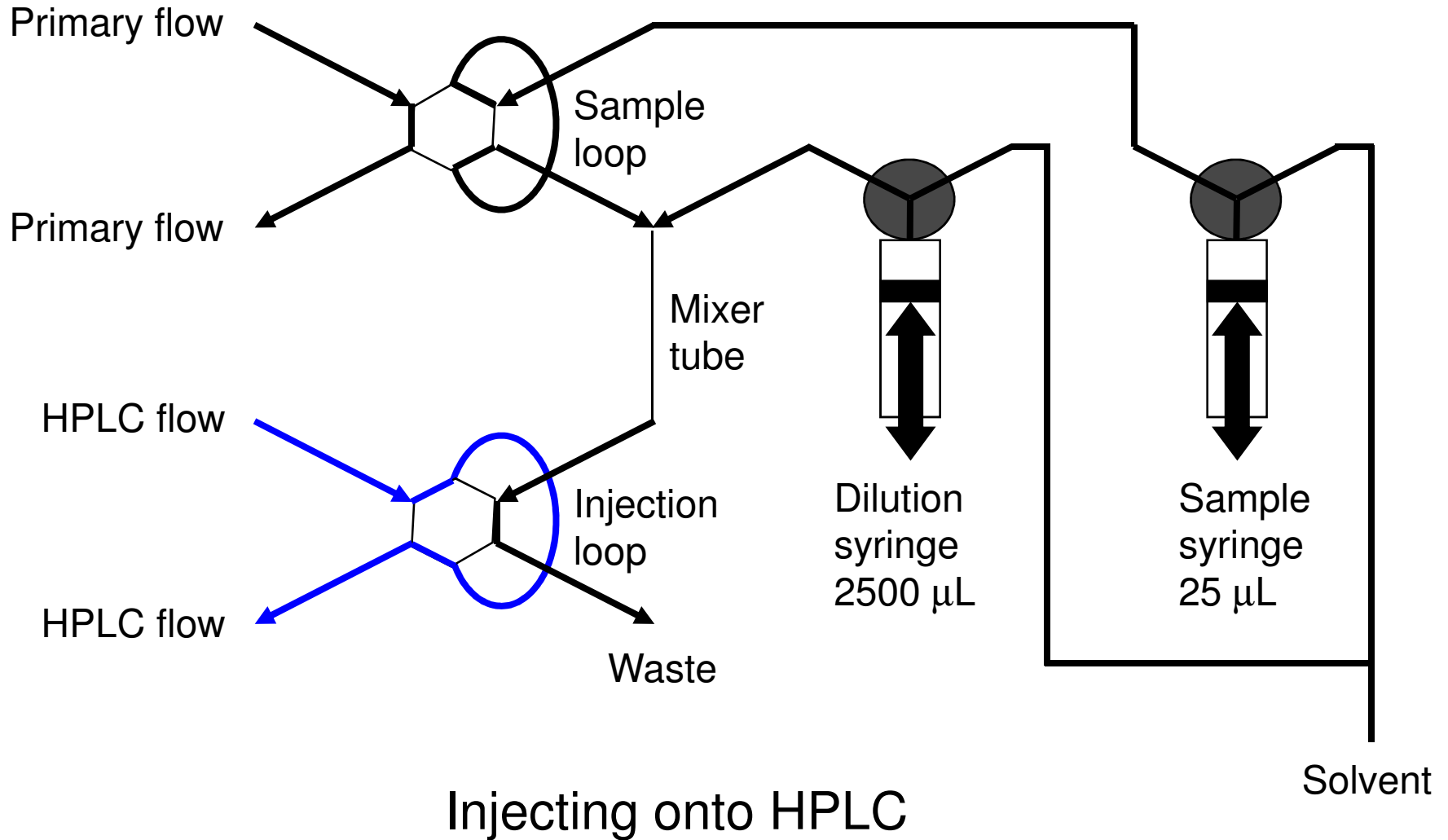


Sampling "Heart Cuts" from the Flowing Segments





Sampling "Heart Cuts" from the Flowing Segments

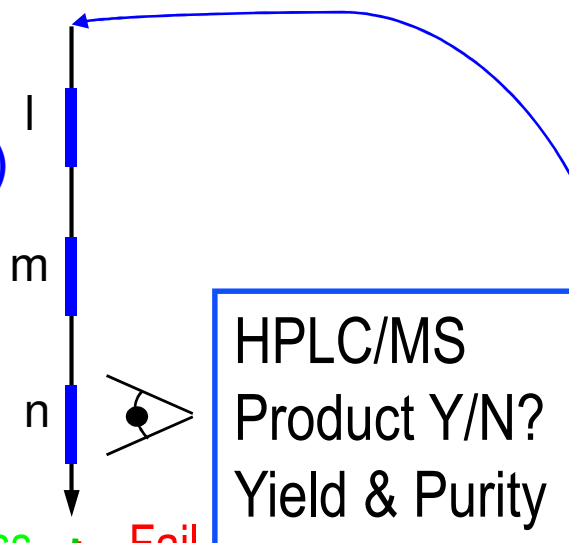




Adding Intelligence to Conjure Flow Reactor

One-size-fits-all initial conditions

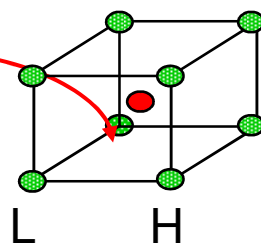
Library elements (Discovery)
Reaction Conditions (Process)
(flowing segments)



Pass Fail

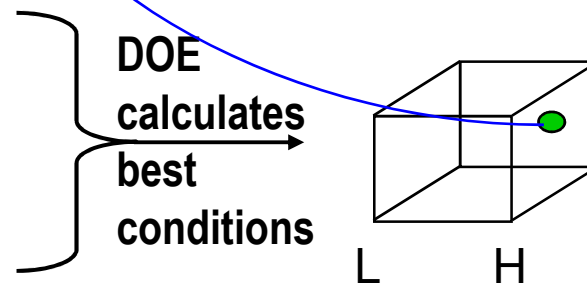
HPLC/MS
Product Y/N?
Yield & Purity

Collect via Fraction Collector (Discovery)
Prep via repetitive segments (Process)



Library Synthesis (Discovery)
Test new conditions optimized
for this library element

Singleton Synthesis (Process)
Test new conditions for this
reagent element



DOE
calculates
best
conditions

Greater percentage of
successful library elements and
easier purifications than from
single condition batch arrays

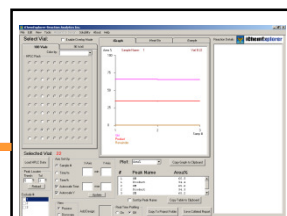
Vary prescribed reaction parameters around initial
conditions. Automatically done based on statistical
optimization tools such as Simplex and DOE.



Conjure Software Workflow

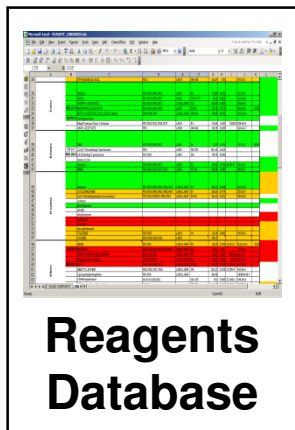
Temp	Equivalents	Yield
100	1	3.41
100	2	5.37
100	3	6.42
150	1	25.29
150	2	35.38
150	3	40.73
150	2	35.41
150	2	35.07
200	1	51.18
200	2	63.25
200	3	66.6

DOE Software

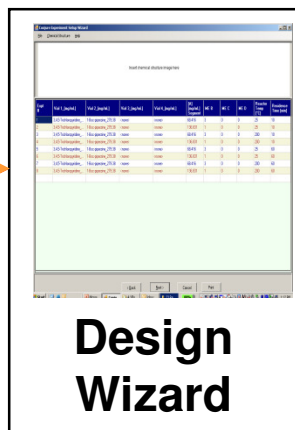


Data Collation and Interpretation

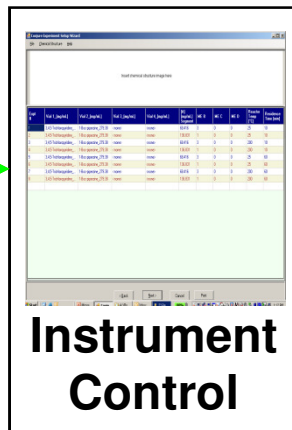
Closing this loop will enable automated reaction optimization POC by 2Q08



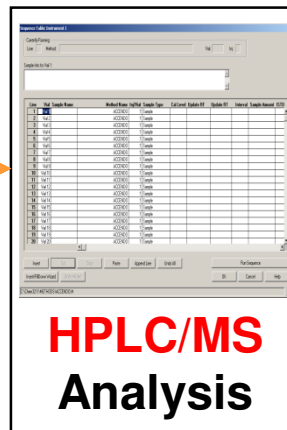
Reagents Database



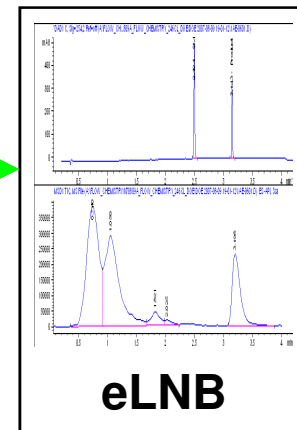
Design Wizard



Instrument Control



HPLC/MS Analysis

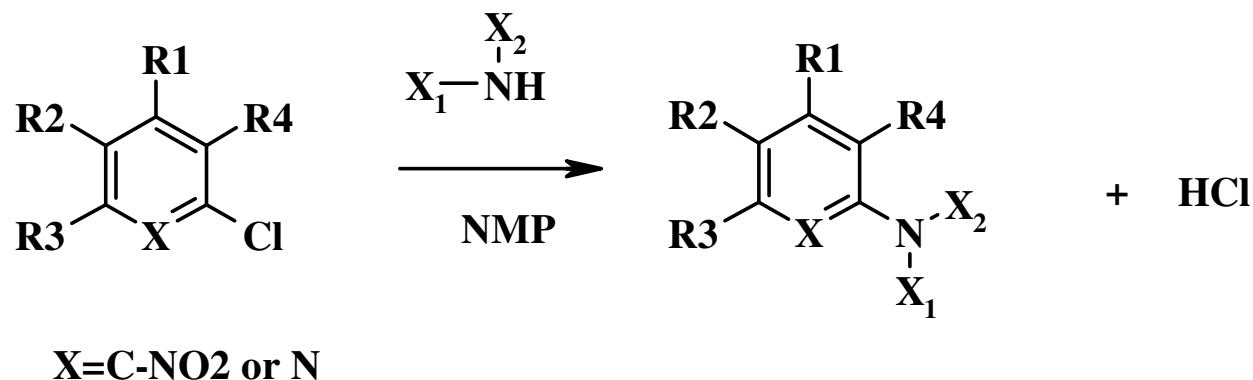


eLNB





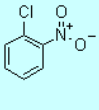
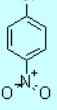
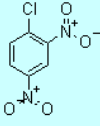


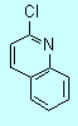
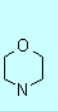
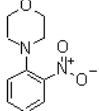
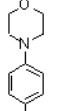
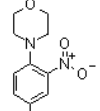
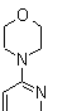
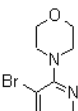
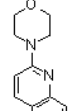
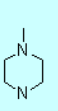
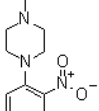
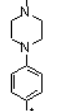
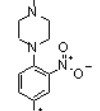
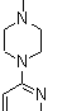
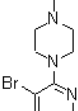
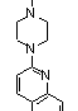
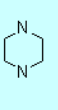
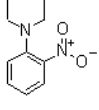
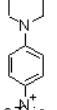
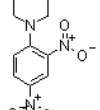
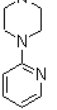
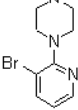
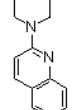
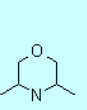
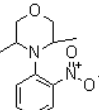
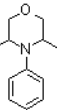
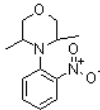
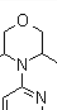
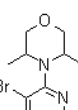
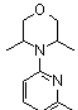
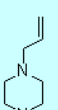
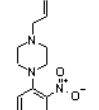
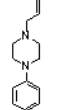
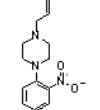
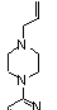
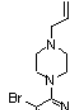
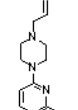
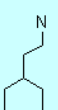
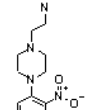
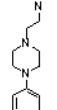
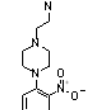
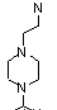
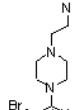
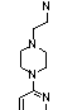
Demonstration S_NAr Library Preparation



- ◆ 6 Amines x 6 Aryls = 36 Library
- ◆ 0.5M Solutions 100uL Each
- ◆ Total Segment Volume = 300uL (50+200+50)
- ◆ 3 Temperatures 150°C, 200°C, 250°C
- ◆ 10 Minute Reaction Time
- ◆ NMP Carrier Solvent
- ◆ 108 Experiments = 15 hours Run
- ◆ On-line HPLC/UV/MS/ELSD Analysis



Demonstration S_NAr Library Preparation



150-250°C in-situ Yield by 254nm HPLC/MS Analysis

150°C - 42%

200°C - 61%

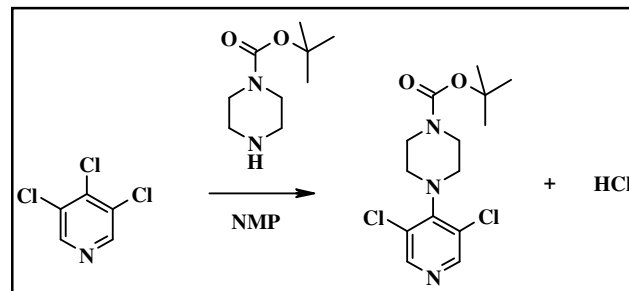
250°C - 22%

Overall Library Success Rate : 88%



Demonstration Singleton DOE Optimisation for Process

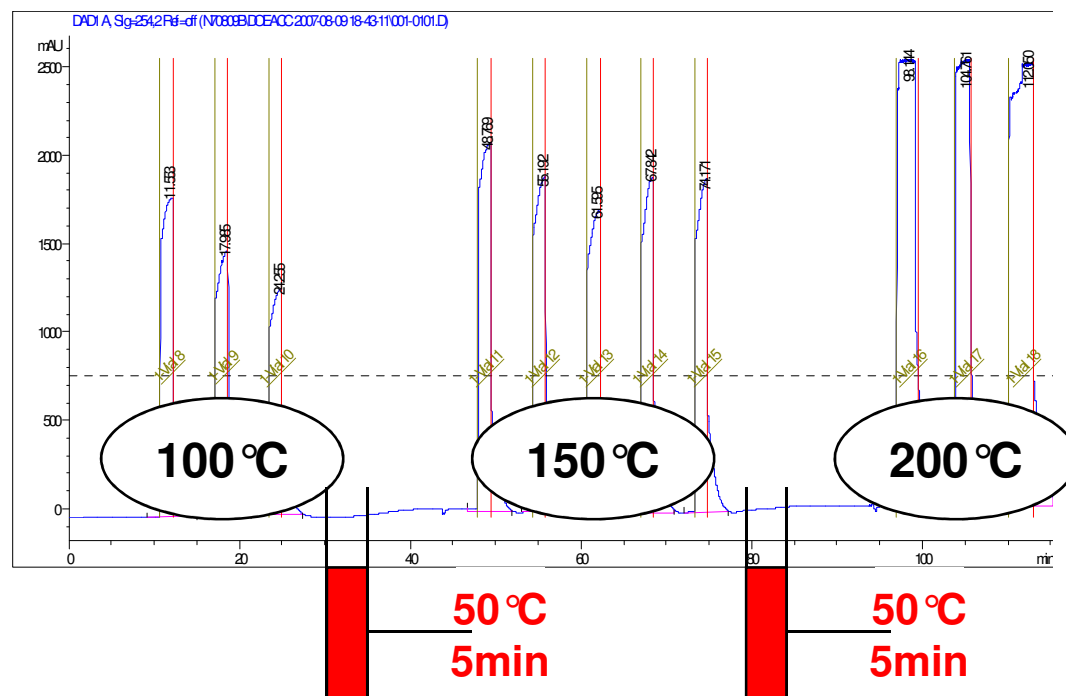
- ◆ **Modde DOE Software**
- ◆ **3 Level 2 Factor Design**
 - Temp – 100°C, 150°C, 200 °C
 - Equivalents – 1eq. 2eq. 3eq.



- ◆ **11 Reactions 13-20mg each**
 - 3 Centre Points

◆ **Total = 184mg**

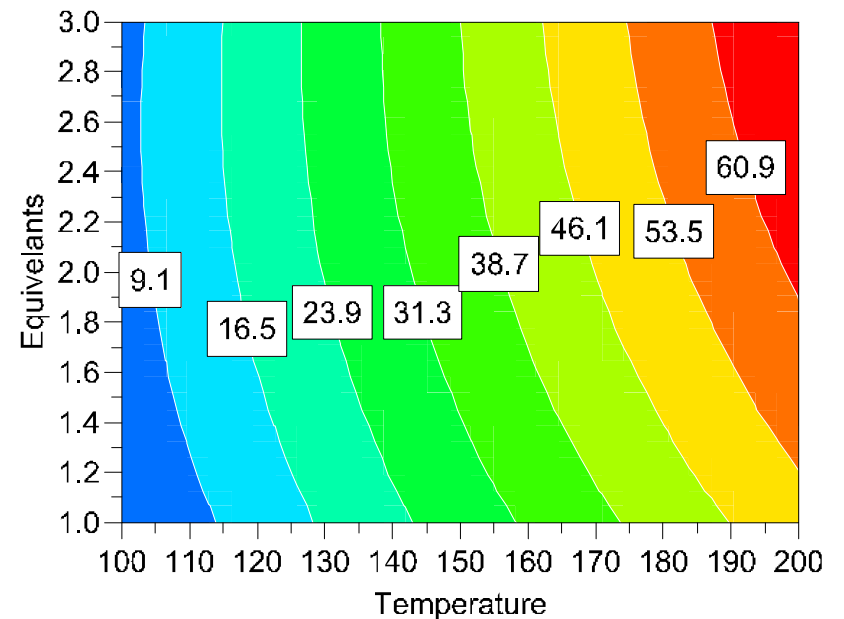
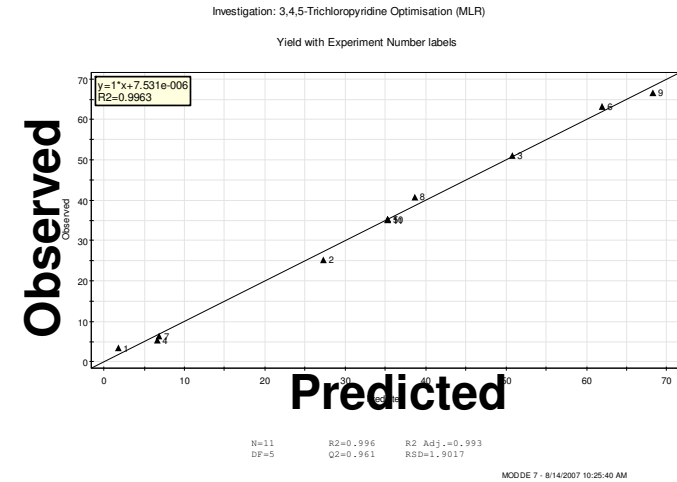
◆ **Total Time = 116 minutes**





Demonstration Singleton DOE Optimisation for Process

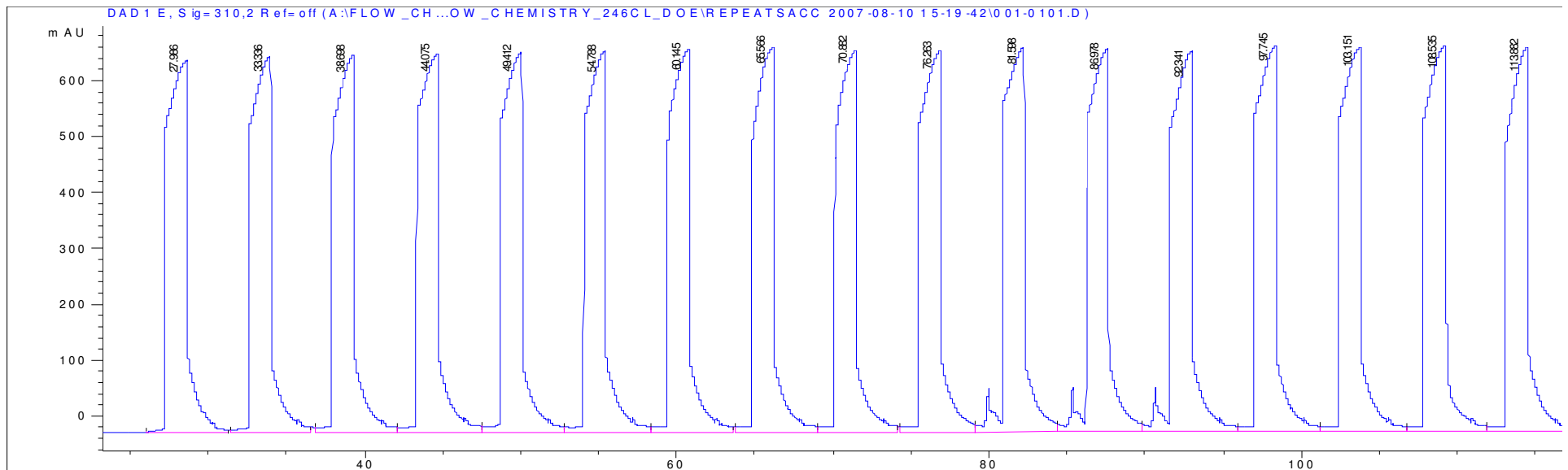
Temp	Equivalents	Yield
100	1	3.41
100	2	5.37
100	3	6.42
150	1	25.29
150	2	35.38
150	3	40.73
150	2	35.41
150	2	35.07
200	1	51.18
200	2	63.25
200	3	66.6





Production Mode

- ◆ Reproduce automatically optimized chemistry
- ◆ Scale out not up as a function of time



- | | |
|----------|-------|
| ◆ 10 min | 500mg |
| ◆ 1hour | 3g |
| ◆ 1day | 72g |
| ◆ 1week | 0.5kg |



Conclusions

◆ Demonstrated

- Preparation of discreet square wave reaction segments
- LC/MS sampling and integration
- Library optimizations (Discovery)
- Singleton optimization (Process)
- Singleton scale-out (Process)

◆ Next steps

- Close DOE loop for total self optimization
- Introduce gaseous reagents
- Multiple step synthesis
- Target 100-300 reactions per day



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Questions
