Preparation of Active Pharmaceutical Ingredients (API) by Continuous Processing

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Why Use Advanced Flow Reactors?

High Throughput Experimentation For…

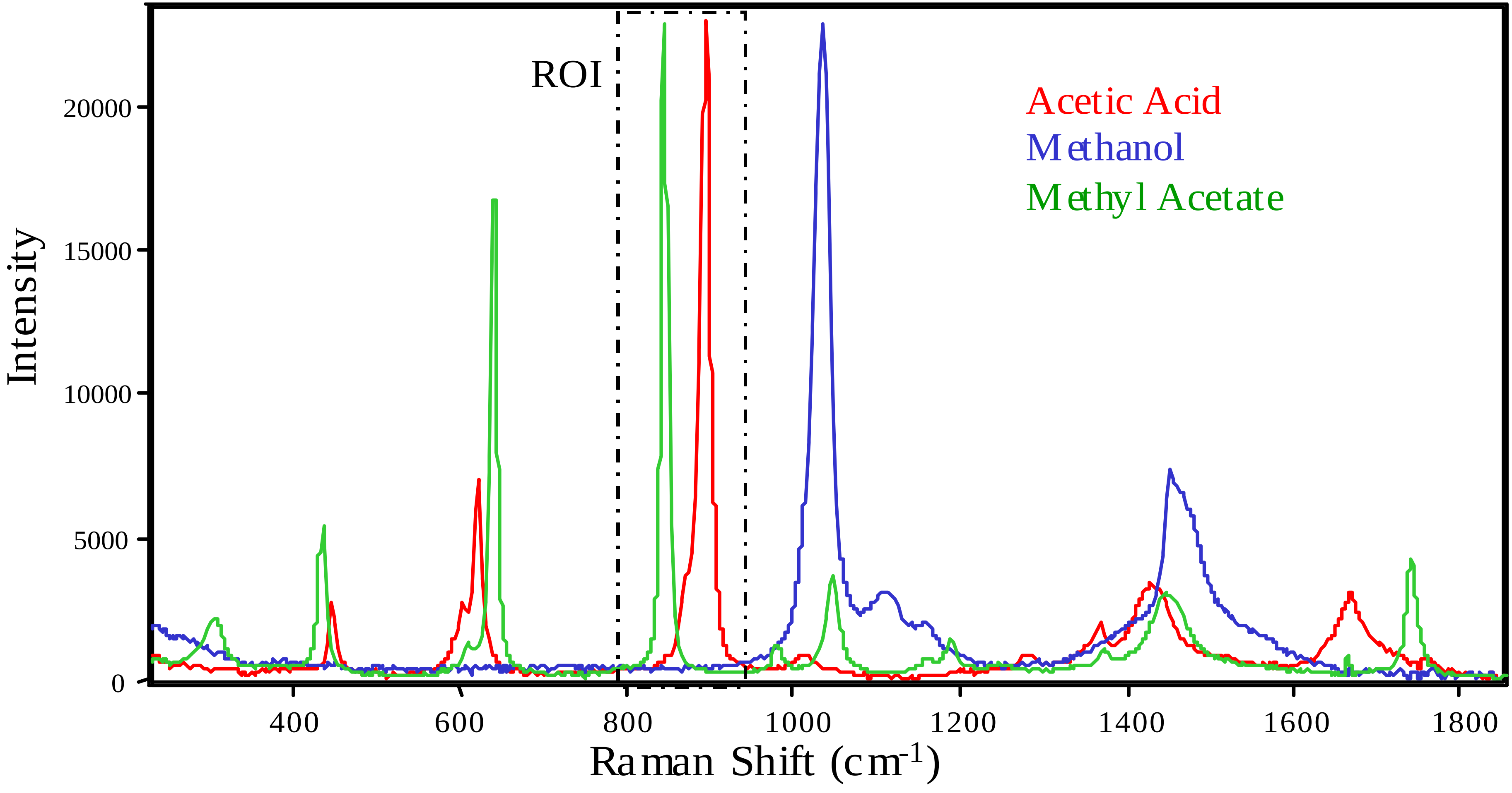
- Discovery and screening
- Process development
- Process optimization
- Process control
- Production?
  - Eliminate chemical engineering production problems related to scaling up batch systems?
  - Increase production through use of many parallel microreactors to achieve volume?

Challenges To Using AF Reactors

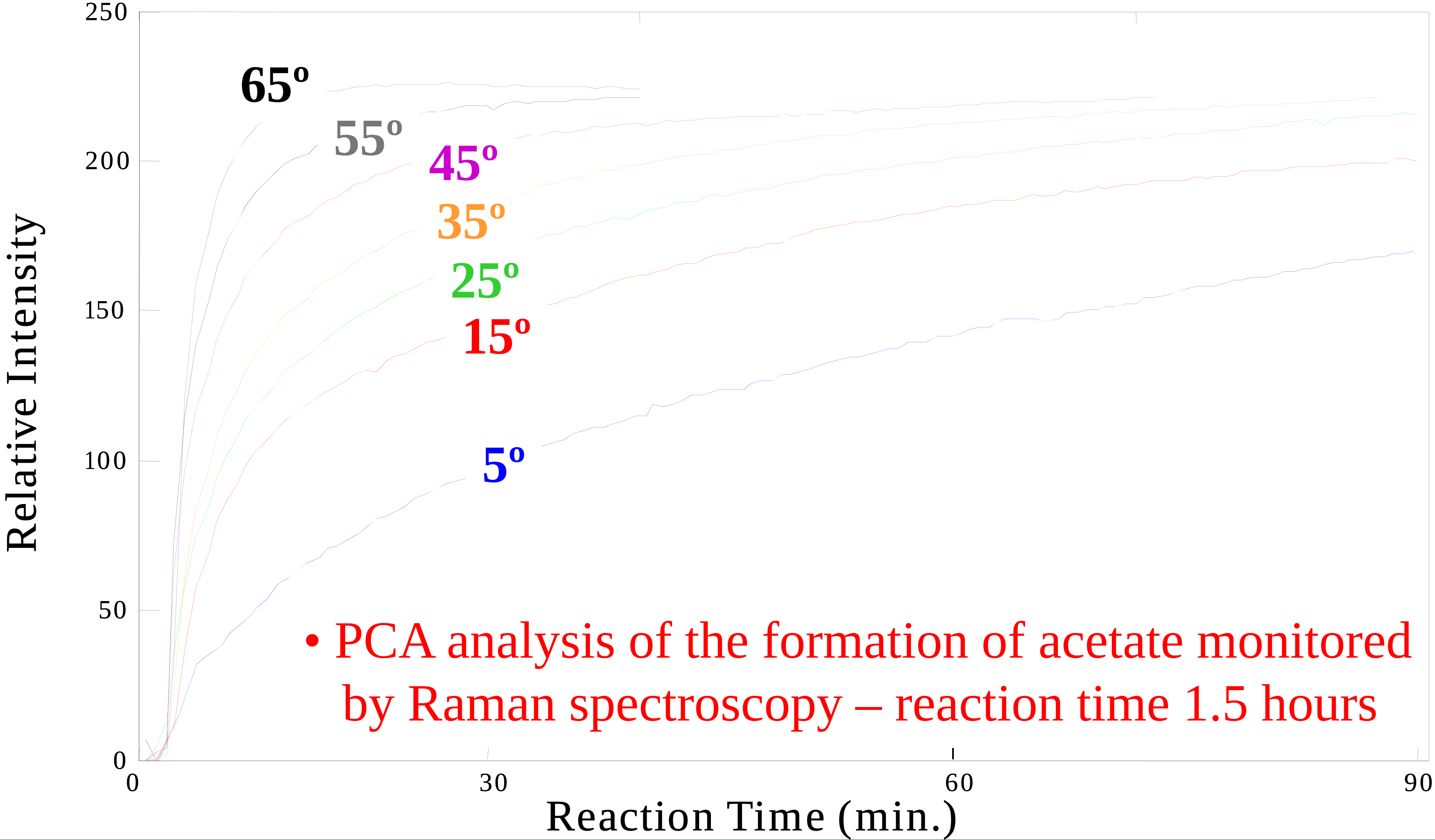
- EDUCATION!!!!!!
- Interfacing modular units
- Sampling and screening
- Analytical characterization
- Data handling
- Process modeling and feed back control (particularly if they are used for production)

Example: Esterification of Methanol

Acetic Acid + Methanol $\xrightarrow{H^+}$ Methyl Acetate + H_2O

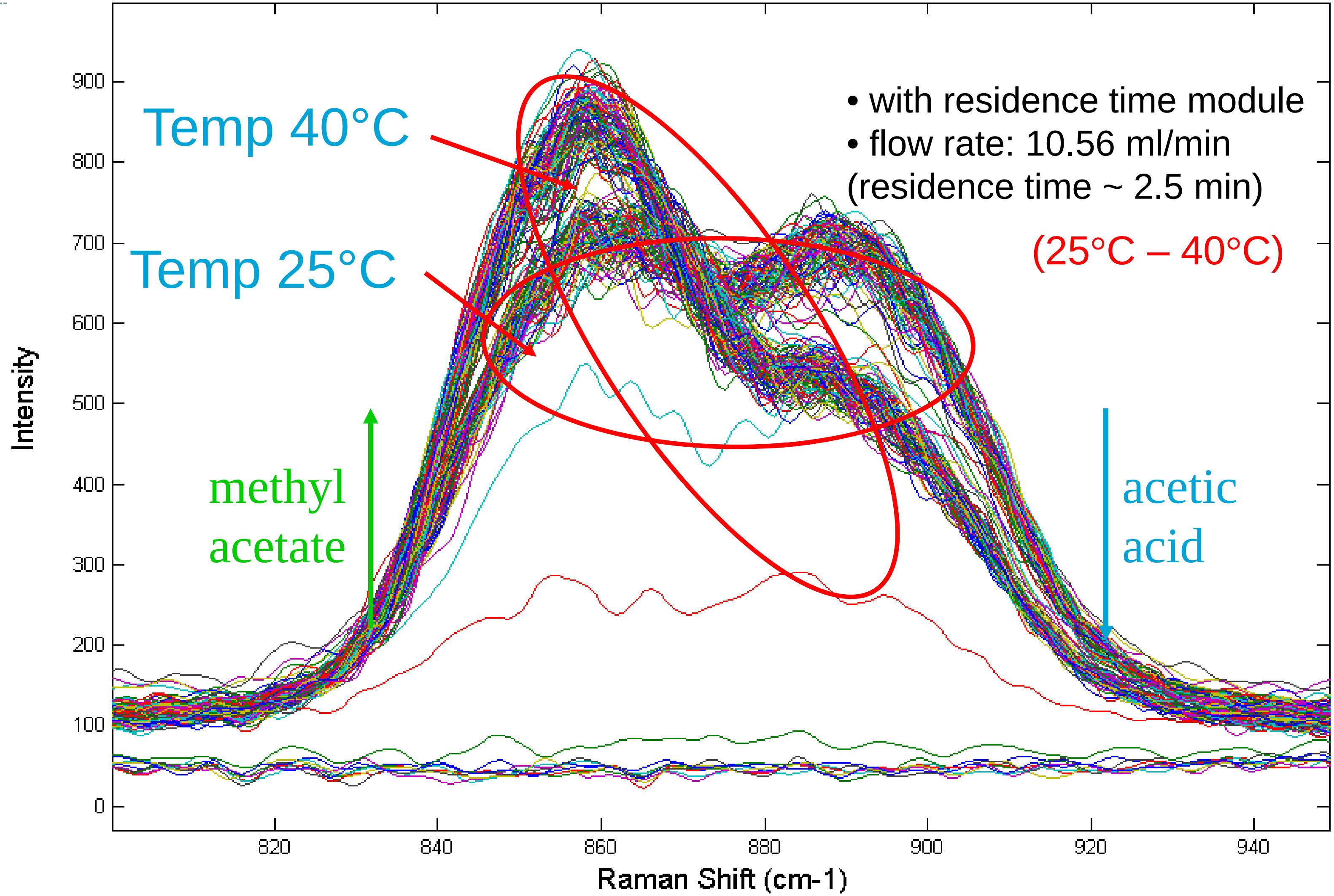


Batch Runs at Different Temperatures



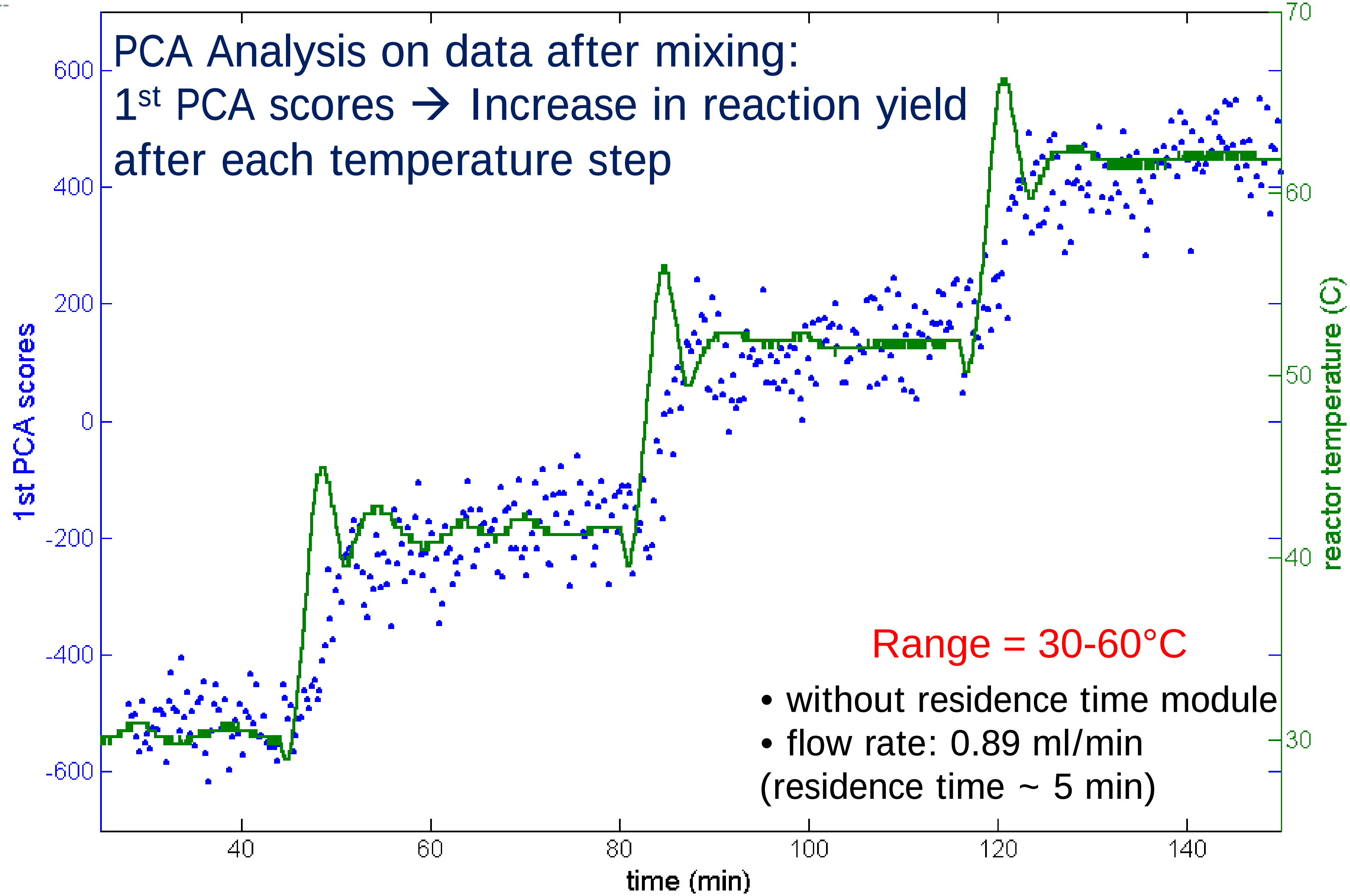
- PCA analysis of the formation of acetate monitored by Raman spectroscopy – reaction time 1.5 hours

Continuous Rxn. with Temp. Step



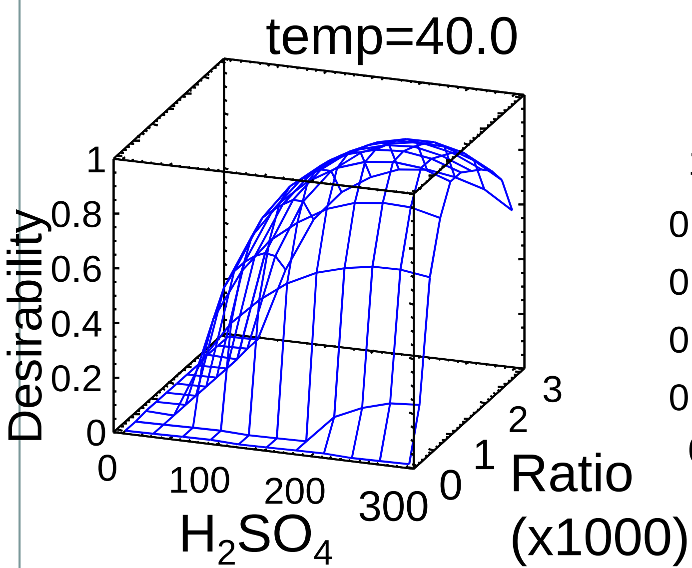
• With control of flow reactor parameters and analytics, fast optimization is possible

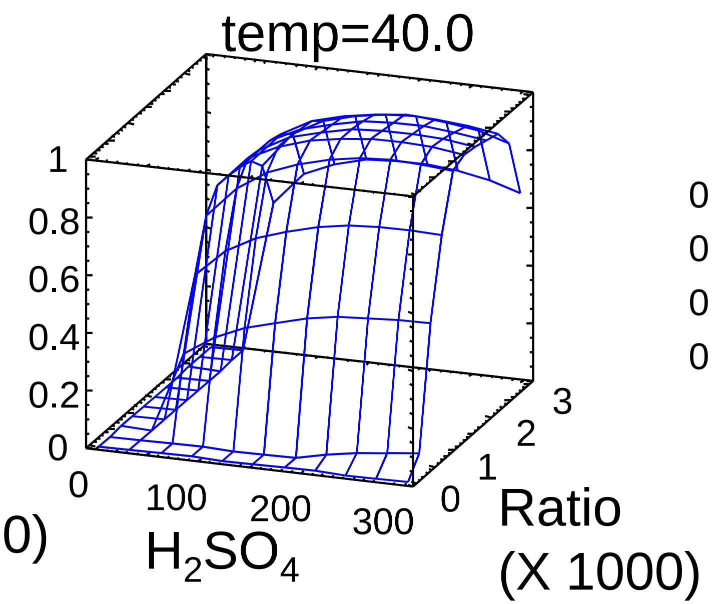
Product Yield vs. Temperature

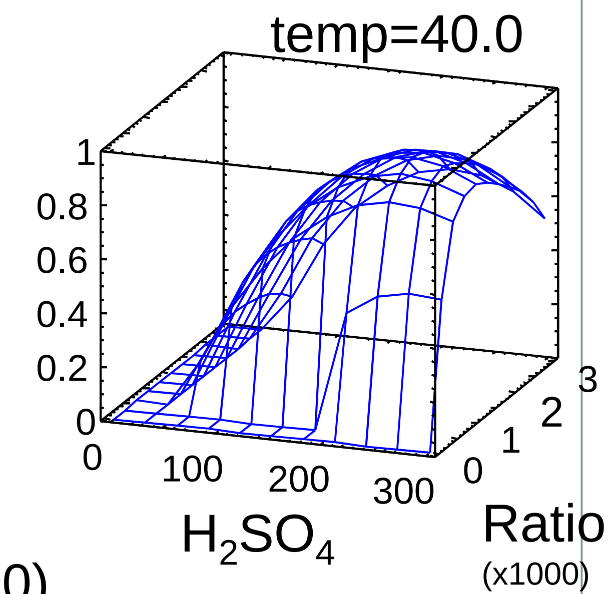


• 2 weeks of batch data reproduced in less than three hours by continuous flow

Result: Estimated Response Surfaces







50% Time - 50% Product
- Optimum response
  - H_2SO_4= 0.230 ml
  - Ratio= 1.35 Ac + 1.65 MeOH
  - Temp = 45ºC

20% Time - 80% Product
- Optimum response
  - H_2SO_4= 0.258 ml
  - Ratio= 1.34 Ac+1.66 MeOH
  - Temp = 46ºC

80% Time - 20% Product
- Optimum response
  - H_2SO_4= 0.141 ml
  - Ratio= 1.45 Ac + 1.55 MeOH
  - Temp = 51.4ºC

- continuous reactors w/analytics allow for fast optimization of design space

Analysis of Continuous Reactors

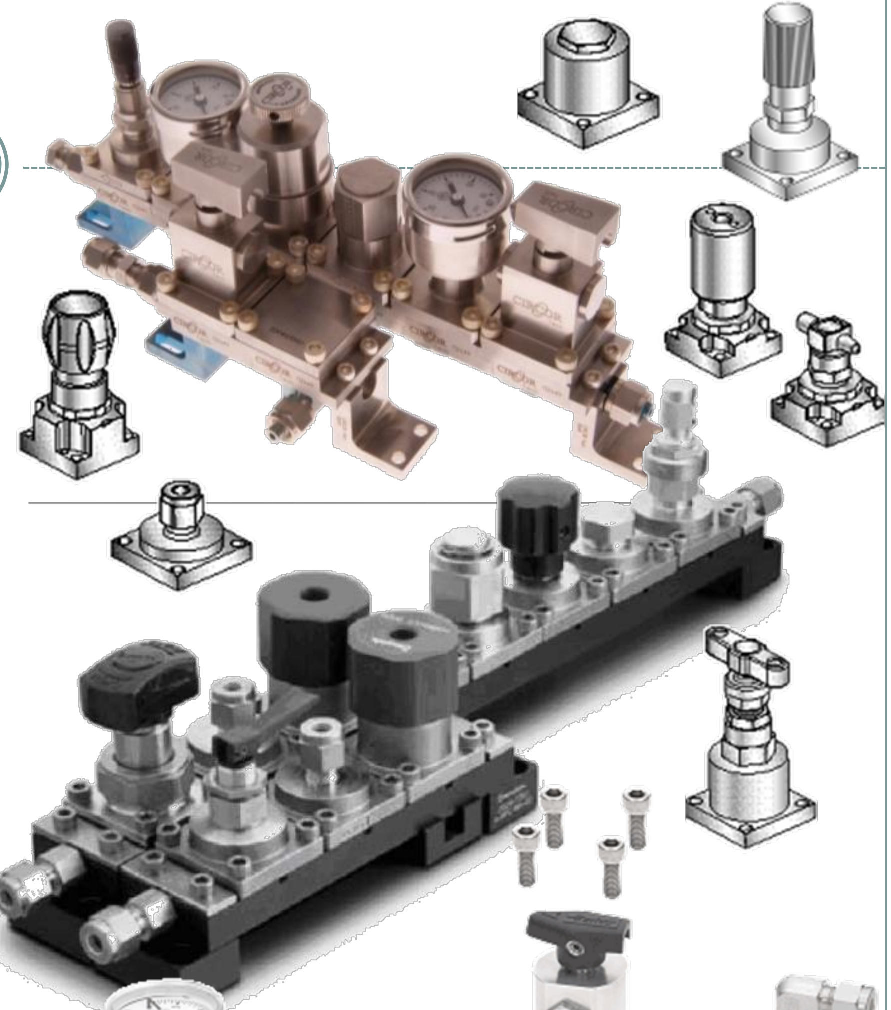
- Problems with performing online measurements
  - Gas formation in sample lines
  - Temperature change before reaching analyzer
  - Phase change between reactor and analyzer
  - Sensor placement at optimal position
  - Automated flow and pressure control
- Most PAT problems are due to sampling not measurement device
- Need better systems to sample processes

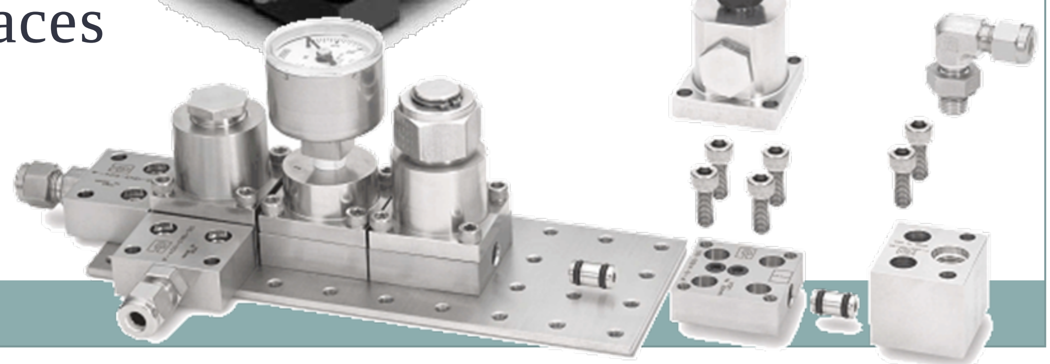
Application of Sampling Systems To Microreactors

- EXAMPLE OF BRINGING ANALYTICS TO A PROCESS AND THE CHALLENGES WITH INTEGRATING THEM

What is NeSSI?

- Industry-driven effort to define and promote a new standardized alternative to sample conditioning systems for analyzers and sensors
  - Standard fluidic interface for modular surface-mount components
    - ISA SP76
  - Standard wiring and communications interfaces
  - Standard platform for micro analytics

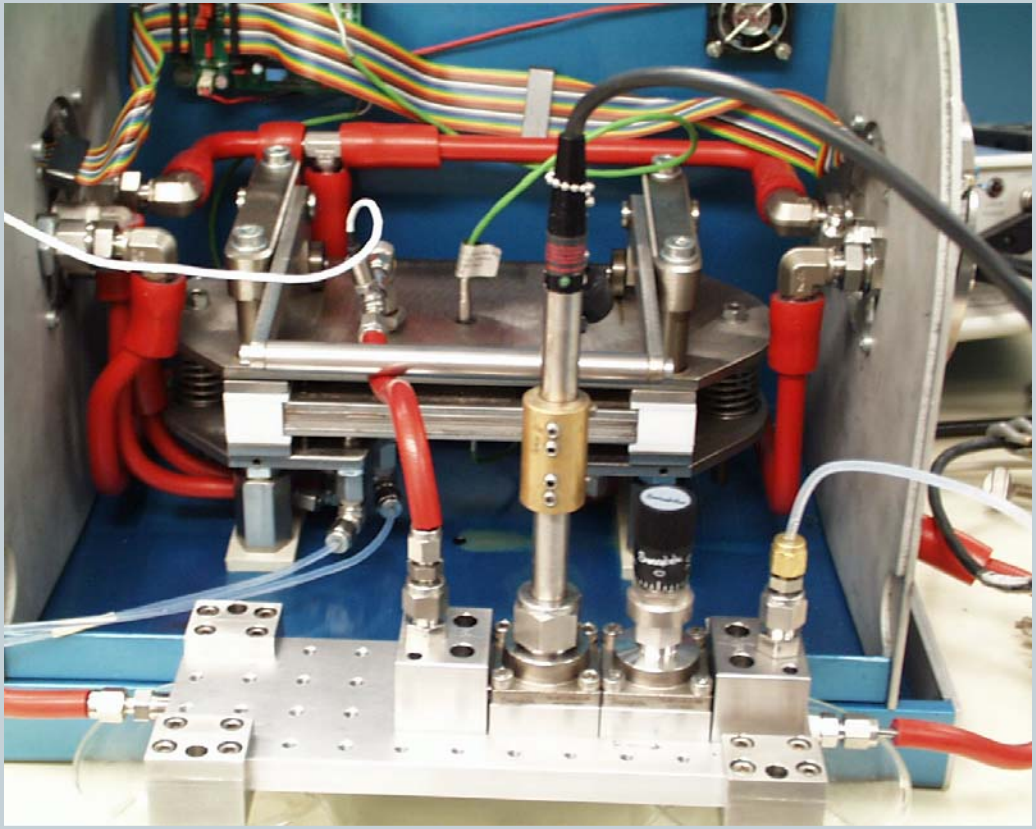


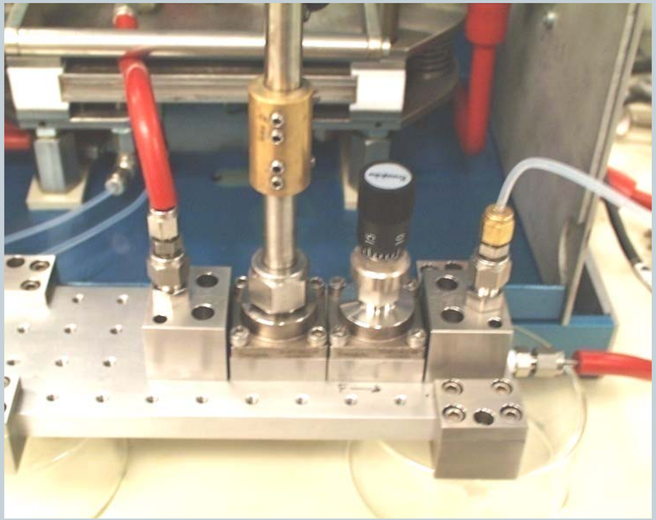


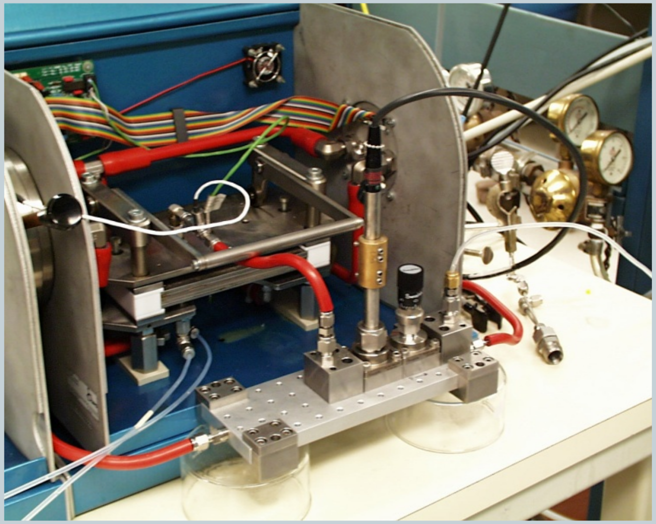
What does NeSSI™ Provide

- Simple "Lego-like" assembly
  - Easy to re-configure
  - No special tools or skills required
- Standardized flow components
  - "Mix-and-match" compatibility between vendors
  - Growing list of components
- Standardized electrical and communication (Gen II)
  - "Plug-and-play" integration of multiple devices
  - Simplified interface for programmatic I/O and control
- Advanced analytics (Gen III)
  - Micro-analyzers
  - Integrated analysis or "smart" systems

NeSSI Raman Sampling Block

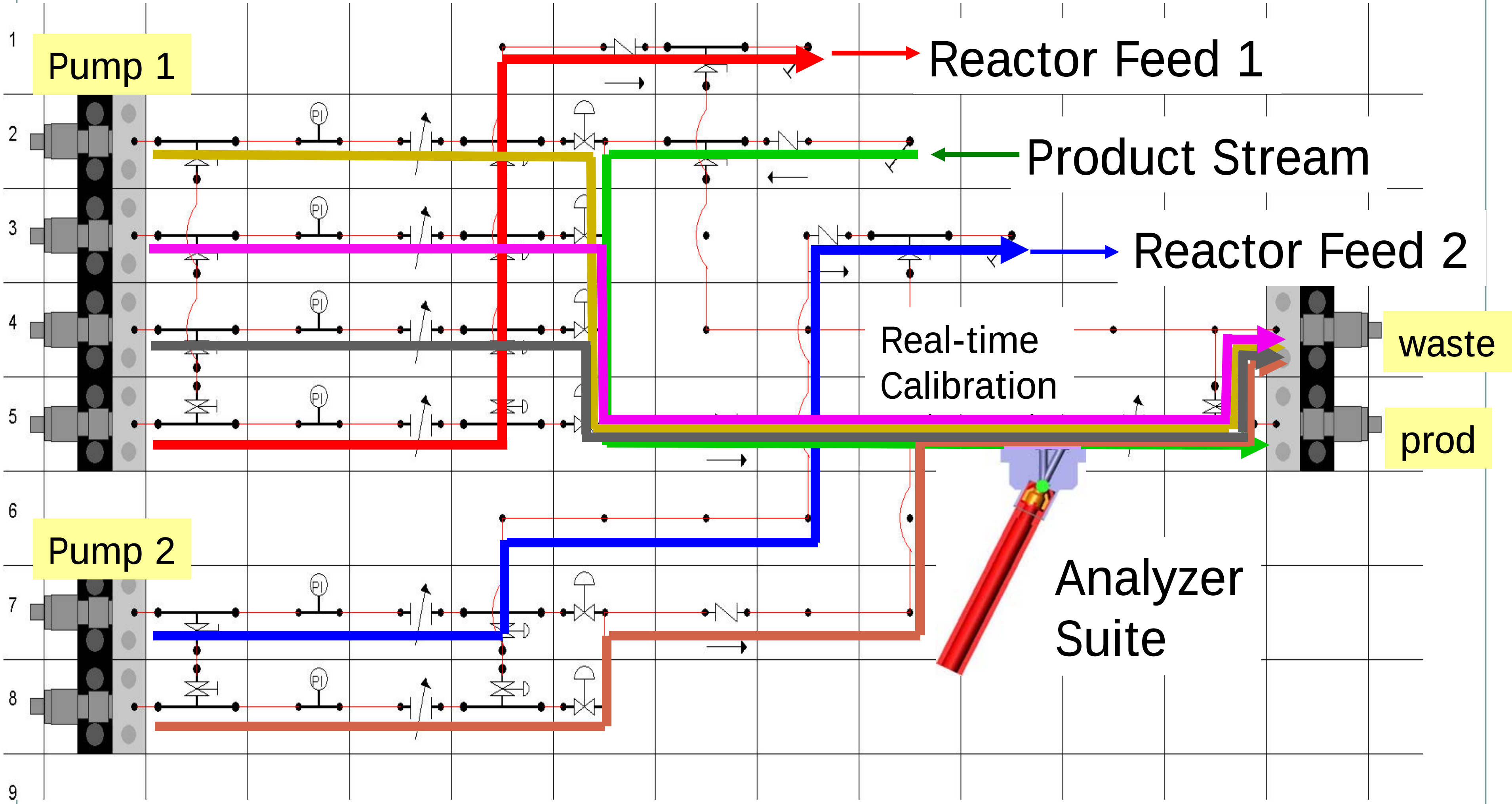






- Parker Intraflow NeSSI substrate
- Sample conditioning to induce backpressure to reduce bubble formation and the heated substrate allows analysis at reactor conditions

NESSI AF Reactor Sampling/Calibration



- Application of sampling systems and analytics to optimize and control AF reactor

FDA Collaboration: Demonstrate the Concept of QbD

- Monitoring an advanced flow reactor (AF Reactor) using NeSSi sampling systems and Raman ballprobe sampling interfaces at various reactor points.

CPAC/FDA/Corning AF Reactor

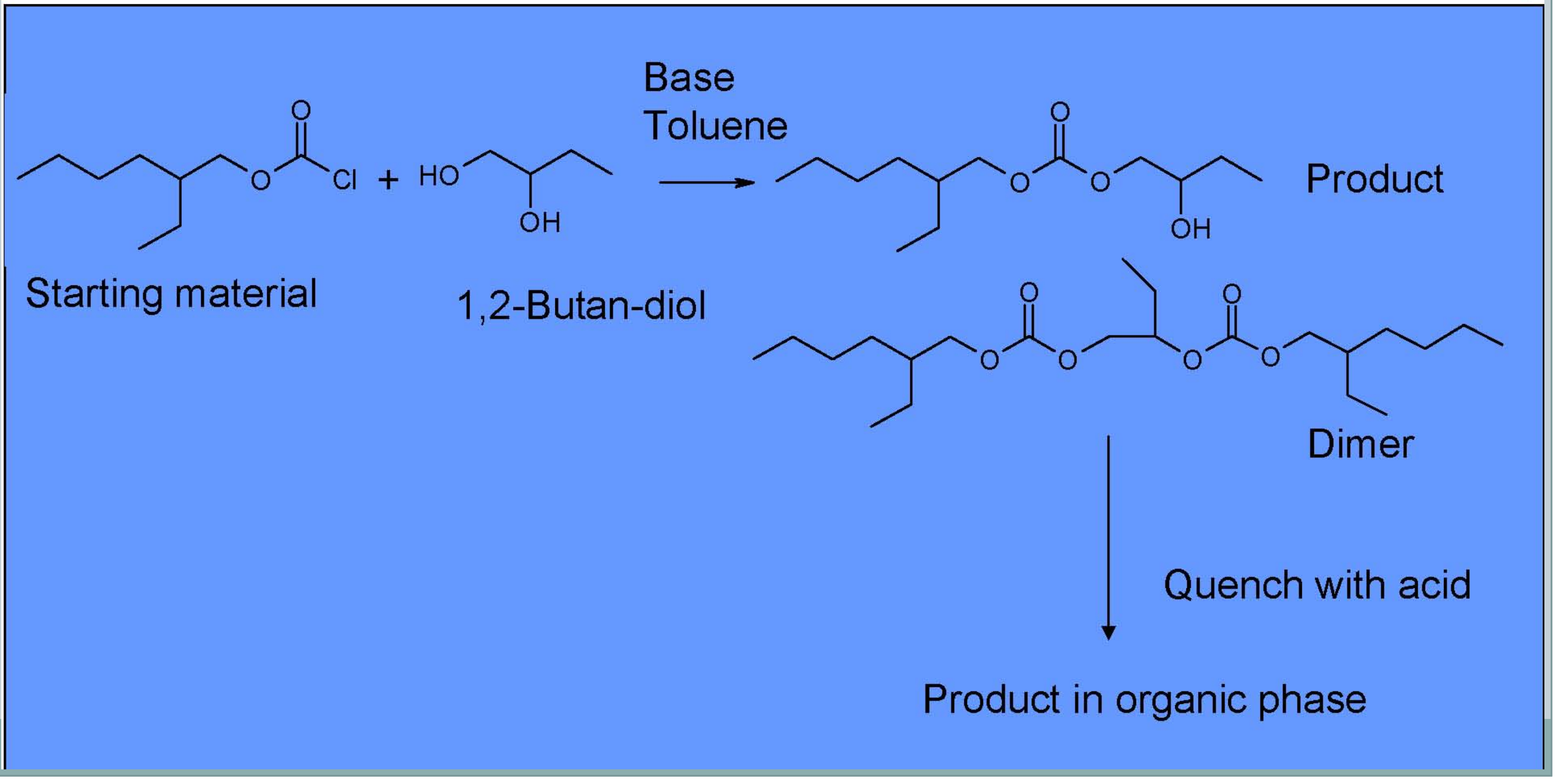
- Goal: to improve reaction development and optimization through the use of continuous glass flow reactors, NeSSI and analytics
- Funded by the FDA to demonstrate the benefits of improved reactor design, effective sampling and online analytics to increase process understanding (QbD)
- Partners: FDA, Corning, CPAC, Kaiser, Parker
- QbD Project began November 2008
- Process Reactions – June 2009

Corning Advanced Flow Reactor

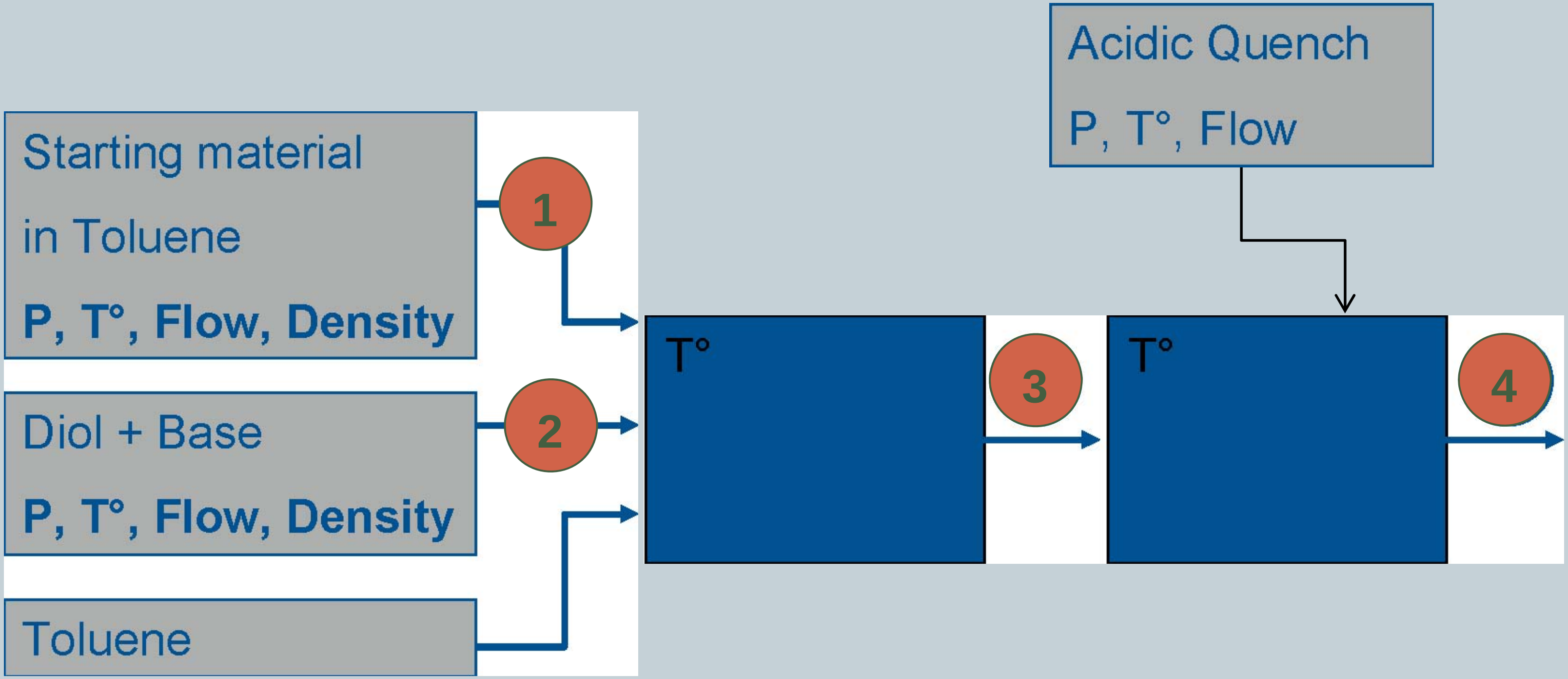
- Continuous reactions are ideal for product and process optimization/ understanding
- Provide predictable and reliable reaction performance, easily customizable and transferable to a production facility
- Application of reactor, sampling and analytics, demonstrates the physical concept of QbD
- Additional analytics easily coupled to reactor through NeSSI substrates
  - 4 channel, Kaiser Optical Systems Rxn2 probes placed in reactor flow path at different points of the reaction

Advanced Flow Reactor Chemistry

Organic Acid Chloride ⟶ Organic Carbonate + dimer



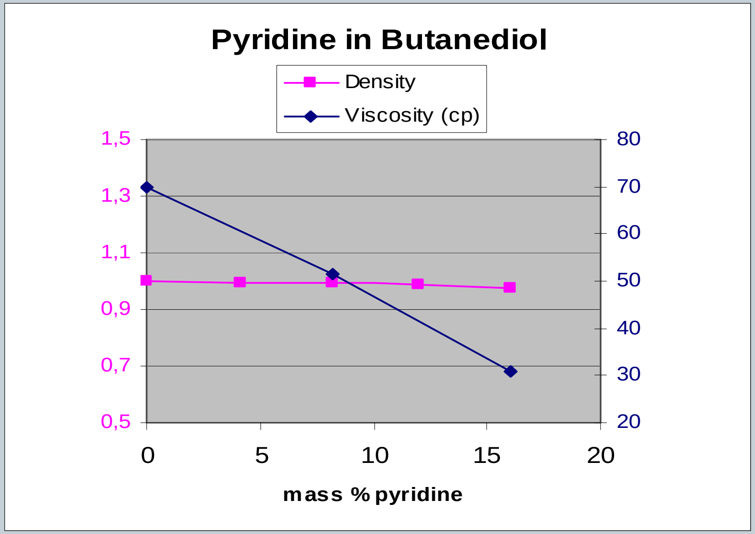
Raman Analysis of AF Reactor

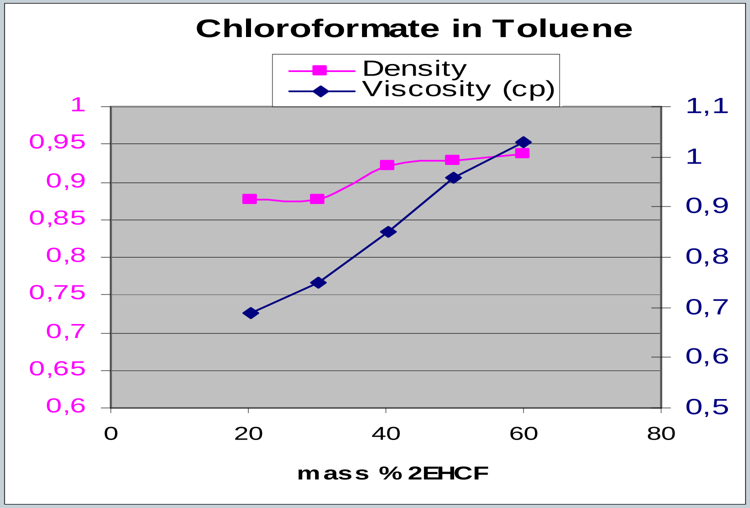


- monitor reaction with 4 channel 785 nm Raman system
- NeSSI sampling systems (1-4) equipped with Raman ballprobes
- Online GC also used as post quench online analyzer (4)

Process on line measurements

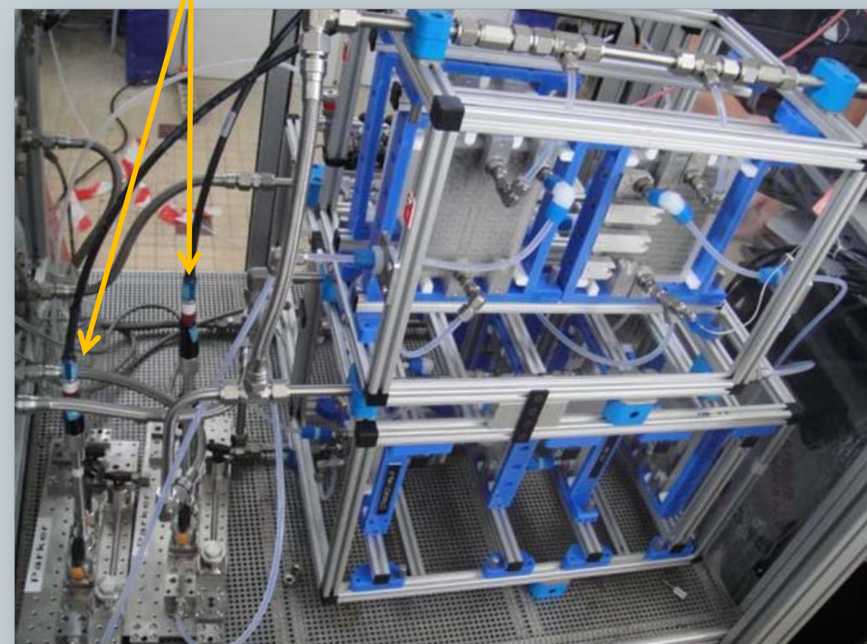
- For each feed :
  - Pressure
  - Mass Flow rate
  - Temperature
  - Density
- Raman Spectroscopy measurements on Feeds, Pre-quench product and Post-quench product
- Density and viscosity measurements were done for Chloroformate/Toluene and Butanediol/Pyridine

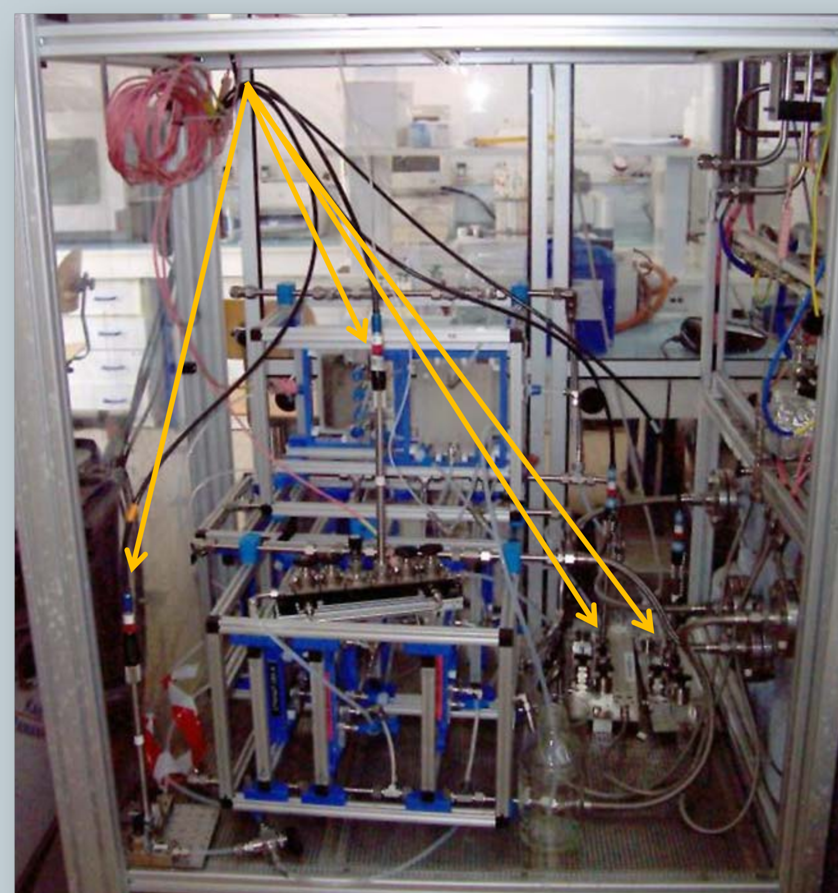




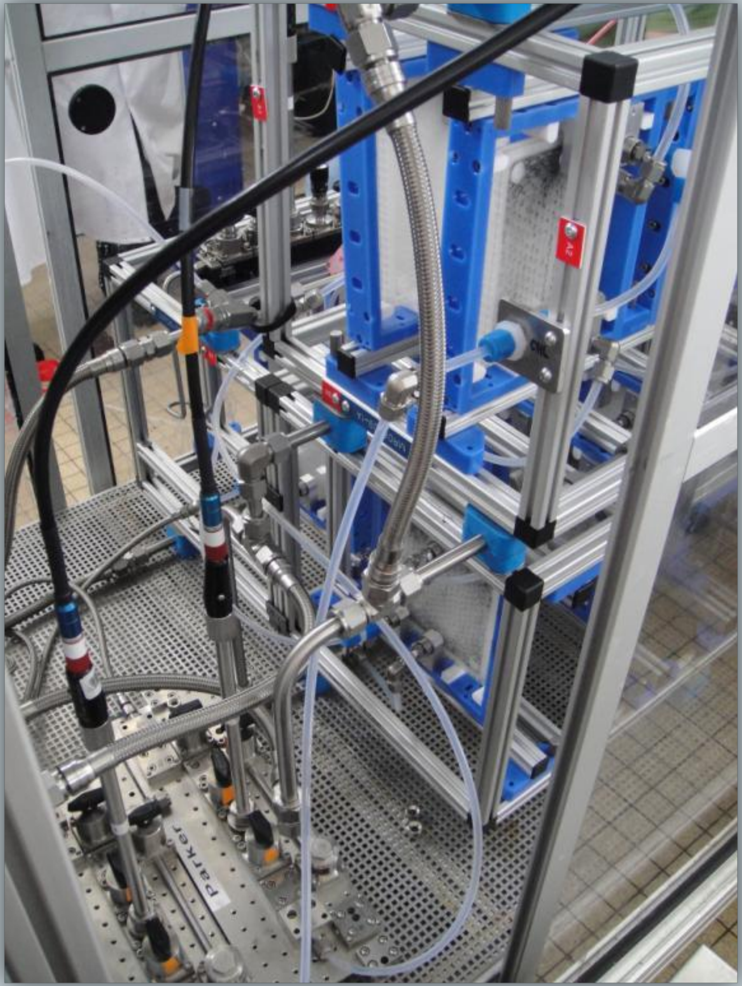
Advanced Flow Reactor Images

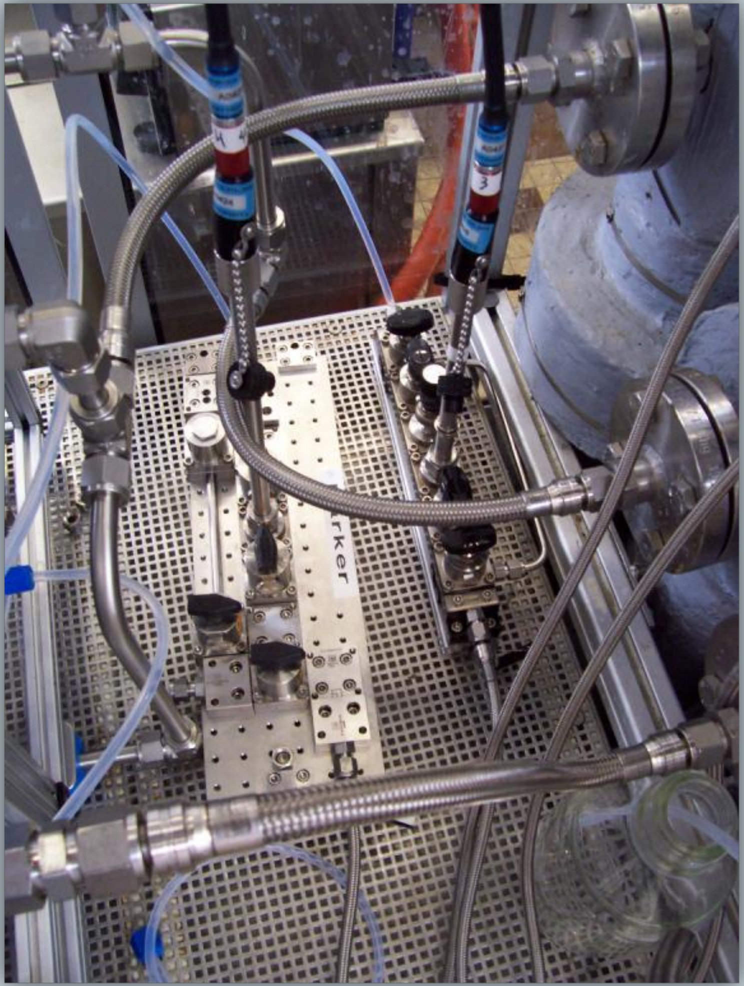
Raman Probes



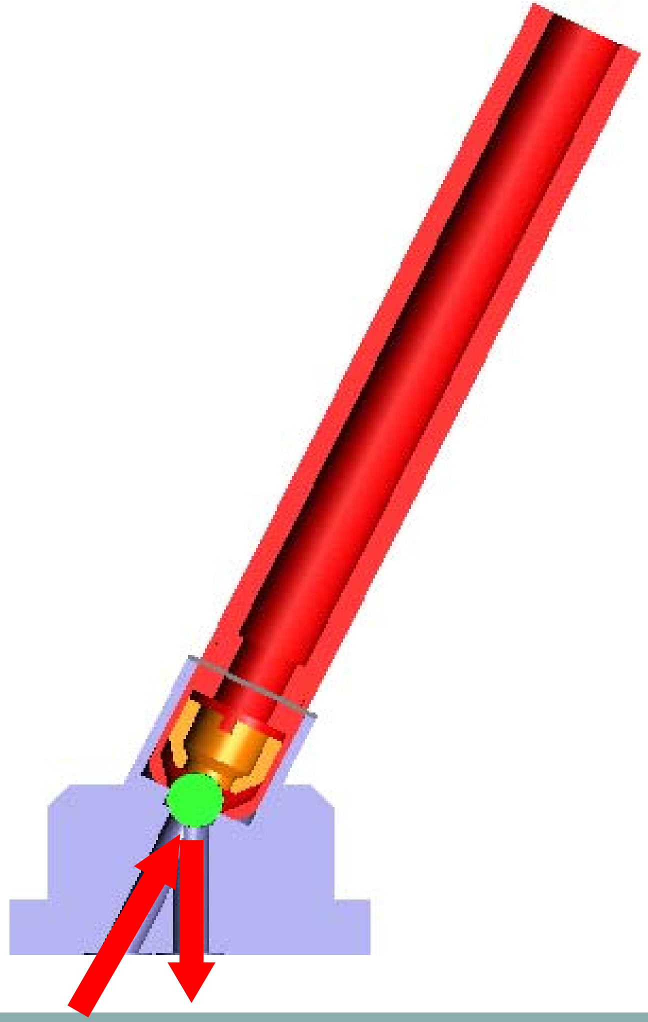


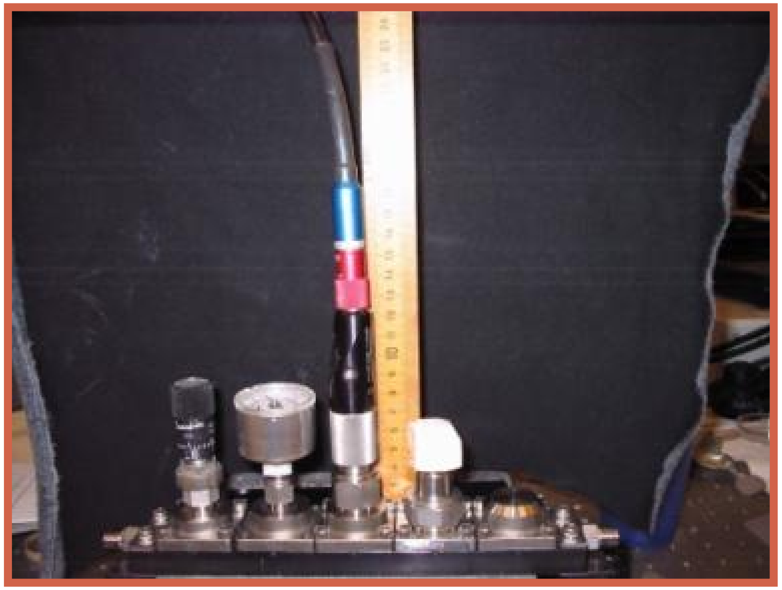
NeSSI Sampling and Raman Probe Images





NeSSI Ballprobe - Raman/NIR/UV

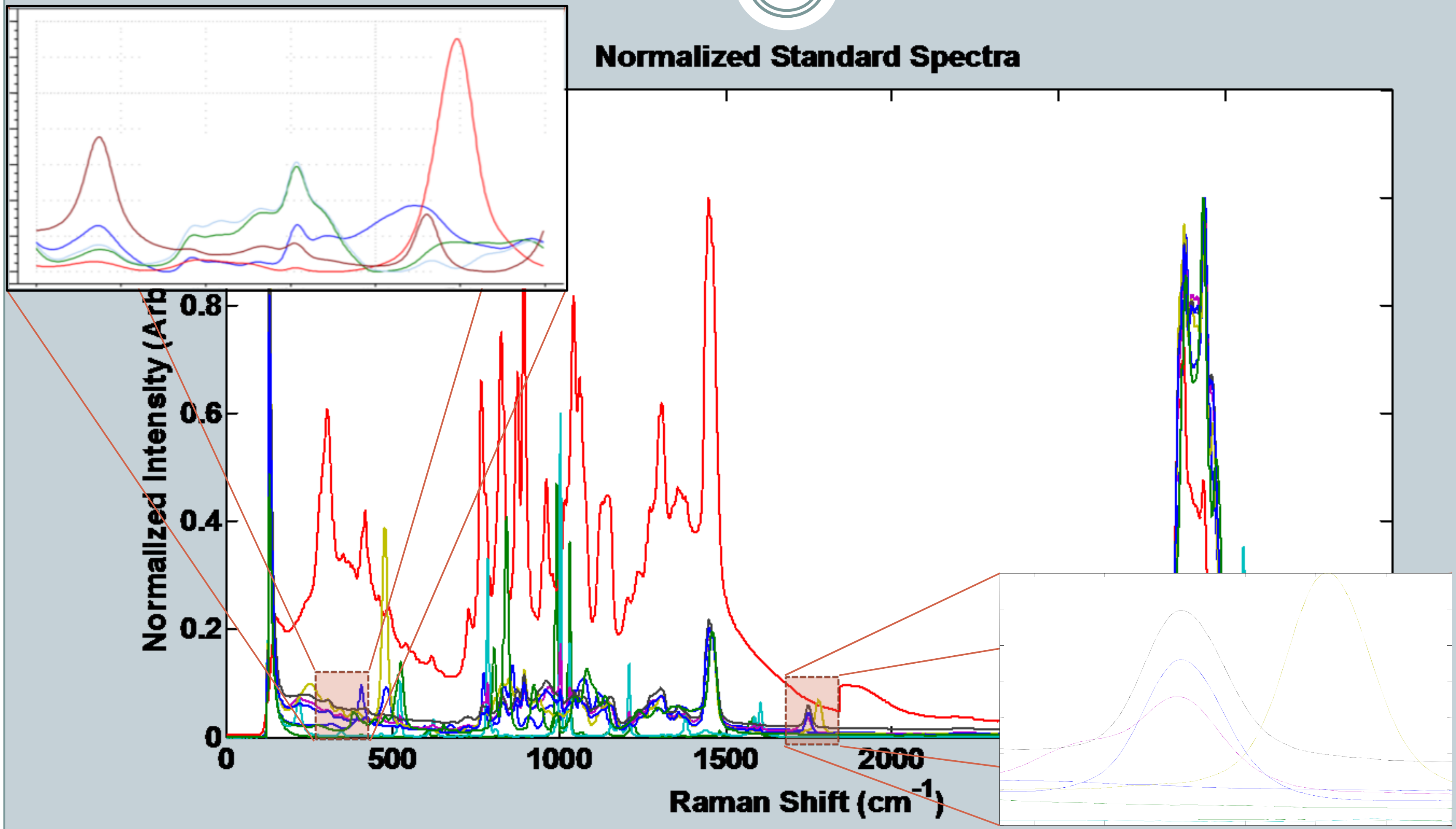




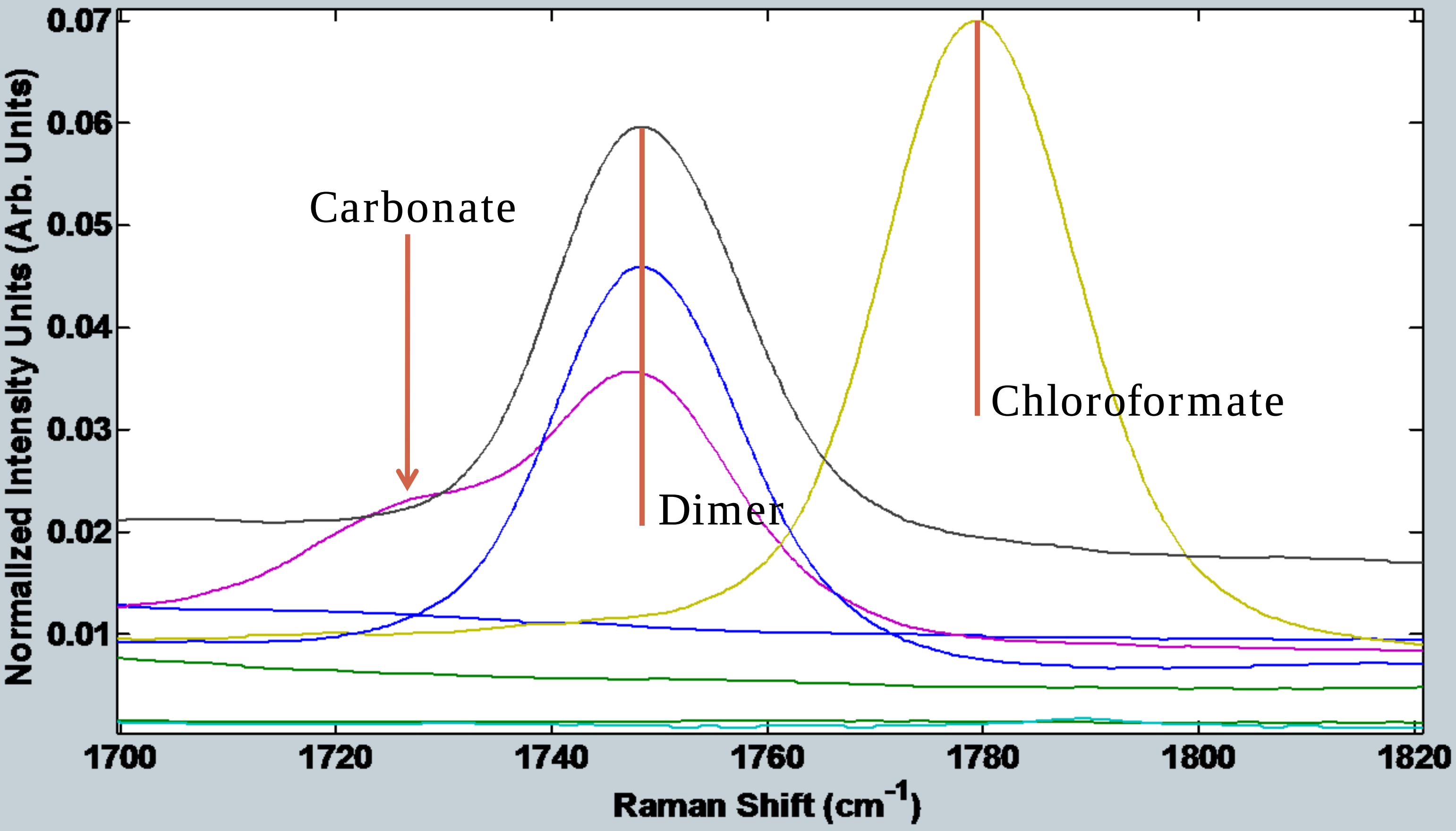
Design of Experiments Information

- 31 Experiments total
  - Temperature steps
  - Reaction with no toluene
  - Changes in butanediol ratio
  - Changes in pyridine ratio
  - Propanediol instead of butanediol
  - Simulated Reactor problems
    - Pump failure
    - Less heat exchange
    - Poor dilution of chloroformate

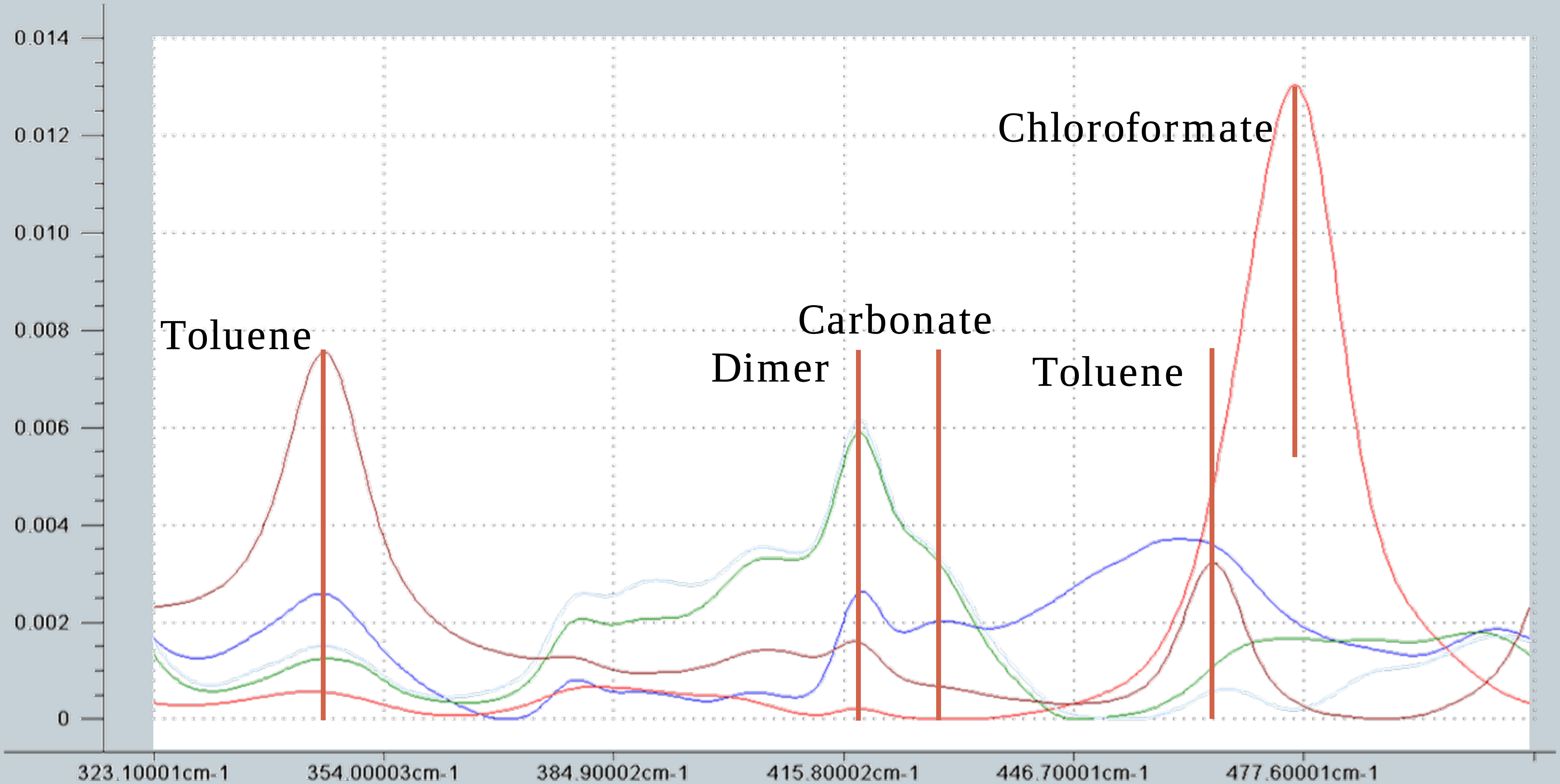
Product Raman Peaks of Interest



Standard Peaks of Interest (High cm^{-1})



Standard Peaks of Interest (Low cm^{-1})



DoE Tests 0 and 3

CFM_RUN1

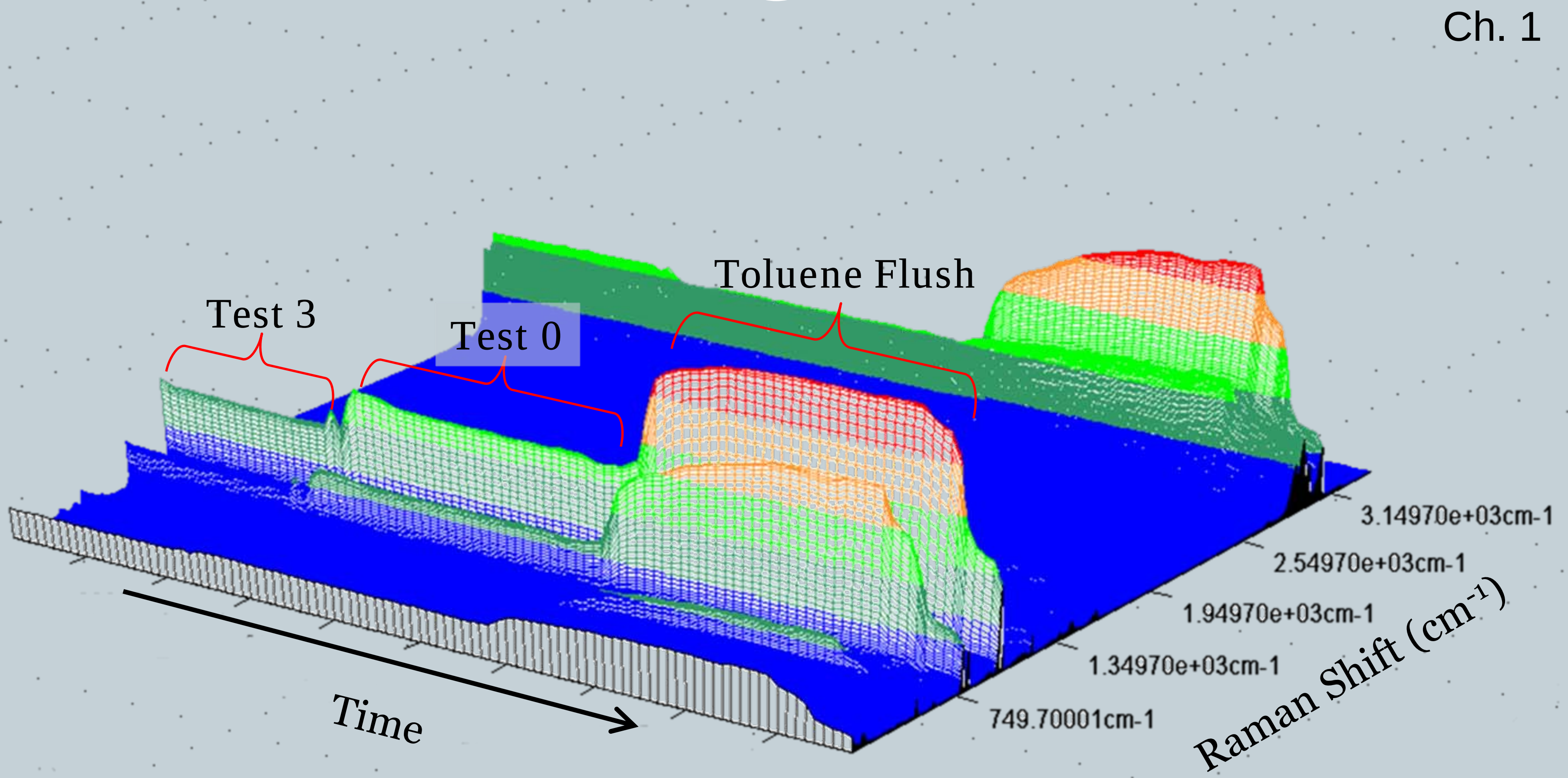
JUNE 9TH, 2009

	T°	Feed A		Feed B				Mass Flow A+B	Feed C		T°	Total Mass Flow
	Reaction	Choloformiate in toluene		Pyridine in butanediol					Acidic solution		Quench	
	°C	g/min	wt%	g/min	wt%	Eq Mol Pyridine	Eq Mol Butanediol	g/min	g/min	wt%	°C	g/min
	Half stoechiometry test											
Test 0	60	10.0	40	10.1	8.1	0.5	5.0	20.1	20.2	10	10	40.3
	Temperature											
Test 1	20	8.0	40.0	16.0	8.1	1.0	9.8	24.0	20.2	10.0	10	44.2
Test 2	40	8.0	40.0	16.0	8.1	1.0	9.8	24.0	20.2	10.0	10	44.2
Test 3	60	8.0	40.0	16.0	8.1	1.0	9.8	24.0	20.2	10.0	10	44.2
	Propanediol instead of butanediol											
Test 15	60	8.0	30.0	16.0	8.1	1.3	15.5	24.0	20.2	10.0	10	44.2
Test 16	85	8.0	30.0	16.0	8.1	1.3	15.5	24.0	20.2	10.0	10	44.2
Test 17	30	8.0	30.0	16.0	8.1	1.3	15.5	24.0	20.2	10.0	10	44.2

GC Results (%)				
R-OH	**2EHCF**	**R-Cl**	**Carbonate**	**Dimer**
2.16	45.84	0.32	51.42	0.59
1.17	0.00	0.26	96.17	2.40

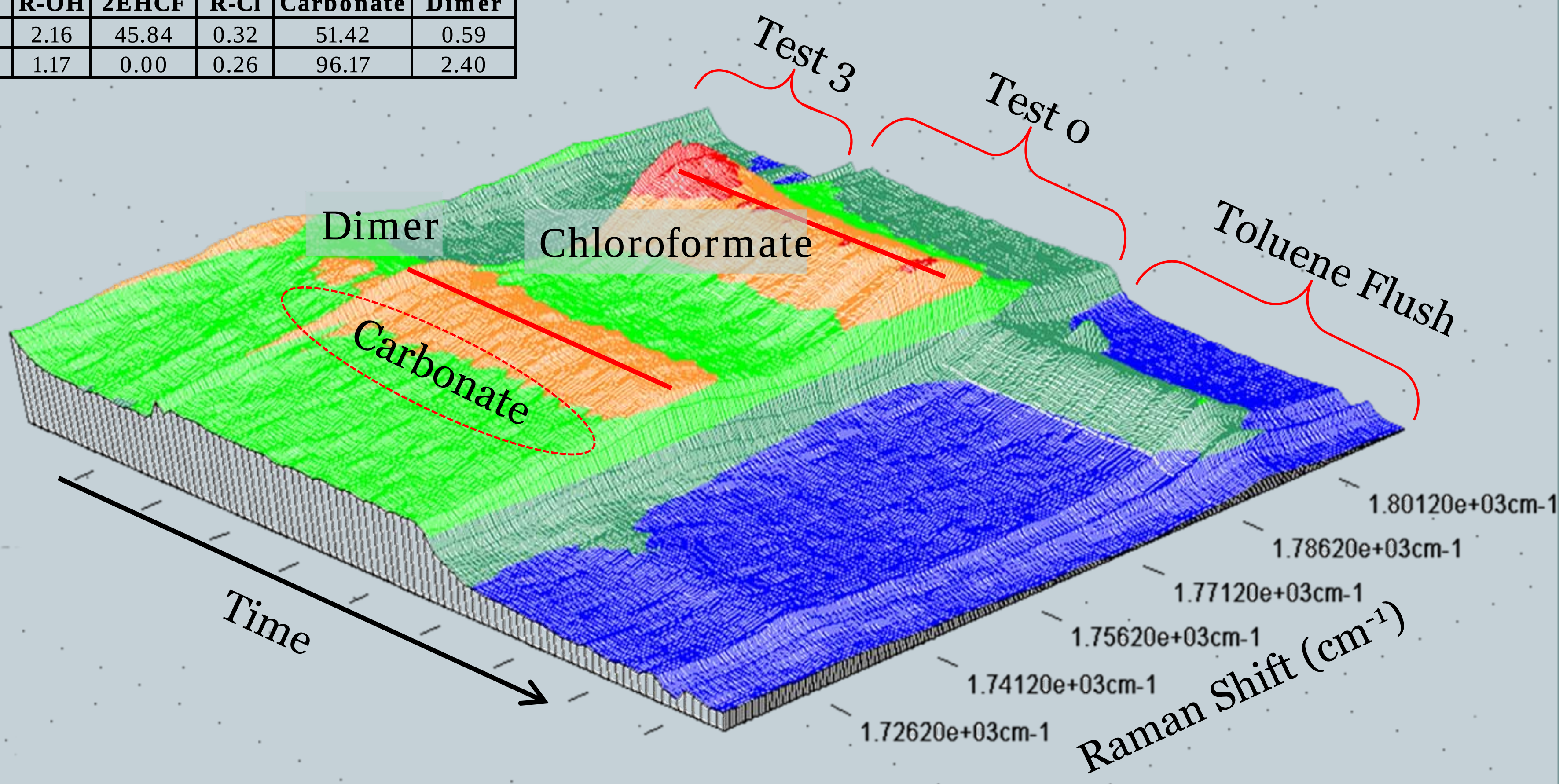
Abbreviation Definitions		
R-OH	**2EHCF**	**R-Cl**
Alcohol formed after quench	Residual, unreacted chloroformate	Natural degradation product of chloroformate

Reaction Easily Followed With Raman



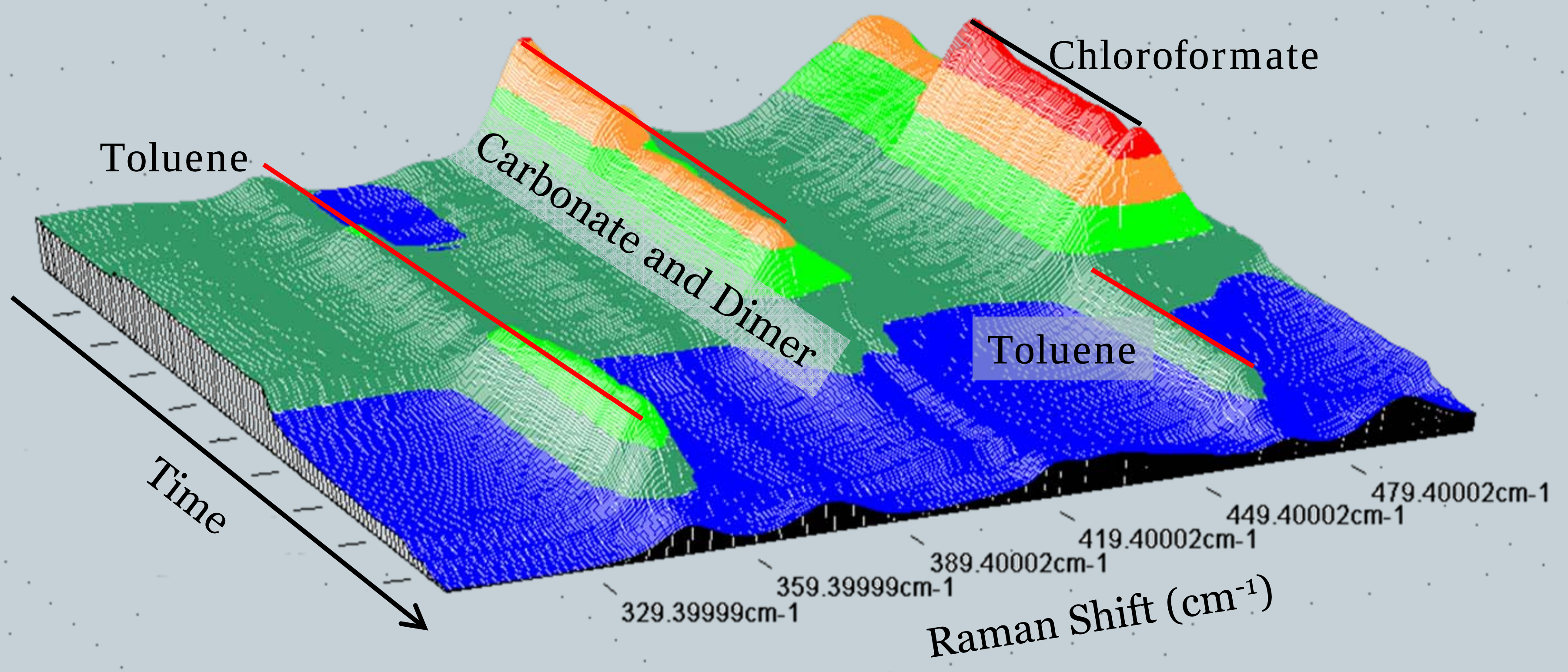
Peaks of Interest (High cm^{-1})

GC Results (%)					
Test	**R-OH**	**2EHCF**	**R-Cl**	**Carbonate**	**Dimer**
0	2.16	45.84	0.32	51.42	0.59
3	1.17	0.00	0.26	96.17	2.40



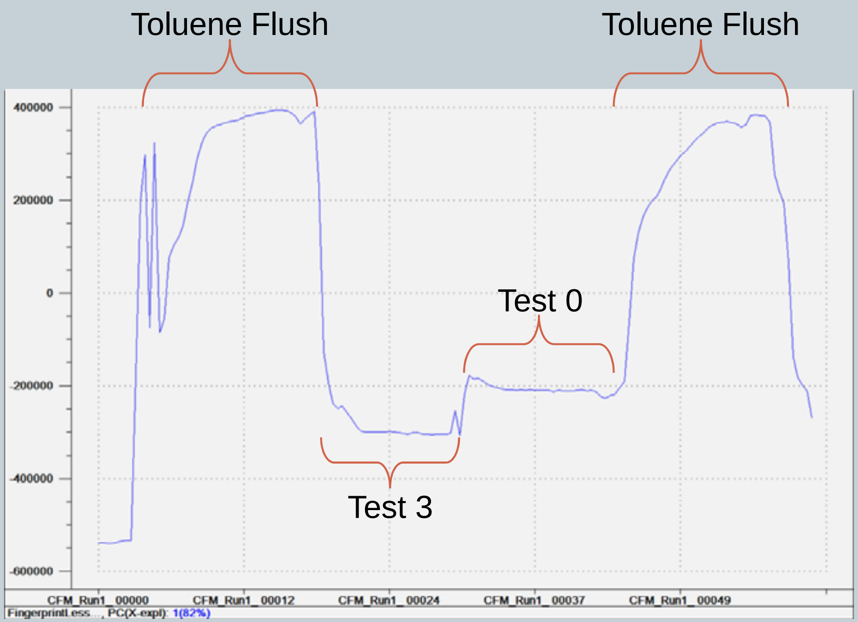
Peaks of Interest (Low cm^{-1})

GC Results (%)					
Test	**R-OH**	**2EHCF**	**R-Cl**	**Carbonate**	**Dimer**
0	2.16	45.84	0.32	51.42	0.59
3	1.17	0.00	0.26	96.17	2.40

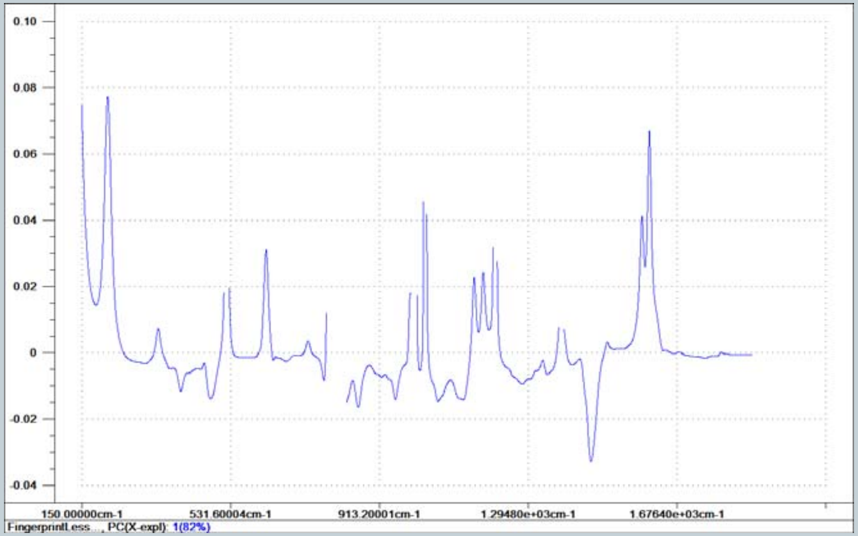


PCA of fingerprint region, PC 1

Toluene peaks removed



Scores



Loadings

Current Status

- Data collected and organized
  - 14 days in Toulouse France
- Analysis started
  - Evaluation of modeling protocols
    - PCA, MCR, ALS
  - Calibrate to GC results (PLS)
- Determine better chemistry for Phase 2
  - More chemical change in reaction space
  - Implement more sensors
  - Acquire reactor at CPAC
- Implement Models for Process Feedback Control

Thanks

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CORNING

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