



Use of Raman for Reaction Monitoring in Lab and Plant

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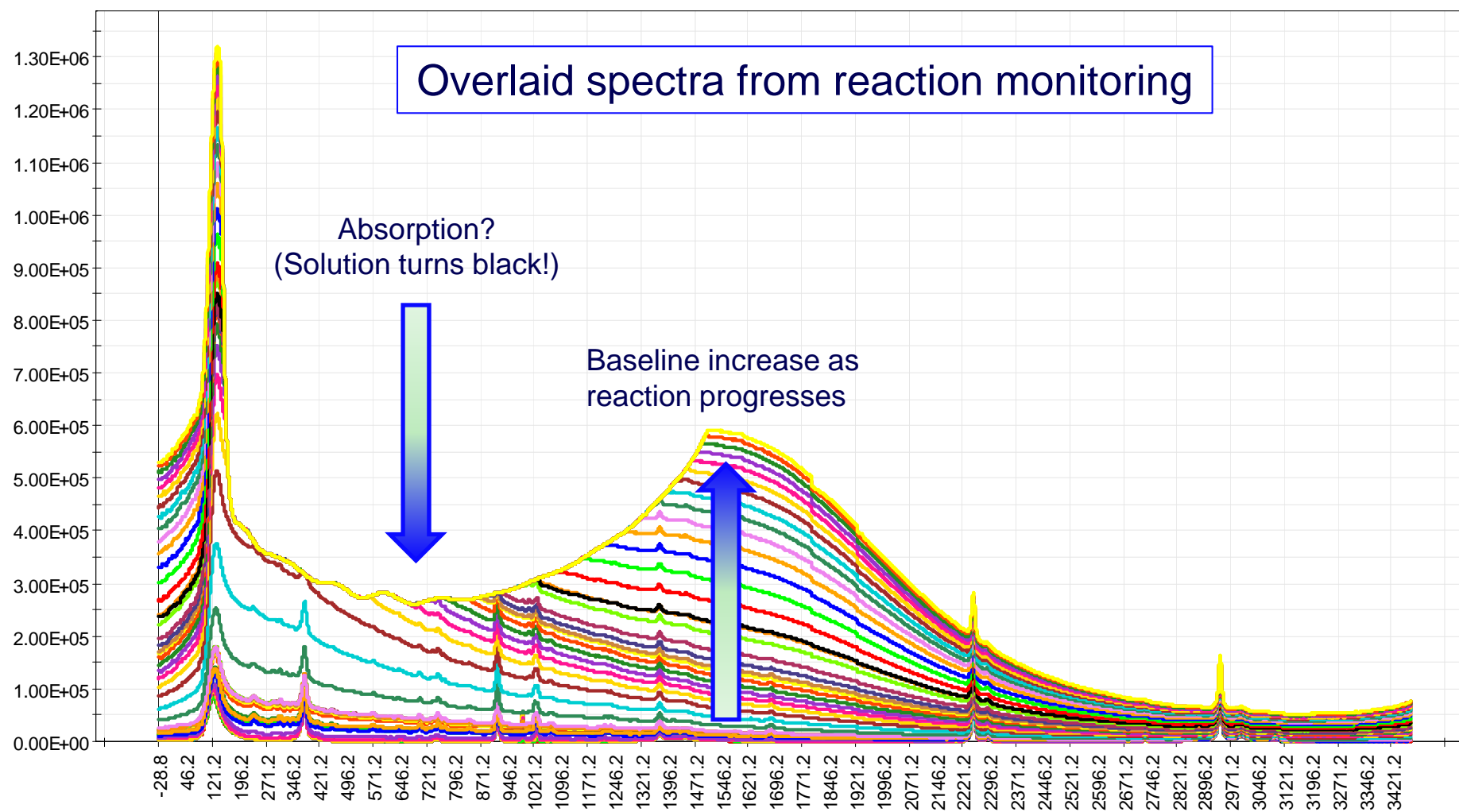
Why Raman for Real-Time Reaction Monitoring?

- Quantitative
 - Compare MidIR
- Spectral resolution and selectivity
 - Compare UV/Vis, NIR
- Can detect solvents, dissolved solutes *and* suspended particulates
 - Compare ATR-based approaches
- Complementary selectivity to MidIR
- Whole spectral range available
 - Compare MidIR limitations due to fibre optic/ATR crystal absorptions
- Insensitive to water content of sample

Disadvantages of Raman

- Fluorescence can interfere
- Less sensitive than MidIR
- Scattering effects from suspensions or emulsions
- Cost of instrumentation

The Problem of Fluorescence

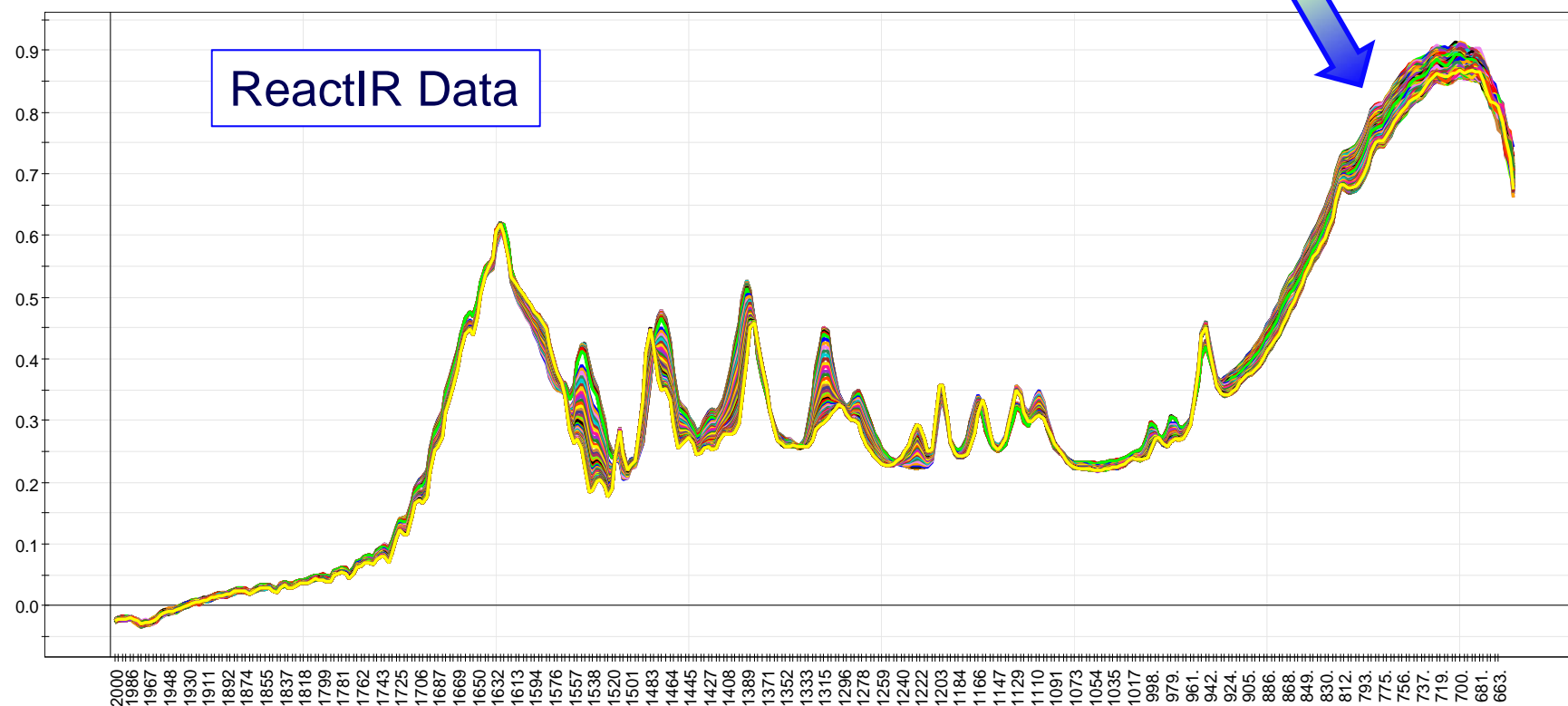


Example 1: Lab Alkylation Reaction Involving Alkyl Chloride

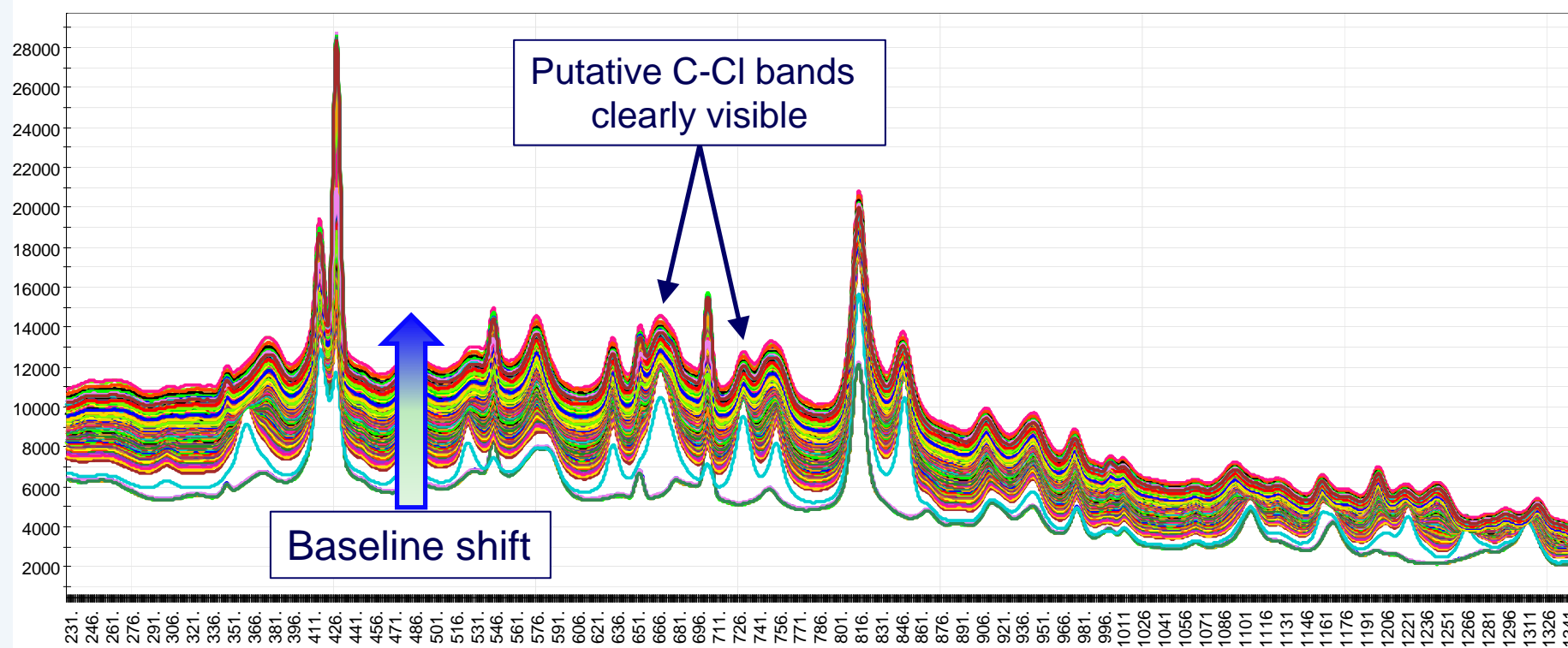
Aim: monitor loss of alkyl chloride

Problem: solvent is iPA:water

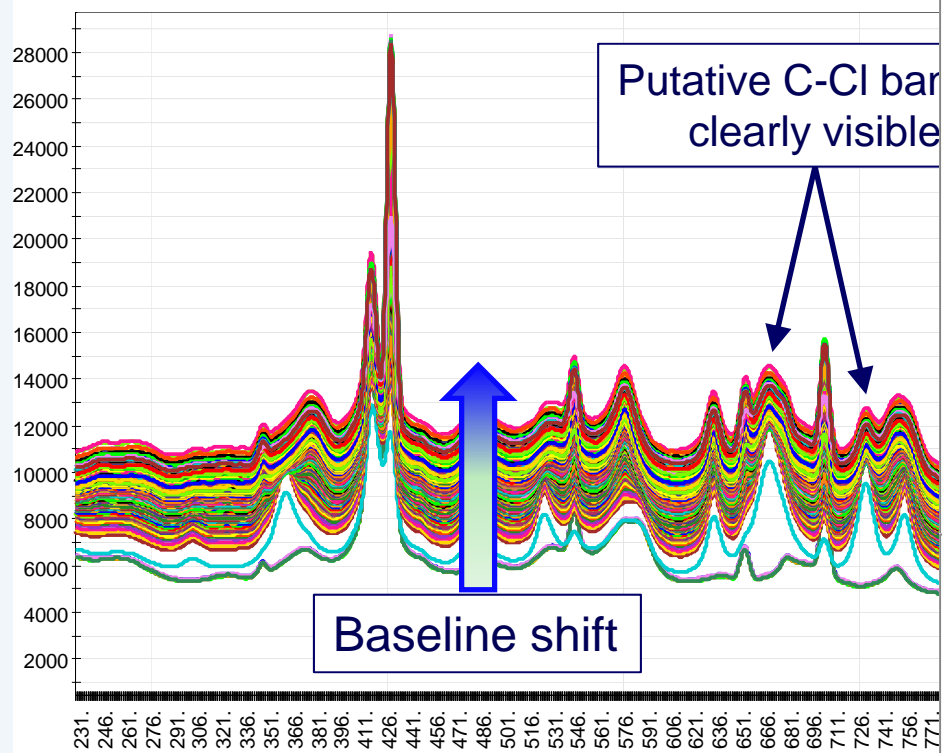
C-Cl bands swamped
by solvent band



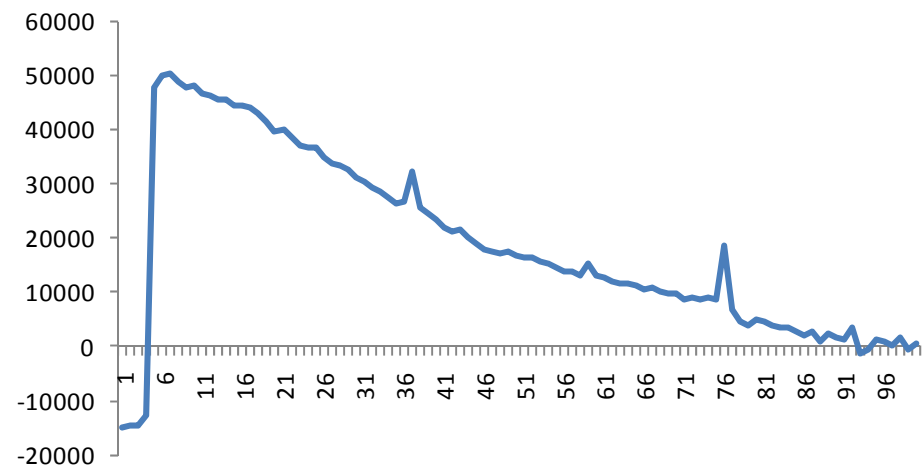
Example 1 Raman Spectra



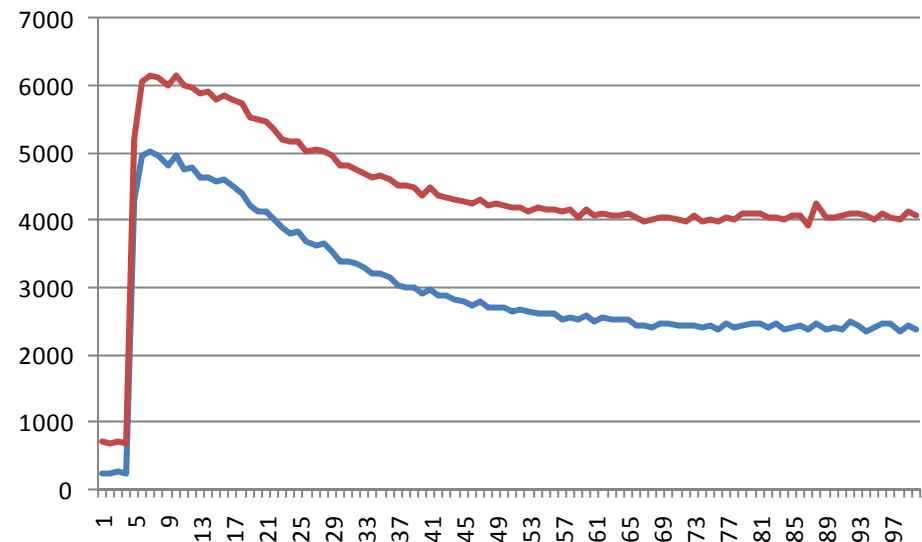
Example 1 Raman Spectra



PCA Score 2

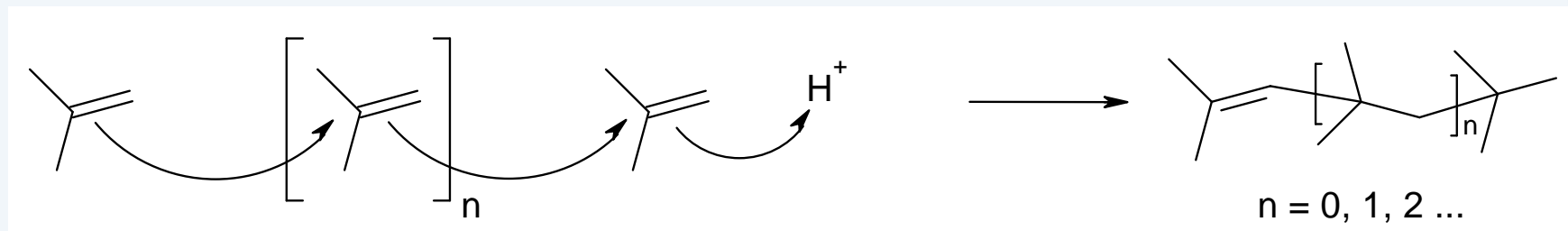


730 cm⁻¹ Baseline Subtracted 670 cm⁻¹ Baseline Subtracted



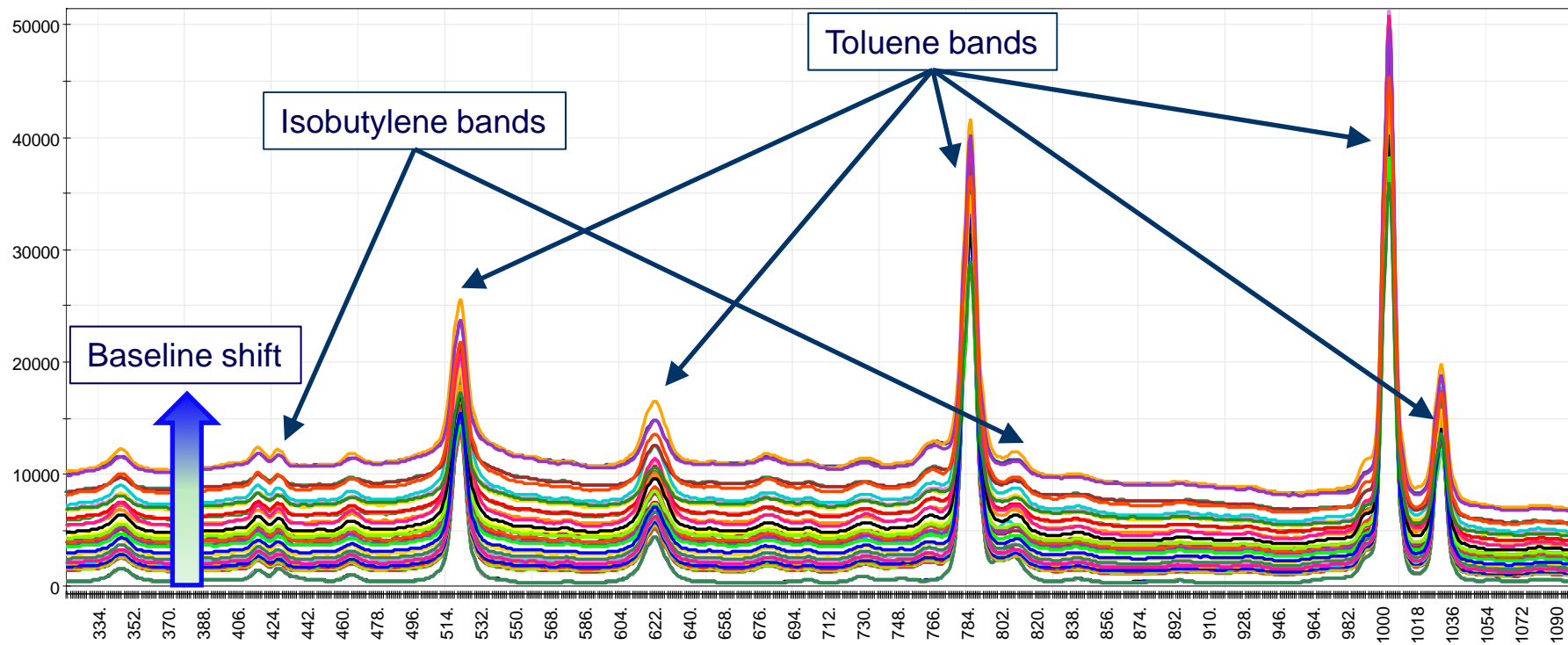
Example 2: Isobutylene Polymerisation Monitoring in Lab

- Isobutylene gas generated during de-Boclation reactions
- Engineers trying to design scrubber to prevent environmental escape
- Acid-catalysed polymerisation evaluated (dimer & above not gaseous)

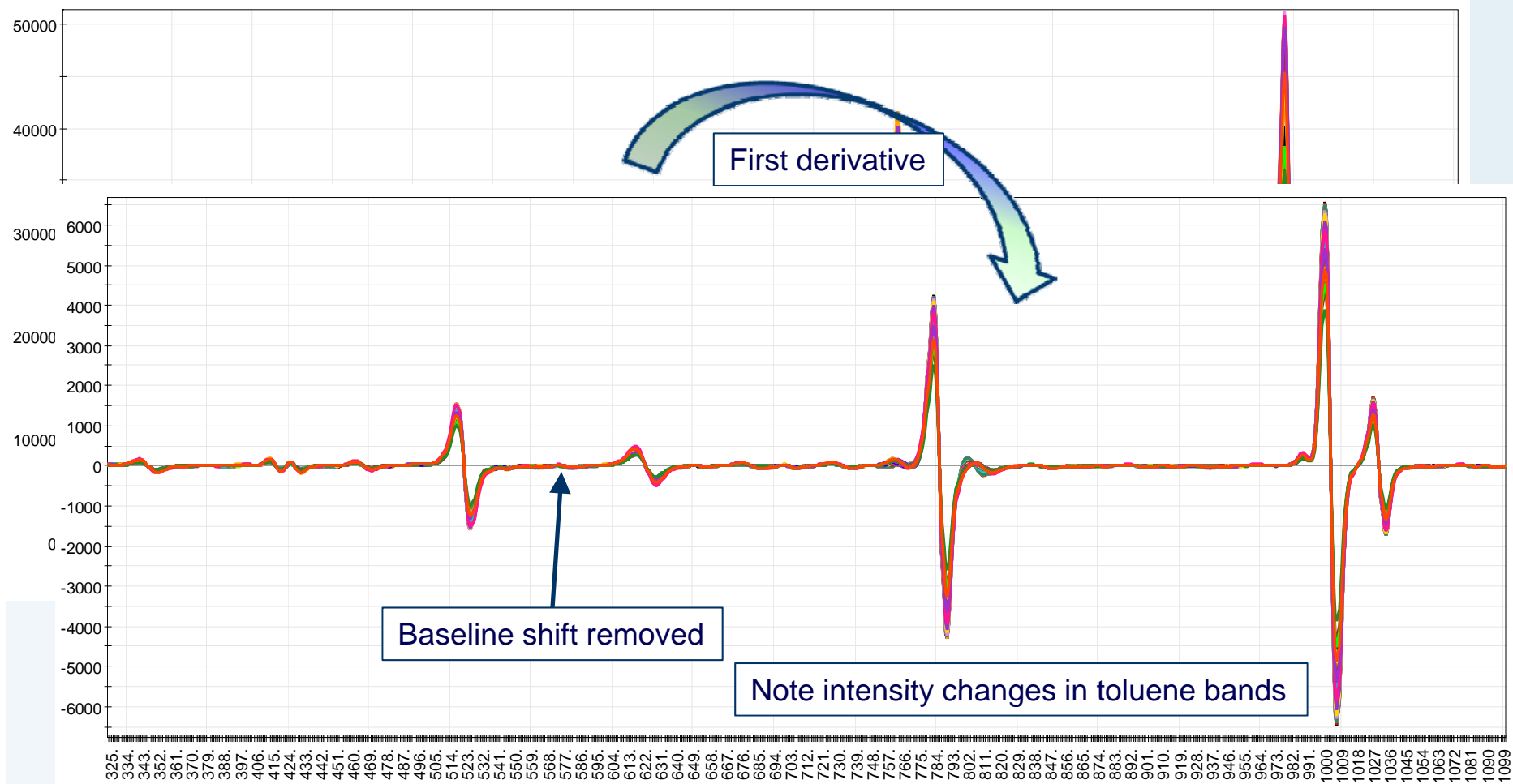


- Required means of monitoring kinetics of reactions
 - Too fast for GC
- Raman spectroscopy was investigated for reaction monitoring
- Methanesulfonic acid immiscible with solvent (toluene) for isobutylene
 - Forms emulsion \Rightarrow scattering \Rightarrow baseline perturbations
 - Requires data pre-processing to resolve

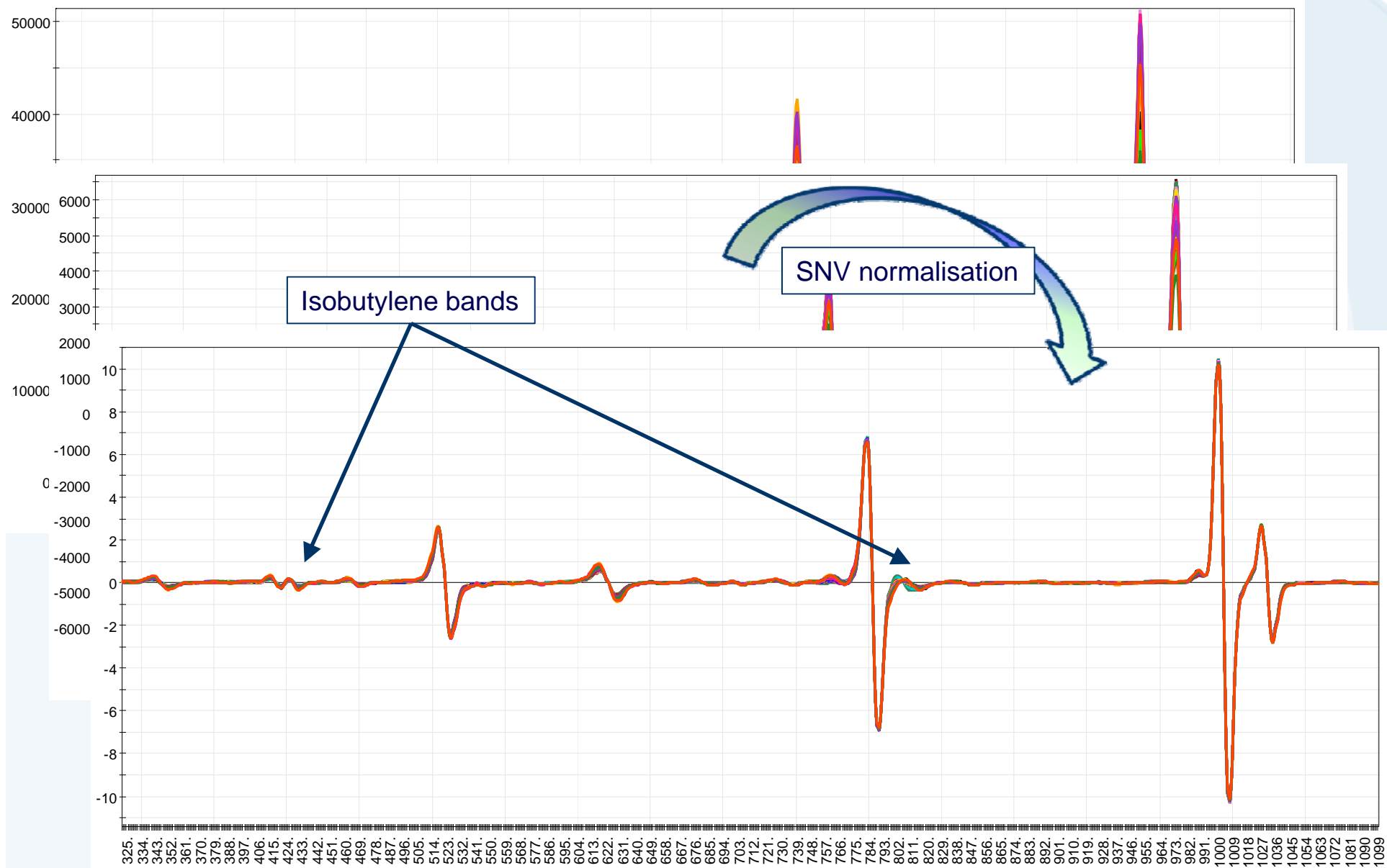
Data Preprocessing



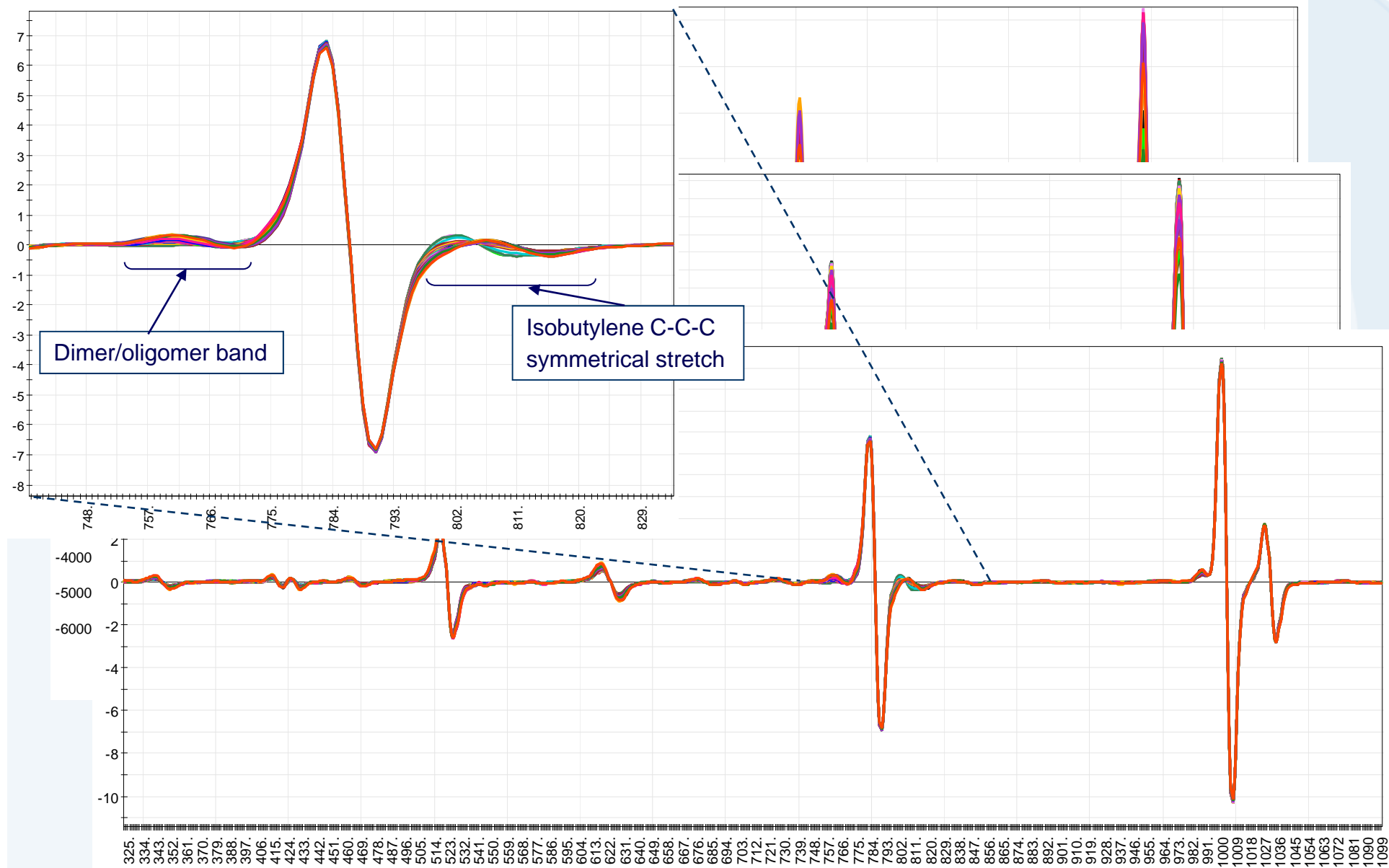
Data Preprocessing



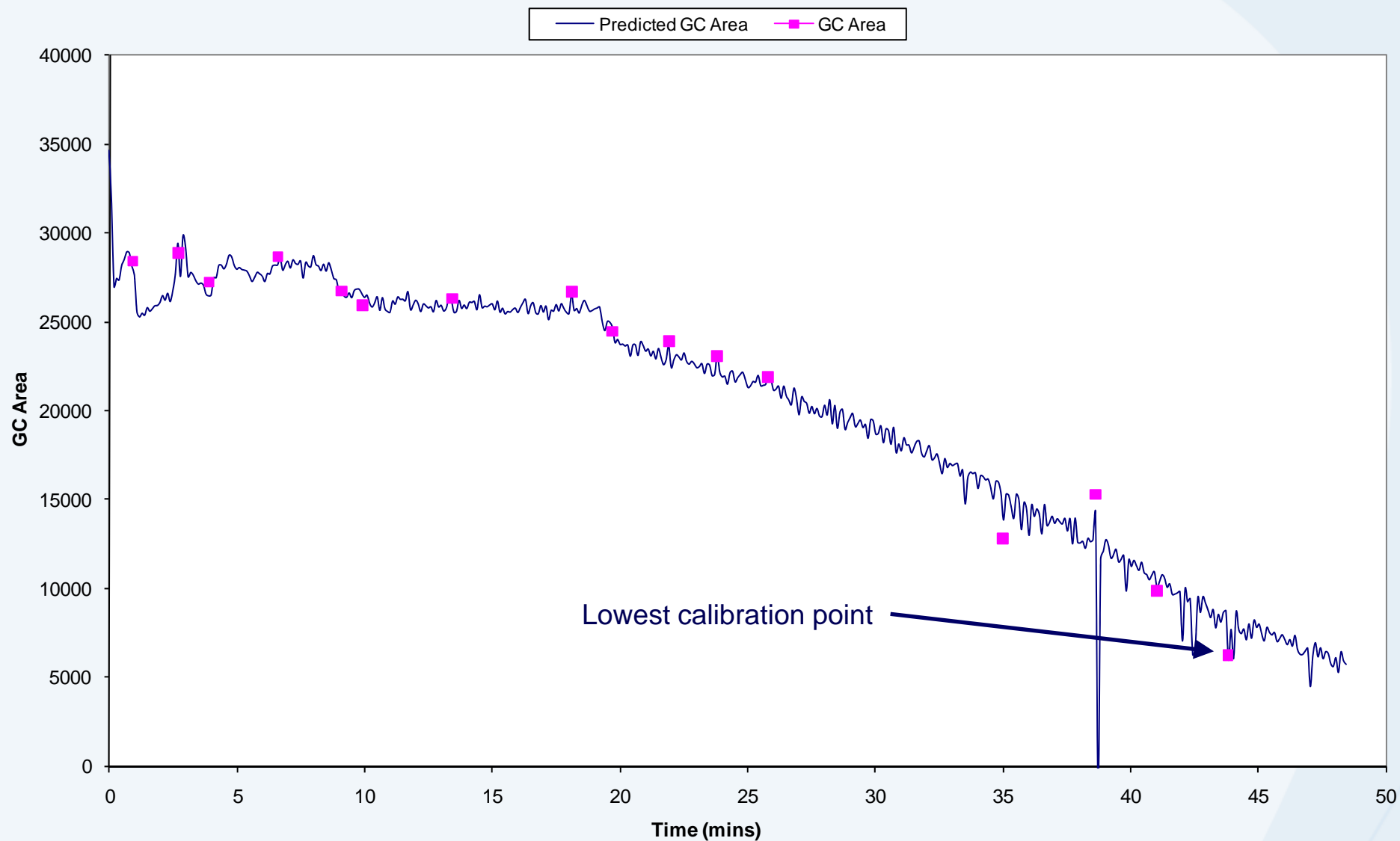
Data Preprocessing



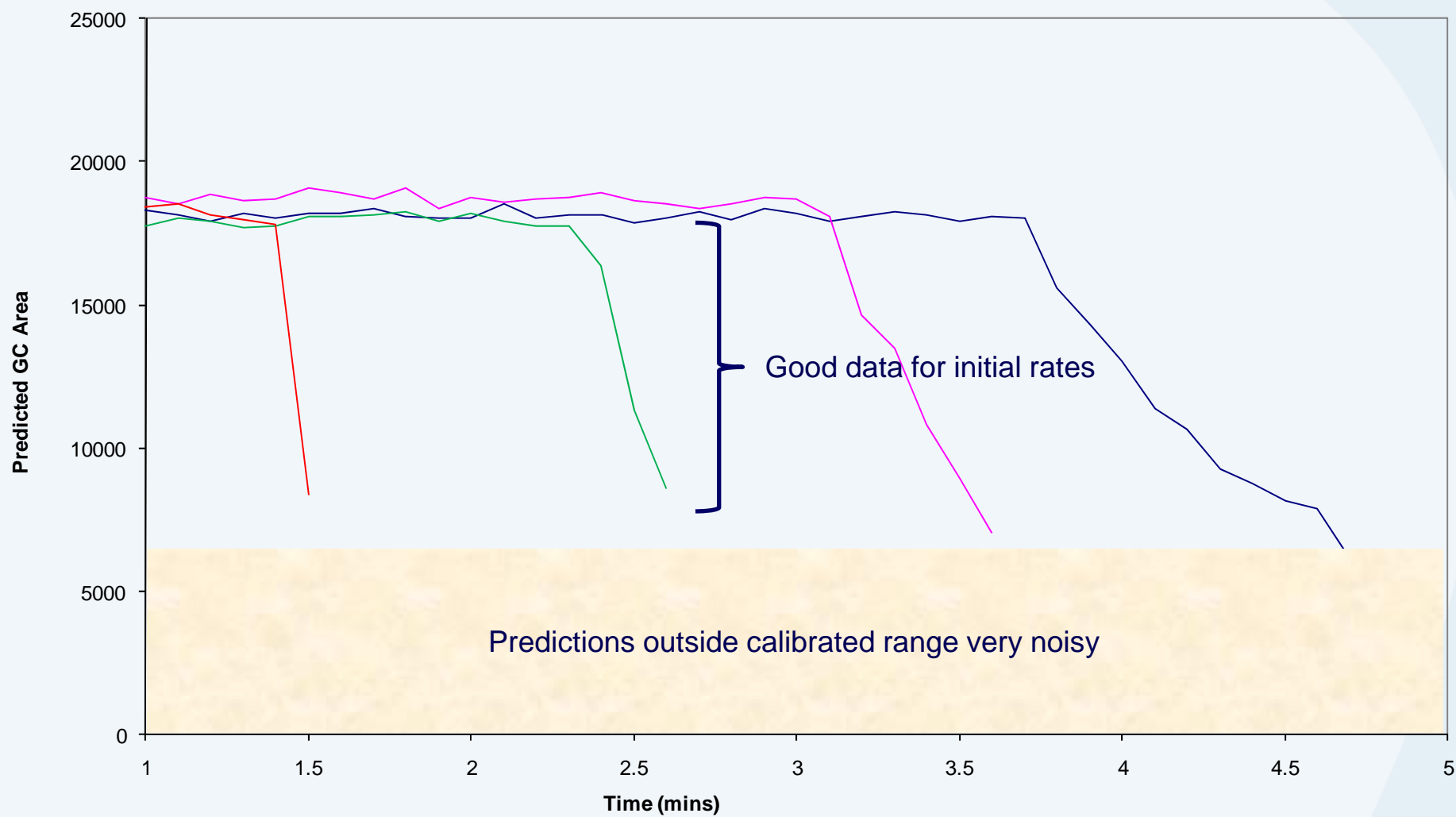
Data Preprocessing



PLS Calibration Data (Slow Reaction)



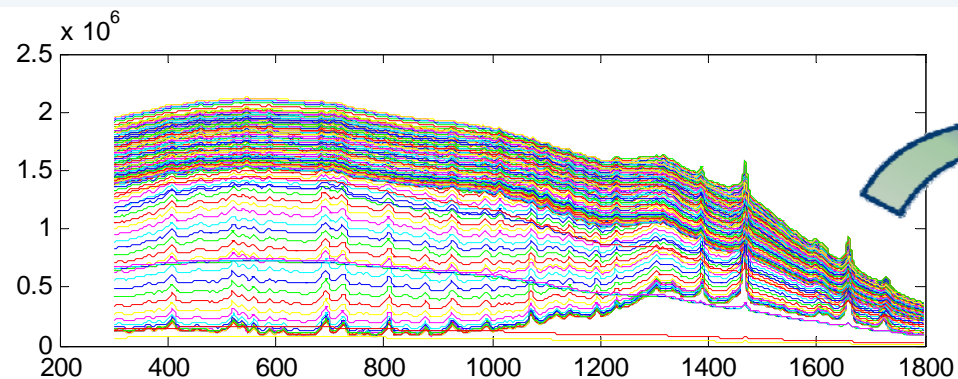
Predictions for Kinetics Experiments



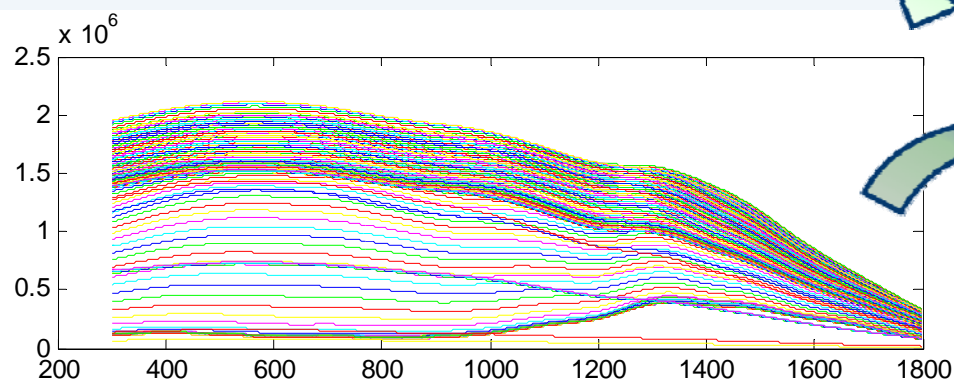
Isobutylene Results

- Good predictions of initial rates
 - Off-line GC would not have been capable
- Suitable for building kinetic model
- Noise in lower level predictions
 - Rapid data acquisition rate: low s:n in raw data
 - 1st derivatives ➡ noise increase
 - Data extrapolated outside calibrated range

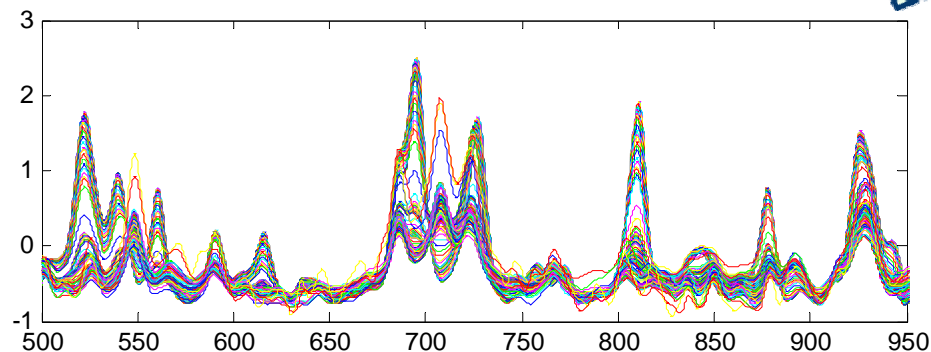
Example 3. Solid State Form Change in Lab



Calculate individual baseline
for each spectrum using
asymmetric least squares
algorithm¹



Subtract baselines



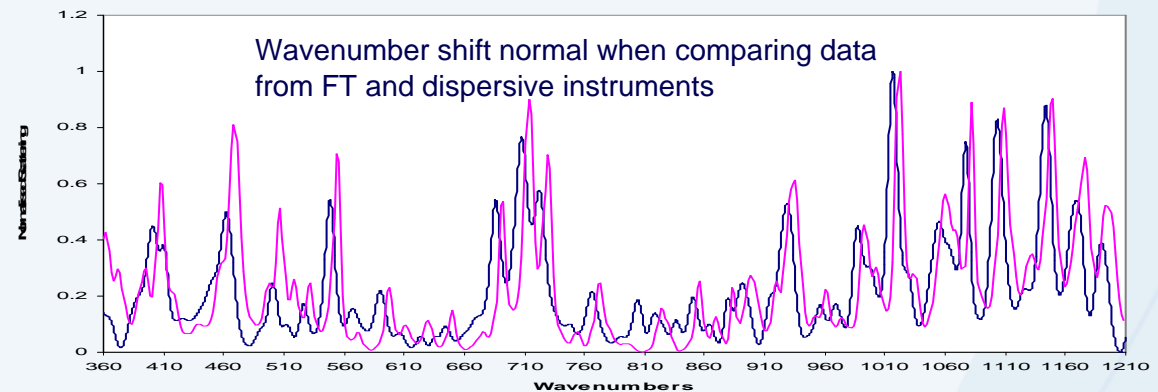
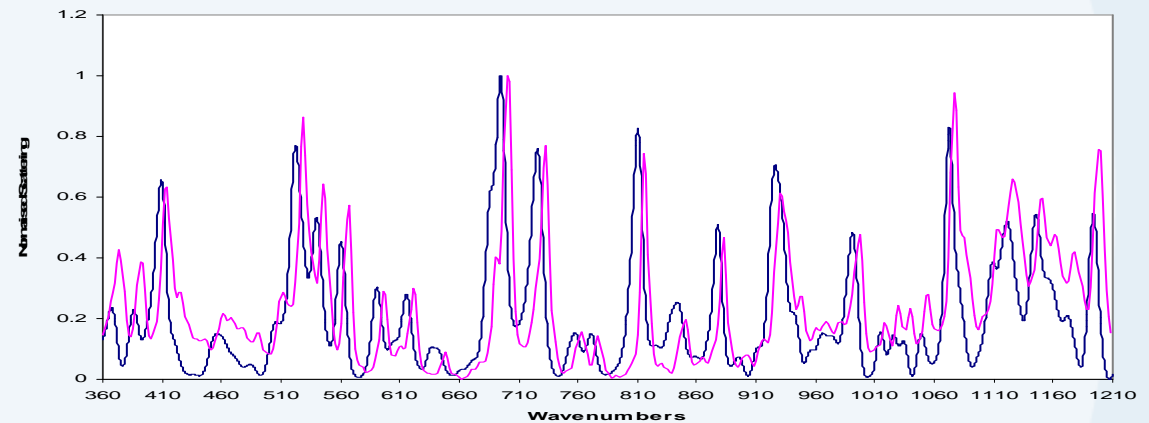
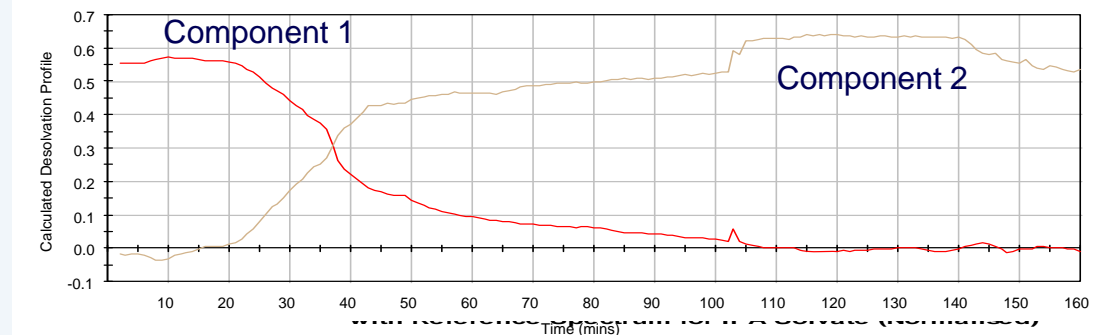
1. Paul Eilers, Anal. Chem. (2004) **76**, 404-411

Example 3: Results

Carried out SNV normalisation followed by multivariate curve resolution (ITTFA)

Calculated spectrum for Component 1 overlaid with reference spectrum of form X

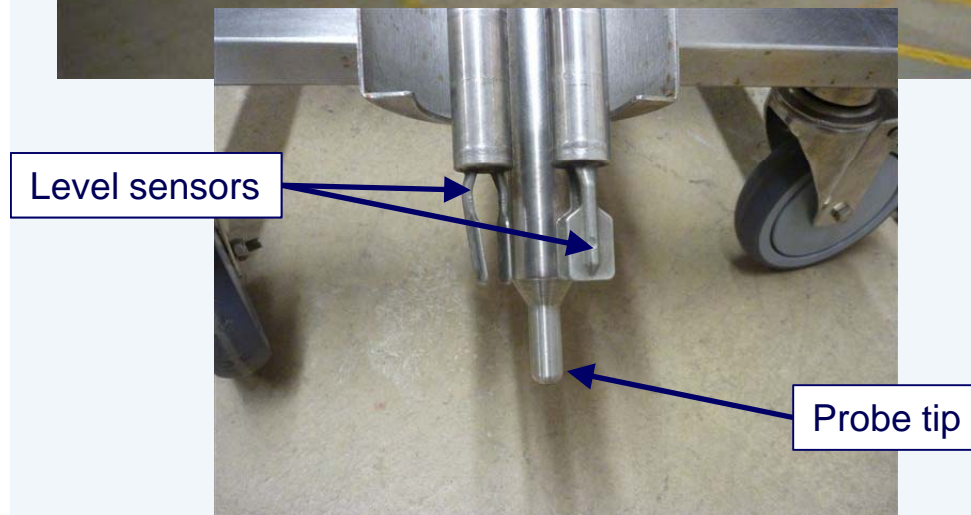
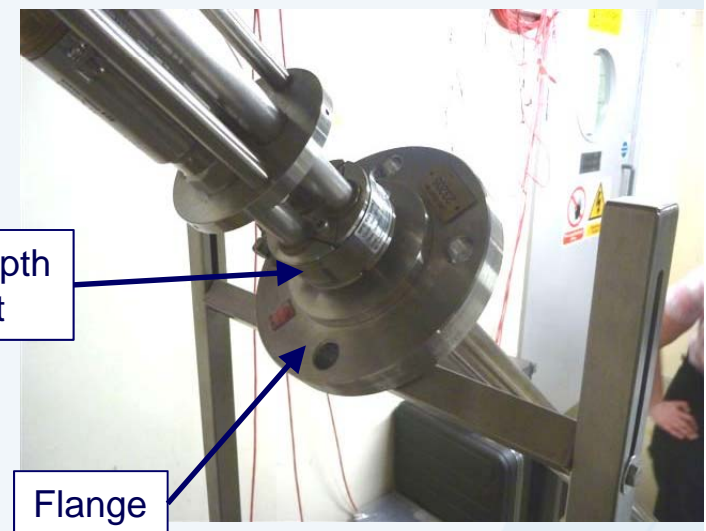
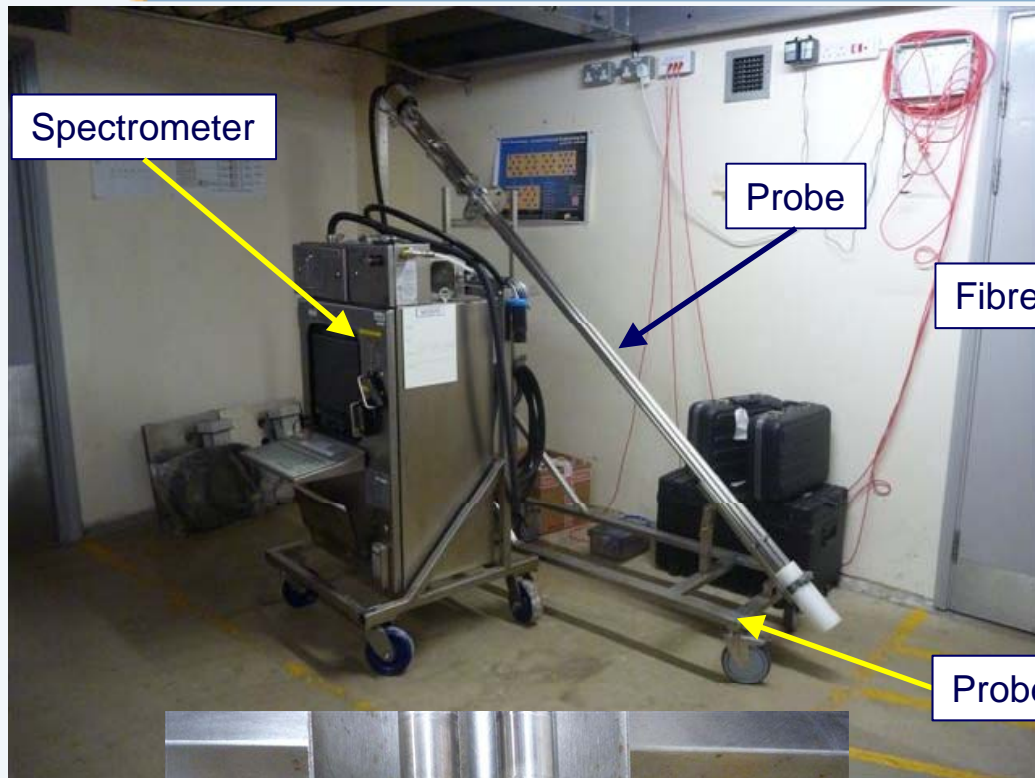
Calculated spectrum for Component 2 overlaid with reference spectrum of form Y



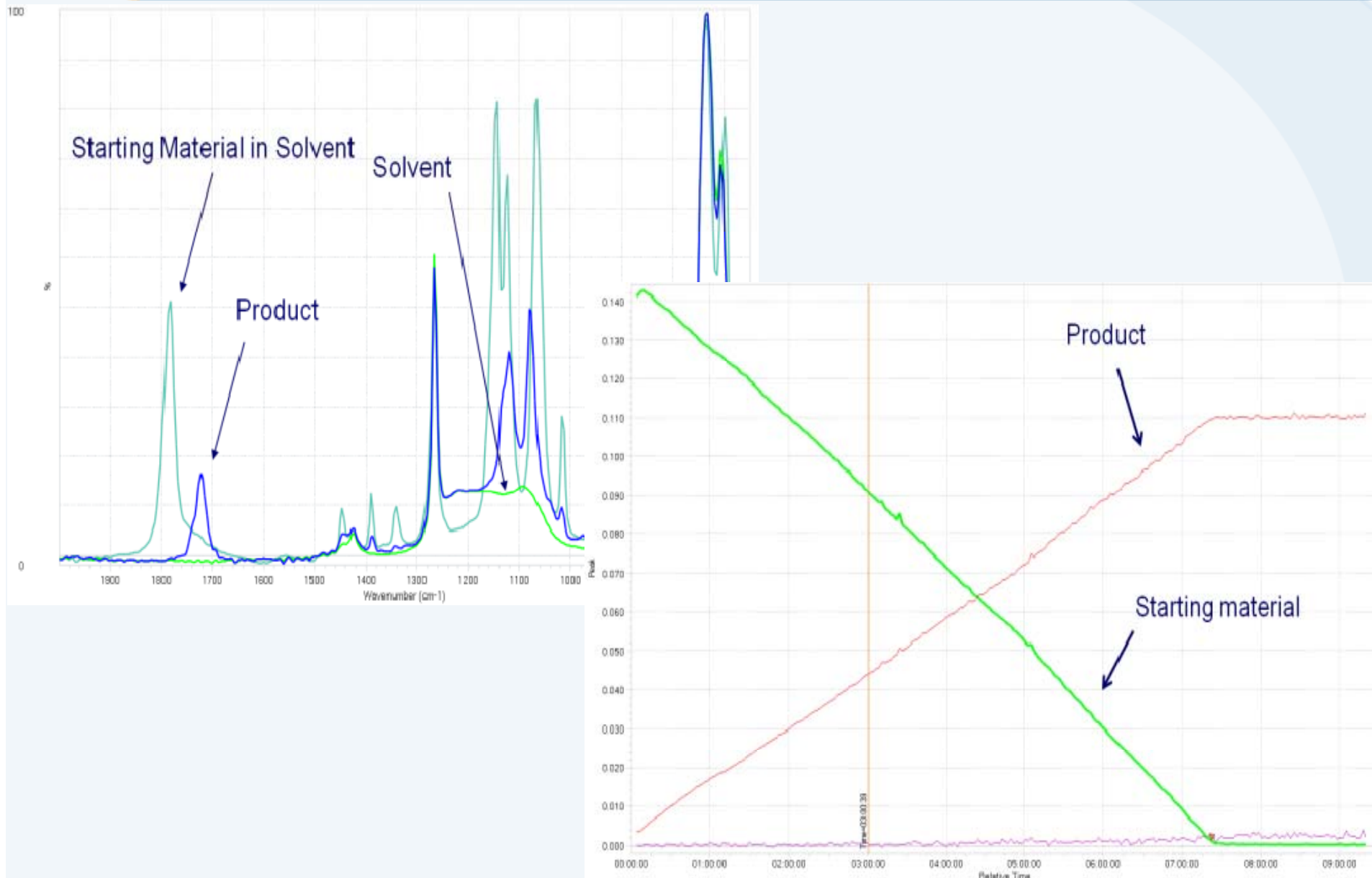
Example 4. Implementing Raman Monitoring in Manufacturing Plant

- Issue: AtEx regulations
 - Class 3 laser constitutes potential ignition source
 - Need to monitor reactions in Zone 0 (vessel) containing potentially flammable solvents
- Solution: Level sensor interlock system
 - Twin, redundant level sensors
 - Set above level of probe tip
 - Interlock to laser power
 - Laser will not strike unless both level sensors are submerged, guaranteeing probe tip is submerged

Solution in Pictures



Reaction Monitoring in Third Party Manufacturing Plant



Result!



Conclusions

- Raman spectroscopy provides practical solutions to real-time reaction monitoring problems
 - Ability to resolve signals from closely related species
 - Differing selectivity from mid-IR
 - Ability to monitor multiphase systems
 - Insensitivity to water
- Approaches to resolving some of the limitations of Raman
 - Preprocessing of data to resolve baseline artifacts
 - Ultimately can't fix the problem in cases of excessive fluorescence
 - Require different excitation wavelengths
- Can implement AtEx-approved plant-based systems

Acknowledgements

Example 1

- Chow San San

Example 2

- Ali Selman

Example 3

- Peter Aspin
- Elaine Smith

Example 4

- Greg Gervasio
- Louise Fido
- Brian Doan
- Marina Duffy
- Duncan Thompson
- Third party contractor staff



GlaxoSmithKline