KEIT spectrometers

Shining a Light on Process Spectroscopy

Obligatory disclaimer slide

The author works for a company that makes and sells FTIR process spectrometers.

He's tried really hard not to be biased…

…sorry if he gets carried away when talking about FTIR.

Why bother with process spectroscopy?

"I don't need spectroscopy"

- I spent ages on scale-up – I understand my chemistry.
- I have temperature and pH probes – they tell me everything I need to know!
- It's expensive!

Benefits of spectroscopy

- Can catch unexpected reactions, intermediates and by-products.
- Monitors levels of contaminants in feedstocks, reagents and solvents.
- Very beneficial for process optimisation.

Difference between laboratory and process spectrometers

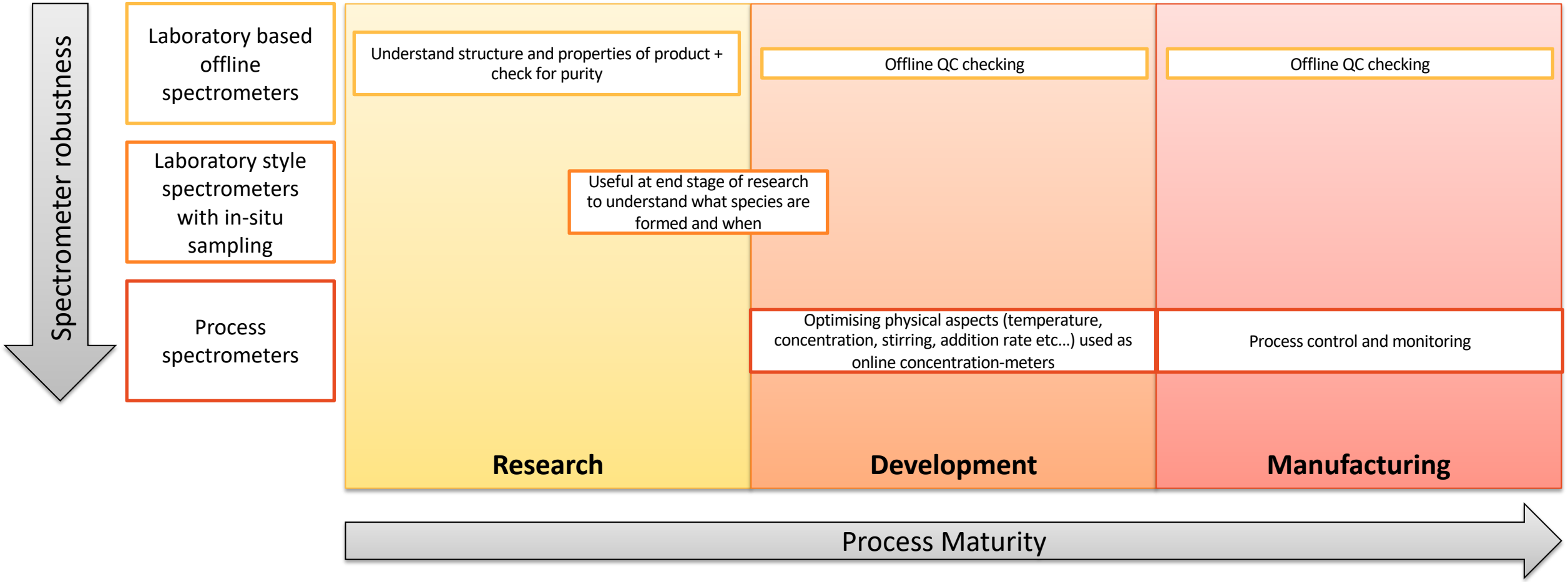
Laboratory

- Safe, controlled, stable environment
- Access to purge gas, liquid nitrogen, specialist handling equipment (i.e. glove box)
- Sample brought to instrument with perfectly designed sampling interface

Process

- Hazardous, uncontrolled and dynamic environment
- Possibly access to purge gas, unlikely access to liquid nitrogen or specialist handling equipment
- Spectrometer brought to sample, with flanged (or similar) interface

Different ways to use spectroscopy



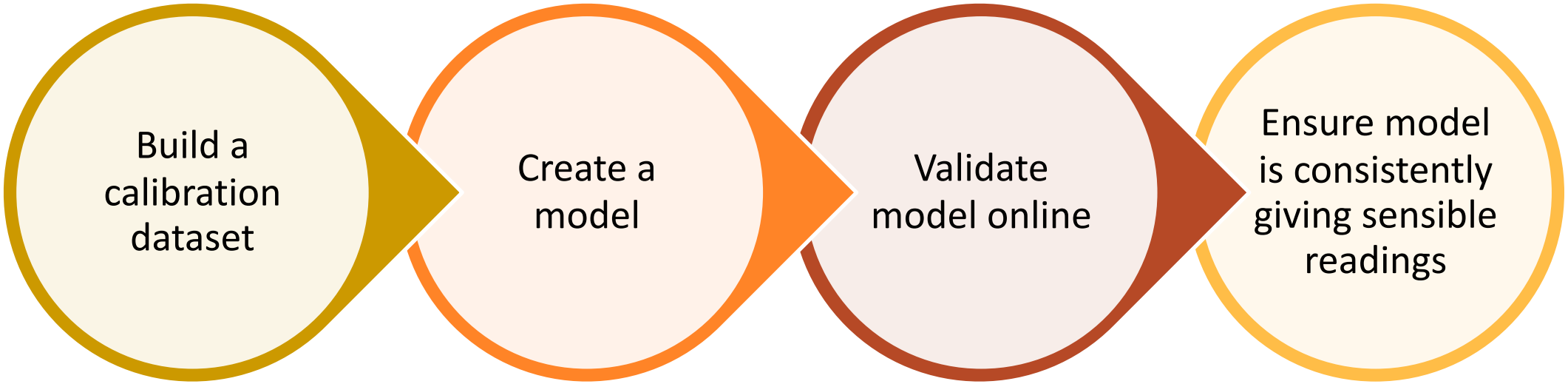
How do you use a spectrometer as a concentration meter?

- By building a calibration model

$$\text{Beer's Law: } A = \varepsilon c l$$

- Univariate Modelling
  - Peak height tracking
  - Concentration = coefficient(Absorbance) + offset
- Multivariate Modelling (chemometrics)
  - Interprets the entire spectrum rather than discrete peaks
  - Can also interpret relationships (i.e. reagent consumption as product is formed)
  - Can be used for non-linear systems if transforms are used (such as SVMR)

How do you actually use a spectrometer as a concentration meter?



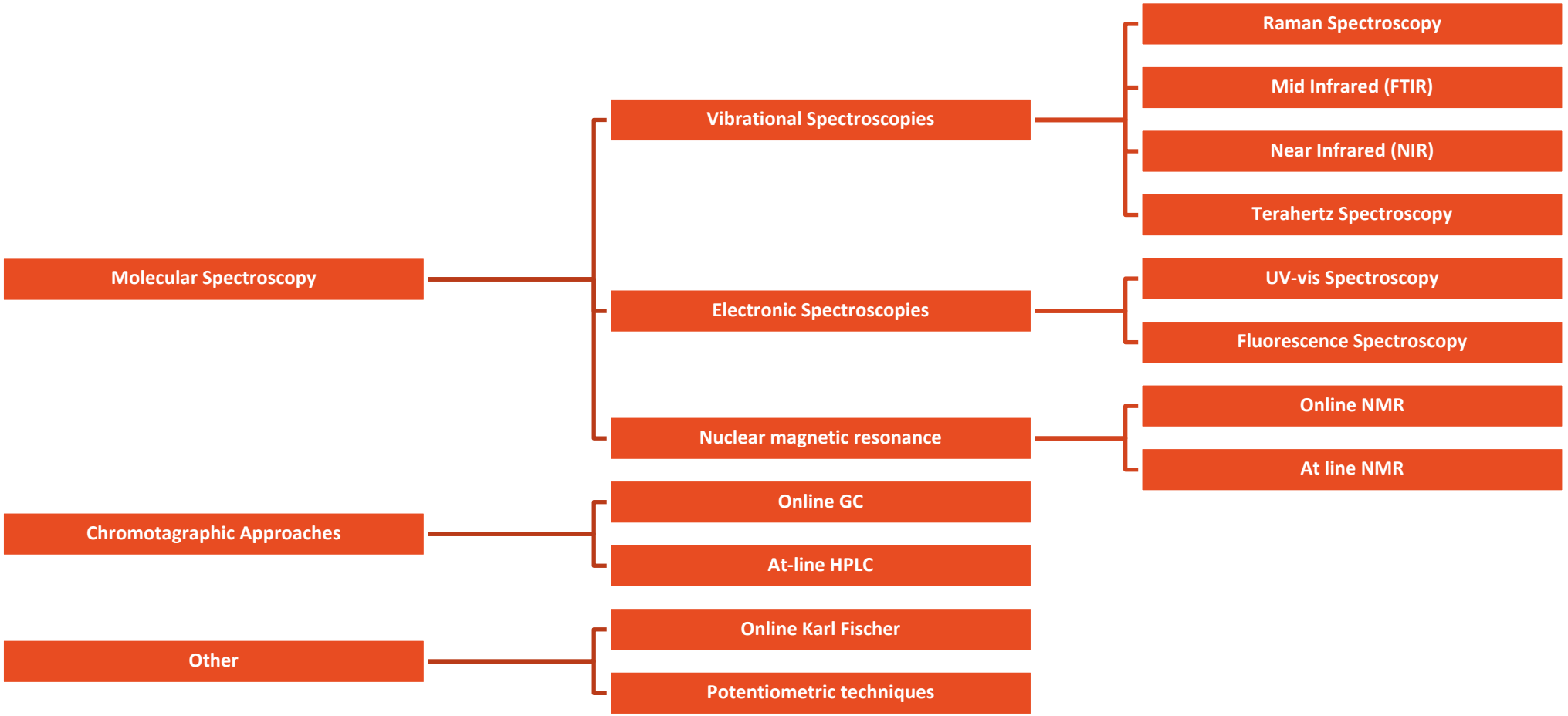
- Using a Design of Experiment methodology
- Running standard processes and taking extracted samples

- Find relationship between peak heights and concentration for univariate modelling (classical method)
- Build chemometric models for compounds of interest (state of the art)

- Install model on online spectrometer
- Periodically check model against offline sampling

- Use offline analysis
- Use online statistical analysis of residuals and Hotelling's T^2

What sorts of spectroscopy are out there?



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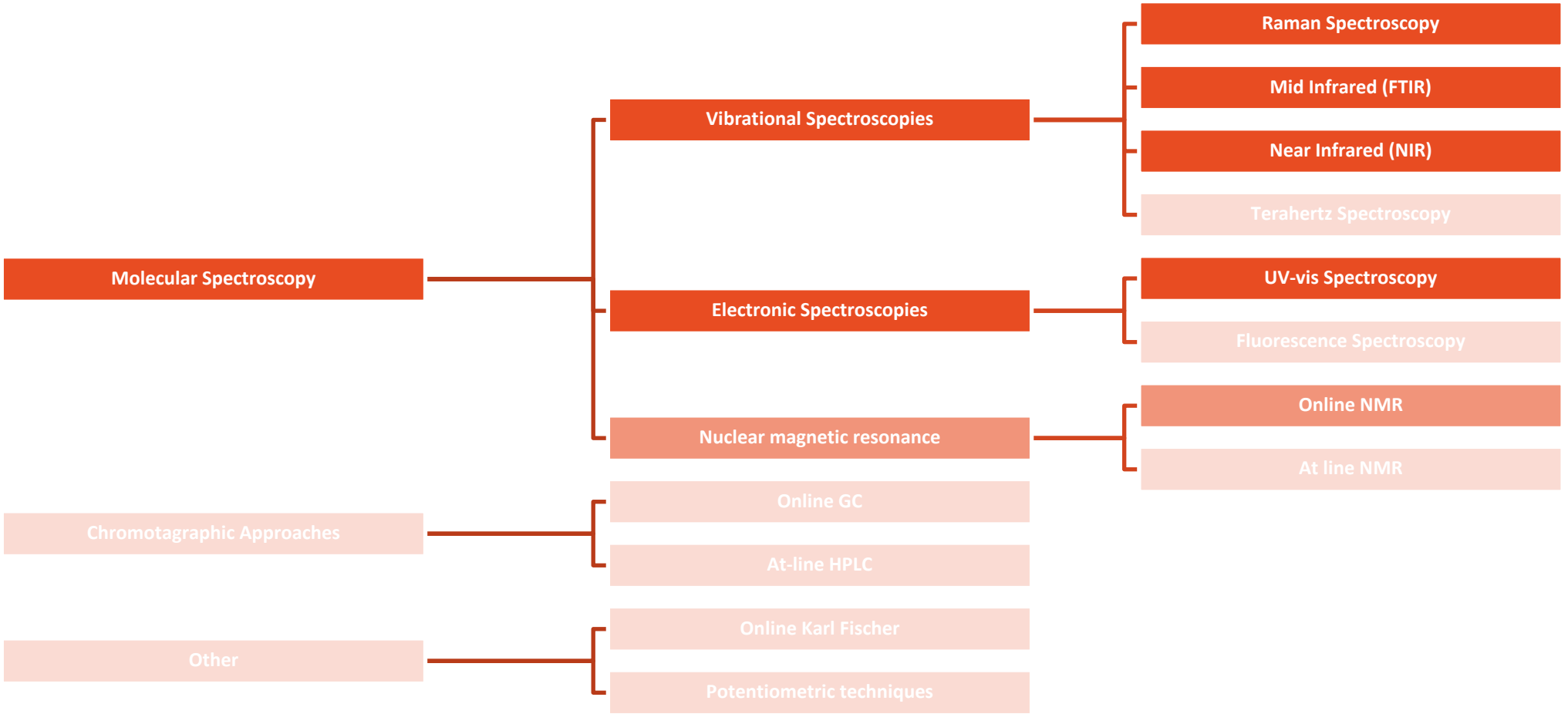


"Online" NMR Spectroscopy

The good

Inherently quantitative (potentially no need for chemometric modelling).

Extremely information rich.

Able to monitor a very wide range of chemistries.

Not really online – more "automated at-line sampling".

Slower sampling times than other techniques.

Not process friendly – definitely not suitable for hazardous zones.

The less good

Ideal applications: early-stage R&D and understanding of reaction kinetics, dynamics, and intermediates.

Raman Spectroscopy

The good

Long fibres allow for placing instrument far away from process if necessary.

ATEX models available.

Small and varied probes accommodate a variety of process conditions and interfaces.

Information rich spectra.

Wide spectral range – especially at the low wavenumber range.

Fluorescence can be a major issue.

Very expensive instruments.

Lasers introduce safety concerns and require additional measures.

Chemometric models can be sensitive to solids loading, turbidity and biomass as Raman is a scattering process.

Not inherently a quantitative process as does not work on basis of absorbance*.

The less good

Ideal applications: anything involving carbon fibre or pyrolytic carbon. Polymorph identification and tablet analysis in pharma.

***Raman is strictly an emission process, but it is possible to build reasonable quantitative models even if it doesn't follow Beer's Law**

NIR Spectroscopy

The good

Long fibres allow for placing instrument far away from process if necessary.

ATEX models available.

Small and varied probes accommodate a variety of process conditions and interfaces.

Can be multiplexed reducing cost to install.

NIR spectrometers are being made smaller and smaller.

Very poor information level.

Requires chemometrics to be interpreted – almost impossible to understand spectra without.

Cannot differentiate between similar chemical structures.

Comparatively poor detection limits.

The less good

Ideal applications: solids analysis in the food and drink industry (i.e. water levels in meat, degree of roast on coffee beans etc…). Tablet analysis to ensure uniform coating in pharma processes.

FTIR Spectroscopy

The good

ATR sensing inherently stable to changing solids content, biomass or bubbles.

ATEX models available.

Established and understood spectral technique that is rich in information.

Sensitive technique with fairly low LoDs.

Traditional fibre-based instruments can be fragile*.

Reasonably costly technique.

Best performance requires purge with either dry air or nitrogen supply.

The less good

Ideal applications: analysis of liquid processes (i.e. chemical reactions, fermentations, continuous manufacturing of drinks and liquid foods etc…)

***New generation of spectrometers with no moving parts has resolved this issue.**

UV-Vis Spectroscopy

The good

Possible to build very small and compact probes.

Can be connected using long and flexible probes.

Minimal interference from complicated mixtures.

Very low LoDs.

Information poor.

Not all chemicals have strong UV-vis signals.

The less good

Ideal applications: analysis of waste water, heavy metal analysis, chromophore analysis.

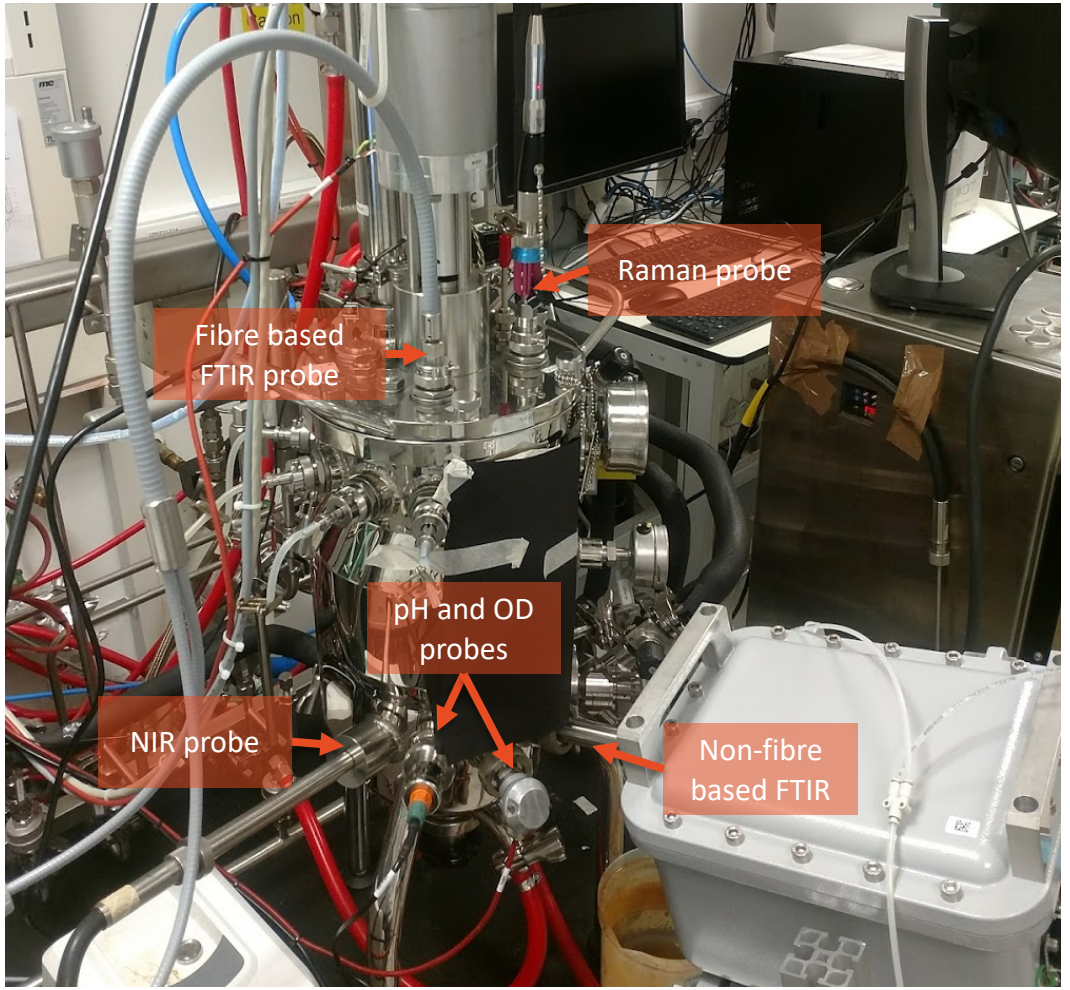
Quick case study as an example

- Monitoring a fermentation process using online spectroscopy
- Different techniques were used simultaneously to gauge suitability

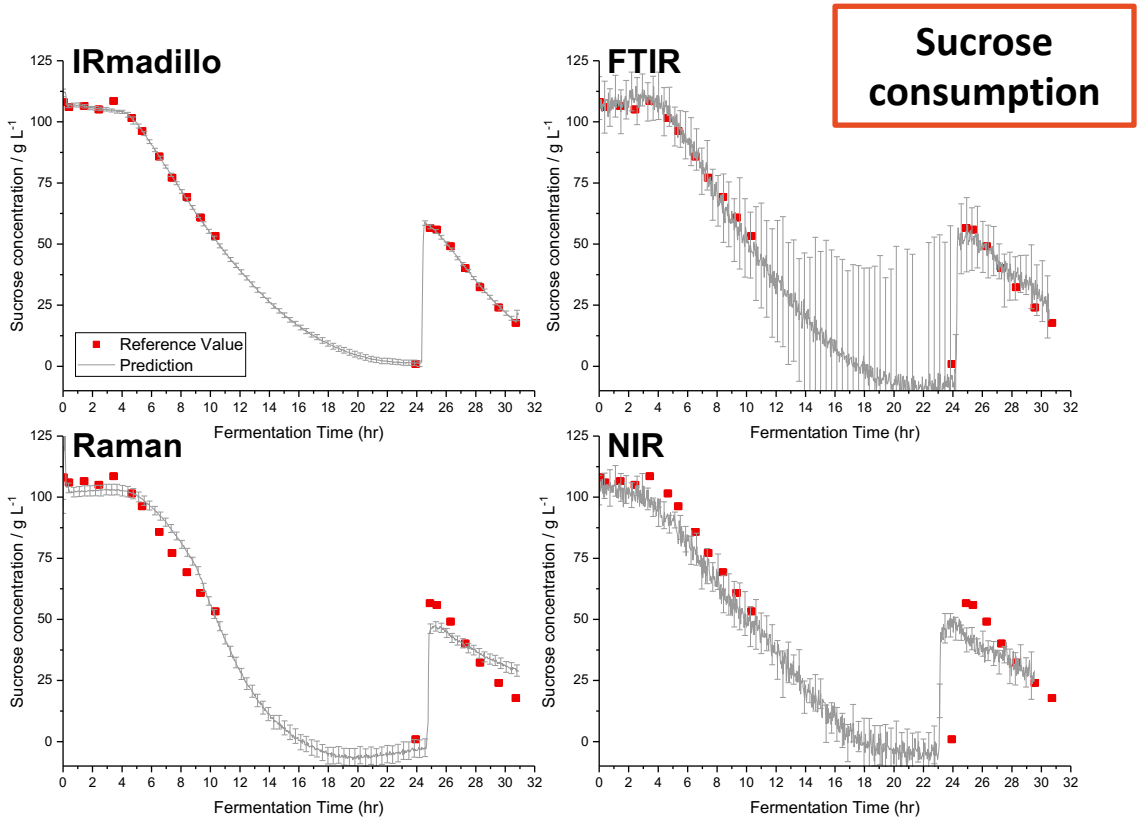
Second disclaimer: the author is presenting this data because he has access to it. There is bound to be other data from other instrument vendors showing how their instruments are suitable for different applications!

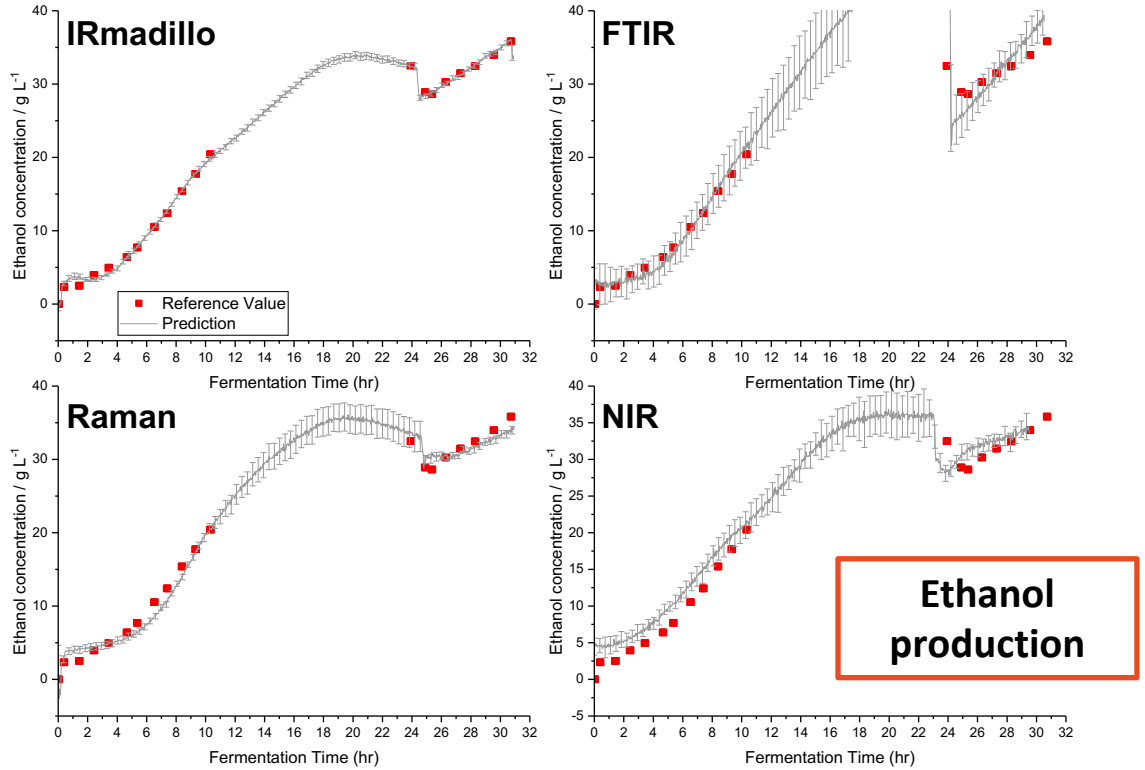
Comparative study at the IBioIC

- Collaboration between **Keit**, **IBioIC** and **CPACT**
  - IBioIC – Industrial Biotechnology Innovation Centre
  - CPACT – Centre Process Analytical Control Technologies
- Online monitoring of sucrose fermentation
- 4 spectrometers would constantly monitor the process and offline HPLC used to gauge capability



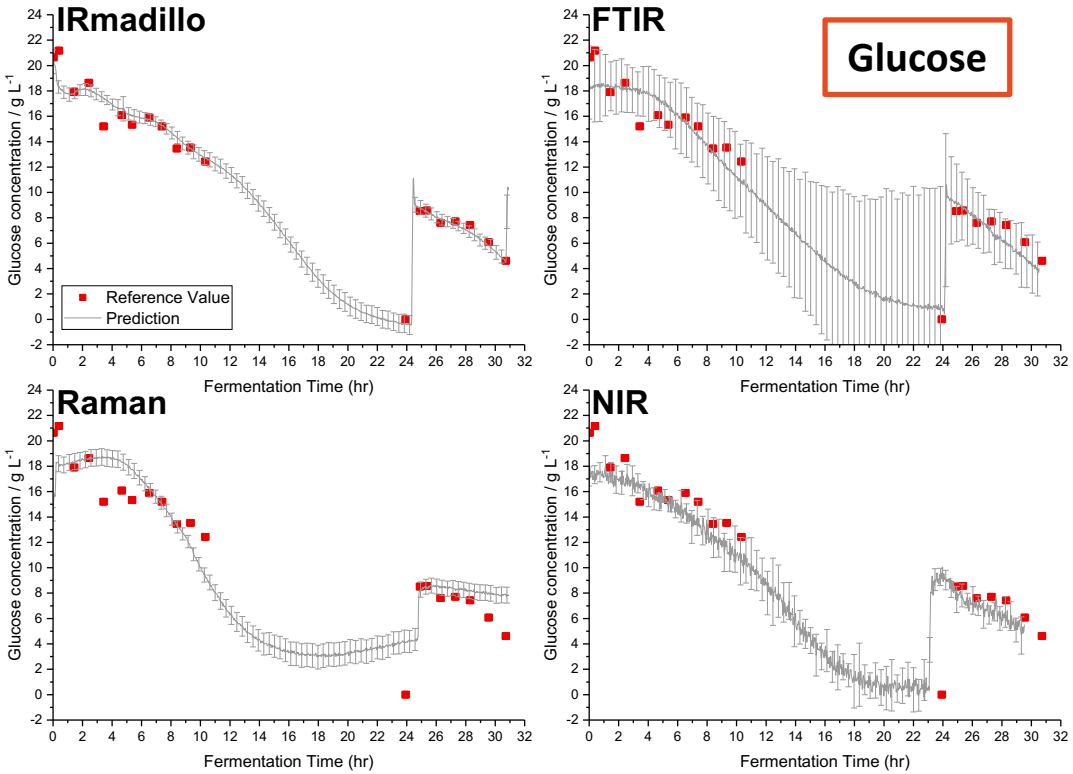
Product and reagent monitoring

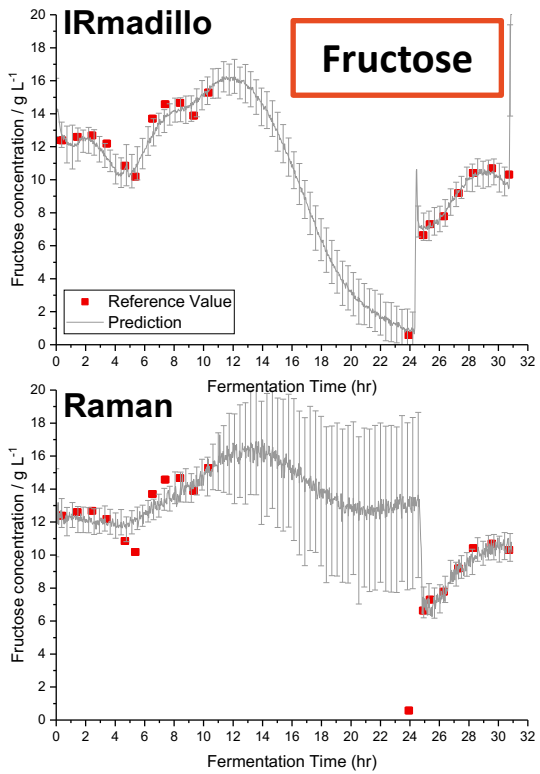


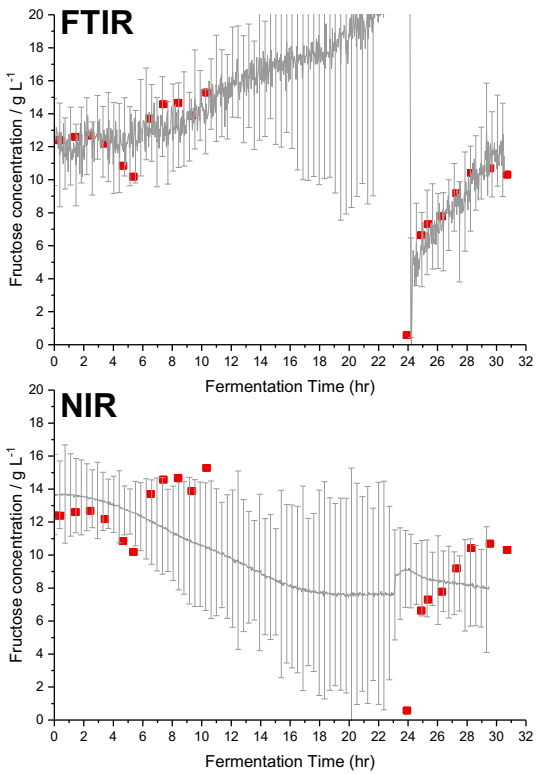


All four instruments are capable of measuring both sucrose consumption and ethanol production over the course of the fermentation. All of the spectrometers show the step change caused by the sucrose addition at 25 hr, but only the IRmadillo and FTIR accurately model the new sucrose concentration afterwards.
FTIR measures unrealistically high values for ethanol.

Sucrose hydrolysis







All four instruments track general consumption of glucose. Uncertainty on FTIR is very large, and Raman struggles to predict absolute concentrations, especially at end stage of fermentation. Neither Raman nor NIR measure the “0” value of glucose.

IRmadillo and Raman both monitor fructose production and consumption accurately. FTIR measures general trends but not accurate concentrations, predicting very high levels of fructose mid run. NIR cannot measure fructose at all, yielding no agreement with the reference values.

“So what”?

- Process Spectroscopy is an important part of modern day chemistry
- Combining spectroscopy with trend analysis and many other sensors is a critical step towards Industry 4.0
- Pick the right spectroscopic technique for the process you want to analyse! There is (unfortunately) no singular universal technique.