Converting Batch to Continuous for Profit as well as Fun

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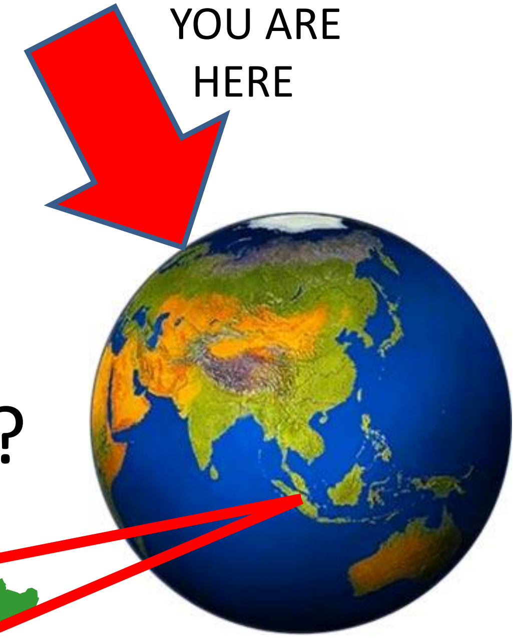
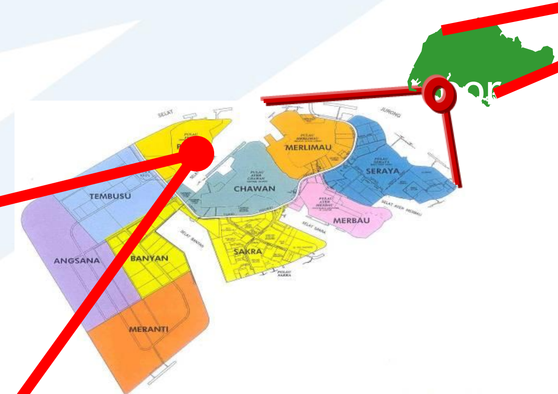
Summary



- Batch and continuous processing
- How can continuous make money?
- Examples
- The hidden gaps



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Why we have batch

- It does most things… badly, but it does them
- It is immensely tolerant of ignorance
- I already have a lot of pots and think I understand them
    - I can clean the pots and use them again
    - My friends have pots I can use in case I don't have enough
- It fits my business model
    - Short time to market
    - Short product life
- I'm still in business – why risk change?

Degussa

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So continuous is better?

- Well of course
  - It's smaller
  - Cheaper
  - Faster
  - Safer
  - Cleaner
  - More efficient
  - Scales up more easily
- How could anybody not see the benefit?

DSM using Corning Microreactors

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So continuous wants to compete?

- Of course there's a catch
- Yes, there may well be benefits

  BUT

  - Lots of exaggerated claims have been made based on selective data
  - Need to deliver at whole process level not just one magical item
  - Need to provide benefit for a sufficient proportion of processes to warrant the resource overhead
  - Need to demonstrate a clear business case for each investment

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Things that a business might want

- Fast time to market;
- Low development effort (as can't afford a large effort with high attrition and margin pressures);
- Low cost exposure if product fails or market prediction is wrong;
- Transferability to contract manufacture;
- A need to use a range of chemistries and complex multistage processes to make products;
- Work under high degrees of regulation of product;
- **ie Ability to implement robust processes quickly and cost-effectively using flexible resources**

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Mythbusters

- There is a lot of misunderstanding around...
- Reactions/crystallisations care about flow
- Microchannels mix fast
- Continuous is inherently safe
    - Remember Bhopal and Flixborough
- All reactions can go fast
- Not many reactions use solids
- **The capabilities of continuous automatically align with business need**
- etc

BEWARE OF THE

BULL

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Making a business case

- The business case for continuous spans a continuum….
  - **"No Brainer"** – why aren't we doing this already?
    - Perhaps 10% of cases
  - **"No Way"** – glad I still have some batch vessels!
    - Perhaps 10-30% of cases
  - **"The Middle Ground"** – maybe… and the battleground is here

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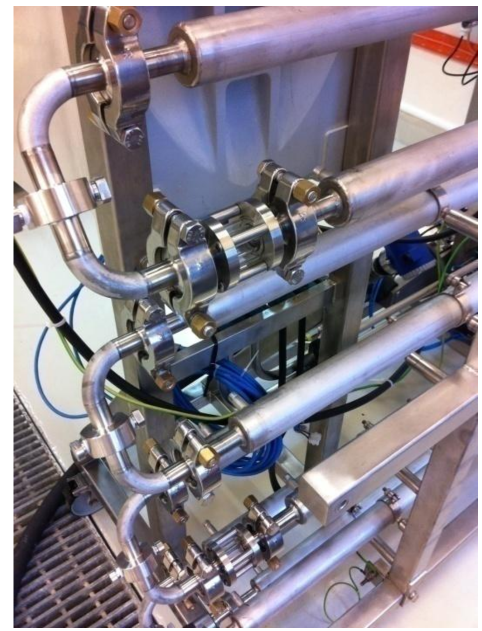
EXAMPLES… THE TECHNICAL BIT

Skids and infrastructure at ICES

Integrated Modular skids

Wiped Film Evaporator

Continuous Oscillatory Baffled Reactor



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Co-located with batch plant

- 60L standard batch plant
- Equivalent continuous scale 20L/h nominal capacity
- And batch vessels can be used as continuous stirred tanks

Batch Reactor
Systems

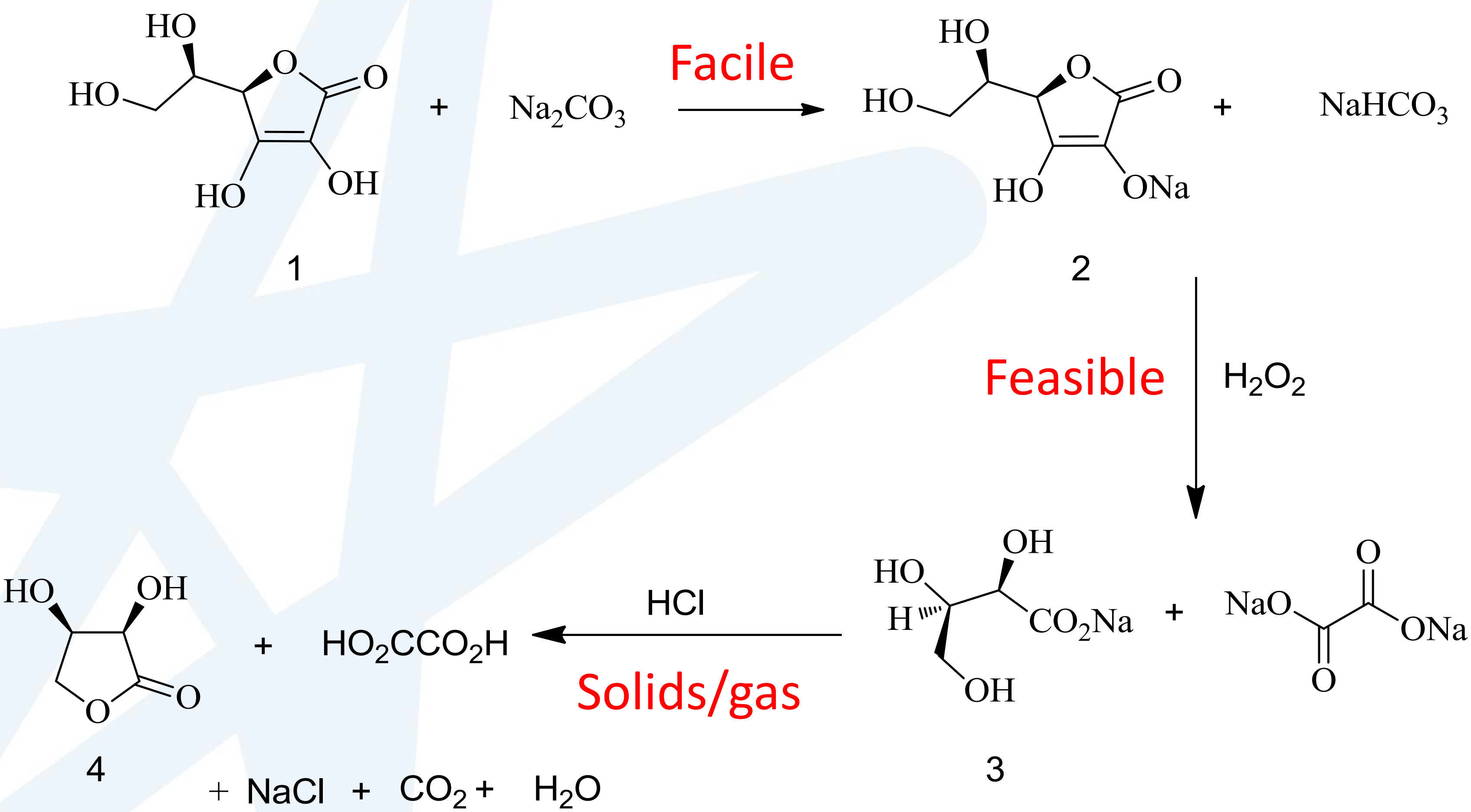
Development tools

APTAC

RC1 with Raman

- Tools as for batch development
- Calorimetry, batch small-scale Reactions, individual behaviour assessment (eg settling velocity)
- Use of PAT tools in development

4,D-erythronolactone



And product recovery is horrific

Process development

- Developed and ran full scale batch process (60L) for comparison
- Carried out minimal additional development for continuous
- Hybrid processing adopted as back end problematic

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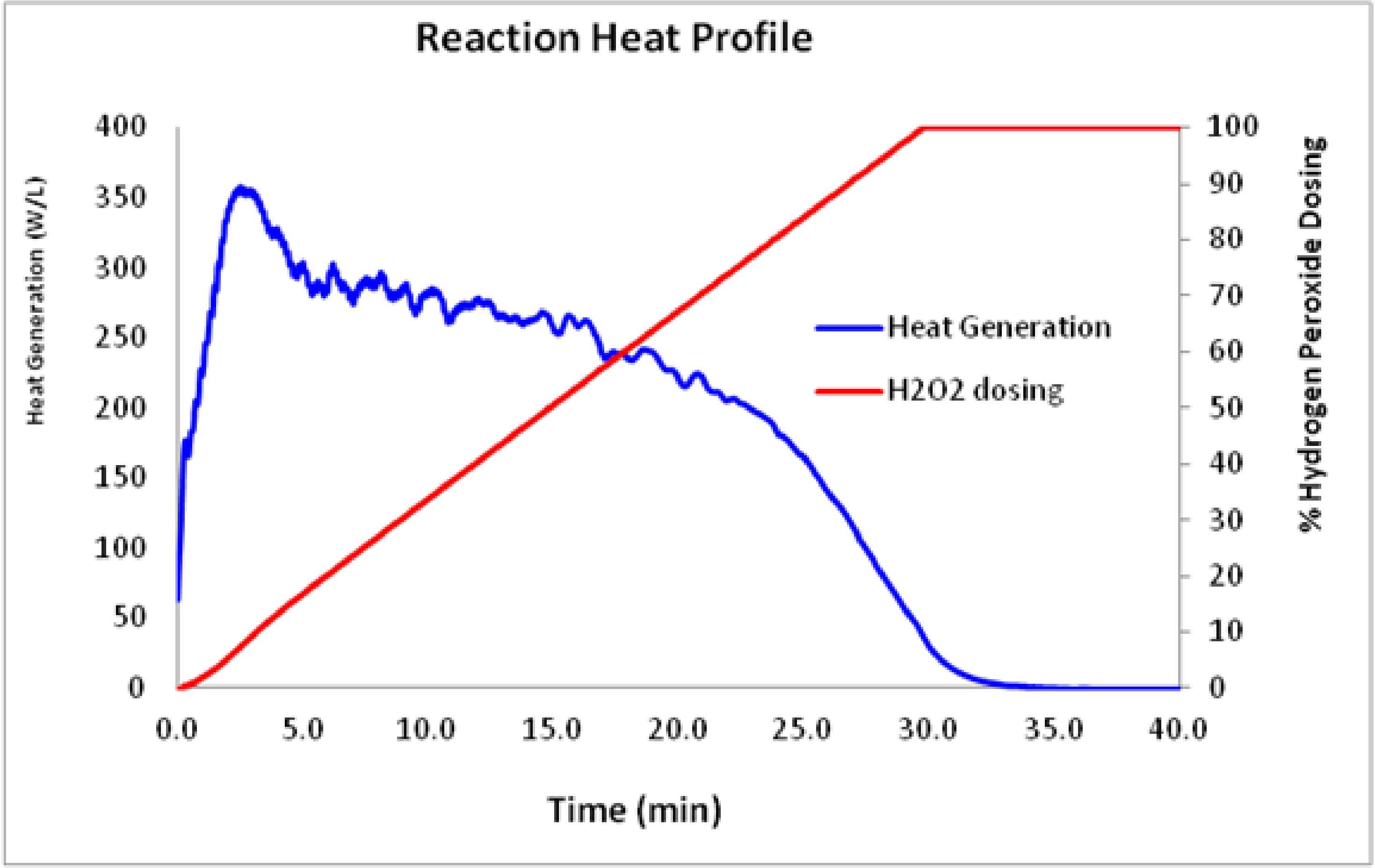
The oxidation reaction

- Batch calorimetry indicates instantaneous reaction



Typical heat release profile for peroxide addition

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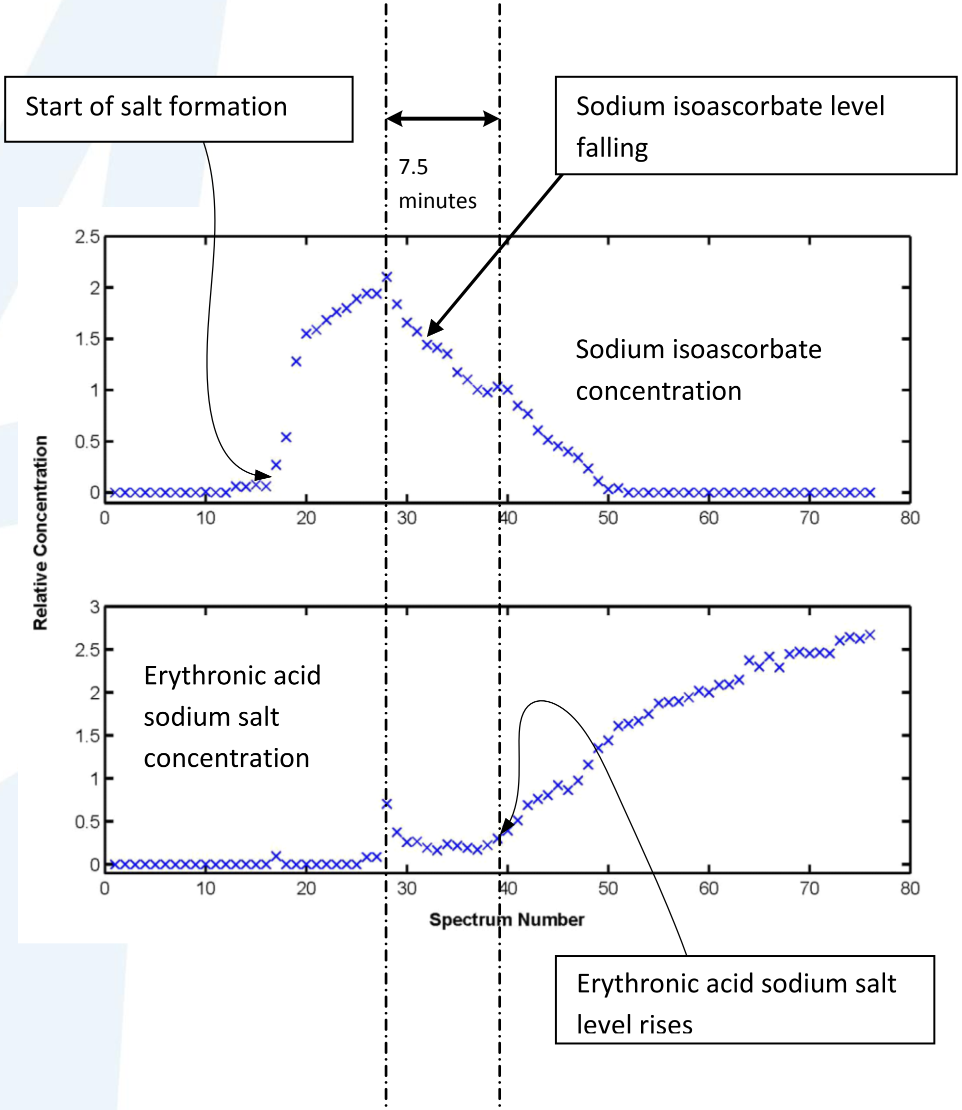
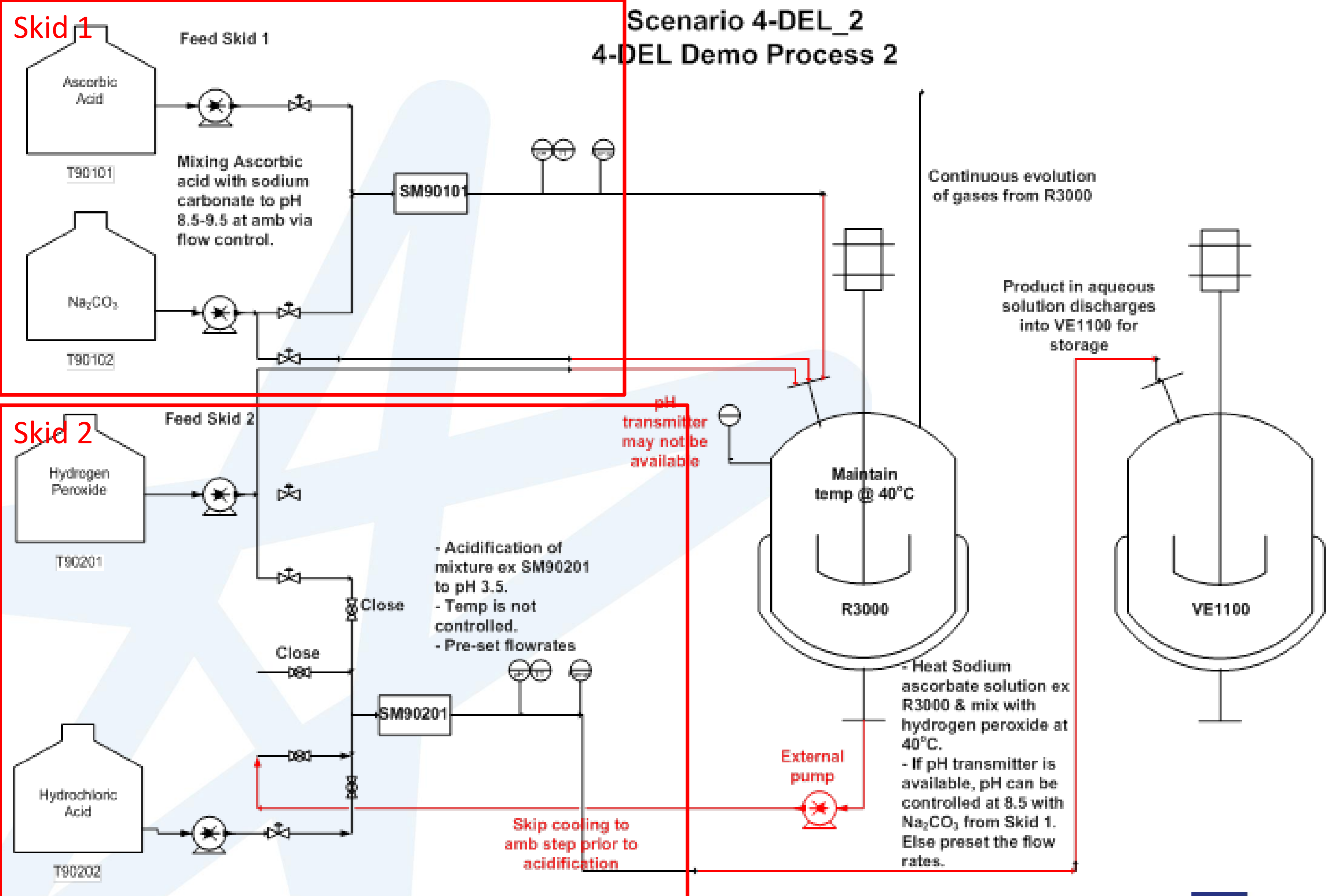
But *in situ* Raman tells a different story



Scenario 4-DEL_2
4-DEL Demo Process 2



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Some results

Stage	Species	%w/w solution	Flowrate (kg/hr)	Flowrate (g/s)		Flowrate (mol/s)	Mol eq	Total mass (kg)
Salt formation (Phases 1 and 3)	D-isoascorbic acid	7.7	9.60	2.67	0.21	0.0012	1.0	19.20
	water				2.46	0.1367		
	sodium carbonate	15	3.30	0.92	0.13	0.0013	1.17	6.6
	water				0.77	0.0434		
Oxidation (Phases 2 and 3)	Hydrogen peroxide	30	1.05	0.29	0.09	0.0026	2.2	2.09
	water				0.20	0.0113		
	sodium carbonate	15	6.38	1.77	0.27	0.0025	2.2	12.76
	water				1.51	0.0837		
Acidification *Batch Phase 4	HCl	18	4.17	1.16	0.21	0.0057	4.9	8.34
	water				0.95	0.0527		

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4DEL learning

- The first part of the process could readily be run continuously and with ease
- The appearance of solids and a solvent swap indicated batch for the back end…
  - We think there is a way, but it's speculative
- **Without end-to-end continuous there is no business case**

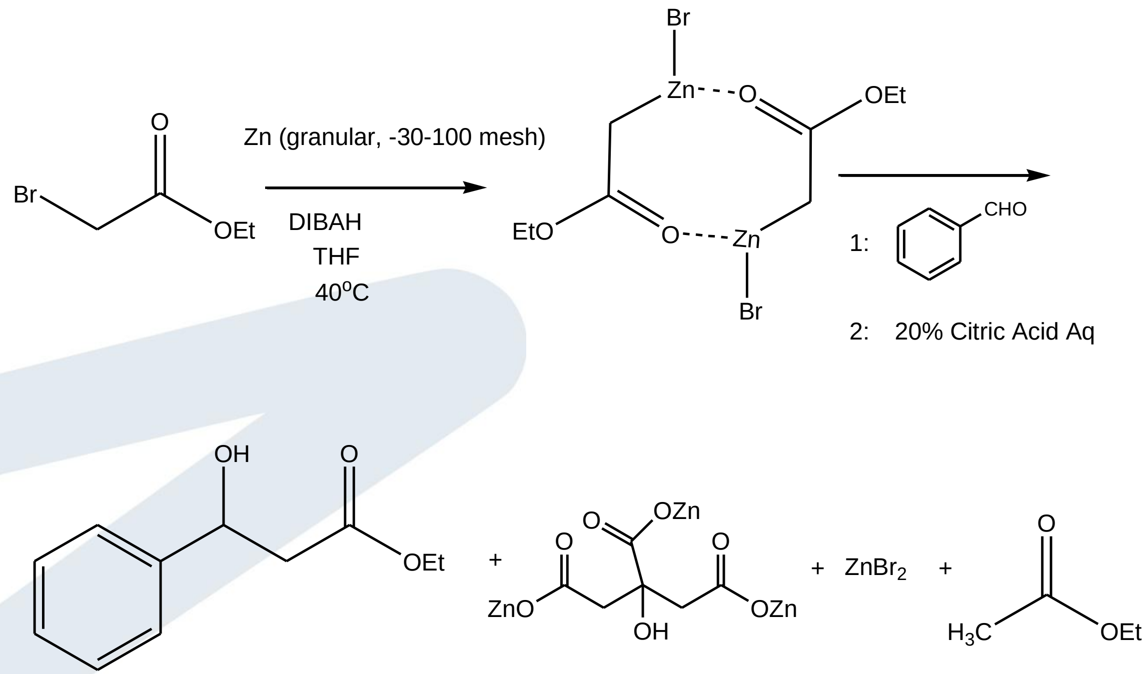
Reformatsky Chemistry in a Miniplant

3 stage process

Stage 1 – Reformatsky reagent formation

Stage 2 – Reformatsky reaction

Stage 3 – Aqueous quench using citric acid



Molecular Weight: 194.23

ethyl 3-hydroxy-3-phenylpropanoate

A Scalable Zinc Activation Procedure Using DIBAL-H in a Reformatsky Reaction, Girgis M.J, Liang J.K., Du Z., Slade J., Prasad K., Organic Process Research & Development **2009,** *13,* 1094–1099

Reformatsky Chemistry

Why continuous processing?

1. Reduced inventory – Inherently safer
2. Increased heat and mass transfer, allowing higher heat removal rate and mixing efficiency
3. Higher thermal inertia of the equipment due to higher mass/volume ratio of equipment including cooling/heating system to reactive mass.
4. Smaller equipment footprint, possible lower capital cost

This one is almost a “no brainer”

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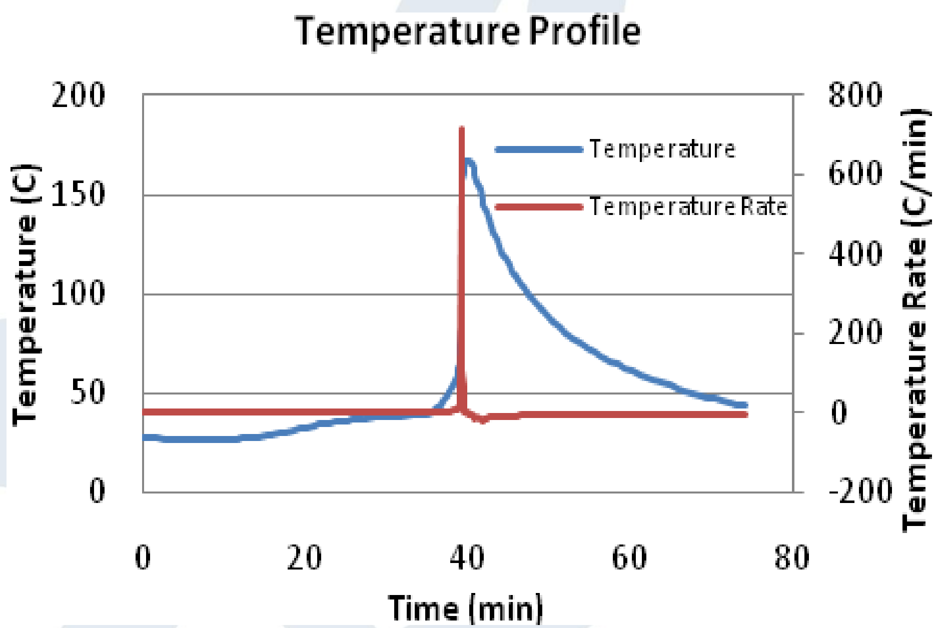
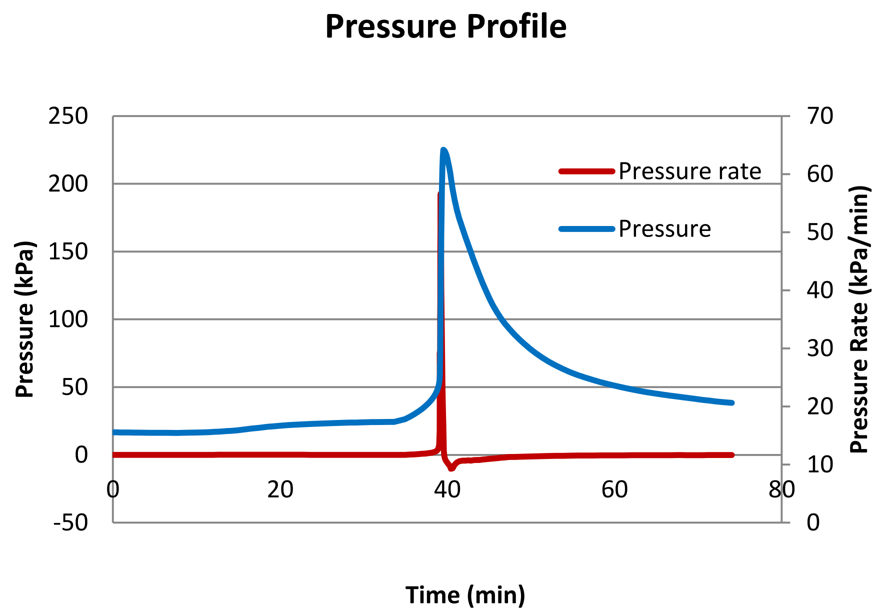
Process Development – Chemical Hazards Evaluation

Reformatsky Reagent





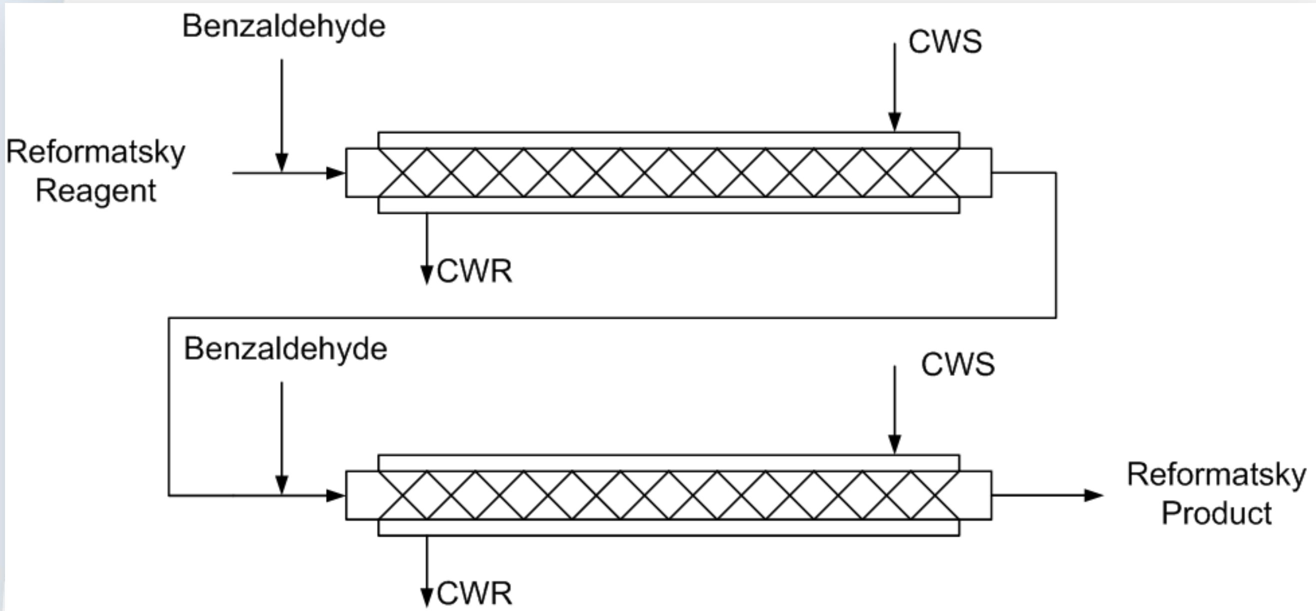
The data showed a rapid increase in both temperature and pressure of about 700˚C/min and 50kPa/min respectively

Process Development

Example issue – insufficient cooling following benzaldehyde addion would give temperature excursion (even in continuous)

Two reactors in series provide:

1. Better distribution of heat across reactors
2. Better heat control
3. Higher surface area to mass ratio
4. Higher thermal inertia



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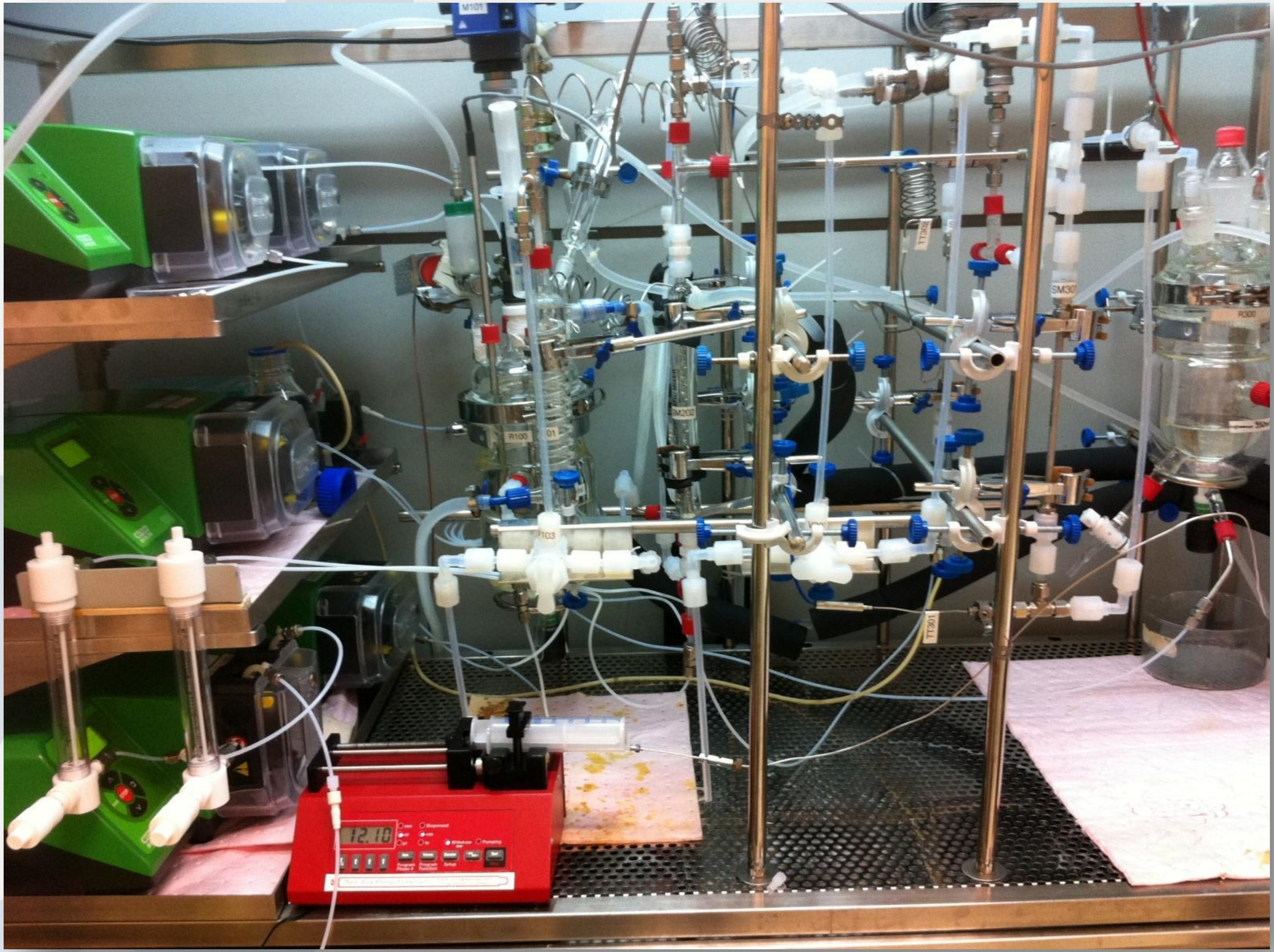
Bench Scale Reactor System



- 400kg/yr throughput

Bench Scale Reactor System

Zinc
Activation

Reagent Formation

Phase
separation

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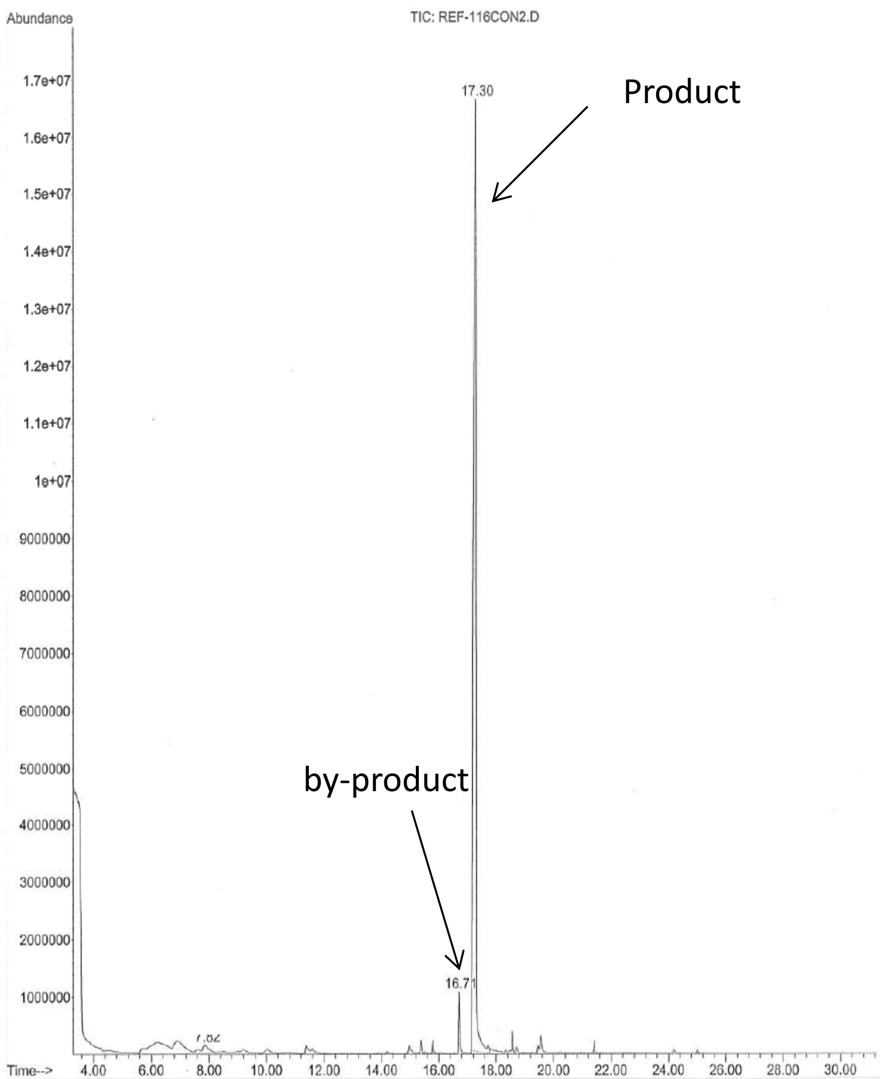
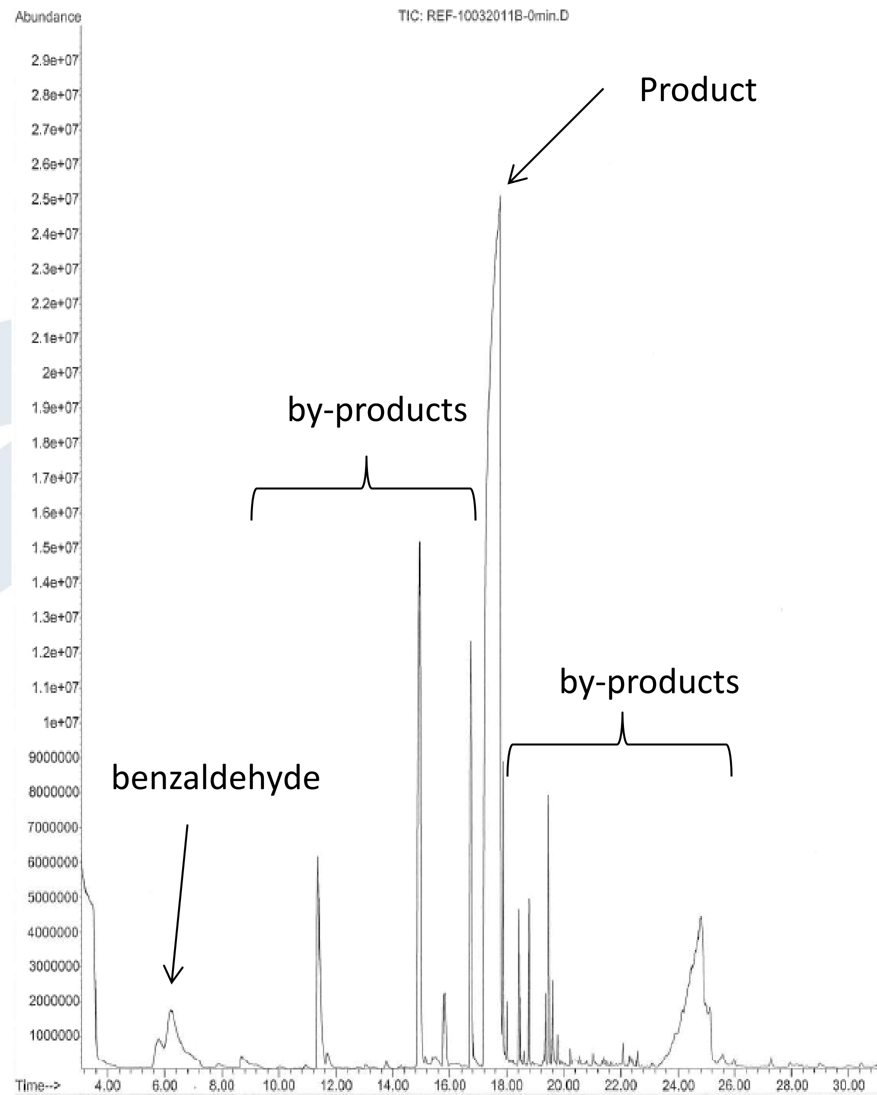
Results – a Happy Surprise

Continuous (10ml/min)



Batch 40ml



Discussion

Benefits of continuous Reformatsky process:

1. Reduced inventory – Inherently safer
2. Increased volumetric heat transfer, giving more robust safety case
3. High throughput - bench scale throughput is comparable to a small/medium size batch plant
4. Higher selectivity and purity

Reformatsky learning

- Give or take some solids control issues the process could readily be run continuously and with ease
- It allowed us to run a process we would not have taken on at 60L scale and to produce at a comparable rate
- **There is a good business case – and encouraged, we are now close to running continuous Grignard including making the reagent**

What we learned about implementation and skills

- While at first the problems seemed daunting, with a little determination they were resolvable
  - Inexperienced technologists delivered successful outcomes in realistic times and without excessive effort.
  - Didn’t need to draw on advanced modeling or simulation.
  - Good quality (standard) experimental and sound chemistry /engineering sufficient.
- The set of equipment and skills we have are flexible enough to take on a good range of processing problems
  - Continuous processing is within the capabilities of many organisations
- Benefits are not automatic from “going continuous”.

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SO WHAT ARE THE BROADER IMPLICATIONS TO DEVELOPMENT?

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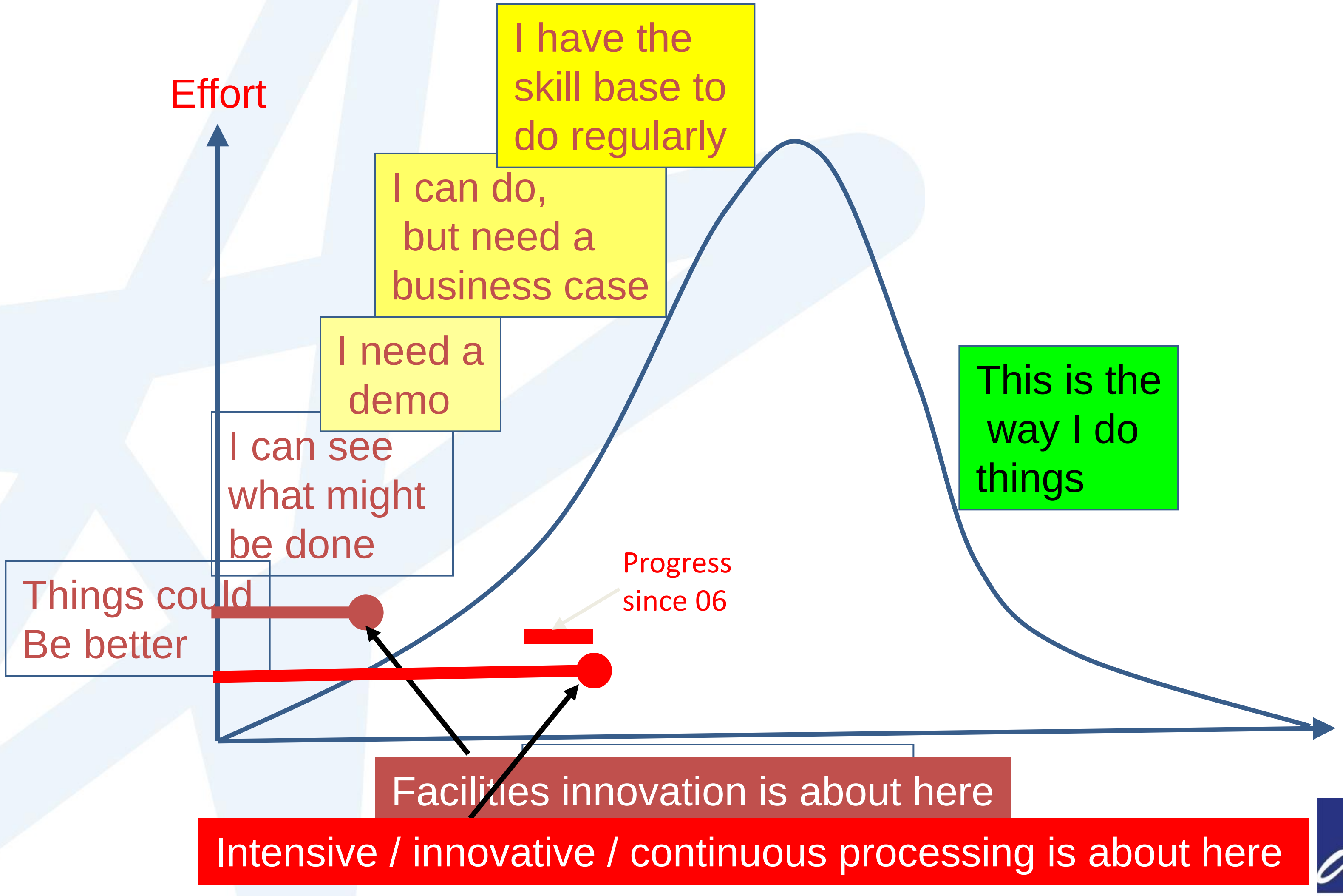
The Innovation Process 2008



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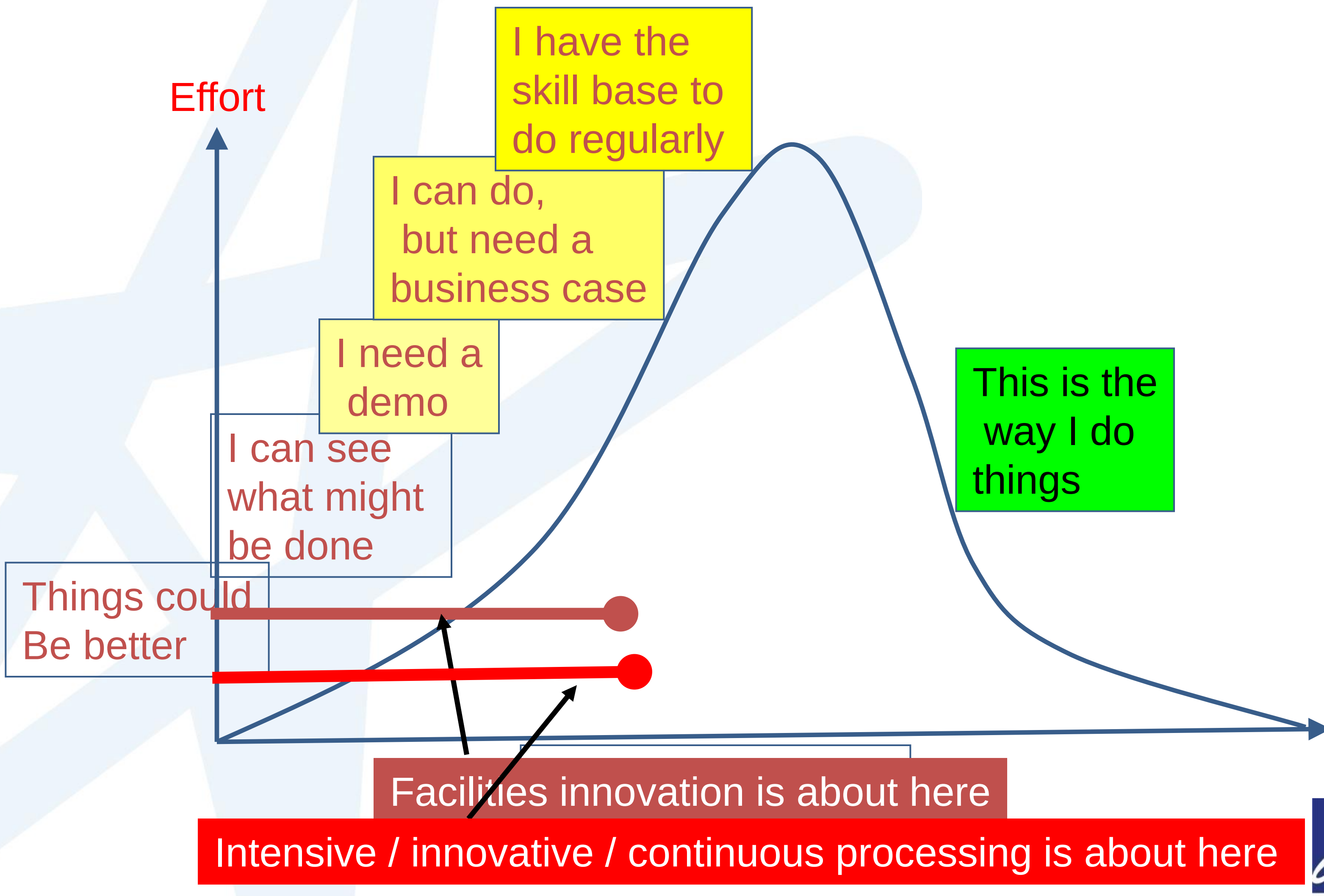
The Innovation Process 2013



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That was fun, could we do it again?

- Delivery of a one-off project by specialists is relatively easy with plenty of time
- Learning from them is harder
- Embedding as a way of working is difficult
  - Skill set changes – adopting new skills where needed (modeling? PAT for control?)
  - Decision making process modifications
  - Laboratory and pilot plant resources and capabilities
  - Integration with other activities – SHE assessment, purchasing and supply
  - Cutting across organisational boundaries

Two key Gaps

- Process understanding
  - How much is enough?
  - How to capture and exploit?
- Design methodology
  - Organising the design activity to be fast and efficient
  - Minimising rework and cost

Gathering and processing understanding

- Mathematical modelling / simulation
  - Viable but very expensive in primary, reliant on good experimental data
  - Tools weak for secondary
- Statistics / OR techniques
  - Links well to experimentation BUT
  - Not understanding based and not design-friendly
  - Too many variables (especially in secondary)
- Structured qualitative approaches
  - Various in house and proprietary methods eg BRITEST
  - Used to capture and exploit understanding in primary and secondary processing

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Design methodology

- The Unit Operation approach?
  - Represent (and even optimise) process as a set of well-defined equipment-based operations. SUMS
  - Much less effective for processes where the properties that define a stream are complex and even undefined
- The way chemists put together a process
  - Recipe-based, quite like cookery. LAB
  - Overly experiential and experimental so likely to miss non-obvious opportunities
- The “A Team” approach
  - Put the best guys on it. LAB+SUMS+SMARTS
  - Not feasible if you want to design a lot of processes

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Conclusions

- The battle now is moving from the business case to having an embedable, teachable method
- Much underpinning work remains to be done to provide the required understanding
  - But it's not seen as sexy
- There are still massive challenges in allowing <u>all</u> developers to "see the big picture"
  - But it is a massively difficult problem

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Thanks to…

- *Teoh Soo Khean, Wong Run Ling, Loretta Wong, Gabriel Loh, Loke Chien Ying, Chew Wee, Tan Suat Teng, David Wang, Salim Shaikh, Steven Mun and Ryo Tanigawara*
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- *BRITEST Limited*
- *GSK, AZ, Pfizer, Foster Wheeler, Genzyme, Shionogi*
- *A*Star Singapore*
- *And many others*

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