The use of automation and machine learning in Flow Chemistry

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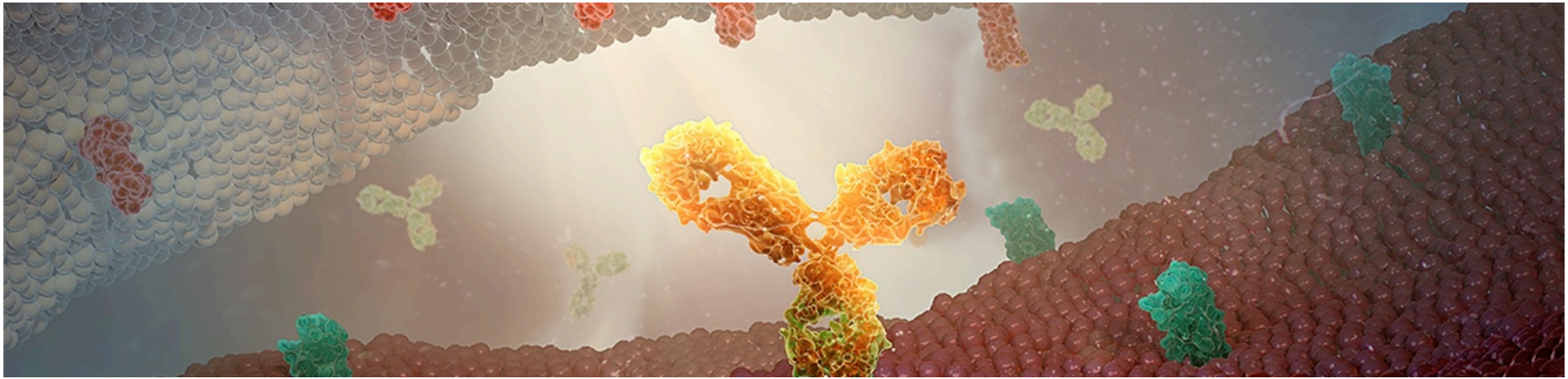
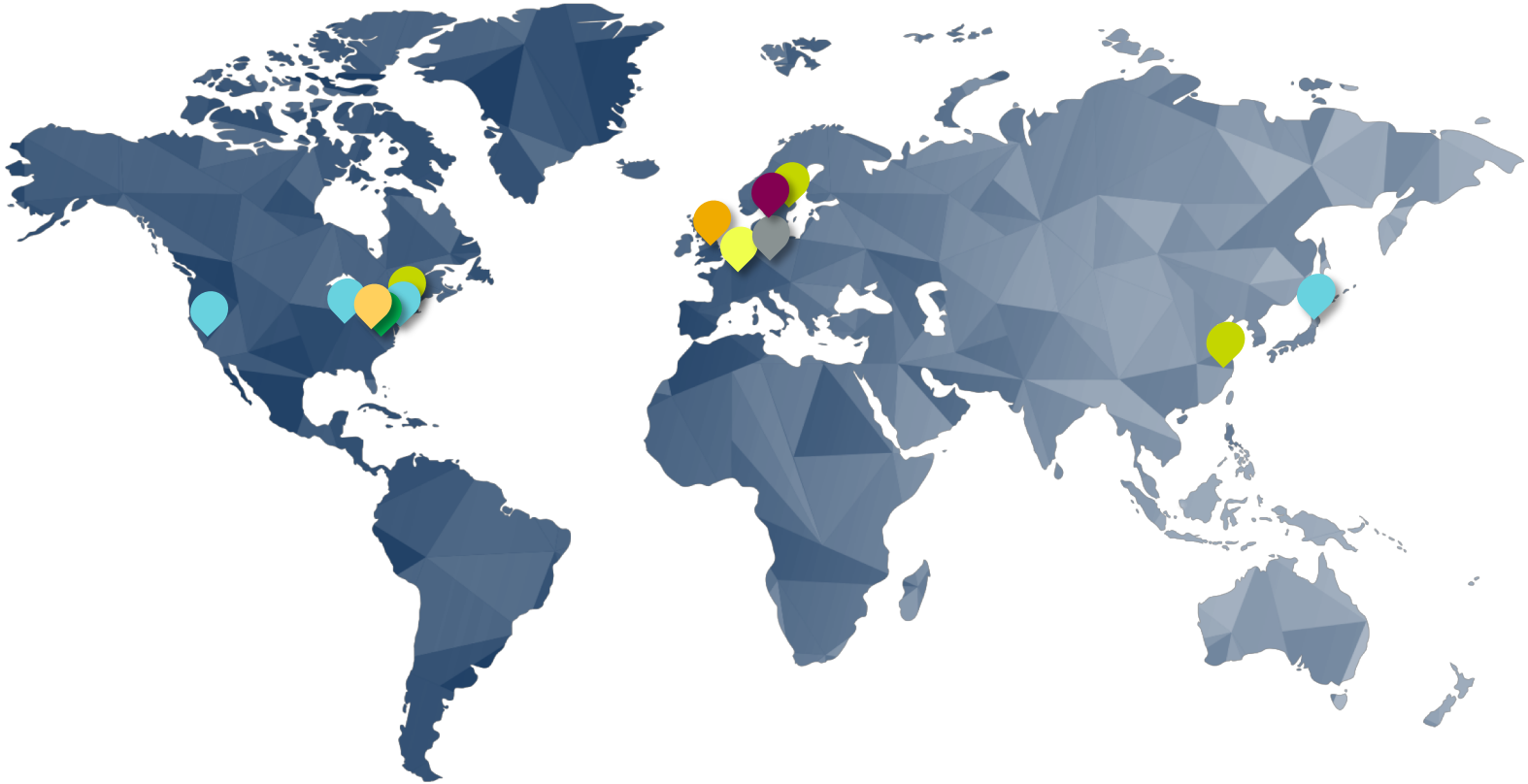
RSC Process Chemistry and Technology Group Launch Symposium

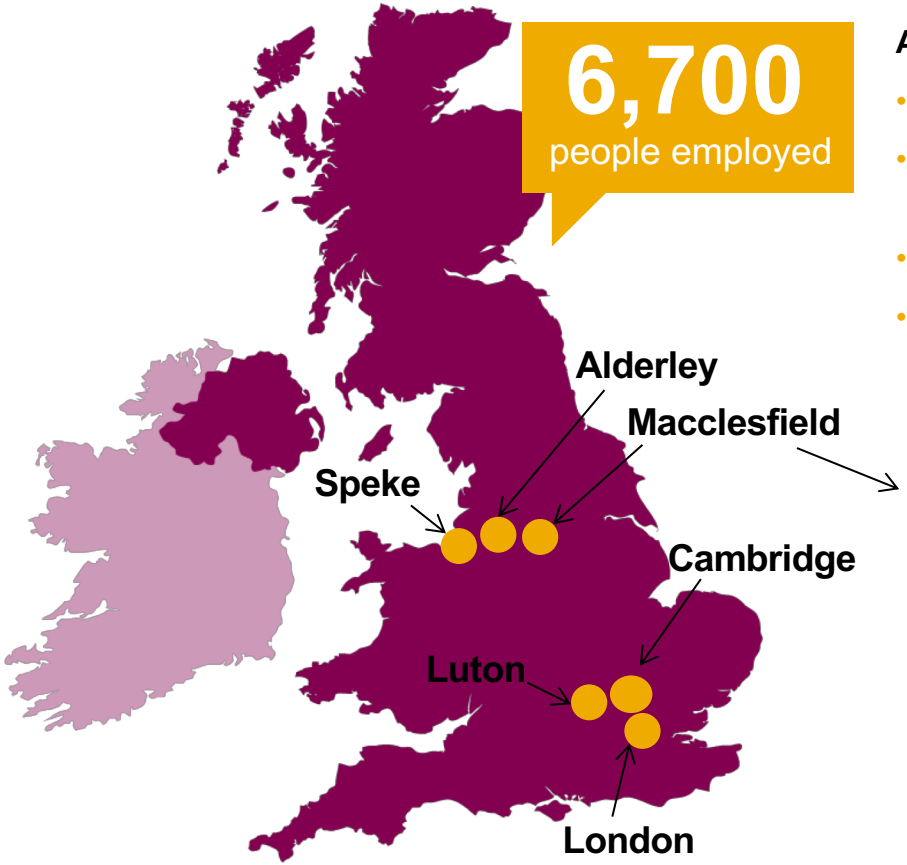
19 November 2018



AstraZeneca



AstraZeneca UK

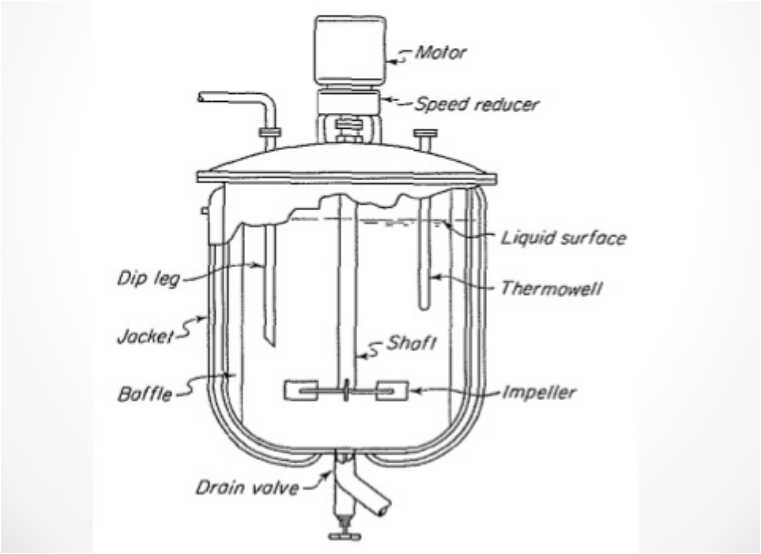


AstraZeneca:

- Creates around £4.5 billion in GVA directly
- Generates direct exports of £7.05 billion representing about 3% of the UK total exports of goods
- Invests £1.3 billion in R&D in the UK annually
- Headquarters located in Cambridge

Batch Chemistry

Batch chemistry mainly employed at AstraZeneca

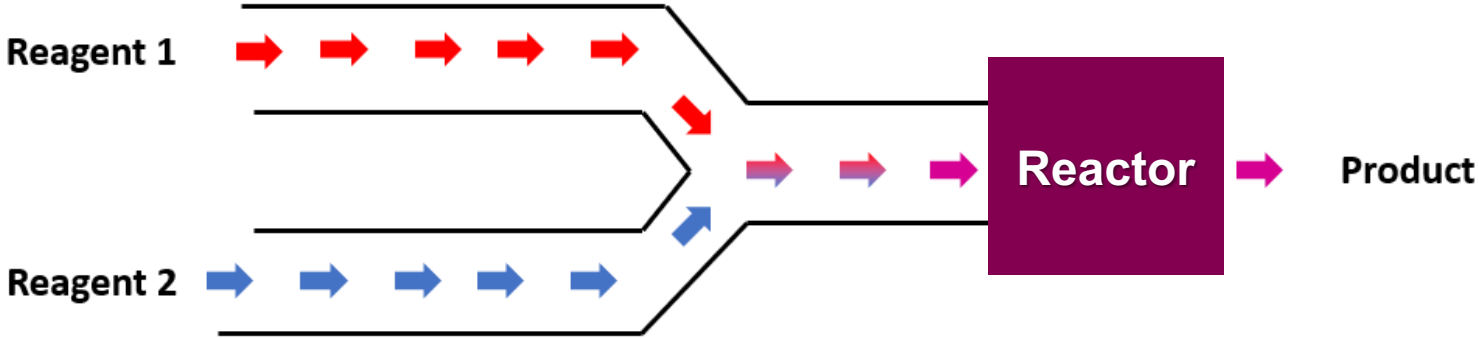


- Thousands of litres of material required when manufacturing on a large scale.
- Some reactions are too dangerous to be considered in batch.
- When things go wrong there is a significant material loss and financial cost.
- Batch chemistry scale up from the laboratory to manufacturing scale can be challenging.

Flow Chemistry

Reagents are continuously pumped through the reactor

Product is continuously collected from end of reactor



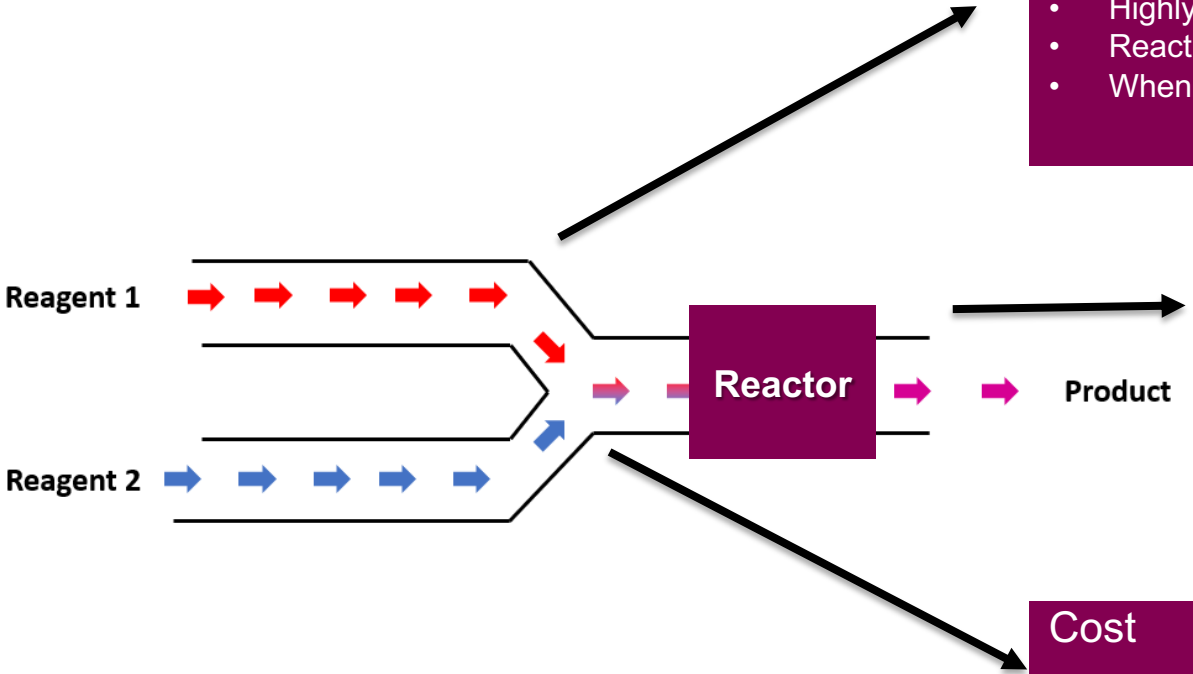
Benefits

- Better heat transfer (larger surface area)
- Much better reaction control than Batch chemistry
- Easier to scale-up than batch chemistry
- Lower inventories (safer)
- Easier to respond to product being out of specification
- Ease of Automation when compared to batch chemistry

AZ Drivers for Flow Chemistry

Safety

- Highly exothermic reactions
- Reactions at high pressures
- When handling hazardous materials



Control

- Unstable intermediates/reactants/products

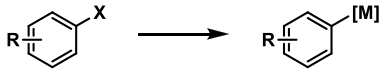
Cost

- Faster reactions
- Reduced process steps
- No need for cryogenic cooling

Targeted Continuous Processing Platforms

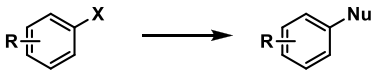
PRIMARY PLATFORMS

Cryogenic



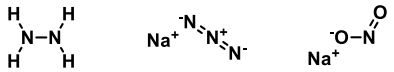
[M] = Li, Mg

S_NAr



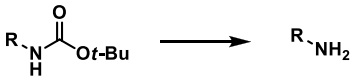
Nu = NHR, NR^1R^2

Hazardous



$Na^+ {}^-C{\equiv}N$ NO_2^+

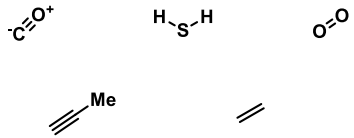
High Temp



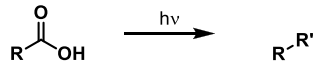
Boc deprotections, Cyclisations, Decarboxylations etc.

DEVELOPING PLATFORMS

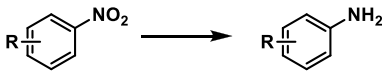
Gas/Liquid



Photoredox

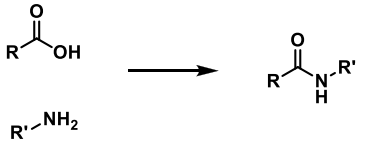


Solid Support

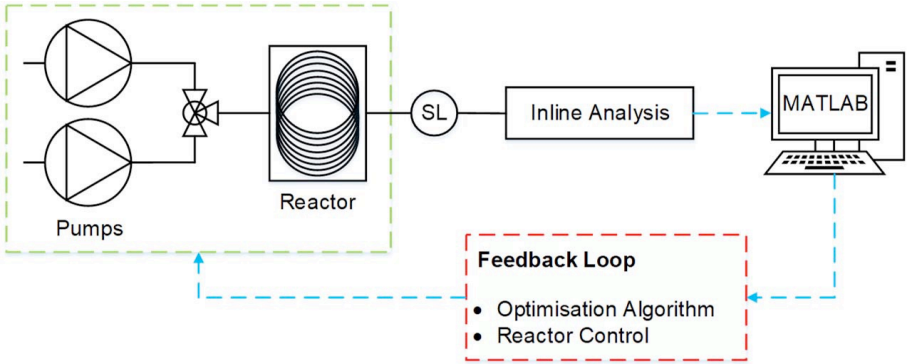


Pd/C reductions, debenzylations

Amide formation

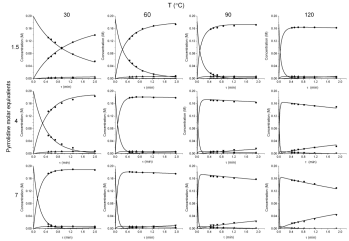


Self-Optimising Flow Reactor (SOFR)



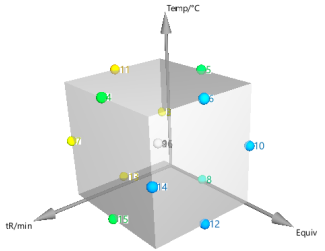
Reaction Kinetics

- Fit rate constants, orders and activation energies



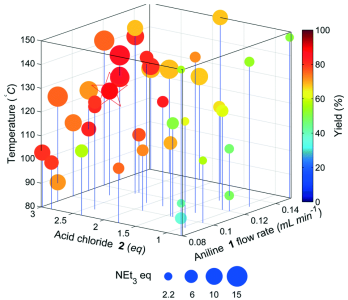
Design of Experiments (DOE)

- Process optimisation and understanding



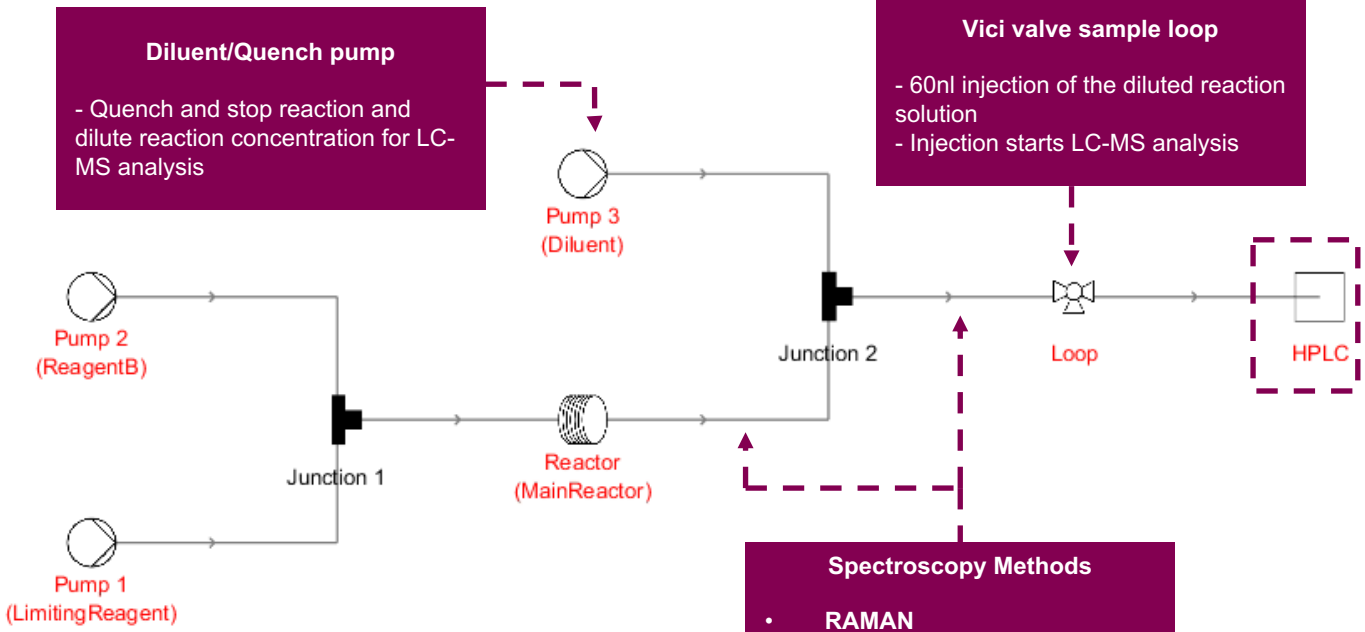
Self-optimisation (AI)

- Self-learning algorithm uses inline analytics to assess reaction space to search for a true optimum



- More likely to find a true optima than DOE
- Quick reaction optimisation with minimal effort

Analytical Techniques for Reaction Assessment



Diluent/Quench pump

- Quench and stop reaction and dilute reaction concentration for LC-MS analysis

Vici valve sample loop

- 60nl injection of the diluted reaction solution
- Injection starts LC-MS analysis

LC/LC-MS/MS

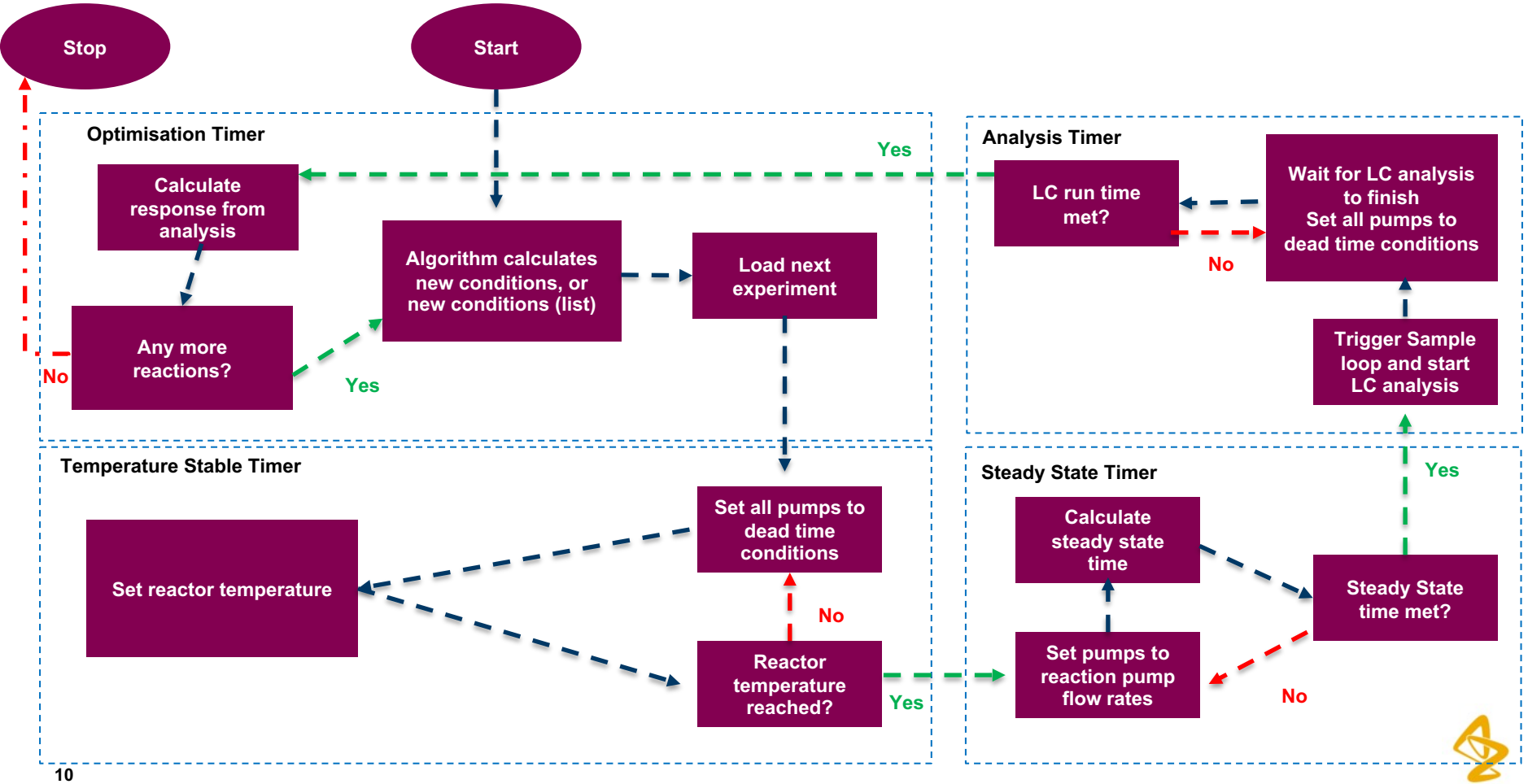
- LC is the main method for assessing reaction quality
- Like to include LC-MS for giving confidence we are creating the right material!
- Can provide insight into impurities formed (further characterisation work then needed)
- Can use MS on its own for analysis if no reaction components not UV active.

Spectroscopy Methods

- **RAMAN**
- **IR**
- **UV**

- Process understanding
- Understanding reaction steady state.
- Monitor Impurities.
- Methods developed at this stage transferred to the LSL for providing real time process evaluation during a manufacture

SOFR System Flow



Advantages of Automation

Efficient Use of Time

	1	2	3	4	5	6	7	8
1	Exp No	Exp Name	Run Order	Incl/Excl	temperature	molar equivalence	residence time	HPLC
2	5	N5	1	Incl	125	4.5	5	
3	8	N8	2	Incl	170	4.5	11	
4	10	N10	3	Incl	147.5	5.5	5	
5	13	N13	4	Incl	147.5	4.5	8	
6	1	N1	5	Incl	125	3.5	8	
7	6	N6	6	Incl	170	4.5	5	
8	11	N11	7	Incl	147.5	3.5	11	
9	3	N3	8	Incl	125	5.5	8	
10	2	N2	9	Incl	170	3.5	8	
11	15	N15	10	Incl	147.5	4.5	8	
12	4	N4	11	Incl	170	5.5	8	
13	7	N7	12	Incl	125	4.5	11	
14	12	N12	13	Incl	147.5	5.5	11	
15	14	N14	14	Incl	147.5	4.5	8	
16	9	N9	15	Incl	147.5	3.5	5	

- System can perform a list of reactions sequentially with in-line analysis overnight.
- Analyse analytical data in the morning.

Automation of DOE design

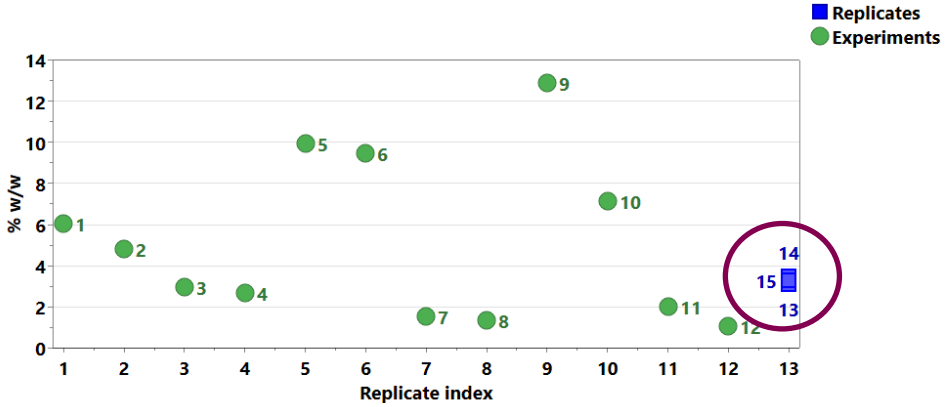
- 16 reactions with a residence time range of 5-11 minutes performed overnight.
- Flow chemist would need 2 days in the lab to do the same.

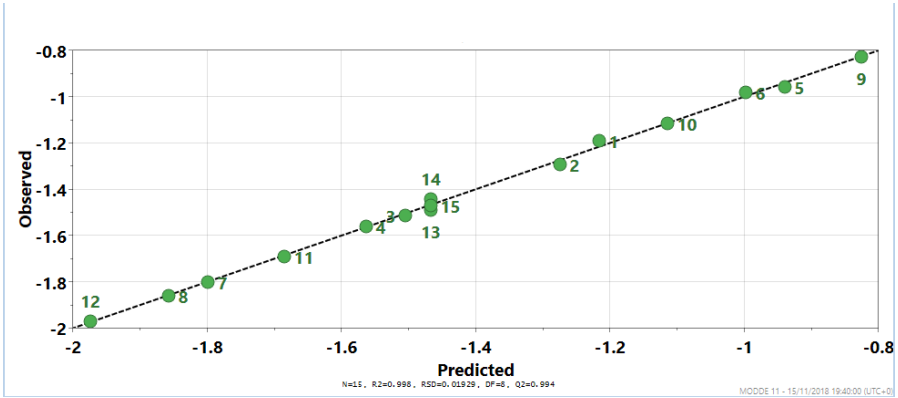
Machine Learning Optimisation

- 80 reactions performed over ~35 hours.
- Fully autonomous self-learning algorithm.
- No human intervention.

Advantages of Automation

Quality of Analytical data



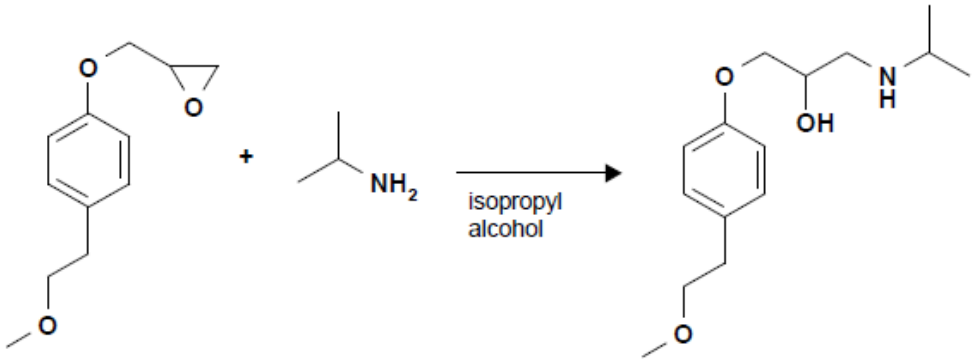


- Excellent repeatability.
- Good quality MLR models.
- Increased confidence in predicting the process and understanding important process parameters.

Removal of human error!

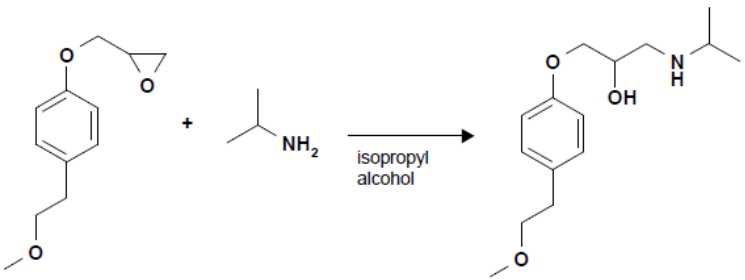
SOFR Case Study 1- Transfer of Batch Reaction to Flow

Developing a Flow Process as an Alternative to Aminolysis Batch Reaction



SOFR Case Study 1- Transfer of Batch Reaction to Flow

Nucleophilic epoxide ring opening reaction



Batch reaction

- Temperature: 60C
- Duration: 4 hours
- 3 molar equivalence of isopropyl amine

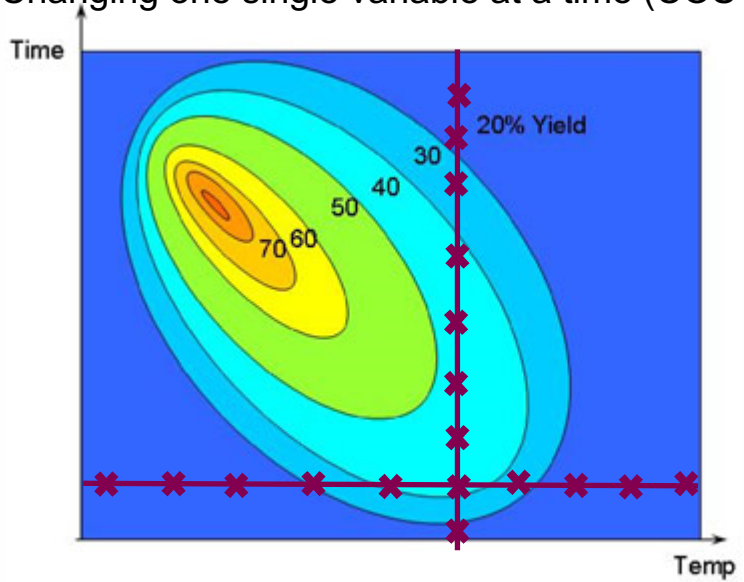
- All-in batch reaction - not inherently safe unless run in a pressure rated batch reactor
- Continuous processing could be an alternative to make the reaction inherently safe (flow reactors have superior pressure rating).

Aims

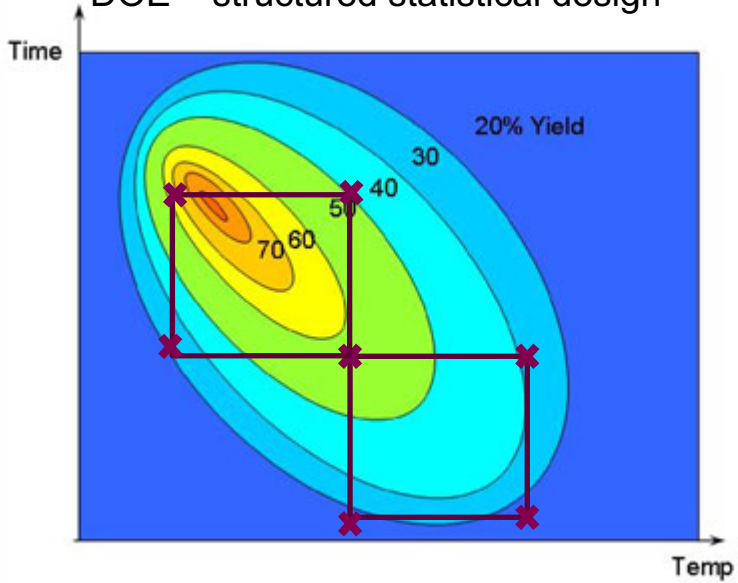
1. Develop flow process using SOFR instrument.
2. Demonstrate the potential of this type of automated flow reactor platform for automating structured statistical designs (design of experiments (DOE)).
3. Find key parameters of the process for driving reaction conversion and maximising product yield.

Design of Experiments (DOE)

Changing one single variable at a time (COST)



DOE – structured statistical design

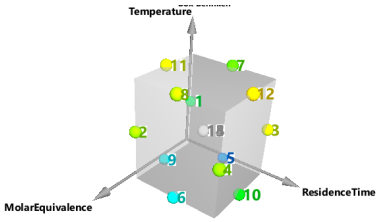


DOE – an efficient way (reduced experimentation) of understanding important parameters and their effect on a process.

SOFR Case Study 1- Transfer of Batch Reaction to Flow

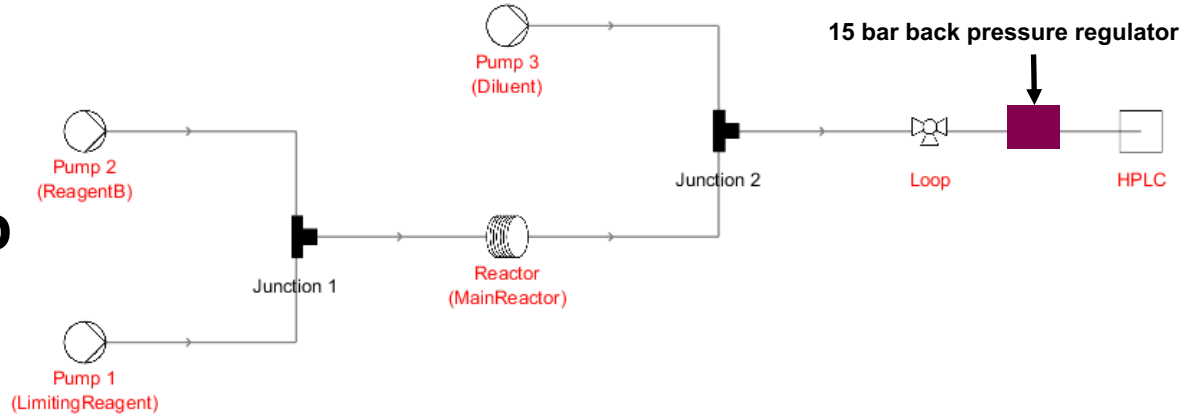
DOE Factors	Ranges
Temperature	125 - 170
Molar equivalence of Isopropyl amine	3.5 – 5.5
Residence time (minutes)	5 - 10

Box Behnken DOE Design (MODDE)



- 16 reactions performed overnight
- Design has 3 factor levels – linear and quadratic responses
- Minimal confounding
- LC-MS used as analytical technique

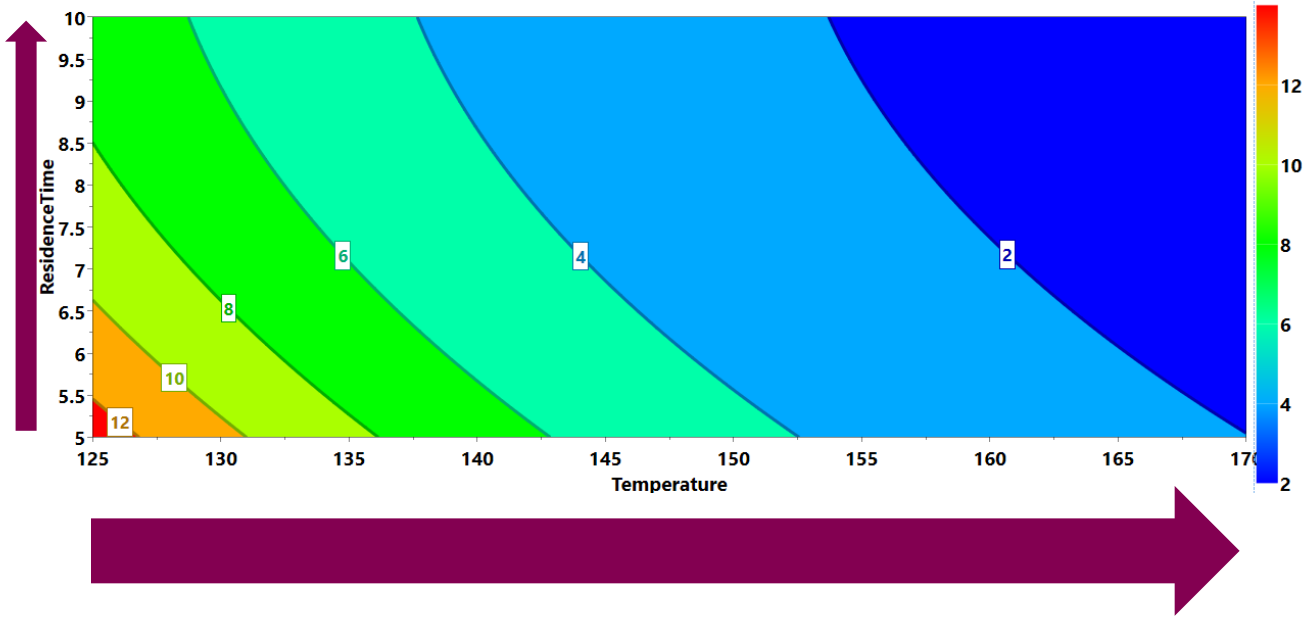
SOFR setup



SOFR Case Study 1- Transfer of Batch Reaction to Flow

Results

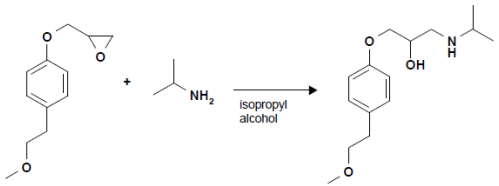
Process parameters driving conversion of limiting reagent?



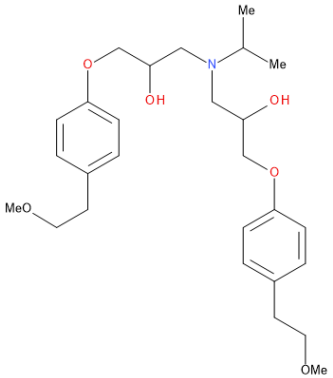
- Increase reactor temperature and reaction residence time
- Increasing both reactor temperature and residence time were also the most significant factors for product yield

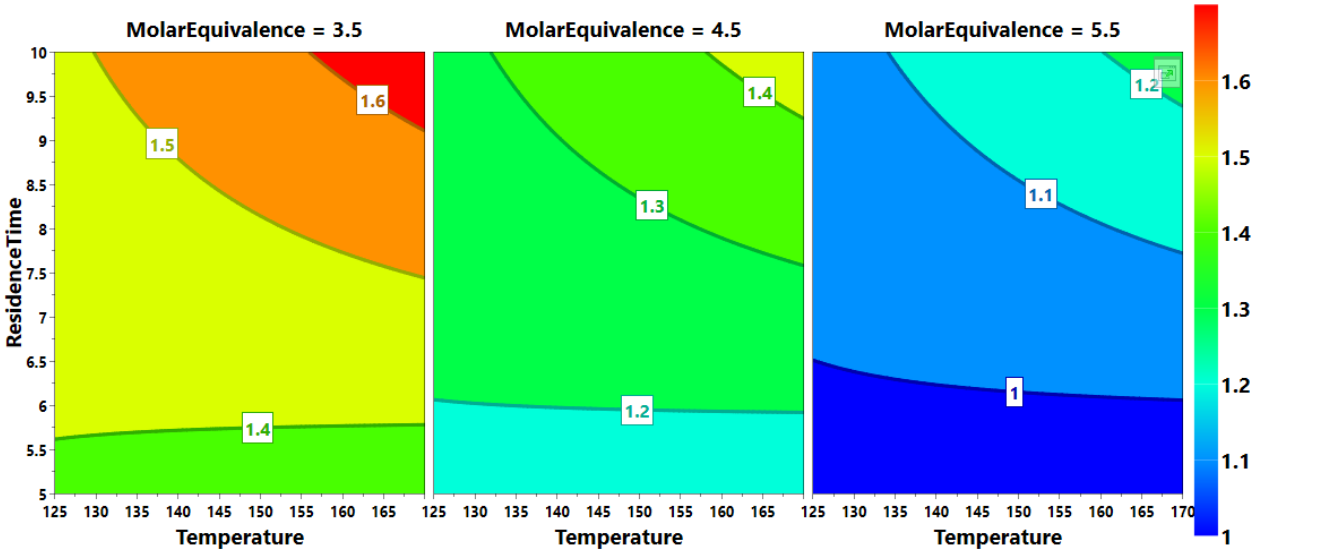
SOFR Case Study 1- Transfer of Batch Reaction to Flow

Process parameters important for the formation of the main impurity?

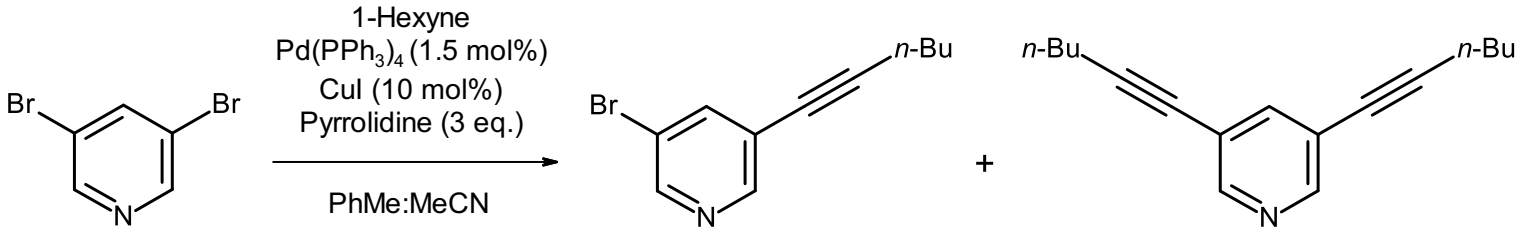


Main impurity





Optimise Sonogashira Coupling Reaction using the PARETO Multi-Objective Self-Learning Algorithm

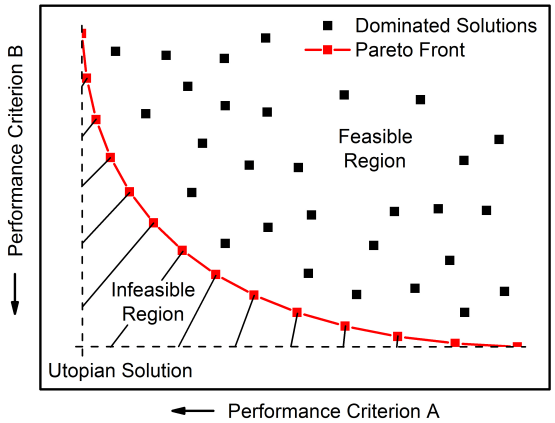


SOFR Case Study 2- Machine Learning for Process Optimisation

Typically more than 1 objective when optimising a process

- Does optimising product yield always give the most appropriate process for the business?
- Could you sacrifice some product yield for a much better throughput when manufacturing (kg/hr)?
- Can the process only handle a certain percent of an impurity formed?

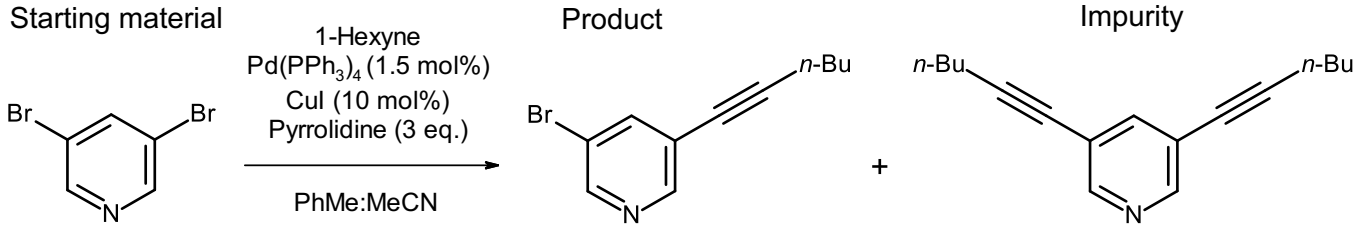
PARETO Multi-Objective Algorithm



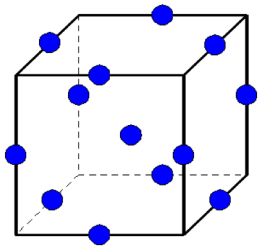
- **Machine learning multi-objective algorithm (TSEMO).**
- **Pareto front solution - One objective cannot be improved without having a detrimental effect on the other .**
- **Pareto front reveals true trade off between conflicting performance criteria.**

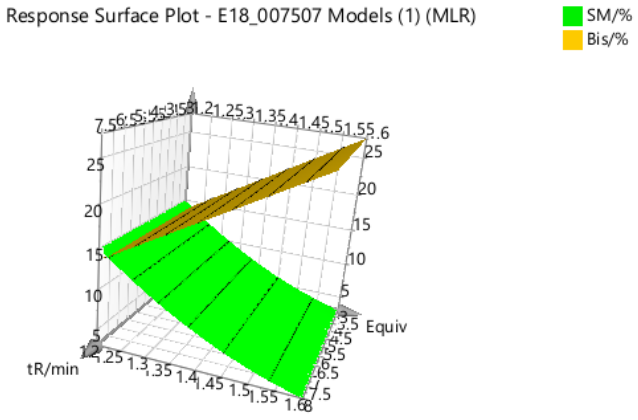
E. Bradford, A.M. Schweidtmann, A. Lapkin, Efficient multiobjective optimization employing Gaussian processes, spectral sampling and a genetic algorithm, J. Global Optim. 71 (2018) 407–438

SOFR Case Study 2- Machine Learning for Process Optimisation



DOE

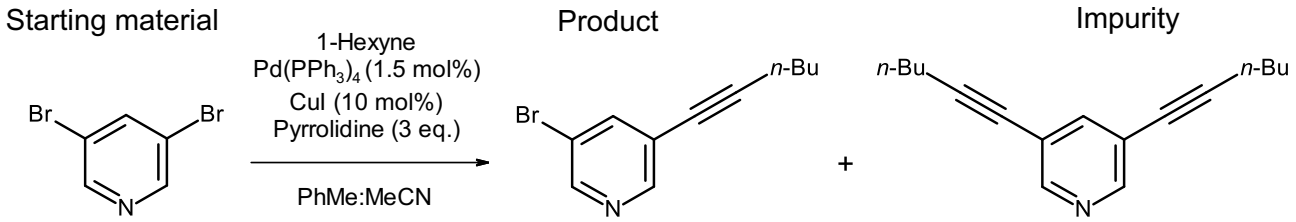




DOE results

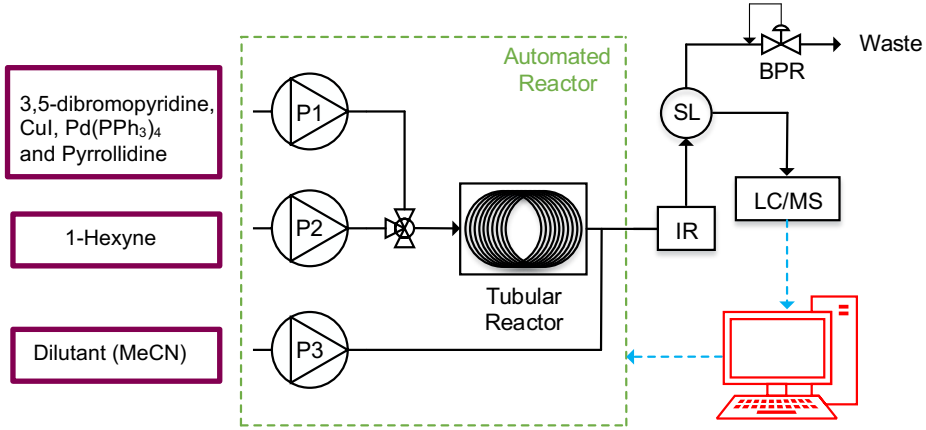
- Increased molar equivalence of Hexyne improves reaction conversion.
- However, increased Hexyne is driving impurity synthesis rather than product
- Trade off between conversion of starting material and product yield?

SOFR Case Study 2- Machine Learning for Process Optimisation



- **Leeds University has shown potential of self-learning pareto multi-objective optimisation algorithm in a recent publication.**

Aim – Use algorithm to assess supposed trade off between product throughput and reaction conversion suggested from DOE work.



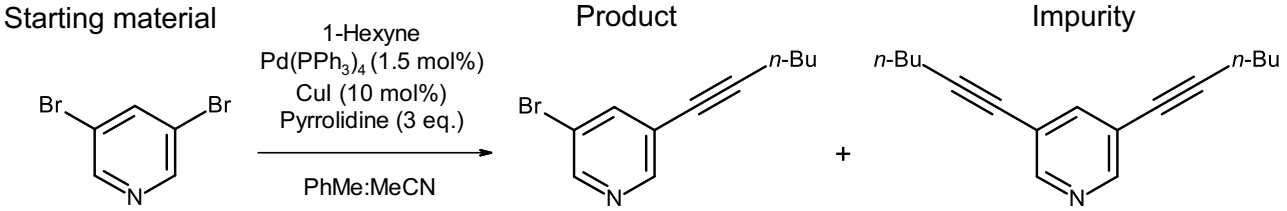
Minimise %w/w of 3,5-dibromopyridine starting material

Maximise product throughput (space time yield)

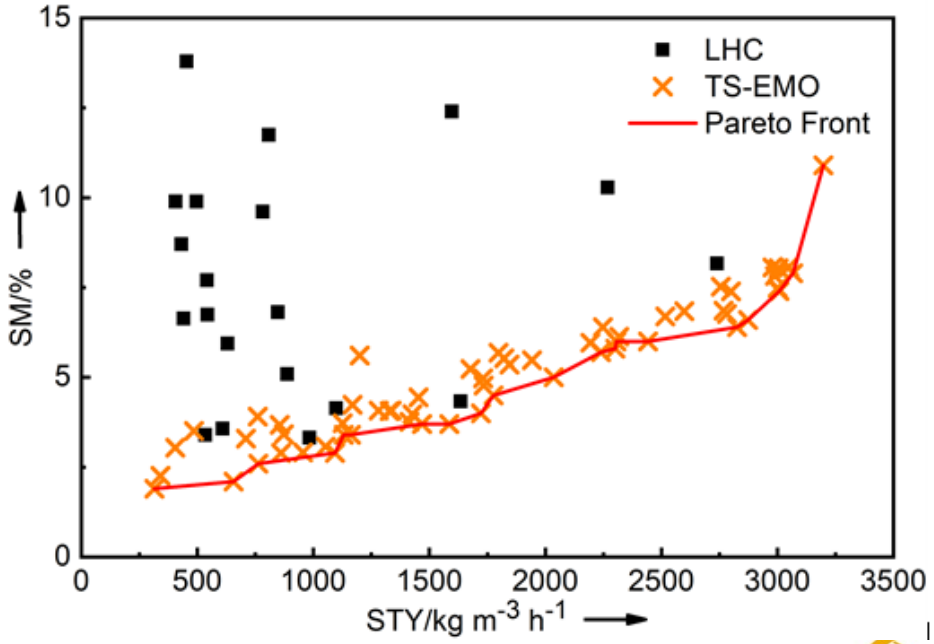
	tR/min	Equiv.	Temp/°C
Lower	1.0	1.2	120
Upper	8.0	1.6	150

Artur M. Schweidtmanna, Adam D. Clayton, Nicholas Holmes, Eric Bradford, Richard A. Bourne, Alexei A. Lapkin, Machine learning meets continuous flow chemistry: Automated optimization towards the Pareto front of multiple objectives, Chemical Engineering Journal 352 (2018) 277–282

SOFR Case Study 2- Machine Learning for Process Optimisation



- 80 reactions completed over ~35 hours
- Clear trade off between product throughput and reaction conversion
- Optimal SM %w/w being 1.9%
- Optimal space time yield 3200 kg m^{-3} h^{-1}



The Future – Automation for Efficient Manufacturing

Cognitive Chemical Manufacturing

- £2.5M Project using Machine Learning to Optimise Chemical Manufacturing starting July-Sept 2018
- EPSRC call on ‘Digital Manufacturing Potential’
- Led by IPRD Leeds (PI: Richard Bourne)
- Academic Partners: University College London, University of Nottingham, Hartree Centre
- Industrial Support: IBM, AstraZeneca, Swagelok and Promethean Particles
- 4 year project with 14 years of PDRA time



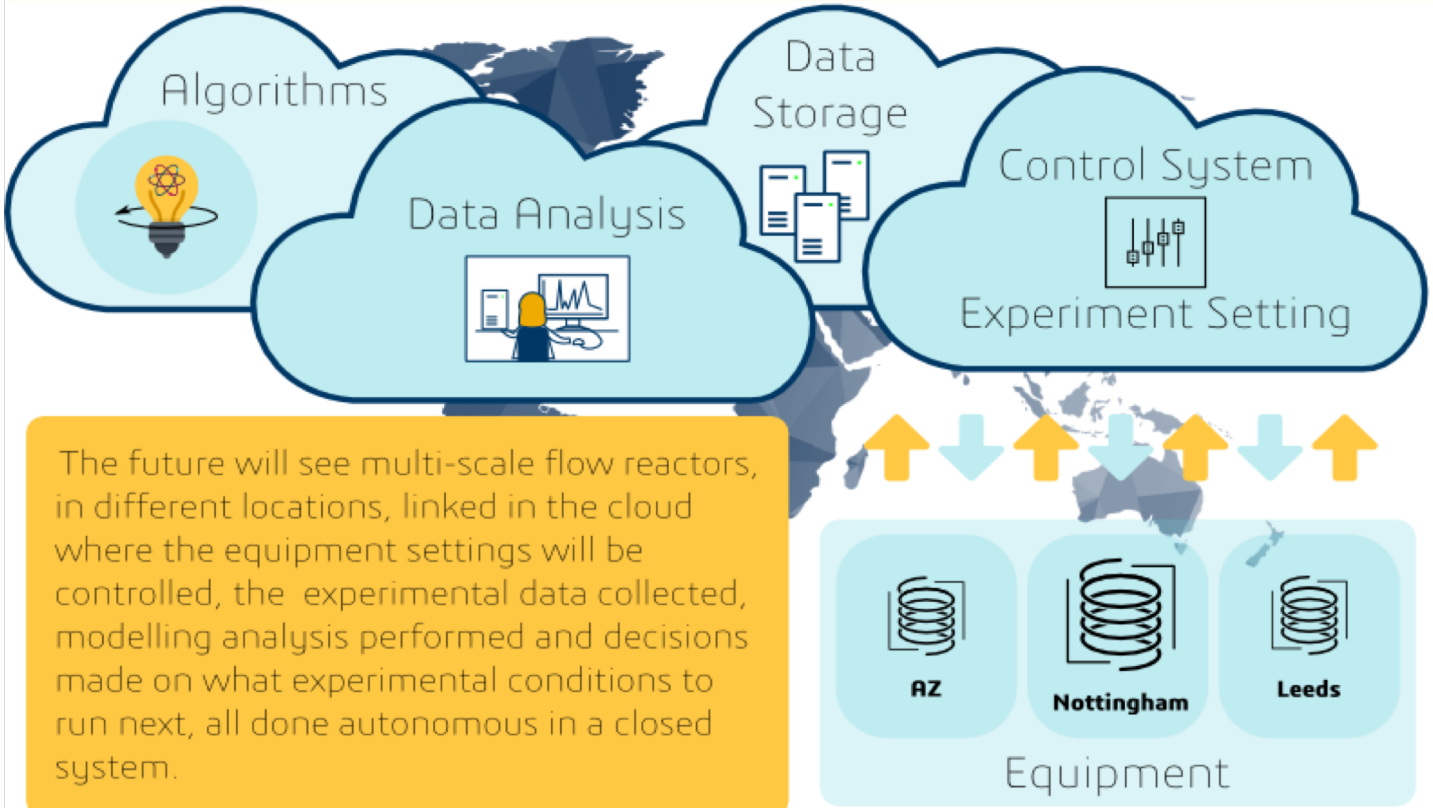








Cognitive Chemistry Manufacturing



The future will see multi-scale flow reactors, in different locations, linked in the cloud where the equipment settings will be controlled, the experimental data collected, modelling analysis performed and decisions made on what experimental conditions to run next, all done autonomous in a closed system.

IBM UCL PrometheanParticles UNIVERSITY OF LEEDS University of Nottingham Swagelok

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Thank You!

Confidentiality Notice