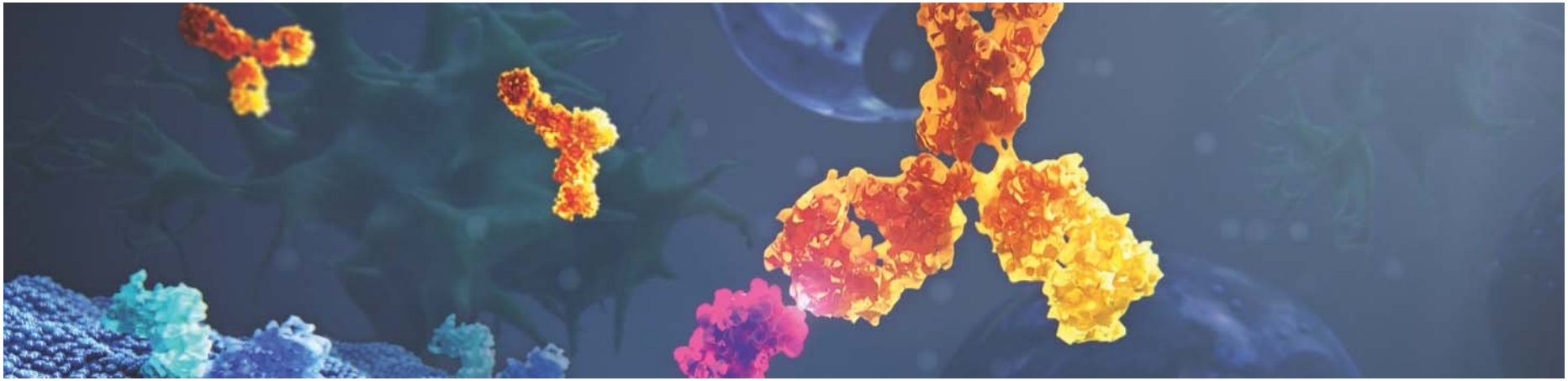
Dial-a-Molecule Technologies at the Industrial (Coal) Face

Simon Yates

Dial-a-Molecule AGM 2019

3rd July 2019



Dial-a-Molecule – The Grand Challenge

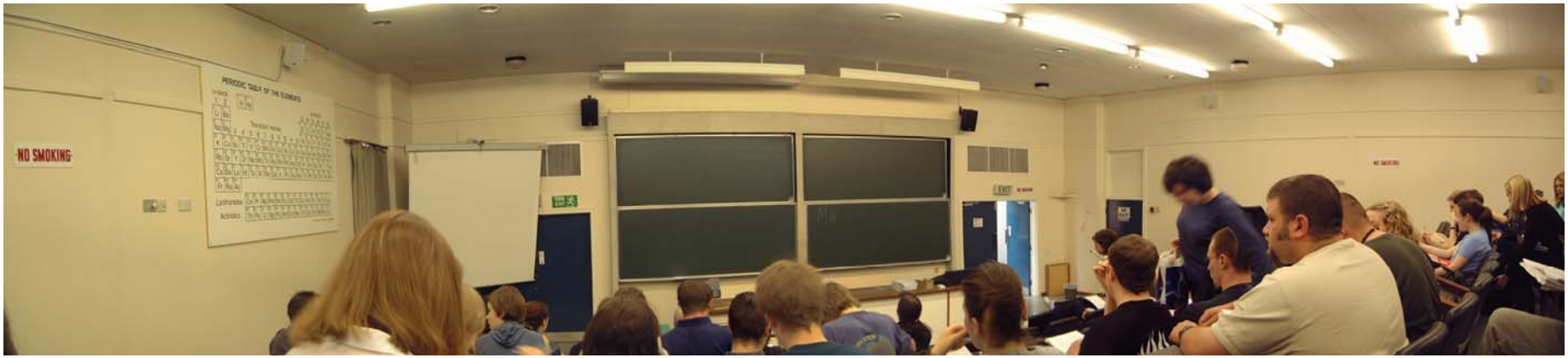
The aim of the Dial-a-Molecule Grand Challenge Network is to make the **synthesis of any desired molecule as easy as dialling a number** thus greatly empowering researchers, and removing a severe constraint to progress, in many fields. A linked aim is to move towards **100% efficient synthesis**. Currently in the production of a molecule many times the mass of the desired product (typically 1000s of times) is produced as waste with consequent disposal and cost implications. With 100% efficient synthesis there would be **no waste** to dispose of and the process would be much cheaper as well as consuming less energy

Back in 2001

Back in 2001

2019

Today



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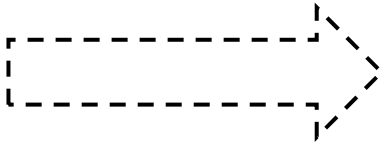
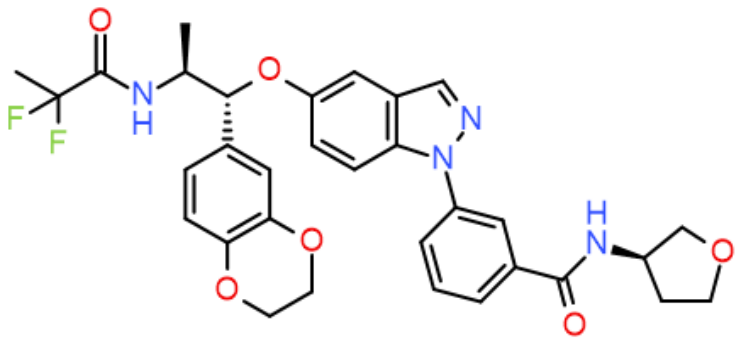


The Industrial Coal Face – Chemical Development at AZ

- Responsible for developing a **synthetic route** to API
- Scale from **mg** to **Kg**
- Processes, **not just reactions**
- Emphasis on **SELECT** criteria
    - Safety
    - Economics
    - Legal
    - Environment
    - Control
    - Throughput
- Supply material for clinical trials through to tech transfer to **commercial**

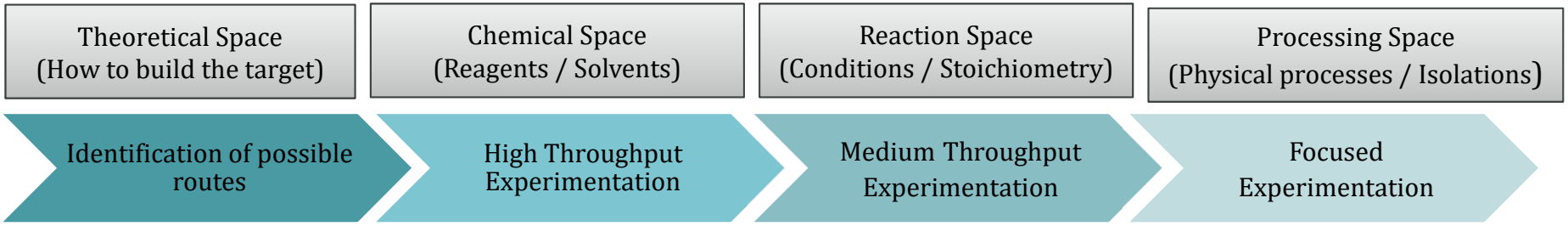


AZD7594

Rapid Route Design of AZD7594, Reaction Chemistry & Engineering, 2019 DOI: 10.1039/C9RE00118B

Synthesis 4.0: Towards an Internet of Chemistry, Reaction Chemistry and Engineering

Plan of attack



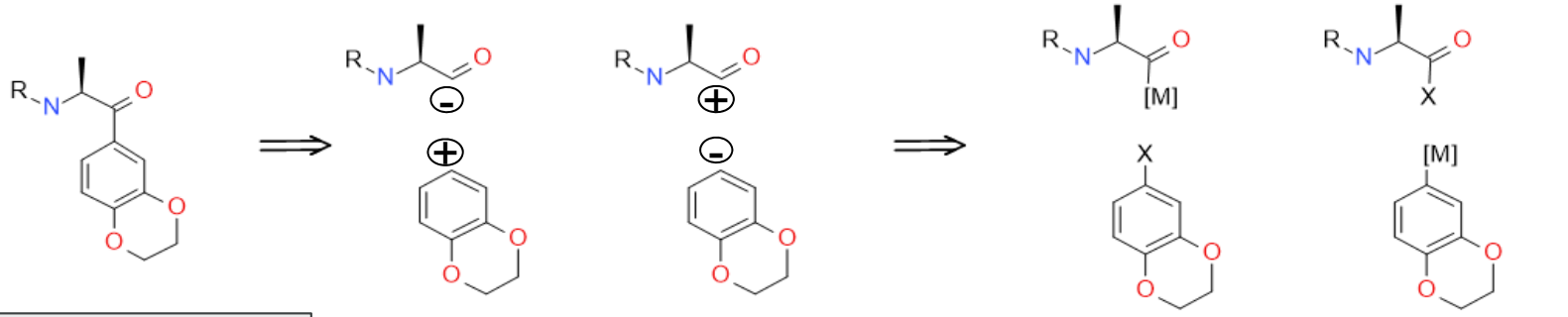
Robust Data Capture, Manipulation and Retention (creating data source for '**Big Data**')

Imagine a world where…

- Identify, visualise and prioritise possible routes in the **theoretical space** quickly and accurately
- We could cover as much **chemical space** as we thought necessary, and then a bit more
- We could explore **reaction space** without the constraints of equipment and time
- All experiments were **uniformly recorded** and raw data, meta data and knowledge stored in an easily visualised and accessible way
- We could apply this across all projects on **all stages of synthesis**

Identification of possible routes

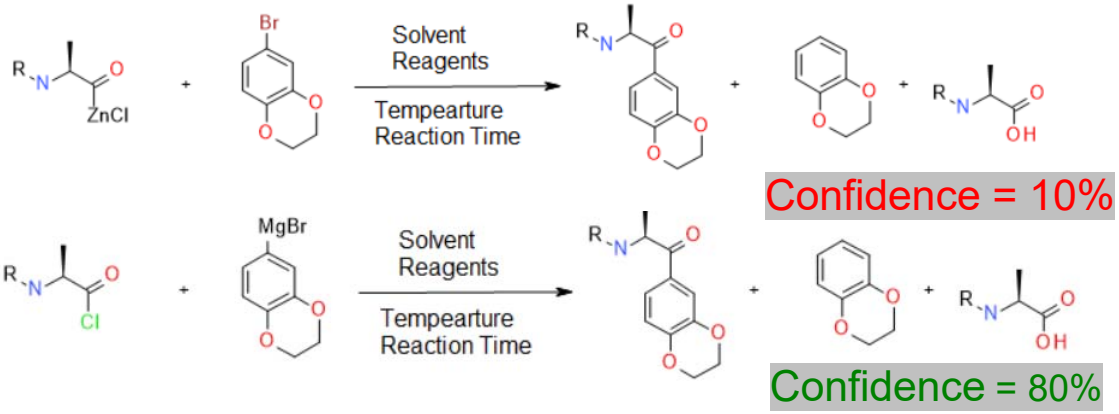
For each step of a synthesis



Break Molecule into smaller parts (easy)

Assign opposite Synthons (easy)

Suggest **functional groups** to make intermediates (medium)



Evaluation and scoring of the forward chemistry

- Does it make the target molecule?
  - In what yield?
  - What else does it make?
- What reagents / solvents needed?
- How fast will it occur? (seconds, weeks?)

(Really, Really Hard)

For each step of a synthesis

Chemist's *Prior Art*

Chemist and Literature Search

Chemist and Computational Retro Synthesis

Application

Predictive Chemistry

Physical Properties

Reaction Class

Chemo selectivity

Regio selectivity

Stereo selectivity

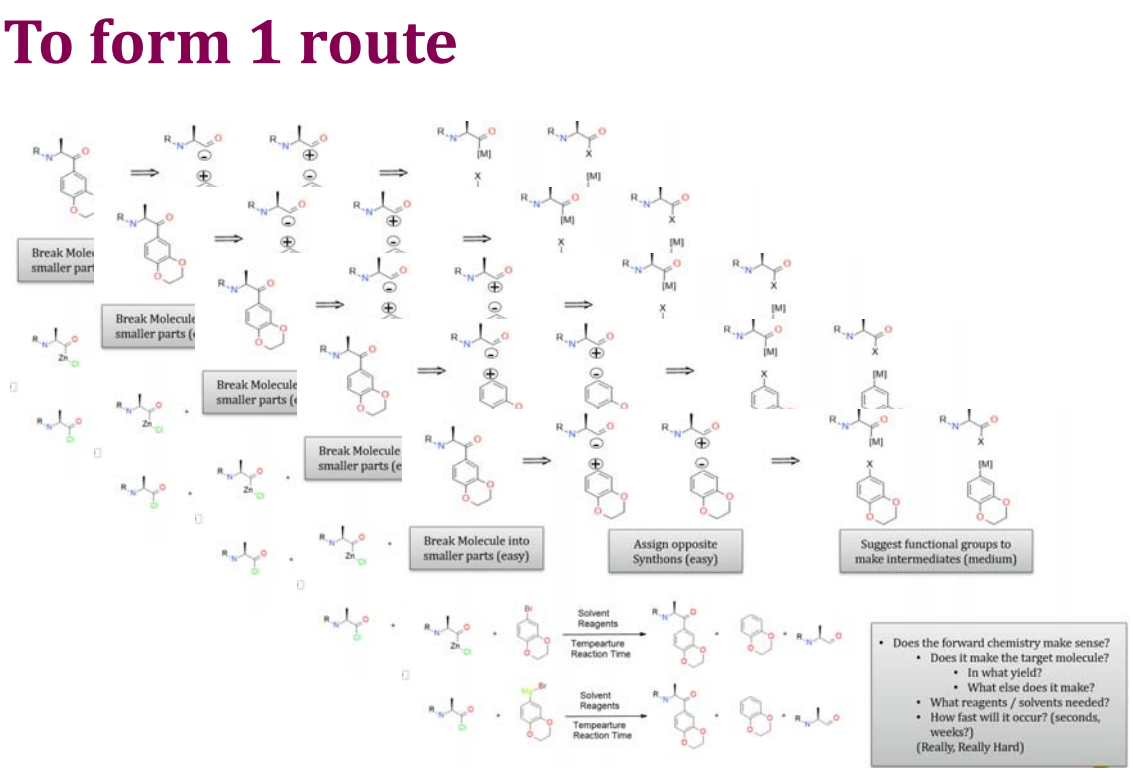
Build a model on data set then validate[1]

In-silico calculations based on QM[2]

Hybrid[3]

1. Solubility Correlations of Common Organic Solvent - Org. Process Res. Dev. 2018, 22, 829–835
2. A Predictive Tool for Electrophilic Aromatic Substitutions Using Machine Learning - J. Org. Chem.2019, 848, 4695-4703
3. Predicting reaction performance in C–N cross-coupling using machine learning – Science. 2018, 360, 186-190

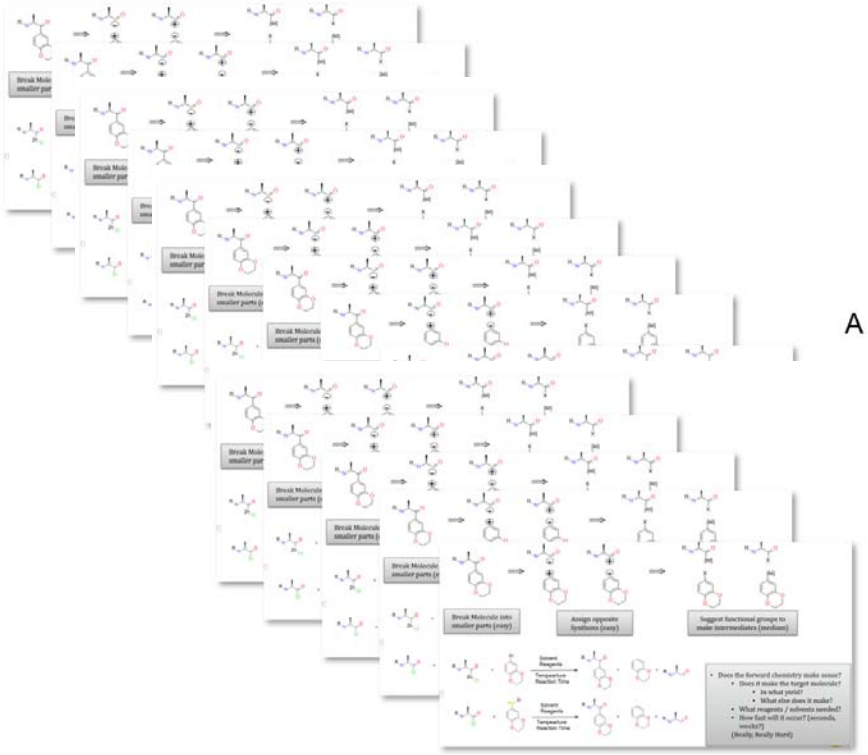
To form 1 route



Identification of possible routes → High Throughput Experimentation → Medium Throughput Experimentation → Focused Experimentation

A → B → C → D → E

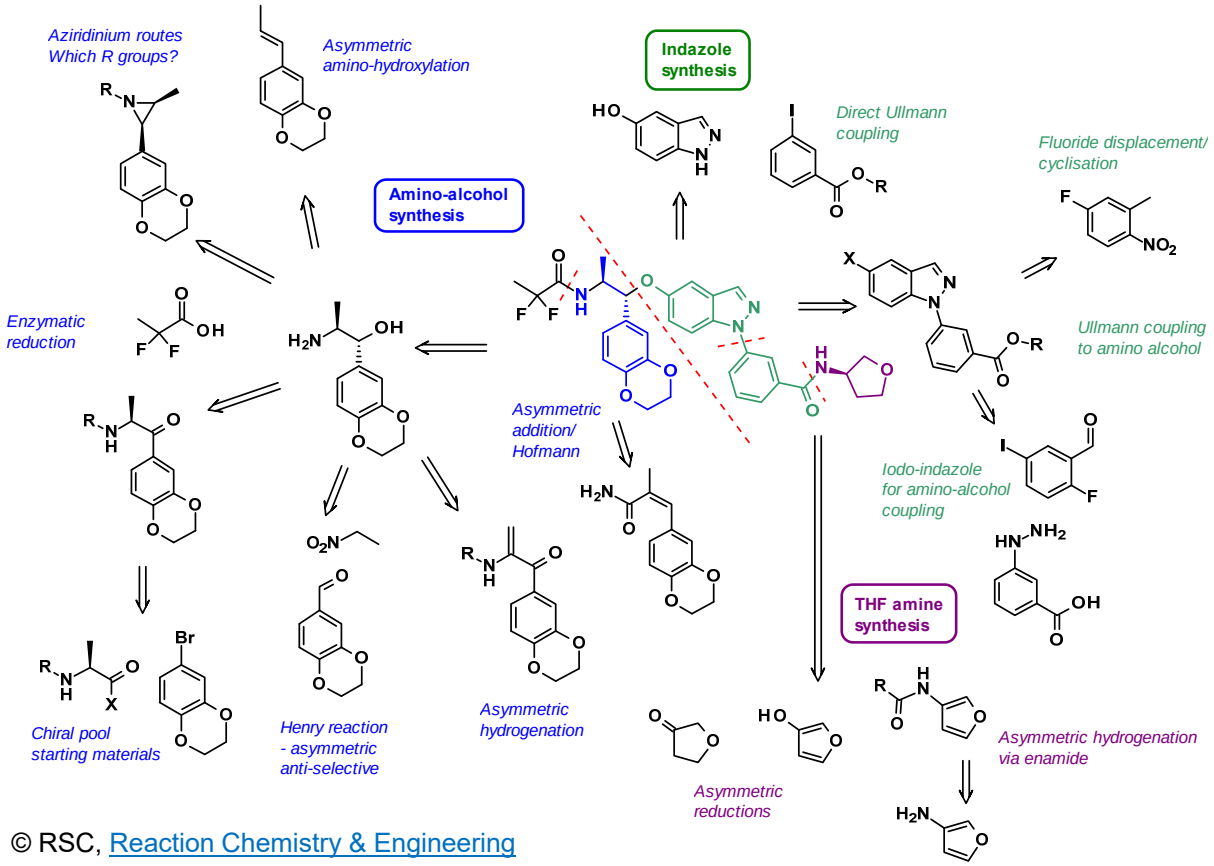
To form all routes



A → B → C → D → E

A → B → C → D → E

AZD7594 Route Selection Options



43 possible routes…..

What to do with all this?

Visualise all the routes

Define success criteria

Rank routes

Prioritise - whole routes or kill reactions for experimentation

Track results

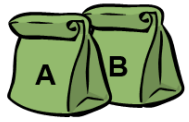
Decision – what to progress

HTE


Identification of possible routes
High Throughput Experimentation
Medium Throughput Experimentation
Focused Experimentation

Chemical Space - HTE

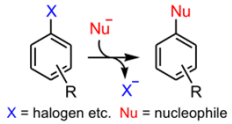
			Catalyst 1	Catalyst 2	Catalyst 3	Catalyst 4	Catalyst 5	Catalyst 6	Catalyst 7	Catalyst 8	Catalyst 9	Catalyst 10	Catalyst 11	Catalyst 12
			1	2	3	4	5	6	7	8	9	10	11	12
Base 1	Solvent 1	A												
Base 2		B												
Base 1	Solvent 2	C												
Base 2		D												
Base 1	Solvent 3	E												
Base 2		F												
Base 1	Solvent 4	G												
Base 2		H												



Discrete variables

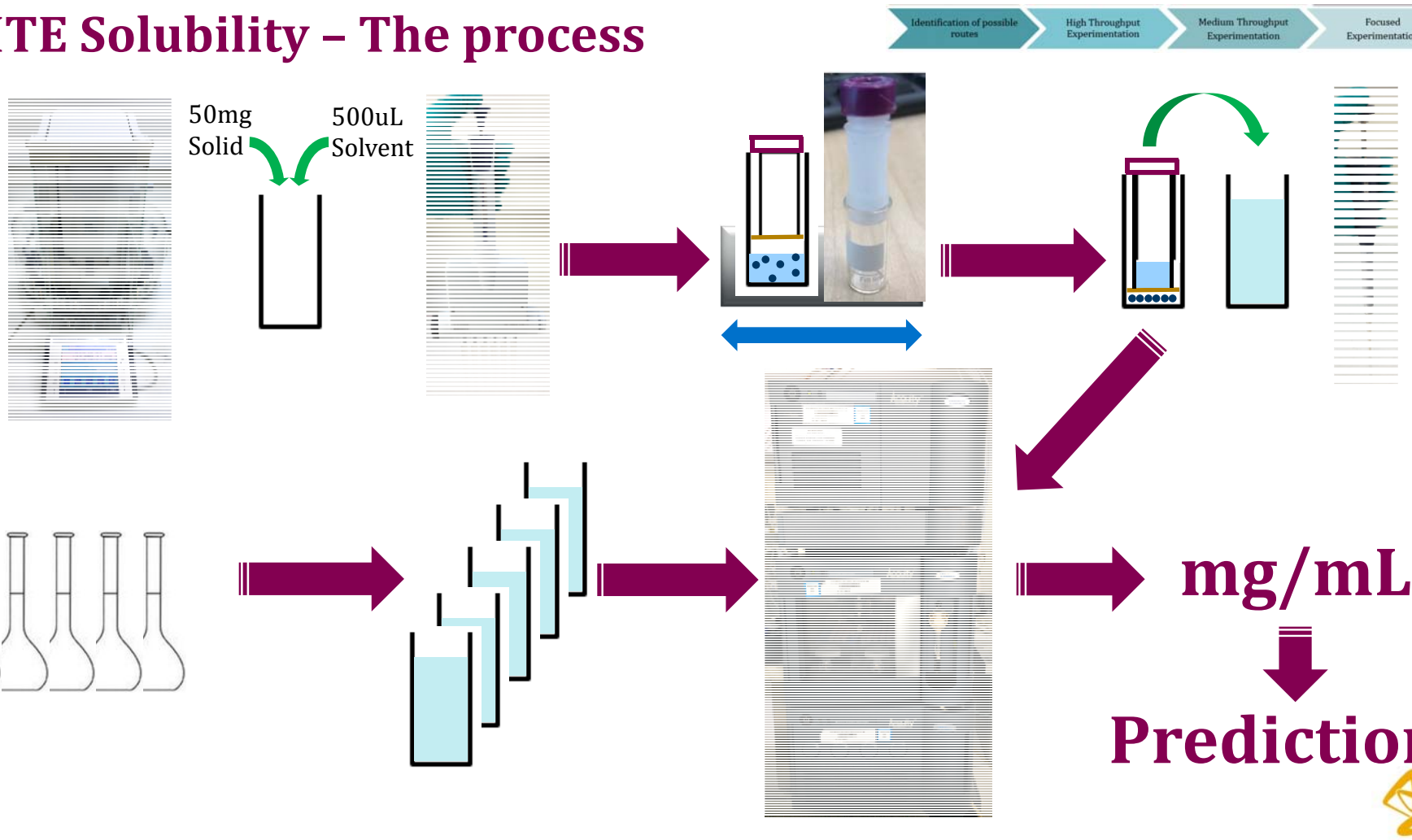
Chemical Space

"I need to see if this novel S_NAr reaction is feasible, to support new route work"

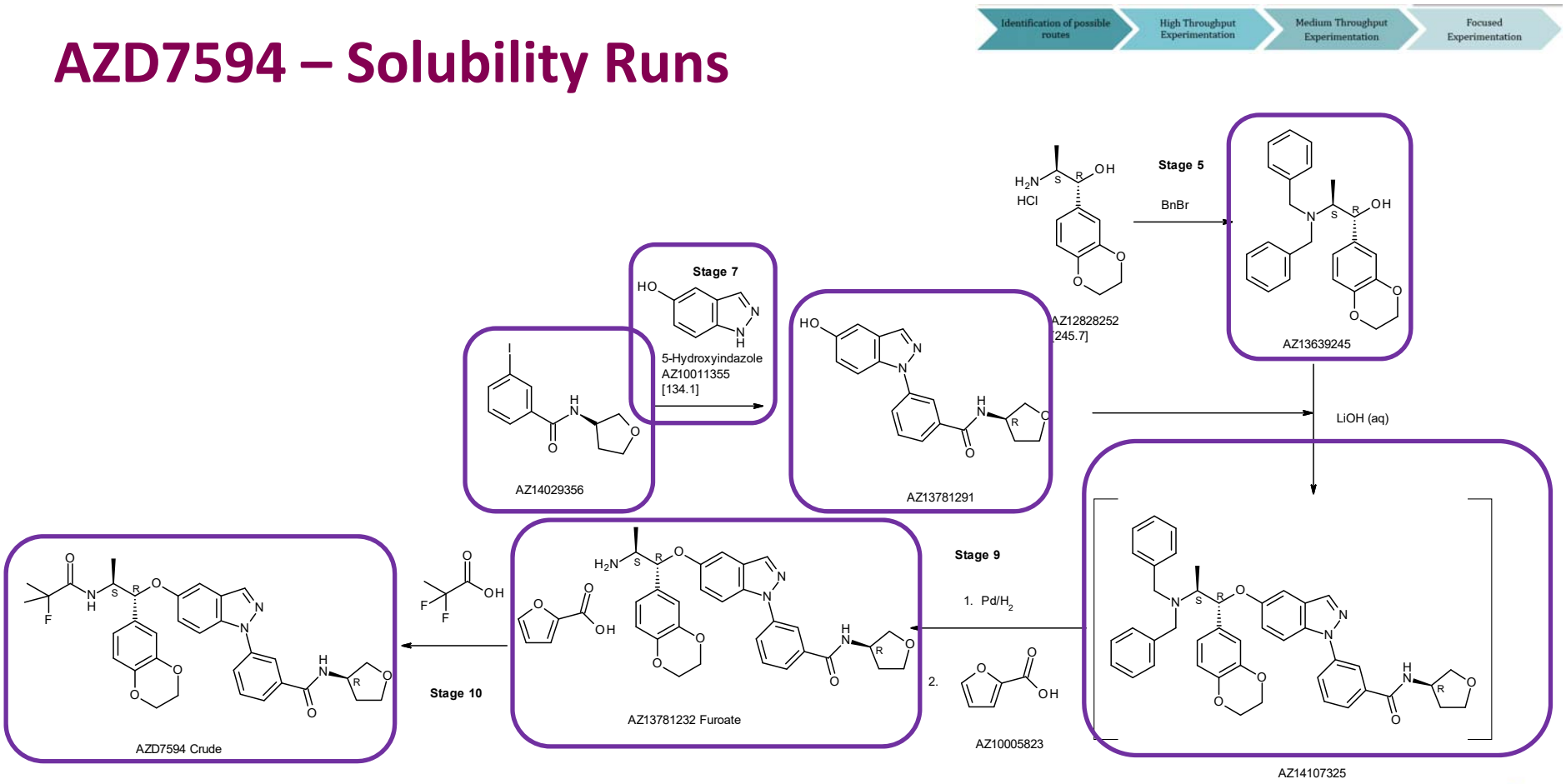


	Possible Impurities	Analytical Methodology	Hazardous combinations	
Solvent Choice	Reagent Choice	Stoichiometry	Conditions	Rate of Reaction
Internal ELNs	Literature	Experience	"AI"	
	Prior Art - Reactivity	Predictive-Reactivity		
		Solubility	pKa	MP / BP	Stability	
Assay	Impurities	Physical Form	Empirical	Prediction
	Batch Information	Physical Properties		
Building an HTE Screen				

HTE Solubility – The process

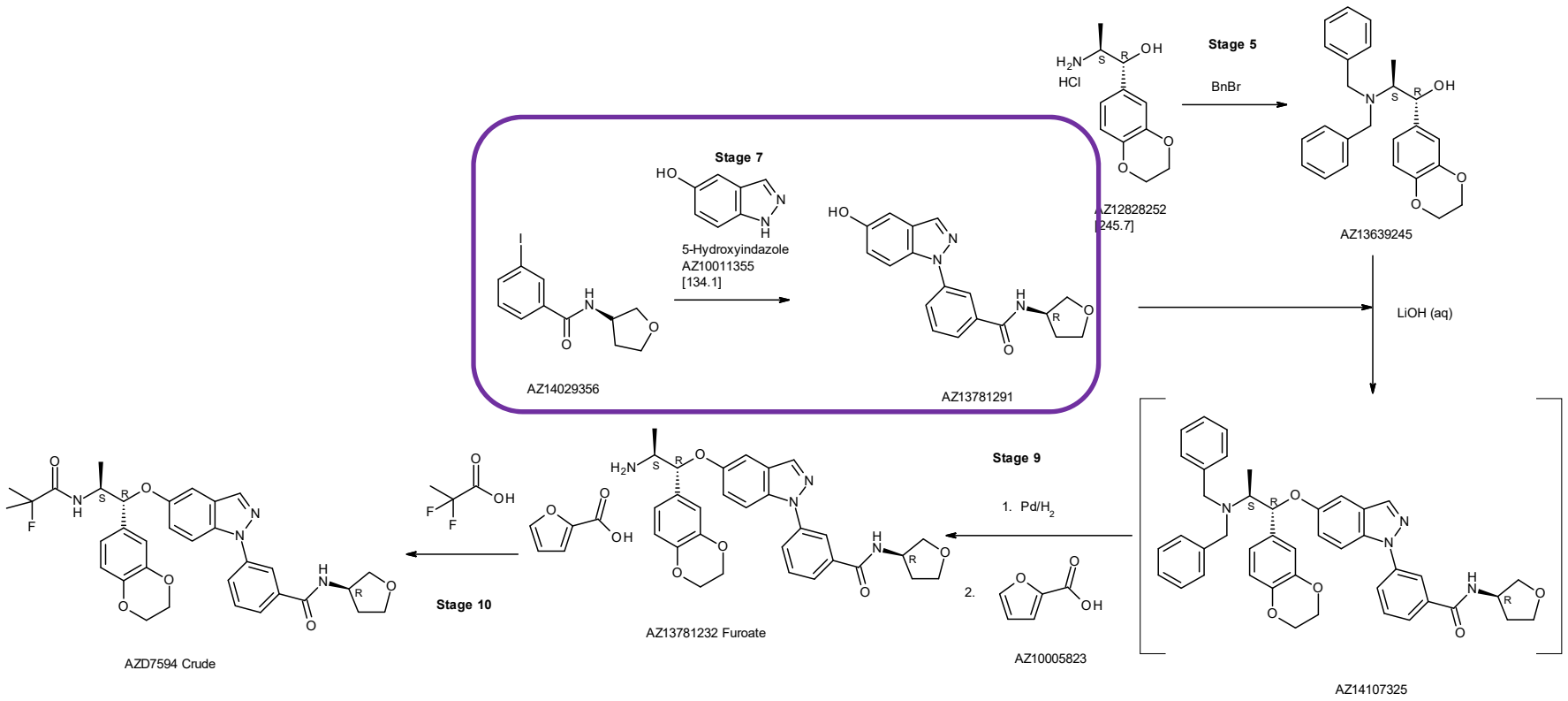


AZD7594 – Solubility Runs

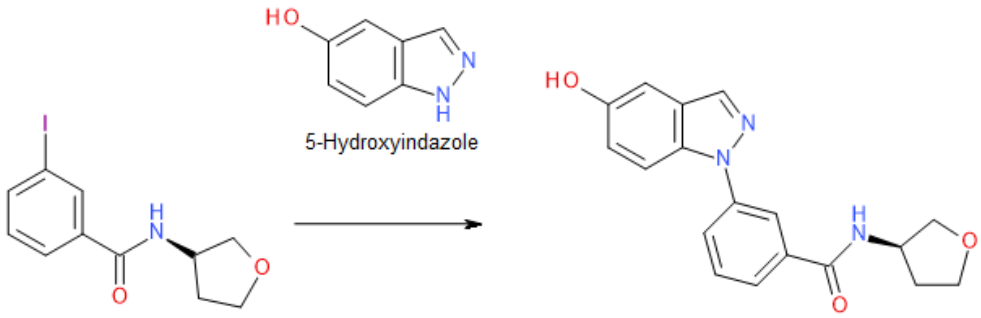


With Holly Carter

AZD7594 – Solubility Runs



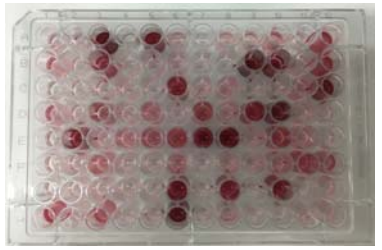
AZD7594 – Ullmann HTE



230 experiments in 4 screens

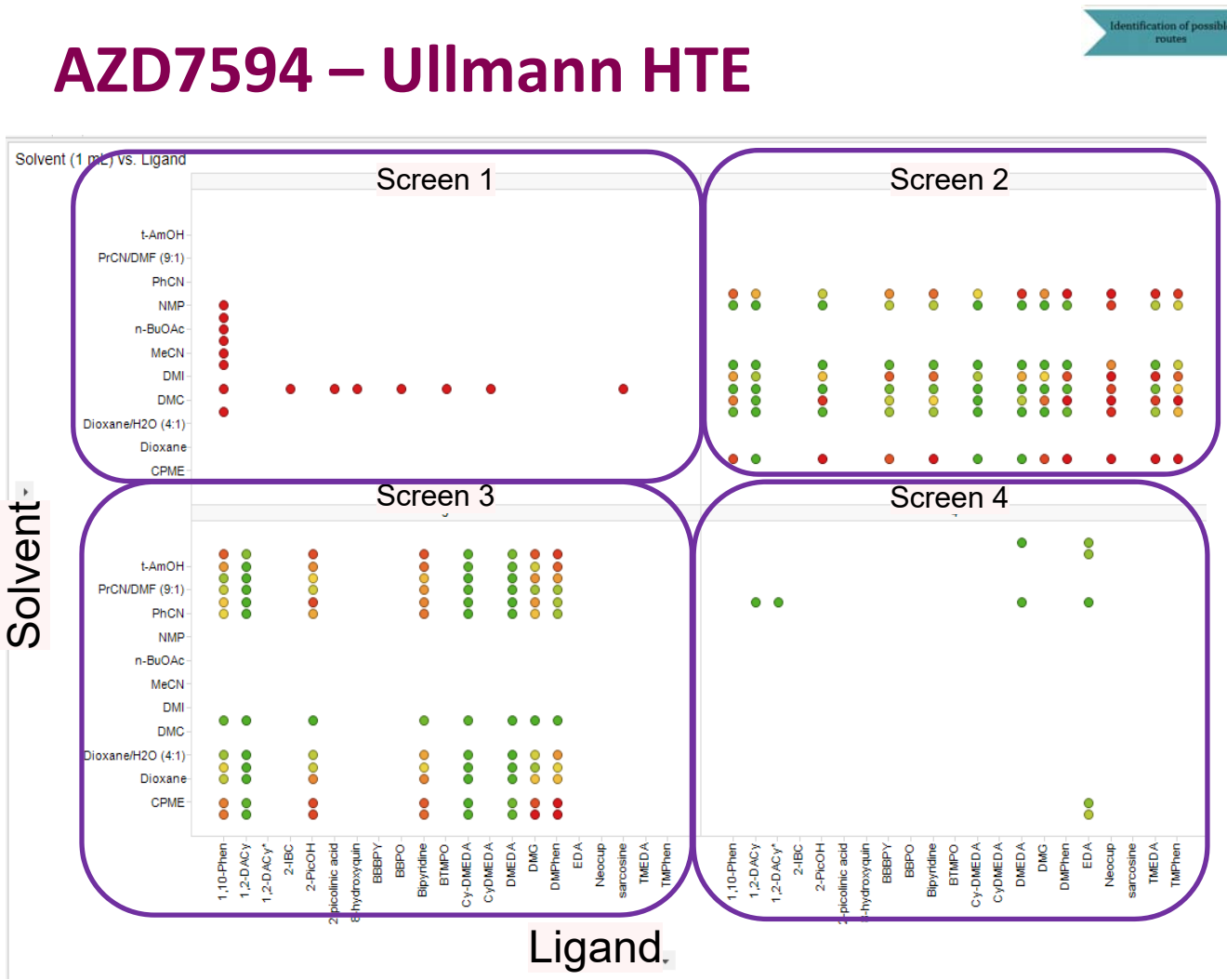
Semi-Manual Workflow

96 well plate, 10mg, 2 samples



The Evolution of High-Throughput Experimentation in Pharmaceutical Development and Perspectives on the Future - https://pubs.acs.org/doi/pdf/10.1021/acs.oprd.9b00140

AZD7594 – Ullmann HTE



Impractical polar aprotic solvents (DMF, NMP)

Butyronitrile and Benzonitrile

Pd / Phosphine ligands

Cu / diamine ligands

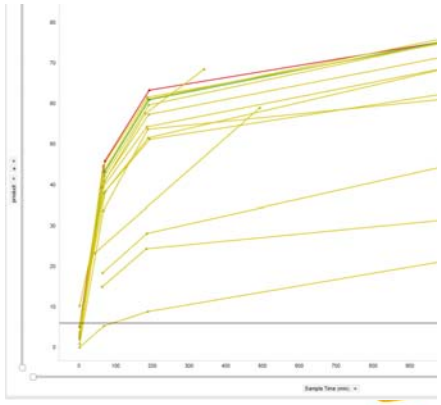
With Tom Ronson

Chemical Space – moving forward

- Well established for catalysis and solubility screening
  - Develop non-catalytic chemistry
  - Automate solubility measurement
  - **Democratise** HTE

- **Break down barriers** to running 96 reactions
  - Semi-Generic designs /workflows
  - Easy to use and reliable kit

- Routinely take 3 or 4 samples per reaction to **allow profiling**
  - Work on getting quicker analysis methods (LC)
  - Education around data handling
  - Deeper understanding derived from all 96 reactions



MTE


Identification of possible routes
High Throughput Experimentation
Medium Throughput Experimentation
Focused Experimentation

Reaction Space - MTE

Continuous variables

Profile reactions

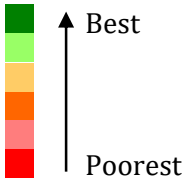
Statistical Analysis

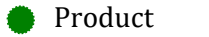
$$\text{Rate} = k[A][B]$$

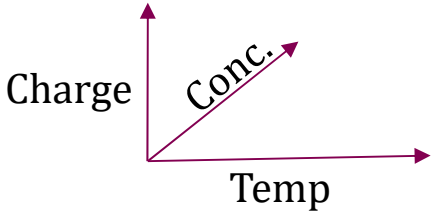
Kinetics

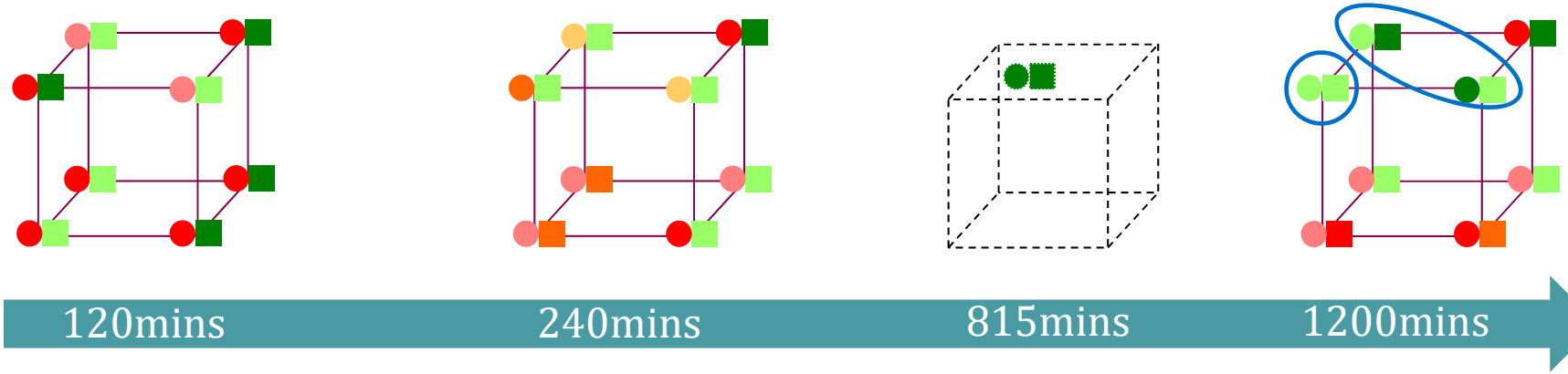
Reaction Space

"I need to optimise my reaction. What set-points do I use? At what time is there maximum product and minimum impurities?"









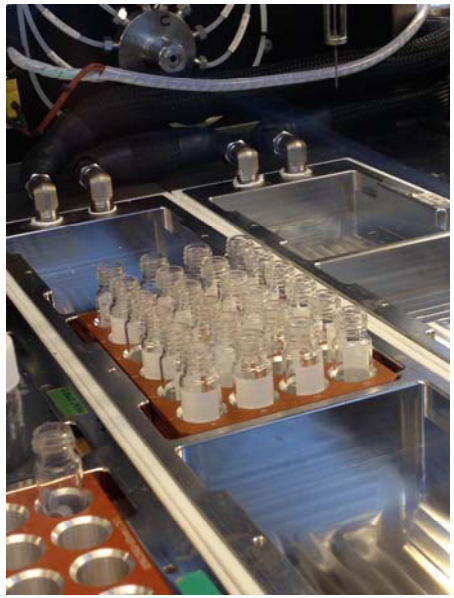
Kinetic Modelling | Statistical Analysis | High Quality Empirical Data

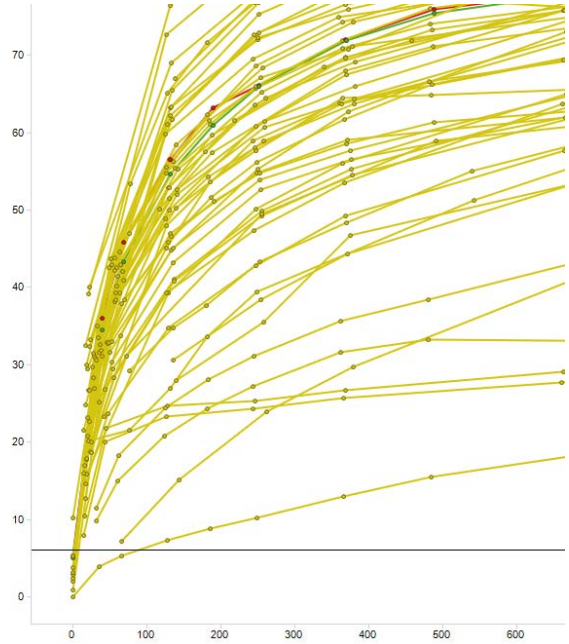
Reaction Space MTE – as it stands

- Within generalist population
  - Experience of test tube reaction systems (20mL)
  - Semi-Automated workflow (Quantos, AmigoChem, Data Export from CDS)

- Within specialist groups
  - Workflow based on 24x3, 4mL vials with multiple samples
  - On a Freeslate CM2, transferring to CM3
  - 5-10 samples per reaction
  - Complex DoE
  - Kinetic experiments
  - Cross over material / parameter screens.

Reaction Space MTE – as it stands

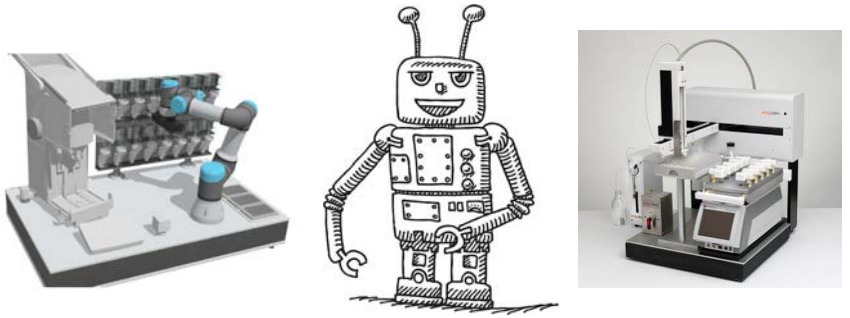




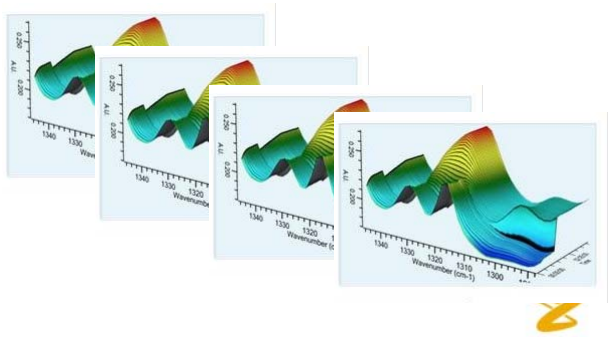
Reaction Space MTE – Future

- Develop Medium Throughput
  - Bridge the gap
  - Equipment not limitation
  - Reduce time to decide

- Define, Test, Release chemist friendly workflows
  - Walk up MTE kit
  - Specialist MTE

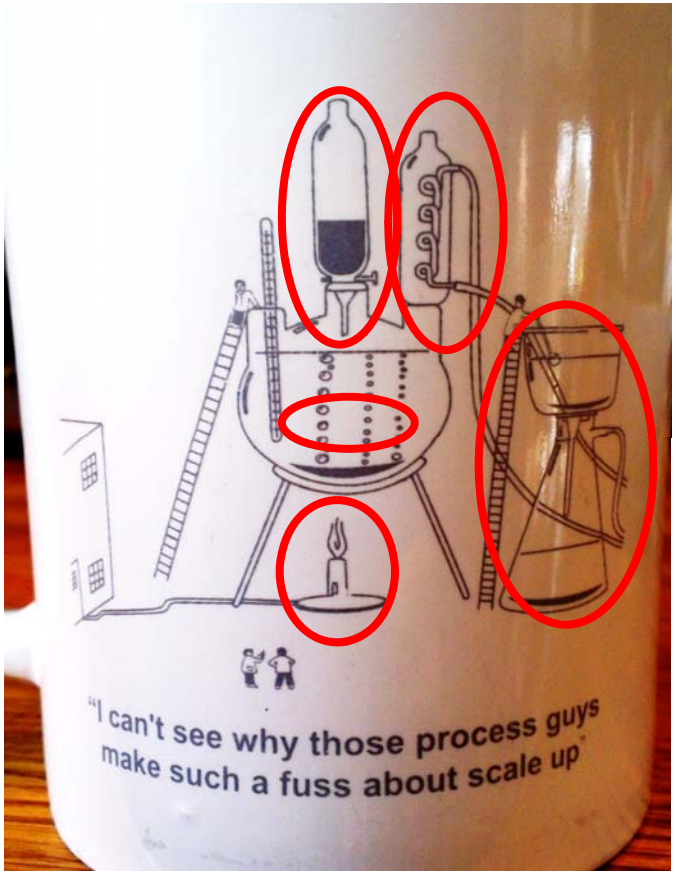


- What else can we do?
  - Multivariate analysis on 10s of reactions?
  - Automated modelling / fitting to determine rate information?



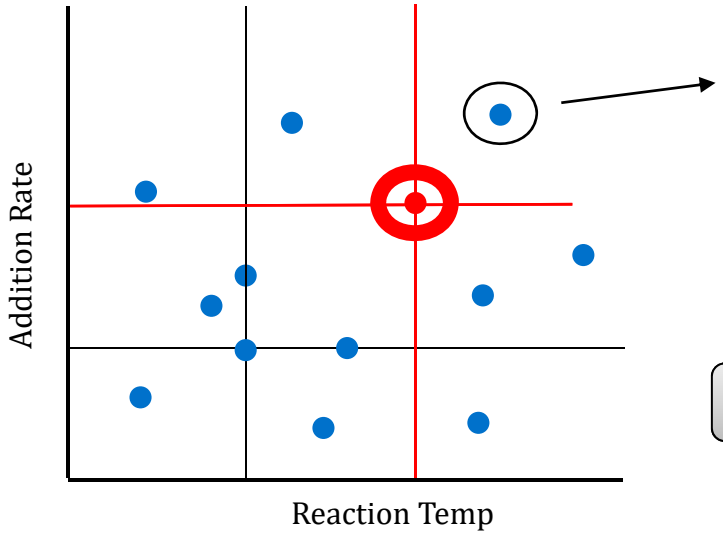
Focused Experimentation

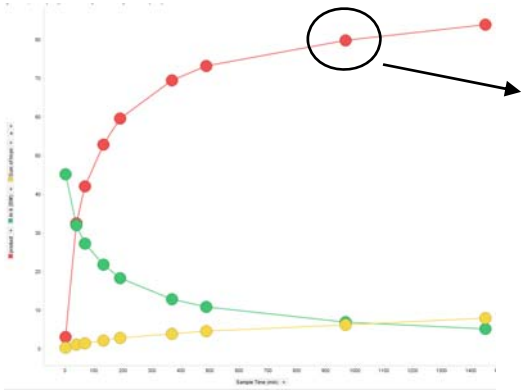
Focused Experimentation

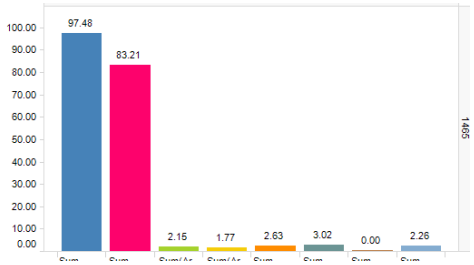


Processing Space

"Help! The addition rate on the plant was twice as fast and the temperature of the vessel is 30DegC higher than set point. How will this affect the reaction?"







ELN ref

LC data | List of parameters | Outcome of single experiment | 'Knowledge' from study

Model 'New' Point

What will the imps be? | Can the route deal with imps? | Can we 'save' the batch?

The Rise of the Automated Lab Reactor

Basic temp loggers

Programmable and logging Temp/addition/pH/stir rate/turbidity/IR

iControl / IC DataCentre

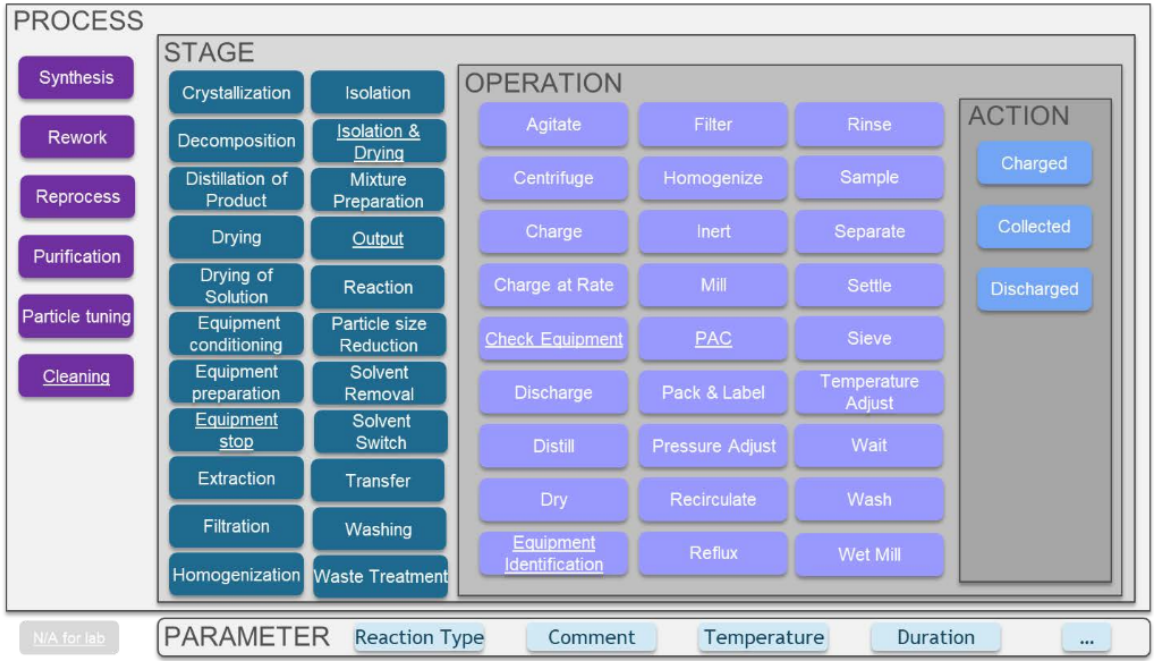
Inhouse control/logging developed for JVs

2000 2010 2014 2020

Processing Space – Data Standard

- Devil is in the detail

- Mettler Toledo, Jansen, AstraZeneca – Project Step Stone
- Develop a open standardised way to capture processing data
- Based on ISA88 (S88) 'process' standard
- XML schema



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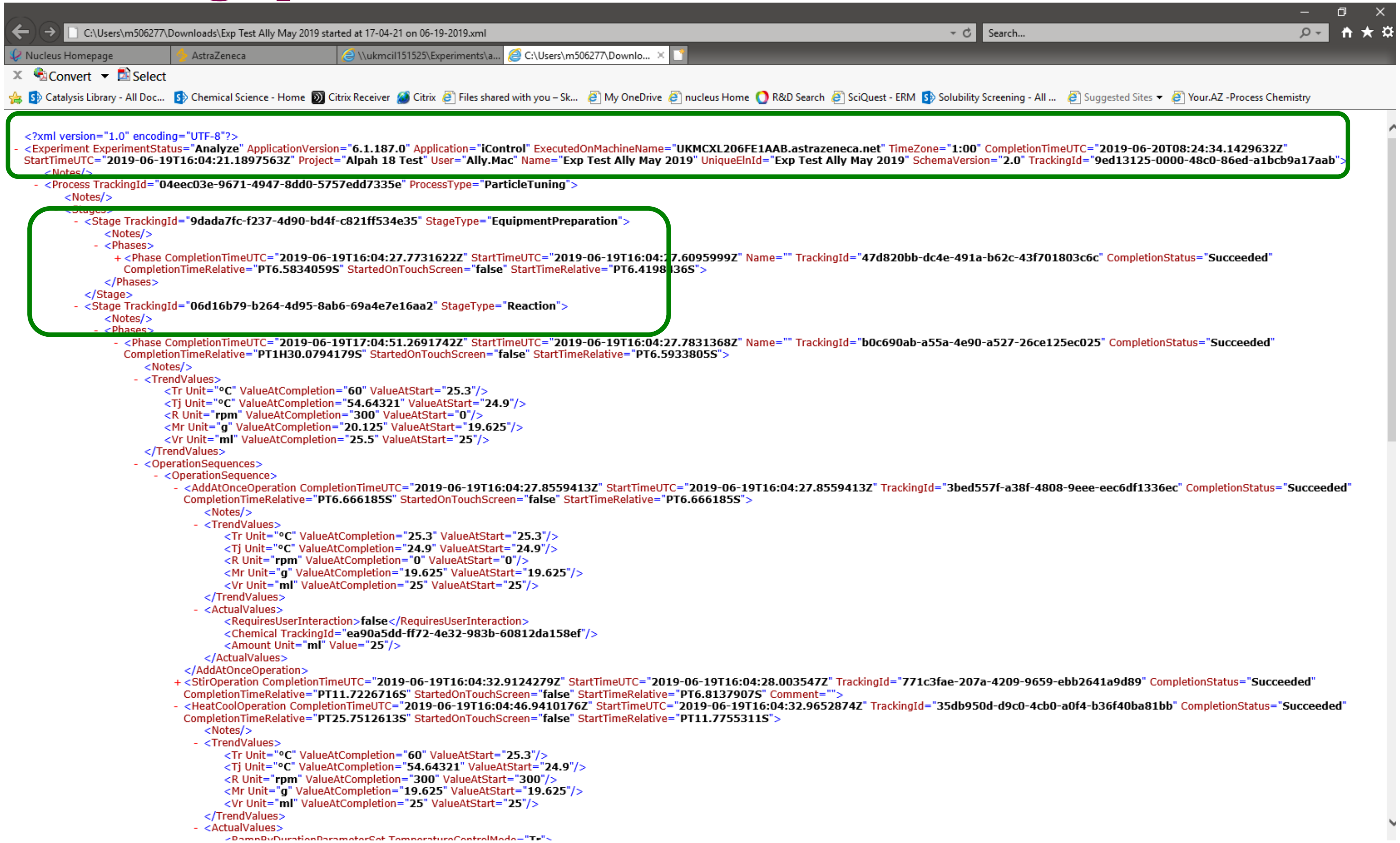

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                      <RampByDurationParameterSet TemperatureControlMode="Tr">
```


•

Processing Space – Data Standard

3 Setup

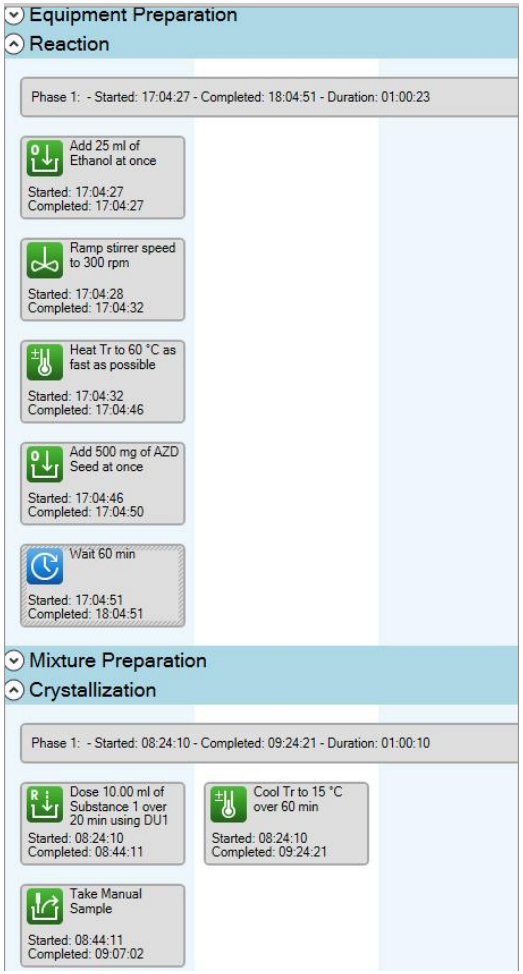
EasyMax 102	Description
Device	EasyMax 102 (Serial #: 12345678 / Firmware: 6.1.0.523)
Reactor	100 ml
Stirrer	Overhead (Pitched-blade down (circular segment), C22, Ø 38mm / Magnetic drive shaft, C22, Length 129mm)
Other	Dosing Unit 1 (50 ml) Tr Sensor, pH Sensor EasySampler (Serial #: B001000001) - Quench solvent: QBenzene - Dilution solvent: DXylene - Reaction solvent: RToluene - Probe type: Type210 - Probe serial number: B001000001 - Probe pocket size: 15 uL

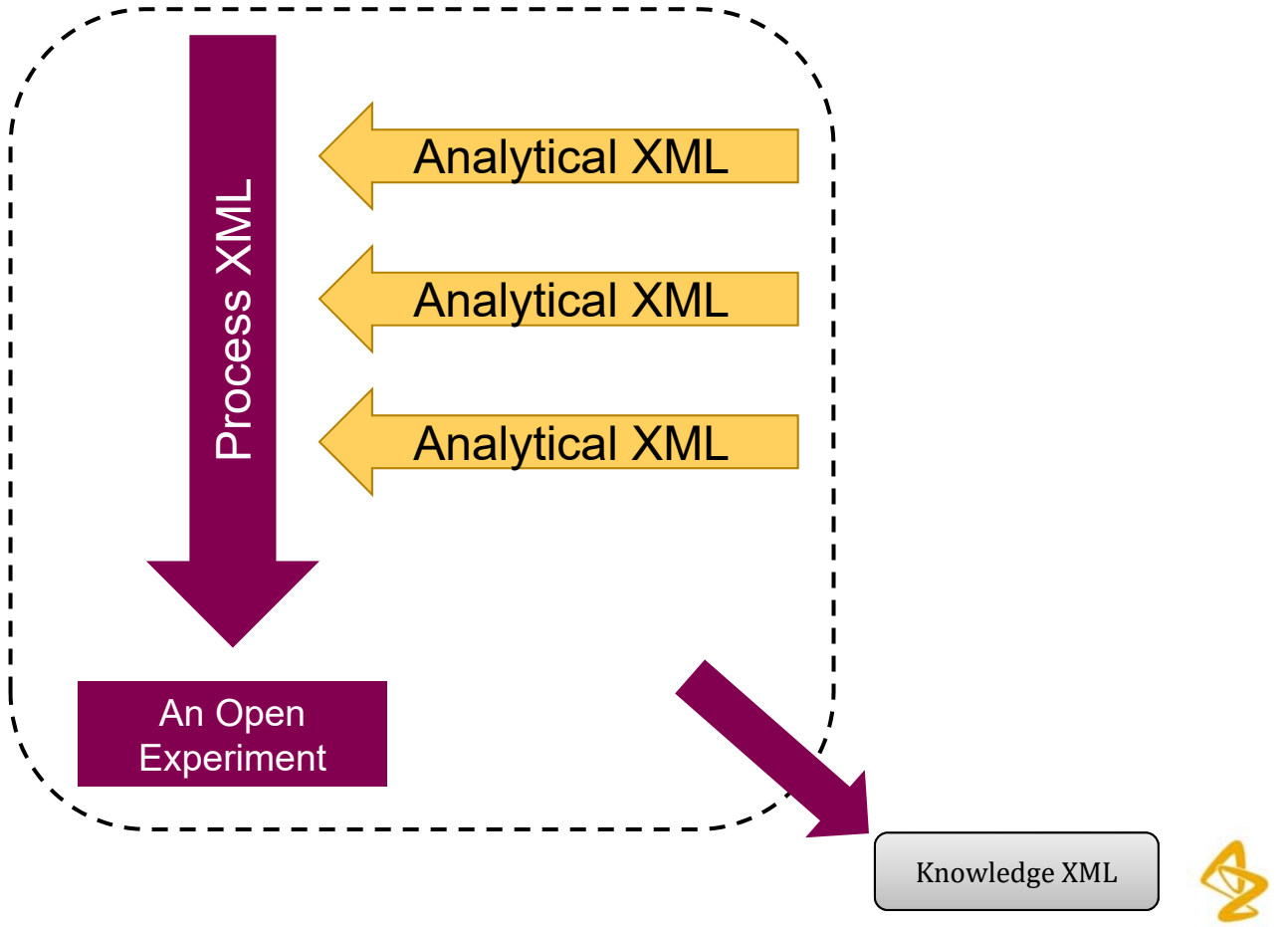
Experiment: Exp Test Ally May 2019
Started: June 19, 2019 17:04 Author: Ally.Mac

4 Recipe

#	Action / Note / Sample	Start Time	End Time
1	Start of experiment on 19/06/2019 at 17:04:22 with thermostat off and stirrer off	19/06/2019 17:04:22	19/06/2019 17:04:27
2	Inert	19/06/2019 17:04:27	
3	Add 25 ml of Ethanol at once	19/06/2019 17:04:27	

Processing Space – Data Standard





What now?

The challenge is clear and accepted

Cross fertilisation of technologies

Application of AI/ML is just at the beginning

People and Innovation

Data streams are bigger than institutions

- Taking the best pictures we can, right now
- Building the technologies to stick them together
- One day a version of the D-a-M dream may come true…..
- Until then we are feeling the beneficial impact of these technologies today.

2000 2020 2040

Acknowledgments

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