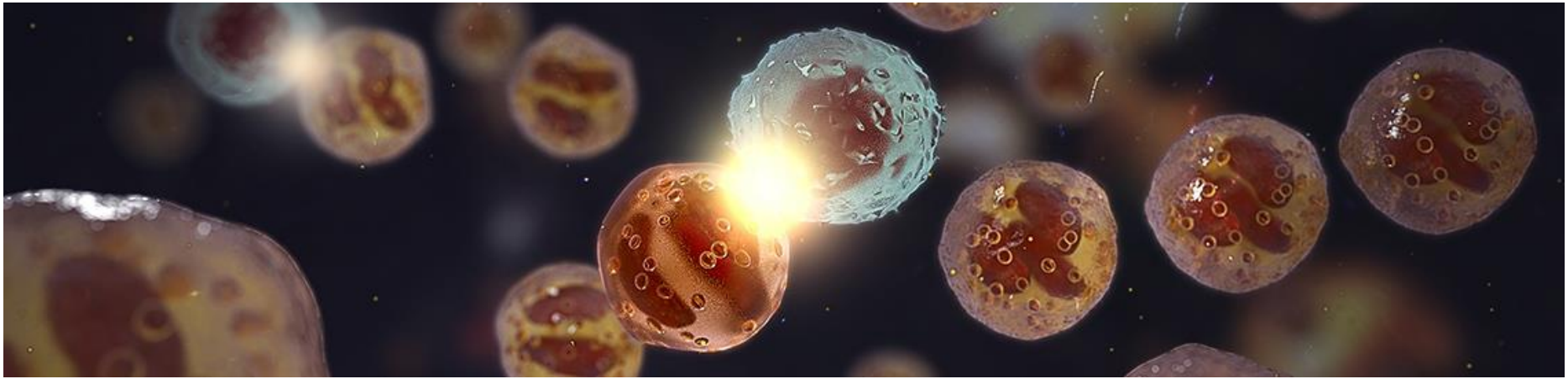
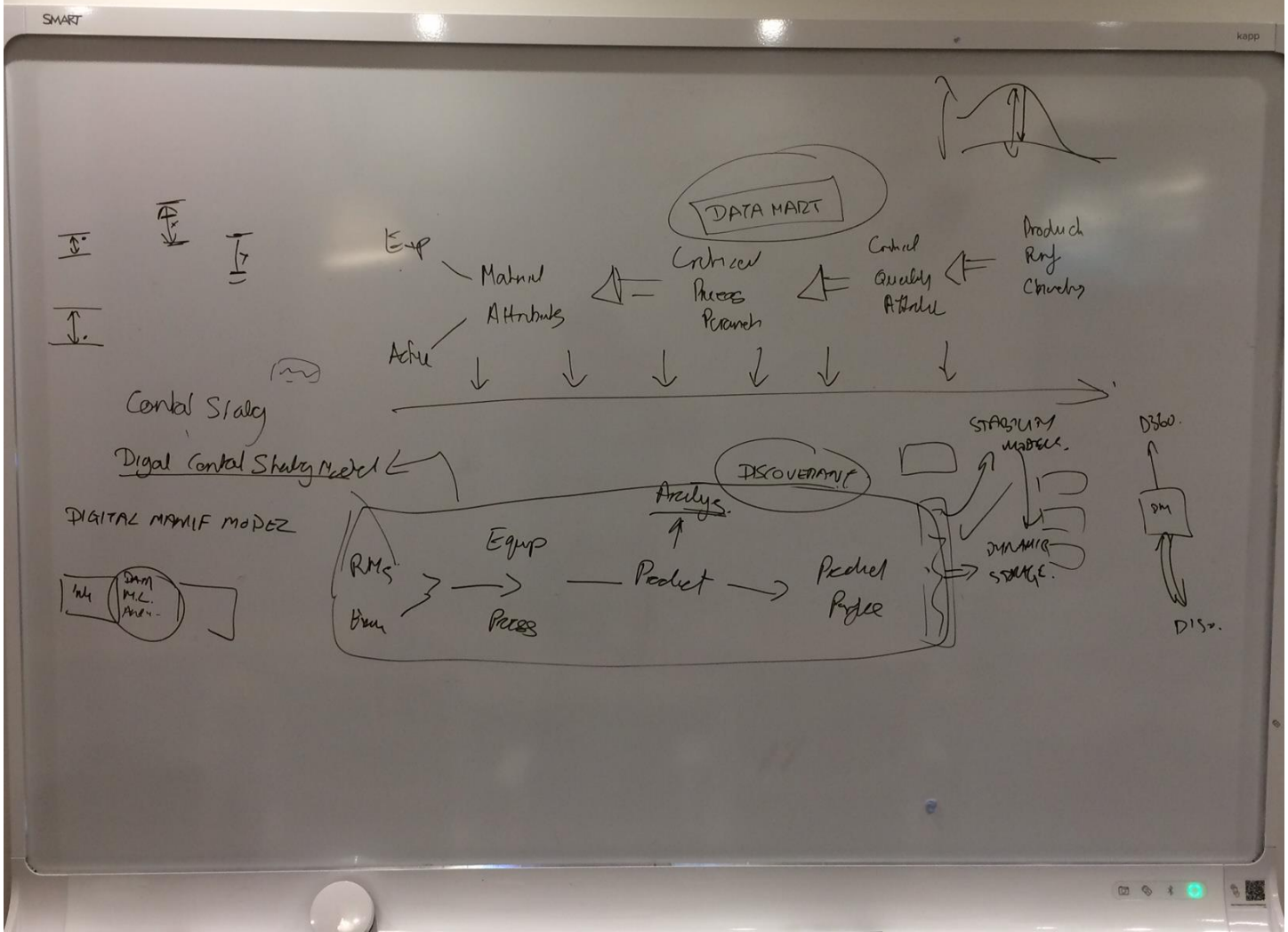
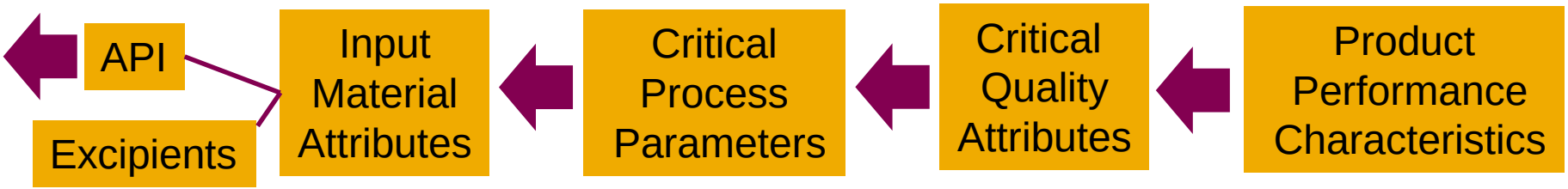
Emerging Technologies to Modernize Pharmaceutical and Bio-processing Development & Manufacture for both small and Large molecules Intelligent Factory - Concept

Andy J Jones




SMART
kapp
DATA MART
Equip
Material Attributes
Active
Critical Process Parameters
Critical Quality Attributes
Product Req Checking
Control Strategy
Digital Control Strategy Model
DIGITAL MANIF MODEL
DISCOVERANT
Analys.
RMs
Equip
Product
Product Perfce
STABILITY MODELS
DYNAMIC STORAGE
DS&D
DM
DISP.

The Development of Process Understanding and Control Strategy



Current Model
Manual and Automated Experiments
Some Automatic Data Capture
Manual data entry to ELN

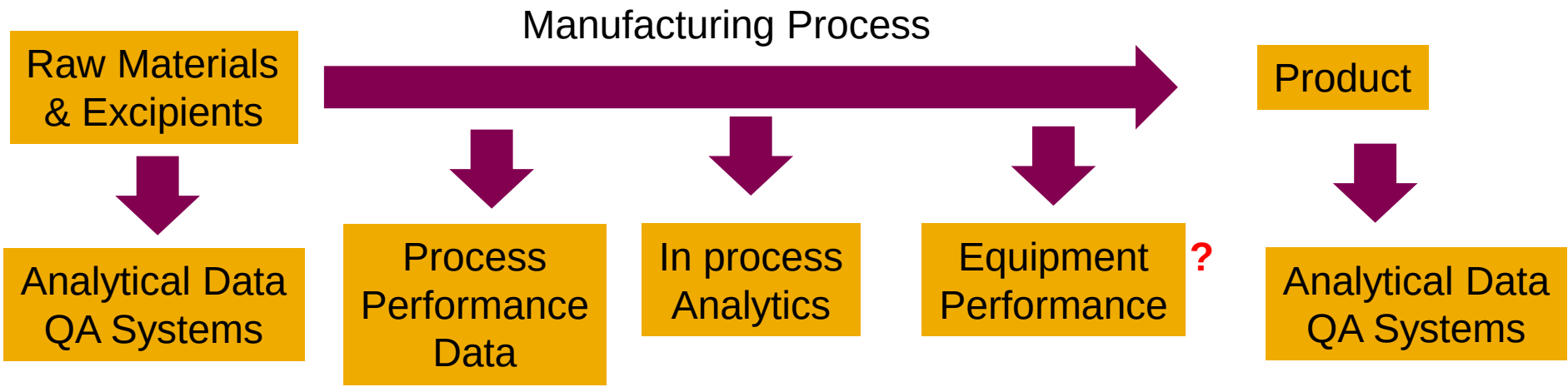
Data Systems:
DATA MART
D360 –IMed Data System

e.g.Times
Temps
Mixing etc.

e.g. Purity
Polymorph
Crystallinity

e.g. Dissolution
Disintegration
Stability etc.

Process Intelligence and CPV



Data Captured in Discoverant, Engineering Systems & QA LIMS Systems

The Opportunity

Can we digitise all our Development Data in order to be able to produce a “ Digital Design Space”?

Can we create a virtual model of the manufacturing Process?

Can we use the process model to define the data capture requirements from the manufacturing information?

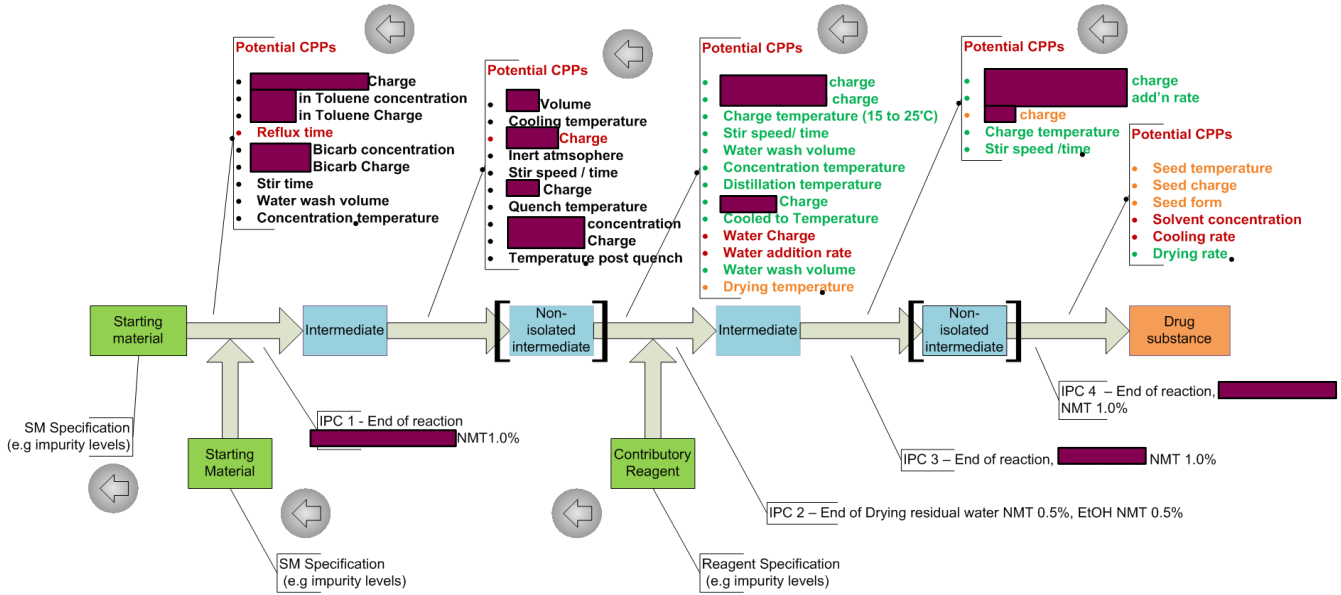
Can we combine this process data with Input Material and Product quality data to drive process optimisation?

Can we combine manufacturing & development data to strengthen the model?

Can we use A.I. to allow the process to learn?

Can we do this continuously, dynamically, and autonomously?

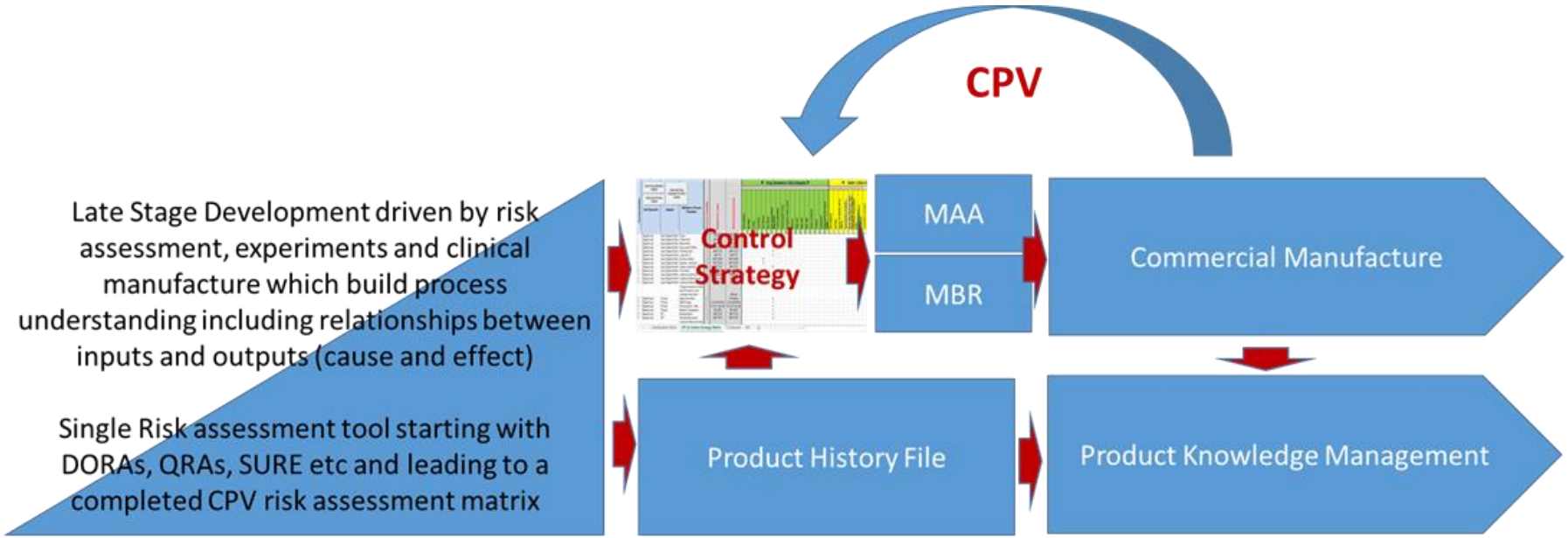
API Control Strategy



Can we digitise all our Development Data in order to be able to produce a " Digital Design Space"?

Hyper Link | Contributory Reagent | Proposed RSM | Intermediate | Drug Substance

Can we use the process model to define the data capture requirements from the manufacturing information?



Innovate UK Project Overview

Demonstration On AstraZeneca Selected Compound

Perceptive Engineering.
Model Predictive Automated Control system

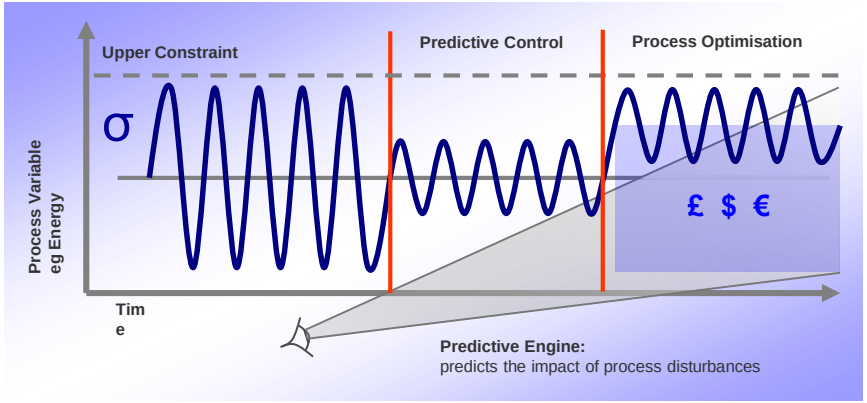
CPI: Corning Advanced Flow Reactor for Continuous Reactions

CMAC: Continuous Oscillatory Baffled Crystalliser (Nitech and CRD)

Advanced Process Control/Model Predictive Control
What does it mean?

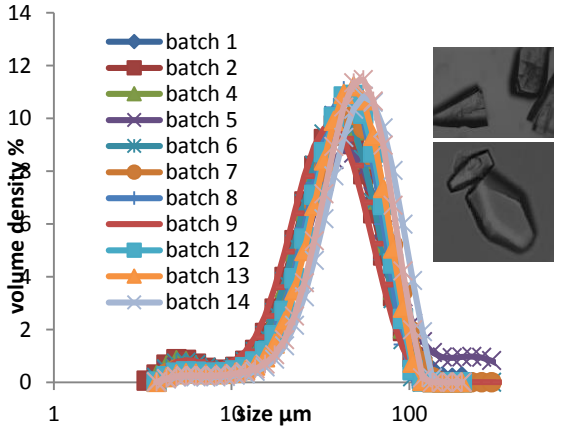
Model Predictive Control (MPC) understands process constraints and complex process interactions:

- Build multivariate correlation between variables and actuators, causes and effects
- Predict impact of known disturbances on operation
- Predict, Advise, Make co-ordinated moves on **multiple** actuators
- Exploit **all** opportunities to push quality / throughput close to constraint / consent



Key Achievements

- ✓ Proven ability to run for 5 days and 26% higher yield (vs batch equivalent) in continuous crystallisation => **improved yield**
- ✓ 2 fold reduction in span of PSD vs stirred tank reactor => **consistent & higher quality**
- ✓ Reduction in crystallisation time from 16 hour to 5 hours => **intensified process**
- ✓ Reduced manpower and waste requirements
- ✓ 'Dial a Particle' capability achieved
- ✓ Batch to continuous methodology developed for crystallisation
- ✓ Advanced Process Control capable of controlling both Crystallisation platforms



The Opportunity

Can we digitise all out Development Data in order to be able to produce a “ Digital Design Space”?

Can we create a virtual model of the manufacturing Process?

Can we use the process model to define the data capture requirements from the manufacturing information?

Can we use this data to drive process optimisation?

Can we combine manufacturing & development data to strengthen the model?

Can we use A.I. to allow the process to learn?

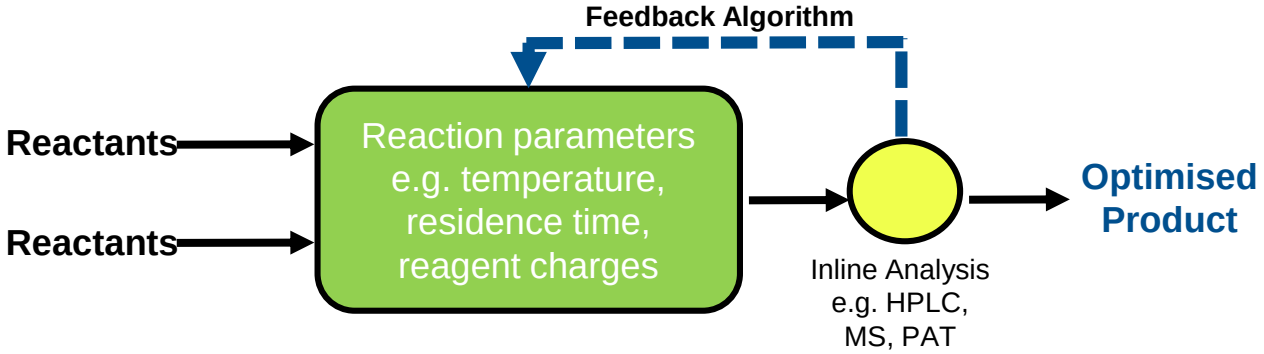
Can we do this continuously, dynamically, and autonomously?

SELF OPTIMISING FLOW REACTOR (SOFR)

An example from the lab

Mubina Mohamed and Graeme Clemens

SOFR Instrument

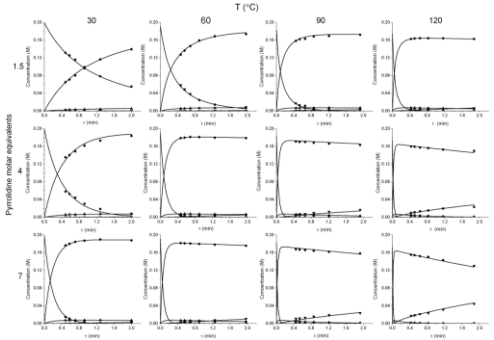


- Fully autonomous experimentation ideal for DOE and kinetic profiling
- Large amount of experimentation at low starting materials/reagents cost
- Large data sets from multiple analytical techniques to give bigger picture of the reaction
- SOFR is a *tool within the flow toolbox* to facilitate quick reaction parameter screen and reaction understanding

SOFR Instrument - What can it do

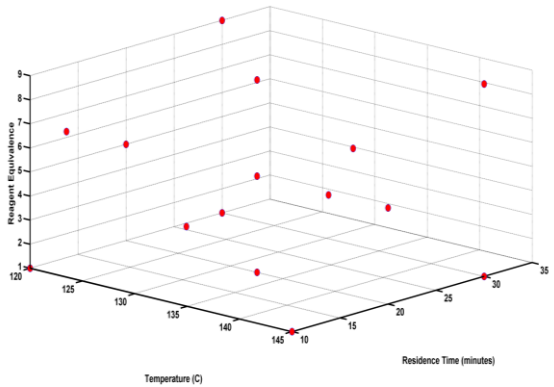
Concentrations Ramps

To produce rapid kinetic profiles of reactions



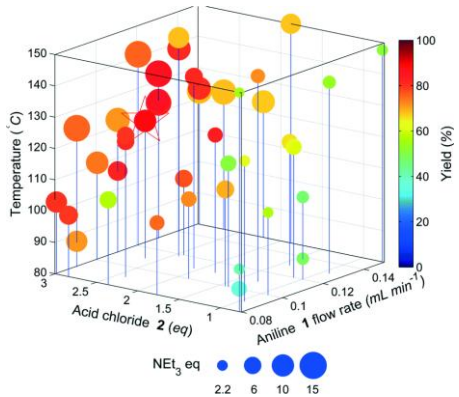
DOEs

Perform DOE experiments in sequence exploring reaction space to find optimum reaction parameters



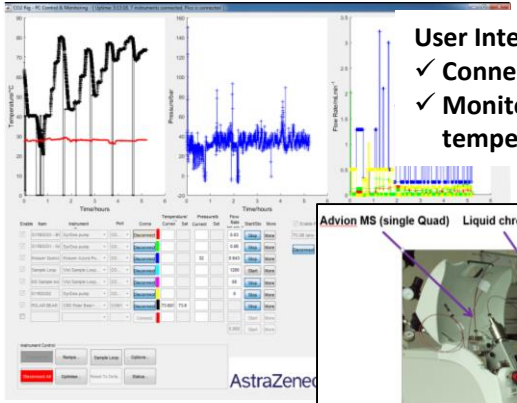
SNOBFIT

Online analysis with a feedback control loop, which uses the optimising SNOBFIT (Stable Noisy Optimisation by Branch and Fit) algorithm to keep generating new conditions until an optimum is reached

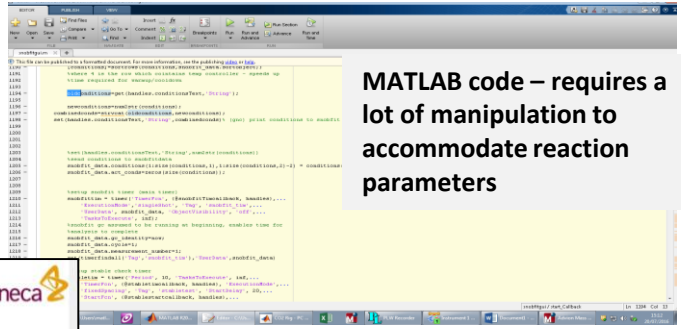


NB: The code is not limited to the above, and is able to accommodate different structured designs

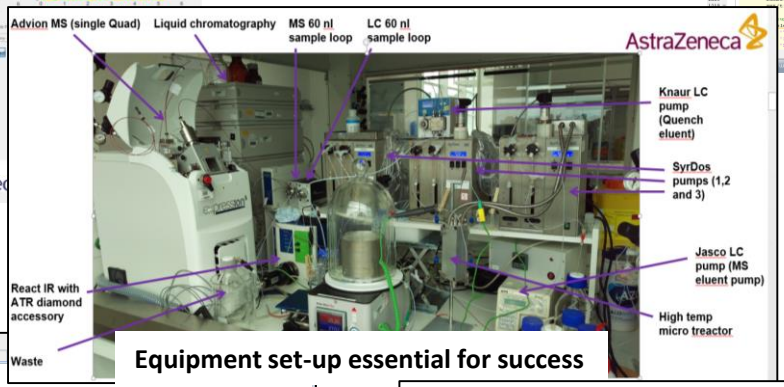
Where do we stand with kit and code



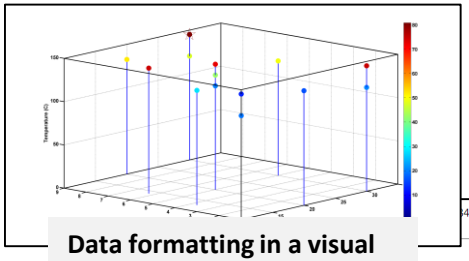
User Interface
- ✓ Connection of equipment
- ✓ Monitor flow rates, system temperature and pressure



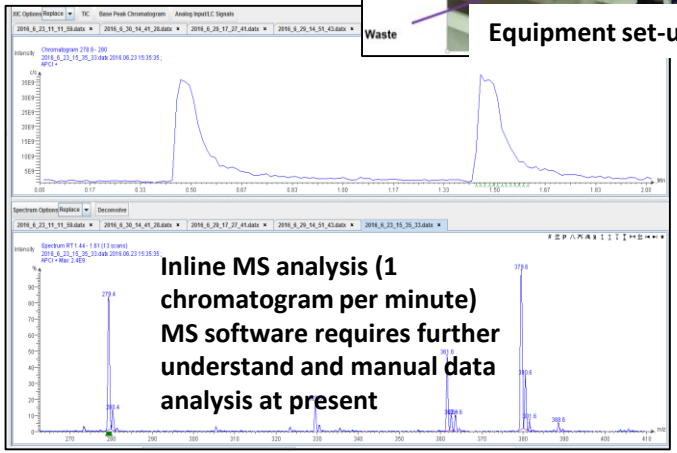
MATLAB code – requires a lot of manipulation to accommodate reaction parameters



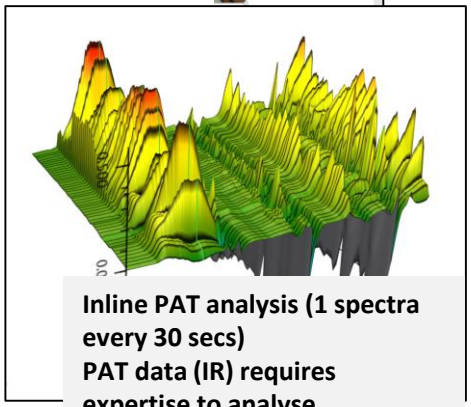
Equipment set-up essential for success



Data formatting in a visual manner for projects

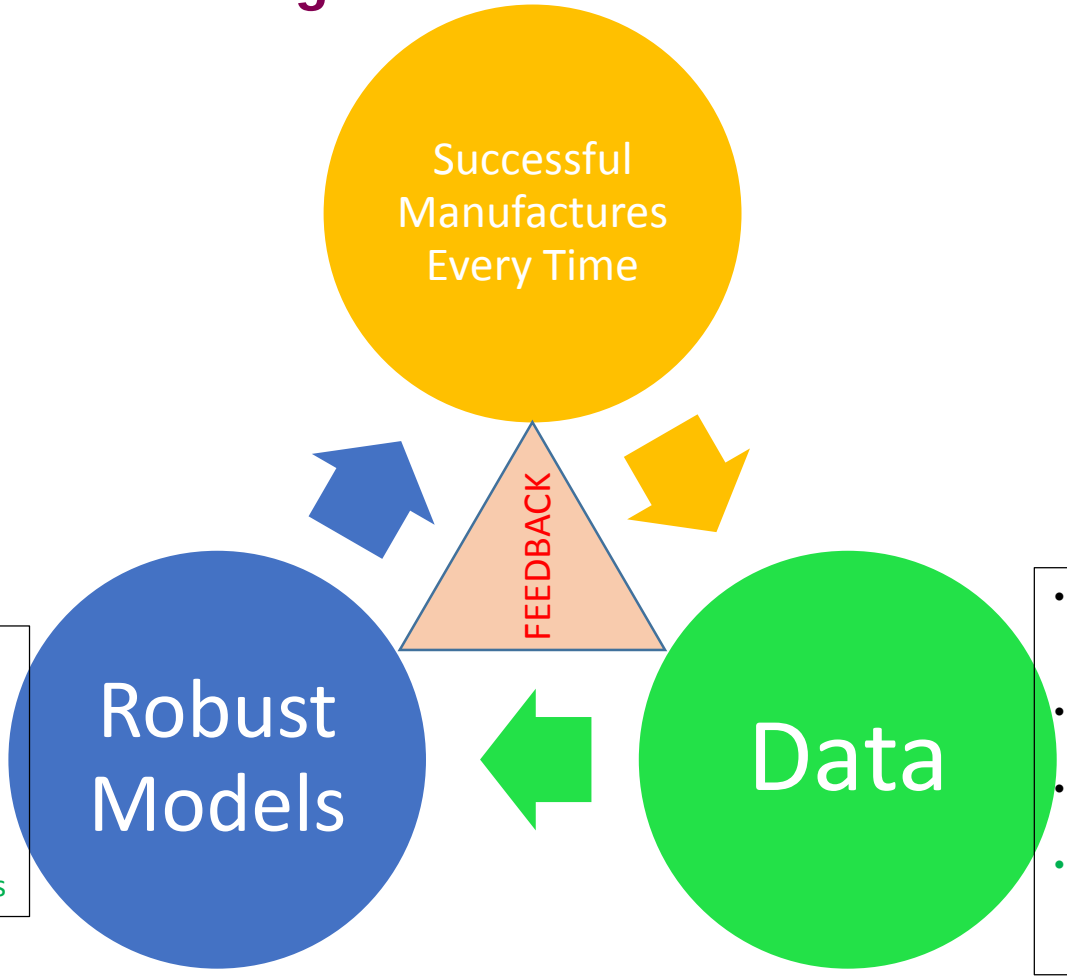


Inline MS analysis (1 chromatogram per minute)
MS software requires further understand and manual data analysis at present



Inline PAT analysis (1 spectra every 30 secs)
PAT data (IR) requires expertise to analyse

SOFR and Manufacturing – Where can we take it?



Good predictions are based on robust models, which are built on variable data sets. Models are updated each time more data is available.
More data = Better models

- Data from all manufacturing processes recorded
- Data about variable input materials
- Data from reaction screening experiments
- All the above can be accomplished in the lab using the SOFR

The Intelligent Factory Vision:
The Big Hairy Audacious Goal The BHAG.

We understand all the critical quality attributes of all our products

We have a virtual Process model for all our processes – a Digital Design Space

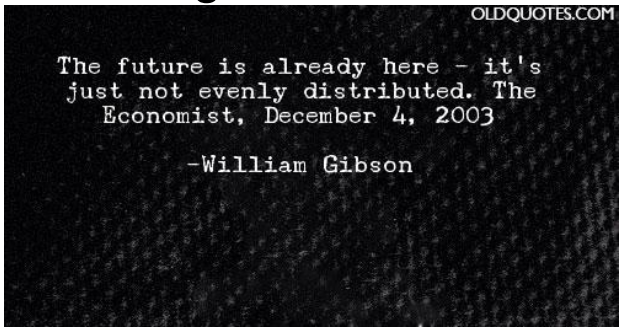
We combine development and commercial data to strengthen the model

The model is used to control manufacture and has the capability to learn

The quality of our products is controlled automatically and the processes are continuously, dynamically and autonomously optimised.

How do we deliver this

- This is a 5 year vision but we have some of these things in place already
  - Process Models
  - Continuous Autonomous optimisation
  - Continuous Processing Options



- We start with One product and maybe one set of CQAs

- We have some systems in place to build on