Driving Process Understanding through a Systematic Approach to Experimentation

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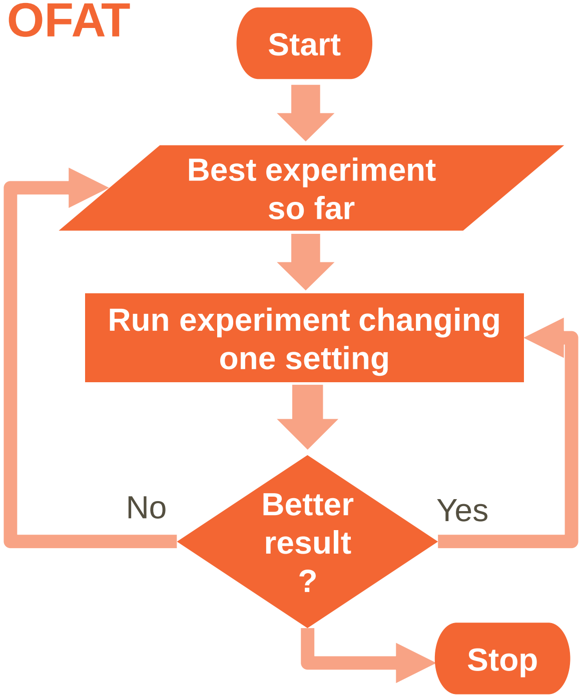
Experimentation in Chemistry

Question for the audience

When you need to improve the yield or selectivity of your reaction what approach are you most likely to take?

1 **OFAT**



2 **NOISE**

Run the same conditions several times before changing anything.

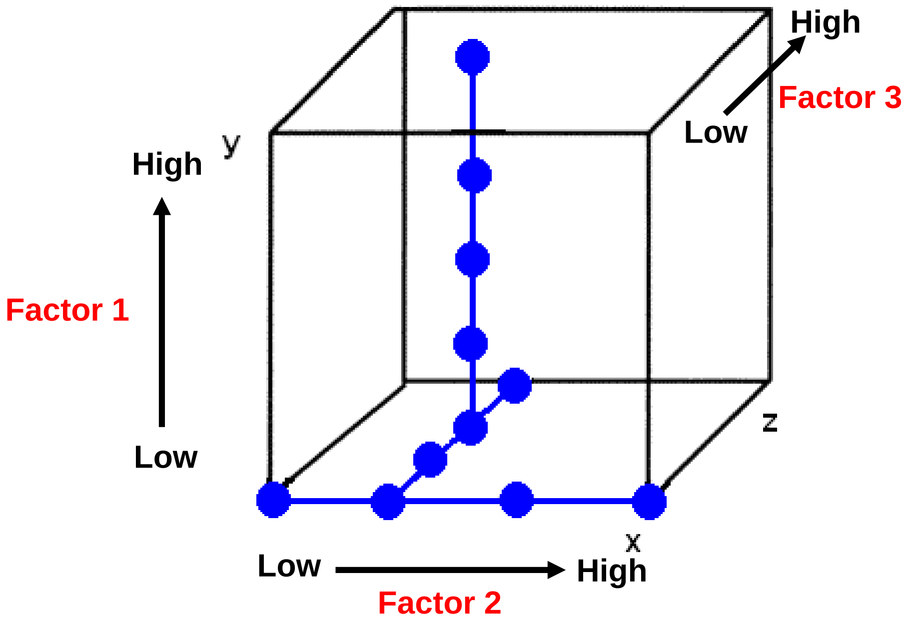
3 **DoE**

Varying everything at once in a systematic way to get a better understanding

OFAT

One Factor at a Time

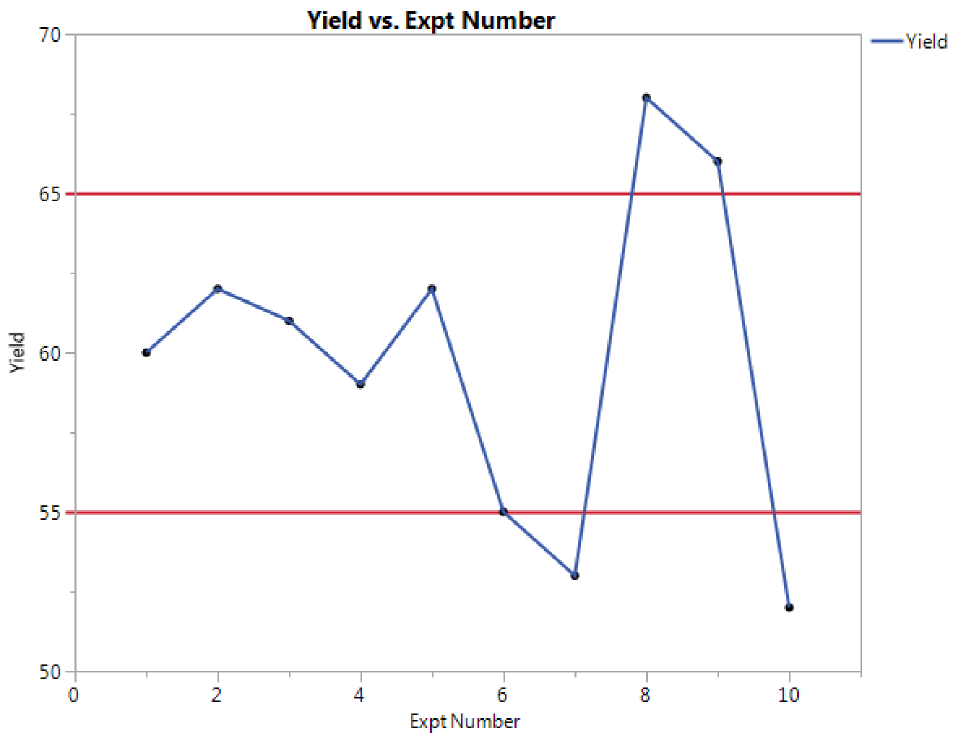
- ☺Taught traditionally
- ☺ Straightforward
- ☹ Does not cover the experimental “space” thoroughly
- ☹ May miss the optimal solution
- ☹ Fails to identify interactions
- ☹ Can be resource intensive



Noise

What could impact the noise?

- The isolation process
- The equipment set-up
- The time before isolation
- Analysis method
- Age of sample
- Batch of reagent
- Batch of solvent
- The chemist/operator
- The analyst
- The ambient humidity
- Exposure to light



…..Anything that you are not controlling

Design of Experiments (DoE)

– What are the advantages and disadvantages?

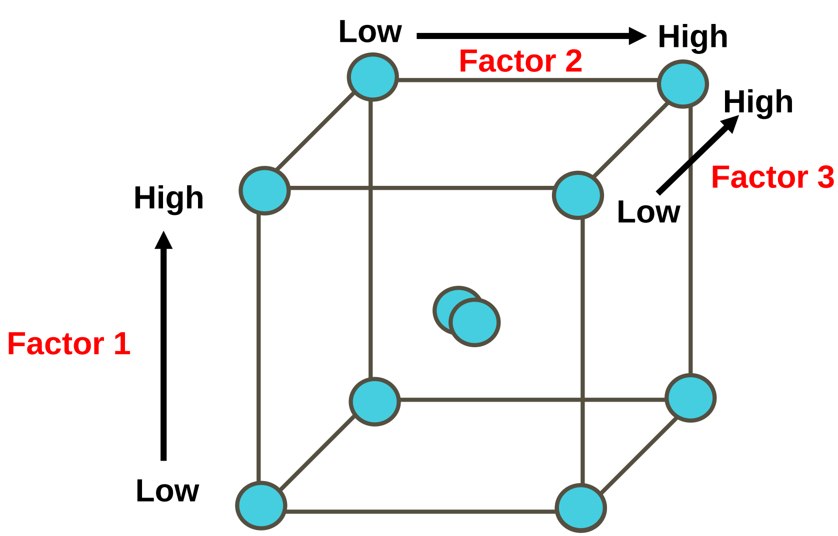
– **DoE using a Factorial Design**

☺ *Systematic:* Thorough coverage of experimental "space"

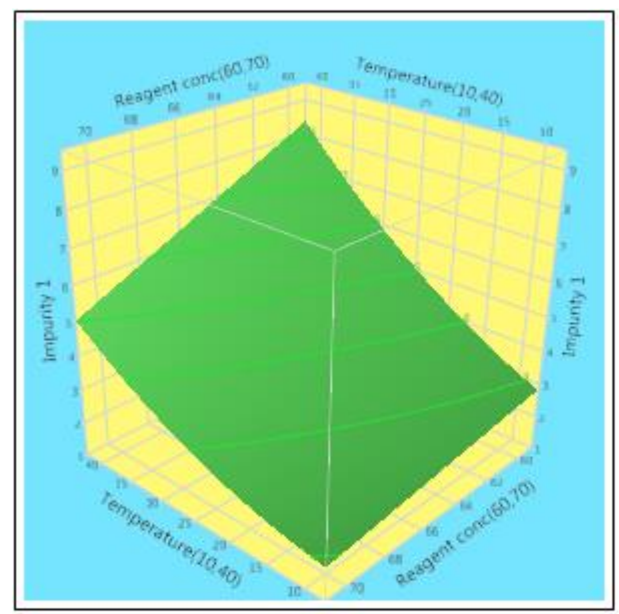
☺ *Efficient:* Able to establish solution with minimal resource

☹ Commit to running a number of experiments up front

☹ You may have to run experiments that you anticipate will give "poor results"



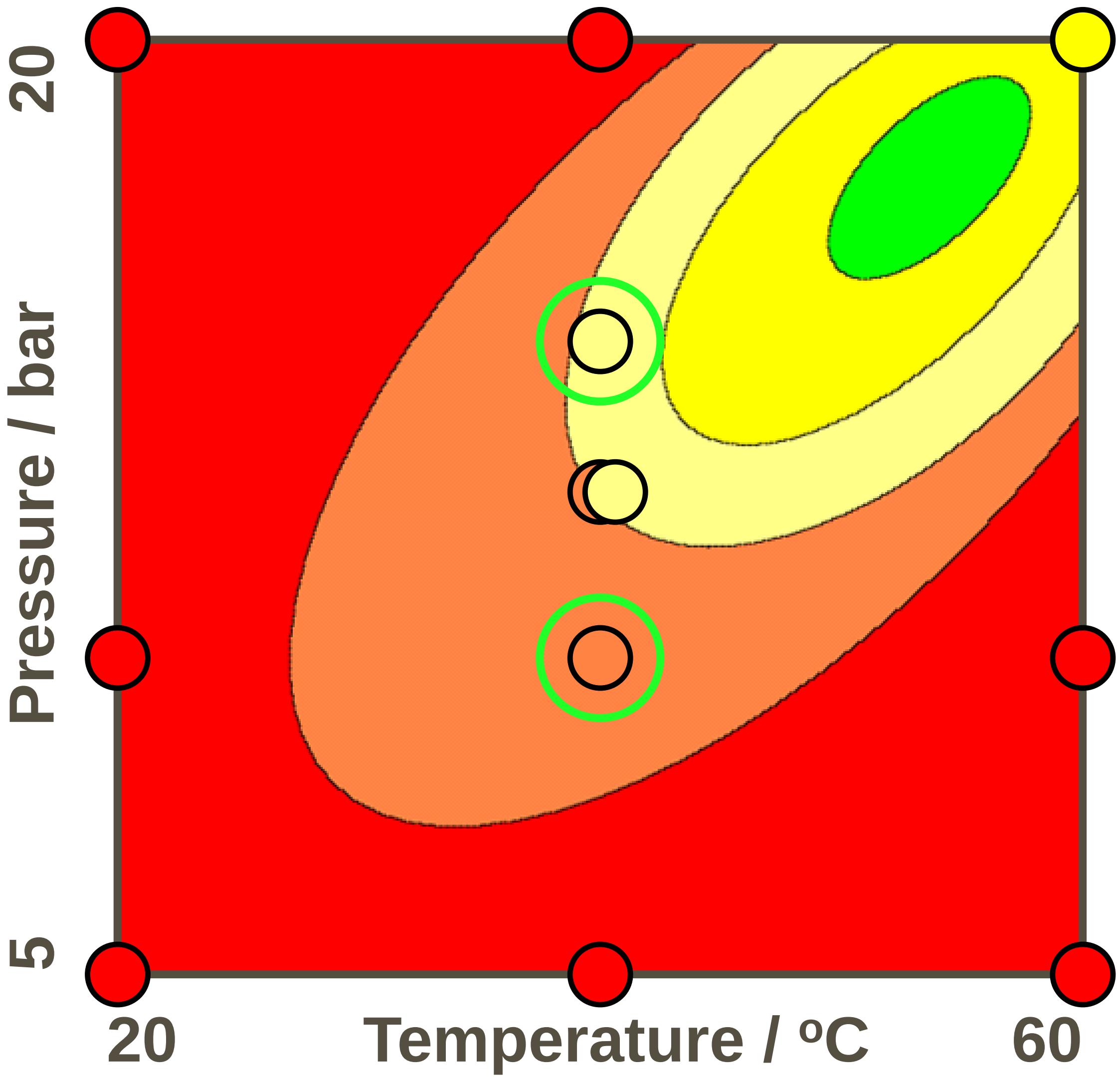
Full Factorial design



DoE in Practice

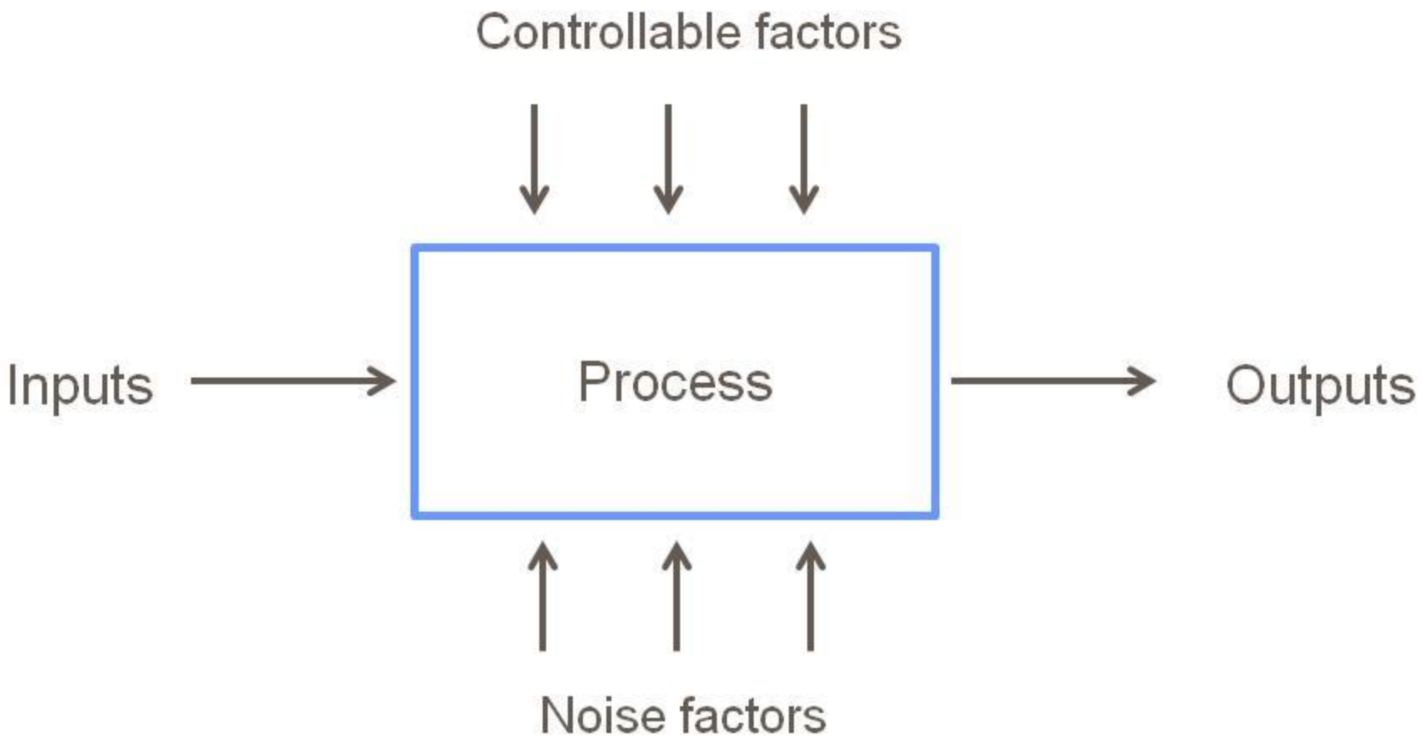
Why DoE?

– What's wrong with One Factor at a Time?



What is a Designed Experiment?

– A **structured** set of tests of a reaction, process or system



Selecting which Factors to Assess

What problem are you trying to solve?

Where do I start?

– Define the target

Then

– Understand the process

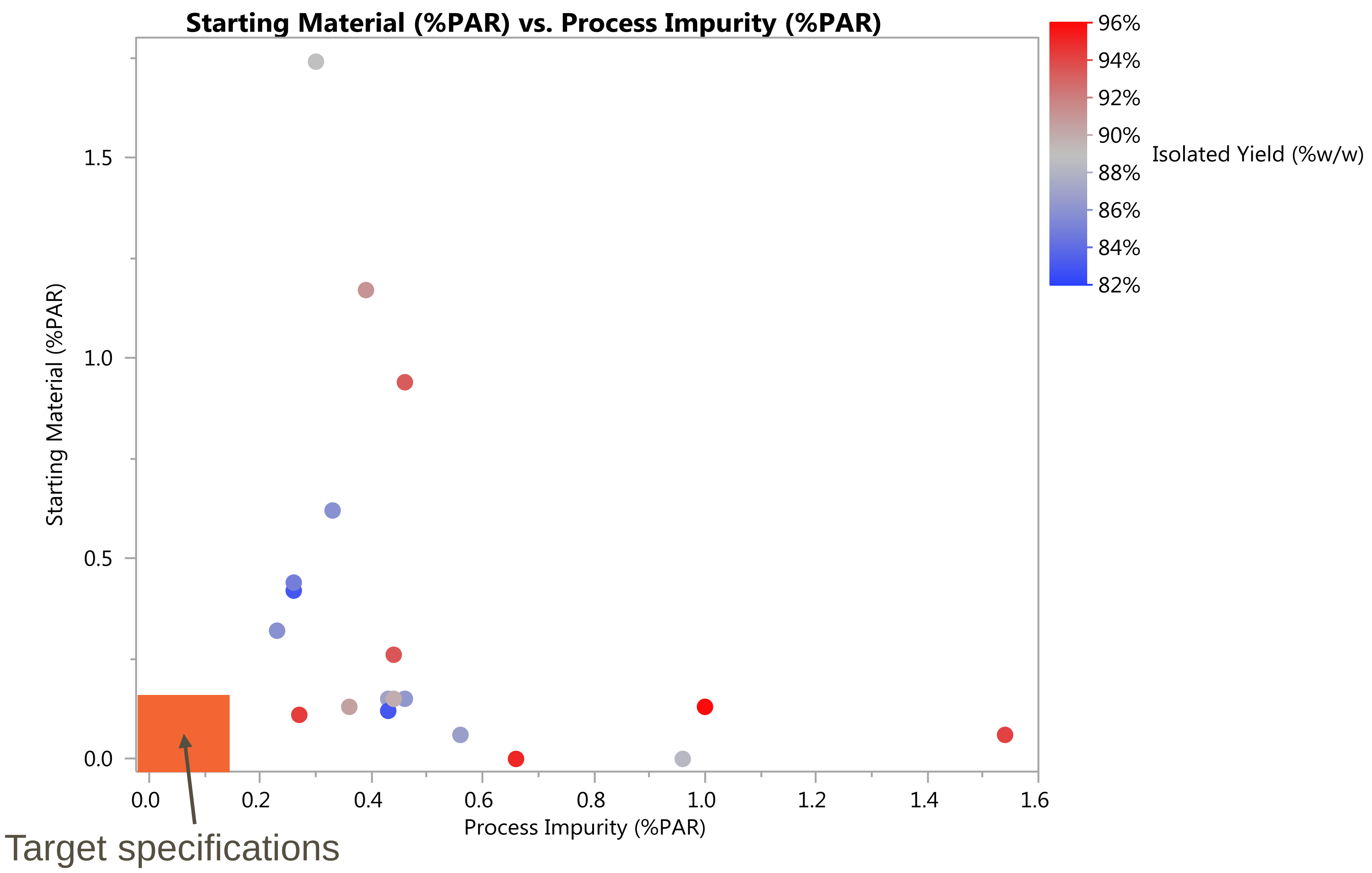
– Control only what is needed

Starting Material —(Reagent / Solvent/Water)→ Product → Impurity

Starting Material	Product	Impurity
<0.15%	maximise	<0.15%

Defining the problem

Initial OFAT lab data



Understanding the Process

Screening Design

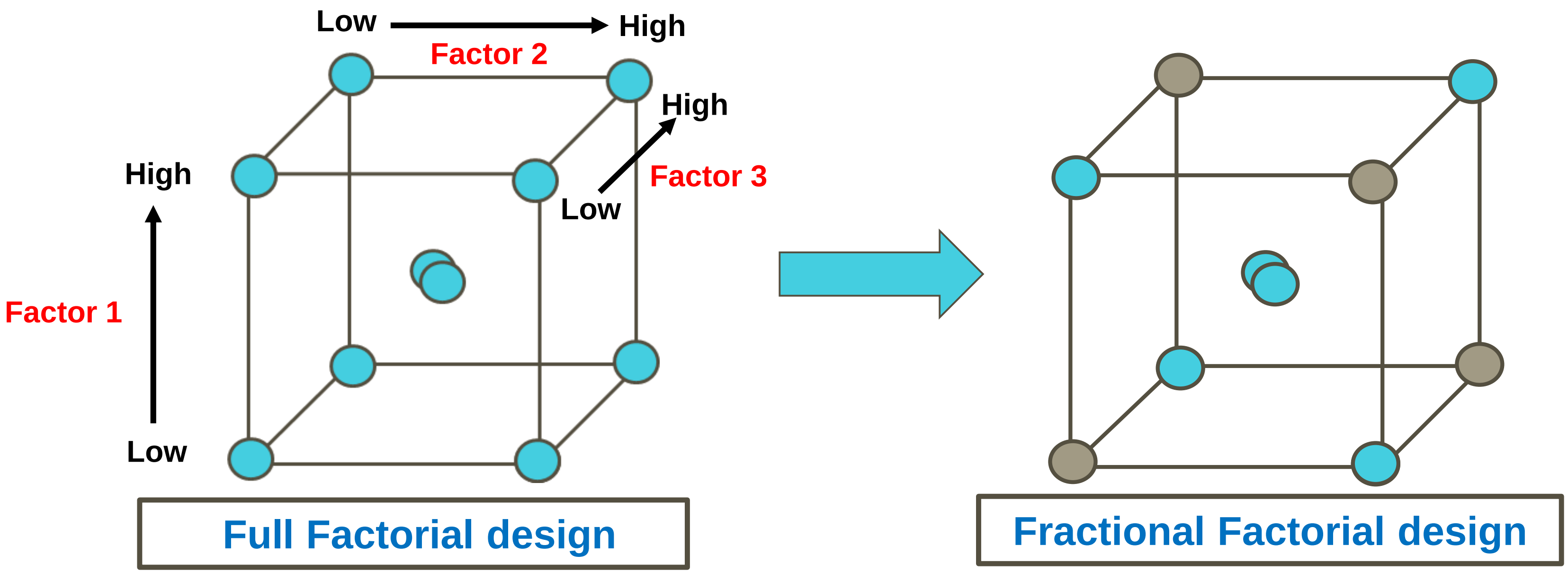
- **Start by brainstorming around the unit operation**
  - What are the potential sources of variation?

Factor	Range	Units
Temperature	0 - 50	ºC
Reaction time	30 – 180	minutes
Water volumes	0 - 3	volumes
Solvent volumes	3 - 7	volumes
Reagent equivalents	1 - 2	equivalents
Addition time	2 - 120	minutes

- And what was kept constant?
  - Amount of starting material, quality of starting material, quality of reagent, concentration of reagent, scale of reaction, vessel fill, mixing…….

The Screening DoE

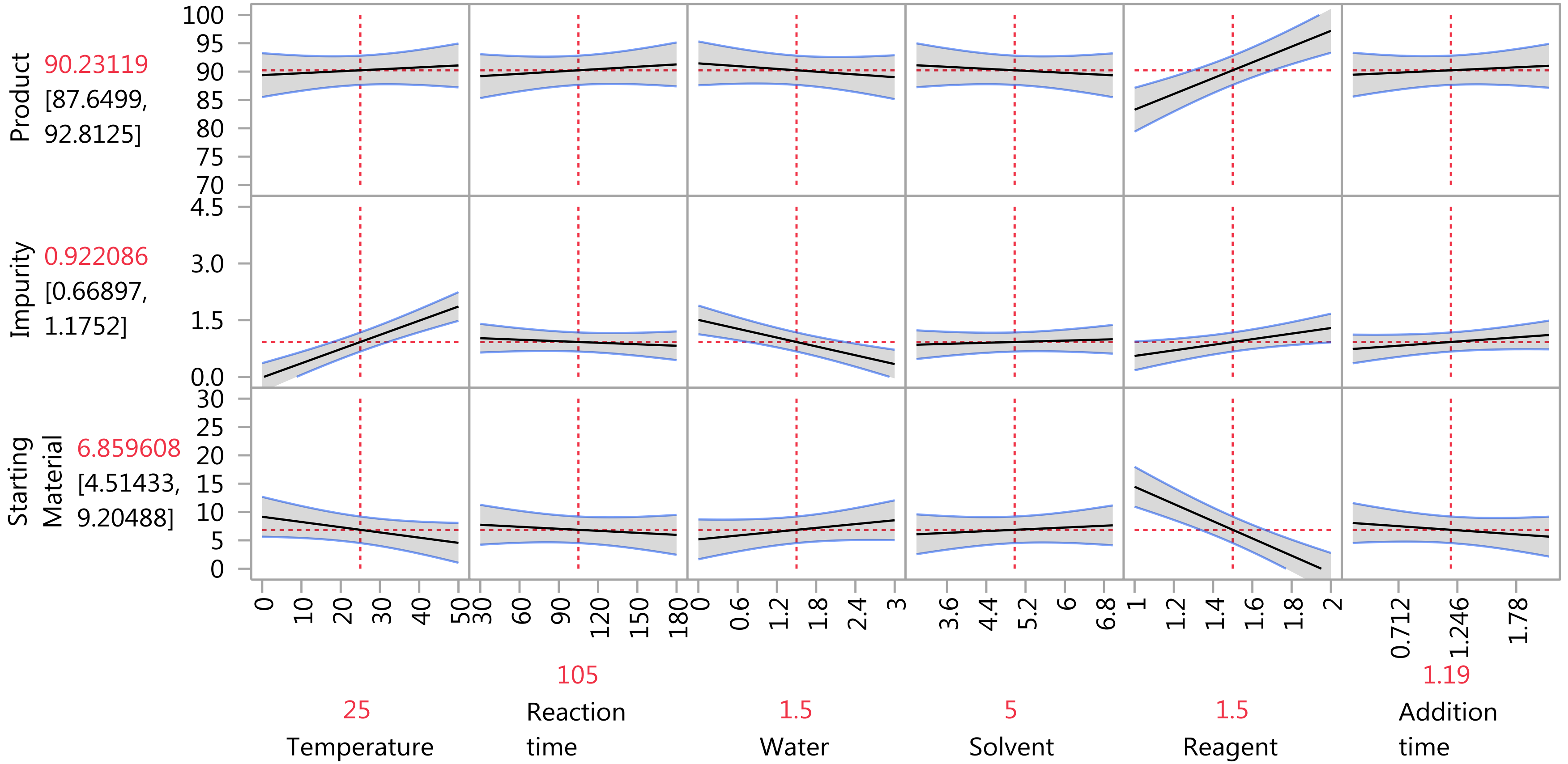
2^{6-2} fractional factorial design



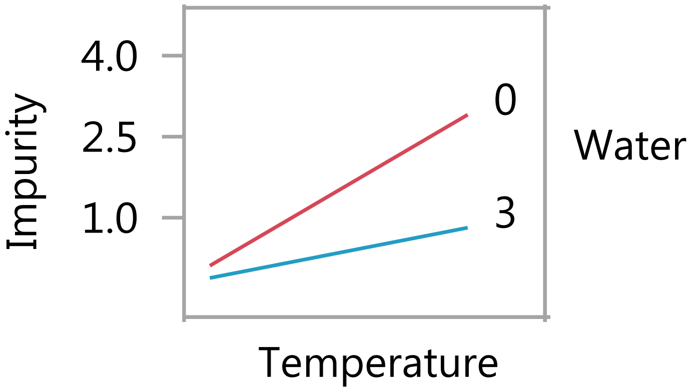
Full factorial with 6 factors would be 64 runs
To save resource ¼ fraction factorial with 6 factors = 16 runs
plus 4 centre-points = 20 runs in total

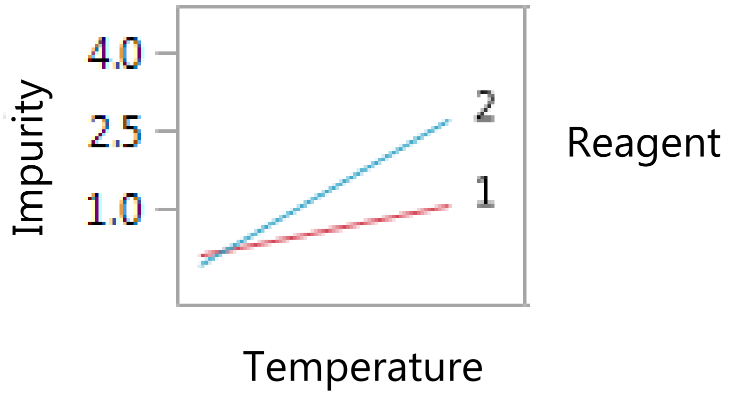
Make sure you randomise your run order to remove systematic effects
– most software will do this for you

The screening effects



The screening interactions





Increasing temperature results in more impurity being produced. At low levels of water this effect is greater

Increasing temperature results in more impurity being produced. At high levels of reagent this effect is greater

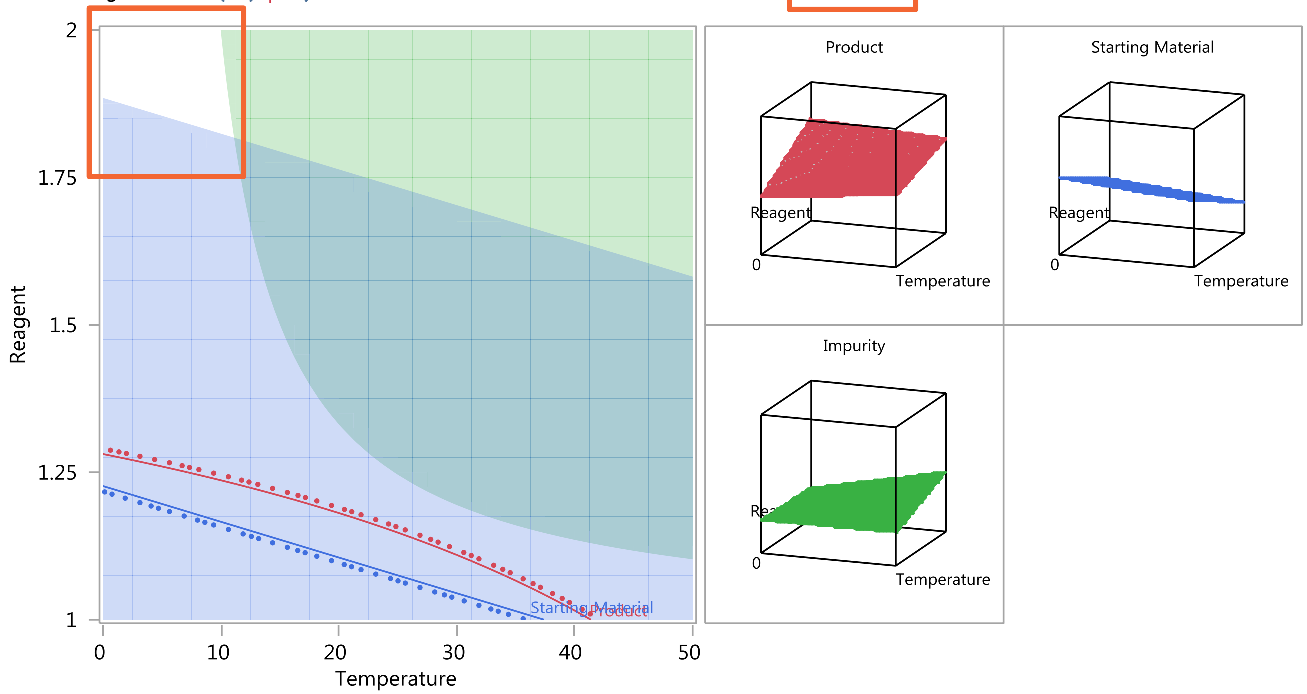
These interactions are not present in the starting material so we can make use of them to optimise our reaction

Results of the screening design

Contour Profiler

Horiz	Vert	Factor		Current X
◉	○	Temperature		25
○	◉	Reagent		1.5
○	○	Reaction time		105
○	○	Water		3
○	○	Solvent		5
○	○	Addition time		1.19

Response		Contour	Current Y	Lo Limit	Hi Limit
Product		85.326	90.231188	.	
Impurity		2.25	0.3376868	.	0.15
Starting Material		15	8.5440372	.	5



The Optimisation DoE

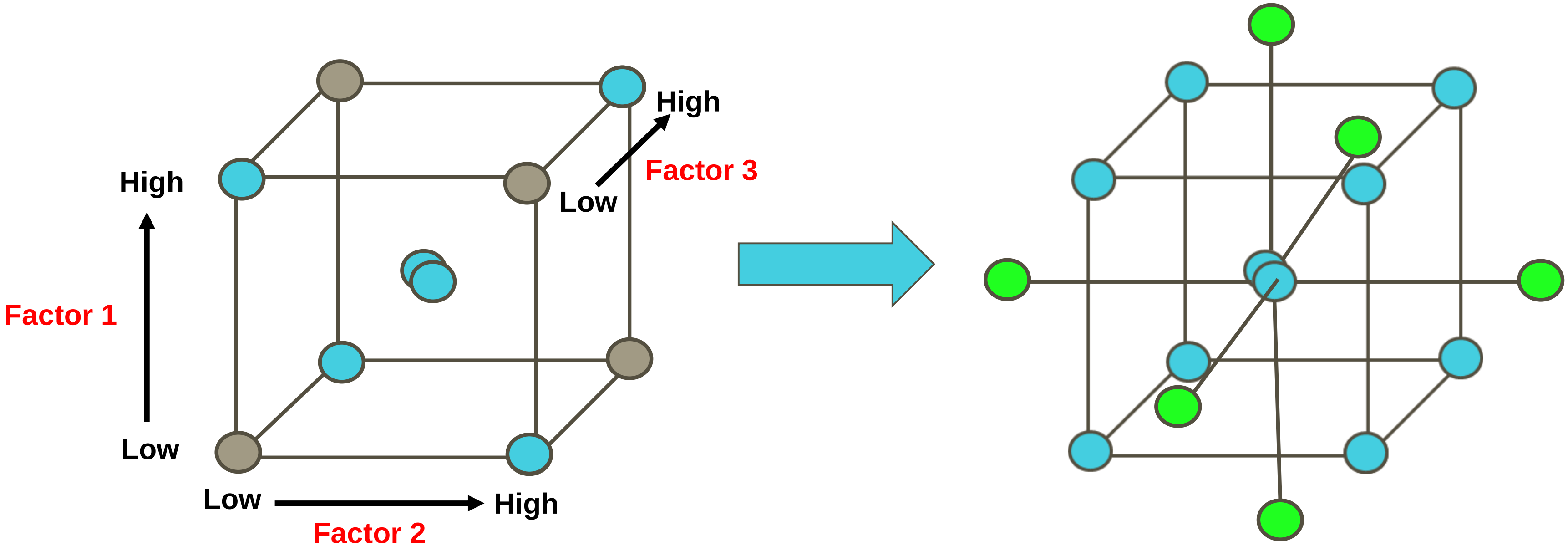
Choose new parameter ranges based on screening design

Factor	Screening Range	Optimisation Range	Units
Temperature	0 - 50	0 - 25	ºC
Reaction time	30 – 180	180	minutes
Water volumes	0 - 3	0 - 3	volumes
Solvent volumes	3 - 7	7	volumes
Reagent equivalents	1 - 2	1.2 – 2.2	equivalents
Addition time	2 - 120	10 - 120	minutes

Focus on the parameters which have the greatest effect, fix the rest.

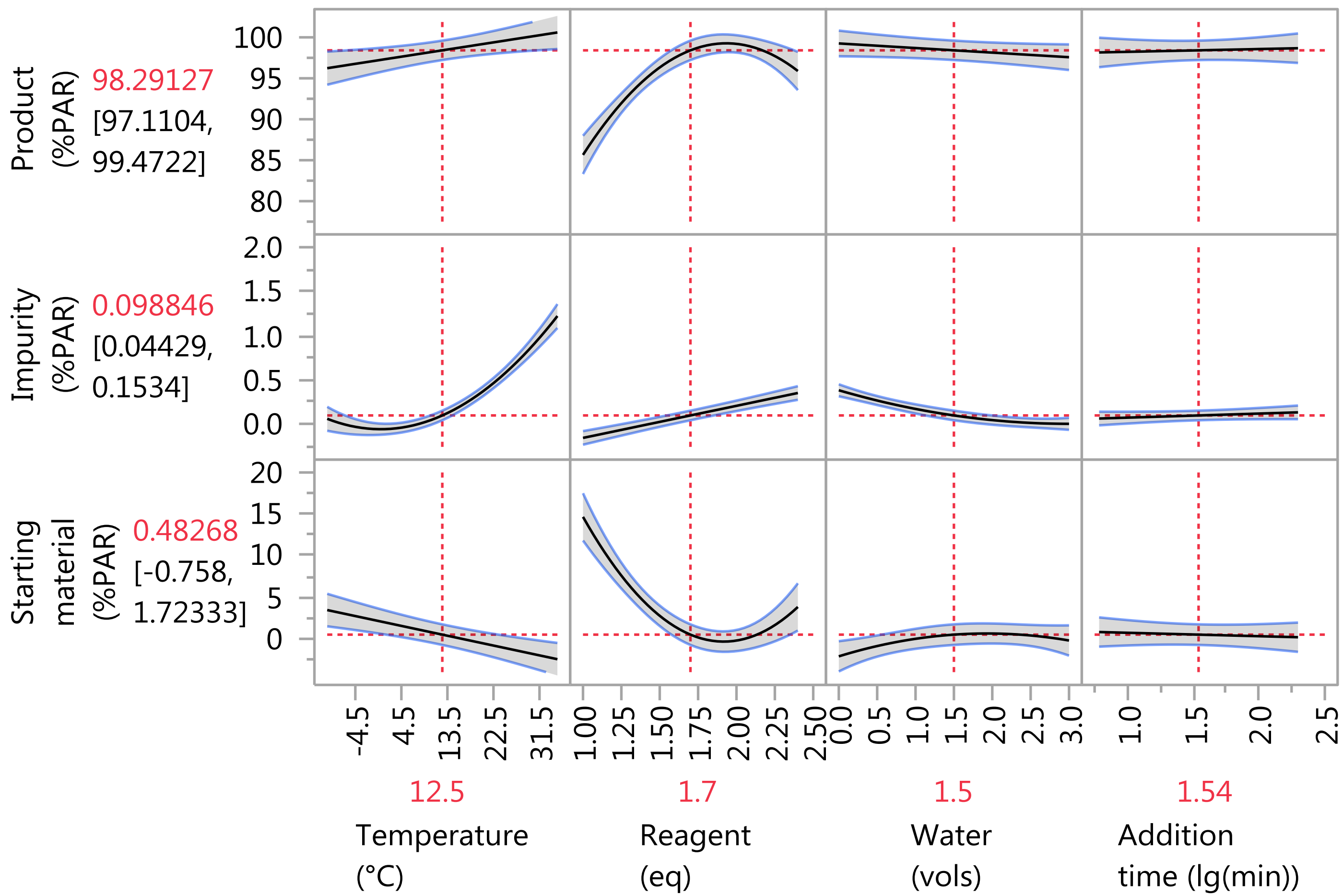
The Optimisation DoE

Response Surface Design



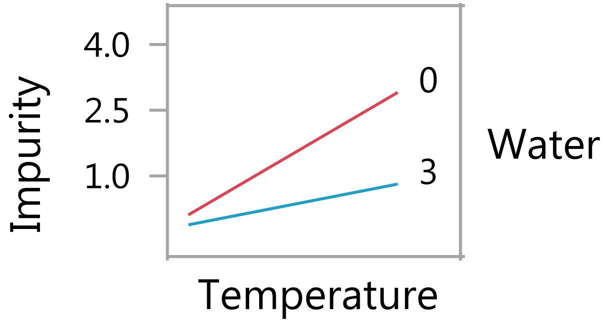
Full response surface with 4 factors would be 24 runs
plus 6 centre-points = 30 runs in total

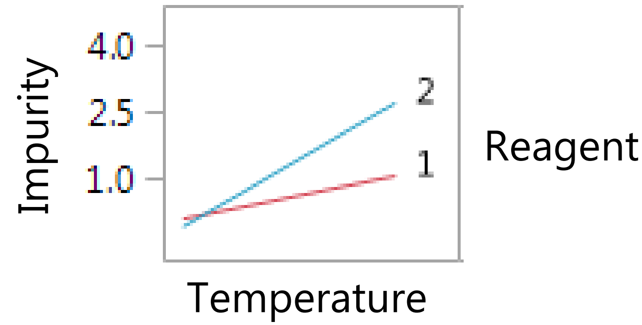
The optimisation effects



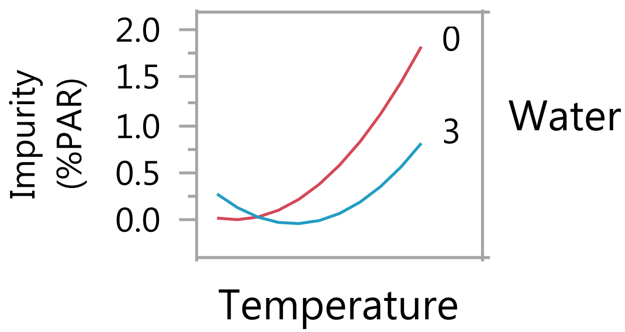
The screening interactions

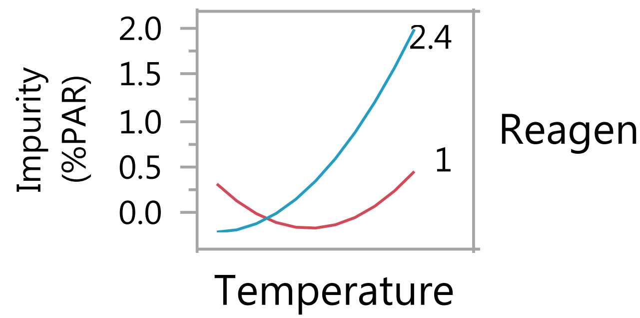
Screening Design

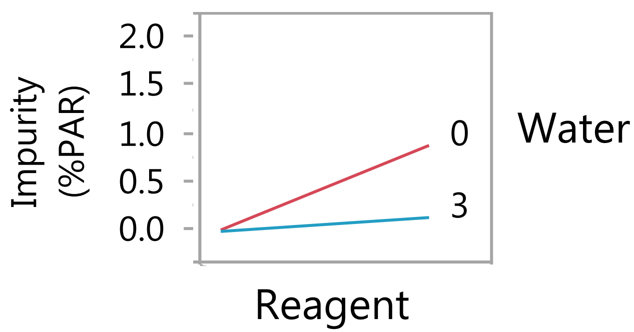




Optimisation Design





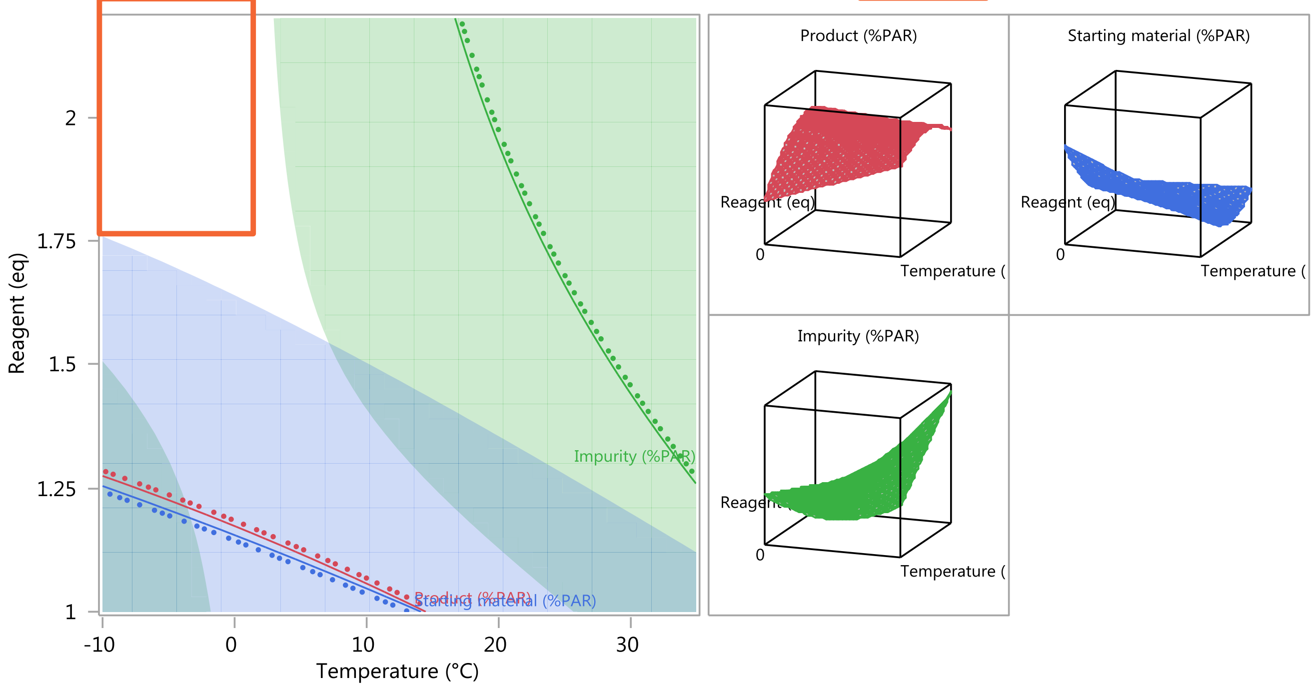


Optimisation of the response surface design

Contour Profiler

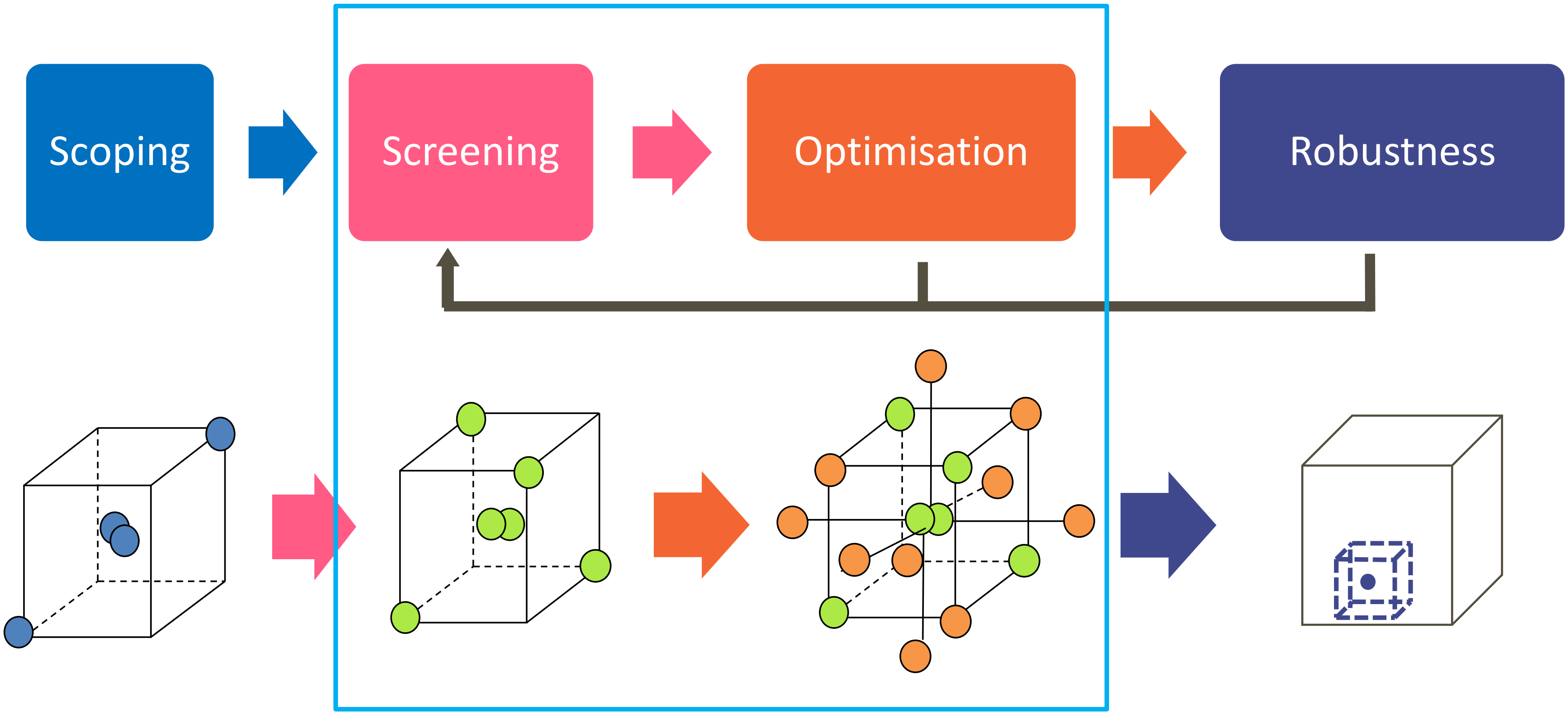
Horiz	Vert	Factor		Current X
◉	○	Temperature (°C)		12.5
○	◉	Reagent (eq)		1.7
○	○	Water (vols)		0
○	○	Addition time (lg(min))		1.54

Response		Contour	Current Y	Lo Limit	Hi Limit
Product (%PAR)		88.75	99.126768	.	
Impurity (%PAR)		1	0.3833828	.	0.15
Starting material (%PAR)		10	-2.129574	.	0.15



Sequential DoE

A Sequential Approach

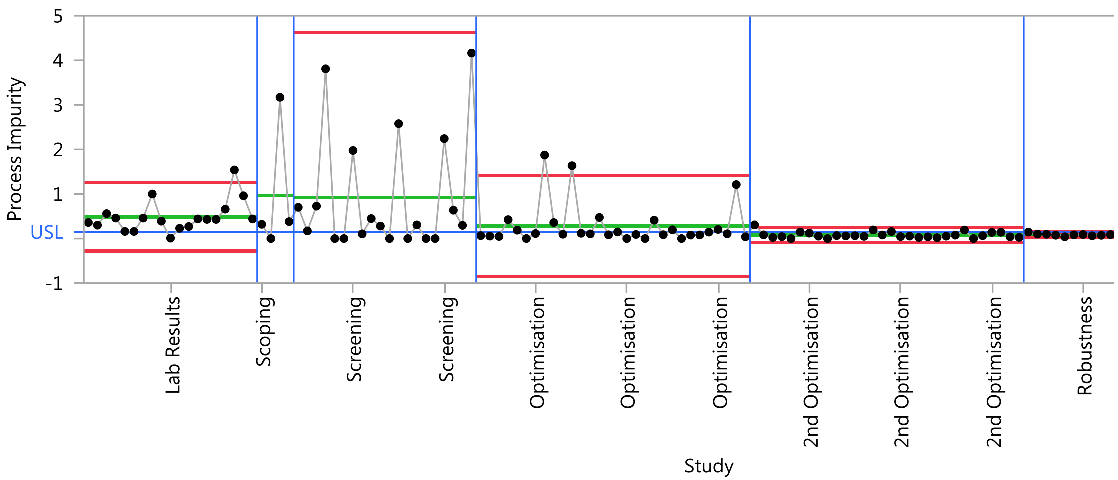


This is what we've covered so far.

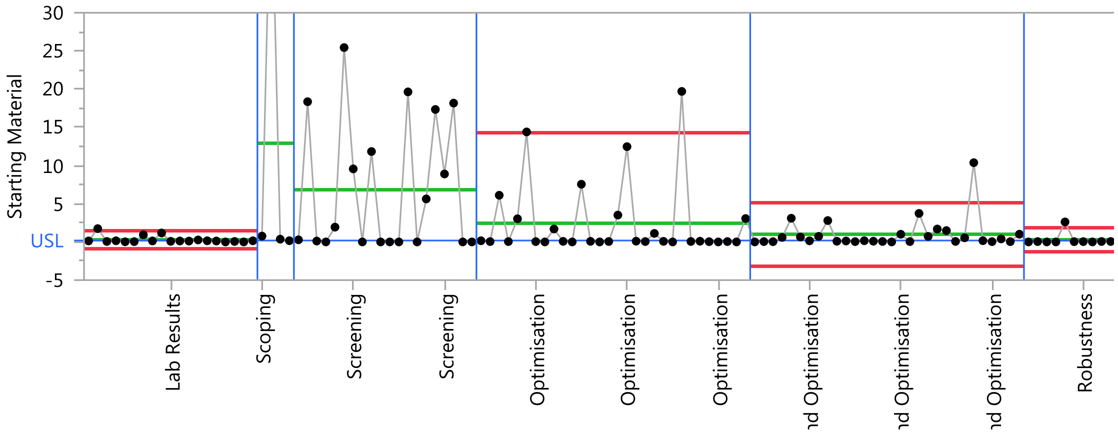
Following the sequential workflow

Trending the data

Individual Measurement of Process Impurity



Individual Measurement of Starting Material



Conclusions

- Define your problem before starting to experiment
- Design of Experiments can help you to understand which factors are important in controlling your process
- Don't forget the noise.
- Following a sequential approach can deliver a robust process

Thank you