Applications of MBDoE techniques to a cloud-based platform for automated chemical manufacturing in flow reactor systems

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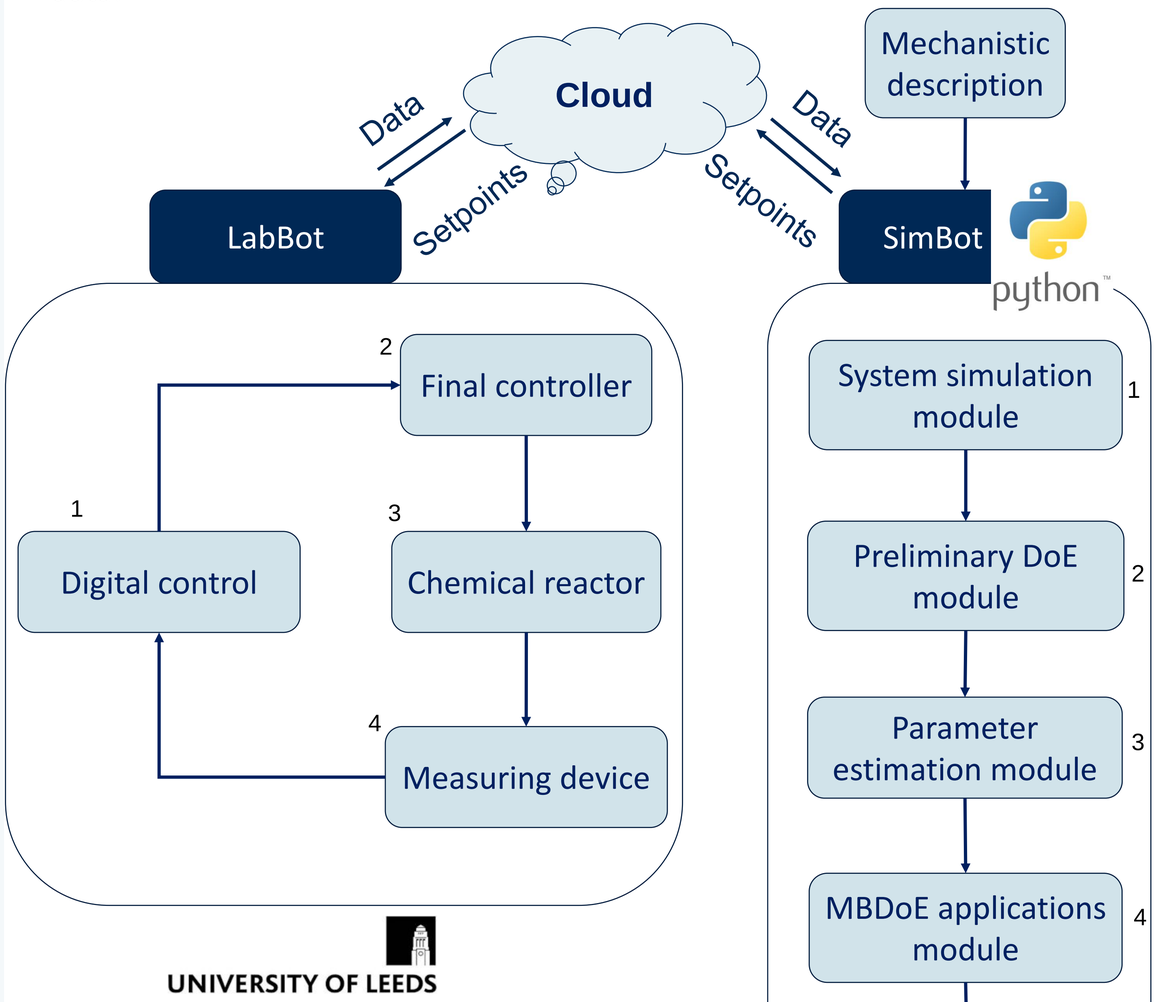
? Introduction and Motivation

- Industry 4.0 has birthed a new era for the chemical manufacturing sector, transforming reactor design and automating process control [1].
- Towards autonomous chemistry development, on-demand manufacturing, and real-time optimization, we have developed a **cloud-based platform driven by model-based design of experiment (MBDoE)**, an optimal experimental design algorithm, to coordinate remotely the LabBot, a smart flow reactor, situated at the University of Leeds.
- The platform has modelled and enriched two pharmaceutically-relevant case studies: nucleophilic aromatic substitution and homogeneous amide formation.

Methodology

- Figure 2.1 illustrates the communication within the cloud-based platform.
- The MBDoE algorithm is Module 4 within the Python-coded SimBot software that computes and sends experimental designs while the LabBot – the experimental setup with 4 compartments – executes and sends experimental data.



Simbot modelling and optimisation structure

- Differential and algebraic equations (DAEs):

$$\boldsymbol{f}(\dot{\boldsymbol{x}}(\tau), \boldsymbol{x}(\tau), \boldsymbol{u}(\tau), \boldsymbol{\theta}, \tau) = \boldsymbol{0} \quad (2.1)$$
$$\hat{\boldsymbol{y}}(t) = \boldsymbol{g}(\boldsymbol{x}(\tau)) \quad (2.2)$$
$$\boldsymbol{x}(0) = \boldsymbol{x}_0 \quad (2.3)$$
$$\boldsymbol{\phi} = [\boldsymbol{u}^T, \tau, \boldsymbol{x}_0{}^T]^T \quad (2.4)$$
$$\boldsymbol{x}(\tau) \in \boldsymbol{\mathcal{X}} \quad (2.5)$$

Eq.(2.1) describes the reactor measured and initialised by Eqs. (2.2) and (2.3) within the design space described by Eqs (2.4) and 2.5) combined.

- Modelling objectives:
  - Parameter estimation (Module 3 for maximizing the likelihood function) [2]:

$$\psi_{PE} = \min_{\boldsymbol{\phi}\in\boldsymbol{\Phi}} (\boldsymbol{y} - \hat{\boldsymbol{y}})^T \boldsymbol{V}^{-1} (\boldsymbol{y} - \hat{\boldsymbol{y}}) \quad (2.6)$$

  - Precision MBDoE (for maximizing a scalar measure of the Fisher information matrix (FIM), in this work the determinant) [3]:

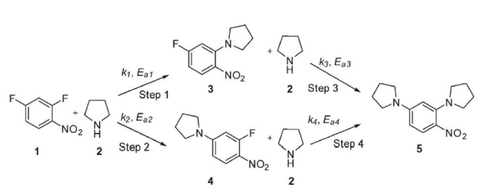
$$\psi_{MBDoE} = \max_{\boldsymbol{\phi}\in\boldsymbol{\Phi}} \sum_{r=1}^{r=n} \sum_{s=1}^{s=n} \sigma_1^{rs} \boldsymbol{Q_r}^T \boldsymbol{Q_s} \quad (2.7)$$

$\boldsymbol{x}(t)$: state variable, $\hat{\boldsymbol{y}}(t)$: measurements, $\boldsymbol{u}(t)$: control variables, $\boldsymbol{\theta}$: parameters, t: time; $\boldsymbol{y}$: model expectation, $\boldsymbol{V}$: response covariance matrix with elements σ_1^{rs}, $\boldsymbol{Q}$: parameter model sensitivities $\partial \boldsymbol{f}/\partial \boldsymbol{\theta}$, ψ: objective function

Results

Case Study 1: Nucleophilic aromatic substitution

- The reaction mechanism in this case study shown below has been reported [4].
- The resulting kinetic model (Module 1) is reported in Eqs. (3.1) – (3.5).
- On applying MBDoE (Module 4), the parameter statistics and model accuracy improved.



Scheme of reaction steps: nucleophilic aromatic substitution of 2,4-difluoronitrobenzene

Kinetic modelling

$$\frac{dc_1}{d\tau} = -r_1 + r_2 \quad (3.1)$$
$$\frac{dc_2}{d\tau} = -r_1 - r_2 - r_3 - r_4 \quad (3.2)$$
$$\frac{dc_3}{d\tau} = r_1 - r_3 \quad (3.3)$$
$$\frac{dc_4}{d\tau} = r_2 - r_4 \quad (3.4)$$
$$\frac{dc_5}{d\tau} = r_3 + r_4 \quad (3.5)$$

c_i i^{th} species concentration; r_j is the reaction rate (mol/s.L) of the j^{th} reaction

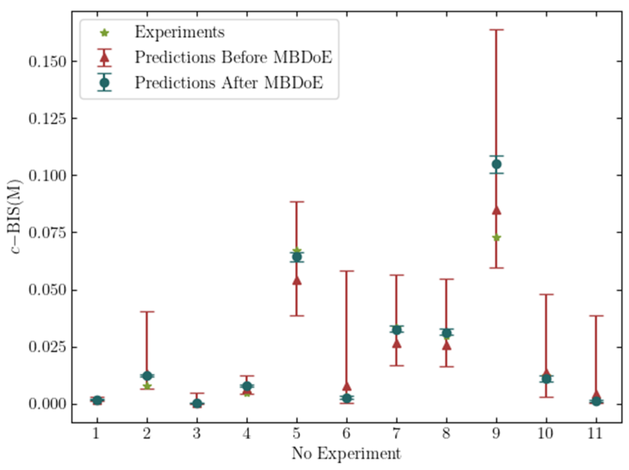


Figure 3.1: Significant reduction in model prediction uncertainty and improved model accuracy impacted by MBDoE

Table 3.1: Parameter values and statistics calculated before and after MBDoE

$k_i(\mathrm{M^{-1}s^{-1}})$/ E_{a_i}(kJ/mol)	k_1	E_{a_1}	k_2	E_{a_2}	k_4	E_{a_4}
Parameter values	1.21	34.53	0.21	27.84	0.057	42.49
t-before (t_{ref} (99%)= 2.68)	9.61	39.04	16.91	5.89	0.45	0.23
t-MBDoE (t_{ref} (99%)= 2.40)	55.04	260.76	136.65	73.08	27.60	15.60

Case Study 2: Homogeneous amide formation

- Two mechanisms can be inferred from literature: forward-step and reversible-step.
- χ^2 lack-of-fit test accepted the reversible model (with 4 parameters) as the best model for the amide formation (Module 3).
- The MBDoE module subsequently selected the most Fisher informative experiment that improved the reversible model precision and predictions as shown below by the validation results (Module 5).

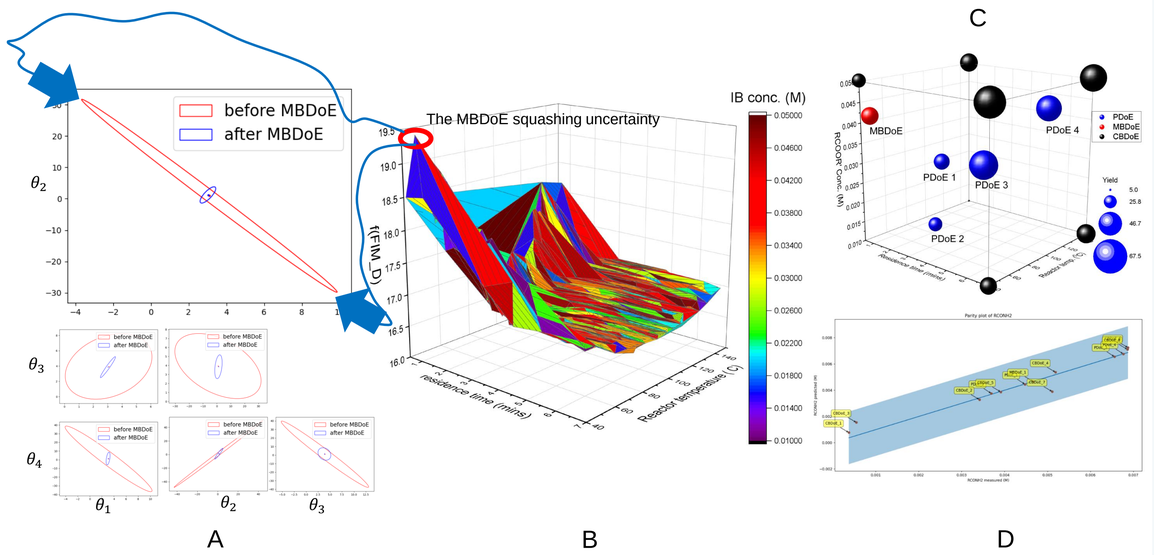


Figure 3.2: A: Parameter precision, B: Fisher information map, C: Design space, and D: Model validation parity plot. PDoE: Preliminary DoE; CBDoE: Control-bound DoE.

Conclusions

- We have developed a novel cloud-based platform driven by MBDoE to remotely coordinate experimentation in a smart flow reactor.
- The platform in few experiments autonomously identified structure and parameters in kinetic models suitable for pharmaceutical applications.

Acknowledgement

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