Application of a novel cloud-based platform for kinetic model identification in pharmaceutical processes

Emmanuel Agunloye[a], Panagiotis Petsagkourakis[a], Muhammad Yusuf[b], Ricardo Labes[b], Thomas Chamberlain[b], Frans L. Muller[b], Richard A. Bourne[b], and Federico Galvanin[a*]

[a]Department of Chemical Engineering, University College London, Torrington Place, London, WC1E 7JE, United Kingdom

[b]School of Chemical and Process Engineering, University of Leeds, Leeds, LS2 9JT, United Kingdom

*corresponding author: f.galvanin@ucl.ac.uk

? Introduction and Motivation

- Recently, the pharmaceutical industry reported alarming rates of drug recalls and expanding time to launch a new drug for relying on outdated technologies [1].
- The industry consequently embraced a new framework to incorporate industry 4.0 technologies into drug manufacturing to guarantee quality and accelerate commercialization [1].
- In accordance, this work presents pharmaceutical applications of a novel cloud-based platform driven by optimal experimental design software deployed from University College London to remotely control experimentation in a smart flow reactor system situated at University of Leeds [2].

Methodology

- Fig. 1 shows the cloud-based platform with the cloud anchoring data and design of experiments (DoEs) communication between the LabBot reactor hardware and the Python-coded SimBot software [2].
- The optimal experimental design software integrates model-free and model-based DoE techniques.

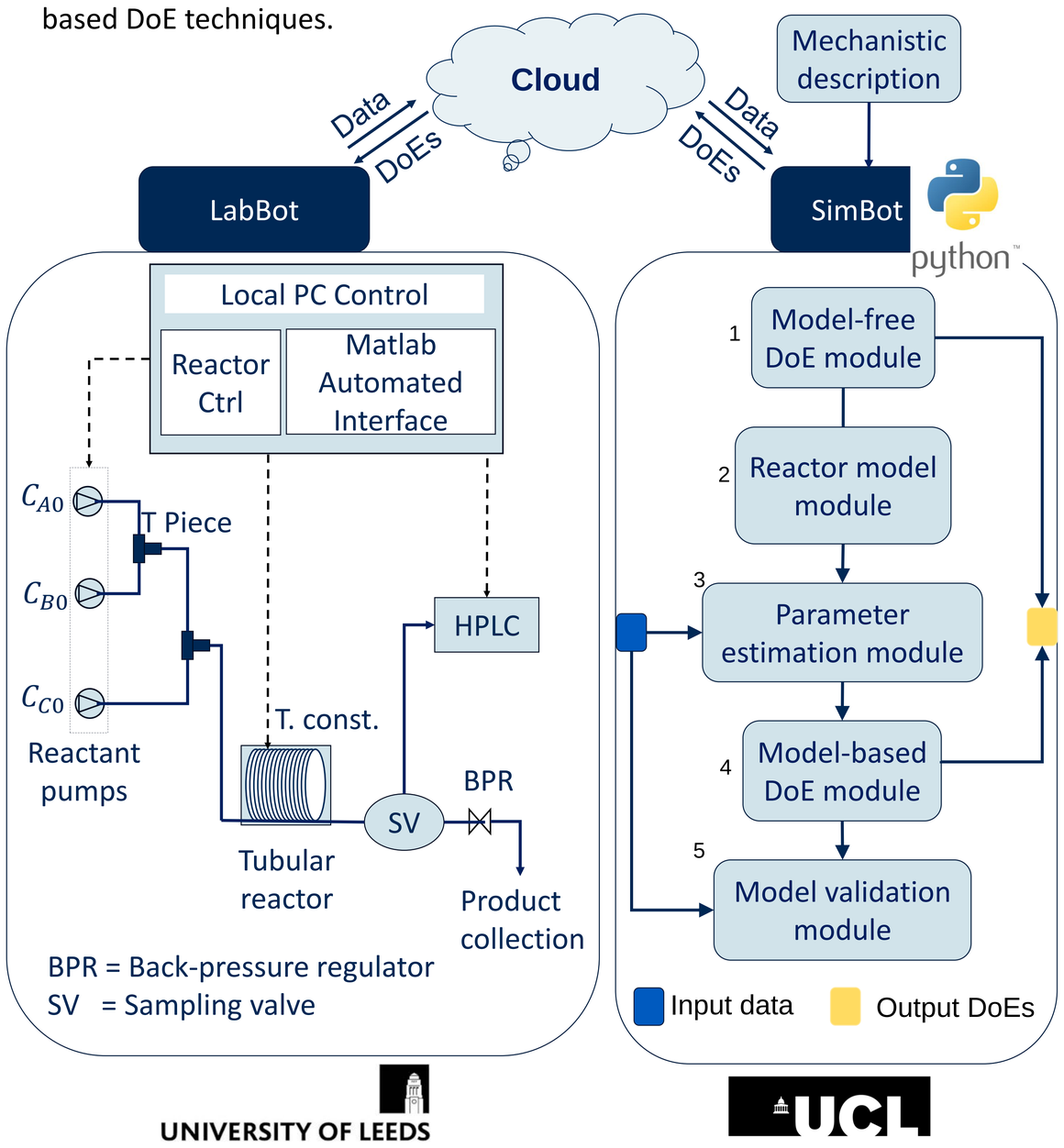

Fig. 1: The novel cloud-based platform

Simbot modelling and optimisation structure

- Differential and algebraic equations (DAEs):

$$\boldsymbol{f}(\dot{\boldsymbol{x}}(\tau), \boldsymbol{x}(\tau), \boldsymbol{u}(\tau), \boldsymbol{\theta}, \tau) = \boldsymbol{0} \qquad \text{Eq. 1}$$

$$\hat{\boldsymbol{y}}(t) = \boldsymbol{g}(\boldsymbol{x}(\tau)); \boldsymbol{x}(0) = \boldsymbol{x}_0 \qquad \text{Eq. 2}$$

$$\boldsymbol{\phi} = [\boldsymbol{u}^T, \tau, {\boldsymbol{x}_0}^T]^T; \boldsymbol{x}(\tau) \in \boldsymbol{\mathcal{X}} \qquad \text{Eq. 3}$$

Eq. 1 describes the reactor DAEs model initialised and measured using Eq. 2 within the design space described by Eq. 3.

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

$$\psi_{PE} = \max_{\boldsymbol{\phi}\in\boldsymbol{\Phi}}(-1)\left[\log(2\pi)^{N_S N_y} + \sum_{s=1}^{N_s}\sum_{k=1}^{N_y}\log\det \boldsymbol{V_y} + (\hat{\boldsymbol{y}} - \boldsymbol{y})^T {\boldsymbol{V_y}}^{-1}(\hat{\boldsymbol{y}} - \boldsymbol{y})\right] \qquad \text{Eq. 4}$$

  - Model-based DoE for model discrimination (for maximizing divergence among rival models):

$$\psi_{MD} = \max_{\boldsymbol{\phi}\in\boldsymbol{\Phi}}\left\{\left(\boldsymbol{y^1} - \boldsymbol{y^2}\right)^T\left[\left(\boldsymbol{V_y^1}\right)^{-1} + \left(\boldsymbol{V_y^2}\right)^{-1}\right]\left(\boldsymbol{y^1} - \boldsymbol{y^2}\right)\right\} \qquad \text{Eq. 5}$$

  - Model-based DoE for model parameter precision (for maximizing a scalar measure of the Fisher information matrix):

$$\psi_{PP} = \max_{\boldsymbol{\phi}\in\boldsymbol{\Phi}}\psi\left[\sum_{r=1}^{r=n}\sum_{s=1}^{s=n}\sigma_1^{rs}\boldsymbol{Q_r}^T\boldsymbol{Q_s}\right] \qquad \text{Eq. 6}$$

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

Results

Case Study 1: Homogeneous amide formation

- Amides are a promising group of organic compounds for producing drugs [4].
- In the homogeneous amide formation, two mechanisms can be inferred from literature: forward-step and reversible-step.
- χ^2 lack-of-fit test integrated in the cloud-based platform (Table 1) accepted the reversible model (with 4 parameters) as the best model for the amide formation (Module 3).
- MBDoE for parameter precision (i.e., robust model performance) subsequently selected the most informative experiment that improved the reversible model predictions as shown in the results in Fig. 2 with full-factorial experimental designs for model validation (Module 5).

Table 1:Two candidate kinetic models of amide formation with their χ^2 performances

	Chemical equations	Rate equations	χ^2 test
Model 1	$RCOOR' + R''NH_2 \longrightarrow RCONH_2 + R''OR'$	$r_f = k_f c_1 c_2$	$\chi^2 = 494.1$ ($\chi^2_{ref} = 23.7$)
Model 2	$RCOOR' + R''NH_2 \rightleftharpoons RCONH_2 + R''OR'$	$r_f = k_f c_1 c_2$ $r_b = k_b c_3 c_4$	$\chi^2 = 7.29 \cdot 10^{-9}$ ($\chi^2_{ref} = 21.03$)
$c_1 = RCOOR'; c_2 = R''NH_2; c_3 = RCONH_2; c_4 = R''OR'$			

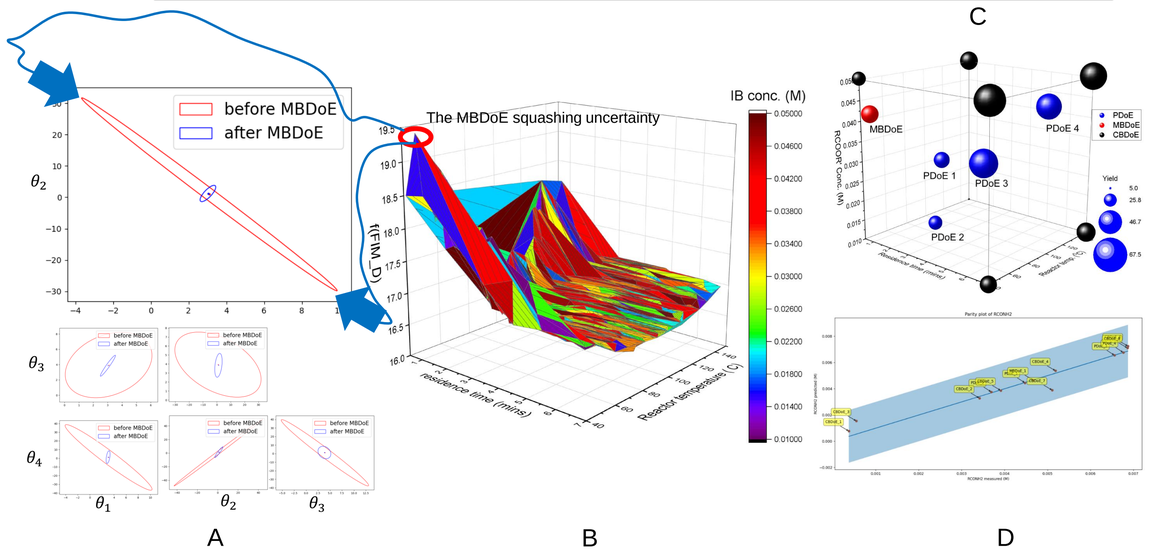

Fig. 2: A: Parameter precision, B: Fisher information map, C: Design space showing the locations of preliminary (blue), MBDoE (red) and validation (black) experiments; and D: Model validation parity plot. PDoE: Preliminary DoE; CBDoE: Control-bound DoE.

Case Study 2: Heterogeneous hydrogen borrowing

- Hydrogen borrowing is a widely used protocol in the pharmaceutical industry to diversify alcohols over several hydrogen borrowing cycles in new drug discovery [5].
- Fig. 3 shows the classical mechanistic theory for describing a hydrogen borrowing cycle [5].
- The platform via sequential parameter estimation and MBDoE for model discrimination, reduced 6 initially tested candidate kinetic models to 2 models with identifiable parameters (Table 2) and allowed to test the latter models in silico for distinguishability (Fig. 4).

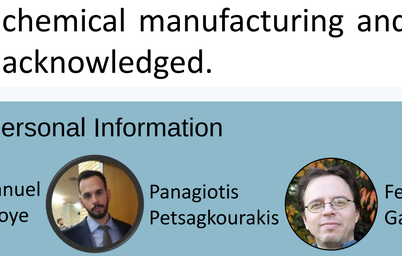

Fig. 3: Classical hydrogen borrowing mechanism [4]

Table 2 χ^2 model adequacy and Fisher information analyses for the six models

	Model	χ^2	χ^2_{ref}	FIM-D
1	Model 1	26.49	60.48	397.00
2	Model 2	26.48	83.68	397.36
3	Model 3	23.01	92.81	0.00
4	Model 4	23.01	101.88	0.00
5	Model 5	23.01	113.15	0.00
6	Model 6	23.02	122.11	0.00

Fig. 4: In-silico divergence region to distinguish Models 1 and 2.

Conclusions

- A novel cloud-based platform for kinetic model identification has been developed, integrating optimal experimental designs software to remotely coordinate experimentation in a smart flow reactor.
- The platform has been demonstrated in two pharmaceutical applications for autonomous model identification, a crucial tool for achieving Quality-by-Design in drug manufacturing.

Acknowledgement

This project received founding from the EPSRC with the grant name: cognitive chemical manufacturing and reference: EP/R032807/1. The support is gratefully acknowledged.

References:

1. Destro, F., Barolo, M., 2022 Inter J. Pharmaceutics, 620, 121715, ISSN 0378-5173, https://doi.org/10.1016/j.ijpharm.2022.121715
2. Agunloye, E., Petsagkourakis, P., Yusuf, M., Labes, R., Chamberlain, T., Muller, F.L., Bourne, R.A., and Galvanin, F., (submitted)
3. Bard, Y. Academic Press **1974**.
4. Boonen et al., 2012. J Ethnopharmacol., 1;142(3):563-90. doi: 10.1016/j.jep.2012.05.038.
5. Reed-Berendt et al., 2021. *ACS Central Sci., 7* (4), 570-585, DOI: 10.1021/acscentsci.1c00125

Personal Information


Emmanuel Agunloye

Panagiotis Petsagkourakis

Federico Galvanin

Sargent Centre for Process Systems Engineering

UCL ENGINEERING Change the world