DEPARTMENT OF CHEMICAL ENGINEERING

Cloud-based MBDoE applications

- for optimal design of experiments to accelerate kinetic model identification

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07 Dec. 2023

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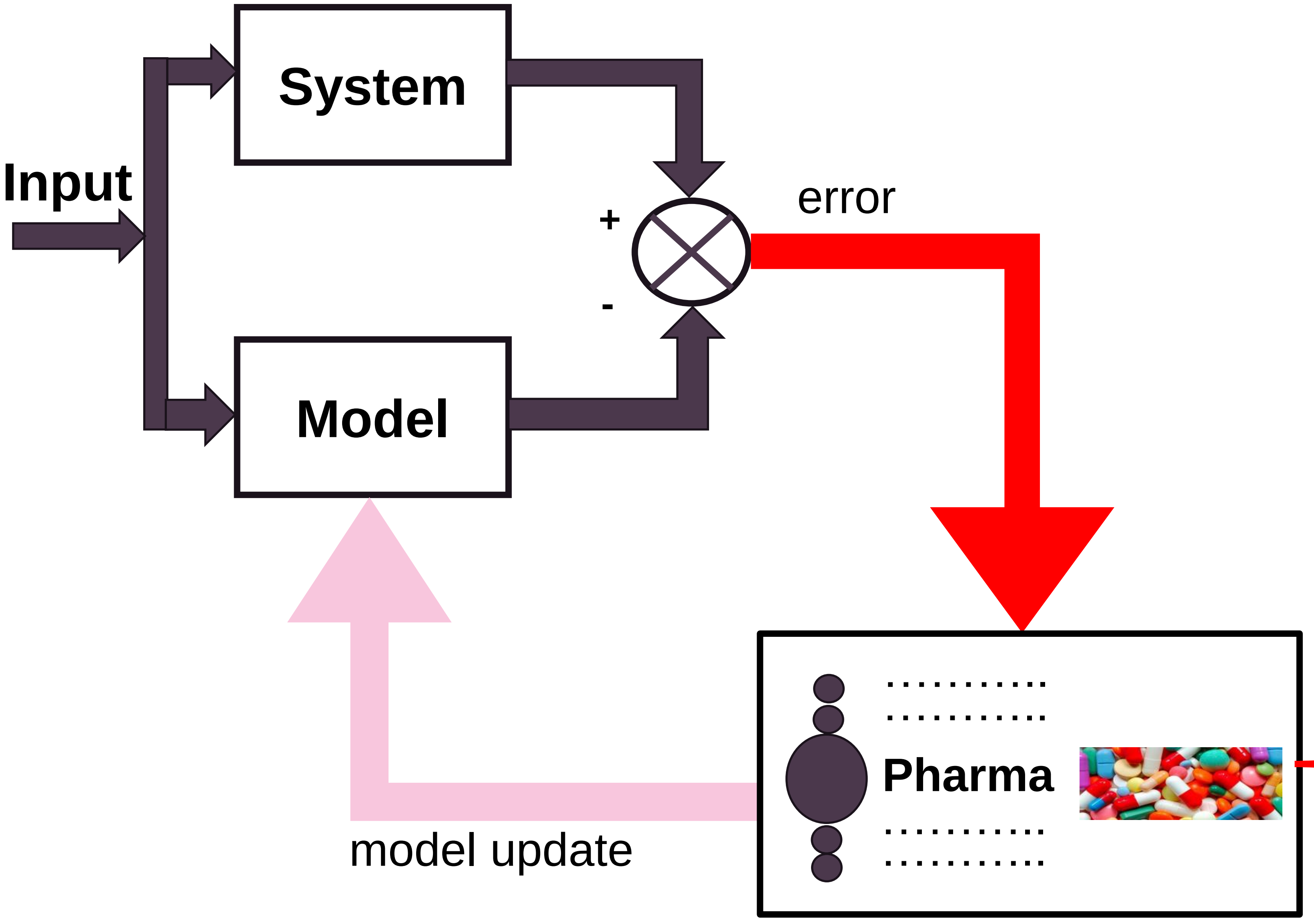
Presentation outline

- Introduction and problem definition
- Methodology
  - Novel cloud-based platform
  - Model-based experimental design software
- Pharmaceutical application
- Conclusions
- Acknowledgements

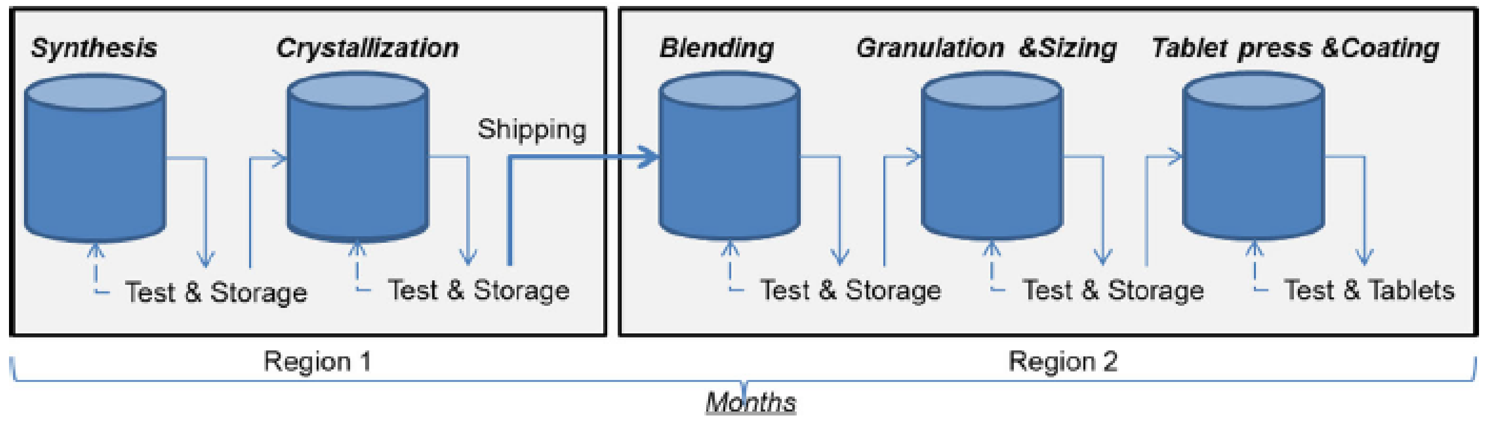
Introduction and problem definition



System identification

1. Technical[1]

A typical batch manufacturing process



2. Regulatory[2]

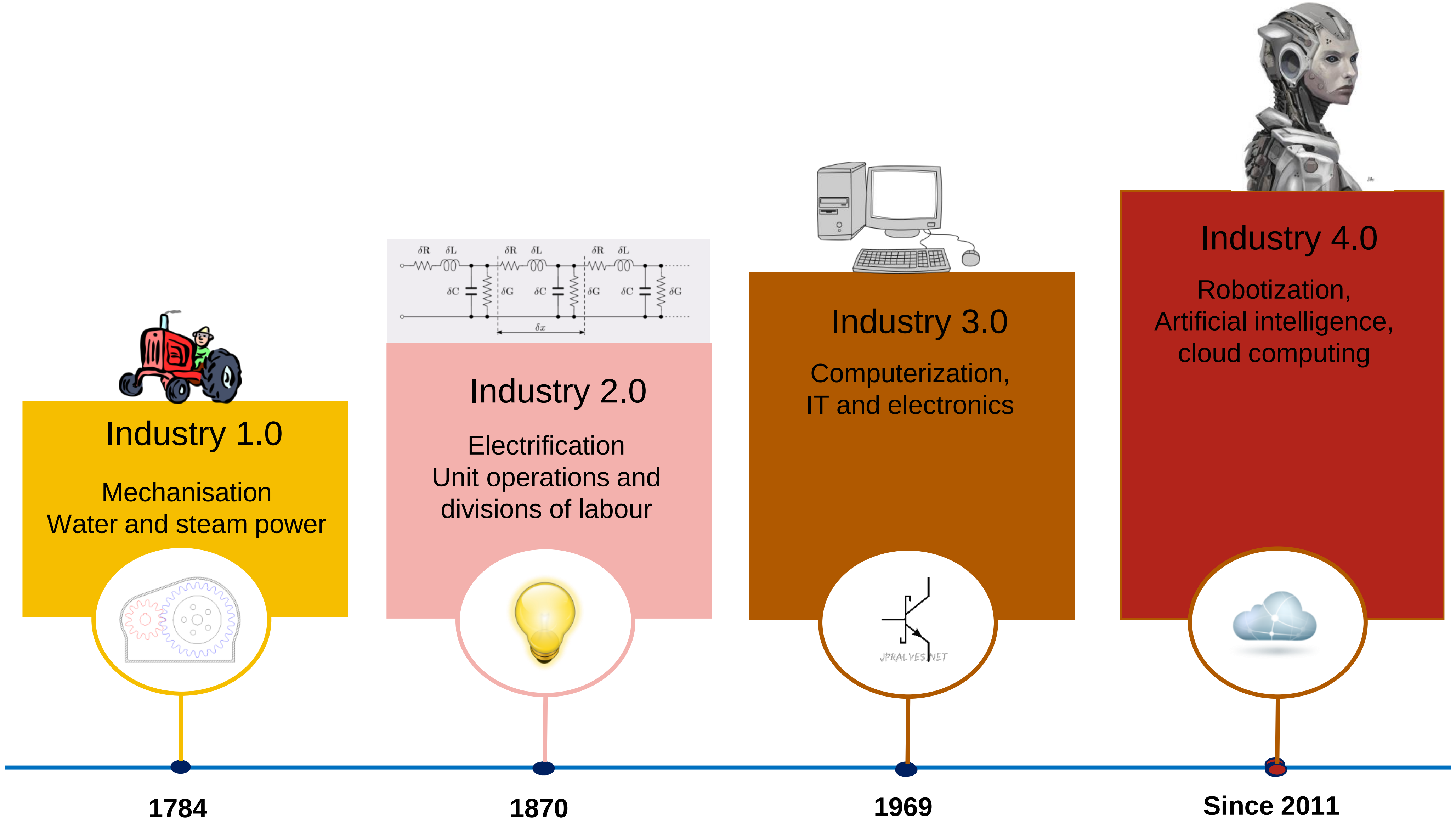
Others

Pharma challenges[1,2]

[1]Lee, O'Connor et al. (2015), J Pharm Innov

[2]Destro, F., Barolo, M. (2022)., International Journal of Pharmaceutics

EPSRC project: cognitive manufacturing



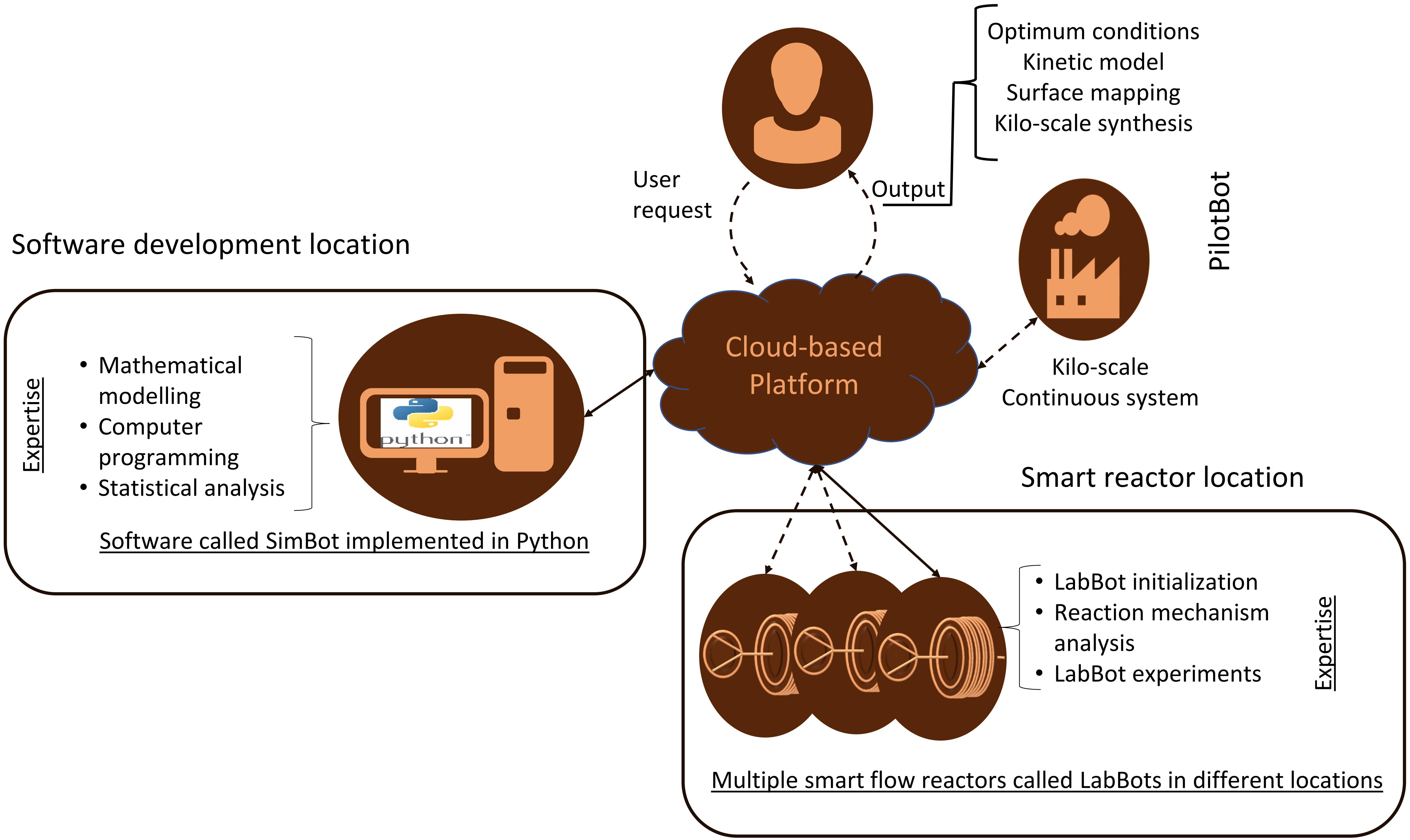
Industrial revolution timeline[3]

Incorporating Industry 4.0 into chemical/pharma manufacturing

Project objective

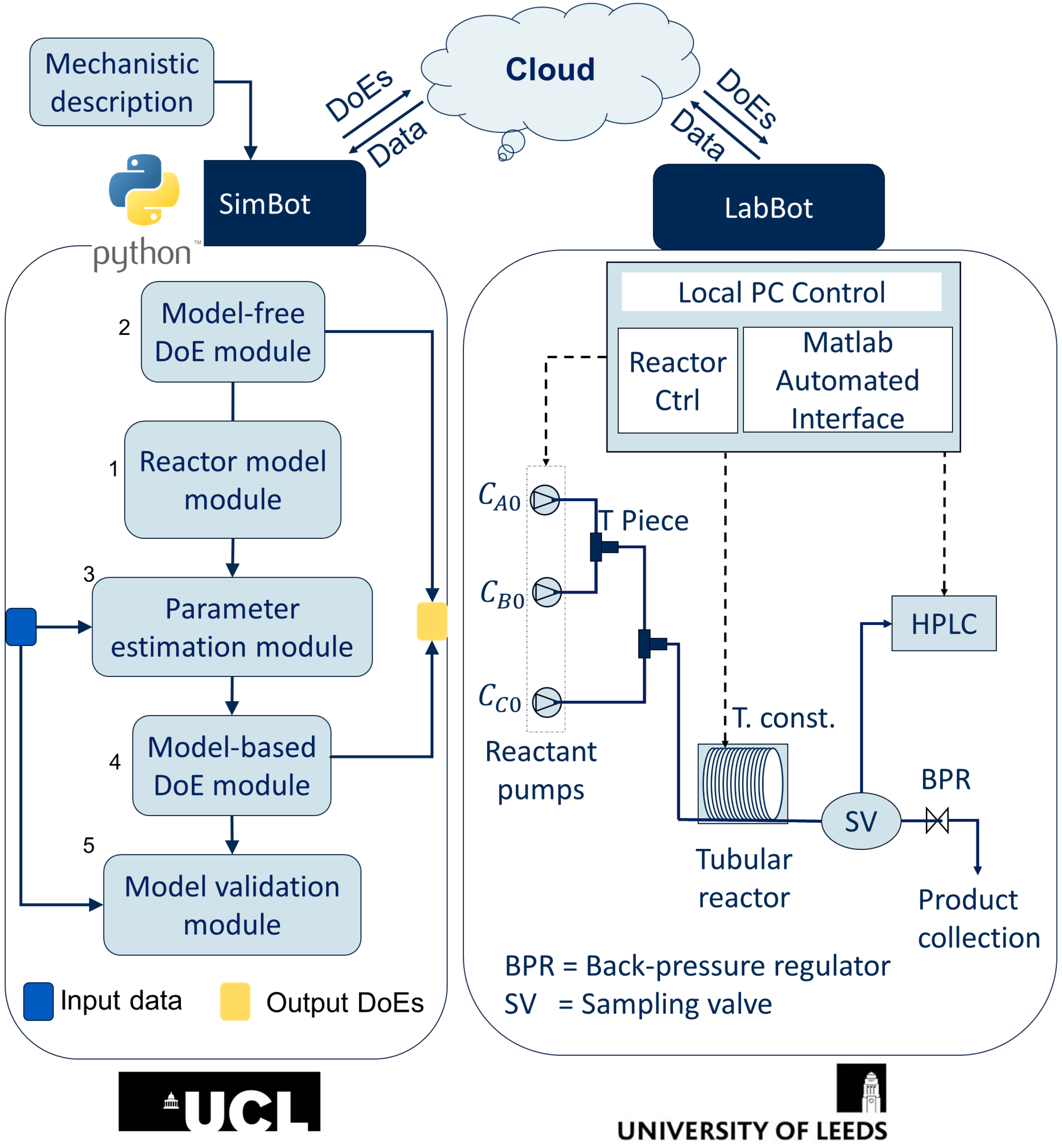
[3]Appsierra, 2022. https://www.appsierra.com/blog/what-is-industry-4-0

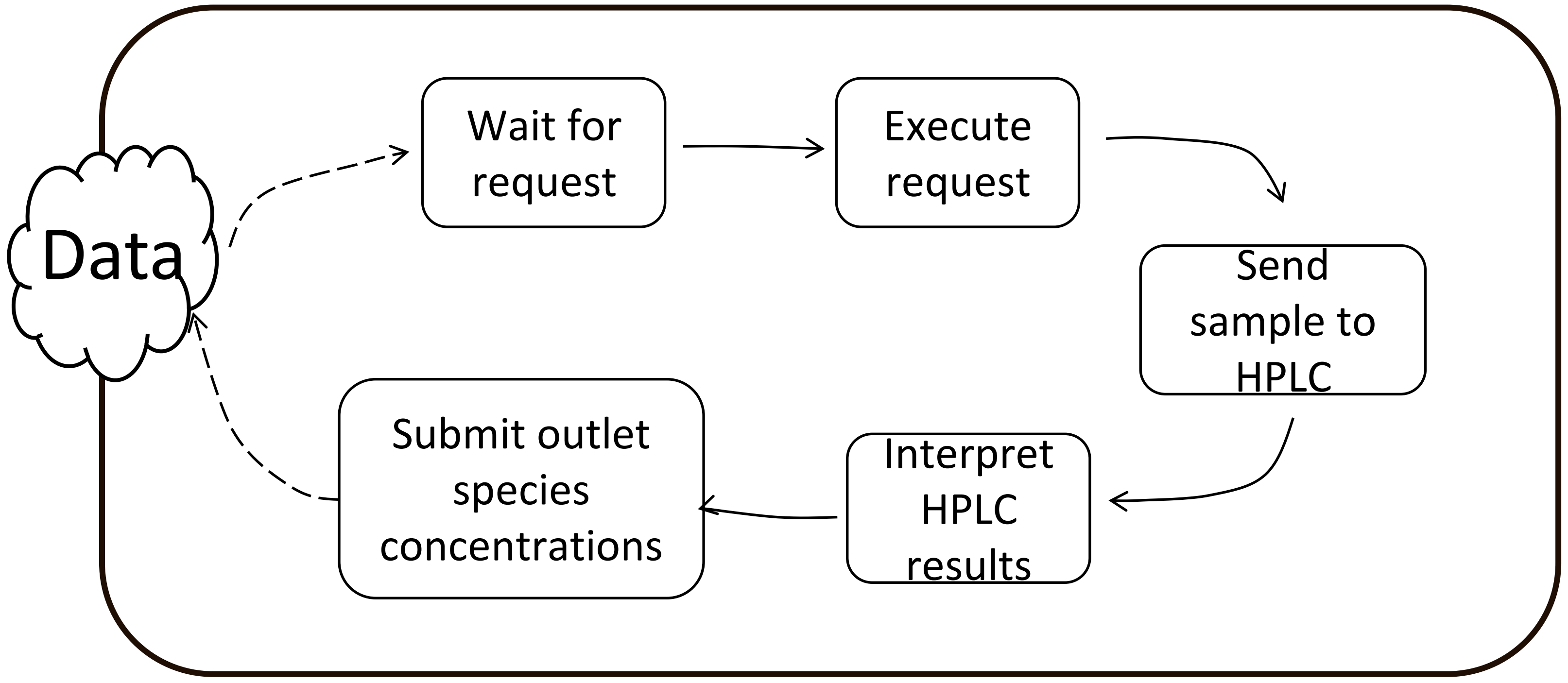
Methodology: novel cloud-based platform[4]



[4]Agunloye, Petsagkourakis, Yusuf, Labes, Chamberlain, Muller, Bourne, and Galvanin, (submitted) React. Chem. Eng.

Cloud-based experimental controls





LabBot automation scheme[4]

[4]Agunloye, Petsagkourakis, Yusuf, Labes, Chamberlain, Muller, Bourne, and Galvanin, (submitted) React. Chem. Eng.

Physics-based model equations in Simbot

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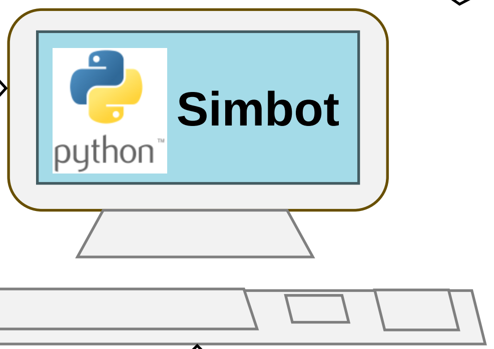
Flow reactor model[4]:

$$\frac{\partial c_i}{\partial t} = \frac{\partial c_i}{\partial \tau} + \sum_{j=1}^{N^r} \nu_{ij} r_j \, ; \quad \forall i = 1, \ldots, NC$$

$$(-r_j) = k_{eff} \prod c_i^{p_i} \, ; \, k_{eff} = k_0 e^{-\frac{E_a}{RT}}$$

1

Experimental data: $\boldsymbol{c_{exp}}$



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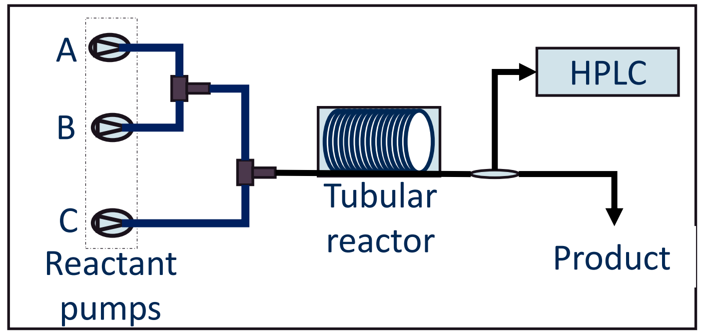
2

Optimisation objectives[4]:

1. Parameter estimation: $MLE(\boldsymbol{\theta}) = \frac{1}{(2\pi)^{N_y N_s/2} |\boldsymbol{V_y}|^{N_s/2}} \exp\left\{ -\frac{1}{2} \sum_i^{N_s} [\boldsymbol{y}_i - \hat{\boldsymbol{y}}_i(\boldsymbol{\theta})]^T \boldsymbol{V_y}^{-1} [\boldsymbol{y}_i - \hat{\boldsymbol{y}}_i(\boldsymbol{\theta})] \right\}$
2. Model discrimination: $\psi_{MD} = \max_{\boldsymbol{\varphi} \in \boldsymbol{\Phi}} \psi [(\boldsymbol{y^1} - \boldsymbol{y^2})^T \left((\boldsymbol{V_y^1})^{-1} + (\boldsymbol{V_y^2})^{-1} \right) (\boldsymbol{y^1} - \boldsymbol{y^2})]$
3. Parameter precision: $\psi_{PP} = \max_{\boldsymbol{\phi} \in \boldsymbol{\Phi}} \psi [\sum_{r=1}^{r=n} \sum_{s=1}^{s=n} \sigma_1^{rs} \boldsymbol{Q_r}^{\boldsymbol{T}} \boldsymbol{Q_s}]$

Experimental designs:
$\boldsymbol{\varphi} = [\boldsymbol{u}^T, \tau, \boldsymbol{c_0}^T]^T$



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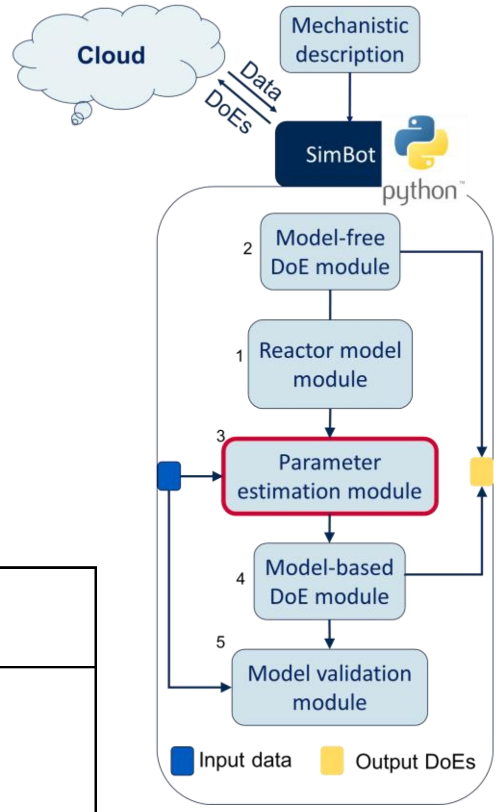
$\boldsymbol{c}(t)$: reactant concentrations, $\hat{\boldsymbol{y}}(t)$: measurements, $\boldsymbol{u}(t)$: control variables, $\boldsymbol{\theta}$: parameters, t: time;
$\boldsymbol{y}$: model expectation, $\boldsymbol{V}$: response covariance matrix, $\boldsymbol{Q}$: parameter sensitivities

[4]Agunloye, Petsagkourakis, Yusuf, Labes, Chamberlain, Muller, Bourne, and Galvanin, (submitted) React. Chem. Eng.

Pharma case study: homogeneous amide formation



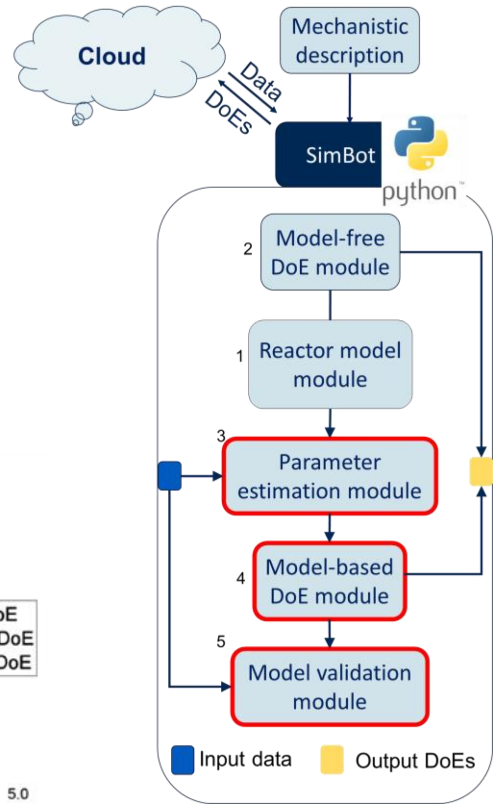
- Two mechanisms can be inferred from literature: forward-step and reversible-step[5,6].
- χ^2 lack-of-fit test performed in Module 3 following parameter estimation accepted the reversible model (with 4 parameters) as the best model for the amide formation as shown in Table 1.

Table 1

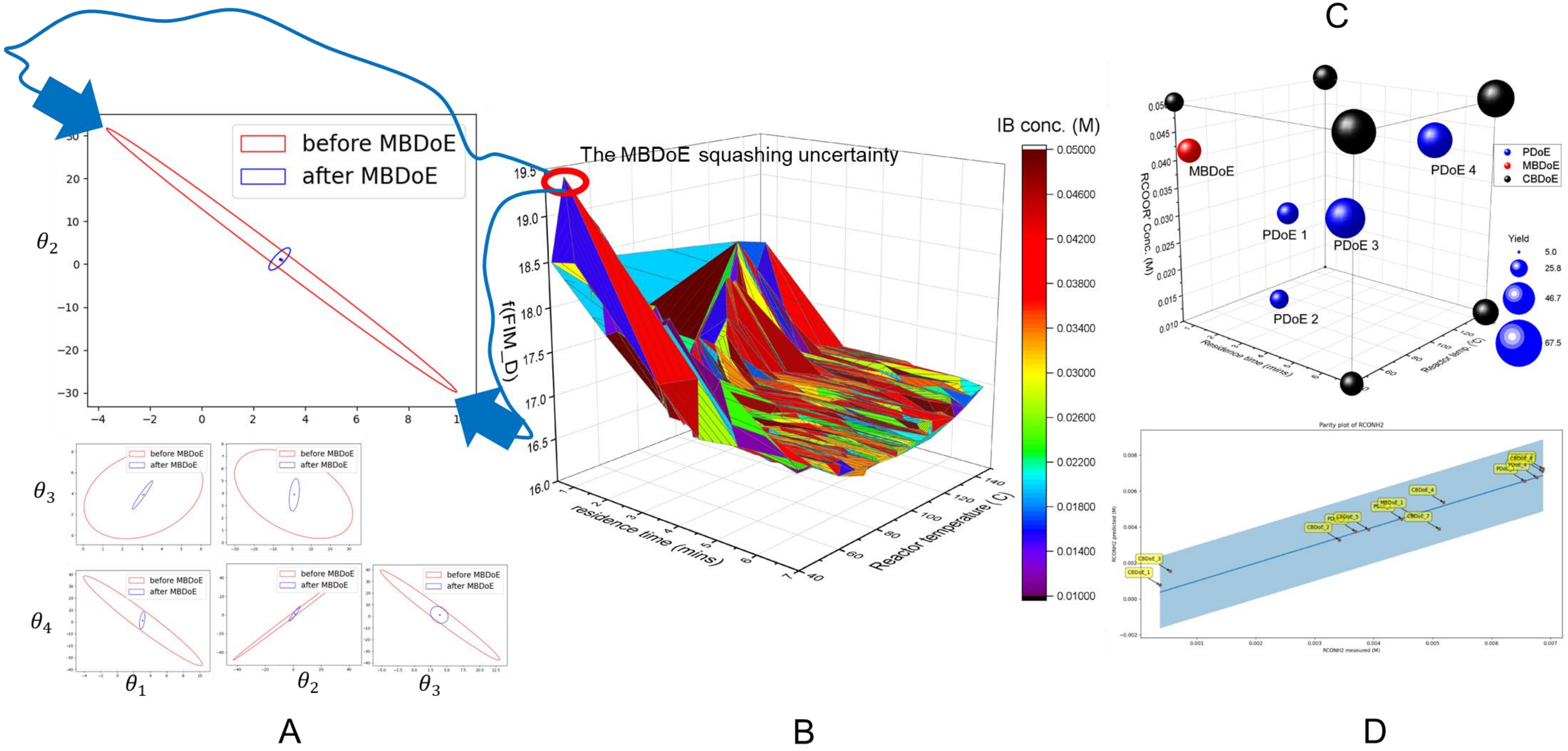
	Chemical equations	Rate equations	χ^2 test
Model 1	$RCOOR' + R''NH_2 \longrightarrow RCONH_2 + R''OR'$	$r_f = k_f c_1 c_2$	$\chi^2 = 494.1$ ($\chi^2_{ref} = 23.7$)
Model 2	$RCOOR' + R''NH_2 \rightleftharpoons RCONH_2 + R''OR'$	$r_f = k_f c_1 c_2$ $r_b = k_b c_3 c_4$	$\chi^2 = 7.29 \cdot 10^{-9}$ ($\chi^2_{ref}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

[5]Nakajima and Ikada (1995) Bioconjugate Chem. 6, 123-130
[6]Clark, Farmer, Kennepohl, Morsch, & Morsch,, (2022) Chemistry of Amides.

Case study: MBDoE results



- 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. C with full-factorial experimental designs for model validation (Module 5).



[4]Agunloye, Petsagkourakis, Yusuf, Labes, Chamberlain, Muller, Bourne, and Galvanin, (submitted) React. Chem. Eng.

Conclusions (1/2)

1

- In conclusion, we have developed a novel cloud-based platform that remotely controls a smart experimental reactor using optimal experimental design software.

2

- The platform has been demonstrated in a number of case studies, including the pharmaceutically relevant amide formation.

3

- The model-based design of experiment techniques identified robust kinetic model with reliable predictions in a few experimental runs.

4

- The developed cloud-based platform will be instrumental in accelerating developments of digital twin platform and on-demand manufacturing for the pharmaceutical sector and the wider chemical industry..

Conclusions (2/2)

1

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Acknowledgements

EPSRC

Engineering and Physical Sciences Research Council

Grant name: Cognitive chemical manufacturing
EPSRC Reference: EP/R032807/1

Galvanin

System Identification Group

http://www.homepages.ucl.ac.uk/~ucecfga/

Collaborators at the University of Leeds:

1. Prof. Richard A Bourne
2. Prof. Frans L. Muller
3. Dr. Thomas Chamberlain
4. Dr. Ricardo Labes
5. Dr Muhammad Yusuf

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