Distinguishing alternative kinetic models for hydrogen borrowing within the model-based design of experiment framework for model discrimination

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? Introduction and Motivation

- Hydrogen borrowing is a widely used protocol in the pharmaceutical industry to diversify alcohols in new drug discovery [1].
- A hydrogen borrowing cycle can be described using three elementary steps: 1) oxidation; 2) addition; 3) reduction → various kinetic models can be developed.
- Available experimental data, however, would constrain the model space to a few kinetic models with estimable parameters [2].
- This work presents a model-based design of experiment (MBDoE) framework for model discrimination applied through a cloud-based system (SimBot) [3] to select the best model for a hydrogen borrowing case study.

Methodology

- Fig. 1 shows the cloud-based SimBot software, which depends on physics-based modelling for model development and employs a sequential parameter estimation technique
- The Python-coded SimBot employs identifiable physics-based models in the model-based design of experiments (MBDoE) for model discrimination.

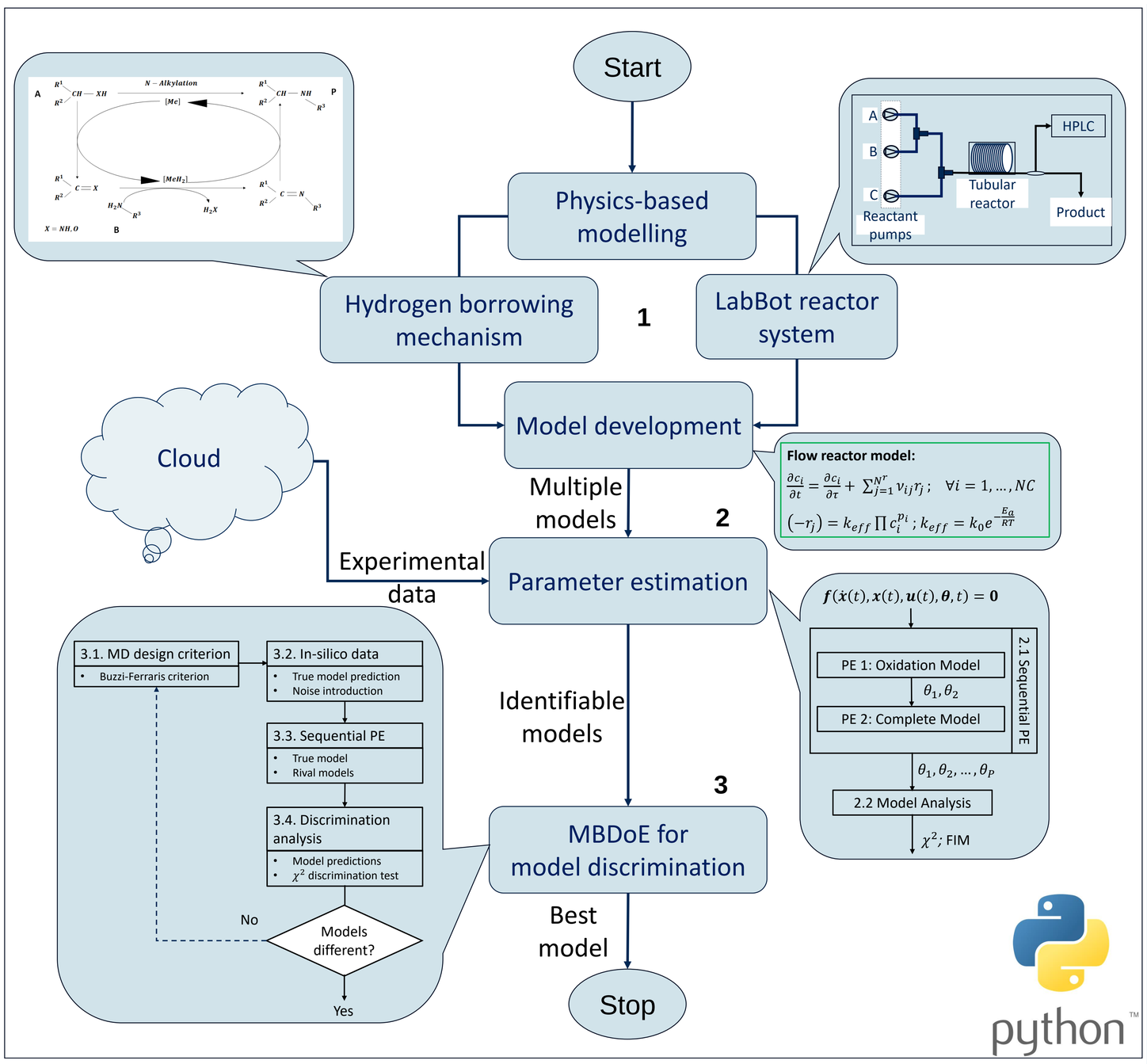

Fig. 1: SimBot kinetic model identification framework for hydrogen borrowing

1 Simbot modelling and optimisation structure

❑Differential and algebraic equations (DAEs):

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

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

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

Eq. 1 describes the reactor DAEs model initialised and measured using Eq. 2 within the design space $\boldsymbol{\Phi}$ described by Eq. 3.

❑Modelling objectives [4]:

- Parameter estimation for maximizing the log-likelihood function (sequentially performed[5]):

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

- Model-based DoE for model discrimination among two rival models using the Buzzi-Ferraris divergence criterion:

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

$\boldsymbol{x}(t)$: state variable, $\hat{\boldsymbol{y}}(t)$: measured responses, $\boldsymbol{u}(t)$: control variables, $\boldsymbol{\theta}$: parameters, t: time; $\boldsymbol{y}$: model expectation, N_s: sampling points, N_y: No of measured responses, $\boldsymbol{V_y}$: response covariance matrix, $\boldsymbol{V_y^i}$: model i prediction covariance matrix, ψ: objective function, $\boldsymbol{\varphi}$: experimental design vector

Results

2 Model calibration and goodness of fit analysis

- The hydrogen borrowing case study involves benzyl alcohol and benzylamine reacting on Ru catalyst in the LabBot reactor to form di-benzylamine and tri-benzylamine (at sufficiently long residence times).
- Six kinetic models describing increasing number of chemical steps and species were developed.
- Table 1 shows the results of the models when tested for χ^2 model adequacy and Fisher information model identifiability ($|FIM|$), identifying the two simplest models.

Table 1:Results from χ^2 model adequacy test and Fisher information analyses for the six candidate kinetic models

Model number	Number of model parameters	χ^2	χ^2_{ref}	$\lvert FIM\rvert$
1	6	26.49	60.48	397.00
2	6	26.48	83.68	397.36
3	8	23.01	92.81	0.00
4	10	23.01	101.88	0.00
5	10	23.01	113.15	0.00
6	12	23.02	122.11	0.00

3 MBDoE for model discrimination in-silico

- Fig. 2A obtained from in-silico model discrimination studies shows the two identifiable models: Models 1 and 2, which are zeroth and first orders, respectively, with respect to the catalyst amount, are similar, i.e., their discrimination probabilities are around 0.50.
- However, a decrease in the catalyst amount (if assumed an experimental design variable, Eq. 3) would provide a clear distinction among Model 1 (True Model) and Model 2 (Rival Model) (Figs 2B,C,D), the discrimination probability surpassing 0.99 at 3% catalyst decrease.

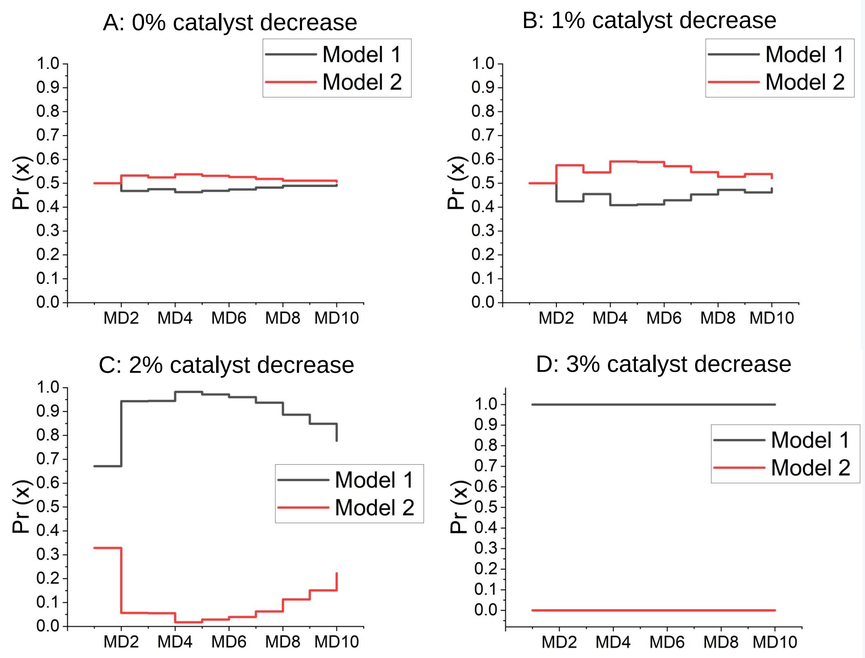

Fig. 2: Model discrimination experiments (MD) via in-silico studies between Models 1 and 2 with catalyst decrease of A. 0%, B. 1%, C. 2% and D. 3%

Conclusions

- Within the cloud-based Simbot framework, two promising kinetic models have been identified among candidates and tested for the hydrogen borrowing.
- In-silico MBDoE study shows that these models can only be distinguished by decreasing the catalyst amount.
- Future validation experiments will be needed to confirm the impact of catalyst decrease on model discrimination and hence the adequacy of Model 2 in representing reaction kinetics in the hydrogen borrowing system.

Acknowledgement

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