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Publication date:
2016

Document Version
Peer reviewed version

A case study on robust optimal experimental design for model calibration of ω-Transaminase

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Abstract

Proper calibration of models describing enzyme kinetics can be quite challenging. This is especially the case for more complex models like transaminase models (Shin and Kim, 1998). The latter fitted model parameters, but the confidence on the parameter estimation was not derived. Hence, the usability of the parameter estimates is difficult to assess.

In this paper, the confidence is derived, using the Fisher Information Matrix (FIM) for the backward reaction (conversion of acetophenone and alanine to α-methylbenzylamine and pyruvate). FIM computation requires local parameter sensitivities and measurement errors. Since the latter was not provided, a conservative standard deviation of 5% was assumed. The confidence analysis yielded that only two (V_r and K_{ac}) out of five parameters were reliable estimates, which means that model predictions and decisions based on them are highly uncertain. The reason behind this problem is practical identifiability, which can be related to both the model structure and/or the information content of the data.

The available data are 25 experiments performed by Shin and Kim, set up in a 5x5 factorial design (2 substrates with 5 concentration levels each) across the experimental space. However, it is expected that more informative experiments can be designed to increase the confidence of the parameter estimates. Therefore, we apply Optimal Experimental Design (OED) to the calibrated model of Shin and Kim (1998). The total number of samples was retained to allow fair comparison with the original experimental design. Using OED led to unique and higher quality parameter estimates for all parameters. This illustrates that OED can increase parameter confidence without increasing the experimental effort.

The main problem which arises when performing OED is that the "real" parameter values are not known before finishing the model calibration. However, it is important that the chosen parameter values are close to the real parameter values, otherwise the OED can possibly yield non-informative experiments. To counter this problem, one can use robust OED. The idea of robust OED is to make the design less dependent on one specific parameter set, but make it suitable for a subset of parameters in a local parameter space.

This robust OED methodology is currently being applied to the backward part of the model of Shin and Kim (1998) to design experiments for the conversion of 1-methyl-2-phenylpropylamine and acetone to benzylacetone and isopropylamine and yield a reliable estimation for all parameters. Details of the outcome will be shown at the conference.

References

Shin, J.-S. and Kim, B.-G. (1998), Kinetic modeling of ω-transamination for enzymatic kinetic resolution of α-methylbenzylamine. Biotechnol. Bioeng., 60: 534–540. doi: 10.1002/(SICI)1097-0290(19981205)60:5<534::AID-BIT3>3.0.CO;2-L