Online Model health Monitoring and Drift correction using NIR spectroscopy and Delayed Measurements in Bioreactors

Keerthana C[1], Nirav P Bhatt[1]*, Guhan Jayaraman[1]

1 Department of Biotechnology, Indian Institute of Technology Madras, India

**niravbhatt@iitm.ac.in*

Highlights

- Real-time monitoring of chemometric model health using T^2 and Q statistics.
- Drift correction using delayed HPLC measurements without process interruption.
- NIR-PLS-PID-based control of glucose concentration in *Lactococcus lactis* fermentation.

1. Introduction

Process analytical technology (PAT) tools are an indispensable part of the quality-by-design (QbD) approach to ensure product quality and safety. Despite the recent advancements, these tools are only as good as the chemometric models when handling complex microbial cells with intrinsic variability. Online signals are vitiated by process or instrumental drifts that are unseen by the chemometric model, leading to faulty predictions. The current work proposes using T^2 and Q statistics to monitor the chemometric model's performance online and rectify it using the infrequently available offline measurements. As a proof of concept, the proposed approach is applied to the data from NIR spectroscopy-PLS (generic and specific model) based monitoring and automatic control of glucose concentration in *Lactococcus lactis* fermentation. The idea is to look for failed predictions and anomalies in the statistics plots and use the delayed measurements from HPLC to correct the drift by implementing Implicit Correction Methods (ICM) [1]. This strategy helps to spot and regulate the sub-optimal performance of the calibration model while the process is still running, thereby improving process robustness and efficiency and eliminating batch failure.

2. Methods

Figure 1 shows the schematics of the experimental setup. Spectrum (average of 32 scans) from the fermentation media is obtained every 5 minutes by the in-situ NIR probe. To review the progress of the process, samples are collected every hour and analyzed in HPLC. The synthetic mixture containing a known concentration of the analyte and a batch of experimental data was used for developing the PLS model and calculating the T^2 threshold [2] with a 0.05 significance level. The Q threshold is approximated by Jackson and Mudholkar [3]. Ideally, the Q statistic value should be zero for the drift-free spectrum or should at least be within the threshold. If violated, a correction spectrum with the corresponding delayed measurement and all the available measurements is added to the calibration set, and the PLS model is re-evaluated. The updated model can be used for further predictions.

3. Results and discussion

Figures 2 and 3 show the comparison between the offline glucose concentration and the predictions made by the model with and without drift correction, respectively. The glucose concentration was predicted using the generic model (1000-1900 nm) in the first experiment, while a glucose-specific model (1120-1350, 1450-1850 nm) was used in the second. After multiple drift corrections, the RMSE values for the model with and without drift correction for experiments 1 and 2 are 1.32 and 0.4095, and 0.4863 and 0.1528, respectively.

4. Conclusions

Online monitoring of chemometric models using T^2 and Q statistics was demonstrated for the glucostat condition in the *Lactococcus lactis* fermentation process. From the RMSE scores, it is evident that the proposed approach effectively maintains the health of the calibration model using delayed

measurements. Future work will focus on adapting this approach for monitoring multivariate models in real-time.

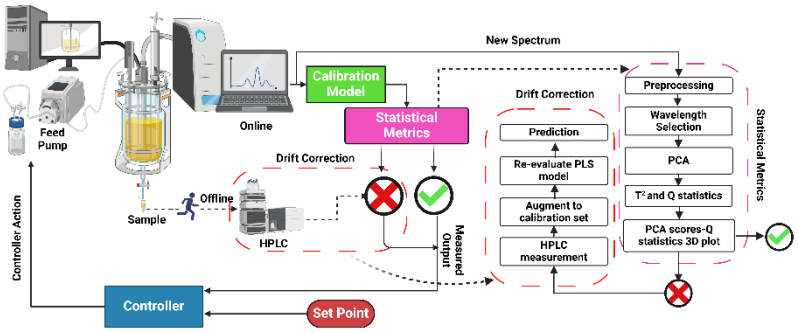

Figure 1. Schematic representation of the experimental setup and the steps followed in chemometric model monitoring and drift correction.

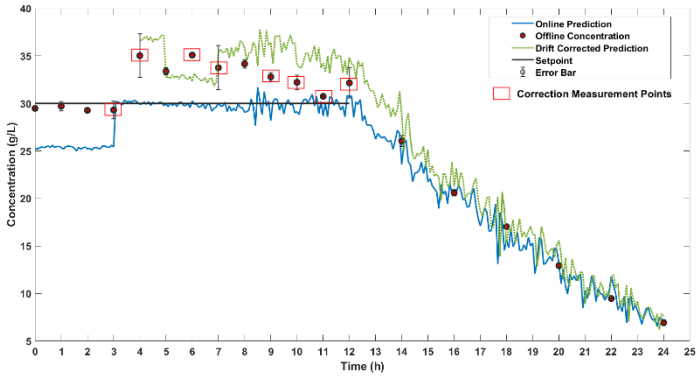

Figure 2. Glucose profile from experiment 1(Generic model).

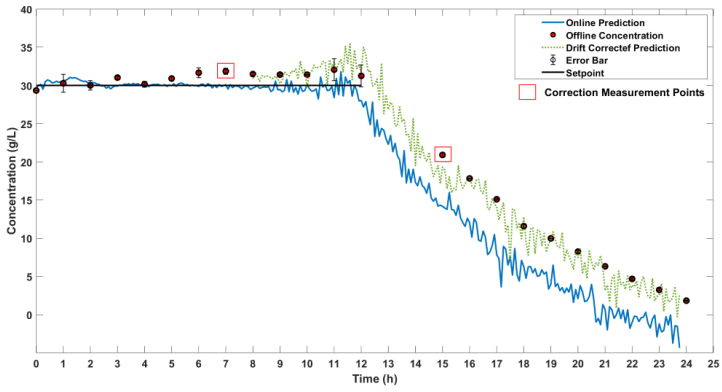

Figure 3. Glucose profile from experiment 2 (Glucose-specific model).

References

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Keywords

Chemometric model health monitoring; NIR spectroscopy; T^2 and Q statistics; Drift correction.