Design of Optimal Experiments for Identification of Yield Coefficients in a Baker's Yeast Model

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The identification problem in bioprocess dynamical modelling is usually twofold: the estimation of the yield coefficients k_i; and the determination of a suitable structure for the reaction rate model r and the estimation of the kinetic coefficients involved in r. Only the former case will be addressed in this work. The main objective of this work is to elaborate methodologies that allow the identification of yield coefficients through complete measurements of the state. Experimental design strategies are proposed in order to optimize the richness of data coming out from the experiments, quantified by indexes related to the Fisher information matrix. The objectives of the experimental planning have been addressed in terms of the programming of input trajectories. The experimental planning is envisaged for baker's yeast aiming at the computation of the substrate feed trajectories.

The reaction network for baker's yeast (*Saccharomyces cerevisiae*) growth on sugar with ethanol production / consumption is usually [1] described by the following three metabolic pathways:

Respiratory growth on sugar: $k_1 S + k_5 C \xrightarrow{r_1} X + k_7 P$

Fermentative growth on sugar: $k_2 S \xrightarrow{r_2} X + k_8 P + k_3 E$

Respiratory growth on ethanol: $k_4 E + k_6 C \xrightarrow{r_3} X + k_9 P$

$$\frac{d}{dt}\begin{bmatrix} X \\ S \\ E \\ O \\ C \end{bmatrix} = \begin{bmatrix} 1 & 1 & 1 \\ -k_1 & -k_2 & 0 \\ 0 & k_3 & -k_4 \\ -k_5 & 0 & -k_6 \\ k_7 & k_8 & k_9 \end{bmatrix} \begin{bmatrix} r_1 \\ r_2 \\ r_3 \end{bmatrix} - D \begin{bmatrix} X \\ S \\ E \\ O \\ C \end{bmatrix} + \begin{bmatrix} 0 \\ DS_{in} \\ 0 \\ OTR \\ -CTR \end{bmatrix}$$

where S, C, X, P, E represent sugar, oxygen, yeast, carbon dioxide, and ethanol respectively, r_1, r_2, r_3 are the reaction rates, D is the dilution rate, S_{in} is the sugar feed concentration, OTR is the oxygen transfer rate, CTR is the CO_2 transfer rate. The yield coefficients k_i are expressed with respect to the production of 1 unit of yeast in each reaction. The associated dynamical model is described above by the mass balance equations written in a matrix form [2].

Yield coefficients were computed by a linear regression technique without any knowledge about the kinetics being necessary, by a reparametrization [3] on the yield coefficients matrix.

To compose a basis for the comparison of different experimental conditions with respect to parameter identification a measure of the preciseness of the estimated parameters is required. This depends on the degree of richness or degree of independence of the regressor. A measure of the accuracy of estimation is the parameter covariance matrix. The asymptotic covariance matrix of any unbiased estimator $\hat{\theta}$ of θ satisfies the inequality: $\mathrm{cov}(\hat{\theta}) \geq F_I^{-1}$ where F_I is the Fisher Information Matrix.

The D-optimality design criterion in the optimal search of experimental conditions is considered. D-optimality corresponds to maximizing the determinant of the Fisher information matrix and is equivalent to minimising the volume of the deviation ellipsoids, a measure of the absolute errors of the estimated value of parameters. To find the input functions that lead to the most informative experiment, the feed rate was discretized into a finite number of node points and considered to be

linear between node points. For the optimization of the input variables at node points, a simplex-simulated annealing approach [4] and an adaptive random search method [5] have been used. Fig. 1 shows an illustration example of the feed profile for a programmed experiment.

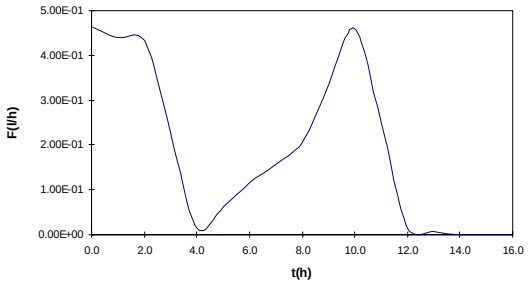

Fig. 1 Computed feed rate profile.

References

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