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SUBAREA 2.2 Automation and Control

Mathematical modeling of a biotechnological process for estimation and control purposes

Introduction and motivation

Biotechnological processes use either microorganisms or enzymes inside a reactor to synthesize complex molecules. One major challenge in the operation of such processes is however that the main process variables of interest, such as the biomass and product mass, are difficult to measure online. Furthermore, the processes are complex and not always entirely understood. Typically, laborious experiments have to be performed until the process runs satisfactorily.

A possible solution would be to use a suited mathematical model that can be used to **estimate** the major process variables, to reduce the experimental effort in finding the **best process conditions** and for **control purposes**.

Goals of the work

The goal is to find a mathematical model for an E. Coli fed-batch process that can predict the biomass growth and product formation, captures the dynamics and is suited for

- **Estimation** – providing online information of biomass and product mass.
- **Process optimization** – selection of optimal temperature, biomass growth rate and induction strength.
- **Process control** – assurance that the optimal process parameters are reached and kept.

Modeling

The model consists of the following set of ordinary differential equations:

$$\begin{aligned}\frac{dX}{dt} &= Y_{XS}q_S X - \frac{F}{V}X \\ \frac{dS}{dt} &= -q_S X + \frac{F_S}{V}S_{in} - \frac{F}{V}S \\ \frac{dI_e}{dt} &= \frac{-rV_{cell} - I_e(F - Y_{XS}q_S V_{cell}) + F_I I_{in}}{V_m} \\ \frac{dI_i}{dt} &= \frac{rV_{cell} - I_i Y_{XS}q_S V_{cell}}{V_{cell}} \\ \frac{dP}{dt} &= Y_{PS}q_S X - \frac{F}{V}P \\ \frac{dV_{cell}}{dt} &= Y_{XS}q_S V_{cell} \\ \frac{dV_m}{dt} &= F - Y_{XS}q_S V_{cell} \\ \frac{dM}{dt} &= \alpha_M \frac{1+K_1 I_i^2}{K+K_1 I_i^2} - (\gamma_M + Y_{XS}q_S)M \\ \frac{dPer}{dt} &= \alpha_P M - (\gamma_P + Y_{XS}q_S)Per\end{aligned}$$

The biomass yield Y_{XS} and product yield Y_{PS} are functions of intracellular inducer concentration I_i , specific substrate consumption rate q_S and temperature T . The inducer transport rate r is a

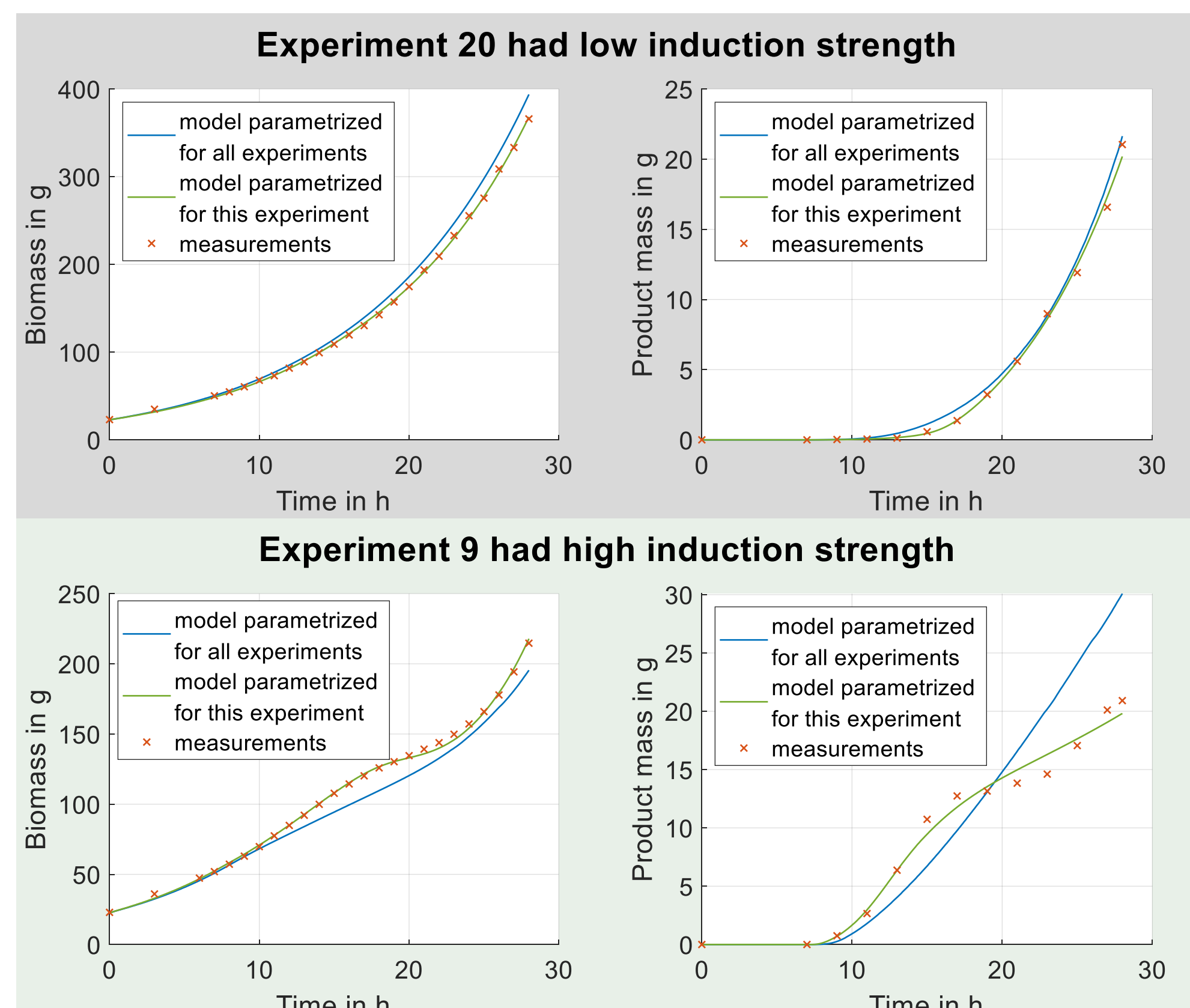


Figure 1: Model validation: Both experiments at 37°C and desired growth rate 0.1 h⁻¹. Good results with Experiment 20 with induction strength of 0.2 µmol inducer per gram cell dry weight. Moderate results with Experiment 9 with 0.9 µmol inducer per gram cell dry weight.

function of the extracellular inducer concentration I_e , the intracellular inducer concentration I_i and the permease concentration Per .

Model parametrization and validation

To find the model parameters, 31 experiments that were performed at different temperatures, substrate feed rates and induction strengths were compared to the model predictions using a quadratic quality measure. The model was parametrized for single

Variable	Description	Unit
X	Biomass concentration	g/l
S	Substrate (glucose) concentration	g/l
I_e	Extracellular inducer concentration	g/l
I_i	Intracellular inducer concentration	g/l
P	Product mass concentration	g/l
V_{cell}	Total cell volume	l
V_m	Medium volume	l
M	mRNA concentration	g/l
Per	Permease concentration	g/l
F	Feed rate	l/h
Y_{XS}	Biomass yield	g/g
Y_{PS}	Product mass yield	g/g
V	Reaction volume	l
q_S	Specific substrate uptake rate	g/(g h)
r	Specific inducer transport rate	g/(l h)
S_{in}	Substrate concentration in feed	g/l
F_S	Substrate feed rate	l/h
I_{in}	Inducer concentration in feed	g/l
F_I	Inducer feed rate	l/h

experiments and for all 31 experiments together and then validated against measured biomass and product mass. Exemplarily, two experiments are shown in Figure 1. Experiment 20 shows a scenario where the overall model fits well. Experiment 9 shows a case where it fits less well. For both examples the model fitted specifically to the experiment fits very well. Generally, the biomass is described better than the product mass. The reason why the overall model deviates stronger for some experiments still needs to be found.

Conclusions & outlook

The developed model succeeds in predicting the biomass but not product mass sufficiently yet. But it is suited for estimation algorithms which can further improve the quality of predicted biomass and product mass. Then the model can be used to find the optimal process conditions and for development of a control algorithm that realizes them.

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