Mec6313 Semester Project

Control of Biological Systems

Stefan Bracher

Presented to: El-Kébir Boukas

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Abstract: Biological systems usually have highly non-linear system dynamics. One approach to solve the control problem of such systems is to linearize them around one or multiple operation points, regard possible changes from these points as uncertainties and use appropriate matrix inequality (LMI) theorems to compute the controller gains. In this report, a short literature review is provided, followed by a practical example of a bio-reactor, where bacteria are used to transform a substrate into a product.

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1. Introduction

Biological systems are systems that contain living organisms or parts of them (enzymes or DNA). Many industrial processes use microorganisms or enzymes to transform chemicals, examples are beer-brewing, waste-water treatment or drug production. This reactions usually take place in bio-reactors. Reactors can range from small size, for a labor setting, to huge tank reactors. The two dominant types used are the batch reactor, a reactor that is completely emptied once the transformation is finished, and the continuous reactor, where there is a steady flow of chemicals trough the reactor.

The system dynamics of this reactors are described by kinetics and usually highly non linear, time varying and can contain time delays. Further on, it is difficult to measure the kinetic constants [7], what results in parameter uncertainties. The design of a robust controller is thus a very difficult and interesting task.

Kinetics

Kinetics describe the transformation speed from two chemicals A and B to a product C. The rate of change of the product concentration [C] is written as a function of the concentrations [A], [B] as well as other parameters. A usual form for the dynamic equation is:

$$\frac{d[C]}{dt} = k(T)[A]^n[B]^m$$

Depending on the parameters, the system is non-linear and time dependent.

2. Literature review

Robust controllers can be obtained using linear matrix inequality (LMI) theorems. The system robustness analysis using LMIs can roughly be divided in two fields: Kim et al. [7], Bakosova et al. [6] and Queinnec et al. [1] use one nominal point, linearize around it and consider system uncertainties, while Jorge et al. [4] and Li et al. [8] [10] linearize the system piecewise and use switching theorems. Sometimes non-linearities of the state are also regarded as norm bounded disturbance [3].

Other approaches that address the problem of non linearity, time variation, parameter uncertainty and delay exist as well. For example, Boubaker et al. [2] use sliding mode control in order to stabilize a bio-reactor for drinking water treatment and Sandoval et al. [5] use fuzzy control to track several system profiles of their bio-reactor.

Linear matrix inequalities can not only be used the design robust controllers. Cosentino et al. [11] use them to identify the system parameters from experimental data and Herrera et al. [9] design an observer in order to reduce the sensors needed.

3. Continuous reactor example

In the following, an example is elaborated where a substrate is transformed into a product by bacteria.

3.1 System dynamics

Notation:

Capital letters S, P and B describe substrate, product and biomass concentration. Small letters m_i, m_{out}, s, p, b, incoming mass flow, outgoing mass flow, substrate flow, product flow and biomass flow with the unit [kg/h]. T is temperature in Kelvin and $\dot{T}_{ex}$ describes the heat exchange rate. M is the total mass content in the tank [kg].

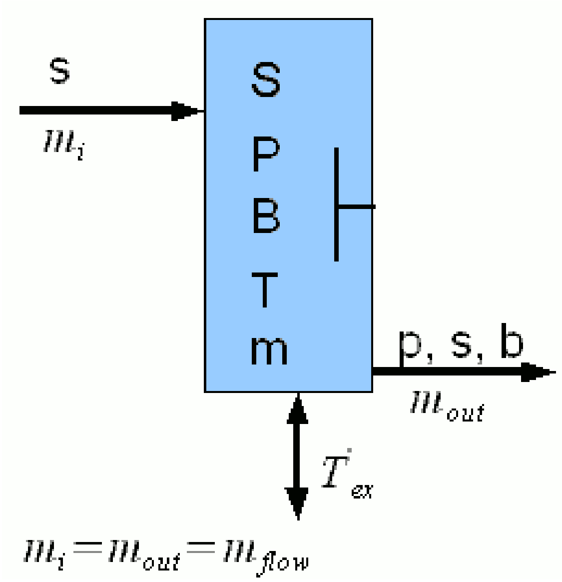

Figure 1: Schematic of the model with inflowing substrate S, that is transformed by the biomass B into product P. Other system parameters are the internal temperature T, the mass flows m_i, m_{out}, the heat exchanger exchange rate $\dot{T}_{ex}$ as well as the total tank content mass M.

Assumptions

The tank is considered to be perfectly isolated. The content is continuously stirred, such as the distribution of product P, substrate S and biomass B can be considered as homogeneous. The total mass of the tank is set as constant, thus whenever some substrate S is added, tank content, consisting of a mix of product, substrate and biomass, has to be removed. No delays in the tank-system are considered. The influx is bounded positive to 10 kg/h and the heat exchanger is modeled as a low-pass system of the form $\frac{s}{0.4s+1}$ and limited to be able to change the tank temperature maximally 50 K/h.

Kinetics

The product concentration increases due to production by the biomass, which is dependent on temperature, biomass and substrate concentration. It decreases with the outflowing mass, which has a product content P:

$$\frac{dP}{dt} = k_p(T) \cdot B \cdot S - \frac{P \cdot m_{flow}}{M} \quad , \quad kp(T) = kpt \cdot T \tag{3.1.1}$$

The biomass concentration increases quadratically with substrate concentration and decreases as well through its content of the outflowing mass. It is regarded as not temperature dependent:

$$\frac{dB}{dt} = k_g \cdot S^2 - \frac{B \cdot m_{flow}}{M}$$

(3.1.2)

As substrate concentration S, biomass concentration B and product concentration C must sum to 1, the change of substrate concentration can be written as:

$$\frac{dS}{dt}=\frac{-dP}{dt}-\frac{dB}{dt}$$

(3.1.3)

The temperature change in the tank is dependent on the temperature of the inflowing and outflowing masses, the heat produced by the bacteria, when transforming the substrate in the product, as well as the heat flow trough the heat exchanger:

$$\frac{dT}{dt}=\frac{c_t\cdot m_{flow}}{M}\cdot\left[T_{inlet}-T\right]+\frac{k_t\cdot k_p(T)\cdot B\cdot S}{M}+\dot{T}_{ex}$$

(3.1.4)

3.2 Linearized state model

The system dynamics are transformed in a linearized state model of the form $\dot{\boldsymbol{x}}=A\boldsymbol{x}+B\boldsymbol{u}$, with states $\boldsymbol{x}=\begin{bmatrix}P & S & B & T\end{bmatrix}^T$ and inputs $\boldsymbol{u}=\begin{bmatrix}m_{flow} & \dot{T}_{ex}\end{bmatrix}^T$. The system matrices become:

$$A=\begin{bmatrix}\frac{-m_{flow}}{M} & k_P(T)\cdot B & k_P(T)\cdot S & 0 & ktp\\ \frac{m_{flow}}{M} & -k_P(T)\cdot B-k_g\cdot 2\cdot S & -k_P(T)\cdot S+\frac{m_{flow}}{M} & 0 & -kpt\\ 0 & 2\cdot k_g\cdot S & \frac{-m_{flow}}{M} & 0 & 0\\ 0 & \frac{k_t\cdot k_p(T)\cdot B}{M} & \frac{k_t\cdot k_p(T)S}{M} & 0 & \frac{-c_t\cdot m_{flow}}{M}\end{bmatrix}$$

(3.2.1)

and

$$B=\begin{bmatrix}\frac{-P}{M} & 0\\ \frac{P+B}{M} & 0\\ \frac{-B}{M} & 0\\ 0 & 1\end{bmatrix}$$

(3.2.2)

The matrices A and B depend on the product, substrate and biomass concentration, the mass flow, the temperature and the overall mass, thus they change at every operating point.

3.3 Open-loop simulation with no mass flow (batch mode)

To simulate the system behavior, a Simulink model of the system dynamics (3.1.1-3.1.4) is made. In a first step, a simulation in "batch-mode" is done. This means that the reactor is filled once and then closed (no mass flow) until the reaction is finished.

Simulation parameters

Initial tank product concentration P:	0
Initial tank biomass concentration B:	0.01
Initial tank substrate concentration S:	0.99
Initial tank temperature:	290 K
Total tank content mass M:	10 kg
Heat production rate kt (see 3.1.4):	1600 K*kg
Bacterial grow coefficient (see 3.1.2):	0.8
Reaction constant kpt (see 3.1.1):	0.008
Heat exchanger:	Off
Mass influx/ out flux:	0

Simulation result

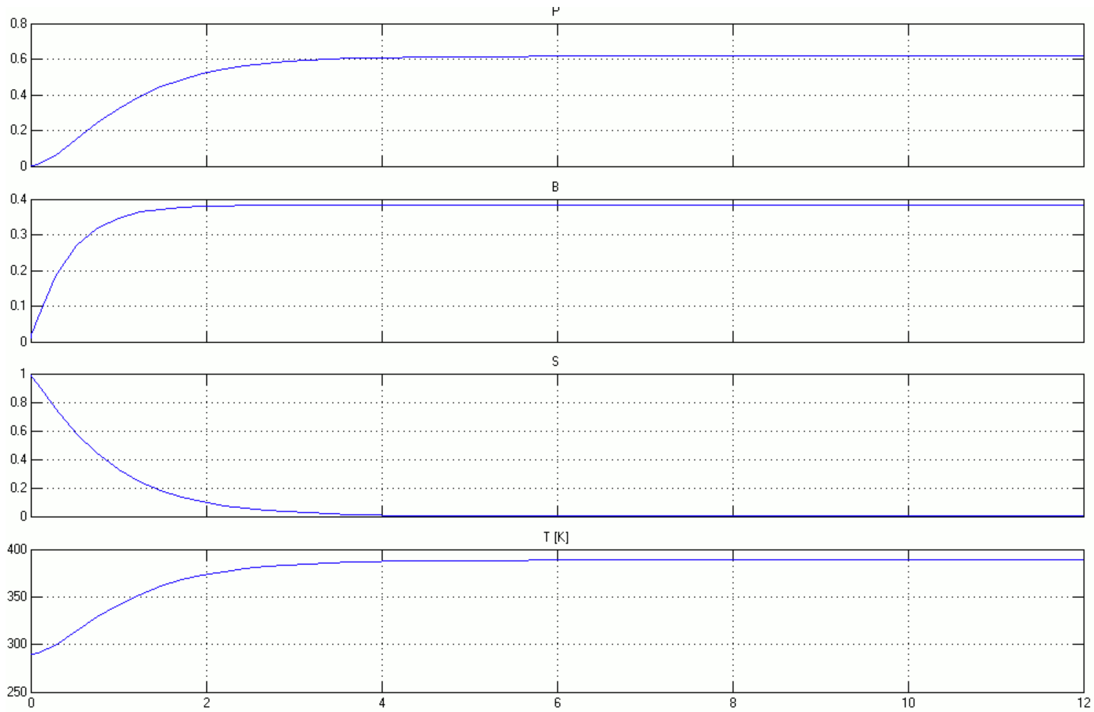

Figure 2: From the top: Product concentration, Biomass concentration, Substrate concentration, Temperature. X-axis: simulated hours

In figure 2 we see the simulation result. In the first two hours there is an enormous bacterial grow, that leads to a maximal transformation rate after about ¾ h. After that, transformation rate and bacterial grow rate become smaller due to the lower substrate concentration. Six hours after the begin of the simulation, almost all substrate is transformed and the system stabilizes.
What also can be observed is the enormous temperature increase up to over 380 Kelvin. At this temperature, a real system would certainly be destroyed, thus the heat exchanger is essentially if the system is used in batch-mode. (See section 4.1)

3.4 Open-loop simulation with constant mass flow (continuous mode)

The simulation is repeated, but this time in continuous mode, with a constant mass flow (inflowing substrate, outflowing mix of substrate, biomass and product) of 1 kg/h.

Simulation parameters

Initial tank product concentration P:	0
Initial tank biomass concentration B:	0.01
Initial tank substrate concentration S:	0.99
Initial tank temperature:	290 K
Total tank content mass:	10 kg
Heat production rate kt (see 3.1.4):	1600 K*kg
Bacterial grow coefficient (see 3.1.2):	0.8
Reaction constant kpt (see 3.1.1):	0.008
Heat exchanger:	Off
Mass influx/ out flux:	1 kg/h
Material heat coefficient ct (see 3.1.4):	4.19
Inflowing substrate temperature	290 K

Simulation result

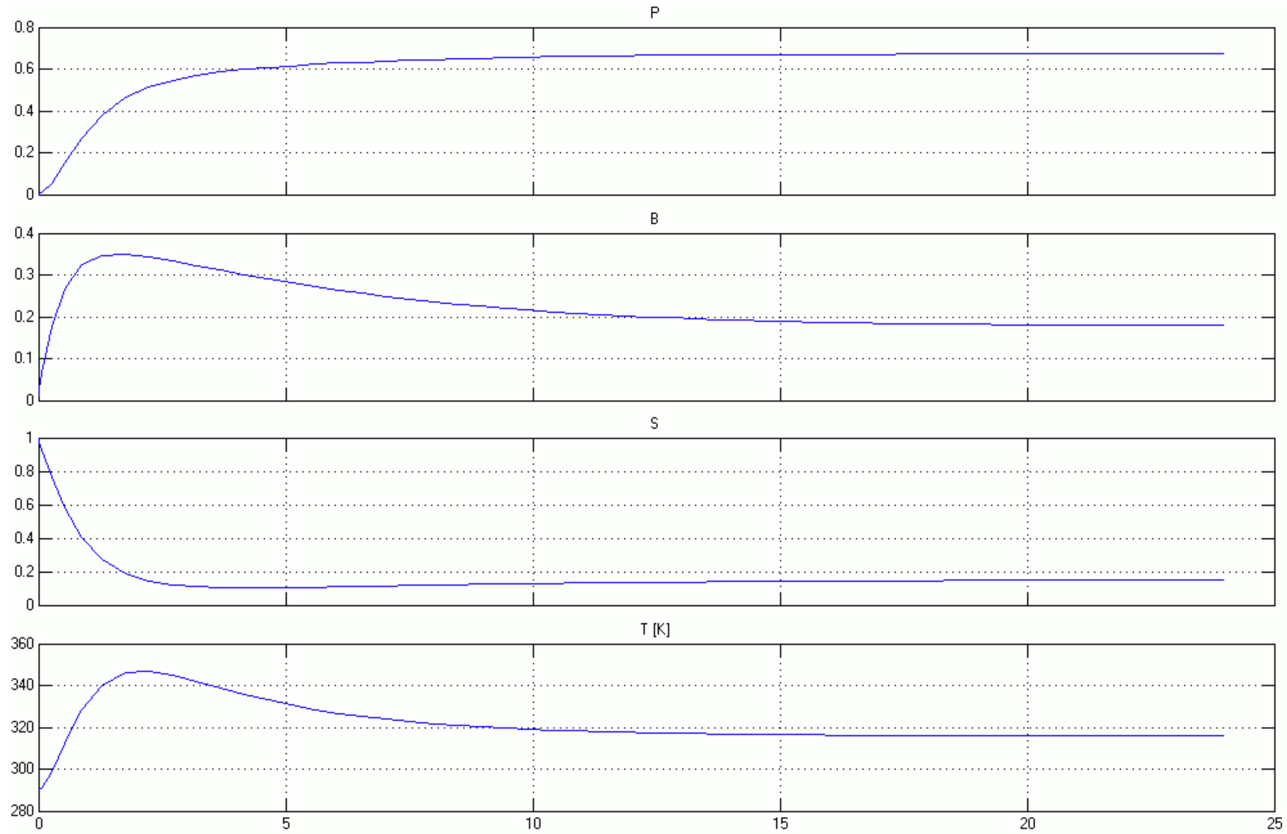

Figure 3: From the top: Product concentration, Biomass concentration, Substrate concentration, Temperature. X-axis: simulated hours (max 24)

Unlike the system without mass flow, after a first increase, the bacterial concentration decreases after time to stabilize around 19%. This is because with the mass flow, the system constantly looses bacteria, the higher their concentration, the more. Interestingly, thanks to the constant substrate influx, the product concentration stabilizes at a higher level than in batch-mode. The incoming mass at 290 K also keeps the temperature at more moderate levels. The drawback of the open-loop continuous mode is, that it needs almost 24h to stabilize.

4. Controller design for the example

4.1 Temperature state feedback control

To keep the temperature within limits, it has to be controlled in closed loop. The idea for the design is to linearize the system around one operating point and regard all changes from this point either as uncertainty or as disturbance.

Model

The model of the temperature becomes, based on (3.1.4):

$$\dot{\boldsymbol{x}} = A\,\boldsymbol{x} + B\,\boldsymbol{u}$$

with

$$x = \begin{bmatrix} \int T \\ T \end{bmatrix},\ u = \dot{T}_{ex}\ ,\ A_{nom} = \begin{bmatrix} 0 & 1 \\ 0 & \dfrac{kt \cdot kpt \cdot T_{nom} \cdot B_{nom} \cdot S_{nom}}{M} \end{bmatrix},\ B = \begin{bmatrix} 0 \\ 1 \end{bmatrix}$$

(4.1.1

The integral of the temperature is added as state to be able to make a control without offset.

The temperature change due to the material flow is neglected, what will not cause any problems as long as the substrate, that is inserted in the tank, is preheated at the desired tank temperature, as in this case it will always help to stabilize the system.

Uncertainties

The variations from the nominal operation point due to changing T, B and S, are modeled as norm bounded uncertainties of the form:

$$A = A_{nom} + D_A F_A E_A$$

with

$$D_A = \begin{bmatrix} 0 \\ 1 \end{bmatrix},\ F_A^2 < 1 \text{ and } E_A = \begin{bmatrix} 0 & \dfrac{kt \cdot kpt \cdot (SB_{max} \cdot T_{up} - T_{nom} \cdot B_{nom} \cdot S_{nom})}{M} \end{bmatrix}$$

(4.1.2

Where SB_{max} is the maximal product of the substrate and biomass concentrations (=1) and T_{up} is the maximal admissible temperature.

Controller gain computation with linear matrix inequalities

The gains of the controller $\boldsymbol{u}=K\cdot(\boldsymbol{x}-\boldsymbol{x}_{des})$ are computed using the following linear matrix inequality theorem by E.K. Boukas [12]:

State-Feedback Stabilization theorem, norm-bounded uncertain systems [12]
There exists a state feedback controller $\dot{x}=(A+BK)\boldsymbol{x}+B\boldsymbol{u}$ that stabilizes the uncertain system if there exist a symmetric and positive-definite matrix X > 0, a matrix Y and positive scalars ϵ_A > 0 and ϵ_B > 0 that satisfy the following LMI's: X>0 $\begin{bmatrix} J & X E_A^T & Y^T E_B^T \\ E_A X & -\epsilon_A I & 0 \\ E_B Y & 0 & -\epsilon_B I \end{bmatrix} < 0$ where $J=X A^T+A X+B Y+Y^T B^T+\epsilon_A D_A D_A^T+\epsilon_B D_B D_B^T$. The controller gain is given by $K=Y X^{-1}$

(4.1.3

Simulation

Simulation parameters

Initial tank product concentration P:	0
Initial tank biomass concentration B:	0.01
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Initial tank temperature:	290 K
Total tank content mass M:	10 kg
Heat production rate kt (see 3.1.4):	1600 K*kg
Bacterial grow coefficient (see 3.1.2):	0.8
Reaction constant kpt (see 3.1.1):	0.008
Heat exchanger:	*On*
Mass influx/ out flux:	1 kg/h
Material heat coefficient ct (see 3.1.4):	4.19
Inflowing substrate temperature	290 K
Desired Temperature T_des:	*290 K*
Upper temperature limit T_up:	*300 K*
Nominal Biomass concentration Bnom:	*0.3*
Nominal Product concentration:	*0.7*
Nominal Substrate concentration:	*0*
Sbmax:	*1*

The solution of (4.1.3) with these parameters, using Yalmip [13] and Sedumi [14] for the controller gains is:

$$K = \begin{bmatrix} -0.0103 & -867.0572 \end{bmatrix} \tag{4.1.4}$$

And the simulation result is:

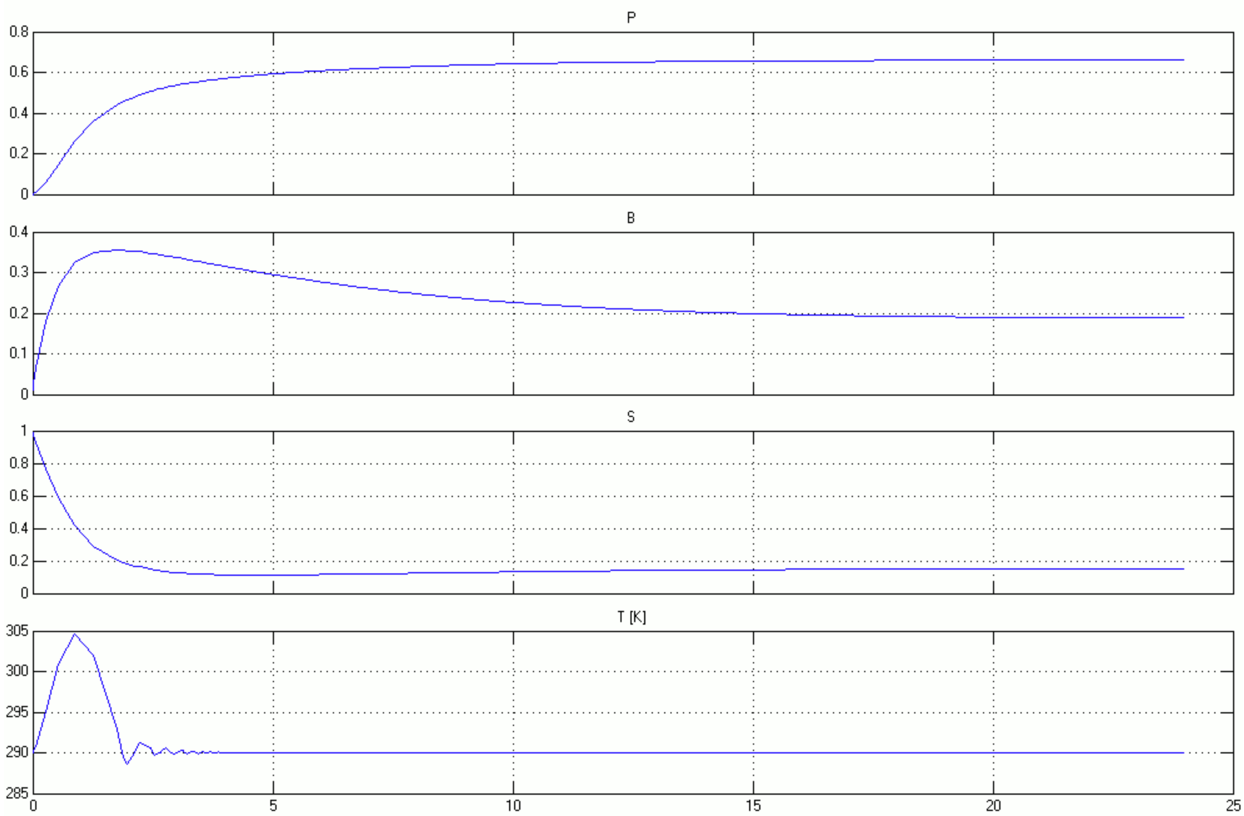

Figure 4: From the top: Product concentration, Biomass concentration, Substrate concentration, Temperature. X-axis: simulated hours (max 24)

It can be seen that, compared to Figure 3, the temperature stays within a reasonable range. The final system concentrations remain almost unchanged.

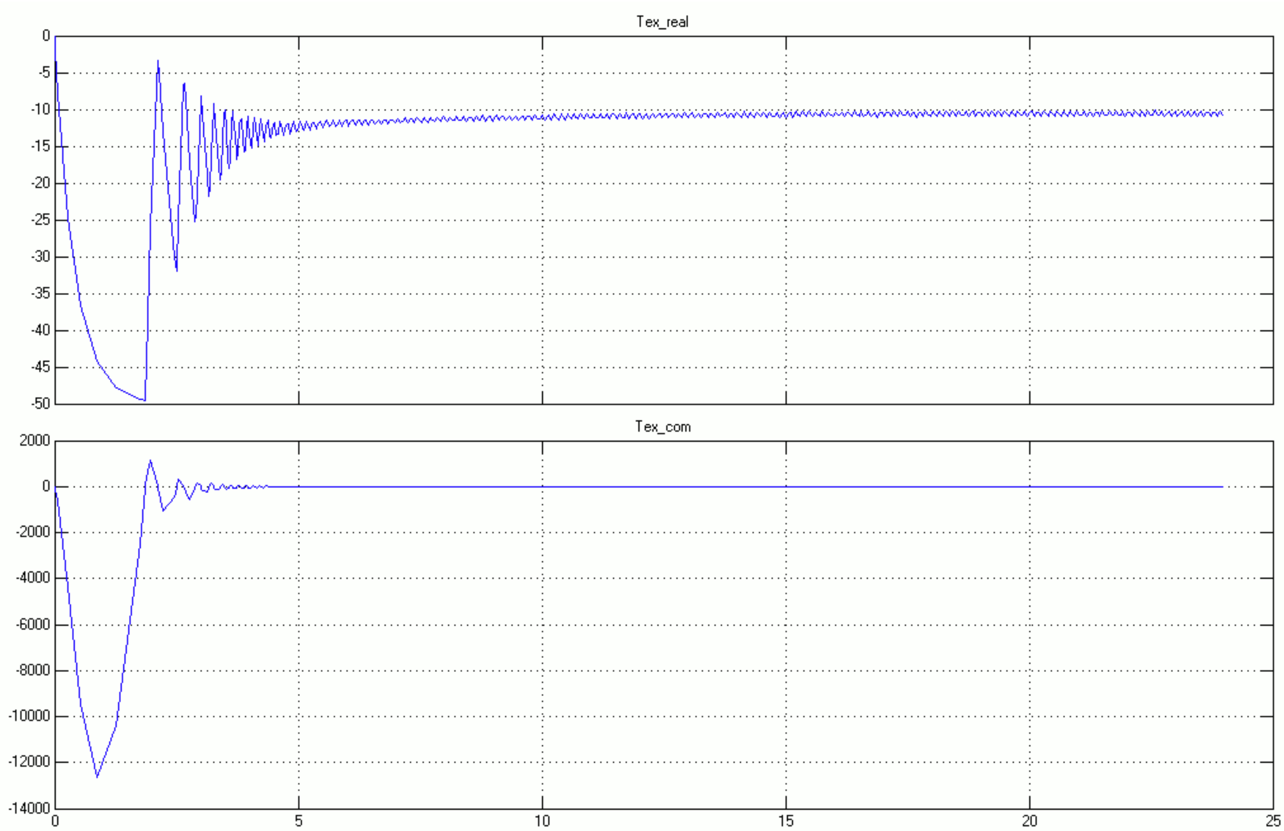

Figure 5: Top: Real heat exchanger flux, Bottom: Commanded heat exchanger flux

Figure 5 shows the effect of modeling the heat exchanger as a low pass of the form $\frac{s}{0.4s+1}$ with a limitation of temperature change capacity of 50 K per hour. The command demands much higher values than are possible, but the system still stabilizes, even with the smaller real values and the delay introduced by the low pass.

4.2 Product concentration control

In the same way as the temperature controller, a product concentration controller is implemented. This might be necessary when this concentration in the output is crucially.

Model

The model is this time based on on (3.1.1) and becomes:

$\dot{\boldsymbol{x}} = A\,\boldsymbol{x} + B\,\boldsymbol{u}$

with

$$x = \begin{bmatrix} \int P \\ P \end{bmatrix},\ u = \dot{m}_{flux},\ A_{nom} = \begin{bmatrix} 0 & 1 \\ 0 & \dfrac{-m_{nom}}{M} \end{bmatrix},\ B = \begin{bmatrix} 0 \\ \dfrac{-P_{nom}}{M} \end{bmatrix}$$

(4.2.1

Again an integral part is added to avoid offsets in the control. The assumption is made that product creation can be regarded as disturbance. That this works can be seen later on. The controller has the form $\boldsymbol{u} = K \cdot (\boldsymbol{x} - \boldsymbol{x}_{des})$

Uncertainties

Again, the derivations from the nominal point are modeled as norm-bounded uncertainty:

$A = A_{nom} + D_A F_A E_A$

with

$$D_A = \begin{bmatrix} 0 \\ 1 \end{bmatrix},\ F_A^2 < 1 \text{ and } E_A = \begin{bmatrix} 0 & \dfrac{-(m_{max} - m_{nom})}{M} \end{bmatrix}$$

(4.2.2)

as well as

$B = B_{nom} + D_B F_B E_B$

with

$$D_B = \begin{bmatrix} 0 \\ 1 \end{bmatrix},\ F_B^2 < 1 \text{ and } E_A = \frac{-(P_{max} - P_{nom})}{M}$$

(4.2.3)

Simulation

Simulation parameters

Initial tank product concentration P:	0
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Bacterial grow coefficient (see 3.1.2):	0.8
Reaction constant kpt (see 3.1.1):	0.008
Heat exchanger:	On
Material heat coefficient ct (see 3.1.4):	4.19
Inflowing substrate temperature	290 K
Desired Temperature T_des:	*290 K*
Upper temperature limit T_up:	300 K
Nominal Biomass concentration Bnom:	0.3
Nominal Product concentration:	0.7
Nominal Substrate concentration:	0
Sbmax:	1
Nominal mass flow	5 kg/h
Maximal admissible mass flow	10 kg/h

The gains calculated by solving (4.1.3) are:

$$K = \begin{bmatrix} -0.0000 & -1.2503 \end{bmatrix}$$

And the simulation, with product concentration control and temperature control at the same time, gives:

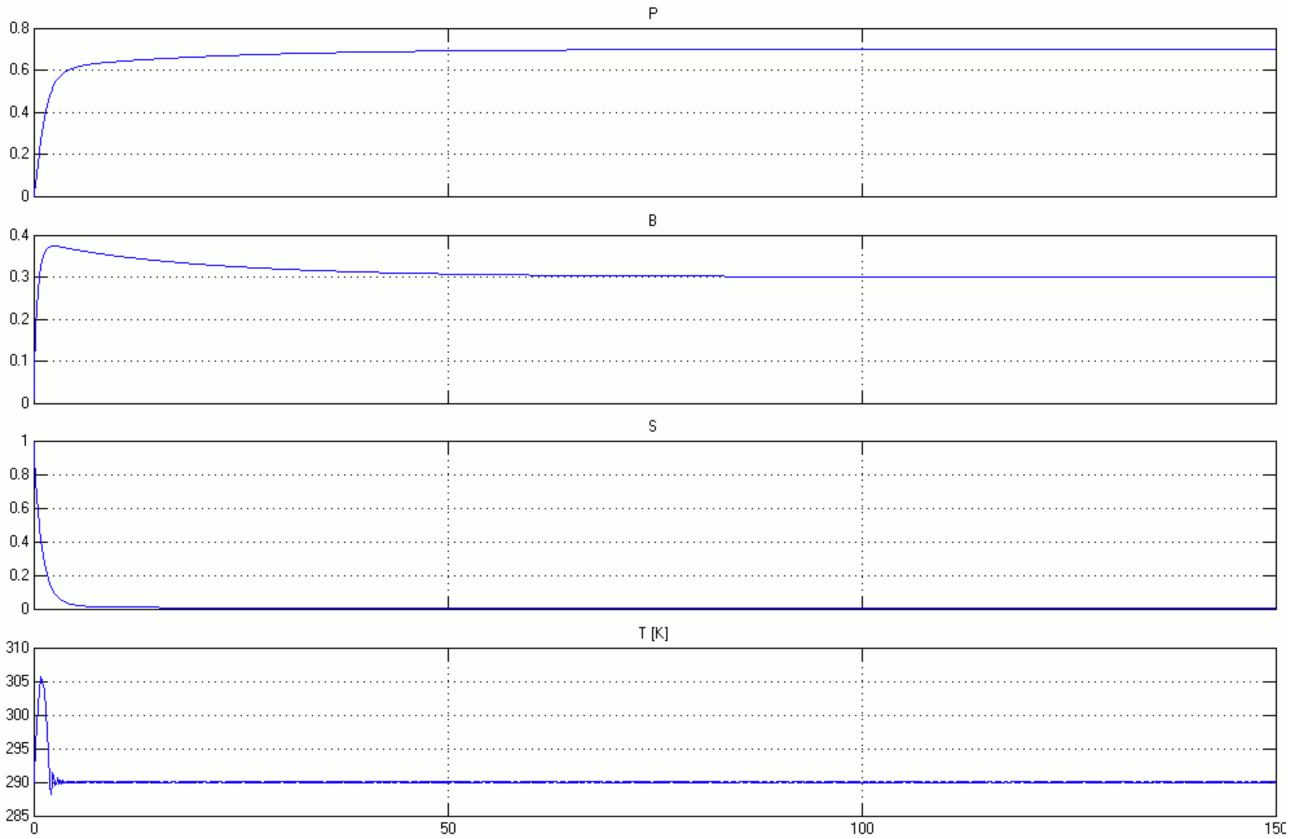


Figure 6: From the top: Product concentration, Biomass concentration, Substrate concentration, Temperature. X-axis: simulated hours (max 24)

The controller is able to attain the desired product concentration, but is very slow. However an unexpected result can be seen looking at the flow rate:

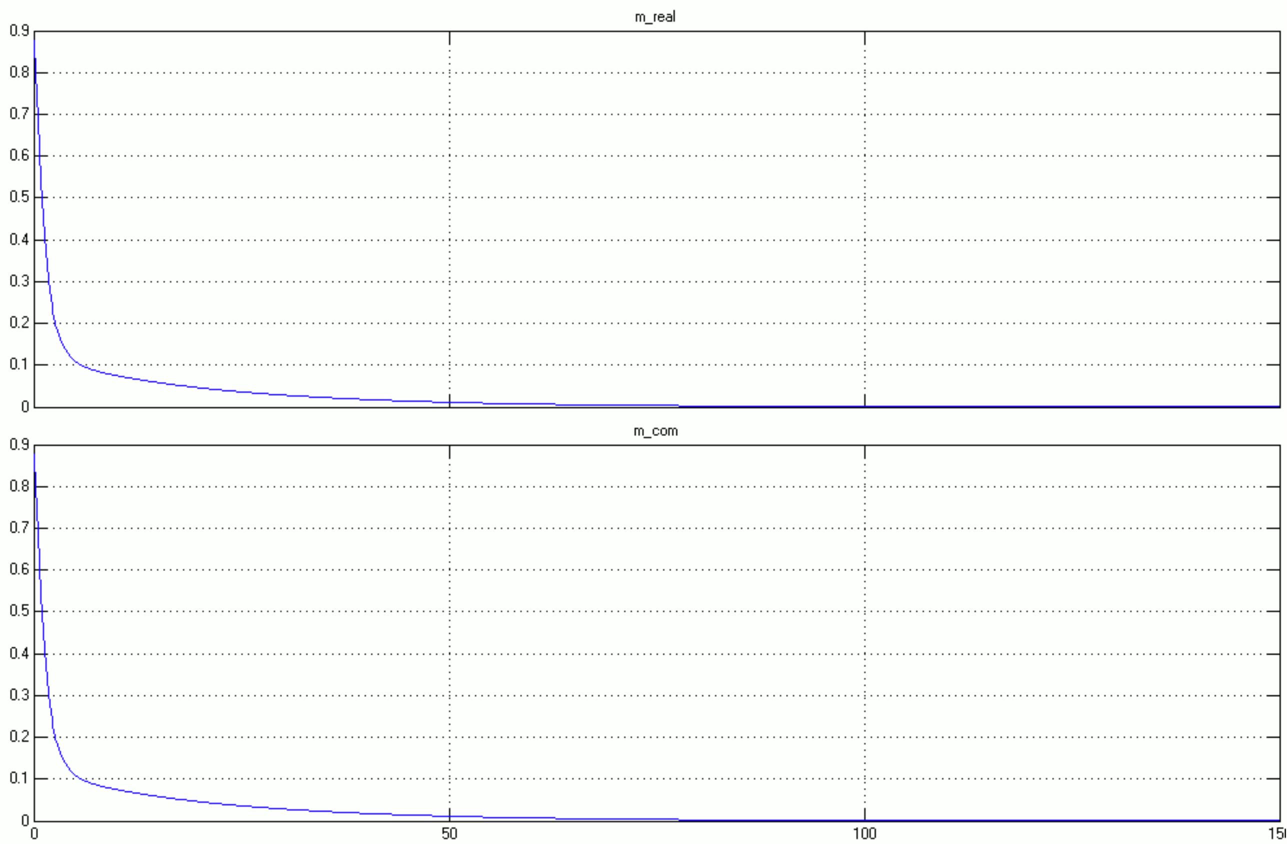


Figure 7: Top: Real material flux, Bottom: Commanded material flux

As it can be seen from figure 7, the material flow is constantly reduced, until it becomes almost zero at the stabilized point with desired product concentration where the control transforms the reactor into a batch-reactor.

4. Discussion

4.1 Model

The model used is still quite basic. Additional features such as bacterial death, bacteria grow rate dependence on temperature et-cetera could be added.

4.2 Controller

The splitting up of the control problem in two SISO problems, one for temperature and one for product concentration, made the uncertainty design very easy. If the whole dynamics in one single MIMO system would have to be considered, the LMI approach should work as well, but it will be much more complicated to account for all the different uncertainties at the same time.

4.3 Unexpected result for product concentration control

The unexpected result of the product concentration control, that the mass flow is constantly reduced the closer the system gets to the desired system point, makes, looking at the used system dynamics, completely sense: Bacteria death is not included in the model, thus, this behavior is actually the easiest way to keep a constant concentration.

4. Conclusion

As shown in the literature review as well as in the example, linear matrix inequality theorems for controller design can be used to overcome the problem of highly non-linear dynamics, that are found in biological systems. By considering multiple system states or by including the possible state variable changes about a nominal point as uncertainties, robustness of the control can be assured, even if the system changes are big.

References

[1] I. Queinnec, A. Trofino, “H-infinity Attenuation of a Bioprocess with Parameter Uncertainty”, 1997

[2] O. Boubaker, J.P. Babary, “On SISO and MIMO Sliding Control of a Distributed Parameter Biological Process”, 1999

[3] I. Queinnec, S. Tarbouriech, H.X. de Araujo, “H2 Disturbance attenuation by dynamic output feedback of a nitrification process submitted to actuator limitations”, 1999

[4] J.M. Gonçalves, “Regions of Stability for Limit Cycle Oscillations in Piecewise Linear Systems”, 2005

[5] P. Garcia-Sandoval, B. Castillo-Toledo, V. Gonzalez-Alvarez, “Fuzzy Robust Tracking of a Bioreactor”, 2005

[6] M. Bakosova, D. Puna, Alojz Mészaros, “Robust Controller Design for a Chemical Reactor”, 2005

[7] J. Kim, D.G. Bates, I. Postlethwaite, L.Ma. P.A. Iglesias, “Robustness analysis of biochemical network models”, 2006

[8] C. Li, L. Chen, K. Aihara, “Stability of Genetic Networks With SUM Regulatory Logic: Lur'e System and LMI Approach”, 2006

[9] E. Herrera, B. Castillo, J. Ramirez, E. C. Ferreira, “Exact Fuzzy Observer for a Baker's Yeast Fed-Batch Fermentation Process”, 2007

[10] C. Li, L. Chen, K. Aihara, “Stochastic Stability of Genetic Networks With Disturbance Attenuation”, 2007

[11] C.Cosentino, W. Curatola, F. Montefusco, M.Bansal, D. di Bernardo, F.Amato, “Linear matrix inequalities approach to reconstruction of biological networks”, 2007

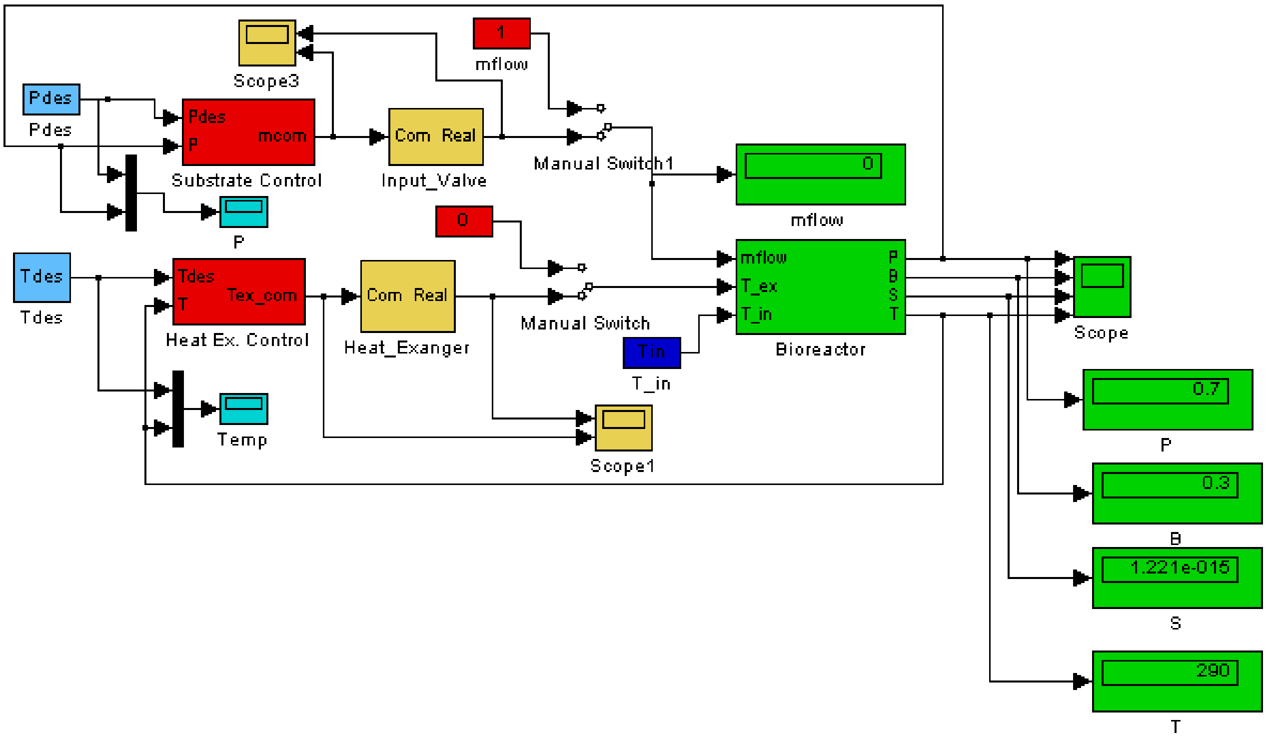
[12] Boukas El-Kebir, “Class Notes MEC6313“, Ecole Polytechnique de Montréal, 2007

[13] Löfberg J., “YALMIP : A Toolbox for Modeling and Optimization in MATLAB.” In Proceedings of the CACSD Conference, Taipei, Taiwan, 2004.

[14] Sedumi: http://sedumi.mcmaster.ca

Appendix

Simulink model screenshot



Matlab Code, Simulink model, referred articles