

BPL_CHO_Fedbatch - demo

This notebook deals with CHO fedbatch cultivation and recombinant protein production is included. We look first at start-up strategy to keep the by-product formation low. After that we look at a whole cultivation and see the impact of feeding strategy on both cell growth and protein production where a trade-off is needed in this case.

The model used takes its inspiration from the microbial bottleneck models [1]. The original model is here expanded with the classical empirical Luedeking-Piret model recombinant protein production.

Interaction with the compiled model as FMU is mainly through the simplified commands: `par()`, `init()`, `newplot()`, `simu()` etc. The last simulation is always available in the workspace and called 'sim_res'. The command `describe()` brings mainly up description information from the actual Modelica code from the FMU but is complemented with information given in the dedicated Python setup-file.

The idea is to demonstrate how simulations and varying conditions can provide some process insight that can support the experimental work. I hope that at the end of this session you are ready to formulate your own questions you want to address with simulations - and you can just go on in this notebook! Just press the field "+Code" in the upper left part of notebook interface and you get a new "cell" where you write your own code. You can copy and paste from cells above using `ctrl-c` and `ctrl-p` as usual and edit the cell. When you are ready to execute the cell just press the "play button" to the left in the cell or press `shift-enter` as in "ordinary" Jupyter notebooks.

After a session you may want to save your own notebook. That you can do on your Google Drive account and I refer to Colab instructions for how to do this. It is easy.

Good luck!

In [1]:

```
run -i BPL_CHO_fedbatch_explore.py
```

Windows - run FMU pre-compiled JModelica 2.14

Model for bioreactor has been setup. Key commands:

- `par()` - change of parameters and initial values
- `init()` - change initial values only
- `simu()` - simulate and plot
- `newplot()` - make a new plot
- `show()` - show plot from previous simulation
- `disp()` - display parameters and initial values from the last simulation
- `describe()` - describe culture, broth, parameters, variables with values / units

Note that both `disp()` and `describe()` takes values from the last simulation

Brief information about a command by `help()`, eg `help(simu)`

Key system information is listed with the command `system_info()`

In [2]:

```
plt.rcParams['figure.figsize'] = [30/2.54, 24/2.54]
```

About the process model

We can get information about the process and liquid phase by the command `describe()`. Here is no gas-phase included. This command can also be used to bring up information about a specific variable or parameter. However, you should use `describe()` after a simulation to get the values used during the simulation.

```
In [3]: describe('culture'); print(); describe('liquidphase')
```

Reactor culture CHO-MAb - cell line HB-58 American Culture Collection ATCC

Reactor broth substances included in the model

```
Cells viable index = 1 molecular weight = 24.6 Da
Cells dead index = 2 molecular weight = 24.6 Da
Glucose index = 3 molecular weight = 180.0 Da
Glutamine index = 4 molecular weight = 146.1 Da
Lactate index = 5 molecular weight = 90.1 Da
Ammonia index = 6 molecular weight = 17.0 Da
Protein index = 7 molecular weight = 15000.0 Da
```

Simulation of different start-up feeding strategies

```
In [ ]:
```

Simulation of recombinant protein production during the whole process

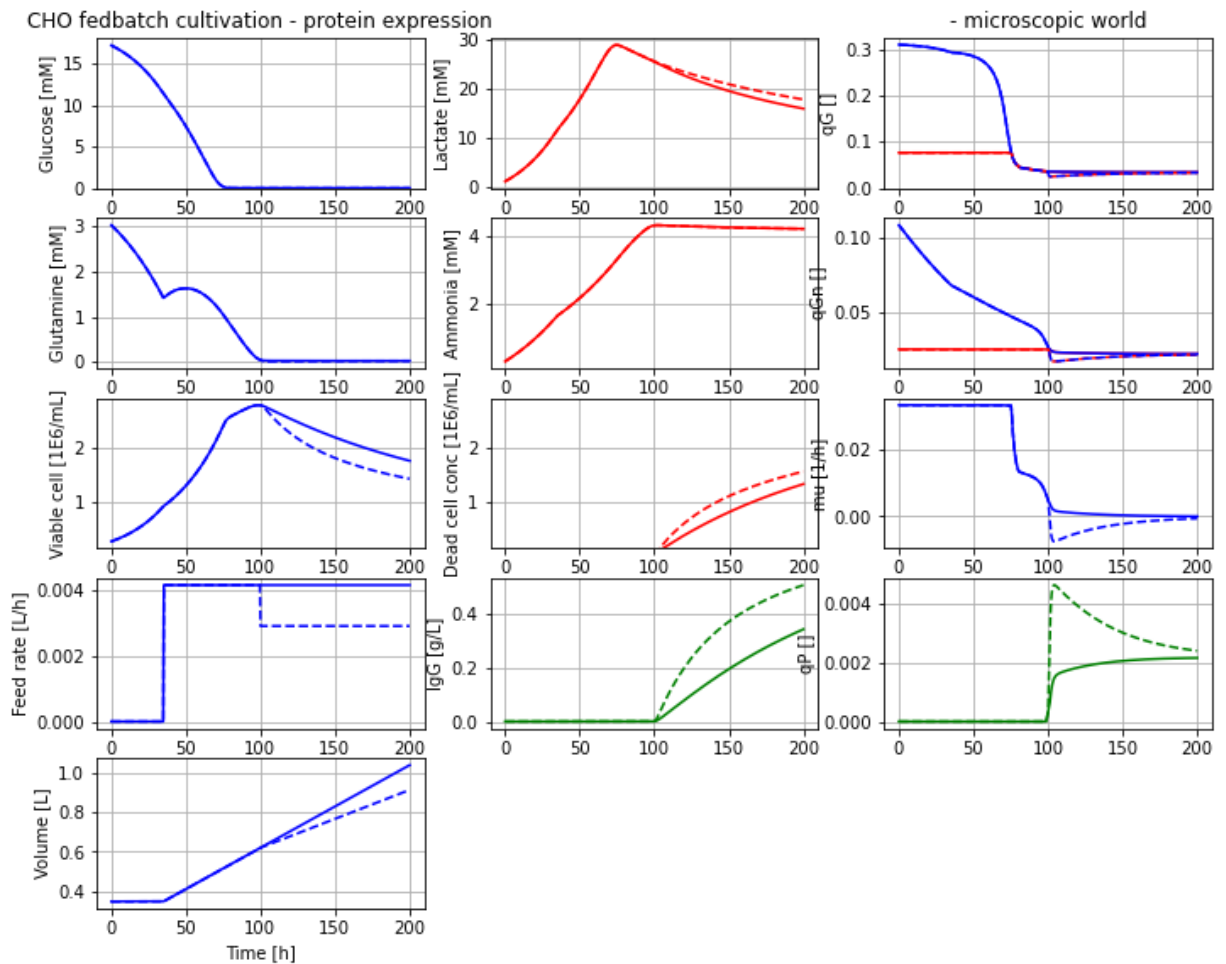
```
In [4]: # Slide 3
newplot('CHO fedbatch cultivation - protein expression', plotType='Textbook_3')

# Data from Table 1 and 2 for experiment 3
V_0=0.35
init(V_0=V_0, VXv_0=V_0*0.29, VXd_0=V_0*0.010)
init(VG_0=V_0*17.17, VGn_0=V_0*3.02, VL_0=V_0*1.12, VN_0=V_0*0.29)

# Feeding
Feed=0.1/24
par(G_in=15, Gn_in=9.3)
par(t0=0, F0=0, t1=35, F1=Feed, t2=100, F2=Feed, t3=300, F3=Feed)

# Culture parameters
par(alpha=-1.0, beta=0.01)

# Simulation
simu(200)
par(t2=100, F2=0.7*Feed, t3=300, F3=0.7*Feed); simu(200)
par(F2=Feed, F3=Feed)
```



Summary

References

- [1] Amribt, Z., Niu, H. and Bogaerts P.: "Macroscopic modelling of overflow metabolism and model based optimization of hybridoma cell fed-batch cultures.", Biochem. Eng. Journal, 2013.
- [2] Niu,H., Amribt, Z., Fickers, P., Tan, W. and Bogaerts P.: "Metabolic pathway analysis and reduction for mammalian cell cultures - towards macroscopic modelling, Chem. Eng. Science, 2013.
- [3] Axelsson, J. P. "Simplified model of CHO-cultivation in Biopros Library for Modelica - some experience", conference paper 22nd NPCW Lyngby, Denmark, August 22-23, 2019.

Appendix

In [5]: `# List of components in the process setup and also a couple of other things like Liq describe('parts')`

`['bioreactor', 'bioreactor.broth_decay', 'bioreactor.culture', 'dosagescheme', 'feed tank', 'liquidphase', 'MSL']`

In [6]: `system_info()`

System information
-OS: Windows

- Python: 3.9.5
- PyFMI: 2.9.5
- FMU by: JModelica.org
- FMI: 2.0
- Type: FMUModelCS2
- Name: BPL_CHO.Fedbatch
- Generated: 2022-08-19T14:17:34
- MSL: 3.2.2 build 3
- Description: Bioprocess Library version 2.1.0 beta
- Interaction: FMU-explore ver 0.9.2

In []: