

BPL IEC validation

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Here I try to reproduce some results from Jonas Månssons master thesis report "Control of chromatography column in production scale", TFRT-5599.

The interaction with the model has changed slightly so that linear flow rate $LF = F/\text{area}$ is used. The column volume is now specified in terms of (cross-section) area times height. Thus by changing area the scale up works fine and what you do in practice. Further the time unit changed from seconds to minutes.

The model has 5 states as listed below, 3 states in liquid mobile phase and 2 states for the gel for bound proteins. In a few of Jonas figures also bound ions of the buffer are plotted but I do not do that. Bound ions of the buffer can be calculated from the difference of total binding capacity Q_{av} and bound protein and bound protein antagonist, see section 5.1 in the report.

The molecular weights listed below are not used in the simulations. They just give typical values and the molecular weight for bound protein and antagonist protein is just arbitrary here.

Parameters of the model in general as well as time scale are all arbitrary and focus is on qualitative aspects of the model.

The height of the column is 20 cm which is a common size in the industry.

```
In [1]: run -i BPL_IEC_fm.py_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 and the command process_diagram() brings up the main configuration

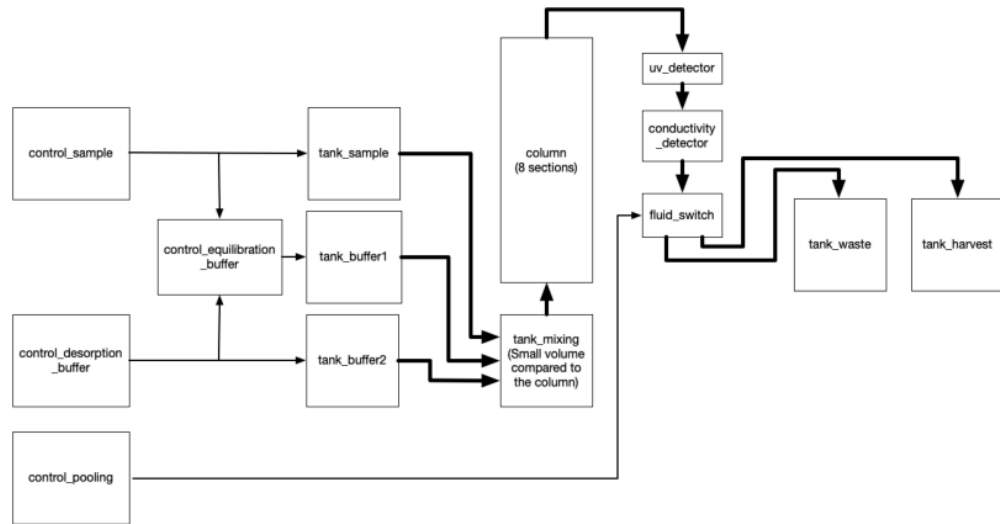
Brief information about a command by help(), eg help(simu)

Key system information is listed with the command system_info()

```
In [2]: plt.rcParams['figure.figsize'] = [30/2.54, 24/2.54]
```

```
In [3]: # The process diagram is made outside Modelica to illustrate the configuration
process_diagram()
```

No processDiagram.png file in the FMU, but try the file on disk.



```
In [4]: describe('chromatography'); print(); #describe('Liquidphase')
```

Ion exchange chromatography controlled with varying salt-concentration. The pH is kept constant.

Loading or adsorption

The parameter notation and values are the same as in the referred report. However the flow rate is here denoted F while q in the report. The column is divided in $n=8$ sections and set at compilation time. The values are arbitrarily chosen in the report and the focus is on qualitative aspects of the model.

The simplified model describe only the column in terms of volume and does not distinguish a high column with a small diameter from a lower with larger diameter.

The parameters k_1 , k_2 , k_3 , k_4 and Q_{av} are given relative volume and with increased column volume a larger capacity is thus obtained.

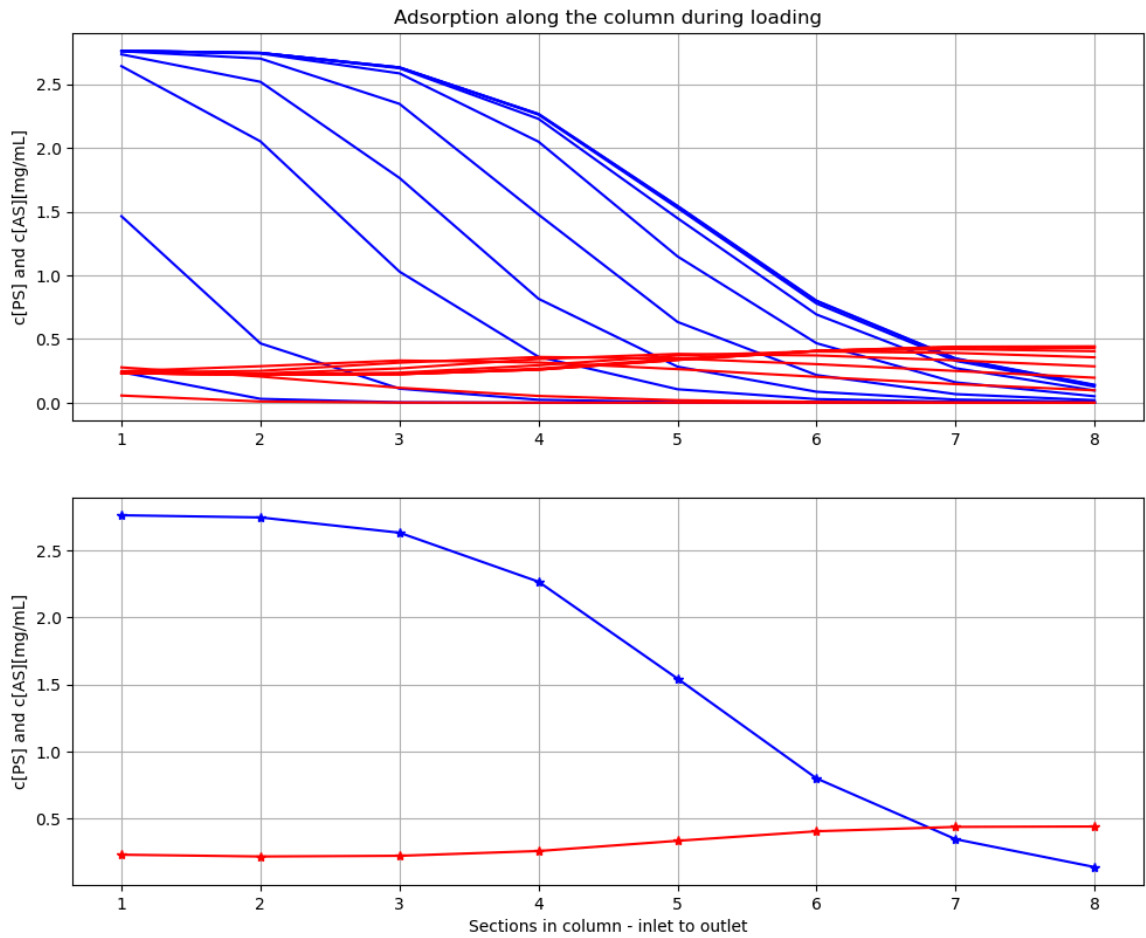
```
In [5]: # Loading of the column - try to reproduce Jonas figure 13.
newplot(title='Adsorption along the column during loading', plotType='Loading')

# Sample
par(P_in=1.0, A_in=1.0, E_in=0)

# Column properties
par(k1=0.3, k2=0.05, k3=0.05, k4=0.3, Q_av=3.0)
par(height=20, diameter=0.714)
par(x_m=0.3)

# Operation
par(E_in_desorption_buffer=8)
par(LFR=12)
par(scale_volume=False)
par(start_adsorption=0, stop_adsorption=50)
par(start_desorption=150, stationary_desorption=450)
par(start_pooling=220, stop_pooling=450)
```

```
# Simulation
simu(100)
```



The results are the same as Figure 13 in [1].

```
In [6]: # We just check that we had the same volume flow rate as Jonas
describe('F')
```

```

-----
TypeError                                Traceback (most recent call last)
Cell In [6], line 2
      1 # We just check that we had the same volume flow rate as Jonas
----> 2 describe('F')

File \\VBoxSvr\Modelica\GitHub\Colab\BPL_IEC_validation\BPL_IEC_fm.py:1066, in describe(name, decimals)
    1063     describe_MSL()
    1065 else:
-> 1066     describe_general(name, decimals)

File \\VBoxSvr\Modelica\GitHub\Colab\BPL_IEC_validation\BPL_IEC_fm.py:1353, in describe_general(name, decimals)
    1351 else:
    1352     description = model_get_variable_description(name)
-> 1353     value = model_get(name)
    1354     try:
    1355         unit = model_get_variable_unit(name)

File \\VBoxSvr\Modelica\GitHub\Colab\BPL_IEC_validation\BPL_IEC_fm.py:1113, in model_get(parLoc, model_description)
    1111     value = start_values[par_var[k].name]
    1112 elif par_var[k].variability in ['constant', 'fixed']:
-> 1113     value = float(par_var[k].start)
    1114 elif par_var[k].variability == 'continuous':
    1115     try:

TypeError: float() argument must be a string or a number, not 'NoneType'

```

In [14]: describe('V')

```

-----
TypeError                                Traceback (most recent call last)
Cell In [14], line 1
----> 1 describe('V')

File \\VBoxSvr\Modelica\GitHub\Colab\BPL_IEC_validation\BPL_IEC_fm.py:1066, in describe(name, decimals)
    1063     describe_MSL()
    1065 else:
-> 1066     describe_general(name, decimals)

File \\VBoxSvr\Modelica\GitHub\Colab\BPL_IEC_validation\BPL_IEC_fm.py:1338, in describe_general(name, decimals)
    1336 elif name in parLocation.keys():
    1337     description = model_get_variable_description(parLocation[name])
-> 1338     value = model_get(parLocation[name])
    1339     try:
    1340         unit = model_get_variable_unit(parLocation[name])

File \\VBoxSvr\Modelica\GitHub\Colab\BPL_IEC_validation\BPL_IEC_fm.py:1113, in model_get(parLoc, model_description)
    1111     value = start_values[par_var[k].name]
    1112 elif par_var[k].variability in ['constant', 'fixed']:
-> 1113     value = float(par_var[k].start)
    1114 elif par_var[k].variability == 'continuous':
    1115     try:

TypeError: float() argument must be a string or a number, not 'NoneType'

```

In [15]: `model_get('column.x_m')`

Out[15]: 0.3

In [16]: `model_get('column.V_m')`

```

-----
TypeError                                Traceback (most recent call last)
Cell In [16], line 1
----> 1 model_get('column.V_m')

File \\VBoxSvr\Modelica\GitHub\Colab\BPL_IEC_validation\BPL_IEC_fm.py:1113, in model_get(parLoc, model_description)
    1111     value = start_values[par_var[k].name]
    1112 elif par_var[k].variability in ['constant', 'fixed']:
-> 1113     value = float(par_var[k].start)
    1114 elif par_var[k].variability == 'continuous':
    1115     try:

TypeError: float() argument must be a string or a number, not 'NoneType'

```

In [17]: `describe('column.n')`

Number of sections of the column : 8.0 [None]

In [7]: `model_get('column.column_section[1].V_m')`

```

-----
TypeError                                Traceback (most recent call last)
Cell In [7], line 1
----> 1 model_get('column.column_section[1].V_m')

File \\VBoxSvr\Modelica\GitHub\Colab\BPL_IEC_validation\BPL_IEC_fm.py:1113, in model_get(parLoc, model_description)
    1111     value = start_values[par_var[k].name]
    1112 elif par_var[k].variability in ['constant', 'fixed']:
-> 1113     value = float(par_var[k].start)
    1114 elif par_var[k].variability == 'continuous':
    1115     try:

TypeError: float() argument must be a string or a number, not 'NoneType'

```

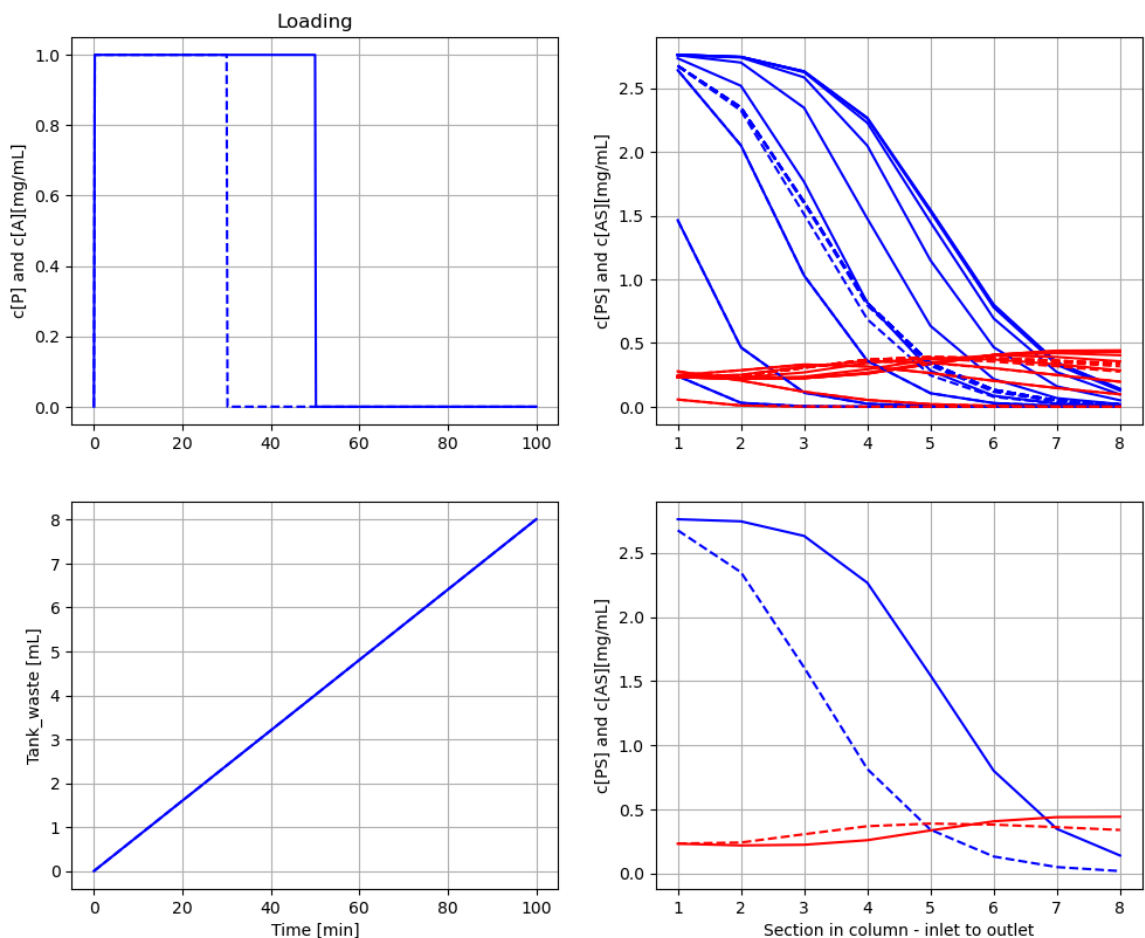
```

In [8]: # Impact of shorter time for loading and then less material
newplot(title='Loading', plotType='Loading-combined')
show()

# Simulation with changed parameter t2
par(stop_adsorption=30); simu(100)

# Reset changed parameter
par(stop_adsorption=50)

```



To the left the inlet loading over time. To the right upper concentration along the column at different times and in steady states finally To the right lower concentrations along the column in steady state.

We see that a shorter time and then less material makes less of the column capacity used.

Note that the flow through the column is constant despite change from sample to just buffer 1, and shown in how the volume of the waste tank increase with time.

Elution or desorption

```
In [9]: # Elution of the column
newplot(title='Elution peaks', plotType='Elution')

# Sample
par(P_in=1, A_in=1.0, E_in=0)

# Operation
par(E_in_desorption_buffer=8)
par(LFR=12.0, start_adsorption=0, stop_adsorption=50, start_desorption=150, stat

# Simulation
simu(550)
```

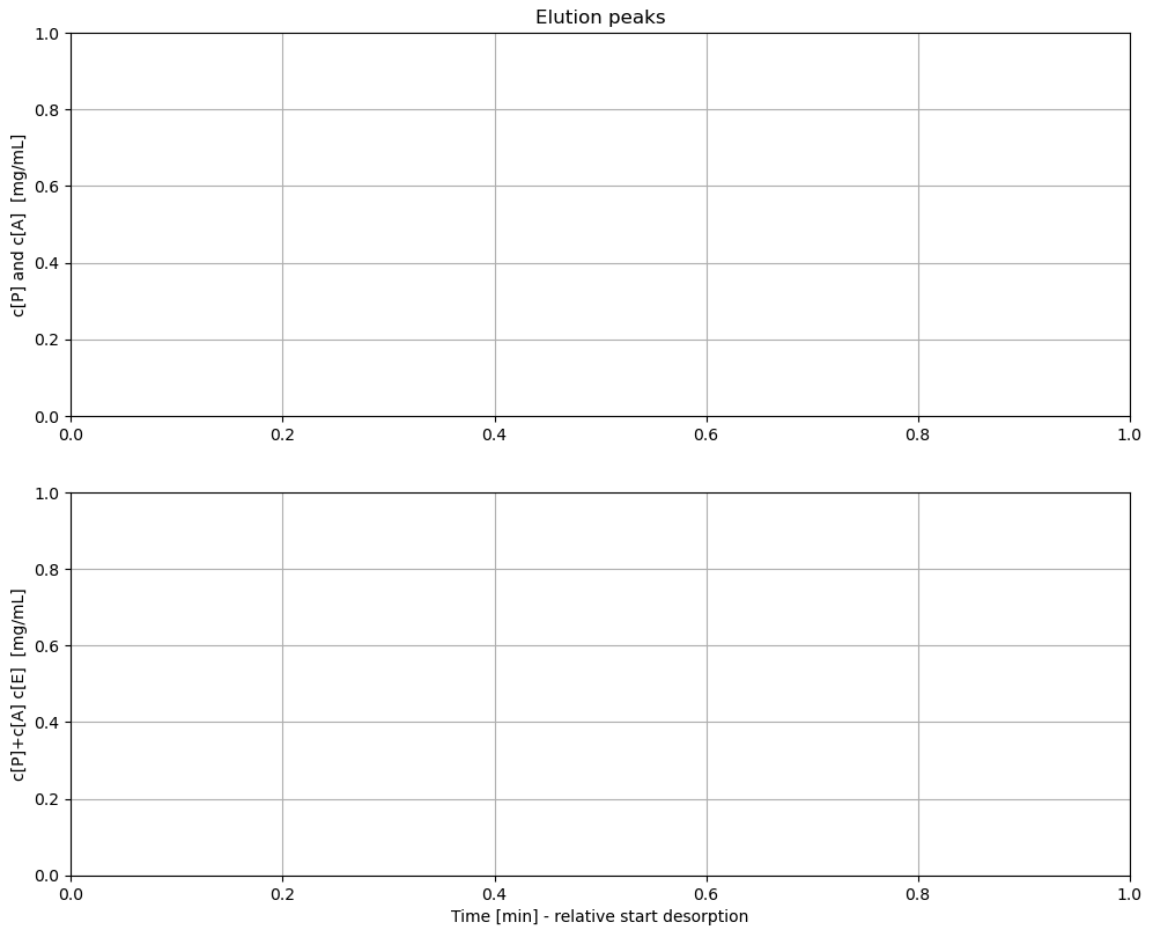
```
-----
TypeError                                Traceback (most recent call last)
Cell In [9], line 12
      9 par(LFR=12.0, start_adsorption=0, stop_adsorption=50, start_desorption=
150, stationary_desorption=450)
     11 # Simulation
--> 12 simu(550)

File \\VBoxSvr\Modelica\Github\Colab\BPL_IEC_validation\BPL_IEC_fm.py:1281, in simu(simulationTime, mode, options, diagrams)
    1277 if simulationDone:
    1278
    1279     # Plot diagrams from simulation
    1280     linetype = next(linecycler)
-> 1281     for command in diagrams: eval(command)
    1283     # Store final state values in stateDict:
    1284     for key in stateDict.keys(): stateDict[key] = model_get(key)

File <string>:1

File \\VBoxSvr\Modelica\Github\Colab\BPL_IEC_validation\BPL_IEC_fm.py:1113, in model_get(parLoc, model_description)
    1111     value = start_values[par_var[k].name]
    1112 elif par_var[k].variability in ['constant', 'fixed']:
-> 1113     value = float(par_var[k].start)
    1114 elif par_var[k].variability == 'continuous':
    1115     try:

TypeError: float() argument must be a string or a number, not 'NoneType'
```



The results are the same as Figure 14 in [1].

The upper diagram shows the column outlet concentrations of P and A over time.

The lower diagram shows the sum (or possibly the UV signal) at column outlet as well as the salt concentration. We have some separation between the two peaks.

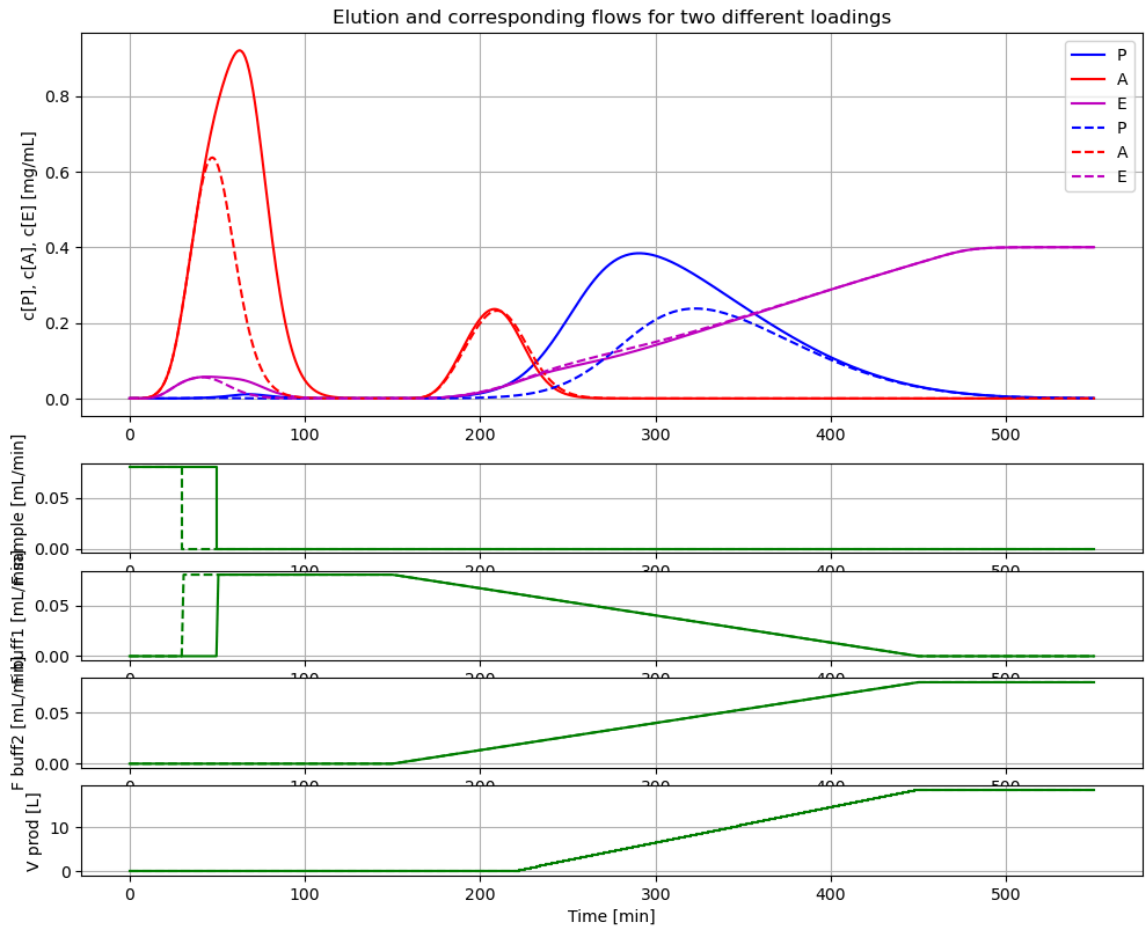
Note that the salt concentration deviates slightly from the linear increase between time 50 to 100. This is due to ion interaction with P and A in the column. This phenomenon can also be seen in real data. The ion-salt concentration is scaled with factor 0.05 to get comparable concentrations to P and A.

I have here simulated time 150 of adsorption and then started elution. Here is time counted as zero at time of start of elutions. Not sure how long Jonas simulated to get steady state before he did elution.

```
In [10]: # More complete visualization of the elution phase and the different flows
newplot(title='Elution and corresponding flows for two different loadings', plot
par(stop_adsorption=50); simu(550)

# Simulation with changed parameter t2
par(stop_adsorption=30); simu(550)

# Reset changed parameter
par(stop_adsorption=50)
```

Here a diagram that shows the peaks at the outlet as shown in the previous diagram. Below the flow rates of the three different sources. Here time is 0 at start of adsorption and elution starts at time 150.

Automatic pooling based on UV-measurement is tested in another notebook.

Change of resin properties

```
In [11]: # Elution of the column
newplot(title='Elution peaks for different resin parameters k1 and k2', plotType

# Sample
par(P_in=1, A_in=0.0, E_in=0)

# Operation
par(E_in_desorption_buffer=8)
par(LFR=12.0, start_adsorption=0, stop_adsorption=50, start_desorption=150, stat

# Simulations
par(k1=0.05, k2=0.50); simu(550)
par(k1=0.05, k2=0.25); simu(550)
par(k1=0.05, k2=0.05); simu(550)
par(k1=0.25, k2=0.05); simu(550)
par(k1=0.50, k2=0.05); simu(550)

# Adjust diagrams
ax1.set_ylim([0, 0.65])
```

```
ax2.set_ylim([0, 0.65])
plt.show()
```

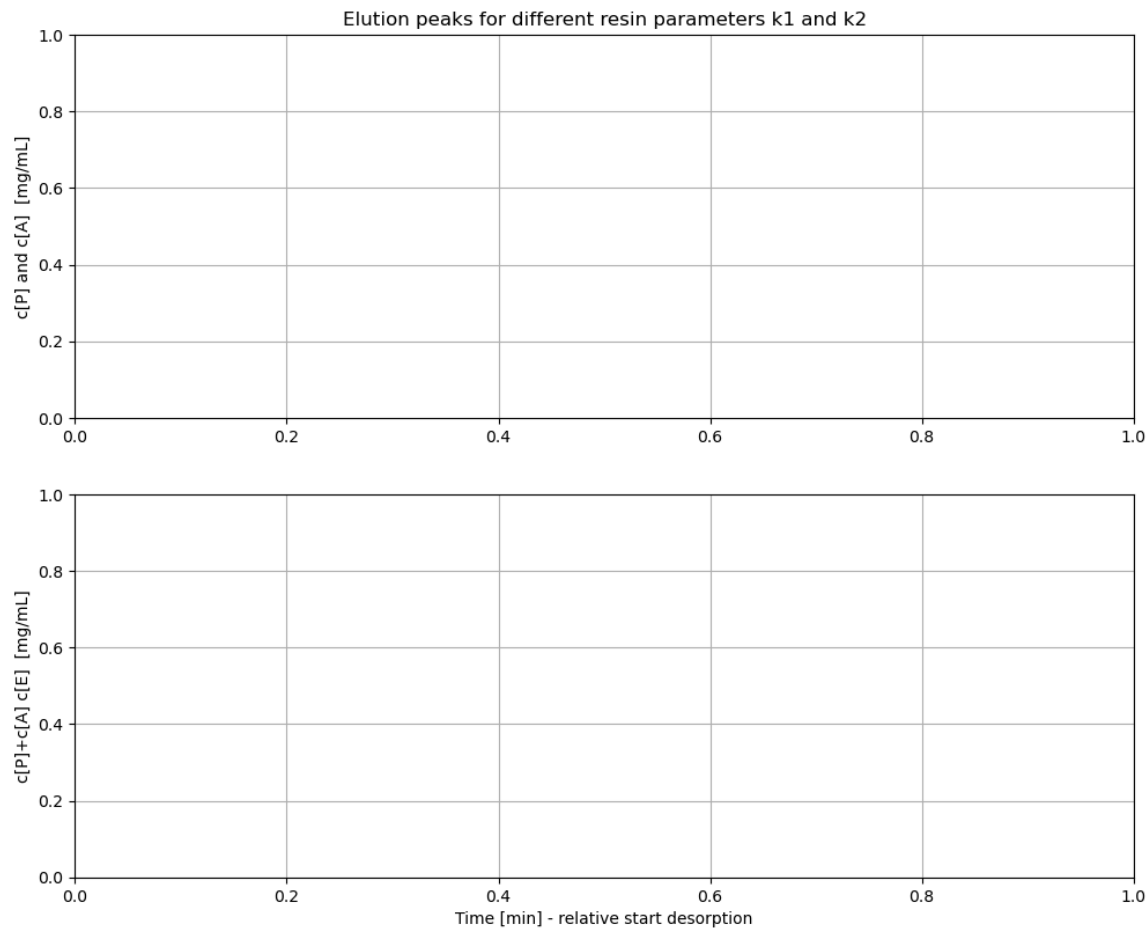
```
-----
TypeError                                Traceback (most recent call last)
Cell In [11], line 12
      9 par(LFR=12.0, start_adsorption=0, stop_adsorption=50, start_desorption=
150, stationary_desorption=450)
     11 # Simulations
--> 12 par(k1=0.05, k2=0.50); simu(550)
     13 par(k1=0.05, k2=0.25); simu(550)
     14 par(k1=0.05, k2=0.05); simu(550)

File \\VBoxSvr\Modelica\Github\Colab\BPL_IEC_validation\BPL_IEC_fm.py_explore.p
y:1281, in simu(simulationTime, mode, options, diagrams)
    1277 if simulationDone:
    1278
    1279     # Plot diagrams from simulation
    1280     linetype = next(linecycler)
-> 1281     for command in diagrams: eval(command)
    1283     # Store final state values in stateDict:
    1284     for key in stateDict.keys(): stateDict[key] = model_get(key)

File <string>:1

File \\VBoxSvr\Modelica\Github\Colab\BPL_IEC_validation\BPL_IEC_fm.py_explore.p
y:1113, in model_get(parLoc, model_description)
    1111     value = start_values[par_var[k].name]
    1112 elif par_var[k].variability in ['constant', 'fixed']:
-> 1113     value = float(par_var[k].start)
    1114 elif par_var[k].variability == 'continuous':
    1115     try:

TypeError: float() argument must be a string or a number, not 'NoneType'
```



The results are the same af Figure 17 in [1].

Summary

Three important diagrams Figure 13, 14 and 17 in the original report [1] were reproduced and the implementation in Modelica used here is considered validated.

The model is now extended with an improved parametrization of the column that match the industrial practice.

Acknowledgement

The author thank Karl Johan Brink for sharing his know-how of chromatography operation. He has especially given input to how to parametrize the model in terms often used in the industrial practice.

References

1. Månsson, Jonas, "Control of chromatography comlumn in production scale", Master thesis TFRT-5599, Department of Automatic Control, LTH, Lund Sweden, 1998.
2. Pharmacia LKB Biotechnology. "Ion Exchange chromatography. Principles and Methods.", 3rd edition, 1991.

3. Jungbauer, Alois and Giorgio Carta, "Protein Chromatography: Process Development and Scale-Up", Wiley 2nd edition, 2020.

Appendix

In [12]: `describe('MSL')`

MSL: RealInput, RealOutput, Constants, Hysteresis, CombiTimeTable, Types

In [13]: `system_info()`

System information
-OS: Windows
-Python: 3.9.16
-Scipy: not installed in the notebook
-FMPy: 0.3.15
-FMU by: JModelica.org
-FMI: 2.0
-Type: CS
-Name: BPL_IEC.Column_system
-Generated: 2024-03-08T09:56:46
-MSL: 3.2.2 build 3
-Description: Bioprocess Library version 2.1.2 prel
-Interaction: FMU-explore for FMPy version 0.9.9

In []: