⌄ BPL_IEC_operation script with PyFMI

The key library PyFMI is installed.

After the installation a small application BPL_IEC_operation is loaded and run. You can continue with this example if you like.

```
!lsb_release -a # Actual VM Ubuntu version used by Google
```

```
⊋  No LSB modules are available.
   Distributor ID: Ubuntu
   Description:    Ubuntu 22.04.4 LTS
   Release:        22.04
   Codename:       jammy
```

```
%env PYTHONPATH=
```

```
⊋  env: PYTHONPATH=
```

```
!python --version
```

```
⊋  Python 3.11.11
```

```
!wget https://repo.anaconda.com/miniconda/Miniconda3-py311_24.11.1-0-Linux-x86_64.sh
!chmod +x Miniconda3-py311_24.11.1-0-Linux-x86_64.sh
!bash ./Miniconda3-py311_24.11.1-0-Linux-x86_64.sh -b -f -p /usr/local
import sys
sys.path.append('/usr/local/lib/python3.11/site-packages/')
```

```
⊋  --2025-02-07 07:10:52--  https://repo.anaconda.com/miniconda/Miniconda3-py311_24.11.1-0-Linux-x86_64.sh
   Resolving repo.anaconda.com (repo.anaconda.com)... 104.16.32.241, 104.16.191.158, 2606:4700::6810:20f1, ...
   Connecting to repo.anaconda.com (repo.anaconda.com)|104.16.32.241|:443... connected.
   HTTP request sent, awaiting response... 200 OK
   Length: 145900576 (139M) [application/octet-stream]
   Saving to: 'Miniconda3-py311_24.11.1-0-Linux-x86_64.sh'

   Miniconda3-py311_24 100%[===================>] 139.14M   115MB/s    in 1.2s

   2025-02-07 07:10:54 (115 MB/s) - 'Miniconda3-py311_24.11.1-0-Linux-x86_64.sh' saved [145900576/145900576]

   PREFIX=/usr/local
   Unpacking payload ...

   Installing base environment...

   Preparing transaction: ...working... done
   Executing transaction: ...working... done
   installation finished.
```

```
!conda update -n base -c defaults conda --yes
```

```
⊋  Channels:
    - defaults
   Platform: linux-64
   Collecting package metadata (repodata.json): done
   Solving environment: done

   ## Package Plan ##

     environment location: /usr/local

     added / updated specs:
       - conda


   The following packages will be downloaded:

       package                    |            build
       ---------------------------|-----------------
       ca-certificates-2024.12.31 |       h06a4308_0         128 KB
       certifi-2025.1.31          |   py311h06a4308_0         163 KB
       ---------------------------------------------------------
                                              Total:         291 KB

   The following packages will be UPDATED:

     ca-certificates                     2024.11.26-h06a4308_0 --> 2024.12.31-h06a4308_0
     certifi                          2024.8.30-py311h06a4308_0 --> 2025.1.31-py311h06a4308_0


   Downloading and Extracting Packages:
```

```
        certifi-2025.1.31     | 163 KB     | :    0% 0/1 [00:00<?, ?it/s]
        ca-certificates-2024  | 128 KB     | :    0% 0/1 [00:00<?, ?it/s]
        certifi-2025.1.31     | 163 KB     | :   39% 0.3936048816230436/1 [00:00<00:00,  3.44it/s]
        ca-certificates-2024  | 128 KB     | :  100% 1.0/1 [00:00<00:00,  2.42it/s]


        Preparing transaction: done
        Verifying transaction: done
        Executing transaction: done
```

```
!conda --version
!python --version
```

```
→▼    conda 24.11.1
      Python 3.11.11
```

```
!conda config --set channel_priority strict
```

```
!conda install -c conda-forge pyfmi --yes # Install the key package
```

→▼

```
        Preparing transaction: done
        Verifying transaction: done
        Executing transaction: done
```

˅ Preparation of BPL_IEC_operation

Now specific installation and the run simulations. Start with connecting to Github. Then upload the two files:

- FMU - BPL_IEC_Column_system_linux_om_me

- Setup-file - BPL_IEC_explore

```bash
%%bash
git clone https://github.com/janpeter19/BPL_IEC_operation
```

```
⊋   Cloning into 'BPL_IEC_operation'...
```

```
%cd BPL_IEC_operation
```

```
⊋   /content/BPL_IEC_operation
```

∨ BPL_IEC_operation

Authors: Karl Johan Brink and Jan Peter Axelsson

In this notebook we show operation of a typical ion-exchange chromatography step. The impact of pH is also illustrated.

The model is based on the simplified model [1].

```
run -i BPL_IEC_explore.py
```

```
⊋   Linux - run FMU pre-compiled OpenModelica

    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()
```
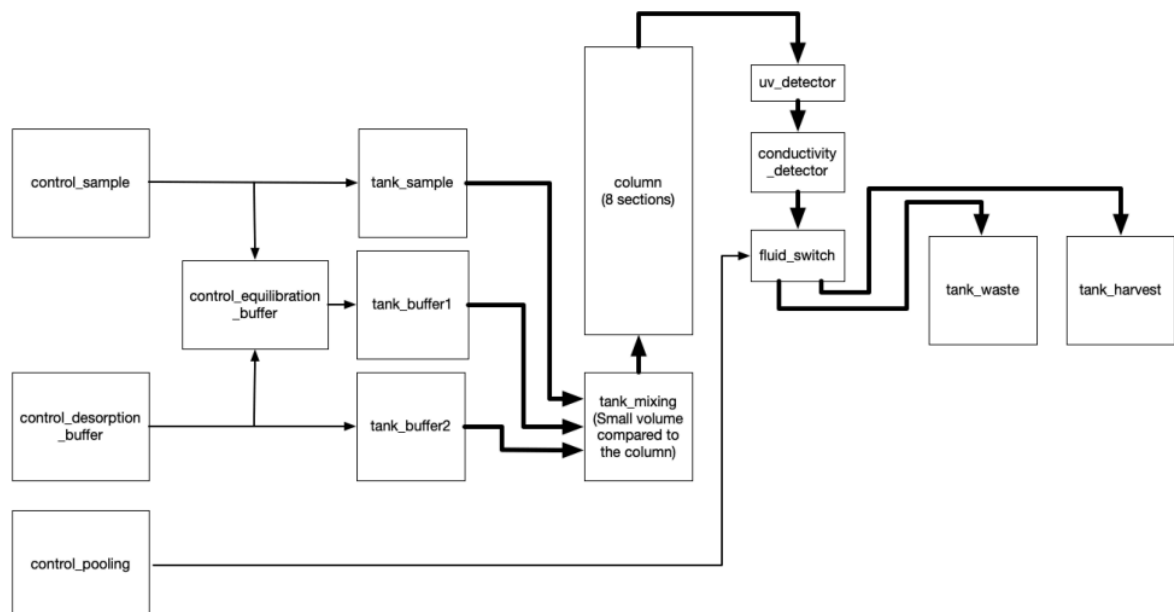
```
%matplotlib inline
plt.rcParams['figure.figsize'] = [36/2.54, 30/2.54]
```

```
# The process diagram is made outside Modelica for illustration of the configuration
process_diagram()
```

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


∨ 1 Typical parameters for a pilot scale ion exchange chromatography column process setup

```
# From  given colunn height (h) diameter (d) and linear flow rate (lfr)
# actual column volume (V) and volume flow rate (VFR) are calculated below.

from numpy import pi
h = 20.0
d = 1.261
a = pi*(d/2)**2
V = h*a
print('V =', np.round(V,1), '[mL]')

lfr = 48
VFR = a*lfr/60
print('VFR =', np.round(VFR,1), '[mL/min]')                          # Pump schedule parameter
```

```
 ⇄  V = 25.0 [mL]
    VFR = 1.0 [mL/min]
```

```
# Sample concentration product P_in and antagonist A_in
par(P_in = 1.0)
par(A_in = 1.0)
par(E_in = 0.0)

# Column properties are described by the size and binding capacity of the resin Q_av
par(height = h)
par(diameter = d)
par(Q_av = 6.0)

# Remaining salt koncentration in the column from prvious batch and eliminated during the initial equilibration period
init(E_start = 50)

# Salt koncentration of the desorption buffer
par(E_in_desorption_buffer = 8.0)

# Flow rate rate through the
par(LFR=lfr)

# Switching points during operation are conveniently described in terms of multiples of the column volume V
CV_ekv = 1.0
CV_ads = 0.5
CV_wash = 1.0
CV_desorb = 3.0
CV_start_pool = 1.2
CV_stop_pool = 4.5
CV_ekv2 = 2.5
par(scale_volume=True, start_adsorption=CV_ekv*V, stop_adsorption=(CV_ekv+CV_ads)*V)
par(start_desorption=(CV_ekv+CV_ads+CV_wash)*V, stationary_desorption=(CV_ekv+CV_ads+CV_wash+CV_desorb)*V)
par(stop_desorption=7.5*V)
par(start_pooling=(CV_ekv+CV_ads+CV_wash+CV_start_pool)*V, stop_pooling=(CV_ekv+CV_ads+CV_wash+CV_stop_pool)*V)

# Simulation and plot of results
newplot(title='Illustration of operation of the chromatgraphy step', plotType='Elution-conductivity-vs-CV-combined-all')
simu((CV_ekv+CV_ads+CV_wash+CV_desorb+CV_ekv2)*V/VFR)
```

```
Could not find cannot import name 'dopri5' from 'assimulo.lib' (/usr/local/lib/python3.11/site-packages/assimulo/lib/__i
Could not find cannot import name 'rodas' from 'assimulo.lib' (/usr/local/lib/python3.11/site-packages/assimulo/lib/__in
Could not find cannot import name 'odassl' from 'assimulo.lib' (/usr/local/lib/python3.11/site-packages/assimulo/lib/__i
Could not find ODEPACK functions.
Could not find RADAR5
Could not find GLIMDA.
```

Illustration of operation of the chromatgraphy step
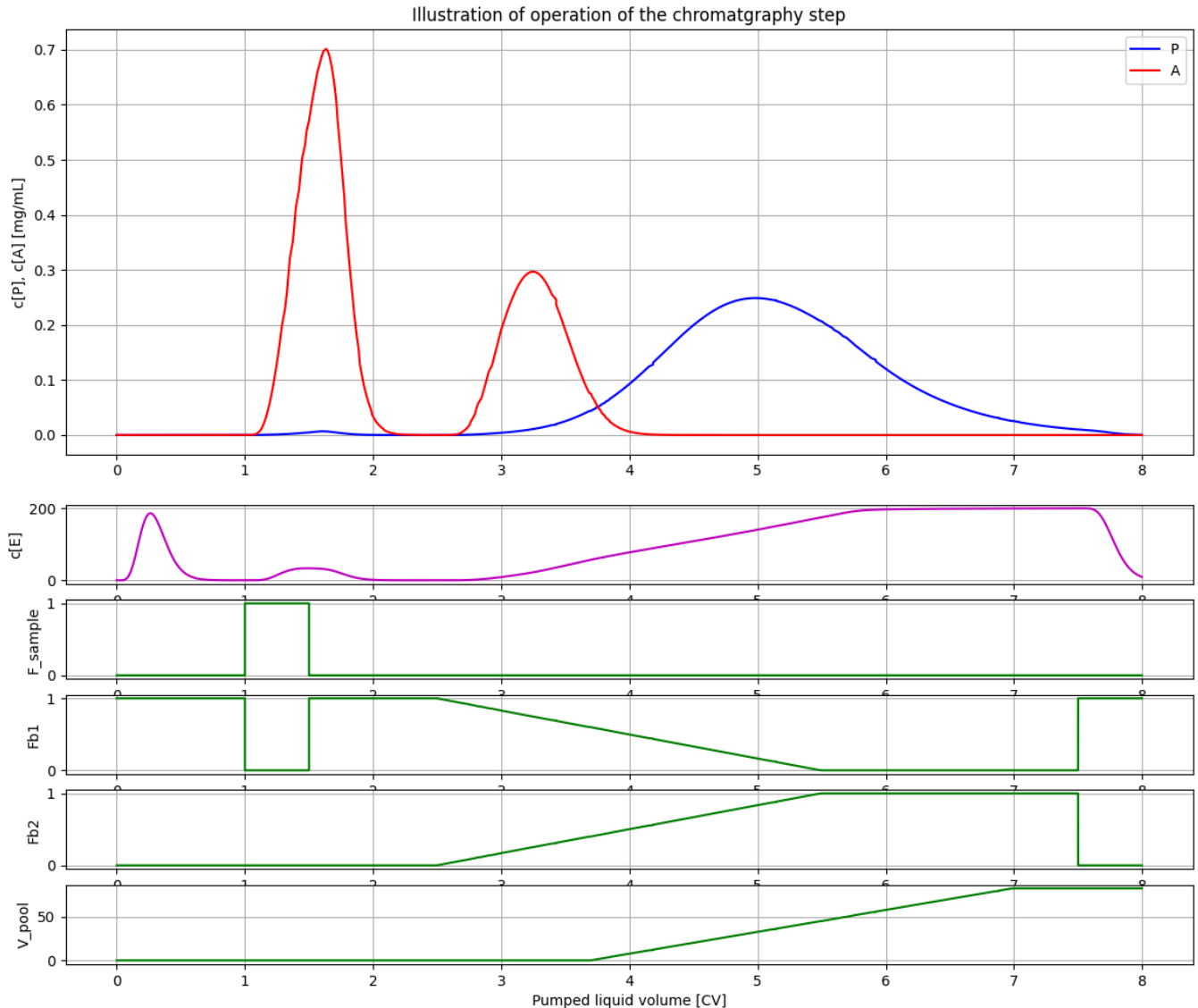
Comments of steps of operations:

1) Time: 0-1 hours - equilibration. Just to illustrate the equilibration process the first part of the column is given an initial value of salt concentration.

2) Time: 1-1.5 hours - sample is loaded on the column. The product P is adsorbed to the columne and just a small amount passes through and goes to the waste. The antagonist A is much less adsrobed.

3) Time: 1.5-2.5 hours - washing 1. The column comes to equilibrium and both antagonist and product comes down to low levels.

4) Time: 2.5-5.5 hours - desorption. A linear gradient of increaseing salt concentration is applied. First the antagonist and later the product comes out.

5) Time: 5.5-7.5 hours - washing 2 The The column has constant salt concentration and stationary desorption.

6) Time: 3.7-7.0 hours - pooling of product. The start- and stop of pooling are chosen with trade-off between maximizing the product pooled and minimize the amount of antagonist in the pooling.

7) Time: 7.5-8.0 hours - desorption stopped and salt is washed out and preparation of the next batch to come.

Note that step 4 and 5 is parallel to step 6.

```
# Check mass-balance of P and A
P_mass = model.get('tank_harvest.m[1]') + model.get('tank_waste.m[1]')
A_mass = model.get('tank_harvest.m[2]') + model.get('tank_waste.m[2]')
print('P_mass [mg] =', P_mass)
print('A_mass [mg] =', A_mass)
```

```
⮕   P_mass [mg] = [12.42212163]
    A_mass [mg] = [12.48878113]
```

These values should be compared with the expected value 12.5 mg, i.e. half a column volume with sample concentration 1 mg/L. The difference is due to numerical errors during simulation.

⌄ 2 The impact of the slope of the desorption gradient

```
# Simulations showing the impact of change of slope of the desorption gradient
newplot(title='Impact of the slope of the gradient', plotType='Elution-conductivity-vs-CV-combined-all')

# Same gradienet as before
par(start_desorption=(CV_ekv+CV_ads+CV_wash)*V, stationary_desorption=(CV_ekv+ CV_ads+CV_wash+CV_desorb)*V)
par(stop_desorption=7.5*V)
simu((CV_ekv+CV_ads+CV_wash+CV_desorb+CV_ekv2)*V/VFR)

# Gradeint finishes after 0.5 of the volume
par(stationary_desorption = (CV_ekv + CV_ads + CV_wash + 0.5*CV_desorb)*V )
simu((CV_ekv+CV_ads+CV_wash+CV_desorb+CV_ekv2)*V/VFR)

# Fradient finishes after 0.25 of the volume
par(stationary_desorption = (CV_ekv + CV_ads + CV_wash + 0.25*CV_desorb)*V )
simu((CV_ekv+CV_ads+CV_wash+CV_desorb+CV_ekv2)*V/VFR)
```
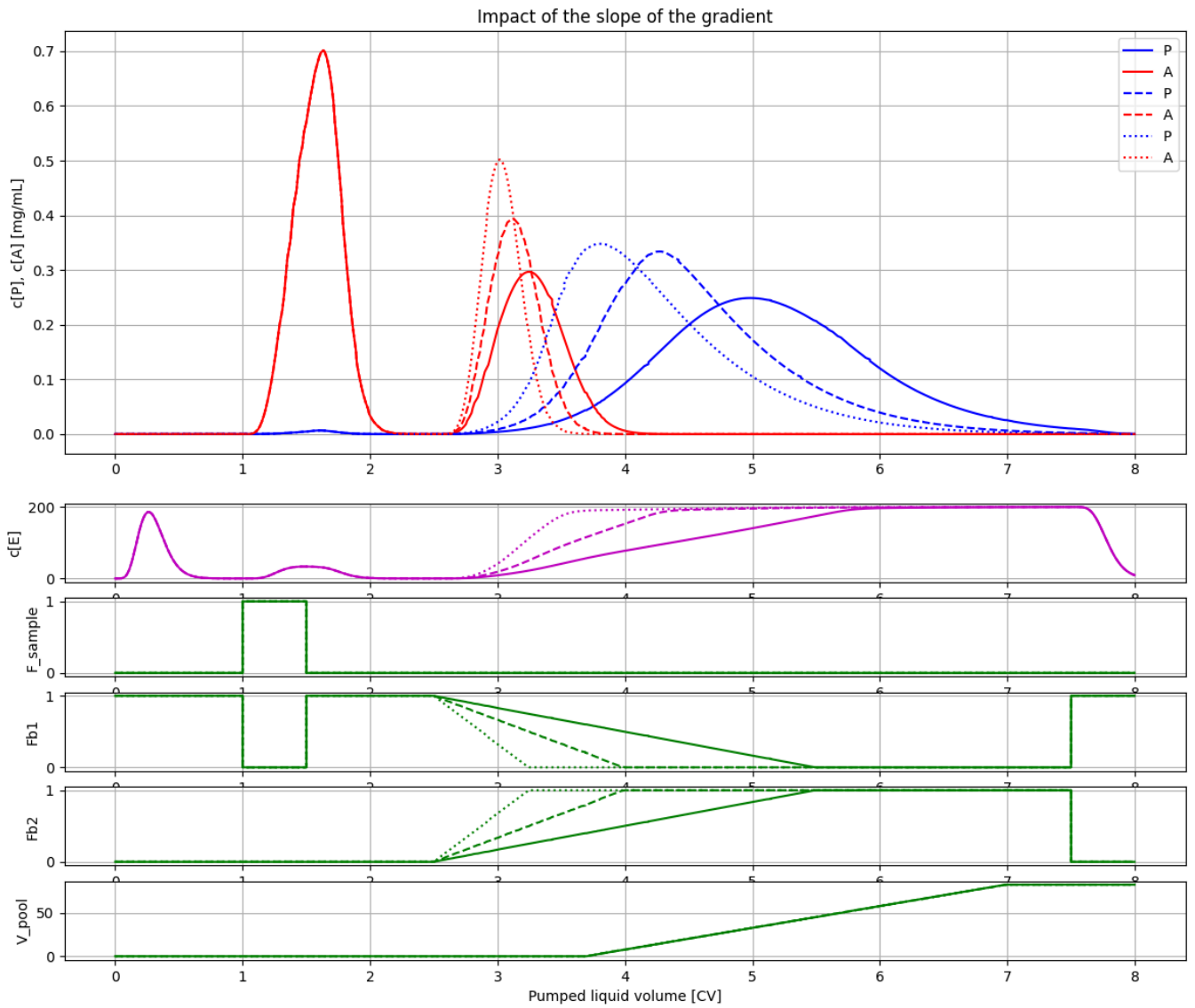
Note the pens shift style for each simulation in the order: solid, dashed, dotted, dash-dotted. The actual simulations done you see in the preceeding cell.
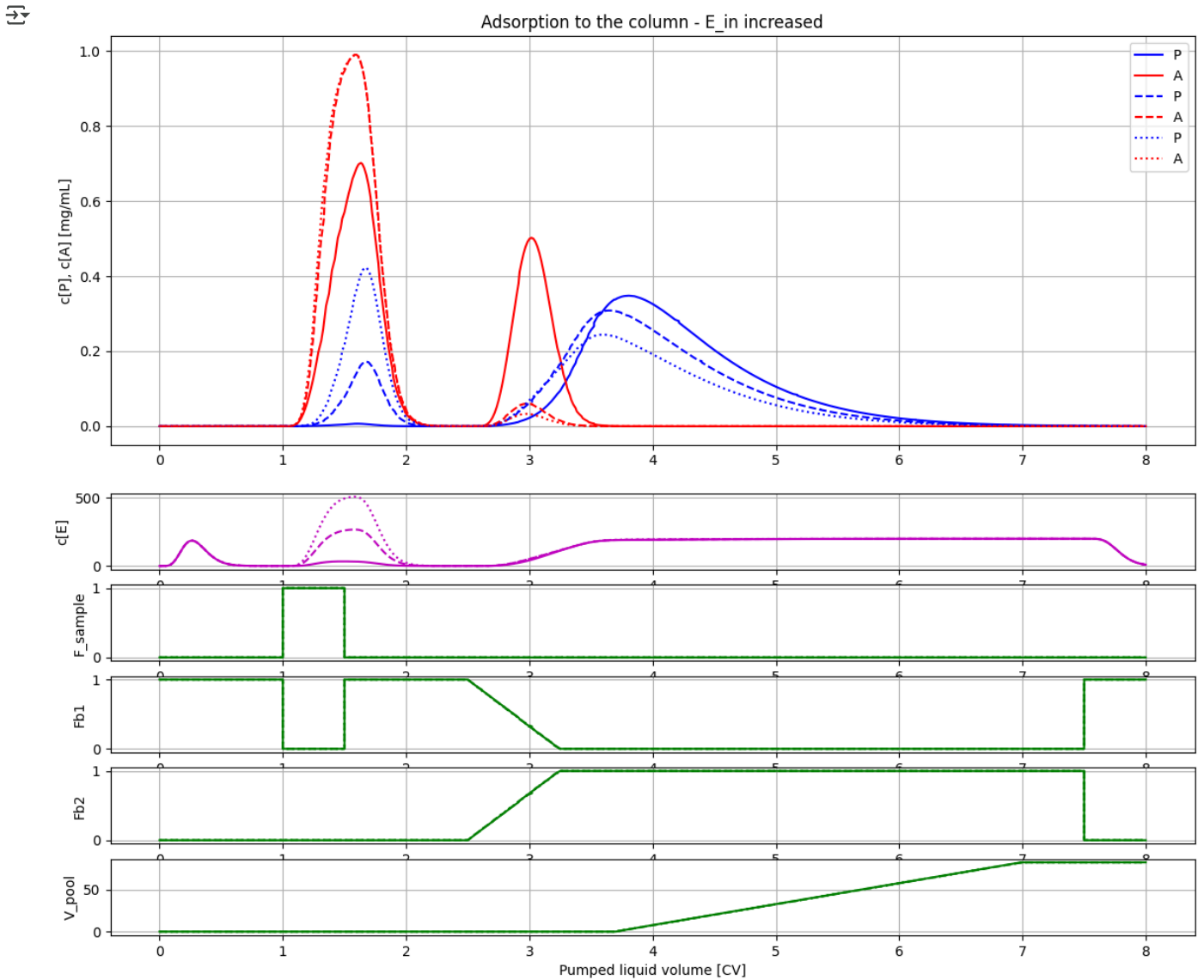
⌄ 3 The impact of salt concentration in the sample

```
# Let us investigate the impact of increasing salt concetration in the sample E_in

# Simulate and plot the results
newplot(title='Adsorption to the column – E_in increased', plotType='Elution-conductivity-vs-CV-combined-all')

for value in [0, 10, 20]:
    par(E_in=value)
    simu((CV_ekv+CV_ads+CV_wash+CV_desorb+CV_ekv2)*V/VFR)

# Restore default values
par(k2=0.05, k4=0.3, E_in=0)
```

Note, that increased salt concentration in the sample affect binding of both proteins. During adsorption less is bound. During desoprtion less product P can be harvested but the fraction of antagonist A may be lowered. Thus, some product is lost but the quality in terms of purity is improved.

4 The impact of change of binding strength due to pH

There are many factors that contribute to the binding strength. A most important factor is the pH-value of the resin and the characteristic iso-electric point of the protein. The binding strenght can be seen as proportional to the difference.

The binding strength of the resin is described by the quotient $KP=k1/k2$ for the protein P and similarly $KA=k3/k4$ for the protein A.

Below a few help-functions that describe this idea of the pH difference and its impact on binding strength in terms of the parameters k1, k2, k3, and k4 of the protein-resin interaction.

```
# Define function that describe the proportionality of binding strength ot
# the pH difference of the iso-electric point and the resin

def KP_pH_sensitivity(pI_P=8.0, pH_resin=7.0):
    coeff_pH = 6.0
    return coeff_pH*(pI_P-pH_resin)

def KA_pH_sensitivity(pI_A=7.1667, pH_resin=7.0):
    coeff_pH = 1.0
    return coeff_pH*(pI_A-pH_resin)
```

```python
def par_pH(pI_P=8.0, pI_A=7.1667, pH_resin=7.0, TP=3.33, TA=20.0):
    if (pI_P > pH_resin) & (pI_A > pH_resin):
        par(k2 = 1/(TP*KP_pH_sensitivity(pI_P=pI_P, pH_resin=pH_resin)))
        par(k4 = 1/(TA*KA_pH_sensitivity(pI_A=pI_A, pH_resin=pH_resin)))
    else:
        print('Both pI_P > pH_resin and pI_A > pH_resin must hold – no parameter change made')


# The default parameters of the column
disp('column')
```

```
diameter : 1.261
height : 20.0
x_m : 0.3
k1 : 0.3
k2 : 0.05
k3 : 0.05
k4 : 0.3
Q_av : 6.0
E_start : 50.0
```
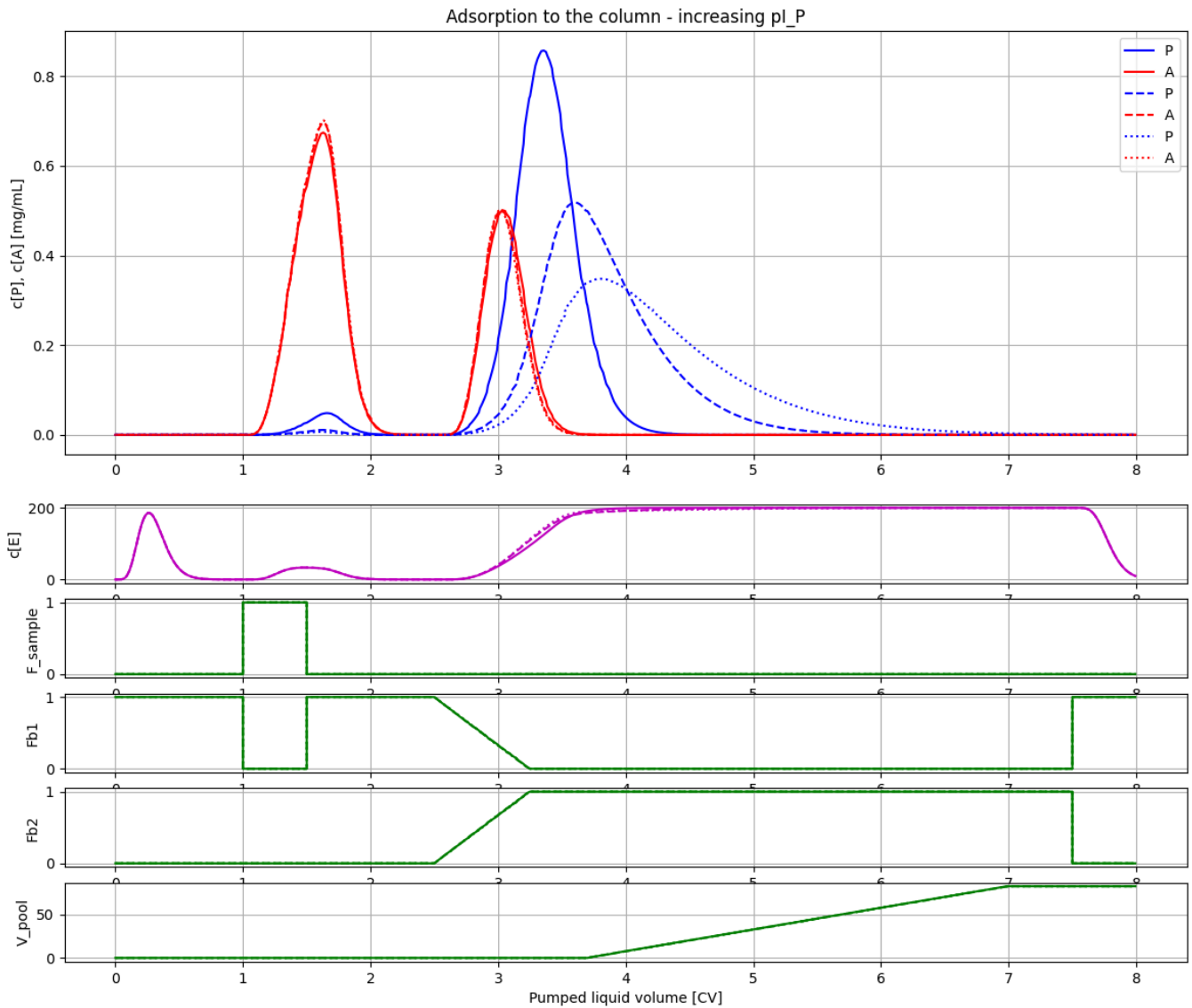
```python
# Let us investigate the impact of change of the iso-electric pH for protein P

# Simulate and plot the results
newplot(title='Adsorption to the column – increasing pI_P', plotType='Elution-conductivity-vs-CV-combined-all')

for value in [7.2, 7.6, 8.0]:
    par_pH(pI_P=value, pI_A=7.1667, pH_resin=7.0)
    simu((CV_ekv+CV_ads+CV_wash+CV_desorb+CV_ekv2)*V/VFR)

# Restore default values
par(k2 = 0.05, k4 = 0.3)
```

Note, with increasing pI_P the binding of P increase which leads less loss of product during adsorption. During desorption the peak height is lower with increasing binding strenght, but the total amoiunt of product P that can be harvested is higher, due to the smaller loss during adsorption.

```
# Let us investigate the impact of pI_P close to pH_resin

# Simulate and plot the results
newplot(title='Adsorption to the column - pI_P close to pH_resin', plotType='Elution-conductivity-vs-CV-combined-all')

for value in [7.0001]:
    par_pH(pI_P=value, pI_A=8)
    simu((CV_ekv+CV_ads+CV_wash+CV_desorb+CV_ekv2)*V/VFR)

# Restore default values
par(k2=0.05, k4=0.3)
```
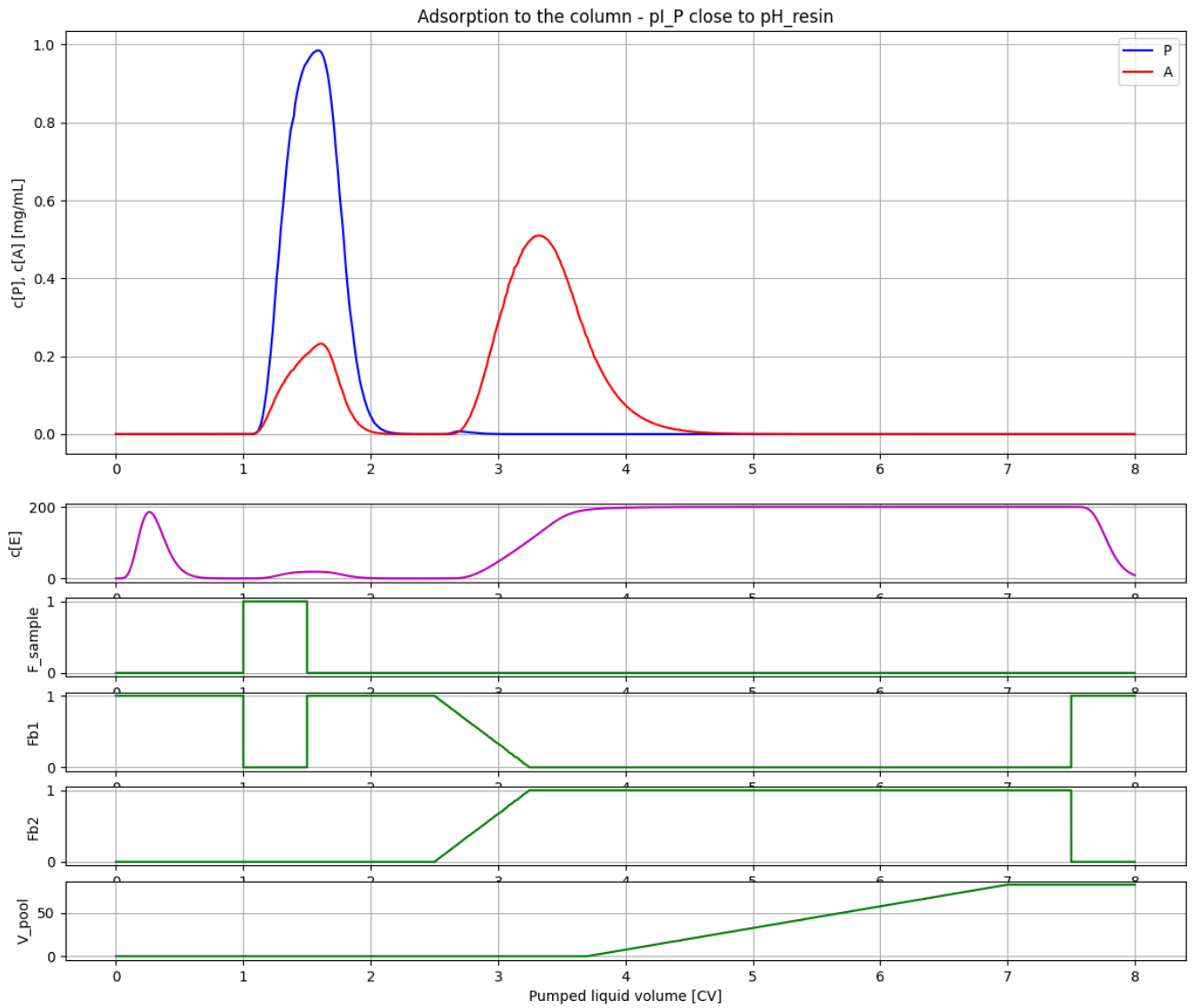
Adsorption to the column - pI_P close to pH_resin

Let us investigate the impact of pI_A close to pH_resin

# Simulate and plot the results
newplot(title='Adsorption to the column – pI_A close to pH_resin', plotType='Elution–conductivity–vs–CV–combined–all')
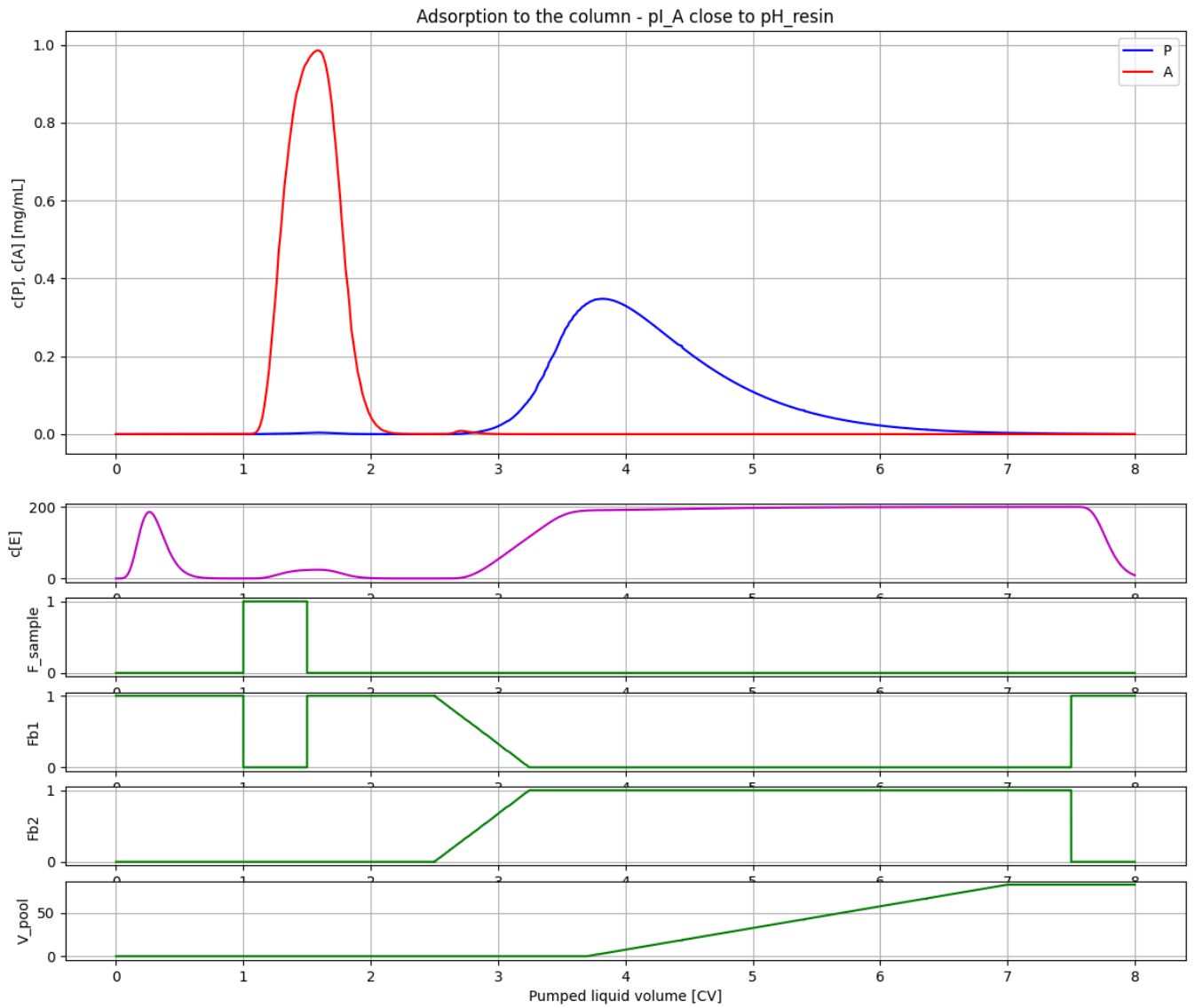
for value in [7.001]:
    par_pH(pI_P=8.0, pI_A=value)
    simu((CV_ekv+CV_ads+CV_wash+CV_desorb+CV_ekv2)*V/VFR)

# Restore default values
par(k2=0.05, k4=0.3)

Adsorption to the column - pI_A close to pH_resin

```
# Let us also investigate the impact of salt concentration of the desorptions buffer

# Simulate and plot the results
newplot(title='Adsorption to the column – desorption buffer salt conc varied', plotType='Elution-conductivity-vs-CV-combined

for value in [8.0, 16.0]:
    par(E_in_desorption_buffer=value)
    par_pH(pI_P=8.0, pI_A=7.001, pH_resin=7.0)
    simu((CV_ekv+CV_ads+CV_wash+CV_desorb+CV_ekv2)*V/VFR)

# Restore default values
par(E_in_desorption_buffer=8.0)
par(k2=0.05, k4=0.3)
```

Adsorption to the column - desorption buffer salt conc varied