Design aspects of Bioprocess Library® *for* Modelica

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Note, “Bioprocess Library” is a registered trademark.

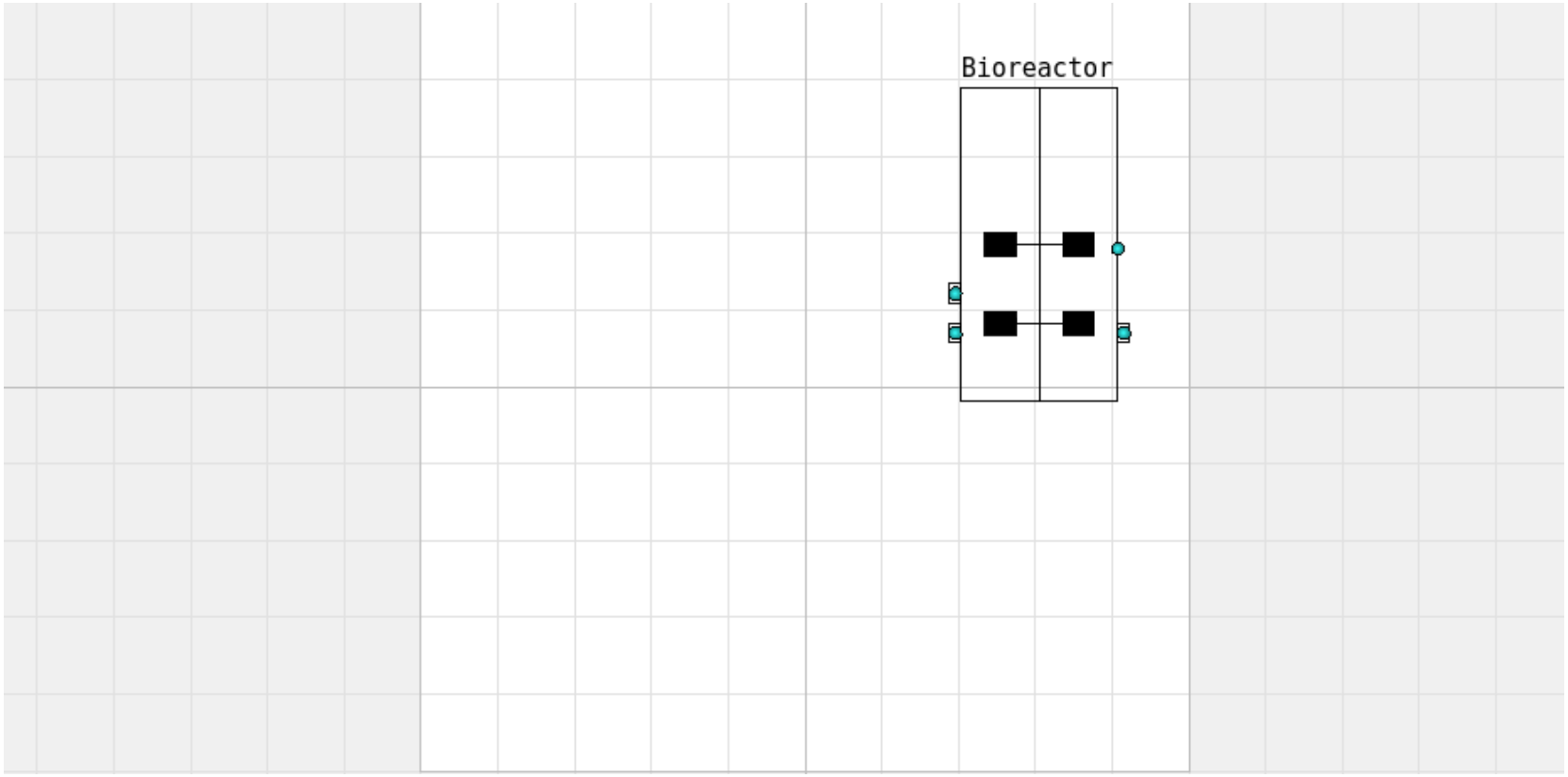
Outline

- Scope
- Structure Library /Application – flexibility needed
- Key is parametrization of the library
  - Media packages
  - Reactor model – part library part application
- Jupyter notebook – Python3, PyFMI, FMU
  - Command line interaction!
- Conclusion

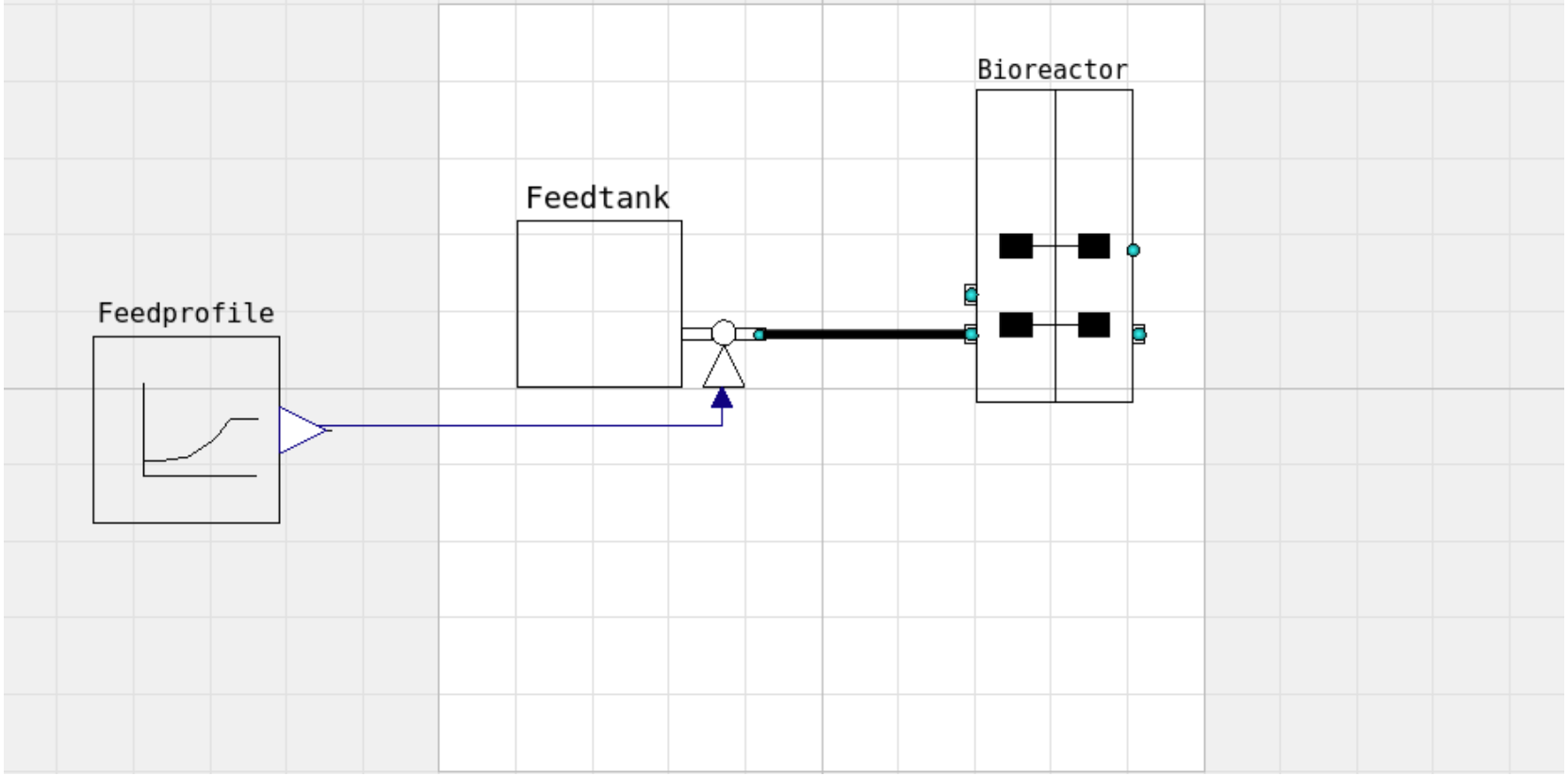
Scope

- Quicker to setup first model – key as consultant
- Document model with focus on the customer
  - Play down standard components
- Clarity of code!
- Useful also in teaching context for biotech-people
- Teach myself Modelica…. ☺

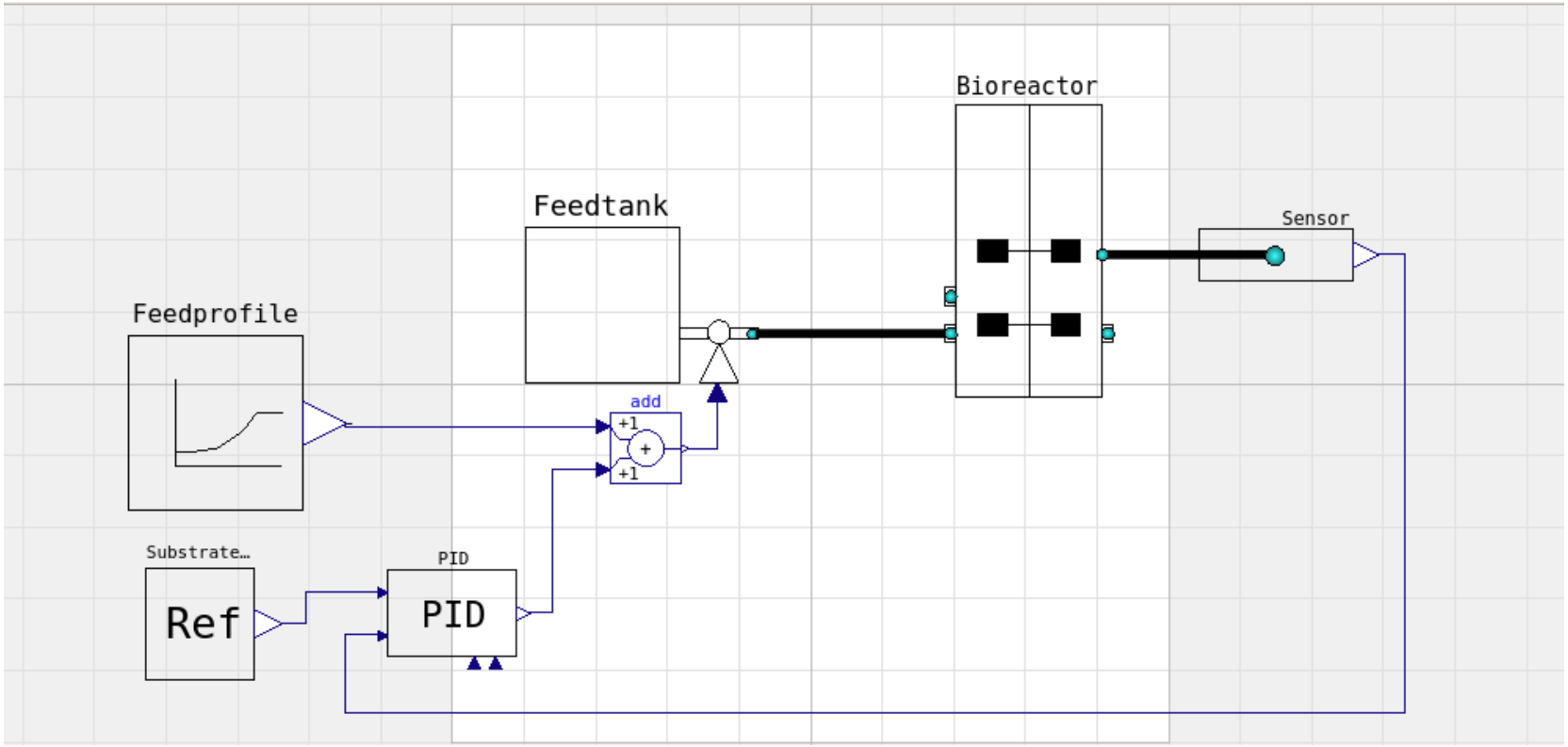
Example: Batch cultivation



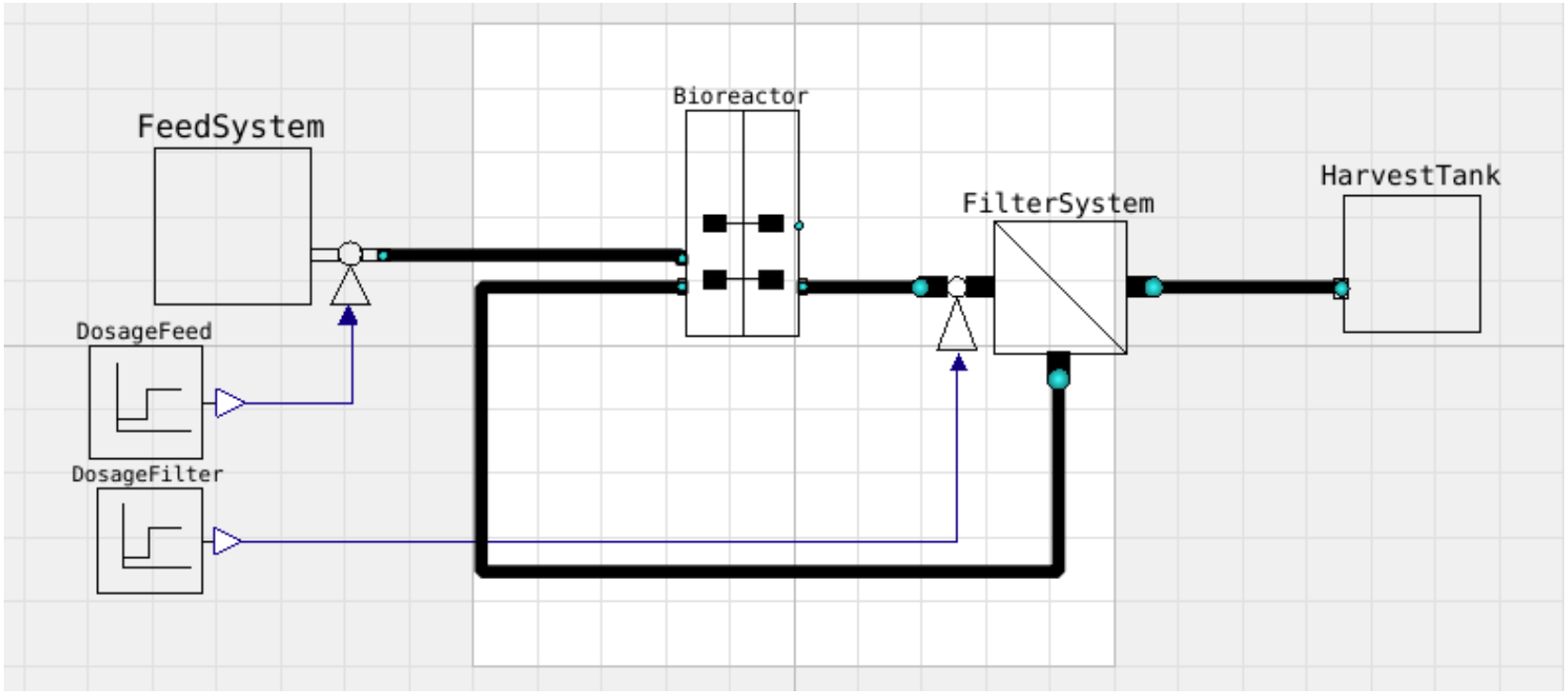
Example: Fedbatch cultivation Fixed feedrate profile



Example: Fedbatch cultivation Feedprofile with on-line control



Example: Perfusion cultivation



Flexibility needed

- Process configuration may vary
  - Batch, Fedbatch, Continous, Perfusion, … (up-stream)
  - Scale-down
  - Later include down-stream processing
- Process control
  - Substrate levels, Dissolved oxygen, pH, temperature…
  - Feeding strategies…
  - Optimization
- Cells cultivated
  - Yeast, Ecoli, CHO…. Hosts for recombinant proteins
  - Liquid- and gas-phase varies

Object orientation... - connectors

- Liquid pipes - LiquidCon
- Gas pipes - GasCon
- Electrical signals - MSL RealInput, RealOutput etc
- Provide flexibility
  - Re-configuration of process setup
  - Change of control systems

- Provide flexibility for different cultures, liquids…?
  - Parametrize EquipmentLib with Application def parts!

Structure of code

Application

Library

- Liquid-, gas-phases
- EquipmentLib
  - Tank
  - Pump
  - Reactor
  - Sensor
  - …
- ControlLib

Structure of code

Application

- LiquidphaseYeast
- GasphaseYeast

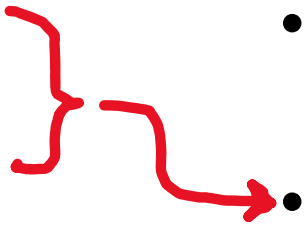
Library

- Liquid-, gas- phases, signals
- EquipmentLib
  - Tank
  - Pump
  - Reactor
  - Sensor
  - …
- ControlLib

Structure of code

Application

- LiquidphaseYeast
- GasphaseYeast



Library

- Liquid-, gas- phases, signals
- EquipmentLib
  - Tank
  - Pump
  - Reactor
  - Sensor
  - …
- ControlLib

Structure of code

Application

- LiquidphaseYeast
- GasphaseYeast

- CultureYeast model
- BufferYeast model
- GasLiquidTransferYeast

Library

- Liquid-, gas- phases, signals
- EquipmentLib
  - Tank
  - Pump
  - Reactor
  - Sensor
  - …
- ControlLib

Structure of code

Application

- LiquidphaseYeast
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Library

- Liquid-, gas- phases, signals
- EquipmentLib
  - Tank
  - Pump
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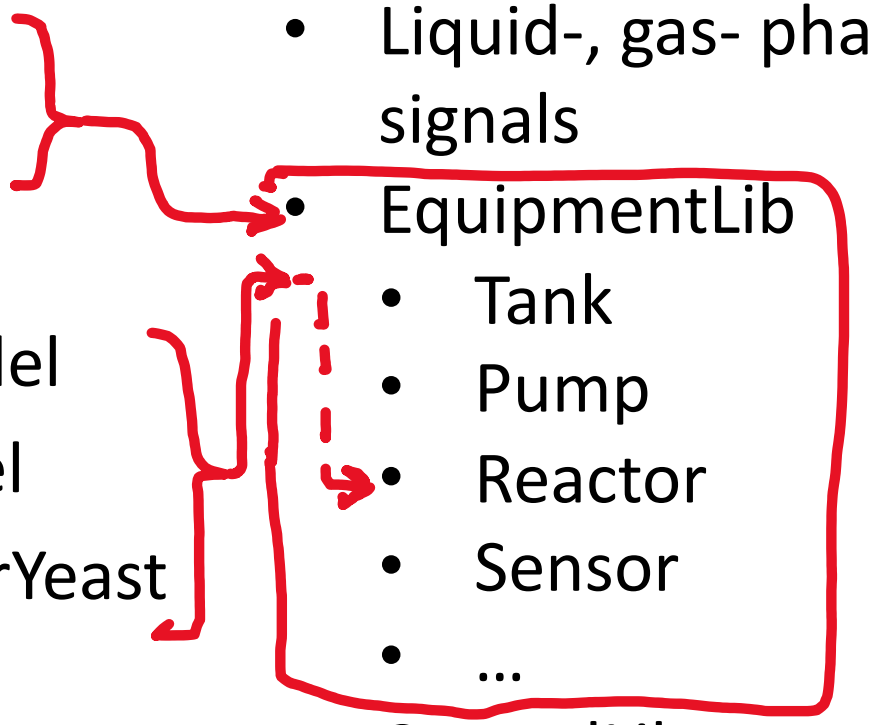
  - Sensor
  - …
- ControlLib



Try to improve…

rently Dymola 7.2 [2] and SimulationX 3.2 [8] support stream connectors. Other tool vendors already announced to support the concept, too.

The streams concept is a big step forward for fluid modeling in Modelica. However, stream connectors are not yet the ultimate solution for fluid modeling because there are still missing features:

- The used medium has currently to be defined for every component. It would be nicer if the medium was defined at one source and the medium definition would then be propagated through the connection structure.
- When components are connected together, the connection semantics ensures that the mass and the energy balance are fulfilled exactly (in the sense of "ideal" mixing). The momentum bal-

Ref Franke et al 2009 "Stream connectors – an extension of Modelica for device-oriented modeling of convective transport phenomena", Proc 7th Modelica, Italy.

Application…
- Yeast in airated reactor

Work from “templates” partial packages, models…

Extend partial package LiquidphaseBase -> LiquidphaseYeast
Extend partial package GasphaseBase -> GasphaseYeast
(Define number of components, provide index etc)

Extend partial model ReactorInterface -> CultureYeast model
Extend partial model ReactorInterface -> GasLiquidTransfer
(Define mappings concentration to flows: c[i] -> q[i] - static or dynamical systems)

Structure: Application - Library

encapsulated package BPL_YEAST_AIR

package LiquidphaseYeast

package GasphaseYeast

model CultureYeast

model GasLiquidTransferYeast

package EquipmentYeast

import BPL.EquipmentLib

…. extend, **redeclare**

model Fedbatch

… configure with **redeclared BPL components**

end BPL_YEAST_AIR;

Application: package Equipment - formal parameters

```
package EquipmentYeast
    import BPL.EquipmentLib;
    extends EquipmentLib(
        redeclare package Liquidphase = LiquidphaseYeast,
        redeclare package Gasphase = GasphaseYeast,
        redeclare model Culture = CultureYeast(
            redeclare package Liquidphase=LiquidphaseYeast),
        redeclare model GasLiquidTransfer=GasLiquidTransferYeast(
            redeclare package Liquidphase=LiquidphaseYeast,
            redeclare packate Gasphase=GasYeast),
        redeclare model Buffer = NoBuffer(
             redeclare package Liquidphase=LiquidphaseYeast));
end EquipmentYeast;
```

Library – formal parameter

```
package BPL
   …
   package EquipmentLib
        replaceable package Liquidphase=LiquidphaseBase
              constrainedby LiquidphaseBase;
        replaceable package Gasphase=GasphaseBase
             constrainedby GasphaseBase;
        replaceable model Culture = NoCulture
             constrainedby ReactorInterface;
         …
    package ControlLib…
end BPL;
```

Liquidphase - ”template”

```
partial package LiquidphaseBase
    constant String name;
    constant Integer nc;
    type Concentration = Real[nc];
end LiquidphaseBase;
```

cont’ Liquidphase

```
package LiquidphaseYeast
    import BPL.LiquidphaseBase;
    extends LiquidphaseBase
        (name=“Yeast medium…”, nc=3);
    constant Integer X=1;
    constant Integer G=2;
    constant Integer E=3;
    constant Real[nc] mw = {24.6, 180.0, 46.0};
 end LiquidphaseYeast;
```

cont’ Liquidphase

Record LiquidphaseYeast_data

    constant String name = **LiquidphaseYeast**.name;

    constant Integer nc = LiquidphaseYeast.nc;

    constant Integer X = LiquidphaseYeast.X;

    …

    constant Real[nc] mw = LiquidphaseYeast.mw

End LiquidphaseYeast_data;

--

Repetious but seems to be needed

Connector LiquidCon - ”template”

```
package EquipmentLib
  replaceable package Liquidphase = LiquidphaseBase
    constrainedby LiquidphaseBase;
  connector LiquidCon
    stream Liquidphase.Concentration c;
    flow Real F;
    Real p;
  end LiquidCon;
  model Pump, Tank, Reactor, Sensor etc
```

BPL ReactorType

General reactor with

- n_inlets, n_outlets, n_ports

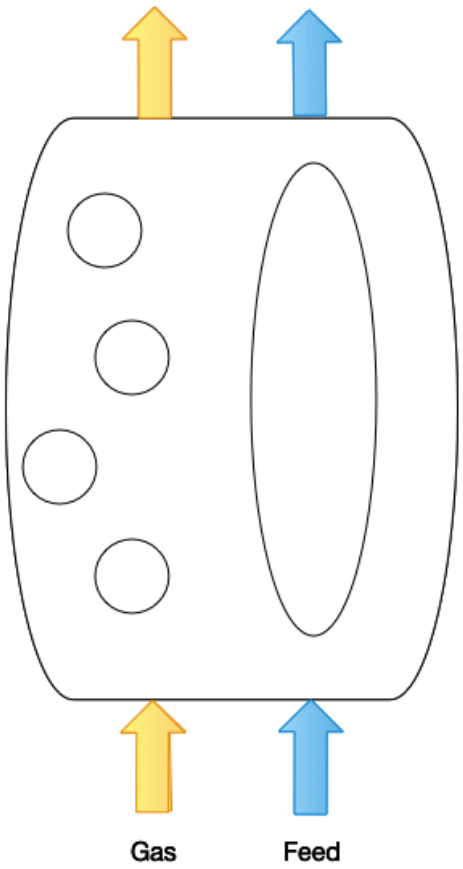
- connector LiquidCon – common for EquipmentLib
- connector GasCon – common for EquipmentLib

- model Culture
- model GasLiquidTransfer
- model Buffer

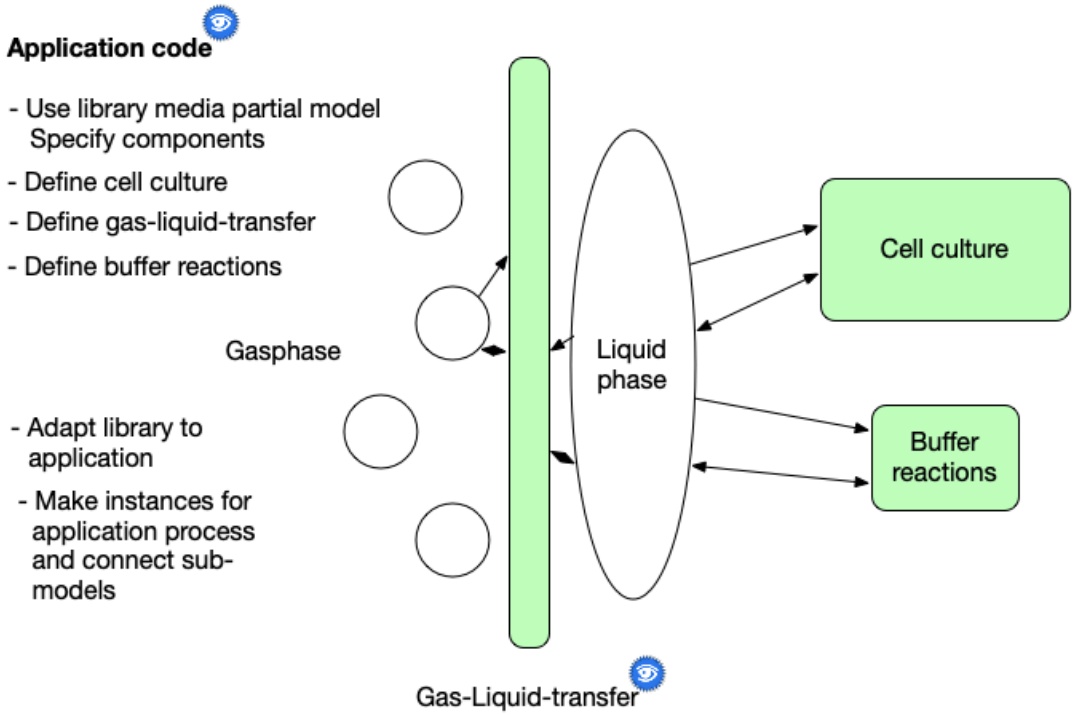
Library

Library code

- Define general liquid- and gas-phases
- Define general reactor
- Define general pumps, tanks, filters, sensors…
- Define controllers…



Application



cont’ BPL ReactorType

Reactor concentration c[i] affects everything
User inner/outer connection to application

- model Culture
- model GasLiquidTransfer
- model Buffer

These models static or dynamic of c[i]

- culture_q[i] – cell specific flow q[i]
- gas_to_liquid_transfer_Q[i] – total flow Q[i]
- liquid_to_gas_transfer_Q[i]
- buffer_Q[i]

cont’ BPL ReactorType

```
// Mass-balance for the liquid phase of the reactor:
for i in 1:Liquidphase.nc loop
    der(m[i]) = culture_q[i]*m[X] + buffer_Q[i]
                    + gas_to_liquid_transfer_Q[i]
                    + sum(actualStream(inlet[j].c[i])*inlet[j].F for j)
                    + sum(c[i]*outlet[k].F for k);
     for j in 1:n_inlets loop inlet[j].c[i] = c[i]; end for;
end for;
der(V)  =  sum(inlet[j].F for j) + sum(outlet[k].F for k);
```

Applications with **Yeast** - processes Batch and Fedbatch

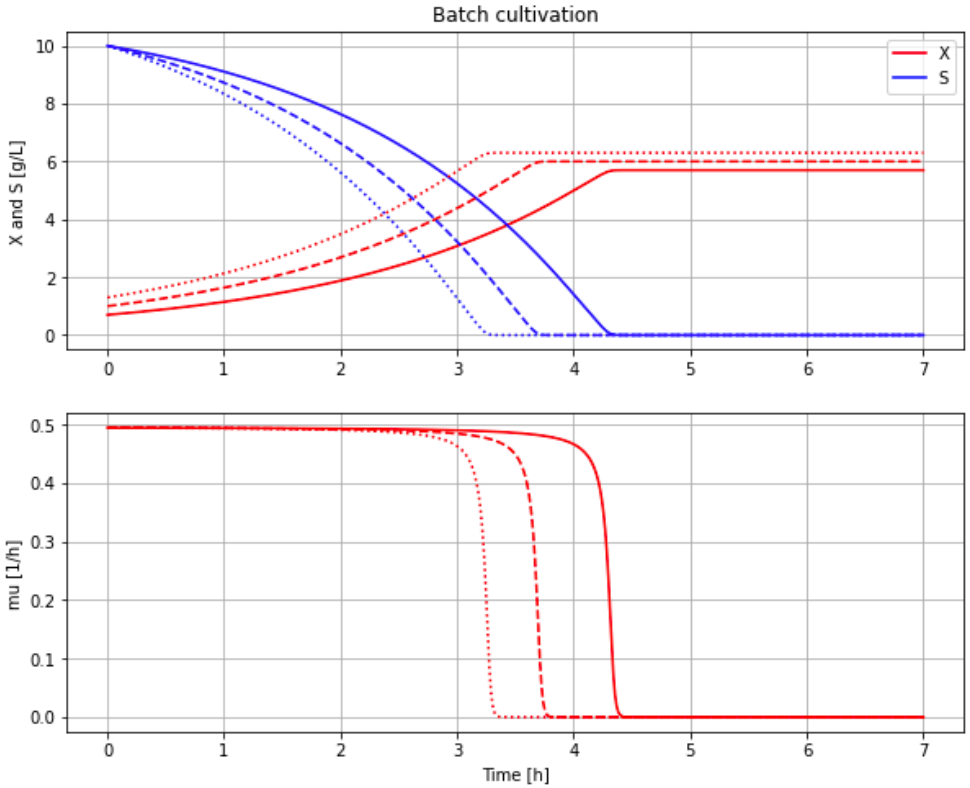
```
package EquipmentYeast
   import BPL.EquipmentLib;
   extends EquipmentLib(redeclare package Liquidphase = LiquidphaseYeast
                                redeclare model Culture = CultureYeast
   …
end EquipmentYeast;
model Batch
   LiquidphaseYeast_data liquidphase;
   EquipmentYeast.ReactorType bioreactor(X=liquidphase.X);
equation
end Batch;
model Fedbatch….
```

… and process Fedbatch

```
model Fedbatch "Fedbatch cultivation of yeast"
    LiquidphaseYeast_data liquidphase;
    EquipmentYeast.ReactorType bioreactor
                                (X=liquidphase.X, n_inlets=1);
    EquipmentYeast.Feedsystem feedtank;
    Control.DosageSchemeExp dosagescheme;
  equation
    connect(bioreactor.inlet[1], feedtank.outlet);
    connect(dosagescheme.F, feedtank.Fsp);
end Fedbatch;
```

Jupyter notebook and Bioprocess Library *for* Modelica

In [3]:
```
newplot()
for x in [0.7, 1.0, 1.3]: init(VX_0=x); simu()
```



In [4]:
```
describe('bioreactor.V')
```

```
Reactor broth volume [ L ]
```

Comment: In the diagram above we see the impact of variation in the initial cell concentration during batch cultivation.

More pedestrian way…

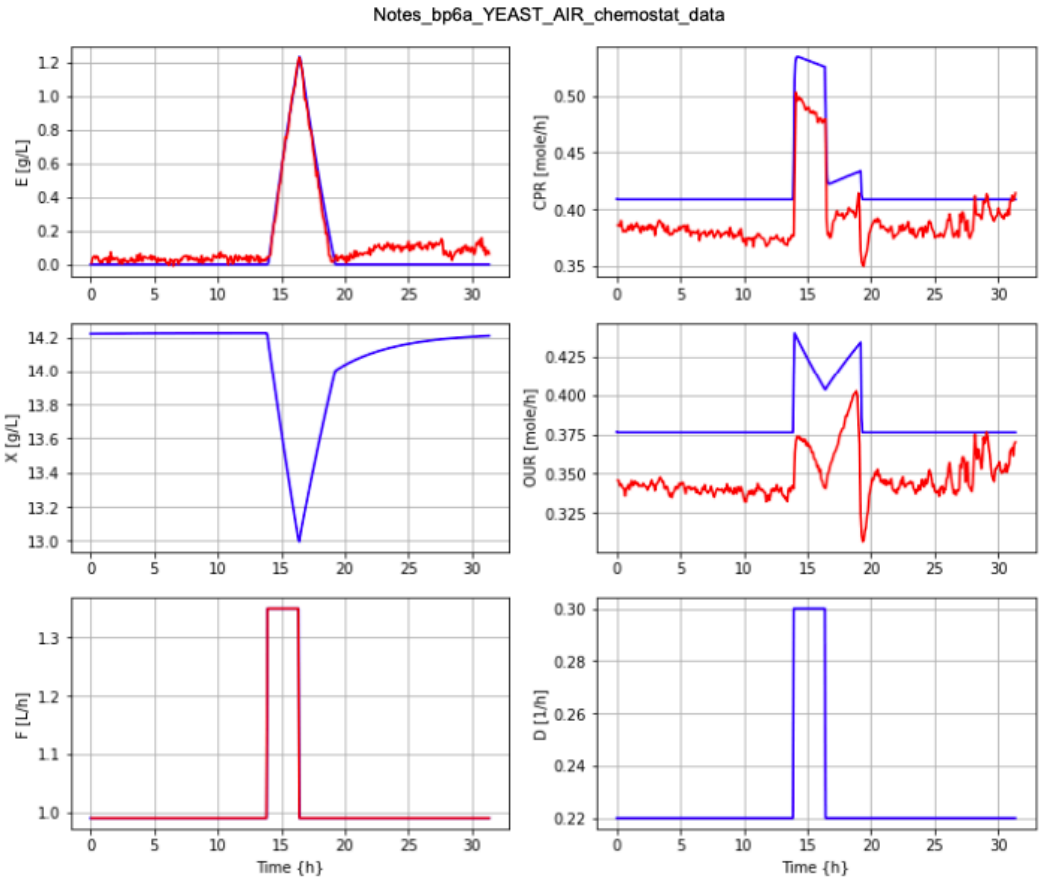
In [5]:
```
# Script bp6a_batch_setup - defines fmu_model, parDict[] and more

# - newplot()
plt.figure()
ax1=plt.subplot(2,1,1); ax1.grid(); ax1.set_ylabel('X and S [g/L]')
ax2=plt.subplot(2,1,2); ax2.grid(); ax2.set_ylabel('mu [1/h]'); ax2.set_xlabel('Time [h]')
lines=['-','--',':']; linecycler = cycle(lines)

for x in [0.7, 1.0, 1.3]:
    # - init(VX_0=x)
    parDict['bioreactor.m_0[1]'] = x
    # - simu(7)
    model = load_fmu(fmu_model)
    for key in parDict.keys(): model.set(key, parDict[key])
    sim_res = model.simulate(0, 7, options=opts)
    linetype = next(linecycler)
    ax1.plot(sim_res['time'], sim_res['bioreactor.c[1]'], color='r', linestyle=linetype); ax1.legend(['X', 'S'])
    ax1.plot(sim_res['time'], sim_res['bioreactor.c[2]'], color='b', linestyle=linetype)
    ax2.plot(sim_res['time'], sim_res['bioreactor.culture_q[1]'], color='b', linestyle=linetype)
```

Jupyter with Python3 and PyFMI

- Jupyter combine: code, diagrams, and text
- PyFMI (Modelon) – runs FMU
  (Modelon but on Github since a year)
- OpenModelica export FMU…
- Teaching – simplify command line interaction
  - newplot()
  - par(), init()
  - simu()
  - disp(), describe()

  Run Modelica as if *Simnon!* (H. Elmqvist, 1975)

Larger example
- Yeast continous (incl gas-phase)



Conclusion

- Application code clearly separated from library
- Got flexibility needed
  - ”Work with structure”
    - Object-orientation, connectors…
  - “Keep structure, change content”
    - Type level: Redeclaration… formal parameter: packages, models … “polymorphism”
    - Instance level: Smaller changes for readability, eg what conc variable is cell conc etc

  Key words: Formal parameter, redeclare, replaceable, see Fritzon section 4.4
- Adapt EquipmentLib at *one* place, cf MSL Fluid differs
  - DRY still difficult…
- Modelica can bring very neat and compact code, cf library ReactorType
- FMU
  - OpenModelica do not propagate constants, cf LiquidphaseYeast.mw etc
  - List of continuous time state variables available, but not discrete time?
- Jupyter notebooks very useful also in teaching context
  - Good to simplify command line interaction!

Acknowledgement Stackoverflow – name: janpeter

- Extending packages and access to the content
- Parametrised Modelica library and possibility to use models as parameters – part 1, 2, 3
- How to construct a balanced connector for liquids in Mocelica

Discussion are around simplified code examples that can be run – **see you there!**

Appendix Modelica 1999
6. Design Rationale – Code Reuse

Code reuse is a desirable but hard-to-reach goal for software development. Modelica contributes to this goal in several ways. Its non-causal equation-based modeling style permits model components to be reused in different contexts, automatically adapting to the data flow order in specific simulation applications, i.e. the Modelica compiler automatically arranges equations for solution with particular inputs or outputs. Object orientation and polymorphism significantly enhances the potential for reuse of Modelica model components.