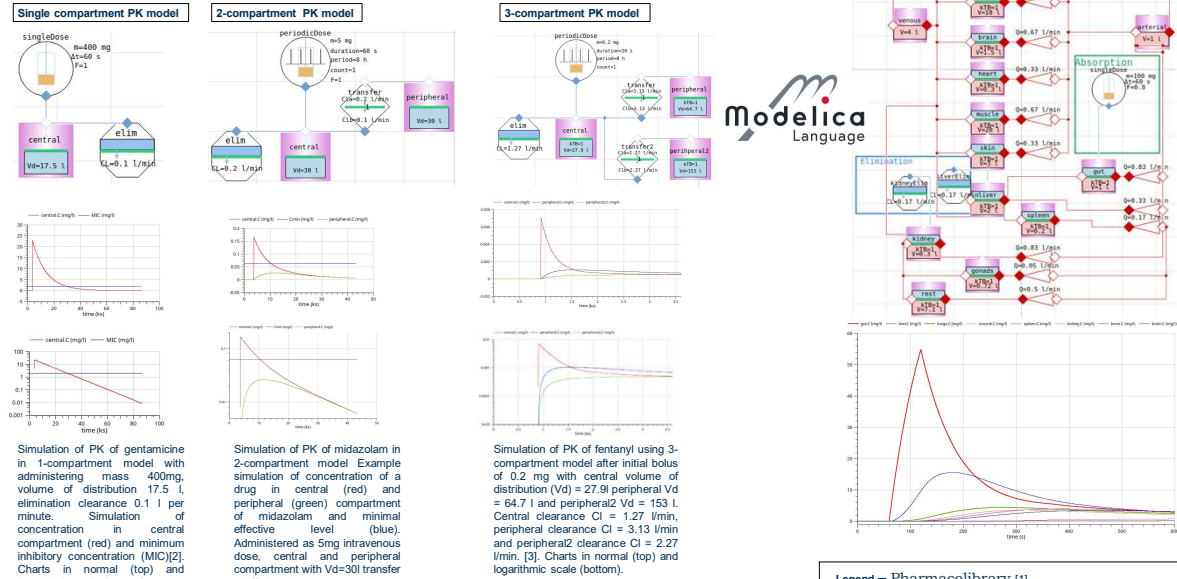


PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELING WITH MODELICA AND FMI: DEMO INTEGRATION WITH PK DATABASE

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Equivalent implementation of single compartment model in equations

```

model AcetaminophenEquations
  Pharmacokinetics.Types.Concentration C(displayUnit = "mg/l")
  "concentration"
  Real M "mass"
  Real Mdot "mass flow rate"
  Real Mdot_in "mass flow rate in"
  Real Mdot_out "mass flow rate out"
  Real Mdot_elim "mass flow rate elimination"
  Real Mdot_dose "mass flow rate dose"
  Real Mdot_perif "mass flow rate peripheral"
  Real Mdot_cent "mass flow rate central"
  parameter Real F = 0.8 "bioavailability"
  parameter Real Dose = 1000 "mg"
  parameter Real Cl = 0.2 "l/min"
  parameter Real Vd = 17.5 "l"
  parameter Real Vd2 = 64.7 "l"
  parameter Real Vd3 = 153 "l"
  parameter Real Cl1 = 1.27 "l/min"
  parameter Real Cl2 = 3.13 "l/min"
  parameter Real Cl3 = 2.27 "l/min"
  equation
    M = if time < 10 then 1 else 0
    Mdot_in = Dose
    Mdot_out = Cl * C
    Mdot_elim = Cl * C
    Mdot_dose = Dose
    Mdot_perif = Cl1 * C
    Mdot_cent = Cl2 * C
    Mdot_cent = Cl3 * C
  end AcetaminophenEquations
  
```

1. Model

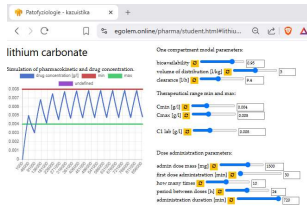
- Standard Modelica language
- Interoperable libraries for multiple domains [1]
- Simple models – equations, semi-complex model – diagrams, complex models – object oriented modeling – combination of components (diagrams/equations) [2]

2. Simulate & Analyze

- EITHER in Modelica tool (all examples in OpenModelica)
- OR Export to FMI standard unit
- Simulate in any environment
- Integrate data from external sources [3]
- Use favorite workflows

3. Visualize

- Export FMU -> WebAssembly
- Integrate as in-browser simulator in static web pages [4]



References:

[1] Pharmacokinetics: <https://github.com/creative-connections/Pharmacokinetics>

[2] T. Kulhánek and J. Kofránek, "Experience with Teaching Different Modeling Techniques on the example of Glucose Insulin Regulation Model," 2020 42nd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC), Montreal, QC, Canada, 2020, pp. 6024-6027. doi: 10.1109/EMBC44109.2020.9176535.

[3] <https://www.pk-db.com> PK-DB: pharmacokinetics database for individualized and stratified computational modeling (Gregorczyk, J., Brandhorst, J., Green, K., Elgether, D., Dupont, Y., Bartsch, J., Kötter, A., de Dey, D., De Angelis, S., König, M. Nucleic Acids Res. 2021 Jan 8;49(D1):D1358-D1364. doi: 10.1093/nar/gkaa990. PMID: 33151297

[4] eGolem pharma demo: <https://egolem.online/pharma/>

Model exported to standard FMI package and simulated using Python

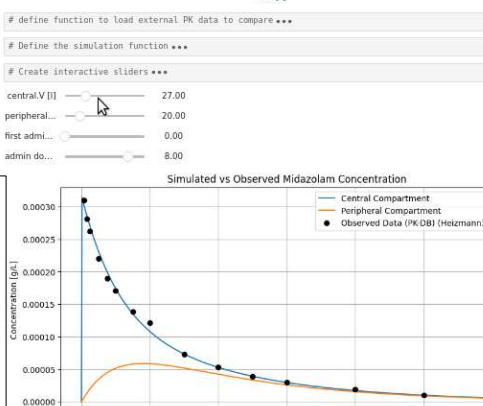
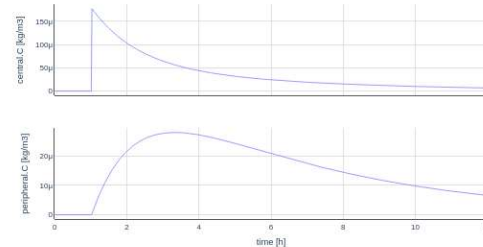
fmPy Python library – to simulate model using FMI standard

json + request Python library – to retrieve data from <https://pk-db.com>

Matplotlib + IPYWidgets – interactive example to fit data and simulation in Jupyter notebook

```

import fmPy
from fmPy import *
filename = 'PK_2C_Midazolam.fmu'
start_values = {
  'central.V': 27.9,
  'peripheral.V': 64.7,
  'peripheral2.V': 153,
}
output = [
  'central.C', # drug mass total
  'peripheral.C', # drug mass total
]
with SuppressNativeOutput():
  result = simulate_fmPy(filename, start_values=start_values, output=output, stop_time=43200, 0)
plot_result(result)
  
```



Legend – Pharmacokinetics [1]

Acasual connector for ConcentrationPort contains the following quantities qm and c defined as follows:

Flow MassFlowRate qm;

MassConcentration c;

when a component is connected using such a connector, Modelica tool following Modelica standard will ensure that flow variable qm is not accumulated in connected connectors by ensuring that

$$\sum_{i=1}^n q_{mi} = 0$$

and also that all non-flow variables - in this case concentration c are equilibrated i.e. $c_1 = c_2 = \dots = c_n$ (n is number of connected components via a connector).

Non-perfused-tissue compartment contains the ConcentrationPort and implements the equation of massflowrate qm:

$$\frac{dM}{dt} = q_m$$

And concentration C of connected port:

$$C = \frac{M}{V}$$

Where M is total mass dissolved in compartment, Vd is parameter of theoretical volume distribution in compartment.

Elimination component contains the ConcentrationPort and delivers outflow of the drug:

$$q_m = CL \cdot c$$

CL – parameter of clearance.

Intercompartmental first order transfer clearance, the drug is transferred from port A to port B at rate:

$$q_m = CL_{AB} \cdot c_A - CL_{BA} \cdot c_B$$

CL_{AB}, CL_{BA} – parameter of clearance from port A (resp. port B)

Administering drug component contains the ConcentrationPort and delivers inflow of the drug in prescribed administration time:

$$q_m = \frac{adminMass}{duration}$$

In other time the qm is 0.

Acasual connector for compartments with perfusion feature contains following quantities qv and c defined as follows:

Flow VolumeFlowRate qv;

Stream MassConcentration c;

For flow variable qv similar rule that it is not accumulated in connectors apply:

$$\sum_{i=1}^n q_{vi} = 0$$

And concentration c as stream variable is ensured to be correctly and physically consistently mixed based on the flow quantities.

Compartment with concentration of a drug and perfusion through it via bloodstream and simple diffusion to tissue by KTB rate:

$$\frac{dM}{dt} = q_{in} \cdot c_a + q_{v0} \cdot c_b + q_m$$

$$c_a = c_b = \frac{M}{V}$$

$$c = \frac{c_a + c_b}{2}$$

Prescribed flow Q through part of circulatory system as from connectors a and b:

$$q_{v0} = -q_{v0} = Q$$

Ground port prescribes ground or basic level concentration within the stream connected components:

$$c = 0$$