pkpd-tutorial

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1 pkpd-tutorial

1.1 Whole-body PKPD model for caffeine

PKPD model for clearance of caffeine by the human liver.

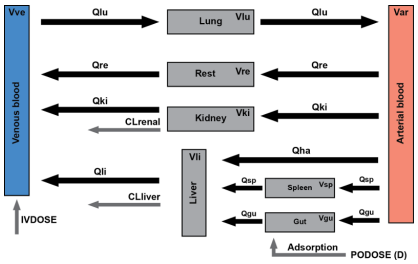


Fig.1 Caffeine PKPD Model

- Caffeine and the primary metabolite paraxanthine are removed from the blood stream by hepatic or renal clearance.
- Caffeine can be given either as intra-venous injection or by oral dose in the model
- The model is used to analyse the effect of smoking on caffeine clearance

This notebook demonstrates some simple use cases of a PKPD model for caffeine in Human. * the ODE equations were generate directly from the SBML of the caffeine model * initial values `X0`, parameter values `pars`, and the ODE system `dxdt` are defined in the `caffeine.py`

This tutorial works in a minimal python environment with * `numpy` * `scipy` * `matplotlib`

For questions contact konigmatt@googlemail.com.

The latest version of the resources is available at https://github.com/matthiaskoenig/pkpd-tutorial with

- caffeine.py https://github.com/matthiaskoenig/pkpd-tutorial/blob/master/notebooks/caffeine.py
- pkpd-tutorial.ipynb https://github.com/matthiaskoenig/pkpd-tutorial/blob/master/notebooks/pkpd-tutorial.ipynb

```
In [1]: # general imports for ode integration
        from __future__ import print_function
        import numpy as np
        import scipy
```

```
from matplotlib import pylab as plt
from scipy.integrate import odeint

# global settings for plots
plt.rcParams.update({
        'axes.labelsize': 'large',
        'axes.labelweight': 'bold',
        'axes.titlesize': 'large',
        'axes.titleweight': 'bold',
        'legend.fontsize': 'small',
        'xtick.labelsize': 'large',
        'ytick.labelsize': 'large',
    })
```

1.2 Import the caffeine model

- initial values `X0`, parameter values `p`, assigned variables `y` and the ODE system `dxdt` are defined in `caffeine.py`
- names for the `x`, `p`, `y` and `dxdt` are defined in `caffeine.py`

```
In [2]: from caffeine import *
        from pprint import pprint

        # load the names
        p_names, y_names, x_names, dx_names = names_caffeine()

        # display the x-variable names of the ODE
        pprint(x_names)
```

```
['A [mg] amount gut caffeine',
 'A [mg] amount kidney caffeine',
 'A [mg] amount liver caffeine',
 'A [mg] amount lung caffeine',
 'A [mg] amount spleen caffeine',
 'A [mg] amount rest caffeine',
 'A [mg] amount arterial blood caffeine',
 'A [mg] amount gut paraxanthine',
 'A [mg] amount kidney paraxanthine',
 'A [mg] amount liver paraxanthine',
 'A [mg] amount lung paraxanthine',
 'A [mg] amount spleen paraxanthine',
 'A [mg] amount rest paraxanthine',
 'A [mg] amount arterial blood paraxanthine',
 'A [mg] amount venous blood caffeine',
 'oral dose caffeine [mg]',
 'DCL_caf',
 'A [mg] amount venous blood paraxanthine',
 'oral dose paraxanthine [mg]',
```

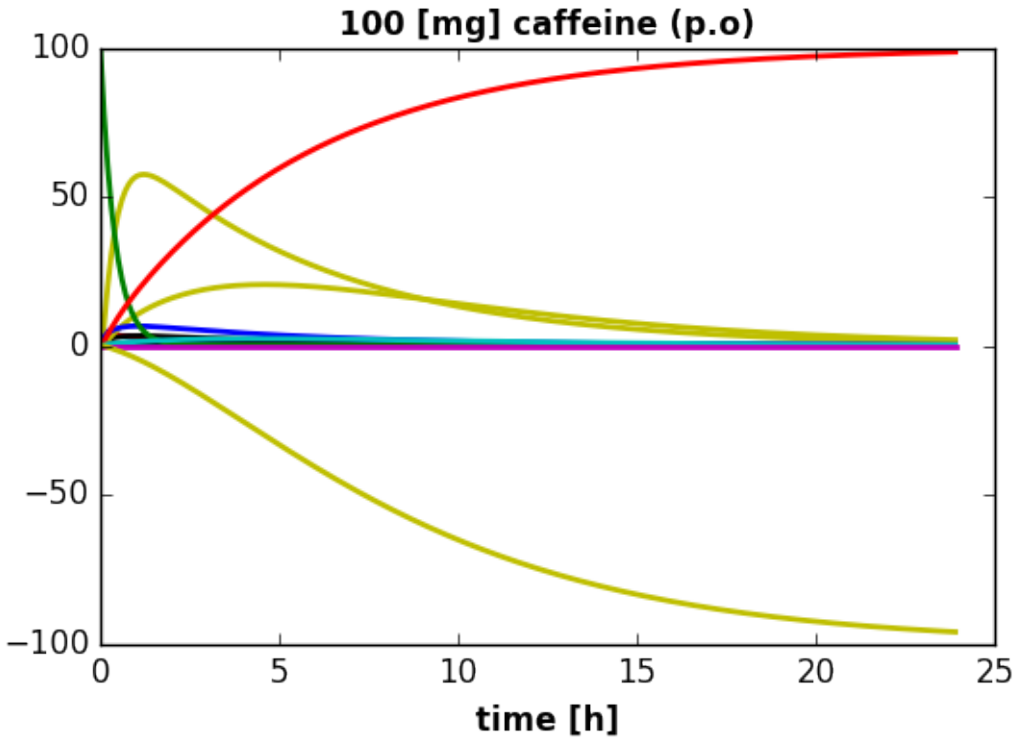
```
 'DCL_px',
 '']
```

1.3 Example simulation

By default the model simulates a 100 [mg] oral dose (p.o) of caffeine. In a first step we perform this simulation and look at some state variables of the model.

```
In [3]: from caffeine import *
        T = np.arange(0, 24, 0.1)
        X0 = X0_caffeine()
        pars = p_caffeine()
        dxdt = dxdt_caffeine
        X = odeint(dxdt, X0, T, args=(pars, ))

        plt.plot(T, X, linewidth=2)
        plt.title('100 [mg] caffeine (p.o)')
        plt.xlabel('time [h]')
        plt.show()
```



1.4 Plot amounts

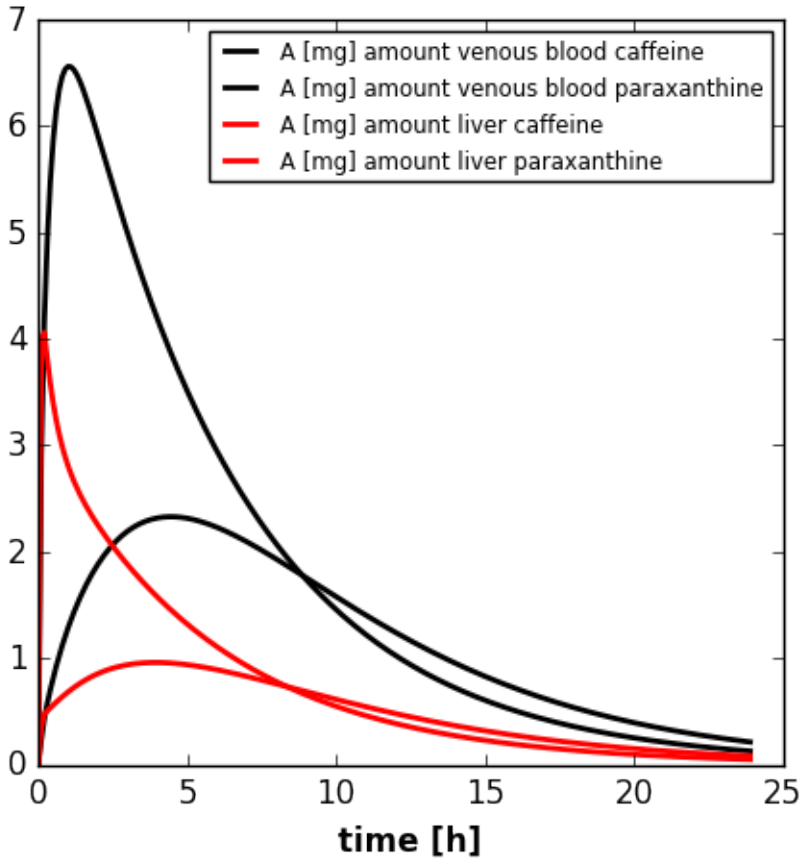
Now we plot the amounts of caffeine and paraxanthine in the venous blood and liver.

In [4]:
```
# plot caffeine and paraxanthine amounts
f1, ax1 = plt.subplots(1, 1, figsize=(5,5), dpi=80)

# venous blood amounts
ax1.plot(T, X[:,14], color='black', linewidth=2, label=x_names[14])
ax1.plot(T, X[:,17], color='black', linewidth=2, label=x_names[17])
# liver blood amounts
ax1.plot(T, X[:,2], color='red', linewidth=2, label=x_names[2])
ax1.plot(T, X[:,9], color='red', linewidth=2, label=x_names[9])

ax1.set_xlabel('time [h]')
ax1.legend()

plt.show()
```



In [5]:
```
# to lookup the indices you can do for instance
dict(zip(x_names, range(len(x_names))))
```

Out[5]:
```
{'': 20,
 'A [mg] amount arterial blood caffeine': 6,
```

```
 'A [mg] amount arterial blood paraxanthine': 13,
 'A [mg] amount gut caffeine': 0,
 'A [mg] amount gut paraxanthine': 7,
 'A [mg] amount kidney caffeine': 1,
 'A [mg] amount kidney paraxanthine': 8,
 'A [mg] amount liver caffeine': 2,
 'A [mg] amount liver paraxanthine': 9,
 'A [mg] amount lung caffeine': 3,
 'A [mg] amount lung paraxanthine': 10,
 'A [mg] amount rest caffeine': 5,
 'A [mg] amount rest paraxanthine': 12,
 'A [mg] amount spleen caffeine': 4,
 'A [mg] amount spleen paraxanthine': 11,
 'A [mg] amount venous blood caffeine': 14,
 'A [mg] amount venous blood paraxanthine': 17,
 'DCL_caf': 16,
 'DCL_px': 19,
 'oral dose caffeine [mg]': 15,
 'oral dose paraxanthine [mg]': 18}
```

1.5 Plot concentrations

The concentrations are derived/calculated values from the ode system. All calculated values, not being state variables are available in `y`.

```
In [6]: # y names
        dict(zip(y_names, range(len(y_names))))
```

```
Out[6]: {'Abody_caf': 51,
         'Abody_px': 52,
         'C caffeine [mg/l] arterial blood': 28,
         'C caffeine [mg/l] gut': 21,
         'C caffeine [mg/l] kidney': 22,
         'C caffeine [mg/l] liver': 23,
         'C caffeine [mg/l] lung': 24,
         'C caffeine [mg/l] rest of body': 26,
         'C caffeine [mg/l] spleen': 25,
         'C caffeine [mg/l] venous blood': 27,
         'C paraxanthine [mg/l] arterial blood': 36,
         'C paraxanthine [mg/l] gut': 29,
         'C paraxanthine [mg/l] kidney': 30,
         'C paraxanthine [mg/l] liver': 31,
         'C paraxanthine [mg/l] lung': 32,
         'C paraxanthine [mg/l] rest of body': 34,
         'C paraxanthine [mg/l] spleen': 33,
         'C paraxanthine [mg/l] venous blood': 35,
         'HLM apparent clearance paraxanthine by hepatic microsomes [mul/min/mg]':
         'Ka [1/hr] absorption paraxanthine': 12,
```

```
 'Venous_caf': 48,
 'Venous_px': 50,
 'arterial blood': 7,
 'arterial plasma': 10,
 'caffeine absorption': 47,
 'cardiac output [L/hr]': 11,
 'free kidney concentration caffeine': 39,
 'free kidney concentration paraxanthine': 44,
 'free liver concentration caffeine': 38,
 'free liver concentration paraxanthine': 43,
 'gut': 1,
 'gut blood flow': 14,
 'hepatic (venous side) blood flow': 16,
 'hepatic artery blood flow': 17,
 'kidney': 2,
 'kidney blood flow': 15,
 'liver': 3,
 'liver clearance caffeine [l/hr]': 40,
 'liver clearance paraxanthine [l/hr]': 45,
 'lung': 4,
 'lung blood flow': 18,
 'paraxanthine absorption': 49,
 'plasma': 8,
 'rate of caffeine change [l/hr]': 41,
 'rate of paraxanthine change [l/hr]': 46,
 'rest of body': 0,
 'rest of body blood flow': 20,
 'spleen': 5,
 'spleen blood flow': 19,
 'venous blood': 6,
 'venous plasma': 9,
 'venous plasma concentration caffeine': 37,
 'venous plasma concentration paraxanthine': 42}
```

In [7]:
```
# first we have to calculate the y values
Y = Y_caffeine(X, pars)
```

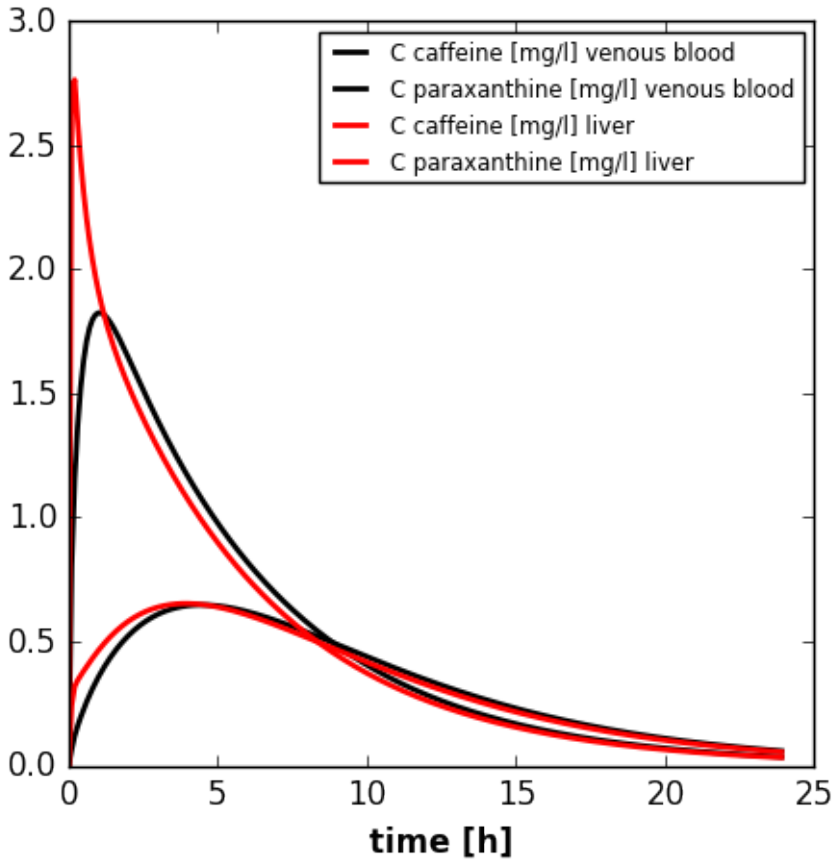
In [8]:
```
# plot caffeine and paraxanthine concentrations
f1, ax1 = plt.subplots(1, 1, figsize=(5,5), dpi=80)

# venous blood concentrations
ax1.plot(T, Y[:,27], color='black', linewidth=2, label=y_names[27])
ax1.plot(T, Y[:,35], color='black', linewidth=2, label=y_names[35])
# liver blood amounts
ax1.plot(T, Y[:,23], color='red', linewidth=2, label=y_names[23])
ax1.plot(T, Y[:,31], color='red', linewidth=2, label=y_names[31])

ax1.set_xlabel('time [h]')
```

```
ax1.legend()

plt.show()
```



2 Exercises

2.1 E1 Your caffeine level

The first exercise is to calculate the timecourse of your caffeine level after you drink some caffeinated beverage.

To estimate the oral dose you can estimate the caffeine content from the following chart

Tee also contains caffeine, it depends on the tee how much it contains.

The oral dose of the model is defined in parameter `p[31] = 100` [mg]. In addition you can also adjust the bodyweight to get a more realistic estimation via the parameter `p[0] = 70` [kg].

What would be your level of caffeine now, if you had two cups of coffee for breakfast this morning?

How would your time course and level of caffeine look if you would take the same amount of caffeine intravenously (I.V)?
(Hint: you have to set the oral dose to 0 and set the respective i.v. dose)

What is the peak time of caffeine in venous blood? What is the peak concentration?

2.2 E2 Interindividual variability

We saw that there is a large variability in caffeine kinetics in the population. Depending on if you are a fast or slow metabolizer of caffeine the timecourses can look very different. In E1 you calculated the mean timecourse for the population. Now we will look at the interindividual differences.

Your caffeine clearance by the liver depends on the activity of CYP1A2 in the liver, the main enzyme metabolizing caffeine. The activity is defined via the apparent clearance caffeine by hepatic microsomes `p[43] = 2` [mul/min/mg].

How would your time course / level of caffeine change if you are a slow metabolizer (small apparent clearance), or if you are a fast metabolizer (large apperent clearance)?

In addition you can simulate the effect of lifestyle changes, like your coffee intake or smoking habit. An overview over the changes in apparent clearance are given in the following table

How would your caffeine timecourse change if you smoke >20 cigarettes per day and drink 1 liter of coffee (the effects are additive) compared to being abstinent?

```
In [ ]:
```

Table 4. Parameter estimates of covariates obtained for logarithmic clearance values using the paraxanthine/caffeine ratio method (equation 1)

Covariate	*Symbol used in equation 5*	*Estimate*	*95% Confidence interval*		*Mean resulting change of clearance (factor)*
			Lower bound	*Upper bound*	
–	Intercept	0.264	–0.015	0.542	–
Coffee intake (litre day^{-1})	$Slope_{coffee}$	0.368	0.287	0.449	1.445
Body mass index (kg m^{-2})	$Slope_{BMI}$	–0.010	–0.018	–0.002	0.990
Cigarettes/day					
Non-smokers	$V_{smoking\ habit\ index}$	0	–	–	Reference
1–5		0.195	0.065	0.324	1.215
6–10		0.383	0.253	0.509	1.467
11–20		0.504	0.386	0.621	1.655
>20		0.543	0.430	0.655	1.721
Oral contraceptives					
No	$V_{oral\ contraceptive\ index}$	0	–	–	Reference
Yes		–0.332	–0.236	–0.428	0.717
Country					
Germany	$V_{country\ of\ residence\ index}$	0	–	–	Reference
Bulgaria		–0.209	–0.356	–0.061	0.811
Slovakia		–0.303	–0.450	–0.156	0.739
Sex					
Male		0	–	–	Reference
Female	$V_{sex\ index}$	–0.111	–0.178	–0.044	0.895

Fig3 Lifestyle Effects