The PBPK model

The (personwise) ordinary differential equation (ODE) as specified in (Bois, Gelman, Jiang, Maszle, Zeise, Alexeef 1996, Data and models) reads

$$\dot{C}_i = \frac{F_i}{V_i}(C_{\text{arterial}} - \frac{C_i}{P_i})$$

for the non-liver compartments and

$$\dot{C}_i = \frac{F_i}{V_i}(C_{\text{arterial}} - \frac{C_i}{P_i}) - \frac{V_{\max} C_i}{K_m + C_i V_i}$$

for the liver compartment, where

- C_i is the PERC mass concentration [mg/l] (in the i-th compartment),
- F_i is the blood flow [l/min] (...),
- V_i is the organ volume [l],
- P_i is the partition coefficient [1],
- $V_{\max}$ is the maximum rate of metabolism [mg/min],
- K_m is the Michaelis-Menten coefficient [mg/l] and
- C_{arterial} is the arterial PERC mass concentration [mg/l].

The "actual" blood flows F_i [l/min] get computed from the statistical parameters, the relative blood flows $\hat{F}_i$ [1], via

$$F_i = \frac{0.7MV}{VPR}\hat{F}_i$$

where

- MV is the "exactly" measured minute volume flow at rest [l/min]
- VPR is the (unknown) ventilation perfusion ratio [1].

The "actual" organ volumes V_i similarly get computed from the statistical parameters, the relative organ volumes $\hat{V}_i$ [1] by multiplication with the "exactly" measured lean body volume [l] (lean body mass gets measured and a lean body density of 1 kg/l is "assumed"). For the volume of body fat the measured body fat mass gets divided by the fat density of 0.92kg/l.

The partition coefficients are just the statistical parameters.

The "actual" maximum rate of metabolism [mg/min] $V_{\max}$ gets upscaled from the statistical parameter by multiplication with $LBM^{0.7}$.

The Michaelis-Menten coefficient [mg/l] is just the statistical parameter.

The arterial PERC mass concentration C_{arterial} is a function of

- the venous PERC mass concentration C_{venous} [mg/l],
- the ventilation perfusion ratio VPR [1],
- the environmental PERC mass concentration C_{inhaled} [mg/l].

The venous PERC mass concentration C_{venous} [mg/l] is just the weighted average of the *outgoing compartmental blood* PERC mass concentrations $C_{out,i}$ [mg/l]:

$$C_{\text{venous}} = \frac{\sum_i C_{out,i} F_i}{\sum_i F_i} = \sum_i C_{out,i} \hat{F}_i$$

with the the *outgoing compartmental blood* PERC mass concentrations $C_{out,i}$ [mg/l] getting computed from the *compartmental* PERC mass concentrations C_i [mg/l] assuming equilibrium between blood and compartment, i.e.

$$C_{out,i} = \frac{C_i}{P_i}.$$

The ventilation perfusion ratio is "fixed," while the environmental PERC mass concentration $C_{\text{alveolar,in}}$ [mg/l] is either 0 (after exposure) or some fixed value (during exposure).

The dependence of the arterial PERC mass concentration on these parameters can then be derived from a simple mass balance, i.e. the PERC mass flows entering the lungs (from the air entering the alveoli and the venous blood) has to equal the PERC mass flow exiting the lungs (via the air exiting the alveoli and the arterial blood). Thus

$$F_{\text{alveolar,in}} C_{\text{alveolar,in}} + F_{\text{venous}} C_{\text{venous}} = F_{\text{alveolar,ex}} C_{\text{alveolar,ex}} + F_{\text{arterial}} C_{\text{arterial}}$$

"Assuming" negligible PERC volume (compared to the volume of in/exhaled air and blood) we have

$$F_{\text{alveolar}} = F_{\text{alveolar,in}} = F_{\text{alveolar,ex}} = 0.7 * MV$$

and

$$F_{\text{blood}} = F_{\text{venous}} = F_{\text{arterial}} = \frac{0.7 * MV}{VPR} = \frac{F_{\text{alveolar}}}{VPR}.$$

Furthermore, assuming equilibrium between exhaled air and arterial blood we get

$$C_{\text{alveolar,ex}} = \frac{C_{\text{arterial}}}{P_{\text{blood/air}}}$$

and then finally

$$F_{\text{alveolar}} C_{\text{alveolar,in}} + F_{\text{blood}} C_{\text{venous}} = F_{\text{alveolar}} \frac{C_{\text{arterial}}}{P_{\text{blood/air}}} + F_{\text{blood}} C_{\text{arterial}}$$

or equivalently

$$C_{\text{arterial}} = \frac{F_{\text{alveolar}} C_{\text{alveolar,in}} + F_{\text{blood}} C_{\text{venous}}}{F_{\text{blood}} + \frac{F_{\text{alveolar}}}{P_{\text{blood/air}}}} = \frac{C_{\text{alveolar,in}} + \frac{C_{\text{venous}}}{VPR}}{\frac{1}{VPR} + \frac{1}{P_{\text{blood/air}}}}.$$

Reformulation and non-identifiability

First, we perform a (linear) change of variables from the *compartmental* PERC mass concentrations C_i [mg/l] to the *outgoing compartmental blood* PERC mass concentrations $C_{out,i}$ [mg/l] by dividing by the respective partition coefficient, which turns

$$\dot{C}_i = \frac{F_i}{V_i}(C_{\text{arterial}} - \frac{C_i}{P_i}) - \delta_{i,4}\frac{V_{\max}C_i}{K_m + C_iV_i}$$

into

$$\frac{\dot{C}_i}{P_i} = \dot{C}_{out,i} = \frac{F_i}{V_iP_i}(C_{\text{arterial}} - \frac{C_i}{P_i}) - \delta_{i,4}\frac{V_{\max}C_i}{P_i(K_m + C_iV_i)}$$

where $\delta_{i,4}$ is one if $i = 4$ and zero otherwise. In terms of these new variables we simplify the ODE to

$$\dot{C}_{out,i} = \frac{F_i}{V_iP_i}(C_{\text{arterial}} - C_{out,i}) - \delta_{i,4}\frac{V_{\max}C_{out,i}}{K_m + C_{out,i}V_iP_i}$$

which immediately reveals the non-identifiability between the compartmental organ volumes V_i and partition coefficients P_i. **The only thing that influences the behavior of the ODE is the product V_iP_i!**

Measurements

Two quantities get measured (noisily):

- the PERC mass concentration in venous blood C_{venous} [mg/l] and
- the PERC mass concentration in *exhaled* air C_{exhaled} [mg/l].

We have already discussed the PERC mass concentration in venous blood C_{venous} [mg/l], which gets computed from the *outgoing compartmental blood* PERC mass concentrations $C_{out,i}$ [mg/l] via

$$C_{\text{venous}} = \sum_i C_{out,i}\hat{F}_i.$$

The PERC mass concentration in *exhaled* air C_{exhaled} is just

$$C_{\text{exhaled}} = 0.7C_{\text{alveolar,ex}} + 0.3C_{\text{inhaled}},$$

with

$$C_{\text{alveolar,ex}} = \frac{C_{\text{arterial}}}{P_{\text{blood/air}}} = \frac{C_{\text{alveolar,in}} + \frac{C_{\text{venous}}}{VPR}}{\frac{P_{\text{blood/air}}}{VPR} + 1}.$$

Neither of these measurements is able to identify the organ volumes or the compartmental partition coefficients!

Strang splitting

We may split the ODE into a linear part and a nonlinear part affecting only the liver compartment. The linear part is just

$$\dot{C}_{out,i,linear} = \frac{F_i}{V_i P_i} \left[C_{\text{arterial}} - C_{out,i} \right]$$

into which we may plug in our expression for the arterial PERC mass concentration C_{arterial} to get

$$\dot{C}_{out,i,linear} = \frac{F_i}{V_i P_i} \left[\frac{F_{\text{alveolar}} C_{\text{alveolar,in}} + F_{\text{blood}} C_{\text{venous}}}{F_{\text{blood}} + \frac{F_{\text{alveolar}}}{P_{\text{blood/air}}}} - C_{out,i} \right]$$

into which we may then plug in our expression for the PERC mass concentration in venous blood C_{venous} [mg/l] to yield

$$\dot{C}_{out,i,linear} = \frac{F_i}{V_i P_i} \left[\frac{F_{\text{alveolar}} C_{\text{alveolar,in}} + F_{\text{blood}} \sum_j C_{out,j} \hat{F}_j}{F_{\text{blood}} + \frac{F_{\text{alveolar}}}{P_{\text{blood/air}}}} - C_{out,i} \right].$$

We may then solve the linear part using a matrix exponential and the nonlinear part using the Lambert W function with which we may build our Strang splitting.

References

Bois, Gelman, Jiang, Maszle, Zeise, Alexeef. 1996. https://stat.columbia.edu/~gelman/research/published/toxicology.pdf.

Gelman, Bois, Jiang. 1996. http://www.stat.columbia.edu/~gelman/bayescomputation/GelmanBoisJIang1996.pdf.