

## How to change the parameterization of a 2-compartment model from $k$ (rate constants) into $CL$ (clearance)

Sometimes it may be convenient to express a 2-compartment model – described by  $[V_c, K_{el}, K_{cp}, K_{pc}]$  in native SAAM II terminology - in terms of  $[V_c, CL, V_p \text{ and } Q]$ . These two parameterizations (volumes and rate constants, or volumes and clearances) are exactly equivalent, and their use in single-subject pharmacokinetic data analysis is often a matter of preference.

So, from FIGURE, let's define  $c$  = central (compartment 1),  $p$  = peripheral (compartment 2),  $el$  = elimination. So, the relevant  $k(i,j)$  are:

$$k(2,1) = K_{cp}$$

$$k(1,2) = K_{pc}$$

$$k(0,1) = K_{el}$$

For example,  $K_{cp}$  is the transfer rate (in inverse time) from the central to the peripheral compartment; in SAAM II native terminology, this is  $k(2,1)$ , the transfer rate from 1 to 2. Now, copy and paste these in the Equations window in SAAM II. When this is done, the PRIMARY model parameters (i.e., the parameters that are directly estimated when fitting data and that are shown in the Parameters window) become:  $K_{cp}$ ,  $K_{pc}$  e  $K_{el}$ . As SAAM II is based on balance of mass, do not forget to set the volume of the central compartment which is accessible to concentration measurements ( $V_c$ ).

We can also write:

$$V_{ss} = V_c + V_p$$

$$K_{el} = CL/V_c$$

$$K_{cp} = Q/V_c$$

$$K_{pc} = Q/V_p$$

In these equations,  $V_{ss}$  is the total volume at steady state (the sum of central and peripheral volumes of distribution) and  $V_p$  is the peripheral compartment volume.  $Q$  is the intercompartmental exchange flow (clearance) between the central and peripheral compartments, which is equal from both central to peripheral and peripheral to central, as is constrained from steady state (equilibrium).

It follows that the clearance from the central compartment is the product of the elimination rate constant and the volume of distribution (and has units of volume over time):

$$CL = K_{el} * V_c$$

Central-to-Peripheral exchange flow is:

$$Q = K_{cp} * V_c = K_{pc} * V_p$$

One may also calculate the elimination (beta) and distribution (alpha) half-lives from the individual  $k(i,j)$ , as:

$$\beta = 0.5 * (k(2,1) + k(1,2) + k(0,1) - \sqrt{(k(2,1) + k(1,2) + k(0,1))^2 - 4 * k(1,2) * k(0,1)})$$

$$\alpha = k(1,2) * k(0,1) / \beta$$

$$T12_{\beta} = \log(2) / \beta$$

$$T12_{\alpha} = \log(2) / \alpha$$

These equations can also be pasted into the Equations window. As a result, once the model is fitted to data, SAAM II will return estimated values of alpha and beta, T12\_alpha and T12\_beta, in the Statistics window.

