Deriving and interpreting PK parameters in a physiological model

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Purpose of this presentation

Two main purposes

1. Tutorial for non-pharmacokineticists on what PK parameters mean
   - We want to investigate the meaning of PK parameters by building a simple physiological model for a fictive compound
   - Based on that model we will define the meaning of the different parameters
   - ..... and compute them using nonparametric methods
2. The second purpose is deferred to the end of the presentation

What PK people compute

If we assume an intravenous bolus (so we know the dose D we give), PK people compute the following parameters:

Parameter	Notation	Formula
Terminal half-life:	$t_{1/2}$	$\ln(2)/k_{el}$
Clearance:	CL	$D/\int_0^\infty C(t)dt$
Mean Residence Time:	MRT	$\int_0^\infty t\,C(t)\,dt/\int_0^\infty C(t)\,dt$
Volume of distribution:	V_d	CL/k_{el}
Volume in steady state:	V_{ss}	$CL\cdot$MRT

Volumes in PK are not true volumes: they are proportionality constants like in

$$\text{Amount drug} = \text{Volume} \cdot \text{Concentration}$$

Our objective is to build a physiological model for drug behaviour that will allow us an interpretation of these.

How drug is handled in the body

- Like all compounds that enter the body, drugs are transported around the body by the blood circulation
- A molecule may leave the circulation and enter different tissues, only to return to blood later
- Tissues are complex structures made up of cells bathing in an interstitial fluid, all held together by different membranes
- There are tissues within the blood as well - the various cells in the blood, notably the red blood cells.
  - When measuring our drug concentration we may choose to do it in whole blood or in extra-cellular compartment only, the plasma
- Finally the drug is removed from the body by either
  - metabolic conversion to something else, that has a similar history in the body, or
  - by being excreted from the body, most often by the kidneys

ADME - the PK steps

- Absorption - will not be addressed, we will assume a simple intravenous bolus dose
- Distribution - this is the description of what happens to the drug from it has entered the system for the first time, until it leaves the system
- Metabolism and Excretion - this is the description of how the drug is eliminated from the body
  - We will assume that our drug is only metabolized, so ignore excretion.

Some notations:

$C(t)$ will denote the plasma concentration of a drug at time t
$C_u(t)$ will be the free concentration of drug at time t

Metabolism

Metabolism usually means that enzymes in the liver break the molecule in some way. Classical enzyme kinetics is described by the chemical reaction

$$S + E \underset{k_{-1}}{\overset{k_1}{\leftrightarrows}} SE \xrightarrow{k_2} P + E,$$

The velocity for this reaction is given by

$$-[S]' = \frac{k_2 E_0 [S]}{k_1 [S] + k_{-1} + k_2} = \frac{v_m [S]}{K_m + [S]}, \quad K_m = \frac{k_{-1} + k_2}{k_1}, v_m = \frac{E_0 k_2}{k_1}.$$

Only free drug is available for elimination (assume one enzyme system):

$$\text{amount eliminated per time unit} = CL_{int} C_u, \quad CL_{int} = \frac{v_m}{K_m + C_u} \approx \frac{v_m}{K_m}$$

if $K_m >> C_u$.

The partition coefficient K_p

- Assume a body in complete steady state (no input/output).
- Assume free concentration C_u the same everywhere
- let $f_{u,i} =$ fraction free in organ i

By definition

$$K_p = \frac{C_{T_i}}{C} = \frac{f_u}{f_{u,i}} \qquad (C_u = f_{u,i} C_{T_i} \quad \Rightarrow \quad f_{u,i} C_{T_i} = f_u C)$$

K_p is determined by type and amount of binding proteins in the organ in question.

$$\text{Amount in body} = \sum_i \text{Amount in organs} = \sum_i V_{T_i} C_{T_i} = (\sum_i K_{p,i} V_{T_i}) C.$$

The volume in steady state is defined by

$$\text{Amount in body } = V_{ss} C \qquad \Rightarrow \qquad V_{ss} = \sum_i K_{p,i} V_{T_i}$$

Events over a well-stirred organ

Over an organ mass-balance considerations shows that

$$\text{flow in} = \text{flow out} + \left\{ \begin{array}{c} \text{rate of change} \\ \text{in amount in organ} \end{array} \right\} + \left\{ \begin{array}{c} \text{elimination rate} \\ \text{from organ} \end{array} \right\}$$

Assume

- Organ well-stirred with drug concentration C_T and volume V_T
- Blood flow Q to organ (and no loss of water)
- That the fraction unbound is constant f_u

$$\Rightarrow \qquad QC_{in} = QC_{out} + V_T C_T' + CL_{int} f_u C_{out}.$$

- assume instantaneous equilibrium on the venous side: $C_{out} = C_T/K_p$, where K_p is the partition coefficient

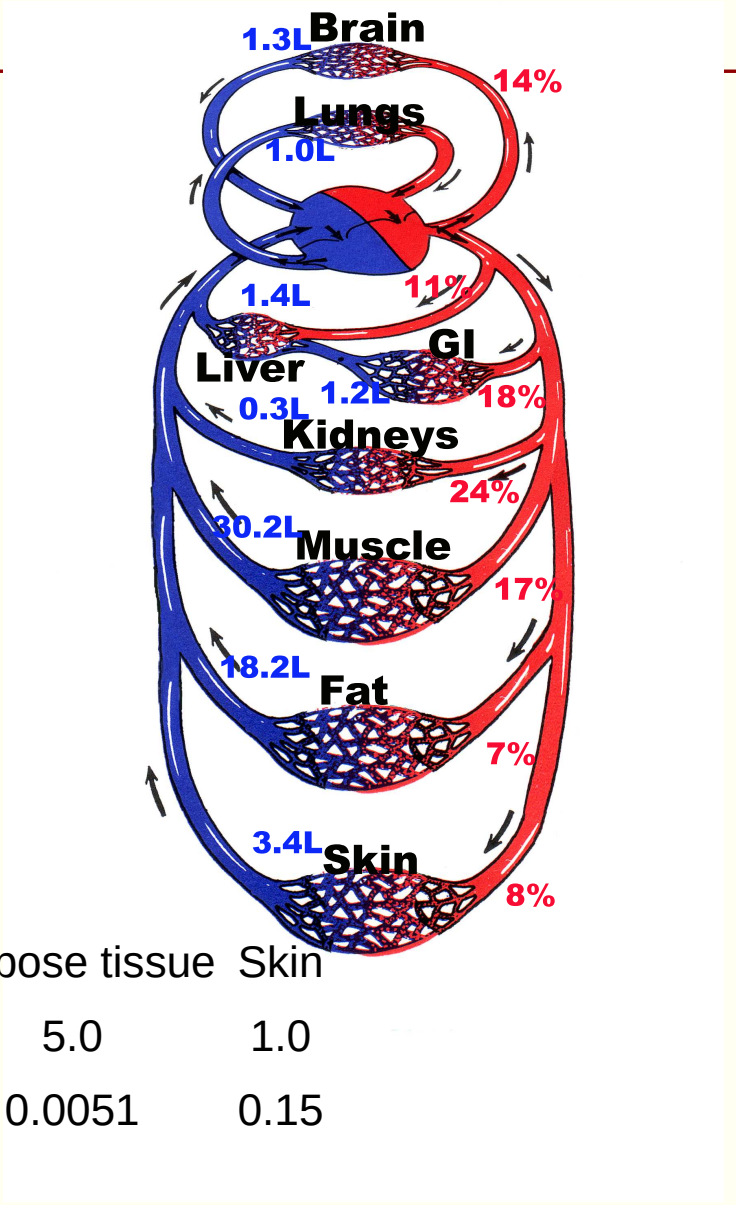
$$\Rightarrow \qquad C_{out}' = \frac{Q}{V_T K_p}(C_{in} - \frac{C_{out}}{1-E}), \quad E = \frac{Q f_u CL_{int}}{Q + f_u CL_{int}}.$$

- E is called the extraction ratio

An alien body

Assume that the body consists only of a
few well-stirred organs connected by a circulatory system.

Organ	Volume (V_T) (mL)	Blood flow (Q) (mL/min)	Perfusion rate (Q/V_T) (mL/min/mL tissue)
Veins	3400	5330	1.57
Arteries	2100	5330	2.54
Liver	1400	1450	1.04
Kidneys	270	1170	4.33
GI tract	1200	880	0.73
Lungs	950	5330	5.61
Brain	1350	690	0.51
Muscles	30200	1050	0.03
Adipose tissue	18200	460	0.03
Skin	3400	510	0.15



Drug specific data:

Organ:	Liver	Kidneys	GI tract	Lungs	Brain	Muscles	Adipose tissue	Skin
K_p:	2.6	1.3	4.1	1.0	1.6	2.1	5.0	1.0
$k_T = Q/V_T K_p$:	0.40	3.3	0.18	5.6	0.32	0.017	0.0051	0.15

We have that $V_{ss} = V_a + V_v + \sum_i V_{T_i} K_{p,i} = 175$ L
(cf 62 L organ volumes)

Model building - differential equations

- For a non-eliminating organ with arterial input we have that ($C_i = C_{out}$ for organ i)

$$V_i K_{p,i} C_i'(t) = Q_i(C_a(t) - C_i(t)),$$

- For the liver we have

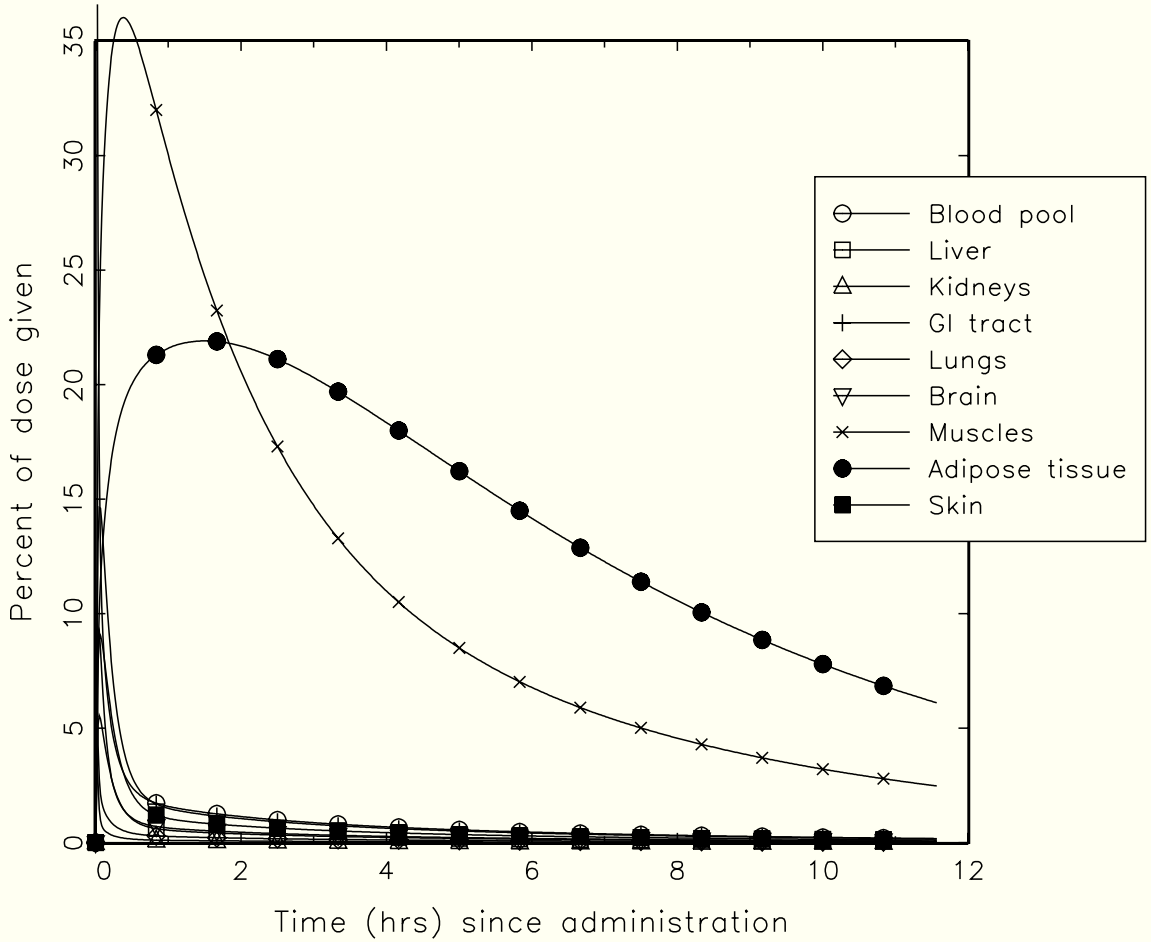
$$V_i K_{p,i} C_i'(t) = Q_1(C_a(t) - C_i(t)) + Q_2(C_{GI}(t) - C_i(t)) - CL'_{int} C_i(t).$$

  - $Q_1 =$ flow of the hepatic artery, with drug concentration $C_a(t)$
  - $Q_2 =$ flow of the portal vein, with concentration $C_{GI}(t)$
  - $CL'_{int} = CL_{int} \times f_u = 1500$ mL/min ($E = 0.51$).

- For veins $V_v C_v'(t) = \sum_{i \in \mathcal{I}} Q_i C_i(t) - Q_c C_v(t)$, where $Q_c = \sum_{i \in \mathcal{I}} Q_i =$ cardiac output and $\mathcal{I}$ a list of all organs that feed into the venous circulation.
- For the lungs, swap C_a and C_v
- For arteries $V_a C_a'(t) = Q_c(C_{lungs}(t) - C_a(t))$.
- Initial condition: i.v. bolus dose $V_c C_v(t) = D$

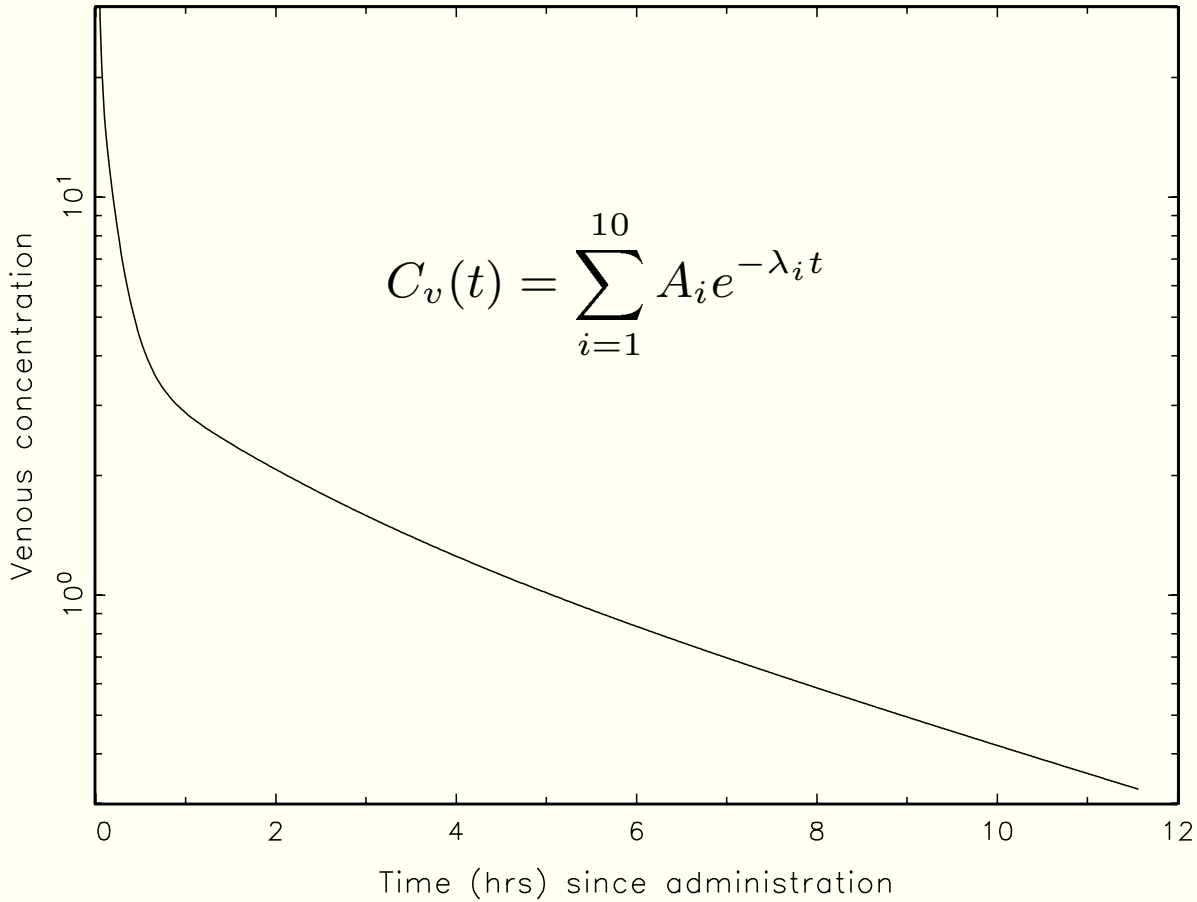
Solution to this system

- The amount of drug in organ $= V_i K_{p,i} C_i(t)$.
- The total amount of drug$= M(t) = V_a C_a(t) + V_v C_v(t) + \sum_i V_i K_{p,i} C_i(t)$.



But we only sample from the veins..

...so the only concentrations we see is what is measured there:



So, how can we derive the modeling assumptions from that concentration curve only?
What information can we obtain?

Distribution volume and Clearance

The distribution volume $V(t)$ of the drug is defined from the formula

$$M(t) = V(t)C_v(t).$$

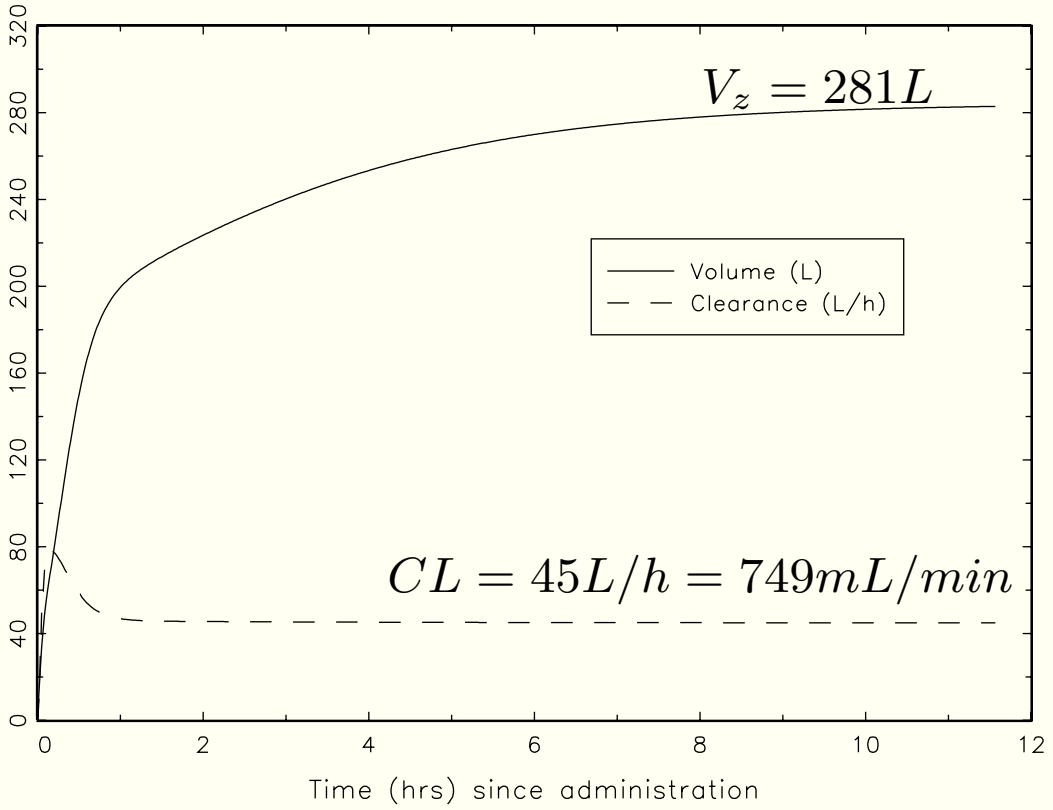
Not a true volume!

Clearance $CL(t)$ is defined from

$$-M'(t) = CL(t)C_v(t)$$

which shows that

$$CL(t) = CL'_{int}C_{liver}(t)/C_v(t).$$



This is time-dependent, since elimination is not from the organ we sample in!

Note that
$D = -\int_0^\infty M'(t)dt = \int_0^\infty CL(t)C_v(t)dt.$

Non-Compartmental Analysis

- Clearance:
  - $D = -(M(\infty) - M(0)) = \int_0^\infty CL(t)C_v(t)dt$
  - $CL_{av} = \frac{\int_0^\infty C_v(t)dt}{D}$
- Mean Residence Time: $T =$ time spent in the body for a drug molecule,
  - with distribution function given by $F_T(t) = (D - M(t))/D = 1 - M(t)/D$ ...
  - ... so the average time spent in the body is given by

$$E(T) = \int_0^\infty tF_T'(t)dt = \frac{1}{D}\int_0^\infty tM'(t)dt = \frac{\int_0^\infty tCL(t)C_v(t)dt}{\int_0^\infty CL(t)C_v(t)dt}$$

$$= \frac{\int_0^\infty tC_v(t)dt}{\int_0^\infty C_v(t)dt} \qquad \text{if clearance is constant.}$$

- Volumes
  - $V_{ss} =$ Time spent in body $\times$ Rate of elimination $=$ MRT·CL
  - $V_z = V(\infty) = \frac{CL}{\lambda_z}$, usually called volume of distribution
  - $V_c = D/C_v(0)$, volume of the central space

Sample and analyze our model

- We assume that we sample at times 1, 2, 5 and 10 minutes, and then every tenth minute up to and including 690 minutes after start (unrealistically rich number of samples).
- To obtain a sample at time $t = 0$ we extrapolate log-linearly backwards, using the first two observed points.

The NCA analysis produces the following list of standard PK parameters:

$t_{1/2}$ (h)	CL (mL/min)	MRT (h)	V_c (L)	V_{ss} (L)	V_z (L)
4.3	756	3.9	6.8	177	282

Everything relates well to what it should be,

- $t_{1/2} = \ln(2)/$smallest eigenvalue of coefficient matrix
- $CL = 749$mL/min from graph, for most of the time
- $V_{ss} = V_{blood} + \sum_i K_{p,i} V_{T_i} = 175L$
- $V_z = 281L$ from previous graph
- We can express MRT in k_T etc, but skip it here
- The only exception to a good fit is V_c which is much greater than the true initial volume, the volume of the veins.

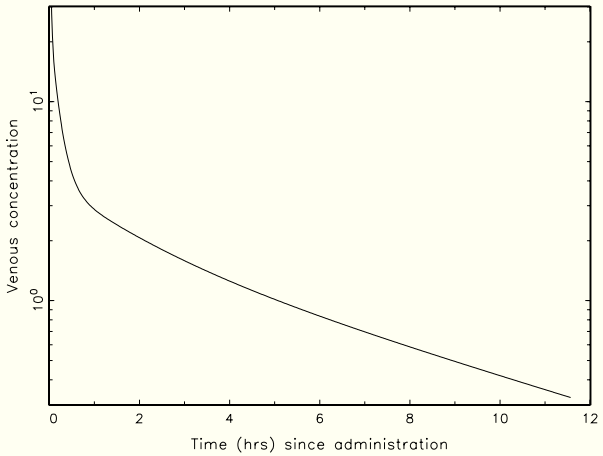
The problem with the central volume

- Is that we allowed recirculation to occur before first data point.
- The definition of V_c rests on blood/plasma and everything in rapid equilibrium with it and will depend on our exact time points of measurement.
- In fact, we can identify what the analysis picks up as the central compartment. Inspecting the tissue rate constants we find that two of them are > 1, those for kidneys and lungs. Also the volume $V_a + V_v + V_{lungs} + K_{kidneys}V_{kidneys}$ agrees with the central volume V_c estimate. So the NCA analysis has identified these four organs as in rapid diffusive equilibrium with a common drug concentration.

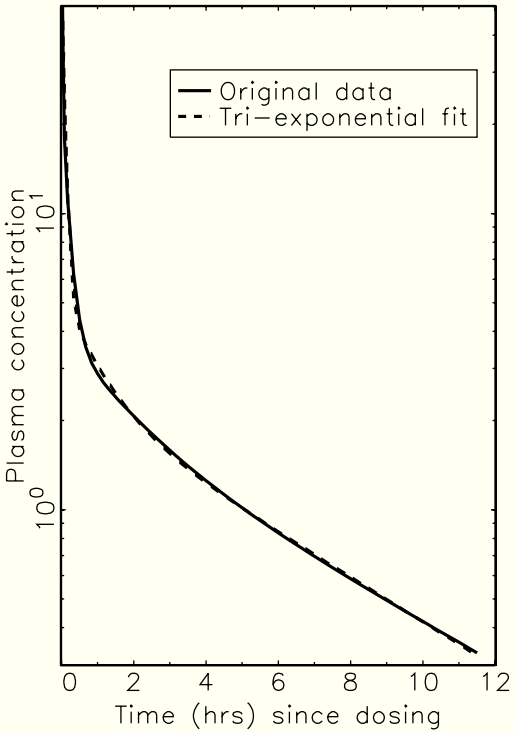
Compartment modelling

The blood
concentration profile is clearly reminiscent of a tri-exponential:

$$C(t) = \sum_{i=1}^{3} A_i e^{-\lambda_i t},$$



as an approximation of the original ten-exponential.



A nonlinear regression fit to the data provides us
with parameter estimates that produces the fit to the left:

- Virtually no visible difference
- From this we can
  build up a simplified model of the body consisting of
  - One compartment identified with adipose,
  - One compartment identified with muscle,
  - One central
    compartment consisting of everything else

The second reason..

for this presentation:
If you want to know more ...

- ...you can order and read