Compartmental Modelling and Differential equations

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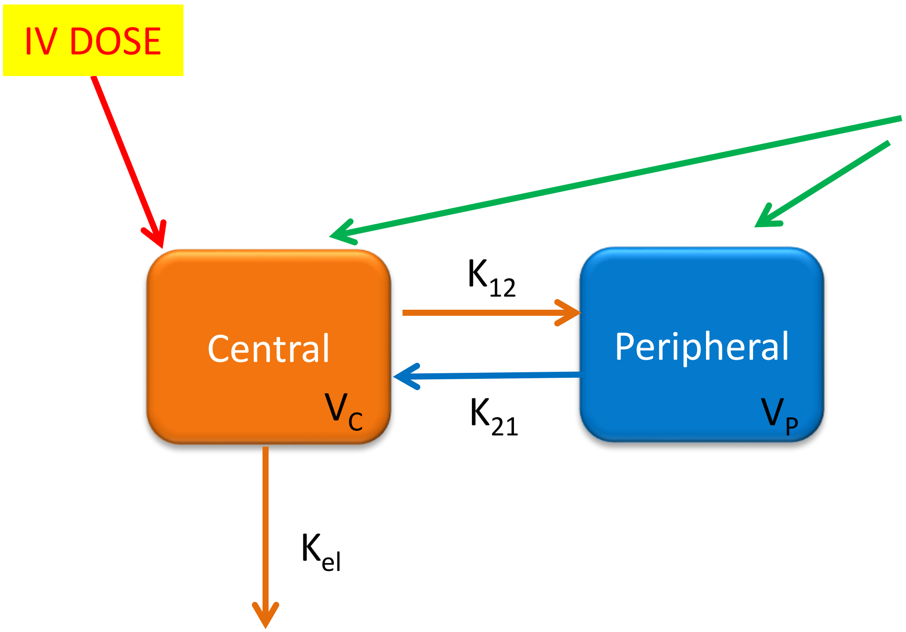
Compartmental Modelling

The system under test is modelled as a set of interconnected compartments.

The amounts in these compartments interact with each other and they change following the rules described by a set of differential equations.

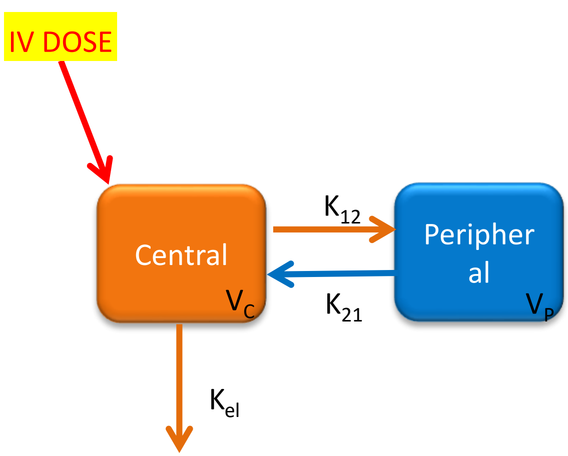


These compartments are only mathematical concepts.
They don't necessarily correspond one-to-one to physical parts of the body and the amount which is contained in them may represent drug concentration, a biomarker value, an effect.

A model as a set of differential equations

For a compartmental model to be completely specified, we need to define its structure, i.e. the number of compartments and the mechanism that describes how the amount in each compartment changes over time.

Mathematically, this is achieved with a set of differential equations, one equation for each compartment in the model.



$$\begin{cases} \frac{dA_1}{dt} = -k_{el} \cdot A_1 - k_{12} \cdot A_1 + k_{21} \cdot A_2 & A_1(t=0) = dose \\ \frac{dA_2}{dt} = k_{12} \cdot A_1 - k_{21} \cdot A_2 & A_2(t=0) = 0 \end{cases}$$

Differential equation: Definition

A differential equation is an equation that contains derivatives, i.e. it **describes the rate of change of a quantity over time**.

If we call A the amount in a compartment - or A(t) to stress that it changes over time - we can consider this simple differential equation

$$\frac{dA(t)}{dt} = f(A(t), t, p)$$

dA/dt denotes the rate of change of A and on the right hand-side there is the function f(.) that describes this rate of change

This function can depend on the instantaneous value of A(t), on the time t, or on other parameters p.

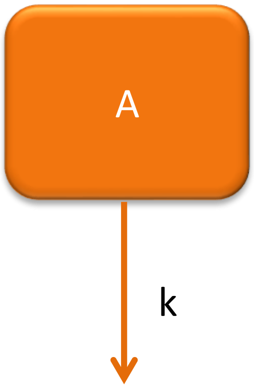
A simple differential equation

Let us have a look at a specific case of differential equation

$$\frac{dA(t)}{dt} = -k \cdot A(t)$$

In this case, at each time t, A(t) is going to decrease with speed proportional to the amount at that specific time, with k being the proportionality constant.

When drawing a scheme of a model, the notation for this kind of equation is simply an arrow exiting a compartment.



Initial conditions

Now we know how the quantity A is changing over time, but we need an initial value to start with.

This is known as **initial condition**, and it is normally defined with the notation shown below

$$A(t = 0) = A_0$$

Solution of a differential equation

This differential equation with this initial condition

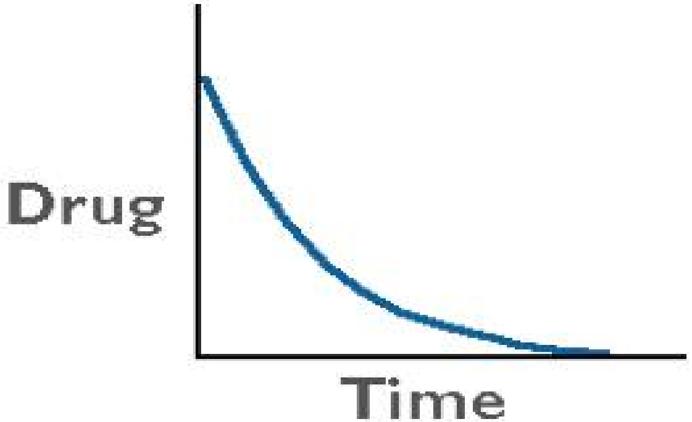
$$\frac{dA(t)}{dt} = -k \cdot A(t) \qquad\qquad A(0) = A_0$$

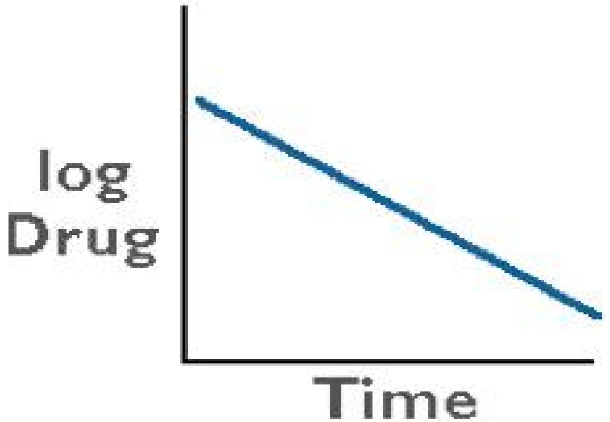
Has the following solution (you can try to derive it and see that it works):

$$A(t) = A_0 \cdot e^{-k \cdot t}$$

which is an exponentially decreasing function.

We can use it to model drug elimination, when it follows linear kinetics, and the initialisation can be used to insert the dose into the system.





Another simple differential equation

Let us try now another simple differential equation

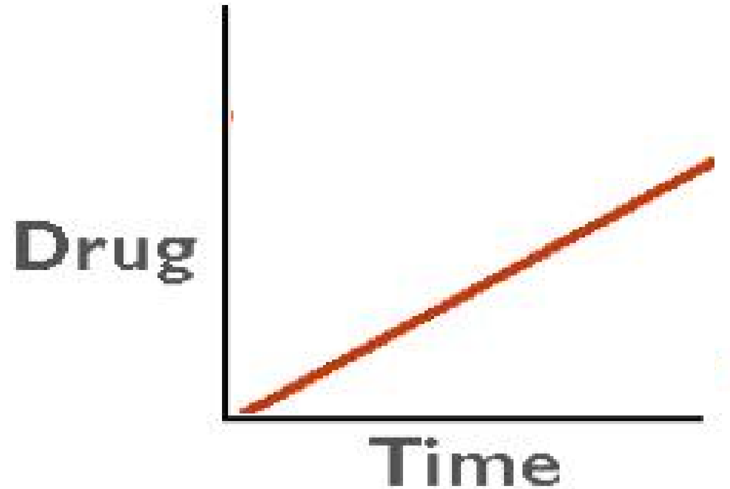
$$\frac{dA(t)}{dt} = R_{in} \qquad A(0) = 0$$

In this case A(t) is 0 at time 0, and then it grows constantly at the same rate.

Solution:

$$A(t) = R_{\text{in}} \cdot t$$

We can use this for drug infusion



Order of differential equations

In most simple PK compartmental models, the rates of change between compartments are similar to the simple equations we have just seen.

They are example of either zero-order (e.g. constant infusion) or first-order (e.g. exponential elimination) kinetics.

The order is determined by the exponent (n) when the differential equation is written in the following form:

$$\frac{dA}{dt} = -k \cdot A^{\boldsymbol{n}}$$

A more complex description is sometimes necessary when saturation is present (Michaelis-Menten).

Saturable kinetics

A hybrid situation in which the system behaves approximately as

- first-order for lower concentrations,
- zero-order for higher concentrations (saturation)

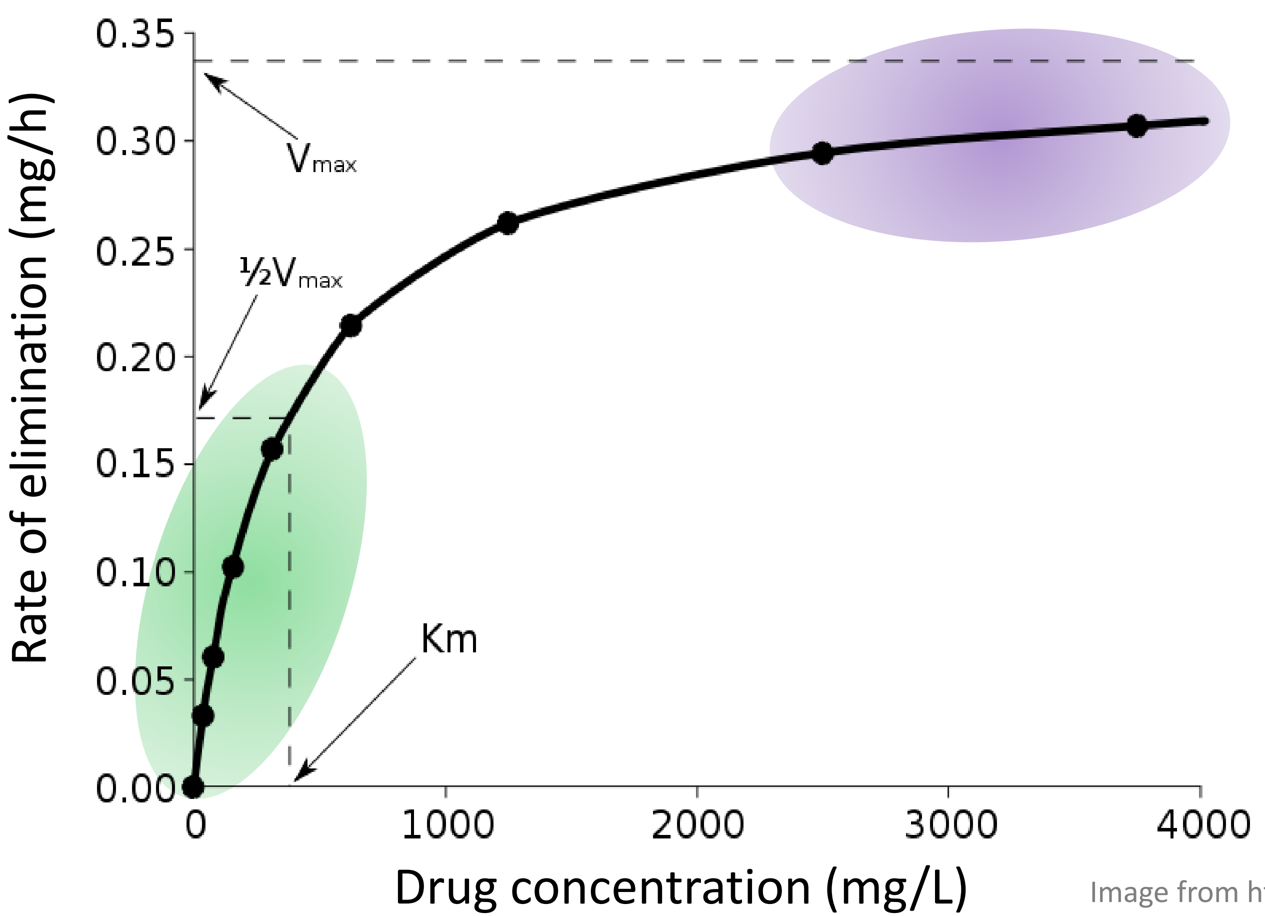


Image from http://en.wikipedia.com

Saturable kinetics

This is normally described by the Michaelis-Menten equation.

If C is the concentration, its rate of change is described by

$$\frac{dC}{dt} = V_{max} \cdot \frac{C}{K_m + C}$$

Maximum rate

Michaelis constant
Concentration at which $V_{max}/2$ is reached

Image from http://en.wikipedia.com

Summary

Summary of most commonly used kinetics, along with their parameters and units

Kinetics	Constants	Units (example)
Zero-order	R_{in}	mg/min
First-order	k	1/min
Michaelis-Menten	V_{max}, k_m	mg/L/min, mg/L

Zero-order vs. First-order

0-order | 1st-order