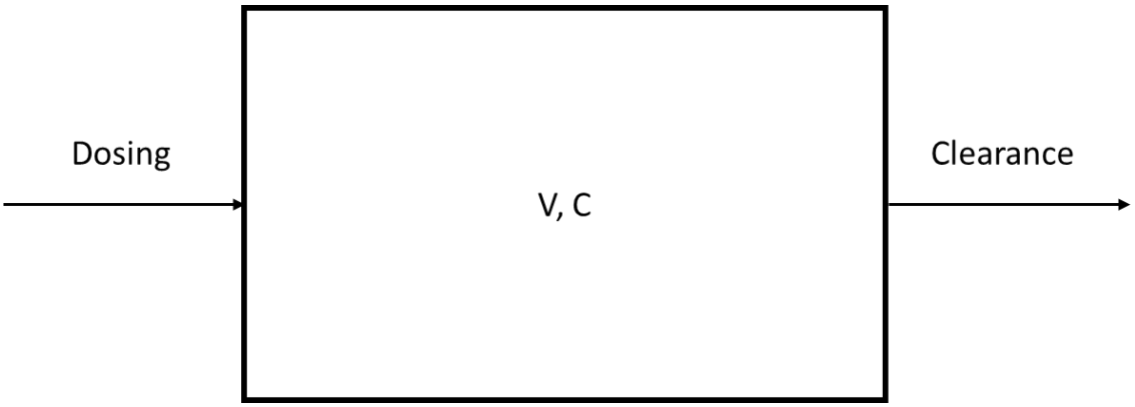
Derivation of a One Compartment Model of a i.v. Bolus Dose

For an i.v. bolus (i.e., drug injected into plasma rapidly) injection of a small molecule/biologic with low peripheral tissue penetration, a one compartment model can be used to predict pharmacokinetics. A simple diagram of a one compartment model is found below.



As seen in the diagram, a one compartment model consists of a single, fixed volume (V) compartment representing the blood where the main model output is the concentration of the delivery therapeutic (C) within the compartment. This concentration is controlled by the dosing method and the systemic clearance of the therapeutic, which typically comes from renal/hepatic clearance or degradation by other cells in the blood. One compartment models are represented by a single mass balance equation with only accumulation, in, and out terms:

$$Accumulation = In - Out$$

$$V\frac{dC}{dt} = dose(C,t) - clearance(C,t)$$

In the case of an i.v. bolus dose, we can neglect the dosing term in the mass balance and instead set the initial amount of therapeutic in the blood to the administered dose amount, leaving us with:

$$V\frac{dC}{Dt} = -clearance(C,t)$$

Clearance is typically modeled as a volumetric clearance rate CL (V/time) multiplied by the concentration, giving us:

$$V\frac{dC}{dt} = -CL * C$$

$$\frac{dC}{dt} = -\frac{CL}{V}C = -k_{CL}C$$

For simplicity, we define the term $k_{CL} = \frac{CL}{V}$, a first order clearance rate constant with respect to therapeutic concentrations. In total, are left with the set of equations:

$$C_0 = \frac{D}{V}$$

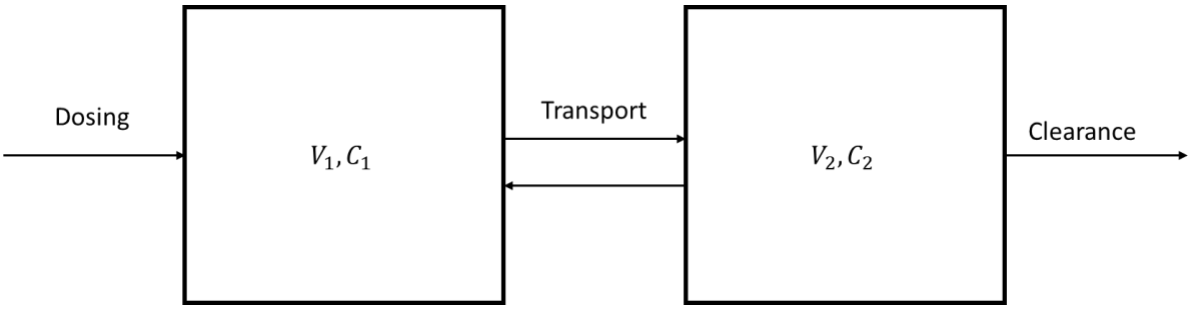
$$\frac{dC}{dt} = -k_{CL}C$$

In this simple case the model can be solved analytically, giving the solution:

$$C(t) = \frac{D}{V}\exp\{-k_{CL}t\}$$

Derivation of a Two Compartment Model of a s.c. Bolus Dose

For a s.c. bolus dose a similar modeling approach can be used; however, a second compartment must be added to represent the subcutaneous compartment and transport to and from the blood. The diagram below illustrates what these models look like.



Mass balances around both compartments are used to derive the equations for the two compartment model. For the subcutaneous compartment (compartment 1), the mass balance includes dosing, transport from the subcutaneous space to the blood, and transport from the blood to the subcutaneous space. Similar to the one compartment model of an i.v. bolus dose, we can model the dosing aspect of this compartment by setting the initial concentration equal to the dose divided by the compartment volume. For small molecules and biologics with a molecular weight smaller than ~16 kDa, transport from the subcutaneous space to the blood occurs via diffusion and can be modeled as:

$$J_{12} = V_1 k_{12}(C_1 - C_2)$$

Where J_{12} is the mass flux from compartment 1 to compartment 2 and k_{12} is the first order transport rate constant. This gives us a mass balance on compartment 1:

$$V_1 \frac{dC_1}{dt} = -V_1 k_{12}(C_1 - C_2)$$

$$\frac{dC_1}{dt} = -k_{12}(C_1 - C_2)$$

Similar to compartment 1, we obtain an equation for the concentration of therapeutic in compartment two considering transport from the subcutaneous space to the blood and clearance as in the one compartment model:

$$V_2 \frac{dC_2}{dt} = V_1 k_{12}(C_2 - C_1) - CL * C$$

$$\frac{dC_2}{dt} = \frac{V_1}{V_2} k_{12}(C_1 - C_2) - k_{CL} C_2$$

Therefore, in total a two compartment model is represented by a system of two ordinary differential equations:

$$\frac{dC_1}{dt} = -k_{12}(C_1 - C_2)$$

$$\frac{dC_2}{dt} = \frac{V_1}{V_2} k_{12}(C_1 - C_2) - k_{CL} C_2$$

Like a one compartment model, analytical solutions for a two compartment model are easily solvable, but typically predictions are made via ODE integration.