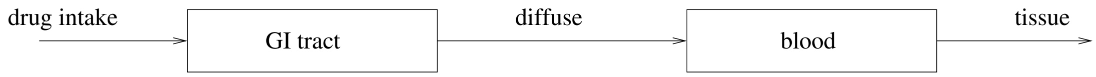
Mathematical modelling: Drug dosing II

Oral dose: Here, we consider drugs that are taken orally. These are usually taken before or after food. These drugs, with digested food in the form of a liquid mixture, arrive in the GI tract. From there, it diffuses into the blood through the GI tract wall and then reaches the tissue. Obviously, it takes time to be effective compared to the intravenous drugs.



Let $x(t)$ be the drug concentration in the GI tract and $y(t)$ be the drug concentration in the blood.

Single dose: A pill for a headache is an example. We assume that the single-dose pill in the form of a liquid mixture with concentration x_0 arrives at the GI tract at time $t = 0$, The governing equations are

$$\begin{aligned} \frac{dx}{dt} &= -k_1 x, \qquad && x(0) = x_0 \\ \frac{dy}{dt} &= k_1 x - k_2 y, && y(0) = 0. \end{aligned}$$

Here, x_0 is the initial concentration of the drug in the GI tract. Further, k_1 and k_2 are the decay constants for the drug in the GI tract and blood, respectively. Solving the first equation, we get

$$x = x_0 \mathrm{e}^{-k_1 t}$$

Substituting into the second and rearranging, we get

$$\frac{dy}{dt} + k_2 y = k_1 x_0 \mathrm{e}^{-k_1 t}$$

Integrating we find

$$y(x) = k_1 x_0 \mathrm{e}^{-k_2 t} \int_0^t \mathrm{e}^{(k_2 - k_1)s}\, ds$$

Thus, we find

$$y(x) = \begin{cases} \frac{k_1 x_0}{k_2 - k_1} \left(\mathrm{e}^{-k_1 t} - \mathrm{e}^{-k_2 t} \right), & k_2 \neq k_1 \\ k x_0 t \mathrm{e}^{-kt}, & k_1 = k_2 = k. \end{cases}$$

Multiple dose: A course of pills for a cold is an example. Let I be the rate of constant input of the drug (by ingestion) into the GI tract.

<u>Model I</u>: The governing equations are

$$\begin{aligned} \frac{dx}{dt} &= I - k_1 x, \qquad && x(0) = 0, \\ \frac{dy}{dt} &= k_1 x - k_2 y, && y(0) = 0. \end{aligned}$$

Solving for x we find

$$x(t) = \frac{I}{k_1}\left(1 - \mathrm{e}^{-k_1 t}\right)$$

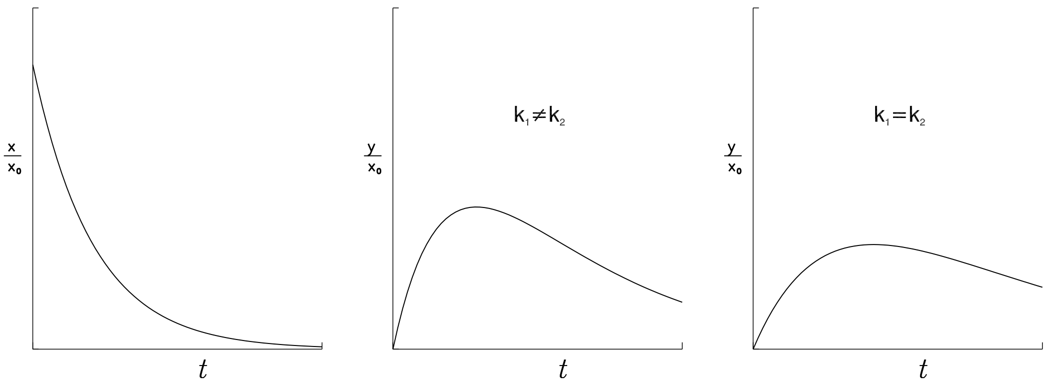
Substituting into the second equation and rearranging, we find

$$\frac{dy}{dt} + k_2 y = I(1 - \mathrm{e}^{-k_1 t}) \implies y(t) = Ie^{-k_2 t}\int_0^t (1 - \mathrm{e}^{-k_1 s})\mathrm{e}^{k_2 s}\, ds$$

Simplifying, we find

$$y(x) = \begin{cases} \frac{I}{k_2}\left[1 - \frac{1}{k_2 - k_1}\left(k_2 \mathrm{e}^{-k_1 t} - k_1 \mathrm{e}^{-k_2 t}\right)\right], & k_2 \neq k_1 \\ \frac{I}{k_2}\left(1 - \mathrm{e}^{-kt} - kt\mathrm{e}^{-kt}\right), & k_1 = k_2 = k. \end{cases}$$

From the solution, we observe that $x(t) \to x^* = \frac{I}{k_1}$ and $y(t) \to y^* = \frac{I}{k_2}$ when $t \to \infty$. Note that (x^*, y^*) is the equilibrium solution of the governing equations.



Model III: Rate of transport of a drug between the GI tract and the bloodstream is more realistically dependent on the difference $x - y$ between the concentrations. Thus, the modified governing equations are

$$\begin{aligned} \frac{dx}{dt} &= I - k_1(x - y), \qquad x(0) = 0, \\ \frac{dy}{dt} &= k_1(x - y) - k_2 y, \quad y(0) = 0. \end{aligned}$$

To solve it, we may use the matrix method for a linear system. Otherwise, we may proceed as follows. Denote $\frac{d}{dt}$ by D and $\frac{d^2}{dt^2}$ by D^2. From the second equation, we get

$$x = \frac{1}{k_1}(D + k_1 + k_2)y.$$

Substituting into the first equation, we arrive at a second-order linear ODE for y:

$$D^2 y + (2k_1 + k_2)Dy + k_1 k_2 y = k_1 I$$

A general solution of this equation is

$$y(t) = C_1 \mathrm{e}^{m_1 t} + C_2 \mathrm{e}^{m_2 t} + \frac{I}{k_2}, \qquad m_{1,2} = \frac{-(2k_1 + k_2) \pm \sqrt{4k_1^2 + k_2^2}}{2}.$$

It is clear that both $m_1 < 0$ and $m_2 < 0$. From the second equation, we also find $\frac{dy}{dt}(0) = 0$. Thus, using the initial condition $y(0) = 0$ and $\frac{dy}{dt}(0) = 0$, we find the constants C_1 and C_2:

$$C_1 = \frac{m_2 I}{k_2(m_1 - m_2)}, \quad C_2 = -\frac{m_1 I}{k_2(m_1 - m_2)}.$$

Once y is found, we get x using the second equation as

$$\begin{aligned} x &= \frac{1}{k_1} Dy + \frac{k_1 + k_2}{k_1} y \\ &= \frac{1}{k_1}\left(C_1 m_1 \mathrm{e}^{m_1 t} + C_2 m_2 \mathrm{e}^{m_2 t}\right) + \frac{k_1 + k_2}{k_1}\left(C_1 \mathrm{e}^{m_1 t} + C_2 \mathrm{e}^{m_2 t} + \frac{I}{k_2}\right) \end{aligned}$$

Since $m_1 < 0$ and $m_2 < 0$, we observe that

$$x(t) \to \left(\frac{1}{k_1} + \frac{1}{k_2}\right) I \quad \text{and} \quad y(t) \to \frac{I}{k_2} \qquad \text{as } t \to \infty.$$

Let us find the equilibrium solutions of the governing system, which are solutions of

$$I - k_1(x - y) = 0 \quad \text{and} \quad k_1(x - y) - k_2 y = 0 \implies y^* = \frac{I}{k_2},\ x^* = \left(\frac{I}{k_1} + \frac{I}{k_2}\right) I.$$

Hence, $x(t) \to x^*$ and $y(t) \to y^*$ as $t \to \infty$. Note that an equilibrium solution does not tell us whether it is stable or unstable. For this, we need to conduct a stability analysis, which involves the eigenvalues of the corresponding matrix for a linear system. Since we can find an exact solution that converges to the equilibrium solution as time increases, we conclude that the equilibrium solution is stable.