Applied Statistical Modelling (STAT 40510)
Main Project
Task 1: Theoretical Characterization of the Models

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TBC

Format of the Project

The main project in PK in STAT 40510 will be made up of several tasks.

- Follow the online lectures independently, attend weekly office hours in Weeks 5-7.
- Over the same time period, complete (in a group) **Tasks 1 and 2** to test your knowledge of what you have learned.
- Again over the same time period, you will be assigned your most challenging task, **Task 3**. You should begin to do background reading to understand what is required here.
- In Week 8, you should present your work to date, the presentation should consist of:
  - The theoretical concepts you have learned in Tasks 1–2;
  - How you will apply these in Task 3.
- The final report (due towards the end of the trimester) will be based entirely on Task 3.

Consider the following set of equations for a two-compartment PK model (IV administration).

$$\frac{\mathrm{d}A_1}{\mathrm{d}t} = -k_{10}A_1 - k_{12}A_1 + k_{21}A_2, \quad (1a)$$

$$\frac{\mathrm{d}A_2}{\mathrm{d}t} = k_{12}A_1 - k_{21}A_2, \quad (1b)$$

with initial conditions

$$A_1(0) = SD, \qquad A_2(0) = 0.$$

1. Using matrix methods for systems of linear ODEs, show that $Cp(t) = A_1/V_1$ satisfies:

   $$Cp(t) = A\mathrm{e}^{-\alpha t} + B\mathrm{e}^{-\beta t}, \quad (2a)$$

   Here, A and B are constants, but they are not arbitrary integration constants; they satisfy:

   $$A = \frac{S \cdot D(\alpha - k_{21})}{V_1(\alpha - \beta)}, \qquad B = \frac{S \cdot D(k_{21} - \beta)}{V_1(\alpha - \beta)}. \quad (2b)$$

   Also,

   $$\alpha = \tfrac{1}{2}\left[(k_{10} + k_{12} + k_{21}) + \sqrt{(k_{10} + k_{12} + k_{21})^2 - 4k_{21}k_{10}}\right], \quad (2c)$$

   $$\beta = \tfrac{1}{2}\left[(k_{10} + k_{12} + k_{21}) - \sqrt{(k_{10} + k_{12} + k_{21})^2 - 4k_{21}k_{10}}\right]. \quad (2d)$$

2. Let

   $$\mathrm{AUC} = \int_0^\infty Cp(t)\mathrm{d}t.$$

   Show that:

   $$\mathrm{AUC} = \frac{A}{\alpha} + \frac{B}{\beta}.$$

3. The clearance for a two-compartment model is defined as $\mathrm{Cl} = k_{10}V_1$. Show that:

   $$\mathrm{Cl} = \frac{S \cdot D}{\mathrm{AUC}}.$$

   Show also that:

   $$V_1 = \frac{D}{A + B}.$$

Suppose now that the patient receives

- An initial dose D,such that:

  $$A_1(0) = SD, \qquad A_2(0) = 0.$$

- A continuous, intravenous infusion at $t > 0$, at a rate $\dot{a}$.

Equations (**??**) (at $t > 0$) are now modified to read:

$$\frac{\mathrm{d}A_1}{\mathrm{d}t} = -k_{10}A_1 - k_{12}A_1 + k_{21}A_2 + \dot{a} \tag{3a}$$

$$\frac{\mathrm{d}A_2}{\mathrm{d}t} = k_{12}A_1 - k_{21}A_2, \tag{3b}$$

At steady state, $\mathrm{d}A_1/\mathrm{d}t = \mathrm{d}A_2/\mathrm{d}t = 0$.

4. Show that at steady state, $A_1 = \dot{a}/k_{10}$, with $Cp_{ss} = A_1/V_1$.

5. Find $Cp(t) = A_1/V_1$ in the non-steady state, for Equation (**??**).

6. If the initial dose D is such that $A_1(0) = \dot{a}/k_{10}$, then D is called the **loading dose**, and denoted by D_L. Show that

$$D_L = \frac{Cp_{ss}V_1}{SF}.$$

7. Lidocaine is an anti-arrhtymic drug that is used in the treatment of premature ventricular contractions. A 70-kg male patient is to receive an intravenous infusion of Lidocaine to maintain a plasma concentration of $2\,\mathrm{mg/L}$. Calculate a loading dose of Lidocaine hydrochloride ($S = 0.87$) to achieve this plasma concentration immediately. Lidocaine has the following volume: $V_1/[\text{patient mass}] = 0.5\,\mathrm{L/kg}$.