ST 762, HOMEWORK 1 SOLUTIONS, FALL 2009

1. We demonstate two ways to solve the system of ODEs.

   (a) First, we use the standard method of Laplace transforms. It is often the case that finding the solution of a complicated system of differential equations may be difficult, but transforming the problem to the Laplace transform "world" makes it easy to solve.

   The Laplace transform of a function $A(t)$ is given by

$$\mathcal{L}\{A(t)\} = \int_0^\infty e^{-st} A(t)\, dt.$$

From this definition, it is easy to see that, under suitable conditions, writing

$$A'(t) = \frac{dA(t)}{dt}$$

for short and using integration by parts, that

$$\mathcal{L}\{A'(t)\} = \int_0^\infty e^{-st} A'(t)\, dt = s\mathcal{L}\{A(t)\} + A(0).$$

Clearly, from the definition, the Laplace transform has a linearity property. We may thus take the Laplace transforms of each side of the system of ODEs in Equation (1) of Homework 1 to arrive at

$$\begin{aligned} s\mathcal{L}\{A(t)\} + A(0) &= k_a\mathcal{L}\{A_a(t)\} - k_e\mathcal{L}\{A(t)\} \\ s\mathcal{L}\{A_a(t)\} + A_a(0) &= -k_a\mathcal{L}\{A_a(t)\} \end{aligned}$$

We may apply the initial conditions to arrive further at

$$\begin{aligned} s\mathcal{L}\{A(t)\} &= k_a\mathcal{L}\{A_a(t)\} - k_e\mathcal{L}\{A(t)\} \\ s\mathcal{L}\{A_a(t)\} + D &= -k_a\mathcal{L}\{A_a(t)\} \end{aligned} \tag{1}$$

We can solve the second equation in (1) for $\mathcal{L}\{A_a(t)\}$ to obtain

$$\mathcal{L}\{A_a(t)\} = \frac{D}{s + k_a}.$$

Substituting this in the first equation in (1) then yields

$$\mathcal{L}\{A(t)\} = \frac{k_a D}{(s + k_a)(s + k_e)}. \tag{2}$$

It may also be shown that Laplace transforms have a uniqueness property; that is, two functions having the same Laplace transform can only differ at isolated points. Hence, for continuous functions, a particular Laplace transform corresponds uniquely to a function of t. Thus, we seek the function $A(t)$ whose Laplace transform is given in (2). Note also by the definition of Laplace transform that, for a constant C,

$$\mathcal{L}\{CA(t)\} = C\{A(t)\}.$$

Luckily, Laplace transforms of many functions are tabulated, so one does not have to derive them oneself. It turns out that the function whose Laplace transform is given by (2) may be found in an extensive such table (easily located using Google) and is given by

$$A(t) = \frac{k_a D}{k_a - k_e}\{\exp(-k_e t) - \exp(-k_a t)\},$$

from whence the result follows.

(b) Alternatively, if we didn't know about Laplace transforms, we could find the solution directly with a little more work. Considering the second equation in Equation (1) of Homework 1, we can rearrange this as

$$\frac{\frac{dA_a(t)}{dt}}{A_a(t)} = -k_a;$$

note that the left hand side is the derivative of $\log\{A_a(t)\}$ with respect to t. Thus, if we integrate both sides, we are led immediately to

$$\log\{A_a(t)\} = -k_a t + C \quad \Rightarrow \quad A_a(t) = \exp(-k_a t + C),$$

where C is some constant whose value we can determine by substituting the initial condition $A_a(0) = D$ to obtain

$$A_a(t) = D\exp(-k_a t).$$

Subsituting this in the first equation in Equation (1) of Homework 1 then yields, rearranging,

$$\frac{dA(t)}{dt} + k_e A(t) = k_a D e^{-k_a t}.$$

This is where a clever trick can be implemented: Multiplying both sides by $e^{k_e t}$ to obtain

$$\frac{dA(t)}{dt}e^{k_e t} + k_e e^{k_e t} A(t) = k_a D e^{-k_a t} e^{k_e t},$$

it is straightforward to observe that the left hand side is equal to

$$\frac{d}{dt}\{A(t)e^{-k_e t}\}$$

so that the expression becomes

$$\frac{d}{dt}\{A(t)e^{k_e t}\} = k_a D e^{(k_e - k_a)t}.$$

Integrating both sides then yields

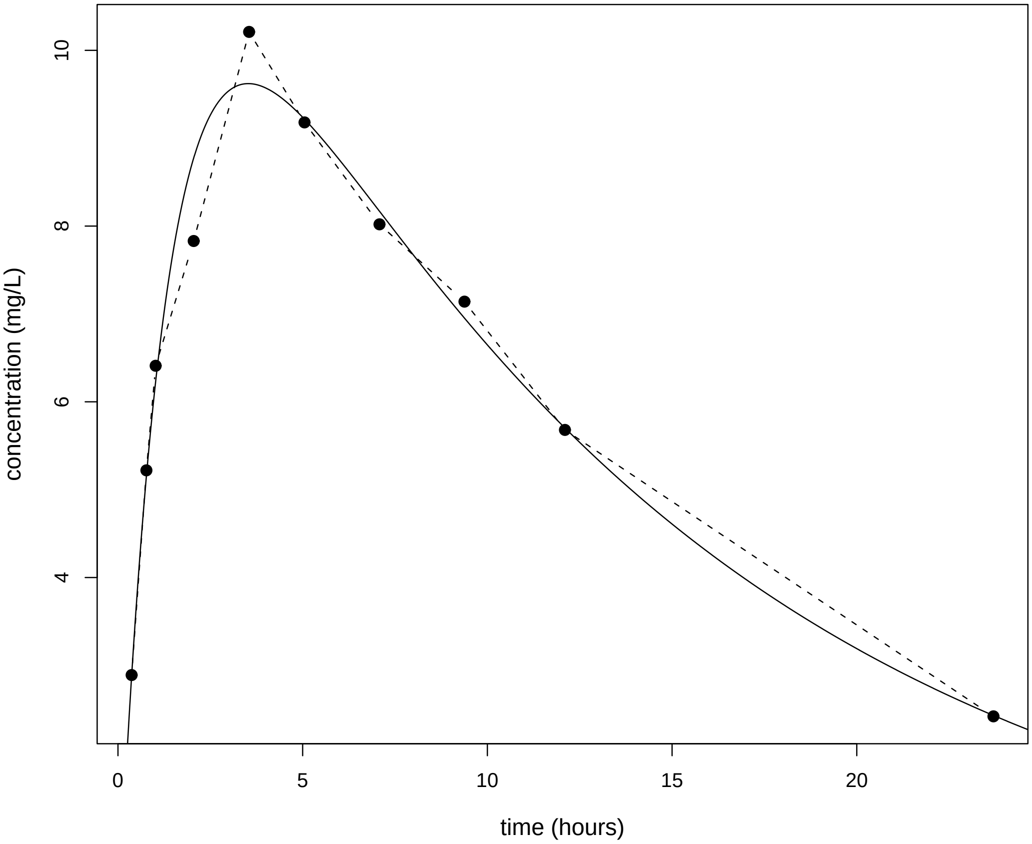
$$A(t) = k_a D e^{-k_e t}\left\{\frac{e^{(k_e-k_a)t}}{k_e - k_a} + C\right\}$$

for some constant C; applying the initial condition $A(0) = 0$ shows that

$$C = \frac{-k_a D}{k_e - k_a}.$$

Substituting this expression and rearranging then leads to the desired result.

2. (a) Here is the plot, with the observations connected by a dashed line.



The solid line is the fit of the one compartment model using GLS with $\theta = 1.0$ superimposed.

(b) See the two `R` programs and their output; they are fairly well-documented, so you should be able to follow them even if you do not know `R`. The programs use analytic derivatives. Note that, as expected, both algorithms lead to the same solutions for each θ.

(c) The theophylline concentration at 15 hours is estimated for this patient by substituting $t = 15$ in Equation (2) in Homework 1 with $\boldsymbol{\beta}$ set equal to the estimate obtained when $\theta = 1.0$. The estimate (see the output) is 4.61 mg/L (it is critical that, whenever you report an estimate of anything, you provide the associated units!)