

ST 762, HOMEWORK 1, FALL 2009

These problems are to be turned in on the due date.

1. Many nonlinear (in parameters) functions used to describe biological and physical phenomena arise as the solution to a system of *ordinary differential equations (ODEs)*. This is the case in pharmacokinetics, as discussed in Chapter 1 of the notes, where compartmental representations of mechanisms taking place over time within a human or animal subject are routinely used to characterize the pharmacokinetic processes of absorption, distribution, metabolism, and excretion. Similar representations are also used to describe processes underlying, for example, the interplay between a virus such as human immunodeficiency virus (HIV) and the immune system of an infected individual.

On the bottom of page 22 of the class notes is a depiction of the one compartment model with first order absorption used to describe the pharmacokinetics of theophylline following oral administration of dose D given at time 0 within a single individual. The compartmental model may be translated into the following system of ODEs:

$$\begin{aligned}\frac{dA(t)}{dt} &= k_a A_a(t) - k_e A(t) \\ \frac{dA_a(t)}{dt} &= -k_a A_a(t),\end{aligned}\tag{1}$$

where $A(t)$ is the amount of drug present in the main “blood” compartment at time $t \geq 0$; and $A_a(t)$ is the amount of drug present in a hypothetical “absorption depot” (e.g., the gut) at time $t \geq 0$, from which it is absorbed into the main compartment at fractional rate of absorption k_a (units of 1/time). At time $t = 0$, it is assumed that the dose D instantaneously fills the “absorption depot,” so that we have the *initial condition* that $A_a(t) = D$. It is also assumed that there is no drug already present in the system, so at time $t = 0$ there is no drug in the main “blood” compartment; that is, we have the initial condition $A(0) = 0$. For simplicity, we will take the bioavailability $F = 1$.

Because so many nonlinear models arise in this way, it is instructive to know something about how such systems of ODEs can be solved (when they can be solved in a closed form, that is). Whether or not you have ever taken a course in differential equations, you will find by doing a little research or by a little clever thinking that it is not too hard to solve this system of equations under the given initial conditions to obtain the expression for the concentration $C(t) = A(t)/V$ present in the main compartment at time t given in (1.5) on page 23 of the notes, where V is the hypothetical volume of the main compartment. Your job in this problem is to give a full, step-by-step argument leading to an expression for the solution for $A(t)$ using any method you choose.

Here are two possible ways to go about this (not the only ways):

- (a) Use the method of *Laplace transforms*, which you can research online or in a standard differential equations text and apply directly to system (1).
- (b) Use “brute force” by carrying out the following steps: (i) solve the second equation in (1), which involves only $A_a(t)$, for $A_a(t)$ by integrating both sides of the equation and making use of the initial condition. (*Hint*: divide both sides of the equation by $A_a(t)$ first.) (ii) Substitute the expression for $A_a(t)$ into (i), rearrange the equation by placing all terms involving $A(t)$ on the left hand side, multiply both sides by a suitable function

of t so that the new left hand side is the derivative of a product, integrate both sides, and make use of the initial condition.

It is up to you to choose a method of solution. Present your argument leading to the solution systematically and with suitable narrative so that a person unfamiliar with differential equations could follow it.

2. In your favorite programming language, write two programs to implement the following methods.
 - (i) The 3-step GLS algorithm on pages 51 and 56 of the notes, where the “weight matrix” \mathbf{W} is held fixed at step (iii), as described in Section 3.2 of the notes. Your program should allow the user to choose the number of iterations C .
 - (ii) IRWLS ($C = \infty$) as described in Section 3.4 of the notes.

Do not mimic the programs in Section 3.7; I want you to write all parts of the algorithm (e.g. the Gauss-Newton scheme) yourself.

Both programs should have the following features:

- Allow the user to supply a starting value $\beta_{(0)}$ to get things going.
- Allow the user to choose a maximum number of iterative updates in step (iii) of the fixed- C algorithm and similarly a maximum number of iterative updates of IRWLS; a reasonable choice would be 500. If iteration continues up to this max number, each program should stop and declare that no convergence was reached.
- Use as the convergence criterion both in step (iii) of the fixed- C algorithm and IRWLS the following rule: If 2 successive iterates $\beta_{(a+1)}$ and $\beta_{(a)}$, say, have a *relative* difference of less than some small constant tol , stop and declare $\beta^{(a+1)}$ to be the solution. That is, stop if

$$\max_{\ell=1, \dots, p} |\beta_{\ell, (a+1)} - \beta_{\ell, (a)}| / |\beta_{\ell, (a)}| < tol$$

as on page 59. For your programs, take $tol = 10^{-8}$.

- Compute an estimate of σ^2 based on the final estimated value for β . Use the version of the estimator “adjusted for loss of degrees of freedom” (with the divisor $(n - p)$) on page 64.

To test your programs, consider the pharmacokinetic data from Subject 10 in the theophylline study discussed in Example 1.8 in the class notes. Here, following oral dose of $D = 5.50$ mg/kg, this subject had blood samples taken at times t_j (hours), $j = 1, \dots, 10$, and on each the concentration of theophylline (mg/L), represented by the random variable Y_j for each j , was measured. Letting $\mathbf{x}_j = (D, t_j)$, the concentration-time relationship at this dose at time t_j is thought to be well represented by the one compartment open model with first order absorption as in Problem 1, which we write in the form

$$f(\mathbf{x}_j, \boldsymbol{\beta}) = \frac{De^{\beta_3}}{e^{\beta_2}(e^{\beta_3} - e^{\beta_1}/e^{\beta_2})} \{\exp(-e^{\beta_1}t_j/e^{\beta_2}) - \exp(-e^{\beta_3}t_j)\}, \quad (2)$$

Note that in (2), comparing to equation (1.5) of the class notes, the model is parameterized in terms of $\beta_1 = \log Cl$, $\beta_2 = \log V$, and $\beta_3 = \log k_a$. The data are given in the file

`theo10.dat`, available on the class web page. The first column is time (hours) and the second is concentration (mg/L).

(a) Make a plot of the data using your favorite software. This will give you a sense of the shape of the concentration-time relationship for this subject.

(b) Assume that the variance model is

$$\text{var}(Y_j|\mathbf{x}_j) = \sigma^2 f^{2\theta}(\mathbf{x}_j, \boldsymbol{\beta}), \quad \theta \text{ known.}$$

For this mean-variance model, try three different fits using each program:

- (i) $\theta = 0.0$ (thus, assuming constant variance and fitting by OLS)
- (ii) $\theta = 0.5$ (“Poisson-like” variance)
- (iii) $\theta = 1.0$ (constant coefficient of variation)

For the three-step GLS algorithm, use $C = 20$ for (ii) and (iii); note that (i) only requires the first step of the algorithm. For IRWLS, note that in (i) $\mathbf{W} = \mathbf{I}_n$. Use the starting value $\boldsymbol{\beta}_{(0)} = \{\log(0.05), \log(0.50), \log(0.75)\}^T$. Please turn in both your programs and their output.

(c) Assuming that theophylline concentrations exhibit approximate constant coefficient of variation, give an estimate of concentration at 15 hours post-dose for this subject.