

ST520, Fall 2011

Homework 2, due: Monday, 9/12/2011

1. (25 pts) Suppose the true dose-toxicity relationship is given by the following equation

$$P[\text{toxicity}|d] = \frac{e^{-4+0.2d}}{1 + e^{-4+0.2d}}, \quad 0 < d < \infty$$

where d is a dose level. Do the following:

- (a) (5 pts) Find the true maximum tolerated dose (MTD). That is, find a dose level D_m such that $P[\text{toxicity}|D_m] = 1/3$.
- (b) (5 pts) Starting with an initial dose level of $D_1 = 4$, prepare a dose schedule $\{D_i\}$ of length 5 using the modified Fibonacci sequence.
- (c) (10 pts) Let us conduct an MTD finding study in this way. Initially we treat 3 patients at D_1 . If no toxicity is seen, the trial moves to D_2 . If more than one patient experiences toxicity, the trial is stopped at D_1 . If exactly one patient has toxicity, then add ONE more patient. If this patient does not experience toxicity, then the trial is moved to D_2 . Otherwise the trial is stopped.

Define A_i to be the event that the trial will be stopped at dose D_i (if the trial reaches the last dose level, the trial will be stopped there), find $P(A_i)$. The dose level at which the trial stops is claimed to be the MTD. Define a random variable $X =$ dose level claimed to be the MTD. Find the distribution of X .

- (d) (5 pts) Find $E(X)$. Comment on this design in general by comparing $E(X)$ to the true MTD.
2. (8 pts) Suppose you are given a data set (t_i, c_i) , $i = 1, 2, \dots, n$, for an individual who participated a PK study, where t_i is the time at which drug concentration c_i is measured. Assume one compartment open model with the known intravenous dose D . Find an estimate of k_e and V for this individual (**Hint**: the true $\log c(t)$ should be a straight line and this implies the least square method after taking log-transformation of c_i).

3. (7 pts) Suppose you are given a one compartment open model with an oral dose D . Assume only half of the dose is available for absorption. Find AUC_{0-T} and $AUC_{0-\infty}$. How are AUC_{0-T} and $AUC_{0-\infty}$ related to T and k_e, k_a the elimination rate constant and absorption rate constant (**Hint:** Just describe how AUC_{0-T} and $AUC_{0-\infty}$ behave if T, k_e, k_a increase)?