AN INTRODUCTION TO STOCHASTIC COMPARTMENTAL MODELS IN PHARMACOKINETICS

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Introduction

Linear compartmental models are being widely used to model pharmacokinetic systems. Most of these models are deterministic and the statistical analysis of such models has been studied extensively. Many deterministic models are illustrated in other papers of this volume, and recent reviews are also given by Gibaldi and Perrier (1982), Godfrey (1983), and Jacquez (1985).

A number of papers have appeared recently in the literature presenting various stochastic models and deriving new methodology based on the stochastic assumptions. Many of these papers are reviewed in the previous references. In addition to their intrinsic appeal of providing a broader theoretical framework, the stochastic models have contributed two major results of interest in pharmacokinetic methodology. One is a new, rigorous approach to statistical moment theory incorporating the assumed compartmental structure of a model. The other is a generalization of the compartmental model to include nonexponential retention time distributions. These new methods have not been adopted rapidly in the literature, perhaps in part due to their perceived complexity.

This paper presents a simplified approach to these new, stochastic models and their related methodology. The objective is first to present a logical development of the results as heuristic extensions of previous well-known findings and then to illustrate the simplicity of the practical application of the methods. The paper may be considered as divided into two parts. The first part, consisting of Sections 1 to 4, reviews the single and multicompartment deterministic models and also a stochastic analog to these models. This part, though presenting some useful insights derived from the stochastic model, is intended primarily to serve as a foundation for the subsequent sections. The second part focuses on the new methodology. Section 5 develops the stochastic one-compartment model from the assumption of an exponential retention time random variable, and Section 6 extends the development to multicompartment models. Section 7 generalizes the stochastic one-compartment model to nonexponential retention time distributions which are common in survival analysis. Section 8 presents a generalized compartmental analysis in which a multicompartment model is assumed to have nonexponential retention time distributions within the compartments.

For the sake of simplicity, all models will assume that the drug enters the system as a bolus (IV injection). Also, it is assumed that the observations are on the total drug, as opposed to the concentration, in the compartments at various times. A matrix approach will be used to formulate all multicompartment models in order to unify the presentation. Many extensions to continuous dosing and concentration variables, and many mathematical proofs using matrix and other solution techniques are given in subsequent references.
I. One-Compartment Deterministic Model

1A Derivation of Model

Consider first the one-compartment deterministic model. It requires the following notation:

Notation Set 1A: Let:

1) \( X(t) \) denote the amount of drug in the compartment at time \( t \), and

2) \( \dot{X}(t) \) denote the derivative of \( X(t) \).

The basic assumption of this model is that the compartment has a constant proportional loss rate. This may be stated symbolically as follows:

Assumption 1A: Assume

\[
\frac{X(t + \Delta t) - X(t)}{\Delta t} = -k \Delta t
\]

where \( \Delta t \) is a small increment of time and \( k \) is a constant.

The constant \( k \) is often called the fractional (or proportional) flow rate. Dividing (1-1) by \( \Delta t \), multiplying by \( X(t) \) and then taking the limit as \( \Delta t \) approaches 0 yields the following model:

Model 1A:

\[
\dot{X}(t) = X(t)(-k)
\]

This differential equation has the familiar solution:

Solution 1A:

\[
X(t) = X(0) \exp(-kt)
\]

where \( X(0) \) is the initial amount (i.e. the dose).

1B Parameter Estimation

Usually the parameter \( k \), and often \( X(0) \) also, are unknown and are estimated from data on the system. Consider now the following additional notation:

Notation Set 1B: Let

1) \( y(t_j) \) denote the observed amount of drug in the compartment at time \( t_j \),

2) \( y = [y(t_1), \ldots, y(t_m)] \) be the (row) vector of observations at \( m \) distinct times,

3) \( Y(k) = [X(t_1), \ldots, X(t_m)] \) be a corresponding vector of the assumed model values with parameter \( k \), and

4) \( \epsilon = [\epsilon_1, \ldots, \epsilon_m] \) be a vector of random errors.

The statistical model which is usually assumed for estimation is:

Assumption 1B: Let

\[
y = Y(k) + \epsilon
\]

with expected values \( E(\epsilon) = 0 \), a vector of 0’s, and variance-covariance matrix \( E[\epsilon'\epsilon] = D \), a diagonal matrix.

Under this assumed model, the \( y(t) \) observations may have different variances, for example one could assume that the variances are proportional to the observed values, however the assumption of a diagonal \( D \) matrix requires that all observations be uncorrelated, which for all practical purposes means that they must be independent. The errors are usually associated with the independent measurement (or sampling) process which takes place in order to ascertain a \( y(t) \) value. The parameters may be estimated by ordinary or by weighted nonlinear least squares, as discussed elsewhere in this volume and in a number of reviews.

II. Multicompartment Deterministic Model

2A Derivation of Model

The subsequent generalization will hold for any \( n \)-compartment model. However, for simplicity, the concepts will be illustrated at times only for the two-compartment case. Consider now the following expanded set of notation: