SIMIODE Systemic Initiative for Modeling Investigations and Opportunities with Differential Equations

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**Article Review and Annotation**

Wagner, J. G. 1967. Computers in pharmacokinetics. *Clinical Pharmacology and Therapeutics*. 8(1)-Part 2: 201-218.

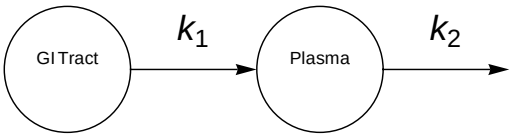
Article Abstract: Analogue, digital, and hybrid computers may be used in two principal ways in the analysis of data from pharmacokinetic studies: (1) for rapid numerical analysis of data and (2) for pharmacokinetic simulation. Simulation may be defined as the act of building a model of a system and observing its performance. In pharmacokinetics, the equations and models elaborated are always oversimplifications and their appropriateness can only be judged by their ability to describe the observed data and the accuracy with which they make predictions of future observed data. Five examples are employed to illustrate the use of computers; the paths from the original observed data to the final answers are shown in detail. The examples are as follows: (1) the relationship between the area under the lincomycin serum concentration curve and the dose of lincomycin administered intramuscularly; (2) the distribution of the half-lives of the antibiotics liricomycin and novobiocin; (3) prediction of multiple dose serum levels of lincomycin observed after constant rate intravenous Infusions with an analogue computer; (4) the fitting of serum levels of tetracycline observed after a single oral dose with a two-term exponential equation; (5) simulation of serum levels produced by depointramuscular preparations of lincomycin with a digital computer.

This is a seminal paper in pharmacokinetics in which the author introduces historic notions and approaches. As can be seen from the abstract there is a variety of material here. In Table VI from the article we extract the data,

**Table VI.** *The lowest serum levels of tetracycline hydrochloride activity observed in a panel of 8 subjects administered Panmycin, 250 mg., after specified breakfast*

| *Time (hours)* | *Serum concentration of tetracycline HCl (mcg./ml.)* |
|---|---|
| 1 | 0.7 |
| 2 | 1.2 |
| 3 | 1.4 |
| 4 | 1.4 |
| 6 | 1.1 |
| 8 | 0.8 |
| 10 | 0.6 |
| 12 | 0.5 |
| 16 | 0.3 |

form a two compartment model as depicted in the diagram, build a linear system of differential equations model,




Let $x_1(t)$ be the concentration of tetracycline (units?) in the gastrointesinal tract.
Let $x_2(t)$ be the concentration of tetracycline (units?) in the plasma.

$$x_1`(t) = - k_1\, x_1(t) \qquad \text{and} \qquad x_2`(t) = k_1\, x_1(t) - k_2\, x_2(t)$$

solve it, and estimate the parameters $k_1$ and $k_2$ from the data. Then we plot the concentration in the plasma to confirm our model.