MATHEMATICAL MODELING OF PHARMACOKINETIC DATA

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PHARMACOKINETICS- DEFINITION AND SCOPE

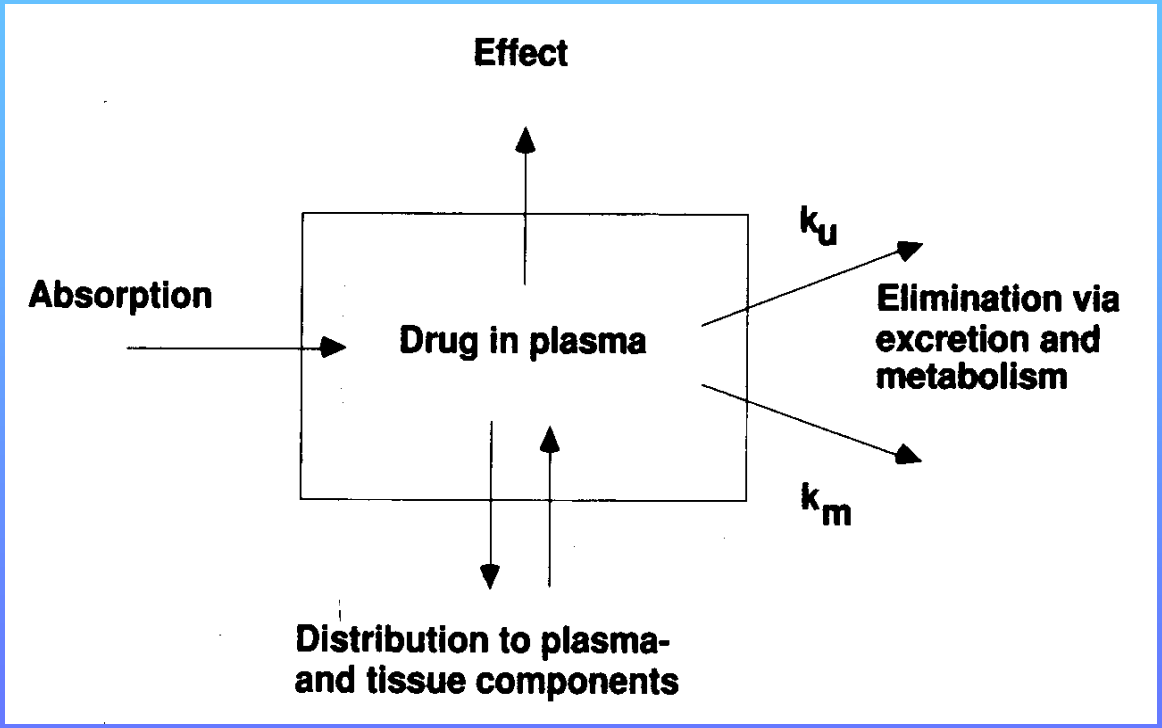
Pharmacon=drug and Kinetics=movement

Mathematical description of biological process affecting drugs and affected by drugs

Important:

- Design and development of new drugs
- Reassessment of old drugs
- Clinical applications (Clin. Pkinetics)
- Evaluating bioavailability and bioequivalence

SHEMATIC REPRESENTATION OF ADME AND PD OF A MOLECULE



REASONS FOR MEASURING BLOOD LEVELS AND URINARY EXCRETION

1. Is the drug absorbed and to what extent?
2. Do other things interfere with absorption of the drug?
3. What is the nature of the dose response curve?
4. How do levels obtained with different routes of administration compare?
5. How is the drug eliminated and how fast?
6. What factors affect rate of elimination?
7. Is the pharmacological action due to the parent drug or a metabolite?
8. Is there a correlation between pharmacologic response and pharmacokinetic data?

WHY DO WE TRY TO FIT DATA WITH EQUATIONS AND DERIVE KINETIC MODELS?

1. To summarize observed data- data exploration
2. To increase understanding of the process or processes involved
3. To be able to make predictions
4. To compare several drugs with similar pharmacological actions
5. To quantitatively relate biological activity with pharmacokinetic data

COMPARTMENT MODELS

A model in pharmacokinetics is a hypothetical structure which can be used to characterize with reproducibility, the behavior and fate of a drug in biological system when given by a certain route of administration and in a particular dosage form.

PHARMACOKINETIC MODELS

Type	No. of Compartments	Mathematical Characteristics
Non-compartmental	0	Curve fitting to data
Compartmental	1-3	Model parameters fit to data
Physiological	4-20	Model parameters fit to priori

PHARMACOKINETIC MODELS

NON-COMPARTMENTAL MODELS

- Offers little insight into the rate or processes involved in drug distribution
- Imposes a model structure and more restrictive than multi-compartmental model

COMPARTMENT MODELS

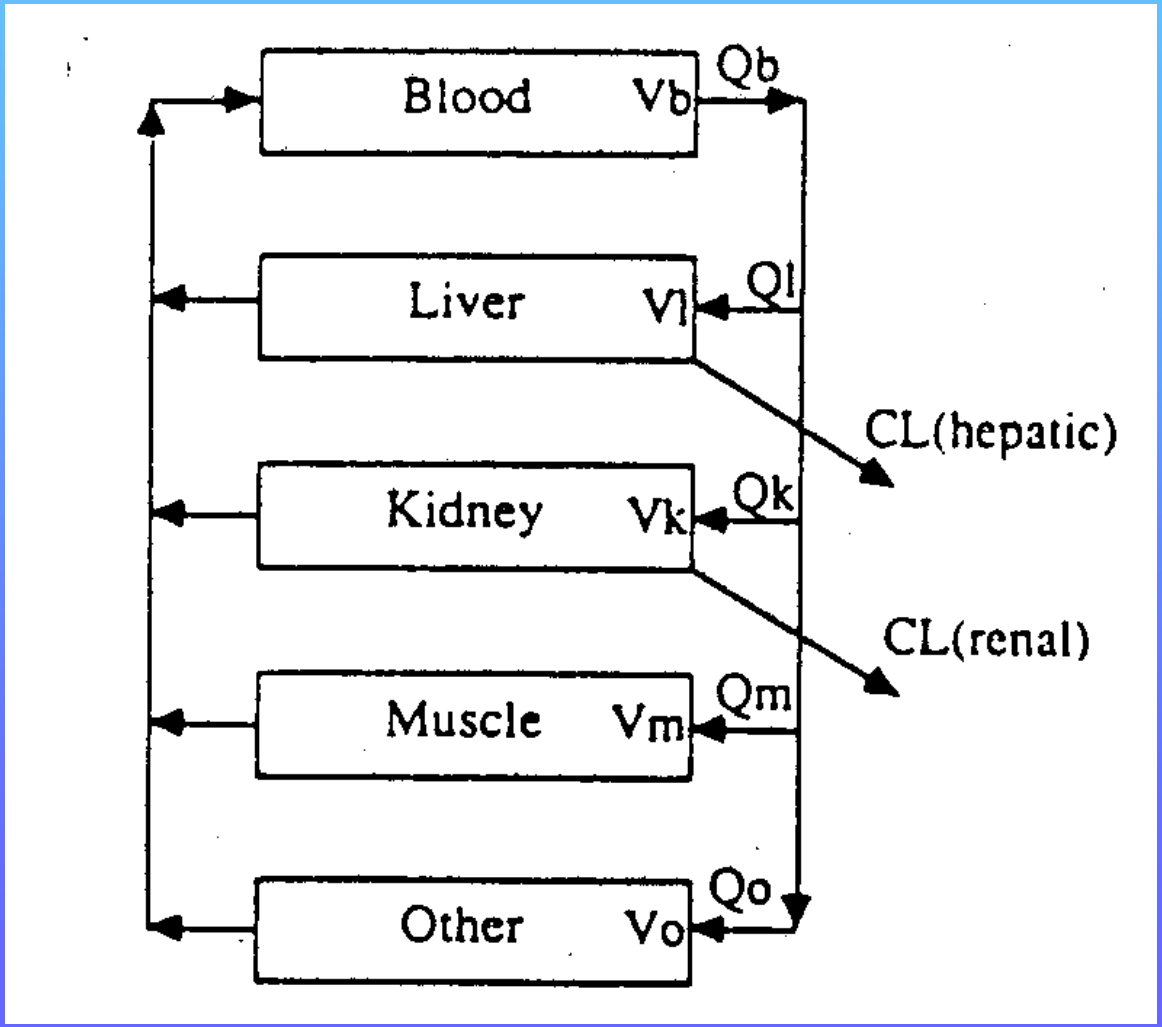
- Catenary and mamillary models

PHYSIOLOGICAL MODELS

- Organ blood flow, volume, partition coefficient, and binding affinity for a particular drug
- Assumes that a fraction of the drug in the body will be extracted form the blood on each pass
- Blood flow is a determental of drug clearance

$$CL = Q.E$$

PHYSIOLOGICAL MODELS



ESTIMATION OF PARAMETERS

1. The statistical problem
2. Numerical methods
3. Computer implementation

NUMERICAL GRAMMAR
(Daniel & Wood, 1971)

1. Use all relevant data
2. Have reasonable parsimony in the number of unknown parameters
3. Take into account the error in the data
4. Provide some measure for the precision of estimates for unknown model parameters
5. Be able to locate systematic deviations in data form the chosen model equations
6. Provide some measure of how well the model will predict future experimental frames

WAGNERs SIX POINT CHECK LIST FOR DERIVING MODELS

1. State the assumption involved
2. Excert caution particularly in making physiological and biochemical inferences
3. Ask yourself whether models could equally as well explain the data
4. Check whether your model agrees with known physiology, pharmacology etc.,
5. Check not only for closeness of fit, but also trends in areas of poor fit
6. Check whether your model provides accurate predictions particularly if the system is perturbed

GENERAL MODELING STRATEGIES

1. Initial model selection
- Start with a plot
- How many linear segments are involved?
2. Obtaining initial estimates
- Curve stripping method
- Computer programs – PCNONLIN, KINETICA etc.,
3. Selection of minimization algorithm
- Gauss-Newton
- Marquardt
- Nelder-Mead Simplex Optimization

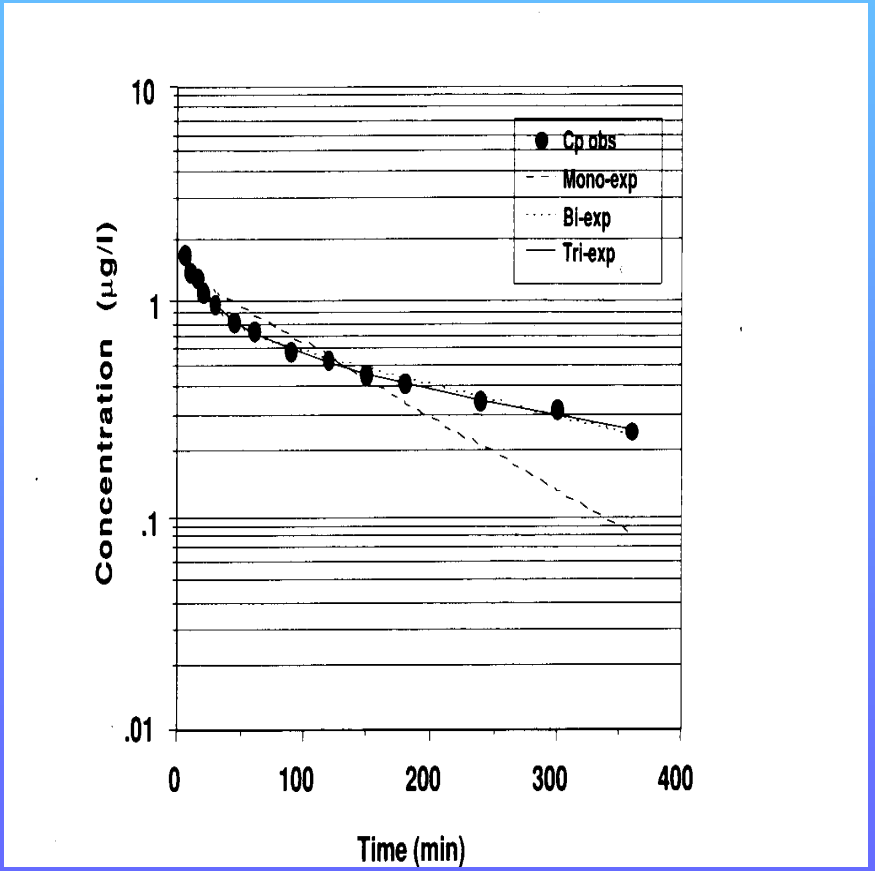
GENERAL MODELING STRATEGIES…continued

4. Assessing the goodness of fit

- AIC
- Correlation between observed and predicted values
- Analysis of residuals

START WITH A PLOT

1. Plot on Log scale
2. See for the number of segments
3. Straight line in the elimination segment- 1 compartment (mono exp)
4. One segment – 2 compartment (bi-exp)
5. Two segments – 3 compartments (Tri-exp)…..



RATE PROCESSES

FIRST ORDER PROCESS

$$\frac{dc}{dt} = -k.C$$

$$C = C_0 . \exp(-k.t)$$

$$\ln C = C_0 - k.t$$

ZERO ORDER PROCESS

$$\frac{dC}{dt} = -k_0$$

$$C = C_0 - k_0.t$$

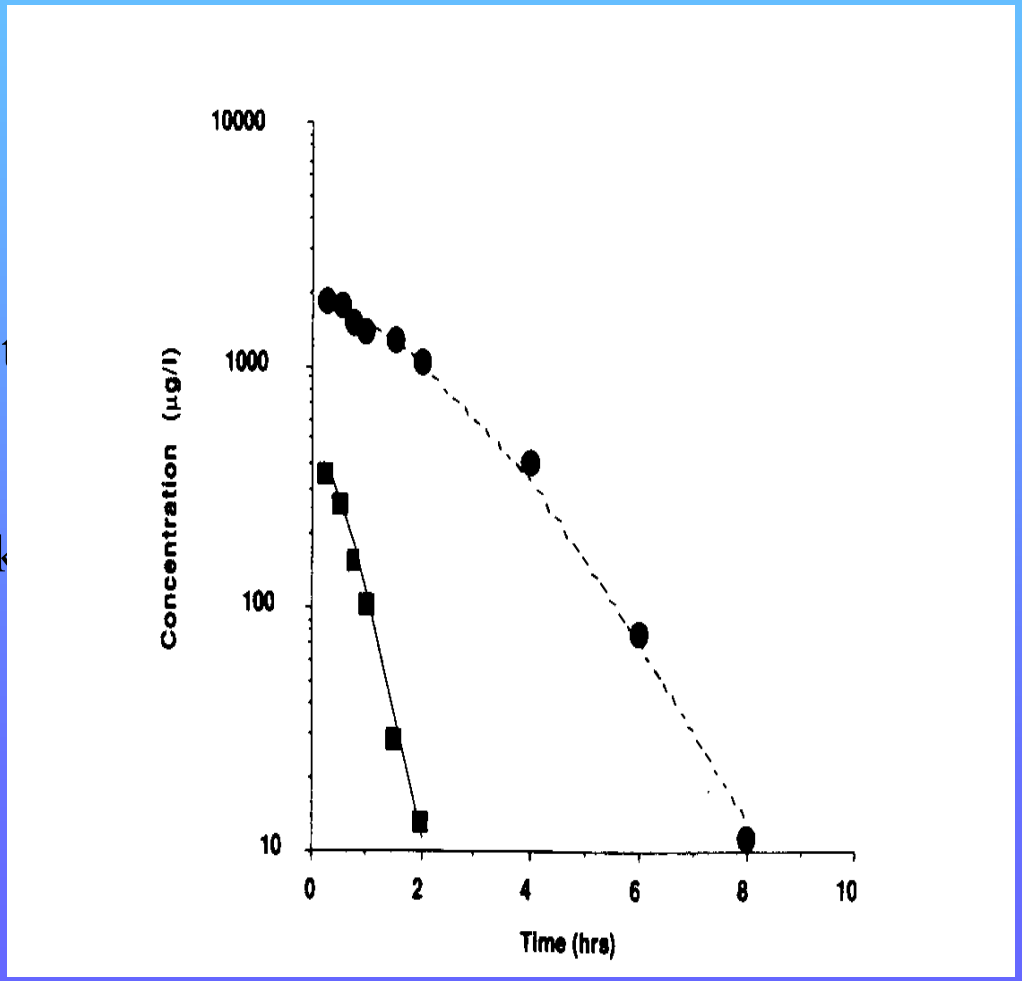
CAPACITY LIMITED PROCESS

$$-\frac{dC}{dt} = \frac{V_{max}.C}{K_m + C}$$

$$\frac{t_{(n-1)} - t_{(n)}}{\ln C_{(n)} - \ln C_{(n+1)}} = \frac{K_m}{V_{max}} + \frac{1}{V_{max}} . \sqrt{C_{(n)} . C_{(n+1)}}$$

CAPACITY LIMITED PROCESS

1. Plot Con Vs Time on log scale at increasing doses
2. Low dose may look like first order plot (indicated non-saturation)
3. At higher doses the plot look like dome shaped (due to saturation)



HOW COMPLICATED MODEL CAN BE FIT TO DATA?

$$NP=2.EX+PE+2.TS+NL$$

NP=No. of parameters

EX=No. of exponentials

PE=No. of elimination or excretory pathways

TS=No. of tissue spaces or binding proteins

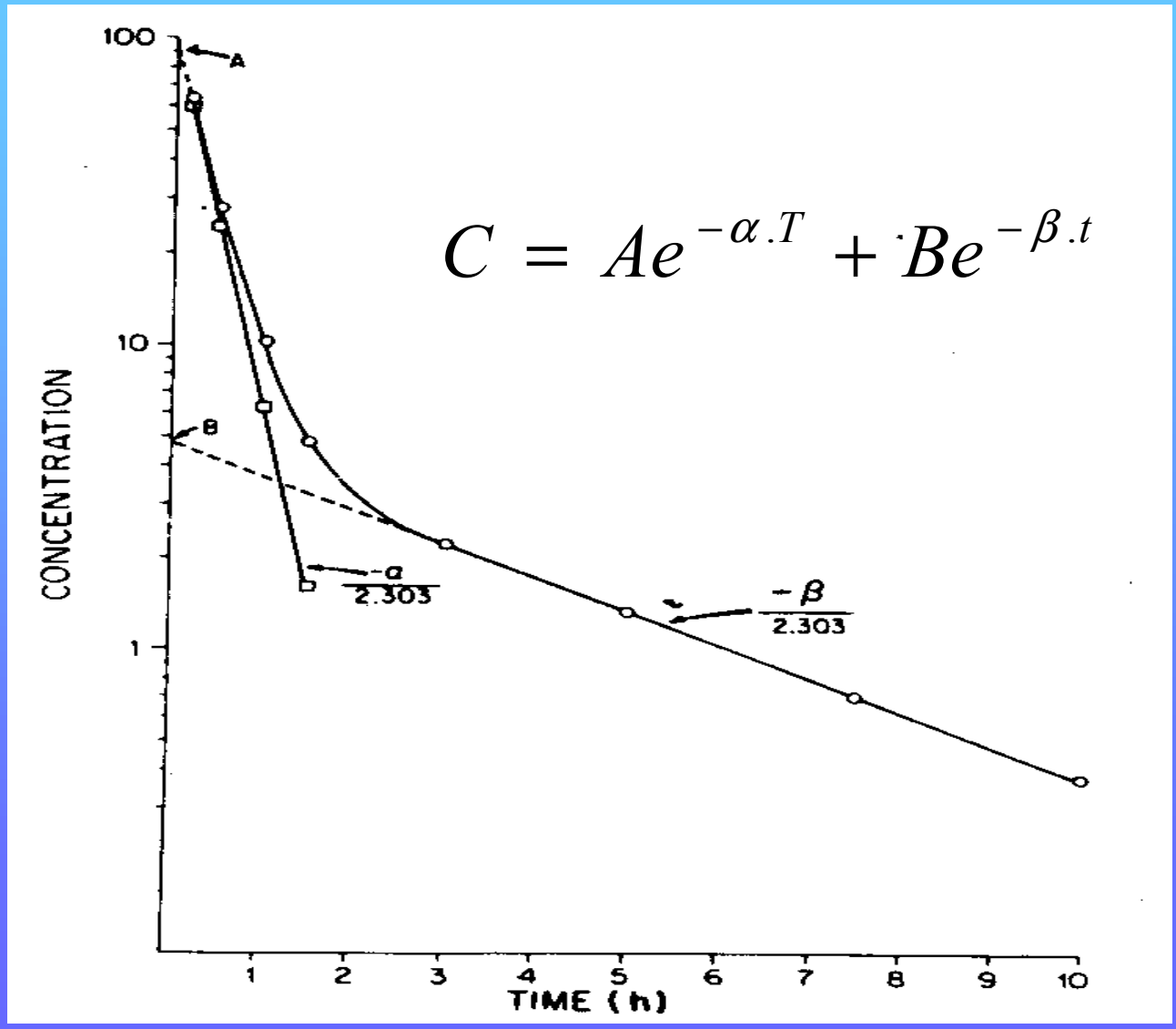
NL=No. of visible non-linear features

Ref.: Jusko, Applied Pharmacokinetics: Principles of TDM, 2nd Edn.1986

OBTAINING INITIAL ESTIMATES

1. RANDOM SEARCH METHODS
2. STRIPPING OR PEELING METHODS
3. LINEARIZATION METHODS

CURVE STRIPPING METHOD



$$C = Ae^{-\alpha.T} + Be^{-\beta.t}$$

LINEARIZATION METHODS

$$\begin{pmatrix} n & \sum x_i \\ \sum x_i & \sum x_i^2 \end{pmatrix} \begin{pmatrix} \beta_0 \\ \beta_1 \end{pmatrix} = \begin{pmatrix} \sum y_i \\ \sum x_i y_i \end{pmatrix}$$

A C B

$$A^{-1}.B = C$$

NORMAL EQUATIONS TO SOLVE LEAST SQUARES

COMPUTER PROGRAMS

A large number of computer programs are available to perform the functions of mathematical modeling. Some are:

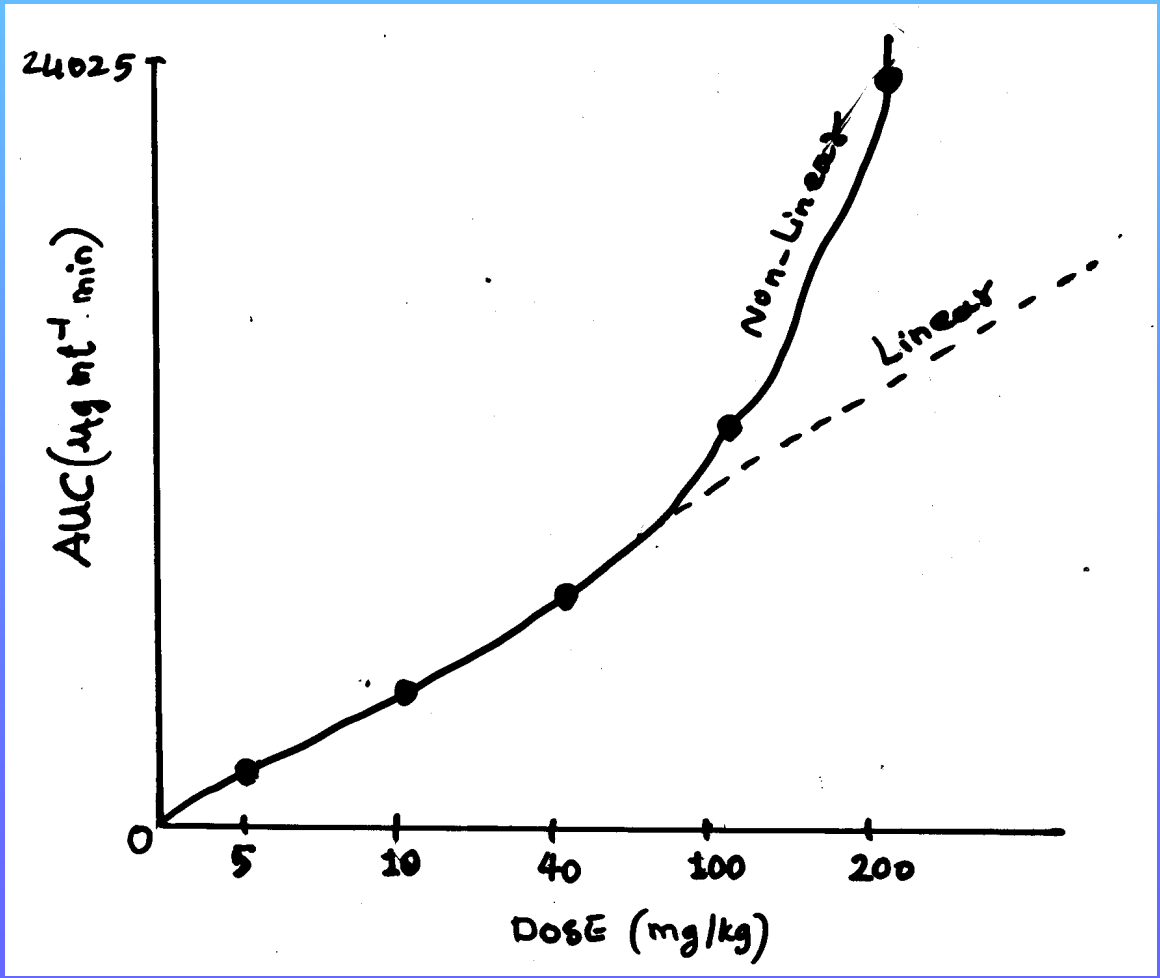
1. ADAPT II – Fortran based by D'Argenio and Schumitzky
2. BOOMER – Fortran Based by WA Bourne
3. MK MODEL- by Holford
4. MULTI – Basic based by Yamaoka et al.
5. WINNONLIN – Industry standard popular program, Windows based.
6. KINETICA – Industry based popular program, Windows based
7. NONMEM – Fortran based by Beal and Sheiner
8. QUICKCALC – Basic based by Shivprakash- 14 models
9. MATHEMATICA – Most advanced programming capabilities, can be used for alpha-numerical programming

CONFUSION BETWEEN MATHS AND BIOLOGY PROCESS

DO NOT GET CONFUSED BETWEEN NON-LINEAR PHARMACOKINETICS AND NON-LINEAR MODELS

Non=Linear Pharmacokinetics is saturation kinetics in which PK parameters are not linear with increasing dose (do not exhibit dose linearity)

NON-LINEAR PHARMACOKINETICS



LINEAR AND NON-LINEAR MODELS

$$Y = \beta_0 + \beta_1 Z_1 + \beta_2 Z_2 + ... + \beta_n Z_n + \varepsilon .....1$$

$$Y = \exp(\theta_1 + \theta_2 t^2) + \varepsilon .....2$$

$$\ln Y = \theta_1 + \theta_2 t^2 + \varepsilon .....3$$

Read: Draper and Smith: Applied Regression analysis

OPTIMIZATION- CRITERIA FOR BEST FIT

These criteria are achieved by minimizing the following quantities:

$$OLS = \sum_{i=1}^{n} (C_i - \hat{C}_i)^2$$

$$WLS = \sum_{i=1}^{n} W_i (C_i - \hat{C}_i)^2$$

$$ELS = \sum_{i=1}^{n} \frac{(C_i - \hat{C}_i)^2}{Var(\hat{C}_i)} + \log_e (Var(\hat{C}_i))$$

Read on Weighting Schemes in PK: Peck CC et al. Drug Met. Rev., 1984

OPTIMIZATION TECHNIQUES

STEEPEST DESCENT METHOD

Seems to be most efficient. Problems arise when translated into computer method.

Large steps- method gets lost

Small steps- too long

Quite slow at minimum

GUASS-NEWTON METHOD

Linear least squares method. Linearisation by first order Taylors expansion. It may lost with poor initial estimates.

OPTIMIZATION TECHNIQUES continued…

MARQUARDT METHOD

$$\chi^2 = \sum_{i=1}^{n} \left[\frac{Y_i - Y(x_i)}{\sigma_i} \right]^2$$

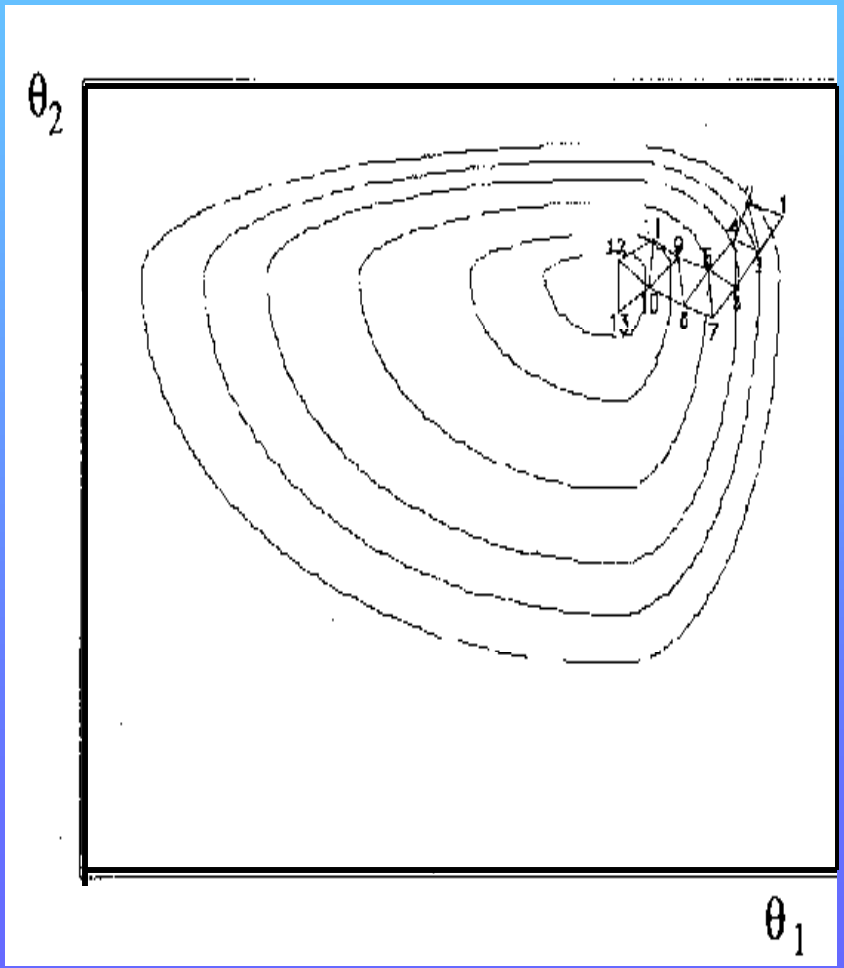
Minimization of χ^2 is used as a criterion of best fit.

SIMPLEX METHOD

SIMPLEX OPTIMIZATION

Contour plot of residual sum of square surface

Ref. :Nelder and Mead, Computing Journal, 1965



MODEL SEECTION CRITERIA

1. THE AKAIKE INFORMATION CRITERIA (AIC)

$$AIC = N.\ln.R_e + 2p$$

$$R_e = \sum_{i=1}^{n} w_i (C_i - \hat{C}_i)^2$$

Minimum AIC value is the best representation of model.

Warning: Improper weight could select wrong equation.

2. F-TEST

$$F = \frac{WSS_1 - WSS_2}{WSS_2} \cdot \frac{df_2}{df_1 - df_2} \qquad (df_1 \rangle df_2)$$

df=(No. of experimental data points)-(No. of parameters)

MODEL SELECTION CRITERION continue…

3. STANDARD DEVIATION OF ESTIMATED PARAMETER

$$S.D = \sqrt{s^2 C_{ii}}$$

$$s^2 = \frac{\sum dev^2}{N - P}$$

$$\sum dev^2 = \sum (Y - \hat{Y})^2$$

N=No. of data points

P= No. of parameters estimated

N-P= degrees of freedom

C_{ii}=i^{th} diagonal element of the variance-covariance matrix of the elements

MODEL SELECTION continue…

4. COEFFICIENT OF DETERMINATION

$$r^2 = 1 - \left[\sum_{i=1}^{n} \frac{w_i (Y - \hat{Y})^2}{S_y^2} \right]$$

$$S_y^2 = \sum_{i=1}^{n} \frac{Y^2 - (\sum Y)^2}{N}$$

5. MODEL SELECTION CRITERION (MSC)

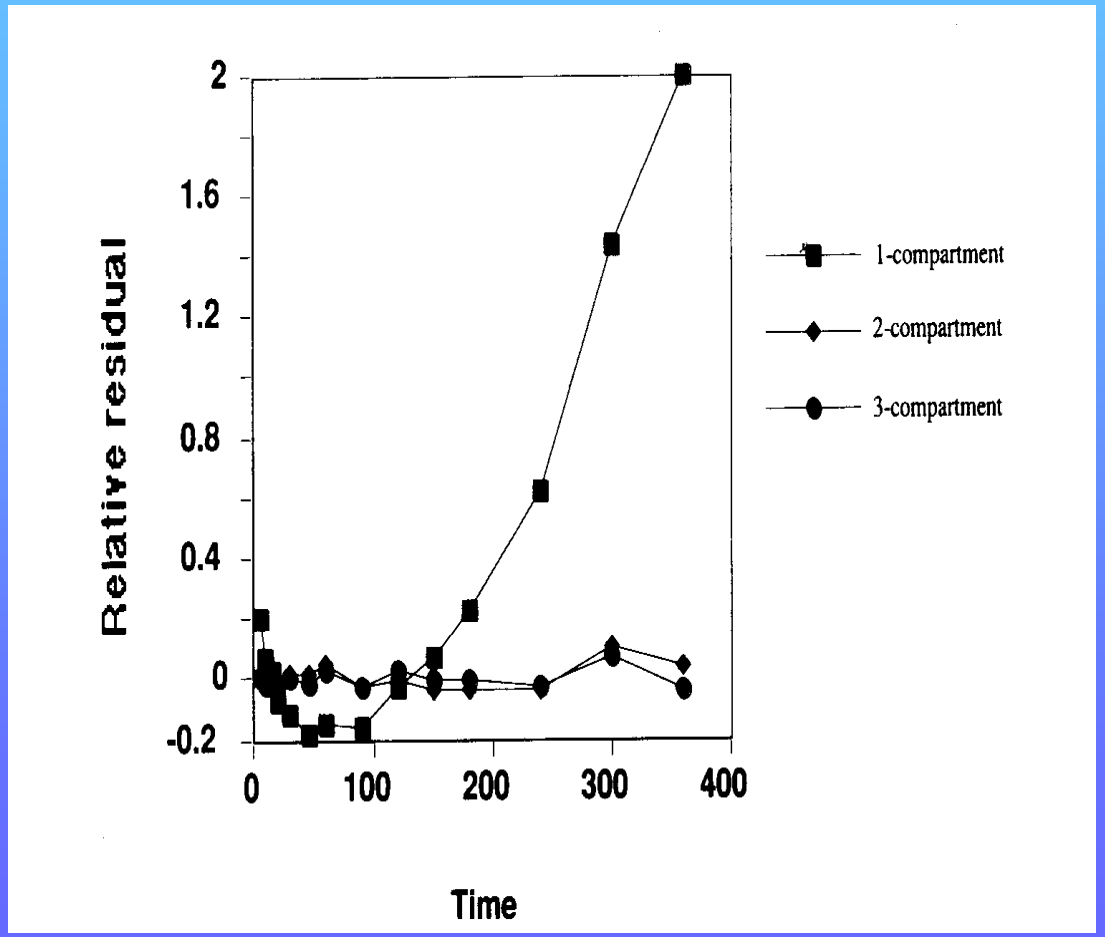
$$MSC = \ln \left[\frac{\sum_{i=1}^{n} w_i (Y_i - \bar{Y})^2}{\sum_{i=1}^{n} w_i (Y_i - \hat{Y})^2} \right] - 2.\frac{P}{N}$$

For equal weight

$$MSC = \ln \left[\frac{S_y^2}{\sum dev^2} \right] - 2.\frac{P}{N}$$

MODEL SELECTION continue…

6. ANALYSIS OF RESIDUALS



MODEL SELECTION continue..

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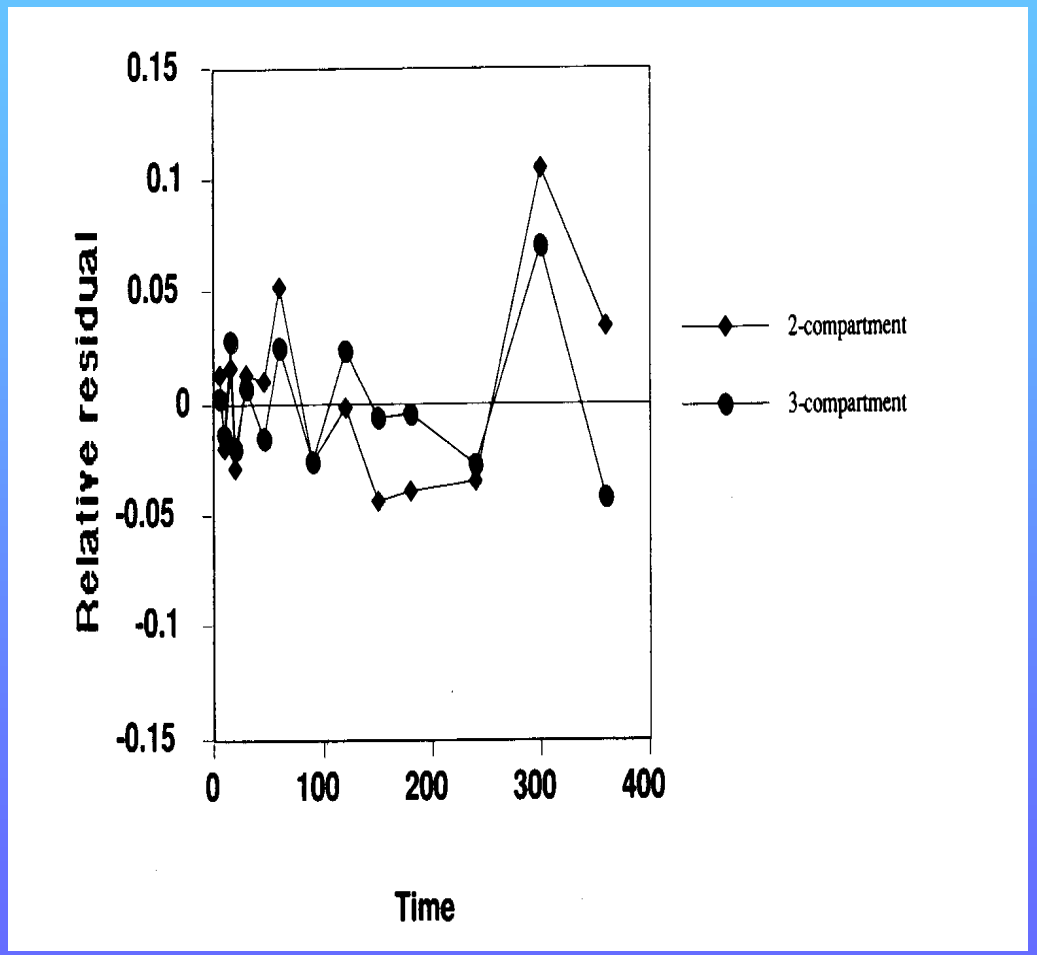

OPPORTUNITY BASED ON SKILLS

- Mathematics – algebra, matrix manipulations, calculus, numerical analysis
- Initial parameter estimation procedures
- Computer programming – learn at least one programming language
- Knowledge of industry standard software's

THANK YOU