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
Schematic representation of ADME and PD of a molecule

Effect

Absorption

Drug in plasma

Elimination via excretion and metabolism

$k_u$

$k_m$

Distribution to plasma- and tissue components
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

<table>
<thead>
<tr>
<th>Type</th>
<th>No. of Compartments</th>
<th>Mathematical Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-compartmental</td>
<td>0</td>
<td>Curve fitting to data</td>
</tr>
<tr>
<td>Compartmental</td>
<td>1-3</td>
<td>Model parameters fit to data</td>
</tr>
<tr>
<td>Physiological</td>
<td>4-20</td>
<td>Model parameters fit to priori</td>
</tr>
</tbody>
</table>
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 detrimental of drug clearance

\[ CL = Q.E \]
PHYSIOLOGICAL MODELS

Diagram showing the flow of substances through different body compartments. The diagram includes:
- **Blood (Vb)**
- **Liver (Vl)**
- **Kidney (Vk)**
- **Muscle (Vm)**
- **Other (Vo)**

Flows indicated by arrows:
- **Qb** from Blood to Liver
- **Ql** from Liver to Kidney
- **Qk** from Kidney to Muscle
- **Qm** from Muscle to Other

Flows designated as:
- **CL(hepatic)**
- **CL(renal)**
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
WAGNER's 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

\[ \frac{dc}{dt} = -k \cdot C \]
\[ C = C_0 \cdot \exp(-k \cdot t) \]
\[ \ln C = C_0 - k \cdot t \]

ZERO ORDER PROCESS

\[ \frac{dC}{dt} = -k_0 \]
\[ C = C_0 - k_0 \cdot t \]

CAPACITY LIMITED PROCESS

\[ \frac{dC}{dt} = \frac{V_{\text{max}} C}{K_m + C} \]
\[ \frac{t_{(n-1)} - t_{(n)}}{\ln C_{(n)} - \ln C_{(n+1)}} = \frac{K_m + 1}{V_{\text{max}}} \sqrt{\frac{C_{(n)} \cdot C_{(n+1)}}{V_{\text{max}}}} \]
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 looks like dome shaped (due to saturation)
HOW COMPLICATED MODEL CAN BE FIT TO DATA?

\[ NP = 2 \cdot \text{EX} + \text{PE} + 2 \cdot \text{TS} + \text{NL} \]

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

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

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

\[A^{-1} \cdot B = C\]

NORMAL EQUATIONS TO SOLVE LEAST SQUARES
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.
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

\[
Y = \beta_0 + \beta_1 Z_1 + \beta_2 Z_2 + \ldots + \beta_n Z_n + \varepsilon \ldots \ldots 1
\]

\[
Y = \exp(\theta_1 + \theta_2 t^2) + \varepsilon \ldots \ldots \ldots \ldots \ldots \ldots 2
\]

\[
\ln Y = \theta_1 + \theta_2 t^2 + \varepsilon \ldots \ldots \ldots \ldots \ldots \ldots 3
\]

Read: Draper and Smith: Applied Regression analysis
OPTIMIZATION- CRITERIA FOR BEST FIT

These criteria are achieved by minimizing the following quantities:

\[
\begin{align*}
    OLS &= \sum_{i=1}^{n} (C_i - \hat{C}_i)^2 \\
    WLS &= \sum_{i=1}^{n} W_i (C_i - \hat{C}_i)^2 \\
    ELS &= \sum_{i=1}^{n} \frac{(C_i - \hat{C}_i)^2}{\text{Var} (\hat{C}_i)} + \log_e (\text{Var} (\hat{C}_i))
\end{align*}
\]

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 \( \chi^2 \) 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 SELECTION CRITERIA

1. THE AKAIKE INFORMATION CRITERIA (AIC)

\[ AIC = N \cdot \ln .R_e + 2p \]
\[ R_e = \sum_{i=1}^{n} w_i (C_i - \hat{C}_i)^2 \]

Minimum AIC value is the best representation of model. Warning: Improper weight could select wrong equation.

2. F-TEST

\[ F = \frac{WSS_1 - WSS_2}{WSS_2} \cdot \frac{df_2}{df_1 - df_2} \quad (df_1 > df_2) \]
\[ df = (\text{No. of experimental data points}) - (\text{No. of parameters}) \]
MODEL SELECTION CRITERION
continue…

3. STANDARD DEVIATION OF ESTIMATED PARAMETER

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

\[ s^2 = \frac{\sum \text{dev}^2}{N - P} \]

\[ \sum \text{dev}^2 = \sum (Y - \hat{Y})^2 \]

N=No. of data points
P=No. of parameters estimated
N-P=degrees of freedom
\( C_{ii} = \text{i}^{\text{th}} \text{ diagonal element of the variance-covariance matrix of the elements} \)
MODEL SELECTION continue…

4. COEFFICIENT OF DETERMINATION

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

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

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

\[ MSC = \ln \left[ \frac{S_y^2}{\sum \text{dev}^2} \right] - 2 \frac{P}{N} \]
MODEL SELECTION continue…

6. ANALYSIS OF RESIDUALS

![Graph showing relative residuals over time for different compartment models.](image)
MODEL SELECTION continue..

6. ANALYSIS OF RESIDUALS

![Graph showing residuals over time for 2-compartment and 3-compartment models.](image)
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