VERSION 3.15

VOLUME 3

METHODS

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1 PATIENT PARAMETERS

1.1 Introduction

The MW\PHARM patient database contains 3 types of data. General patient data (e.g. name, sex, age, weight, etc.), a medication history (list of dosing events and plasma levels), and individual pharmacokinetic parameters. The general patient data are accessed in 3 different screens. First, the patient registration screen (figure 1.1) which contains mostly administrative data. Here only the age is of direct influence on the pharmacokinetics (see paragraph 1.4).

```
                    PATIENT REGISTRATION

        patient number      : 1
        name and initials   : MW
        date of birth       : 04-12-1939
        address             :
        postcode/zipcode    :

        city                :
        family doctor       :
        requesting physician:
        ward                :
        room number         :

        age                 :   55 years

        last medication     :




F10 F1 ↑↓ ^f=find ^+=next ^-=previous ^Del=erase ^Ins=save ^s=st.pat. BS
```

Figure 1.1. Patient registration screen

Other patient parameters which have a pronounced effect on the pharmacokinetics of drugs are listed in figures 1.2 (pathology screen) and figure 1.4 (kidney function screen).

1.2 Lean Body Mass

The lean body mass (LBM) is defined as body weight minus the weight of fat tissue. We speak of obesity if the actual body weight is more than 20% higher than the lean body mass (figure 1.2).

```
PATHOLOGY/STATUS DATA INFLUENCING PHARMACOKINETICS


1  weight        :    70.0 kg ┐
2  height        :    175  cm ┤──> BSA = 1.85 m²  LBM =  70.0 kg
3  sex           :    M       ┘                   LBMc=  70.0 kg

4  renal function :    CLcr =  89.5 ml/min/1.73m²
                                95.6 ml/min

5  pathology     :    ████████████████████




Enter value for body weight in kg [Enter = 70 ]   75



 F10 = continue │ F1 = main menu │ 1-5 = change │
```

Figure 1.2. Pathology screen.

The lean body mass of patients is calculated according to the equation of Chennavasin (Eur. J. Clin. Pharmacol., 1982, 22, 91-94) which is in fact the 'cm-version' of the equation of Devine (Am. J. Hosp. Pharm. 1980, 37, 225-231).

Symbol	Unit	Description
LBM	kg	Lean body mass
LBM_c	kg	Lean body mass corrected for fat distribution
BW	kg	Body weight
BH	cm	Body height
f_d	$-$	Fat distribution factor

Chennavasin *(Eur. J. Clin. Pharmacol., 1982, 22, 91-94)*

$$LBM_c = (BW - LBM) \cdot f_d + LBM$$

Age > 20:

Male: $LBM = 50.0 + 0.9 \cdot (BH - 152)$

Female: $LBM = 45.5 + 0.9 \cdot (BH - 152)$

Age ≤ 20: $LBM_c = BW$

☞ Note if the value of `LBM` exceeds that of `BW`, the `LBM` is set to the value of `BW`.

Both `LBM` and `BW` are used for normalizing pharmacokinetic drug parameters like clearance (`L/h/kg`) and `LBM`$_c$ is used for normalizing the volume of distribution (`L/kg`).

1.3 Body Surface Area

Also the body surface area is used for parameter normalization. E.g. the creatinine clearance is expressed in `mL/min/1.73m`^{2}. The body surface area is calculated according to the formula of Dubois and Dubois (Am. J. Hosp. Pharm. 1980, 37, 225-231):

Symbol	Unit	Description
BW	*kg*	Body weight
BH	*cm*	Body height
BSA	*m²*	Body surface area

Dubois and Dubois *(Am. J. Hosp. Pharm. 1980, 37, 225-231)*

$$BSA = BW^{0.425} \cdot BH^{0.725} \cdot 0.007184$$

1.4 Renal Function

The creatinine clearance of a patient is taken as a measure for the patient's renal function. MwPharm offers up to 4 methods for calculating the creatinine clearance from one or more creatinine levels. Figure 1.2 lists 3 of them (Cockcroft and Gault, Jelliffe 1 and Jelliffe 2).

☞ The Schwartz children formula is only available if the subject is younger than 20. It is the only available method if the subject is younger than 18.

```
                RENAL FUNCTION (creatinine clearance)


     1  calculate from 1 serum creatinine level
     2  calculate from 2 serum creatinine levels and time interval
     3  enter value for creatinine clearance (ml/min/1.73m²)

     4  Cockcroft & Gault      CLcr =   97.7 ml/min/1.73m²  =  104.4 ml/min
     5  Jelliffe I             CLcr =   88.4 ml/min/1.73m²  =   94.4 ml/min
     6  Jelliffe II            CLcr =   89.5 ml/min/1.73m²  =   95.6 ml/min



 serum creatinine =   70   µmol/l   creatinine clearance =  89.5 ml/min/1.73m²
                     0.79 mg/dl                             95.6 ml/min



 unit of serum creatinine:  >20 = µMol/l,  <=20 = mg/dl

 Enter value for serum creatinine [Enter = 70 ]



  F10 = continue | F1 = main menu | 1-3 = change | <──┘ = enter | 4-6 = CLcr
```

Figure 1.4-A. Kidney function screen.

Symbol	Unit	Description
Y	$Years$	Age
LBM	kg	Lean body mass
BH	cm	Body height
BSA	m^2	Body surface area
Cr	$\mu mol/L$	Creatinine plasma concentration
CL_{cr}	$mL/min/1.73m^2$	Creatine clearance
F_{sex}	$–$	Sex factor

Cockcroft and Gault *(Nephron 16: 31-41, 1979)*

$$CL_{cr} = F_{sex} \cdot \frac{(140-Y) \cdot LBM}{72 \cdot Cr} \cdot 88.5 \cdot \frac{1.73}{BSA} \qquad F_{male} = 1.00$$
$$F_{female} = 0.85$$

Jelliffe 1 (Ann. Int. Med. 79: 604, 1973)

$$CL_{cr} = F_{sex} \cdot \frac{98-0.8 \cdot (Y-20)}{Cr} \cdot 88.5 \qquad F_{male} = 1.00$$
$$F_{female} = 0.90$$

Jelliffe 2 (Math. Biosc. 14: 17-24, 1972)

$$F_1 = (29.305 - 0.203 \cdot Y) \cdot LBM \cdot \frac{(1344.3 - 43.76 \cdot \frac{\Delta Cr}{2})}{(1344.3 - 43.76 \cdot 1.1)} \cdot 0.85 \cdot F_{sex}$$

$$F_2 = 4 \cdot LBM \cdot \frac{\Delta Cr}{\Delta t} \qquad F_3 = \frac{\Delta Cr}{2} \cdot 1440 \qquad \Delta Cr = \frac{(Cr_1 - Cr_2)}{88.5}$$

$$CL_{cr} = \frac{F_1 - F_2}{F_3} \cdot 100 \cdot \frac{1.73}{BSA} \qquad F_{male} = 1.00$$
$$F_{female} = 0.90$$

Δt is the time (`days`) between two successive creatinine level measurements Cr_1 and Cr_2 (`µmol/L`).

Schwartz (Pediatrics 58: 259-263, 1976)

$$CL_{cr} = \frac{0.55 \cdot BH}{Cr} \cdot 88.5$$

☞ The Cockcroft & Gault and Jelliffe 2 methods take the lean body mass (LBM) as an argument instead of body weight (BW) because the creatinine production is dependent on the amount of muscle tissue but independent from fat tissue. This ensures that the formula also performs well for people with overweight.

☞ The Jelliffe 2 method is suitable for calculating the creatinine clearance in case of an instable kidney function. It is the only method that takes the non-renal creatinine clearance into account with patients suffering from a chronic bad kidney function.

MW\PHARM automatically assigns a unit to an entered creatinine level depending on its magnitude. If the entered value is larger than *20*, the unit is assumed to be $\mu mol/L$. If the entered value is smaller than *20*, the unit is assumed to be *mg/dL*.

For every available method both the absolute creatinine clearance expressed in *mL/min* as well as the normalized creatinine clearance expressed in $mL/min/1.73m^2$ are displayed. Both these values are displayed separately again for the currently selected method.

Should any of the previous described methods give unsatisfactory results (e.g. in the case of a bad liver function) the option is given to estimate the patient's creatinine clearance manually (option 3).

date time	dose	roa	no	interv.	T(inf)	conc.	weight	creat	Q(EC)
DD-MM-YY HH:MM	[mg]	i/e		[h]	[h]	[mg/l]	[kg]	[µM]	[ml/min]
21-03-90 08:00	90	iv	1		0.5		68	100	
21-03-90 20:00	60	iv	5	12	0.5				
22-03-90 21:00						8.2			
23-03-90 07:55						2.4			
24-03-90 08:00	60	iv	11	24	0.5		70	97	
25-03-90 07:55						1.5			
25-03-90 09:00						7.3			
26-03-90 07:55						1.3	68	110	
29-03-90 09:00			4	24	2				250

```
One or more SD values missing: weighting relative                      →
Bayes ('b'):  ON        Conc. at t=0 ('c')  0              Algorithm ('a'):  Marquardt
F10=continue F1 ↑↓→←,PgUp,PgDn Del Ins ^→ p=date +=+1 -=-1 F4=reg.d F6=recalc.d
```

Figure 1.4-B. Medication history screen.

PATIENT PARAMETERS

The in the medication history screen (figure 1.4-B) entered creatinine levels will be processed using the currently selected kidney function evaluation method unless the creatinine clearance has been estimated manually in which case the creatinine levels in the medication history screen are ignored all together. Creatinine levels at any time point are obtained by linear interpolation of the two nearest known creatinine levels. Values are never obtained by means of extrapolation. If interpolation is not possible the value of the last known creatinine level is used. The same interpolation approach is used for obtaining body weight values at any time point.

Age is an important factor when calculating the renal function as can be seen from the different kidney function equations. As a rule of thumb the normal creatinine clearance decreases with 10% for every 10 years above 40 years. Normally the age is calculated from the patients birthdate and the computer system date. However, when dealing with a medication history the patient age at any history moment is determined from the actually entered dosing event dates. This approach ensures that results from calculations involving a medication history are independent of the date and time of data collection.

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2 DRUG PARAMETERS

2.1 Introduction

In the medication data screen you can access all data present in the drug database. There are in fact 2 medication data screens. One contains general drug data like the available dosages, desired maximum and minimum concentrations, unit of dose, unit of concentration, etc. (figure 2.1-A). The second one contains the pharmacokinetic population parameters (figure 2.1-B).

Figure 2.1-A. Medication data screen I

The first medication screens contains parameters and settings which are important for dosage calculations (available dosages, target levels, route of administration, etc.) and the way data are presented (units, graphics, etc.). Settings that affect the way in which the parameters in the second medication screen are used are also listed here (no. compartments, normalization method, etc.).

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```
Name of drug         : gentamicin                    28-11-94

                       1 comp. data      2 comp. data      3 comp. data
kelm (1/h)       : .015  ± 0     .015  ± 0        0     ± 0
Km   (mg/l)      : 0     ± 0     0     ± 0        0     ± 0
Vmax (mg/h/1.85m²): 0    ± 0     0     ± 0        0     ± 0
kelr (1/h/(ml/min)): .0024 ± 0   .0024 ± 0        0     ± 0
V1   (l/kg)      : .21   ± 0     .21   ± 0        0     ± 0
k12  (1/h)       :                .03  ± 0        0     ± 0
k21  (1/h)       :                .008 ± 0        0     ± 0
k13  (1/h)       :                                0     ± 0
k31  (1/h)       :                                0     ± 0

oral    ka (1/h): 0    ± 0    F (0-1): 0    ± 0    ┌──────────────┐
i.m.    ka (1/h): 3    ± 0    F (0-1): 1    ± 0    │   patient    │
                                                   │              │
Distribution into fat     (0-1) : .4               │ CL    3.38 l/h│
Fraction unbound (fu)     (0-1) : .9   ± 0         │ V    14.70  l │
Extraction ratio EC clearance   : 0               │ t½    3.02  h │
Metabolising constant     (1/h) : 0    ± 0         │ fe    0.9347  │
SD concentration measurement (%): 0               └──────────────┘
               +   (mg/l) : 0         normal
Distribution kinetic parameters :    normal

F10=continue F1 ↑↓→← PgUp ^f=find ^+=+1 ^-=-1 ^Del=erase ^Ins=save Esc BS
```

Figure 2.1-B. Medication data screen II

The second medication screen can display population or individual pharmacokinetic parameters. In the latter case the "***date of last change***" (upper left corner) has been replaced with the label ***"individual data"***.

2.2 Pharmacokinetic Models

MwPharm supports several kinetic models (figure 2.2). These include 1, 2 and 3 compartment kinetics, non-linear elimination kinetics (Michaelis-Menten or saturation kinetics), extracorporeal elimination (dialysis) and several routes of administration, like intravenous injections and infusions but also oral and intramuscular administrations. Different dosage forms may be administered simultaneously. All supported types of elimination can be active in parallel. Due to the extracorporeal clearance facility you can predict plasma levels and calculate adequate dosage regimens even when the patients are being dialysed or hemoperfused. All kinetic calculations can be based on total or free (not protein bound) concentrations.

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ADMINISTRATION

intravascular

extravascular (k_a,F)

2
'shallow'
peripheral
compartment

k_{12}

k_{21}

1
central
compartment
(volume V_1)

k_{13}

k_{31}

3
'deep'
peripheral
compartment

k_{10} renal

k_{10} metabolic

k_{10} extracorporeal

V_{max} ,K_m metabolic

ELIMINATION
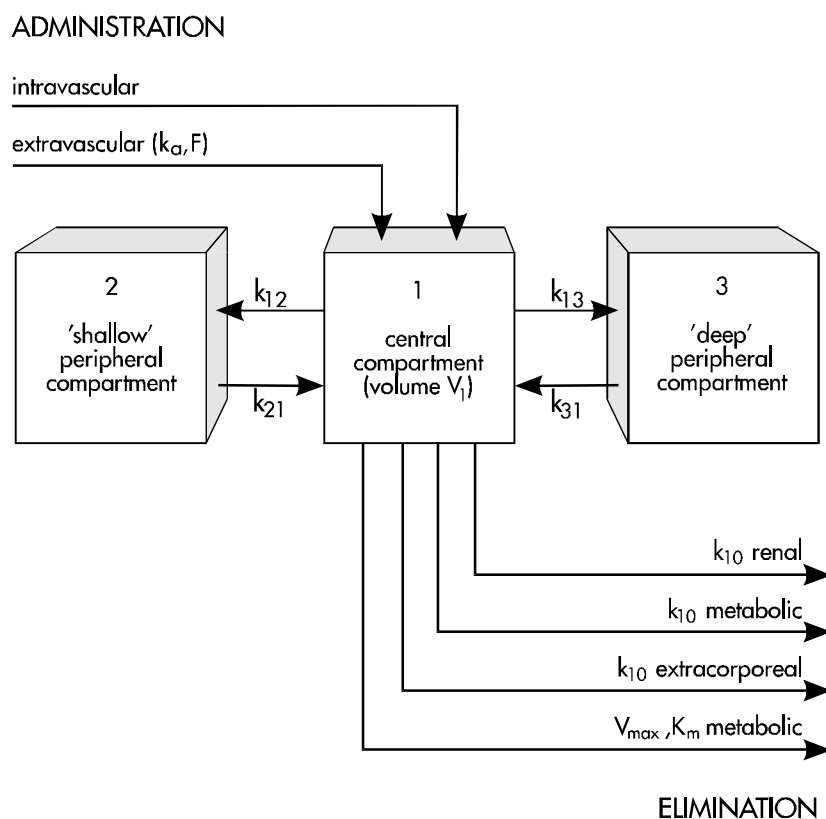
Figure 2.2. MW\PHARM Compartment model.

2.3 Parameter Normalisation

Once a pharmacokinetic model is selected, it is useful to establish functional relationships between pharmacokinetic parameters and patient characteristics. We call this parameter normalisation. E.g. volume of distribution is commonly referenced to body weight, and drug elimination or clearance may be a function of creatinine clearance (figure 2.3-A and 2.3-B). Most MW\PHARM parameters are normalised this way based on one or more patient characteristics that are then formally cast into the pharmacokinetic model by de-normalization. When adding your own drug parameters to the MW\PHARM drug database you must bear in mind that these parameters must be normalised. Appendix B gives some examples of entering literature pharmacokinetic data into the MW\PHARM drug database.

$$CL = CL_{nr} + CL_r = CL_{nr} + fr \cdot CL_{cr}$$

$fr = slope$

$CL_{nr} = intercept$
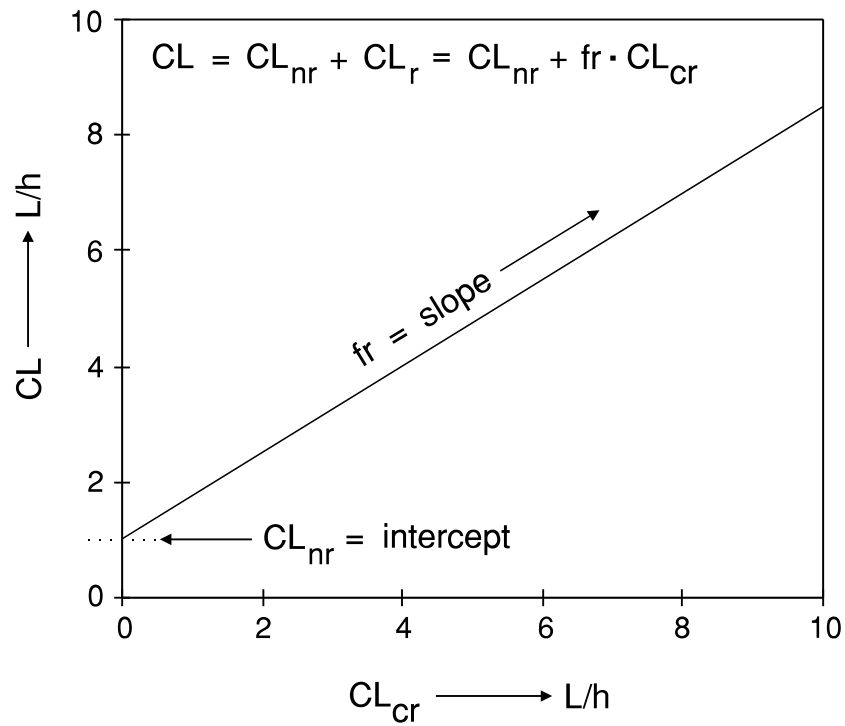
Figure 2.3-A. Normalisation of the total body clearance CL using CL_{cr}

$$k_{el} = k_{elm} + k_{elr} \cdot CL_{cr}$$

$k_{elr} = slope$

$k_{elm} = intercept$
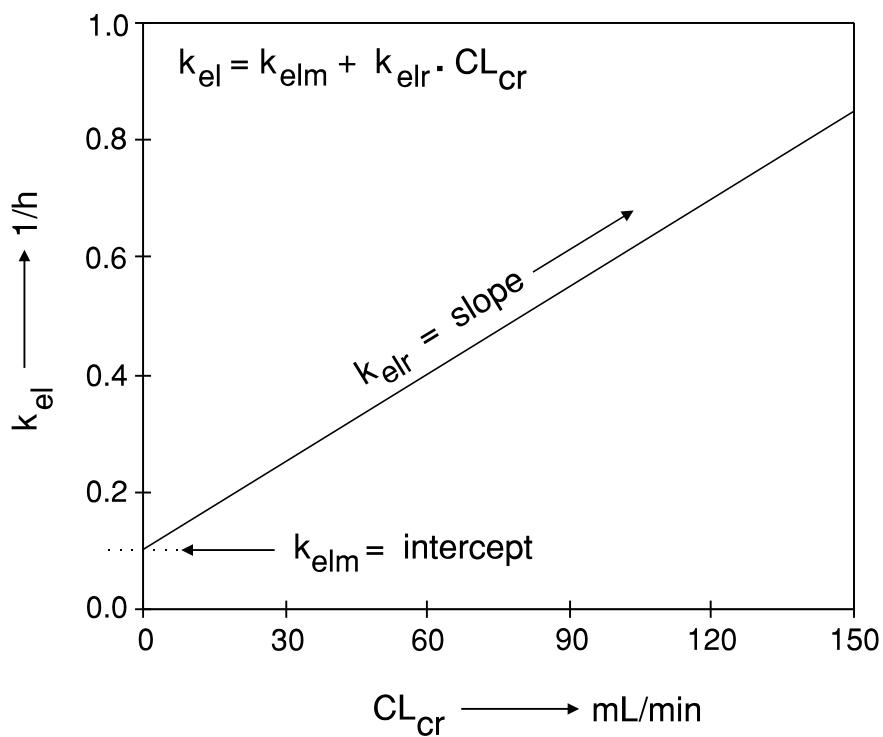
Figure 2.3-B. Normalisation of the elimination rate constant k_{el} using CL_{cr}

MW\PHARM's pharmacokinetic parameters are normalized based on the so called standard patient. The standard patient has the following characteristics:

MW\PHARM Standard Patient:

```
Number              : 1
Name                : MW
Sex                 : Male
Age                 : 55    years
Weight and LBM      : 70    kg
Height              : 175   cm
Body surface area   : 1.85  m²
Serum creatinine    : 70.0  μmol/L        (0.79 mg/dL)
Creatinine clearance      : 95.6 mL/min          (89.5
              mL/min/1.73m²)
```

2.4 Clearance

Clearance is the loss of drug across an organ of elimination. Figure 2.4 shows the classification of different clearance types as used by MW\PHARM.

Figure 2.4-A. Different clearance types in MW\PHARM.

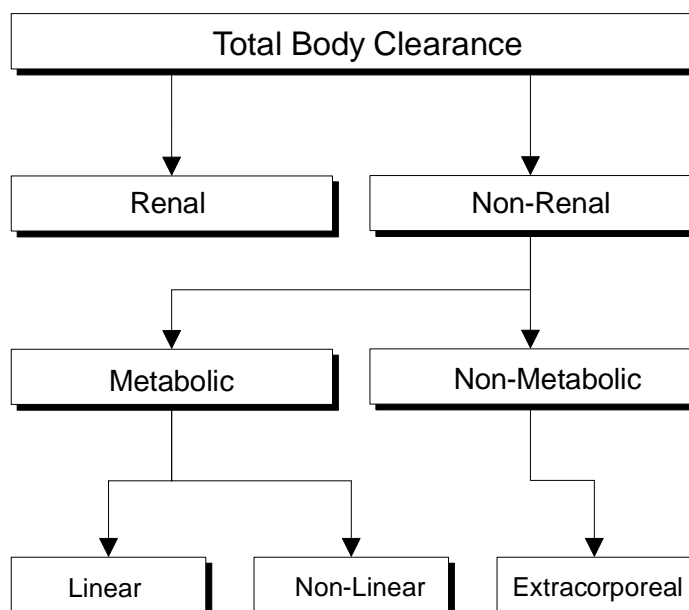| Symbol	Unit	Description
CL	L/h	Total body clearance
CL_r	L/h	Renal clearance
CL_{nr}	L/h	Non-renal clearance
CL_m	L/h	Metabolic clearance (linear)
CL_{mm}	L/h	Metabolic clearance (non-linear)
CL_{ec}	L/h	Extracorporeal clearance (EC)
CL_{cr}	L/h	Creatinine clearance
f_r	–	Drug clearance - creatinine clearance ratio
k_{el}	$1/h$	Total elimination rate constant
k_{elr}	$1/h/RCU*$	Renal elimination rate constant
k_{elm}	$1/h$	Metabolic elimination rate constant
V_{max}	mg/h	Maximal rate of enzymatic transformation
K_m	mg/L	Michaelis-Menten constant
C	mg/L	Plasma concentration
Q_{ec}	mL/min	Extracorporeal device flow
E_{ec}	–	Extracorporeal extraction ratio
LBM	kg	Lean body mass
LBM_c	kg	Lean body mass corrected
BSA	m^2	Body surface area
V_1	L/kg	Volume of distribution central compartment

$*RCU$ = renal clearance units = $ml/min/1.73m^2$

In terms of equations figure 2.4-A can be written as:

Total Body Clearance

$$CL = CL_r + CL_{nr}$$

$$CL_{nr} = CL_m + CL_{mm} + CL_{ec}$$

Most pharmacokinetic parameters are normalised to one or more patient characteristics like weight, lean body mass, body surface area and renal function. Two basic methods for normalising the drug clearance are displayed in figures 2.3-A and 2.3-B. In total MwPharm offers four principle clearance normalisation methods which can be selected in the first medication screen.

Method $I: kel = kelm + kelr.CLcr$

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$$CL = (k_{elm} + k_{elr} \cdot CL_{cr}) \cdot V_1 \cdot LBM_c + \frac{V_{\max} \cdot \frac{BSA}{1.85}}{(K_m + C)} + Q_{ec} \cdot E_{ec} \cdot \frac{60}{1000}$$

$k_{elm} \rightarrow 1/h$ $CL_{cr} \rightarrow RCU*$

$k_{elr} \rightarrow 1/h/RCU*$ $V_{max} \rightarrow mg/h/1.85m^2$

$*RCU$ = renal clearance units = $ml/min/1.73m^2$

Method II: CL = CLm.BSA/1.85 + fr.CLcr

$$CL = CL_m \cdot \frac{BSA}{1.85} + f_r \cdot CL_{cr} + \frac{V_{\max} \cdot \frac{BSA}{1.85}}{(K_m + C)} + Q_{ec} \cdot E_{ec} \cdot \frac{60}{1000}$$

$CL_m \rightarrow L/h/1.85m^2$ $CL_{cr} \rightarrow L/h$

$f_r \rightarrow -$ $V_{max} \rightarrow mg/h/1.85m^2$

Method III: CL = CLm.BW/70 + fr.CLcr

$$CL = CL_m \cdot \frac{BW}{70} + f_r \cdot CL_{cr} + \frac{V_{\max} \cdot \frac{BW}{70}}{(K_m + C)} + Q_{ec} \cdot E_{ec} \cdot \frac{60}{1000}$$

$CL_M \rightarrow L/h/70kg$ $CL_{cr} \rightarrow L/h$

$f_r \rightarrow -$ $V_{max} \rightarrow mg/h/70kg$

Method IV: CL = CLm.LBM/70 + fr.CLcr

$$CL = CL_m \cdot \frac{LBM}{70} + f_r \cdot CL_{cr} + \frac{V_{\max} \cdot \frac{LBM}{70}}{(K_m + C)} + Q_{ec} \cdot E_{ec} \cdot \frac{60}{1000}$$

$CL_M \rightarrow L/h/70kg$ $CL_{cr} \rightarrow L/h$

$f_r \rightarrow -$ $V_{max} \rightarrow mg/h/70kg$

All units are listed in the previous table unless indicated otherwise.
Method I is based on the assumption that:

DRUG PARAMETERS

- Elimination rate constant is related to the creatinine clearance according to figure 2.3-B.
- V_{max} is linearly related to body surface area (BSA).

Method II is based on the assumption that:

- Clearance is related to the creatinine clearance according to figure 2.3-A.
- Metabolic (non-renal) clearance is linearly related to body surface area (BSA).
- V_{max} is linearly related to body surface area (BSA).

Method III is based on the assumption that:

- Clearance is related to the creatinine clearance according to figure 2.3-A.
- Metabolic (non-renal) clearance is linearly related to body weight (BW).
- V_{max} is linearly related to body weight (BW).

Method IV is based on the assumption that:

- Clearance is related to the creatinine clearance according to figure 2.3-A.
- Metabolic (non-renal) clearance is linearly related to lean body mass (LBM).
- V_{max} is linearly related to lean body mass (LBM).

You can switch between the 4 methods in the first medication data screen (figure 2.1-A). The relationship between k_{elm} & CL_m and k_{elr} & f_r is given in the equations below.

Method parameter conversion

$$CL_m = k_{elm} \cdot V_1 \cdot LBM_c \cdot \frac{1.85}{BSA}$$

$$f_r = k_{elr} \cdot V_1 \cdot LBM_c \cdot \frac{1000}{60} \cdot \frac{1.73}{BSA}$$

The BSA and LBM_C parameters in the conversion formulae refer to:

- the characteristics of the actual patient, if individual parameters have been estimated by a fitting procedure (indicated by '*individual*' in the upper right corner of the medication data screen);
- the characteristics of the standard patient, in other cases.

This conversion formulae causes the different methods to generate identical results when dealing with the so called standard patient (see paragraph 2.3). For patients with deviating characteristics, the dose recommendations may vary. In particular for infants and children the differences may be significant.

Generally speaking, drug clearance is proportional to body surface area, and therefore method II is recommended as the standard method. Method I is widely used, among others, by Dr. R. Jelliffe. However, this approach may lead to too low doses in infants and children. Methods III and IV yield results close to that obtained with method I in case of linear kinetics. Methods III and IV will yield different values only in the case of obese patients. In case of non-linear (Michaelis-Menten) kinetics methods I and II yield the same results, whereas methods III and IV will give lower doses in infants and children.

It should be noted that the choice of the method also depends how the population data were obtained. Most sources of pharmacokinetic data give population means expressed per kg body weight, and method III might seem the appropriate method, although even in this case method II may yield more accurate results in infants and children **if the population data refer to adults**. However, if for a particular drug the population value for clearance **in infants and / or children** is expressed per kg body weight, method III should be used!. In this case the clearance should be entered in the medication data screen after multiplication by 70 kg. These data can than be used only for infants and / or children in the age for which the clearance was given. Extrapolation to adults will lead to overdosing!

The general clearance equation also contains a term for non-linear elimination or Michaelis-Menten kinetics. In the case of non-linear elimination ($V_{max} > 0$ and $K_m > 0$) the total body clearance and elimination half-life change over time and are therefore not defined. This is indicated in the so called patient box by the label `n.d.`

Michaelis-Menten kinetics (non-linear elimination)

$$CL_{mm} = \frac{V_{max} \cdot \frac{BSA}{1.85}}{(K_m + C)} \qquad \text{or} \qquad CL_{mm} = \frac{V_{max} \cdot \frac{LBM}{70}}{(K_m + C)}$$

☞ Non-linear elimination is taken into account in the drug dosing screen (regular dosage screen) and the medication history screen (irregular dosage screen).
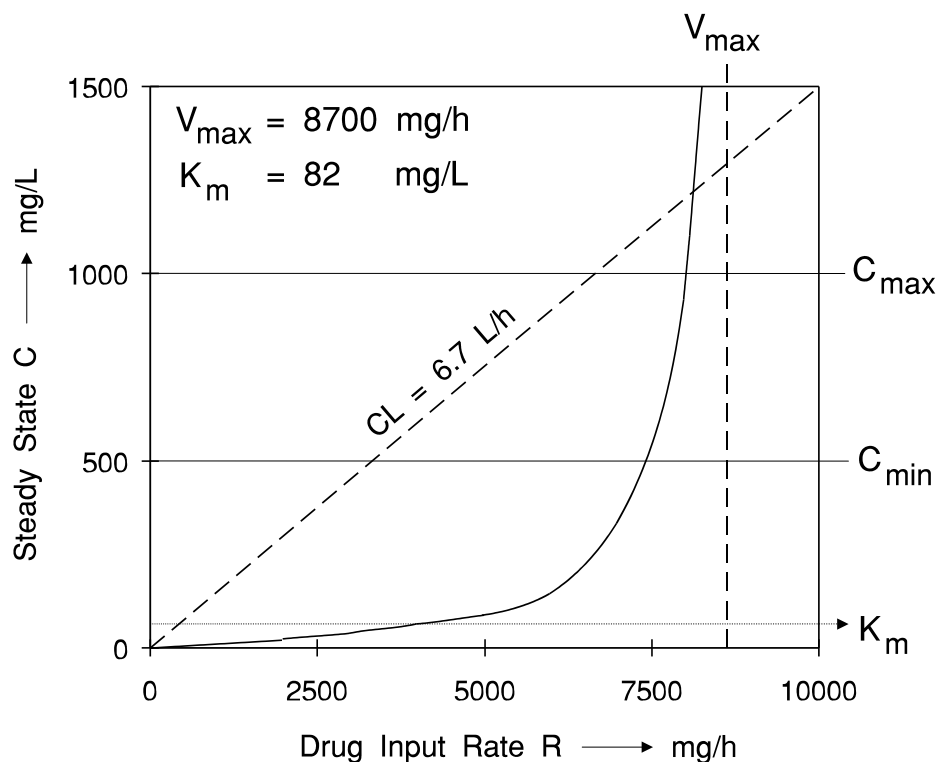

Figure 2.4-B. Relation between input rate R and steady state concentration C in case of non-linear kinetics.

Figure 2.4-B nicely demonstrates some important aspects of non-linear pharmacokinetics. The dashed diagonal in figure 2.4-B represents the expected steady state levels in relation to drug input rate R in the case of standard linear kinetics. The clearance in this ex-

ample equals 10000 mg/h divided by 1500 mg/L which amounts to 6.7 L/h. The clearance remains constant over the whole range of drug input rates. If the input rate increases by a factor 2 the corresponding steady state level also increases by a factor 2.

The solid line in figure 2.4-B represents the expected steady state levels in relation to different input rates R in the case of non-linear kinetics. The drug clearance is dependent on the drug concentration and therefore changes with input rate and time. If the input rate increases by a factor 2 the corresponding state state level may increase by a factor 10 depending on the initial input rate. A magical border is formed by V_{max}. If the Input rate is larger than V_{max} ($R>V_{max}$) no steady state is defined and drug will be accumulating indefinitely.

The extracorporeal clearance facility enables the user to predict the effect of an extracorporeal clearance (dialysis, hemoperfusion, etc.) on measured drug and creatinine plasma levels.

Extracorporeal clearance

$$CL_{ec} = Q_{ec} \cdot E_{ec} \cdot \frac{60}{1000}$$

☞ Extracorporeal elimination is only taken into account in the medication history screen (irregular dosage screen). It can not be used in drug dosing screen (regular dosage screen)

The Q_{ec} variable represents the perfusion or dialysis flow through the extracorporeal elimination device and E_{ec} is the observed extraction ratio. If the user wants to work with the extracorporeal clearance facility a drug E_{ec} value must be specified in the second medication screen (default 0) and the creatinine E_{ec} value (default 1) must be specified in the calculation options screen. The exact value of E_{ec} is dependent on the characteristics of the dialysis membrane. The Q_{ec} variable can be entered in the medication history screen (figure 2.4-C).

date	time	dose	roa	no	interv.	T(inf)	conc.	weight	creat	Q(EC)
DD-MM-YY	HH:MM	[mg]	i/e		[h]	[h]	[mg/l]	[kg]	[µM]	[ml/min]
21-03-90	08:00	90	iv	1		0.5		68	100	
21-03-90	20:00	60	iv	5	12	0.5				
22-03-90	21:00						8.2			
23-03-90	07:55						2.4			
24-03-90	08:00	60	iv	11	24	0.5		70	97	
25-03-90	07:55						1.5			
25-03-90	09:00						7.3			
26-03-90	07:55						1.3	68	110	
29-03-90	09:00			4	24	2				250
05-04-90	08:00									

```
One or more SD values missing: weighting relative          →
Bayes ('b'): ON     Conc. at t=0 ('c') 0        Algorithm ('a'): Marquardt
F10=continue|F1|↑↓→←,PgUp,PgDn|Del|Ins|^→|p=date|+=+1|-=-1|F4=reg.d|F6=recalc.d
```

Figure 2.4-C. Medication history containing dialysis periods.
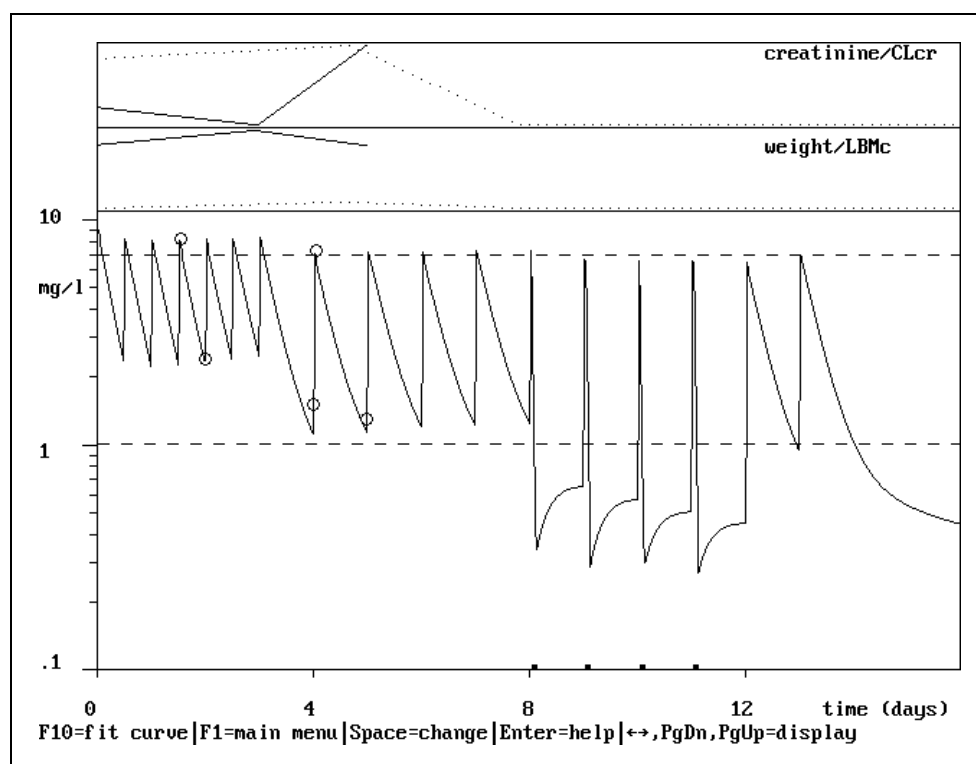

Figure 2.4-D. Simulated medication history of figure 2.4-B.

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The number of extracorporeal clearance periods must be specified in the `no` column. The duration of every period is specified in the `T(inf)` column. The flow through the extracorporeal clearance device must be specified in the `Q(EC)` column. In the example of figure 2.4-C, the first dialysis period started at `29-03-90` at `09:00`. In total `4` dialysis sessions of `2` hours with a flow of `250 mL/min` occured at `24` hour intervals . This means that every dialysis period started `1 h` after the administration of drug. Please note the redistribution phenomenon after every dialysis period (figure 2.4-D).

2.5 Distribution

Distribution refers to the reversible transport of drug from one location to another within the body.

Symbol	Unit	Description
V_1	L *or* L/kg	Volume of distribution central compartment
V_{ss}	L	Volume of distribution during steady state
V_β	L	Volume of distribution in terminal phase
LBM_c	kg	Lean body mass corrected
CL	L/h	Total body clearance
k_{xy}	/h	Rate constant from comp. x to comp. y
L_x	/h	x^{th} exponent in polyexponential equation

The volume of distribution of the central compartment is normalised to the corrected lean body mass.

Volume of distribution of central compartment

$$V_1^{'} = V_1 \cdot LBM_c$$

Besides the volume of the central compartment (V_1) MW\PHARM identifies two more volumes of distribution. These are the volume of distribution during steady state (V_{ss}) and the volume of distribution in the terminal phase (V_β).

Volume of distribution during steady state

Compartments:

1
$$V_{ss} = V_1$$

2
$$V_{ss} = V_1 \cdot (1 + \frac{k_{12}}{k_{21}})$$

3
$$V_{ss} = V_1 \cdot (1 + \frac{k_{12}}{k_{21}} + \frac{k_{13}}{k_{31}})$$

Volume of distribution in terminal phase

Compartments:

1
$$V_\beta = \frac{CL}{L_1} = V_{ss} = V_1$$

2
$$V_\beta = \frac{CL}{L_2}$$

3
$$V_\beta = \frac{CL}{L_3}$$

Figure 2.5 is a magnified section of the medication screen forming the so called patient box which shows the CL, V_1 and V_β (displayed as V) parameters.

Figure 2.5. Patient box in the medication data screen.

2.6 Derived Parameters

Figure 2.5 displays also two secondary or derived parameters. These are the half-life ($t_{\frac{1}{2}}$) and fraction excreted unchanged (f_e).

Symbol	Unit	Description
$t_{\frac{1}{2}x}$	/h	Half-life of xth phase
L_x	/h	x^{th} exponent in polyexponential equation
f_r	–	Drug clearance - creatinine clearance ratio
f_e	–	Fraction excreted unchanged
k_{10}	/h	Elimination rate constant
V_1	L	Volume of distribution
CL	L/h	Total body clearance
CL_r	L/h	Renal clearance

Half-life

$$t_{\frac{1}{2}_x} = \frac{\ln(2)}{L_x}$$

Fraction excreted unchanged

$$f_e = \frac{CL_r}{CL} = \frac{f_r \cdot CL_{cr}}{CL}$$

The elimination rate constant, which is internally used in MW\PHARM's differential equations (see chapter 3), is calculated as follows.

Elimination rate constant

$$k_{10} = \frac{CL}{V_1}$$

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3 PHARMACOKINETIC SIMULATIONS

3.1 Introduction

The prediction of plasma levels can be done by means of pharmacokinetic simulations. MW\PHARM employs two different simulation methods. One is based on 'normal' equations and the other is based on differential equations. The basic form and applications of these methods is displayed in the table below.

Differential Equations　　　　　　　**Normal Equations**

$$A(t) = \int\limits_{t=0}^{t} -k_{10} \cdot A(t) \cdot dt \qquad\qquad A(t) = A_0 \cdot e^{-k_{10} \cdot t}$$

❍ Dose calculation (non-lin.)　　❍ Dose calculation (lin.)

❍ Irregular dosing (e.g. split dosing)　　❍ Regular dosing

❍ Extracorporeal clearance　　❍ KinFit

❍ All graphics

The method based on differential equations is more flexible but also slower than the method based on normal equations. Therefore the method based on normal equations is used as much as possible unless it cannot be applied for a certain problem (e.g. non-linear kinetics, irregular dosing and extracorporeal clearance).

For the graphical representation of plasma curves only the method based on differential equations is used. Thus a dosage regimen that was calculated using normal equations is graphically simulated using differential equations. This can be viewed upon as a kind of internal control.

3.2 Differential Equations

Symbol	Unit	Description
A	mg	Amount
$A0$	mg	Amount at absorption site 0
$A1$	mg	Amount in central compartment 1
$A2$	mg	Amount in peripheral compartment 2
$A3$	mg	Amount in peripheral compartment 3
A_m	mg	Amount of metabolite
CL	L/h	Total drug clearance
V_1	L	Distribution volume central compartment 1
k_{xy}	$/h$	Rate constants
k_a	$/h$	Absorption rate constant
k_m	$/h$	Metabolising constant
t	h	Time since first dose administration
T_{inf}	h	Infusion duration
R	mg/h	Infusion rate
D	mg	Dose
O	mg	Error term of numerical integration

MW\PHARM keeps track of the amount of drug at 4 different locations of the body by using a set of 4 differential equations. These locations are the absorption site (intestine), central compartment (plasma) and 2 peripheral compartments (tissue).

Differential equations

$$\frac{dA1(t)}{dt} = -\frac{dA0(t)}{dt} - \frac{dA2(t)}{dt} - \frac{dA3(t)}{dt} - k_{10} \cdot A1(t)$$

$$\frac{dA0(t)}{dt} = -k_{01} \cdot A0(t)$$

$$\frac{dA2(t)}{dt} = k_{12} \cdot A1(t) - k_{21} \cdot A2(t) \qquad k_{10} = \frac{CL}{V_1}$$

$$\frac{dA3(t)}{dt} = k_{13} \cdot A1(t) - k_{31} \cdot A3(t) \qquad k_{01} = k_a$$

Dosing events cause an abrupt change in the amount of drug at the absorption site (oral dose) or in plasma (bolus dose).

Dosing Events

$$\textbf{\textit{Extravascular}} \quad : A0(t) = A0(t) + F \cdot D$$

$$\textbf{\textit{I.V. Bolus}} \qquad : A1(t) = A1(t) + D$$

$$\textbf{\textit{I.V. Infusion}} \qquad : \frac{dA1(t)}{dt} = \frac{dA1(t)}{dt} + R \qquad\qquad R = \frac{D}{T_{\text{inf}}}$$

The differential equations in MW\PHARM are solved by numerical integration using the 4th order Runge-Kutta method.

Numerical Integration: 4th order Runge-Kutta

$$f'(t_n, A_n) = \frac{dA(t_n)}{dt} \qquad\qquad \delta t = t_{n+1} - t_n$$

$$\delta a = \delta t \cdot f'(t_n, A_n) \qquad\qquad \delta b = \delta t \cdot f'(t_n + \tfrac{\delta t}{2}, A_n + \tfrac{\delta a}{2})$$

$$\delta c = \delta t \cdot f'(t_n + \tfrac{\delta t}{2}, A_n + \tfrac{\delta b}{2}) \qquad \delta d = \delta t \cdot f'(t_n + \delta t, A_n + \delta c)$$

$$A(t_{n+1}) = A(t_n) + \frac{\delta a}{6} + \frac{\delta b}{3} + \frac{\delta c}{3} + \frac{\delta d}{6} + O(\delta t^5)$$

The error term O is dependent on the stepsize δt which is adapted automatically so that the relative accuracy of the results is always better than 0.1% of the accuracy factor dt specified in the options menu (default value dt = 1.0).

Also the formation of metabolites is expressed by means of a differential equation. Metabolite formation is a part of the total drug elimination (see chapter 2) and is included in the total drug clearance. Therefore the value of k_m does not affect the concentration of the parent drug.

Metabolite formation

$$\frac{dA_m(t)}{dt} = k_m \cdot A1(t)$$

The metabolising constant k_m takes into account the difference in molecular weight of the metabolite and the parent compound.
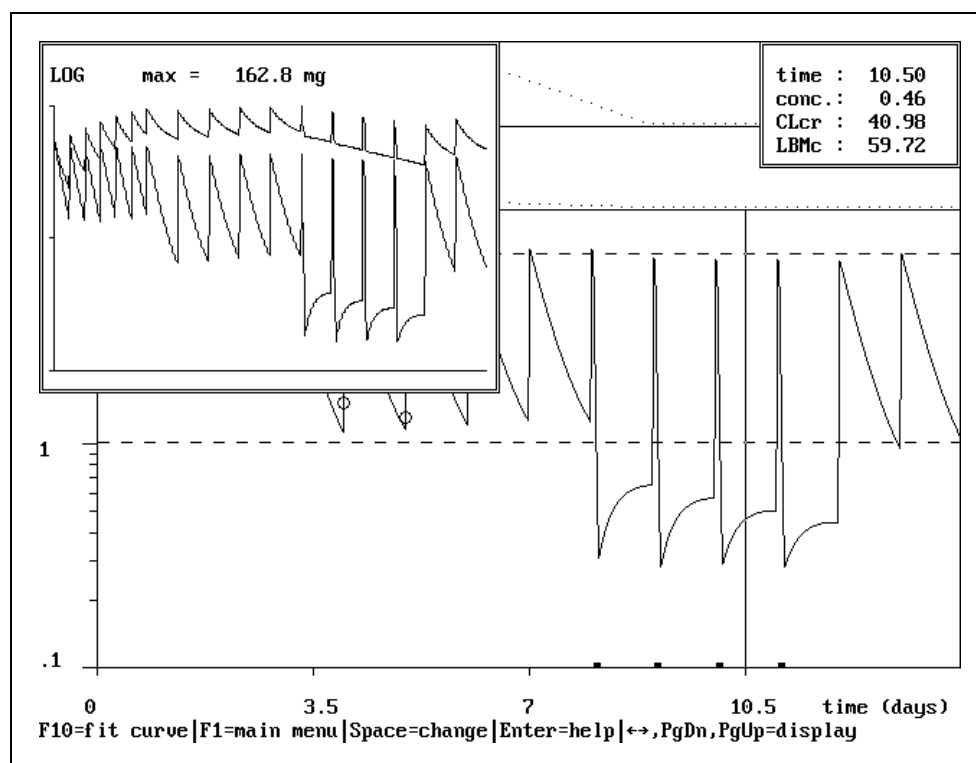
Figure 3.2   Effect of dialysis on the amount of drug in plasma and the total amount of drug present in the body.

Figure 3.2 demonstrates a patient case that could not be simulated without the use of differential equations. Initially the patient was put on a regimen of 60 mg gentamycin every 12 hours. After a peak-trough measurement the regimen was changed into 60 mg gentamycin every 24 hours. After 4 days of using this regimen the patient was also dialysed. In total 4 dialysis sessions took place, each with a duration of 2 hours. Every dialysis period started 30 min after stopping the gentamycin infusion. The main windows displays the plasma concentration over time. The small popup window in the upper left corner shows 2 curves. The lower curve represents the amount in plasma while the upper curves represents the total amount in the body. The highest value of this total amount in body curve is also displayed in the popup window. Please note the redistribution phenomenon after every dialysis period. This way of data

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presentation is very suitable for judging the efficiency of dialysis treatments in the case of intoxications.

3.3 Normal Equations

MW\PHARM uses normal equations for dose calculations (linear kinetics only) and in the KinFit module. The following symbols are used in the upcoming paragraphs.

Symbol	Unit	Description
AUC	$h.mg/L$	Area under the curve
CL	L/h	Total drug clearance
V_1	L	Volume of distribution central compartment
V_{ss}	L	Volume of distribution during steady state
V_β	L	Volume of distribution in terminal phase
D	mg	Dose
C	mg/L	Plasma concentration
C_i	mg/L	i^{th} plasma concentration
C_0	mg/L	Plasma concentration at $t=0$
C_x	mg/L	x^{th} coefficient in polyexponential equation
L_x	$/h$	x^{th} exponent in polyexponential equation
Q_x	$-$	Accumulation factor x^{th} term
Q_a	$-$	Accumulation factor absorption term
n	$-$	Number of doses
N	$-$	Number of compartments
N_c	$-$	Number of concentrations
t	h	Time since first dose administration
t_r	h	Time since last dose administration
t_0	h	Absorption lag-time
$t_{\frac{1}{2}x}$	h	Half-life phase x
T_{inf}	h	Infusion duration
k_{xy}	$/h$	Rate constants
k_{10}	$/h$	Total elimination rate constant
k_a	$/h$	Absorption rate constant
MRT	h	Mean residence time
MAT	h	Mean absorption time

The parameters C_x (C_1, C_2, C_3) and L_x (L_1, L_2, L_3) of the polyexponential equation are sometimes referred to as **macro** constants whereas the parameters k_{xy} (k_{01}, k_{10}, k_{21}, k_{21}, k_{13}, k_{31}) which are used in the differential equations are sometimes called **micro** constants.

PHARMACOKINETIC SIMULATIONS

MW\PHARM uses the following equations for predicting plasma levels at any moment in time after multiple (regular) administrations of drug using one specific route of administration

I.V. Bolus

$$C(t) = \sum_{x=1}^{N} \{C_x \cdot Q_x \cdot e^{-L_x \cdot t_r}\}$$

I.V. Infusion

$$C(t) = \sum_{x=1}^{N} \{C_x \cdot \frac{1}{L_x \cdot T_{\text{inf}}} \cdot (Q_x - Q_x \cdot e^{-L_x \cdot t_r})\}$$

I.V. Post-Infusion

$$C(t) = \sum_{x=1}^{N} \{C_x \cdot \frac{1}{L_x \cdot T_{\text{inf}}} \cdot (Q_x \cdot e^{-L_x \cdot (t_r - T_{\text{inf}})} - Q_x \cdot e^{-L_x \cdot t_r})\}$$

E.V. Oral & Intramuscular

$$C(t) = \sum_{x=1}^{N} \{C_x \cdot \frac{k_a}{k_a - L_x} \cdot (Q_x \cdot e^{-L_x \cdot (t_r - t_0)} - Q_a \cdot e^{-k_a \cdot (t_r - t_0)})\}$$

I.V. & E.V. Multiple dose factors

$$Q_x = \frac{(1 - e^{-n \cdot L_i \cdot T_{\text{int}}})}{(1 - e^{-L_i \cdot T_{\text{int}}})} \qquad Q_a = \frac{(1 - e^{-n \cdot k_a \cdot T_{\text{int}}})}{(1 - e^{-k_a \cdot T_{\text{int}}})}$$

$$t_r = t - (n-1) \cdot T_{\text{int}}$$

The following parameter limits must be taken into account for both micro and macro constants.

Parameter limits

$$k_{xy} > 0 \qquad\qquad C_x > 0 \qquad\qquad L_1 > L_2 > L_3 > 0$$

The half-life of every x^{th} phase in the plasma curve is simply obtained by dividing the natural logarithm of 2 by the value of xth exponent of the polyexponential equation.

Half-life

$$t_{\frac{1}{2}_x} = \frac{\ln(2)}{L_x}$$

3.4 Constant Conversion: Micro → Macro

The pharmacokinetic population parameters listed in the medication data screen are all in fact so called micro parameters that can be directly used (after normalization) in differential equations. If we want to use these pharmacokinetic parameters in normal equations we will have to convert them into macro parameters.

First the elimination rate constant is calculated from the denormalized clearance and denormalized volume of distribution.

Elimination rate constant

$$k_{10} = \frac{CL}{V_1}$$

On the next page the conversion formulae are listed for 1, 2 and 3 compartment systems.

PHARMACOKINETIC SIMULATIONS

1 compartment macro constants

$$L_1 = k_{10} \qquad\qquad C_1 = C_0 = \frac{D}{V_1}$$

2 compartment macro constants

$$a = k_{10} + k_{12} + k_{21} \qquad\qquad b = a^2 - 4 \cdot k_{10} \cdot k_{21}$$

$$C_0 = \frac{D}{V_1}$$

$$L_1 = \frac{1}{2} \cdot (a + \sqrt{b}) \qquad\qquad C_1 = C_0 \cdot \frac{(k_{21} - L_1)}{(L_2 - L_1)}$$

$$L_2 = a - L_1 \qquad\qquad C_2 = C_0 - C_1$$

3 compartment macro constants

$$a = k_{10} + k_{12} + k_{21} + k_{13} + k_{31}$$
$$b = k_{10} \cdot k_{21} + k_{10} \cdot k_{31} + k_{12} \cdot k_{31} + k_{13} \cdot k_{21} + k_{21} \cdot k_{31}$$
$$c = k_{10} \cdot k_{21} \cdot k_{31}$$

$$aa = \frac{1}{3}a \qquad bb = aa^2 - \frac{1}{3}b \qquad cc = aa^3 + \frac{1}{2}(c - aa \cdot b)$$

$$\varphi = \frac{1}{3} atn\left(\sqrt{\frac{bb^3}{cc^2} - 1}\right) \qquad\qquad C_0 = \frac{D}{V_1}$$

$$L_x = aa + 2 \cdot \sqrt{bb} \cdot \cos\left(\varphi + \frac{2}{3}\pi \cdot (x - 1)\right)$$

$$C_1 = C_0 \cdot \frac{(k_{21} - L_1)}{(L_2 - L_1)} \cdot \frac{(k_{31} - L_1)}{(L_3 - L_1)}$$

$$C_2 = C_0 \cdot \frac{(k_{21} - L_2)}{(L_1 - L_2)} \cdot \frac{(k_{31} - L_2)}{(L_3 - L_2)}$$

$$C_3 = C_0 - C_1 - C_2$$

3.5 Constant Conversion: Macro → Micro

MW\PHARM must also be able to do the reverse, that is obtaining micro constants from macro constants. This is for instance required after a fitting plasma levels in the KinFit module. KinFit will look for those values of C_x and L_x that minimize the sum of squared differences of predicted and measured concentrations (see chapter 6 for details). First the area under the curve, the volume of distribution and the half-life are calculated from the fitted macro parameters.

Area under the curve

$$AUC_t = \int_{t=0}^{t} C(t) \cdot dt \qquad AUC_\infty = \int_{t=0}^{\infty} C(t) \cdot dt = \sum_{x=1}^{N} \frac{C_x}{L_x}$$

$$\textit{Trapezium Rule:} \qquad AUCT_t = \sum_{i=1}^{N_c} \frac{(C_i + C_{i-1}) \cdot (t_i - t_{i-1})}{2}$$

Volume of distribution and half-life

$$V_1 = \frac{F \cdot D}{C_0} \qquad C_0 = \sum_{x=1}^{N} C_x \qquad t_{\frac{1}{2}x} = \frac{\ln(2)}{L_x}$$

The area under the curve from time zero to infinity is then used for the calculation of the clearance.

Clearance

$$CL = \frac{F \cdot D}{AUC_\infty}$$

The micro constants can now be calculated as follows:

PHARMACOKINETIC SIMULATIONS

1 compartment micro constants

$$C_0 = C_1 \qquad\qquad k_{10} = L_1$$

2 compartment micro constants

$$C_0 = C_1 + C_2 \qquad\qquad k_{21} = \frac{(C_1 \cdot L_2 + C_2 \cdot L_1)}{C_0}$$

$$k_{10} = \frac{L_1 \cdot L_2}{k_{21}} \qquad\qquad k_{12} = L_1 + L_2 - (k_{21} + k_{10})$$

3 compartment micro constants

$$C_0 = C_1 + C_2 + C_3$$

$$a = L_1 + L_2 + L_3$$

$$b = \frac{(C_3 \cdot L_1 + C_2 \cdot L_1 + C_1 \cdot L_3 + C_2 \cdot L_3 + C_1 \cdot L_2 + C_3 \cdot L_2)}{-C_0}$$

$$c = \frac{(C_3 \cdot L_1 \cdot L_2 + C_2 \cdot L_1 \cdot L_3 + C_1 \cdot L_2 \cdot L_3)}{C_0}$$

$$k_{31} = \frac{-b - \sqrt{(b^2 - 4c)}}{2} \qquad k_{21} = -b - k_{31} \qquad k_{10} = \frac{L_1 \cdot L_2 \cdot L_3}{k_{21} \cdot k_{31}}$$

$$k_{12} = \frac{(L_2 \cdot L_3 + L_1 \cdot L_2 + L_1 \cdot L_3 - k_{21} \cdot a - k_{10} \cdot k_{31} + k_{21}^2)}{(k_{31} - k_{21})}$$

$$k_{13} = a - (k_{10} + k_{12} + k_{21} + k_{31})$$

The calculation of the volume of distribution at steady state and in the terminal phase was explained in chapter 2.

The mean residence time (MRT) and the mean absorption time (MAT) are calculated as follows.

Mean residence time

$$\textbf{\textit{Intravenous}} \quad : MRT = \frac{\int\limits_{t=0}^{\infty} C(t) \cdot t \cdot dt}{\int\limits_{t=0}^{\infty} C(t) \cdot dt} = \frac{AUMC}{AUC} = \frac{V_{ss}}{CL}$$

$$\textbf{\textit{Extravascular}} \quad : MRT = MAT + \frac{V_{ss}}{CL}$$

$$MAT = \frac{1}{k_a} + t_0$$

```
Dose                        [mg]    :  100.00

Area Under the Curve (AUC)  [h.mg/l] :   31.51
AUC polyexponential   (t= 8)         :   24.38
AUC trapezoidal rule  (t= 8)         :   24.26
Clearance (CL)              [l/h]   :    3.174
Volume of distribution comp.1 [l]   :    6.566
Volume of distr. steady state [l]   :   16.79
Volume of distribution      [l]     :   17.85
Half-life phase 1           [h]     :    0.1351
Half-life phase 2           [h]     :    3.899
Rate constant k10           [1/h]   :    0.4834
Rate constant k12           [1/h]   :    2.938
Rate constant k21           [1/h]   :    1.887
Mean Residence Time (MRT)   [h]     :    5.289




 F10 = continue │ F1 = Kinfit menu │
```

Figure 3.5 KinFit report of calculated micro constants.

4 DOSAGE REGIMENS

4.1 Introduction

Given a set of pharmacokinetic parameters C_x and L_x, the design of a dosage regimen can be viewed upon as finding those values for D_m and T_{int} that generate a model output (response) that satisfies the selected targets of C_{max} and C_{min} (or C_{av}).

Symbol	Unit	Description
n	–	Number of doses
L_x	/h	x^{th} exponent in polyexponential equation
C_x	mg/L	x^{th} coefficient in polyexponential equation
C	mg/L	Concentration
C_{id}	mg/L	Target concentration of type id
C_{id}^n	mg/L	Concentration of type id after n^{th} dose
T_{id}^n	h	Time of type id after n^{th} dose
T_{int}	h	Dosing interval time
t_r	h	Time since last dose administration
CL	L/h	Clearance
AUC	h.mg/L	Area under the curve
F	–	Bioavailability
D	mg	Loading (D_l) or maintenance dose (D_m)
R	mg/h	Dosing rate
Z	/L	General $C(t)$ function divided by dose D
Z'	/h/L	First derivative of $Z()$ function
$SS\%$	%	Percentage steady state

id	description
max	Maximum concentration
min	Minimum concentration
av	Average concentration
$peak$	Highest measured/sampled concentration
$trough$	Lowest measured/sampled concentration

We will first deal with the general case that describes a model containing any number of compartments combined with any route of administration. In order to do so we must first rewrite the normal simulation equations as described in chapter 3. This rewrite consists of separating the given dose (*D*) from the coefficients of the polyexponential equation. The remaining part of all equations we summarize in a single term called *Z()*. This term is a function of simulation time, dosing interval time and the number of given doses.

Generalised normal equation

$$C(t) = D \cdot Z(t_r, T_{\text{int}}, n)$$

4.2 Minimum and Maximum Target Levels

If the calculation of a dosage regimen must be based on the minimum and maximum targets the interval time is calculated from the ratio of the minimum and maximum target concentrations at steady state (*n=◎*). The required time of maximum is obtained by taking the first derivative of the generalised normal equation and assigning it to zero. Note that in both equations the dose variable *D* has been eliminated.

Dosing interval time

$$\textit{Find } T_{\text{max}}^{\infty} \quad : \quad \frac{dC(t)}{dt} = Z'(T_{\text{max}}^{\infty}, T_{\text{int}}, \infty) = 0$$

$$\textit{Find } T_{\text{int}} \quad : \quad \frac{C_{\text{min}}}{C_{\text{max}}} = \frac{Z(T_{\text{int}}, T_{\text{int}}, \infty)}{Z(T_{\text{max}}^{\infty} . T_{\text{int}}, \infty)}$$

The values of T_{int} and T_{max}^{∞} are defined implicitly because they cannot be isolated from the equations in which the are contained. Therefore these parameters must be solved by an iterative proce-

dure. In this case a modified bisection method is applied that has been optimised for this type of problems.

Once T_{int} and T_{max}^{∞} have been determined the maintenance dose D_m can be calculated as follows.

Maintenance dose

$$D_m = \frac{C_{\max}}{Z(T_{\max}^{\infty}, T_{\text{int}}, \infty)}$$

For the calculation of the loading dose D_l two criteria are possible. The first criterion is to make sure that the maximum concentration after the first dose ($n=1$) is equal to the final maximum target, that is the maximum concentration at steady state ($n=\circledcirc$). The required time of maximum is obtained by taking the first derivative of the generalised normal equation and assigning it to zero.

Loading Dose I

Find $T_{\max}^{1}$ $\quad : \dfrac{dC(t)}{dt} = Z'(T_{\max}^{1}, T_{\text{int}}, 1) = 0$

Calc D_l $\quad : D_l = \dfrac{C_{\max}}{Z(T_{\max}^{1}, T_{\text{int}}, 1)}$

The T_{max}^{1} parameter is once again defined implicitly and must therefore be solved in the derivative equation by using an iterative procedure.

The second criterion is to make sure that the minimum concentration after the first dose ($n=1$) is equal to the final minimum target, that is the minimum concentration at steady state ($n=\circledcirc$).

Loading Dose II

$$D_l = \frac{C_{\min}}{Z(T_{\text{int}}, T_{\text{int}}, 1)}$$

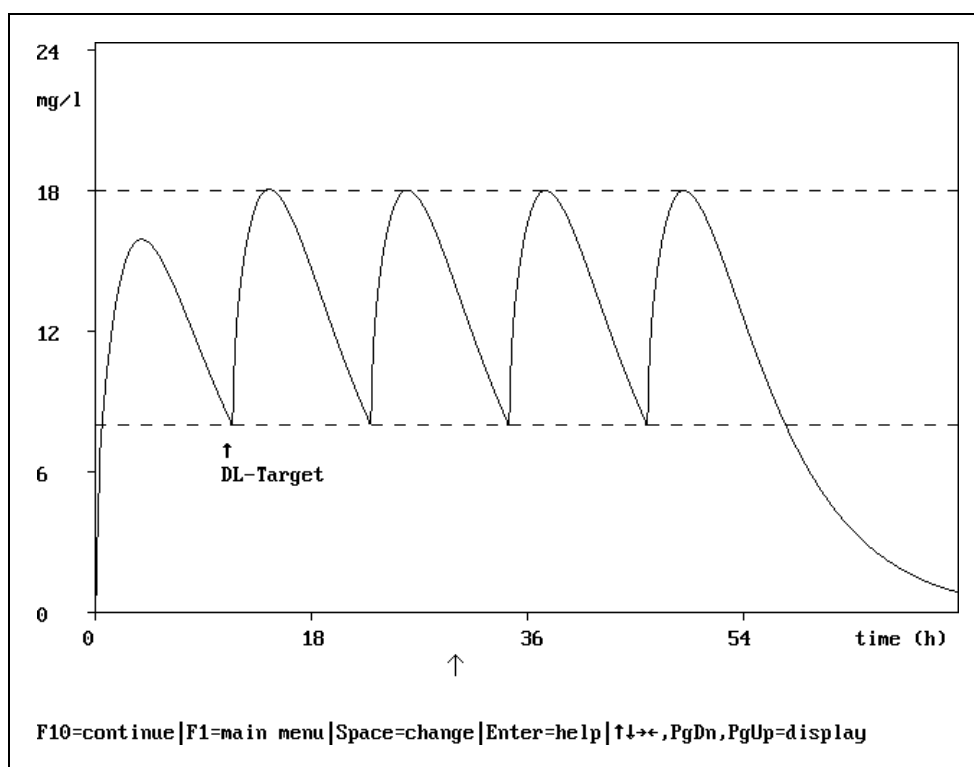*Figure 4.2-A. Oral regimen of theophylline (2-comp) using C_{min} as a target for the loading dose.*
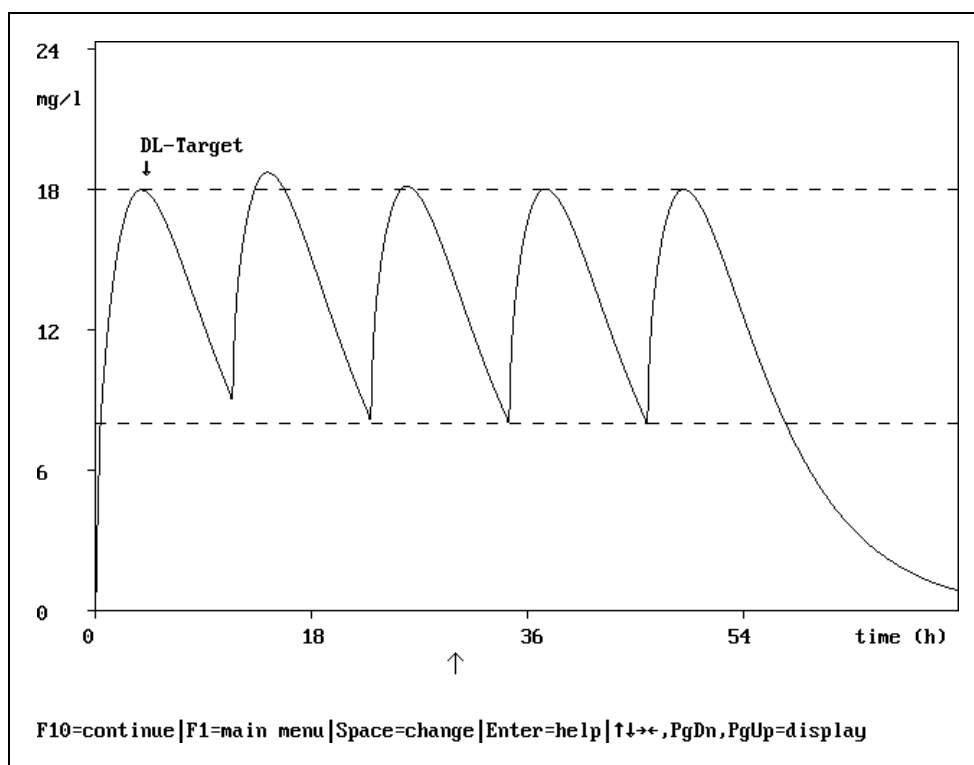

Figure 4.2-B. Oral regimen of theophylline (2-comp) using C_{max} as a target for the loading dose.
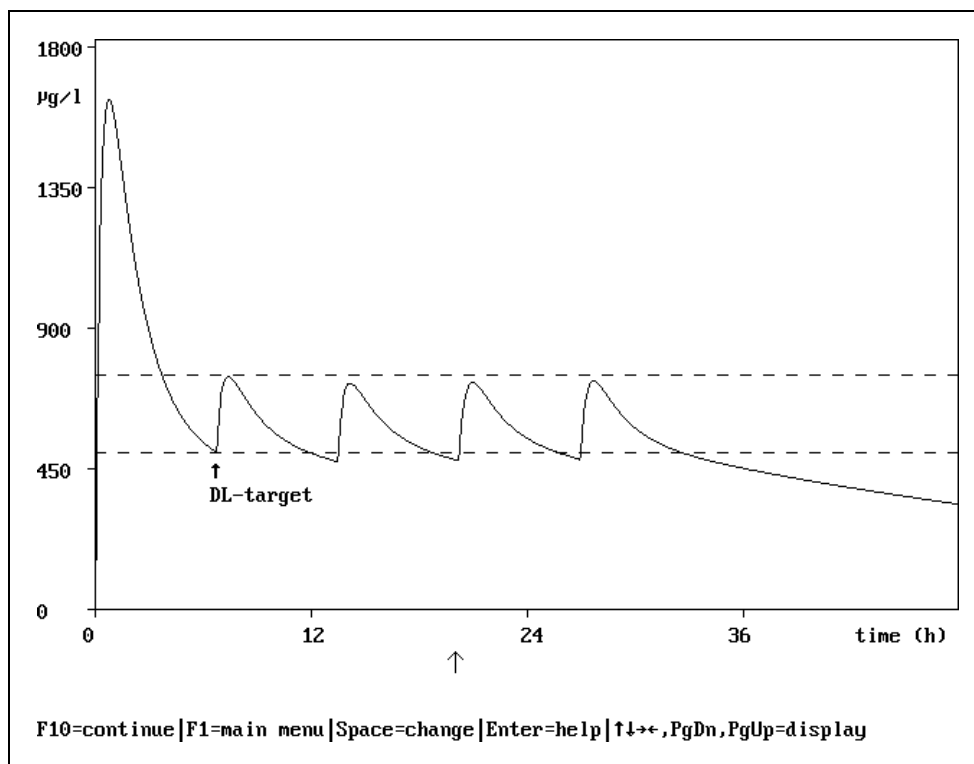
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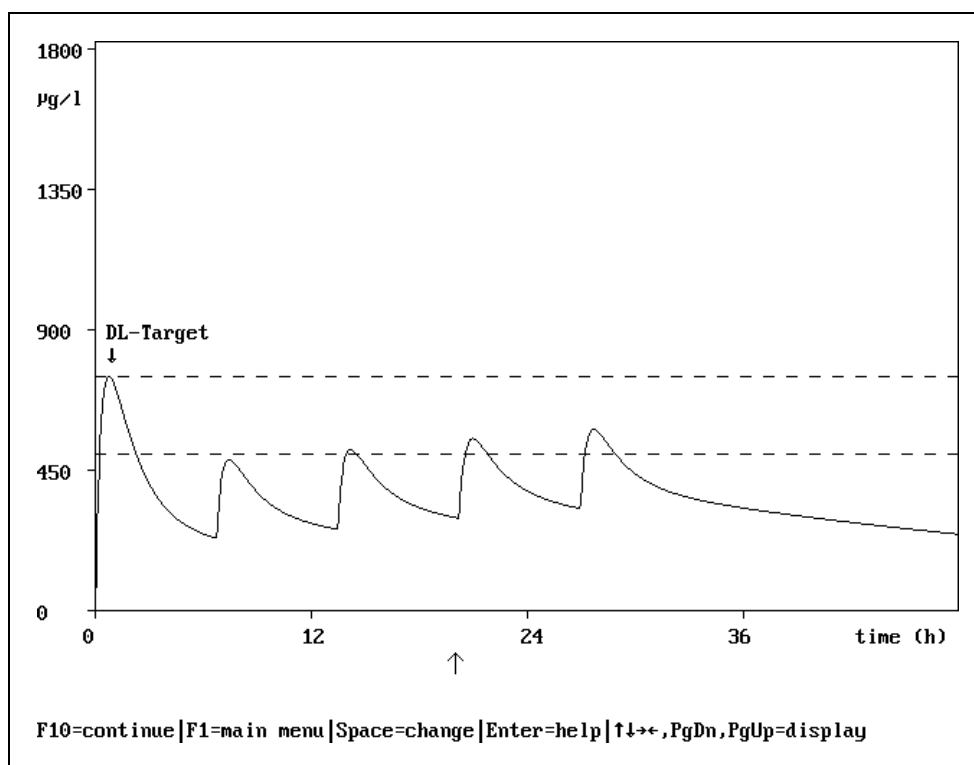*Figure 4.2-C. Oral regimen of diazepam (2-comp) using C_{min} as a target for the loading dose.*

Figure 4.2-D. Oral regimen of diazepam (2-comp) using C_{max} as a target for the loading dose.

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☞ MW\PHARM calculates both loading doses but only the lowest loading dose is selected for the dosage regimen. The reason for this is explained in figure 4.2.

Figures 4.2-A and 4.2-B represent an oral theophylline dosage regimen based on a 2-compartment model. In figure 4.2-A a loading dose was given causing a minimum concentration after the first dose that exactly matches the target minimum concentration. In figure 4.2-B a loading dose was given causing a maximum concentration after the first dose that exactly matches the target maximum concentration. In figure 4.2-A the maximum concentration after the second dose (first maintenance dose) matches exactly the desired target maximum concentration whereas in figure 4.2-B the maximum concentration after the second dose is higher than the target maximum concentration.

☞ These types of overshoots can occur if the absorption rate constant is lower then the elimination rate constant and is not related to the 2 compartment nature of the model. Thus in this particular example a loading dose based on the minimum concentration target is optimal.

Figures 4.2-C and 4.2-D represent an oral diazepam dosage regimen based on a 2-compartment model. In figure 4.2-C a loading dose was given causing a minimum concentration after the first dose that exactly matches the target minimum concentration. In figure 4.2-D a loading dose was given causing a maximum concentration after the first dose that exactly matches the target maximum concentration. From figure 4.2-C it becomes clear that in order to reach the minimum concentration target after the first gift a huge loading dose must be given. Therefore it is better to use the maximum target concentration for calculating the loading dose.

☞ This type of behaviour is typical for 2 compartment systems and is not related to the route of administration. Thus in this particular example a loading dose based on the maximum concentration target is optimal.

4.3 Average Target Level

If the calculation of a dosage regimen must be based on an average concentration level the maintenance dose and the dosing interval are determined simultaneously using a iterative procedure based on the so the called bisection method.

Dosing interval time and maintenance dose

$$\frac{D_m}{T_{\text{int}}} = C_{av} \cdot \frac{CL}{F} = AUC \cdot \frac{CL}{F}$$

Condition I: $D_m \cdot Z(T_{\max}^{\infty}, T_{\text{int}}, \infty) = C_{\max}$

Condition II: $D_m \cdot Z(T_{\text{int}}, T_{\text{int}}, \infty) = C_{\min}$

The parameters C_{av}, CL and F are all known. An iterative procedure searches for values of T_{int} and D_m that satisfy condition I or condition II. It is difficult to predict which condition will be satisfied first because this depends on the shape of the curve. The closer the average target level is to one of the extreme target levels the higher the change that this extreme level becomes part of the dosage regimen. This has been illustrated if figure 4.3 Figure 4.3-A and 4.3-B both show an oral dosage regimen of theophylline based on a target average plasma level. In both examples the target maximum level was set to 20.0 mg/L and the target minimum level was set to 10.0 mg/L. In figure 4.3-A the average target level was set to 12.5 mg/L while in figure 4.3-B it was set to 17.5 mg/L.

Dosage regimes based on average concentrations can be of interest in the following situations.

- In concentration controlled clinical trials (CCCT's) as compared to dosage controlled clinical trials (DCCT's).

- In the absence of a clear relation between plasma levels and the observed therapeutic or toxic effect. This situation might occur when the effect is correlated with the concentration in a peripheral compartment or when the effect is caused indirectly (e.g. cyclosporine).
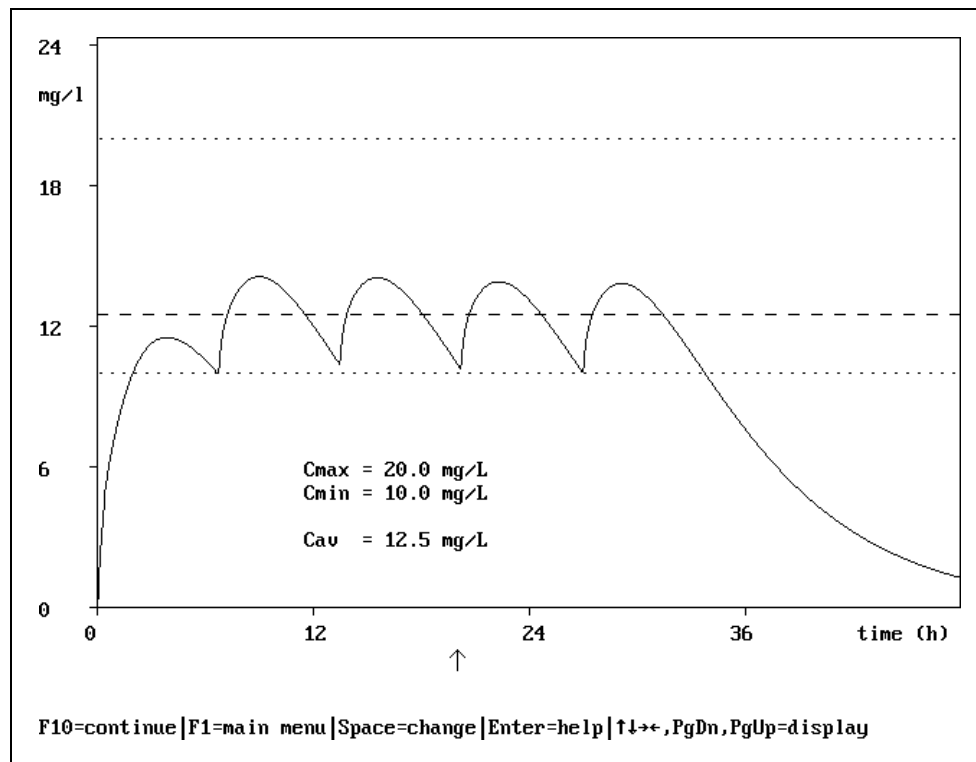
Figure 4.3-A. Dosage regimen based on average and minimum target plasma levels.
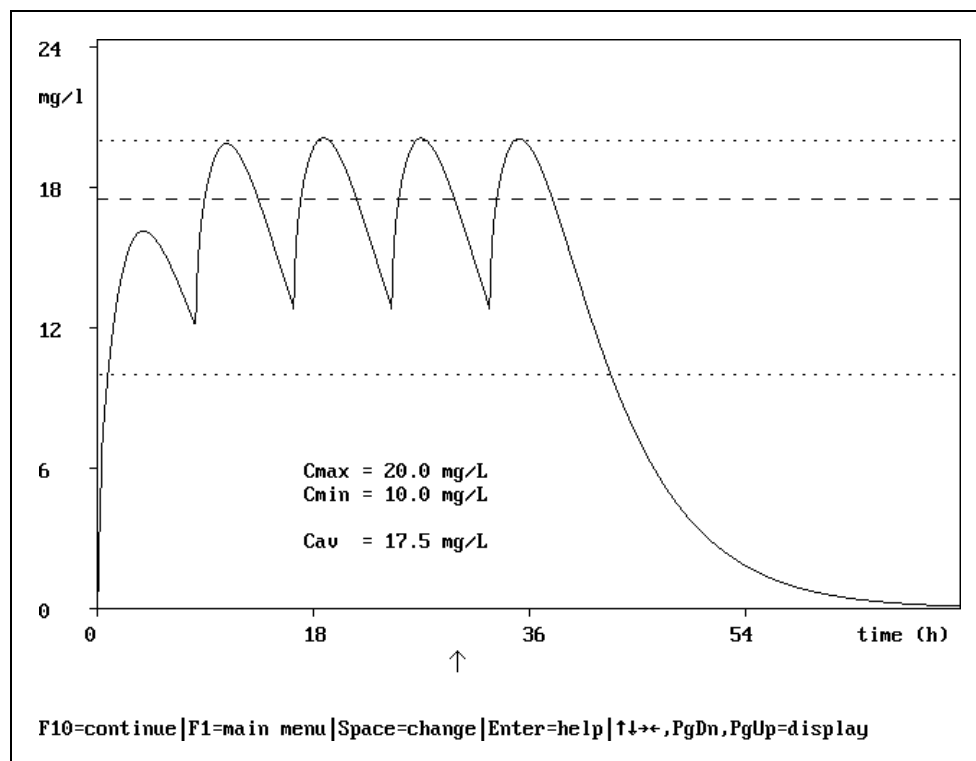
Figure 4.3-B. Dosage regimen based on average and maximum target plasma levels.

The loading dose is calculated in the same way as described in paragraph 4.2. MW\PHARM imposes the following limits on all target levels.

Target level limits

$$C_{\max} > 1.1 \cdot C_{\min} \qquad C_{av} > 1.1 \cdot C_{\min} \qquad C_{av} < 0.9 \cdot C_{\min}$$

☞ Note: The dosage regimen calculation of a single constant rate infusion is always based on C_{av} independent of the selected method (C_{av} or $C_{min}-C_{max}$. The mean value of C_{min} and C_{max} will be used if no value for C_{av} has been specified in the medication screen.

4.4 Non-Linear Kinetics

Several drugs exhibit non-linear kinetics. Examples are ethanol, phenytoin, probenecid, salicylate and high doses of theophylline.

The methods discussed until now for designing a dosage regimen, only work in the case of linear kinetics. In the case of non-linear kinetics MW\PHARM must use differential equations. Although the basic strategy for finding a dosage regimen is more or less the same, the equations involved are quite different. It involves state of the art numerical programming which is beyond the scope of this manual.

☞ Note: In the case of non-linear kinetics a dosage regimen can only be based on $C_{min}-C_{max}$.

Figure 4.4 displays a dosage regimen of ethanol given orally. The targets were set to 1000 mg/L and 500 mg/L respectively. The concentration scale is logarithmic. Note the shape of the curve during the elimination phase. This is typical for non-linear kinetics.
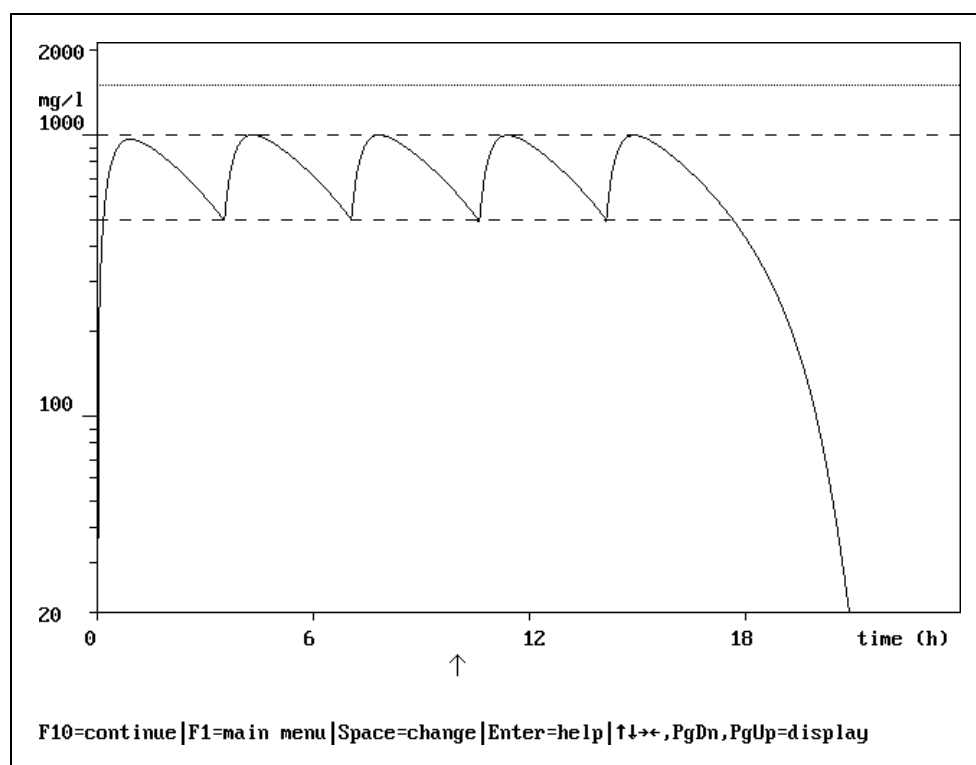
Figure 4.4. Dosage regimen of ethanol using non-linear kinetics.

4.5 Practical Dosage Regimens

With the methods described so far we were able to calculate an exact dosage regimen. An exact regimen is characterised by the fact that the calculated maintenance dose and interval time cause steady state levels that exactly match the pre-set target levels

Very seldom an exact dosage regimen is also practical. E.g. a regimen subscribing 1347.5 mg every 16.31 h can hardly be called practical. MW\PHARM is able to convert exact dosage regimens into practical dosage regimens based on convenient interval times and available dosages (see fig. 4.5).

From figure 4.5. you can see that there are 4 principle practical alternatives to a single exact dosage regimen (vancomycin). Practical interval times are chosen so that they are convenient for the medical personal administrating the dosages. The available dosages mentioned do not represent commercially available dosages but

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dosages that the hospital pharmacist is willing to prepare himself. These available dosages are listed in the drug database of MW\PHARM.

The practical dosage suggested by MW\PHARM is based on one or a combination of maximally two available dosages. Thus in the example of figure 4.5 MW\PHARM will never suggest the (better) regimen of 1750 mg / 24 h because the amount of 1750 mg must be constructed from three available dosages (1000 + 500 + 250).
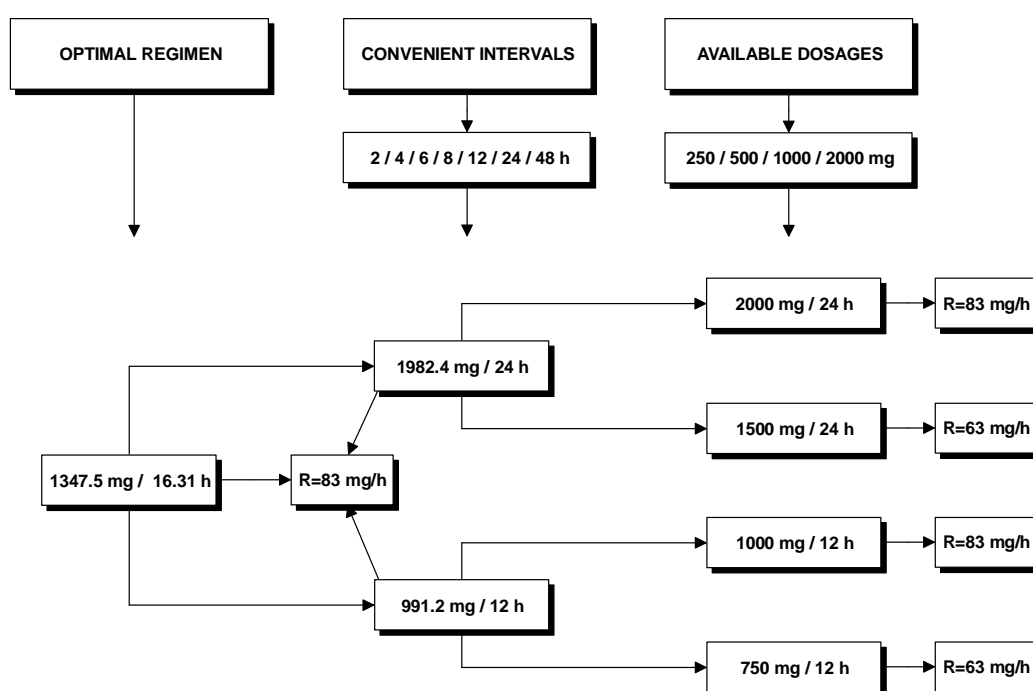
Figure 4.5. Generation of practical dosage regimens.

Figures 4.5-ABCD display the concentration time profiles of the practical vancomycin regimens displayed in figure 4.5. As you can see from these figures, dosage regimens with the same input rate R (mg/h) will cause identical average plasma levels. However, the difference between the maximum and minimum plasma levels (amplitude) increases with longer interval times.

☞ MW\PHARM sorts the different practical dosage regimen alternatives based on the value of the maintenance dose and not on the deviation of the desired and actually reached plasma levels.
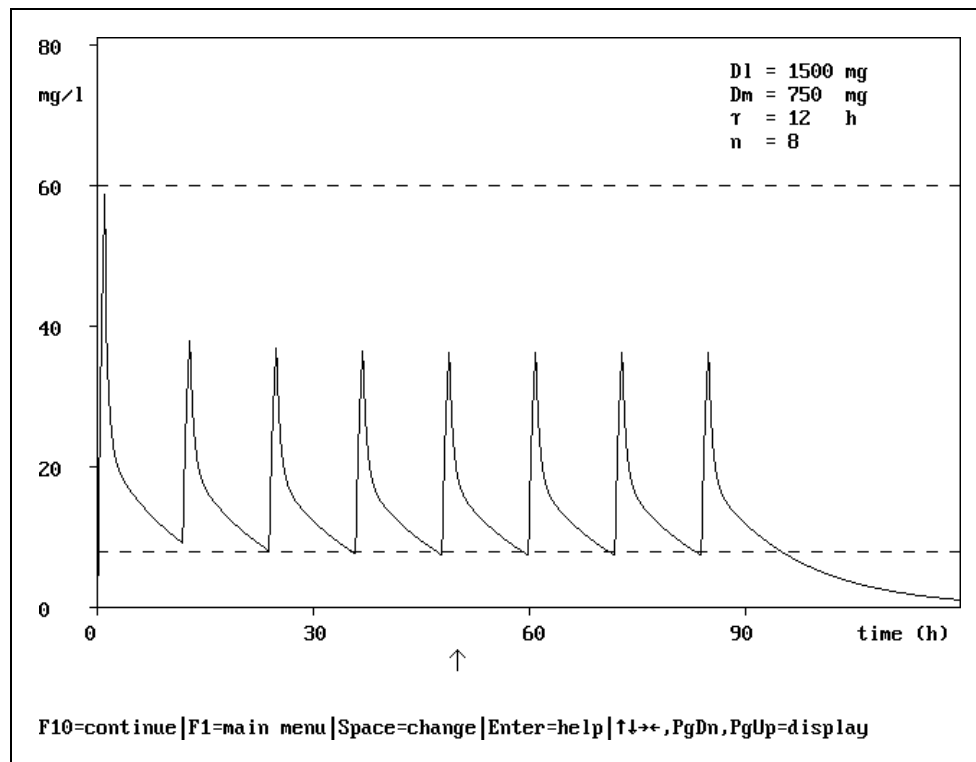
Figure 4.5-A. Vancomycin regimen of 750 mg every 12 h.
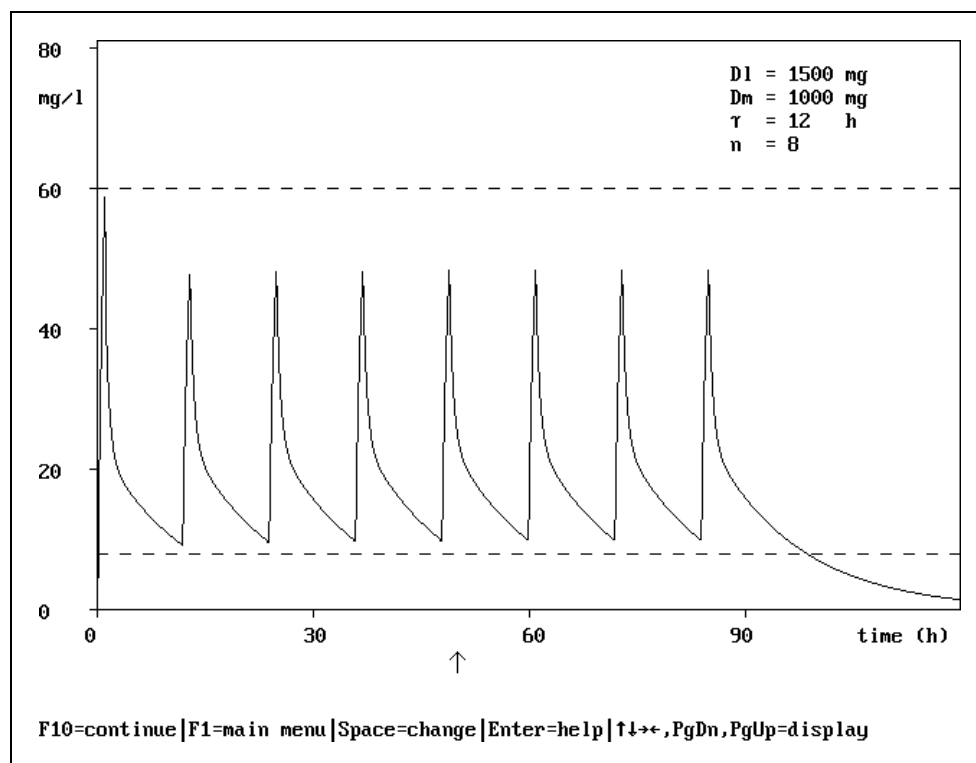
Figure 4.5-B. Vancomycin regimen of 1000 mg every 12 h.
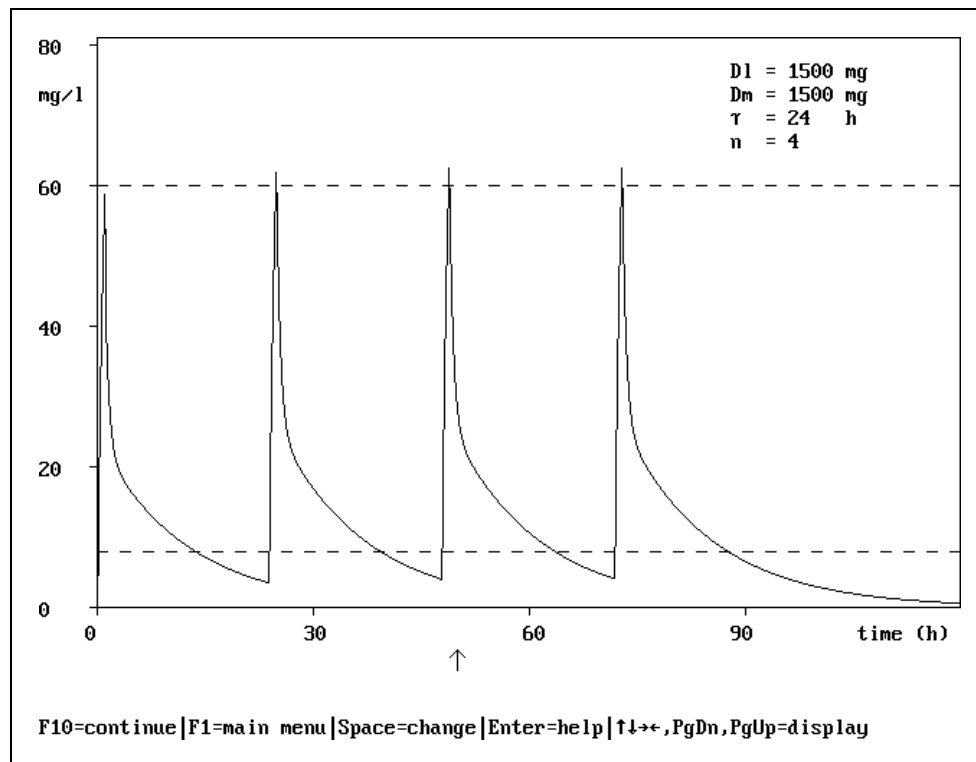
Figure 4.5-C. Vancomycin regimen of 1500 mg every 24 h.
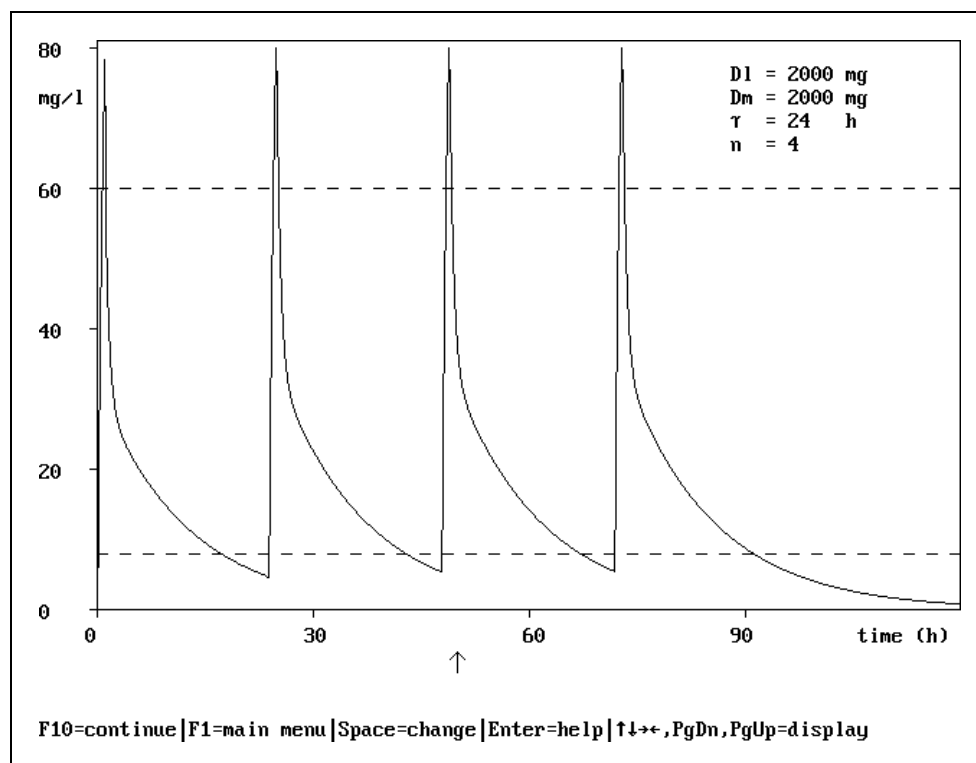
Figure 4.5-D. Vancomycin regimen of 2000 mg every 24 h.

4.6 Prediction of Plasma Levels

The dosage regimen screen visible in figure 4.6 does not only display the calculated exact and practical dosage regimens but also the effects of these regimens in terms of predicted plasma levels.

```
┌─────────────────────────────────────────────────────────────────────┐
│ vancomycin (adult)              MW                       08-01-1940   │
├──────────────────────┬──────────┬──────────┬─────────────────────────┤
│ Infusion (repeated)  │ Selected │  Exact   │         Practical        │
├──────────────────────┼──────────┼──────────┼──────┬──────┬──────┬─────┤
│ Loading dose      mg │  1536.4  │  1536.4  │ 1500 │ 1500 │ 1500 │2000 │
│ Maint. dose       mg │  1347.5  │  1347.5  │  750 │ 1000 │ 1500 │2000 │
│ Infusion time      h │     1.00 │     1.00 │ 1.00 │ 1.00 │ 1.00 │1.00 │
│ Dosing interval    h │    16.31 │    16.31 │   12 │   12 │   24 │  24 │
│ Total duration     h │    49    │    49    │   48 │   48 │   48 │  48 │
│ Number of doses      │     3    │     3    │    4 │    4 │    2 │   2 │
├──────────────────────┼──────────┼──────────┼──────┼──────┼──────┼─────┤
│ C_max_ss        mg/l │    60.00 │    60.00 │36.15 │48.20 │62.35 │83.14│
│ C_min_ss        mg/l │     8.00 │     8.00 │ 7.44 │ 9.92 │ 4.09 │5.46 │
│ C_av_ss         mg/l │    18.30 │    18.30 │13.85 │18.46 │13.85 │18.46│
│ Steady state       % │    99    │    99    │  101 │  100 │   98 │  98 │
├──────────────────────┼──────────┼──────────┼──────┼──────┼──────┼─────┤
│ C_peak          mg/l │    23.98 │    23.98 │16.05 │21.05 │22.77 │30.36│
│ C_trough        mg/l │     7.64 │     7.64 │ 7.70 │ 9.82 │ 3.50 │4.67 │
│ T_peak             h │     3.00 │     3.00 │ 3.00 │ 3.00 │ 3.00 │3.00 │
│ T_trough           h │     0.00 │     0.00 │ 0.00 │ 0.00 │ 0.00 │0.00 │
└──────────────────────┴──────────┴──────────┴──────┴──────┴──────┴─────┘

 F10=continue F1=main menu F3=adapt F4=copy F5=print F6=recalc. F7=roa ↓
```

Figure 4.6. Dosage regimen screen.

The upper part of the dosage regimen screen lists the dosage regimen parameters (loading dose, maintenance dose, interval time, duration and the number of doses). The middle part of the dosage regimen screen contains the predicted plasma levels at steady state (steady state output parameters). The levels reported here are the highest and lowest levels possible (extremes). The lower part of the screen contains the plasma levels after the last given dose (current state parameters). The levels are predicted at the pre-set sampling times which are also listed.

All these predictions are obtained using the generalised normal equation which was derived in paragraph 4.2.

Predicted steady state concentrations

C_max_ss $: C_{\max}^{\infty} = D_m \cdot Z(T_{\max}^{\infty}, T_{\mathrm{int}}, \infty)$

C_min_ss $: C_{\min}^{\infty} = D_m \cdot Z(T_{\mathrm{int}}, T_{\mathrm{int}}, \infty)$

C_av_ss $: C_{av}^{\infty} = \dfrac{D_m}{T_{\mathrm{int}}} \cdot \dfrac{F}{CL}$

$Steady\ state$ $: SS\% = \dfrac{Z(T_{\max}^{n}, T_{\mathrm{int}}, n)}{Z(T_{\max}^{\infty}, T_{\mathrm{int}}, \infty)} \cdot 100\%$

Predicted current state concentrations

C_peak $: C_{peak}^{n} = D_m \cdot Z(T_{peak}^{n}, T_{\mathrm{int}}, n)$

C_trough $: C_{trough}^{n} = D_m \cdot Z(T_{trough}^{n}, T_{\mathrm{int}}, n)$

T_peak $: T_{peak}^{n}$

T_trough $: T_{trough}^{n}$

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BEFORE REPRODUCTION

5 INDIVIDUALIZATION

5.1 Introduction

Symbol	Unit	Description
n	–	Number of doses
N_c	–	Number of measured concentrations
N_p	–	Number of fitted parameters
k_{xy}	$/h$	Rate constants
L_x	$/h$	x^{th} exponent in polyexponential equation
C_x	mg/L	x^{th} coefficient in polyexponential equation
C	mg/L	Concentration
C_{id}	mg/L	Target concentration of type id
C_{id}^{n}	mg/L	Concentration of type id after n^{th} dose
T_{id}^{n}	h	Time of type id after n^{th} dose
T_{int}	h	Dosing interval time
T_{inf}	h	Infusion duration
D	mg	Loading (D_l) or maintenance dose (D_m)
Z	$/L$	General $C(t)$ function divided by dose D
Cm_i	mg/L	Measured i^{th} concentration
Ce_i	mg/L	Estimated i^{th} concentration
Pp_i	–	Observed i^{th} population parameter
Pe_i	–	Estimated i^{th} individual parameter
SS	–	Sum of squares
SS_c	–	Sum of squares (concentrations only)
SS_p	–	Sum of squares (parameters only)
SDc	mg/L	Standard deviation of all concentrations
SDp_i	–	Standard deviation of ith pop. parameter
LOD	mg/L	Limit of detection

id	description
max	Maximum concentration
min	Minimum concentration
av	Average concentration
$peak$	Highest measured/sampled concentration
$trough$	Lowest measured/sampled concentration

Individualization is the process of characterizing the pharmacokinetic parameters of an individual patient based on the measurement of one or more plasma levels. MW\PHARM offers a 2-point and a multi-point individualization method. The characteristics of these methods are listed in the table below.

Individualization Methods	Initial	2-Point		Multi-Point	
	dose	norm.	bayes	norm.	bayes
❑ Minimal nr. of required samples	0	2^{*}	2	2^{*}	1
❑ Maximal nr. of compartments	3	1	2	3	3
❑ Route of administration					
○ intravascular	+	+	+	+	+
○ extravascular	+	-	$-^{**}$	+	+
❑ Pharmacokinetics					
○ linear	+	+	+	+	+
○ non-linear	+	-	$-^{**}$	+	+
❑ Dosage regimen					
○ regular	+	+	+	+	+
○ irregular	-	-	-	+	+
❑ Weight and kidneyfunction					
○ constant	+	+	+	+	+
○ variable	-	-	-	+	+

  *Equals minimal number of model parameters: V1 & k10
  **This not a principle but a design limitation

Both methods have their advantages and disadvantages. We will start with the 2-point method first.

5.2 Two-Point Method

With the 2-point method only 2 plasma samples are used for the calculation of individual pharmacokinetic parameters. Therefore the application of this method is limited to 1 compartment systems and intravascular administrations. MW\PHARM supports both peak-trough (figure 5.2-A) and trough-peak (figure 5.2-B) measurements.

Using the generalised normal equation derived in chapter 4 (dosage regimens) MW\PHARM constructs 2 equations in order to solve the 2 unknown (individual) model parameters.

1 compartment: general case (non-steady state)

unknown 1	$: V_1 \rightarrow \qquad C_1 = \dfrac{D_m}{V_1}$
unknown 2	$: CL \rightarrow \qquad L_1 = \dfrac{CL}{V_1} = k_{10}$
equation 1	$: C_{peak}^n = D_m \cdot Z(T_{peak}^n, T_{int}, n)$
equation 2a	$: C_{trough}^n = D_m \cdot Z(T_{trough}^n, T_{int}, n)$
equation 2b	$: C_{trough}^{n-1} = D_m \cdot Z(T_{int} + T_{trough}^{n-1}, T_{int}, n-1)$
Signs	$: T_{trough}^{n-1} \leq 0 \qquad T_{trough}^n > 0$

Equation 2a is used in the case of peak-trough measurements whereas equation 2b is used in the case of trough-peak measurements. This set of non-steady state equations cannot be solved explicitly and is therefore solved using an iterative procedure.

☞ Note: The 2-point method in MW\PHARM does not assume steady state conditions and can therefore be applied after any number of given doses.

Figure 5.2-A. Peak-Trough 2-Point Method

$$0 \le T_{max}^n \le T_{peak}^n \le T_{trough}^n \le T_{int}$$

60
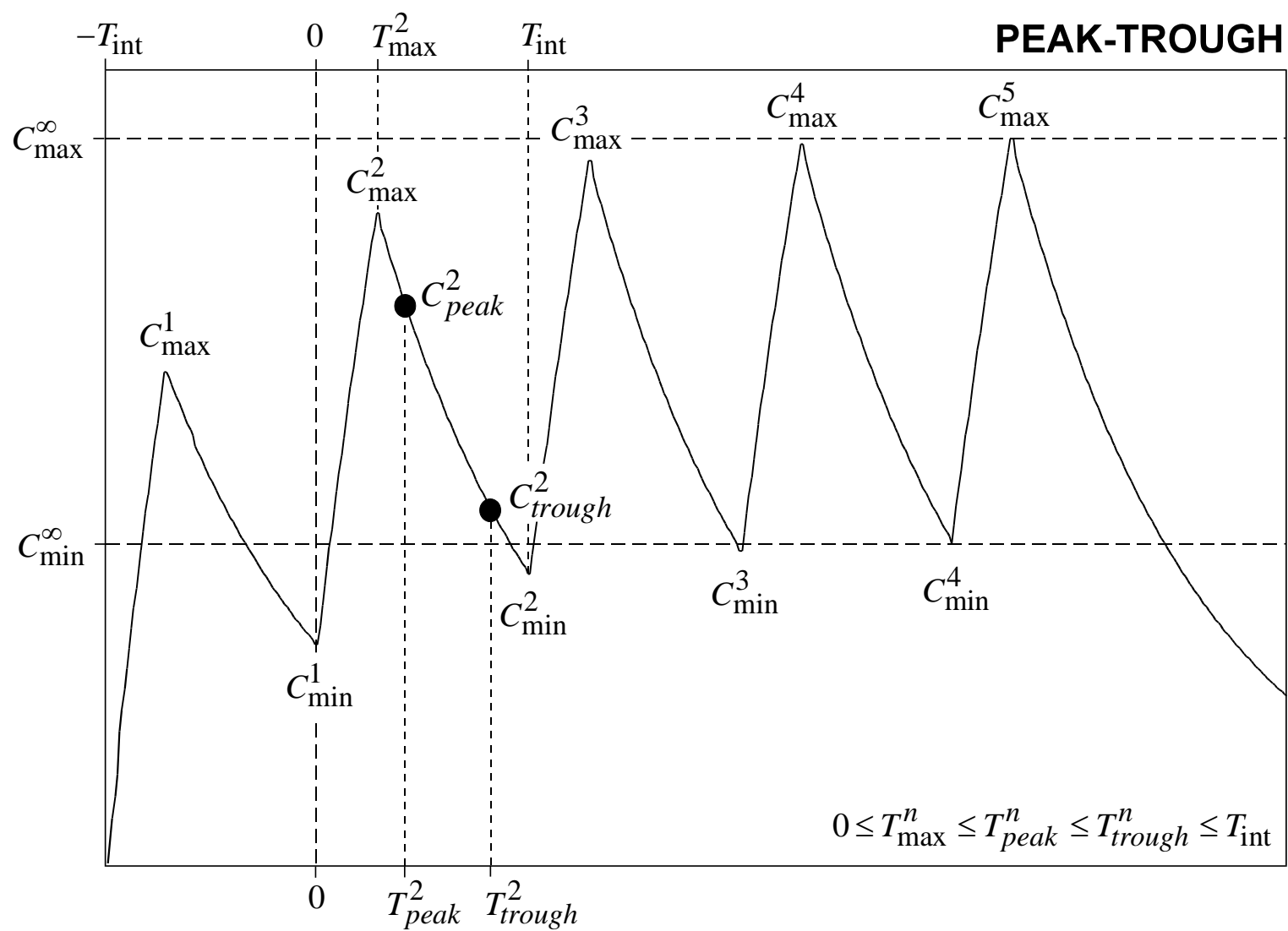
Figure 5.2-B. Trough-Peak 2-Point Method

TROUGH-PEAK

$-T_{int}$ $\quad 0 \quad$ T^2_{max} $\quad$ T_{int}

C^∞_{max}

C^4_{max} $\qquad$ C^5_{max}

C^3_{max}

C^2_{max}

C^2_{peak}

C^1_{max}

C^∞_{min}

C^1_{trough}

C^3_{min} $\qquad$ C^4_{min}

C^2_{min}

C^1_{min}

$$0 \le T^n_{max} \le T^n_{peak} \le T_{int} + T^{n-1}_{trough} \le T_{int}$$

T^1_{trough} $\quad 0 \quad$ T^2_{peak}

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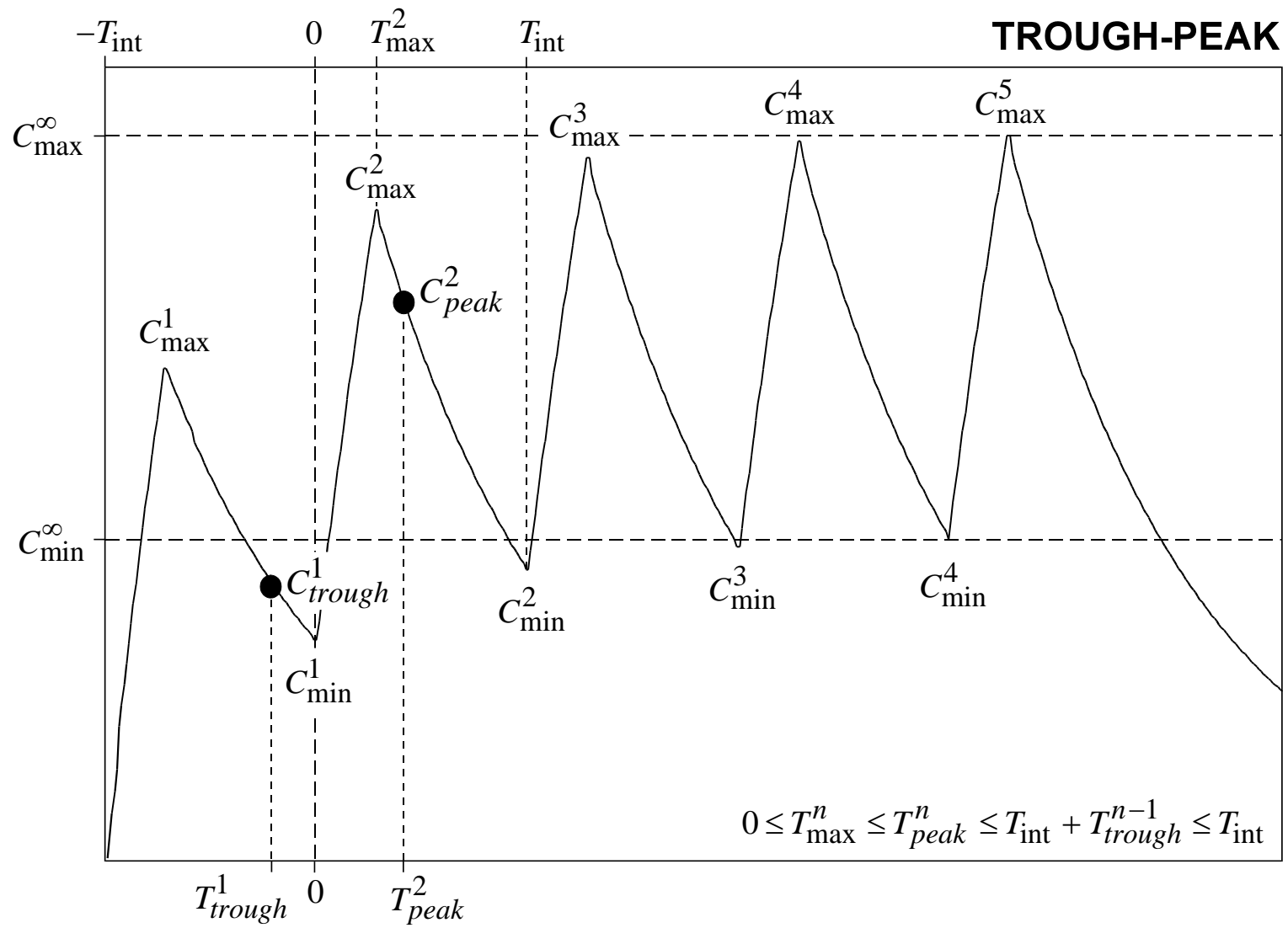
The method of Sawchuk and Zaske (J. Pharmacokin. Biopharm. 1976, 4, 183-195) which is often employed in classical calculator programs employs the steady state approximation rule in which a trough-peak measurement can be treated as peak-trough measurement.

Steady state approximation

$$C_{trough}^{n-1} = C_{trough}^{n} = C_{trough}^{\infty}$$

However in non-steady state conditions this could lead to severe errors in the calculated pharmacokinetic parameters. In non-steady state conditions the drug is still accumulating. When treating the trough-peak measurement as a peak-trough measurement the trough level is estimated too low causing an overestimation of the drug clearance. The dosage regimen based on the overestimated drug clearance may easily lead to toxic plasma levels.

If the steady state rule is used, the set of 2 equations and 2 unknowns can be solved explicitly. For demonstration purposes we will show this for the case of multiple injections and multiple infusions.

1 compartment: multiple injections & steady state

$$k_{10} = \frac{(\ln(C_{peak}^{\infty}) - \ln(C_{trough}^{\infty}))}{(T_{trough}^{\infty} - T_{peak}^{\infty})}$$

$$C_{max}^{\infty} = C_{peak}^{\infty} \cdot e^{+k_{10} \cdot T_{peak}^{\infty}}$$

$$C_{min}^{\infty} = C_{trough}^{\infty} \cdot e^{-k_{10} \cdot (T_{int} - T_{trough}^{\infty})}$$

$$V_1 = \frac{D_m}{(C_{max}^{\infty} - C_{min}^{\infty})}$$

1 compartment: multiple infusions & steady state

$$k_{10} = \frac{(\ln(C_{peak}^{\infty}) - \ln(C_{trough}^{\infty}))}{(T_{trough}^{\infty} - T_{peak}^{\infty})}$$

$$C_{\max}^{\infty} = C_{peak}^{\infty} \cdot e^{+k_{10} \cdot (T_{peak}^{\infty} - T_{\inf})}$$

$$C_{\min}^{\infty} = C_{trough}^{\infty} \cdot e^{-k_{10} \cdot (T_{int} - T_{trough}^{\infty})}$$

$$V_1 = \frac{D_m}{(C_{\max}^{\infty} - C_{\min}^{\infty} \cdot e^{-k_{10} \cdot T_{\inf}})} \cdot \frac{(1 - e^{-k_{10} \cdot T_{\inf}})}{k_{10} \cdot T_{\inf}}$$

The sampling times and measured concentrations can be directly entered in the dosage regimen screen (figure 5.3-C).


```
 gentamicin                        MW                    04-12-1939

 Infusion (repeated)   Recalc.

 Loading dose      mg    120.0
 Maint. dose       mg    120.0
 Infusion time      h     0.50
 Dosing interval    h    12.00
 Total duration     h       36
 Number of doses             3




 C_peak          mg/l     8.00
 C_trough        mg/l     1.00
 T_peak             h     1.00
 T_trough           h    -0.50


 F6=calculate parameters  time in h (decimal)  ↓
```

Figure 5.3-C. Entering 2-point data in the dosage regimen screen.

After the 2-point calculation is finished the old and new model parameters (CL and V_1) are displayed at the bottom of the screen.

```
┌─individual data─────────────────────────────────────────────────┐
│ gentamicin                    MW                      04-12-1939  │
│ ┌──────────────────┬─────────┬────────┬───────────────────────┐  │
│ │Infusion (repeated)│ Selected│ Exact  │        Practical      │  │
│ ├──────────────────┼─────────┼────────┼───────────────────────┤  │
│ │Loading dose    mg│  120.0  │ 105.0  │ 100   100   100   120 │  │
│ │Maint. dose     mg│  120.0  │  91.4  │  60    80   100   120 │  │
│ │Infusion time    h│   0.50  │  0.50  │ 0.50  0.50  0.50  0.50│  │
│ │Dosing interval  h│  12.00  │ 10.39  │   8     8    12    12 │  │
│ │Total duration   h│   36    │  21    │  24    24    24    24 │  │
│ │Number of doses   │    3    │   2    │   3     3     2     2 │  │
│ ├──────────────────┼─────────┼────────┼───────────────────────┤  │
│ │C_max_ss      mg/l│   8.83  │  7.00  │ 5.05  6.73  7.36  8.83│  │
│ │C_min_ss      mg/l│   0.92  │  1.00  │ 1.15  1.54  0.77  0.92│  │
│ │C_av_ss       mg/l│   3.56  │  3.13  │ 2.67  3.56  2.97  3.56│  │
│ │Steady state     %│  100    │ 100    │ 101   100    99    99 │  │
│ ├──────────────────┼─────────┼────────┼───────────────────────┤  │
│ │C_peak        mg/l│   8.00  │  6.34  │ 4.64  6.10  6.61  7.94│  │
│ │C_trough      mg/l│   1.01  │  1.10  │ 1.36  1.69  0.77  0.92│  │
│ │T_peak           h│   1.00  │  1.00  │ 1.00  1.00  1.00  1.00│  │
│ │T_trough         h│  -0.50  │ -0.50  │-0.50 -0.50 -0.50 -0.50│  │
│ t½ (h)   3.02 ->   3.52═V1 (l)  14.70 -> 14.29═CL (l/h)  3.38 ->  2.81│
│ ADVICE:  Waiting time after the last dose (give maintenance dose) :   11.57 h │
│    OR:  Reloading dose after the last dose (after 1 interval)    :   91.21 mg │
│ F10=continue F1=main menu F3=adapt F4=copy F5=print F6=recalc. F7=roa ↓       │
└──────────────────────────────────────────────────────────────────┘
```

Figure 5.2-D. Dosage regimen screen after an 2-point procedure.

Also a new set of exact and practical dosage regimens will be displayed after a 2-point procedure. These regimens are based on the new individual parameter values.

In order to switch optimally from the old to the new dosage regimen a waiting time or a reload dose is suggested. MW\PHARM suggests a waiting time relative to the start of the last given dose when the measured trough level is above the desired minimum level (figure 5.2-E). After the waiting time is over the new regimen (new maintenance dose and new interval time) may be applied. When the measured trough level is below the desired minimum level, a reloading dosing is suggested (figure 5.2-F). The reloading dose must be given at one interval time (old regimen) after the last given dose. One interval time (new regimen) after the reloading dose the therapy may be continued using the new dosage regimen (new maintenance dose and new interval time).
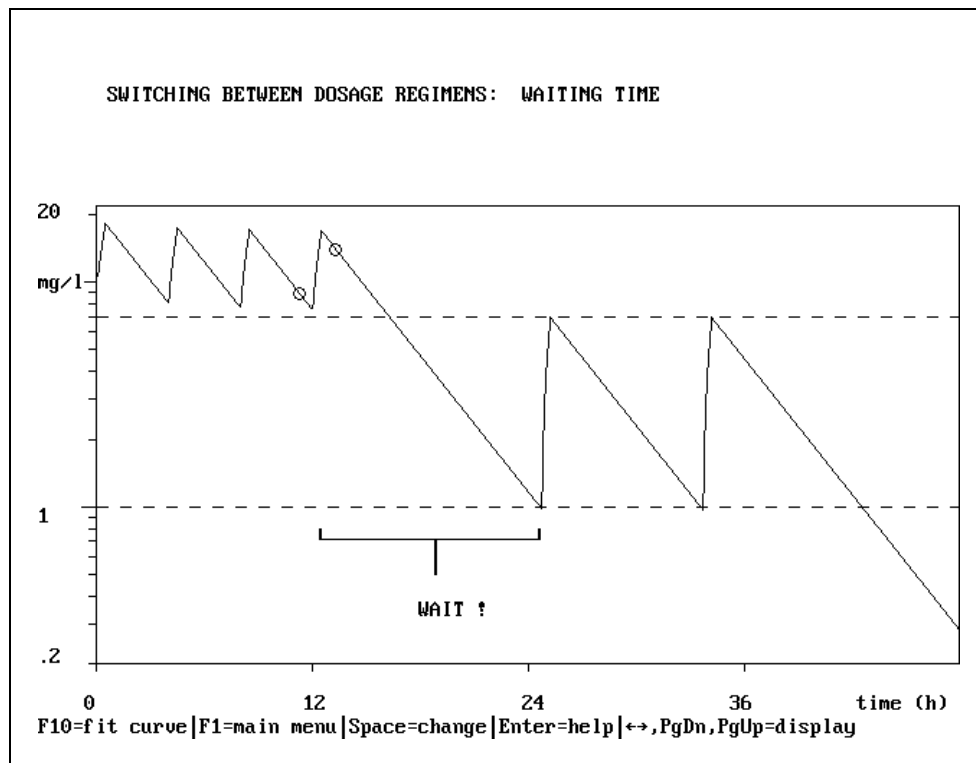
Figure 5.2-E. Example of the "waiting time" principle.
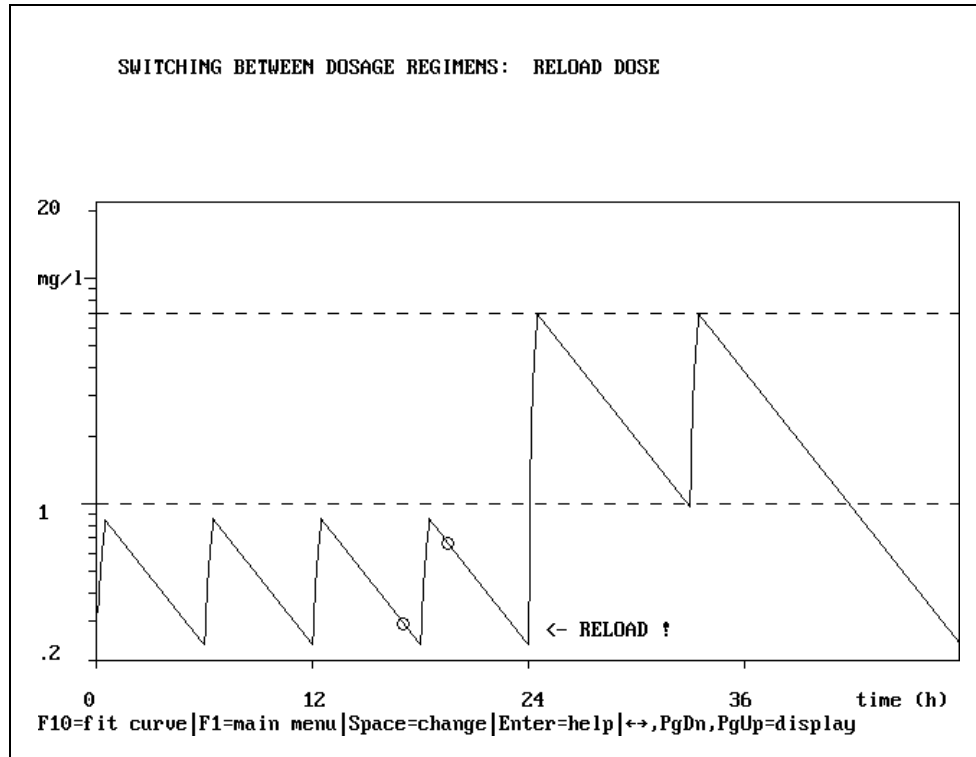
Figure 5.2-F. Example of the "reload dose" principle.

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The 2-point method can also be performed using the so called Bayesian population feedback technique. If so, the 2-point method is mathematically treated as a special case of the multi-point method with Bayesian feedback enabled.

☞ The 2-point method using bayesian feedback is treated as a special case of the multi-point method with bayesian feedback.

☞ The 2-point method can only be employed for 2-compartment systems if the Bayesian feedback option has been enabled.

With the Bayesian population feedback method not only the value and distribution of the observed plasma levels are taken into account (a posteriori knowledge) but also the value and distribution of the pharmacokinetic population parameters (a priori knowledge).

The effect of Bayesian feedback can nicely be demonstrated by using two imaginative 2-point scenarios. In scenario I the SD's of the measured concentrations are small (1%) and the SD's of the population parameters are large (100%). In scenario II just the opposite is true.

I	CL_m	V_1	C_{peak}	C_{trough}
Initial	1.00 ± 1.00	1.00 ± 1.00	18.0	8.0
Input	-	-	25.0 ± 0.25	10.0 ± 0.10
Fitted	0.82	0.82	25.0	10.0

II	CL_m	V_1	C_{peak}	C_{trough}
Initial	1.00 ± 0.01	1.00 ± 0.01	18.0	8.0
Input	-	-	25.0 ± 25.0	10.0 ± 10.0
Fitted	1.00	1.00	18.0	8.0

As can be seen from the table above, the more accurate a parameter or concentration is known (small SD) the more influence it will have on the final results.

5.3 Multi-Point Method

With the multi-point method 1 to 99 plasma samples can be used for the calculation of individual pharmacokinetic parameters. The data for this method can be entered in the so called medication history screen (figure 5.3-A).

date	time	dose	roa	no	interv.	T(inf)	conc.	weight	creat	Q(EC)
DD-MM-YY	HH:MM	[mg]	i/e		[h]	[h]	[mg/l]	[kg]	[µM]	[ml/min]
12-05-87	08:00	90	iv	3	8	2		60	100	
13-05-87	08:00						0.522			
14-05-87	08:00	60	iv	3	8	2	0.209			
15-05-87	08:00	70	iv	9	8	2	0.195			
17-05-87	08:00						0.378			
18-05-87	08:00	50	iv	9	8	2				
20-05-87	08:00						0.271			
21-05-87	08:00	60	iv	3	8	2	0.209			
22-05-87	08:00	120	iv	1	8	2	0.188			
22-05-87	08:10						0.221			
22-05-87	08:20						0.216			
22-05-87	08:30						0.291			
22-05-87	08:45						0.706			
22-05-87	09:00						1.043			
22-05-87	10:00						2.081			
22-05-87	11:00						0.751			
22-05-87	12:00						0.507			
22-05-87	13:00						0.309			
22-05-87	14:00						0.358			
22-05-87	15:00						0.238			

One or more SD values missing: weighting relative →
Bayes ('b'): ON   Conc. at t=0 ('c') 0   Algorithm ('a'): Marquardt
F10=continue | F1 | ↑↓→←, PgUp, PgDn | Del | Ins | ^→ | p=date | +=+1 | -=-1 | F4=reg.d | F6=recalc.d

Figure 5.3-A. Medication history screen.

If the Bayesian feedback option is disabled the number of required plasma samples must be equal or larger than the number of model parameters. If the Bayesian feedback method option is enabled already 1 plasma sample is sufficient.

The multi-point method is based on differential equations combined with a non-linear fitting algorithm for the minimization of the so

called fitting criterion. The fitting criterion always contains the sum of the squared deviations between observed and measured plasma levels. If Bayesian feedback has been enabled also the squared deviations between the population and estimated parameters is included.

Sum of squares

standard fit $\qquad$: $SS = SS_c$

bayesian fit $\qquad$: $SS = SS_c + SS_p$

A weight factor will be used for the calculation of the sum of squares if the standard deviations of all measured concentrations and used population parameters are known. The user can also specify if the parameters or concentrations are distributed in a normal or a log-normal fashion.

Weighing of concentrations

normal distribution $\qquad$: $SS_c = \sum\limits_{i=1}^{N_c} \left(\dfrac{Cm_i - Ce_i}{SDc \cdot Ce_i + LOD} \right)^2$

log-normal distribution $\qquad$: $SS_c = \sum\limits_{i=1}^{N_c} \left(\dfrac{\ln(Cm_i/Ce_i)}{SDc + LOD/Ce_i} \right)^2$

one or more sd's unknown $\qquad$: $SS_c = \sum\limits_{i=1}^{N_c} \left(\ln(\dfrac{Cm_i}{Ce_i}) \right)^2$

Weighing of parameters

normal distribution $\qquad$: $SS_p = \sum\limits_{i=1}^{N_p} \left(\dfrac{Pp_i - Pe_i}{SDp_i} \right)^2$

$$\textit{log-normal distribution} \qquad : SS_p = \sum_{i=1}^{N_p} \left(\frac{\ln(Pp_i / Pe_i)}{SDp_i / Pe_i} \right)^2$$

$$\textit{one or more sd's unknown} \qquad : SS_p = \sum_{i=1}^{N_c} \left(\ln(\frac{Pp_i}{Pe_i}) \right)^2$$

If the medication history contains only extravascular administrations you will be prompted with the following questions:

```
p.o.:  ka_po   fit or keep constant? (f/c)
i.m.:  ka_im   fit or keep constant? (f/c)
```

Here you must specify if you want to fit the absorption rate constant (*ka_po* or *ka_im*) or not (keep constant).

MW\PHARM is able to also estimate bioavailability if the medication history contains both extravascular and intravascular administrations. If so, you will be prompted with the following questions:

```
p.o.:  ka_po & F_po   fit or keep constant? (f/c)
i.m.:  ka_im & F_im   fit or keep constant? (f/c)
```

Here you must specify if you want to fit the absorption rate constant (*ka_po* and or *ka_im*) and the bioavailability constant (*F_po* and *F_im*) or not (keep constant).

A medication history can even be fitted if it is not completely known. This has been accomplished by offering the user the option to fit the starting concentration (time zero in the graph) of the medication history. If this option is selected you will be prompted with the following questions:

```
 Enter value for estimated concentration at t=0 (C(0)) ?
```

> Enter value for non-absorbed dose at t=0 (D(0)) ?

If you enter non-zero values for C(0) and D(0) (first estimates) these parameters will also be estimated during the fitting process.

The user may select from two algorithms for the minimization of the sum of squares fitting criterion. First the so called Simplex method (Nelder and Mead, Comput. J., 1965, 7, 308-313) which is very robust but also a bit slow. Second, the so called Marquardt method (Marquardt, J. Soc. Ind. Appl. Math., 1963, 11, 431-441) which is very fast but a bit less robust.

☞ Always try the Marquardt method first. It will work nicely in the majority of cases. If not, try the Simplex method.

After the fitting procedure has been completed the population, initial and fitted parameter values are displayed at the top of the graphics screen (figure 5.3-B).
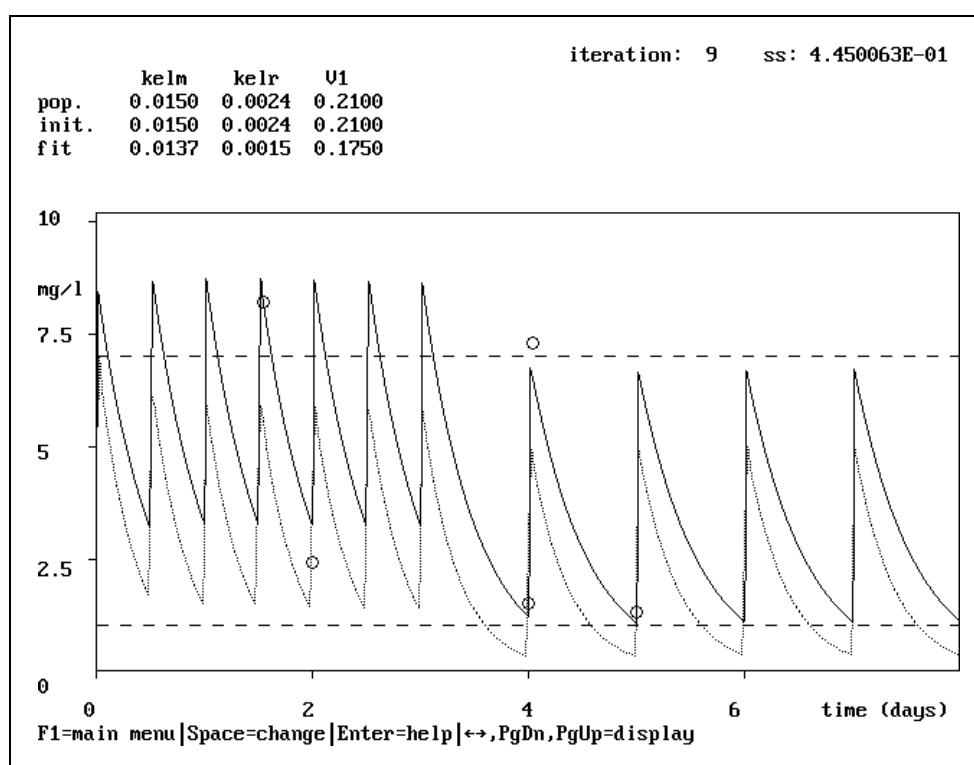
Figure 5.3-B. Fitted medication history (multi-point method).
Also the final sum of squares and number of required iterations are displayed here.

A more detailed report can also be generated (figure 5.3-C) .

```
     MwPharm 3.15E UK Demo Version

MW\PHARM  fit of patient history

name            : TEST-E
patient number  : 1234
medication      : gentamicin

weighting       : OFF (weighting relative)
Bayes           : ON

         kelm    kelr    V1
pop.    0.0150  0.0024  0.2100
init.   0.0150  0.0024  0.2100
fit     0.0137  0.0015  0.1750

sum of squares :  4.450063E-01 including parameters
                  2.033705E-01 only concentrations

                      time          C(obs)          C(est)
22-03-90 21:00       37.0000        8.2000          8.3511
23-03-90 07:55       47.9167        2.4000          3.2820
25-03-90 07:55       95.9167        1.5000          1.2242
25-03-90 09:00       97.0000        7.3000          6.4897
26-03-90 07:55      119.9167        1.3000          1.0720
```

Figure 5.3-C. Report after a multi-point fit (medication history)

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6 KINFIT

6.1 Introduction

KinFit is a very easy to use yet extremely powerful MW\PHARM module for fitting and analysing single dose administrations. The module offers two analysis methods:

- HPSTRIP : Automated curve stripping
- KINFIT : Non-linear curve fitting

Both methods are based on a least squares method. KINFIT employs the very robust Simplex method for minimising the weighted sum of squares (SS) fitting criterion whereas HPSTRIP uses a linear regression method.

One of the main problems with non-linear curve fitting programs are the first estimates that have to be entered by the user. Most programs get stuck (sometimes even crash) if the first estimates are far away from the final estimates.

☞ KINFIT solved the first estimates problem by presenting the user default first estimates that were automatically taken (behind the scenes) from the HPSTRIP module.

Symbol	Unit	Description
C_x	mg/L	x^{th} coefficient in polyexponential equation
L_x	$/h$	x^{th} exponent in polyexponential equation
t_r	h	Time since last dose administration
t_0	h	Absorption lag-time
T_{inf}	h	Infusion duration
N	–	Number of compartments
N_c	–	Number of measured concentrations
N_p	–	Number of fitted parameters
Cm_i	mg/L	Measured i^{th} concentration
Ce_i	mg/L	Estimated i^{th} concentration
SS_c	–	Sum of squares (concentrations only)

Symbol	Unit	Description
SS_p	–	Sum of squares (parameters only)
df	–	Degrees of freedom
r^2	–	Coefficient of determination
RMS	–	Root means square error
v	–	Exponent in general error model

6.2 Polyexponential Equations

Both HPSTRIP and KINFIT use polyexponential equations for the representation of plasma time curves. These equations are identical to the ones we derived in chapter 3. The only difference is that here only single administrations are allowed. As a consequence no accumulation factors are required.

I.V. Bolus

$$C(t) = \sum_{x=1}^{N} \{ C_x \cdot e^{-L_x \cdot t_r} \}$$

I.V. Infusion

$$C(t) = \sum_{x=1}^{N} \{ C_x \cdot \frac{1}{L_x \cdot T_{\text{inf}}} \cdot (1 - e^{-L_x \cdot t_r}) \}$$

I.V. Post-Infusion

$$C(t) = \sum_{x=1}^{N} \{ C_x \cdot \frac{1}{L_x \cdot T_{\text{inf}}} \cdot (e^{-L_x \cdot (t_r - T_{\text{inf}})} - e^{-L_x \cdot t_r}) \}$$

E.V. Oral & Intramuscular

$$C(t) = \sum_{x=1}^{N} \{ C_x \cdot \frac{k_a}{k_a - L_x} \cdot (e^{-L_x \cdot (t_r - t_0)} - e^{-k_a \cdot (t_r - t_0)}) \}$$

6.3 Fitting Criterion

As mentioned earlier, both KINFIT and HPSTRIP use the sum of squared deviations between the measured and estimated concentrations as the main fitting criterion. Three types of weighing procedures can be selected for the calculation of the sum of squares.

Absolute error independent of the concentration

$$SS_c = \sum_{i=1}^{N_c} (Cm_i - Ce_i)^2 \qquad S_w = N_c$$

$$S_c = \sum_{i=1}^{N_c} Cm_i \qquad S_{cc} = \sum_{i=1}^{N_c} (Cm_i)^2$$

Relative error independent of the concentration

$$SS_c = \sum_{i=1}^{N_c} \left(\ln(\frac{Cm_i}{Ce_i}) \right)^2 \qquad S_w = N_c$$

$$S_c = \sum_{i=1}^{N_c} \ln(Cm_i) \qquad S_{cc} = \sum_{i=1}^{N_c} (\ln(Cm_i))^2$$

General error model

$$SS_c = \sum_{i=1}^{N_c} \frac{(Cm_i - Ce_i)^2}{(Cm_i)^v} \qquad S_w = \sum_{i=1}^{N_c} \frac{1}{(Cm_i)^v}$$

$$S_c = \sum_{i=1}^{N_c} \frac{Cm_i}{(Cm_i)^v} \qquad S_{cc} = \sum_{i=1}^{N_c} \frac{(Cm_i)^2}{(Cm_i)^v}$$

6.4 Curve Stripping

With manual curve stripping the data points are plotted on logarithmic paper. Then the data points in the terminal phase of the curve (β-phase) are connected by a straight line. This has been demonstrated for an intravenous administration in figure 6.3-A.

$$C(t) = C_1 \cdot e^{-L_1 \cdot t} + C_2 \cdot e^{-L_2 \cdot t}$$
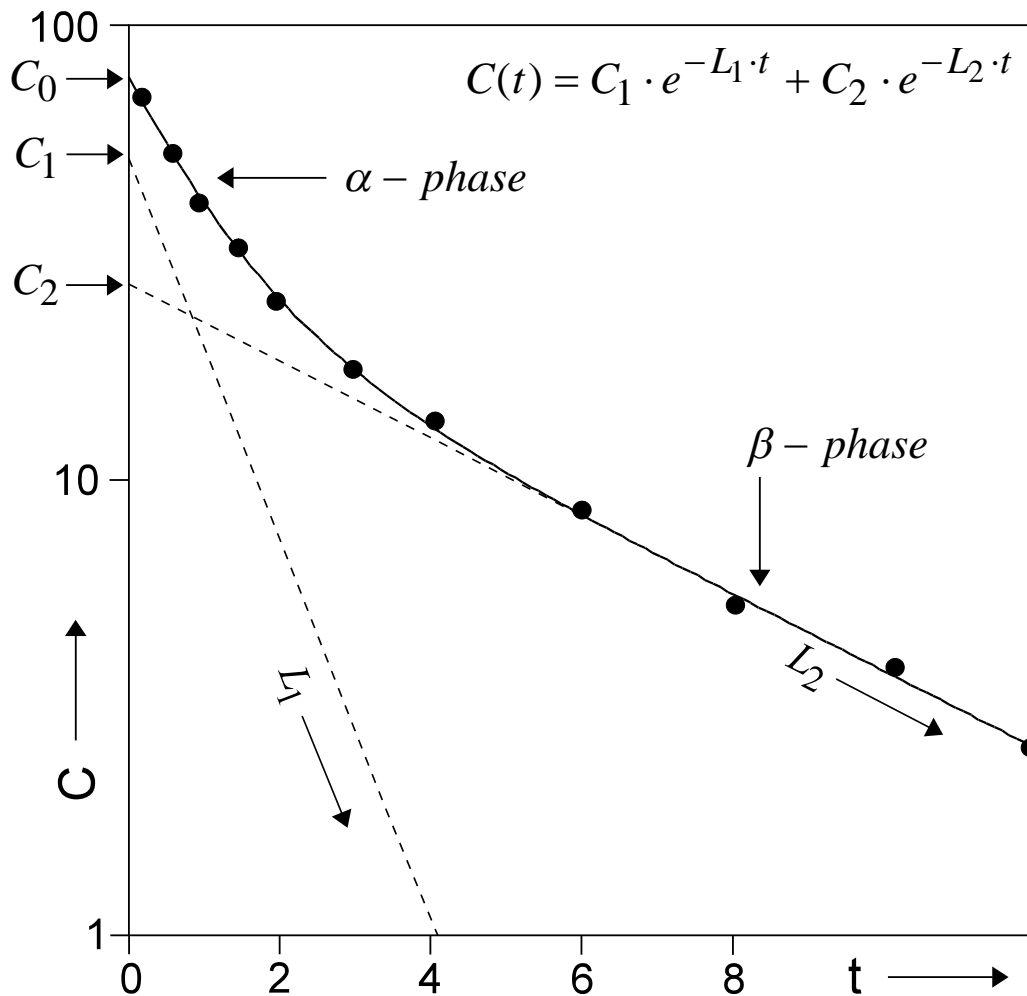
Figure 6.3-A. Curve stripping of an i.v. bolus curve.

This line is then extrapolated towards the y-axis (intercept C_2, slope L_2). From all the original data points this extrapolated curve is subtracted generating a new straight line that represents the distribution phase (intercept C_1, slope L_1). The same procedure is demonstrated in figure 6.3-B for an extravascular administration.

$$C(t) = C_1^e \cdot (e^{-L_1 \cdot t} - e^{-k_a \cdot t})$$

$$C_1^e = C_1 \cdot \frac{k_a}{k_a - L_1}$$

$$k_a > L_1$$
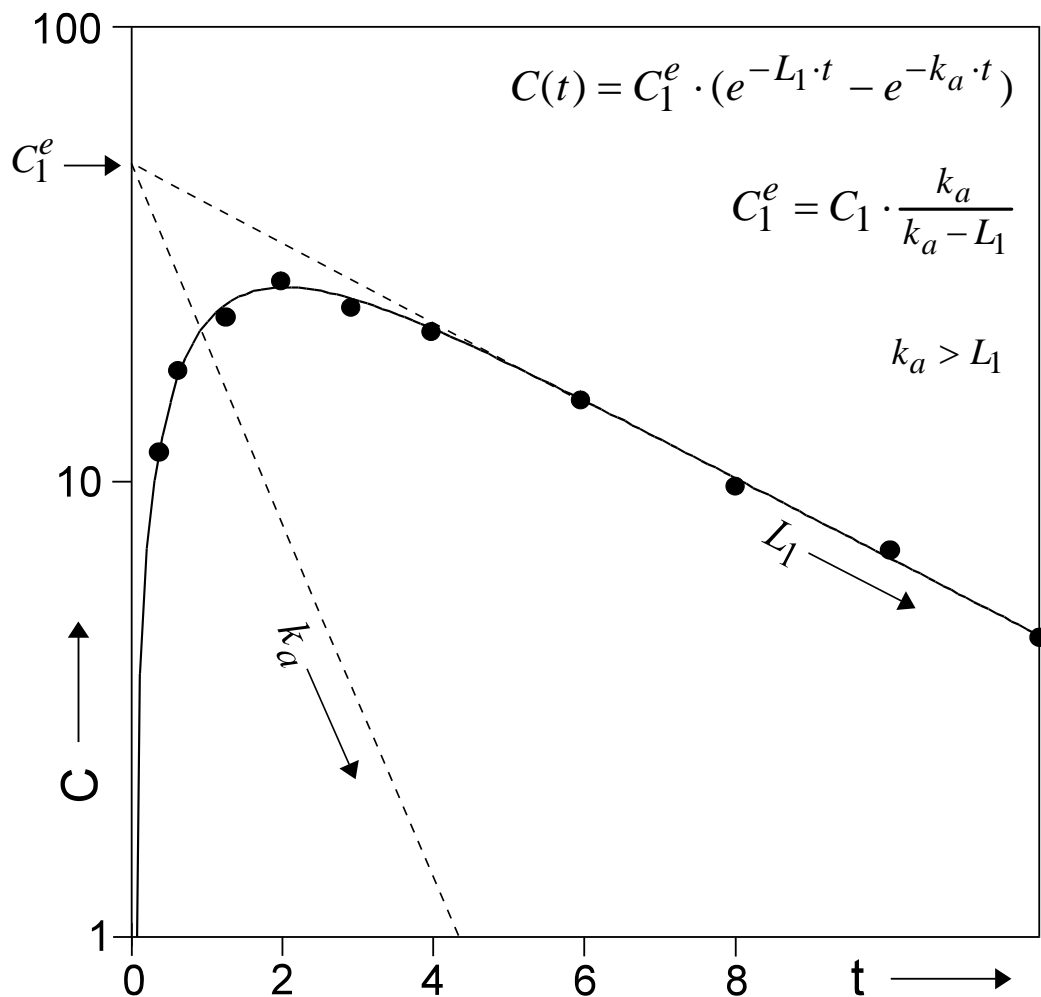
Figure 6.3-B. Curve stripping of an oral curve.

HPSTRIP is able to perform the above explained procedure fully automatically using a linear regression technique. It will attempt strips assuming 1, 2, 3 and 4 exponents. If n exponents are to be accounted for HPSTRIP tries to divide the complete data set into n adjacent subgroups. The subdivision generating the lowest sum of squares is finally chosen.

☞ For infusions only the post infusion data are used.

The results of every strip are displayed graphically (figures 6.3-C to 6.3-F) together with the maximal number of detectable exponents.
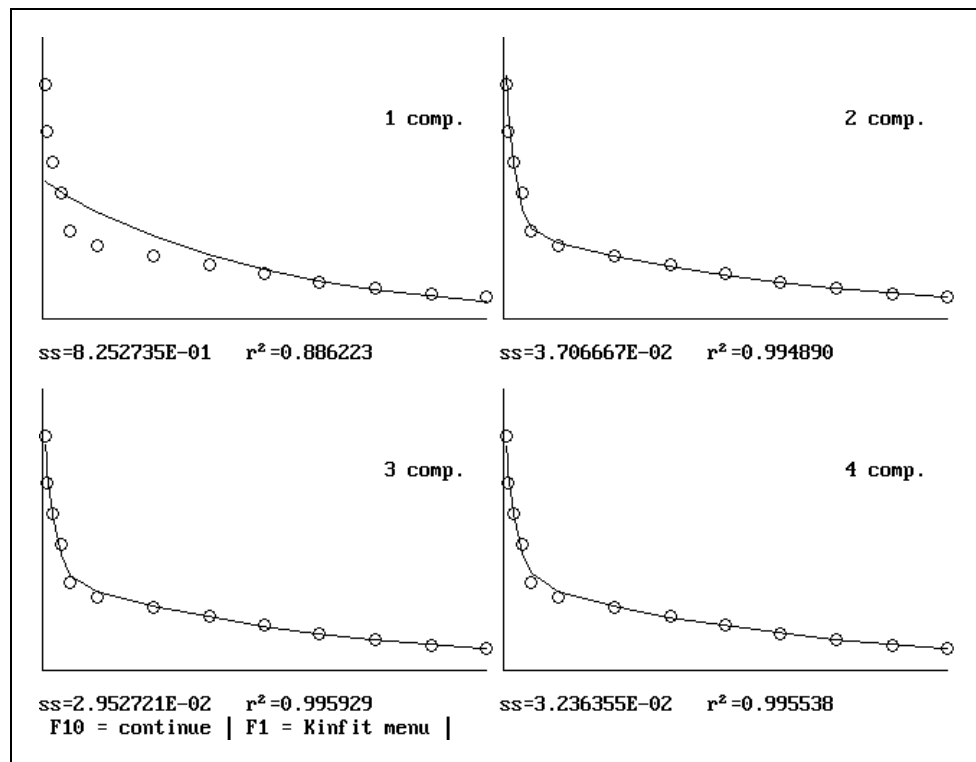
Figure 6.3-C. Curve stripping of an i.v. bolus curve.
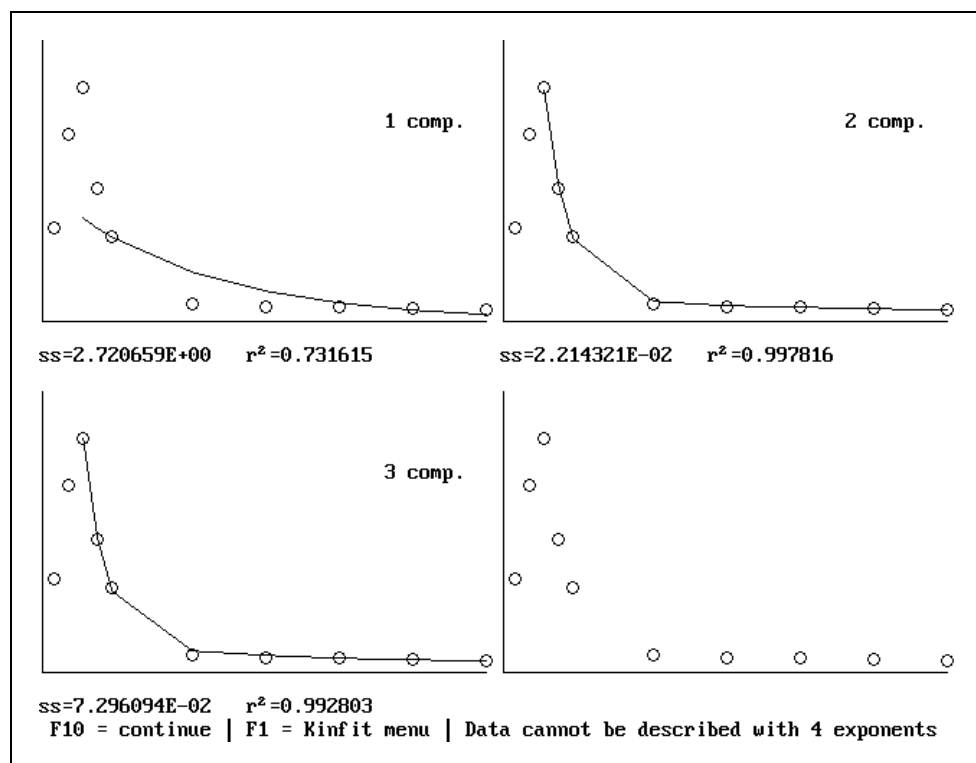
Figure 6.3-D. Curve stripping of an i.v. infusion curve.

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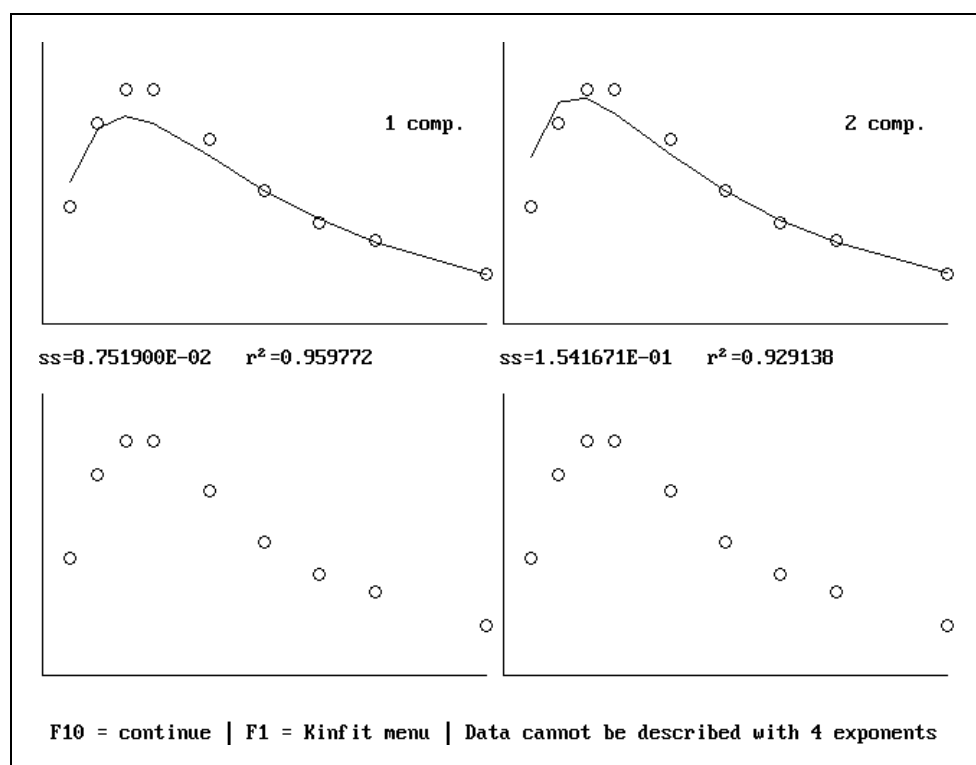
Figure 6.3-E. Curve stripping of an oral curve (no lag-time)
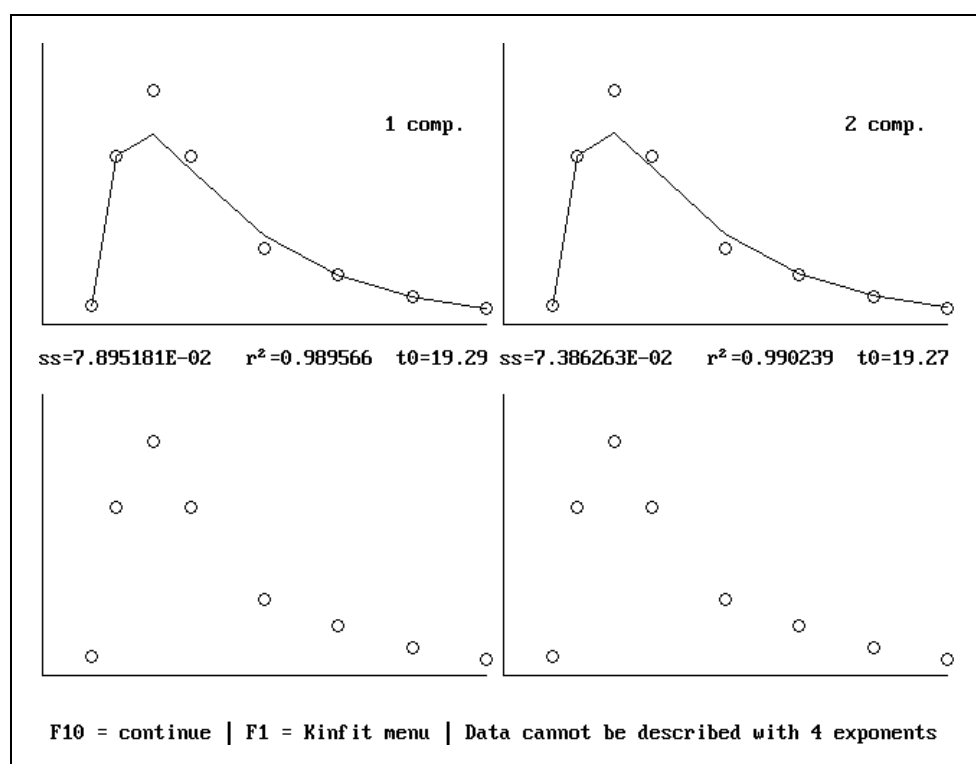
Figure 6.3-F. Curve stripping of an oral curve (with lag-time)

A more detailed report can also be generated (figure 6.3-G).

```
     ----------------------------------------------------------------
        MwPharm 3.15E UK Demo Version

 MW\PHARM  HPstrip

 datafile : DEMO
 model     : intravenous
 weighting : relative error independent of concentration

     ----------------------------------------------------------------

 phase      coefficient        exponent       number of data points
  1          8.155092          0.255622           13

 sum of squares (ss)     8.252735E-01
 correlation coeff.(r²)  0.886223
 ----------------------------------------------------------------

 phase      coefficient        exponent       number of data points
  1         11.805344          6.478902            5
  2          5.325573          0.179991            8

 sum of squares (ss)     3.706667E-02
 correlation coeff.(r²)  0.994890
 ----------------------------------------------------------------

 phase      coefficient        exponent       number of data points
  1          9.817389          5.811537            3
  2          0.545891          0.429427            7
  3          5.065450          0.174385            3

 sum of squares (ss)     2.952721E-02
 correlation coeff.(r²)  0.995929
 ----------------------------------------------------------------

 phase      coefficient        exponent       number of data points
  1          6.580704          7.492894            3
  2          3.563424          3.202461            3
  3          0.285299          0.235627            4
  4          5.065450          0.174385            3

 sum of squares (ss)     3.236355E-02
 correlation coeff.(r²)  0.995538
 ----------------------------------------------------------------
```

Figure 6.3-G. Example of a curve strip report.

6.5 Curve Fitting

The KINFIT module also uses the sum of squares as a fitting criterion. In contrast to the linear regression technique employed by HPSTRIP, KINFIT minimizes the sum of squares using a non-linear fitting algorithm based on the so called Simplex method (Nelder and Mead, Comput. J., 1965, 7, 308-313).

For demonstration purposes the data sets of the previous strip examples are also analysed using KINFIT. The results are displayed in figures 6.4-A to 6.4-D.

Figure 6.4-E shows a statistical analysis of a 2-compartment fit. Besides the calculation of the usual statistical parameters such as the determination coefficient and the root mean square error, also two statistical tests are performed. First, a so called runs test which checks if the distribution of data points around the curve (above or below) is random. Second, a F-test that compares the current fit (2-compartment model) with the previous fit (1-compartment model). In our example the 2-compartment model describes the data set significantly better than the 1-compartment model.

Degrees of freedom

$$df = N_c - N_p$$

Coefficient of determination

$$r^2 = 1 - \frac{SS_c}{(S_{cc} - (S_c)^2 / S_w)}$$

Root mean square error

$$RMS = \sqrt{\frac{SS_c}{df}}$$

concentration   LOG concentration

parameter estimates

C1 =   9.973385
L1 =   5.130852
C2 =   5.256179
L2 =   0.177796   iteration   62

                                      sum of squares =   2.321408E-02

                                      correlation coeff.(r²) 0.996800

 F10 = continue | F1 = Kinfit menu |
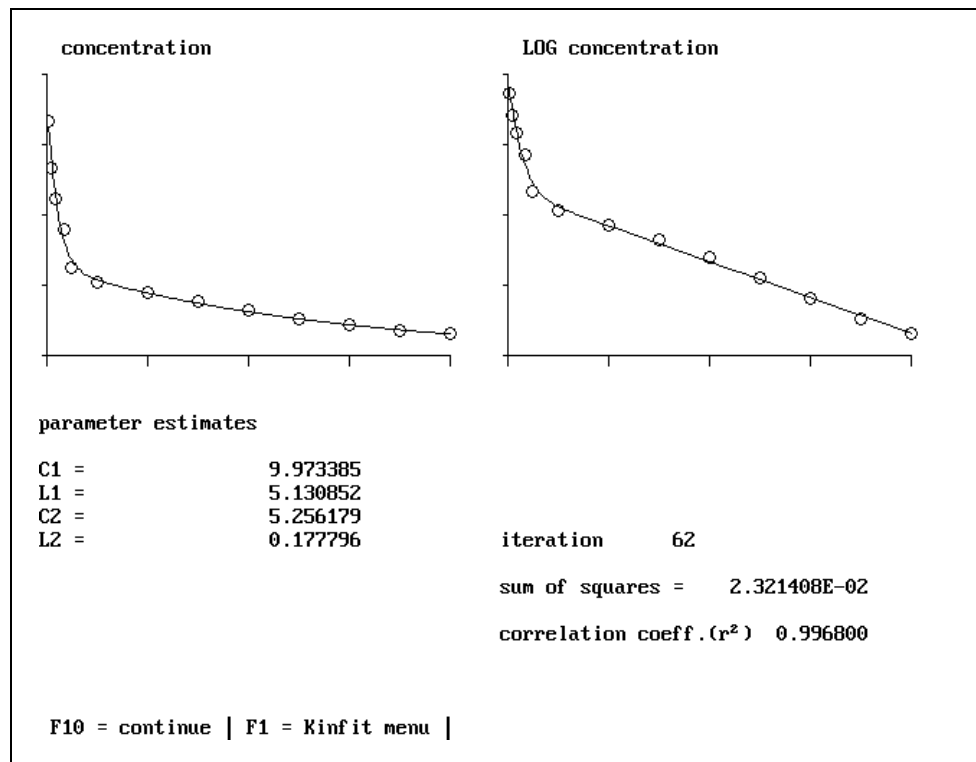
Figure 6.4-A. Curve fitting of an i.v. bolus curve.

concentration   LOG concentration

parameter estimates

C1 =   0.381537
L1 =   0.259694
C2 =   0.037845
L2 =   0.259749   iteration   199
C3 =   0.017616
L3 =   0.004566   sum of squares =   3.998659E-02

                                      correlation coeff.(r²) 0.997007

 F10 = continue | F1 = Kinfit menu |
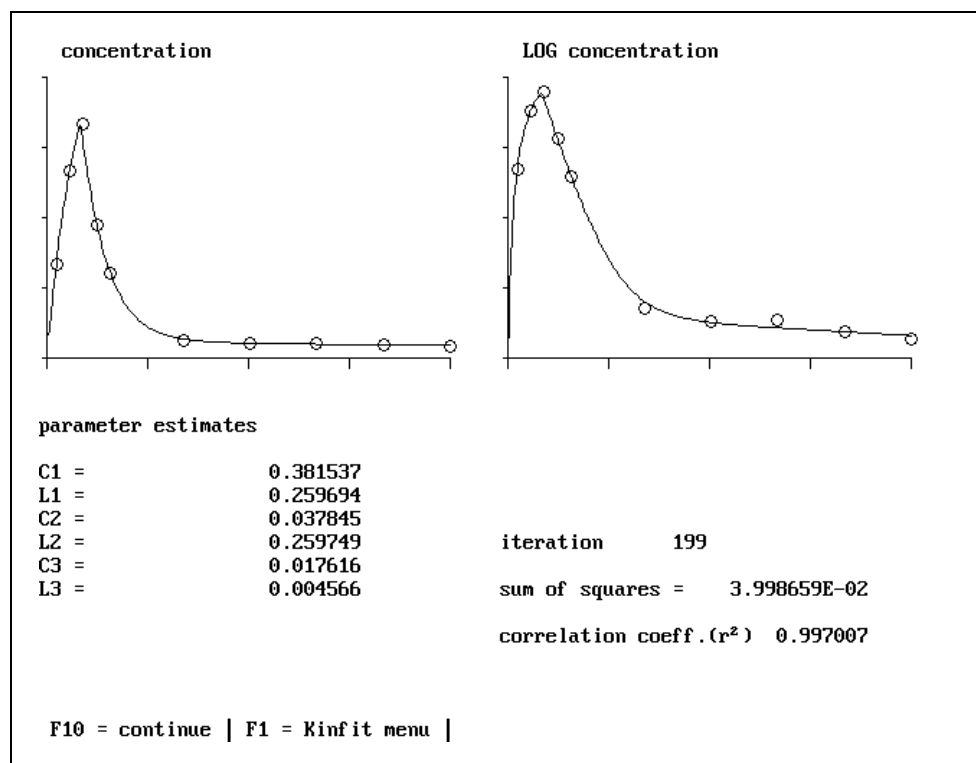
Figure 6.4-B. Curve fitting of an i.v. infusion curve.
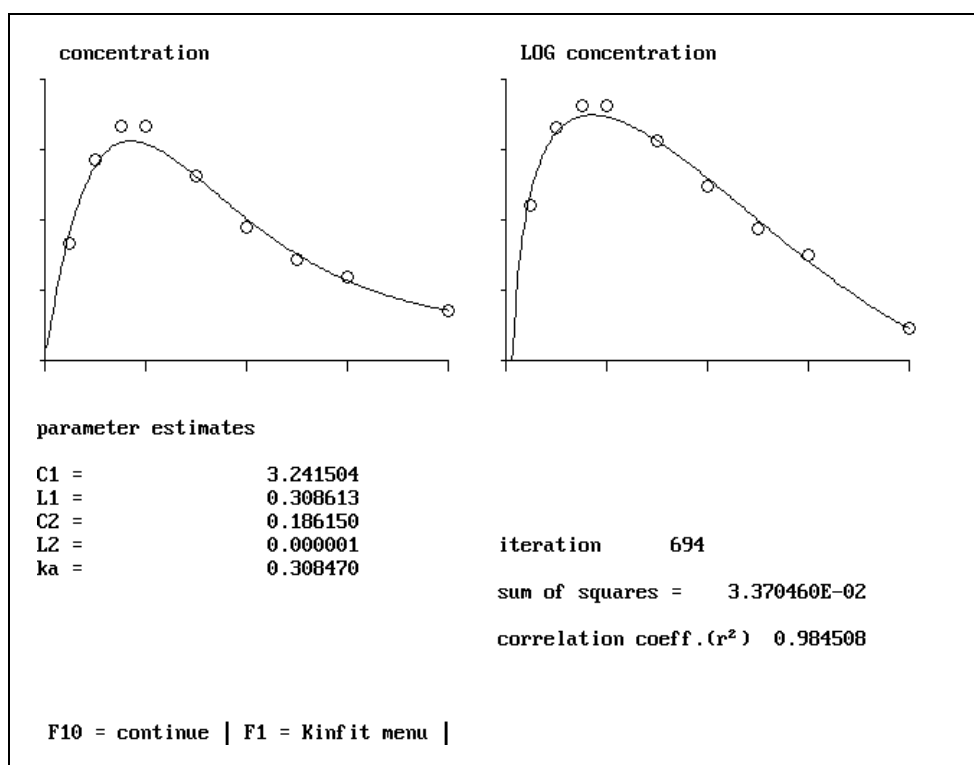
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Figure 6.4-C. Curve fitting of an oral curve (no lag-time)
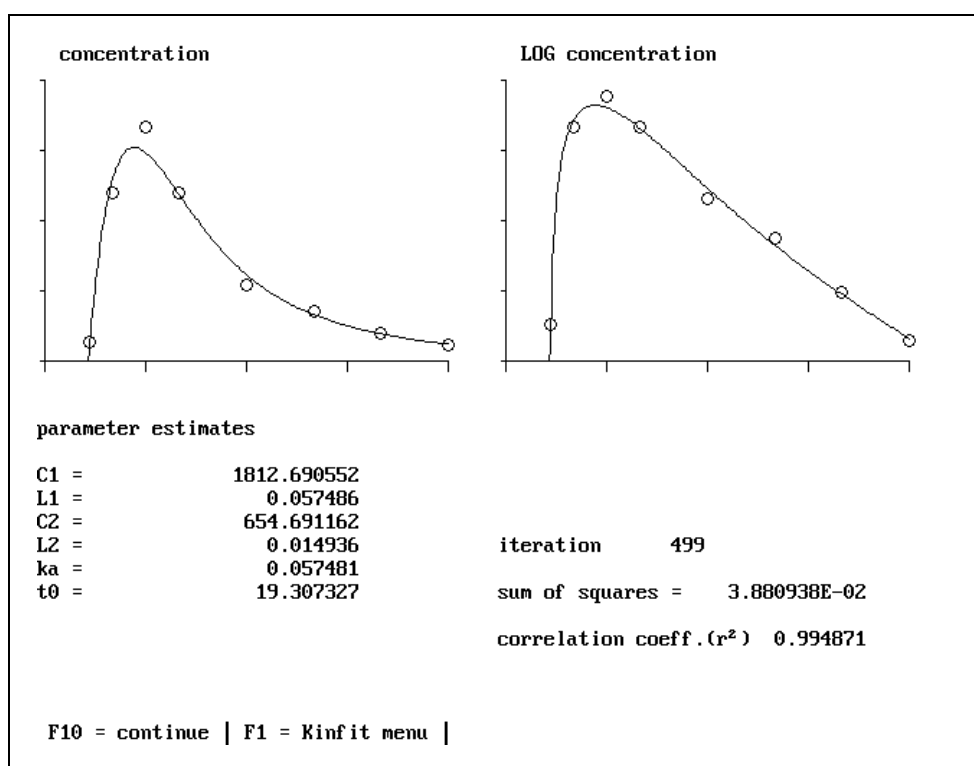

Figure 6.4-D. Curve fitting of an oral curve (with lag-time)

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```
STATISTICS

Number of data points     N   = 13
Number of parameters      P   = 4
Degrees of freedom        df  = 9
Sum of Squares            ss  = 2.321408E-02
Root Mean Square error    RMS = 5.078723E-02   ( 5.08%)
Correlation coefficient   r²  = 0.996800

RUNS TEST

Number of runs    =  7
Run profile       =  +--+--++++--+   (p>=0.05)

EXTRA PARAMETER SIGNIFICANCE

                   ss              df              r²

Previous fit       8.252736E-01    11              0.886223
Current fit        2.321408E-02     9              0.996800

F =  155.4775      p = 0.0000      (p<0.001)


┌─────────────┬────────────────┐
│ F10 = continue │ F1 = Kinfit menu │
└─────────────┴────────────────┘
```

Figure 6.4-E. Statistics report screen

The F-value for the F-test is calculated using the following formula:

F-test

$$F = \frac{(SS_{c1} - SS_{c2})/(df_1 - df_2)}{SS_{c2}/df_2}$$

Here SS_c refers to the weighted residual sum of squares, and df refers to the number of degrees of freedom (number of observations - number of parameters). The subscript 1 refers to the fit with the fewer parameters, i.e. the simpler model. A P-value is obtained from the F-value by consulting a standard table using (df_1-df_2) and df_2 degrees of freedom. A small P-value ($P<0.05$) indicates that the more complex model fits the data significantly better than the simpler model. The F-test can only be applied if the two models belong to the same family of models. Furthermore, the weighting schemes of the two models must be same in order to make a valid comparison possible.

KINFIT only fits the coefficients and exponents of the multi-exponential equation which was presented earlier. These parameters are often called macro parameters. After entering a value for the actual given dose, KINFIT is able to convert these macro parameters into micro parameters (figure 6.4-F) using formulas derived in chapter 3.

```
Dose                          [mg]    :  100.00

Area Under the Curve (AUC)    [h.mg/l] :   31.51
AUC polyexponential    (t= 8)         :   24.38
AUC trapezoidal rule   (t= 8)         :   24.26
Clearance (CL)                [l/h]   :    3.174
Volume of distribution comp.1 [l]     :    6.566
Volume of distr. steady state [l]     :   16.79
Volume of distribution        [l]     :   17.85
Half-life phase 1             [h]     :    0.1351
Half-life phase 2             [h]     :    3.899
Rate constant k10             [1/h]   :    0.4834
Rate constant k12             [1/h]   :    2.938
Rate constant k21             [1/h]   :    1.887
Mean Residence Time (MRT)     [h]     :    5.289




 F10 = continue │ F1 = Kinfit menu │
```

Figure 6.4-F. Report of fitted parameters.

After the fitting procedure has been completed the derived pharmacokinetic parameters can be transferred to the main MW\PHARM module as inidvidual parameters. This is option is only given if in the main program a drug was selected. If you want to transfer the parameters you must specify a value for the fraction excreted unchanged because of the fact that the main program module discriminates between renal and non-renal clearance whereas the KINFIT module does not.

All results can also be printed (figures 6.4-G and 6.4-H).

```
      MwPharm 3.15E UK Demo Version

 MW\PHARM  KinFit

 datafile : CICLO
 model    : infusion / post-infusion  duration  4  h
 weighting : relative error independent of concentration


 during      infusion      :          C1/(Tinf*L1)*(1-exp(-L1*t))      +
C2/(Tinf*L2)*(1-exp(-L2*t)) +                     C3/(Tinf*L3)*(1-exp(-
L3*t))

 after infusion  :  C1/(Tinf*L1)*(exp(-L1*(t-Tinf))-exp(-L1*t)) +
                    C2/(Tinf*L2)*(exp(-L2*(t-Tinf))-exp(-L2*t)) +
                    C3/(Tinf*L3)*(exp(-L3*(t-Tinf))-exp(-L3*t))


 parameter estimates
 C1 =    3.874E+03
 L1 =      4.077
 C2 =  224.4
 L2 =    0.2743
 C3 =   49.48
 L3 =    0.04078



 no.    time      C(obs)      C(est)    C(obs)-C(est)   ln C(obs)-ln C(est)
 ---  -------   ---------   ---------   -------------   -------------------
  1    0.500    216.000     238.940      -22.940            -0.101
  2    1.000    328.000     294.688       33.312             0.107
  3    1.500    298.000     323.988      -25.988            -0.084
  4    2.000    379.000     347.569       31.431             0.087
  5    3.000    406.000     387.148       18.852             0.048
  6    4.000    409.000     419.415      -10.415            -0.025
  7    4.500    182.000     194.423      -12.423            -0.066
  8    6.000    123.000     120.846        2.154             0.018
  9    8.000     89.000      84.250        4.750             0.055
 10   10.000     60.000      62.013       -2.013            -0.033
 11   16.000     32.000      33.052       -1.052            -0.032
 12   22.000     24.000      22.889        1.111             0.047
 13   28.000     17.000      17.345       -0.345            -0.020



 STATISTICS

 Number of data points      N   = 13
 Number of parameters       P   =  6
 Degrees of freedom         df  =  7
 Sum of Squares             ss  =  5.150105E-02
 Root Mean Square error     RMS =  8.577467E-02   (  8.58%)
 Correlation coefficient    r²  =  0.996648

 RUNS TEST

 Number of runs    =  9
 Run profile       =  -+-++--++--+-  (p>=0.05)


EXTRA PARAMETER SIGNIFICANCE

                    ss                df              r²

 Previous fit     1.926723E-01        9             0.987458
 Current fit      5.150105E-02        7             0.996648

 F =    9.5940     p = 0.0099        (p<0.01)


 Dose                          [mg]     : 1000.0
```

```
Area Under the Curve (AUC)      [h.mg/l] :   2.981E+03
AUC polyexponential   (t= 28)          :   2.560E+03
AUC trapezoidal rule  (t= 28)          :   2.620E+03
Clearance (CL)                  [l/h]  :   0.3354
Volume of distribution comp.1   [l]    :   0.2411
Volume of distr. steady state   [l]    :   3.709
Volume of distribution          [l]    :   8.226
Half-life phase 1               [h]    :   0.1700
Half-life phase 2               [h]    :   2.527
Half-life phase 3               [h]    :  17.00
Rate constant k10               [1/h]  :   1.391
Rate constant k12               [1/h]  :   1.718
Rate constant k21               [1/h]  :   0.5039
Rate constant k13               [1/h]  :   0.7140
Rate constant k31               [1/h]  :   0.06506
Mean Residence Time (MRT)       [h]    :  11.06
```

Figure 6.4-G. Printed KINFIT report (bolus dose).

```
      MwPharm 3.15E UK Demo Version

MW\PHARM  KinFit

datafile  : ORAL
model     : extravascular with lag-time
weighting : relative error independent of concentration


Ce1*exp(-L1*(t-t0)) +
Ce2*exp(-L2*(t-t0)) -
(Ce1+Ce2)*exp(-ka*(t-t0))
Ce1 = C1*ka/(ka-L1) Ce2 = C2*ka/(ka-L2)

parameter estimates
C1 =    1.813E+03
L1 =    0.05749
C2 =  654.7
L2 =    0.01494
ka =    0.05748
t0 =   19.31


no.   time      C(obs)      C(est)    C(obs)-C(est)  ln C(obs)-ln C(est)
--- -------  ---------   ---------   -------------  -------------------
 1  20.000     95.000      94.779       0.221           0.002
 2  30.000    814.000     878.131     -64.131          -0.076
 3  45.000   1135.000    1011.932     123.068           0.115
 4  60.000    816.000     805.159      10.841           0.013
 5  90.000    372.000     419.100     -47.100          -0.119
 6 120.000    242.000     226.015      15.985           0.068
 7 150.000    135.000     132.541       2.459           0.018
 8 180.000     80.000      81.775      -1.775          -0.022


STATISTICS


Number of data points      N   =  8
Number of parameters       P   =  6
Degrees of freedom         df  =  2
Sum of Squares             ss  =  3.880938E-02
Root Mean Square error     RMS =  1.393007E-01   ( 13.93%)
Correlation coefficient    r²  =  0.994871
```

```
RUNS TEST

Number of runs   =  6
Run profile      =  +-++-++-  (p>=0.05)

EXTRA PARAMETER SIGNIFICANCE

                  ss                df                      r²

Previous fit      6.902971E-02       4                      0.990878
Current fit       3.880938E-02       2                      0.994871

F =    0.7787     p = 0.5622        (p>=0.05)



Dose                          [mg]     : 1000.0
Bioavailability  (F)          [-]      :    1.000

Area Under the Curve (AUC)    [h.mg/l] :   7.537E+04
AUC polyexponential   (t= 180)         :   7.139E+04
AUC trapezoidal rule  (t= 180)         :   7.066E+04
Clearance (CL)                [l/h]    :   0.01327
Volume of distribution comp.1 [l]      :   0.4053
Volume of distr. steady state [l]      :   0.6132
Volume of distribution        [l]      :   0.8884
Half-life phase 1             [h]      :   12.06
Half-life phase 2             [h]      :   46.41
Rate constant k10             [1/h]    :   0.03274
Rate constant k12             [1/h]    :   0.01346
Rate constant k21             [1/h]    :   0.02623
Mean Residence Time (MRT)     [h]      :   82.92

Absorption rate constant (ka) [1/h]    :   0.05748
Absorption half-life          [h]      :   12.06
Lag-time                      [h]      :   19.31
Time to peak        Tmax      [h]      :   39.89
Peak concentration  Cmax      [mg/l]   :   1.036E+03
```

Figure 6.4-H. Printed KINFIT report (oral dose).

APPENDIX A

List Of Symbols And Abbreviations

Symbol	Unit[1]	Description
A	mg	Total amount in the body
A_0	mg	Total amount in the body at $t=0$
$A0$	mg	Amount at absorption site 0
$A1$	mg	Amount in central compartment 1
$A2$	mg	Amount in peripheral compartment 2
$A3$	mg	Amount in peripheral compartment 3
A_m	mg	Amount of metabolite
AUC	$h.mg/L$	Area under the concentration-time curve
$AUC_\odot$	$h.mg/L$	AUC calculated by integration of the fitted curve from $t=0$ to $t=\odot$
AUC_t	$h.mg/L$	AUC calculated by integration of the fitted curve from $t=0$ to $t=t$
$AUCT_t$	$h.mg/L$	AUC obtained from the observed data using the trapezoidal rule
BH	cm	Body height
BW	kg	Body weight

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Symbol	Unit[1]	Description	
BSA	m^2	Body surface area calculated from bodyweight and bodyheight	
C	mg/L	Plasma concentration	
C_0	mg/L	Plasma concentration at $t=0$	
Cm_i	mg/L	Measured i^{th} concentration	
Ce_i	mg/L	Estimated i^{th} concentration	
C_{tox}	mg/L	Toxic concentration	
C_{max}	mg/L	Target maximum concentration	
C_{min}	mg/L	Target minimum concentration	
C_{av}	mg/L	Target average concentration	
C_{max}^n	mg/L	Predicted maximum concentration after n^{th} dose	
C_{min}^n	mg/L	Predicted minimum concentration after n^{th} dose	
C_{av}^n	mg/L	Predicted minimum concentration after n^{th} dose	
C_{peak}^n	mg/L	Measured peak concentration after n^{th} dose	
C_{trough}^n	mg/L	Measured trough concentration after n^{th} dose	
C_max_ss	mg/L	Predicted maximum concentration at steady state	$=C_{max}^\infty$
C_min_ss	mg/L	Predicted minimum concentration at steady state	$=C_{min}^\infty$
C_av_ss	mg/L	Predicted average concentration at steady state	$=C_{av}^\infty$
C_peak	mg/L	Measured peak concentration at after n^{th} dose	$=C_{peak}^n$
C_trough	mg/L	Measured trough concentration at after n^{th} dose	$=C_{trough}^n$

Symbol	Unit[1]	Description
C_x	mg/L	x^{th} coefficient in polyexponentional equation (i.v.)
C_{ex}	mg/L	x^{th} coefficient in polyexponentional equation (e.v.)
CL	L/h	Total body clearance
CL_m	L/h	Metabolic clearance (linear)
CL_{mm}	L/h	Metabolic clearance (non-linear)
CL_r	L/h	Renal clearance
CL_{ec}	L/h	Extracorporeal clearance
CL_{cr}	mL/min	Creatinine clearance
Cr	$\mu mol/L$	Creatinine plasma concentration
Dl	mg	Loading dose
Dm	mg	Maintenance dose
dt	–	Accuracy factor for numerical integration
df	–	Degrees of freedom
E_{ec}	–	Drug extraction ratio of extracoropeal clearance
F	–	Bioavailability
F_{sex}	–	Sex dependent correction factor used in the calculation of CL_{cr}

Symbol	Unit[1]	Description
f_d	–	Fat distribution factor
f_e	–	Fraction excreted unchanged
f_r	–	Drug clearance - creatinine clearance ratio
f_u	–	Fraction unbound
K_m	mg/L	Michealis-Menten constant
k_m	$/h$	Rate of metabolite formation (metabolizing constant)
k_a	$/h$	Absorption rate constant
k_{el}	$/h$	Total elimination rate constant
k_{elm}	$/h$	Metabolic elimination rate constant
k_{elr}	$/h/RCU*$	Renal elimination rate constant
k_{xy}	$/h$	Rate constant for drug transport from compartment x to compartment y
LBM	kg	Lean body mass
LBM_c	kg	Lean body mass corrected for fat distribution
LOD	mg/L	Lower limit of detection
L_x	$/h$	x^{th} exponent in polyexponential equation (i.v. & e.v.)
MRT	h	Mean residence time
MAT	h	Mean absorption time

Symbol	Unit[1]	Description
n	–	Number of given dosages
N	–	Number of model compartments
N_c	–	Number of measured concentrations
N_p	–	Number of fitted parameters
Pp_i	#	Observed i^{th} population parameter
Pe_i	#	Estimated i^{th} individual parameter
Q_{ec}	ml/min	Flow through extracorporeal clearance device
R	mg/h	Infusion rate (also dosing rate)
r^2	–	Coefficient of determination
RMS	–	Root mean square error
SDc	mg/L	Standard deviation of all plasma concentrations
SDp_i	#	Standard deviation of ith population parameter
SS_c	–	Sum of squares (concentrations)
SS_p	–	Sum of squares (parameters)
$SS\%$	%	Percentage steady state after n^{th} dose

Symbol	Unit[1]	Description
T_{max}^{n}	h	Predicted time of maximum concentration after the nth dose
T_{min}^{n}	h	Predicted time of minimum concentration after the nth dose
T_{peak}^{n}	h	Sampling time of peak concentration after n^{th} dose
T_{trough}^{n}	h	Sampling time of trough concentration after n^{th} dose
$T_{\_peak}$	h	Sampling time of peak concentration after n^{th} dose
$T_{\_trough}$	h	Sampling time of trough concentration after n^{th} dose
T_{inf}	h	Infusion duration
T_{int}	h	Dosing interval time (also ♦)
t	h	Time since first dose administration (simulation time)
t_r	h	Time since last dose administration (reduced time)
t_0	h	Absorption lag-time
$t_{½x}$	h	Elimination half-life x^{th} phase

Symbol	Unit[1]	Description
V	L	Volume of distribution in terminal phase (also V_β)
V_1	L	Volume of distribution of central compartment
V_{ss}	L	Volume of distribution during steady state
V_β	L	Volume of distribution in terminal phase (also V)
V_{max}	mg/h	Maximum rate of enzymatic transformation
Y	$Years$	Patient age

[1]In the MwPharm medication screen all mg units can be forced to $\bigcirc g$ units.
*RCU = renal clearance units = $ml/min/1.73m^2$
#Exact unit depends on type of parameter.

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APPENDIX B

Pharmacokinetic Parameters in Literature

In this section we will present five examples in which we demonstrate how to transform pharmacokinetic population parameters found in literature so that they can be used in MW\PHARM. A transformation is often required before the parameters can be entered into the MW\PHARM drug database.

On of the first steps is to write down the basic equations as given by the literature and as used by MW\PHARM. In order to do so we must select one of four possible clearance normalization methods available in MW\PHARM. Therefore the clearance normalization method is always clearly stated. The equation used in literature is denoted by L and the equation used in MW\PHARM is denoted by M.

Basic Equations

L: Literature equation
M: MW\PHARM equation

Wrong units are one of the largest error sources with these type of calculations. Therefore the units are always explicitly displayed in every equation.

Example I

The following table lists the pharmacokinetic population parameters of vancomycin as found by Garrelts et. al.

Garrelts et. al. (Clin. Pharm., 1987, 6, 795-799):   Vancomycin in adults

Parameter	Unit	Value	Remark
V_{ss}	L/kg	0.47 (± 20%)	-
CL	mL/min/kg	$0.04 + 0.0075 (± 50\%) \triangleleft CL_{cr}$	CL_{cr} in mL/min

The literature clearance parameters are normalized with respect to body weight. The easiest way to transform these parameters would be to select a similar clearance normalization method in MW\PHARM (method III). However, in this example we shall use body surface area for the normalization of clearance (method II)

Clearance equations

L: CL (mL/min/kg) $= intercept$ (mL/min/kg) $+ slope$ (1/kg) $\triangleleft CL_{cr}$ (mL/min)

M: CL (L/h) $= CL_M$ (L/h/1.85m^2) $\triangleleft BSA$ (m^2) / 1.85 (-) $+ f_r$ (-) $\triangleleft CL_{cr}$ (L/h)
(Method II)

Calculation V_1

We are dealing with a 1 compartment system here:

V_1 (L/kg) = V_{ss} (L/kg) = **0.47 ± 0.094** (L/kg)

Calculation of CL_m

L: CL_M (L/h) = $intercept$ (mL/min/kg) ◄ LBM (kg) ◄ 60 (min/h) / 1000 (mL/L)

M: CL_M (L/h) = CL_M (L/h/1.85m^2) ◄ BSA (m^2) / 1.85 (-)

Assigning the upper to the lower equation yields:

CL_M (L/h/1.85m^2) = $intercept$ (ml/min/kg) ◄ LBM (kg) ◄ 60 (min/h) / 1000 (mL/L) / BSA (m^2) ◄ 1.85 (-)

For LBM and BSA we will assume the values of the MW\PHARM standard patient (70 kg and 1.85 m^2)

CL_M (L/h/1.85m^2) = 0.04 ◄ 70 ◄ 60 / 1000 / 1.85 ◄ 1.85 = **0.168** (L/h/1.85m^2)

Calculation of f_r

L: $\quad CL_R$ (L/h) = $slope$ (1/kg) $\times$ LBM (kg) $\times$ CL_{cr} (L/h)

M: $\quad CL_R$ (L/h) = f_r (-) $\times$ CL_{cr} (L/h)

Assigning the upper to the lower equation yields:

f_r (-) = $slope$ (1/kg) $\times$ LBM (kg)

For LBM we will assume the value of the MW\PHARM standard patient (70 kg)

$\mathbf{f_r}$ (-) = 0.0075 $\times$ 70 = **0.525 ± 0.263** (-)

After selection of the correct clearance normalization method the calculated parameters V_1, CL_M and f_r may be entered into the MW\PHARM drug database.

Example II

The following table lists the pharmacokinetic population parameters of vancomycin as found by Rodvold et. al.

Rodvold et. al. Ther. Drug Monit. 1989, 11, 269-275:   Vancomycin in adults

Parameter	Unit	Value		Remark
V_c	L/kg	0.21 (± 20%)		-
CL	mL/min/kg	0.05 (± 20%) + 0.75 (± 33%) $\triangleleft CL_{cr}$		CL_{cr} in mL/min/kg
k_{12}	/h	1.12 (± 25%)		-
k_{21}	/h	0.48 (± 25%)		-

The literature clearance parameters are normalized with respect to body weight. The easiest way to transform these parameters would be to select a similar clearance normalization method in MW\PHARM (method III). However, in this example we shall use body surface area for the normalization of clearance (method II)

Clearance equations

L: CL (mL/min/kg) = $intercept$ (mL/min/kg) + $slope$ (-) $\triangleleft CL_{cr}$ (mL/min/kg)

M: CL (L/h) = CL_M (L/h/1.85m^2) $\triangleleft BSA$ (m^2) / 1.85 (-) + f_r (-) $\triangleleft CL_{cr}$ (L/h) (Method II)

Calculation V_1

The value for V_1 can be taken directly from the table:

V_1 (L/kg) = **0.21 ± 0.042** (L/kg)

Calculation of CL_m

L: CL_M (L/h) = $intercept$ (mL/min/kg) $\times$ LBM (kg) $\times$ 60 (min/h) / 1000 (mL/L)

M: CL_M (L/h) = CL_M (L/h/1.85m^2) $\times$ BSA (m^2) / 1.85 (-)

Assigning the upper to the lower equation yields:

CL_M (L/h/1.85m^2) = $intercept$ (ml/min/kg) $\times$ LBM (kg) $\times$ 60 (min/h) / 1000 (mL/L) / BSA (m^2) $\times$ 1.85 (-)

For LBM and BSA we will assume the values of the MW\PHARM standard patient (70 kg and 1.85 m^2)

CL_M (L/h/1.85m^2) = 0.05 $\times$ 70 $\times$ 60 / 1000 / 1.85 $\times$ 1.85 = **0.21 ± 0.042** (L/h/1.85m^2)

Calculation of f_r

L: CL_R (L/h) = $slope$ (-) $\times$ CL_{cr} (L/h)

M: CL_R (L/h) = f_r (-) $\blacktriangleleft$ CL_{cr} (L/h)

Assigning the upper to the lower equation yields:

f_r (-) = $slope$ (-)

$\boldsymbol{f_r}$ (-) = **0.75 ± 0.25** (-)

Calculation of micro constants

The values for k_{12} and k_{21} can be taken directly from the table:

k_{12} (/h) = **1.12 ± 0.28** (/h)

k_{21} (/h) = **0.48 ± 0.12** (/h)

Example III

The following table lists the pharmacokinetic population parameters of vancomycin as found by Matzke et. al.

Matzke et. al., Antimicrob. Agents Chemother 1984, 25, 433-437: Vancomycin in adults

Parameter	Unit	Value	Remark
k_{el}	/h	$0.0044 + 0.00085 \times CL_{cr}$	CL_{cr} in mL/min/1.73m^2

The elimination rate is normalized with respect to body surface area. Therefore we will select the corresponding normalzation method in MW\PHARM (method I).

Calculation of k_{elm} and k_{elr}

The values for k_{elm} and k_{elr} can be taken directly from the equation listed in the table:

k_{elm} (/h) $\quad\quad\quad\quad\quad\quad\quad$ = **0.0044** (/h)

k_{elr} (/(mL/min/1.73m^2)/h) $\quad$ = **0.00085** (/(mL/min/1.73m^2)/h)

Example IV

The following table lists the pharmacokinetic population parameters of vancomycin as found by Blevins et. al.

Blevins et. al., Antimicrob. Agents Chemother 1984, 25, 603-606: Vancomycin in dialysis patients

Parameter	Unit	Value	Remark
CL	mL/min	5.0	10% renal
V_{ss}	L/kg	0.8	-

We will make the following assumptions.

Assumptions

Parameter	Unit	Value	Remark
CL_{cr}	mL/min	5.0	-
BSA	m^2	1.85	Standard patient
k_{12}	/h	1.12	Rodvold 1989
k_{21}	/h	0.48	Rodvold 1989

Calculation V_1

V_1 (L/kg) = V_{ss} (L/kg) / (1 + k_{12} (/h) / k_{21} (/h))

V_1 (L/kg) = 0.8 / (1 + 1.12 / 0.48) = **0.24** (L/kg)

Calculation of CL_M

If 10% of the clearance is renal then 90% is non-renal. When using method II normalization this yields:

CL_M (L/h/1.85m^2) = (1 - 0.1) $\cdot$ CL (mL/min) $\cdot$ 60 (min/h) / 1000 (mL/L) / BSA (1.85m^2) $\cdot$ 1.85 (-)

CL_M (L/h/1.85m^2) = 0.9 $\cdot$ 5 $\cdot$ 60 / 1000 /1.85 $\cdot$ 1.85= **0.27** (L/h/1.85m^2)

Calculation of f_r

f_r (-) = CL_R (mL/min) / CL_{cr} (mL/min)

f_r (-) = 0.1 $\cdot$ 5 / 5 = **0.1** (-)

Example V

The following table lists the pharmacokinetic population parameters of vancomycin as found by Rotschafer et. al.

Rotschafer et. al., Antimicrob. Agents Chemother 1982, 22, 391-394:   Vancomycin in adults

Parameter	Unit	Value	Remark
CL_{cr}	mL/min	184.1	-
CL	mL/min/kg	1.26	-
$t\frac{1}{2}_{\alpha}$	h	0.5	first phase (fast)
$t\frac{1}{2}_{\beta}$	h	5.6	second phase (slow)
V_c	L/kg	0.14	central compartment
V_{dss}	L/kg	0.62	steady state

We want to use MW\PHARMS's clearance normalization method II. Furthermore we assume that 95% of the clearance is renal and that the population from which these data were obtained had an average BSA of 1.85m^2 and an average LBM of 70 kg.

In order to convert the macro parameters $t\frac{1}{2}_{\alpha}$ and $t\frac{1}{2}_{\beta}$ into the micro parameters k_{12} and k_{21} it is essential to have knowledge about the distribution volume of the central compartment (V_1) and the distribution volume at steady state (V_{ss}).

 Calculation of micro constants

L_α (/h) = ln(2) / t½$_\alpha$ (h) = 0.693 / 0.5 = 1.386 (/h)

L_β (/h) = ln(2) / t½$_\alpha$ (h) = 0.693 / 5.6 = 0.124 (/h)

k_{21} (/h) = L_α (/h) · L_β (/h) · V_1 (L/kg) / CL (L/h/kg) = 1.386 · 0.124 · 0.14 / (1.26 · 60 / 1000) = **0.318** (/h)

k_{12} (/h) = k_{21} · (V_{ss} (L/kg) / V_1 (L/kg) - 1) = 0.318 · (0.62 / 0.14 - 1) = **1.090** (/h)

Calculation of CL_M

CL_M (L/h/1.85m^2) = (1 - 0.95) · CL (mL/min/kg) · LBM (kg) / BSA (m^2) · 1.85 (-) · 60 (min/h) / 1000 (mL/L)

CL_M (L/h/1.85m^2) = (1 - 0.95) · 1.26 · 70 / 1.85 · 1.85 · 60 / 1000 = **0.265**

Calculation of f_r

f_r (-) = 0.95 · CL (mL/min/kg) · LBM (kg) / CL_{cr} (mL/min/)

f_r (-) = 0.95 · 1.26 · 70 / 184.1 = **0.455** (-)

APPENDIX C

Export File Formats

The curves and data points which are visible in the different graphics screens can be exported to plain ASCII files. This appendix lists the used file formats.

Symbol	Unit	Description
t	h	Time (since first dose)
$A1$	mg	Amount in central compartment 1
$A2$	mg	Amount in peripheral compartment 2
$A3$	mg	Amount in peripheral compartment 3
C	mg/L	Concentration (fitted curve)
C_m	mg/L	Concentration (measured data)
CL_{cr}	ml/min	Creatinine clearance
LBM	kg	Exponent in general error model
TAB	–	Total amount in body ($A1+A2+A3$)
X	–	First/Last data point in series
$..$	–	Intermediate data points in series

In order to import these files into a graphics package specify one of the following import settings.

Import Settings:
- ❍ no header info
- ❍ fixed width fields (14 positions)
- ❍ delimited fields (comma)

The units for time, concentration and amount are dependent on the units which are used in the graph.
The number of points used to represent the fitted curve (resolution) can be specified by the user. The maximum resolution is 600.

MwPharm Graphics Screens (TAB-Window not visible)

t (h)	$C^{\#}$ (mg/L)	CL_{cr}* (ml/min)	LBM* (kg)	C_m (mg/L)
x	x	x	x	
..	..	..	..	
x	x	x	x	
x				x
..				..
x				x

$^{\#}$Exported for every visible curve
*Exported only in the irregular graphics screen.

MwPharm Graphics Screens (TAB-Window visible)

t (h)	A1 (mg)	A1+A2+A3 (mg)*
x	x	x
..	..	..
x	x	x

*Total amount in body

KinFit Graphics Screens

t (h)	C (mg/L)	C_m (mg/L)
x		x
..		..
x		x
x	x	
..	..	
x	x	