PK01

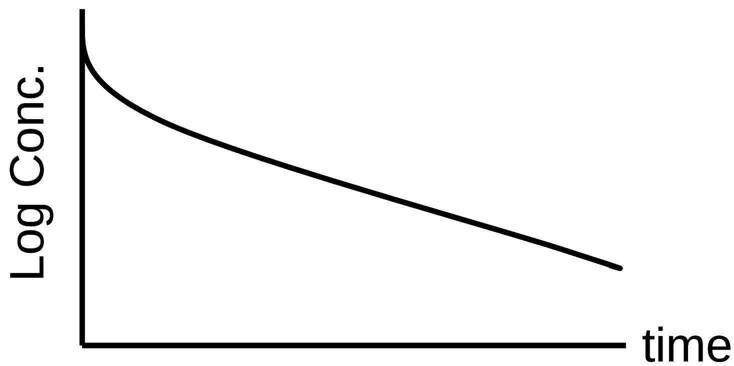
Solution 1-1 – Library model FitMicroIVBolus for dataset 1

The one compartment IV Bolus can be characterized by a simple differential equation:

$$\frac{dx}{dt} = -ax$$

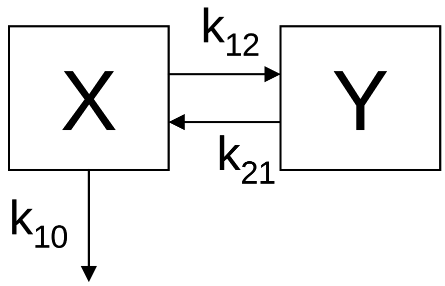
This equation simply describes a profile wherein the rate of decay or elimination is proportional to the amount x. In Kinetica, this form of equation is also called micro. This equation is mathematically equivalent to $x(t) = x_0e^{-at}$, where x_0 is the initial estimate at t = 0; this algebraic form is known as macro in Kinetica.

The elimination of many drugs follows the behavior that can be characterized by exponential decay. Let us take for example a graph of log concentration versus time, as shown in the picture below. Since this curve is not totally a straight line in the log scale, this curve can be described by the sum of more than one exponentials, perhaps two exponentials, such as $C = Ae^{-\alpha t} + Be^{-\beta t}$.



The variables A, B, α, and β are called the macro constants. At time zero, A + B = C_0. Thus the concentration at time = 0 has both A and B component. The B component can be determined by extrapolating the terminal elimination phase of the curve to the intercept at t=0. The A component at the zero time point is simply the difference between C_0 and the extrapolated B. The constants α and β are approximated from the two slopes of the curve.

The same curve in the picture above can be described by a set of differential equations. Assuming a two-compartment model, we will draw boxes and arrows that represent compartments and movement between compartments, respectively. The arrows coming into a compartment are represented by positive rate constants and the arrows going out of a compartment are negative rate constants. For the X compartment, k_{21} is positive while k_{10} and k_{12} are both negative, while k12 is positive and k21 is negative for the Y compartment.



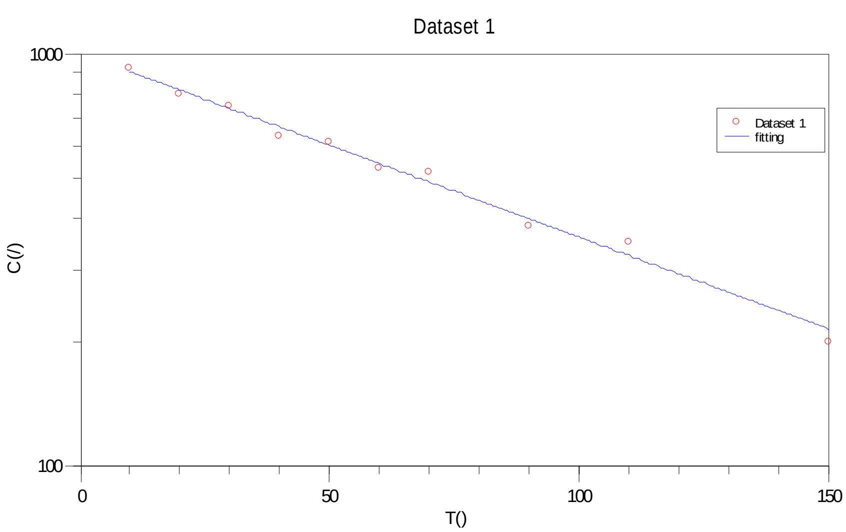
Note that all compartmental models are based on the assumption that the eliminating compartment is the input or first compartment, similar to the one shown in the diagram above. The same diagram can be mathematically represented by differential equations:

$$\frac{dX}{dt} = k_{21}Y - (k_{10} + k_{12})X$$
$$\frac{dY}{dt} = k_{12}X - k_{21}Y$$

Unlike in a one compartment model, the relationship between macro and micro constants in a two or more compartment models are not as intuitive. We will not discuss in details the methods to convert one from the other. One of the methods is Laplace transformation. You may consult any textbooks on ordinary differential equations for more details.

The method FitMicroIVBolus is the primary method to fit the data. The structural model assumes that the concentration data is taken from the first or central compartments. With the option to select for 1, 2 or 3 compartments, this model assumes that both the second and third compartments are connected of the first, thus the rate constants Kel, K12, K21, K13 and K31, representing the rate constants for the elimination, first to second, second to first, first to third, and third to the first compartment, respectively. In Kinetica, the hard-coded pharmacokinetic methods do not require the user to input initial parameter estimates. A built-in algorithm generates excellent initial parameter estimates.

Plot of the Fitting



Method Option Summary

Number of compartments: 1
Weighting: 1 (uniform)
Plot curve: Yes
Execution: Fitting

Parameter	Initial Estimates
Vc	10
Kel	0.023

Fitting Summary

solution found in 8 iterations

Objective function: 4327.38
Akaike criteria: 87.7272
Schwartz criteria: 86.0298

Parameter	Mean	S.D.	C.V.(%)
Vc	9.97846	0.205238	2.05681
Kel	0.010256	0.000433127	4.22316

Correlation Matrix

	Vc	Kel
Vc	1	
Kel	-0.806891	1

T	C	C calc	Residuals	Weighted Res.
10	920	904.472	15.5277	15.5277
20	800	816.308	-16.3081	-16.3081
30	750	736.738	13.2622	13.2622
40	630	664.924	-34.9236	-34.9236
50	610	600.11	9.89035	9.89035
60	530	541.613	-11.6134	-11.6134
70	520	488.819	31.1808	31.1808
90	380	398.168	-18.1676	-18.1676
110	350	324.327	25.6726	25.6726
150	200	215.188	-15.1884	-15.1884

	Without weights	With weights
Sum	-0.667578	-0.667578
Mean	-0.0667578	-0.0667578
SumOfSquares	4327.38	4327.38
Std. dev.	21.9275	21.9275

Summary of Estimated Parameters

Numerical Field Name	Units	Data Field
dose		10000
Vc		9.97846
Kel		0.010256
K12		
K21		
K13		
K31		
AUC		97714.5
AUMC		9.52756e+006
MRT		97.5041
Lz		0.010256
Cmax calc		1002.16
Tmax calc		0
A		1002.16
Alpha		0.010256
B		
Beta		
C		
Gamma		
Vss		9.97846
Vz		9.97846
Cl		0.102339

Solution 2-1 – User-created clearance model for dataset 1

For user-created method, initial parameter estimates should be input to assist the optimization algorithm (Marquardt) to find a global minimum. In the example of the user-created method (modelpk1b), the main equation is called funct, which represents the equation:

$$C(t) = \frac{Dose_{iv}}{V} e^{-\frac{Cl}{V} \bullet t}$$

The secondary parameter k which is the elimination rate constant is derived from dividing Cl by V.

Method Name: modelpk1b

```
Dim X as InputColumn
Dim Y as ColumnToFit
Dim Ycalc as ComputedColumn

Dim V as Parameter
Dim Cl as Parameter

Dim k as OutputNumber

dim funct as double

SUB modelpk1b ()
```

```
Dim i as Integer

dim T as double

    For i=1 To X_count

        If X_status(i)=0 Then
              T=x(i)
              funct= (10000/V)*exp(-(cl/V)*T)
            If Y_status(i)=0 Then
                Ycalc(i) = funct      ' corresponding computed value for IV
                Ycalc_status(i) = 0
            Else
                Ycalc_status(i) = 3
            End if
        End if
    Next i
    Ycalc_unit = Y_unit
 k=cl/v
End Sub
```

Method Option Summary

Weighting: 1 (uniform)
Execution: Fitting

Parameter	Initial Mean
V	10
Cl	1

Fitting Summary

solution found in 1 iterations

Objective function: 4327.48
Akaike criteria: 87.7274
Schwartz criteria: 86.03

Parameter	Mean	S.D.	C.V.(%)
V	9.98066	0.20524	2.05637
Cl	0.102303	0.0029046	2.8392

Correlation Matrix

	V	Cl
V	1	
Cl	-0.476938	1

T	C	Ycalc	Residuals	Weighted Res.
10	920	904.325	15.6747	15.6747
20	800	816.223	-16.223	-16.223

30	750	736.704	13.2961	13.2961
40	630	664.932	-34.9318	-34.9318
50	610	600.152	9.84806	9.84806
60	530	541.683	-11.6832	-11.6832
70	520	488.911	31.0894	31.0894
90	380	398.288	-18.2885	-18.2885
110	350	324.464	25.5364	25.5364
150	200	215.329	-15.329	-15.329

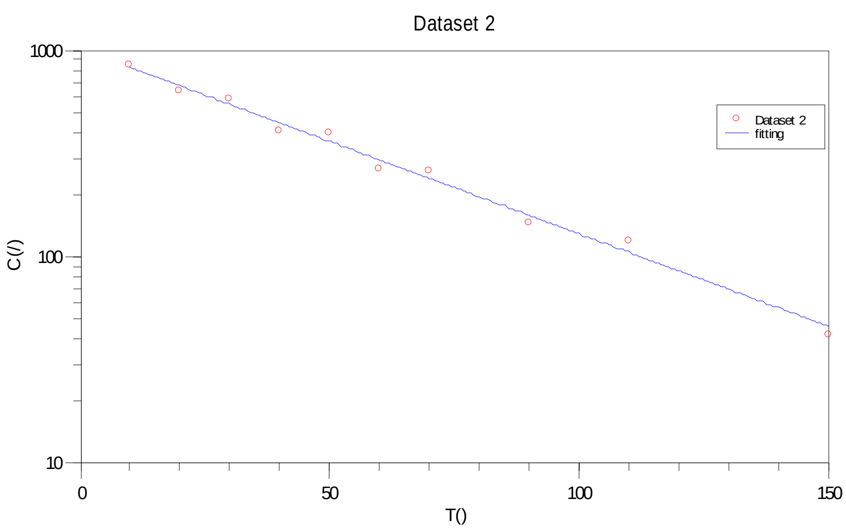
	Without weights	With weights
Sum	-1.01076	-1.01076
Mean	-0.101076	-0.101076
SumOfSquares	4327.48	4327.48
Std. dev.	21.9276	21.9276

Summary of Estimated Parameters

Numerical Field Name	Units	Data Field
Cl		0.102303
V		9.98066
K		0.0102502

Solution 1-2 – Library model FitIVBolus for dataset 2

Plot of the Fitting



Method Option Summary

Number of compartments: 1
Weighting: 1 (uniform)
Plot curve: Yes

Execution: Fitting

Parameter	Initial Mean
Vc	10
Kel	0.023

Fitting Summary

solution found in 4 iterations

Objective function: 7539.74
Akaike criteria: 93.2794
Schwartz criteria: 91.582

Parameter	Mean	S.D.	C.V.(%)
Vc	9.81725	0.36889	3.75757
Kel	0.0206566	0.00113298	5.48484

Correlation Matrix

	Vc	Kel
Vc	1	
Kel	-0.811007	1

T	C	C calc	Residuals	Weighted Res.
10	850	828.513	21.4869	21.4869
20	630	673.89	-43.8897	-43.8897
30	580	548.123	31.8767	31.8767
40	410	445.828	-35.8283	-35.8283
50	400	362.624	37.3756	37.3756
60	270	294.949	-24.9487	-24.9487
70	260	239.903	20.0969	20.0969
90	145	158.714	-13.7138	-13.7138
110	120	105.001	14.999	14.999
150	42	45.957	-3.95695	-3.95695

	Without weights	With weights
Sum	3.49755	3.49755
Mean	0.349755	0.349755
SumOfSquares	7539.74	7539.74
Std. dev.	28.9415	28.9415

Summary of Estimated Parameters

Numerical Field Name	Units	Data Field
dose		10000
Vc		9.81725
Kel		0.0206566
K12		

K21		
K13		
K31		
AUC		49311.8
AUMC		2.38721e+006
MRT		48.4106
Lz		0.0206566
Cmax calc		1018.61
Tmax calc		0
A		1018.61
Alpha		0.0206566
B		
Beta		
C		
Gamma		
Vss		9.81725
Vz		9.81725
Cl		0.202791

Solution 2-2 – User-created clearance model for dataset 2

This example utilizes the same user-created method modelpk1b.

Method Option Summary

Weighting: 1 (uniform)
Execution: Fitting

Parameter	Initial Mean
V	10
Cl	1

Fitting Summary

solution found in 11 iterations

Objective function: 7539.72
Akaike criteria: 93.2794
Schwartz criteria: 91.582

Parameter	Mean	S.D.	C.V.(%)
V	9.81622	0.368675	3.75577
Cl	0.202815	0.00665766	3.28262

Correlation Matrix

	V	Cl
V	1	
Cl	-0.211153	1

T	C	Ycalc	Residuals	Weighted Res.
10	850	828.562	21.4381	21.4381
20	630	673.898	-43.8982	-43.8982
30	580	548.105	31.8952	31.8952
40	410	445.793	-35.7927	-35.7927
50	400	362.579	37.4213	37.4213
60	270	294.898	-24.8978	-24.8978
70	260	239.851	20.1494	20.1494
90	145	158.664	-13.6644	-13.6644
110	120	104.959	15.0414	15.0414
150	42	45.9299	-3.9299	-3.9299

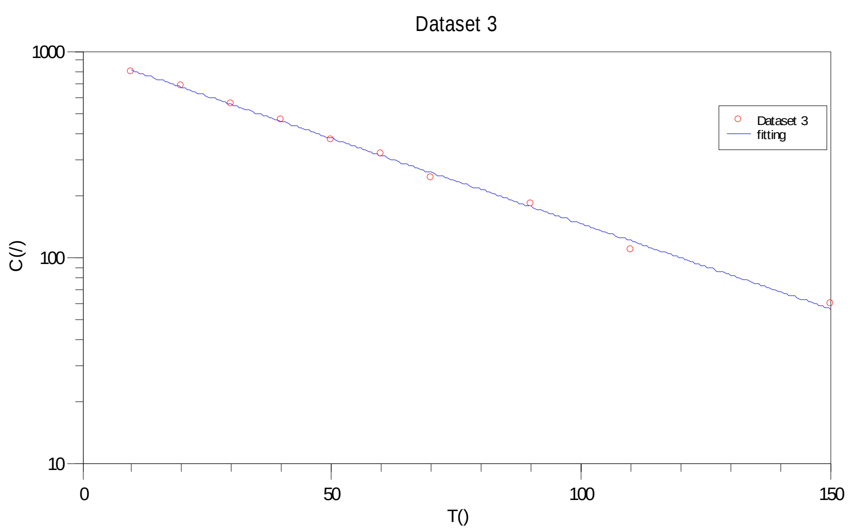
	Without weights	With weights
Sum	3.76231	3.76231
Mean	0.376231	0.376231
SumOfSquares	7539.72	7539.72
Std. dev.	28.9411	28.9411

Summary of Estimated Parameters

Numerical Field Name	Units	Data Field
Cl		0.202815
V		9.81622
K		0.0206613

Solution 1-3 – Library model FitIVBolus for dataset 3

Plot of the Fitting



Method Option Summary

Number of compartments: 1
Weighting: 1 (uniform)
Plot curve: Yes
Execution: Fitting

Parameter	Initial Estimates
Vc	10
Kel	0.023

Fitting Summary

solution found in 4 iterations

Objective function: 770.605
Akaike criteria: 70.4718
Schwartz criteria: 68.7743

Parameter	Mean	S.D.	C.V.(%)
Vc	10.2235	0.121909	1.19243
Kel	0.0190338	0.000342524	1.79956

Correlation Matrix

	Vc	Kel
Vc	1	
Kel	-0.809611	1

T	C	C calc	Residuals	Weighted Res.
10	800	808.605	-8.60488	-8.60488
20	680	668.457	11.5426	11.5426
30	550	552.6	-2.60021	-2.60021
40	465	456.823	8.17654	8.17654
50	370	377.647	-7.64674	-7.64674
60	320	312.193	7.80705	7.80705
70	245	258.084	-13.0836	-13.0836
90	185	176.374	8.62577	8.62577
110	110	120.534	-10.5341	-10.5341
150	60	56.2936	3.70638	3.70638

	Without weights	With weights
Sum	-2.61112	-2.61112
Mean	-0.261112	-0.261112
SumOfSquares	770.605	770.605
Std. dev.	9.24916	9.24916

Summary of Estimated Parameters

Numerical Field Name	Units	Data Field

dose		10000
Vc		10.2235
Kel		0.0190338
K12		
K21		
K13		
K31		
AUC		51389.5
AUMC		2.69991e+006
MRT		52.5382
Lz		0.0190338
Cmax calc		978.135
Tmax calc		0
A		978.135
Alpha		0.0190338
B		
Beta		
C		
Gamma		
Vss		10.2235
Vz		10.2235
Cl		0.194592

Solution 2-3 – User-created clearance model for dataset 3

This example utilizes the same user-created method modelpk1b.

Method Option Summary

Weighting: 1 (uniform)
Execution: Fitting

Parameter	Initial Mean
V	10
Cl	1

Fitting Summary

solution found in 11 iterations

Objective function: 770.51
Akaike criteria: 70.4705
Schwartz criteria: 68.7731

Parameter	Mean	S.D.	C.V.(%)
V	10.2229	0.121858	1.192
Cl	0.194659	0.00211984	1.089

Correlation Matrix

	V	Cl

V	1	
Cl	-0.243557	1

T	C	Ycalc	Residuals	Weighted Res.
10	800	808.591	-8.59099	-8.59099
20	680	668.395	11.6054	11.6054
30	550	552.506	-2.50596	-2.50596
40	465	456.711	8.28949	8.28949
50	370	377.524	-7.52441	-7.52441
60	320	312.068	7.93211	7.93211
70	245	257.96	-12.9604	-12.9604
90	185	176.263	8.73699	8.73699
110	110	120.44	-10.4396	-10.4396
150	60	56.2322	3.76776	3.76776

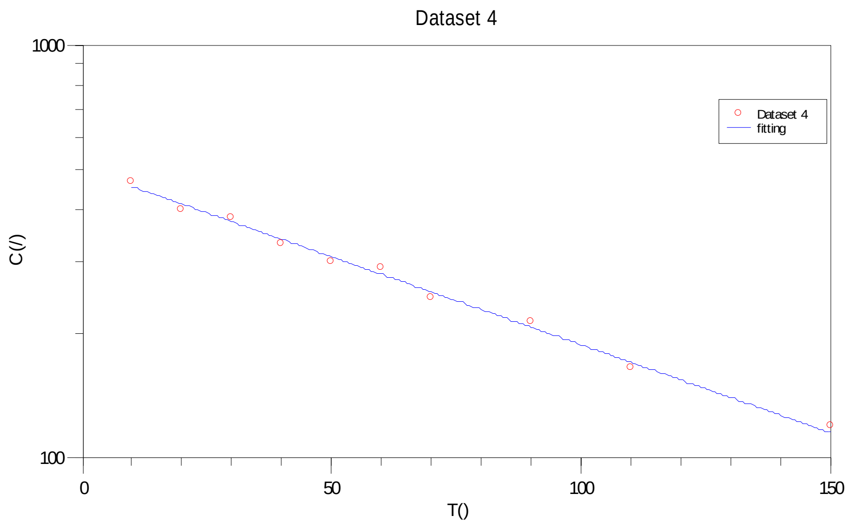
	Without weights	With weights
Sum	-1.68966	-1.68966
Mean	-0.168966	-0.168966
SumOfSquares	770.51	770.51
Std. dev.	9.25097	9.25097

Summary of Estimated Parameters

Numerical Field Name	Units	Data Field
Cl		0.194659
V		10.2229
K		0.0190414

Solution 1-4 – Library model FitIVBolus for dataset 4

Plot of the Fitting



Method Option Summary

Number of compartments: 1
Weighting: 1 (uniform)
Plot curve: Yes
Execution: Fitting

Parameter	Initial Estimates
Vc	10
Kel	0.023

Fitting Summary

solution found in 6 iterations

Objective function: 721.939
Akaike criteria: 69.8194
Schwartz criteria: 68.122

Parameter	Mean	S.D.	C.V.(%)
Vc	19.947	0.329496	1.65186
Kel	0.00981417	0.000341645	3.48114

Correlation Matrix

	Vc	Kel
Vc	1	
Kel	-0.807132	1

T	C	C calc	Residuals	Weighted Res.
10	465	454.466	10.5344	10.5344
20	400	411.982	-11.9824	-11.9824
30	380	373.47	6.52957	6.52957
40	330	338.559	-8.55858	-8.55858

50	300	306.91	-6.91027	-6.91027
60	290	278.22	11.7796	11.7796
70	245	252.213	-7.21252	-7.21252
90	215	207.263	7.73697	7.73697
110	165	170.324	-5.32447	-5.32447
150	120	115.024	4.97627	4.97627

	Without weights	With weights
Sum	1.56857	1.56857
Mean	0.156857	0.156857
SumOfSquares	721.939	721.939
Std. dev.	8.95478	8.95478

Summary of Estimated Parameters

Numerical Field Name	Units	Data Field
dose		10000
Vc		19.947
Kel		0.00981417
K12		
K21		
K13		
K31		
AUC		51082.2
AUMC		5.20495e+006
MRT		101.893
Lz		0.00981417
Cmax calc		501.33
Tmax calc		0
A		501.33
Alpha		0.00981417
B		
Beta		
C		
Gamma		
Vss		19.947
Vz		19.947
Cl		0.195763

Solution 2-4 – User-created clearance model for dataset 4

This example utilizes the same user-created method modelpk1b.

Method Option Summary

Weighting: 1 (uniform)
Execution: Fitting

Parameter	Initial Mean

V	10
Cl	1

Fitting Summary

solution found in 11 iterations

Objective function: 721.94
Akaike criteria: 69.8194
Schwartz criteria: 68.122

Parameter	Mean	S.D.	C.V.(%)
V	19.9482	0.32945	1.65153
Cl	0.195748	0.00461975	2.36005

Correlation Matrix

	V	Cl
V	1	
Cl	-0.491465	1

T	C	Ycalc	Residuals	Weighted Res.
10	465	454.443	10.5572	10.5572
20	400	411.967	-11.9673	-11.9673
30	380	373.462	6.53817	6.53817
40	330	338.555	-8.55537	-8.55537
50	300	306.912	-6.91152	-6.91152
60	290	278.225	11.7747	11.7747
70	245	252.22	-7.22038	-7.22038
90	215	207.275	7.72489	7.72489
110	165	170.339	-5.33901	-5.33901
150	120	115.04	4.96021	4.96021

	Without weights	With weights
Sum	1.56154	1.56154
Mean	0.156154	0.156154
SumOfSquares	721.94	721.94
Std. dev.	8.9548	8.9548

Summary of Estimated Parameters

Numerical Field Name	Units	Data Field
Cl		0.195748
V		19.9482
K		0.00981281

Solution 3-1 – Differential equation model for dataset 1

In the example of the user-created method (modelpk1c), the central compartment Z1 at time 0 has the original concentration Dose/V. In this model, the subroutine Sub Deriv is where the user codes the differential equation:

$$\frac{dZ_1}{dt} = -\frac{Cl}{V} Z_1$$

DZ1 is equivalent to $\frac{dZ_1}{dt}$. The function NewInteg is a built-in numerical solution that utilizes either the Runge Kutta or the Livermore algorithms as its ordinary differential equation and stiff differential equation solvers, respectively. The function DeclareComp takes in three arguments, namely hmod, Z1, and DZ1.

Method Name: modelpk1c

```
Dim X as InputColumn
Dim Y1 as ColumnToFit
Dim Y1calc as ComputedColumn
Dim Dose as InputNumber
Dim V as Parameter
Dim cl as Parameter
Dim k as outputnumber
Dim Z1 as Double
Dim DZ1 as Double


SUB modelpk1c ()
  Dim i as Integer
  Dim ret as Integer
  Dim hmod as long

  hmod = NewInteg("Deriv")
  ret = DeclareComp(hmod, Z1, DZ1)

  Z1 = Dose/V

  For i=1 To X_count            ' For each time
    If X_status(i)=0 Then       ' Check time status and if OK
      ret = IntegTo(hmod, X(i))   ' Compute new comp values
      If Y1_status(i)=0 Then   ' If there is an observation
        Y1calc(i) = Z1       ' Get corresponding computed value
        Y1calc_status(i) = 0 ' code for Normal value
      Else
        Y1calc_status(i) = 3 ' code for Missing value
      End if
    End if
  Next i
  Y1calc_unit = Y1_unit   ' Set units for computed column

      k=cl/v
End Sub

Sub Deriv (Byval t as double)

  DZ1 = -Z1*cl/V
```

```
End Sub
```

Method Option Summary

Weighting: 1 (uniform)
Execution: Fitting

Parameter	Initial Mean
V	10
cl	0.1

Fitting Summary

solution found in 3 iterations

Objective function: 4327.39
Akaike criteria: 87.7272
Schwartz criteria: 86.0298

Parameter	Mean	S.D.	C.V.(%)
V	9.97931	0.205203	2.05628
cl	0.102316	0.00290425	2.8385

Correlation Matrix

	V	cl
V	1	
cl	-0.476853	1

T	Y	Ycalc	Residuals	Weighted Res.
10	920	904.425	15.5749	15.5749
20	800	816.291	-16.2913	-16.2913
30	750	736.746	13.2541	13.2541
40	630	664.952	-34.9516	-34.9516
50	610	600.154	9.84624	9.84624
60	530	541.67	-11.6703	-11.6703
70	520	488.886	31.1143	31.1143
90	380	398.247	-18.2468	-18.2468
110	350	324.413	25.5868	25.5868
150	200	215.273	-15.2725	-15.2725

	Without weights	With weights
Sum	-1.05626	-1.05626
Mean	-0.105626	-0.105626
SumOfSquares	4327.39	4327.39
Std. dev.	21.9274	21.9274

Summary of Estimated Parameters

Numerical Field Name	Units	Data Field
Cl		0.102316
V		9.97931
dose		10000
k		0.0102528

PK03

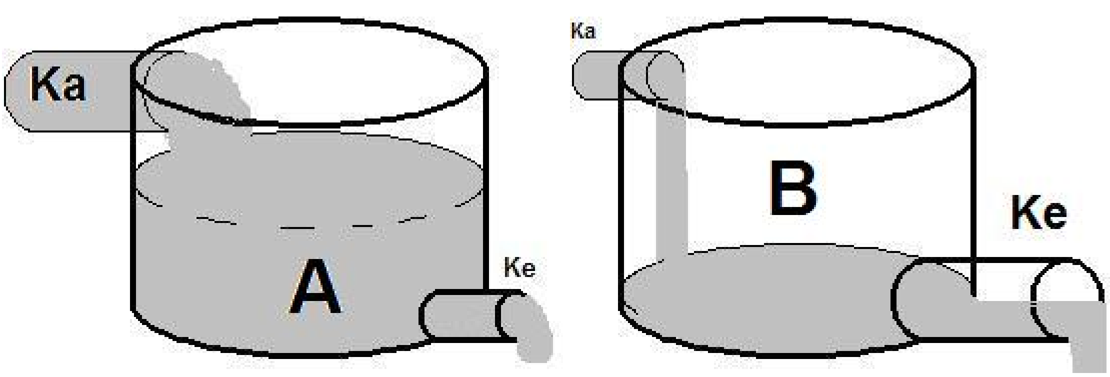
Solution I – First-order absorption

The user-created model called modelpk3a is similar to the hard-coded method FitMicroExtravascular for 1 compartment model in the previous exercise. The model assumes that the bioavailability factor is a component of the volume of distribution; the equation funct in the code does not contain a separate parameter for bioavailability. For models that are created by users such as the one in this example, the user is required to enter initial parameter estimates for Kinetica to fit the data.

This section descries strategies to derive initial parameter estimates for compartmental modeling. One can easily derive a rough estimate of the elimination rate constant Ke from the time-concentration profile. We see that the concentration dropped from about 90 to 45 µg/L in 2 hours; the terminal phase half-life of the drug is approximately 2 hours. The relationship between half-life and elimination rate constant is an inverse proportionality such that Ke = $\log_n(2)$ / half-life. In this case, the Ke is 0.35. As for the estimate of the lag time, we know that lag time has to be less than 0.5 h since there was already a concentration of 10 µg/L at time 0.5 h. We will use 200 for the volume of distribution; this value should be less than Dose/Cmax (~200), since the profile is an extravascular route. If the drug were to be administered as an IV bolus, the volume of distribution would simply be dose divided by the extrapolated concentration at t = 0 hours.

The initial estimate for Ka is perhaps the most difficult one to derive. Frequently, the numerical deconvolution of the oral data with the intravenous bolus data as reference is used to determine the rate constant for absorption. However, the intravenous data is not available in this example. Assuming that the profile is not a flip-flop situation, the absorption rate constant should generally be larger than the elimination rate constant otherwise one would not observe any concentration in the body. The simple explanation is that drug coming into the body should be faster than drug leaving the body in order to keep the drug in the body.

An illustration will help explain the relative magnitude of the absorption and elimination rate constants. Two tanks of similar volume have different diameter of pipes bringing water into and out of tank. In tank A, the pipe coming into the tank has a larger diameter and accommodates a flow rate of 10 liters per hour while the pipe leaving the same tank can only allow water to flow at a maximum rate of 2 liters per hour. Tank A will eventually be filled since the flow rate coming into the tank is greater than that leaving the tank. In tank B, the diameter sizes of the input and output pipes are switched. Flow rate of the input is 2 liters per hour while the output flow rate has the capacity of 10 liters per hour. In this scenario, tank B will not retain any of the water that comes in.



The same concept applies to the relative magnitude of the pharmacokinetic rate constants. In a non-flip-flop situation, Ka should be larger than Ke to observe a drug concentration in the body. We will provide an arbitrary value 1 for the initial estimate for Ka; the value should be greater than 0.35. In summary, the initial estimates for the example model are as follows:

Ka = 1 (h^{-1})
Ke = 0.35 (h^{-1})
Tlag = 0.3 (h)
V/F = 200 (L)

Method Name: modelpk3a

```
Dim X as InputColumn
Dim Y as ColumnToFit
Dim Ycalc as ComputedColumn

Dim ka as Parameter
Dim ke as Parameter
Dim VF as Parameter
Dim Tlag as Parameter
dim dose as inputnumber
dim funct as double
dim coeff as double

SUB modelpk3a ()
Dim i as Integer

dim T as double

For i=1 To X_count

    If X_status(i)=0 Then
        T=x(i)

            if t <= tlag then
                funct=0
            else
                COEFF=(KA/VF)*Dose/(KA-KE)
                funct = COEFF*(EXP(-KE*(T-TLAG))-EXP(-KA*(T-TLAG)))
            end if
      If Y_status(i)=0 Then
        Ycalc(i) = funct
        Ycalc_status(i) = 0
      Else
        Ycalc_status(i) = 3
      End if
    End if
Next i
  Ycalc_unit = Y_unit
End Sub
```

Method Option Summary

Weighting: 1 (uniform)
Execution: Fitting

Parameter	Initial Mean
ka	1
ke	0.35

VF	200
Tlag	0.3

Fitting Summary

solution found in 30 iterations

Objective function: 1126.66
Akaike criteria: 92.3241
Schwartz criteria: 89.2939

Parameter	Mean	S.D.	C.V.(%)
ka	0.44701	2.41356	539.936
ke	0.401943	2.11785	526.903
VF	104.871	541.328	516.187
Tlag	0.393445	0.160859	40.8848

Standard deviation of some parameters is high
NB : check data for possible outliers

Correlation Matrix

	ka	ke	VF	Tlag
ka	1			
ke	-0.999251	1		
VF	0.999531	-0.999834	1	
Tlag	0.470032	-0.451494	0.45539	1

Very high correlation between parameters
Possible overparametrization

T	C	Ycalc	Residuals	Weighted Res.
0.5	10	8.6821	1.3179	1.3179
1	46	39.9724	6.02762	6.02762
1.5	56	58.9821	-2.98212	-2.98212
2	56	69.2658	-13.2658	-13.2658
3	66	73.5356	-7.53558	-7.53558
4	87	66.5892	20.4108	20.4108
5	69	55.6726	13.3274	13.3274
6	45	44.3597	0.640268	0.640268
7	29	34.227	-5.22698	-5.22698
8	15	25.8081	-10.8081	-10.8081
9	10	19.1269	-9.12686	-9.12686
10	9	13.9863	-4.98627	-4.98627

	Without weights	With weights
Sum	-12.2078	-12.2078
Mean	-1.01731	-1.01731
SumOfSquares	1126.66	1126.66
Std. dev.	10.0645	10.0645

Summary of Estimated Parameters

Numerical Field Name	Units	Data Field
Dose		20000
Ka		0.44701
Kel		0.401943
VF		104.871
Tlag		0.393445

Solution II – Zero-order absorption

The user-created model called modelpk3b is equivalent to the hard-coded method FitMicro0orderinput or FitMicroIVInf for 1 compartment model. In the model, the duration of infusion or Tabs is a parameter output from the fit of data. The equation at time prior to Tabs consists of a linear function subtracted by an exponential function $C(t) = \frac{F}{K_e V}(1 - e^{-K_e t})$. The rate of infusion is the linear function and the exponential decay accounts for the drug elimination. The combination of the two functions is responsible for the curvilinear increase of the drug. For time greater than Tabs, the equation, $C(t) = \frac{F}{K_e V}(1 - e^{-K_e Tabs})(e^{-K_e(t-Tabs)})$, is equivalent to $C(t) = \frac{F}{K_e V} e^{-K_e(t-Tabs)} - \frac{F}{K_e V} e^{-K_e t}$. This equation is simply a mono-exponential decay with a shift in time subtract from a separate monoexponential decay without the shift. In essence, the previous linear increasing function is replaced by an exponential decay.

The initial parameters for this model are fairly easy to determine. For the Tabs which is the duration of infusion, we will use the Tmax value, assuming that the infusion stops at this point. The half-life of the drug is approximately 2 to 2.5 hours; the initial estimate for Ke will be 0.4, which is the natural logarithm of 2 divided by the half-life.

The fit of the data using a zero-order input resulted in lower objective function, Akaike and Schwartz criteria than the fitting of the same data using the first-order absorption model. In addition, the coefficients of variation of the estimated parameters are approximately 50-fold smaller. The current model produces a tighter fit of the data than the first-order absorption model.

Method Name: modelpk3b

```
Dim X as InputColumn
Dim Y1 as ColumnToFit
Dim Y1calc as ComputedColumn

Dim Dose as InputNumber

Dim Tabs as Parameter
Dim VF as Parameter
Dim ke as Parameter
dim funct as double
dim finf as double

SUB modelpk3b ()

    Dim i as Integer
```

```
    For i=1 To X_count            ' For each time
      T=x(i)
      finf = dose/tabs
             If X_status(i)=0 Then
                    If X(i)<=Tabs Then
                           Funct =(FINF/(Ke*VF))*(1. - EXP(-Ke*T))
                    else
                           Funct=(FINF/(Ke*VF))*(1.-EXP(-Ke*Tabs))*EXP(-Ke*(T-Tabs))

                    End If
                    If Y1_status(i)=0 Then   ' If there is an observation
                           Y1calc(i) = funct    ' Get corresponding computed value
                           Y1calc_status(i) = 0 ' code for Normal value
                    Else
                           Y1calc_status(i) = 3 ' code for Missing value
                    End if
             End if
   Next i

   Y1calc_unit = Y1_unit   ' Set units for computed column

 End Sub
```

Method Option Summary

Weighting: 1 (uniform)
Execution: Fitting

Parameter	Initial Mean
Tabs	4
VF	100
Ke	0.35

Fitting Summary

solution found in 10 iterations

Objective function: 347.517
Akaike criteria: 76.2097
Schwartz criteria: 73.9371

Parameter	Mean	S.D.	C.V.(%)
Tabs	4.54493	0.240082	5.28241
VF	96.1941	10.997	11.4321
ke	0.465809	0.0630736	13.5406

Correlation Matrix

	Tabs	VF	ke
Tabs	1		
VF	-0.779085	1	

ke	0.763898	-0.941297	1

T	Y	Ycalc	Residuals	Weighted Res.
0.5	10	20.4047	-10.4047	-10.4047
1	46	36.57	9.43005	9.43005
1.5	56	49.3765	6.62349	6.62349
2	56	59.5222	-3.52224	-3.52224
3	66	73.9277	-7.92771	-7.92771
4	87	82.969	4.03102	4.03102
5	69	69.8843	-0.884322	-0.884322
6	45	43.8613	1.13871	1.13871
7	29	27.5285	1.47147	1.47147
8	15	17.2776	-2.27765	-2.27765
9	10	10.8439	-0.843917	-0.843917
10	9	6.80594	2.19406	2.19406

	Without weights	With weights
Sum	-0.971761	-0.971761
Mean	-0.08098	-0.08098
SumOfSquares	347.517	347.517
Std. dev.	5.62008	5.62008

Summary of Estimated Parameters

Numerical Field Name	Units	Data Field
Dose		20000
Vf		96.1941
Tabs		4.54493
Ke		0.465809