38 Slides Presenting: Getting Started with WinSAAM
What it does and how we prepare Models and Data

Ray Boston and Darko Stefanovski

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Priming Examples Illustrating the Use of WinSAAM
… Learning by Doing …

What to reflect on as we go through these examples:

- The layout of the Problem Specification
- The use of Modeling Constructs … objects defining the model
- The use of Operational Units … objects affecting processing steps
- The specification of Data Uncertainty
- The specification of Categories
- The association of Categories with Components
- The specification of Compartments
- The specification of object Adjustability, Dependency and Invariance
- The Fields associated with object specification

The 3 C's of WinSAAM Category, Component, and Compartment, by Loren Zech

Slides 19,20, and 21, in this module will show you how the linearly adjustable, scale-factor, parameter, K(J), can help you with fitting your data.

Be aware though, of the following two points:
1. There are often units attached to K(J) … e.g. volume of distribution inverse [L^{-1}]. In this case the value of $K(J)^{-1}$ will represent the Volume of Distribution.
2. There are 2 sets of K's within WinSAAM: those linked to Components (K(1) to K(75)), and those as simply, free to use, or non-assigned, linear, fixed, or linearly adjustable parameters (K(77) to K(99)). This set is NOT linked to components.

Our presentation will only discuss the K's linked to Components.
Here K(J) will apply the value of the Jth, K parameter, automatically via multiplication and that value will be applied to the computed values, QC(J), associated with the Category of Component J. J viz: 104 in the presence of an adjustable K(4) will yield the Category values, K(4)*Category(4)

In a nutshell
'101 L(I,J)', as a data specification line in your 'WinSAAM Deck', means that the Category, or calculated values, of L(I,J), are applied to Component '01', or '1', and, L(I,J), as usual, reflects the fractional rates of transfer of items, of interest, from Compartment J to Compartment I

Solving a model for Steady State

… Example 1 Steady state .. No kinetic data

WinSAAM Input

```
A SAAM31    Example 1: Steady state
c
c Simple steady state calculations subject
c to known l(i,j) and an input
c
H PAR
   l(2,1)    .4
   l(1,2)    .1
   l(0,2)    .02
H STE
   u(1)=4/(60*24)
   m(1)
H DAT
110
   m(1)
   m(2)
   r(1,2)
   r(2,1)
   r(0,2)
```

Fields

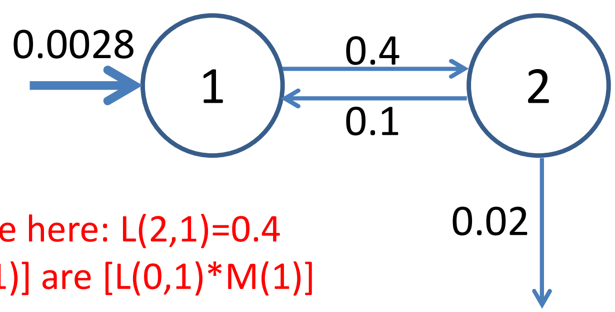
Model Constructs

1000

Component (10)

Categories m(1) etc.

Model Graphic Showing Compartments 1 and 2



Note here: L(2,1)=0.4
[U(1)] are [L(0,1)*M(1)]

Manipulating the model in WinSAAM

> deck .. compile the model
> solv .. solve the model
> m(i) .. display the pool sizes

```
> deck
UPDATE?
* DECK BEING PROCESSED
***ALL WEIGHTS=1.*2*
PRE-PROCESSING TIME :      0.000 SECS
> solv
*** MODEL CODE 10 SOLUTION
***COMPS ISOLATED IN STEADY STATE *8*
***   TC( 0)-  3  4  5  6  7  8  9 10
***NO ADJUSTABLE PARAMETERS**67*
SOLUTION TIME :      0.000 SECS
> m(i)
M( 1)    4.1667E-02
M( 2)    1.3889E-01
> r(i,j)
R(  2, 1)  1.6667E-02   F
R(  1, 2)  1.3889E-02   F
R(  0, 2)  2.7778E-03   F
> u(i)
U( 1)    2.7778E-03
```

Achieving Steady State for Linear Systems: 3 methods

Example 2 Steady state … no kinetic data

WinSAAM input file

```
A SAAM31    Example 2: Steady state
C
C Using an input function to drive
C a system to steady state.  Steady
C state is compared with solution
C values for driven responses
C
H PAR
   l(2,1)   .4
   l(1,2)   .1
   l(0,2)   .02
   uf(1)=4/(60*24)
h ste
   u(1)=uf(1)
   m(1)         // <42 spaces> 10000
H DAT
x g(12)=l(1,2)*f(2)
x g(21)=l(2,1)*f(1)
x g(02)=l(0,2)*f(2)
   u(1)
   m(1)
   m(2)
   r(0,2)
   r(1,2)
   r(2,1)
101
            inf
102 g(12)
            inf
103 g(21)
            inf
104 g(02)
            inf
```

Comments are important

Steady state solution request .. also see uf … what does this tell us about uf, and u? Hint: names

x is needed if a function is time dependent

Note g(12)=R(1,2)
g(12)=l(1,2)*f(2)

inf is entered in the time field of data.
It is the largest value a real number can have, typically 1.0E+35

Manipulating the model in WinSAAM

```
> deck
UPDATE?
* DECK BEING PROCESSED
***ALL WEIGHTS=1.*2*
PRE-PROCESSING TIME :      0.000 SECS
>
** NO LINE NEXT
> solv
*** MODEL CODE 10 SOLUTION
***COMPS ISOLATED IN STEADY STATE *8*
***   TC( 0)-  3  4
***NO ADJUSTABLE PARAMETERS**67*
SOLUTION TIME :      0.000 SECS
> m(i)
M( 1)    4.1667E-02
M( 2)    1.3889E-01
> r(i,j)
R(  1, 2)  1.3889E-02   F
R(  2, 1)  1.6667E-02   F
R(  0, 2)  2.7778E-03   F
> prin qc(1,2,3,4)
*** NAME :    1
#  COMP  TC  CATEGORY       T     M1      QC
  7    1   0  F ( 1)    1.000E+35   4.167E-02
*** NAME :    2
#  COMP  TC  CATEGORY       T     M2      QC
  8    2   0  G (12)    1.000E+35   1.389E-02
*** NAME :    3
#  COMP  TC  CATEGORY       T     R21     QC
  9    3   0  G (21)    1.000E+35   1.667E-02
*** NAME :    4
#  COMP  TC  CATEGORY       T     R02     QC
 10    4   0  G ( 2)    1.000E+35   2.778E-03
```

Fitting Steady State with WinSAAM

Example 3 … Kinetic data .. Draw the model

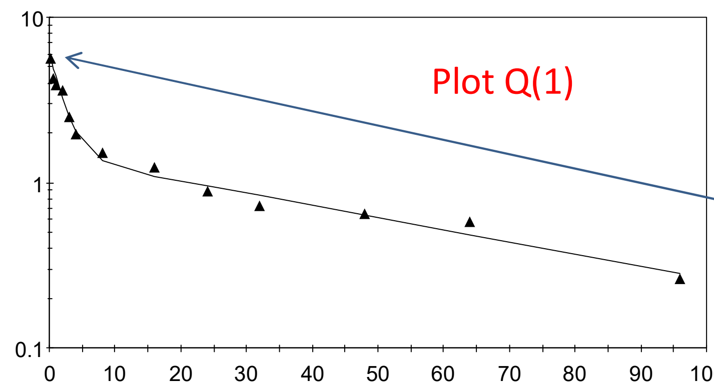
WinSAAM Model

```
A SAAM31     Example 3: Fitting w Steady state
C
C Fitting data based on specific activity values
C Kinetic parameters estimated from dynamic data
C
2       25
H PAR
   l(2,1)   .4                             10
   l(1,2)   .1                             10
   l(0,2)   .02                            10
   ic(1)    100
   p(1)     .92                            10
H STE
   u(1)=p(1)
   m(1)                                    1000
H DAT
110
   g(12)=m(1)+m(2)
   g(12)                   66              5
   r(2,1)                  5.8             .6
   m(1)                    14.2            1
   u(1)                    1               .1
101 SA                                     fsd=.1
            .2             5.67
            .7             4.24
            1              3.89
            2              3.64
            3              2.51
            4              1.98
            8              1.52
            16             1.24
            24             0.89
            32             0.72
            48             0.65
            64             0.58
            96             0.26
```

SA(1)=F(1)/M(1)

SD's

Estimates



Plot Q(1)

SA(1,0)=ic(1)/m(1)=100/15.83

Thus SA(1,0) = 6.32 and

QC(1,0) = 6.32

Kinetics

```
> saam
* DECK BEING PROCESSED
***COMPS ISOLATED IN STEADY STATE *8*
***   TC( 0)-   3   4   5   6   7   8   9  10

CONVERGENCE MEASURES
 IMPROVEMENT IN SUM OF SQUARES =    61.50(%)
 FINAL VALUE OF CONAB =    1.060E+00
 LARGEST CHANGE (    12.49 %) WAS IN PAR( 1, 0)
...
PARAMETER     VALUE       ERROR       FSD
L ( 2, 1)   3.765E-01   3.351E-02   8.899E-02
L ( 1, 2)   1.010E-01   1.116E-02   1.105E-01
L ( 0, 2)   2.169E-02   1.700E-03   7.838E-02
P ( 1, 0)   1.054E+00   3.854E-02   3.658E-02
CORRELATION MATRIX
 COLUMN    1      2      3      4
ROW 1   1.00   0.64   0.04   0.08
ROW 2   0.64   1.00   0.61   0.07
ROW 3   0.04   0.61   1.00   0.53
ROW 4   0.08   0.07   0.53   1.00
> plot q(1)
```

Steady State

```
> m(i) and u(i)
U(1)     1.0540E+00
M(1)     1.5832E+01
M(2)     4.8578E+01
> r(i,j)
R(2,1)    5.9613E+00 A
R(1,2)    4.9077E+00 A
R(0,2)    1.0536E+00 A
```

Fitting Kinetics with 'limited' Steady State Data

Example 4

```
A  SAAM31
2        25
c
c Estimation of pool size and transference of this
c information to enable Specific Activity to be
c calculated
c
H PAR
   L(2,1)     3.221028E-01  0.000000E+00   1.000000E+01
   L(1,2)     9.931703E-02  0.000000E+00   1.000000E+01
   L(0,2)     2.290499E-02  0.000000E+00   1.000000E+01
   ic(1)    100
   P(2)       1.769928E+01  0.000000E+00   1.000000E+02
H STE
   m(1)=p(2)
   U(1)       1.068392E+00                  1000
H DAT
x g(1)=f(1)/p(2)
x g(2)=m(1)+m(2)
110
   g(2)
   r(2,1)
   m(1)
   u(1)
101 g(1)                                    fsd=.1
            .2            5.67
            .7            4.24
            1             3.89
            2             3.64
            3             2.51
            4             1.98
            8             1.52
            16            1.24
            24            0.89
            32            0.72
            48            0.65
            64            0.58
            96            0.26
```

Note that m(1)=p(2)
But we fit g(1)=f(1)/p(2)
to the observations ..
cf sa=f(1)/m(1)

Model Manipulation

```
> saam
* DECK BEING PROCESSED
***TC( 0) DEPENDENCE EQUATIONS DEFINE:
***       M(I),I=  1,
***COMPS ISOLATED IN STEADY STATE *8*
***  TC( 0)-   3   4   5   6   7   8   9 10

CONVERGENCE MEASURES
 IMPROVEMENT IN SUM OF SQUARES =     0.00(%)
 FINAL VALUE OF CONAB =    1.023E+00
 LARGEST CHANGE (     0.14 %) WAS IN PAR( 2, 1)


CONVERGENCE MEASURES
 IMPROVEMENT IN SUM OF SQUARES =     0.05(%)
 FINAL VALUE OF CONAB =    8.203E+00
 LARGEST CHANGE (     0.84 %) WAS IN PAR( 2, 1)


PARAMETER     VALUE      ERROR       FSD
P ( 2, 0)  1.778E+01  1.379E+00  7.753E-02
L ( 2, 1)  3.190E-01  5.257E-02  1.648E-01
L ( 1, 2)  9.914E-02  1.739E-02  1.754E-01
L ( 0, 2)  2.294E-02  2.397E-03  1.045E-01
```

Note m(1)=p(2)

```
> prin qc(10)
-------------------------------------------------
*** NAME :   10
CURRENT KOMN
 #   COMP  TC   CATEGORY        T            QC
  1   10    0   G ( 2)       0.000E+00    6.424E+01
  2   10    0   R ( 2, 1)    0.000E+00    5.672E+00
  3   10    0   M ( 1)       0.000E+00    1.778E+01
  4   10    0   U ( 1)       0.000E+00    1.066E+00
>
```

Comparing Steady State solutions of models 3 and 4

```
PARAMETER      VALUE       ERROR       FSD
L ( 2, 1)  3.765E-01  3.351E-02  8.899E-02
L ( 1, 2)  1.010E-01  1.116E-02  1.105E-01
L ( 0, 2)  2.169E-02  1.700E-03  7.838E-02
P ( 1, 0)  1.054E+00  3.854E-02  3.658E-02

> m(i)
M( 1)    1.5832E+01
M( 2)    4.8578E+01
> prin q(10)
----------------------------------------------------------------------
*** NAME :   10
CURRENT KOMN
 #  COMP  TC  CATEGORY        T          QC          QO        QC/QO
  1  10    0  G (12)      0.000E+00  6.441E+01  0.000E+00       ****
  2  10    0  G (12)      0.000E+00  6.441E+01  6.600E+01     0.9759
  3  10    0  R ( 2, 1)   0.000E+00  5.961E+00  5.800E+00     1.0278
  4  10    0  M ( 1)      0.000E+00  1.583E+01  1.420E+01     1.1149
  5  10    0  U ( 1)      0.000E+00  1.054E+00  1.000E+00     1.0536
```

The numbers from the two sets of calculations are quite close but different, never the less

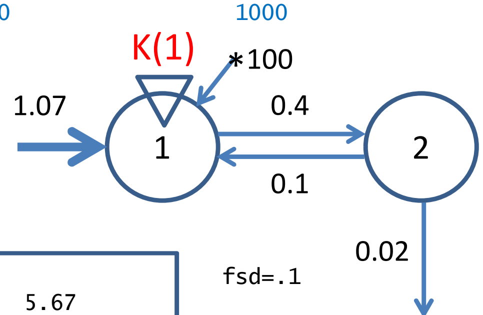
```
PARAMETER      VALUE       ERROR       FSD
P ( 2, 0)  1.778E+01  1.379E+00  7.753E-02
L ( 2, 1)  3.190E-01  5.257E-02  1.648E-01
L ( 1, 2)  9.914E-02  1.739E-02  1.754E-01
L ( 0, 2)  2.294E-02  2.397E-03  1.045E-01

> m(i)
M( 1)    1.7781E+01
M( 2)    4.6458E+01
> prin q(10)
----------------------------------------------------------------------
*** NAME :   10
CURRENT KOMN
 #  COMP  TC  CATEGORY        T          QC          QO        QC/QO
  1  10    0  G ( 2)      0.000E+00  6.424E+01  0.000E+00       ****
  2  10    0  R ( 2, 1)   0.000E+00  5.672E+00  0.000E+00       ****
  3  10    0  M ( 1)      0.000E+00  1.778E+01  0.000E+00       ****
  4  10    0  U ( 1)      0.000E+00  1.066E+00  0.000E+00       ****
```

```
Model 3
> ss(i)
SS( 1)    9.5946E-02
SS(10)    2.0352E-02

Model 4
SS( 1)    6.1212E-02
No Informative Priors
```

Fitting with a Linear Adjustable K

Example 5

```
A SAAM31     Example 5: SS using Linear Adjustables
2        25
c
c No steady state information.  All steady state inferred
c from the tracer results.  The data fitted is the label
c data.
c
H PAR
   L(2,1)     3.221028E-01  0.000000E+00   1.000000E+01
   L(1,2)     9.931703E-02  0.000000E+00   1.000000E+01
   L(0,2)     2.290499E-02  0.000000E+00   1.000000E+01
   IC(1)      100
   K(1)       .1                           1.000000E+02
H STE
   m(1)=1/k(1)
   U(1)       1.068392E+00                 1000
H DAT
x g(2)=m(1)+m(2)
110
   g(2)
   r(2,1)
   r(1,2)
   r(0,2)
   m(1)
   u(1)
101
           .2             5.67
           .7             4.24
           1              3.89
           2              3.64
           3              2.51
           4              1.98
           8              1.52
           16             1.24
           24             0.89
           32             0.72
           48             0.65
           64             0.58
           96             0.26
```



fsd=.1

Steady state solution

```
> saam
* DECK BEING PROCESSED
***TC( 0) DEPENDENCE EQUATIONS DEFINE:
***        M(I),I=  1,
***COMPS ISOLATED IN STEADY STATE *8*
***   TC( 0)-  3  4  5  6  7  8  9 10
***COMPS ISOLATED IN STEADY STATE *8*
***   TC( 0)-  3  4  5  6  7  8  9 10
```

```
prin qc(10)
------------------------------------------------
*** NAME :   10
CURRENT KOMN
 #  COMP TC   CATEGORY       T           QC
 1   10   0   G ( 2)     0.000E+00   6.448E+01
 2   10   0   R ( 2, 1)  0.000E+00   5.685E+00
 3   10   0   R ( 1, 2)  0.000E+00   4.615E+00
 4   10   0   R ( 0, 2)  0.000E+00   1.070E+00
 5   10   0   M ( 1)     0.000E+00   1.789E+01
 6   10   0   U ( 1)     0.000E+00   1.070E+00
```

Data section 101 implies component ‘01’ or ‘1’

PARAMETER	VALUE	ERROR	FSD
L (2, 1)	3.178E-01	5.231E-02	1.646E-01
L (1, 2)	9.908E-02	1.752E-02	1.768E-01
L (0, 2)	2.297E-02	2.395E-03	1.043E-01
K (1, 0)	5.590E-02	4.338E-03	7.760E-02

QC(J,T) = K(J).F(J,T)

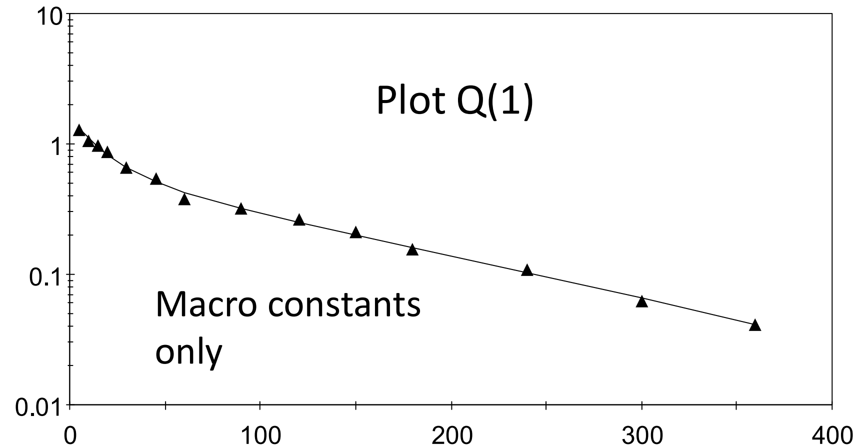
Note that 1/k(1)=17.89 and m(1)=17.89. Thus k(1) does reflect a component involvement with m(1) … what is a component?

Pharmacokinetics Indices fitted with K's and P's

Example 6A PK2 in G&W Edn 1

```
A SAAM31    Ex. 6 Gabrielsson and Wiener Exp Model
2       10
C [GW1:PK2] A bolus of 496 ug of drug
C administered IV to a human volunteer
C Plasma concentrations were measured
C during 6 hours and presented as below
c Given the subject's weight of 80 Kg is
c the data plausible?
C Note the inclusion of uncertainty in the
c subject's weight
c
H PAR
   K(77)     9.532784E-01  0.000000E+00   1.000000E+02
   K(78)     5.488275E-01  0.000000E+00   1.000000E+02
   P(1)      4.809079E-02  0.000000E+00   1.000000E+01
   P(2)      6.754539E-03  0.000000E+00   1.000000E+01
c DIV Set as below in G & W PK2 Edn 1
   P(3)=496
 p(11)=k(77)/p(1)+k(78)/p(2)
 p(12)=p(3)/p(11)
 p(13)=p(3)/(k(77)+k(78))
 p(14)=k(77)/p(1)**2+k(78)/p(2)**2
 p(15)=p(14)/p(11)
 p(16)=p(12)*p(15)
c
 p(17)=(k(77)*p(2)+k(78)*p(1))/(k(77)+k(78))
 p(18)=p(1)*p(2)/p(17)
 p(19)=p(1)+p(2)-p(17)-p(18)
c
c k(77)=A
c k(78)=B
c p(1) =a
c p(2) =b
c
c p(03)=Dose IV [ug]
c p(11)=AUC     [ug.min]
c p(12)=Cl      [L/min]
c p(13)=Vd      [L]
c p(14)=AUMC    [ug.min^2]
c p(15)=MRT     [min]
c p(16)=Vss     [L]
c
c p(17)=l(1,2)  [/min]
c p(18)=l(0,1)  [/min]
c p(19)=l(2,1)  [/min]
c
H DAT
   k(77)
   k(78)
   p(1)
   p(2)
   p(11)
   p(12)
   p(13)
```

```
   p(14)
   p(15)
   p(16)
c
   p(17)
   p(18)
   p(19)
c
x g(1)=k(77)*exp(-p(1)*t) +
       k(78)*exp(-p(2)*t)

101 g(1)                                  fsd=.4
c          [min]          [ug/L]
             5             1.29
            10             1.07
            15             .969
            20             .875
            30             .652
            45             .539
            60             .378
            90             .317
           120             .267
           150             .209
           180             .157
           240             .108
           300             .063
           360             .041
```

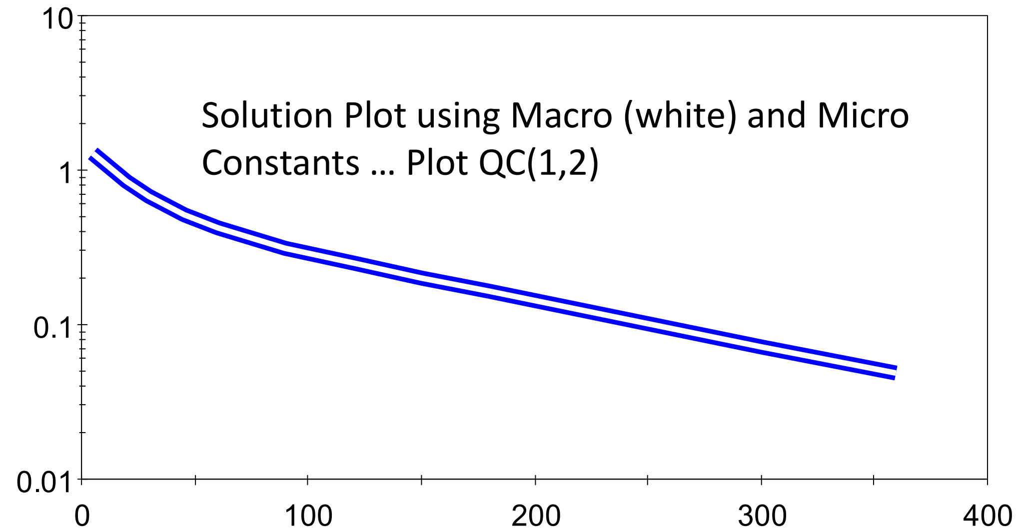


Error propagation from adjustables to dependencies using the Delta Method

-CAT-		Value	FSD
K	77	9.52997E-01	5.210E-02
K	78	5.49029E-01	1.198E-01
P	1	4.80908E-02	1.206E-01
P	2	6.75864E-03	1.261E-01
P	11	1.01050E+02	3.884E-02
P	12	4.90845E+00	3.903E-02
P	13	3.30221E+02	2.021E-02
P	14	1.24313E+04	1.413E-01
P	15	1.23021E+02	1.036E-01
P	16	6.03842E+02	6.649E-02
P	17	2.18666E-02	1.864E-01
P	18	1.48642E-02	4.613E-02
P	19	1.81187E-02	1.249E-01

```
A SAAM31    Ex. 6 Gabrielsson and Wiener Exp Model
2       10
C [GW1:PK2] A bolus of 50 ug of drug
C administered IV to a human volunteer
C Plasma concentrations were measured
C during 6 hours and presented as below
C Given the subject's weight of 80 Kg is
c the data plausible?
C Note the inclusion of uncertainty in the
c subject's weight
c
H PAR
   K(77)     9.532784E-01  0.000000E+00   1.000000E+02
   K(78)     5.488275E-01  0.000000E+00   1.000000E+02
   P(1)      4.809079E-02  0.000000E+00   1.000000E+01
   P(2)      6.754539E-03  0.000000E+00   1.000000E+01
c DIV Set as below in G & W PK2 Edn 1
   P(3)=496
 p(11)=k(77)/p(1)+k(78)/p(2)
 p(12)=p(3)/p(11)
 p(13)=p(3)/(k(77)+k(78))
 p(14)=k(77)/p(1)**2+k(78)/p(2)**2
 p(15)=p(14)/p(11)
 p(16)=p(12)*p(15)
c
 p(17)=(k(77)*p(2)+k(78)*p(1))/(k(77)+k(78))
 p(18)=p(1)*p(2)/p(17)
 p(19)=p(1)+p(2)-p(17)-p(18)
c
c k(77)=A
c k(78)=B
c p(1) =a
c p(2) =b
c
c p(03)=Dose IV [ug]
c p(11)=AUC     [ug.min]
c p(12)=Cl      [L/min]
c p(13)=Vd      [L]
c p(14)=AUMC    [ug.min^2]
c p(15)=MRT     [min]
c p(16)=Vss     [L]
c
```

```
c p(17)=l(1,2)  [/min]
c p(18)=l(0,1)  [/min]
c p(19)=l(2,1)  [/min]
c
   ic(1)=K(77)+k(78)
   l(1,2)=p(17)
   l(0,1)=p(18)
   l(2,1)=p(19)
H DAT
   k(77)
   k(78)
   p(1)
   p(2)
   p(11)
   p(12)
   p(13)
   p(14)
   p(15)
   p(16)
c
   p(17)
   p(18)
   p(19)
```




```
c
x g(1)=k(77)*exp(-p(1)*t) +
      k(78)*exp(-p(2)*t)
102 g(1)                              sd=.04
c          [min]        [ug/L]
            5            1.29
            10           1.07
            15           .969
            20           .875
            30           .652
            45           .539
            60           .378
            90           .317
            120          .267
            150          .209
            180          .157
            240          .108
            300          .063
            360          .041
```

```
101
            5            1.29
            10           1.07
            15           .969
            20           .875
            30           .652
            45           .539
            60           .378
            90           .317
            120          .267
            150          .209
            180          .157
            240          .108
            300          .063
            360          .041
```

Some Important Macro Model Relationships: G/W 1st Edn 1994

- C_p = Plasma Concentration by Time .. g(1)
- CL = Clearance .. P(12)
- V_C = Volume of the Central Pool .. P(13)
- AUC = Area Under C_P .. P(11)
- AUMC = Area Under First Moment .. P(14)
- MRT = Mean Residence Time .. P(15)
- V_{SS} = Steady State Volume of Distribution .. P(16)

- D_{IV} = IV Dose .. P(3)
- α = Fast Slope … a .. P(1)
- β = Second Phase .. b .. P(2)
- A = Coefficient of Fast Slope .. K(77)
- B = Coefficient of Second Phase .. K(78)

$$C_p = A.e^{-\alpha.t} + B.e^{-\beta t}$$

$$CL = D_{IV} / (A/\alpha + B/\beta)$$

$$V_C = D_{IV} / (A + B)$$

$$AUC = A/\alpha + B/\beta$$

$$AUMC = A/\alpha^2 + B/\beta^2$$

$$MRT = AUMC/AUC$$

$$V_{SS} = MRT.CL$$

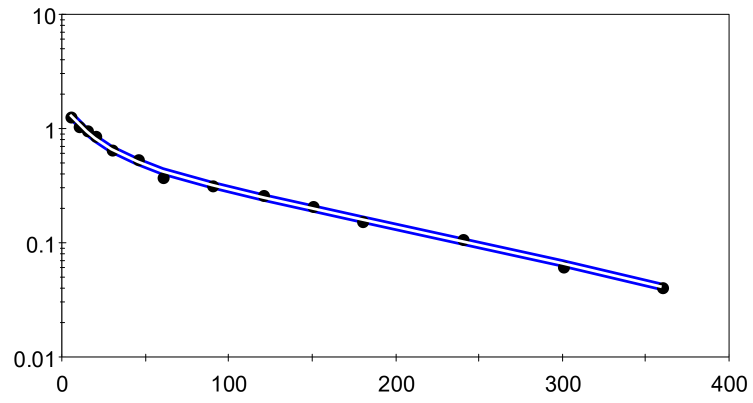
Check of a model using Macro and Micro Constants

Example 7 .. slightly abridged .. this model is the reverse of 6

```
A SAAM31     Ex 7: G & W LCM
2        10
C See example 6
H PAR
   l(2,1)    .1                              10
   l(1,2)    .02                             10
   l(0,1)    .01                             10
 ic(1)=p(1)
   p(1)      50                              100
   k(1)      .1                              100
 p(3)=1/k(1)
 p(2)=l(2,1)*p(3)/l(1,2)
 p(4)=l(2,1)*p(3)
 p(5)=l(1,2)*p(2)
 p(6)=l(0,1)*p(3)
 p(7)=p(2)+p(3)
 p(8)=p(3)*(1+l(2,1)/l(1,2))
c
 p(9)=l(2,1)+l(1,2)+l(0,1)
 p(10)=(p(9)-sqrt(p(9)**2-4*l(1,2)*l(0,1)))/2
 p(11)=l(1,2)*l(0,1)/p(10)
 p(12)=p(1)*(p(11)-l(1,2))/(p(11)-p(10))/p(3)
 p(13)=p(1)*(p(10)-l(1,2))/(p(10)-p(11))/p(3)
c
c p1 = IV Dose 50 [mg]
c p2 = Vt          [dl]
c p3 = Vc          [dl]
c p4 = Clc         [dl/min]
c p5 = Clt         [dl/min]
c p6 = Cl          [dl/min]
c p7 = VT          [dl]
c p8 = Vss         [dl]
c p9 = Sum{Lij}    [/min]
c p10= b           [/min]
c p11= a           [/min]
c p12= A           [mg/dl]
c p13= B           [mg/dl]
c
H DAT
   l(0,1)
   l(1,2)
   l(2,1)
```

Here we plot f1 and g11 to see if the micro and macro constant models agree

plot q(1,11)




```
c
   p(1)
...
   p(13)
c
   p(1)                     51              10
x g(2)=f(2)/p(3)
x g(11)=p(12)*exp(-p(11)*t)+p(13)*exp(-p(10)*t)
101 f(1)                                    fsd=.1
c         Time [min]     Conc. [mg/dl]
            5               1.29
... data from example 6
            360             .041
111 g(11)                                   fsd=.1
c         Time [min]     Conc. [mg/dl]
            5               1.29
... data from example 6
            360             .041
```

Note:
q(1)=k(1)*f(1) and
q(11)=g(11)

```
A SAAM31  Ex: 9 Bayesian estimation
2       25
C
C 4 g/d of Ca are fed to a dog where a prior
C kinetic experiment had exposed the Ca kinetics
C Calculate the pool sizes and fluxes under
C these conditions
C
H PAR
   L(2,1)   .4           1.333333E-01   1.200000E+00
   L(1,2)   .1           3.333334E-02   3.000000E-01
   L(0,2)   .02          6.666666E-03   6.000000E-02
H STE
   u(1)=4/(24*60)
   m(1)                              1000
H DAT
110
   m(1)                  .04            .01
   m(2)                  .13            .02
   u(1)                  .003           .001
   r(1,2)                .014           .003
   r(2,1)                .018           .003
   r(0,2)                .0025          .001
```

Kinetic parameters resolved from Bayesian information applied to Steady state parameters Example 9

Model manipulation

```
> saam
* DECK BEING PROCESSED
***COMPS ISOLATED IN STEADY STATE *8*
***   TC( 0)-   3   4   5   6   7   8   9 10

CONVERGENCE MEASURES
 IMPROVEMENT IN SUM OF SQUARES =    61.84(%)
 FINAL VALUE OF CONAB =    1.185E+00
 LARGEST CHANGE (    11.15 %) WAS IN PAR( 1, 2)
...
PARAMETER     VALUE       ERROR       FSD
L ( 2, 1)  4.340E-01  3.216E-02  7.409E-02
L ( 1, 2)  1.125E-01  6.296E-03  5.594E-02
L ( 0, 2)  2.139E-02  8.794E-04  4.112E-02
```

Priors for m(1), m(2), and u(1), etc

m(1) = *N*(0.04, 0.01)

m(2) = *N*(0.13, 0.02)

u(1) = *N*(0.003, 0.001) … etc for r(i,j)

N(a,b) => Normal (Mean(a), SD(b))

Without data how can we estimate the L(I,J) and their uncertainties

Fitting parameters without kinetic data … is there anything we can't do with WinSAAM?

Bayesian weighting of steady state observations
Considering prior information .. what is the relationship between E{m(1)}, and SD {m(1)} for weighting effects?

m(1)	.04	.01
m(2)	.13	.02
u(1)	.003	.001
r(1,2)	.014	.003
r(2,1)	.018	.003
r(0,2)	.0025	.001

It used to be believed that an identifiable status based on kinetic data was a requirement. Bayesian weighting debunks this

```
> saam
* DECK BEING PROCESSED
***COMPS ISOLATED IN STEADY STATE *8*
***  TC( 0)-  3  4  5  6  7  8  9 10

CONVERGENCE MEASURES
 IMPROVEMENT IN SUM OF SQUARES =   61.84(%)
 FINAL VALUE OF CONAB =   1.185E+00
 LARGEST CHANGE (   11.15 %) WAS IN PAR( 1, 2)
...
PARAMETER    VALUE      ERROR      FSD
L ( 2, 1)  4.340E-01  3.216E-02  7.409E-02
L ( 1, 2)  1.125E-01  6.296E-03  5.594E-02
L ( 0, 2)  2.139E-02  8.794E-04  4.112E-02
```

Reading Bayesian Statistics

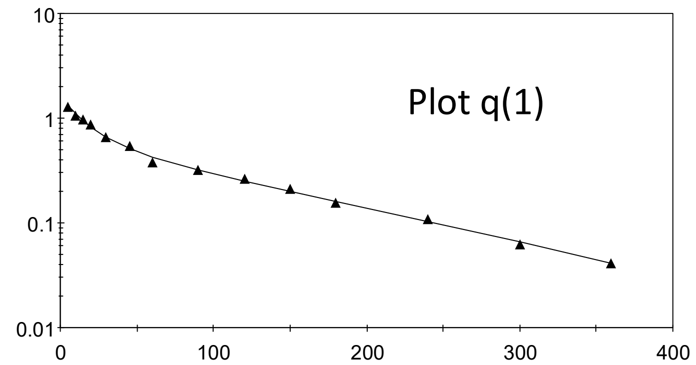
Priors for m(1), m(2), and u(1), etc
m(1) = *N*(0.04, 0.01)
m(2) = *N*(0.13, 0.02)
u(1) = *N*(0.003, 0.001) … etc for r(i,j)
N(a,b) => Normal (Mean(a), SD(b))

Priors, as expressed via Bayesian statistics, puts to work the concept that ..
There is nothing we know nothing about ….

Numerical integration of functions of the response of a linear compartmental system

Example 10

```
A SAAM31  Ex. 7: G & W LCM
2       10
C A bolus of 496 mg of drug
C administered IV to a human volunteer
C Plasma concentrations were measured
C during 6 hours and presented as below
H PAR
   l(2,1)   .1                       10
   l(1,2)   .02                      10
   l(0,1)   .01                      10
   ic(1)=496
   k(1)     .1                       100
 p(1)=1/k(1)
 p(2)=p(1)*l(0,1)
H DAT
x uf(11)=f(1)*k(1)
x uf(12)=t*f(1)*k(1)
x g(11)=f(12)/f(11)
x g(12)=ic(1)/f(11)
102 f(11)
            360
102 f(12)
            360
102 g(11)
            360
102 g(12)
            360
102
    p(1)
101 f(1)                             fsd=.1
C         Time [min]     Conc. [mg/dl]
            5              1.29
            10             1.07
            15             .969
            20             .875
            30             .652
            45             .539
            60             .378
            90             .317
            120            .267
            150            .209
            180            .157
            240            .108
            300            .063
            360            .041
```

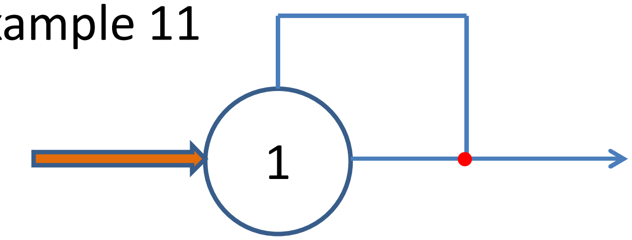



```
> iter
* PARTIALS ESTIMATED
* CORRECTION VECTOR ESTIMATED

CONVERGENCE MEASURES
 IMPROVEMENT IN SUM OF SQUARES =   98.90(%)
 FINAL VALUE OF CONAB =   3.824E-01
 LARGEST CHANGE (  727.76 %) WAS IN PAR( 2, 1)
```

Index				Estimate	FSD	
AUC	F	11	T	9.31334E+01	4.725E-02	[mg/dl.min]
AUMC	F	12	T	8.52720E+03	5.330E-02	[mg/dl.min^2]
MRT	G	11		9.15590E+01	1.123E-02	[min]
CL	G	12		5.32569E+00	4.729E-02	[dl/min]

Nonlinear Steady State: Example 11

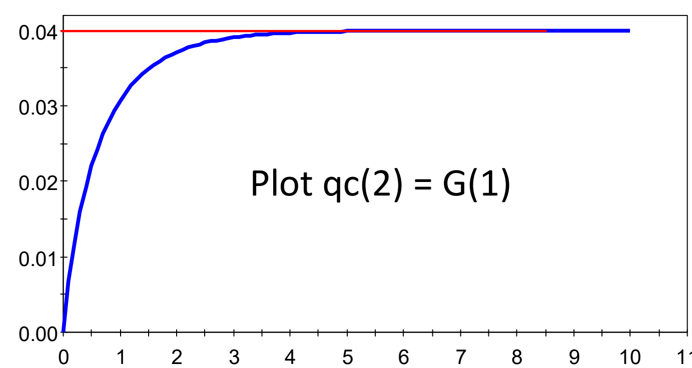
```
A SAAM31
H PAR
C
C Here we demonstrate nonlinear steady solutions
C We consider the Wagner Alcohol Model
C M(1) =4 [gm/L] from nonlinear steady state solver
C F(1) =4 [gm/L] by driving the system to steady state
C P(10)=4 [gm/L] by manually solving F`=-G1.F+UF1 = 0
C
C Vmax = 18 mg/dL/hr = 0.18 gm/L/h
C Km   =  5 mg/dl    = 0.05 gm/L
C P(1) = Vmax
C P(2) = Km
C P(3) = Alcohol input rate         [gm/hr]
C P(4) = Alcohol distribution space [L]
C P(5) = Alcohol absorption = 1
C
C [UF1] = [gm/L/hr]
C [F1]  = [gm/L]
C [G1]  = [/hr]
C
 P(1)=0.18
 P(2)=0.05
 P(3)=4
 P(4)=50
 P(5)=1
 p(10)=P(3)*P(2)/(P(1)*P(4)-P(3))
 L(0,1)     1                                        *G 1
H STE
 U(1)=UF(1)
   M(1)                             10000
H DAT
X G(1)=P(1)/(P(2)+F(1))
X UF(1)=P(3)/P(4)
C Note UF(1) describes the input rate of
C alcohol into compartment 1
H DAT
101
            0
2           .1                      100
102 G(1)
            0
2           .1                      100
```



f1` = uf1 – g1.f1 (=Vmax.f1/(Km+f1)

```
> saam
* DECK BEING PROCESSED
***ALL WEIGHTS=1.*2*
***COMPS ISOLATED IN STEADY STATE *8*
***  TC( 0)-  2
***COMPS ISOLATED IN STEADY STATE *8*
***  TC( 0)-  2
*** STEADY STATE CONVERGED IN  1 ITERATIONS.*50*
***NO ADJUSTABLE PARAMETERS**67*
```

```
> m(i)
M( 1)    3.9981E-02
> p(10)
  *   4.0000E-02  D
>
```



The 3 C's of WinSAAM **Category, Component, and Compartment**, by Loren Zech

The next three slides will hopefully show you how the **linearly adjustable, scale-factor, parameter, K(J)**, can assist with fitting your data.

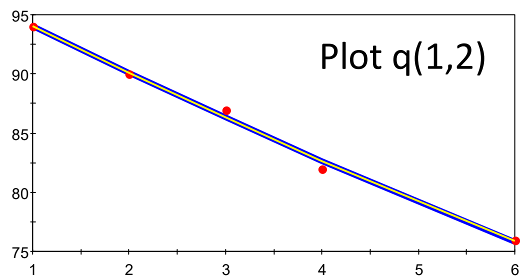
Be aware though of the following two points:
1. There are often **units** attached to K(J) … e.g. volume of distribution inverse [$Liter^{-1}$]. In this case the value of $K(J)^{-1}$ may provide a good estimate of the Volume of Distribution.
2. There are 2 sets of K's within WinSAAM: those linked to **Components** (K(1) to K(75)), and those as simply free for you to use as **non pre-assigned**, linear, fixed, or linearly adjustable parameters (K(77) to K(99)). This set is NOT linked to components.

Our presentation will only discuss the K's linked to Components.
Here K(J) will apply the value of the Jth, K parameter, **automatically** via multiplication and that value will be applied to the computed values, QC(J), associated with the Category of Component J. J viz: 104 in the presence of an adjustable K(4) will yield the Category values, K(4)*Category(4)

In a nutshell
'101 L(I,J)', as a data **specification** line in your 'WinSAAM Deck', means that the **Category**, or calculated values, of L(I,J), are applied to **Component** '01', or '1', and, L(I,J), as usual, reflects the fractional rates of transfer of items, of interest, from Compartment J to Compartment I

Components, K and Units Example 12

```
A SAAM31
H PAR
   ic(1)     100
   l(0,1)    0.1                          100
   k(1)      1                            100
C
   p(1)      1                            100
H DAT
x g(1)=p(1)*f(1)
101                                       fsd=.2
             1             94
             2             90
             3             87
             4             82
             6             76
102 g(1)                                  fsd=.2
             1             94
             2             90
             3             87
             4             82
             6             76
```




```
 1 > deck
 2 > k(i)
 3   K(  1, 0)  1.0000E+00 A
 4 > solv
 5   K(  1, 0)  1.1620E+00 A
 6 > iter
...
    CONVERGENCE MEASURES
 7  IMPROVEMENT IN SUM OF SQUARES =    99.59(%)
    FINAL VALUE OF CONAB =    8.863E-01
    LARGEST CHANGE (  116.07 %) WAS IN PAR( 0, 1)
…
 8 > k(i)
 9   K(  1, 0)  9.8225E-01 A
10 > iter
…
11 > fsd(i)
12 * VALUES MAY NOT RELATE TO CURRENT PARAMETERS
13 * P ( 1)       9.821E-01     FSD( 1)   4.314E-03
14 * L ( 0, 1)    4.308E-02     FSD( 2)   2.495E-02
15 * K ( 1)       9.821E-01     FSD( 3)   3.475E-01
```

Note the following here:

1. K1 has the initial value of 1
2. K1 changes to 1.162 during the solve
3. K1 is never referred to mathematically in the WinSAAM model
4. P1 reaches an identical value to K1
5. P1 is an f1 scale factor
6. The solutions are identical despite no K1 reference Plot
7. No category is specified in the ‘101’ line implying a K(1)

Components, K and Units .. 2 .. Example 13

```
A SAAM31
H PAR
   ic(1)     100
   l(0,1)    0.1                         100
   k(2)      1                           100
C
   p(1)      1                           100
H DAT
x g(1)=p(1)*f(1)
101 g(1)                                 fsd=.2
             1             94
             2             90
             3             87
             4             82
             6             76
102 f(1)                                 fsd=.2
             1             94
             2             90
             3             87
             4             82
             6             76
```

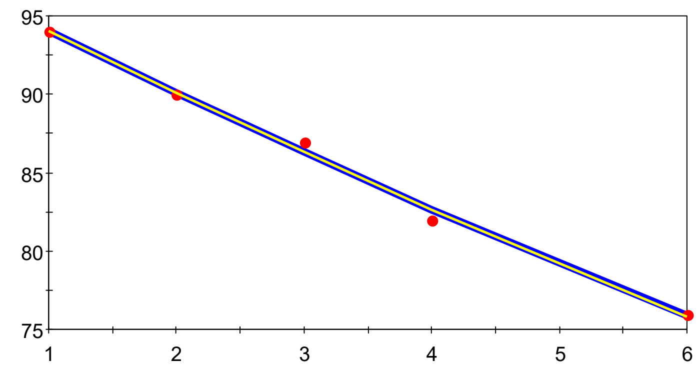
Notice the subtle changes to our model.
Will this model produce identical results to our last model?
We are testing the following principles

1. K's are connected to **components** not categories
2. Categories can be **arbitrarily** assigned to components
3. Compartments have only **passing** connection with components. They **may** not need not be identified if the compartment and component indexes are the same

Note that we converged to identical estimates of the three adjustable params

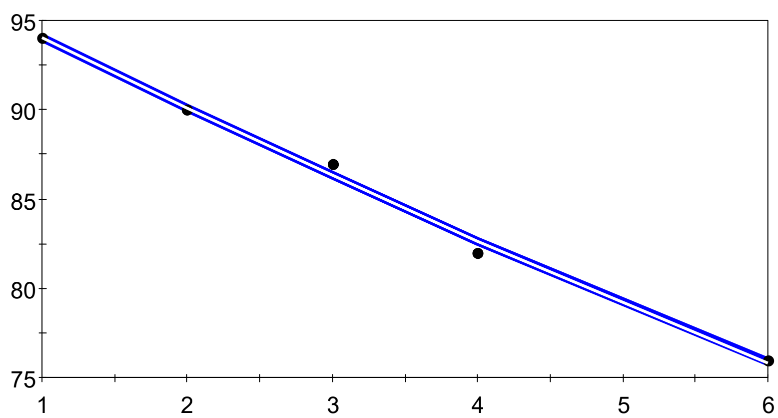
```
> deck
> solv
> iter
 CONVERGENCE MEASURES
 IMPROVEMENT IN SUM OF SQUARES =   99.59(%)
...
fsd(i)
* VALUES MAY NOT RELATE TO CURRENT PARAMETERS
* P ( 1)      9.821E-01     FSD( 1)   4.314E-03
* L ( 0, 1)   4.307E-02     FSD( 2)   2.495E-02
* K ( 2)      9.821E-01     FSD( 3)   2.252E+00
```

Again identical fits, and also identical to our last demonstration



Components, K and Units .. 3 Example 14

```
A SAAM31
H PAR
   ic(1)    100
   l(0,1)   0.1                          100
   k(2)     1                            100
C
   p(1)     1                            100
H DAT
X g(1)=f(1)
X g(2)=p(1)*f(1)
101 g(2)                                 fsd=.2
            1             94
            2             90
            3             87
            4             82
            6             76
102 g(1)                                 fsd=.2
            1             94
            2             90
            3             87
            4             82
            6             76
```



K(J) belongs to Component J

```
> deck
> k(2)
  *  1.0000E+00 A
> solv
> k(2)
  *  1.1620E+00 A
> iter
* PARTIALS ESTIMATED
* CORRECTION VECTOR ESTIMATED

CONVERGENCE MEASURES
 IMPROVEMENT IN SUM OF SQUARES =   99.59(%)
 FINAL VALUE OF CONAB =   8.864E-01
 LARGEST CHANGE (  116.09 %) WAS IN PAR( 0, 1)

> k(i)
K(  2, 0)  9.8207E-01 A


> saam
…
PARAMETER    VALUE      ERROR       FSD
P ( 1, 0)  9.821E-01  4.237E-03  4.314E-03
L ( 0, 1)  4.307E-02  1.075E-03  2.495E-02
K ( 2, 0)  9.821E-01  4.240E-03  4.318E-03
CORRELATION MATRIX
 COLUMN   1     2     3
ROW 1  1.00  0.80  0.63
ROW 2  0.80  1.00  0.80
ROW 3  0.63  0.80  1.00
```

Results are identical as when K(j) was connected to F(j) .. ie it the category is not the determinant

Fitting a kinetic model using both Kinetic and Steady State data

Example 15 see also 3

```
A SAAM31    Example 3: Fitting w Steady state
c
c Fitting data based on specific activity values
c Kinetic parameters estimated from dynamic data
c
2       25
H PAR
   l(2,1)    .4                          10
   l(1,2)    .1                          10
   l(0,2)    .02                         10
   ic(1)     100
   p(1)      .92                         10
H STE
   u(1)=p(1)
   m(1)                                  1000
H DAT
x g(1)=f(1)/m(1)
110
   g(12)=m(1)+m(2)
   g(12)               66                5
   r(2,1)              5.8               .6
   m(1)                14.2              1
   u(1)                1                 .1
101 sa                                   fsd=.1
             .2        5.67
             .7        4.24
             1         3.89
             2         3.64
             3         2.51
             4         1.98
             8         1.52
             16        1.24
             24        0.89
             32        0.72
             48        0.65
             64        0.58
             96        0.26
103 g(1)
             .2
             .7
```

Why is R(0,2)=P(1)?

```
> prin q(1,3)
*** NAME :     1
CURRENT KOMN
  #  COMP  TC  CATEGORY       T          QC          QO         QC/QO
  6    1    0  SA         2.000E-01  5.863E+00  5.670E+00     1.0340
  8    1    0  SA         7.000E-01  4.901E+00  4.240E+00     1.1559
 10    1    0  SA         1.000E+00  4.425E+00  3.890E+00     1.1375
 12    1    0  SA         2.000E+00  3.248E+00  3.640E+00     0.8923
 14    1    0  SA         3.000E+00  2.513E+00  2.510E+00     1.0011
 16    1    0  SA         4.000E+00  2.050E+00  1.980E+00     1.0356
 18    1    0  SA         8.000E+00  1.356E+00  1.520E+00     0.8924
 20    1    0  SA         1.600E+01  1.096E+00  1.240E+00     0.8839
 22    1    0  SA         2.400E+01  9.555E-01  8.900E-01     1.0736
 24    1    0  SA         3.200E+01  8.343E-01  7.200E-01     1.1587
 26    1    0  SA         4.800E+01  6.357E-01  6.500E-01     0.9779
 28    1    0  SA         6.400E+01  4.843E-01  5.800E-01     0.8351
 30    1    0  SA         9.600E+01  2.812E-01  2.600E-01     1.0814
*** NAME :     3
CURRENT KOMN
  #  COMP  TC  CATEGORY       T          QC          QO         QC/QO
  7    3    0  G ( 1)     2.000E-01  5.863E+00  0.000E+00       ****
  9    3    0  G ( 1)     7.000E-01  4.901E+00  0.000E+00       ****
 11    3    0  G ( 1)     1.000E+00  4.425E+00  0.000E+00       ****
 13    3    0  G ( 1)     2.000E+00  3.248E+00  0.000E+00       ****
 15    3    0  G ( 1)     3.000E+00  2.513E+00  0.000E+00       ****
 17    3    0  G ( 1)     4.000E+00  2.050E+00  0.000E+00       ****
 19    3    0  G ( 1)     8.000E+00  1.356E+00  0.000E+00       ****
 21    3    0  G ( 1)     1.600E+01  1.096E+00  0.000E+00       ****
 23    3    0  G ( 1)     2.400E+01  9.555E-01  0.000E+00       ****
 25    3    0  G ( 1)     3.200E+01  8.343E-01  0.000E+00       ****
 27    3    0  G ( 1)     4.800E+01  6.357E-01  0.000E+00       ****
 29    3    0  G ( 1)     6.400E+01  4.843E-01  0.000E+00       ****
 31    3    0  G ( 1)     9.600E+01  2.812E-01  0.000E+00       ****
```

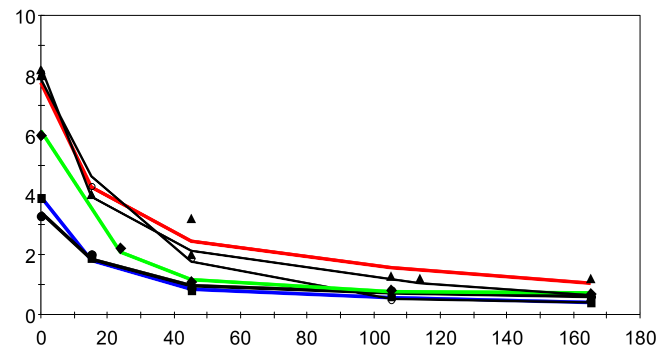
Kinetics

PARAMETER	VALUE	ERROR	FSD
L (2, 1)	3.765E-01	3.351E-02	8.899E-02
L (1, 2)	1.010E-01	1.116E-02	1.105E-01
L (0, 2)	2.169E-02	1.700E-03	7.838E-02
P (1, 0)	1.054E+00	3.854E-02	3.658E-02

Steady state

```
> m(i)
M( 1)      1.5832E+01
M( 2)      4.8578E+01
> r(i,j)
R(  2, 1)   5.9613E+00 A
R(  1, 2)   4.9077E+00 A
R(  0, 2)   1.0536E+00 A
```

Example 17
Simultaneously fitting the lactate disposition of 6 horses using macro models.
We see the plots breaking into 3 dose groups .. Red cluster, Blue cluster, and Green cluster




```
A SAAM31                                   Example 17
2      10
C Insert Control lines 2,3,4 here as needed
H PAR
   P(1)      4.590284E+00  0.000000E+00   1.000000E+02
   P(2)      7.820775E-02  0.000000E+00   1.000000E+01
   P(3)      3.154558E+00  0.000000E+00   1.000000E+02
   P(4)      6.719415E-03  0.000000E+00   1.000000E+02
C
   P(5)      3.012392E+00  0.000000E+00   1.000000E+02
   P(6)      7.651587E-02  0.000000E+00   1.000000E+01
   P(7)      9.349019E-01  0.000000E+00   1.000000E+02
   P(8)      4.992981E-03  0.000000E+00   1.000000E+02
C
   P(9)      7.426307E+00  0.000000E+00   1.000000E+02
   P(10)     3.819059E-02  0.000000E+00   1.000000E+01
   P(11)     4.385362E-01  0.000000E+00   1.000000E+02
   P(12)     9.999998E-04  9.999998E-04   1.000000E+02
C
   P(13)     2.491849E+00  0.000000E+00   1.000000E+02
   P(14)     6.362862E-02  0.000000E+00   1.000000E+01
   P(15)     9.206057E-01  0.000000E+00   1.000000E+02
   P(16)     2.388272E-03  0.000000E+00   1.000000E+02
C
   P(17)     5.295347E+00  0.000000E+00   1.000000E+02
   P(18)     5.951259E-02  0.000000E+00   1.000000E+01
   P(19)     8.342069E-01  0.000000E+00   1.000000E+02
   P(20)     9.850096E-04  9.999998E-05   1.000000E+02
C
   P(21)     5.088596E+00  0.000000E+00   1.000000E+02
   P(22)     9.785010E-02  0.000000E+00   1.000000E+01
   P(23)     3.182503E+00  0.000000E+00   1.000000E+02
   P(24)     9.725116E-03  0.000000E+00   1.000000E+02
C
H DAT
x g(1)=p(1)*exp(-p(2)*t)+p(3)*exp(-p(4)*t)
x g(2)=p(5)*exp(-p(6)*t)+p(7)*exp(-p(8)*t)
x g(3)=p(9)*exp(-p(10)*t)+p(11)*exp(-p(12)*t)
x g(4)=p(13)*exp(-p(14)*t)+p(15)*exp(-p(16)*t)
x g(5)=p(17)*exp(-p(18)*t)+p(19)*exp(-p(20)*t)
x g(6)=p(21)*exp(-p(22)*t)+p(23)*exp(-p(24)*t)
```

```
101 g(1)                              fsd=.1
            0            8
            15           4
            45           3.2
            105          1.3
            165          1.2
102 g(2)                              fsd=.1
            0            3.9
            15           1.9
            45           .8
            105          .6
            165          .4
103 g(3)                              fsd=.1
            0            8.1
            15           4.3
            45           1.9
            105          .5
            165          .4
104 g(4)                              fsd=.1
            0            3.3
            15           2
            45           .9
            105          .8
            165          .6
105 g(5)                              fsd=.1
            0            6
            24           2.2
            45           1.1
            105          .8
            165          .7
106 g(6)                              fsd=.1
            0            8.2
            15           4
            45           2
            114          1.2
            165          .608696
```

The final estimates of the **macro** rate parameters and their **errors** in the table to the left. Each block of 4 parameters represents the fitted disposition coefficients for the specific horses.

Below are the 6 models, and, below that, the pattern of correlation between the sets of 6 parameters

PARAMETER	VALUE	ERROR	FSD
P (2, 0)	7.821E-02	3.060E-02	3.913E-01
P (1, 0)	4.590E+00	1.029E+00	2.242E-01
P (4, 0)	6.719E-03	1.881E-03	2.800E-01
P (3, 0)	3.155E+00	7.322E-01	2.321E-01
P (6, 0)	7.652E-02	1.980E-02	2.587E-01
P (5, 0)	3.012E+00	4.042E-01	1.342E-01
P (8, 0)	4.993E-03	1.720E-03	3.446E-01
P (7, 0)	9.349E-01	2.144E-01	2.293E-01
P (10, 0)	3.819E-02	6.323E-03	1.656E-01
P (9, 0)	7.426E+00	6.484E-01	8.731E-02
P (12, 0)	1.000E-03	4.829E-03	4.829E+00
P (11, 0)	4.385E-01	3.435E-01	7.832E-01
P (14, 0)	6.363E-02	2.055E-02	3.229E-01
P (13, 0)	2.492E+00	3.687E-01	1.480E-01
P (16, 0)	2.388E-03	1.996E-03	8.358E-01
P (15, 0)	9.206E-01	2.553E-01	2.773E-01
P (18, 0)	5.951E-02	1.050E-02	1.765E-01
P (17, 0)	5.295E+00	6.196E-01	1.170E-01
P (20, 0)	9.850E-04	2.346E-03	2.382E+00
P (19, 0)	8.342E-01	2.763E-01	3.312E-01
P (22, 0)	9.785E-02	3.432E-02	3.507E-01
P (21, 0)	5.089E+00	9.526E-01	1.872E-01
P (24, 0)	9.725E-03	1.376E-03	1.415E-01
P (23, 0)	3.183E+00	5.591E-01	1.757E-01

```
H DAT
x g(1)=p(1)*exp(-p(2)*t)+p(3)*exp(-p(4)*t)
x g(2)=p(5)*exp(-p(6)*t)+p(7)*exp(-p(8)*t)
x g(3)=p(9)*exp(-p(10)*t)+p(11)*exp(-p(12)*t)
x g(4)=p(13)*exp(-p(14)*t)+p(15)*exp(-p(16)*t)
x g(5)=p(17)*exp(-p(18)*t)+p(19)*exp(-p(20)*t)
x g(6)=p(21)*exp(-p(22)*t)+p(23)*exp(-p(24)*t)
```

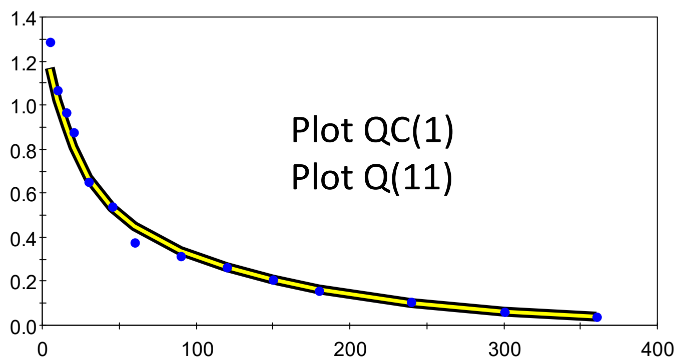
CORRELATION MATRIX

COLUMN	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
ROW 1	1.00	-0.19	0.68	0.73	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ROW 2	-0.19	1.00	-0.62	-0.64	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ROW 3	0.68	-0.62	1.00	0.96	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ROW 4	0.73	-0.64	0.96	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ROW 5	0.00	0.00	0.00	0.00	1.00	0.05	0.70	0.76	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ROW 6	0.00	0.00	0.00	0.00	0.05	1.00	-0.35	-0.35	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ROW 7	0.00	0.00	0.00	0.00	0.70	-0.35	1.00	0.96	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ROW 8	0.00	0.00	0.00	0.00	0.76	-0.35	0.96	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ROW 9	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.26	0.81	0.85	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ROW10	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.26	1.00	-0.13	-0.10	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ROW11	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.81	-0.13	1.00	0.99	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ROW12	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.85	-0.10	0.99	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ROW13	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	-0.18	0.77	0.82	0.00	0.00	0.00
ROW14	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-0.18	1.00	-0.50	-0.51	0.00	0.00	0.00
ROW15	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.77	-0.50	1.00	0.97	0.00	0.00	0.00
ROW16	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.82	-0.51	0.97	1.00	0.00	0.00	0.00
ROW17	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.05	0.77
ROW18	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.05	1.00	-0.32
ROW19	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.77	-0.32	1.00
ROW20	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.81	-0.33	0.98
ROW21	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ROW22	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ROW23	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ROW24	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Example 18 Macro and Micro Rate Constants. Dependencies from Text in the Spreadsheet: Data and Param

```
a_[/min]        P(11)          D            0.0534422
A_[mg/dl]       P(12)          D            0.675143
b_[/min]        P(10)          D            0.00786248
Cl_[dl/min]     P(6)           D            0.513533
Clc_[dl/min]    P(4)           D            0.634758
IV_Dose50_[mg]  P(1)           A            50.541
Sum{Lij}_[/min]P(9)            D            0.0613047
Vc_[dl]         P(3)           D            37.4482
Vss_[dl]        P(8)           D            58.164
Vt_[dl]         P(2)           D            20.7158
VT_[dl]         P(7)           D            58.164
B_[mg/dl]       P(13)          D            0.674483
```

```
A SAAM31    Ex 7: G & W LCM
2       10
C See example 6
H PAR
c
c# IV_Dose50_[mg]=p(1)
c# Vt_[dl]=p(2)
c# Vc_[dl]=p(3)
c# Clc_[dl/min]=p(4)
c# Clt_[dl/min]=p(5)
c# Cl_[dl/min]=p(6)
c# VT_[dl]=p(7)
c# Vss_[dl]=p(8)
c# Sum{Lij}_[/min]=p(9)
c# b_[/min]=p(10)
c# a_[/min]=p(11)
c# A_[mg/dl]=p(12)
c# B_[mg/dl]=p(13)
c
   L(2,1)     1.695031E-02  0.000000E+00   1.000000E+01
   L(1,2)     3.064119E-02  0.000000E+00   1.000000E+01
   L(0,1)     1.371318E-02  0.000000E+00   1.000000E+01
 ic(1)=p(1)
   P(1)       5.054100E+01  0.000000E+00   1.000000E+02
   K(1)       2.670357E-02  0.000000E+00   1.000000E+02
 p(3)=1/k(1)
 p(2)=l(2,1)*p(3)/l(1,2)
 p(4)=l(2,1)*p(3)
 p(5)=l(1,2)*p(2)
 p(6)=l(0,1)*p(3)
 p(7)=p(2)+p(3)
 p(8)=p(3)*(1+l(2,1)/l(1,2))
c
 p(9)=l(2,1)+l(1,2)+l(0,1)
 p(10)=(p(9)-sqrt(p(9)**2-4*l(1,2)*l(0,1)))/2
 p(11)=l(1,2)*l(0,1)/p(10)
 p(12)=p(1)*(p(11)-l(1,2))/(p(11)-p(10))/p(3)
 p(13)=p(1)*(p(10)-l(1,2))/(p(10)-p(11))/p(3)
```



Micro and Macro rate constants Micro fitted and Macro evaluated.

Note agreement between the two models … heavy blue line and thin white line

```
H DAT
  l(0,1)
  l(1,2)
  l(2,1)
  p(1)
  p(2)
  p(3)
  p(4)
  p(5)
  p(6)
  p(7)
  p(8)
  p(9)
  p(10)
  p(11)
  p(12)
  p(13)

g(11)=p(12)*exp(-p(10)*t)+p(13)*exp(-p(11)*t)
 f(1)                                        fsd=.1
        [min]          [ug/L]
         5              1.29
         10             1.07
         15             .969
         20             .875
         30             .652
         45             .539
         60             .378
         90             .317
         120            .267
         150            .209
         180            .157
         240            .108
         300            .063
         360            .041
111 g(11)                                    fsd=.1
c       [min]          [ug/L]
         5              1.29
         10             1.07
         15             .969
         20             .875
         30             .652
         45             .539
         60             .378
         90             .317
         120            .267
         150            .209
         180            .157
         240            .108
         300            .063
         360            .041
```

After iteration and FSD Capture

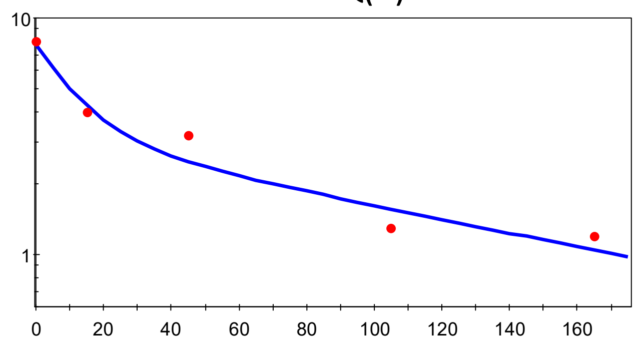
Name	Param	Value	FSD
a_[/min]	P(11)	0.0532772	0.190977
A_[mg/dl]	P(12)	0.674935	0.0469508
b_[/min]	P(10)	0.00787324	0.026955
B_[mg/dl]	P(13)	0.675812	0.0489115
Cl_[dl/min]	P(6)	0.514932	0.1461
Clc_[dl/min]	P(4)	0.632677	0.273729
IV_Dose50_[mg]		P(1)	50.72331
Sum{Lij}_[/min]		P(9)	0.061150
Vc_[dl]	P(3)	37.552	0.151973
Vss_[dl]	P(8)	58.2345	0.147191
Vt_[dl]	P(2)	20.6825	0.162856
VT_[dl]	P(7)	58.2345	0.14719

Differences <0.1%

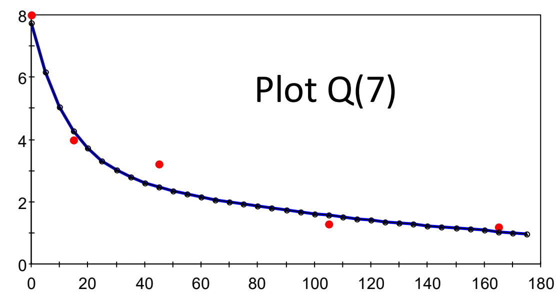
Example 19 Macro and Micro Rate Constants

```
A SAAM31
2       10
C Insert Control lines 2,3,4 here as needed
H PAR
   P(1)      4.590284E+00
   P(2)      7.820775E-02
   P(3)      3.154558E+00
   P(4)      6.719415E-03
C
   L(7,8)    3.573663E-02  0.000000E+00   1.000000E+01
   L(8,7)    3.431543E-02  0.000000E+00   1.000000E+01
   L(0,7)    1.464702E-02  0.000000E+00   1.000000E+01
   K(7)      7.740561E+00  0.000000E+00   1.000000E+02
   ic(7)=1
H DAT
x g(1)=p(1)*exp(-p(2)*t)+p(3)*exp(-p(4)*t)
x qo(7)=g(1)
101 g(1)
            0
2           5                             35
101 g(1)                                  sd=.1
            0             8
            15            4
            45            3.2
            105           1.3
            165           1.2
107                                       sd=.1
            0
2           5                             35
```

Plot Q(1)




```
> deck
* DECK BEING PROCESSED
PRE-PROCESSING TIME :      0.000 SECS
> solv
*** MODEL CODE 10 SOLUTION
SOLUTION TIME :      0.000 SECS
> iter
* PARTIALS ESTIMATED
•  CORRECTION VECTOR ESTIMATED

CONVERGENCE MEASURES
 IMPROVEMENT IN SUM OF SQUARES =     0.00(%)
 FINAL VALUE OF CONAB =    1.000E+01
 LARGEST CHANGE (    0.04 %) WAS IN PAR( 8, 7)
* CORRECTION VECTOR ESTIMATED

CONVERGENCE MEASURES
 IMPROVEMENT IN SUM OF SQUARES =     0.00(%)
 FINAL VALUE OF CONAB =    1.000E+01
 LARGEST CHANGE (    0.03 %) WAS IN PAR( 8, 7)

ITERATION TIME :      0.000 SECS

DISTRIBUTION OF SQUARES
 COMP   SUM OF SQUARES
   1     7.6844E-01
   7     2.0895E-05
> fsd(i)
* VALUES MAY NOT RELATE TO CURRENT PARAMETERS
* L ( 7, 8)     3.574E-02     FSD( 1)    8.019E-02
* L ( 8, 7)     3.434E-02     FSD( 2)    5.655E-02
* L ( 0, 7)     1.465E-02     FSD( 3)    2.925E-02
* K ( 7)        7.742E+00     FSD( 4)    1.177E-02
```



A Nonlinear Model
A 1 Unit Challenge is Abruptly Introduced into Compartment 3 at T=5, and then Immediately Fed to Compartment 2 … how is all this achieved?
Example 8

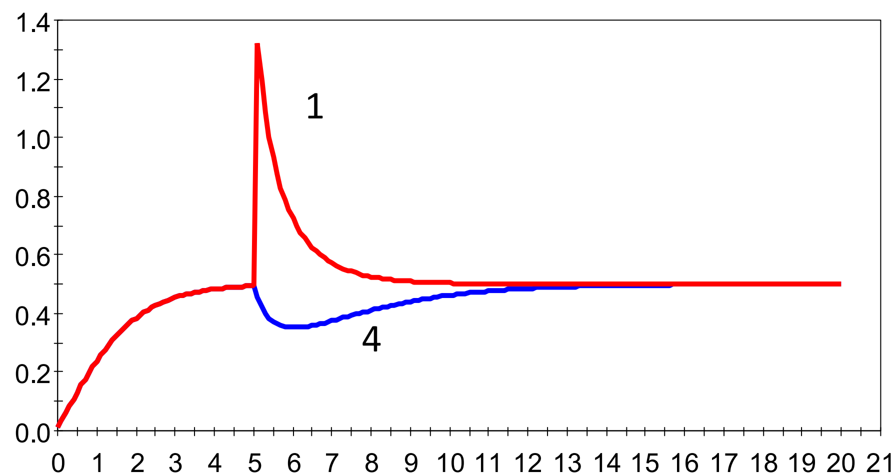
```
A SAAM31
H PAR
   P(1)      1
   P(2)      .25
   L(2,3)    1000
   ic(1)=.01
H DAT
X G(1)=p(1)*(F(1)+F(2))**2
X G(2)=(F(1)+F(2))
x uf(1)=P(2)-f(1)*g(2)*P(1)
x uf(2)=-f(2)*g(2)*P(1)
101
            0
2           .1                             200
102
            0
2           .1                             200
104 G(2)
            0
2           .1                             200
103 QO
            5             1
105 G(1)
            0
2           .1         //     200
```

f1`=p2-f1*p1/(f1+f2)

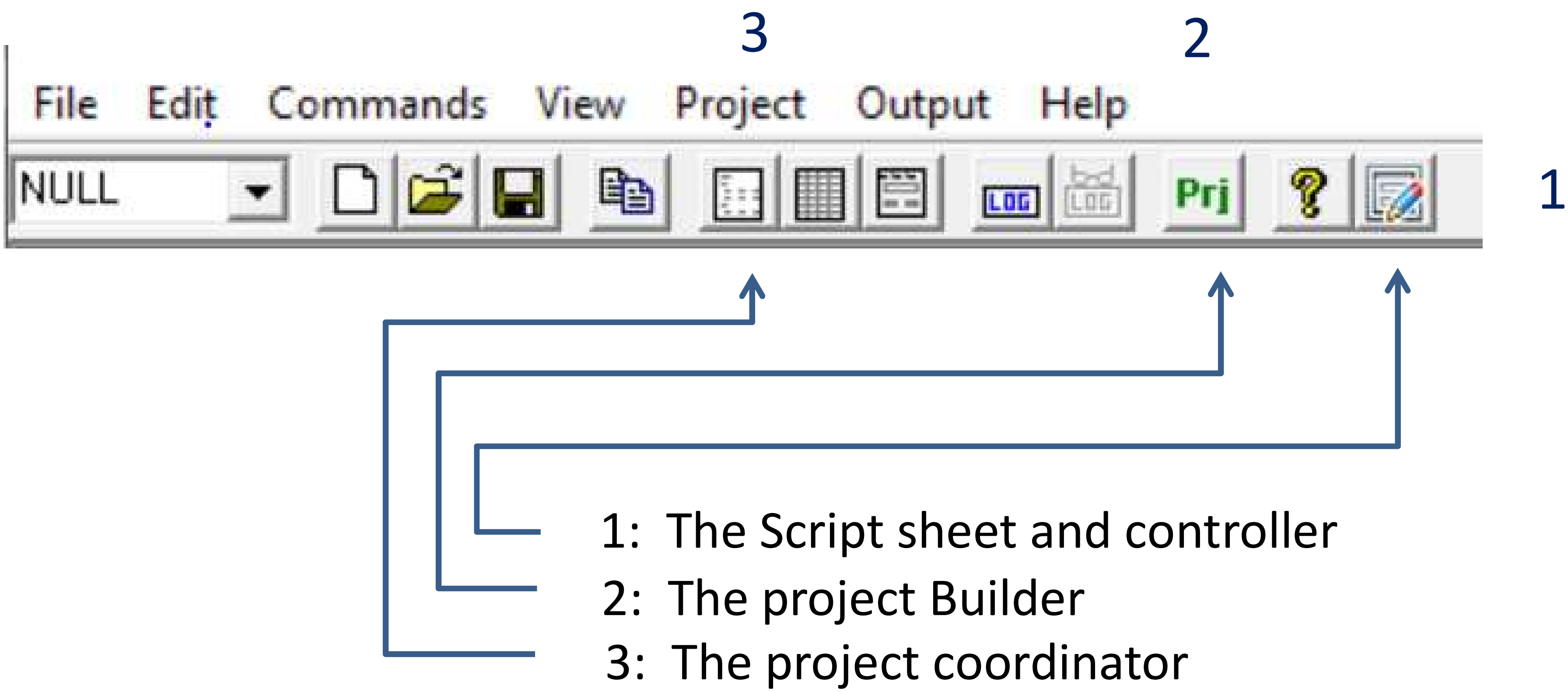
f2`=-f2*p1/(f1+f2)+1000*1 (at t=5)

g1=p1.(f1+f2)**2

Plot qc(1,4)



Some new and less commonly used features in WinsAAM:
Scripting and Project Management



Scripting commands for WinSAAM

… WinSAAM 3.2 …

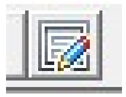
```
c# Load file
file
deck
c:\winsaam\macro_testing\morphine_1.saam
deck

solv
iter
p deck
prin q(1)
plot q(1)
iter
fsd(i)
plot q(1)
rand q(1)/fsd=.8
prin q(1)
p(i)
deck

solv
calc li
calc fcr li
fcr(i,j)
calc li
calc tr li
tr(i,j)
calc li
li(i,j)
l(i,j)
calc eig li
egv(i)
eig(i,j)
```

A Script is any sequence of WinSAAM commands stored in a text file with extension '.sams' for SAM Script.

A typical script might be the one shown here. Commands here include:
file, deck, solv, iter, p, prin, plot, fsd, rand, calc, fcr, tr, li, l, egv, and eig.

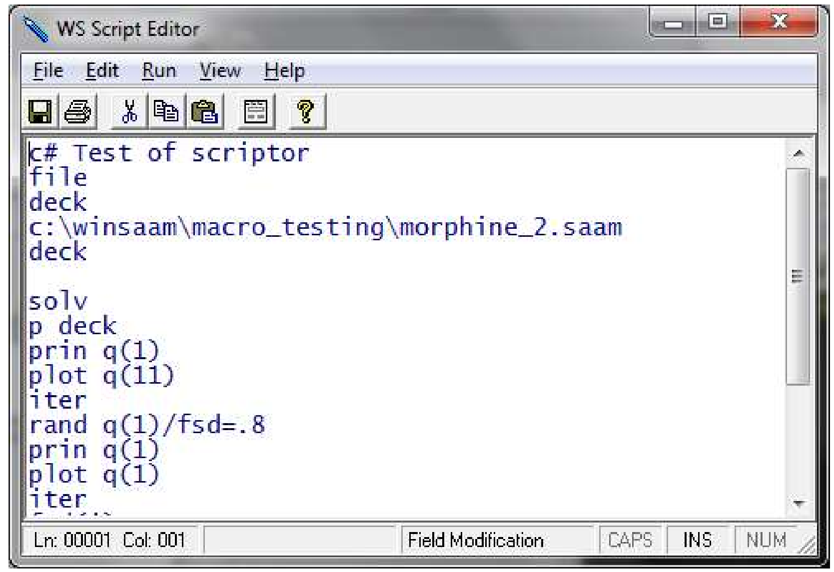
Of course the arguments of the command must make sense in the problem context and in the command syntax

Creating a script:

Invoke the script tool  and start typing into the displayed 'editor'

Saving the new script:

Use the file command and save option

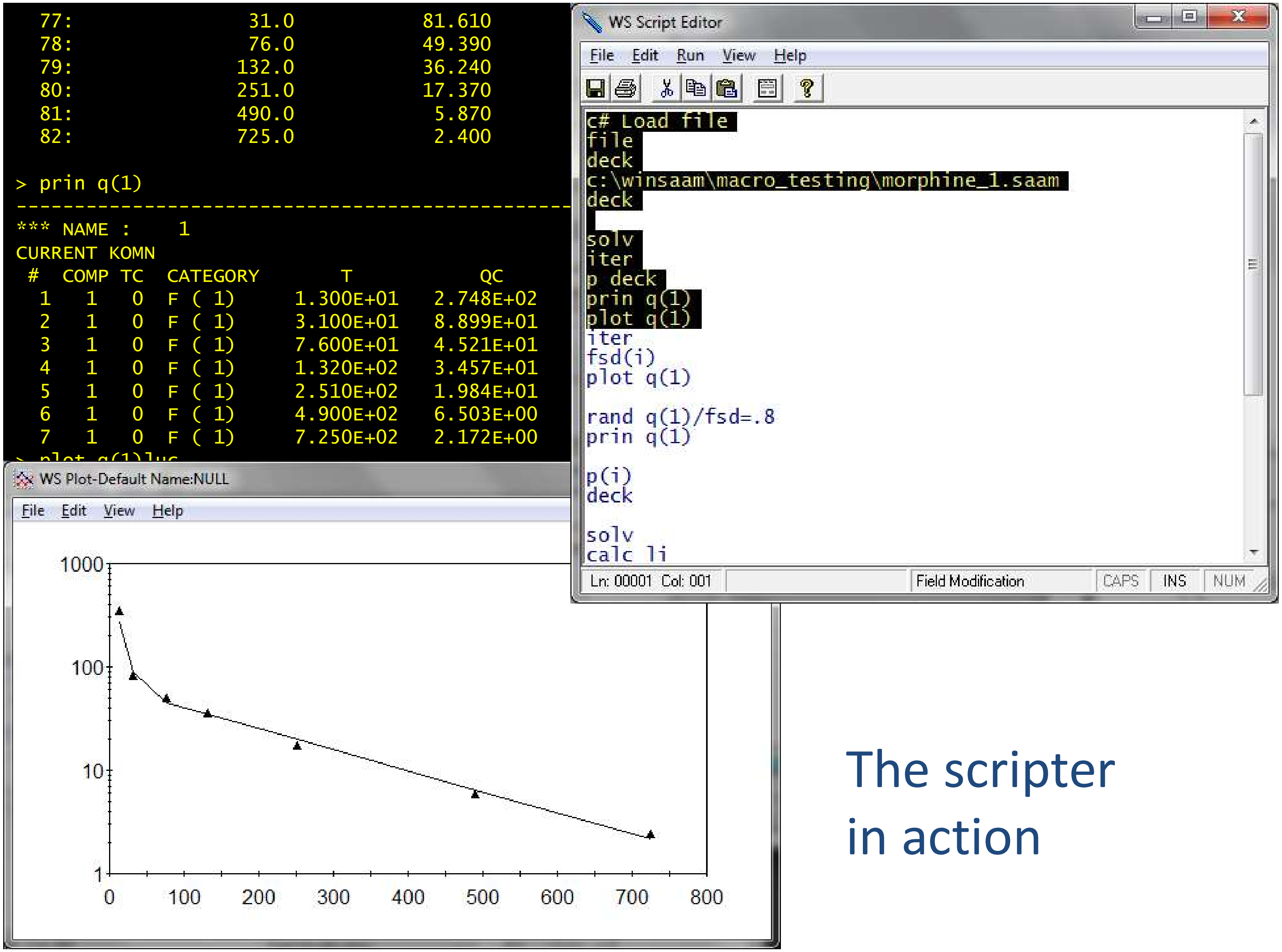


Editing the script:

Simply edit in the script editor

Invoking the script

Select Run fro the Script editor … the results will be directed to the WinSAAM console, or the plot window as dictated by the command



The scripter in action

Labeling WinSAAM Objects
… WinSAAM 3.2 …

A typical WinSAAM input job with object labeling

```
A  SAAM31                                        Sub_1
2         10
H  PAR
C
c#  Vd=p(1)
c#  Cl=p(2)
c#  Cmax=p(3)
c#  t1/2=p(4)
c#  AUC=p(5)
c#  AUMC=p(6)
c#  MRT=p(7)
c#  Cmax=p(8)
c#  Elim Rate=L(0,1)
c#  Scale factor=K(1)
C
   K(1)      1.011269E-01  0.000000E+00   1.000000E+04
   L(0,1)    1.049099E-02  0.000000E+00   1.000000E+04
   ic(1)    10000
 p(1)=1/k(1)
 p(2)=p(1)*l(0,1)
 p(3)=ic(1)*k(1)
 p(4)=alog(2)/l(0,1)
 p(5)=k(1)*ic(1)/l(0,1)
 p(6)=k(1)*ic(1)/l(0,1)/l(0,1)
 p(7)=p(6)/p(5)
 p(8)=K(1)*ic(1)
H  DAT
   p(1)
   p(2)
   p(3)
   p(4)
   p(5)
   p(6)
   p(7)
   p(8)
   l(0,1)
   k(1)
101                                       fsd=.4
            10             920
            20             800
...
            90             380
            110            350
            150            200
```


```
C
c#  Vd=p(1)
c#  Cl=p(2)
c#  Cmax=p(3)
c#  t1/2=p(4)
c#  AUC=p(5)
c#  AUMC=p(6)
c#  MRT=p(7)
c#  Cmax=p(8)
c#  Elim Rate=L(0,1)
c#  Scale factor=K(1)
C
```


Note:

Labeling lines begin with '*c#<space>*'

Labeling lines end with '*= internal object*'

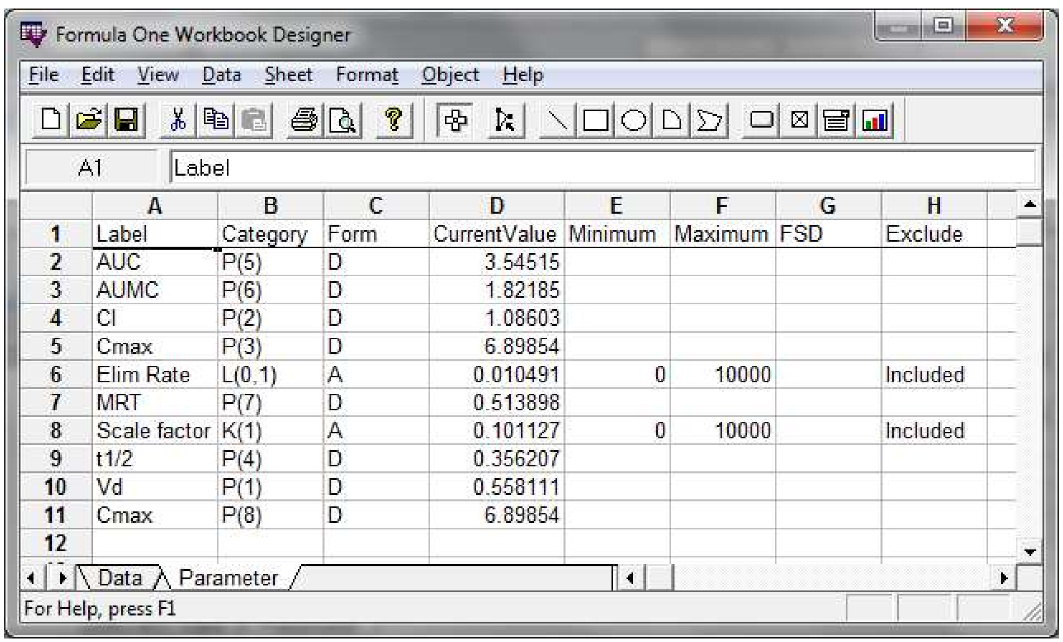
No spaces allowed in labels

Underscores '_' are allowed

For example '*c# Vd_[L/Kg]=p(1)*' labels '*p(1)*' in all spreadsheet tables as '*Vd_[L/Kg]*'

Object labels are accessible in the Spreadsheet tool when the input is compiled (deck). Names are also available in the Project manager processes if a project job includes them

Label	Category	Form	Current
AUC	P(5)	D	3.54515
AUMC	P(6)	D	1.82185
Cl	P(2)	D	1.08603
Cmax	P(3)	D	6.89854
Elim Rate	L(0,1)	A	0.010491
MRT	P(7)	D	0.513898
Scale factor	K(1)	A	0.101127
t1/2	P(4)	D	0.356207
Vd	P(1)	D	0.558111
Cmax	P(8)	D	6.89854



	A	B	C	D	E	F	G	H
1	Label	Category	Form	CurrentValue	Minimum	Maximum	FSD	Exclude
2	AUC	P(5)	D	3.54515				
3	AUMC	P(6)	D	1.82185				
4	Cl	P(2)	D	1.08603				
5	Cmax	P(3)	D	6.89854				
6	Elim Rate	L(0,1)	A	0.010491	0	10000		Included
7	MRT	P(7)	D	0.513898				
8	Scale factor	K(1)	A	0.101127	0	10000		Included
9	t1/2	P(4)	D	0.356207				
10	Vd	P(1)	D	0.558111				
11	Cmax	P(8)	D	6.89854				
12								

Spreadsheet Data Labeling

a_[/min]	0	P(11)	0	0	0.0534422
A_[mg/dl]	0	P(12)	0	0	0.675143
b_[/min]	0	P(10)	0	0	0.00786248
B_[mg/dl]	0	P(13)	0	0	0.674483
Cl_[dl/min]	0	P(6)	0	0	0.513533
Clc_[dl/min]	0	P(4)	0	0	0.634758
Clt_[dl/min]	0	P(5)	0	0	0.634758
IV_Dose50[mg]	0	P(1)	0	0	50.541
Sum{Lij}_[/min]	0	P(9)	0	0	0.0613047
Vc_[dl]	0	P(3)	0	0	37.4482
Vss_[dl]	0	P(8)	0	0	58.164
Vt_[dl]	0	P(2)	0	0	20.7158
VT_[dl]	0	P(7)	0	0	58.164

Spreadsheet Parameter Labeling

a_[/min]	0	P(11)	0	0	0.0534422
A_[mg/dl]	0	P(12)	0	0	0.675143
b_[/min]	0	P(10)	0	0	0.00786248
B_[mg/dl]	0	P(13)	0	0	0.674483
Cl_[dl/min]	0	P(6)	0	0	0.513533
Clc_[dl/min]	0	P(4)	0	0	0.634758
Clt_[dl/min]	0	P(5)	0	0	0.634758
IV_Dose50[mg]	0	P(1)	0	0	50.541
Sum{Lij}_[/min]	0	P(9)	0	0	0.0613047
Vc_[dl]	0	P(3)	0	0	37.4482
Vss_[dl]	0	P(8)	0	0	58.164
Vt_[dl]	0	P(2)	0	0	20.7158
VT_[dl]	0	P(7)	0	0	58.164

Manipulation of Nonlinear Systems at Steady State?

Consider the Minimal Model

For insulin: $X` = - p2.X + p3.\delta I$ $\qquad$ $\delta I = I - Ib$

At steady state: $X` = 0$ and thus $X = SI \cdot \delta I$ $\qquad$ $SI = P3/P2$

For glucose: $G` = - G.(X + Sg) + Gb.Sg + G_{inf}$

At steady state: $G` = 0$ and thus $0 = - G_{ss}.(X + Sg) + Gb.Sg + G_{inf}$

Hence: $G_{ss.}Sg + G_{ss}.SI.\delta I = Gb.Sg + G_{inf}$ $\qquad$ G_{ss} = Steady State Glucose

Rearranging: $Sg.(G_{ss} - Gb) = - SI.\delta I.G_{ss} + G_{inf}$

Thus: $\delta G = (- SI.\delta I.G_{ss} + G_{inf})/Sg$ $\qquad$ $\delta G = G_{ss} - Gb$

Or: $\delta G \approx G_{inf}/Sg - SI/Sg.\ \delta I.G_{ss}$

Here we see that if $\delta G = 0$, then: $X \approx G_{inf} / G_{ss}$

Thank You