Micro and Macro Constants …
Maneuvering between Data Invariants

Modeling Drug Metabolism and Disposition In Sections

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Achieving a Balance or Striking a Chord … Macro v Micro

The Macro Constants version of PK data captures **almost all** there is to be obtained from (linear drug) disposition data .. (Rowlands and Tozer)

Hence Macro Constant versions of PK data **may** provide effective bases from which other **summaries** of disposition data can be advanced

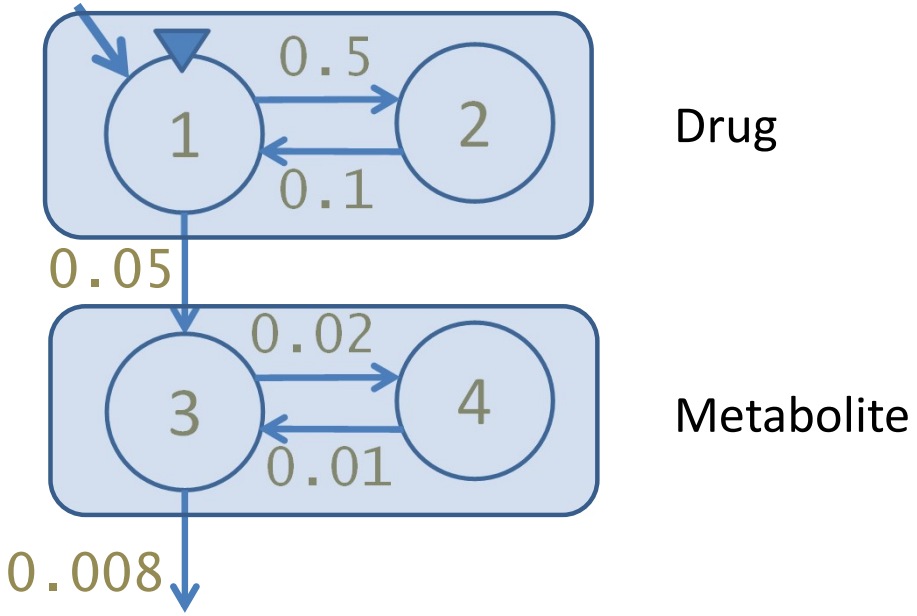
On the other hand, it is quite **cumbersome** to explore **disposition** patterns for alternate **administrations** (routes of delivery) with Macro Constant models

The ideal way to advance study design includes **Macro and Micro** model deployment. The Macro constants capturing the model generating base and the Micro rate constants capturing **plausible** mechanisms and drug **delivery** implications for a challenge.

Here using a simple 2 compt. **drug** sub model and a 2 compt. **metabolite** sub model we will show some of the key features of 1) responses of a **linear** system, and 2) Macro ⇔ Micro model interconversion using WinSAAM's **matrix** management facility

Drug and Metabolite Model

```
A SAAM31
H PAR
c Drug
   l(2,1)   .5
   l(1,2)   .1
c Metabolism
   l(3,1)   .05
c Metabolite
   l(4,3)   .02
   l(3,4)   .01
c Elimination
   l(0,3)   .008
H DAT
```



Convert Micro to Macro

```
> deck
> ic(1)=100
> calc li
> calc inv li
> calc eig inv
STOPPED AFTER    9 ITERATIONS
** EIGENVECTORS PRESENTLY UNNORMALIZED.
```

Four Eigenvalues

```
> egv(i)
EGV( 1) =   6.4221E-01
EGV( 2) =   7.7856E-03
EGV( 3) =   3.5763E-02
EGV( 4) =   2.2369E-03
```

Coefficients … eigenvectors

```
> deck
> ic(1)=100
> calc li
> calc eig li
STOPPED AFTER    8 ITERATIONS
> eig(i,j)
         1             2             3             4
 1  8.5465E+01   8.7249E-07   1.4535E+01   1.6587E-07
 2 -7.8811E+01   5.6706E-07   7.8811E+01   5.2872E-06
 3 -6.9608E+00  -1.4547E+01  -1.0367E+01   3.1875E+01
 4  2.2020E-01   1.1293E+01  -9.3632E+01   8.2119E+01
```

Compiling all responses … note the pervasive presence of the Macro Constants

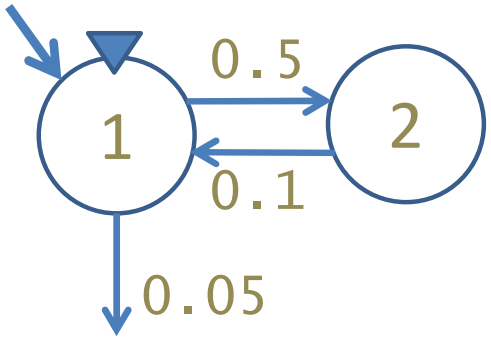
```
> egv(i)
EGV( 1) =   6.4221E-01
EGV( 2) =   7.7856E-03
EGV( 3) =   3.5763E-02
EGV( 4) =   2.2369E-03
```

$f1(t)=85.47e^{-0.64t}+14.53e^{-0.036t}$

$f2(t)=-78.81e^{-0.64t}+78.811e^{-0.036t}$

$f3(t)=-6.96e^{-0.64t}-14.55e^{-0.0078t}-10.37e^{-0.036t}+31.88e^{-0.0022t}$

$f4(t)=0.22e^{-0.64t}+11.29e^{-0.0078t}-93.63e^{-0.036t}+82.21e^{-0.0022t}$



Looking at the Drug

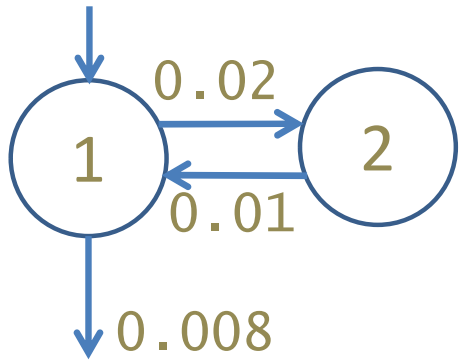
```
A SAAM31
H PAR
c Drug
   l(2,1)   .5
   l(1,2)   .1
c Metabolism
   l(0,1)   .05
```

```
> deck
> ic(1)=100
> solv
> calc li
> calc inv li
> calc eig inv
STOPPED AFTER    4 ITERATIONS
** EIGENVECTORS UNNORMALIZED.
> egv(i)
EGV( 1) =   6.4222E-01
EGV( 2) =   7.7856E-03
```

```
EGV( 1) =   6.4221E-01
EGV( 2) =   7.7856E-03
```

Looking at the Metabolite

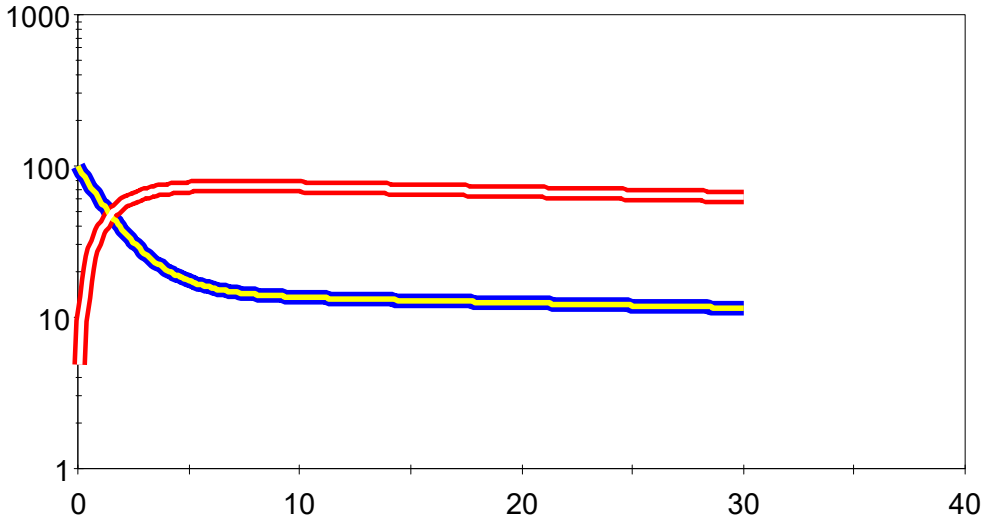
```
A SAAM31
H PAR
c Metabolite
   l(2,1)   .02
   l(1,2)   .01
c Elimination
   l(0,1)   .008
H DAT
```




```
> deck
> solv
> calc li
> calc inv li
> calc eig inv
STOPPED AFTER    4 ITERATIONS
** EIGENVECTORS PRESENTLY UNNORMALIZED.
> egv(i)
EGV( 1) =   3.5763E-02                EGV( 3) =   3.5763E-02
EGV( 2) =   2.2369E-03                EGV( 4) =   2.2369E-03
```

Checking Accounts of Drug Disposition

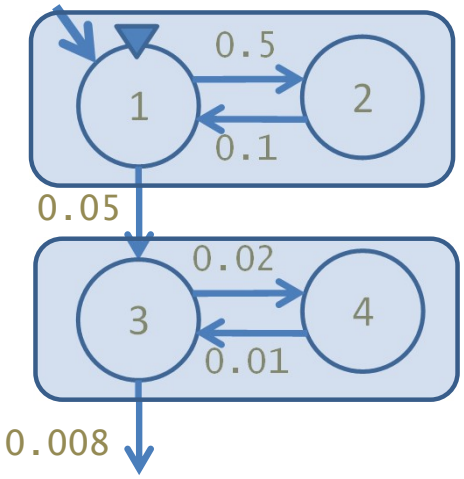
Blue and White, f1 and g1 respectively, and
Red and Yellow, f2 and g2 respectively




```
A SAAM31
H PAR
c Drug
   ic(1)    100
   l(2,1)   .5
   l(1,2)   .1
c Metabolism
   l(3,1)   .05
c Metabolite
   l(4,3)   .02
   l(3,4)   .01
c Elimination
   l(0,3)   .008
H DAT
X g(1)= 85.47*exp(-0.642*t)+14.54*exp(-0.00778*t)
x g(2)=-78.81*exp(-0.642*t)+78.81*exp(-0.00778*t)
101
            0
2           .1                              300
102
            0
2           .1                              300
111 g(1)
            0
2           .1                              300
112 g(2)
            0
2           .1                              300
```

Some important features of the responses of linear systems

All exchanging compartments of a linear system share the same eigenvalues.



Drug

Metabolite

For example compts. 1 and 2 share the same eigenvalues and compts 3 and 4 share the same eigenvalues.

Compts 1 and 2 share a subset of the eigenvalues of compts. 3 and 4.

We say that compts. 3 and 4 SEE compts. 1 and 2 but compts 1 and 2 do NOT SEE compts. 3 and 4

The **share** of eigenvalues (or exponentials) in each compartment is given by the **eigenvectors** for that compt.

These facts hold for any input to the system … however for an **infusion** the pattern is most evidently manifest in the elution.

If we have **multiple inputs** to a linear system then the response of the system is the sum of the **responses** to the separate inputs. If the inputs are offset then the separate responses need to be similarly offset.

Without easy access to general matrix manipulation facilities it is ‘tricky’ to move from Macro PK models to Micro models and from Micro models of one topology to another

Here we demonstrate a few tricks for achieving either of these objectives quite easily … and without recourse to serious ‘math’ Using simulated data and model fitting

The model here specifies the data to be fitted in an **inverse exponential** form meaning that the data (Wagner, JD, 2000) is in **Macro constant** form
The fitting model is in **Micro constant** form, each adjustable parameter initialized near to the final estimates.

```
A SAAM31
2       25
C
H PAR
 ic(1)=100
   l(2,1)   .3                                  10
   l(1,2)   .06                                 10
   l(3,1)   .02                                 10
   l(1,3)   .005                                10
   l(0,1)   .04                                 10
C
c l(2,1)=.2
c l(1,2)=.05
c l(3,1)=.01
c l(1,3)=.004
c l(0,1)=.03
C
H DAT
x g(1)=84.415*exp(-t/3.53292)+11.335*exp(-t/118.5582)+
       4.2503*exp(-t/397.9088)
x qo(1)=g(1)
101                                          sd=.2
            0
2           1                                1024
```

Our goal is to fit the Micro model to the Macro 'data' and to show that the fitted Micro model has the eigenvalues of the Macro model.

Note the use of the QO construct … generating data using an equation

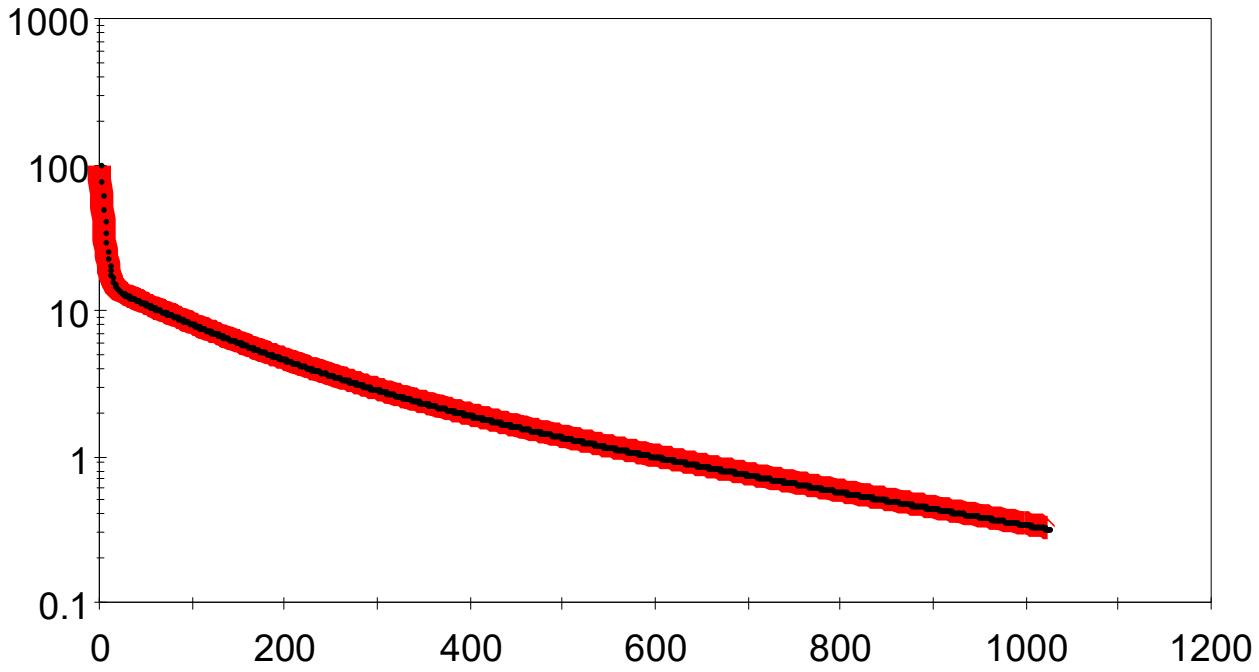
```
> saam
* DECK BEING PROCESSED
...
CONVERGENCE MEASURES
 IMPROVEMENT IN SUM OF SQUARES =   99.44(%)
 FINAL VALUE OF CONAB =   7.521E-01
 LARGEST CHANGE (   70.26 %) WAS IN PAR( 3, 1)
...

PARAMETER    VALUE      ERROR       FSD
L ( 2, 1)  2.000E-01  1.986E-07  9.929E-07
L ( 1, 2)  5.000E-02  9.495E-08  1.899E-06
L ( 3, 1)  1.000E-02  8.741E-08  8.741E-06
L ( 1, 3)  4.000E-03  6.124E-08  1.531E-05
L ( 0, 1)  3.000E-02  3.403E-08  1.134E-06
CORRELATION MATRIX
 COLUMN   1     2     3     4     5
ROW 1  1.00  0.30 -0.24 -0.28 -0.17
ROW 2  0.30  1.00  0.73  0.58  0.29
ROW 3 -0.24  0.73  1.00  0.74  0.26
ROW 4 -0.28  0.58  0.74  1.00  0.73
ROW 5 -0.17  0.29  0.26  0.73  1.00
> calc li
*** MODEL CODE 10 SOLUTION
SOLUTION TIME :      0.000 SECS
> calc eig li
STOPPED AFTER    4 ITERATIONS
> egv(i)
EGV( 1) =   3.5331E+00
EGV( 2) =   1.1855E+02
EGV( 3) =   3.9789E+02
```

Recover eigenvalues

x g(1)=84.415*exp(-t/3.53292)+
11.335*exp(-t/118.5582)+
4.2503*exp(-t/397.9088)

Fit of the Micro model (red outline) to the Macro data (small dark dots) showing consistent agreement between the two forms



Thank You

A strategy for the analysis of drug disposition following a moderately complicated administration

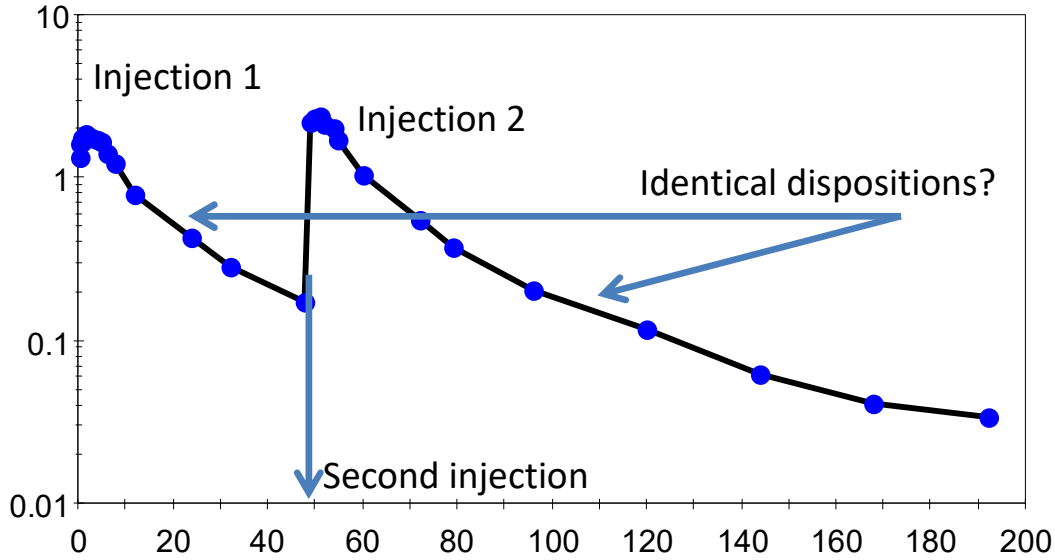
Drug administration can follow a variety of routes
… and take a variety of delivery methods

Typical routes:	Typical delivery methods
IV,	Bolus
Oral, PO	Infusion
IM	Repeat injections
Sublingual	Priming injection and infusion
IA	Intra-articular

If a drug is linearly metabolized and its disposition is linear then how we model the drug disposition should be based on where we obtain the **clearest** picture of the drug response.

All exchanging pools in the passage of the drug elimination see entirely the same **kinetic** invariants

Plot of Blood Spiramycin levels in response to administration below



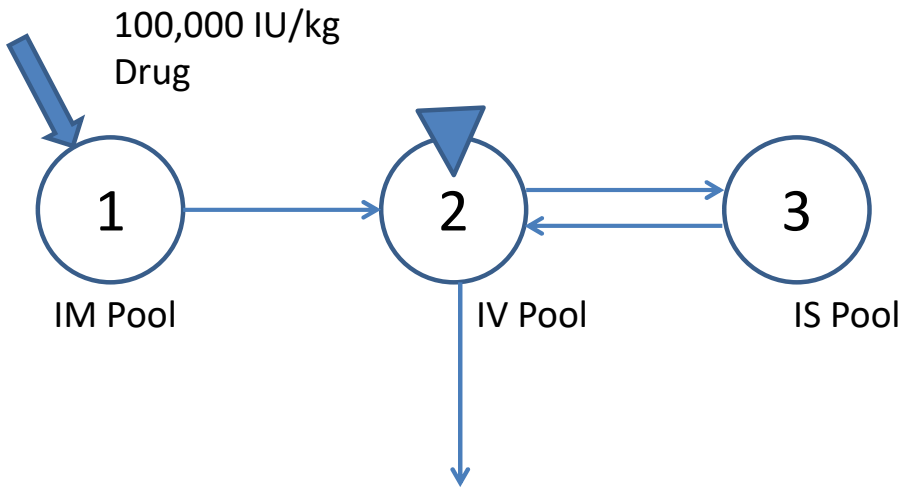
Young cattle (mean bodyweight = 250 kg) were given two intramuscular injections of Spiramycin (each injection was 100,000 IU of Spiramycin/kg bodyweight).

One milligram of Spiramycin is equal to 4133 IU of Spiramycin.

The first injection was given at 0 hours and the second injection was given at 48 hours.

An untested model of Spiramycin Disposition

Our challenge is to accommodate the complex drug administration and fit the blood appearance consistently

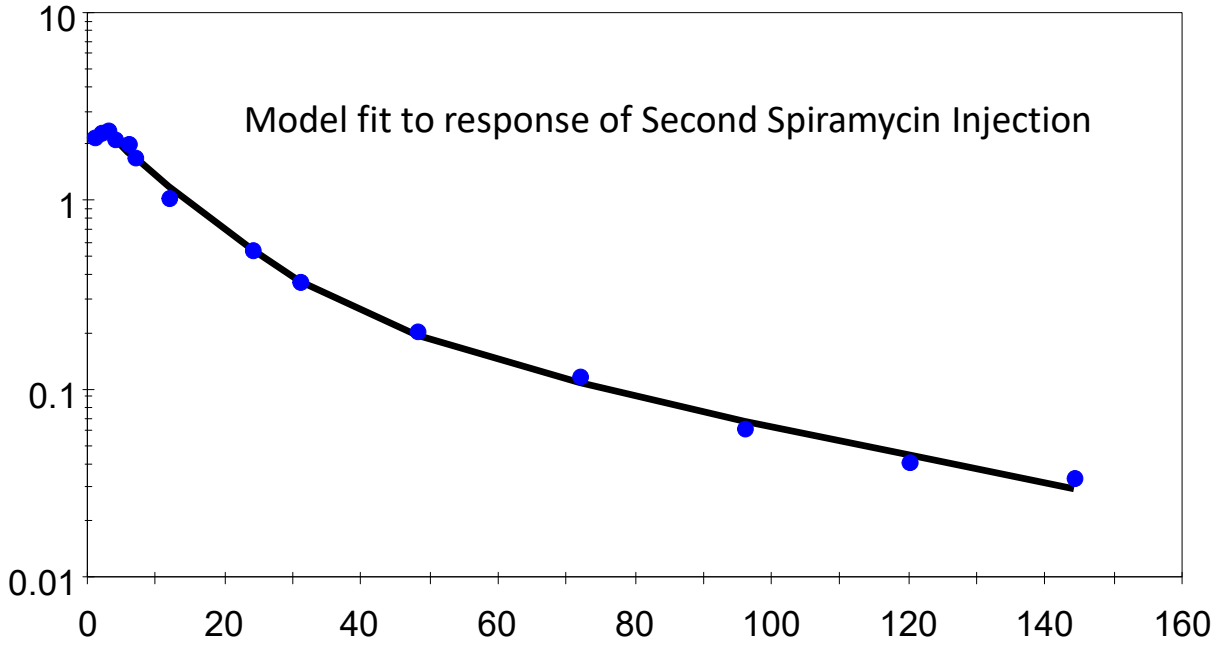


Gaining better control for estimation by fitting the second Spiramycin injection first

PARAMETER	VALUE	ERROR	FSD
L (2, 1)	1.791E+00	2.958E-01	1.652E-01
L (0, 2)	5.769E-02	1.693E-03	2.934E-02
L (3, 2)	2.083E-02	2.051E-03	9.846E-02
L (2, 3)	2.590E-02	2.329E-03	8.995E-02
K (2, 0)	4.576E-07	1.305E-08	2.851E-02

CORRELATION MATRIX

COLUMN	1	2	3	4	5
ROW 1	1.00	-0.50	-0.39	-0.23	-0.37
ROW 2	-0.50	1.00	0.81	0.51	0.87
ROW 3	-0.39	0.81	1.00	0.80	0.62
ROW 4	-0.23	0.51	0.80	1.00	0.38
ROW 5	-0.37	0.87	0.62	0.38	1.00



WinSAAM Model for Second Spiramycin Injection

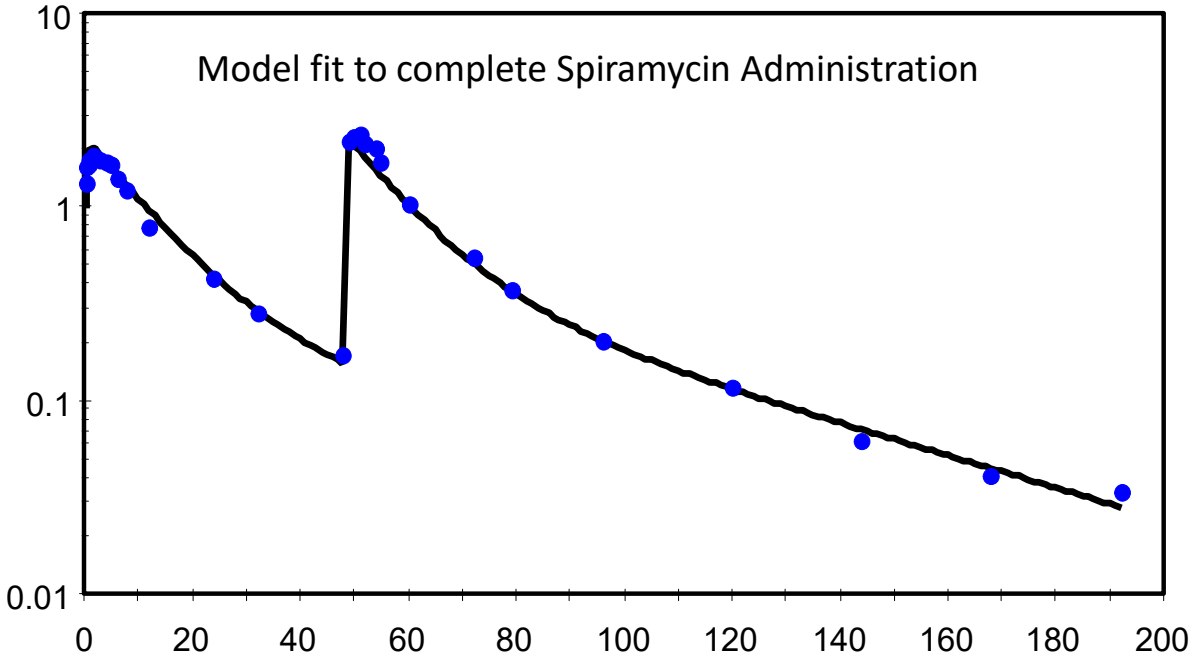
```
A SAAM31
2       12
H PAR
C Injection t=0,  100000 IU/Kg
C Injection t=48, 100000 IU/Kg
C Cow weight 250 Kg
C 1 mg = 4133 IU
C Dose=100000/4133*250*1000 ug
   ic(1)=p(1)
   L(2,1)    1.838549E+00  0.000000E+00   1.000000E+02
   L(0,2)    5.688424E-02  0.000000E+00   1.000000E+02
   L(3,2)    2.019770E-02  0.000000E+00   1.000000E+02
   L(2,3)    2.536828E-02  0.000000E+00   1.000000E+02
   p(1)=100000/4133*1000*250
   K(2)      4.516785E-07  0.000000E+00   1.000000E+04
H DAT
102         -48                          fsd=.05
            49            2.204
            50            2.337
            51            2.395
            52            2.146
            54            1.995
            55            1.694
            60            1.036
            72            0.55
            79            0.376
            96            0.201
            120           0.117
            144           0.062
            168           0.041
            192           0.034
```

Fit to data from both Spiramycin injections.

PARAMETER	VALUE	ERROR	FSD
L (2, 1)	2.288E+00	8.390E-02	3.667E-02
L (0, 2)	5.902E-02	1.080E-03	1.829E-02
L (3, 2)	2.012E-02	1.797E-03	8.931E-02
L (2, 3)	2.877E-02	2.038E-03	7.084E-02
K (2, 0)	3.775E-07	5.049E-09	1.337E-02

CORRELATION MATRIX

COLUMN	1	2	3	4	5
ROW 1	1.00	-0.28	-0.18	-0.10	-0.41
ROW 2	-0.28	1.00	0.72	0.44	0.97
ROW 3	-0.18	0.72	1.00	0.86	0.60
ROW 4	-0.10	0.44	0.86	1.00	0.36
ROW 5	-0.41	0.97	0.60	0.36	1.00



WinSAAM Model for First and Second Spiramycin Injection

```
A SAAM31
2       12
H PAR
C Injection t=0,  100000 IU/Kg
C Injection t=48, 100000 IU/Kg
C Cow weight 250 Kg
C 1 mg = 4133 IU
C Dose=100000/4133*250*1000 ug
   ic(1)=p(1)
   L(2,1)    2.113826E+00  0.000000E+00   1.000000E+02       .1
   L(0,2)    5.961749E-02  0.000000E+00   1.000000E+02       .01
   L(3,2)    2.093800E-02  0.000000E+00   1.000000E+02       .01
   L(2,3)    2.944792E-02  0.000000E+00   1.000000E+02       .01
   p(1)=100000/4133*1000*250
   K(2)      3.817573E-07  0.000000E+00   1.000000E+04       .0000001
 p(11)=1/k(2)/1000/250
 p(12)=p(11)*l(0,2)
H DAT
   p(1)
   p(11)
   p(12)
102                                          fsd=.05
c           Time (h)      Spiramycin (ug/ml)
            0.25          1.347
            0.5           1.609
            0.75          1.644
            1             1.758
            1.5           1.872
            2             1.803
            3             1.741
            4             1.689
            5             1.64
            6             1.389
            8             1.219
            12            0.779
            24            0.424
            32            0.286
            48            0.173
102
            0
2           1                          48
```

```
h dat                     tc(1)
102                                          fsd=.05
            49            2.204
            50            2.337
            51            2.395
            52            2.146
            54            1.995
            55            1.694
            60            1.036
            72            0.55
            79            0.376
            96            0.201
            120           0.117
            144           0.062
            168           0.041
            192           0.034
102
            49
2           1                                143
h icc                     tc(1)
 +  2        6000000
```

Table of finally adjusted parameters showing the leveraging gained from fitting the **second Spiramycin dose disposition first**. For each pair of parameters the second is the fit to the **complete study** .. the first relates to the fit to the second injection

PARAMETER	VALUE	ERROR	FSD
L (2, 1)	1.791E+00	2.958E-01	1.652E-01
L (2, 1)	2.288E+00	8.390E-02	3.667E-02
L (0, 2)	5.769E-02	1.693E-03	2.934E-02
L (0, 2)	5.902E-02	1.080E-03	1.829E-02
L (3, 2)	2.083E-02	2.051E-03	9.846E-02
L (3, 2)	2.012E-02	1.797E-03	8.931E-02
L (2, 3)	2.590E-02	2.329E-03	8.995E-02
L (2, 3)	2.877E-02	2.038E-03	7.084E-02
K (2, 0)	4.576E-07	1.305E-08	2.851E-02
K (2, 0)	3.775E-07	5.049E-09	1.337E-02

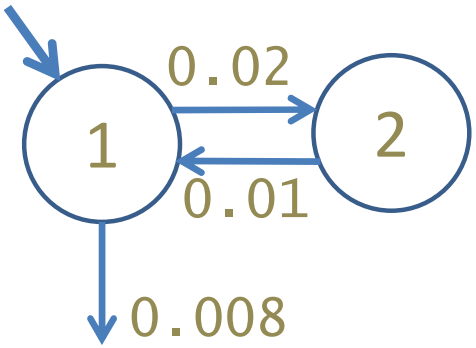
CORRELATION MATRIX

COLUMN	1	2	3	4	5
ROW 1	1.00	-0.50	-0.39	-0.23	-0.37
ROW 2	-0.50	1.00	0.81	0.51	0.87
ROW 3	-0.39	0.81	1.00	0.80	0.62
ROW 4	-0.23	0.51	0.80	1.00	0.38
ROW 5	-0.37	0.87	0.62	0.38	1.00

COLUMN	1	2	3	4	5
ROW 1	1.00	-0.28	-0.18	-0.10	-0.41
ROW 2	-0.28	1.00	0.72	0.44	0.97
ROW 3	-0.18	0.72	1.00	0.86	0.60
ROW 4	-0.10	0.44	0.86	1.00	0.36
ROW 5	-0.41	0.97	0.60	0.36	1.00

Thank You

The relationship between the Micro Rate constants and the Macro constants



$$L = A.a.A^{-1}$$

$$L = \begin{bmatrix} L11 & L12 \\ L21 & L22 \end{bmatrix}$$

$$L11 = L21 + L01$$

$$L22 = L12$$

Macro constants

A is the eigenvector matrix

a is the eigenvalue matrix

$$A = \begin{bmatrix} A11 & A12 \\ A21 & A22 \end{bmatrix}$$

$$A11 + A12 = IC(1)$$

$$A21 + A22 = 0$$

Micro rate constants

L is the fractional transfer matrix

$$a = \begin{bmatrix} a1 & \\ & a2 \end{bmatrix}$$