PK – PD Modeling with WinSAAM …
and the model translation process

… modeling objects
… protocol emulation
… data weighting
… numerical methods

Six Demonstrations from Gabrielsson and Weiner .. Varying Complexity

Ray Boston, 2012/2020

PK and PD Models are Ubiquitous in the Exploration of Drug Movement and Action

WinSAAM offers **unique** support for these types of investigation:

- **simple**, efficient modeling **platform**
- **fast**, flexible **optimizer** suite
- **intuitive** array of powerful prefabricated modeling **constructs**
- **flexible** tools to emulate **protocols**
- onboard **Population** modeling
- onboard **Bayesian** tools
- simple error **Propagation** to dependencies
- …

Model utility hinges, in part, on the ease of **model translation** and verification

Some simple **approaches** can expedite the process

… PK – PD Data Analysis: Concepts and Applications
Johan Gabrielsson and Dan Weiner 4th Edn. , 2006

In translating one model setting to another ….

Start by getting a familiarity with the model … e.g.

- its **purpose**
- the study/responses it **captures**
- the **objects** germane to the model
- how **initial** estimates of model parameters were derived
- **assumptions** implicit in the model

Next isolate how modeling constructs at your disposal (WinSAAM) will **substitute** for those used in the original 'rendition'
Here, '**faithful**' translation is critical … the closer the object alignment the better

Run the model **comparing** your results with those published

If you fail to reproduce the published results use a **divide and conquer** approach to locate and correct the inconsistent model section (Y/Y-)

Once the model produces the same pattern of results explore data **fitting, simplification, and enhancements**.

Some modeling environments have different 'natural' **construct** metrics ($L_{i,j}$) than others ($A_{i,j}$ α_i)

An important consideration

All PK-PD models are specified in one of **three** metrics:

Macro constants, **Micro** rate constants and **Physiological** constants

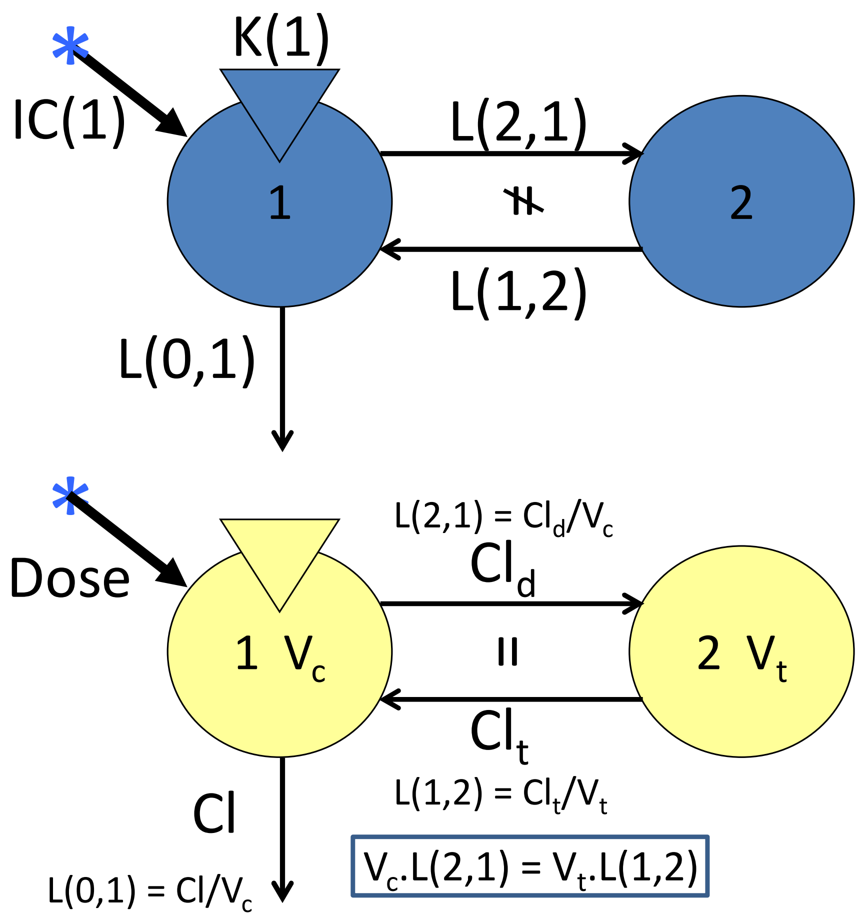
The features of each metric are as follows:

Metric	**Example**	**Connecting relationship**	**Advantages**	**Disadvantages**
Macro constants	A, α, B, β (two pool)	AUC=A/α + B/β $t_{1/2\alpha} = \ln(2)/\alpha$	The invariant properties of the data	No intrinsic biological context
Micro rate constants	L(0,1), L(1,2), L(2,1) (two pool), K(1)	$L = A\ \alpha\ A^{-1}$, R=L.M, $[L^{ii}] = \mathrm{diag}(L^{-1})$, $K(1)^{-1}$	Units and interpretation natural	Need* to be derived from Macro rate constants
Physiological constants	V, Cl, K.	L(0,1)*Vc=Cl Vc.L(2,1)=Vt.L(1,2) Cld=Clt	Units and interpretation natural	Somewhat contrived from L(I,j) for interpretation

Three representations of a two-compartment model

$$F(t) = Ae^{-a.t} + Be^{-b.t}$$

Macro Constant model



Micro Rate Constant model
with loss from compt. ‘1’

Physiologic Constant model
with loss from compt. ‘1’

Our agenda

- Model **translation** methodologies
- Demonstrating how certain modeling **tasks** are accomplished with WinSAAM
- Highlighting the **flexibility** of WinSAAM to support **PK-PD** analysis
- Demonstrating **error** propagation to model **dependencies** on data fitting
- Demonstrating setting up somewhat **complex** study Protocols

The demonstration models

GW Code	Admin Route	Admin Form	Response Model	Sample Sites	Sample Rate	Sample Duration	Subtlety
PK4	Oral	Repeat Boluses	Linear One Compt.	Plasma	Feq. [h] Baseline Last Admin	24 h	TC Negotiation
$PK6_{macro}$ $PK6_{micro}$	Oral and IV	Bolus	Linear One Compt.	Plasma and Urine	Plasma freq Urine 2 samples	168 h	Absorption Delay Consideratn
PK11	IV	Repeat Boluses	Linear one comp & Emax effect	Plasma and PD Site	Plasma freq PD Site freq	60 h, 250 h	UF – QO Admin machinery
PK12	Oral and IV	Bolus Oral Infusion IV*	Linear two Compt.	Plasma	Three hourly or so	144 h	Detecting oral input PK indices
PK18	Alcohol IV	30 min infusion	Linear two Compt. Nonlinear metab	Plasma	Five minute obs.	6 h	Fitting Wilkinson Alc metab model
PK33	Transdermal Patch	Burst and Maint. Release	Linear One Compt.	Plasma	Approx. hourly	24 h	Resolving durat and amt. of doses

Demonstration features

1. PK4: One compartment response model, **Oral** dosing Multiple dose administration using simulated T-interrupt. Absorption delay

2. PK6: One compartment response model: **Oral and IV** dosing. Observations in the **urine and plasma** . Data investigated in two metrics, **macro** constants, and **micro** rate constants

3. PK11: Two compartment response model and repeated PO (tid) dosing. Effect of drug captured with an Emax model. The **administration** of the drug was modeled using the **QO resetting function**

4. PK12: Intravenous and Oral dosing: An **oral** dose of a drug is given and then **60 minutes later** an IV infusion of the drug is administered. Model demonstrates the joint use of **UF and QO** to deliver an input

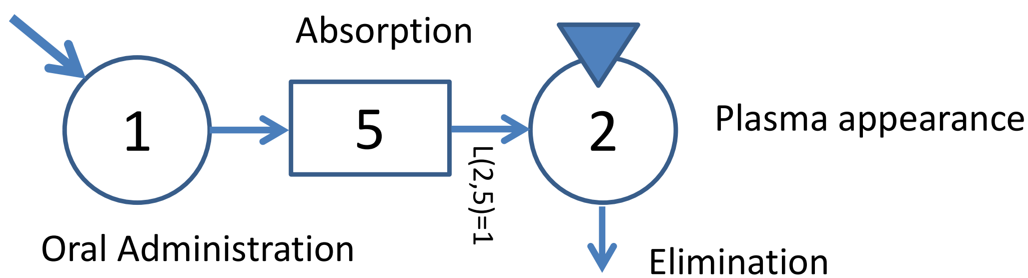
5. PK18: Ethanol kinetics – Capacity II: Exchanging two pool approach to examine **Ethanol** metabolism .. see assignment

6. PK33: Transdermal input kinetics: Exploration of nicotine release from **Burst**, and **Maintenance**, deliveries from a composite (fast and slow) nicotine patch. **Zeroth** order nicotine release

PK4 .. One-compartment oral dosing

Details ... An oral **dose** of 352.3 μg of a drug formulated as a controlled release, CR, **tablet** was given at each of 0, 24, 48, 72, 98, 120, 144, 168, 192, and 216 h.

A **plasma** concentration profile was obtained from samples during the **first** and **last** doses. Purpose for inclusion .. model translation and multiple oral administrations




```
H PAR
   IC(1)=352.3
   DT(5)      7.398961E-01   0.000000E+00   1.000000E+01
   DN(5)=2
   L(5,1)     1.220064E-01   0.000000E+00   1.000000E+02
   L(2,5)=1
   L(0,2)     1.993174E-01   0.000000E+00   1.000000E+02
   K(2)       2.490848E-02   0.000000E+00   1.000000E+02
 P(1)=1/K(2)
```

Observations associated with the first time block

Administration of oral doses

```
A SAAM31
2       10
H PAR
   ic(1)=352.3
   DT(5)     7.398961E-01  0.000000E+00   1.000000E+01
   dn(5)=2
   L(5,1)    1.220064E-01  0.000000E+00   1.000000E+02
   l(2,5)=1
   L(0,2)    1.993174E-01  0.000000E+00   1.000000E+02
   K(2)      2.490848E-02  0.000000E+00   1.000000E+02
 p(1)=1/k(2)
H DAT
102                                      sd=.02
            1             .3622
            2             1.14
            3             1.7
            4             2.1
            5             2.35
            6             2.4
            7             2.5
            8             2.4
            10            2.3
            12            2.1
            14            1.7
            23.9          .65
102                                      wt=0
            0
2           .1                           239
h icc                     tc(2)
 +  1       352.3
h icc                     tc(3)
 +  1       352.3
h icc                     tc(4)
 +  1       352.3
h icc                     tc(5)
 +  1       352.3
h icc                     tc(6)
 +  1       352.3
h icc                     tc(7)
 +  1       352.3
h icc                     tc(8)
 +  1       352.3
h icc                     tc(9)
 +  1       352.3
h icc                     tc(10)
 +  1       352.3
```

```
h dat                     tc(2)
102
            24
2           1                           23
h dat                     tc(3)
102
            48
2           1                           23
h dat                     tc(4)
102
            72
2           1                           23
h dat                     tc(5)
102
            96
2           1                           23
h dat                     tc(6)
102
            120
2           1                           23
h dat                     tc(7)
102
            144
2           1                           23
h dat                     tc(8)
102
            168
2           1                           23
h dat                     tc(9)
102
            192
2           1                           23
            215.9
h dat                     tc(10)
102                                     sd=.02
            216           .74
            216.5         .70
            217           .74
            218           1.8
            219           2.1
            220           2.6
            221           2.6
            222           2.8
            223           2.7
            224           2.8
            226           2.4
            228           2.3
            230           1.9
            240           0.8
```

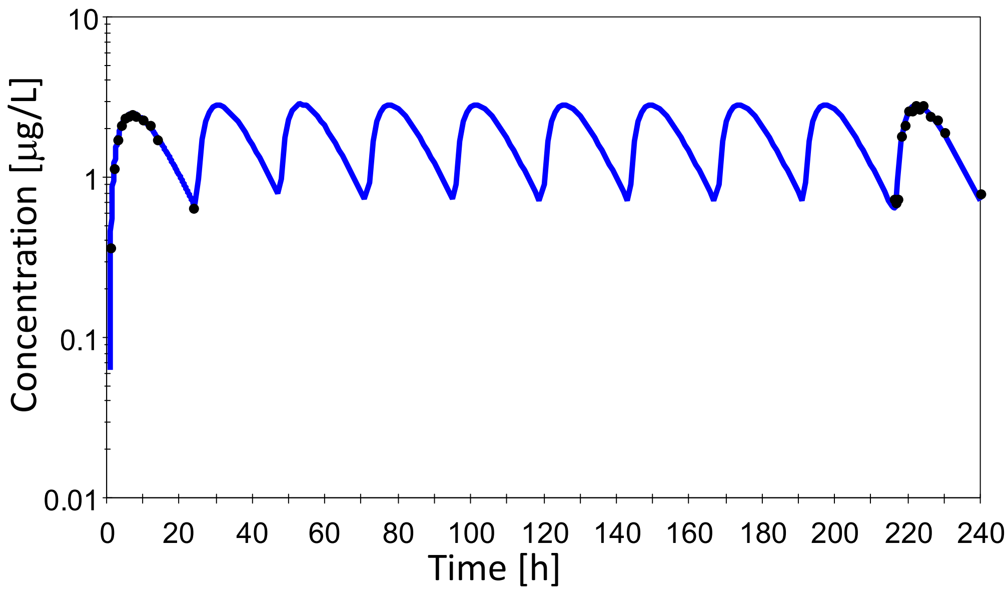
Hours spanned for each time block

Samples taken for the final time block

Final estimates of the adjustable parameters

PARAMETER	VALUE	ERROR	FSD	
DT(5, 0)	7.399E-01	1.259E-02	1.702E-02	... *0.697 tlag*
L (5, 1)	1.220E-01	1.206E-03	9.888E-03	... *0.123 K*
L (0, 2)	1.993E-01	2.439E-03	1.223E-02	... *0.196 Ka*
K (2, 0)	2.491E-02	2.502E-04	1.004E-02	... *0.02 (F/V)*[*]

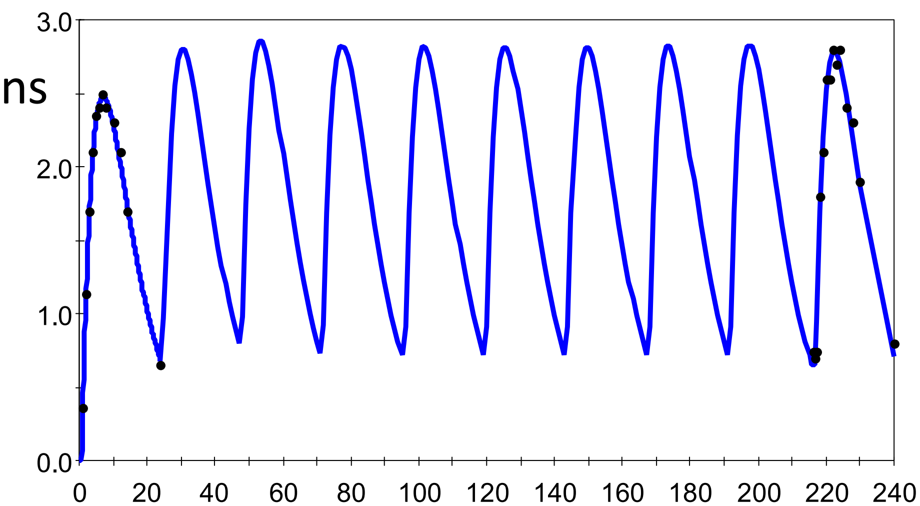
[*] Unidentified

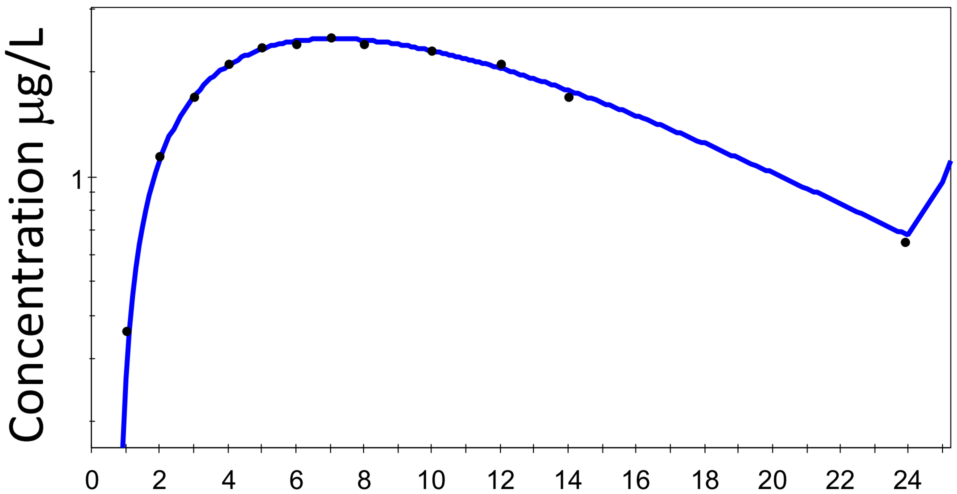


Semi log plot of observed and predicted responses. Note where lines only appear where there was no measurement **reported**.
Measurements are only **reported** in during the **first** and **last** 24 hour administrations.
All times shown are in the unit of hour.

Model fit to the observations

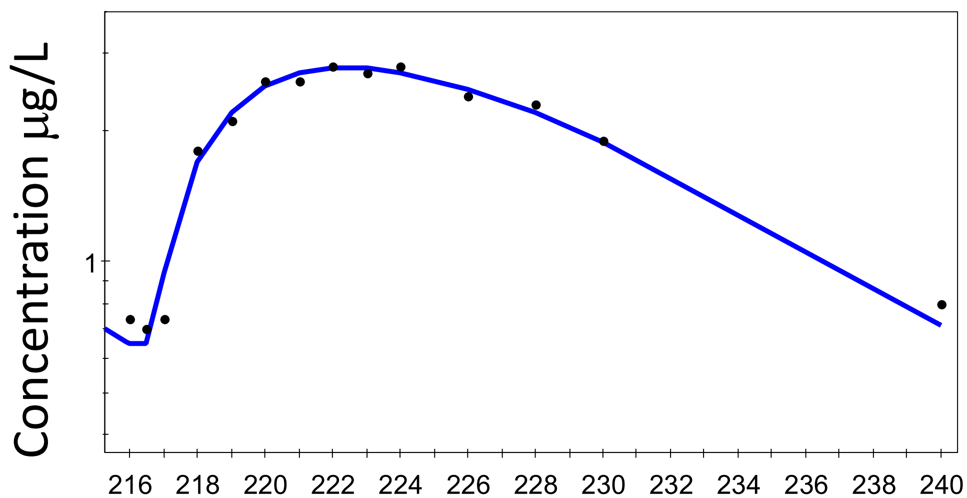
Linear plot of observed and predicted values





First and last 24 hour intense sampling patterns

Semi log Plots



Two Intense Sampling Periods 0<t<24, TC(0), and 216<=t<=240, TC(10)

```
h dat
102                                          sd=.02
         1          .3622
         2          1.14
         3          1.7
         4          2.1
         5          2.35
         6          2.4
         7          2.5
         8          2.4
         10         2.3
         12         2.1
         14         1.7
         23.9       .65
102                                          wt=0
         0
2        .1                                  239
```

```
h dat                 tc(10)
102                               sd=.02
         216          .74
         216.5        .70
         217          .74
         218          1.8
         219          2.1
         220          2.6
         221          2.6
         222          2.8
         223          2.7
         224          2.8
         226          2.4
         228          2.3
         230          1.9
         240          0.8
```

Pulses of oral administration of drug

Note: temporal context of icc comes from matching 'h dat tc(j)'
Note: at each tc(j) start 352.3 units of drug are **added** to compt. 1

```
h icc                   tc(2)
 +  1       352.3
h icc                   tc(3)
 +  1       352.3
h icc                   tc(4)
 +  1       352.3
h icc                   tc(5)
 +  1       352.3
h icc                   tc(6)
 +  1       352.3
h icc                   tc(7)
 +  1       352.3
h icc                   tc(8)
 +  1       352.3
h icc                   tc(9)
 +  1       352.3
h icc                   tc(10)
 +  1       352.3
```

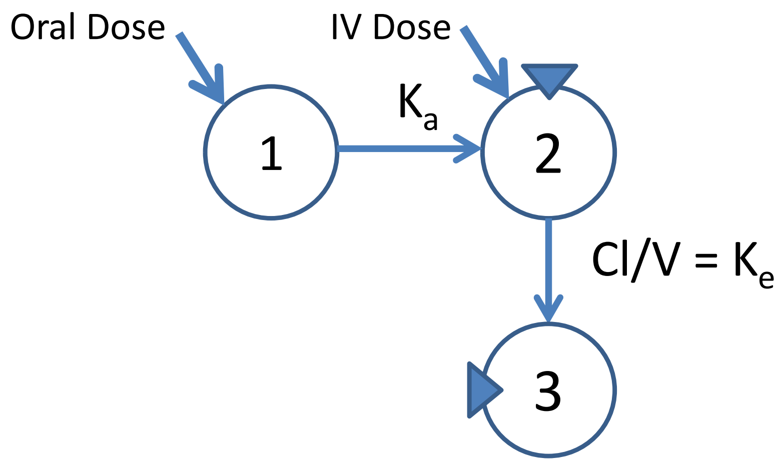
Here we see the epoch association of each tc(j) and the request for storage of each tc(j) calculations

```
h dat
102
            24
2           1                             23
h dat                     tc(2)
102
            24
2           1                             23
h dat                     tc(3)
102
            48
2           1                             23
h dat                     tc(4)
102
            72
2           1                             23
h dat                     tc(5)
102
            96
2           1                             23
h dat                     tc(6)
102
            120
2           1                             23
h dat                     tc(7)
102
            144
2           1                             23
h dat                     tc(8)
102
            168
2           1                             23
h dat                     tc(9)
102
            192
2           1                             23
            215.9
```

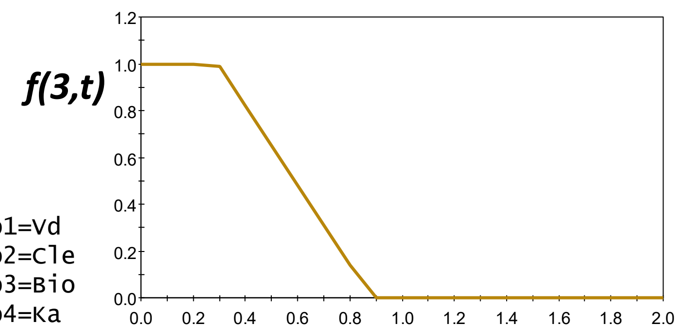
Points to Ponder:

1. The implementation of the administration seemed rather cumbersome … can you think of a better approach?
2. Recode this problem using the QO construct as in problem PK11.
3. Refit the data using this revised administration emulation … how do your results agree with those reported above?
4. Which results do you believe?
5. Which administration emulation do you believe?
6. Why?
7. Is there a compromise between the two approaches, or anything else you can think of that will help you arbitrate fairly and objectively here?
8. What other considerations need to be taken into account here?
9. What weighting scheme is used in conjunction with data fitting?
10. Is this a scheme you would endorse?
11. Try a different scheme and decide which is preferable

PK6: One compartment IV Plasma and Oral Dosing, and Plasma and Urine sampling
Administrations: 25 mg of drug in 10 ml (oral) and 12.5 mg of drug in 5 ml (IV) on two separate occasions. IV administered as 1 ml/min over 5 min modeled as bolus.
Purpose for inclusion: Multiple dose sites and multiple sample sites



Oral administration
IV administration
IV and **Urinary** observations




```
c
c  p1=Vd
c  p2=Cle
c  p3=Bio
c  p4=Ka
c  p5=Tlag
c  p6=Fe
c  p7=Ke
c
```

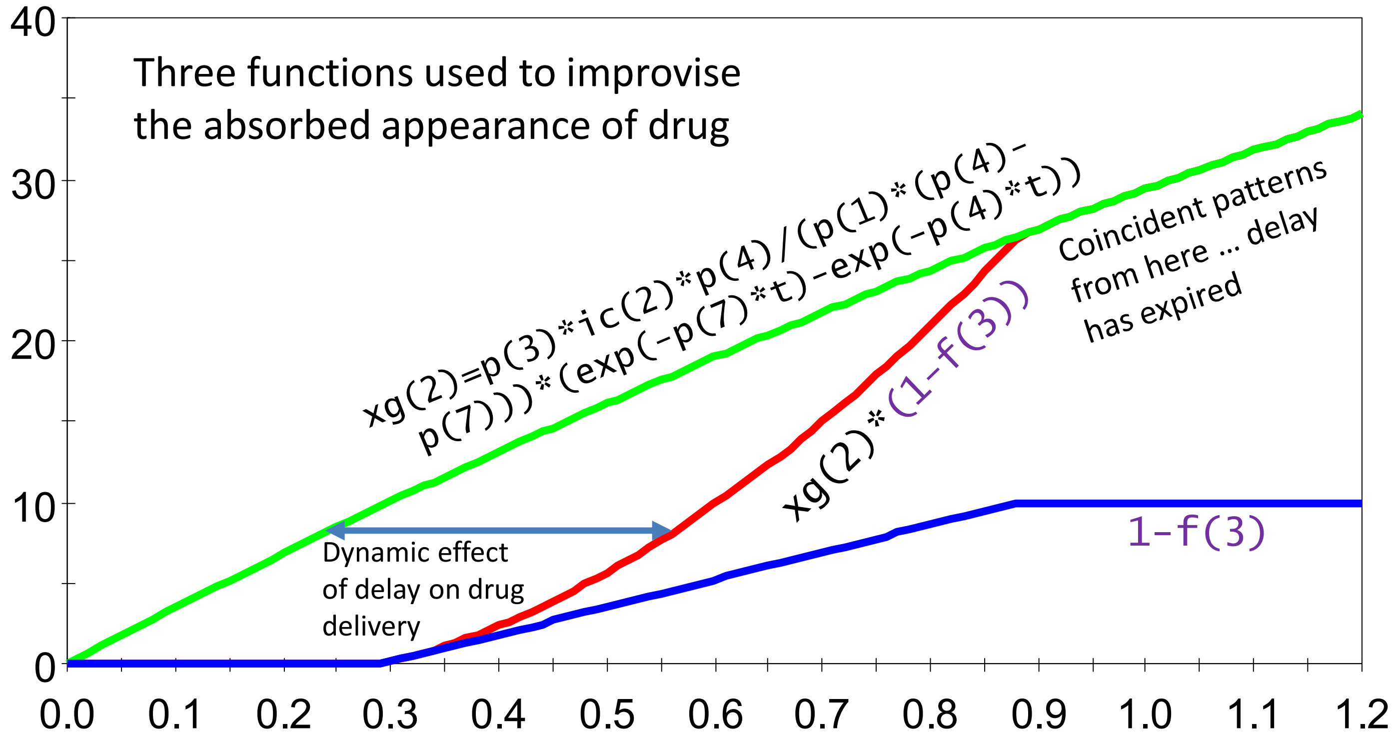
To isolate the time for the oral intake to reach the plasma, and, following that, urine, we use a delay system.
Responses multiplied by ***1-f(3,t)*** are weighted to zero before the delay detects the arrival of the drug from oral route.

```
x  g(2)=p(3)*ic(2)*p(4)/(p(1)*(p(4)-p(7)))*
     (exp(-p(7)*t)-exp(-p(4)*t))*(1-f(3))
```

Plasma response, Oral Admin

```
H PAR
   ic(3)=1
   l(0,3)=1
   dt(3)=p(5)
   dn(3)=2
   p(5)       5.886292E-01  0.000000E+00   1.000000E+00
...
H DAT
x g(3)=p(3)*ic(2)*p(4)/(p(1)*(p(4)-p(7)))*(exp(-p(7)*t)-exp(-p(4)*t))*(1-f(3))
```

Using a delay when there is NO intrinsic dynamic response coupling .. model expressed in the form of Macro constants an Physiological constants



```
...
   P(1)      2.866957E+02  0.000000E+00   1.000000E+03
   P(2)      6.040593E+00  0.000000E+00   1.000000E+03
   P(3)      1.139411E+00  0.000000E+00   1.000000E+01
   P(4)      3.556780E-01  0.000000E+00   1.000000E+00
   P(5)      5.886292E-01  0.000000E+00   1.000000E+00
   P(6)      6.914110E-02  0.000000E+00   1.000000E+00
c
   ic(3)=1
   l(0,3)=1
   dt(3)=p(5)
   dn(3)=2

   p(7)=p(2)/p(1)
   p(11)=p(1)/p(2)
   p(12)=3.3*alog(2)/p(7)
   p(13)=alog(2)/p(7)
   p(14)=p(6)*p(2)
   p(15)=alog(10)/(p(4)-p(7))*alog(p(4)/p(7))+p(5)
   p(16)=p(3)*(ic(2)/p(1))*exp(-p(7)*p(15))
   p(17)=alog(2)/p(4)
c
H DAT
c
c g1=f1
c g2=f2
c g3=f3
c g4=f4
c g5=Rest
c
x g(1)=(ic(1)/p(1))*exp(-(p(2)/p(1))*t)
x g(2)=p(3)*ic(2)*p(4)/(p(1)*(p(4)-p(7)))*
    (exp(-p(7)*t)-exp(-p(4)*t))*(1-f(3))
x g(3)=p(6)*ic(1)*(1-exp(-p(2)/p(1)*t))
x g(5)=(p(2)/p(1))*exp(-p(4)*t)/(p(4)*(p(2)/p(1)-
       p(4)))*(1-f(3))
x g(4)=p(6)*p(4)*p(3)*ic(2)*(1/p(4)+exp(-p(2)/
  p(1)*t)/(p(2)/p(1)-p(4))-g(5))*(1-f(3))
c
101 g(1)                                sd=1
            .333          47.5
...
```

WinSAAM Macro/Physiologic Model to Explain Observations

```
c               c
c p1=Vd          c p11=MRT
c p2=Cle         c p12=T90%
c p3=Bioeq       c p13=T1/2
c p4=Ka          c p14=Clr
c p5=Tlag        c p15=Tmax
c p6=Fe          c p16=Cmax
c p7=Ke          c p17=T1/2ka
```

Model equations in explicit form

```
x g(1)=(ic(1)/p(1))*exp(-(p(2)/p(1))*t)
x g(2)=p(3)*ic(2)*p(4)/(p(1)*(p(4)-p(7)))*
    (exp(-p(7)*t)-exp(-p(4)*t))*(1-f(3))
x g(3)=p(6)*ic(1)*(1-exp(-p(2)/p(1)*t))
x g(5)=(p(2)/p(1))*exp(-p(4)*t)/(p(4)*(p(2)/p(1)-
       p(4)))*(1-f(3))
x g(4)=p(6)*p(4)*p(3)*ic(2)*(1/p(4)+exp(-p(2)/
  p(1)*t)/(p(2)/p(1)-p(4))-g(5))*(1-f(3))
```

101 g(1)			sd=1
	.333	47.5	
	.6667	46.2	
	1	46.5	
	2	42.9	
	3	45.9	
	4	44.8	
	6	40.5	Plasma response IV Administration
	8	38	
	24	26.3	
	48	14.2	
	72	8.8	
	96	5.72	
	168	1.5	
102 g(2)			sd=1
	.333	.94	
	.6667	13.1	
	1	27.9	
	2	38	
	3	71.9	
	4	76.1	
	6	83.9	
	8	75	Plasma response Oral Administration
	24	51.6	
	48	34.9	
	72	23.4	
	96	14.5	
	168	4.5	
103 g(3)			sd=1
	24	340	
	48	550	Urinary response Oral Administration
104 g(4)			sd=1
	24	705	
	48	1210	Urinary response IV Administration

Final Results .. G & W In Italics

PARAMETER	VALUE	ERROR	FSD	
P (1, 0)	2.867E+02	1.895E+00	6.611E-03	*290 L*
P (2, 0)	6.041E+00	4.665E-02	7.723E-03	*6.03 L.h^{-1}*
P (3, 0)	1.139E+00	2.379E-03	2.088E-03	*1.14 Bioavail*
P (4, 0)	3.557E-01	7.361E-03	2.070E-02	*0.42 h^{-1}*
P (6, 0)	6.914E-02	4.327E-04	6.258E-03	*0.069 Absorpt*
P (5, 0)	5.887E-01	2.474E-02	4.203E-02	*0.31 tlag, h*

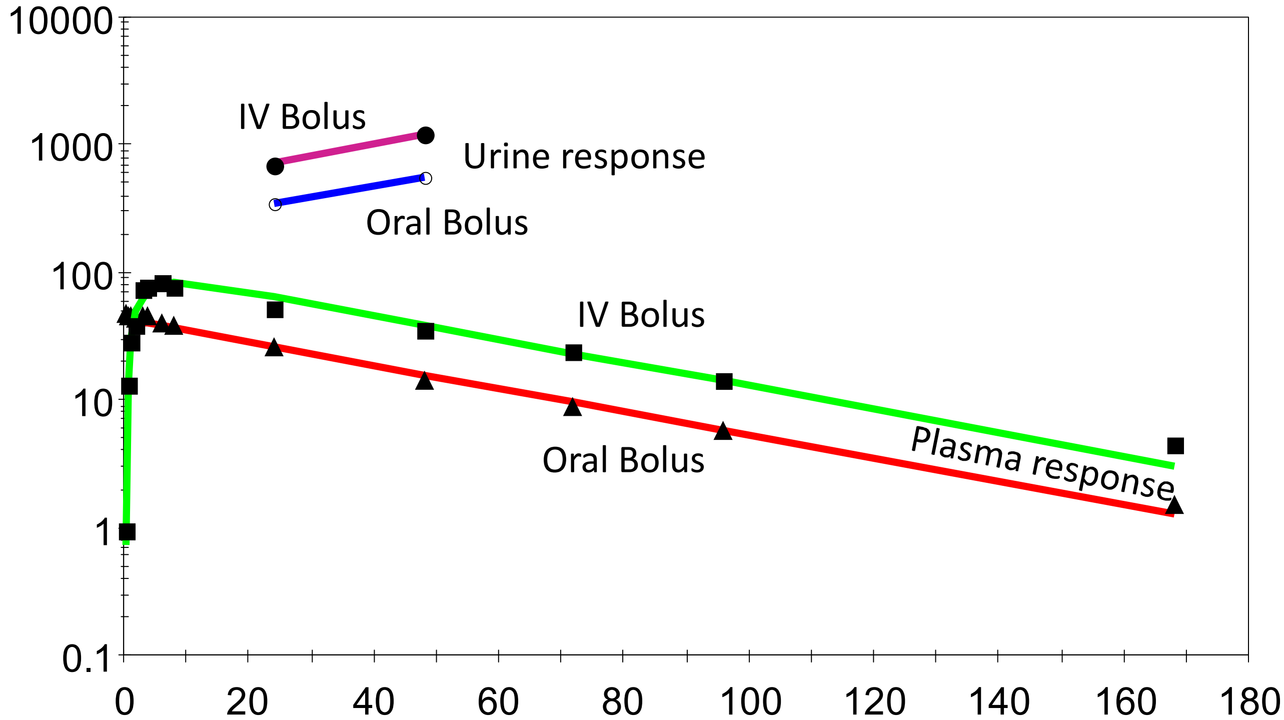
CORRELATION MATRIX

COLUMN	1	2	3	4	5	6
ROW 1	1.00	0.13	-0.24	0.66	0.54	0.06
ROW 2	0.13	1.00	0.25	-0.28	-0.73	-0.07
ROW 3	-0.24	0.25	1.00	-0.59	-0.55	-0.09
ROW 4	0.66	-0.28	-0.59	1.00	0.67	0.16
ROW 5	0.54	-0.73	-0.55	0.67	1.00	0.10
ROW 6	0.06	-0.07	-0.09	0.16	0.10	1.00

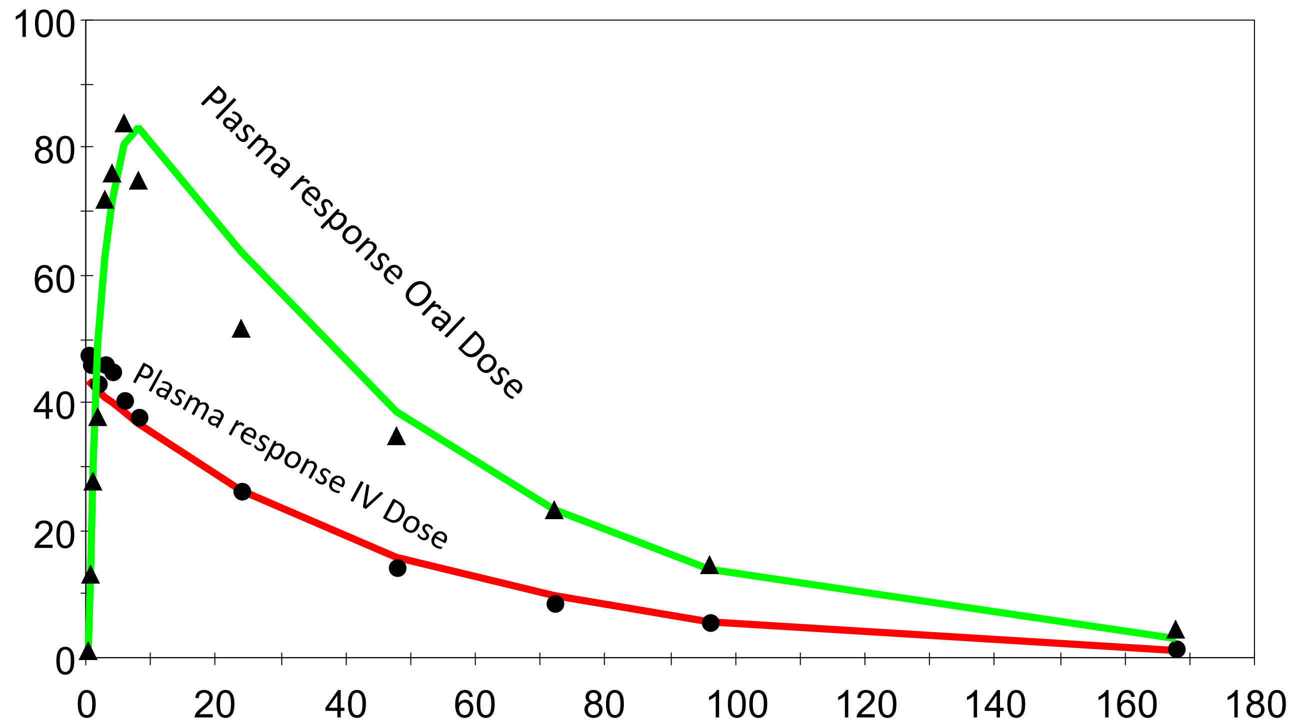
```
c
c p1=Vd
c p2=Cle
c p3=Bio
c p4=Ka
c p5=Tlag
c p6=Fe
c p7=Ke
c
```

Semi log plot of fits to each of the 4 datasets

Plot q(1,2,3,4)



Sometimes linear plots give a more critical perspective



Dependent Parameters and their Errors .. G&W in Bold Italics

INITIAL COMPONENT VALUES

1= 1.2500E+04 2= 2.5000E+04 3= 1.0000E+00

D	C	---CAT--		QC	FSD	
1	11	P	1	2.86695E+02	6.611E-03	***290***
2	11	P	2	6.04057E+00	7.723E-03	***6.0***
3	11	P	3	1.13940E+00	2.088E-03	***1.13***
4	11	P	4	3.55690E-01	2.070E-02	***0.42***
5	11	P	5	5.88661E-01	4.203E-02	***0.31***
6	11	P	6	6.91417E-02	6.258E-03	***0.069***
7	11	P	7	2.10697E-02	9.471E-03	
8	11	P	11	4.74616E+01	9.454E-03	***48***
9	11	P	12	1.08563E+02	9.454E-03	***110***
10	11	P	13	3.28979E+01	9.454E-03	***33***
11	11	P	14	4.17655E-01	5.294E-03	***0.42***
12	11	P	15	2.00365E+01	1.232E-02	***18***
13	11	P	16	6.51411E+01	5.283E-03	***67***
14	11	P	17	1.94874E+00	2.049E-02	***1.7***

C	DATA	SS	NORM.SS	MEAN SD	MEAN FSD
1	13	9.9760E+01	7.6739E+00	2.7702E+00	7.6205E-02
2	13	4.7215E+02	3.6319E+01	6.0265E+00	1.3266E-01
3	2	9.1820E+00	4.5910E+00	2.1427E+00	4.4970E-03
4	2	7.5968E+00	3.7984E+00	1.9489E+00	2.1794E-03

```
c
c p1=Vd
c p2=Cle
c p3=Bio
c p4=Ka
c p5=Tlag
c p6=Fe
c p7=ke
c
c p11=MRT
c p12=T90%
c p13=T1/2
c p14=Clr
c p15=Tmax
c p16=Cmax
c p17=T1/2ka
c
   ic(1)=12500
   ic(2)=25000
c ic1=IV dose
c ic2=PO dose
```

Model equations from G & W (6:1 – 6:4) in Mathematical Form

$$C = \frac{D_{IV}}{V}\exp(-\frac{Cl}{V}.t)$$

Plasma Response IV Bolus dose

$$X_u = f_e D_{IV}[1 - \exp(-\frac{Cl}{V}.t)]$$

Corresponding Cumul. Urine Response

$$C = \frac{K_a F D_{PO}}{V(K_a - \frac{Cl}{V})}[\exp(-\frac{Cl}{V}.(t - t_{lag})) - \exp(-K_a.(t - t_{lag}))]$$

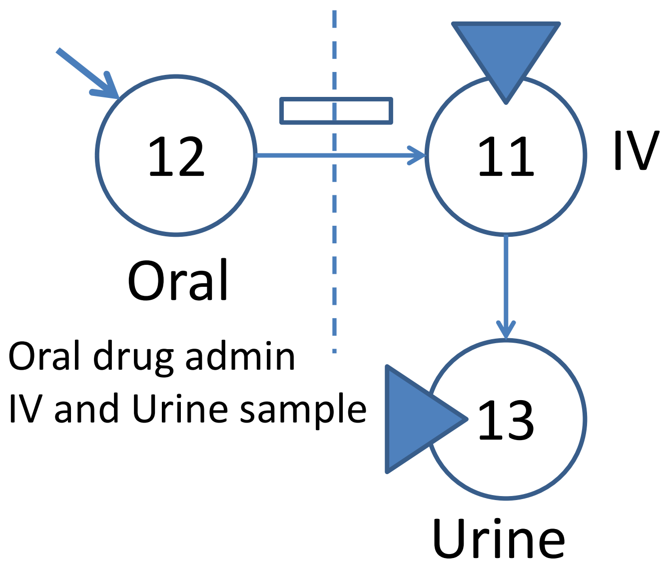
Plasma Response after Extravasc. Admin.

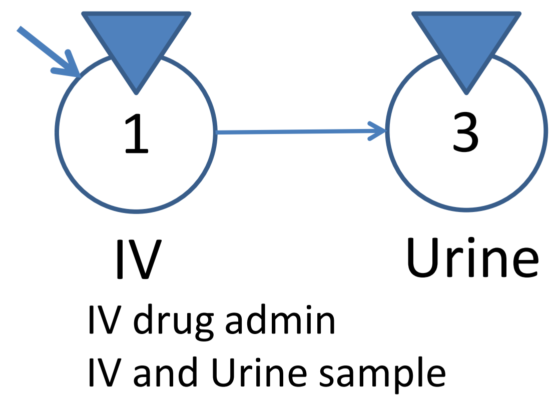
$$X_u = f_e K_a F D_{PO}[\frac{1}{K_a} + \frac{\exp(-\frac{Cl}{V}.(t - t_{lag}))}{\frac{Cl}{V} - K_a} - \frac{\frac{Cl}{V}\exp(-K_a.(t - t_{lag}))}{K_a(\frac{Cl}{V} - K_a)}]$$

Corresponding Cumul. Urine Response

Investigating this data in another (more natural) metric

Perspectives on Data and Data Collection





It is possible to reproduce this model with conventional WinSAAM constructs (natural metric) and derive ALL the ancillary indices

```
A SAAM31
2       10
H PAR
c
 ic(1)=12500
 ic(12)=25000
 ic(5)=1

   l(0,5)=1
   DT(5)      6.008196E-01  0.000000E+00   1.000000E+02
   DN(5)=2
   K(1)       3.696602E-03  0.000000E+00   1.000000E+03

   k(11)=k(1)
   K(3)       7.101075E-02  0.000000E+00   1.000000E+04
   K(13)      8.070253E-02  0.000000E+00   1.000000E+04
   L(3,1)     2.013443E-02  0.000000E+00   1.000000E+03
   L(13,11)=l(3,1)
   L(11,12)   4.038501E-01  0.000000E+00   1.000000E+03

 p(1)=1/k(1)
 p(2)=p(1)*l(3,1)
 p(3)=k(13)/k(3)
 p(4)=L(11,12)
 p(5)=dt(5)
 p(6)=k(3)
 p(7)=l(3,1)
 p(21)=p(1)/p(2)
 p(22)=3.3*alog(2)*p(21)
 p(23)=alog(2)*p(21)
 p(24)=p(6)*p(2)
 p(25)=(alog(10)/(p(4)-p(7)))*alog(p(4)/p(7))+p(5)
 p(26)=p(3)*(ic(12)/p(1))*exp(-p(7)*p(25))
 p(27)=alog(2)/p(4)

H DAT
x g(11)=f(11)*(1-f(5))
x uf(7)=f(1)
x uf(8)=f(11)
x g(40)=f(8)*ic(1)/f(7)/ic(12)
```

```
c p1=Vd
c p2=Cle
c p3=Bio
c p4=Ka
c p5=Tlag
c p6=Fe
c p7=ke
c
c p21=MRT
c p22=T90%
c p23=T1/2
c P24=Clr
c P25=Tmax
c P26=Cmax
c P27=T1/2Ka
c
```

PARAMETER	VALUE	ERROR	FSD
DT(5, 0)	6.008E-01	2.481E-02	4.130E-02
L (3, 1)	2.014E-02	1.836E-04	9.116E-03
L (11,12)	4.037E-01	8.344E-03	2.067E-02
K (1, 0)	3.696E-03	2.407E-05	6.511E-03
K (3, 0)	7.101E-02	4.271E-04	6.015E-03
K (13, 0)	8.068E-02	4.271E-04	5.294E-03

Another perspective of the WinSAAM model using Micro Rate Constants

```
A  SAAM31
2       10
H  PAR
c
c  p1=Vd
c  p2=Cle
c  p3=Bio
c  p4=Ka
c  p5=Tlag
c  p6=Fe
c  p7=ke
c
c  p21=MRT
c  p22=T90%
c  p23=T1/2
c  P24=Clr
c  P25=Tmax
c  P26=Cmax
c  P27=T1/2Ka
c
   ic(1)=12500
   ic(12)=25000
   ic(5)=1
c
   l(0,5)=1
   DT(5)     6.008196E-01  0.000000E+00   1.000000E+02
   dn(5)=2
c
   K(1)      3.696602E-03  0.000000E+00   1.000000E+03
   k(11)=k(1)
   K(3)      7.101075E-02  0.000000E+00   1.000000E+04
   K(13)     8.070253E-02  0.000000E+00   1.000000E+04
c
   L(3,1)    2.013443E-02  0.000000E+00   1.000000E+03
   L(13,11)=l(3,1)
   L(11,12)  4.038501E-01  0.000000E+00   1.000000E+03
```

Dependencies

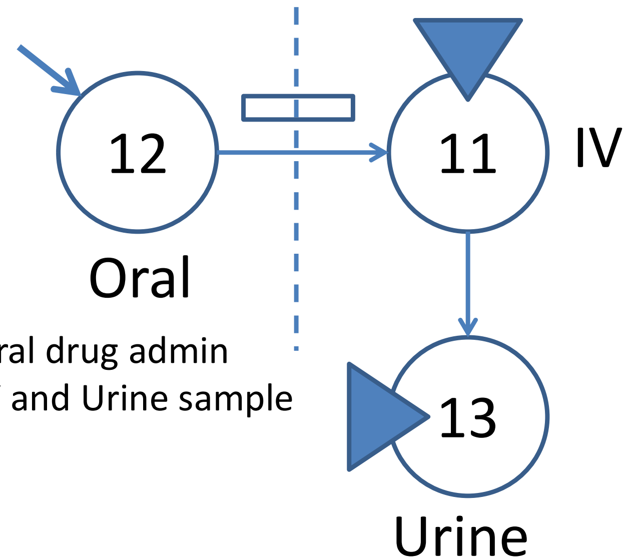
```
c
 p(1)=1/k(1)
 p(2)=p(1)*l(3,1)
 p(3)=k(13)/k(3)
 p(4)=L(11,12)
 p(5)=dt(5)
 p(6)=k(3)
 p(7)=l(3,1)
 p(21)=p(1)/p(2)
 p(22)=3.3*alog(2)*p(21)
 p(23)=alog(2)*p(21)
 p(24)=p(6)*p(2)
 p(25)=(alog(10)/(p(4)-p(7)))*alog(p(4)/p(7))+p(5)
 p(26)=p(3)*(ic(12)/p(1))*exp(-p(7)*p(25))
 p(27)=alog(2)/p(4)
H DAT
x g(11)=f(11)*(1-f(5))
x uf(7)=f(1)
x uf(8)=f(11)
x g(40)=f(8)*ic(1)/f(7)/ic(12)
120 g(40)
            1000
121
   p(1)
   p(2)
   p(3)
   p(4)
   p(5)
   p(6)
   p(7)
   p(21)
   p(22)
   p(23)
   p(24)
   p(25)
   p(26)
   p(27)
```

Perspectives on Data and Data Collection

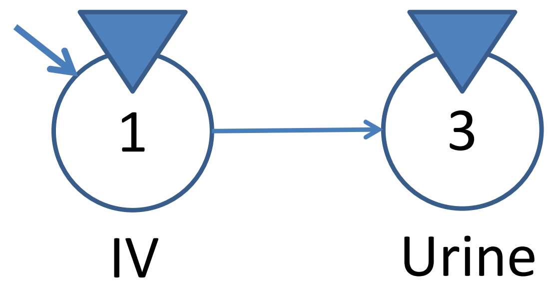
	101			sd=1
		.333	47.5	
		.6667	46.2	
		1	46.5	
		2	42.9	
		3	45.9	
		4	44.8	
IV Admin		6	40.5	
		8	38	
		24	26.3	
		48	14.2	
		72	8.8	
		96	5.72	
		168	1.5	
	111 g(11)			sd=1
		.333	.94	
		.6667	13.1	
		1	27.9	
		2	38	
		3	71.9	
Oral Admin		4	76.1	
		6	83.9	
		8	75	
		24	51.6	
		48	34.9	
		72	23.4	
		96	14.5	
		168	4.5	
	103			sd=1
IV Admin		24	340	
		48	550	
	113			sd=1
Oral Admin		24	705	
		48	1210	

IV Samples Taken

Urine Samples



Oral drug admin
IV and Urine sample



IV drug admin
IV and Urine sample

Results from Macro Constant and Micro Rate Constant Modeling cf G&W (Right)

INITIAL COMPONENT VALUES

1= 1.2500E+04   5= 1.0000E+00   12= 2.5000E+04

D	C	---CAT--		QC	FSD	D	C	---CAT--		QC	FSD	
1	21	P	1	2.70539E+02	4.592E-03	1	11	P	1	2.86695E+02	6.611E-03	*290*
2	21	P	2	5.44771E+00	6.023E-03	2	11	P	2	6.04057E+00	7.723E-03	*6.0*
3	21	P	3	1.13620E+00	9.704E-04	3	11	P	3	1.13940E+00	2.088E-03	*1.13*
4	21	P	4	4.03705E-01	2.067E-02	4	11	P	4	3.55690E-01	2.070E-02	*0.42*
5	21	P	5	6.00820E-01	4.130E-02	5	11	P	5	5.88661E-01	4.203E-02	*0.31*
6	21	P	6	7.10061E-02	5.813E-03	6	11	P	6	6.91417E-02	6.258E-03	*0.069*
7	21	P	7	2.01365E-02	9.116E-03	7	11	P	7	2.10697E-02	9.471E-03	*0.021*
8	21	P	21	4.96611E+01	9.028E-03	8	11	P	11	4.74616E+01	9.454E-03	*48*
9	21	P	22	1.13594E+02	9.028E-03	9	11	P	12	1.08563E+02	9.454E-03	*110*
10	21	P	23	3.44224E+01	9.028E-03	10	11	P	13	3.28979E+01	9.454E-03	*33*
11	21	P	24	3.86820E-01	2.736E-03	11	11	P	14	4.17655E-01	5.294E-03	*0.42*
12	21	P	25	1.85989E+01	1.271E-02	12	11	P	15	2.00365E+01	1.232E-02	*18*
13	21	P	26	7.21960E+01	1.583E-03	13	11	P	16	6.51411E+01	5.283E-03	*67*
14	21	P	27	1.71696E+00	2.045E-02	14	11	P	17	1.94874E+00	2.049E-02	*1.7*

C	DATA	SS	NORM.SS	MEAN SD	MEAN FSD
1	13	4.0405E+01	3.1081E+00	1.7630E+00	6.9616E-02
3	2	3.2850E-02	1.6425E-02	1.2816E-01	3.1327E-04
11	13	4.0190E+02	3.0916E+01	5.5602E+00	1.3869E-01
13	2	7.2734E+00	3.6367E+00	1.9070E+00	2.2089E-03

SUM SQUARES AFTER 2 ITERATIONS IS 4.49615143E+02

COMP 1= 4.0405483E+01

COMP 3= 3.2849588E-02

COMP 11= 4.0190338E+02

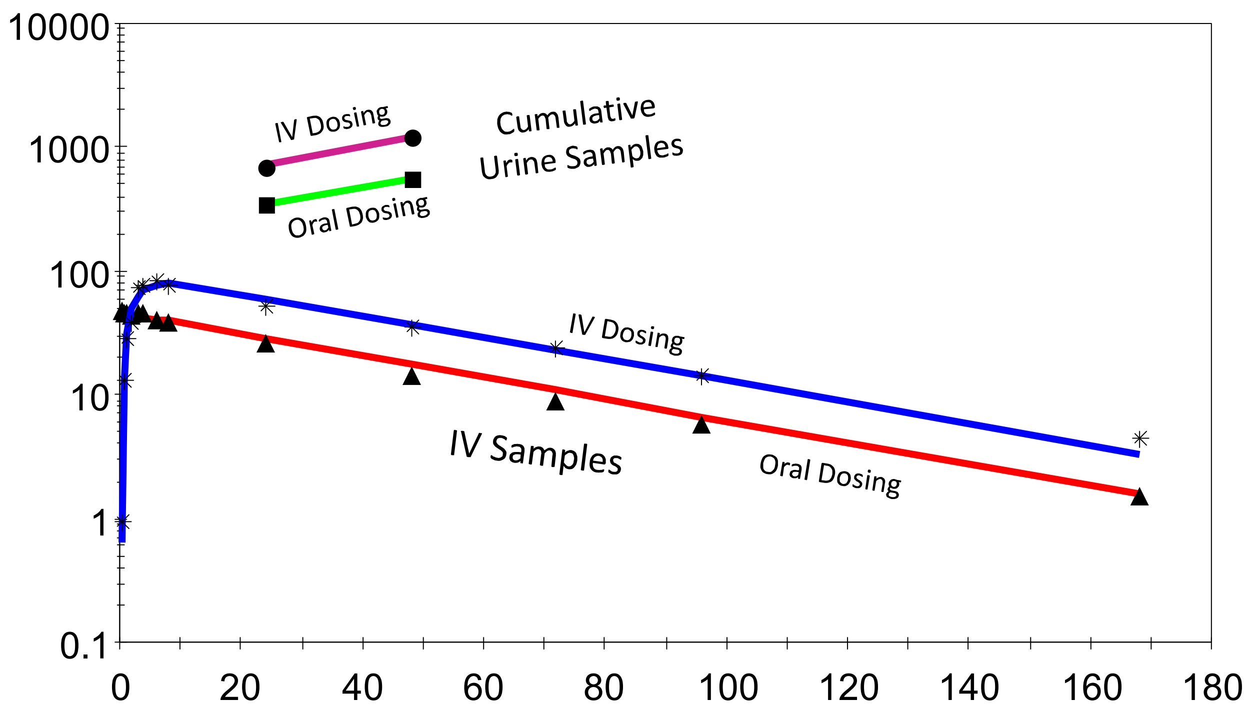
COMP 13= 7.2734337E+00

SIG AFTER 2 ITERATIONS IS 1.00000000E+00

ADJUSTABLE PARAMETERS				SD	FSD
1	DT(5, 0)=	6.0082048E-01	+OR-	2.4811685E-02	4.1296E-02
2	L (3, 1)=	2.0136490E-02	+OR-	1.8357337E-04	9.1165E-03
3	L (11,12)=	4.0370536E-01	+OR-	8.3443206E-03	2.0669E-02
4	K (1, 0)=	3.6963234E-03	+OR-	2.4066861E-05	6.5110E-03
5	K (3, 0)=	7.1006060E-02	+OR-	4.2711216E-04	6.0152E-03
6	K (13, 0)=	8.0676891E-02	+OR-	4.2712584E-04	5.2943E-03

```
c p1=Vd
c p2=Cle
c p3=Bio
c p4=Ka
c p5=Tlag
c p6=Fe
c p7=ke
c
c p21=MRT
c p22=T90%
c p23=T1/2
c P24=Clr
c P25=Tmax
c P26=Cmax
c P27=T1/2Ka
```

Fitted model agreeing with observations at least as well as G&W



WinSAAM Version of PK6

```
A SAAM31
2       10
H PAR
c
c p1=Vd
c p2=Cle
c p3=Bio
c p4=Ka
c p5=Tlag
c p6=Fe
c p7=ke
c
c p21=MRT
c p22=T90%
c p23=T1/2
c P24=Clr
c P25=Tmax
c P26=Cmax
c P27=T1/2Ka
c
   ic(1)=12500
   ic(12)=25000
   ic(5)=1
c Comp  1, 11 .. Plasma IV, Plasma Oral
c Comp 12,     .. Gut
c Comp  3, 13 .. Urine  IV, Urine  Oral
   l(0,5)=1
   DT(5)     6.008196E-01  0.000000E+00   1.000000E+02
   dn(5)=2
c
   K(1)      3.696602E-03  0.000000E+00   1.000000E+03
   k(11)=k(1)
   K(3)      7.101075E-02  0.000000E+00   1.000000E+04
   K(13)     8.070253E-02  0.000000E+00   1.000000E+04
c
   L(3,1)    2.013443E-02  0.000000E+00   1.000000E+03
   L(13,11)=l(3,1)
   L(11,12)  4.038501E-01  0.000000E+00   1.000000E+03
c
 p(1)=1/k(1)
 p(2)=p(1)*l(3,1)
 p(3)=k(13)/k(3)
 p(4)=L(11,12)
 p(5)=dt(5)
 p(6)=k(3)
 p(7)=l(3,1)
 p(21)=p(1)/p(2)
 p(22)=3.3*alog(2)*p(21)
 p(23)=alog(2)*p(21)
 p(24)=p(6)*p(2)
 p(25)=(alog(10)/(p(4)-p(7)))*alog(p(4)/p(7))+p(5)
 p(26)=p(3)*(ic(12)/p(1))*exp(-p(7)*p(25))
 p(27)=alog(2)/p(4)
H DAT
x g(11)=f(11)*(1-f(5))
x uf(7)=f(1)
x uf(8)=f(11)
x g(40)=f(8)*ic(1)/f(7)/ic(12)
120 g(40)
            1000
121
   p(1)
   p(2)
   p(3)
   p(4)
   p(5)
   p(6)
   p(7)
   p(21)
   p(22)
   p(23)
   p(24)
   p(25)
   p(26)
   p(27)
101                                     sd=1
            .333          47.5
            .6667         46.2
            1             46.5
            2             42.9
            3             45.9
            4             44.8
            6             40.5
            8             38
            24            26.3
            48            14.2
            72            8.8
            96            5.72
            168           1.5
111 g(11)                               sd=1
            .333          .94
            .6667         13.1
            1             27.9
            2             38
            3             71.9
            4             76.1
            6             83.9
            8             75
            24            51.6
            48            34.9
            72            23.4
            96            14.5
            168           4.5
103                                     sd=1
            24            340
            48            550
113                                     sd=1
            24            705
            48            1210
```

Translation PK6 from G & W
.. with minor variations

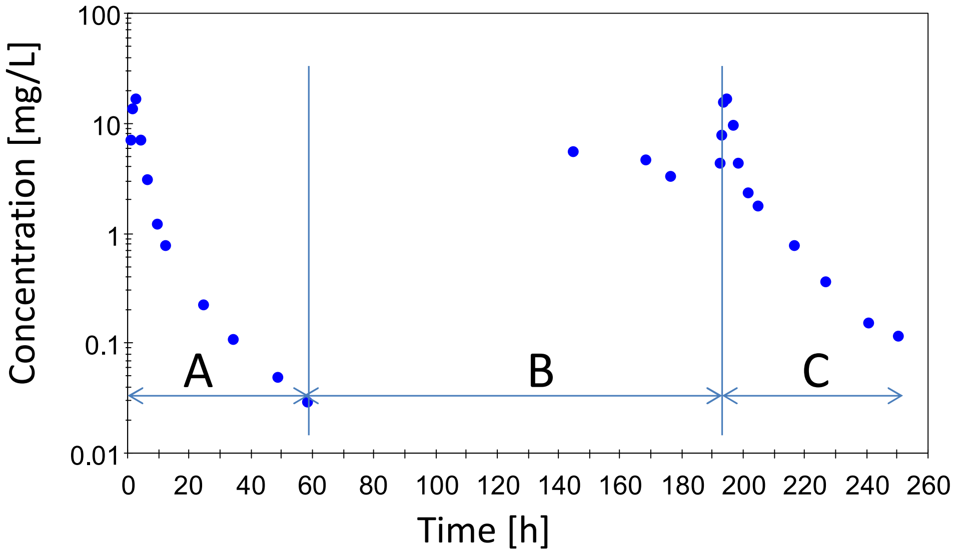
```
A SAAM31
2       10
H PAR
c
c p1=Vd
c p2=Cle
c p3=Bio
c p4=Ka
c p5=Tlag
c p6=Fe
c p7=ke
c
c p11=MRT
c p12=T90%
c p13=T1/2
c p14=Clr
c p15=Tmax
c p16=Cmax
c p17=T1/2ka
c
   ic(1)=12500
   ic(2)=25000
c ic1=IV dose
c ic2=PO dose
   P(1)      2.866957E+02  0.000000E+00   1.000000E+03
   P(2)      6.040593E+00  0.000000E+00   1.000000E+03
   P(3)      1.139411E+00  0.000000E+00   1.000000E+01
   P(4)      3.556780E-01  0.000000E+00   1.000000E+00
   P(5)      5.886292E-01  0.000000E+00   1.000000E+00
   P(6)      6.914110E-02  0.000000E+00   1.000000E+00
c
   ic(3)=1
   l(0,3)=1
   dt(3)=p(5)
   dn(3)=2
   p(7)=p(2)/p(1)
   p(11)=p(1)/p(2)
   p(12)=3.3*alog(2)/p(7)
   p(13)=alog(2)/p(7)
   p(14)=p(6)*p(2)
   p(15)=alog(10)/(p(4)-p(7))*alog(p(4)/p(7))+p(5)
   p(16)=p(3)*(ic(2)/p(1))*exp(-p(7)*p(15))
   p(17)=alog(2)/p(4)
c
H DAT
111
   p(1)
   p(2)
   p(3)
   p(4)
   p(5)
   p(6)
   p(7)
   p(11)
   p(12)
   p(13)
   p(14)
   p(15)
   p(16)
   p(17)
c g1=f1
c g2=f2
c g3=f3
c g4=f4
c g5=Rest
x g(1)=(ic(1)/p(1))*exp(-(p(2)/p(1))*t)
x g(2)=p(3)*ic(2)*p(4)/(p(1)*(p(4)-p(7)))*
    (exp(-p(7)*t)-exp(-p(4)*t))*(1-f(3))
x g(3)=p(6)*ic(1)*(1-exp(-p(2)/p(1)*t))
x g(5)=(p(2)/p(1))*exp(-p(4)*t)/(p(4)*(p(2)/p(1)-
       p(4)))*(1-f(3))
x g(4)=p(6)*p(4)*p(3)*ic(2)*(1/p(4)+exp(-p(2)/
  p(1)*t)/(p(2)/p(1)-p(4))-g(5))*(1-f(3))
c
101 g(1)                                  sd=1
            .333          47.5
            .6667         46.2
            1             46.5
            2             42.9
            3             45.9
            4             44.8
            6             40.5
            8             38
            24            26.3
            48            14.2
            72            8.8
            96            5.72
            168           1.5
102 g(2)                                  sd=1
            .333          .94
            .6667         13.1
            1             27.9
            2             38
            3             71.9
            4             76.1
            6             83.9
            8             75
            24            51.6
            48            34.9
            72            23.4
            96            14.5
            168           4.5
103 g(3)                                  sd=1
            24            340
            48            550
104 g(4)                                  sd=1
            24            705
            48            1210
```

Questions and suggestions

1. How was the absorption lag implemented in the Micro Rate Constant model of this system?
2. Can you suggest why this was done?
3. What are the alternatives?
4. Have you ever had a situation where the temporal resolution of your data interfered with the detection of a delay?
5. Do you think that this might have been the case here?
6. Re enter the Micro Rate Constant version of this system and explore the use of different configurations of the absorption delay. Think carefully as you explore alternatives … balance between reality, practicality, precision, and plausibility

PK11-Edn. 1 Volunteers were administered orally 400 mg on day 1 of a trial for a new drug and on day 5 (at 96 h) they were started on an oral 400 mg t.i.d. (**tid=three times a day**) for 5 days (days 5 thru 9 of the study .. only receiving the AM oral dose on day 9). The purpose of this analysis was to explore the possibility of resolving **PK** and PD consequences of the drug.

Our specific agenda was to explore the use of **resetting functions** to achieve the drug delivery schedule modeling the system in WinSAAM.



Observed conc. time data showing the three phases of the study …

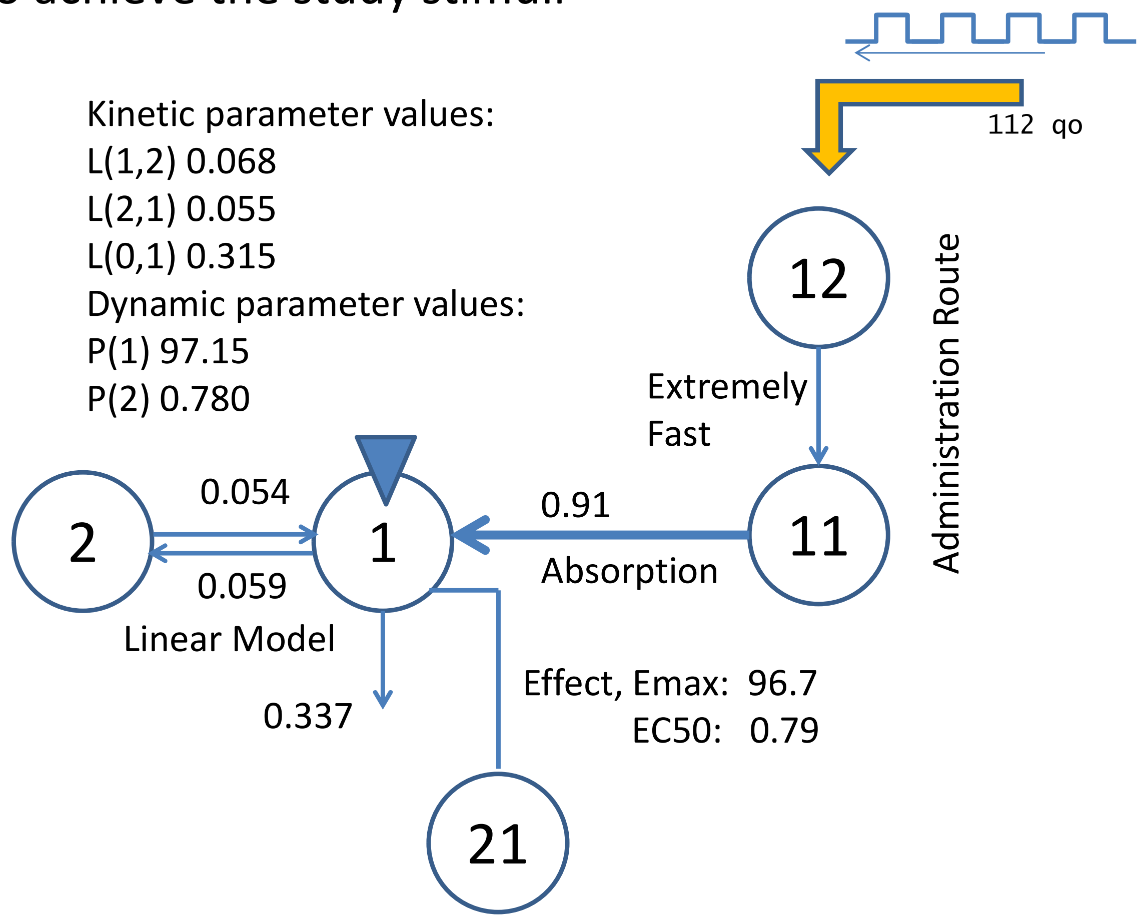
A: **First phase** (One 400 mg Oral dose),

B: **Repetitive phase** (5 Days 5-9, Oral 400 mg ***tid*** (3 times/day), and

C: **Final phase** (One 400 mg Oral dose AM)

Using the resetting function ‘QO’ to achieve the study stimuli

Kinetic parameter values:
L(1,2) 0.068
L(2,1) 0.055
L(0,1) 0.315
Dynamic parameter values:
P(1) 97.15
P(2) 0.780



0	400
0.1	0
96	400
96.1	0
104	400
104.1	0
112	400
112.1	0
120	400
120.1	0
128	400
128.1	0
136	400
136.1	0
144	400
144.1	0
152	400
152.1	0
160	400
160.1	0
168	400
168.1	0
176	400
176.1	0
184	400
184.1	0
192	400
192.1	0

```
A SAAM31 PK 11, REPETITIVE ORAL ADMINISTRATION
2       10
H PAR
   L(1,11)    9.107984E-01  0.000000E+00   1.000000E+02
   L(2,1)     5.382920E-02  0.000000E+00   1.000000E+02
   L(1,2)     5.953036E-02  0.000000E+00   1.000000E+02
   L(0,1)     3.370228E-01  0.000000E+00   1.000000E+02
   l(11,12) 1000
   K(1)       5.921686E-02
   P(1)       9.656172E+01  0.000000E+00   1.000000E+04
   P(2)       7.903673E-01  0.000000E+00   1.000000E+00
H DAT
X G(1) = k(1)*f(1)
X G(21)=P(1)*g(1)/(P(2)+g(1))
112 qo
            0           400
            0.1         0
            96          400
            96.1        0
            104         400
            104.1       0
            112         400
            112.1       0
            120         400
            120.1       0
            128         400
            128.1       0
            136         400
            136.1       0
            144         400
            144.1       0
            152         400
            152.1       0
            160         400
            160.1       0
            168         400
            168.1       0
            176         400
            176.1       0
            184         400
            184.1       0
            192         400
            192.1       0
```

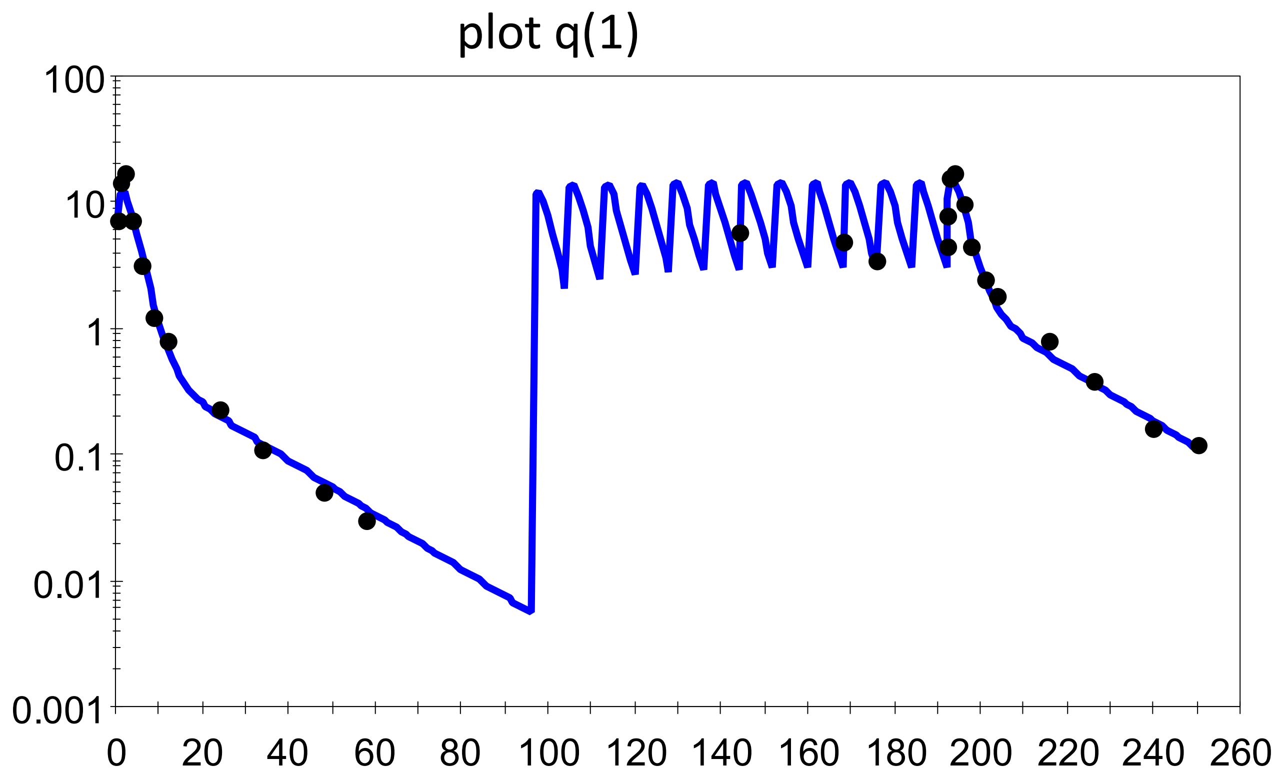
WinSAAM Code for this Investigation
Note fast delivery using QO resetter

```
101                                  FSD=.05
        0.5        7.24
        1          14.21
        2          17.2
        4          7.27
        6          3.18
        9          1.25
        12         0.8
        24         0.23
        34         0.11
        48         0.05
        58         0.03
        144        5.79
        168        4.86
        176        3.45
        192        4.53
        192.5      8.01
        193        15.87
        194        17.01
        196        9.84
        198        4.47
        201        2.42
        204        1.81
        216        0.8
        226        0.38
        240        0.16
        250        0.12
121 G(21)                            fsd=.05
        0.5        85.69
        1          93.9
        2          94.43
        4          85.2
        6          74.62
        9          50.48
        12         42.31
        24         20.85
        34         9.95
        144        84.83
        168        81.21
        176        78.14
        192        78.51
        192.5      89.43
        193        93.92
        194        93.71
        196        91.78
        198        81.94
        201        70.46
        204        71.24
        216        46.33
        226        28.51
        240        30.68
        250        26.69
101
        0
2       1                            250
```

Linear Kinetic Data

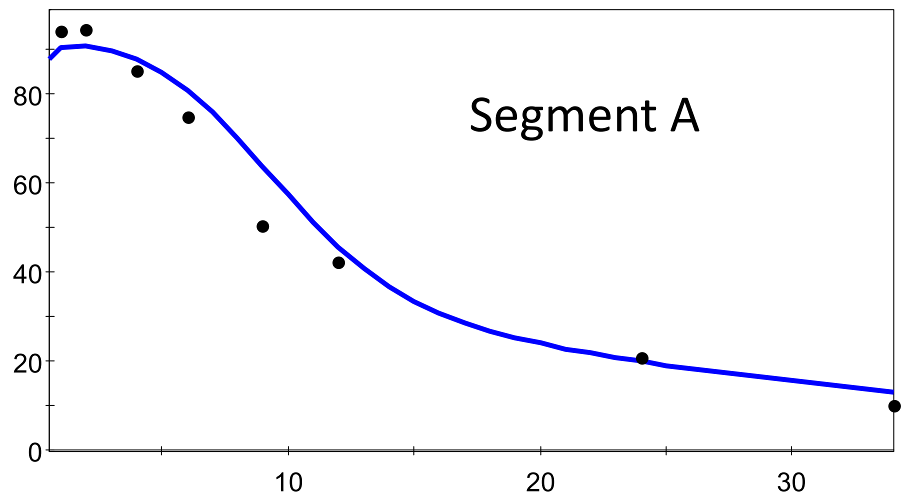
Dynamic Emax Data

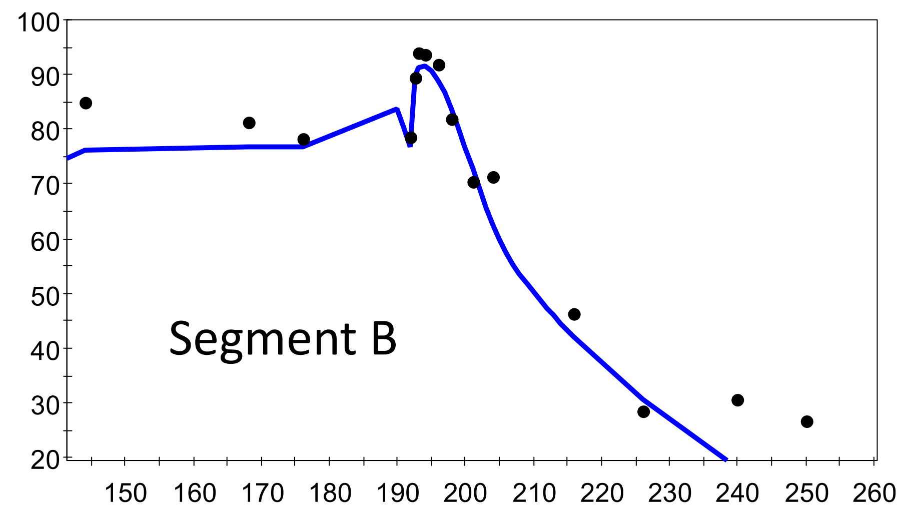
Fit of the kinetic model to the three phases of the study for one subjects



plot q(21)

Two segments of the dynamic response of the system





Final estimates and errors of adjustable parameters

PARAMETER	VALUE	ERROR	FSD		
					Dynamic
P (1, 0)	9.643E+01	1.558E+00	1.615E-02	97	EMAX Model
P (2, 0)	7.852E-01	3.460E-02	4.407E-02	.78	EC50
L (1,11)	9.115E-01	3.250E-02	3.565E-02		
L (2, 1)	5.328E-02	2.362E-03	4.434E-02	Linear* Kinetic Model	
L (1, 2)	5.916E-02	1.545E-03	2.611E-02	0.33	Tlag .. (L2,1)
L (0, 1)	3.370E-01	3.484E-03	1.034E-02	0.05	β

CORRELATION MATRIX#

COLUMN	1	2	3	4	5	6
ROW 1	1.00	0.73	-0.03	0.20	0.12	0.11
ROW 2	0.73	1.00	-0.02	0.35	0.29	0.02
ROW 3	-0.03	-0.02	1.00	-0.33	-0.06	-0.62
ROW 4	0.20	0.35	-0.33	1.00	0.79	0.63
ROW 5	0.12	0.29	-0.06	0.79	1.00	0.18
ROW 6	0.11	0.02	-0.62	0.63	0.18	1.00

* G&W Only report Macro Elements here a=0.38 h^{-1} and b=0.05 h^{-1}
All L's proximal to G&W

Level of elements of Correlation Matrix reinforce identifiability of param estimates

Questions and suggestions:

Compare and contrast problems PK11 and PK4 in regard to emulation of the administration …

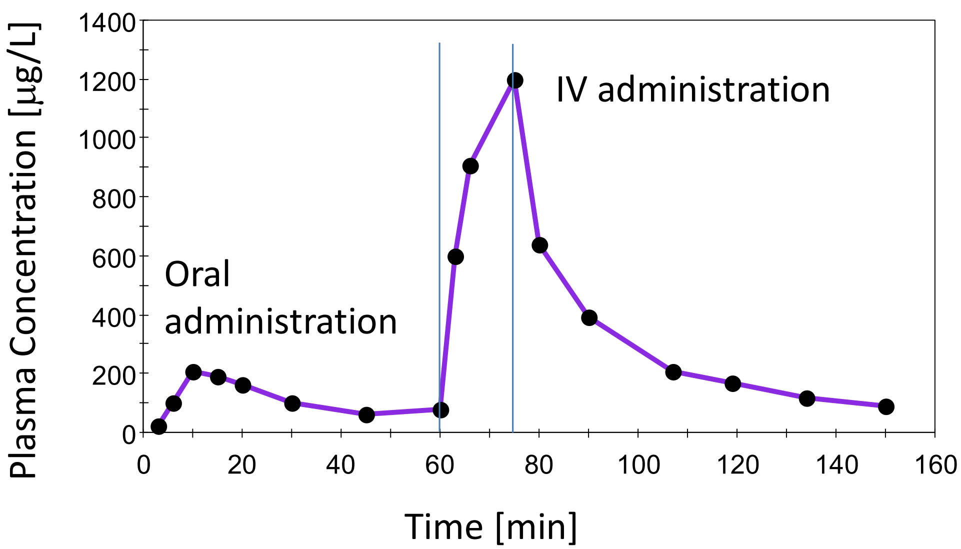
1. which is more easily controlled?
2. which is more accurate?
3. how does one approach offer greater accuracy than the other?
4. are advantages of one approach over the other large enough that the accuracy issue may be relegated for a while
5. what would you consider the better approach for exploring the system response
6. use the administration approach implemented in PK4 with the study described in PK11 and compare the results … does this change your ideas about the issue of loss of precision

PK12 – Intravenous and Oral Drug Dosing

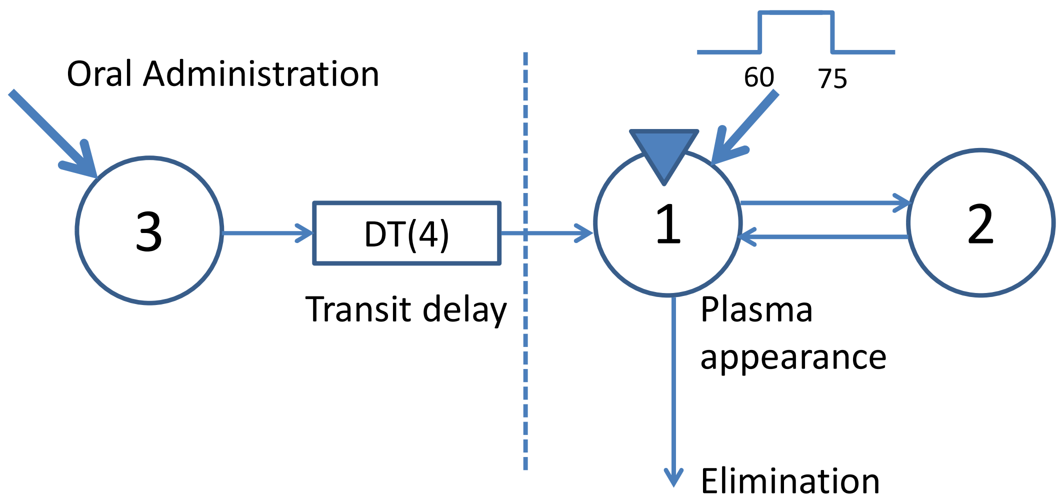
In this example the provision of **short intervals** between **IV and Oral** administrations to facilitate the **estimation** of absolute **bioavailability** are demonstrated using a sequence of challenges that provide a basis for such estimation.

2.5 mg/kg of a drug is administered orally followed, 60 minutes later, by a 15 minute IV infusion of 0.5 mg/kg of the drug.

Purpose: We will demonstrate how **all** common PK **parameters** (clearances, volumes of distribution, bioavailability, absorption, and oral latency) are estimable using the natural metric of the WinSAAM simulation software



Plasma observations of drug disposition



PARAMETER	VALUE	ERROR	FSD
L (0, 1)	1.209E-01	2.245E-03	1.856E-02
L (2, 1)	1.743E-01	6.729E-03	3.860E-02
L (1, 2)	7.627E-02	2.728E-03	3.577E-02
L (4, 3)	1.049E-01	4.733E-03	4.510E-02
DT(4, 0)	4.653E+00	9.600E-02	2.063E-02
P (2, 0)	4.628E-02	1.018E-03	2.200E-02
K (1, 0)	8.303E+00	1.323E-01	1.594E-02

WinSAAM model of drug study

```
A SAAM31
2      10
H PAR
c
c PK12 GW-4
c
c p11=Vd
c p12=Cl
c p13=Vt
c p14=Cld
c
 p(11)=1/k(1)
 p(12)=p(11)*l(0,1)
 p(13)=p(11)*l(2,1)/l(1,2)
 p(14)=p(13)*l(1,2)
c
   K(1)      7.895522E+00  0.000000E+00   1.000000E+04
   L(0,1)    1.137547E-01  0.000000E+00   1.000000E+01
   L(2,1)    1.453584E-01  0.000000E+00   1.000000E+01
   L(1,2)    5.819302E-02  0.000000E+00   1.000000E+01
c
   L(4,3)    9.967976E-02  0.000000E+00   1.000000E+01
   DT(4)     4.545013E+00  0.000000E+00   1.000000E+01
   dn(4)=2
   l(1,4)=1
   P(2)      4.692819E-02  0.000000E+00   1.000000E+02
c
 ic(3)=2500*p(2)
 p(1)=500/15
 p(3)=dt(4)
H DAT
   k(1)
   l(2,1)
   l(1,2)
   l(0,1)
   l(4,3)
   p(2)
   p(3)
   p(11)
   p(12)
   p(13)
   p(14)
```

```
c
x uf(1)=p(1)*f(5)
105 qo
            0            0
            60           1
            75           0
101                                   SD=5
            3            20
            6            100
            10           210
            15           190
            20           160
            30           100
            45           60
            60           80
            63           600
            66           910
            75           1200
            80           640
            90           390
            107          210
            119          170
            134          120
            150          90
101
            0
2           .1                        1500
```

Parameters from WinSAAM and G&W

```
INITIAL COMPONENT VALUES
  3=  1.1571E+02
```

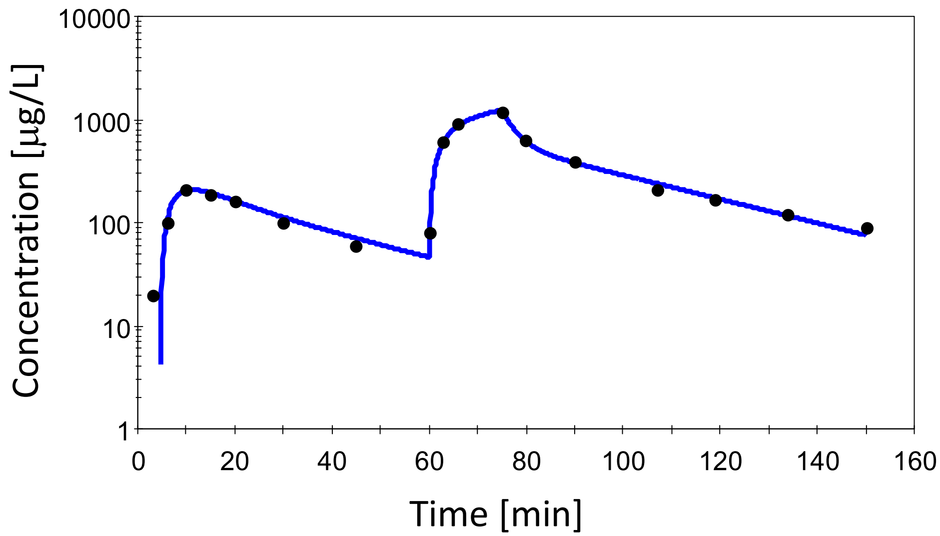
D	C	---CAT--			QC		FSD	*Common PK Parameters	
1	0	K	1		8.30339E+00	*	1.571E-02		
2	0	L	2	1	1.74324E-01		3.860E-02		
3	0	L	1	2	7.62720E-02		3.577E-02		
4	0	L	0	1	1.20942E-01		1.856E-02		
5	0	L	4	3	1.04945E-01		4.510E-02	*0.103*	*Ka /min*
6	0	P	2		4.62825E-02		2.200E-02	*0.0462*	*Bioavail.*
7	0	P	3		4.65318E+00		2.063E-02	*4.68*	*Tlag min*
8	0	P	11		1.20433E-01		1.583E-02	*0.1209*	*Vc L/kg*
9	0	P	12		1.45653E-02		6.641E-03	*0.0145*	*Cl L/min/kg*
10	0	P	13		2.75255E-01		2.010E-02	*0.2759*	*Vt L/kg*
11	0	P	14		2.09943E-02		2.454E-02	*0.0209*	*Cld L/min/kg*

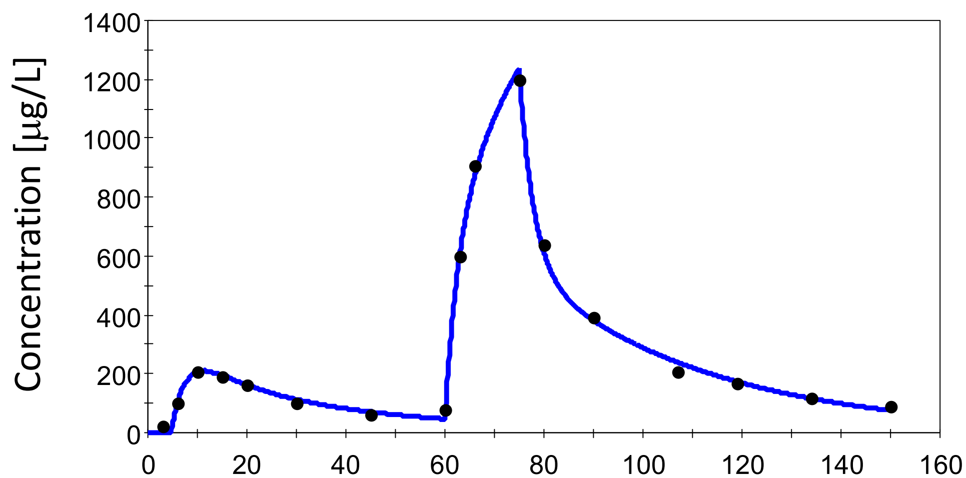
* G&W Present a combination of Physiological and Macro Parameters. (α and β, for example) .. no Micro Parameters

```
c p02=Bioavailability
c p03=Absorption lag
c p11=Vc
c p12=Cl
c p13=Vt
c p14=Cld
c
 p(11)=1/k(1)
 p(12)=p(11)*l(0,1)
 p(13)=p(11)*l(2,1)/l(1,2)
 p(14)=p(13)*l(1,2)
 ic(3)=2500*p(2)
  P(2)      4.692819E-02  0.000000E+00   1.000000E+02
```

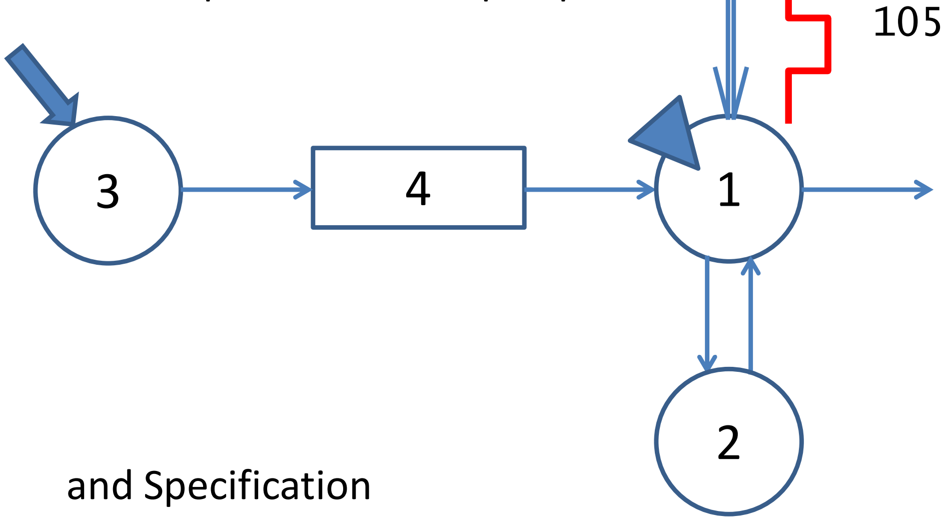
```
c
c p11=Vd
c p12=Cl
c p13=Vt
c p14=Cld
c
 p(11)=1/k(1)
 p(12)=p(11)*l(0,1)
 p(13)=p(11)*l(2,1)/l(1,2)
 p(14)=p(13)*l(1,2)
```

Linear and Semi logarithmic displays of model fits to plasma observations





Model Graphic … another perspective




```
c
x uf(1)=p(1)*f(5)
105 qo
          0          0
          60         1
          75         0
```

```
c PK12 GW-4
c
c p11=Vd
c p12=Cl
c p13=Vt
c p14=Cld
c
 p(11)=1/k(1)
 p(12)=p(11)*l(0,1)
 p(13)=p(11)*l(2,1)/l(1,2)
 p(14)=p(13)*l(1,2)
c
```

and Specification

```
c
   K(1)       7.895522E+00  0.000000E+00   1.000000E+04
   L(0,1)     1.137547E-01  0.000000E+00   1.000000E+01
   L(2,1)     1.453584E-01  0.000000E+00   1.000000E+01
   L(1,2)     5.819302E-02  0.000000E+00   1.000000E+01
c
   L(4,3)     9.967976E-02  0.000000E+00   1.000000E+01
   DT(4)      4.545013E+00  0.000000E+00   1.000000E+01
   DN(4)=2
   L(1,4)=1
   P(2)       4.692819E-02  0.000000E+00   1.000000E+02
c
 IC(3)=2500*P(2)
 P(1)=500/15
 P(3)=DT(4)
H DAT
```

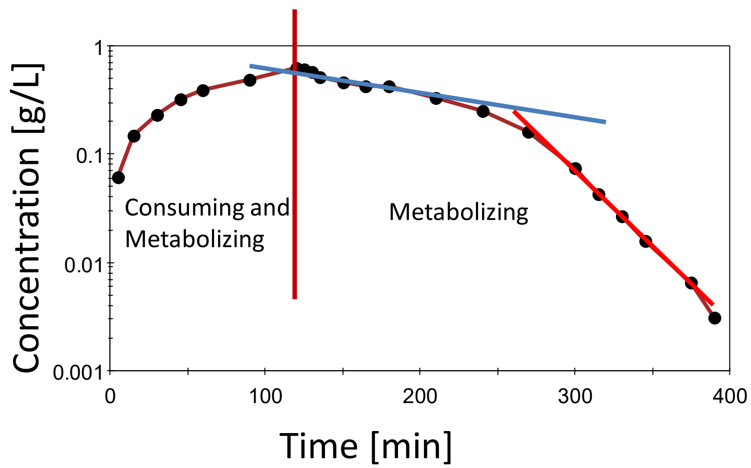
Some questions and extensions:

1. How was the PO administration offset from the IV one?
2. How was the IV administration implemented?
3. Does the implementation of the IV administration seem plausible?
4. What made you decide how you responded to question 3?
5. How did we achieve the display of the PO absorption delay?
6. Did that make sense?
7. Implement another version of this model using all the information
8. Is there any way we could take account of the protracted IV administration?
9. Consider other features of our implementation of this system that you might change and implement them for yourself

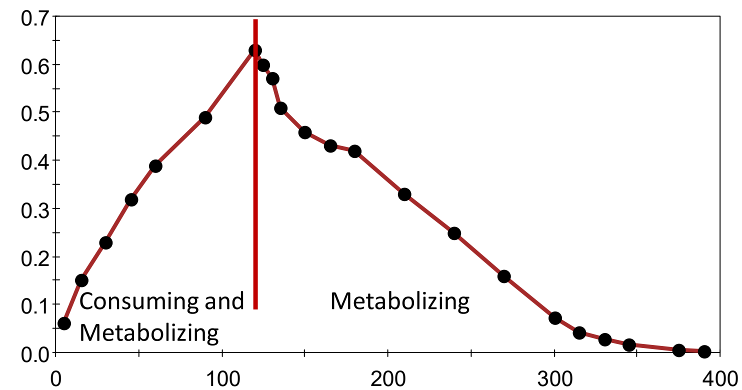
PK18 Ethanol kinetics … Wilkinson's (1976) approach

A total of **45 g of alcohol** was infused into an individual over approximately 2 hours and during that time and **4.5 hours beyond** blood concentrations (g/L) of alcohol were recorded. Our challenge is to resolve the infusion duration and the key metabolic parameters for alcohol from the data.

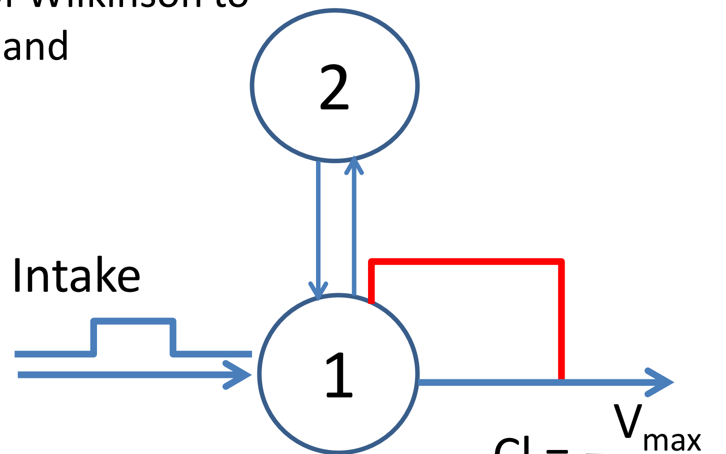
Purpose: Nonlinear kinetics



Linear and semilog plots of alcohol intake and disposition

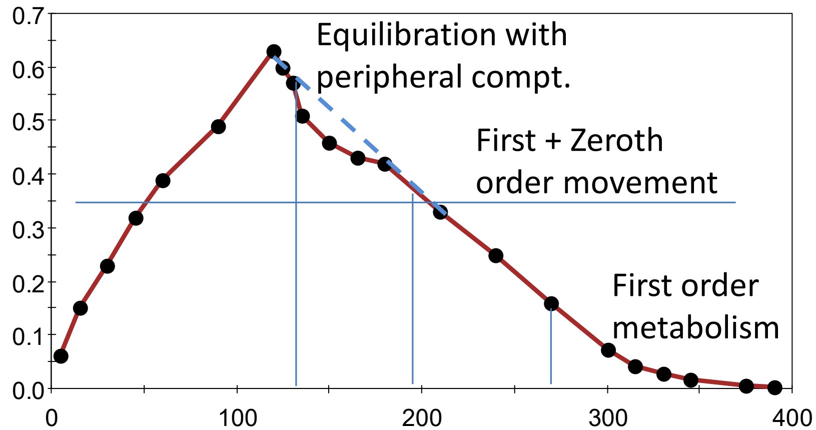


The **two pool approach** of Wilkinson to describe the metabolism and distribution of alcohol



$$Cl = \frac{V_{max}}{K_m + C}$$

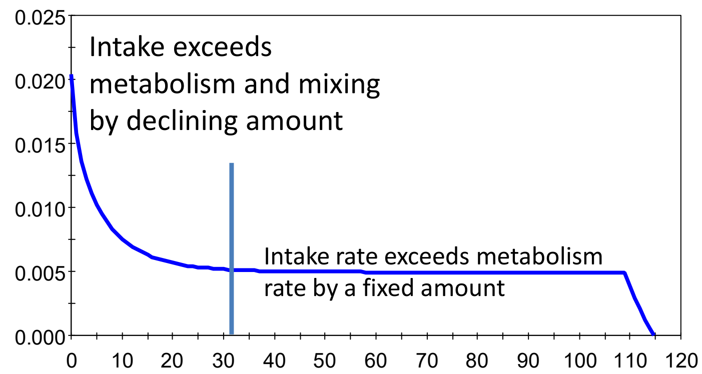
Clearance is **Michaelis Menten** Function of Concentration



```
A SAAM31                              PK18_2
2      10
H PAR
c p1=Vc
c p2=Vmax
c p3=Km
c p4=Cld
c p5=VT
c p6=Vss
c p7=MRT
c p8=Tz
c p9=Dose
c p10=Vmax/Km
c p11=MRT
c p12=Tz
   P(1)      2.185354E+01  0.000000E+00   1.000000E+02
   P(2)      1.604767E-01  0.000000E+00   1.000000E+00
   P(3)      4.240005E-02  0.000000E+00   1.000000E+00
   P(4)      1.180391E+00  0.000000E+00   1.000000E+01
   P(5)      2.599861E+01  0.000000E+00   1.000000E+02
 p(9)=45.77
 p(6)=p(1)+p(5)
 p(10)=p(2)/p(3)
 p(11)=p(6)/p(10)
   ic(5)=1
   dn(5)=12
   DT(5)     1.187991E+02  0.000000E+00   1.000000E+03
   l(0,5)=1
   p(7)=dt(5)
H DAT
   p(1)
   p(2)
   p(3)
   p(4)
   p(5)
   p(6)
   p(7)
   p(9)
   p(10)
   p(11)
x g(1)=f(5)*p(9)/dt(5)
x g(2)=p(2)/(p(3)+f(1))
x uf(1)=(g(1)-g(2)*f(1)-p(4)*f(1)+p(4)*f(2))/p(1)
x uf(2)=(p(4)*f(1)-p(4)*f(2))/p(5)
```

Model used to describe this study. Note that the functional portrayal of the model is very closely as in Gabrielsson and Weiner

Net intake rate (uf(1)) of alcohol in compartment ‘1’ [g/L/min]



Creating the model's dynamic equations

```
x g(1)=f(5)*p(9)/dt(5)
x g(2)=p(2)/(p(3)+f(1))
x uf(1)=(g(1)-g(2)*f(1)-p(4)*f(1)+p(4)*f(2))/p(1)
x uf(2)=(p(4)*f(1)-p(4)*f(2))/p(5)
```

```
c p1=Vc
c p2=Vmax
c p3=Km
c p4=Cld
c p5=VT
c p6=Vss
c p7=MRT
c p8=Tz
c p9=Dose
c p10=Vmax/Km
c p11=MRT
c p12=Tz
```

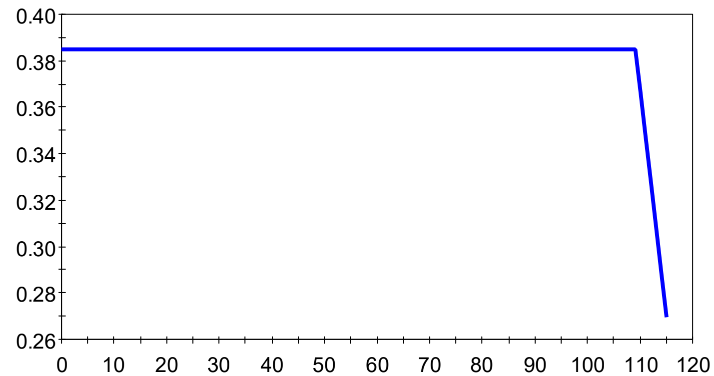
$[f1] = [f2] = g.L^{-1}$

$[uf1] = [uf2] = g.L^{-1}.min^{-1}$

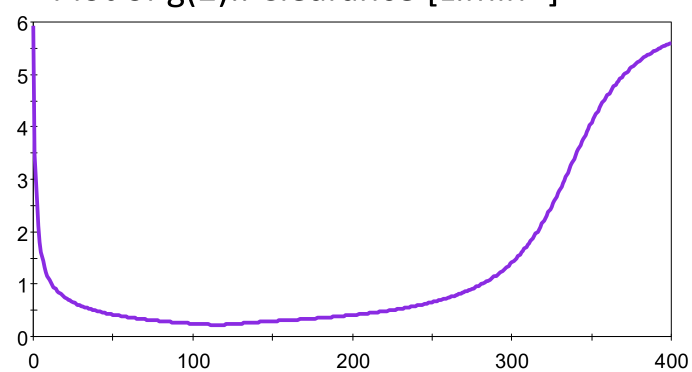
$[g1] = g.min^{-1}$

$[g2] = L.min^{-1}$

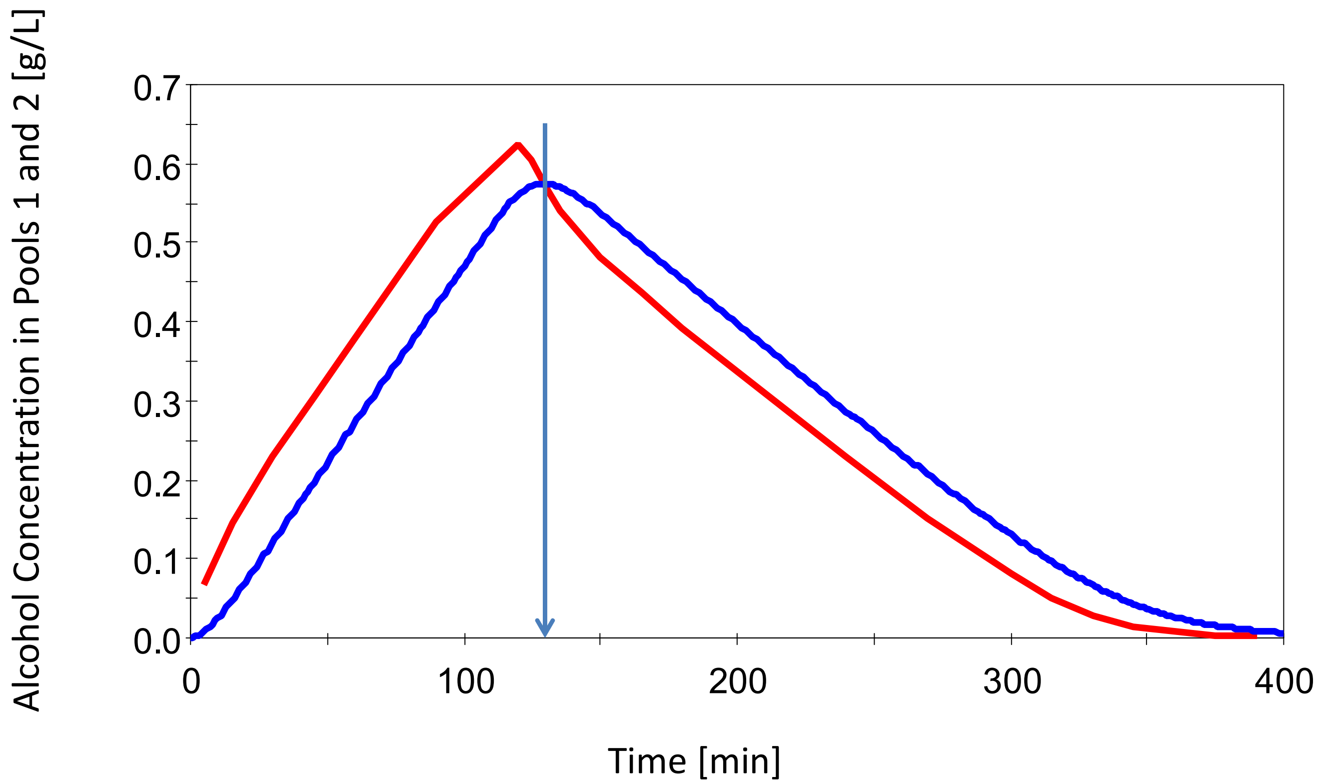
Plot of g(1) .. 2 hr. infusion [g/L/min]



Plot of g(2).. Clearance [$L.min^{-1}$]



Central (red) and Peripheral (blue) pool concentrations [g/L] showing how long it takes to achieve equilibration between these two pools



c dt5=tlag
c p1=Vc
c p2=Vmax
c p3=Km
c p4=Cld
c p5=VT

PARAMETER	VALUE	ERROR	FSD		
DT(5, 0)	1.189E+02	2.990E+00	2.515E-02	*120	tlag[min]
P (2, 0)	1.481E-01	6.680E-03	4.510E-02	0.151	Vmax[$g.min^{-1}$]
P (3, 0)	2.488E-02	8.116E-03	3.261E-01	0.030	Km[$g.L^{-1}$]
P (4, 0)	1.423E+00	3.626E-01	2.548E-01	1.43	Cld[$L.min^{-1}$]
P (1, 0)	1.891E+01	3.770E+00	1.994E-01	19.0	Vc[L]
P (5, 0)	3.051E+01	3.745E+00	1.227E-01	30.5	Vt[L]

CORRELATION MATRIX

COLUMN	1	2	3	4	5	6
ROW 1	1.00	-0.41	-0.36	-0.03	-0.49	0.60
ROW 2	-0.41	1.00	0.98	0.43	0.08	-0.42
ROW 3	-0.36	0.98	1.00	0.37	0.09	-0.40
ROW 4	-0.03	0.43	0.37	1.00	-0.75	0.51
ROW 5	-0.49	0.08	0.09	-0.75	1.00	-0.92
ROW 6	0.60	-0.42	-0.40	0.51	-0.92	1.00

*See List of Results Tabulated Page 646 G&W 4^{th} Edn. Wilkinson PK 1976

Observations and weighting assigned … note request for net intake rate calculations to be stored in QC(2)

```
101                                                          rqo=.02
            5              .062
            15             .15
            30             .23
            45             .32
            60             .39
            90             .49
            120            .63
            125            .6
            130            .57
            135            .51
            150            .46
            165            .43
            180            .42
            210            .33
            240            .25
            270            .16
            300            .074
            315            .043
            330            .027
            345            .016
            375            .0066
            390            .0031
102 uf(1)
            0
2           1                                                115
```

Final Parameter Estimates from the SAAM command

D	C	---CAT--		QC	FSD		
1	0	P	1	1.89101E+01	1.994E-01		c p1=Vc
2	0	P	2	1.48120E-01	4.510E-02		c p2=Vmax
3	0	P	3	2.48843E-02	3.261E-01		c p3=Km
4	0	P	4	1.42333E+00	2.548E-01		c p4=Cld
5	0	P	5	3.05079E+01	1.227E-01		c p5=VT
6	0	P	6	4.94180E+01	3.092E-02	*49.5	c p6=Vss
7	0	P	7	1.18863E+02	2.515E-02		c p8=Tz
8	0	P	9	4.57700E+01	0.000E+00	45.7	c p9=Dose
9	0	P	10	5.95233E+00	3.401E-01	5.95	c p10=Vmax/Km
10	0	P	11	8.30229E+00	2.727E-01	9.5	c p11=MRT

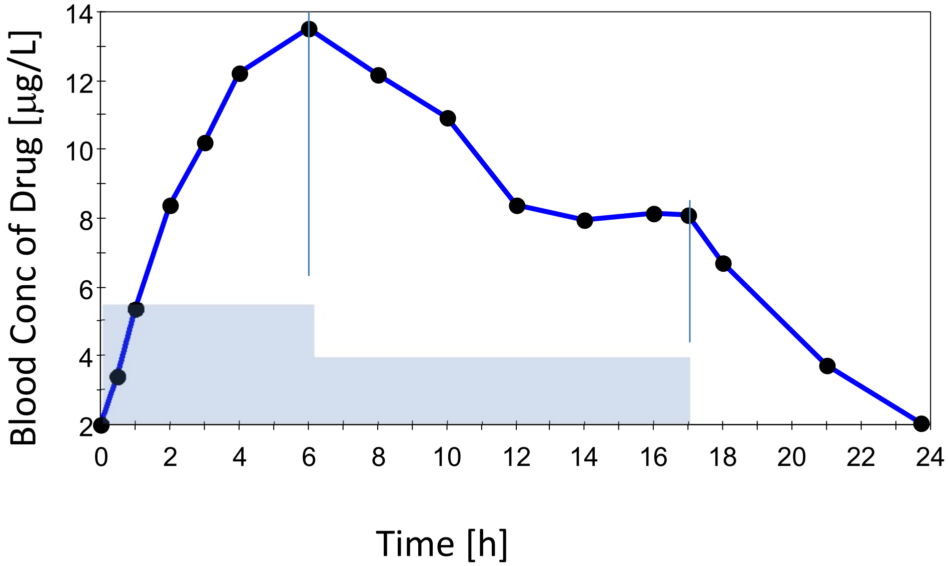
Question: use the original Wagner alcohol model
without a peripheral compartment to model this data

Points to ponder

1. In PK18 we explored ethanol metabolism using Wilkinson's model and in this model there is a peripheral compartment involved.
2. How would you describe the kinetics of the exchange between the central and the peripheral compartments?
3. Prior to Wilkinson's we had Wagner's model and in this model there was no peripheral compartment … just a single plasma pool. Wagner identified the metabolic parameters of his model as Vmax = 0.18 [gm/L/hr], Km = 0.05 [gm/L]. The volume of distribution of was 50 L. Explore how well Wagner's model explains the observations in the study reported in PK18
4. If you allow Wagner's parameters to adjust is the fit improved? What about the resolution of the parameters?
5. Do you see an opportunity of stabilizing the Wagner parameters using Bayesian considerations. What works against that idea? How will you address that?

PK33 Transdermal input kinetics

This demonstration shows how **transdermal** drug and **hormonal** delivery systems are easily emulated in the constructs supported by WinSAAM and it is even possible to estimate delivery rates and delivery durations when fast and slow releasing agents are merged



A nicotine patch was applied to volunteers for 17-18 hr for **5 consecutive days**. Plasma conc. data were obtained on days 1 and 5. This data is for **day 5 only**.

The est. total release of nicotine was **15890 μg** and this comprised of a burst release, and a maintenance release.

All release was assumed to exhibit **zeroth order kinetics** and the plasma response was modeled using a **single** pool system.

Units of nicotine [$\mu g.L^{-1}$].

Note: IC(1)=2 .. T_0 Nicotine

The WinSAAM Representation of this Study

```
c
c p1=V
c p2=Cl
c p3=Dinf
c dt21=Tfst
c dt11=Tinf

   p(1)      3.292584E+02  0.000000E+00   1.000000E+03
   p(2)      8.129505E+01  0.000000E+00   1.000000E+03
   p(3)      1.035365E+04  0.000000E+00   1.000000E+05
   p(11)=15890

 ic(1)=2
 ic(11)=1
 ic(21)=1

 l(0,11)=1
 l(0,21)=1
 dn(11)=20
 dn(21)=20
   dt(11)    1.780342E+01  0.000000E+00   1.000000E+02
   dt(21)    6.536426E+00  0.000000E+00   1.000000E+02
H DAT
x g(1)=f(11)*p(3)/dt(11)
x g(2)=f(21)*(p(11)-p(3))/dt(21)
x uf(1)=(g(1)+g(2)-p(2)*f(1))/p(1)
x g(3)=(g(1)+g(2))/p(1)
```

Setting up the common adjustable parameters

```
c p1=V
c p2=Cl
c p3=Dinf
c p11=Total nicotine micro gm
c dt21=Tfst
c dt11=Tinf

   p(1)       3.292584E+02  0.000000E+00   1.000000E+03
   p(2)       8.129505E+01  0.000000E+00   1.000000E+03
   p(3)       1.035365E+04  0.000000E+00   1.000000E+05
   p(11)=15890
```

Setting up the burst (dt21, yellow) and maintenance (dt11, grey) duration determinations

```
 ic(1)=2
 ic(11)=1
 l(0,11)=1
 dn(11)=20
   dt(11)     1.780342E+01  0.000000E+00   1.000000E+02
 ic(21)=1
 l(0,21)=1
 dn(21)=20
   dt(21)     6.536426E+00  0.000000E+00   1.000000E+02
```

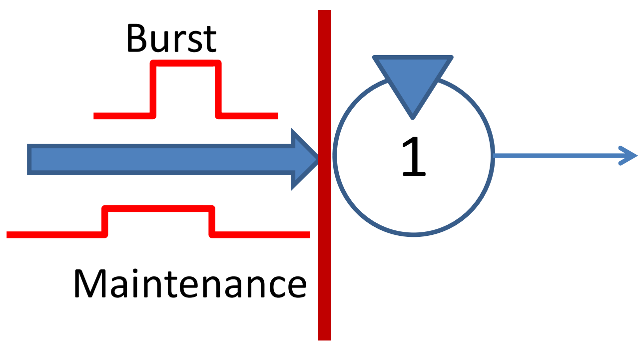
Dynamic equations modeling release of nicotine

```
x g(1)=f(11)*p(3)/dt(11)
x g(2)=f(21)*(p(11)-p(3))/dt(21)
x uf(1)=(g(1)+g(2)-p(2)*f(1))/p(1)
x g(3)=(g(1)+g(2))/p(1)
```

$$f1` = (g1 + g2 – p2*f1)/p1$$

g1 = burst release, [μg/h] duration dt21
g2 = slow release, [μg/h] duration dt11
p3 = burst size [μg]
p11-p3 = slow release size [μg]
g3 is the total release [μg/h/L]
uf1 = net rate of entry [μg/h/L]
f1 = nicotine level in its distn space [μg/L]

```
c p1=V
c p2=Cl
c p3=Dinf
c p11=Total nicotine micro gm
c dt21=Tfst
c dt11=Tinf
```



Some questions:
What does f11)/dt(11) achieve?
What does f(21)/dt(21) achieve?
What is p(1) and why does it popup often?
What are the units of p(2)*f(1)?

Final parameter estimates

```
PARAMETER      VALUE        ERROR        FSD
P ( 3, 0)  9.996E+03  3.611E+02  3.612E-02  DINF 10086 [μg]
DT(11, 0)  1.775E+01  3.084E-01  1.738E-02  TINF 18.25 [hr]
DT(21, 0)  6.349E+00  2.405E-01  3.788E-02  TFST 6.54  [hr]
P ( 2, 0)  8.085E+01  8.599E-01  1.064E-02  CL   80.16 [L.hr-1]
P ( 1, 0)  3.589E+02  2.391E+01  6.663E-02  V    337   [L]
CORRELATION MATRIX
 COLUMN    1      2      3      4      5
ROW 1  1.00   0.35   0.07   0.19  -0.73
ROW 2  0.35   1.00   0.56  -0.17  -0.74
ROW 3  0.07   0.56   1.00  -0.16  -0.60
ROW 4  0.19  -0.17  -0.16   1.00   0.06
ROW 5 -0.73  -0.74  -0.60   0.06   1.00
```

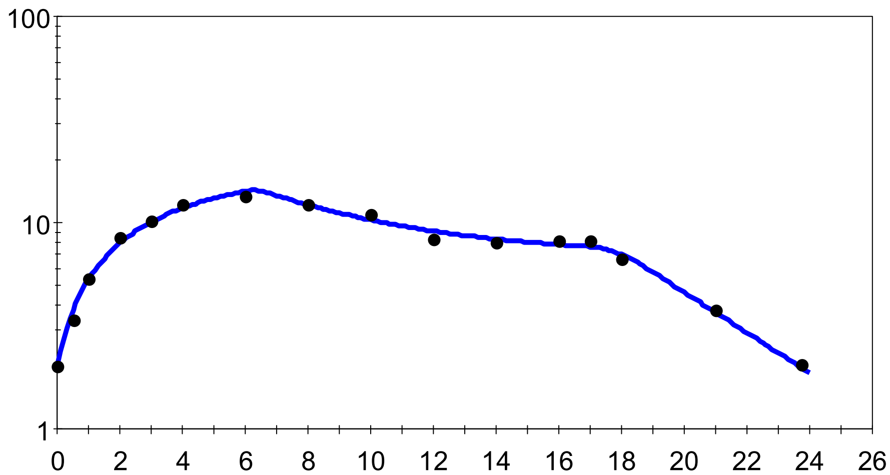
P3: Dinf .. Dose Infused

DT11: Tinf .. Slow Infusion [hr]

DT21: Tfst .. Fast Infusion [hr]

P2: Cl .. Clearance [L.hr^{-1}]

P1: Vd .. Volume of Distrib. [L]

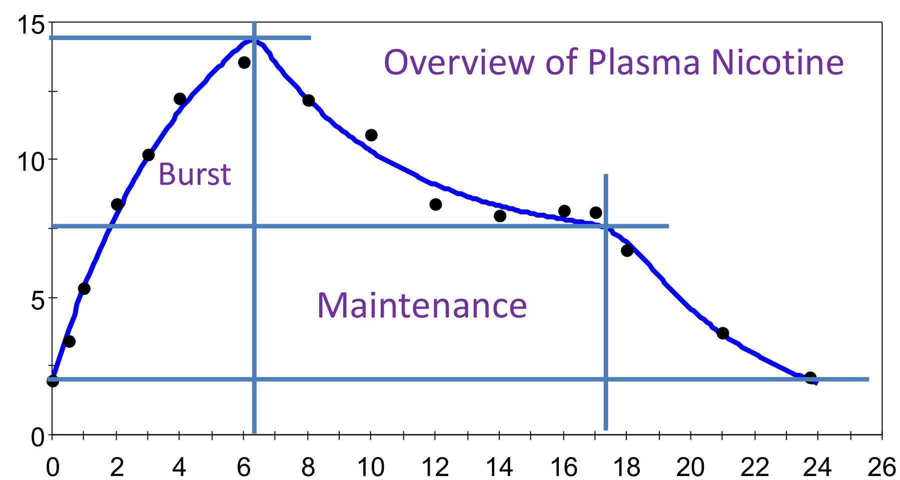


Question: how could we model this system if there were no overlap between the burst and maintenance administrations?

Linear and Semi log plots of Observed and Estimated Nicotine levels [μg/L] by time

Note that our plots of predicted Nicotine release are smoothed by seeking 1/10th hourly model solutions for our 24 hr observation range, viz:

```
102 g(3)
              0
2             .1            //            240
```



Patch Model, System Equations, and Data

```
A SAAM31
2       10
H PAR
c
c p1=V
c p2=Cl
c p3=Dinf
c DT21=Tfst
c Dt11=Tinf
c
   P(1)      3.292584E+02  0.000000E+00   1.000000E+03
   P(2)      8.129505E+01  0.000000E+00   1.000000E+03
   P(3)      1.035365E+04  0.000000E+00   1.000000E+05
 p(11)=15890
 ic(1)=2
 ic(11)=1
 l(0,11)=1
 dn(11)=20
   DT(11)    1.780342E+01  0.000000E+00   1.000000E+02
 ic(21)=1
 l(0,21)=1
 dn(21)=20
   DT(21)    6.536426E+00  0.000000E+00   1.000000E+02
```

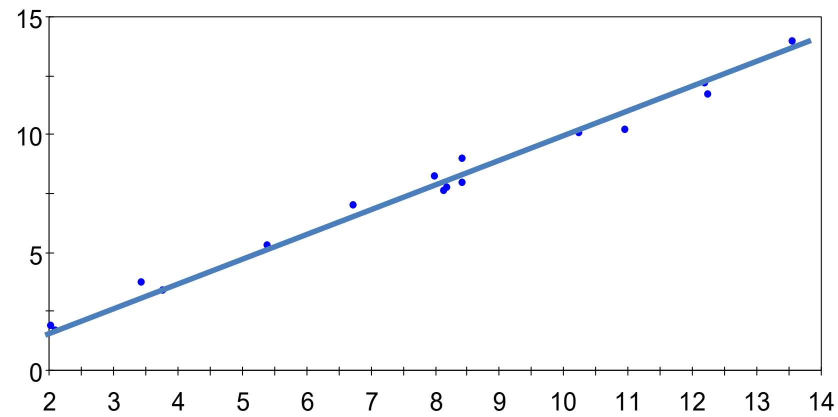
```
H DAT
x g(1)=f(11)*p(3)/dt(11)
x g(2)=f(21)*(p(11)-p(3))/dt(21)
x uf(1)=(g(1)+g(2)-p(2)*f(1))/p(1)
x g(3)=(g(1)+g(2))/p(1)
101                                       sd=.1
            0             2
            .5            3.4
            1             5.36
            2             8.4
            3             10.2
            4             12.22
            6             13.53
            8             12.17
            10            10.93
            12            8.39
            14            7.97
            16            8.15
            17            8.1
            18            6.7
            21            3.74
            23.73         2.07
102 g(3)
            0
2           .1                            240
```

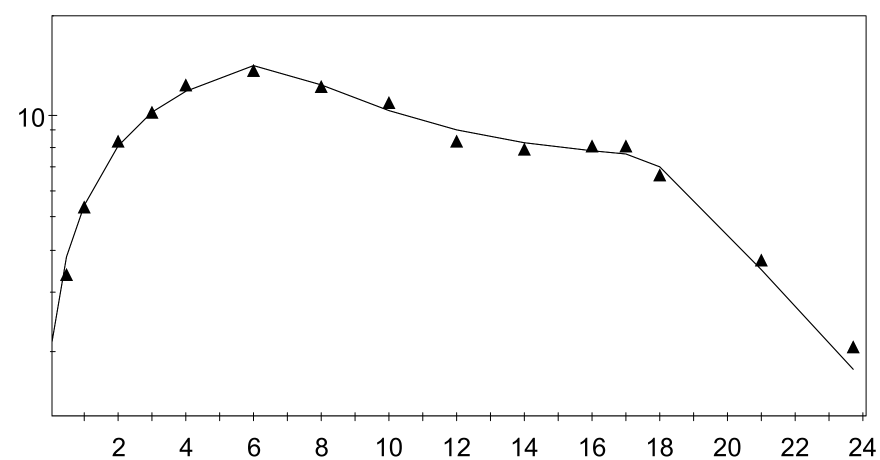
Table of Observed and Predicted versus Time

```
> prin q(1)
----------------------------------------------------------------------
*** NAME :    1
CURRENT KOMN
```

#	COMP	TC	CATEGORY	T	QC	QO	QC/QO
1	1	0	F (1)	0.000E+00	2.000E+00	2.000E+00	1.0000
7	1	0	F (1)	5.000E-01	3.809E+00	3.400E+00	1.1202
13	1	0	F (1)	1.000E+00	5.407E+00	5.360E+00	1.0088
24	1	0	F (1)	2.000E+00	8.069E+00	8.400E+00	0.9605
36	1	0	F (1)	3.000E+00	1.015E+01	1.020E+01	0.9949
47	1	0	F (1)	4.000E+00	1.177E+01	1.222E+01	0.9634
68	1	0	F (1)	6.000E+00	1.403E+01	1.353E+01	1.0371
89	1	0	F (1)	8.000E+00	1.229E+01	1.217E+01	1.0100
109	1	0	F (1)	1.000E+01	1.029E+01	1.093E+01	0.9414
130	1	0	F (1)	1.200E+01	9.068E+00	8.390E+00	1.0808
151	1	0	F (1)	1.400E+01	8.322E+00	7.970E+00	1.0441
172	1	0	F (1)	1.600E+01	7.866E+00	8.150E+00	0.9652
183	1	0	F (1)	1.700E+01	7.708E+00	8.100E+00	0.9516
194	1	0	F (1)	1.800E+01	7.067E+00	6.700E+00	1.0548
225	1	0	F (1)	2.100E+01	3.496E+00	3.740E+00	0.9348
254	1	0	F (1)	2.373E+01	1.782E+00	2.070E+00	0.8607

PLOT OC(1)





Two plots to the right:
Upper: Plotting Observed vs Predicted .. dots, pine represents a smoothed fit
Lower: Extracted Semi-lg Plot of Observed and Predicted versus time
Extraction obtained by shift-dragging a plot section

Points to ponder

1. What role did the delays play in this investigation of a dual loaded patch?
2. How were we able to estimate the size of the burst and the maintenance nicotine administrations?
3. Do you think that the information forming the basis for uncoupling the two administrations was appropriate? What additional information would you seek here?
4. How well were the model parameters resolved in conjunction with data fitting?
5. What data weighting was used for data fitting?
6. Does this seem sensible?
7. See if different weighting schemes lead to large changes in the parameters estimates
8. How good a job did we do translating the model from Gabrielsson and Weiner? Do an exact translation and critique the two approaches. Which is the preferred?
9. What do we learn from the first and last observation?

Thank You

On balance …

If we obtain the same/similar results using two distinct codings
for a problems which approach is better?

First: replicate the coding approach of the published model

Next: explore a metric for which you, or your software, are best suited*

Explore variations only when your results corroborate the published ones

*WinSAAM was the first modeling software enable kinetic modeling from the basis of the micro rate constants. It is still the only system for which this metric is still the best performing and the most flexible