Modeling Dosing Regimens: Propofol Kinetics in Children

Real World Biomedical Modeling Techniques Through Case Studies – Module 5

IEEE/EMBS and BMES Pre-Conference Workshop

October 22, 2002 • Westin Galleria • Houston, TX

Modeling Complex Infusion Rates

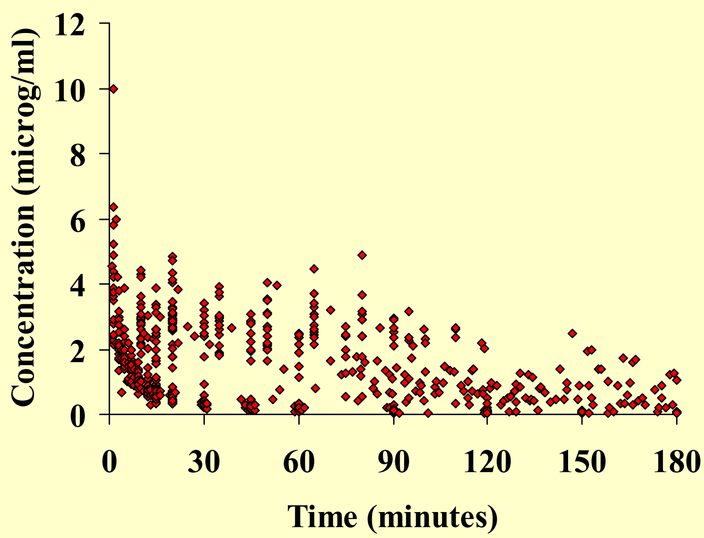
- Example: propofol pharmacokinetics
- Data are from: Kataria BK, Ved SA, Nicodemus HF, Hoy GR, Lea D, Dubois MY, Mandema JW, Shafer SL. The pharmacokinetics of propofol in children using three different data analysis approaches. Anesthesiology. 1994 Jan;80(1):104-22.

vicini@u.washington.edu

Propofol Pharmacokinetics

- 53 healthy, unpremedicated children
- Twenty children only received an initial loading dose of 3 mg/kg intravenous propofol. In the remaining 33 children, an initial intravenous propofol dose of 3.5 mg/kg was followed by one or two propofol maintenance infusion
- Correct modeling of the infusion rates is crucial for pharmacokinetic estimates

Propofol Measurements (N=53)



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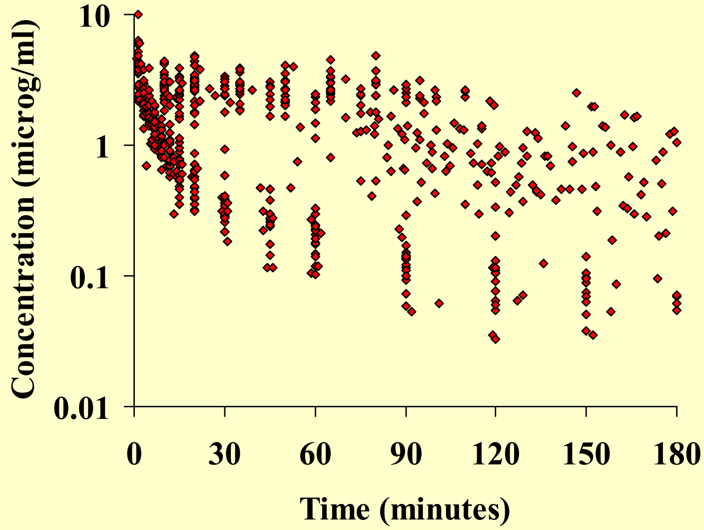
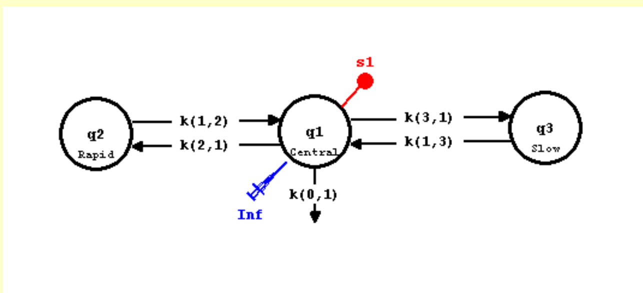
Propofol Measurements (N=53)



Three Compartment Model



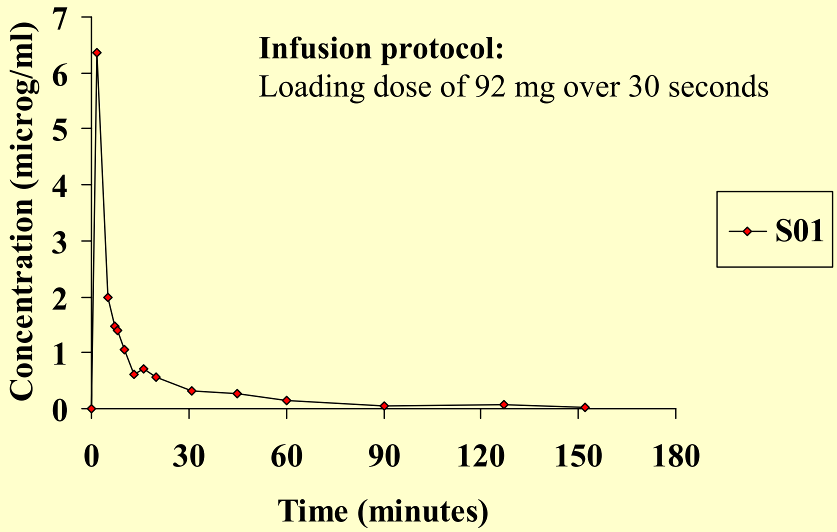
$$\frac{dq_1}{dt} = -[k(0,1) + k(2,1) + k(3,1)]q_1(t) + k(1,2)q_2(t) + k(1,3)q_3(t) + Inf(t)$$

$$\frac{dq_2}{dt} = +k(2,1)q_1(t) - k(1,2)q_2(t)$$

$$\frac{dq_3}{dt} = +k(3,1)q_1(t) - k(1,3)q_3(t)$$

vicini@u.washington.edu

Back to the Data…



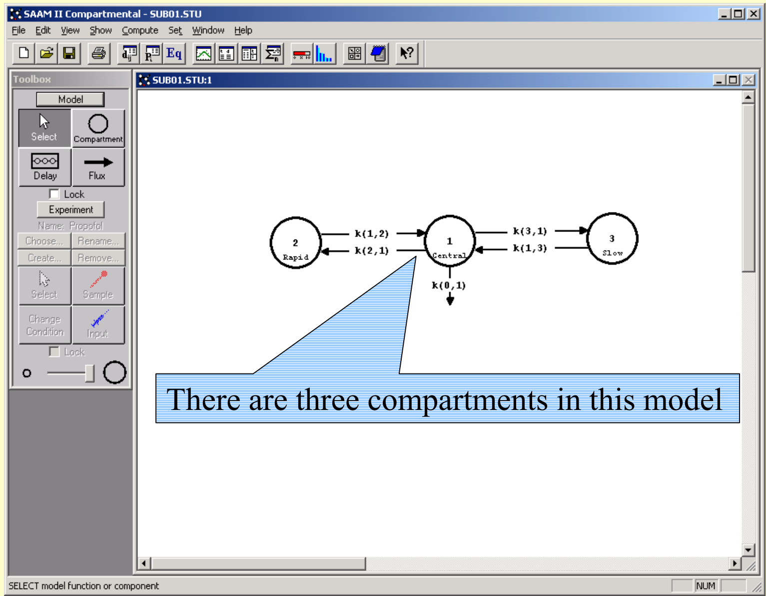
Data Format

```
# TID 1
DATA
(FSD 0.1)
t        dat
1.5      6.37
5        2
7        1.47
8        1.41
10       1.06
13       0.604
16       0.714
20       0.574
31       0.314
45       0.272
60       0.146
90       0.0589
127      0.0645
152      0.035
END
```

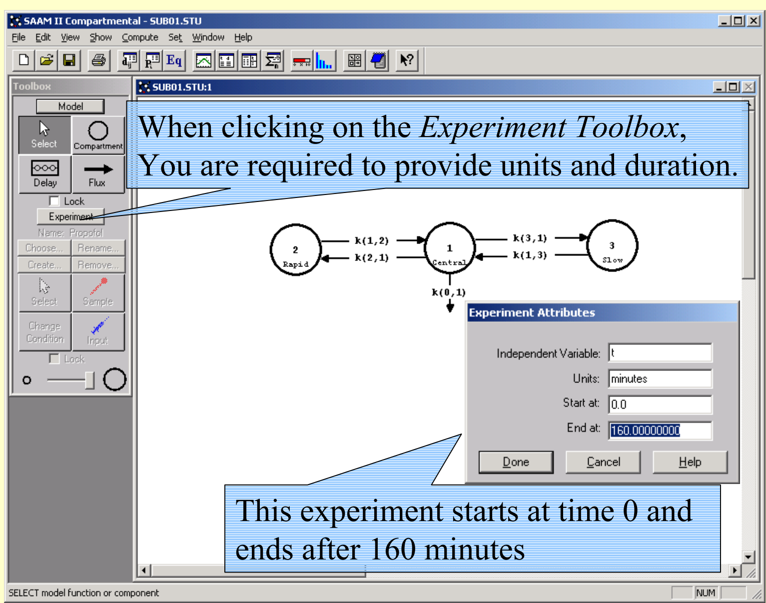
- Data are in column format, as we have seen
- Units are: minutes for time, micrograms/ml for propofol concentration
- The data measurement error is constant fractional standard deviation (FSD) equal to 10% of the measurement value
- We will use model-based weights for this exercise

vicini@u.washington.edu

Define Your System Model



Define the Experiment Duration…



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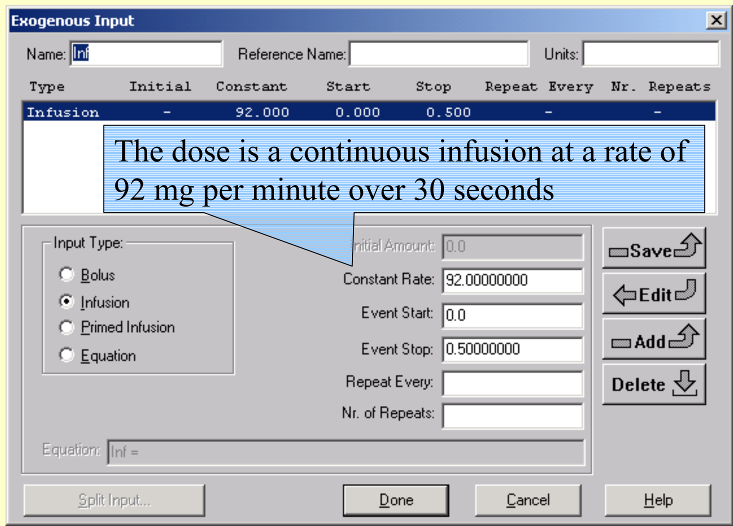
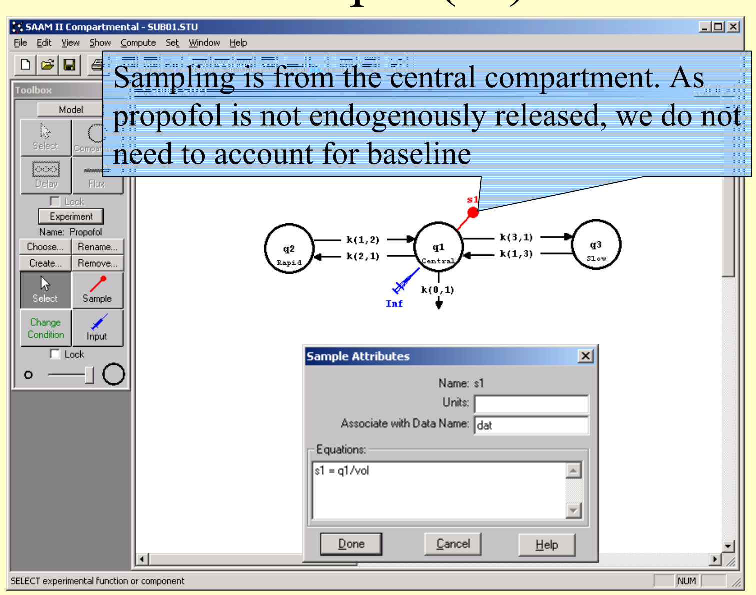
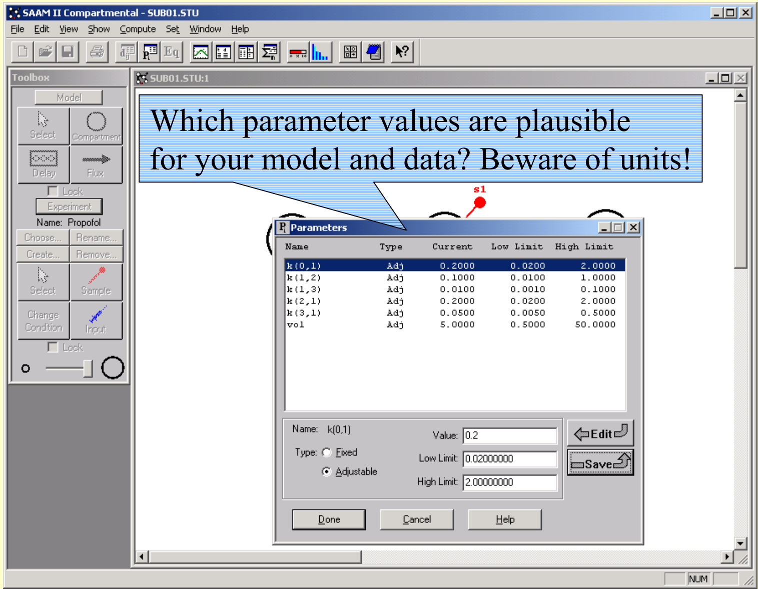
Exogenous Input (Inf)



Sample (s1)

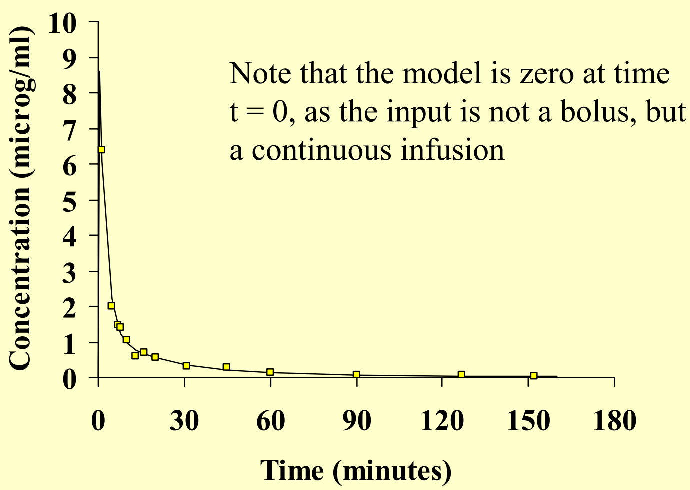


Provide Parameter Values



Model Fit

(remember to use Model-based Weights)



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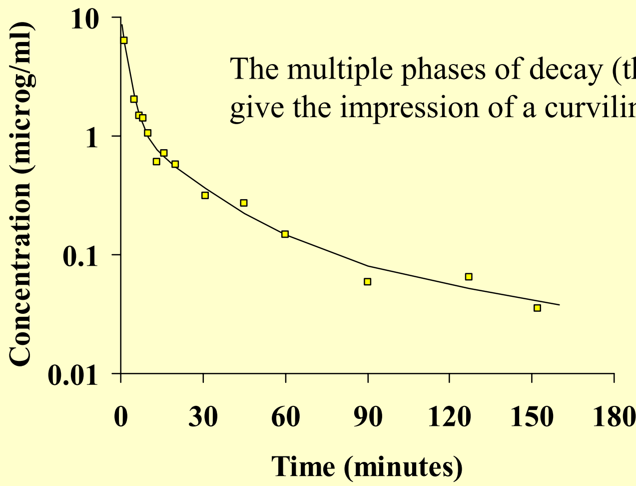
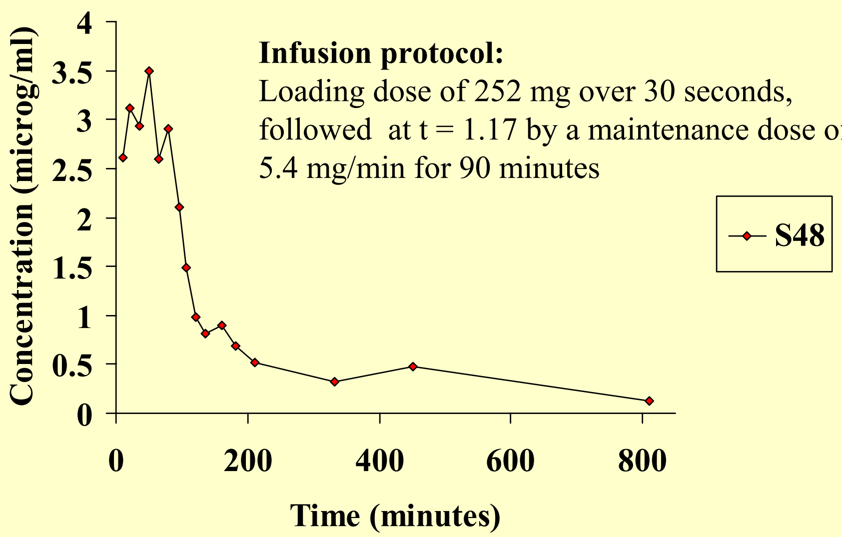
Model Fit

(semilog scale)



The multiple phases of decay (three) give the impression of a curvilinear plot

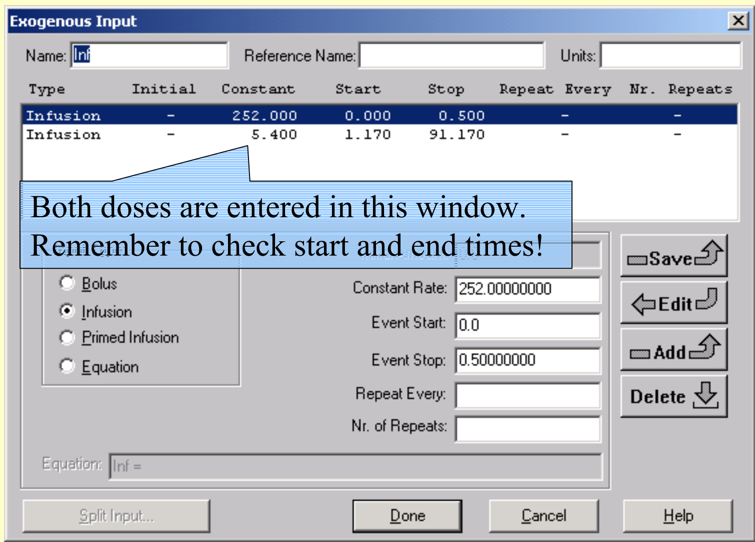
Another Example



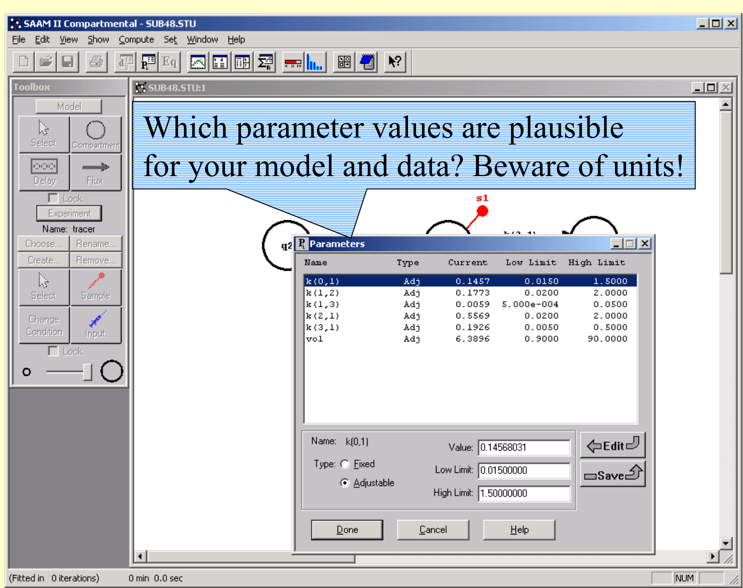
Infusion protocol:
Loading dose of 252 mg over 30 seconds, followed at t = 1.17 by a maintenance dose of 5.4 mg/min for 90 minutes

vicini@u.washington.edu

Exogenous Input (Inf)



Provide Parameter Values



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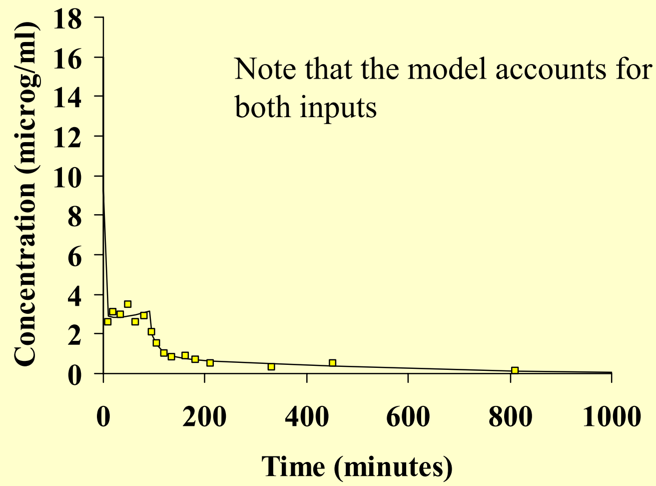
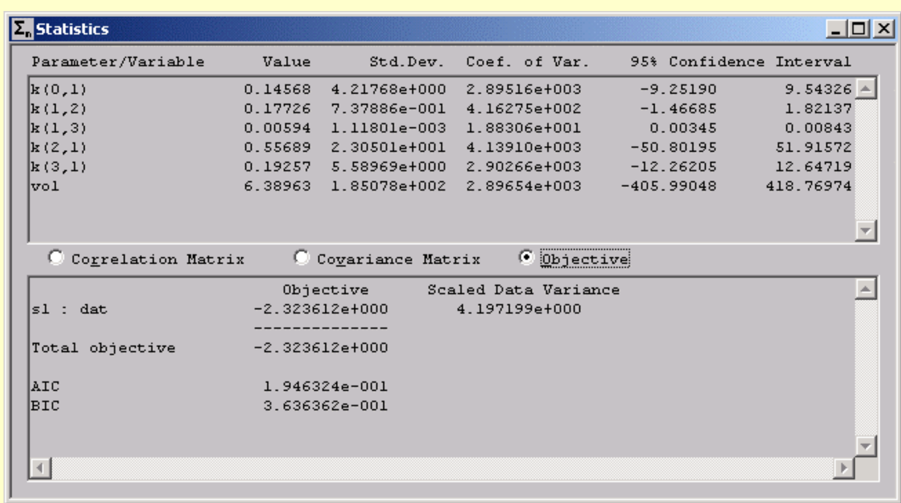
Model Fit

(remember to use Model-based Weights)



What About the Statistics?



Statistics

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
k(0,1)	0.14568	4.21768e+000	2.89516e+003	-9.25190	9.54326
k(1,2)	0.17726	7.37886e-001	4.16275e+002	-1.46685	1.82137
k(1,3)	0.00594	1.11801e-003	1.88306e+001	0.00345	0.00843
k(2,1)	0.55689	2.30501e+001	4.13910e+003	-50.80195	51.91572
k(3,1)	0.19257	5.58969e+000	2.90266e+003	-12.26205	12.64719
vol	6.38963	1.85078e+002	2.89654e+003	-405.99048	418.76974

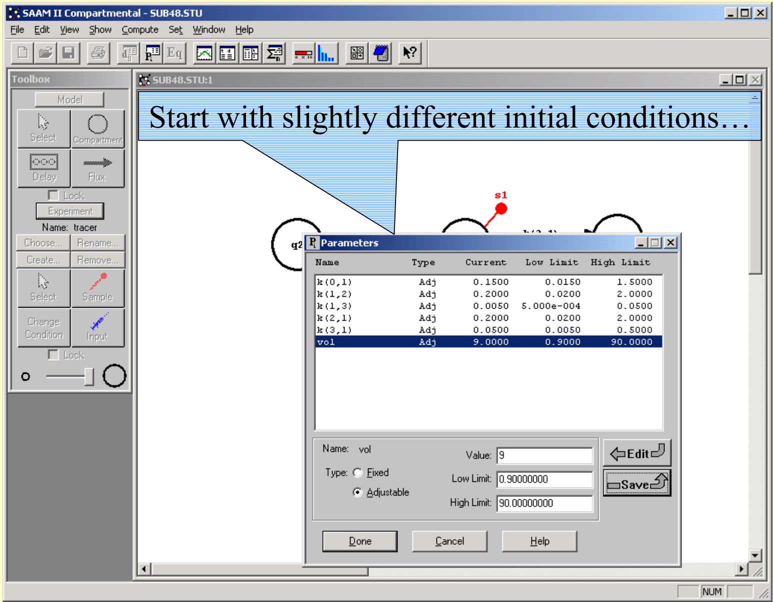
Correlation Matrix   Covariance Matrix   Objective

	Objective	Scaled Data Variance
s1 : dat	-2.323612e+000	4.197199e+000
Total objective	-2.323612e+000	
AIC	1.946324e-001	
BIC	3.636362e-001	

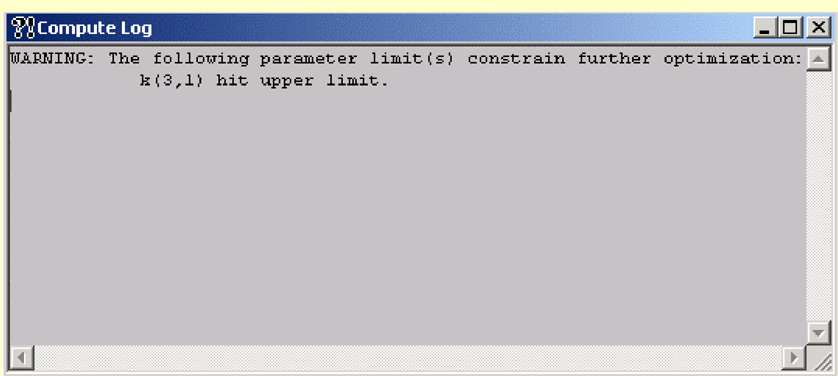
Unacceptable…

vicini@u.washington.edu

This Fit Is Not Robust!



Warning Message



Solution: adjust (reset) upper and lower limits for k(3,1)

vicini@u.washington.edu

Another Warning Message

Compute Log

```
ERROR:   While fitting, the optimizer was unable to find any
         combination of parameter values that would satisfy the
         convergence criteria.  Try changing the computational
         settings.
```

Solution: There is none! The fit is not robust!

What About the Statistics?

Statistics

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
k(0,1)	0.43413	2.61273e-001	6.01839e+001	-0.14803	1.01628
k(1,2)	0.16275	1.62808e-001	1.00036e+002	-0.20001	0.52551
k(1,3)	0.00587	1.17054e-003	1.99326e+001	0.00326	0.00848
k(2,1)	1.76213	1.94477e+000	1.10365e+002	-2.57110	6.09536
k(3,1)	0.57112	3.68432e-001	6.45106e+001	-0.24980	1.39203
vol	2.13298	1.34317e+000	6.29714e+001	-0.85978	5.12575

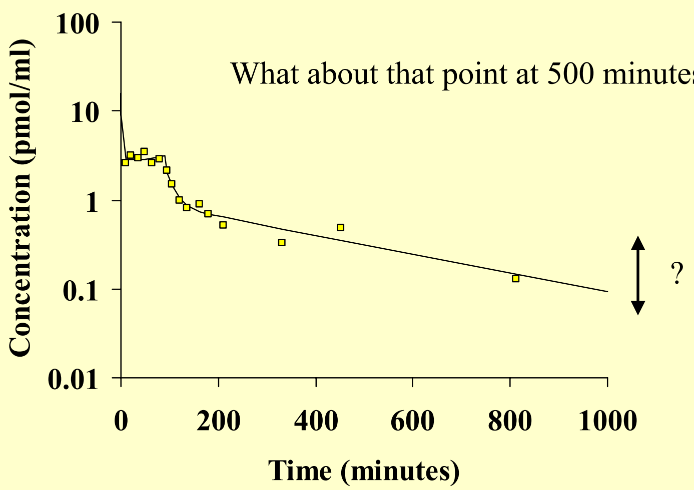
○ Correlation Matrix ○ Covariance Matrix ● Objective

	Objective	Scaled Data Variance
s1 : dat	-2.330687e+000	4.153780e+000
Total objective	-2.330687e+000	
AIC	1.910950e-001	
BIC	3.600988e-001	

Still unacceptable…

Model Fit

(semilog scale)



Unweighting Measurements

```
# ID 48
DATA
(FSD 0.1)
t       dat
10      2.61
20      3.11
35      2.94
50      3.49
65      2.6
80      2.9
96.2    2.11
106.2   1.49
121.2   0.979
136.2   0.82
161.2   0.896
181.2   0.692
211.2   0.52
331.2   0.325
451.2   0.482 (-)
811.2   0.128
END
```

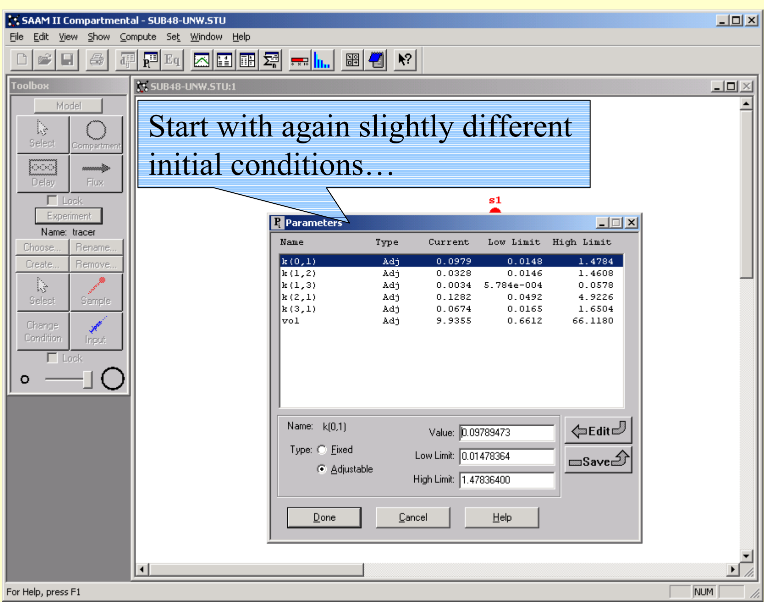
- Sometimes, it is of interest to try fitting data when unweighting (or neglecting) some measurements
- There may be many reasons for this:
  - It is believed that the measurement is an outlier (i.e. a very unlikely outcome of the measurement process)
  - The measurement may have an unreasonable value, or an unreasonable amount of noise
  - One wants to *test* how sensitive the fit is to the removal of a single measurement

vicini@u.washington.edu

Should We Just Take Out Data That Do Not Fit the Model?

- Answer: *it depends*
- Lack of model fit may not be a compelling enough reason to delete data
- On the other hand, it sometimes is apparent that some points are outliers, i.e. other errors may have been involved in data collection
- It often is a judgment call, but it should be *supported* by *independent*, *verifiable* evidence

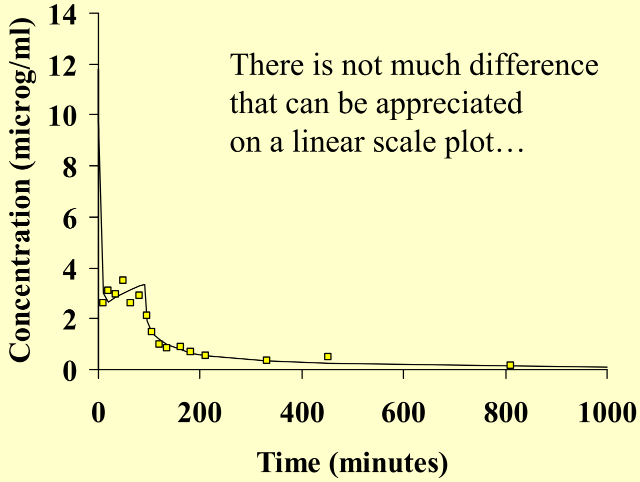
Modified Initial Conditions



vicini@u.washington.edu

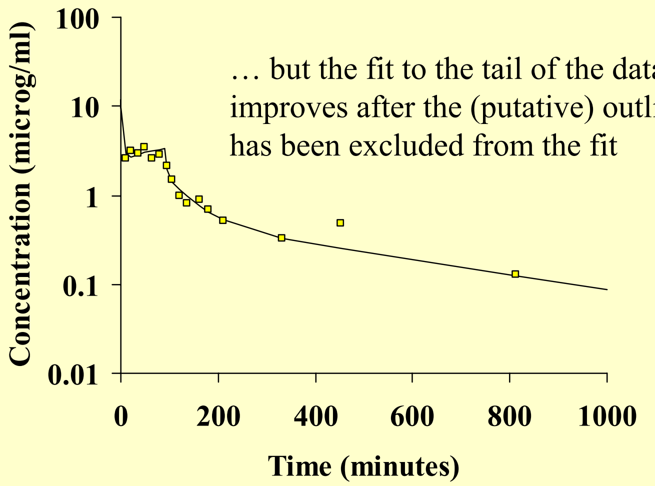
Modified Dataset Fit

(start from the modified initial conditions)



Modified Dataset Fit

(start from the modified initial conditions)



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What About the Statistics?

Statistics

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
k(0,1)	0.09789	4.15000e-002	4.23925e+001	0.00402	0.19177
k(1,2)	0.03277	1.37487e-002	4.19514e+001	0.00167	0.06387
k(1,3)	0.00338	1.21425e-003	3.59307e+001	6.32591e-004	0.00613
k(2,1)	0.12816	6.52798e-002	5.09372e+001	-0.01952	0.27583
k(3,1)	0.06744	3.05756e-002	4.53404e+001	-0.00173	0.13660
vol	9.93551	4.42099e+000	4.44969e+001	-0.06549	19.93650

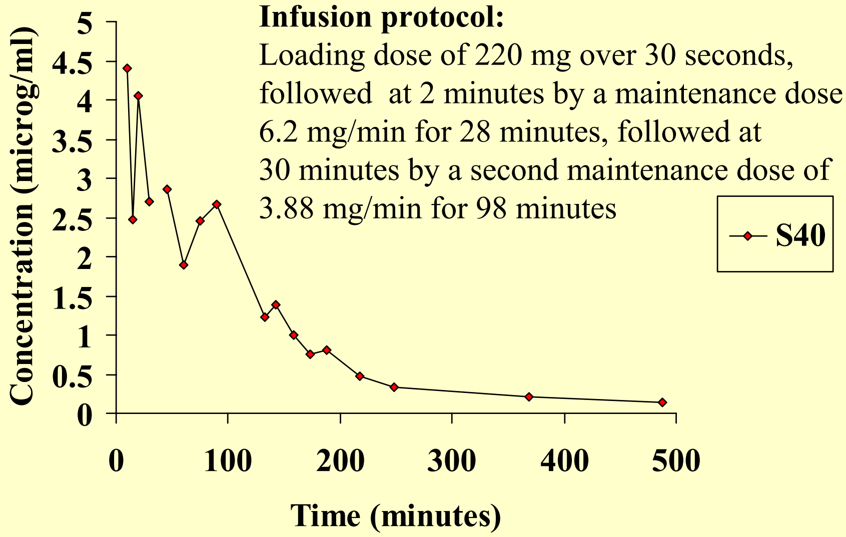
○ Correlation Matrix ○ Covariance Matrix ◉ Objective

	Objective	Scaled Data Variance
s1 : dat	-2.851435e+000	2.322461e+000

Total objective	-2.851435e+000	
AIC	-4.011245e-002	
BIC	1.250993e-001	

They improved substantially

Hands-On: Propofol Infusion



Infusion protocol:
Loading dose of 220 mg over 30 seconds, followed at 2 minutes by a maintenance dose of 6.2 mg/min for 28 minutes, followed at 30 minutes by a second maintenance dose of 3.88 mg/min for 98 minutes

vicini@u.washington.edu

Hands-On: Propofol Infusion

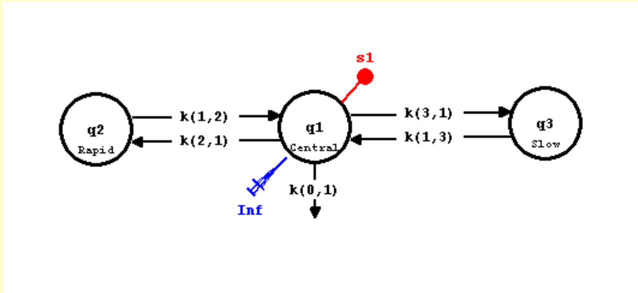
- Define the infusion protocol
- Find appropriate starting values
- Fit the data
- Report the statistics

Model Reparameterization

- Multicompartmental models are often parameterized in terms of rate constants k(i,j) and volumes
- A sometimes more useful parameterization is based on clearances and volumes
- Clearances are defined as the product of the rate constant k(i,j) times the volume of distribution of the originating compartment

vicini@u.washington.edu

Three Compartment Model



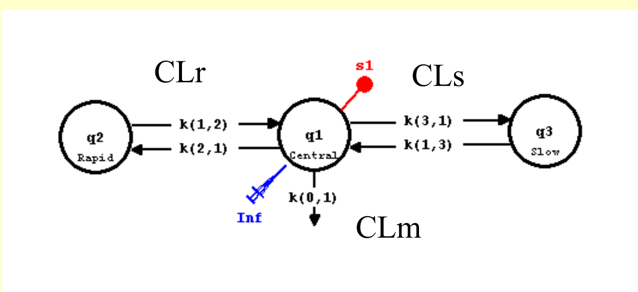
$$\frac{dq_1}{dt} = -[k(0,1) + k(2,1) + k(3,1)]q_1(t) + k(1,2)q_2(t) + k(1,3)q_3(t) + Inf(t)$$

$$\frac{dq_2}{dt} = +k(2,1)q_1(t) - k(1,2)q_2(t)$$

$$\frac{dq_3}{dt} = +k(3,1)q_1(t) - k(1,3)q_3(t)$$

Three Compartment Model

- There are three clearances:
  - Metabolic (elimination) Clm
  - Rapid peripheral, CLr
  - Slow peripheral, CLs



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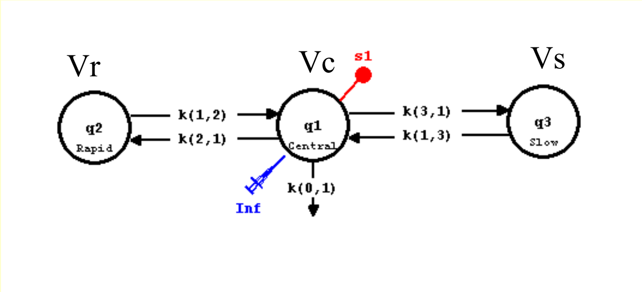
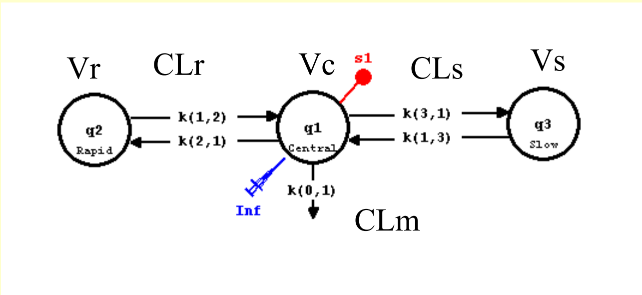
Three Compartment Model

- There are three volumes:
  - Central, Vc
  - Rapid peripheral, Vr
  - Slow peripheral, Vs



Reparameterization

- Fundamental equations are:
  - CLr = k(1,2)Vr = k(2,1)Vc
  - CLs = k(1,3)Vs = k(3,1)Vc
  - CLm = k(0,1)Vc



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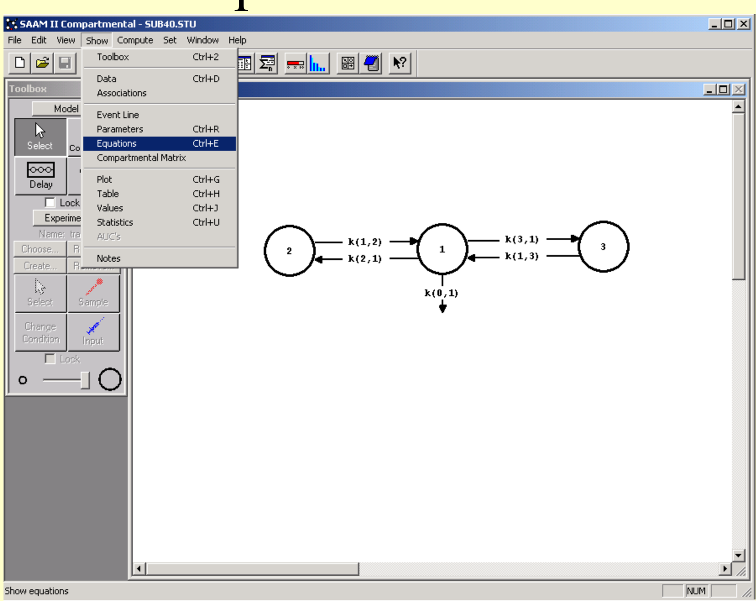
Reparameterization

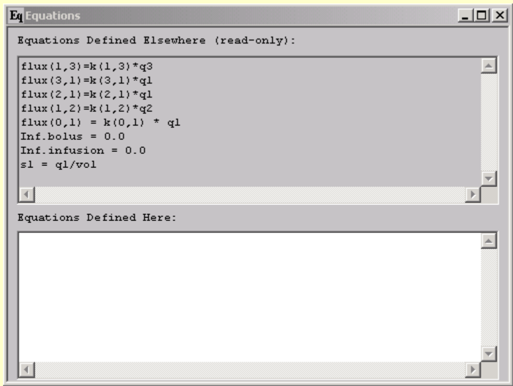
- Thus, we can express the rate constants as functions of the clearances, and make the clearances primary parameters:
  - k(1,2) = CLr / Vr
  - k(2,1) = CLr / Vc
  - k(1,3) = CLs / Vs
  - k(3,1) = CLs / Vc
  - k(0,1) = CLm / Vc
- This reparameterization can be accomplished in the Equations window of SAAM II

The Equations Window



vicini@u.washington.edu

The Equations Window

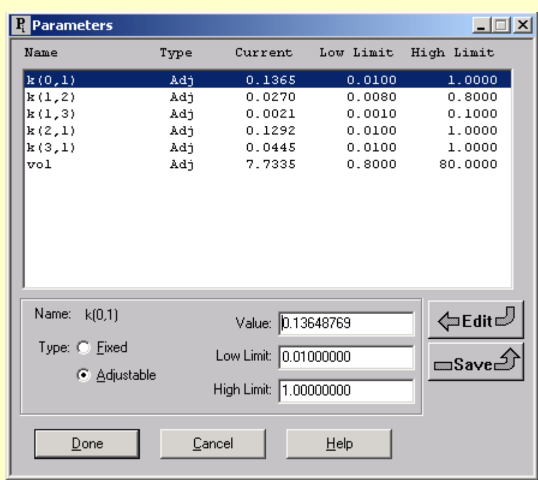


- The top window shows predefined (by the graphical model) equations
- The bottom window is available for user-defined equations
- Any equation is feasible
- The right hand side must contain only terms that have been defined beforehand

Primary Parameters

(directly estimated)

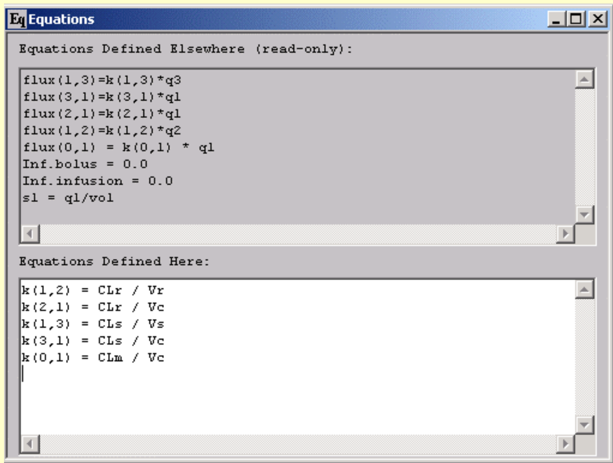
- Those that appear in the Parameter Window



User-Defined Equations

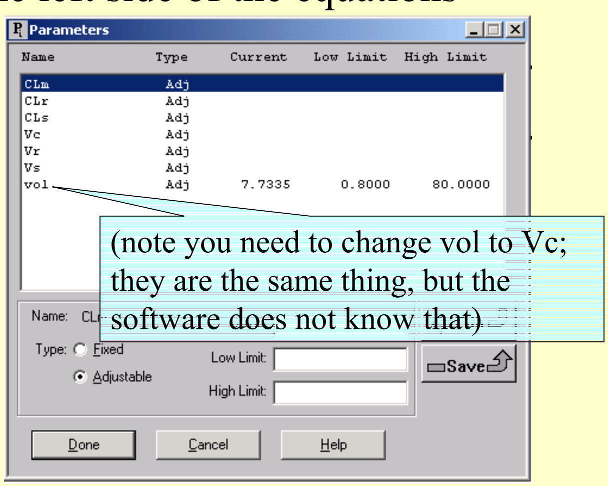
(in the Equation Window)

- These equations redefine the primary parameters



New Parameter Window

- The primary parameters have become those on the left side of the equations



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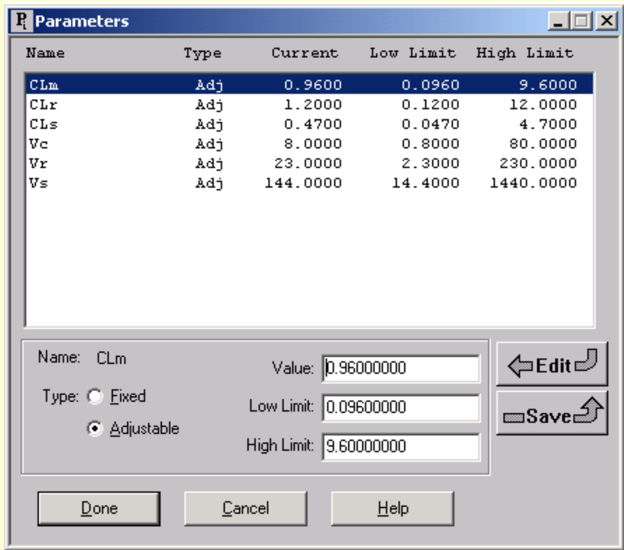
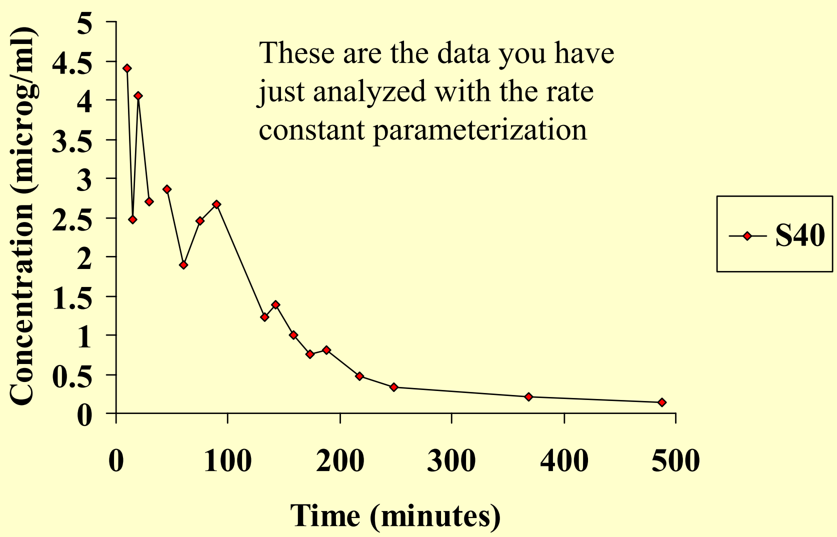
Initial Estimates



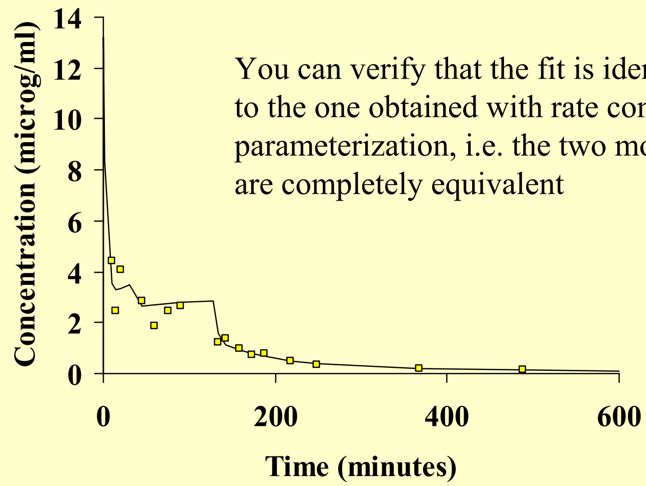
Example Dataset



These are the data you have just analyzed with the rate constant parameterization

vicini@u.washington.edu

Model Fit



You can verify that the fit is identical to the one obtained with rate constant parameterization, i.e. the two models are completely equivalent

What About the Statistics?

- There are Derived Variables!

Statistics

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
CLm	1.05750	4.18427e-001	3.95676e+001	0.12519	1.98981
CLr	1.00217	2.96406e-001	2.95764e+001	0.34174	1.66260
CLs	0.34337	2.27381e-001	6.62206e+001	-0.16327	0.85001
Vc	7.70407	4.92547e+000	6.39334e+001	-3.27057	18.67872
Vr	36.85425	1.99650e+001	5.41730e+001	-7.63065	81.33915
Vs	157.64754	5.19425e+002	3.29485e+002	-999.70364	1314.99872
Derived Variables					
k(0,1)	0.13726	9.80455e-002	7.14280e+001	-0.08119	0.35572

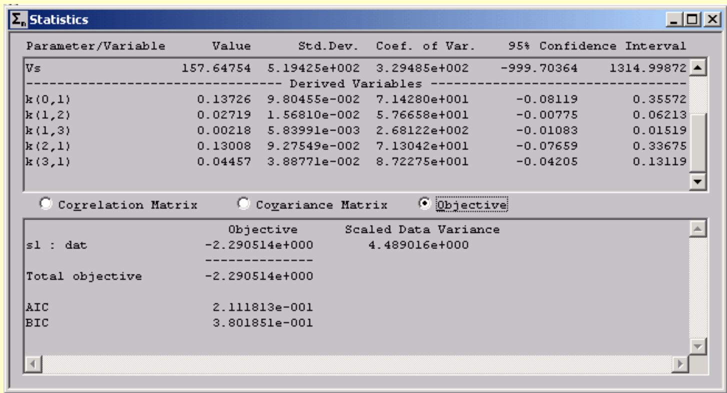
Correlation Matrix Covariance Matrix Objective

	Objective	Scaled Data Variance
s1 : dat	-2.290514e+000	4.489016e+000
Total objective	-2.290514e+000	
AIC	2.111813e-001	
BIC	3.801851e-001	

vicini@u.washington.edu

What About the Statistics?

- The rate constant estimates are all available (with their confidence interval) under the 'Derived Variables' heading


Statistics

Parameter/Variable	Value	Std.Dev.	Coef. of Var.	95% Confidence Interval	
Vs	157.64754	5.19425e+002	3.29485e+002	-999.70364	1314.99872
Derived Variables					
k(0,1)	0.13726	9.80455e-002	7.14280e+001	-0.08119	0.35572
k(1,2)	0.02719	1.56810e-002	5.76658e+001	-0.00775	0.06213
k(1,3)	0.00218	5.83991e-003	2.68122e+002	-0.01083	0.01519
k(2,1)	0.13008	9.27549e-002	7.13042e+001	-0.07659	0.33675
k(3,1)	0.04457	3.88771e-002	8.72275e+001	-0.04205	0.13119

Correlation Matrix Covariance Matrix Objective

	Objective	Scaled Data Variance
s1 : dat	-2.290514e+000	4.489016e+000
Total objective	-2.290514e+000	
AIC	2.111813e-001	
BIC	3.801851e-001	

What Have We Learned?

- Defining complex dosing administrations
- Dealing with lack of robustness in a fit
- Interpreting SAAM II warnings
- Reparameterizing models

vicini@u.washington.edu