# PopKinetics Tutorials and Simulations

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## Introduction

A variety of test conditions can be encountered today during the various phases of experimental design and analysis in biomedical research. Some of the experimental design variables include the size of the tested populations, richness of the test data, inter-subject variability in the data, different sampling regimes, and different combinations of some or all of these areas of variability. Analytic techniques available today to the investigators include sophisticated parameter estimation methodology and the use of Bayesian priors incorporating prior beliefs. For example, advanced modeling techniques are routinely applied during drug development and administration regimen design, where they are used to investigate and quantify the variability across subjects of drug absorption, disposition, and effectiveness.

These tutorials and accompanying simulations demonstrate many of the capabilities of the SAAM Institute population kinetics application (PopKinetics) including the use and relative capabilities of both Standard Two Stage (STS) and Iterated Two Stage (ITS) analysis methods, use of the Simulator, and the ability to calculate Confidence Intervals. The tutorials cover the use of PopKinetics under various instances of model complexity, population size, and data/sampling regime richness. They also portray the flexibility and robustness of the SAAM II/PopKinetics software suite.

The simplest approach to studying the population pharmacokinetics of a group of individuals is to administer specific dose of a drug to a number of individual subjects, to monitor the level of the drug in each subject's body over a period of time, and to estimate the pharmacokinetic parameters for each subject using a single subject modeling program such as SAAM II. Afterwards, sample averages and variances of the kinetics from the individual subjects are then computed across the population to determine the statistics of that population. This is the Standard Two-Stage (STS) method in PopKinetics.

Computational Considerations. Despite the simplicity of the method, the shortcomings of the Standard Two-Stage Method are rather evident:

- no information is gained by the fact that the subjects belong to the same population;
- the inter-individual variability given by the Individual Covariance Matrix $C_i$ is not taken into account, and this can lead to an overestimation of the Population Covariance Matrix D;
- no measure of the precision of the estimates of Population Parameter Mean m and Population Covariance Matrix D are available.

Large between-subject variability can lead to errors in the statistics for the population when this method is used.

In the SAAM II Population Kinetics application (PopKinetics), the Iterated Two-Stage (ITS) method uses a simple recursion formula that takes the results of an STS analysis, converts all unfixed model parameters to Bayesian, and again analyzes the population. This analysis/substitution of results /analysis cycle is continued until a user-defined level of convergence is achieved. This process addresses the shortcomings of the STS method while providing a method to refine both single subject and population analyses. See the Mathematical Background section of the HELP system for additional discussion on the STS and ITS methods.

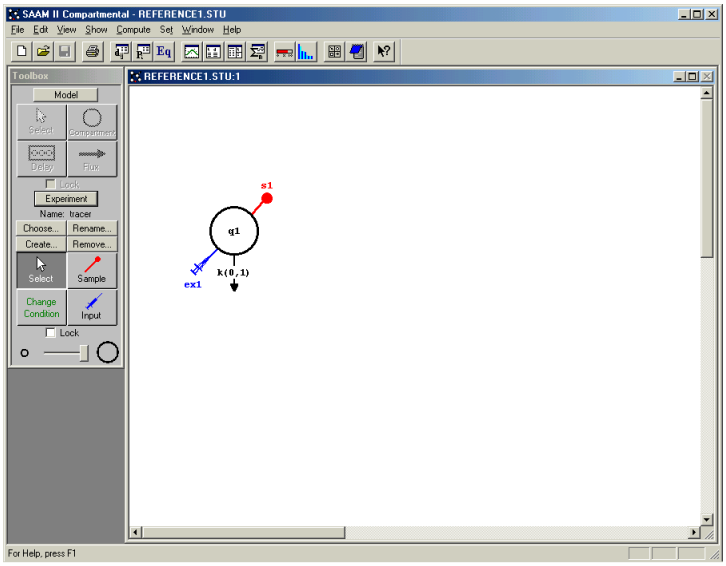
The SAAM Institute thanks Dr. Paolo Vicini both for his contributions to the development of PopKinetics and for these tutorials that illustrate some of the program’s capabilities.

## Simulation 1: Population analysis with low noise and many subjects

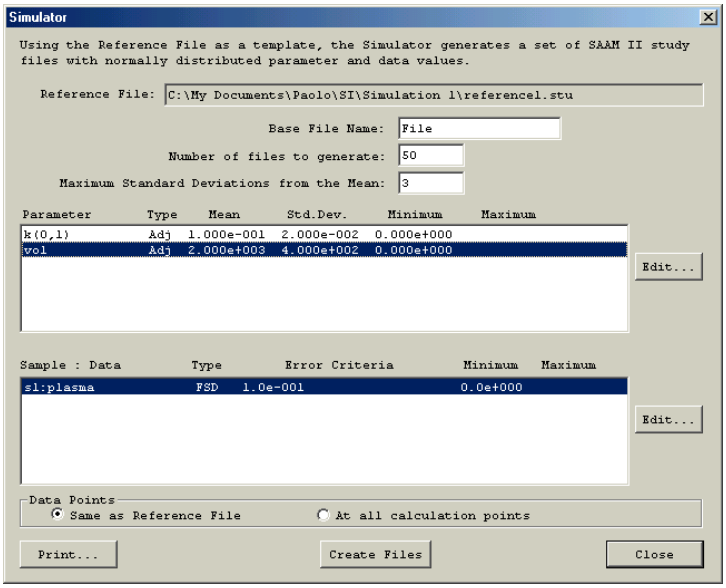
Purposes:

- Demonstrate the differences in Results from an STS Analysis and an ITS Analysis for the same large population.
- Demonstrate the effects of choosing model-based weighting or data-based weighting on the results of an analysis of a large population with low data noise.

This model is a one-compartment model that can be used to analyze data after an IV injection in the plasma compartment. We chose a dose of $1.08 \pm 10^8$ units and sampling (s1 = q1/vol) from the plasma compartment at 0.007, 0.125, 1.0, 4.0, 7.0, 9.0, 12.0 and 14.0 days. Parameter values are k(0,1) = 0.1 and vol = 2000.




We used PopKinetics to simulate 50 subjects with error in the data equal to FSD 3% and variability in the parameters equal to 20% (i.e., the parameters were k(0,1) = 0.10±0.02 and vol = 2000±400. The variances of k(0,1) and vol were thus respectively 0.004 = 4E-03 and 160000 = 1.6E+05. This was accomplished by using the reference file reference1.stu and the following settings in the Create Population menu item (note that reference1.stu is set to use model-based weights):



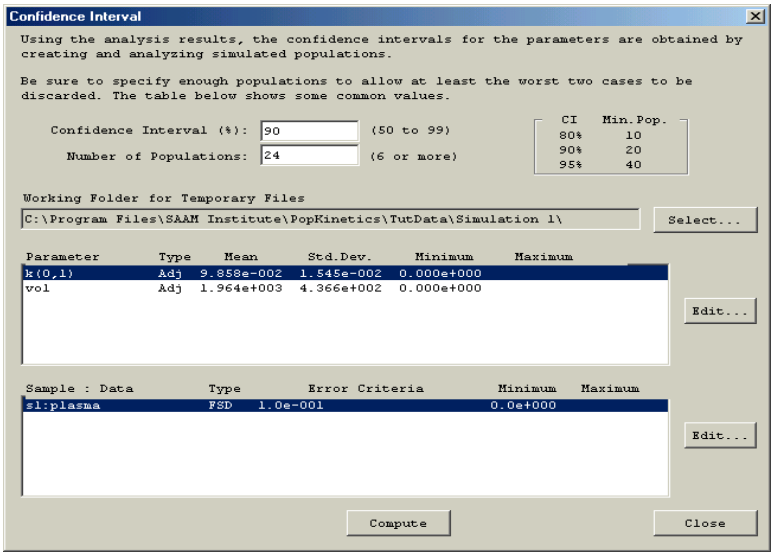
We chose a maximum of 3 standard deviations from the mean in the simulations. To do an STS analysis on the simulated data, we can load the settings in **simulation1_1.pkn**. The resulting means and standard deviations from the STS analysis are displayed after the analysis ends:

| Parameter | Type | Mean | Std.Deviation | Confidence Interval |
|---|---|---|---|---|
| k(0,1) | Adj | 9.85800e-002 | 1.54499e-002 | -- Not Available -- |
| vol | Adj | 1.96365e+003 | 4.36576e+002 | -- Not Available - |

The covariance matrix is:

| | k(0,1) | vol |
|---|---|---|
| k(0,1) | 2.3870e-004 | -8.4415e-001 |
| vol | -8.4415e-001 | 1.9060e+005 |

Do these means and variances and covariances reflect at all the original ones? We could run a confidence interval analysis on all the parameters and see if the resulting intervals always include the true values. Using PopKinetics one can calculate the confidence interval on the parameters from any analysis, not just ITS but also STS.




The Analysis Results now contain the Confidence Interval information.

| Parameter | Type | Mean | Std. Deviation | Confidence Interval |
|---|---|---|---|---|
| k(0,1) | Adj | 9.85800e-002 | 1.54499e-002 | 9.57037e-002 to 1.02691e-001 |
| vol. | Adj | 1.96365e+003 | 4.36576e+002 | 1.85322e+003 to 2.03211e+003 |

The ITS analysis is (load **simulation1_2.pkn** for the right settings):

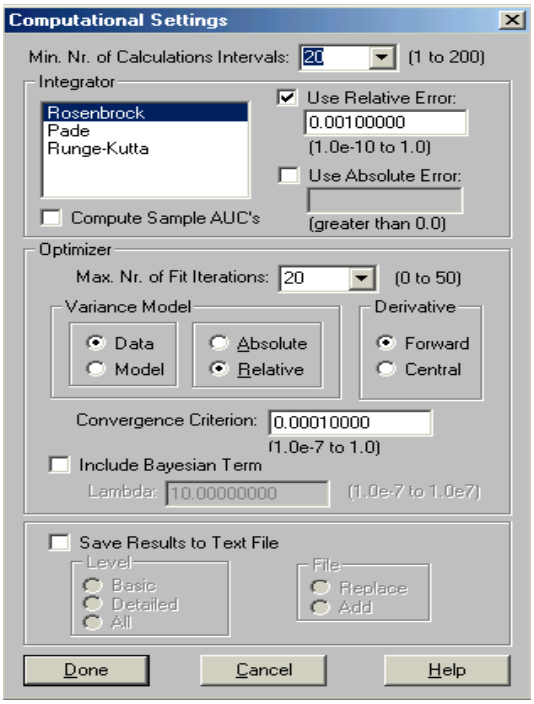
| Parameter | Type | Mean | Std.Deviation | Confidence Interval |
|---|---|---|---|---|
| k(0,1) | Bay | 9.91396e-002 | 1.16676e-002 | 9.6996e-002 to 1.0175e-001 |
| vol | Bay | 1.94799e+003 | 4.03687e+002 | 1.8561e+003 to 2.0631e+003 |

The covariance matrix is:

| | k(0,1) | vol |
|---|---|---|
| k(0,1) | 1.3613e-004 | 4.4769e-001 |
| vol | 4.4769e-001 | 1.6296e+005 |

This is just one simulation, but note how the values for the variances (and thus the standard deviations) of the parameters are closer to the actual, simulated value.

This analysis was run with Model-Based weighting. Which is more accurate, model-based or data-based weighting? We could repeat this analysis using data-based weights. Remember that you can change the weighting model by opening the Reference File in SAAM II, clicking on Compute/Settings, and changing the Variance Model settings to Data. Insure that you have selected Use Values in Reference File in the Initial Parameter Values and Limits frame of the Main PopKinetics window.




The reference file is reference2.stu, and the PopKinetics file is **simulation1_3.pkn**. STS gives the answers:

| Parameter | Type | Mean | Std.Deviation | Confidence Interval |
|---|---|---|---|---|
| k(0,1) | Adj | 9.83841e-002 | 1.52815e-002 | 9.57297e-002 to 1.02283e-001 |
| vol | Adj | 1.99581e+003 | 4.39946e+002 | 1.92672e+003 to 2.12385e+003 |

The covariance matrix is:

| | k(0,1) | vol |
|---|---|---|
| k(0,1) | 2.3353e-004 | -6.6827e-001 |
| vol | -6.6827e-001 | 1.9355e+005 |

which shows that there is not much difference between data-based and model-based weights in this situation of low data noise. With ITS (the PopKinetics file is **simulation1_4.pkn** ) we have:

| Parameter | Type | Mean | Std.Deviation | Confidence Interval |
|---|---|---|---|---|
| k(0,1) | Bay | 9.89750e-002 | 1.18644e-002 | 9.68993e-002 to 1.01972e-001 |
| vol | Bay | 1.98156e+003 | 4.09549e+002 | 1.83522e+003 to 2.07567e+003 |

and the covariance matrix:

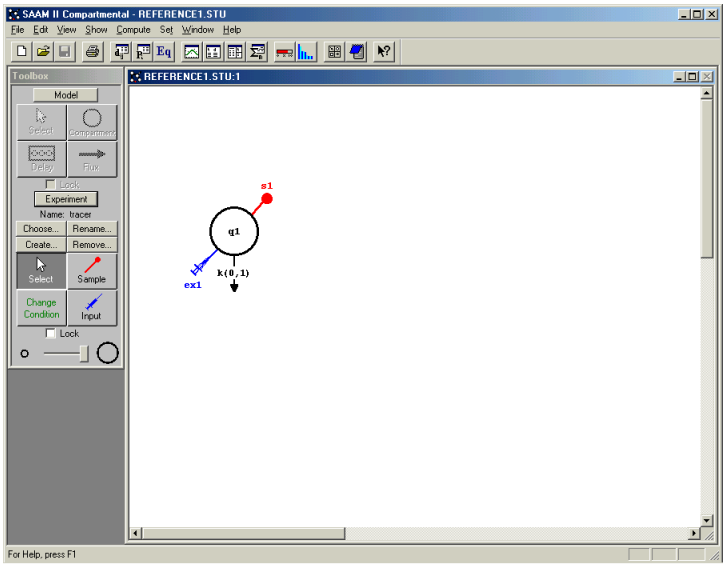
| | k(0,1) | vol |
|---|---|---|
| k(0,1) | 1.4076e-004 | 4.9827e-001 |
| vol | 4.9827e-001 | 1.6773e+005 |

Note how these results parallel those obtained with model-based weights, but the standard deviations have been reduced.

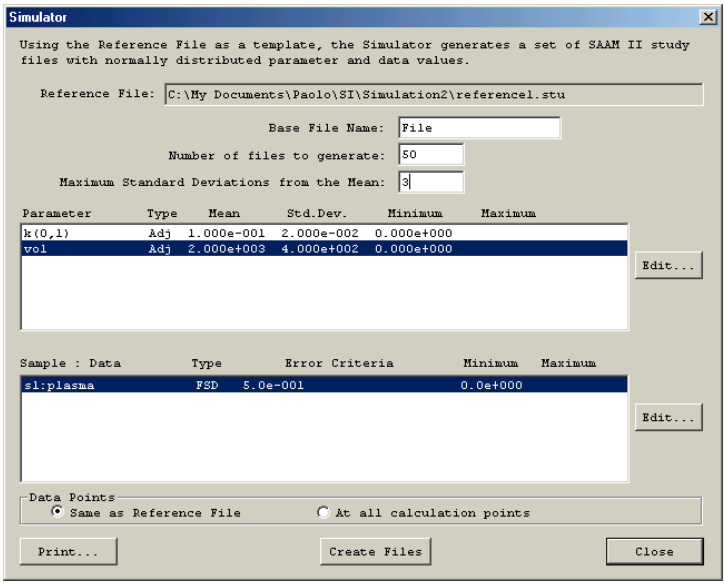
## Simulation 2: Effect of Data Weights

Purpose: To demonstrate the effect of high data noise on a population analysis and suggest the preferred weighting model to obtain a solution.

This model has the same structure as the model in Simulation 1. It is a one-compartment model with injection in the plasma compartment. We have chosen a dose of 1.08 ± $10^8$ units and sampling (s1 = q1/vol) from the plasma compartment at 0.007, 0.125, 1.0, 4.0, 7.0, 9.0, 12.0 and 14.0 days. Parameter values are k(0,1) = 0.1 and vol = 2000.




We used PopKinetics to simulate 50 subjects with error in the data equal to FSD 50% and variability in the parameters equal to 20% (i.e., the parameters were k(0,1) = 0.10±0.02 and vol = 2000±400). The reference file is reference1.stu, and the PopKinetics file is **simulation2_1.pkn**. Here is the Create Population window:




Let us run a STS analysis using model-based weights. Recall that setting the variance model for the reference file in SAAM II Compartmental under Compute/Settings can set the variance model for the population and then choose Use Reference File Values in the Initial Parameters Values and Limits frame in PopKinetics. The results are for the means and SDs:

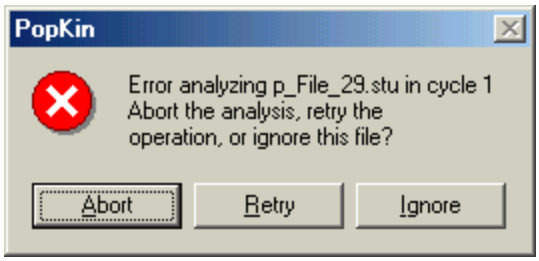
```
Parameter    Type      Mean        Std.Deviation        Confidence Interval
-----------  ----  -------------  -------------  ------------------------------

k(0,1)        Adj   1.10021e-001   3.10612e-002    1.0333e-001 to  1.1324e-001
vol           Adj   1.98037e+003   5.68984e+002    1.9453e+003 to  2.1226e+003
```

and for the covariance matrix:

```
                 k(0,1)           vol
k(0,1)         9.6480e-004  -9.2769e+000
vol           -9.2769e+000   3.2374e+005
```

Using reference2.stu, and the PopKinetics file **simulation2_2.pkn** for data-based weighting, we have an error in p_File_29.stu:




By inspection, we see that the first two data points are obviously outliers:

```
DATA
(FSD  5.00000e-001)
            t          plasma
 7.00000e-003   2.61397e+004(-)
 1.00000e+000   6.91172e+003(-)
 4.00000e+000   8.49702e+004
 5.00000e+000   7.07800e+004
 7.00000e+000   4.62941e+004
 9.00000e+000   1.62127e+004
 1.10000e+001   1.77876e+004
 1.20000e+001   2.27559e+004
 1.40000e+001   2.08666e+004
END
```

(the same happens for p_File_30.stu at t=5 and p_File_40.stu at t=4 and p_File_43.stu at t=7). Analysis results are:

```
Parameter         Type        Mean      Std.Deviation        Confidence Interval
---------------  ----  -------------  -------------  ------------------------------
k(0,1)            Adj   1.50276e-001   1.00322e-001        -- Not Available --
vol               Adj   2.75289e+003   1.66974e+003        -- Not Available -
```

for the means and standard deviations, and

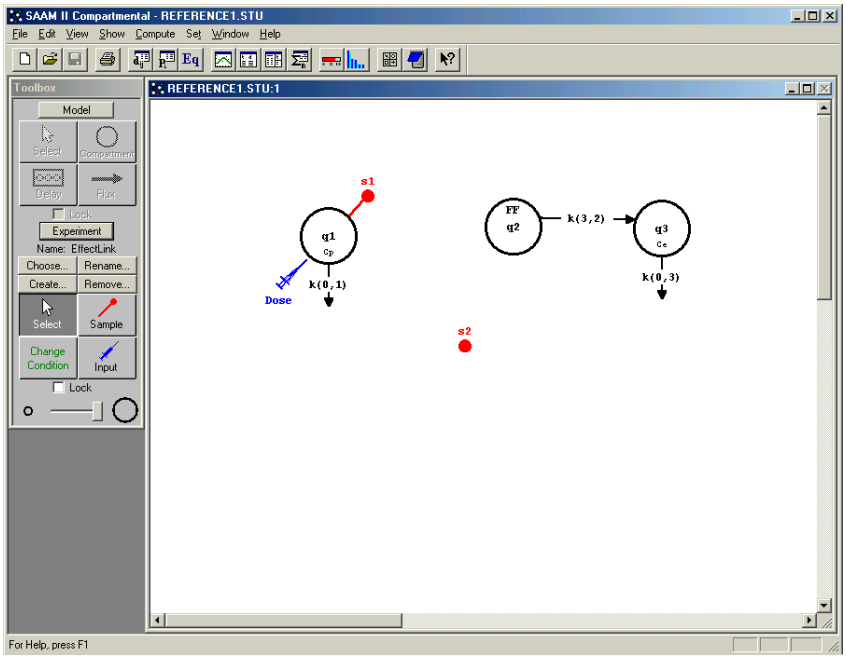
```
                   k(0,1)       vol
k(0,1)         1.0064e-002  -6.9554e+001
vol           -6.9554e+001   2.7880e+006
```

for the covariance matrix. These results suggest that, with this high level of noise, model-based weighting is preferable.

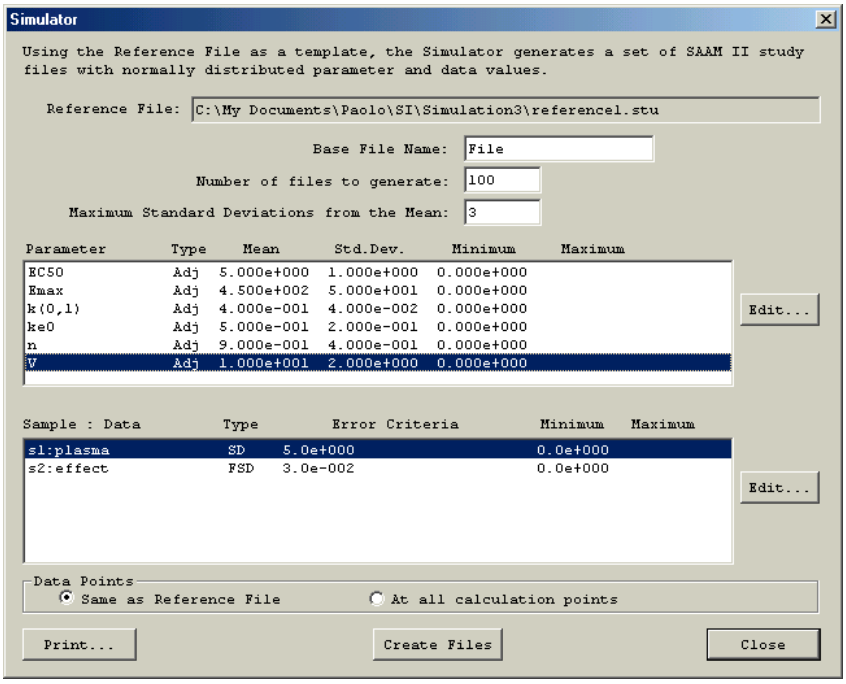
## Simulation 3: Population analysis of a PK/PD model

Purpose: To compare results on an STS analysis and an ITS analysis of a population containing a very rich sampling schedule.

The model is an effect-link model where the pharmacokinetics of a compound after IV administration of a bolus dose of 1000 units follow a one-compartment disposition with k(0,1)=0.4 and V=10. The measured concentration is s1=q1/V. The pharmacodynamic model is a link model where concentration in a remote, effect compartment is linked to the effect through the equation s2 = Emax*Ce^n/(Ce^n + EC50^n), where Emax=450.0, n=0.9 and EC50=0.5. Ce=q3 is computed from the differential equation q3' = + k(3,2)*q2.FF - k(0,3)*q3, where k(3,2)=k(0,3)=ke0=0.5 and q2.FF=s1. Measurement error was constant SD=5 for the PK and constant FSD=0.03 for the PD. The original reference file is in reference.stu.




We simulated 100 experimental subjects for this dataset. Simulated parameter values were as follows:



For the analysis, increase the number of iterations in the reference file to 50 and use central differencing (the settings are in reference1.stu and, for the population analysis, in **simulation3_1.pkn**). We start with a STS analysis. We skip files #48, #63 and #95, where the simulation resulted in an unlikely combination of parameters. From the remaining 97 files, the STS analysis gives:

| Parameter | Type | Mean | Std.Deviation | Confidence Interval |
|---|---|---|---|---|
| EC50 | Adj | 5.59984e+000 | 6.49054e+000 | -- Not Available -- |
| Emax | Adj | 4.44427e+002 | 5.97240e+001 | -- Not Available -- |
| V | Adj | 1.02204e+001 | 2.06604e+000 | -- Not Available -- |
| k(0,1) | Adj | 3.96624e-001 | 5.09430e-002 | -- Not Available -- |
| ke0 | Adj | 5.50985e-001 | 2.47054e-001 | -- Not Available -- |
| n | Adj | 9.56350e-001 | 4.01957e-001 | -- Not Available - |

(to be compared to the original parameters which were EC50=5±1, Emax=450±50, V=10±2, k(0,1)=0.40±0.04, ke0=0.5±0.2 and n=0.9±0.4) and for the covariance matrix:

| | EC50 | Emax | V | k(0,1) | ke0 | n |
|---|---|---|---|---|---|---|
| EC50 | 4.2127e+001 | 1.4267e+002 | -1.6242e+000 | -2.2182e-002 | -8.6925e-002 | -5.9348e-001 |
| Emax | 1.4267e+002 | 3.5670e+003 | -1.1779e+001 | 5.8458e-002 | 1.5906e-001 | 2.3370e-001 |
| V | -1.6242e+000 | -1.1779e+001 | 4.2685e+000 | -8.8659e-003 | 3.3407e-002 | -5.6772e-002 |
| k(0,1) | -2.2182e-002 | 5.8458e-002 | -8.8659e-003 | 2.5952e-003 | 1.1095e-005 | -7.3031e-004 |
| ke0 | -8.6925e-002 | 1.5906e-001 | 3.3407e-002 | 1.1095e-005 | 6.1036e-002 | 2.4229e-003 |
| n | -5.9348e-001 | 2.3370e-001 | -5.6772e-002 | -7.3031e-004 | 2.4229e-003 | 1.6157e-001 |

There are some differences, especially for ke0 and n. The discrepancies are not dramatic, however the question arises if we can improve this result using ITS. Conditions for this PopKinetics run are in **Simulation3_2.pkn**. Results of the ITS run are:

| Parameter | Type | Mean | Std.Deviation | Confidence Interval |
|---|---|---|---|---|
| EC50 | Bay | 4.77597e+000 | 9.51370e-001 | -- Not Available -- |
| Emax | Bay | 4.45864e+002 | 4.84649e+001 | -- Not Available -- |
| V | Bay | 1.01916e+001 | 1.98985e+000 | -- Not Available -- |
| k(0,1) | Bay | 3.96403e-001 | 3.53682e-002 | -- Not Available -- |
| ke0 | Bay | 5.40074e-001 | 2.22619e-001 | -- Not Available -- |
| n | Bay | 9.43838e-001 | 3.98846e-001 | -- Not Available -- |

and for the covariance matrix:

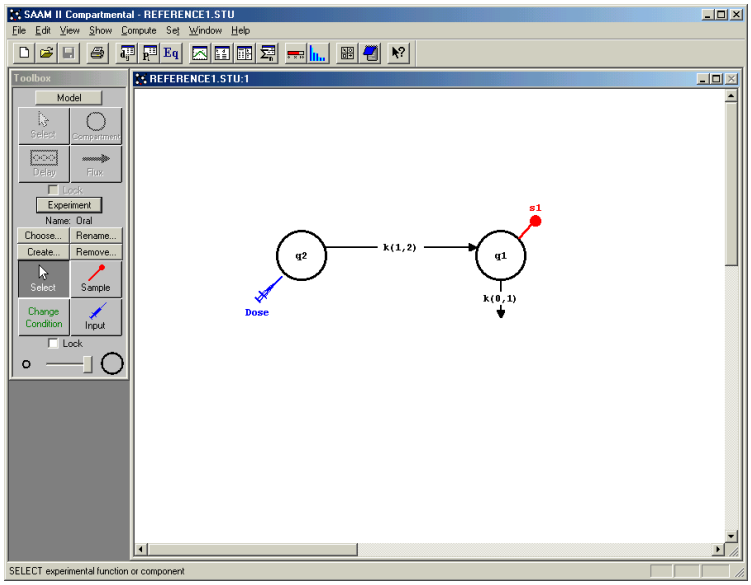
| | EC50 | Emax | V | k(0,1) | ke0 | n |
|---|---|---|---|---|---|---|
| EC50 | 9.0511e-001 | -1.4743e+001 | -3.8058e-002 | 9.0454e-004 | 1.5798e-002 | -3.3412e-002 |
| Emax | -1.4743e+001 | 2.3488e+003 | -5.9356e+000 | -3.2010e-001 | 3.2131e-001 | 1.8825e-003 |
| V | -3.8058e-002 | -5.9356e+000 | 3.9595e+000 | 4.0682e-003 | 9.2052e-003 | -7.1240e-002 |
| k(0,1) | 9.0454e-004 | -3.2010e-001 | 4.0682e-003 | 1.2509e-003 | 1.7957e-003 | 1.1868e-003 |
| ke0 | 1.5798e-002 | 3.2131e-001 | 9.2052e-003 | 1.7957e-003 | 4.9559e-002 | 1.0703e-003 |
| n | -3.3412e-002 | 1.8825e-003 | -7.1240e-002 | 1.1868e-003 | 1.0703e-003 | 1.5908e-001 |

The conclusion is that, with this very rich sampling schedule, we cannot improve significantly on the estimation of the parameters using ITS. However, we can reduce the standard deviations of the parameter means using an ITS analysis.

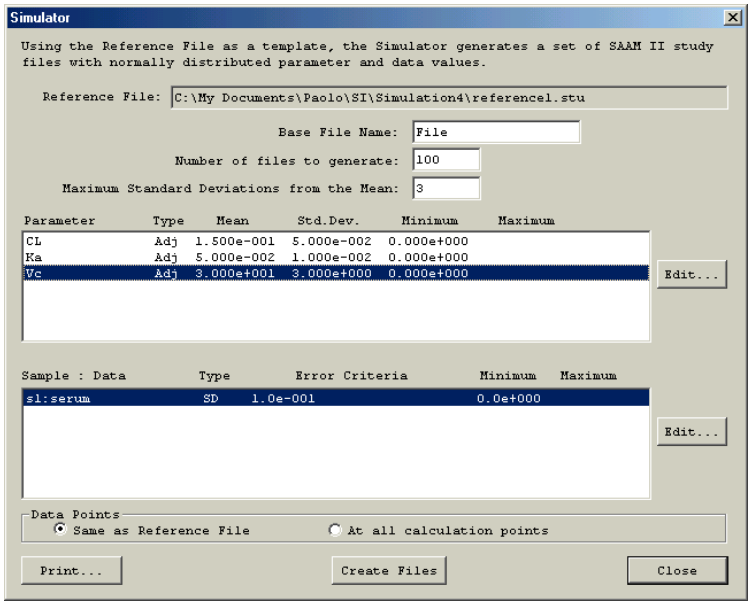
## Simulation 4: Population analysis of a pharmacokinetic model with rich sampling schedule

Purpose: To compare results on an STS analysis and an ITS analysis of a population containing a very rich sampling schedule.

The model is a one-compartment model with first-order absorption, suitable for modeling oral dosing pharmacokinetic data. We have chosen a dose of 100 units and sampling (s1 = q1/vol) from the serum compartment at 5, 10, 50, 100, 150, 200, 300 and 390 minutes. Parameter values are CL = k(0,1)*Vc = 0.15, Vc = 30 and Ka = k(1,2) = 0.05. Bioavailability of the compound is assumed equal to 100%.




We used PopKinetics to simulate 100 subjects with error in the data equal to SD 0.1 and variability in the parameters given by CL = 0.15±0.05, Ka = 0.05±0.01 and Vc = 30±3. The reference file is reference1.stu. Here is the Create Population window:




Analyzing the population in population analysis **simulation4_1.pkn** with STS, we obtain:

| Parameter | Type | Mean | Std.Deviation | 90% Confidence Interval |
|---|---|---|---|---|
| CL | Adj | 1.51204e-001 | 4.64049e-002 | 1.4651e-001 to 1.5739e-001 |
| Ka | Adj | 4.94166e-002 | 1.09128e-002 | 4.7900e-002 to 5.0815e-002 |
| Vc | Adj | 2.94190e+001 | 3.24756e+000 | 2.8851e+001 to 2.9914e+001 |

and for the covariance matrix:

| | CL | Ka | Vc |
|---|---|---|---|
| CL | 2.1534e-003 | -8.7138e-006 | -8.6352e-003 |
| Ka | -8.7138e-006 | 1.1909e-004 | 2.6939e-003 |
| Vc | -8.6352e-003 | 2.6939e-003 | 1.0547e+001 |

With ITS in population analysis **simulation4_2.pkn**, the results are very similar for means:

| Parameter | Type | Mean | Std.Deviation | 90% Confidence Interval |
|---|---|---|---|---|
| CL | Bay | 1.51229e-001 | 4.56499e-002 | 1.4717e-001 to 1.6030e-001 |
| Ka | Bay | 4.88009e-002 | 9.29470e-003 | 4.6526e-002 to 4.9553e-002 |
| Vc | Bay | 2.92934e+001 | 2.72023e+000 | 2.8673e+001 to 2.9571e+001 |

and the covariance matrix:

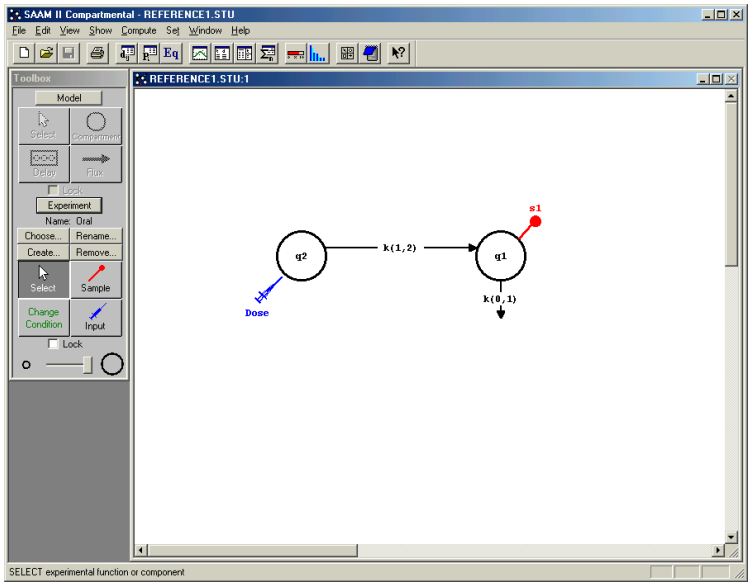
| | CL | Ka | Vc |
|---|---|---|---|
| CL | 2.0839e-003 | 4.4391e-006 | -3.6305e-003 |
| Ka | 4.4391e-006 | 8.6391e-005 | -4.1232e-003 |
| Vc | -3.6305e-003 | -4.1232e-003 | 7.3996e+000 |

When the sampling is rich as in this case, population analysis methods do not significantly improve the goodness of the estimates. However, we can reduce the parameter mean standard deviations using an ITS analysis. As expected, the STS results remain within the ITS results Confidence Intervals

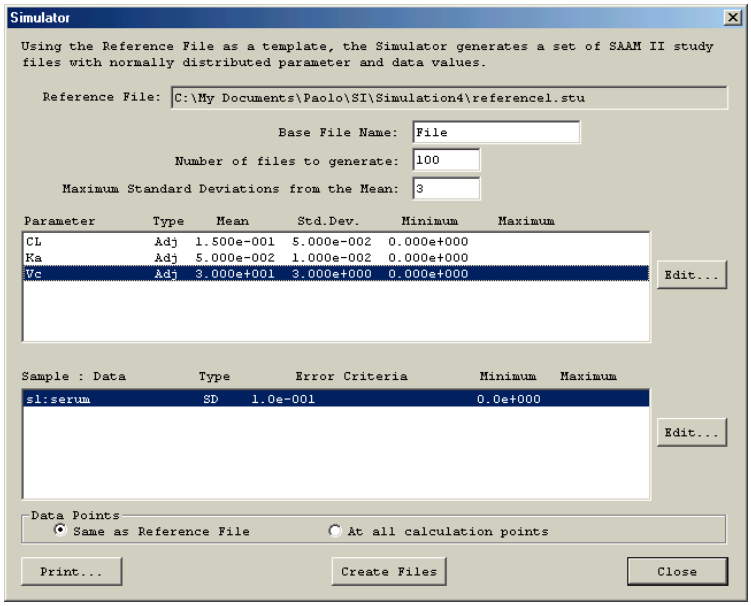
## Simulation 5: Population analysis of a pharmacokinetic model with parsimonious sampling schedule and small variability

Purpose: To demonstrate the value of an ITS analysis on a population with parsimonious sampling schedule and small variability when compared to an STS analysis.

The model is a one-compartment model with first-order absorption, suitable for modeling oral dosing pharmacokinetic data. We have chosen a dose of 100 units and sampling (s1 = q1/vol) from the serum compartment at 10, 50, 100, and 390 minutes. Parameter values are CL = k(0,1)*Vc = 0.15, Vc = 30 and Ka = k(1,2) = 0.05. Bioavailability of the compound is assumed equal to 100%.




We used PopKinetics to simulate 100 subjects with error in the data equal to SD 0.1 and variability in the parameters given by CL = 0.15±0.05, Ka = 0.05±0.01 and Vc = 30±3. The reference file is reference1.stu. Here is the Create Population window:




Note that four points is the absolute minimum to analyze such a model. Analyzing the data with STS, we have to skip file #12, where the last data point is an outlier. Settings are in Simulation5_1.pkn. We obtain:

| Parameter | Type | Mean | Std.Deviation | 77% Confidence Interval |
|---|---|---|---|---|
| CL | Adj | 1.41416e-001 | 5.23884e-002 | 1.3376e-001 to 1.4717e-001 |
| Ka | Adj | 5.15066e-002 | 1.42340e-002 | 5.0276e-002 to 5.3536e-002 |
| Vc | Adj | 3.03556e+001 | 3.86837e+000 | 2.9937e+001 to 3.0877e+001 |

and for the covariance matrix:

| | CL | Ka | Vc |
|---|---|---|---|
| CL | 2.7445e-003 | 5.1889e-005 | -8.3153e-004 |
| Ka | 5.1889e-005 | 2.0261e-004 | 1.1871e-002 |
| Vc | -8.3153e-004 | 1.1871e-002 | 1.4964e+001 |

With ITS (settings are in Simulation5_2.pkn) we still have to ignore #12. The results are very similar for the means, but the standard deviations are somewhat closer to the actual values:

| Parameter | Type | Mean | Std.Deviation | 75% Confidence Interval |
|---|---|---|---|---|
| CL | Bay | 1.41169e-001 | 5.15701e-002 | 1.3385e-001 to 1.4821e-001 |
| Ka | Bay | 5.11595e-002 | 1.32463e-002 | 5.0632e-002 to 5.3316e-002 |
| Vc | Bay | 3.03068e+001 | 3.44124e+000 | 3.0238e+001 to 3.0626e+001 |

The covariance matrix is:

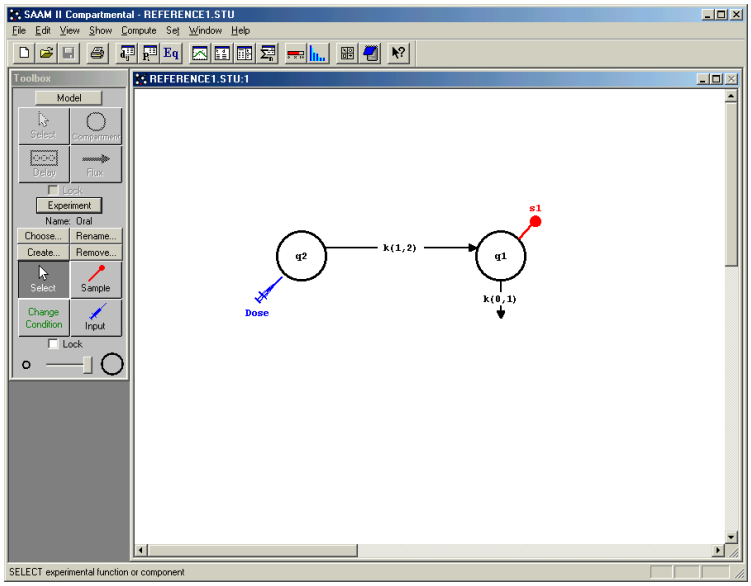
| | CL | Ka | Vc |
|---|---|---|---|
| CL | 2.6595e-003 | 6.9060e-005 | 5.0511e-003 |
| Ka | 6.9060e-005 | 1.7546e-004 | 4.3630e-003 |
| Vc | 5.0511e-003 | 4.3630e-003 | 1.1842e+001 |

As expected, the STS parameter means are within the ITS Confidence Interval.

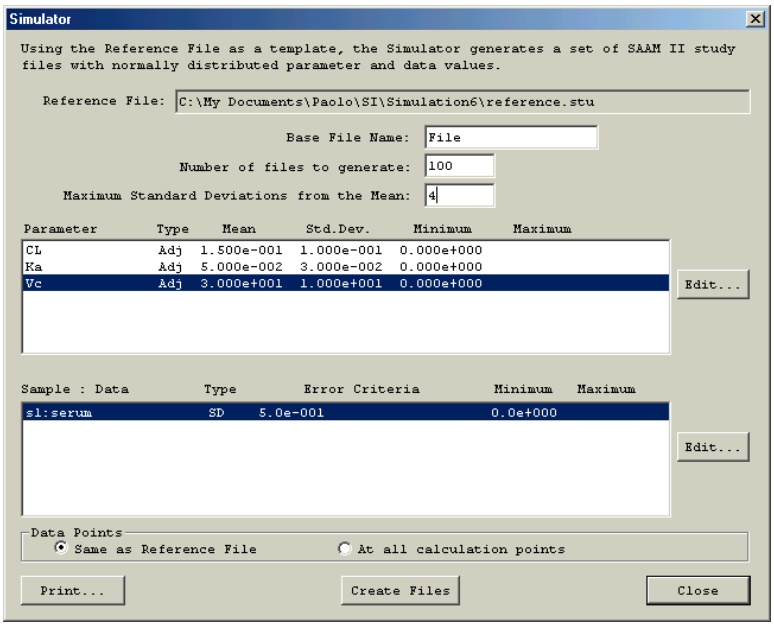
## Simulation 6: Population analysis of a pharmacokinetic model with parsimonious sampling schedule and large variability

Purpose: To demonstrate the value of an ITS analysis on a population with parsimonious sampling schedule and large variability when compared to an STS analysis.

The model is a one-compartment model with first-order absorption, suitable for modeling oral dosing pharmacokinetic data. We have chosen a dose of 100 units and sampling (s1 = q1/vol) from the serum compartment at 10, 50, 100, and 390 minutes. Parameter values are CL = k(0,1)*Vc = 0.15, Vc = 30 and Ka = k(1,2) = 0.05. Bioavailability of the compound is assumed equal to 100%.




We used PopKinetics to simulate 100 subjects with error in the data equal to SD 0.5 (increased with respect to the previous example) and variability in the parameters given by CL = 0.15±0.10, Ka = 0.05±0.03 and Vc = 30±10. This time, we also tolerate 4 standard deviations from the mean, as opposed to 3. The reference file is reference.stu. Here is the Create Population window:




Note that four points is the absolute minimum to analyze such a model. Analyzing the data with STS, we have to skip file 2, 7, 8, 20, 21, 22, 27, 31, 32, 42, 49, 52, 57, 60, 67, 69, 70, 80, 84, 96, 98, 99 and 100 (23 files out of 100). Settings are in **Simulation6_1.pkn.** We obtain:

| Parameter | Type | Mean | Std.Deviation | Confidence Interval |
|---|---|---|---|---|
| CL | Adj | 1.31218e-001 | 8.50544e-002 | -- Not Available -- |
| Ka | Adj | 8.37675e-002 | 5.24761e-002 | -- Not Available -- |
| Vc | Adj | 3.35566e+001 | 1.70196e+001 | -- Not Available - |

and for the covariance matrix:

| | CL | Ka | Vc |
|---|---|---|---|
| CL | 7.2343e-003 | 3.3139e-004 | 2.7434e-002 |
| Ka | 3.3139e-004 | 2.7537e-003 | 2.3422e-001 |
| Vc | 2.7434e-002 | 2.3422e-001 | 2.8967e+002 |

With ITS (settings are in **Simulation6_2.pkn**) we still have to ignore the same files (the setting in Simulation6_2.pkn is to skip the file with error and continue). The results are very similar for the means, but note how the standard deviations have been reduced:

| Parameter | Type | Mean | Std.Deviation | Confidence Interval |
|---|---|---|---|---|
| CL | Bay | 1.30331e-001 | 7.01776e-002 | -- Not Available -- |
| Ka | Bay | 6.92999e-002 | 2.63854e-002 | -- Not Available -- |
| Vc | Bay | 3.10279e+001 | 1.18780e+001 | -- Not Available - |

The covariance matrix is:

| | CL | Ka | Vc |
|---|---|---|---|
| CL | 4.9249e-003 | 2.3855e-004 | -6.5492e-002 |
| Ka | 2.3855e-004 | 6.9619e-004 | -7.1118e-003 |
| Vc | -6.5492e-002 | -7.1118e-003 | 1.4109e+002 |

Also, the means for Ka and Vc have become closer to the true values we defined in the simulation.

## Simulation 7: Simulating and analyzing log-normally distributed populations

Purpose: To demonstrate the value of an ITS analysis on a population with parameters with a log-normal distribution when compared to an STS analysis.

Sometimes, parameters in a population are distributed log-normally as opposed to normally. This means that the logarithm of the parameter follows a log-normal distribution, as opposed to the parameter itself. Let us consider a one-compartment model with first-order absorption, suitable for modeling oral dosing pharmacokinetic data. Let us choose a dose of 100 units and sampling (s1 = q1/vol) from the serum compartment at 10, 50, 100, and 390 minutes. Parameters are CL = k(0,1)*Vc, Vc and Ka = k(1,2). Bioavailability of the compound is assumed equal to 100%. Let us assume that CL and Ka are log-normally distributed. This means that log[CL] and log[Ka] are normally distributed. One can simulate log-normal distributions in PopKinetics, and choose whether to analyze the data with normal or log-normal assumptions. Note that for coefficients of variation close to 5% or less, the log-normal and the normal distributions essentially coincide.

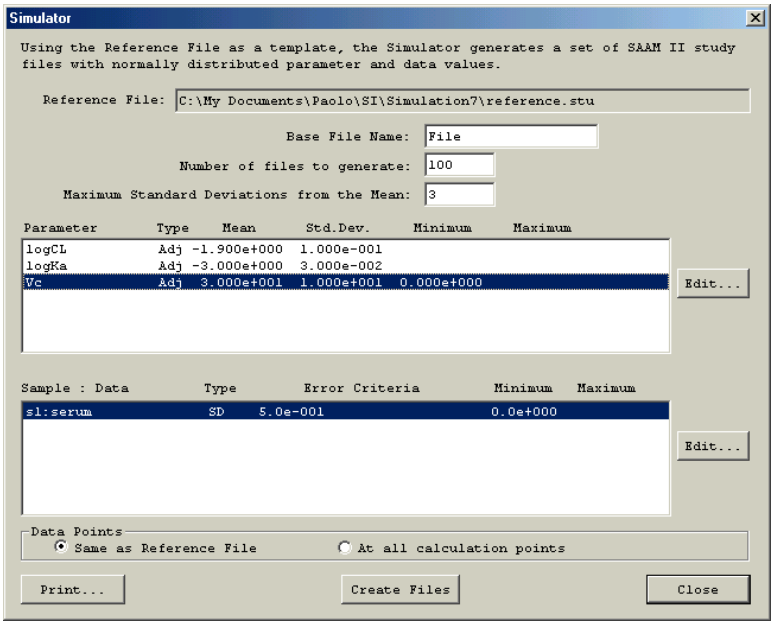
We have modeled a log-normal distribution with medians 0.15 and 0.05 respectively by writing the following equations in the Equation Window of the reference file reference.stu:

```
CL = exp(logCL)
Ka = exp(logKa)
```

Note that CL and Ka can never be negative: that's an advantage of this parameterization. If `logCL` and `logKa` are normally distributed, then the logarithm of CL and Ka is also normally distributed, as we can write:

```
log[CL] = logCL
log[Ka] = logKa
```

We chose the random effects to be mean zero and standard deviation 0.1 for `logCL` and 0.03 for `logKa`. The simulation window is as follows:




One can choose to analyze the files assuming either a Gaussian or a log-normal distribution. The results would be different as these are two different population models. Let us analyze these simulated data with the original parameterization. We can use reference.stu for this purpose. Files 8, 15, 16, 17, 18, 30, 32, 38, 44, 48, 50, 54, 56, 61, 62, 70, 76, 80, 86, 97, 98 and 100 (22 files out of 100) did not converge and were skipped. STS analysis (setup in **Simulation7_1.pkn**) gives:

| Parameter | Type | Mean | Std.Deviation | Confidence Interval |
|---|---|---|---|---|
| Vc | Adj | 3.25823e+001 | 1.20141e+001 | -- Not Available -- |
| logCL | Adj | -2.01868e+000 | 3.46139e-001 | -- Not Available -- |
| logKa | Adj | -2.83932e+000 | 5.11667e-001 | -- Not Available - |

and for the covariance matrix:

| | Vc | logCL | logKa |
|---|---|---|---|
| Vc | 1.4434e+002 | -8.1223e-001 | 2.6455e+000 |
| logCL | -8.1223e-001 | 1.1981e-001 | 4.9105e-004 |
| logKa | 2.6455e+000 | 4.9105e-004 | 2.6180e-001 |

ITS analysis (settings are in **Simulation7_2.pkn**) improves considerably the estimation of the standard deviations of logCL and Vc:

| Parameter | Type | Mean | Std.Deviation | Confidence Interval |
|---|---|---|---|---|
| Vc | Bay | 3.21717e+001 | 8.15831e+000 | -- Not Available -- |
| logCL | Bay | -1.98037e+000 | 1.90126e-001 | -- Not Available -- |
| logKa | Bay | -2.78198e+000 | 2.71313e-001 | -- Not Available - |

and for the covariance matrix:

| | Vc | logCL | logKa |
|---|---|---|---|
| Vc | 6.6558e+001 | 1.6945e-001 | 3.0848e-001 |
| logCL | 1.6945e-001 | 3.6148e-002 | 1.6880e-002 |
| logKa | 3.0848e-001 | 1.6880e-002 | 7.3611e-002 |

Note how the standard deviation estimates are reduced with ITS with respect to STS. Also, the means for Ka and Vc are closer to the true values we defined in the simulation.

## Simulation 8: Monte Carlo simulations of individual data sets

Purpose: To provide an example of the Monte Carlo simulation capability contained in PopKinetics.

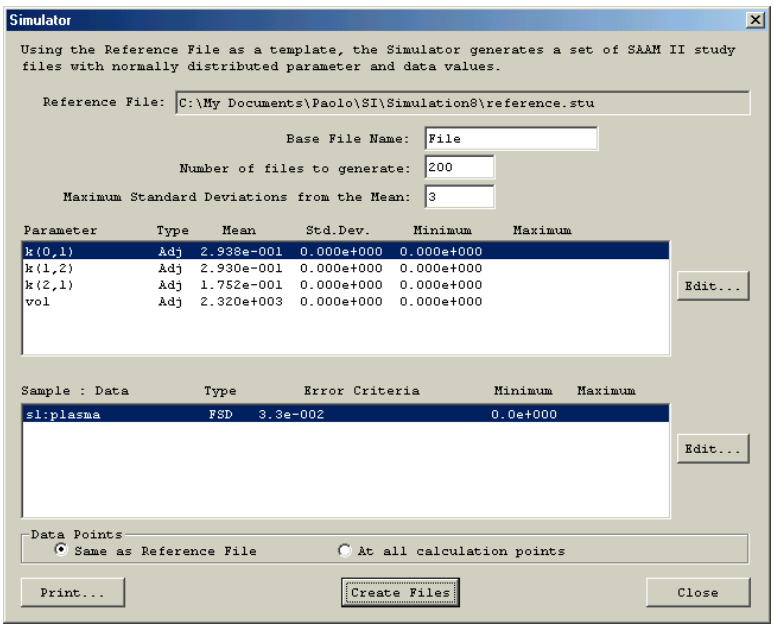
Monte Carlo simulation can be used to calculate better confidence intervals for an individual analysis than those available from asymptotic statistics like those available from the Statistics Window in SAAM II. We will use for this purpose the example file study_0.stu distributed with SAAM II. If one fits that file using model-based relative weights and `(FSD 0.1)` in the Data window, the information from the Statistics Window is:

| Parameter/Variable | Value | Std. Dev. | Coef. Of Var. | 95% Confidence Interval | |
|---|---|---|---|---|---|
| k(0,1) | 0.29384 | 1.40311e-002 | 4.77513e+000 | 0.26295 | 0.32472 |
| k(1,2) | 0.29299 | 7.66637e-002 | 2.61658e+001 | 0.12426 | 0.46173 |
| k(2,1) | 0.17524 | 1.90604e-002 | 1.08767e+001 | 0.13329 | 0.21719 |
| vol | 2320.07572 | 3.84341e+001 | 1.65659e+000 | 2235.48258 | 2404.66885 |

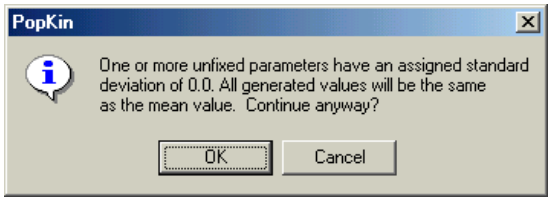
and the objective function information is:

| | Objective | Scaled Data Variance |
|---|---|---|
| s1 : plasma | 1.337451e+001 | 1.120733e-001 |
| Total objective | 1.337451e+001 | |
| AIC | 7.939526e+000 | |
| BIC | 8.057534e+000 | |

Suppose one wonders if the statistics are adequate and the confidence intervals for the parameters are well calculated. Monte Carlo simulation allows testing such a hypothesis, provided the statistics of the measurement error are known. It is based on simulating a large number of synthetic data sets and calculating the average estimate for all the synthetic data sets. For the simulation, we will use a measurement error based on our initial estimate in the data file (FSD 10%) and the Scaled Data Variance from the solution Objective Function information (0.1120733). The simulation measurement error, or relative error, is thus sqrt (0.1120733) x 0.10 for a simulation data error of FSD 0.3347735. in the file reference.stu. The simulation window is as follows:




As we are interested only in the effect of the measurement error, we do not allow the parameters to vary (there is no between-individual variation). This warning will appear:




but we will proceed and click "OK". STS analysis (setup in **Simulation8_1.pkn**) of the simulated data gives:

| Parameter | Type | Mean | Std.Deviation | Confidence Interval |
|---|---|---|---|---|
| k(0,1) | Adj | 2.91144e-001 | 1.47694e-002 | -- Not Available -- |
| k(1,2) | Adj | 2.93114e-001 | 6.95022e-002 | -- Not Available -- |
| k(2,1) | Adj | 1.79673e-001 | 1.78971e-002 | -- Not Available -- |
| vol | Adj | 2.31999e+003 | 3.72195e+001 | -- Not Available - |

thus showing that, under these circumstances of rather low data noise, the asymptotic error for the parameter estimates is quite appropriate.