MetidaNCA validation report

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2021-07-11

1 Introduction and package description

Non-compartment anlysis software.

See documentation: https://pharmcat.github.io/MetidaNCA.jl/dev/

1.1 Validation purpose

The main validation purpose is confirmation by examination and provision of objective evidence that software specifications conform to user needs and intended uses, and that the particular requirements implemented through software can be consistently fulfilled.

1.2 Requirements

- Julia 1.5.* (or higher) installed

- Julia packages from dependence list installed (see Project.toml)

1.3 Developer software life cycle

- Development stage

- Testing procedures development

- Performing testing procedures on local machine

- Push to master branch

- Performing testing procedures with GitHub Actions

- Make pull request to the official registry of general Julia packages (if nessesary)

- Make release (if previous completed)

1.3.1 Versions

- X.Y.Z - patch release (no breaking changes)

- X.Y.# - minor release (may include breaking changes)

- X.#.# - major release (breaking changes, changes in public API)

- 0.#.# - no stable public API

- $\geq$1.#.# - stable public API

1.4 Build support

1.4.1 Tier 1

- julia-version: 1.5, 1.6

- julia-arch: x64

- os: ubuntu-18.04, macos-10.15, windows-2019

2 Installation

2.1 System information

- Julia version: v"1.4.2"

- Current machine: "x86_64-pc-linux-gnu"

2.2 Installation method

MetidaNCA.jl can be installed by executing the following command in REPL.

```
import Pkg; Pkg.add("MetidaNCA")
```

2.3 Version check

The installation process is checking within each testing job via GitHub Actions. Also GitHub Action chek performed before merging into JuliaRegistries/General repository (see Automatic merging of pull requests).

Current package version:

"0.1.2"

3 Operation qualification

This part of validation based on testing procedures entails running software products under known conditions with defined inputs and documented outcomes that can be compared to their predefined expectations. All documented public API included in testing procedures and part of critical internal methods.

3.1 Coverage

Code coverage report available on Codecov.io. Test procedures include all public API methods check.

- Coverage goal: $\geq 90.0\%$

3.2 Data

Validation data available in the repository and included in the package. See Appendix 1.

3.3 Testing results

```
Pkg.test("MetidaNCA")
```

```
Test Summary:                                           | Pass  Total
  Simple test                                           |    2      2
Test Summary:                                           | Pass  Total
  Linear trapezoidal, Dose 100, Dosetime 0, no tau      |   18     18
Test Summary:                                           | Pass  Total
  Linear up Log down, Dose 120, Dosetime 0, tau 12      |   17     17
Test Summary:                                           | Pass  Total
  Log trapezoidal ATM, Dose 120, Dosetime 0, tau 12     |    5      5
Test Summary:                                           | Pass  Total
  Linear up Log down ATM, Dose 120, Dosetime 0, tau 12  |    4      4
Test Summary:                                           | Pass  Total
  Linear up Log down, Dose 100, Dosetime 0.25, tau 9    |    8      8
Test Summary:                                           | Pass  Total
  Linear trapezoidal, Dose 100, Dosetime 2.0, tau 10    |   15     15
Test Summary:                                           | Pass  Total
  Linear trapezoidal, Dose 100, Dosetime 0.0, tau 100   |   15     15
Test Summary:                                           | Pass  Total
  Linear trapezoidal, Dose 120, Dosetime 0.0, tau 12    |    4      4
Test Summary:                                           | Pass  Total
  set-get*! tests                                       |    7      7
Test Summary:                                           |
  applylimitrule!                                       | No tests
Test Summary:                                           |
  kel                                                   | No tests
Test Summary:                                           |
  Output                                                | No tests
```

4 Performance qualification

Purpose of this testing procedures to demonstrate performance for some critical tasks.

4.1 Parameter's names description

```
.------------.-------------------------------.
|       Name |                   Description |
|     String |                        String |
:------------+-------------------------------:
|       Cmax |         Maximum concentration |
|       Tmax |                  Time at Cmax |
|      Cdose |     Concentration at dose time |
|      Clast |     Last non-zero concentration |
|    AUClast |                   AUC to Clast |
|   AUMClast |                  AUMC to Clast |
|     AUCall |            AUC with all values |
|        Rsq |                      r square |
|       ARsq |             Adjusted r square |
|        Kel | Terminal elimination constant |
|         HL |              Half live or T1/2 |
|      LZint |                     Intercept |
| Clast_pred |                Predicted Clast |
|     AUCinf |    AUC extrapolated to infinity |
|     AUCpct | Percentage AUClast from AUCinf |
|    MRTlast |      Mean Residence Time (last) |
|     MRTinf |       Mean Residence Time (inf) |
|      Clinf |                     Clearence |
|      Vzinf |         Volume of distribution |
'------------'-------------------------------'
```

4.2 Results

4.2.1 Linear-trapezoidal rule; Extravascular

Cmax

Subjct	Value	Reference	Difference
Float64	Float64	Float64	Float64
1.0	190.869	190.869	0.0
2.0	261.177	261.177	0.0
3.0	105.345	105.345	0.0
4.0	208.542	208.542	0.0
5.0	169.334	169.334	0.0
6.0	154.648	154.648	0.0
7.0	153.254	153.254	0.0
8.0	138.327	138.327	0.0
9.0	167.347	167.347	0.0
10.0	125.482	125.482	0.0

Tmax

Subjct	Value	Reference	Difference
Float64	Float64	Float64	Float64
1.0	1.0	1.0	0.0
2.0	1.0	1.0	0.0
3.0	1.5	1.5	0.0
4.0	1.0	1.0	0.0

Subjct	Value	Reference	Difference
5.0	4.0	4.0	0.0
6.0	2.5	2.5	0.0
7.0	2.5	2.5	0.0
8.0	4.0	4.0	0.0
9.0	3.0	3.0	0.0
10.0	2.0	2.0	0.0

Cdose

Subjct	Value	Reference	Difference
Float64	Float64	Float64	Float64
1.0	0.0	0.0	0.0
2.0	0.0	0.0	0.0
3.0	0.0	0.0	0.0
4.0	0.0	0.0	0.0
5.0	0.0	0.0	0.0
6.0	0.0	0.0	0.0
7.0	0.0	0.0	0.0
8.0	0.0	0.0	0.0
9.0	0.0	0.0	0.0
10.0	0.0	0.0	0.0

Clast

Subjct	Value	Reference	Difference
Float64	Float64	Float64	Float64
1.0	112.846	112.846	0.0
2.0	85.241	85.241	0.0
3.0	67.901	67.901	0.0
4.0	97.625	97.625	0.0
5.0	110.778	110.778	0.0
6.0	69.501	69.501	0.0
7.0	58.051	58.051	0.0
8.0	74.437	74.437	0.0
9.0	93.44	93.44	0.0
10.0	42.191	42.191	0.0

AUClast

Subjct	Value	Reference	Difference
Float64	Float64	Float64	Float64
1.0	9585.42	9585.42	0.0
2.0	10112.2	10112.2	0.0
3.0	5396.55	5396.55	0.0
4.0	9317.84	9317.84	0.0
5.0	9561.26	9561.26	0.0
6.0	6966.6	6966.6	0.0
7.0	7029.57	7029.57	0.0
8.0	7110.67	7110.67	0.0
9.0	8315.08	8315.08	0.0
10.0	5620.89	5620.89	0.0

AUMClast

Subjct	Value	Reference	Difference
Float64	Float64	Float64	Float64
1.0	333582.0	333582.0	0.0
2.0	298701.0	298701.0	0.0
3.0	186032.0	186032.0	0.0
4.0	313956.0	313956.0	0.0
5.0	315182.0	315182.0	0.0
6.0	226977.0	226977.0	0.0
7.0	219798.0	219798.0	0.0
8.0	240526.0	240526.0	0.0
9.0	277614.0	277614.0	0.0
10.0	154893.0	154893.0	0.0

AUCall

Subjct	Value	Reference	Difference
Float64	Float64	Float64	Float64
1.0	9585.42	9585.42	0.0
2.0	10112.2	10112.2	0.0
3.0	5396.55	5396.55	0.0
4.0	9317.84	9317.84	0.0
5.0	9561.26	9561.26	0.0
6.0	6966.6	6966.6	0.0
7.0	7029.57	7029.57	0.0
8.0	7110.67	7110.67	0.0
9.0	8315.08	8315.08	0.0
10.0	5620.89	5620.89	0.0

Rsq

Subjct	Value	Reference	Difference
Float64	Float64	Float64	Float64
1.0	0.786077	0.786077	0.0
2.0	0.992764	0.992764	0.0
3.0	0.813589	0.813589	0.0
4.0	0.918859	0.918859	0.0
5.0	0.85336	0.85336	0.0
6.0	0.950119	0.950119	0.0
7.0	0.970312	0.970312	0.0
8.0	0.947969	0.947969	0.0
9.0	0.947538	0.947538	0.0
10.0	0.880923	0.880923	0.0

ARsq

Subjct	Value	Reference	Difference
Float64	Float64	Float64	Float64
1.0	0.714769	0.714769	0.0
2.0	0.990351	0.990351	0.0
3.0	0.776307	0.776307	0.0

4.0	0.837717	0.837717	0.0
5.0	0.82892	0.82892	0.0
6.0	0.925179	0.925179	0.0
7.0	0.960416	0.960416	0.0
8.0	0.921954	0.921954	0.0
9.0	0.921307	0.921307	0.0
10.0	0.863912	0.863912	0.0

Kel

Subjct	Value	Reference	Difference
Float64	Float64	Float64	Float64
1.0	0.00338474	0.00338474	0.0
2.0	0.0141063	0.0141063	0.0
3.0	0.00329143	0.00329143	0.0
4.0	0.00769534	0.00769534	0.0
5.0	0.00681333	0.00681333	0.0
6.0	0.00769228	0.00769228	0.0
7.0	0.012459	0.012459	0.0
8.0	0.00893008	0.00893008	0.0
9.0	0.00564586	0.00564586	0.0
10.0	0.0171897	0.0171897	0.0

HL

Subjct	Value	Reference	Difference
Float64	Float64	Float64	Float64
1.0	204.786	204.786	0.0
2.0	49.1374	49.1374	0.0
3.0	210.591	210.591	0.0
4.0	90.0736	90.0736	0.0
5.0	101.734	101.734	0.0
6.0	90.1095	90.1094	0.0001
7.0	55.6345	55.6345	0.0
8.0	77.6194	77.6194	0.0
9.0	122.771	122.771	0.0
10.0	40.3233	40.3233	0.0

Clast_pred

Subjct	Value	Reference	Difference
Float64	Float64	Float64	Float64
1.0	117.306	117.306	0.0
2.0	82.5367	82.5367	0.0
3.0	66.9311	66.9311	0.0
4.0	100.768	100.768	0.0
5.0	105.298	105.298	0.0
6.0	71.9399	71.9399	0.0
7.0	61.1727	61.1727	0.0
8.0	75.6043	75.6043	0.0
9.0	93.7618	93.7618	0.0
10.0	38.8109	38.8109	0.0

AUCinf

Subjct	Value	Reference	Difference
Float64	Float64	Float64	Float64
1.0	42925.0	42925.0	0.0
2.0	16154.9	16154.9	0.0
3.0	26026.2	26026.2	0.0
4.0	22004.1	22004.1	0.0
5.0	25820.3	25820.3	0.0
6.0	16001.8	16001.8	0.0
7.0	11689.0	11689.0	0.0
8.0	15446.2	15446.2	0.0
9.0	24865.2	24865.2	0.0
10.0	8075.32	8075.32	0.0

AUCpct

Subjct	Value	Reference	Difference
Float64	Float64	Float64	Float64
1.0	77.6694	77.6694	0.0
2.0	37.405	37.405	0.0
3.0	79.2649	79.2649	0.0
4.0	57.6541	57.6541	0.0
5.0	62.97	62.97	0.0
6.0	56.4636	56.4636	0.0
7.0	39.8614	39.8614	0.0
8.0	53.9649	53.9649	0.0
9.0	66.5594	66.5594	0.0
10.0	30.3942	30.3942	0.0

MRTlast

Subjct	Value	Reference	Difference
Float64	Float64	Float64	Float64
1.0	34.801	34.801	0.0
2.0	29.5388	29.5388	0.0
3.0	34.4724	34.4724	0.0
4.0	33.6941	33.6941	0.0
5.0	32.9644	32.9644	0.0
6.0	32.5808	32.5808	0.0
7.0	31.2676	31.2676	0.0
8.0	33.8261	33.8261	0.0
9.0	33.3868	33.3868	0.0
10.0	27.5567	27.5567	0.0

MRTinf

Subjct	Value	Reference	Difference
Float64	Float64	Float64	Float64
1.0	293.162	293.162	0.0
2.0	71.9379	71.9379	0.0

```
 3.0   305.041    305.041          0.0
 4.0     130.7      130.7          0.0
 5.0   149.967    149.967          0.0
 6.0   128.241    128.241          0.0
 7.0   79.4983    79.4983          0.0
 8.0   114.857    114.857          0.0
 9.0   176.978    176.978          0.0
10.0   58.7464    58.7464          0.0
```

Clinf

```
 Subjct       Value    Reference   Difference
Float64      Float64      Float64      Float64

 1.0   0.00232964   0.00232964          0.0
 2.0   0.00619006   0.00619006          0.0
 3.0   0.00384228   0.00384228          0.0
 4.0   0.00454461   0.00454461          0.0
 5.0   0.00387293   0.00387293          0.0
 6.0   0.00624931   0.00624931          0.0
 7.0   0.00855509   0.00855509          0.0
 8.0   0.00647408   0.00647408          0.0
 9.0   0.00402168   0.00402168          0.0
10.0    0.0123834    0.0123834          0.0
```

Vzinf

```
 Subjct       Value    Reference   Difference
Float64      Float64      Float64      Float64

 1.0   0.688278    0.688278          0.0
 2.0   0.438815    0.438815          0.0
 3.0    1.16736     1.16736          0.0
 4.0   0.590566    0.590566          0.0
 5.0   0.568434    0.568434          0.0
 6.0   0.812414    0.812414          0.0
 7.0   0.686662    0.686662          0.0
 8.0   0.724974    0.724974          0.0
 9.0   0.712323    0.712323          0.0
10.0   0.720395    0.720395          0.0
```

5 Glossary

- Installation qualification (IQ) - Establishing confidence that process equipment and ancillary systems are compliant with appropriate codes and approved design intentions, and that manufacturer's recommendations are suitably considered.

- Operational qualification (OQ) Establishing confidence that process equipment and sub-systems are capable of consistently operating within established limits and tolerances.

- Product performance qualification (PQ) - Establishing confidence through appropriate testing that the finished product produced by a specified process meets all release requirements for functionality and safety.

- Repository - GitHub repository: https://github.com/PharmCat/MetidaNCA.jl

- Master branch - main branch on GitHub ([link](#)).

- Current machine - pc that used for validation report generating.

6   Reference

- [General Principles of Software Validation; Final Guidance for Industry and FDA Staff](#)
- [Guidance for Industry Process Validation: General Principles and Practices](#)
- [Glossary of Computer System Software Development Terminology](#)

7   Appendix 1

| Subject | Formulation | Time | Concentration |
Int64	String	Float64	Float64
1	T	0.0	0.0
1	T	0.5	178.949
1	T	1.0	190.869
1	T	1.5	164.927
1	T	2.0	139.962
1	T	2.5	129.59
1	T	3.0	131.369
1	T	4.0	150.854
1	T	5.0	121.239
1	T	6.0	139.229
1	T	8.0	128.52
1	T	10.0	143.243
1	T	12.0	144.964
1	T	24.0	133.16
1	T	48.0	137.271
1	T	72.0	112.846
2	R	0.0	0.0
2	R	0.5	62.222
2	R	1.0	261.177
2	R	1.5	234.063
2	R	2.0	234.091
2	R	2.5	222.881
2	R	3.0	213.896
2	R	4.0	196.026
2	R	5.0	199.634
2	R	6.0	196.037
2	R	8.0	213.352
2	R	10.0	200.088
2	R	12.0	196.035
2	R	24.0	160.338
2	R	48.0	110.28
2	R	72.0	85.241
3	R	0.0	0.0
3	R	0.5	49.849
3	R	1.0	77.367

	3		R		1.5		105.345
	3		R		2.0		100.943
	3		R		2.5		72.746
	3		R		3.0		69.985
	3		R		4.0		93.565
	3		R		5.0		91.981
	3		R		6.0		82.71
	3		R		8.0		84.205
	3		R		10.0		85.342
	3		R		12.0		76.027
	3		R		24.0		81.259
	3		R		48.0		70.107
	3		R		72.0		67.901
	4		R		0.0		0.0
	4		R		0.5		52.421
	4		R		1.0		208.542
	4		R		1.5		188.923
	4		R		2.0		165.177
	4		R		2.5		146.996
	4		R		3.0		152.701
	4		R		4.0		154.345
	4		R		5.0		128.398
	4		R		6.0		149.807
	4		R		8.0		151.066
	4		R		10.0		136.819
	4		R		12.0		132.257
	4		R		24.0		141.247
	4		R		48.0		129.138
	4		R		72.0		97.625
	5		T		0.0		0.0
	5		T		0.5		0.0
	5		T		1.0		9.545
	5		T		1.5		153.964
	5		T		2.0		152.34
	5		T		2.5		151.452
	5		T		3.0		161.312
	5		T		4.0		169.334
	5		T		5.0		162.907
	5		T		6.0		166.651
	5		T		8.0		168.668
	5		T		10.0		155.103
	5		T		12.0		154.066
	5		T		24.0		162.974
	5		T		48.0		109.814
	5		T		72.0		110.778
	6		T		0.0		0.0
	6		T		0.5		57.882
	6		T		1.0		100.498
	6		T		1.5		138.651
	6		T		2.0		147.287
	6		T		2.5		154.648
	6		T		3.0		122.316
	6		T		4.0		132.857
	6		T		5.0		126.067
	6		T		6.0		140.466
	6		T		8.0		115.542
	6		T		10.0		102.16
	6		T		12.0		113.751
	6		T		24.0		101.049

	6	T	48.0	92.55
	6	T	72.0	69.501
	7	R	0.0	0.0
	7	R	0.5	19.95
	7	R	1.0	128.405
	7	R	1.5	136.807
	7	R	2.0	113.109
	7	R	2.5	153.254
	7	R	3.0	123.606
	7	R	4.0	142.655
	7	R	5.0	112.347
	7	R	6.0	139.919
	7	R	8.0	105.513
	7	R	10.0	134.408
	7	R	12.0	123.37
	7	R	24.0	110.511
	7	R	48.0	90.291
	7	R	72.0	58.051
	8	R	0.0	0.0
	8	R	0.5	136.91
	8	R	1.0	126.646
	8	R	1.5	118.5
	8	R	2.0	134.926
	8	R	2.5	113.213
	8	R	3.0	130.896
	8	R	4.0	138.327
	8	R	5.0	22.724
	8	R	6.0	53.774
	8	R	8.0	55.107
	8	R	10.0	102.871
	8	R	12.0	134.133
	8	R	24.0	108.021
	8	R	48.0	98.466
	8	R	72.0	74.437
	9	T	0.0	0.0
	9	T	0.5	113.362
	9	T	1.0	128.273
	9	T	1.5	125.395
	9	T	2.0	146.933
	9	T	2.5	140.559
	9	T	3.0	167.347
	9	T	4.0	157.504
	9	T	5.0	141.35
	9	T	6.0	140.282
	9	T	8.0	105.438
	9	T	10.0	164.843
	9	T	12.0	135.58
	9	T	24.0	117.125
	9	T	48.0	109.745
	9	T	72.0	93.44
	10	R	0.0	0.0
	10	R	0.5	13.634
	10	R	1.0	62.561
	10	R	1.5	112.655
	10	R	2.0	125.482
	10	R	2.5	116.255
	10	R	3.0	112.674
	10	R	4.0	116.986
	10	R	5.0	119.81

```
|    10 |        R |     6.0 |       107.557 |
|    10 |        R |     8.0 |       120.479 |
|    10 |        R |    10.0 |       124.171 |
|    10 |        R |    12.0 |       106.476 |
|    10 |        R |    24.0 |       116.508 |
|    10 |        R |    48.0 |        45.204 |
|    10 |        R |    72.0 |        42.191 |
'---------'----------'--------'---------------'
```

8   Appendix 2

8.1   Reference values 1: Linear-trapezoidal rule; Extravascular

```
WinNonlin 8.0.0.3176
Subject=1,Formulation=T
```

```
                                      Date:      9/09/2019
                                      Time:      18:03:23
```

```
                WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
                             8.0.0.3176
                     Core Version 22August2017
```

```
Settings
--------
Model:  Plasma Data, Extravascular Administration
Number of nonmissing observations:   16
Dose time:        0.00
Dose amount:       100.00
Calculation method:  Linear Trapezoidal with Linear Interpolation
Weighting for lambda_z calculations:  Uniform weighting
Lambda_z method:  Find best fit for lambda_z,  Log regression
```

```
Summary Table
-------------
```

Time	Conc.	Pred.	Residual	AUC	AUMC	Weight
0.0000	0.0000			0.0000	0.0000	
0.5000	178.9			44.74	22.37	
1.000	190.9			137.2	92.45	
1.500	164.9			226.1	202.0	
2.000	140.0			302.4	333.8	
2.500	129.6			369.8	484.8	
3.000	131.4			435.0	664.3	
4.000	150.9			576.1	1163.	
5.000	121.2			712.1	1768.	
6.000	139.2			842.4	2489.	
8.000	128.5			1110.	4352.	

```
   10.00 *       143.2       144.7      -1.453       1382.       6813.       1.000
   12.00 *       145.0       143.7       1.244       1670.       9985.       1.000
   24.00 *       133.2       138.0      -4.840       3339.   3.960e+04       1.000
   48.00 *       137.3       127.2      10.04        6584.   1.570e+05       1.000
   72.00 *       112.8       117.3      -4.460       9585.   3.336e+05       1.000
```

*) Starred values were included in the estimation of Lambda_z.

Final Parameters

```
N_Samples                                     16
Dose                                     100.0000
Rsq                                        0.7861
Rsq_adjusted                               0.7148
Corr_XY                                   -0.8866
No_points_lambda_z                            5
Lambda_z                                   0.0034
Lambda_z_intercept                         5.0085
Lambda_z_lower                            10.0000
Lambda_z_upper                            72.0000
HL_Lambda_z                              204.7857
Span                                       0.3028
Tlag                                       0.0000
Tmax                                       1.0000
Cmax                                     190.8690
Cmax_D                                     1.9087
Tlast                                     72.0000
Clast                                    112.8460
Clast_pred                               117.3058
AUClast                                 9585.4218
AUClast_D                                 95.8542
AUCall                                  9585.4218
AUCINF_obs                             42925.0191
AUCINF_D_obs                             429.2502
AUC_%Extrap_obs                           77.6694
Vz_F_obs                                   0.6883
Cl_F_obs                                   0.0023
AUCINF_pred                            44242.6313
AUCINF_D_pred                            442.4263
AUC_%Extrap_pred                          78.3344
Vz_F_pred                                  0.6678
Cl_F_pred                                  0.0023
AUMClast                              333582.4808
AUMCINF_obs                         12583994.9366
AUMC_%Extrap_obs                          97.3492
AUMCINF_pred                        13068142.7409
AUMC_%Extrap_pred                         97.4474
```

```
MRTlast                                        34.8010
MRTINF_obs                                    293.1622
MRTINF_pred                                   295.3744



WinNonlin 8.0.0.3176
Subject=2,Formulation=R


                                     Date:    9/09/2019
                                     Time:    18:03:23


          WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
                        8.0.0.3176
                  Core Version 22August2017

Settings
--------

Model:  Plasma Data, Extravascular Administration
Number of nonmissing observations:   16
Dose time:        0.00
Dose amount:      100.00
Calculation method:  Linear Trapezoidal with Linear Interpolation
Weighting for lambda_z calculations:  Uniform weighting
Lambda_z method:  Find best fit for lambda_z,  Log regression


Summary Table
-------------
      Time       Conc.      Pred.     Residual       AUC        AUMC       Weight
----------------------------------------------------------------------------------
     0.0000     0.0000                             0.0000     0.0000
     0.5000     62.22                              15.56      7.778
     1.000      261.2                              96.41      80.85
     1.500      234.1                              220.2      233.9
     2.000      234.1                              337.3      438.7
     2.500      222.9                              451.5      695.1
     3.000      213.9                              560.7      994.8
     4.000      196.0                              765.7      1708.
     5.000      199.6                              963.5      2599.
     6.000      196.0                              1161.      3686.
     8.000      213.4                              1571.      6569.
     10.00 *    200.1       197.9      2.174       1984.      1.028e+04    1.000
     12.00 *    196.0       192.4      3.626       2380.      1.463e+04    1.000
     24.00 *    160.3       162.4      -2.108      4519.      5.183e+04    1.000
     48.00 *    110.3       115.8      -5.512      7766.      1.615e+05    1.000
     72.00 *    85.24       82.54      2.704    1.011e+04    2.987e+05     1.000


                              15
```

*) Starred values were included in the estimation of Lambda_z.

Final Parameters

```
N_Samples                              16
Dose                           100.0000
Rsq                              0.9928
Rsq_adjusted                     0.9904
Corr_XY                         -0.9964
No_points_lambda_z                    5
Lambda_z                         0.0141
Lambda_z_intercept               5.4289
Lambda_z_lower                  10.0000
Lambda_z_upper                  72.0000
HL_Lambda_z                     49.1374
Span                             1.2618
Tlag                             0.0000
Tmax                             1.0000
Cmax                           261.1770
Cmax_D                           2.6118
Tlast                           72.0000
Clast                           85.2410
Clast_pred                      82.5367
AUClast                      10112.1755
AUClast_D                      101.1218
AUCall                       10112.1755
AUCINF_obs                   16154.9301
AUCINF_D_obs                   161.5493
AUC_%Extrap_obs                 37.4050
Vz_F_obs                         0.4388
Cl_F_obs                         0.0062
AUCINF_pred                  15963.2209
AUCINF_D_pred                  159.6322
AUC_%Extrap_pred                36.6533
Vz_F_pred                        0.4441
Cl_F_pred                        0.0063
AUMClast                    298701.3885
AUMCINF_obs                1162152.0263
AUMC_%Extrap_obs                74.2976
AUMCINF_pred               1134758.6551
AUMC_%Extrap_pred               73.6771
MRTlast                         29.5388
MRTINF_obs                      71.9379
MRTINF_pred                     71.0858
```

```
                                        Date:      9/09/2019
                                        Time:       18:03:23


                    WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
                                   8.0.0.3176
                          Core Version 22August2017
```

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 16
Dose time: 0.00
Dose amount: 100.00
Calculation method: Linear Trapezoidal with Linear Interpolation
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time	Conc.	Pred.	Residual	AUC	AUMC	Weight
0.0000	0.0000			0.0000	0.0000	
0.5000	49.85			12.46	6.231	
1.000	77.37			44.27	31.80	
1.500	105.3			89.94	90.65	
2.000	100.9			141.5	180.6	
2.500	72.75			184.9	276.6	
3.000	69.99			220.6	374.5	
4.000	93.57			302.4	666.6	
5.000	91.98			395.2	1084.	
6.000 *	82.71	83.17	-0.4609	482.5	1562.	1.000
8.000 *	84.21	82.63	1.580	649.4	2732.	1.000
10.00 *	85.34	82.08	3.259	819.0	4259.	1.000
12.00 *	76.03	81.54	-5.518	980.3	6024.	1.000
24.00 *	81.26	78.39	2.872	1924.	2.320e+04	1.000
48.00 *	70.11	72.43	-2.326	3740.	8.698e+04	1.000
72.00 *	67.90	66.93	0.9699	5397.	1.860e+05	1.000

*) Starred values were included in the estimation of Lambda_z.

Final Parameters

```

```
N_Samples                              16
Dose                              100.0000
Rsq                                 0.8136
Rsq_adjusted                        0.7763
Corr_XY                            -0.9020
No_points_lambda_z                       7
Lambda_z                            0.0033
Lambda_z_intercept                  4.4406
Lambda_z_lower                      6.0000
Lambda_z_upper                     72.0000
HL_Lambda_z                       210.5915
Span                                0.3134
Tlag                                0.0000
Tmax                                1.5000
Cmax                              105.3450
Cmax_D                              1.0535
Tlast                              72.0000
Clast                              67.9010
Clast_pred                         66.9311
AUClast                          5396.5498
AUClast_D                          53.9655
AUCall                           5396.5498
AUCINF_obs                      26026.1826
AUCINF_D_obs                      260.2618
AUC_%Extrap_obs                    79.2649
Vz_F_obs                            1.1674
Cl_F_obs                            0.0038
AUCINF_pred                     25731.4952
AUCINF_D_pred                     257.3150
AUC_%Extrap_pred                   79.0275
Vz_F_pred                           1.1807
Cl_F_pred                           0.0039
AUMClast                       186032.0553
AUMCINF_obs                   7939045.7669
AUMC_%Extrap_obs                   97.6567
AUMCINF_pred                  7828296.5609
AUMC_%Extrap_pred                  97.6236
MRTlast                            34.4724
MRTINF_obs                        305.0407
MRTINF_pred                       304.2301



WinNonlin 8.0.0.3176
Subject=4,Formulation=R


                              Date:     9/09/2019
                              Time:      18:03:23
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                   WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
                              8.0.0.3176
                         Core Version 22August2017


  Settings
  --------

  Model:  Plasma Data, Extravascular Administration
  Number of nonmissing observations:   16
  Dose time:       0.00
  Dose amount:       100.00
  Calculation method:  Linear Trapezoidal with Linear Interpolation
  Weighting for lambda_z calculations:  Uniform weighting
  Lambda_z method:  Find best fit for lambda_z,  Log regression



  Summary Table
  -------------
        Time        Conc.       Pred.     Residual       AUC        AUMC        Weight
  -------------------------------------------------------------------------------------
         0.0000     0.0000                             0.0000      0.0000
         0.5000     52.42                              13.11       6.553
         1.000      208.5                              78.35       65.24
         1.500      188.9                              177.7       188.2
         2.000      165.2                              266.2       341.7
         2.500      147.0                              344.3       516.1
         3.000      152.7                              419.2       722.5
         4.000      154.3                              572.7       1260.
         5.000      128.4                              714.1       1890.
         6.000      149.8                              853.2       2660.
         8.000      151.1                              1154.       4768.
        10.00       136.8                              1442.       7344.
        12.00       132.3                              1711.       1.030e+04
        24.00 *     141.2       145.8      -4.547      3352.       4.016e+04      1.000
        48.00 *     129.1       121.2       7.930      6597.       1.552e+05      1.000
        72.00 *     97.63       100.8      -3.143      9318.       3.140e+05      1.000


  *) Starred values were included in the estimation of Lambda_z.


  Final Parameters
  ----------------

  N_Samples                                          16
  Dose                                         100.0000
  Rsq                                            0.9189
  Rsq_adjusted                                   0.8377
  Corr_XY                                       -0.9586
  No_points_lambda_z                                  3
```

```
Lambda_z                                        0.0077
Lambda_z_intercept                              5.1669
Lambda_z_lower                                 24.0000
Lambda_z_upper                                 72.0000
HL_Lambda_z                                    90.0736
Span                                            0.5329
Tlag                                            0.0000
Tmax                                            1.0000
Cmax                                          208.5420
Cmax_D                                          2.0854
Tlast                                          72.0000
Clast                                          97.6250
Clast_pred                                    100.7679
AUClast                                      9317.8358
AUClast_D                                      93.1784
AUCall                                       9317.8358
AUCINF_obs                                  22004.0779
AUCINF_D_obs                                  220.0408
AUC_%Extrap_obs                                57.6541
Vz_F_obs                                        0.5906
Cl_F_obs                                        0.0045
AUCINF_pred                                 22412.4980
AUCINF_D_pred                                 224.1250
AUC_%Extrap_pred                               58.4257
Vz_F_pred                                       0.5798
Cl_F_pred                                       0.0045
AUMClast                                   313955.9048
AUMCINF_obs                               2875926.0451
AUMC_%Extrap_obs                               89.0833
AUMCINF_pred                              2958405.9609
AUMC_%Extrap_pred                              89.3877
MRTlast                                        33.6941
MRTINF_obs                                    130.6997
MRTINF_pred                                   131.9980
```

WinNonlin 8.0.0.3176
Subject=5,Formulation=T

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
8.0.0.3176
Core Version 22August2017

Settings

```
--------
Model:  Plasma Data, Extravascular Administration
Number of nonmissing observations:   16
Dose time:        0.00
Dose amount:      100.00
Calculation method:  Linear Trapezoidal with Linear Interpolation
Weighting for lambda_z calculations:  Uniform weighting
Lambda_z method:  Find best fit for lambda_z,  Log regression
```

Summary Table

Time	Conc.	Pred.	Residual	AUC	AUMC	Weight
0.0000	0.0000			0.0000	0.0000	
0.5000	0.0000			0.0000	0.0000	
1.000	9.545			2.386	2.386	
1.500	154.0			43.26	62.51	
2.000	152.3			119.8	196.4	
2.500	151.5			195.8	367.2	
3.000	161.3			274.0	582.9	
4.000	169.3			439.3	1164.	
5.000 *	162.9	166.2	-3.309	605.4	1909.	1.000
6.000 *	166.7	165.1	1.563	770.2	2817.	1.000
8.000 *	168.7	162.9	5.815	1106.	5166.	1.000
10.00 *	155.1	160.6	-5.546	1429.	8066.	1.000
12.00 *	154.1	158.5	-4.409	1738.	1.147e+04	1.000
24.00 *	163.0	146.0	16.94	3641.	4.603e+04	1.000
48.00 *	109.8	124.0	-14.19	6914.	1.562e+05	1.000
72.00 *	110.8	105.3	5.480	9561.	3.152e+05	1.000

*) Starred values were included in the estimation of Lambda_z.

Final Parameters

N_Samples	16
Dose	100.0000
Rsq	0.8534
Rsq_adjusted	0.8289
Corr_XY	-0.9238
No_points_lambda_z	8
Lambda_z	0.0068
Lambda_z_intercept	5.1474
Lambda_z_lower	5.0000
Lambda_z_upper	72.0000
HL_Lambda_z	101.7340
Span	0.6586

```
Tlag                                                    0.5000
Tmax                                                    4.0000
Cmax                                                  169.3340
Cmax_D                                                  1.6933
Tlast                                                  72.0000
Clast                                                 110.7780
Clast_pred                                            105.2983
AUClast                                              9561.2600
AUClast_D                                              95.6126
AUCall                                               9561.2600
AUCINF_obs                                          25820.2749
AUCINF_D_obs                                           258.2027
AUC_%Extrap_obs                                        62.9700
Vz_F_obs                                                0.5684
Cl_F_obs                                                0.0039
AUCINF_pred                                         25016.0160
AUCINF_D_pred                                          250.1602
AUC_%Extrap_pred                                       61.7794
Vz_F_pred                                               0.5867
Cl_F_pred                                               0.0040
AUMClast                                           315181.5625
AUMCINF_obs                                       3872185.0137
AUMC_%Extrap_obs                                       91.8604
AUMCINF_pred                                      3696236.3722
AUMC_%Extrap_pred                                      91.4729
MRTlast                                                32.9644
MRTINF_obs                                            149.9668
MRTINF_pred                                           147.7548
```

WinNonlin 8.0.0.3176
Subject=6,Formulation=T

Date: 9/09/2019
Time: 18:03:23

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
8.0.0.3176
Core Version 22August2017

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 16
Dose time: 0.00
Dose amount: 100.00
Calculation method: Linear Trapezoidal with Linear Interpolation

Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time	Conc.	Pred.	Residual	AUC	AUMC	Weight
0.0000	0.0000			0.0000	0.0000	
0.5000	57.88			14.47	7.235	
1.000	100.5			54.07	39.60	
1.500	138.7			113.9	116.7	
2.000	147.3			185.3	242.4	
2.500	154.6			260.8	412.6	
3.000	122.3			330.1	601.0	
4.000	132.9			457.6	1050.	
5.000	126.1			587.1	1631.	
6.000	140.5			720.4	2368.	
8.000	115.5			976.4	4135.	
10.00	102.2			1194.	6081.	
12.00 *	113.8	114.1	-0.3825	1410.	8467.	1.000
24.00 *	101.0	104.1	-3.021	2699.	3.121e+04	1.000
48.00 *	92.55	86.53	6.024	5022.	1.136e+05	1.000
72.00 *	69.50	71.94	-2.439	6967.	2.270e+05	1.000

*) Starred values were included in the estimation of Lambda_z.

Final Parameters

N_Samples	16
Dose	100.0000
Rsq	0.9501
Rsq_adjusted	0.9252
Corr_XY	-0.9747
No_points_lambda_z	4
Lambda_z	0.0077
Lambda_z_intercept	4.8297
Lambda_z_lower	12.0000
Lambda_z_upper	72.0000
HL_Lambda_z	90.1095
Span	0.6659
Tlag	0.0000
Tmax	2.5000
Cmax	154.6480
Cmax_D	1.5465
Tlast	72.0000
Clast	69.5010

```
Clast_pred                                          71.9399
AUClast                                           6966.5980
AUClast_D                                           69.6660
AUCall                                            6966.5980
AUCINF_obs                                       16001.7597
AUCINF_D_obs                                        160.0176
AUC_%Extrap_obs                                      56.4636
Vz_F_obs                                              0.8124
Cl_F_obs                                              0.0062
AUCINF_pred                                      16318.8233
AUCINF_D_pred                                       163.1882
AUC_%Extrap_pred                                     57.3094
Vz_F_pred                                             0.7966
Cl_F_pred                                             0.0061
AUMClast                                         226977.0608
AUMCINF_obs                                      2052083.8596
AUMC_%Extrap_obs                                     88.9392
AUMCINF_pred                                     2116130.8466
AUMC_%Extrap_pred                                    89.2740
MRTlast                                              32.5808
MRTINF_obs                                          128.2411
MRTINF_pred                                         129.6742
```

WinNonlin 8.0.0.3176
Subject=7,Formulation=R

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
8.0.0.3176
Core Version 22August2017

Settings

Model: Plasma Data, Extravascular Administration
Number of nonmissing observations: 16
Dose time: 0.00
Dose amount: 100.00
Calculation method: Linear Trapezoidal with Linear Interpolation
Weighting for lambda_z calculations: Uniform weighting
Lambda_z method: Find best fit for lambda_z, Log regression

Summary Table

Time	Conc.	Pred.	Residual	AUC	AUMC	Weight
0.0000	0.0000			0.0000	0.0000	
0.5000	19.95			4.988	2.494	
1.000	128.4			42.08	37.09	
1.500	136.8			108.4	120.5	
2.000	113.1			170.9	228.3	
2.500	153.3			237.4	380.7	
3.000	123.6			306.7	569.2	
4.000	142.7			439.8	1040.	
5.000	112.3			567.3	1606.	
6.000	139.9			693.4	2307.	
8.000	105.5			938.9	3990.	
10.00 *	134.4	132.4	1.964	1179.	6178.	1.000
12.00 *	123.4	129.2	-5.814	1437.	9003.	1.000
24.00 *	110.5	111.2	-0.7336	2840.	3.380e+04	1.000
48.00 *	90.29	82.49	7.798	5249.	1.176e+05	1.000
72.00 *	58.05	61.17	-3.122	7030.	2.198e+05	1.000

*) Starred values were included in the estimation of Lambda_z.

Final Parameters

```
N_Samples                                    16
Dose                                   100.0000
Rsq                                      0.9703
Rsq_adjusted                             0.9604
Corr_XY                                 -0.9850
No_points_lambda_z                            5
Lambda_z                                 0.0125
Lambda_z_intercept                       5.0107
Lambda_z_lower                          10.0000
Lambda_z_upper                          72.0000
HL_Lambda_z                             55.6345
Span                                     1.1144
Tlag                                     0.0000
Tmax                                     2.5000
Cmax                                   153.2540
Cmax_D                                   1.5325
Tlast                                   72.0000
Clast                                   58.0510
Clast_pred                              61.1727
AUClast                               7029.5735
AUClast_D                               70.2957
AUCall                                7029.5735
AUCINF_obs                           11688.9527
AUCINF_D_obs                           116.8895
```

```
AUC_%Extrap_obs                              39.8614
Vz_F_obs                                      0.6867
Cl_F_obs                                      0.0086
AUCINF_pred                               11939.5116
AUCINF_D_pred                               119.3951
AUC_%Extrap_pred                             41.1234
Vz_F_pred                                     0.6723
Cl_F_pred                                     0.0084
AUMClast                                 219797.7073
AUMCINF_obs                              929251.3075
AUMC_%Extrap_obs                             76.3468
AUMCINF_pred                             967402.2944
AUMC_%Extrap_pred                            77.2796
MRTlast                                      31.2676
MRTINF_obs                                   79.4983
MRTINF_pred                                  81.0253



WinNonlin 8.0.0.3176
Subject=8,Formulation=R


                                   Date:     9/09/2019
                                   Time:      18:03:23



          WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
                        8.0.0.3176
                 Core Version 22August2017


   Settings
   --------
   Model:  Plasma Data, Extravascular Administration
   Number of nonmissing observations:   16
   Dose time:       0.00
   Dose amount:        100.00
   Calculation method:  Linear Trapezoidal with Linear Interpolation
   Weighting for lambda_z calculations:  Uniform weighting
   Lambda_z method:  Find best fit for lambda_z,  Log regression


   Summary Table
   -------------
```

Time	Conc.	Pred.	Residual	AUC	AUMC	Weight
0.0000	0.0000			0.0000	0.0000	
0.5000	136.9			34.23	17.11	
1.000	126.6			100.1	65.89	
1.500	118.5			161.4	142.0	

2.000	134.9			224.8	253.9	
2.500	113.2			286.8	392.1	
3.000	130.9			347.8	561.0	
4.000	138.3			482.4	1034.	
5.000	22.72			563.0	1368.	
6.000	53.77			601.2	1586.	
8.000	55.11			710.1	2349.	
10.00	102.9			868.1	3819.	
12.00 *	134.1	129.2	4.939	1105.	6457.	1.000
24.00 *	108.0	116.1	-8.045	2558.	3.167e+04	1.000
48.00 *	98.47	93.68	4.791	5036.	1.195e+05	1.000
72.00 *	74.44	75.60	-1.167	7111.	2.405e+05	1.000

*) Starred values were included in the estimation of Lambda_z.

Final Parameters

```
N_Samples                                        16
Dose                                        100.0000
Rsq                                           0.9480
Rsq_adjusted                                  0.9220
Corr_XY                                      -0.9736
No_points_lambda_z                               4
Lambda_z                                      0.0089
Lambda_z_intercept                            4.9685
Lambda_z_lower                               12.0000
Lambda_z_upper                               72.0000
HL_Lambda_z                                  77.6194
Span                                          0.7730
Tlag                                          0.0000
Tmax                                          4.0000
Cmax                                        138.3270
Cmax_D                                        1.3833
Tlast                                        72.0000
Clast                                        74.4370
Clast_pred                                   75.6043
AUClast                                    7110.6745
AUClast_D                                    71.1067
AUCall                                     7110.6745
AUCINF_obs                                15446.2103
AUCINF_D_obs                                154.4621
AUC_%Extrap_obs                              53.9649
Vz_F_obs                                      0.7250
Cl_F_obs                                      0.0065
AUCINF_pred                               15576.9232
AUCINF_D_pred                               155.7692
AUC_%Extrap_pred                             54.3512
```

```
Vz_F_pred                                                  0.7189
Cl_F_pred                                                  0.0064
AUMClast                                              240526.0538
AUMCINF_obs                                          1774106.9508
AUMC_%Extrap_obs                                          86.4424
AUMCINF_pred                                         1798155.6519
AUMC_%Extrap_pred                                         86.6237
MRTlast                                                   33.8261
MRTINF_obs                                               114.8571
MRTINF_pred                                              115.4372



WinNonlin 8.0.0.3176
Subject=9,Formulation=T


                                            Date:    9/09/2019
                                            Time:    18:03:23



                   WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
                                  8.0.0.3176
                          Core Version 22August2017


Settings
--------
Model:  Plasma Data, Extravascular Administration
Number of nonmissing observations:    16
Dose time:        0.00
Dose amount:       100.00
Calculation method:  Linear Trapezoidal with Linear Interpolation
Weighting for lambda_z calculations:  Uniform weighting
Lambda_z method:  Find best fit for lambda_z,  Log regression



Summary Table
-------------
       Time       Conc.     Pred.     Residual      AUC       AUMC      Weight
--------------------------------------------------------------------------------
      0.0000     0.0000                            0.0000    0.0000
      0.5000     113.4                             28.34     14.17
      1.000      128.3                             88.75     60.41
      1.500      125.4                             152.2     139.5
      2.000      146.9                             220.2     260.0
      2.500      140.6                             292.1     421.3
      3.000      167.3                             369.1     634.7
      4.000      157.5                             531.5     1201.
      5.000      141.4                             681.0     1869.
      6.000      140.3                             821.8     2643.
```

```
  8.000        105.4                                   1067.      4328.
  10.00        164.8                                   1338.      6820.
  12.00 *      135.6      131.6       4.014             1638.   1.010e+04      1.000
  24.00 *      117.1      122.9      -5.823             3154.   3.672e+04      1.000
  48.00 *      109.7      107.4       2.377             5877.   1.337e+05      1.000
  72.00 *      93.44      93.76      -0.3218            8315.   2.776e+05      1.000
```

*) Starred values were included in the estimation of Lambda_z.


```
Final Parameters
---------------
N_Samples                                   16
Dose                                   100.0000
Rsq                                      0.9475
Rsq_adjusted                             0.9213
Corr_XY                                 -0.9734
No_points_lambda_z                           4
Lambda_z                                 0.0056
Lambda_z_intercept                       4.9473
Lambda_z_lower                          12.0000
Lambda_z_upper                          72.0000
HL_Lambda_z                            122.7708
Span                                     0.4887
Tlag                                     0.0000
Tmax                                     3.0000
Cmax                                   167.3470
Cmax_D                                   1.6735
Tlast                                   72.0000
Clast                                   93.4400
Clast_pred                              93.7618
AUClast                               8315.0803
AUClast_D                               83.1508
AUCall                                8315.0803
AUCINF_obs                           24865.2460
AUCINF_D_obs                           248.6525
AUC_%Extrap_obs                         66.5594
Vz_F_obs                                 0.7123
Cl_F_obs                                 0.0040
AUCINF_pred                          24922.2366
AUCINF_D_pred                          249.2224
AUC_%Extrap_pred                        66.6359
Vz_F_pred                                0.7107
Cl_F_pred                                0.0040
AUMClast                            277613.9778
AUMCINF_obs                        4400604.1747
AUMC_%Extrap_obs                        93.6915
AUMCINF_pred                       4414801.7328
```

```
AUMC_%Extrap_pred                                        93.7117
MRTlast                                                  33.3868
MRTINF_obs                                              176.9781
MRTINF_pred                                             177.1431



WinNonlin 8.0.0.3176
Subject=10,Formulation=R


                                             Date:    9/09/2019
                                             Time:    18:03:24



              WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM
                             8.0.0.3176
                      Core Version 22August2017

Settings
--------

Model:  Plasma Data, Extravascular Administration
Number of nonmissing observations:   16
Dose time:      0.00
Dose amount:    100.00
Calculation method:  Linear Trapezoidal with Linear Interpolation
Weighting for lambda_z calculations:  Uniform weighting
Lambda_z method:  Find best fit for lambda_z,  Log regression



Summary Table
-------------
      Time        Conc.      Pred.     Residual       AUC        AUMC       Weight
--------------------------------------------------------------------------------
     0.0000      0.0000                             0.0000      0.0000
     0.5000      13.63                              3.409       1.704
     1.000       62.56                              22.46       19.05
     1.500       112.7                              66.26       76.93
     2.000       125.5                              125.8       181.9
     2.500       116.3                              186.2       317.3
     3.000       112.7                              243.5       474.5
     4.000  *    117.0       124.9     -7.925       358.3       877.5       1.000
     5.000  *    119.8       122.8     -2.972       476.7       1411.       1.000
     6.000  *    107.6       120.7     -13.13       590.4       2033.       1.000
     8.000  *    120.5       116.6      3.868       818.4       3642.       1.000
     10.00  *    124.2       112.7      11.50       1063.       5848.       1.000
     12.00  *    106.5       108.9     -2.386       1294.       8367.       1.000
     24.00  *    116.5       88.57      27.94       2632.      3.281e+04    1.000
     48.00  *    45.20       58.63     -13.43       4572.      9.240e+04    1.000
     72.00  *    42.19       38.81      3.380       5621.      1.549e+05    1.000
```

*) Starred values were included in the estimation of Lambda_z.

Final Parameters

```
N_Samples                              16
Dose                             100.0000
Rsq                                0.8809
Rsq_adjusted                       0.8639
Corr_XY                           -0.9386
No_points_lambda_z                      9
Lambda_z                           0.0172
Lambda_z_intercept                 4.8964
Lambda_z_lower                     4.0000
Lambda_z_upper                    72.0000
HL_Lambda_z                       40.3233
Span                               1.6864
Tlag                               0.0000
Tmax                               2.0000
Cmax                             125.4820
Cmax_D                             1.2548
Tlast                             72.0000
Clast                             42.1910
Clast_pred                        38.8109
AUClast                         5620.8945
AUClast_D                         56.2089
AUCall                          5620.8945
AUCINF_obs                      8075.3242
AUCINF_D_obs                      80.7532
AUC_%Extrap_obs                   30.3942
Vz_F_obs                           0.7204
Cl_F_obs                           0.0124
AUCINF_pred                     7878.6869
AUCINF_D_pred                     78.7869
AUC_%Extrap_pred                  28.6570
Vz_F_pred                          0.7384
Cl_F_pred                          0.0127
AUMClast                      154893.0605
AUMCINF_obs                   474396.5944
AUMC_%Extrap_obs                  67.3495
AUMCINF_pred                  448799.4879
AUMC_%Extrap_pred                 65.4872
MRTlast                           27.5567
MRTINF_obs                        58.7464
MRTINF_pred                       56.9637
```