Pumas NCA Tutorial - Multiple dose IV administration

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```
using Pumas, PumasTutorials, CSV
```

1 Introduction

In this tutorial, we will cover the fundamentals of performing an NCA analysis with Pumas of an example dataset in which multiple intravenous (IV) bolus doses were administered.

2 The dataset

- Four IV bolus doses of 2000 mg were administered every 24 hours to 24 different subjects.
- Samples were collected every 30 minutes.

Let's start reading the dataset. By using the `missingstring` option we are specifying how the missing values are labeled in our dataset.

```
data = PumasTutorials.tutorial_data("data/nca","multiple_dose_IVbolus_7BLQ_test")
data = CSV.read(data,missingstring="NA")
first(data,10)
```

	ID	time	DV	BLQ	DOSE	Formulation	OCC
	Int64	Float64	Float64	Int64	Int64	String	Int64
1	1	0.0	0.0	0	2000	iv	1
2	1	0.5	35.2364	0	0	iv	1
3	1	1.0	33.008	0	0	iv	1
4	1	1.5	27.6	0	0	iv	1
5	1	2.0	25.4196	0	0	iv	1
6	1	2.5	22.0718	0	0	iv	1
7	1	3.0	20.4286	0	0	iv	1
8	1	3.5	18.2746	0	0	iv	1
9	1	4.0	16.4594	0	0	iv	1
10	1	4.5	13.4711	0	0	iv	1

This will be an abbreviated tutorial as the main difference is in the specification of the `read_nca` function. For a complete listing of all NCA options, please check the first tutorial on single oral dose administration

3 Defining the units

```
timeu = u"hr"
concu = u"mg/L"
amtu  = u"mg"
```

```
mg
```

4 Defining the population object

The standard requirements of `read_nca` as specified in other tutorials exist. In this mulitple dose example, since subjects visit in more than once occasion, we need to use an `occasion=` variable to speify the multiple dose nature.

```
pop = read_nca(data, id=:ID, time=:time, conc=:DV, amt=:DOSE, ii=24timeu,
    route=:Formulation, occasion=:OCC,timeu=timeu, concu=concu, amtu=amtu,llq=0.4concu)
```

```
NCAPopulation (24 subjects):
  ID: [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 2
0, 21, 22, 23, 24]
    concentration: mg L^-1
    time:          hr
    auc:           mg hr L^-1
    aumc:          mg hr^2 L^-1
    λz:            hr^-1
    dose:          mg
```

Key features of the syntax above:

- `route=` is mapped to the `Formulation` column that should specify `ev`
- LLOQ was set to 0.4 by `llq=0.4concu`
- `occasion=:OCC` provides a way to specify multiple dosing

To check how occasion works, lets calculate the AUC

```
NCA.auc(pop,auctype=:last,method=:linear)
```

	id	occasion	auc
	Int64	Int64	Unitful
1	1	1	163.68 mg hr L^-1
2	1	2	160.974 mg hr L^-1
3	1	3	164.558 mg hr L^-1
4	1	4	164.068 mg hr L^-1
5	2	1	166.032 mg hr L^-1
6	2	2	164.343 mg hr L^-1
7	2	3	161.089 mg hr L^-1
8	2	4	161.579 mg hr L^-1
9	3	1	160.923 mg hr L^-1
10	3	2	162.922 mg hr L^-1
11	3	3	164.856 mg hr L^-1
12	3	4	161.433 mg hr L^-1
13	4	1	164.836 mg hr L^-1
14	4	2	162.72 mg hr L^-1
15	4	3	162.746 mg hr L^-1
16	4	4	162.166 mg hr L^-1
17	5	1	163.018 mg hr L^-1
18	5	2	163.12 mg hr L^-1
19	5	3	165.067 mg hr L^-1
20	5	4	161.667 mg hr L^-1
21	6	1	161.696 mg hr L^-1
22	6	2	159.946 mg hr L^-1
23	6	3	163.047 mg hr L^-1
24	6	4	162.84 mg hr L^-1
25	7	1	164.272 mg hr L^-1
26	7	2	163.815 mg hr L^-1
27	7	3	165.911 mg hr L^-1
28	7	4	165.304 mg hr L^-1
29	8	1	165.518 mg hr L^-1
30	8	2	162.504 mg hr L^-1
31	8	3	166.277 mg hr L^-1
32	8	4	162.89 mg hr L^-1
33	9	1	161.58 mg hr L^-1
34	9	2	162.975 mg hr L^-1
35	9	3	160.198 mg hr L^-1
36	9	4	161.877 mg hr L^-1
37	10	1	157.204 mg hr L^-1
38	10	2	163.842 mg hr L^-1
39	10	3	160.282 mg hr L^-1
40	10	4	162.828 mg hr L^-1
41	11	1	158.61 mg hr L^-1
42	11	2	165.16 mg hr L^-1
43	11	3	161.69 mg hr L^-1
44	11	4	165.415 mg hr L^-1
45	12	1	162.856 mg hr L^-1
46	12	2	165.709 mg hr L^-1
47	12	3	164.991 mg hr L^-1
48	12	4	162.054 mg hr L^-1
49	13	1	162.286 mg hr L^-1
50	13	2	163.225 mg hr L^-1
51	13	3	161.898 mg hr L^-1
52	13	4	163.755 mg hr L^-1

All other NCA function work on this grouped variable. Let's directly print the NCA report.

```
report = NCAReport(pop)
report = NCA.to_dataframe(report)
```

	id	occasion	doseamt	lambda_z	half_life	tmax	cmax	c0
	Int64	Int64	Unitful	Unitful	Unitful	Unitful	Unitful	Unitful
1	1	1	2000 mg	0.236704 hr^-1	2.92833 hr	0.5 hr	35.2364 mg L^-1	0.0 mg L^-1
2	1	2	2000 mg	-1.17489 hr^-1	-0.589967 hr	0.5 hr	33.306 mg L^-1	0.0 mg L^-1
3	1	3	2000 mg	0.06432 hr^-1	10.7766 hr	0.5 hr	34.5143 mg L^-1	0.0 mg L^-1
4	1	4	2000 mg	0.409752 hr^-1	1.69163 hr	0.5 hr	34.8824 mg L^-1	0.0 mg L^-1
5	2	1	2000 mg	-2.99033 hr^-1	-0.231796 hr	0.5 hr	34.627 mg L^-1	0.0 mg L^-1
6	2	2	2000 mg	0.240855 hr^-1	2.87786 hr	0.5 hr	38.2251 mg L^-1	0.0 mg L^-1
7	2	3	2000 mg	-1.33799 hr^-1	-0.518051 hr	0.5 hr	34.988 mg L^-1	0.0 mg L^-1
8	2	4	2000 mg	-1.50247 hr^-1	-0.461338 hr	1.0 hr	33.6303 mg L^-1	0.0 mg L^-1
9	3	1	2000 mg	0.302713 hr^-1	2.28978 hr	0.5 hr	36.3163 mg L^-1	0.0 mg L^-1
10	3	2	2000 mg	0.255137 hr^-1	2.71676 hr	0.5 hr	36.3201 mg L^-1	0.0 mg L^-1
11	3	3	2000 mg	0.2357 hr^-1	2.9408 hr	0.5 hr	39.4983 mg L^-1	0.0 mg L^-1
12	3	4	2000 mg	0.272468 hr^-1	2.54396 hr	0.5 hr	36.1206 mg L^-1	0.0 mg L^-1
13	4	1	2000 mg	0.403583 hr^-1	1.71748 hr	0.5 hr	35.1015 mg L^-1	0.0 mg L^-1
14	4	2	2000 mg	0.141683 hr^-1	4.89225 hr	0.5 hr	32.9845 mg L^-1	0.0 mg L^-1
15	4	3	2000 mg	0.338564 hr^-1	2.04732 hr	0.5 hr	35.6927 mg L^-1	0.0 mg L^-1
16	4	4	2000 mg	3.28624 hr^-1	0.210924 hr	0.5 hr	34.9361 mg L^-1	0.0 mg L^-1
17	5	1	2000 mg	0.206833 hr^-1	3.35124 hr	0.5 hr	33.4501 mg L^-1	0.0 mg L^-1
18	5	2	2000 mg	0.347514 hr^-1	1.99459 hr	0.5 hr	36.1562 mg L^-1	0.0 mg L^-1
19	5	3	2000 mg	0.290097 hr^-1	2.38936 hr	0.5 hr	38.2094 mg L^-1	0.0 mg L^-1
20	5	4	2000 mg	0.328371 hr^-1	2.11087 hr	1.0 hr	33.0145 mg L^-1	0.0 mg L^-1
21	6	1	2000 mg	0.222834 hr^-1	3.11059 hr	0.5 hr	34.9312 mg L^-1	0.0 mg L^-1
22	6	2	2000 mg	0.150069 hr^-1	4.61885 hr	0.5 hr	34.6846 mg L^-1	0.0 mg L^-1
23	6	3	2000 mg	-0.589922 hr^-1	-1.17498 hr	0.5 hr	37.5062 mg L^-1	0.0 mg L^-1
24	6	4	2000 mg	2.1836 hr^-1	0.317433 hr	0.5 hr	36.161 mg L^-1	0.0 mg L^-1
25	7	1	2000 mg	-0.956457 hr^-1	-0.724703 hr	0.5 hr	34.5898 mg L^-1	0.0 mg L^-1
26	7	2	2000 mg	-0.419205 hr^-1	-1.65348 hr	0.5 hr	35.7611 mg L^-1	0.0 mg L^-1
27	7	3	2000 mg	-0.616704 hr^-1	-1.12395 hr	0.5 hr	36.129 mg L^-1	0.0 mg L^-1
28	7	4	2000 mg	-1.25204 hr^-1	-0.553613 hr	0.5 hr	36.8566 mg L^-1	0.0 mg L^-1
29	8	1	2000 mg	-0.354887 hr^-1	-1.95315 hr	0.5 hr	33.8534 mg L^-1	0.0 mg L^-1
30	8	2	2000 mg	-3.0391 hr^-1	-0.228076 hr	0.5 hr	35.8865 mg L^-1	0.0 mg L^-1
31	8	3	2000 mg	0.425534 hr^-1	1.62889 hr	0.5 hr	35.5282 mg L^-1	0.0 mg L^-1
32	8	4	2000 mg	-1.4873 hr^-1	-0.466045 hr	0.5 hr	36.5292 mg L^-1	0.0 mg L^-1
33	9	1	2000 mg	0.207726 hr^-1	3.33684 hr	0.5 hr	36.2625 mg L^-1	0.0 mg L^-1
34	9	2	2000 mg	0.19937 hr^-1	3.47669 hr	0.5 hr	37.0738 mg L^-1	0.0 mg L^-1
35	9	3	2000 mg	-1.12323 hr^-1	-0.617102 hr	0.5 hr	33.2595 mg L^-1	0.0 mg L^-1
36	9	4	2000 mg	-0.625497 hr^-1	-1.10815 hr	0.5 hr	34.9065 mg L^-1	0.0 mg L^-1
37	10	1	2000 mg	0.461541 hr^-1	1.50181 hr	0.5 hr	34.3046 mg L^-1	0.0 mg L^-1
38	10	2	2000 mg	0.30748 hr^-1	2.25428 hr	0.5 hr	36.62 mg L^-1	0.0 mg L^-1
39	10	3	2000 mg	0.173232 hr^-1	4.00127 hr	1.0 hr	31.2395 mg L^-1	0.0 mg L^-1
40	10	4	2000 mg	-0.956167 hr^-1	-0.724923 hr	0.5 hr	34.3694 mg L^-1	0.0 mg L^-1
41	11	1	2000 mg	0.193065 hr^-1	3.59023 hr	0.5 hr	33.9653 mg L^-1	0.0 mg L^-1
42	11	2	2000 mg	0.152989 hr^-1	4.5307 hr	0.5 hr	37.381 mg L^-1	0.0 mg L^-1
43	11	3	2000 mg	0.420169 hr^-1	1.64969 hr	0.5 hr	37.2582 mg L^-1	0.0 mg L^-1
44	11	4	2000 mg	-0.34515 hr^-1	-2.00825 hr	0.5 hr	35.2926 mg L^-1	0.0 mg L^-1
45	12	1	2000 mg	0.206919 hr^-1	3.34984 hr	0.5 hr	36.2307 mg L^-1	0.0 mg L^-1
46	12	2	2000 mg	0.117211 hr^-1	5.91367 hr	0.5 hr	35.6457 mg L^-1	0.0 mg L^-1
47	12	3	2000 mg	0.91501 hr^-1	0.75753 hr	0.5 hr	36.2055 mg L^-1	0.0 mg L^-1
48	12	4	2000 mg	1.42541 hr^-1	0.486279 hr	0.5 hr	33.3409 mg L^-1	0.0 mg L^-1
49	13	1	2000 mg	0.0776993 hr^-1	8.92089 hr	0.5 hr	35.9369 mg L^-1	0.0 mg L^-1
50	13	2	2000 mg	0.287828 hr^-1	2.4082 hr	0.5 hr	37.0267 mg L^-1	0.0 mg L^-1

Below is a listing of all the NCA parameters in the report

```
names(report)
```

```
49-element Array{Symbol,1}:
 :id
 :occasion
 :doseamt
 :lambda_z
 :half_life
 :tmax
 :cmax
 :c0
 :clast
 :clast_pred
 ⋮
 :rsq
 :rsq_adjusted
 :corr_xy
 :no_points_lambda_z
 :lambda_z_intercept
 :lambda_z_lower
 :lambda_z_upper
 :span
 :route
```

Finally, we can save this data frame as a csv file if desired.

```
CSV.write("./tutorials/nca/report_MD_IVbolus_7BLQ.csv", report)
```