Pumas NCA Tutorial - Single dose ORAL administration 2 analytes

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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 a single oral dose was administered and the concentration of two analytes (parent and metabolite) was measured.

2 The dataset

- Single oral dose of 2000 mg administered 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","SD_oral_2analytes")
data = CSV.read(data,missingstring="NA")
first(data,10)
```

	ID	time	DV	Analyte	BLQ	DOSE	Formulation
	Int64	Float64	Float64	String	Int64	Int64	String
1	1	0.0	0.0	Metabolite	0	2000	ev
2	1	0.5	0.677881	Metabolite	0	0	ev
3	1	1.0	2.13233	Metabolite	0	0	ev
4	1	1.5	3.56769	Metabolite	0	0	ev
5	1	2.0	4.77554	Metabolite	0	0	ev
6	1	2.5	5.94978	Metabolite	0	0	ev
7	1	3.0	7.13593	Metabolite	0	0	ev
8	1	3.5	6.94463	Metabolite	0	0	ev
9	1	4.0	7.32453	Metabolite	0	0	ev
10	1	4.5	7.6625	Metabolite	0	0	ev

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 example since parent and metabolite concentrations were measured, we need to specify the grouping variable so that the PK parameters are calculated for both analytes (`group=`).

```
pop = read_nca(data, id=:ID, time=:time, conc=:DV, amt=:DOSE, ii=24timeu, group=:Analyte,
    route=:Formulation, timeu=timeu, concu=concu, amtu=amtu,lloq=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]
  Group: Pair{String,String}["Analyte"=>"Metabolite", "Analyte"=>"Parent"]
    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`
- `group=:Analyte` provides a way to peform NCA on two different analytes

To check if the grouping works, lets calculate the AUC

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

	id	Analyte	auc
	Int64	String	Unitful
1	1	Metabolite	81.6192 mg hr L^-1
2	2	Metabolite	81.9052 mg hr L^-1
3	3	Metabolite	83.3829 mg hr L^-1
4	4	Metabolite	82.0563 mg hr L^-1
5	5	Metabolite	81.0593 mg hr L^-1
6	6	Metabolite	83.0437 mg hr L^-1
7	7	Metabolite	84.1976 mg hr L^-1
8	8	Metabolite	82.6067 mg hr L^-1
9	9	Metabolite	82.4071 mg hr L^-1
10	10	Metabolite	82.3146 mg hr L^-1
11	11	Metabolite	81.1287 mg hr L^-1
12	12	Metabolite	81.8532 mg hr L^-1
13	13	Metabolite	82.7287 mg hr L^-1
14	14	Metabolite	83.6679 mg hr L^-1
15	15	Metabolite	82.162 mg hr L^-1
16	16	Metabolite	81.5886 mg hr L^-1
17	17	Metabolite	81.3252 mg hr L^-1
18	18	Metabolite	82.517 mg hr L^-1
19	19	Metabolite	83.5749 mg hr L^-1
20	20	Metabolite	83.0247 mg hr L^-1
21	21	Metabolite	82.418 mg hr L^-1
22	22	Metabolite	81.514 mg hr L^-1
23	23	Metabolite	83.5594 mg hr L^-1
24	24	Metabolite	79.7166 mg hr L^-1
25	1	Parent	101.678 mg hr L^-1
26	2	Parent	101.841 mg hr L^-1
27	3	Parent	103.924 mg hr L^-1
28	4	Parent	101.85 mg hr L^-1
29	5	Parent	100.914 mg hr L^-1
30	6	Parent	103.36 mg hr L^-1
31	7	Parent	104.645 mg hr L^-1
32	8	Parent	102.618 mg hr L^-1
33	9	Parent	102.766 mg hr L^-1
34	10	Parent	102.224 mg hr L^-1
35	11	Parent	100.61 mg hr L^-1
36	12	Parent	101.917 mg hr L^-1
37	13	Parent	102.827 mg hr L^-1
38	14	Parent	103.845 mg hr L^-1
39	15	Parent	102.082 mg hr L^-1
40	16	Parent	101.73 mg hr L^-1
41	17	Parent	101.307 mg hr L^-1
42	18	Parent	102.803 mg hr L^-1
43	19	Parent	103.963 mg hr L^-1
44	20	Parent	103.336 mg hr L^-1
45	21	Parent	102.498 mg hr L^-1
46	22	Parent	101.161 mg hr L^-1
47	23	Parent	104.269 mg hr L^-1
48	24	Parent	99.3001 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	Analyte	doseamt	lambda_z	half_life	tmax	tlag	cmax
	Int64	String	Unitful	Unitful	Unitful	Unitful	Unitful	Unitful
1	1	Metabolite	2000 mg	0.375321 hr^-1	1.84681 hr	5.0 hr	0.0 hr	8.37565 mg L^-1
2	2	Metabolite	2000 mg	0.289601 hr^-1	2.39345 hr	5.5 hr	0.0 hr	8.17628 mg L^-1
3	3	Metabolite	2000 mg	0.193229 hr^-1	3.58718 hr	5.0 hr	0.0 hr	8.46302 mg L^-1
4	4	Metabolite	2000 mg	0.397353 hr^-1	1.74441 hr	5.5 hr	0.0 hr	8.00777 mg L^-1
5	5	Metabolite	2000 mg	-0.253963 hr^-1	-2.72932 hr	6.0 hr	0.0 hr	8.44586 mg L^-1
6	6	Metabolite	2000 mg	0.245656 hr^-1	2.82162 hr	4.0 hr	0.0 hr	8.35883 mg L^-1
7	7	Metabolite	2000 mg	0.207358 hr^-1	3.34276 hr	4.0 hr	0.0 hr	8.66713 mg L^-1
8	8	Metabolite	2000 mg	0.369532 hr^-1	1.87574 hr	6.0 hr	0.0 hr	8.03436 mg L^-1
9	9	Metabolite	2000 mg	0.313687 hr^-1	2.20968 hr	5.5 hr	0.0 hr	7.94585 mg L^-1
10	10	Metabolite	2000 mg	0.278758 hr^-1	2.48655 hr	5.5 hr	0.0 hr	8.10679 mg L^-1
11	11	Metabolite	2000 mg	-0.796943 hr^-1	-0.869758 hr	4.0 hr	0.0 hr	7.8671 mg L^-1
12	12	Metabolite	2000 mg	0.282085 hr^-1	2.45722 hr	4.0 hr	0.0 hr	8.27367 mg L^-1
13	13	Metabolite	2000 mg	0.22053 hr^-1	3.1431 hr	4.5 hr	0.0 hr	8.52225 mg L^-1
14	14	Metabolite	2000 mg	0.179082 hr^-1	3.87057 hr	4.0 hr	0.0 hr	7.93562 mg L^-1
15	15	Metabolite	2000 mg	0.147145 hr^-1	4.71066 hr	5.0 hr	0.0 hr	8.25264 mg L^-1
16	16	Metabolite	2000 mg	0.888041 hr^-1	0.780535 hr	5.5 hr	0.0 hr	8.00715 mg L^-1
17	17	Metabolite	2000 mg	0.377237 hr^-1	1.83743 hr	6.0 hr	0.0 hr	8.08663 mg L^-1
18	18	Metabolite	2000 mg	0.16821 hr^-1	4.12072 hr	4.5 hr	0.0 hr	7.88359 mg L^-1
19	19	Metabolite	2000 mg	0.333248 hr^-1	2.07998 hr	5.0 hr	0.0 hr	8.73993 mg L^-1
20	20	Metabolite	2000 mg	0.36101 hr^-1	1.92002 hr	4.0 hr	0.0 hr	7.79501 mg L^-1
21	21	Metabolite	2000 mg	0.221688 hr^-1	3.12667 hr	4.5 hr	0.0 hr	7.9931 mg L^-1
22	22	Metabolite	2000 mg	1.11474 hr^-1	0.621802 hr	6.0 hr	0.0 hr	7.57312 mg L^-1
23	23	Metabolite	2000 mg	0.800884 hr^-1	0.865478 hr	5.0 hr	0.0 hr	8.16937 mg L^-1
24	24	Metabolite	2000 mg	-0.890666 hr^-1	-0.778235 hr	4.5 hr	0.0 hr	7.7859 mg L^-1
25	1	Parent	2000 mg	0.376974 hr^-1	1.83871 hr	3.0 hr	0.0 hr	10.3017 mg L^-1
26	2	Parent	2000 mg	0.287911 hr^-1	2.4075 hr	3.5 hr	0.0 hr	10.0397 mg L^-1
27	3	Parent	2000 mg	0.195978 hr^-1	3.53686 hr	3.0 hr	0.0 hr	10.8176 mg L^-1
28	4	Parent	2000 mg	0.394215 hr^-1	1.7583 hr	3.5 hr	0.0 hr	9.85971 mg L^-1
29	5	Parent	2000 mg	0.133014 hr^-1	5.21108 hr	5.0 hr	0.0 hr	10.0102 mg L^-1
30	6	Parent	2000 mg	0.245908 hr^-1	2.81873 hr	4.0 hr	0.0 hr	10.7972 mg L^-1
31	7	Parent	2000 mg	0.208447 hr^-1	3.32529 hr	4.0 hr	0.0 hr	11.29 mg L^-1
32	8	Parent	2000 mg	0.366268 hr^-1	1.89246 hr	4.0 hr	0.0 hr	10.2454 mg L^-1
33	9	Parent	2000 mg	0.312375 hr^-1	2.21896 hr	3.5 hr	0.0 hr	10.6356 mg L^-1
34	10	Parent	2000 mg	0.277981 hr^-1	2.4935 hr	3.0 hr	0.0 hr	10.4033 mg L^-1
35	11	Parent	2000 mg	-0.756411 hr^-1	-0.916364 hr	4.0 hr	0.0 hr	10.2241 mg L^-1
36	12	Parent	2000 mg	0.280981 hr^-1	2.46688 hr	4.0 hr	0.0 hr	10.8172 mg L^-1
37	13	Parent	2000 mg	0.175111 hr^-1	3.95834 hr	4.0 hr	0.0 hr	11.1044 mg L^-1
38	14	Parent	2000 mg	0.18069 hr^-1	3.83611 hr	3.0 hr	0.0 hr	10.8373 mg L^-1
39	15	Parent	2000 mg	0.150714 hr^-1	4.59908 hr	5.0 hr	0.0 hr	10.137 mg L^-1
40	16	Parent	2000 mg	0.864551 hr^-1	0.801742 hr	4.0 hr	0.0 hr	10.0995 mg L^-1
41	17	Parent	2000 mg	0.375308 hr^-1	1.84688 hr	3.5 hr	0.0 hr	10.321 mg L^-1
42	18	Parent	2000 mg	0.171226 hr^-1	4.04815 hr	3.5 hr	0.0 hr	10.2012 mg L^-1
43	19	Parent	2000 mg	0.329593 hr^-1	2.10304 hr	3.0 hr	0.0 hr	11.2275 mg L^-1
44	20	Parent	2000 mg	0.355591 hr^-1	1.94928 hr	3.0 hr	0.0 hr	10.5528 mg L^-1
45	21	Parent	2000 mg	0.222483 hr^-1	3.1155 hr	4.0 hr	0.0 hr	10.1598 mg L^-1
46	22	Parent	2000 mg	1.08696 hr^-1	0.637695 hr	3.5 hr	0.0 hr	9.99851 mg L^-1
47	23	Parent	2000 mg	0.783621 hr^-1	0.884544 hr	4.0 hr	0.0 hr	10.3031 mg L^-1
48	24	Parent	2000 mg	-0.841545 hr^-1	-0.823661 hr	3.5 hr	0.0 hr	10.0945 mg L^-1

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

```
CSV.write("./tutorials/nca/report_SD_oral_2analytes.csv", report)
```

```
using PumasTutorials
PumasTutorials.tutorial_footer(WEAVE_ARGS[:folder],WEAVE_ARGS[:file])
```

4.1 Appendix

These tutorials are part of the PumasTutorials.jl repository, found at: https://github.com/JuliaDiffEq/Di

To locally run this tutorial, do the following commands:

```
using PumasTutorials
PumasTutorials.weave_file("nca","SD_ORAL_2ANALYTES.jmd")
```

Computer Information:

```
Julia Version 1.1.1
Commit 55e36cc308 (2019-05-16 04:10 UTC)
Platform Info:
  OS: Windows (x86_64-w64-mingw32)
  CPU: Intel(R) Core(TM) i7-8550U CPU @ 1.80GHz
  WORD_SIZE: 64
  LIBM: libopenlibm
  LLVM: libLLVM-6.0.1 (ORCJIT, skylake)
Environment:
  JULIA_EDITOR = "C:\Users\accou\AppData\Local\atom\app-1.38.2\atom.exe"  -a
  JULIA_NUM_THREADS = 4
```

Package Information:

```
Status `C:\Users\accou\.julia\environments\v1.1\Project.toml`
[621f4979-c628-5d54-868e-fcf4e3e8185c] AbstractFFTs 0.4.1
[c52e3926-4ff0-5f6e-af25-54175e0327b1] Atom 0.8.8
[f0abef60-9ec0-11e9-27de-db6506a91768] AutoOffload 0.1.0
[6e4b80f9-dd63-53aa-95a3-0cdb28fa8baf] BenchmarkTools 0.4.2
[4ece37e6-a012-11e8-38cd-91247efc2c34] Bioequivalence 0.1.0
[336ed68f-0bac-5ca0-87d4-7b16caf5d00b] CSV 0.5.9
[c5f51814-7f29-56b8-a69c-e4d8f6be1fde] CUDAdrv 3.0.1
[be33ccc6-a3ff-5ff2-a52e-74243cff1e17] CUDAnative 2.2.1
[49dc2e85-a5d0-5ad3-a950-438e2897f1b9] Calculus 0.5.0
[7057c7e9-c182-5462-911a-8362d720325c] Cassette 0.2.5
[34da2185-b29b-5c13-b0c7-acf172513d20] Compat 2.1.0
[3a865a2d-5b23-5a0f-bc46-62713ec82fae] CuArrays 1.1.0
[667455a9-e2ce-5579-9412-b964f529a492] Cubature 1.4.0
[a93c6f00-e57d-5684-b7b6-d8193f3e46c0] DataFrames 0.18.4
[82cc6244-b520-54b8-b5a6-8a565e85f1d0] DataInterpolations 0.2.0
```

```
[31a5f54b-26ea-5ae9-a837-f05ce5417438] Debugger 0.5.0
[bcd4f6db-9728-5f36-b5f7-82caef46ccdb] DelayDiffEq 5.9.1
[2b5f629d-d688-5b77-993f-72d75c75574e] DiffEqBase 5.16.3
[ebbdde9d-f333-5424-9be2-dbf1e9acfb5e] DiffEqBayes 1.2.0
[31c91b34-3c75-11e9-0341-95557aab0344] DiffEqBenchmarks 0.1.0
[459566f4-90b8-5000-8ac3-15dfb0a30def] DiffEqCallbacks 2.5.2+
[f3b72e0c-5b89-59e1-b016-84e28bfd966d] DiffEqDevTools 2.13.0
[01453d9d-ee7c-5054-8395-0335cb756afa] DiffEqDiffTools 0.14.0
[aae7a2af-3d4f-5e19-a356-7da93b79d9d0] DiffEqFlux 0.6.0
[071ae1c0-96b5-11e9-1965-c90190d839ea] DiffEqGPU 0.1.0
[c894b116-72e5-5b58-be3c-e6d8d4ac2b12] DiffEqJump 6.1.1+
[8f2b45d5-b17b-5532-9e92-98ae0077e2e3] DiffEqMachineLearning 0.1.0
[78ddff82-25fc-5f2b-89aa-309469cbf16f] DiffEqMonteCarlo 0.15.1
[77a26b50-5914-5dd7-bc55-306e6241c503] DiffEqNoiseProcess 3.3.1
[9fdde737-9c7f-55bf-ade8-46b3f136cc48] DiffEqOperators 3.5.0
[055956cb-9e8b-5191-98cc-73ae4a59e68a] DiffEqPhysics 3.2.0
[a077e3f3-b75c-5d7f-a0c6-6bc4c8ec64a9] DiffEqProblemLibrary 4.3.0
[41bf760c-e81c-5289-8e54-58b1f1f8abe2] DiffEqSensitivity 3.3.0
[6d1b261a-3be8-11e9-3f2f-0b112a9a8436] DiffEqTutorials 0.1.0
[0c46a032-eb83-5123-abaf-570d42b7fbaa] DifferentialEquations 6.6.0
[31c24e10-a181-5473-b8eb-7969acd0382f] Distributions 0.20.0
[e30172f5-a6a5-5a46-863b-614d45cd2de4] Documenter 0.23.0
[587475ba-b771-5e3f-ad9e-33799f191a9c] Flux 0.8.3
[f6369f11-7733-5829-9624-2563aa707210] ForwardDiff 0.10.3+
[ba82f77b-6841-5d2e-bd9f-4daf811aec27] GPUifyLoops 0.2.5
[c91e804a-d5a3-530f-b6f0-dfbca275c004] Gadfly 1.1.0
[bc5e4493-9b4d-5f90-b8aa-2b2bcaad7a26] GitHub 5.1.1
[7073ff75-c697-5162-941a-fcdaad2a7d2a] IJulia 1.18.1
[42fd0dbc-a981-5370-80f2-aaf504508153] IterativeSolvers 0.8.1
[033835bb-8acc-5ee8-8aae-3f567f8a3819] JLD2 0.1.2
[e5e0dc1b-0480-54bc-9374-aad01c23163d] Juno 0.7.0
[2d691ee1-e668-5016-a719-b2531b85e0f5] LIBLINEAR 0.5.1
[7f56f5a3-f504-529b-bc02-0b1fe5e64312] LSODA 0.4.0
[6f1fad26-d15e-5dc8-ae53-837a1d7b8c9f] Libtask 0.3.0
[c7f686f2-ff18-58e9-bc7b-31028e88f75d] MCMCChains 0.3.10
[33e6dc65-8f57-5167-99aa-e5a354878fb2] MKL 0.0.0
[cc2ba9b6-d476-5e6d-8eaf-a92d5412d41d] MLDataUtils 0.5.0
[eb30cadb-4394-5ae3-aed4-317e484a6458] MLDatasets 0.3.0
[961ee093-0014-501f-94e3-6117800e7a78] ModelingToolkit 0.5.0
[4886b29c-78c9-11e9-0a6e-41e1f4161f7b] MonteCarloIntegration 0.0.1
[2774e3e8-f4cf-5e23-947b-6d7e65073b56] NLsolve 4.0.0
[872c559c-99b0-510c-b3b7-b6c96a88d5cd] NNlib 0.6.0
[8faf48c0-8b73-11e9-0e63-2155955bfa4d] NeuralNetDiffEq 0.1.0
[09606e27-ecf5-54fc-bb29-004bd9f985bf] ODEInterfaceDiffEq 3.3.1
[1dea7af3-3e70-54e6-95c3-0bf5283fa5ed] OrdinaryDiffEq 5.12.0
[65888b18-ceab-5e60-b2b9-181511a3b968] ParameterizedFunctions 4.2.0
[14b8a8f1-9102-5b29-a752-f990bacb7fe1] PkgTemplates 0.6.1
[91a5bcdd-55d7-5caf-9e0b-520d859cae80] Plots 0.25.3
[92933f4c-e287-5a05-a399-4b506db050ca] ProgressMeter 1.0.0
```

```
[d7b8c89e-ad89-52e0-b9fd-d0ed321fa021] Pumas 0.1.0
[b7b41870-aa11-11e9-048a-09266ec4a62f] PumasTutorials 0.0.1
[438e738f-606a-5dbb-bf0a-cddfbfd45ab0] PyCall 1.91.2
[d330b81b-6aea-500a-939a-2ce795aea3ee] PyPlot 2.8.1
[1fd47b50-473d-5c70-9696-f719f8f3bcdc] QuadGK 2.1.0
[612083be-0b0f-5412-89c1-4e7c75506a58] Queryverse 0.3.1
[6f49c342-dc21-5d91-9882-a32aef131414] RCall 0.13.3
[731186ca-8d62-57ce-b412-fbd966d074cd] RecursiveArrayTools 0.20.0
[37e2e3b7-166d-5795-8a7a-e32c996b4267] ReverseDiff 0.3.1
[295af30f-e4ad-537b-8983-00126c2a3abe] Revise 2.1.6
[2b6d1eac-7baa-5078-8adc-e6a3e659f14f] SingleFloats 0.1.3
[47a9eef4-7e08-11e9-0b38-333d64bd3804] SparseDiffTools 0.5.0
[90137ffa-7385-5640-81b9-e52037218182] StaticArrays 0.11.0
[4c63d2b9-4356-54db-8cca-17b64c39e42c] StatsFuns 0.8.0
[f3b207a7-027a-5e70-b257-86293d7955fd] StatsPlots 0.11.0
[9672c7b4-1e72-59bd-8a11-6ac3964bc41f] SteadyStateDiffEq 1.5.0
[789caeaf-c7a9-5a7d-9973-96adeb23e2a0] StochasticDiffEq 6.6.0
[c3572dad-4567-51f8-b174-8c6c989267f4] Sundials 3.6.1
[fd094767-a336-5f1f-9728-57cf17d0bbfb] Suppressor 0.1.1
[6fc51010-71bc-11e9-0e15-a3fcc6593c49] Surrogates 0.1.0
[9f7883ad-71c0-57eb-9f7f-b5c9e6d3789c] Tracker 0.2.2
[fce5fe82-541a-59a6-adf8-730c64b5f9a0] Turing 0.6.18
[1986cc42-f94f-5a68-af5c-568840ba703d] Unitful 0.16.0
[44d3d7a6-8a23-5bf8-98c5-b353f8df5ec9] Weave 0.9.1
[e88e6eb3-aa80-5325-afca-941959d7151f] Zygote 0.3.2
```