Pumas NCA Tutorial - Crossover IV/oral to estimate bioavailability

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

1 Introduction

In this tutorial, we will cover the fundamentals of performing an NCA analysis with Pumas using an example dataset in which a crossover IV/oral study was conducted to estimate bioavailability.

2 The dataset

- Crossover design
- Single 2000 mg oral dose to 24 subjects
- Washout period
- Single 2000 mg IV dose to the same 24 subjects
- Blood samples for pharmacokinetic analysis were collected every 30 minutes

2.0.1 `CSV.read()`

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_crossover_IV_oral")
data = CSV.read(data,missingstring="NA")
first(data,10)
```

	ID	time	DV	Formulation	BLQ	OCC	DOSE
	Int64	Float64	Float64	String	Int64	Int64	Int64
1	1	0.0	0.0	iv	0	1	2000
2	1	0.5	37.9249	iv	0	1	0
3	1	1.0	34.8935	iv	0	1	0
4	1	1.5	29.115	iv	0	1	0
5	1	2.0	24.684	iv	0	1	0
6	1	2.5	24.4861	iv	0	1	0
7	1	3.0	20.6901	iv	0	1	0
8	1	3.5	19.1516	iv	0	1	0
9	1	4.0	16.9928	iv	0	1	0
10	1	4.5	14.9779	iv	0	1	0

Please, note that the `DOSE` column must only contain a value at the time the dose was administered.

3 Defining the units

Next we can define time, concentration and dose units so the report includes the units for the pharmacokinetic parameters. The general syntax for units are `u` followed by the unit in quotes `""`.

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

```
mg
```

4 Defining the NCA population object

4.0.1 `read_nca`

Using the `read_nca` function, the next step would be to define the population that we are going to use for the NCA. The following are the key arguments to this function that maps the column names from the dataset:

- subject identifier (`id=`),
- time column (`time=`),
- concentration column (`conc=`),
- dose column (`amt=`),
- interdose interval (`ii=`) multiplied by the time units,
- route of administration (`route=`). In this example, since two different formulations were administered, we will specify two different routes of administration.
- occasion column (`occasion=`) that defines the different dosing events. In this example, occasion 1 is IV administration and occasion 2 is oral administration

- column (`occasion=`) needs to be specified (occasion 1 is IV administration and occasion 2 is oral administration).

There are additional arguments that will be discussed later.

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

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
```

Please, note that column mapped to the `route=` argument, in this case the `:Formulation` column can include "iv" or "ev" to represent intravenous or extravacular dosing. This is a required format.

Also note that in the function above by default the lower limit of quantification (LLQ) is 0 and concentrations that are" below LLQ (BLQ) are dropped.

Let's say we want to specify a LLQ value of 0.4 mg/L, then we need to add `llq=0.4concu` to the function above:

```
pop = read_nca(data, id=:ID, time=:time, conc=:DV, amt=:DOSE, ii=24timeu,
    route=:Formulation, occasion=:OCC,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]
    concentration: mg L^-1
    time:          hr
    auc:           mg hr L^-1
    aumc:          mg hr^2 L^-1
    λz:            hr^-1
    dose:          mg
```

5 Single dose PK parameter calculation

We can use different functions to calculate single dose PK parameters. For example, we can calculate the area under the concentration curve from time 0 to the last observation using the linear trapezoidal rule (default method) by writing the following code.

5.0.1 NCA.auc

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

	id	occasion	auc
	Int64	Int64	Unitful
1	1	1	168.732 mg hr L−1
2	1	2	67.7066 mg hr L−1
3	2	1	166.212 mg hr L−1
4	2	2	68.0361 mg hr L−1
5	3	1	161.161 mg hr L−1
6	3	2	69.1506 mg hr L−1
7	4	1	167.056 mg hr L−1
8	4	2	68.0634 mg hr L−1
9	5	1	161.954 mg hr L−1
10	5	2	67.1759 mg hr L−1
11	6	1	167.442 mg hr L−1
12	6	2	69.0235 mg hr L−1
13	7	1	163.307 mg hr L−1
14	7	2	69.9351 mg hr L−1
15	8	1	162.685 mg hr L−1
16	8	2	68.4222 mg hr L−1
17	9	1	162.797 mg hr L−1
18	9	2	68.226 mg hr L−1
19	10	1	162.496 mg hr L−1
20	10	2	68.1991 mg hr L−1
21	11	1	162.913 mg hr L−1
22	11	2	67.0183 mg hr L−1
23	12	1	164.579 mg hr L−1
24	12	2	68.0837 mg hr L−1
25	13	1	160.217 mg hr L−1
26	13	2	68.4954 mg hr L−1
27	14	1	163.966 mg hr L−1
28	14	2	69.6355 mg hr L−1
29	15	1	163.177 mg hr L−1
30	15	2	68.1921 mg hr L−1
31	16	1	163.015 mg hr L−1
32	16	2	67.6805 mg hr L−1
33	17	1	161.263 mg hr L−1
34	17	2	67.4557 mg hr L−1
35	18	1	164.504 mg hr L−1
36	18	2	68.3944 mg hr L−1
37	19	1	161.852 mg hr L−1
38	19	2	69.2667 mg hr L−1
39	20	1	163.759 mg hr L−1
40	20	2	69.1756 mg hr L−1
41	21	1	159.881 mg hr L−1
42	21	2	68.3122 mg hr L−1
43	22	1	164.178 mg hr L−1
44	22	2	67.579 mg hr L−1
45	23	1	163.119 mg hr L−1
46	23	2	69.4551 mg hr L−1
47	24	1	165.01 mg hr L−1
48	24	2	65.9071 mg hr L−1