Pumas.jl Workshop Solutions

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1 Fitting a PK model

In this tutorial we will go through the steps required to fit a model in Pumas.jl.

1.1 The dosage regimen

We start by simulating a population from a two compartment model with oral absorption, and then we show how to fit and do some model validation using the fit output.

```
using Pumas, Plots, Random
Random.seed!(0);
```

The dosage regimen is an dose of 100 into `Depot` at time 0, followed by two additional (`addl=2`) doses every fourth hour

```
repeated_dose_regimen = DosageRegimen(100, time=0, ii=4, addl=2)
```

```
Pumas.DosageRegimen(1×9 DataFrames.DataFrame. Omitted printing of 2 columns
 Row   time      cmt     amt       evid   ii        addl    rate
       Float64   Int64   Float64   Int8   Float64   Int64   Float64


 1     0.0       1       100.0     1      4.0       2       0.0      )
```

As ususal, let's define a function to choose body weight randomly per subject

```
choose_covariates() = (Wt = rand(55:80),)
```

```
choose_covariates (generic function with 1 method)
```

and generate a population of subjects with a random weight generated from the covariate function above

```
pop = Population(map(i -> Subject(id = i,
                                  evs = repeated_dose_regimen,
                                  obs=(dv=Float64[],),
                                  cvs = choose_covariates()),
                                  1:24))
```

```
Population
  Subjects: 24
  Covariates: Wt
  Observables: dv
```

We now have 24 subjects equipped with a weight and a dosage regimen.

1.2 The PK model of drug concentration and elimination

To simulate a data set and attempt to estimate the data generating parameters, we have to set up the actual pharmacokinetics (PK) model and simulate the data. We use the closed form model called `Depots1Central1Periph1` which is a two compartment model with first order absorption. This requires `CL`, `Vc`, `Ka`, `Vp`, and `Q` to be defined in the `@pre`-block, since they define the rates of transfer between (and out of) the compartments

```
mymodel = @model begin
  @param   begin
    cl ∈ RealDomain(lower = 0.0, init = 1.0)
    tv ∈ RealDomain(lower = 0.0, init = 10.0)
    ka ∈ RealDomain(lower = 0.0, init = 1.0)
    q  ∈ RealDomain(lower = 0.0, init = 0.5)
    Ω  ∈ PDiagDomain(init = [0.9,0.07, 0.05])
    σ_prop ∈ RealDomain(lower = 0,init = 0.03)
  end

  @random begin
    η ~ MvNormal(Ω)
  end

  @covariates Wt

  @pre begin
    CL = cl * (Wt/70)^0.75 * exp(η[1])
    Vc = tv * (Wt/70) * exp(η[2])
    Ka = ka * exp(η[3])
    Vp = 30.0
    Q  = q
  end

  @dynamics Depots1Central1Periph1

  @derived begin
      cp := @. 1000*(Central / Vc) # We use := because we don't want simobs to store
with variable
      dv ~ @. Normal(cp, sqrt(cp^2*σ_prop))
    end
end
```

```
PumasModel
  Parameters: cl, tv, ka, q, Ω, σ_prop
  Random effects: η
  Covariates: Wt
  Dynamical variables: Depot, Central, Peripheral
  Derived: dv
  Observed: dv
```

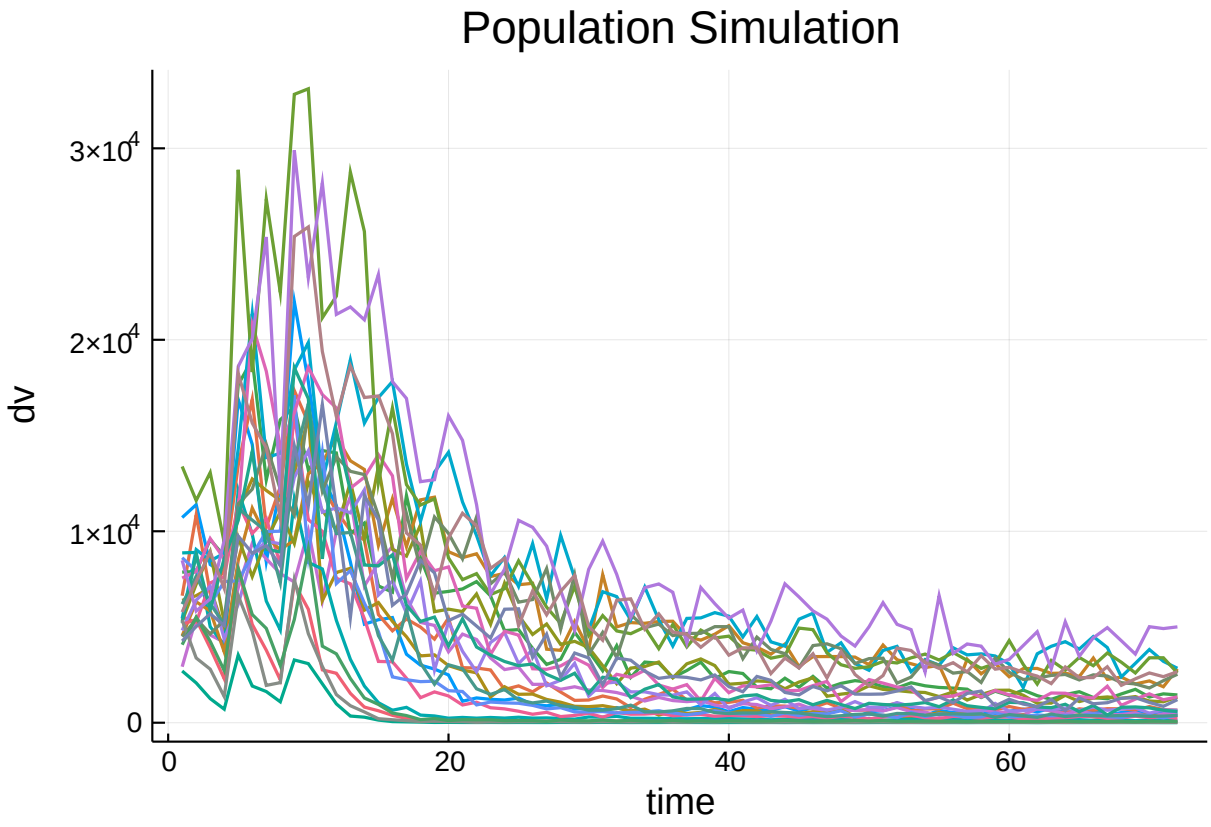
Some parameters are left free by giving them domains in the `@param`-block, and one PK parameter (the volume of distribution of the peripheral compartment) is fixed to 20.0.

1.3 Simulating the indiviual observations

The `simobs` function is used to simulate individual time series. We input the model, the population of Subjects that currently only have dosage regimens and covariates, the parameter vector and the times where we want to simulate. Since we have a proportional error

model we avoid observations at time zero to avoid degenerate distributions of the dependent variable. Let's use the default parameters, as set in the `@param`-block, and simulate the data

```
param = init_param(mymodel)
obs = simobs(mymodel, pop, param, obstimes=1:1:72)
plot(obs)
```



1.4 Fitting the model

To fit the model, we use the `fit` function. It requires a model, a population, a parameter vector and a likelihood approximation method.

```
result = fit(mymodel, Subject.(obs), param, Pumas.FOCEI())
```

```
FittedPumasModel

Successful minimization:                 true

Likelihood approximation:        Pumas.FOCEI
Deviance:                          21021.224
Total number of observation records:    1728
Number of active observation records:   1728
Number of subjects:                       24

---------------------
           Estimate
---------------------
cl          1.0227
tv          9.5343
ka          1.0145
q           0.49597
```

```
Ω_1,_1        1.055
Ω_2,_2        0.070262
Ω_3,_3        0.012696
σ_prop      0.032052
---------------------
```

Of course, we started the fitting at the true parameters, so let us define our own starting parameters, and fit based on those values

```
alternative_param = (
    cl = 0.5,
    tv = 9.0,
    ka = 1.3,
    q  = 0.3,
    Ω  = Diagonal([0.18,0.04, 0.03]),
    σ_prop = 0.04)

fit(mymodel, read_pumas(DataFrame(obs); cvs=[:Wt]), alternative_param, Pumas.FOCEI())

FittedPumasModel

Successful minimization:                true

Likelihood approximation:        Pumas.FOCEI
Deviance:                          21021.224
Total number of observation records:    1728
Number of active observation records:   1728
Number of subjects:                       24

---------------------
           Estimate
---------------------
cl           1.0227
tv           9.5343
ka           1.0145
q            0.49597
Ω_1,_1         1.0551
Ω_2,_2         0.070262
Ω_3,_3         0.012698
σ_prop       0.032052
---------------------
```

and we see that the estimates are essentially the same up to numerical noise.

To augment the basic information listed when we print the results, we can use `infer` to provide RSEs and confidence intervals

```
infer(result)

Calculating: variance-covariance matrix. Done.
FittedPumasModelInference

Successful minimization:                true

Likelihood approximation:        Pumas.FOCEI
Deviance:                          21021.224
Total number of observation records:    1728
Number of active observation records:   1728
Number of subjects:                       24
```

```
------------------------------------------------------------
          Estimate        RSE                  95.0% C.I.
------------------------------------------------------------
cl          1.0227      21.038          [ 0.60098 ;  1.4444  ]
tv          9.5343       5.3913         [ 8.5269  ; 10.542   ]
ka          1.0145       6.1097         [ 0.89303 ;  1.136   ]
q           0.49597      1.2063         [ 0.48424 ;  0.5077  ]
Ω_1,_1        1.055       24.993          [ 0.53821 ;  1.5718  ]
Ω_2,_2        0.070262    23.947          [ 0.037284;  0.10324 ]
Ω_3,_3        0.012696   253.1            [-0.050283;  0.075675]
σ_prop      0.032052     3.2071         [ 0.030037;  0.034067]
------------------------------------------------------------
```

So as we observed earlier, the parameters look like they have sensible values. The confidence intervals are a bit wide, and especially so for the random effect variability parameters. To see how we can use simulation to better understand the statistical properties of our model, we can simulate a much larger population and try again

```
pop_big = Population(map(i -> Subject(id = i,
                                      evs = repeated_dose_regimen,
                                      obs=(dv=Float64[],),
                                      cvs = choose_covariates()),
                                      1:100))
obs_big = simobs(mymodel, pop_big, param, obstimes=1:1:72)
result_big = fit(mymodel, read_pumas(DataFrame(obs_big); cvs=[:Wt]), param,
Pumas.FOCEI())
infer(result_big)
```

```
Calculating: variance-covariance matrix. Done.
FittedPumasModelInference

Successful minimization:                true

Likelihood approximation:         Pumas.FOCEI
Deviance:                           89083.738
Total number of observation records:    7200
Number of active observation records:   7200
Number of subjects:                      100

------------------------------------------------------------------
          Estimate         RSE                  95.0% C.I.
------------------------------------------------------------------
cl          0.94532       9.5818          [0.76779 ;  1.1229  ]
tv          9.8171        2.4967          [9.3367  ; 10.297   ]
ka          1.0214        3.2221          [0.9569  ;  1.0859  ]
q           0.49987       0.55044         [0.49447 ;  0.50526 ]
Ω_1,_1        0.91804      12.395           [0.695   ;  1.1411  ]
Ω_2,_2        0.059452     15.078           [0.041883;  0.077021]
Ω_3,_3        0.04182      27.988           [0.018879;  0.06476 ]
σ_prop      0.029622       1.6237          [0.02868 ;  0.030565]
------------------------------------------------------------------
```

This time we see similar estimates, but much narrower confidence intervals across the board.

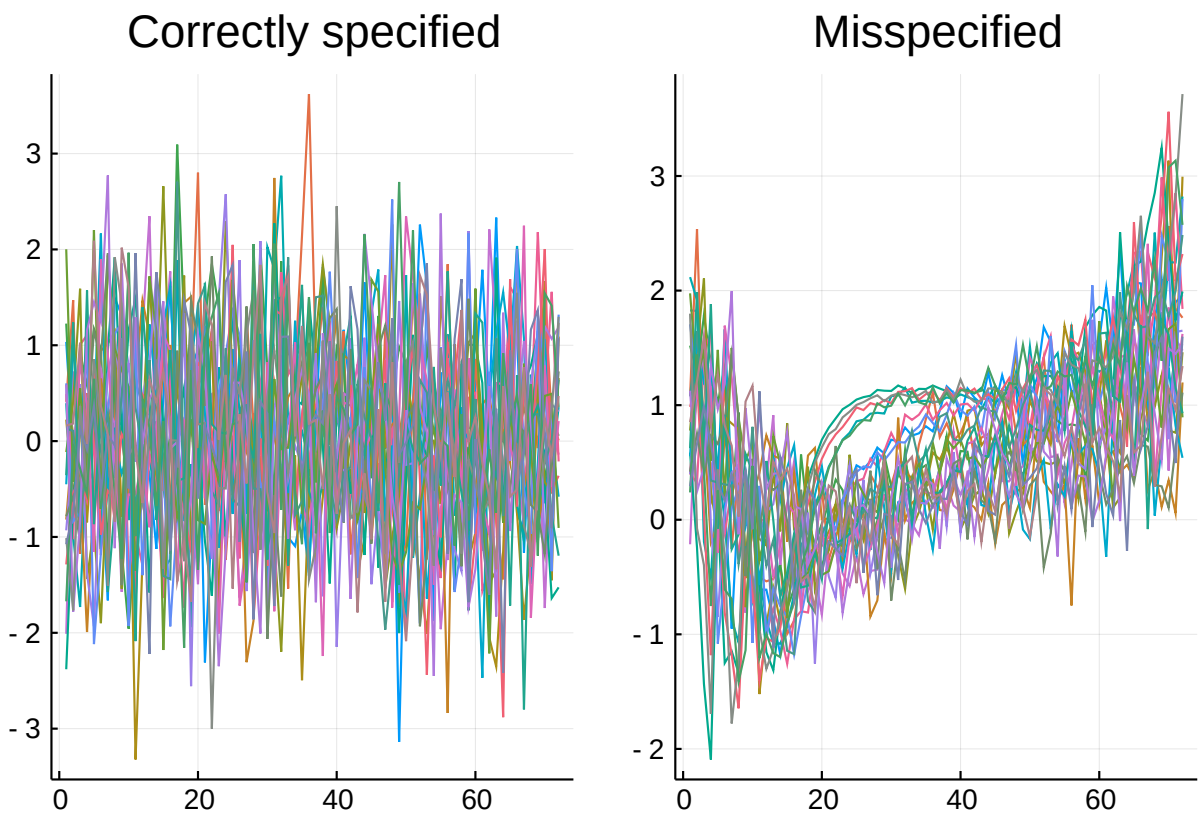
1.5 Estimating a misspecified model

```
mymodel_misspec = @model begin
  @param   begin
```

```
    cl ∈ RealDomain(lower = 0.0, init = 1.0)
    tv ∈ RealDomain(lower = 0.0, init = 20.0)
    ka ∈ RealDomain(lower = 0.0, init = 1.0)
    Ω  ∈ PDiagDomain(init = [0.12, 0.05, 0.08])
    σ_prop ∈ RealDomain(lower = 0, init = 0.03)
  end

  @random begin
    η ~ MvNormal(Ω)
  end

  @pre begin
    CL = cl * (Wt/70)^0.75 * exp(η[1])
    V = tv * (Wt/70) * exp(η[2])
    Ka = ka * exp(η[3])
  end
  @covariates Wt

  @dynamics Depots1Central1

  @derived begin
      cp = @. 1000*(Central / V)
      dv ~ @. Normal(cp, sqrt(cp^2*σ_prop))
    end
end

PumasModel
  Parameters: cl, tv, ka, Ω, σ_prop
  Random effects: η
  Covariates: Wt
  Dynamical variables: Depot, Central
  Derived: cp, dv
  Observed: cp, dv

result_misspec = fit(mymodel_misspec, read_pumas(DataFrame(obs); cvs=[:Wt]),
alternative_param, Pumas.FOCEI())

FittedPumasModel

Successful minimization:                true

Likelihood approximation:        Pumas.FOCEI
Deviance:                          25683.256
Total number of observation records:    1728
Number of active observation records:   1728
Number of subjects:                       24

---------------------
           Estimate
---------------------
cl          1.3772
tv         25.856
ka          5.5109e6
Ω_1,_1        0.49845
Ω_2,_2        0.14961
Ω_3,_3        0.043069
σ_prop      0.31598
---------------------
```

First off, the absorption flow parameters `ka` is quite off the charts, so that would be a warning sign off the bat, but let us try to use a tool in the toolbox to asses the fit: the weighted residuals. We get these by using the `wresiduals` function

```
wres = wresiduals(result)
wres_misspec = wresiduals(result_misspec)
p1 = plot([w.wres.dv for w in wres], title="Correctly specified", legend=false)
p2 = plot([w.wres.dv for w in wres_misspec], title = "Misspecified", legend=false)
plot(p1, p2)
```



The weighted residuals should be standard normally distributed with throughout the time domain. We see that this is the case for the correctly specified model, but certainly not for the misspecified model. That latter has a very clear pattern in time. This comes from the fact that the one compartment model is not able to capture the change in slope as time progresses, so it can never accurately capture the curves generated by a two compartment model.

1.5.1 Conclusion

This tutorial showed how to use fitting in Pumas.jl based on a simulated data set. There are many more models and simulation experiments to explore. Please try out `fit` on your own data and model, and reach out if further questions or problems come up.