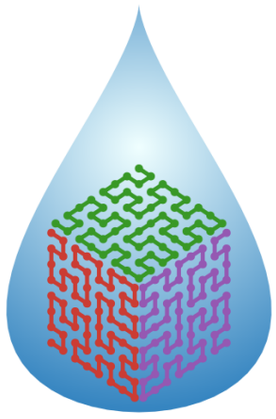


Nonlinear Mixed Effects Modelling with Pumas.jl

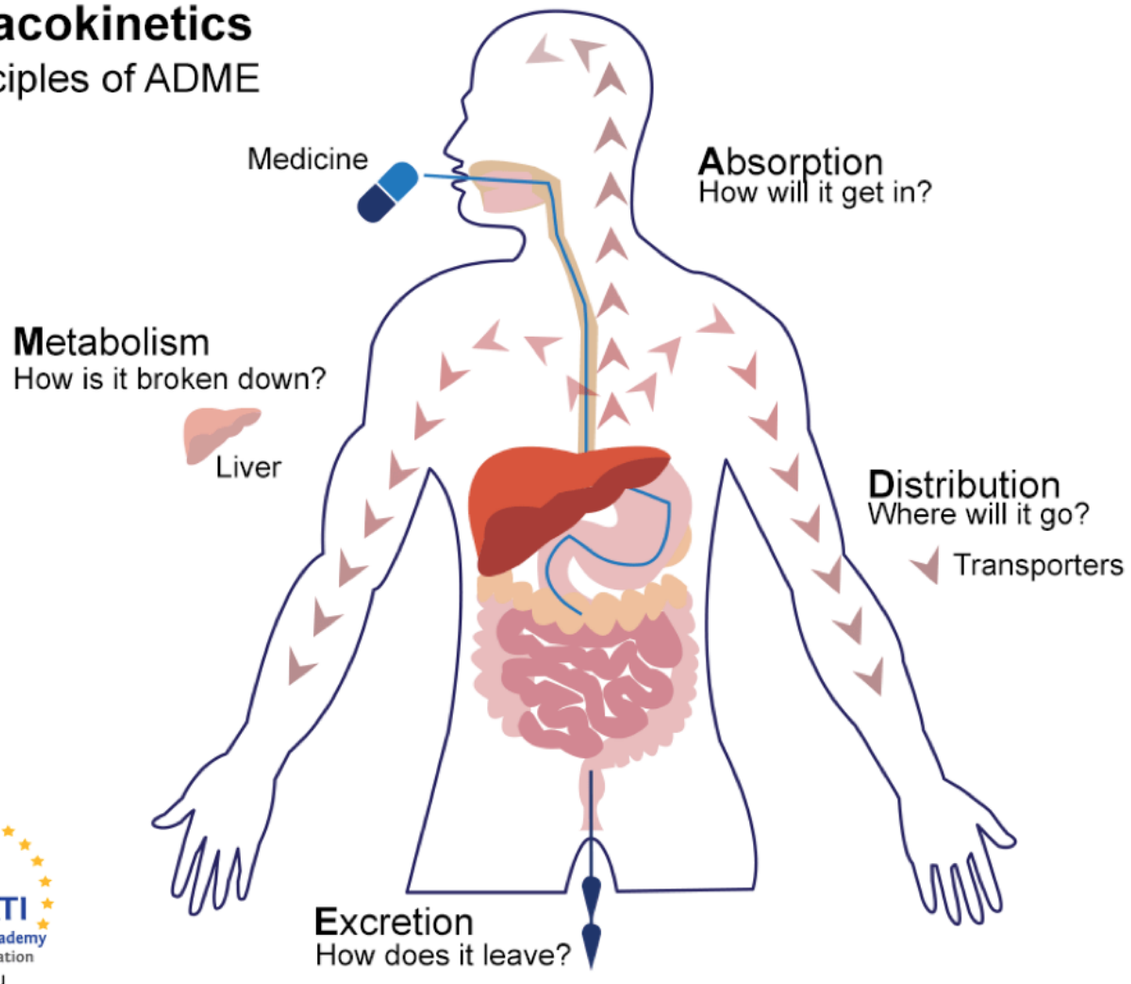
https://pumas.ai

Vaibhav Kumar Dixit

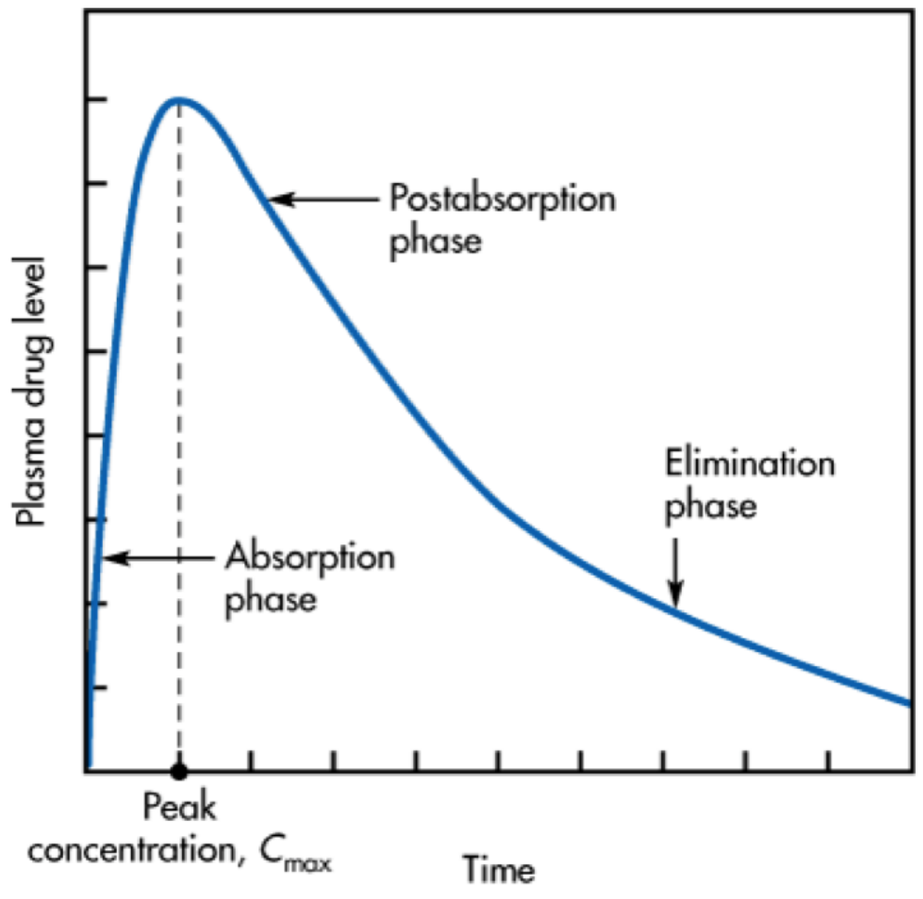
@Vaibhavdixit02

Pharmacokinetics

The principles of ADME



EUPATI
European Patients' Academy on Therapeutic Innovation
www.eupati.eu



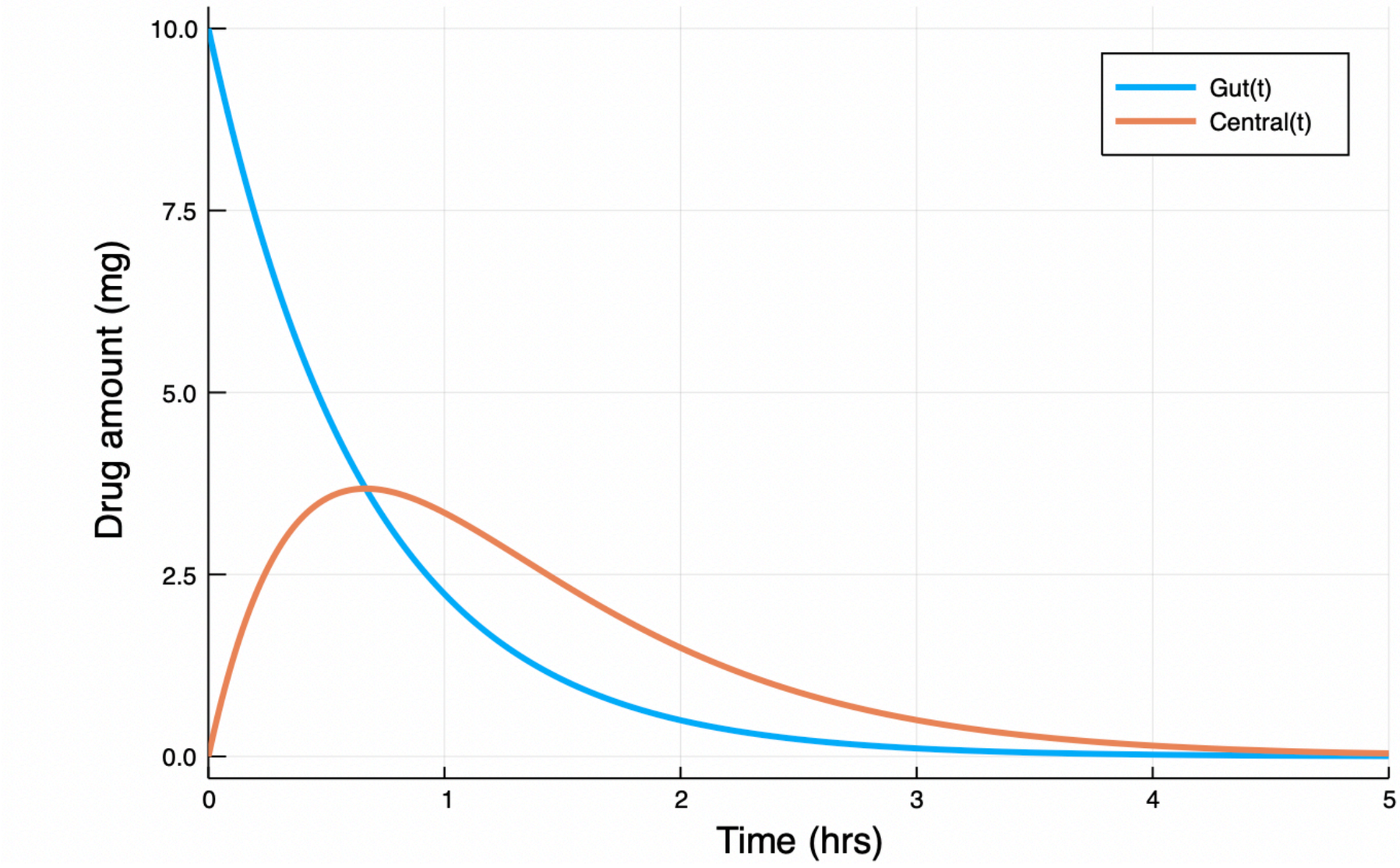
Source: Shargel L, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics 6th Edition*: www.accesspharmacy.com

https://blog.biogeniq.ca/hubfs/figure1-article-alexe2-EN.png

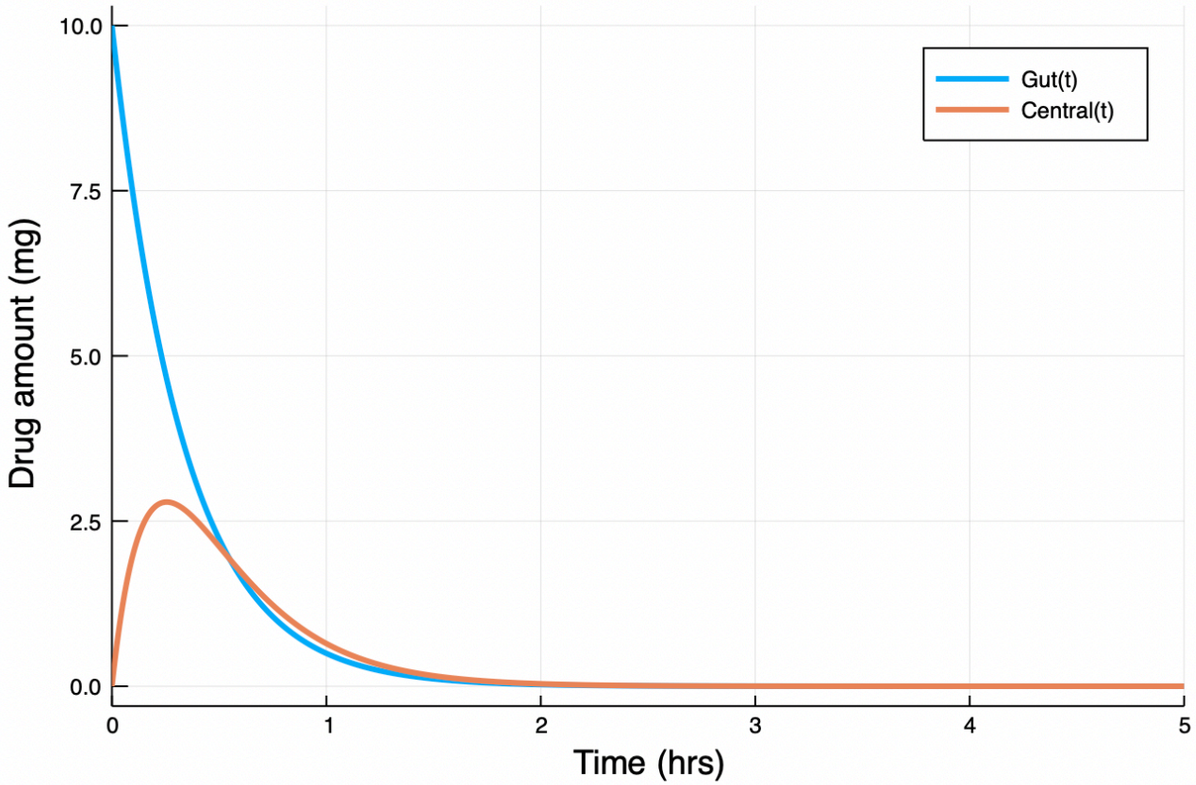
Modelling the drug amount in the body

$$\frac{dGut}{dt} = -Ka \times Gut$$

$$\frac{dCentral}{dt} = Ka \times Gut - \frac{CL}{V} \times Central$$

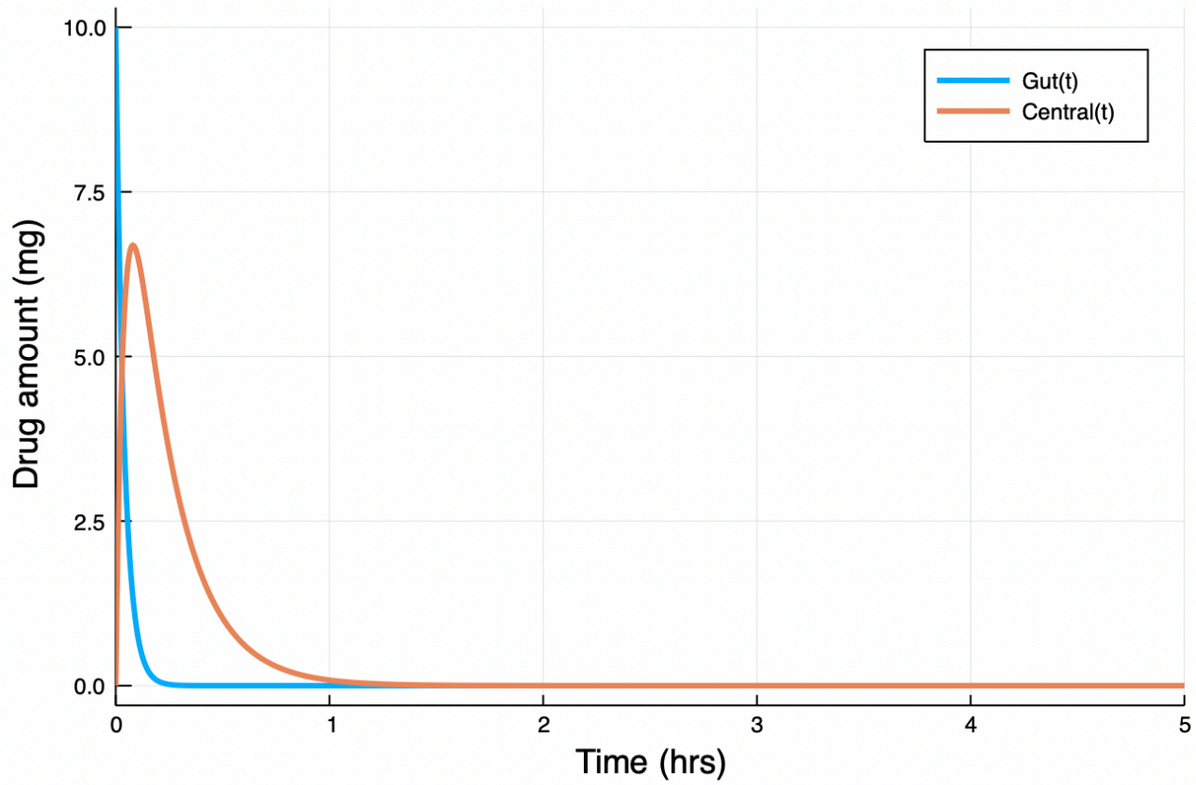


But the parameters?



$K_a = 3$

$CL/V = 5$



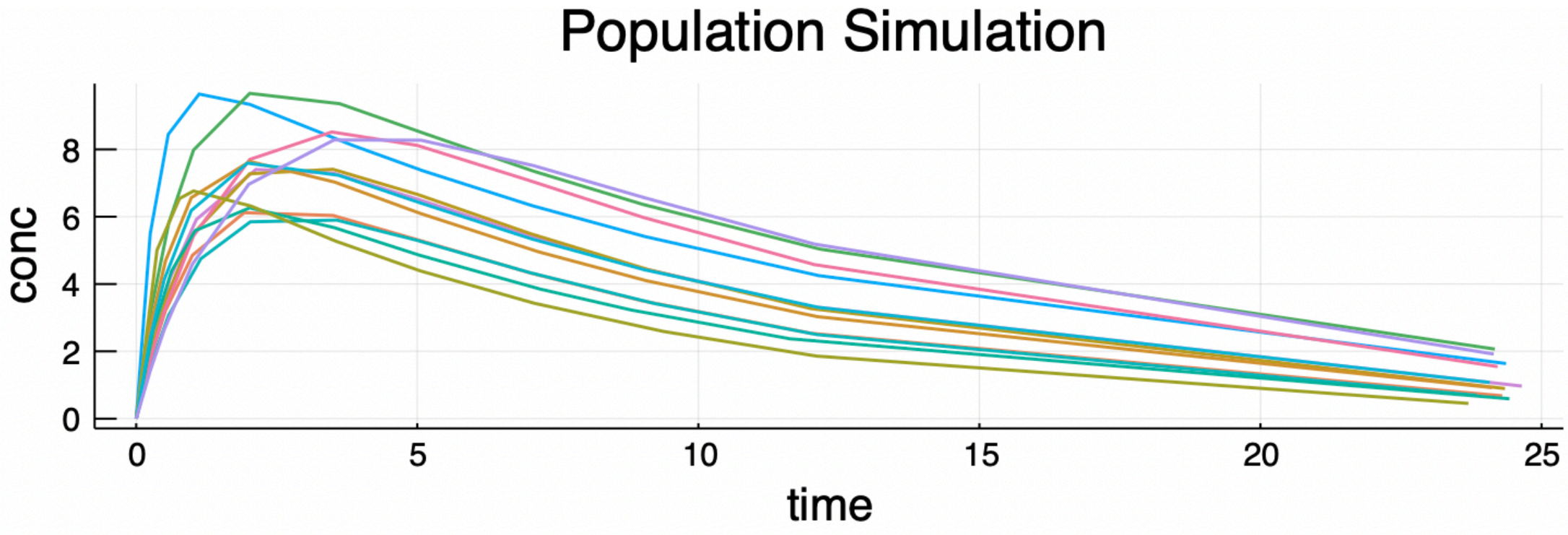
$K_a = 25$

$CL/V = 5$

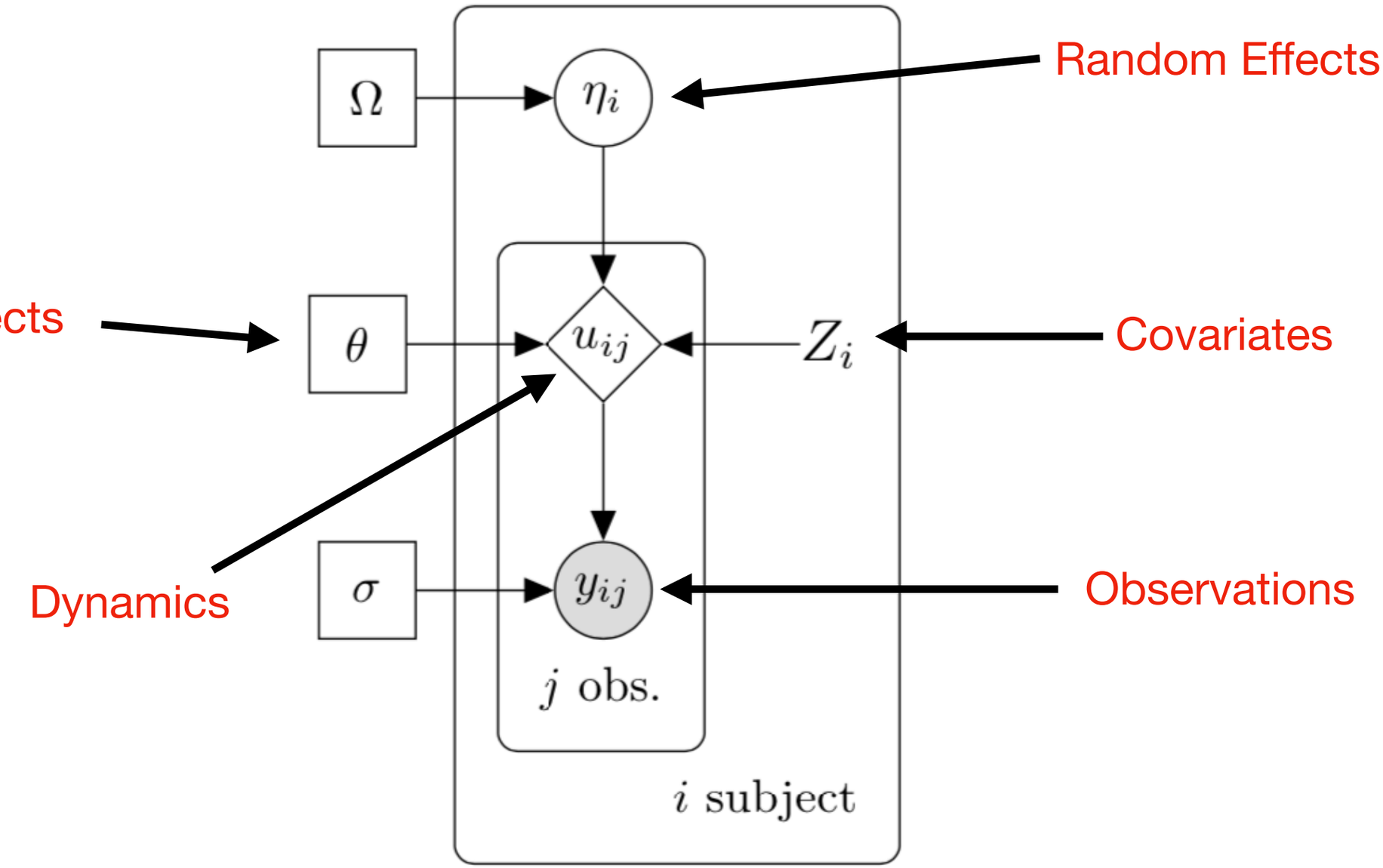
Moving from an individual to a population

So the same dose, same model, but different concentration profiles for different individuals because of the variation in the parameters that define a subject.

How do we capture this variability?



Non Linear Mixed Effects Models



Defining NLME Models in Pumas

```
nlme_model = @model begin
  @param begin
      θ ∈ VectorDomain(3,init=[3.24467E+01, 8.72879E-02, 1.49072E+00])
      Ω ∈ PSDDomain(init=Matrix{Float64}([ 1.93973E-02  1.20854E-02  5.69131E-02
                                           1.20854E-02  2.02375E-02 -6.47803E-03
                                           5.69131E-02 -6.47803E-03  4.34671E-01]))
      Σ ∈ PDiagDomain(init=[1.70385E-02, 8.28498E-02])
  end

  @random begin
      η ~ MvNormal(Ω)
  end

  @pre begin
      V  = θ[1] * exp(η[1])
      Ke = θ[2] * exp(η[2])
      Ka = θ[3] * exp(η[3])
      CL = Ke * V
  end

  @vars begin
      conc = Central / V
  end

  @dynamics begin
      Gut'   = -Ka*Gut
      Central' =  Ka*Gut - Ke*Central
  end

  @derived begin
      dv ~ @. Normal(conc,sqrt(conc^2 *Σ.diag[1] + Σ.diag[end])+eps())
  end
end
```

`@param`: Model parameters (Population averages)

```
@param begin
    θ1 ∈ RealDomain(lower=0.1,   init=2.77,   upper=5.0)
    θ2 ∈ RealDomain(lower=0.008, init=0.0781, upper=0.5)
    θ3 ∈ RealDomain(lower=0.004, init=0.0363, upper=0.9)
    Ω  ∈ PSDDomain(2, init=diagm([5.55, 0.515]))
    σ2 ∈ RealDomain(lower=0.0, init=0.388)
end
```

This specifies the parameters of the model, and their domains:

- `RealDomain`: real values (possibly subject to upper/lower bounds)
- `VectorDomain`: vector of real values
- `PSDDomain`: symmetric positive-definite matrices (e.g. for covariance matrices)
- `PDiagDomain`: postive-valued diagonal matrices

`@random`: Random effects (Individual differences)

```
@random begin
    η ~ MvNormal(Ω)
end
```

Specifies the random effects, dependent on parameters. The random effects are defined by a distribution from Distributions.jl.

`@pre`: pre-processing

```
@pre begin
    Ka = θ1*exp(η[1])
    K  = θ2
    CL = θ3*wt*exp(η[2])
    V  = CL/K
    SC = V/wt
end
```

This determines how the model parameters, random effects and covariates are combined before the differential equations solver.

`@init`: Initial values (optional)

```
@init begin
    Depot   = 0.0
    Central = 0.0
end
```

Specifies the starting values of the differential equations at the time of first dose.

`@covariates`: Covariates

```
1 @covariates sex wt
```

Specifies the covariate terms from the dataset.

`@dynamics`: ODE specification

```
1 @dynamics begin
2     dDepot   = -Ka*Depot
3     dCentral =  Ka*Depot - K*Central
4 end
```

Specifies the system of differential equations. Differential variables are declared by having a line defining their derivative.

Also provide special cases for known closed-form solutions, e.g.

```
1 @dynamics OneCompartmentModel
```

`@derived`: post-processing

```
@derived begin
    dv ~ @. Normal(conc,sqrt(conc^2 *Σ.diag[1] + Σ.diag[end])+eps())
end
```

The derived block specifies variables that can be used for post-processing of results. It can be an continuous distribution shown above or a discrete one like

```
@derived begin
    dv ~ @. Poisson(baseline*(1-dose/(dose + d50)))
end
```

Let’s suppose that there was clinical trial for a new exciting drug JuliaCon, it relieves you of headaches due to using other languages.

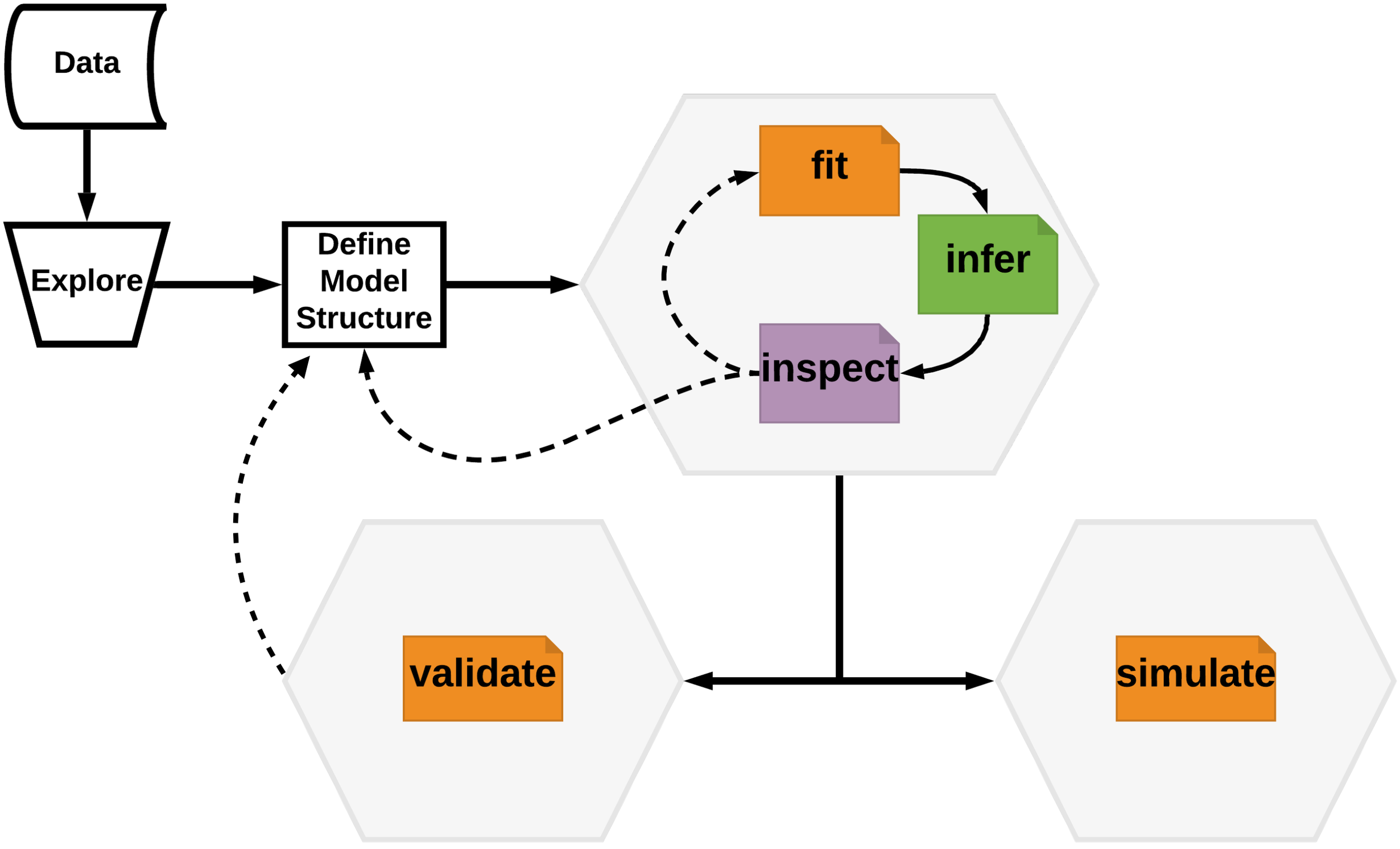
We observed the concentrations but we did not see the response we wanted. We think that the dosage we were giving, say 100mg was not sufficient, we need to ramp it up.

The question arises, what if I increase the dose to say, 200mg, does that fix the problem? What about 150mg would that work?

To answer this question we would have to run the entire clinical trial again with these different doses.

That is slow and costs a lot!

So how do we answer this question?


Data
Explore
Define
Model
Structure
fit
infer
inspect
validate
simulate

Define the model

```
model = @model begin
  @param   begin
    tvcl ∈ RealDomain(lower=0, init = 4.0)
    tvv ∈ RealDomain(lower=0, init = 70)
    pmoncl ∈ RealDomain(lower = -0.99, init= -0.7)
    Ω ∈ PDiagDomain(init=[0.09,0.09])
    σ_prop ∈ RealDomain(lower=0,init=0.04)
  end

  @random begin
    η ~ MvNormal(Ω)
  end

  @pre begin
    CL = tvcl * (1 + pmoncl*isPM) * (wt/70)^0.75 * exp(η[1])
    V  = tvv * (wt/70) * exp(η[2])
  end
  @covariates wt isPM

  @dynamics ImmediateAbsorptionModel
    #@dynamics begin
    #    Central' =  - (CL/V)*Central
    #end

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

Read the data

```
julia> data = read_pumas(simdf,cvs=[:isPM, :wt])
Population
  Subjects: 10
  Covariates: isPM, wt
  Observables: dv
```

Use this data to estimate the parameters of our model.

```
julia> res = fit(model,data,param,Pumas.FOCEI())
FittedPumasModel

Successful minimization:                      true

Likelihood approximation:            Pumas.FOCEI
Objective function value:                 8084.54
Total number of observation records:      1210
Number of active observation records:     1210
Number of subjects:                         10

-----------------
       Estimate
-----------------
tvcl     4.8809
tvv      89.739
pmoncl  -0.73558
Ω₁,₁     0.10822
Ω₂,₂     0.051508
σ_prop   0.042149
-----------------
```

https://docs.pumas.ai/dev/basics/estimation/#Maximum-Likelihood-Estimation-1
https://docs.pumas.ai/dev/basics/estimation/#Bayesian-Estimation-1


```
julia> infer(res)
Calculating: variance-covariance matrix
. Done.
FittedPumasModelInference

Successful minimization:                      true

Likelihood approximation:           Pumas.FOCEI
Objective function value:                8084.54
Total number of observation records:        1210
Number of active observation records:       1210
Number of subjects:                           10

-----------------------------------------------------
       Estimate       RSE            95.0% C.I.
-----------------------------------------------------
tvcl    4.8809     12.932  [ 3.6438   ;   6.1181  ]
tvv    89.739       7.3011 [76.898    ; 102.58    ]
pmoncl -0.73558    -7.9587 [-0.85032  ;  -0.62084 ]
Ω₁,₁    0.10822    26.546  [ 0.051913 ;   0.16452 ]
Ω₂,₂    0.051508   41.275  [ 0.0098391;   0.093176]
σ_prop  0.042149    3.3957 [ 0.039344 ;   0.044954]
-----------------------------------------------------
```

https://docs.pumas.ai/dev/analysis/diagnostics/#The-infer-Function-1

Predictions: The difference between the observations and the model expectation

- Population - EPRED, PRED, CPRED, CPREDI
- Individual - IPRED, CIPRED, CIPREDI, EIPRED

Residuals:

- Population - NPDE, WRES, CWRES, CWRESI
- Individual - IWRES, ICWRES, ICWRESI, EIWRES

ɳshrinkage, ɛshrinkage, AIC, BIC

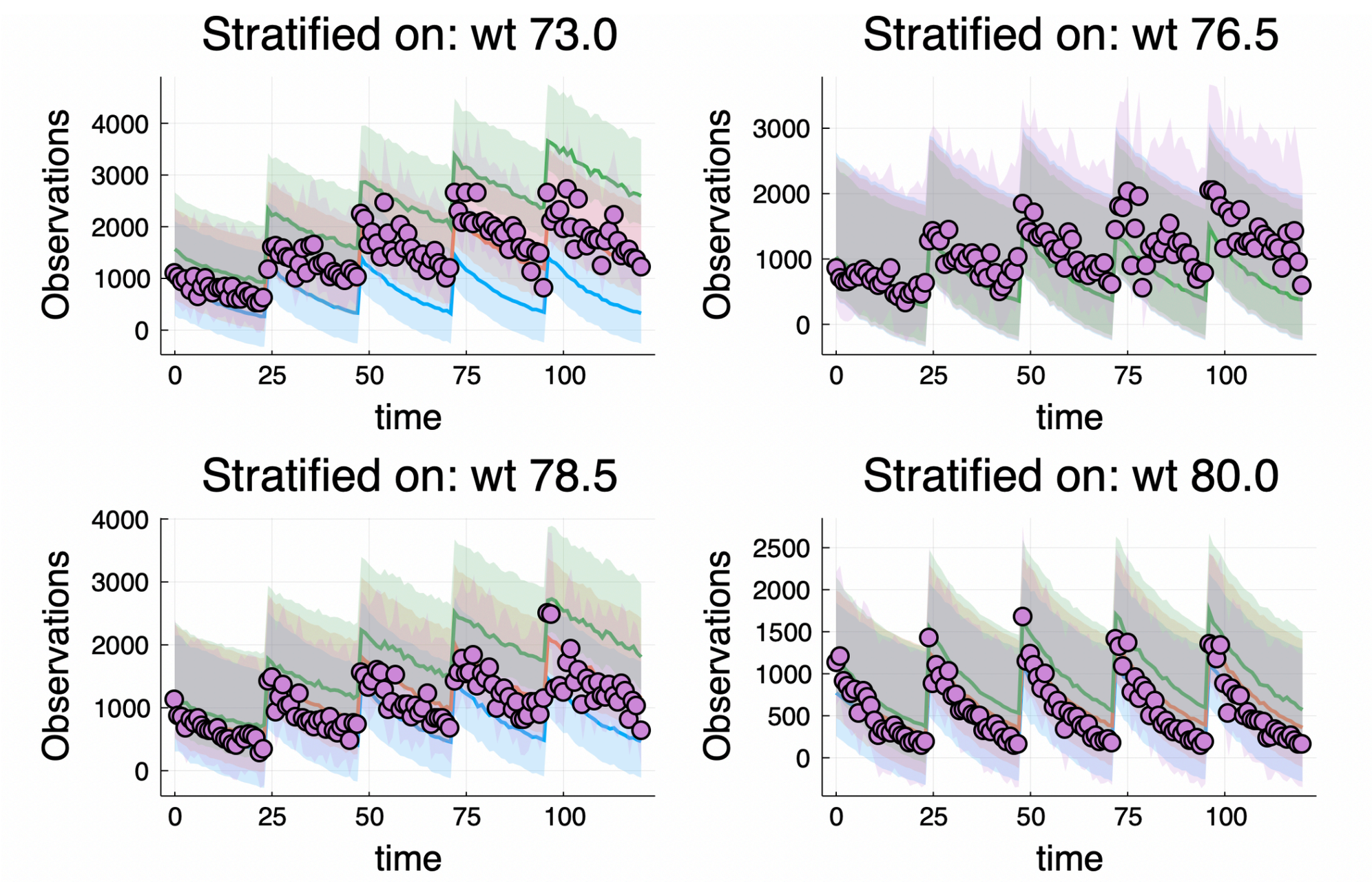
```
julia> resout = DataFrame(inspect(res))
julia> first(resout, 6)
6×13 DataFrame
```

Row	id	time	isPM	wt	pred	ipred	pred_approx	wres	iwres	wres_approx	ebe_1	ebe_2	ebes_approx
	String	Float64	Int64	Int64	Float64	Float64	Pumas.FOCEI	Float64	Float64	Pumas.FOCEI	Float64	Float64	Pumas.FOCEI
1	1	0.0	0	68	1326.95	1290.5	FOCEI()	0.0141867	0.164838	FOCEI()	-0.273173	0.0282462	FOCEI()
2	1	1.0	0	68	1255.42	1236.44	FOCEI()	0.247655	0.414528	FOCEI()	-0.273173	0.0282462	FOCEI()
3	1	2.0	0	68	1187.56	1184.65	FOCEI()	-1.44113	-1.53356	FOCEI()	-0.273173	0.0282462	FOCEI()
4	1	3.0	0	68	1123.17	1135.03	FOCEI()	-0.66784	-1.10145	FOCEI()	-0.273173	0.0282462	FOCEI()
5	1	4.0	0	68	1062.1	1087.49	FOCEI()	-0.67988	-1.29264	FOCEI()	-0.273173	0.0282462	FOCEI()
6	1	5.0	0	68	1004.17	1041.94	FOCEI()	1.14917	0.521982	FOCEI()	-0.273173	0.0282462	FOCEI()

https://docs.pumas.ai/dev/analysis/diagnostics/#Model-Diagnostic-Functions-1

validate

```
julia> vpc(res,200;stratify_on=[:wt]) |> plot
```



https://docs.pumas.ai/dev/analysis/diagnostics/#The-Visual-Predictive-Check-(vpc)-Function-1

We run the simulation with a simobs call

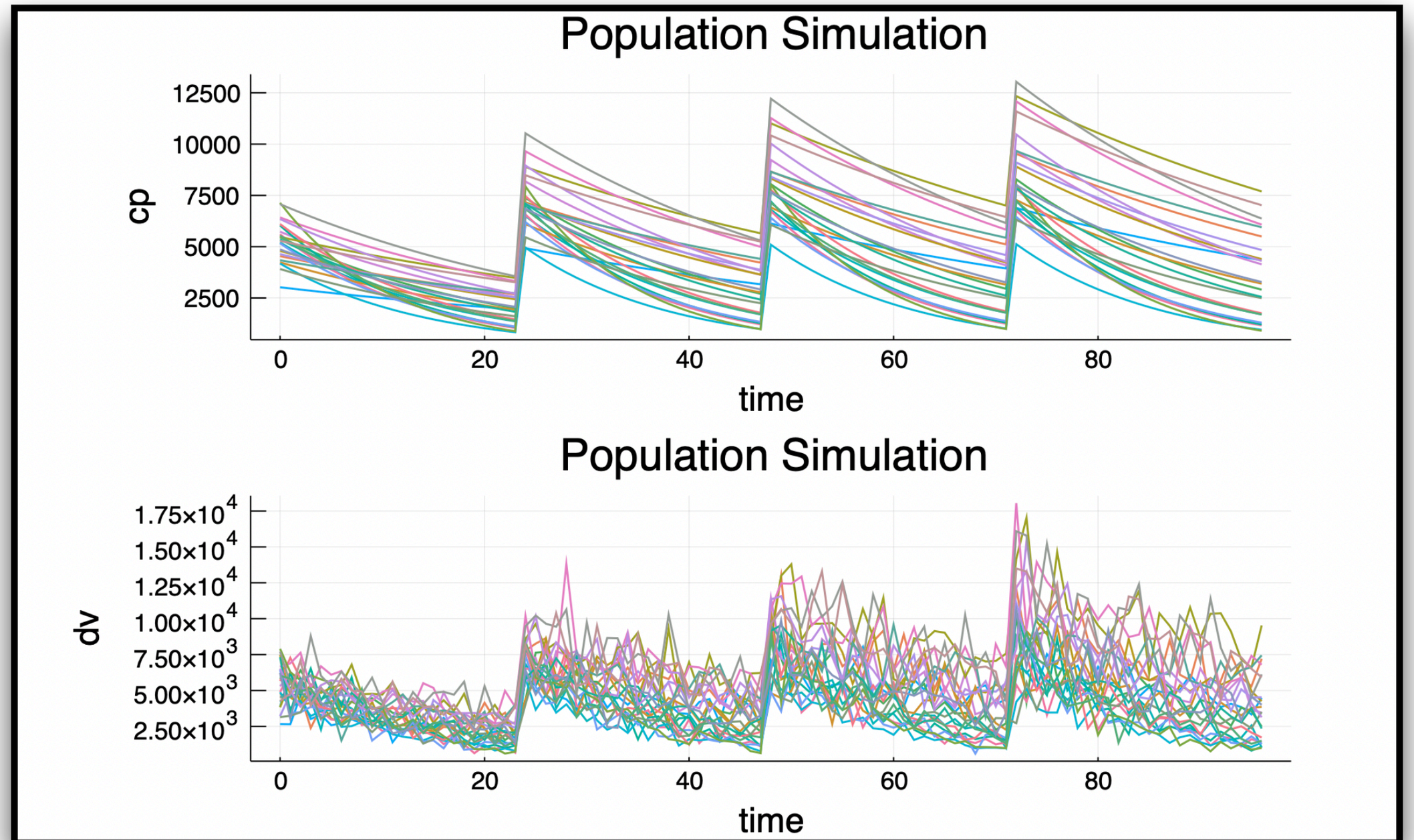
```
julia> sim1 = simobs(m_diffeq, ev1, p; abstol=1e-14, reltol=1e-14)
```

The subject wise simulation output

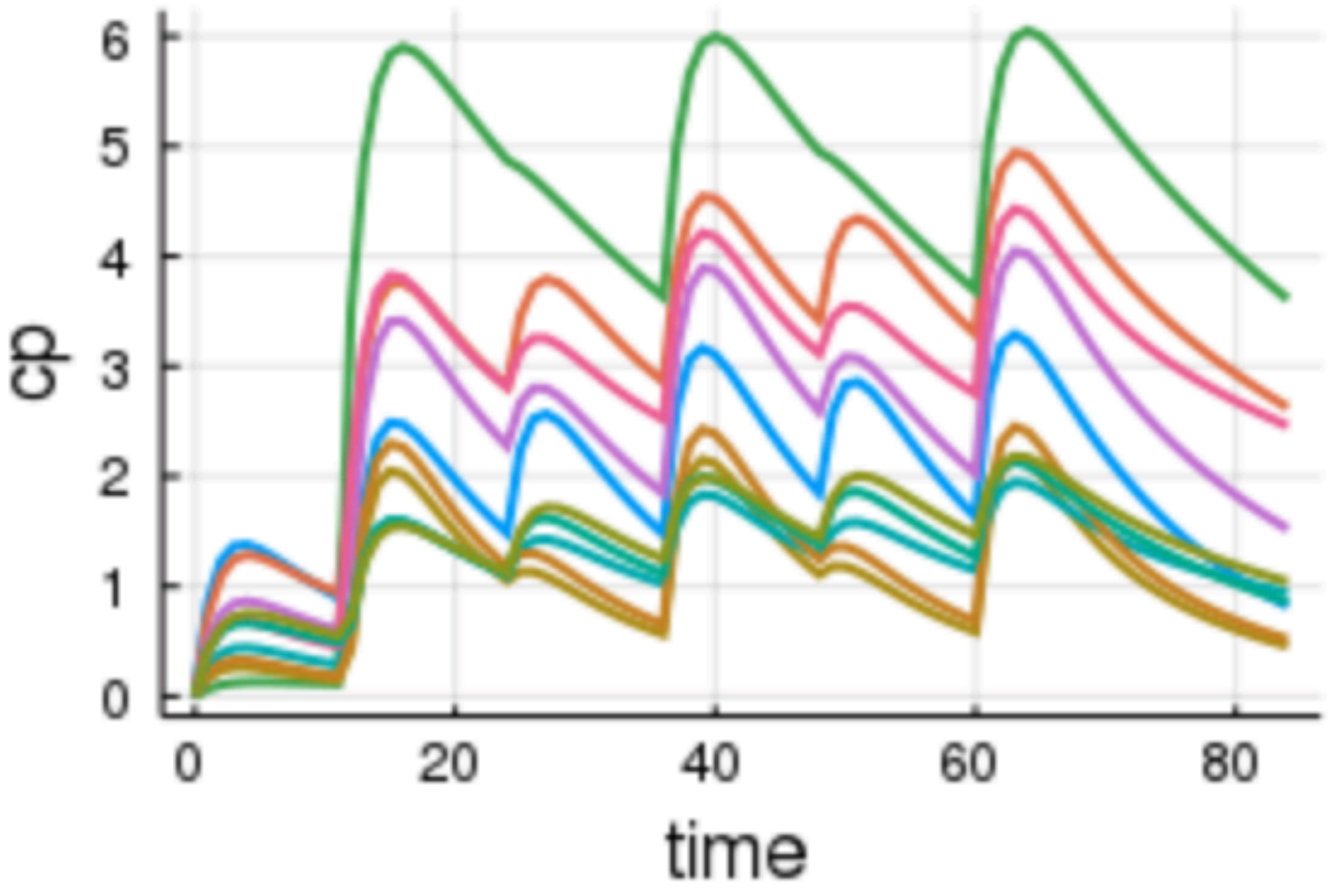
```
Subject
  ID: 1
  Events: 4
, 0.0:1.0:96.0, (cp = [4114.33, 4057.56, 4001.57, 3946.35, 3891.9, 3838.2, 3785.24, 3733.0,
3681.5, 3630.7  …  8676.2, 8556.49, 8438.42, 8321.98, 8207.15, 8093.91, 7982.22, 7872.08, 7763.46,
7656.33], dv = [3254.99, 1998.61, 3497.23, 4780.26, 3041.26, 2604.17, 3277.17, 3295.85, 4776.44,
3386.44  …  8335.86, 8939.89, 10491.5, 7646.75, 7337.47, 8872.07, 5317.99, 6404.97, 7250.41,
9919.32]))
```

https://docs.pumas.ai/dev/basics/simulation/#Simulation-of-Pumas-Models-1

```
julia> plot(sim1)
```



To answer the question, just change the dosage regimen and plug it into the simobs function to simulate different scenarios.



Why use Pumas?

- Pharmacometrics is a discipline where we need to know what the code we are running is doing, what the mathematics says and we need to validate everything. However, the libraries that we are calling are generally written in other languages and treated as an undebuggable black-box. If you're interested in adding a hook in R's deSolve ODE solvers for some new QsP model, or want to dig in and find out why Stan's Bayesian estimation is missing a peak, you will not find R code. Instead, you will find that the core of these libraries are written in FORTRAN 77/90 and C++, and investigating what they are doing requires using opaque and non-interactive languages.
- Drug development
  De-risking investment and expedite time to market.
- Patient Care
  US spends $ 4 Trillion dollars on healthcare, Pumas will take one step closer to enhancing the treatment success.

Acknowledgments

- Vijay Ivaturi
- Chris Rackauckas
- Andreas Noack
- Patrick Mogensen
- Joga Gobburu
- JC Bangalore Team
- Simon Byrne