Indirect Response Models

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1 Introduction

This is an introduction to how to excute individual and population level simulations for indirect response models driven by continuous PK. For the following simulation, we have chosen use an oral drug formulation that is intended to

- inhibit the production of a potential biomarker - `irm1`
- inhibit of degredation of a potential biomarker - `irm2`
- stimulate the production of a potential biomarker - `irm3`
- stimulate the degredation of a potential biomarker - `irm4`

1.1 Getting Started

```
using Pumas, LinearAlgebra, Plots
```

1.2 Model Code

The following provides specifics to the model code:

- One compartment pharmacokinetic model was used to drive pharmacodynamics
- `Cp` is defined in "derived" and represents the plasma concentration in the central compartment
- `IMAX`/`EMAX` parameter was fixed to 1 for maximal inhibition/simulation
- Random effects on `Ka1`, `CL`, `Vc`, `Kin`, `Kout`, and `IC50`, `EC50` were assumed to follow a log-normal distribution

1.3 irm1

```
irm1 = @model begin
    @param begin
        θ ∈ VectorDomain(6)
        Ω ∈  PDiagDomain(5)
    end

    @random begin
        η ~ MvNormal(Ω)
    end

    @pre begin
        Ka      = θ[1]
        CL      = θ[2]*exp(η[1])
        Vc      = θ[3]*exp(η[2])
        Kin     = θ[4]*exp(η[3])
        Kout    = θ[5]*exp(η[4])
        IC50    = θ[6]*exp(η[5])
        IMAX    = 1
    end

    @init begin
        Resp = Kin/Kout
    end

    @vars begin
        cp = Cent/Vc
        inhibition = 1-(IMAX*cp/(IC50+cp))
    end

    @dynamics begin
        Gut'    = -Ka*Gut
        Cent'   =  Ka*Gut - (CL/Vc)*Cent
        Resp'   =  Kin*inhibition - Kout*Resp
    end

    @derived begin
        cp     = Cent / Vc
        resp   = Resp
    end
end
```

1.4 Specified Parameters

The initial estimates of the parameters to simulate from. The fixed effects are provided in the θ vector and the between-subject variability parameteres are provided in the Ω vector as variances. A variance of 0.04 suggests a 20% coefficient of variation.

```
param = (θ = [
          0.5, # Ka Absorption rate constant 1 (1/time)
          5, # CL Clearance (volume/time)
          30, # Vc Central volume (volume)
          10, # Kin Response in rate constant (1/time)
          0.02, # Kout Response out rate constant (1/time)
          10, # IC50 Concentration for 50% of max inhibition (mass/volume)
          1, # IMAX Maximum inhibition
          ],
    Ω = Diagonal([0.04,0.04,0.04,0.04,0.04]));
```

1.5 Simulation

For the purpose of this tutorial, a simulation of a single subject receiving a single oral dose is shown below:

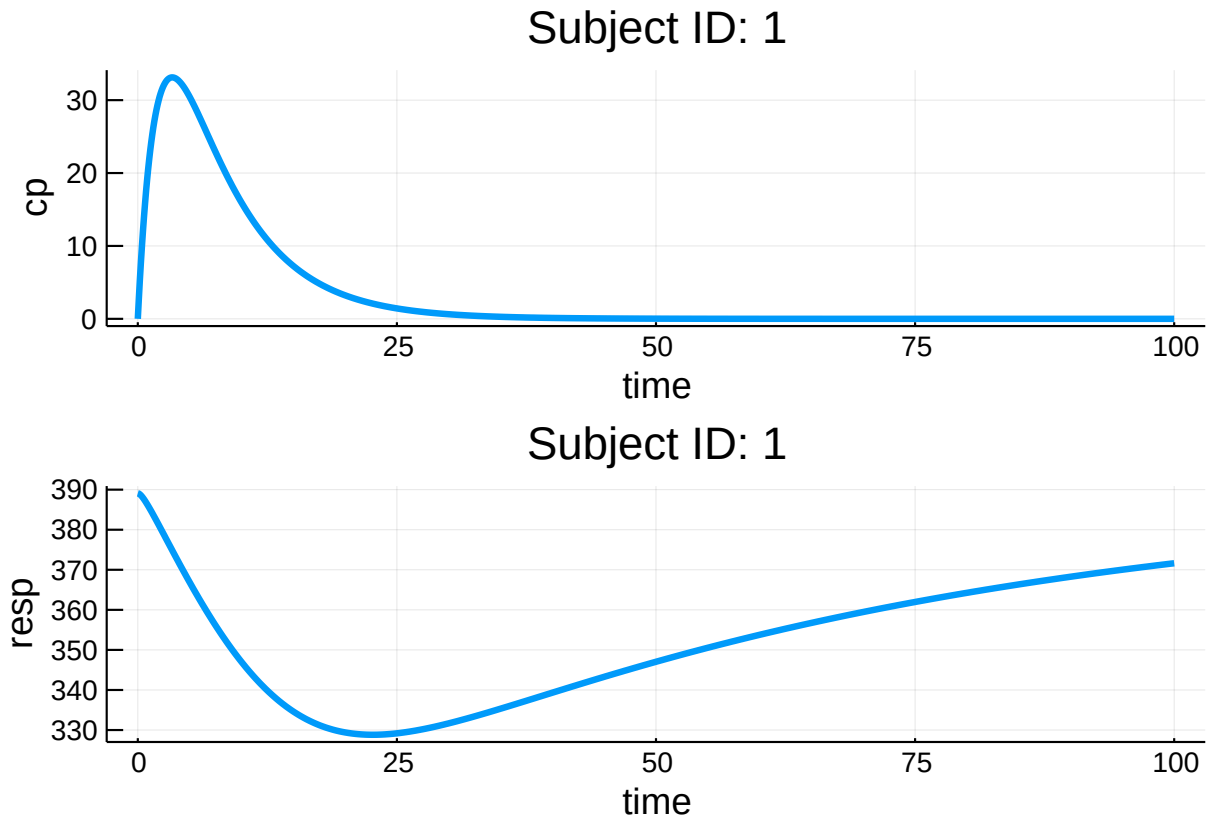
- `regimen1` provides the single oral dose at `time=0` into the gut compartment (`cmt=1`)
- `subject1` provides a single subject receiving regimen1

```
regimen1 = DosageRegimen(1500, time=0,cmt=1)
subject1 = Subject(id=1,evs=regimen1)
```

```
Subject
  ID: 1
  Events: 1
```

The simobs function will call in the model object `irm1`, subject characteristics, parameters. For this simulation, a 100 hour simulation legnth was selected, with observations at every 0.1 hours. The `plot()` function can be used to visualize the simulation output.

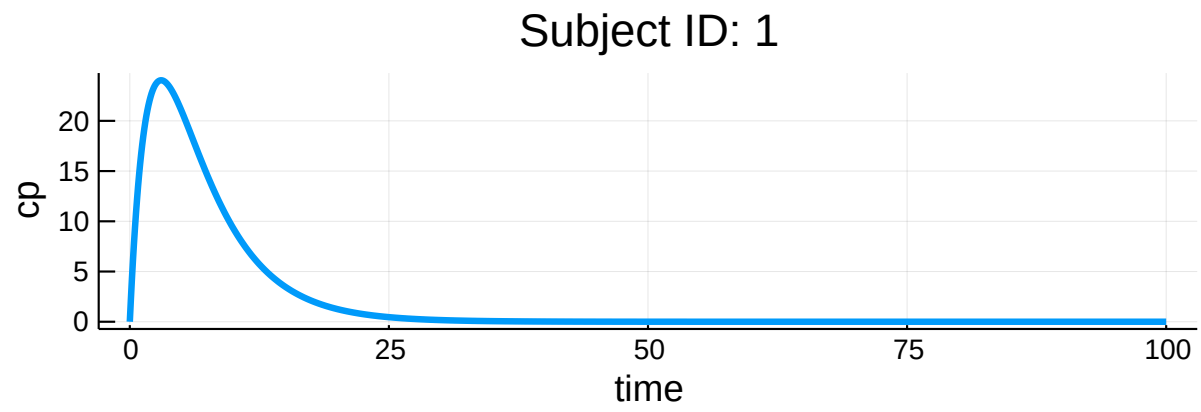
```
sim = simobs(irm1,subject1,param,obstimes=0:0.1:100)
plot(sim, obsnames=[:cp,:resp])
```

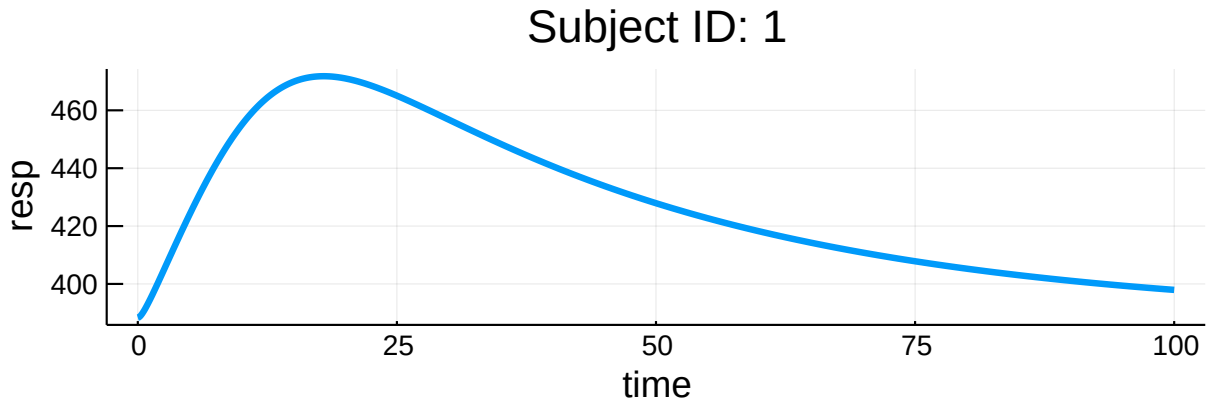


You can now try out the other indirect response models by changing the `@dynamics`.

1.6 `irm2`

```
irm2 = @model begin
    @param begin
        θ ∈ VectorDomain(6)
        Ω ∈  PDiagDomain(5)
    end

    @random begin
        η ~ MvNormal(Ω)
    end

    @pre begin
        Ka      = θ[1]
        CL      = θ[2]*exp(η[1])
        Vc      = θ[3]*exp(η[2])
        Kin     = θ[4]*exp(η[3])
        Kout    = θ[5]*exp(η[4])
        IC50    = θ[6]*exp(η[5])
        IMAX    = 1
    end

    @init begin
        Resp = Kin/Kout
    end

    @vars begin
        cp = Cent/Vc
        inhibition = 1-(IMAX*cp/(IC50+cp))
    end

    @dynamics begin
        Gut'    = -Ka*Gut
        Cent'   =  Ka*Gut - (CL/Vc)*Cent
        Resp'   =  Kin - Kout*inhibition*Resp
    end

    @derived begin
        cp     = Cent / Vc
        resp   = Resp
    end
end

PumasModel
  Parameters: θ, Ω
  Random effects: η
  Covariates:
  Dynamical variables: Gut, Cent, Resp
  Derived: cp, inhibition, resp
  Observed: cp, inhibition, resp

sim = simobs(irm2,subject1,param,obstimes=0:0.1:100)
plot(sim, obsnames=[:cp,:resp])
```





1.7 irm3

Change IMAX and IC50 to EMAX and EC50 in the `@param` block and the subsequent equations

```
irm3 = @model begin
    @param begin
        θ ∈ VectorDomain(6)
        Ω ∈  PDiagDomain(5)
    end

    @random begin
        η ~ MvNormal(Ω)
    end

    @pre begin
        Ka      = θ[1]
        CL      = θ[2]*exp(η[1])
        Vc      = θ[3]*exp(η[2])
        Kin     = θ[4]*exp(η[3])
        Kout    = θ[5]*exp(η[4])
        EC50    = θ[6]*exp(η[5])
        EMAX    = 1
    end

    @init begin
        Resp = Kin/Kout
    end

    @vars begin
        cp = Cent/Vc
        stimulation = 1 + (EMAX*cp/(EC50+cp))
```