Global Sensitivity Analysis on Voriconazole model

2021-04-26

```
using Pumas, CairoMakie, PumasPlots, GlobalSensitivity
```

0.1 Introduction

In this tutorial, we will cover running global sensitivity analysis on the Voriconazole model published here https://github.com/metrumresearchgroup/Voriconazole-PBPK/

0.1.1 Model Code

```
model = @model begin
    @param begin
        Fup ∈ RealDomain(init = 0.42)
        fumic ∈ RealDomain(init = 0.711)
        WEIGHT ∈ RealDomain(init = 73)
        MPPGL ∈ RealDomain(init = 30.3)
        MPPGI ∈ RealDomain(init = 0)
        C_OUTPUT ∈ RealDomain(init = 6.5)
        VmaxH ∈ RealDomain(init = 40)
        VmaxG ∈ RealDomain(init = 40)
        KmH ∈ RealDomain(init = 9.3)
        KmG ∈ RealDomain(init = 9.3)
        bp ∈ RealDomain(init = 1)
        kpad ∈ RealDomain(init = 9.89)
        kpbo ∈ RealDomain(init = 7.91)
        kpbr ∈ RealDomain(init = 7.35)
        kpgu ∈ RealDomain(init = 5.82)
        kphe ∈ RealDomain(init = 1.95)
        kpki ∈ RealDomain(init = 2.9)
        kpli ∈ RealDomain(init = 4.66)
        kplu ∈ RealDomain(init = 0.83)
        kpmu ∈ RealDomain(init = 2.94)
        kpsp ∈ RealDomain(init = 2.96)
        kpre ∈ RealDomain(init = 4)
        MW ∈ RealDomain(init = 349.317)
        logP ∈ RealDomain(init = 2.56)
        s_lumen ∈ RealDomain(init = 0.39*1000)
        L ∈ RealDomain(init = 280)
        d ∈ RealDomain(init = 2.5)
        PF ∈ RealDomain(init = 1.57)
        VF ∈ RealDomain(init = 6.5)
        MF ∈ RealDomain(init = 13)
```

```
        ITT ∈ RealDomain(init = 3.32)
        A ∈ RealDomain(init = 7440)
        B ∈ RealDomain(init = 1e7)
        alpha ∈ RealDomain(init = 0.6)
        beta ∈ RealDomain(init = 4.395)
        fabs ∈ RealDomain(init = 1)
        fdis ∈ RealDomain(init = 1)
        fperm ∈ RealDomain(init = 1)
        vad ∈ RealDomain(init = 18.2)
        vbo ∈ RealDomain(init =10.5)
        vbr ∈ RealDomain(init =1.45)
        vguWall ∈ RealDomain(init =0.65)
        vgulumen ∈ RealDomain(init =0.35)
        vhe ∈ RealDomain(init =0.33)
        vki ∈ RealDomain(init =0.31)
        vli ∈ RealDomain(init =1.8)
        vlu ∈ RealDomain(init =0.5)
        vmu ∈ RealDomain(init =29)
        vsp ∈ RealDomain(init =0.15)
        vbl ∈ RealDomain(init =5.6)
        FQad ∈ RealDomain(lower = 0.0, init = 0.05, upper = 1.0) #add bounds to
parameters for estimation
        FQbo ∈ RealDomain(lower = 0.0, init = 0.05, upper = 1.0)
        FQbr ∈ RealDomain(lower = 0.0, init = 0.12, upper = 1.0)
        FQgu ∈ RealDomain(lower = 0.0, init = 0.16, upper = 1.0)
        FQhe ∈ RealDomain(lower = 0.0, init = 0.04, upper = 1.0)
        FQki ∈ RealDomain(lower = 0.0, init = 0.19, upper = 1.0)
        FQli ∈ RealDomain(lower = 0.0, init = 0.255, upper = 1.0)
        FQmu ∈ RealDomain(lower = 0.0, init = 0.17, upper = 1.0)
        FQsp ∈ RealDomain(lower = 0.0, init = 0.03, upper = 1.0)
    end
    @pre begin
        Vgu = vguWall + vgulumen
        Vve = 0.705*vbl
        Var = 0.295*vbl
        Vre = WEIGHT - (vli+vki+vsp+vhe+vlu+vbo+vbr+vmu+vad+vguWall+vbl)
        CO = C_OUTPUT*60
        Qad = FQad*CO
        Qbo = FQbo*CO
        Qbr = FQbr*CO
        Qgu = FQgu*CO
        Qhe = FQhe*CO
        Qki = FQki*CO
        Qli = FQli*CO
        Qmu = FQmu*CO
        Qsp = FQsp*CO
        Qha = Qli - (Qgu+Qsp)
        Qtot = Qli+Qki+Qbo+Qhe+Qmu+Qad+Qbr
        Qre = CO - Qtot
        Qlu = CO
        Vgulumen = vgulumen
        S_lumen = s_lumen
        VguWall = vguWall
        Kpgu = kpgu
        BP = bp
        Vad = vad
        Kpad = kpad
        Vbr = vbr
        Kpbr = kpbr
```

```
        Vhe = vhe
        Kphe = kphe
        Vki = vki
        Kpki = kpki
        fup = Fup
        Vsp = vsp
        Kpsp = kpsp
        Vli = vli
        Kpli = kpli
        Vlu = vlu
        Kplu = kplu
        Kpmu = kpmu
        Kpre = kpre
        Vmu = vmu
        Vbl = vbl
        Vbo = vbo
        Kpbo = kpbo
        SA_abs = pi*L*d*PF*VF*MF*1e-4
        SA_basal = pi*L*d*PF*VF*1e-4
        MA = 10^logP
        MW_eff = MW - (3*17)
        Peff = fperm*A*(((MW_eff^(-alpha-beta))*MA)/((MW_eff^(-alpha)) +
B*(MW_eff^(-beta))*MA) * 1e-2 * 3600)
        kd = fdis*Peff*SA_abs*1000/vgulumen
        ka = fabs*Peff*SA_basal*1000/VguWall
        kt = 1/ITT
        scale_factor_H = MPPGL*Vli*1000
        scale_factor_G = MPPGI*VguWall*1000
        CLintHep = ((VmaxH/KmH)*scale_factor_H*60*1e-6)/fumic
        CLintGut = ((VmaxG/KmG)*scale_factor_G*60*1e-6)/fumic
        #CLintHep = CLintHep/fumic
        #CLintGut = CLintGut/fumic
        CLrenal = 0.096
        f = 1
    end
    @dynamics begin
        GUTLUMEN' = -kd*Vgulumen*(f*(GUTLUMEN/Vgulumen) + (1-f)*S_lumen) -
            kt*GUTLUMEN
        GUTWALL' = kd*Vgulumen*(f*(GUTLUMEN/Vgulumen) + (1-f)*S_lumen) -
            ka*GUTWALL - CLintGut*(GUTWALL/VguWall)
        GUT' = ka*GUTWALL + Qgu*((ART/Var) - (GUT/VguWall)/(Kpgu/BP))
        ADIPOSE' = Qad*((ART/Var) - (ADIPOSE/Vad)/(Kpad/BP))
        BRAIN' = Qbr*((ART/Var) - (BRAIN/Vbr)/(Kpbr/BP))
        HEART' = Qhe*((ART/Var) - (HEART/Vhe)/(Kphe/BP))
        KIDNEY' = Qki*((ART/Var) - (KIDNEY/Vki)/(Kpki/BP)) -
            CLrenal*(((KIDNEY/Vki)*fup)/(Kpki/BP))
        LIVER' = Qgu*((GUT/VguWall)/(Kpgu/BP)) + Qsp*((SPLEEN/Vsp)/(Kpsp/BP)) +
            Qha*(ART/Var) - Qli*((LIVER/Vli)/(Kpli/BP)) -
            CLintHep*(((LIVER/Vli)*fup)/(Kpli/BP))
        LUNG' = Qlu*((VEN/Vve) - (LUNG/Vlu)/(Kplu/BP))
        MUSCLE' = Qmu*((ART/Var) - (MUSCLE/Vmu)/(Kpmu/BP))
        SPLEEN' = Qsp*((ART/Var) - (SPLEEN/Vsp)/(Kpsp/BP))
        BONE' = Qbo*((ART/Var) - (BONE/Vbo)/(Kpbo/BP))
        REST' = Qre*((ART/Var) - (REST/Vre)/(Kpre/BP))
        VEN' = Qad*((ADIPOSE/Vad)/(Kpad/BP)) + Qbr*((BRAIN/Vbr)/(Kpbr/BP)) +
            Qhe*((HEART/Vhe)/(Kphe/BP)) + Qki*((KIDNEY/Vki)/(Kpki/BP)) +
            Qli*((LIVER/Vli)/(Kpli/BP)) + Qmu*((MUSCLE/Vmu)/(Kpmu/BP)) +
            Qbo*((BONE/Vbo)/(Kpbo/BP)) + Qre*((REST/Vre)/(Kpre/BP)) -
            Qlu*(VEN/Vve)
```

```
        ART' = Qlu*((LUNG/Vlu)/(Kplu/BP) - (ART/Var))
    end
    @derived begin
        Cvenn = VEN./Vve
        cp ~ @. Normal(Cvenn, 0.1) #for estimation
    end
end
```

```
PumasModel
  Parameters: Fup, fumic, WEIGHT, MPPGL, MPPGI, C_OUTPUT, VmaxH, VmaxG, KmH
, KmG, bp, kpad, kpbo, kpbr, kpgu, kphe, kpki, kpli, kplu, kpmu, kpsp, kpre
, MW, logP, s_lumen, L, d, PF, VF, MF, ITT, A, B, alpha, beta, fabs, fdis,
fperm, vad, vbo, vbr, vguWall, vgulumen, vhe, vki, vli, vlu, vmu, vsp, vbl,
 FQad, FQbo, FQbr, FQgu, FQhe, FQki, FQli, FQmu, FQsp
  Random effects:
  Covariates:
  Dynamical variables: GUTLUMEN, GUTWALL, GUT, ADIPOSE, BRAIN, HEART, KIDNE
Y, LIVER, LUNG, MUSCLE, SPLEEN, BONE, REST, VEN, ART
  Derived: Cvenn, cp
  Observed: Cvenn, cp
```

Let's create a subject to study the model

```
regimen_s = DosageRegimen(200, time=0, addl=13, ii=12, cmt=1, ss=1)
sub_s = Subject(id=1, events=regimen_s)
```

```
Subject
  ID: 1
  Events: 14
```

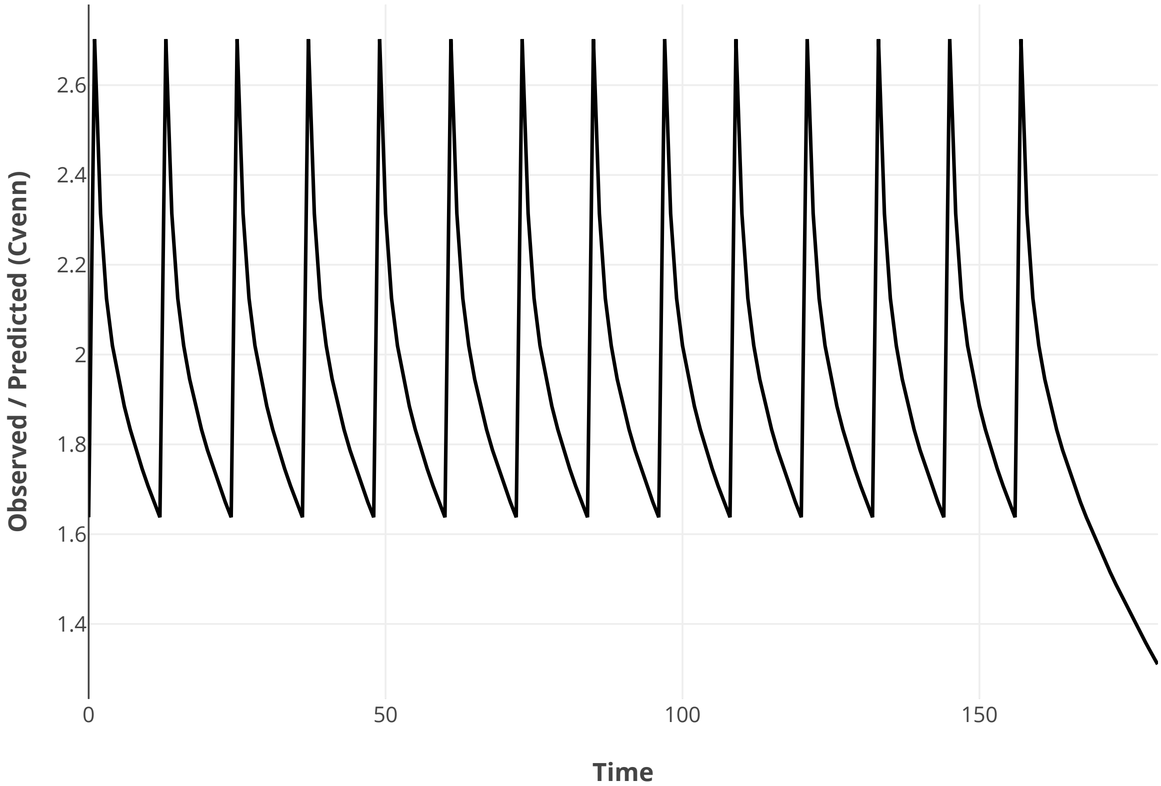
Below are setting the initial estimates of the parameters in the model

```
p = (Fup = 0.42, fumic = 0.711, WEIGHT = 73, MPPGL = 30.3, MPPGI = 0,
    C_OUTPUT = 6.5, VmaxH = 40, VmaxG = 40, KmH = 9.3, KmG = 9.3, bp = 1,
    kpad = 9.89, kpbo = 7.91, kpbr = 7.35, kpgu = 5.82, kphe = 1.95, kpki = 2.9,
    kpli = 4.66, kplu = 0.83, kpmu = 2.94, kpsp = 2.96, kpre = 4, MW = 349.317,
    logP = 2.56, s_lumen = 0.39*1000, L = 280, d = 2.5, PF = 1.57, VF = 6.5,
    MF = 13, ITT = 3.32, A = 7440, B = 1e7, alpha = 0.6, beta = 4.395, fabs = 1,
    fdis = 1, fperm = 1, vad = 18.2, vbo = 10.5, vbr = 1.45, vguWall = 0.65,
    vgulumen = 0.35, vhe = 0.33, vki = 0.31, vli = 1.8, vlu = 0.5, vmu = 29,
    vsp = 0.15, vbl = 5.6, FQad = 0.05, FQbo = 0.05, FQbr = 0.12, FQgu = 0.16,
    FQhe = 0.04, FQki = 0.19, FQli = 0.255, FQmu = 0.17, FQsp = 0.03)
```

```
(Fup = 0.42, fumic = 0.711, WEIGHT = 73, MPPGL = 30.3, MPPGI = 0, C_OUTPUT
= 6.5, VmaxH = 40, VmaxG = 40, KmH = 9.3, KmG = 9.3, bp = 1, kpad = 9.89, k
pbo = 7.91, kpbr = 7.35, kpgu = 5.82, kphe = 1.95, kpki = 2.9, kpli = 4.66,
 kplu = 0.83, kpmu = 2.94, kpsp = 2.96, kpre = 4, MW = 349.317, logP = 2.56
, s_lumen = 390.0, L = 280, d = 2.5, PF = 1.57, VF = 6.5, MF = 13, ITT = 3.
32, A = 7440, B = 1.0e7, alpha = 0.6, beta = 4.395, fabs = 1, fdis = 1, fpe
rm = 1, vad = 18.2, vbo = 10.5, vbr = 1.45, vguWall = 0.65, vgulumen = 0.35
, vhe = 0.33, vki = 0.31, vli = 1.8, vlu = 0.5, vmu = 29, vsp = 0.15, vbl =
 5.6, FQad = 0.05, FQbo = 0.05, FQbr = 0.12, FQgu = 0.16, FQhe = 0.04, FQki
 = 0.19, FQli = 0.255, FQmu = 0.17, FQsp = 0.03)
```

Let's take a look at the simulation of the model to ensure everything is working as expected.

```
simdata = simobs(model, [sub_s], p)
sim_plot(model, simdata, observations=[:Cvenn])
```



We can run parameter estimation on the PBPK model with the `fit` function, we'll use the simulated data to run the estimation here `FQad`, `FQbo`, `FQbr`, `FQgu`, `FQhe`, `FQki`, `FQli`, `FQmu` and `FQsp` will be estimated within the bounds specified and the other parameters will be fixed.

```
data = read_pumas(DataFrame(simdata), observations = [:cp])
ft = fit(model, data, p, Pumas.NaivePooled(),
    constantcoef = (
        Fup = 0.42, fumic = 0.711, WEIGHT = 73, MPPGL = 30.3, MPPGI = 0,
        C_OUTPUT = 6.5, VmaxH = 40, VmaxG = 40, KmH = 9.3, KmG = 9.3, bp = 1,
        kpad = 9.89, kpbo = 7.91, kpbr = 7.35, kpgu = 5.82, kphe = 1.95,
        kpki = 2.9, kpli = 4.66, kplu = 0.83, kpmu = 2.94, kpsp = 2.96,
        kpre = 4, MW = 349.317, logP = 2.56, s_lumen = 0.39*1000, L = 280,
        d = 2.5, PF = 1.57, VF = 6.5, MF = 13, ITT = 3.32, A = 7440, B = 1e7,
        alpha = 0.6, beta = 4.395, fabs = 1, fdis = 1, fperm = 1, vad = 18.2,
        vbo = 10.5, vbr = 1.45, vguWall = 0.65, vgulumen = 0.35, vhe = 0.33,
        vki = 0.31, vli = 1.8, vlu = 0.5, vmu = 29, vsp = 0.15, vbl = 5.6),
    ensemblealg=EnsembleThreads())
```

```
Iter     Function value   Gradient norm
     0     3.682016e+03     2.752213e+02
 * time: 6.198883056640625e-5
     1     3.252025e+03     4.512975e+02
 * time: 0.4183320999145508
     2     2.343474e+03     5.140776e+02
 * time: 0.7970240116119385
     3     1.766600e+03     1.200491e+02
 * time: 1.1807188987731934
     4     1.695758e+03     6.517564e+01
 * time: 1.5688560009002686
     5     1.571057e+03     1.089599e+02
```

```
* time: 1.9491629600524902
    6     1.388413e+03     1.741696e+02
* time: 2.4055609703063965
    7     1.334351e+03     3.132303e+02
* time: 2.8494529724121094
    8     1.206765e+03     8.085562e+02
* time: 3.2726891040802
    9     1.028465e+03     9.440923e+01
* time: 3.7250359058380127
   10     1.011599e+03     3.657840e+01
* time: 4.110250949859619
   11     1.005571e+03     2.707605e+01
* time: 4.4939069747924805
   12     9.968068e+02     7.390553e+00
* time: 4.883265972137451
   13     9.955940e+02     4.583467e+00
* time: 5.368079900741577
   14     9.950436e+02     1.395316e+01
* time: 5.80047607421875
   15     9.944541e+02     2.221676e+01
* time: 6.185312986373901
   16     9.933581e+02     2.684005e+01
* time: 6.572652101516724
   17     9.925532e+02     1.810444e+01
* time: 7.623115062713623
   18     9.923363e+02     1.217759e+01
* time: 8.003284931182861
   19     9.921507e+02     7.880794e+00
* time: 8.384046077728271
   20     9.919460e+02     3.910831e+00
* time: 8.763987064361572
   21     9.918746e+02     1.856312e+00
* time: 9.145912885665894
   22     9.918594e+02     5.778782e-01
* time: 9.52832293510437
   23     9.918563e+02     6.030107e-01
* time: 9.911438941955566
   24     9.918552e+02     6.843451e-01
* time: 10.29286003112793
   25     9.918543e+02     6.338827e-01
* time: 10.676716089248657
   26     9.918533e+02     7.920941e-01
* time: 11.060359954833984
   27     9.918514e+02     9.417454e-01
* time: 11.444878101348877
   28     9.918472e+02     1.073079e+00
* time: 11.827600955963135
   29     9.918381e+02     1.113643e+00
* time: 12.211363077163696
   30     9.918214e+02     9.769528e-01
* time: 12.59877896308899
   31     9.917985e+02     1.080627e+00
* time: 12.9826180934906
   32     9.917786e+02     8.564848e-01
* time: 13.366760015487671
   33     9.917363e+02     1.767720e+00
* time: 13.751688003540039
   34     9.916116e+02     5.550372e+00
* time: 14.134628057479858
```

```
   35     9.914442e+02     1.629176e+01
* time: 14.518476009368896
   36     9.912107e+02     1.914126e+01
* time: 14.902476072311401
   37     9.909221e+02     1.818566e+00
* time: 15.29062795639038
   38     9.907569e+02     1.334672e+00
* time: 15.673218011856079
   39     9.891721e+02     3.625843e+00
* time: 16.057929039001465
   40     9.873604e+02     8.709680e+00
* time: 16.510833024978638
   41     9.853998e+02     1.721744e+01
* time: 16.966166973114014
   42     9.827862e+02     3.346704e+01
* time: 17.48515510559082
   43     9.808133e+02     3.868350e+01
* time: 17.8686580657959
   44     9.799189e+02     1.230831e+01
* time: 18.256328105926514
   45     9.789635e+02     8.525065e+00
* time: 18.645689010620117
   46     9.787814e+02     1.170915e+00
* time: 19.031748056411743
   47     9.787113e+02     8.322856e-01
* time: 19.957097053527832
   48     9.786777e+02     1.542617e+00
* time: 20.339303970336914
   49     9.786629e+02     1.973609e+00
* time: 20.72168803215027
   50     9.786532e+02     2.149714e+00
* time: 21.106795072555542
   51     9.786342e+02     2.332614e+00
* time: 21.48783302307129
   52     9.785897e+02     2.740712e+00
* time: 21.869559049606323
   53     9.784831e+02     3.213833e+00
* time: 22.249927043914795
   54     9.782695e+02     3.918206e+00
* time: 22.63142991065979
   55     9.781810e+02     1.392242e+01
* time: 23.01122498512268
   56     9.780437e+02     3.907756e+00
* time: 23.389700889587402
   57     9.779749e+02     3.637655e+00
* time: 23.768632888793945
   58     9.779138e+02     5.239207e+00
* time: 24.150371074676514
   59     9.778386e+02     4.021796e+00
* time: 24.532577991485596
   60     9.777753e+02     1.528757e+00
* time: 24.917359113693237
   61     9.777552e+02     4.086616e+00
* time: 25.368921995162964
   62     9.777179e+02     1.984431e+00
* time: 25.755944967269897
   63     9.777034e+02     1.097987e+00
* time: 26.14190101623535
   64     9.776927e+02     2.070626e+00
```

```
 * time: 26.5276460647583
    65     9.776884e+02     1.606587e-01
 * time: 27.04797101020813
    66     9.776875e+02     2.689506e-01
 * time: 27.426809072494507
    67     9.776872e+02     1.312477e-01
 * time: 27.804589986801147
    68     9.776872e+02     9.005929e-03
 * time: 28.18191695213318
    69     9.776872e+02     9.003301e-03
 * time: 28.822920083999634
    70     9.776872e+02     9.003301e-03
 * time: 29.74469494819641
FittedPumasModel

Successful minimization:                      true

Likelihood approximation:        Pumas.NaivePooled
Log-likelihood value:                   -977.68717
Number of subjects:                              1
Number of parameters:         Fixed      Optimized
                                 50              9
Observation records:         Active        Missing
    cp:                         181              0
    Total:                      181              0

-------------------------
             Estimate
-------------------------
Fup           0.42
fumic         0.711
WEIGHT       73.0
MPPGL        30.3
MPPGI         0.0
C_OUTPUT      6.5
VmaxH        40.0
VmaxG        40.0
KmH           9.3
KmG           9.3
bp            1.0
kpad          9.89
kpbo          7.91
kpbr          7.35
kpgu          5.82
kphe          1.95
kpki          2.9
kpli          4.66
kplu          0.83
kpmu          2.94
kpsp          2.96
kpre          4.0
MW          349.32
logP          2.56
s_lumen     390.0
L           280.0
d             2.5
PF            1.57
VF            6.5
MF           13.0
```

```
ITT           3.32
A          7440.0
B             1.0e7
alpha         0.6
beta          4.395
fabs          1.0
fdis          1.0
fperm         1.0
vad          18.2
vbo          10.5
vbr           1.45
vguWall       0.65
vgulumen      0.35
vhe           0.33
vki           0.31
vli           1.8
vlu           0.5
vmu          29.0
vsp           0.15
vbl           5.6
FQad          6.0121e-98
FQbo          3.6745e-82
FQbr          0.032632
FQgu          0.030202
FQhe          0.023345
FQki          1.7398e-11
FQli          0.62779
FQmu          0.26102
FQsp          0.97984
-------------------------
```

0.1.2 GSA

We'll run the GSA on the AUC and Cmax output of the `Cvenn` variable and therefore redefine the model to include the NCA calculation.

```
model = @model begin
    @param begin
        Fup ∈ RealDomain(init = 0.42)
        fumic ∈ RealDomain(init = 0.711)
        WEIGHT ∈ RealDomain(init = 73)
        MPPGL ∈ RealDomain(init = 30.3)
        MPPGI ∈ RealDomain(init = 0)
        C_OUTPUT ∈ RealDomain(init = 6.5)
        VmaxH ∈ RealDomain(init = 40)
        VmaxG ∈ RealDomain(init = 40)
        KmH ∈ RealDomain(init = 9.3)
        KmG ∈ RealDomain(init = 9.3)
        bp ∈ RealDomain(init = 1)
        kpad ∈ RealDomain(init = 9.89)
        kpbo ∈ RealDomain(init = 7.91)
        kpbr ∈ RealDomain(init = 7.35)
        kpgu ∈ RealDomain(init = 5.82)
        kphe ∈ RealDomain(init = 1.95)
        kpki ∈ RealDomain(init = 2.9)
        kpli ∈ RealDomain(init = 4.66)
        kplu ∈ RealDomain(init = 0.83)
        kpmu ∈ RealDomain(init = 2.94)
        kpsp ∈ RealDomain(init = 2.96)
```

```
    kpre ∈ RealDomain(init = 4)
    MW ∈ RealDomain(init = 349.317)
    logP ∈ RealDomain(init = 2.56)
    s_lumen ∈ RealDomain(init = 0.39*1000)
    L ∈ RealDomain(init = 280)
    d ∈ RealDomain(init = 2.5)
    PF ∈ RealDomain(init = 1.57)
    VF ∈ RealDomain(init = 6.5)
    MF ∈ RealDomain(init = 13)
    ITT ∈ RealDomain(init = 3.32)
    A ∈ RealDomain(init = 7440)
    B ∈ RealDomain(init = 1e7)
    alpha ∈ RealDomain(init = 0.6)
    beta ∈ RealDomain(init = 4.395)
    fabs ∈ RealDomain(init = 1)
    fdis ∈ RealDomain(init = 1)
    fperm ∈ RealDomain(init = 1)
    vad ∈ RealDomain(init = 18.2)
    vbo ∈ RealDomain(init =10.5)
    vbr ∈ RealDomain(init =1.45)
    vguWall ∈ RealDomain(init =0.65)
    vgulumen ∈ RealDomain(init =0.35)
    vhe ∈ RealDomain(init =0.33)
    vki ∈ RealDomain(init =0.31)
    vli ∈ RealDomain(init =1.8)
    vlu ∈ RealDomain(init =0.5)
    vmu ∈ RealDomain(init =29)
    vsp ∈ RealDomain(init =0.15)
    vbl ∈ RealDomain(init =5.6)
    FQad ∈ RealDomain(lower = 0.0, init = 0.05, upper = 1.0)
    FQbo ∈ RealDomain(lower = 0.0, init = 0.05, upper = 1.0)
    FQbr ∈ RealDomain(lower = 0.0, init = 0.12, upper = 1.0)
    FQgu ∈ RealDomain(lower = 0.0, init = 0.16, upper = 1.0)
    FQhe ∈ RealDomain(lower = 0.0, init = 0.04, upper = 1.0)
    FQki ∈ RealDomain(lower = 0.0, init = 0.19, upper = 1.0)
    FQli ∈ RealDomain(lower = 0.0, init = 0.255, upper = 1.0)
    FQmu ∈ RealDomain(lower = 0.0, init = 0.17, upper = 1.0)
    FQsp ∈ RealDomain(lower = 0.0, init = 0.03, upper = 1.0)
end
@pre begin
    Vgu = vguWall + vgulumen
    Vve = 0.705*vbl
    Var = 0.295*vbl
    Vre = WEIGHT - (vli+vki+vsp+vhe+vlu+vbo+vbr+vmu+vad+vguWall+vbl)
    CO = C_OUTPUT*60
    Qad = FQad*CO
    Qbo = FQbo*CO
    Qbr = FQbr*CO
    Qgu = FQgu*CO
    Qhe = FQhe*CO
    Qki = FQki*CO
    Qli = FQli*CO
    Qmu = FQmu*CO
    Qsp = FQsp*CO
    Qha = Qli - (Qgu+Qsp)
    Qtot = Qli+Qki+Qbo+Qhe+Qmu+Qad+Qbr
    Qre = CO - Qtot
    Qlu = CO
    Vgulumen = vgulumen
```

```
        S_lumen = s_lumen
        VguWall = vguWall
        Kpgu = kpgu
        BP = bp
        Vad = vad
        Kpad = kpad
        Vbr = vbr
        Kpbr = kpbr
        Vhe = vhe
        Kphe = kphe
        Vki = vki
        Kpki = kpki
        fup = Fup
        Vsp = vsp
        Kpsp = kpsp
        Vli = vli
        Kpli = kpli
        Vlu = vlu
        Kplu = kplu
        Kpmu = kpmu
        Kpre = kpre
        Vmu = vmu
        Vbl = vbl
        Vbo = vbo
        Kpbo = kpbo
        SA_abs = pi*L*d*PF*VF*MF*1e-4
        SA_basal = pi*L*d*PF*VF*1e-4
        MA = 10^logP
        MW_eff = MW - (3*17)
        Peff = fperm*A*(((MW_eff^(-alpha-beta))*MA)/((MW_eff^(-alpha)) +
B*(MW_eff^(-beta))*MA) * 1e-2 * 3600)
        kd = fdis*Peff*SA_abs*1000/vgulumen
        ka = fabs*Peff*SA_basal*1000/VguWall
        kt = 1/ITT
        scale_factor_H = MPPGL*Vli*1000
        scale_factor_G = MPPGI*VguWall*1000
        CLintHep = ((VmaxH/KmH)*scale_factor_H*60*1e-6)/fumic
        CLintGut = ((VmaxG/KmG)*scale_factor_G*60*1e-6)/fumic
        #CLintHep = CLintHep/fumic
        #CLintGut = CLintGut/fumic
        CLrenal = 0.096
        f = 1
    end
    @dynamics begin
        GUTLUMEN' = -kd*Vgulumen*(f*(GUTLUMEN/Vgulumen) + (1-f)*S_lumen) -
            kt*GUTLUMEN
        GUTWALL' = kd*Vgulumen*(f*(GUTLUMEN/Vgulumen) + (1-f)*S_lumen) -
            ka*GUTWALL - CLintGut*(GUTWALL/VguWall)
        GUT' = ka*GUTWALL + Qgu*((ART/Var) - (GUT/VguWall)/(Kpgu/BP))
        ADIPOSE' = Qad*((ART/Var) - (ADIPOSE/Vad)/(Kpad/BP))
        BRAIN' = Qbr*((ART/Var) - (BRAIN/Vbr)/(Kpbr/BP))
        HEART' = Qhe*((ART/Var) - (HEART/Vhe)/(Kphe/BP))
        KIDNEY' = Qki*((ART/Var) - (KIDNEY/Vki)/(Kpki/BP)) -
            CLrenal*(((KIDNEY/Vki)*fup)/(Kpki/BP))
        LIVER' = Qgu*((GUT/VguWall)/(Kpgu/BP)) + Qsp*((SPLEEN/Vsp)/(Kpsp/BP)) +
            Qha*(ART/Var) - Qli*((LIVER/Vli)/(Kpli/BP)) -
            CLintHep*(((LIVER/Vli)*fup)/(Kpli/BP))
        LUNG' = Qlu*((VEN/Vve) - (LUNG/Vlu)/(Kplu/BP))
        MUSCLE' = Qmu*((ART/Var) - (MUSCLE/Vmu)/(Kpmu/BP))
```

```
        SPLEEN' = Qsp*((ART/Var) - (SPLEEN/Vsp)/(Kpsp/BP))
        BONE' = Qbo*((ART/Var) - (BONE/Vbo)/(Kpbo/BP))
        REST' = Qre*((ART/Var) - (REST/Vre)/(Kpre/BP))
        VEN' = Qad*((ADIPOSE/Vad)/(Kpad/BP)) + Qbr*((BRAIN/Vbr)/(Kpbr/BP)) +
            Qhe*((HEART/Vhe)/(Kphe/BP)) + Qki*((KIDNEY/Vki)/(Kpki/BP)) +
            Qli*((LIVER/Vli)/(Kpli/BP)) + Qmu*((MUSCLE/Vmu)/(Kpmu/BP)) +
            Qbo*((BONE/Vbo)/(Kpbo/BP)) + Qre*((REST/Vre)/(Kpre/BP)) -
            Qlu*(VEN/Vve)
        ART' = Qlu*((LUNG/Vlu)/(Kplu/BP) - (ART/Var))
    end
    @derived begin
        Cvenn = VEN./Vve
        #capturing NCA metrics for evaluations
        nca := @nca Cvenn
        auc =  last(NCA.auc(nca))
        cmax = last(NCA.cmax(nca))
    end
end
```

```
PumasModel
  Parameters: Fup, fumic, WEIGHT, MPPGL, MPPGI, C_OUTPUT, VmaxH, VmaxG, KmH
, KmG, bp, kpad, kpbo, kpbr, kpgu, kphe, kpki, kpli, kplu, kpmu, kpsp, kpre
, MW, logP, s_lumen, L, d, PF, VF, MF, ITT, A, B, alpha, beta, fabs, fdis,
fperm, vad, vbo, vbr, vguWall, vgulumen, vhe, vki, vli, vlu, vmu, vsp, vbl,
 FQad, FQbo, FQbr, FQgu, FQhe, FQki, FQli, FQmu, FQsp
  Random effects:
  Covariates:
  Dynamical variables: GUTLUMEN, GUTWALL, GUT, ADIPOSE, BRAIN, HEART, KIDNE
Y, LIVER, LUNG, MUSCLE, SPLEEN, BONE, REST, VEN, ART
  Derived: Cvenn, auc, cmax
  Observed: Cvenn, auc, cmax
```

To run the GSA we'll define the parameter ranges for our parameters of interest.

```
p_range_low = (fperm=1/3, s_lumen=390/3, ITT = 3.32/3, MPPGI=1.44/3, )

p_range_high = (fperm=1*3, s_lumen=390*3, ITT = 3.32*3, MPPGI=1.44*3, )
```

```
(fperm = 3, s_lumen = 1170, ITT = 9.959999999999999, MPPGI = 4.32)
```

Now, we are ready to run GSA on our model.

The Sobol Method We will run the Sobol method for 1000 iterations, please note that this takes a couple of hours to finish because of the complexity of the model.

```
regimen_s = DosageRegimen(200, time=0, addl=13, ii=12, cmt=1, ss=1, route =
Pumas.NCA.IVInfusion)
sub_s = Subject(id=1, events=regimen_s)
sobol_ = Pumas.gsa(model, sub_s, p, GlobalSensitivity.Sobol(), [:cmax,:auc],
p_range_low,p_range_high, N=1000, obstimes=0.0:1.0:30.0)
```

```
Sobol Sensitivity Analysis

First Order Indices
2×5 DataFrame
 Row   dv_name   fperm     s_lumen   ITT         MPPGI
       Any       Float64   Float64   Float64     Float64

   1   cmax      0.505844      0.0   0.00157097  0.444075
```

```
  2   auc      0.550181      0.0  0.0014958   0.388602

Total Order Indices
2×5 DataFrame
 Row   dv_name  fperm     s_lumen  ITT          MPPGI
       Any      Float64   Float64  Float64      Float64

   1   cmax     0.561158      0.0  -0.00111054  0.468542
   2   auc      0.611066      0.0  -0.00114236  0.430997
```

We can use scatter plot the result to visualize the result.

```
keys_ = keys(p_range_low)
cmax_s1 = [sobol_.first_order[1,:][key] for key in keys_]
cmax_st = [sobol_.total_order[1,:][key] for key in keys_]

fig = Figure(resolution = (1200, 800))
plot_cmax_s1 = scatter(fig[1,1], 1:4, cmax_s1, axis = (yticks = 0:1, xticks = (1:4,
[string.(keys_)...]), label = "First Order", title="Cmax"))
plot_cmax_st = scatter(fig[1,2], 1:4, cmax_st, axis = (yticks = 0:1, xticks = (1:4,
[string.(keys_)...]), label = "Total Order"), marker=:utriangle)

auc_s1 = [sobol_.first_order[2,:][key] for key in keys_]
auc_st = [sobol_.total_order[2,:][key] for key in keys_]

plot_auc_s1 = scatter(fig[2,1], 1:4, auc_s1, axis = (yticks = 0:1, xticks = (1:4,
[string.(keys_)...]), label = "First Order", title="AUC"))
plot_auc_st = scatter(fig[2,2], 1:4, auc_st, axis = (yticks = 0:1, xticks = (1:4,
[string.(keys_)...]), label = "Total Order"), marker=:utriangle)
display(fig)
```

```
Scene (1200px, 800px):
  72 Plots:
      AbstractPlotting.Poly{Tuple{Vector{Vector{GeometryBasics.Point{2, Flo
at32}}}}}
      AbstractPlotting.LineSegments{Tuple{Vector{GeometryBasics.Point{2, Fl
oat32}}}}
      AbstractPlotting.LineSegments{Tuple{Vector{GeometryBasics.Point{2, Fl
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      AbstractPlotting.Lines{Tuple{Vector{GeometryBasics.Point{2, Float32}}
}}
      AbstractPlotting.Text{Tuple{String}}
  4 Child Scenes:
      Scene (535px, 289px)
      Scene (535px, 289px)
      Scene (535px, 289px)
      Scene (535px, 289px)
```

0.1.3 The eFAST method

eFAST method allows the estimation of first order and total Sobol indices in a more computationaly efficient way.

```
eFAST_ = Pumas.gsa(model, sub_s, p, GlobalSensitivity.eFAST(), [:cmax,:auc],
p_range_low, p_range_high, n=1000, obstimes=0.0:1.0:30.0)

eFAST Sensitivity Analysis

First Order Indices
2×5 DataFrame
 Row   dv_name  fperm     s_lumen     ITT          MPPGI
       Any      Float64   Float64     Float64      Float64


   1   cmax     0.514625  1.87655e-7  0.000242629  0.445391
   2   auc      0.561104  3.74151e-7  0.000215824  0.395535

Total Order Indices
2×5 DataFrame
 Row   dv_name  fperm     s_lumen     ITT         MPPGI
       Any      Float64   Float64     Float64     Float64

   1   cmax     0.553051  0.0017257   0.00184638  0.470818
   2   auc      0.603181  0.00182715  0.001919    0.42781
```

We can use scatter plot the result to visualize the result.

```
keys_ = keys(p_range_low)
cmax_s1 = [eFAST_.first_order[1,:][key] for key in keys_]
cmax_st = [eFAST_.total_order[1,:][key] for key in keys_]

fig = Figure(resolution = (1200,800))
plot_cmax_s1 = scatter(fig[1,1], 1:4, cmax_s1, axis = (yticks = 0:1, xticks = (1:4,
[string.(keys_)...]), label = "First Order", title="Cmax"))
plot_cmax_st = scatter(fig[1,2], 1:4, cmax_st, axis = (yticks = 0:1, xticks = (1:4,
[string.(keys_)...]), label = "Total Order"), marker=:utriangle)

auc_s1 = [eFAST_.first_order[2,:][key] for key in keys_]
auc_st = [eFAST_.total_order[2,:][key] for key in keys_]

plot_auc_s1 = scatter(fig[2,1], 1:4, auc_s1, axis = (yticks = 0:1, xticks = (1:4,
[string.(keys_)...]), label = "First Order", title="AUC"))
plot_auc_st = scatter(fig[2,2], 1:4, auc_st, axis = (yticks = 0:1, xticks = (1:4,
[string.(keys_)...]), label = "Total Order"), marker=:utriangle)
display(fig)

Scene (1200px, 800px):
  72 Plots:
      AbstractPlotting.Poly{Tuple{Vector{Vector{GeometryBasics.Point{2, Flo
at32}}}}}
      AbstractPlotting.LineSegments{Tuple{Vector{GeometryBasics.Point{2, Fl
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oat32}}}}
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oat32}}}}
      AbstractPlotting.LineSegments{Tuple{Vector{GeometryBasics.Point{2, Fl
oat32}}}}
      AbstractPlotting.LineSegments{Tuple{Vector{GeometryBasics.Point{2, Fl
oat32}}}}
      AbstractPlotting.Annotations{Tuple{Vector{Tuple{String, GeometryBasic
s.Point{2, Float32}}}}}
      AbstractPlotting.Text{Tuple{String}}
      AbstractPlotting.Lines{Tuple{Vector{GeometryBasics.Point{2, Float32}}
}}
      AbstractPlotting.LineSegments{Tuple{Vector{GeometryBasics.Point{2, Fl
oat32}}}}
      AbstractPlotting.LineSegments{Tuple{Vector{GeometryBasics.Point{2, Fl
oat32}}}}
      AbstractPlotting.Annotations{Tuple{Vector{Tuple{String, GeometryBasic
s.Point{2, Float32}}}}}
      AbstractPlotting.Text{Tuple{String}}
      AbstractPlotting.Lines{Tuple{Vector{GeometryBasics.Point{2, Float32}}
}}
      AbstractPlotting.Lines{Tuple{Vector{GeometryBasics.Point{2, Float32}}
}}
      AbstractPlotting.Lines{Tuple{Vector{GeometryBasics.Point{2, Float32}}
}}
      AbstractPlotting.Text{Tuple{String}}
  4 Child Scenes:
```

```
Scene (535px, 289px)
Scene (535px, 289px)
Scene (535px, 289px)
Scene (535px, 289px)
```

0.2 Conclusion

We observe for both AUC and Cmax `fperm` and `MPPGI` show high values for both First and Total Order indices of Sobol whereas `s_lumen` and `ITT` have no effect at all and show a value of zero for the indices.