

# PBPK in PuMaS, A Model for ACAT

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6th November 2018

## 1 Introduction

## 2 Code

```
using PuMaS, LinearAlgebra, DiffEqSensitivity, Distributions, Optim, QuadGK

pbpkmodel = @model begin
    @param begin
        GER ∈ ConstDomain(0.066)
        ρ ∈ ConstDomain(5e-6)
        r ∈ ConstDomain(1)
        T ∈ ConstDomain(3e-5)
        d ∈ ConstDomain(1e-4)
        SST ∈ ConstDomain(5.5)
        kilST ∈ ConstDomain(0.5)
        kaST ∈ ConstDomain(14040.00076)
        kaGU ∈ ConstDomain(14040.000063)
        kt ∈ ConstDomain(0.035)
        SGU1 ∈ ConstDomain(5.5)
        SGU2 ∈ ConstDomain(5.5)
        SGU3 ∈ ConstDomain(5.5)
        SGU4 ∈ ConstDomain(5.5)
        SGU5 ∈ ConstDomain(5.5)
        SGU6 ∈ ConstDomain(5.5)
        SGU7 ∈ ConstDomain(5.5)
        kilGU1 ∈ ConstDomain(0.5 )
        kilGU2 ∈ ConstDomain(0.5)
        kilGU3 ∈ ConstDomain(0.5)
        kilGU4 ∈ ConstDomain(0.5)
        kilGU5 ∈ ConstDomain(0.5)
        kilGU6 ∈ ConstDomain(0.5)
        kilGU7 ∈ ConstDomain(0.5)
        EHR ∈ ConstDomain(0 )
        kbi1 ∈ ConstDomain(0.0)
        VLI ∈ ConstDomain(1690)
        Kp ∈ ConstDomain(1.3)
        ktCO ∈ ConstDomain(0.0007)
        SCO ∈ ConstDomain(5.5)
        VCO ∈ ConstDomain(700)
        kilCO ∈ ConstDomain(0.0007)
        kaCO ∈ ConstDomain(14040.0000542)
        CP ∈ ConstDomain(0)
        QLU ∈ ConstDomain(5233)
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VLU ∈ ConstDomain(1172)
VST1 ∈ ConstDomain(50)
VST2 ∈ ConstDomain(154)
VGU ∈ ConstDomain(1650)
VAR ∈ ConstDomain(1698)
AIR ∈ ConstDomain(0.0)
VVE ∈ ConstDomain(3396)
VIR ∈ ConstDomain(0.0)
QBR ∈ ConstDomain(700)
VBR ∈ ConstDomain(1450)
QLI ∈ ConstDomain(1650)
QKI ∈ ConstDomain(1100)
QHR ∈ ConstDomain(150)
VHR ∈ ConstDomain(310)
QMU ∈ ConstDomain(750)
VMU ∈ ConstDomain(35000)
QAD ∈ ConstDomain(260)
VAD ∈ ConstDomain(10000)
QSK ∈ ConstDomain(300)
VSK ∈ ConstDomain(7800)
QBO ∈ ConstDomain(250)
VBO ∈ ConstDomain(4579)
QTH ∈ ConstDomain(80)
VTH ∈ ConstDomain(29)
QST ∈ ConstDomain(38)
QGU ∈ ConstDomain(1100)
Ker ∈ ConstDomain(0.0)
QPA ∈ ConstDomain(133)
VPA ∈ ConstDomain(77)
QSP ∈ ConstDomain(77)
VSP ∈ ConstDomain(192)
CLint ∈ ConstDomain(0)
QHA ∈ ConstDomain(302)
VKI ∈ ConstDomain(280)
R ∈ ConstDomain(1)
end

@random begin
  η ~ MvNormal(Matrix(1.0I,2,2))
end

@dynamics begin
  #Absorption compartments
  #Stomach compartment
  AUNDST' = -GER * AUNDST - (((3*d)/(ρ*r*T)) * AUNDST*(SST - (ADIST/VST1)))
  ADIST' = -GER * ADIST + (((3*d)/(ρ*r*T)) * AUNDST*(SST - (ADIST/VST1))) - kilST*
ADIST -kaST *ADIST
  ADEGST' = -GER * ADEGST + kilST * ADIST
  AABSST' = kaST * ADIST

  #GU1 small intestinal compartment
  AUNDGU1' = GER * AUNDST - kt * AUNDGU1 - (((3*d)/(ρ*r*T)) * AUNDGU1 *(SGU1 -
(ADISGU1/VGU))
  ADISGU1' = GER * ADIST - kt * ADISGU1 + (((3*d)/(ρ*r*T)) * AUNDGU1 *(SGU1 -
(ADISGU1/VGU)) - kilGU1*ADISGU1 - kaGU*ADISGU1 + (EHR*kbi1*CLI *VLI)/( Kp)
  ADEGGU1' = GER * ADEGST - kt * ADEGGU1 + kilGU1 * ADISGU1
  AABSGU1' = kaGU * ADISGU1

  # Other small intestinal compartments (GU2-GU7)

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AUNDGU2' = kt * AUNDGU1 - kt * AUNDGU2 - ((3*d)/(ρ*r*T)) * AUNDGU2 * (SGU2 -
(ADISGU2/VGU))
ADISGU2' = kt * ADISGU1 - kt * ADISGU2 + ((3*d)/(ρ*r*T)) * AUNDGU2 * (SGU2 -
(ADISGU2/VGU)) - kilGU2*ADISGU2 - kaGU*ADISGU2
ADEGGU2' = kt*ADEGGU1 - kt*ADEGGU2 + kilGU2 * ADISGU2
AABSGU2' = kaGU * ADISGU2

AUNDGU3' = kt * AUNDGU2 - kt * AUNDGU3 - ((3*d)/(ρ*r*T)) * AUNDGU3 * (SGU3 -
(ADISGU3/VGU))
ADISGU3' = kt * ADISGU2 - kt * ADISGU3 + ((3*d)/(ρ*r*T)) * AUNDGU3 * (SGU3 -
(ADISGU3/VGU)) - kilGU3*ADISGU3 - kaGU*ADISGU3
ADEGGU3' = kt*ADEGGU2 - kt*ADEGGU3 + kilGU3 * ADISGU3
AABSGU3' = kaGU * ADISGU3

AUNDGU4' = kt * AUNDGU3 - kt * AUNDGU4 - ((3*d)/(ρ*r*T)) * AUNDGU4 * (SGU4 -
(ADISGU4/VGU))
ADISGU4' = kt * ADISGU3 - kt * ADISGU4 + ((3*d)/(ρ*r*T)) * AUNDGU4 * (SGU4 -
(ADISGU4/VGU)) - kilGU4*ADISGU4 - kaGU*ADISGU4
ADEGGU4' = kt*ADEGGU3 - kt*ADEGGU4 + kilGU4 * ADISGU4
AABSGU4' = kaGU * ADISGU4

AUNDGU5' = kt * AUNDGU4 - kt * AUNDGU5 - ((3*d)/(ρ*r*T)) * AUNDGU5 * (SGU5 -
(ADISGU5/VGU))
ADISGU5' = kt * ADISGU4 - kt * ADISGU5 + ((3*d)/(ρ*r*T)) * AUNDGU5 * (SGU5 -
(ADISGU5/VGU)) - kilGU5*ADISGU5 - kaGU*ADISGU5
ADEGGU5' = kt*ADEGGU4 - kt*ADEGGU5 + kilGU5 * ADISGU5
AABSGU5' = kaGU * ADISGU5

AUNDGU6' = kt * AUNDGU5 - kt * AUNDGU6 - ((3*d)/(ρ*r*T)) * AUNDGU6 * (SGU6 -
(ADISGU6/VGU))
ADISGU6' = kt * ADISGU5 - kt * ADISGU6 + ((3*d)/(ρ*r*T)) * AUNDGU6 * (SGU6 -
(ADISGU6/VGU)) - kilGU6*ADISGU6 - kaGU*ADISGU6
ADEGGU6' = kt*ADEGGU5 - kt*ADEGGU6 + kilGU6 * ADISGU6
AABSGU6' = kaGU * ADISGU6

AUNDGU7' = kt * AUNDGU6 - kt * AUNDGU7 - ((3*d)/(ρ*r*T)) * AUNDGU7 * (SGU7 -
(ADISGU7/VGU))
ADISGU7' = kt * ADISGU6 - kt * ADISGU7 + ((3*d)/(ρ*r*T)) * AUNDGU7 * (SGU7 -
(ADISGU7/VGU)) - kilGU7*ADISGU7 - kaGU*ADISGU7
ADEGGU7' = kt*ADEGGU6 - kt*ADEGGU7 + kilGU7 * ADISGU7
AABSGU7' = kaGU * ADISGU7

# Colon compartment
AUNDCO' = kt * AUNDGU7 - ktCO * AUNDCO - ((3*d)/(ρ*r*T)) * AUNDCO * (SCO -
(ADISCO/VC0))
ADISCO' = kt * ADISGU7 - kt * ADISCO + ((3*d)/(ρ*r*T)) * AUNDCO * (SCO -
(ADISCO/VC0)) - kilCO*ADISCO - kaCO*ADISCO + (CP*CLI*VLI*kbil)/(Kp)
ADEGCO' = kt * ADEGGU7 - ktCO * ADEGGU7 + kilCO * ADISCO
AABSCO' = kaCO * ADISGU7

#Total intestinal absorption (IA)
AIA' = kaGU*ADISGU1 + kaGU*ADISGU2 + kaGU*ADISGU3 + kaGU*ADISGU4 + kaGU*ADISGU5
+ kaGU*ADISGU6 + kaGU*ADISGU7

#Somatic Compartments
# Lungs
CLU' = (QLU/VLU) * (CVE - (CLU*R)/(Kp))

#Arterial blood (AR)

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CAR' = (1/VAR) * (QLU*(((CLU*R)/(Kp)) -CAR) + AIR)

# Venous blood (VE)
CVE' = (1/VVE) * (((QBR *CBR*R)/( Kp)) + ((QLI *CLI*R)/( Kp)) + ((QKI *CKI*R)/(
Kp)) + ((QHR *CHR*R)/( Kp)) + ((QMU *CMU*R)/( Kp)) + ((QAD *CAD*R)/( Kp)) + ((QSK
*CSK*R)/( Kp)) + ((QBO *CBO*R)/( Kp)) +((QTH *CTH*R)/( Kp)) - QLU * CVE + VIR)

#Brain
CBR' = (QBR/VBR)* (CAR - (CBR*R)/( Kp))
#Heart
CHR' = (QHR/VHR)* (CAR - (CHR*R)/( Kp))
#Muscle
CMU' = (QMU/VMU)* (CAR - (CMU*R)/( Kp))
#Adipose
CAD' = (QAD/VAD)* (CAR - (CAD*R)/( Kp))
#Skin
CSK' = (QSK/VSK)* (CAR - (CSK*R)/( Kp))
#Bone
CBO' = (QBO/VBO)* (CAR - (CBO*R)/( Kp))
#Thymus
CTH' = (QTH/VTH)* (CAR - (CTH*R)/( Kp))
#Pancreas
CPA' = (QPA/VPA)* (CAR - (CPA*R)/( Kp))
#Spleen
CSP' = (QSP/VSP)* (CAR - (CSP*R)/( Kp))

#Stomach
CST' = (1/VST2) * (QST*(CAR - ((CST*R)/(Kp))) + AABSST)
#Gut
CGU' = (1/VGU) * (QGU*(CAR - ((CGU*R)/(Kp))) + AIA)
#Kidney
CKI' = ((1/VKI) * QKI*(CAR - ((CKI*R)/(Kp)))) - ((CKI*Ker)/Kp)
#Liver
CLI' = (1/VLI)*(QHA*CAR + ((QGU *CGU*R)/( Kp)) + ((QPA *CPA*R)/( Kp)) + ((QSP
*CSP*R)/( Kp)) + ((QST *CST*R)/( Kp)) - ((QLI *CLI*R)/( Kp)) - (CLI*CLint)/Kp )
end
end

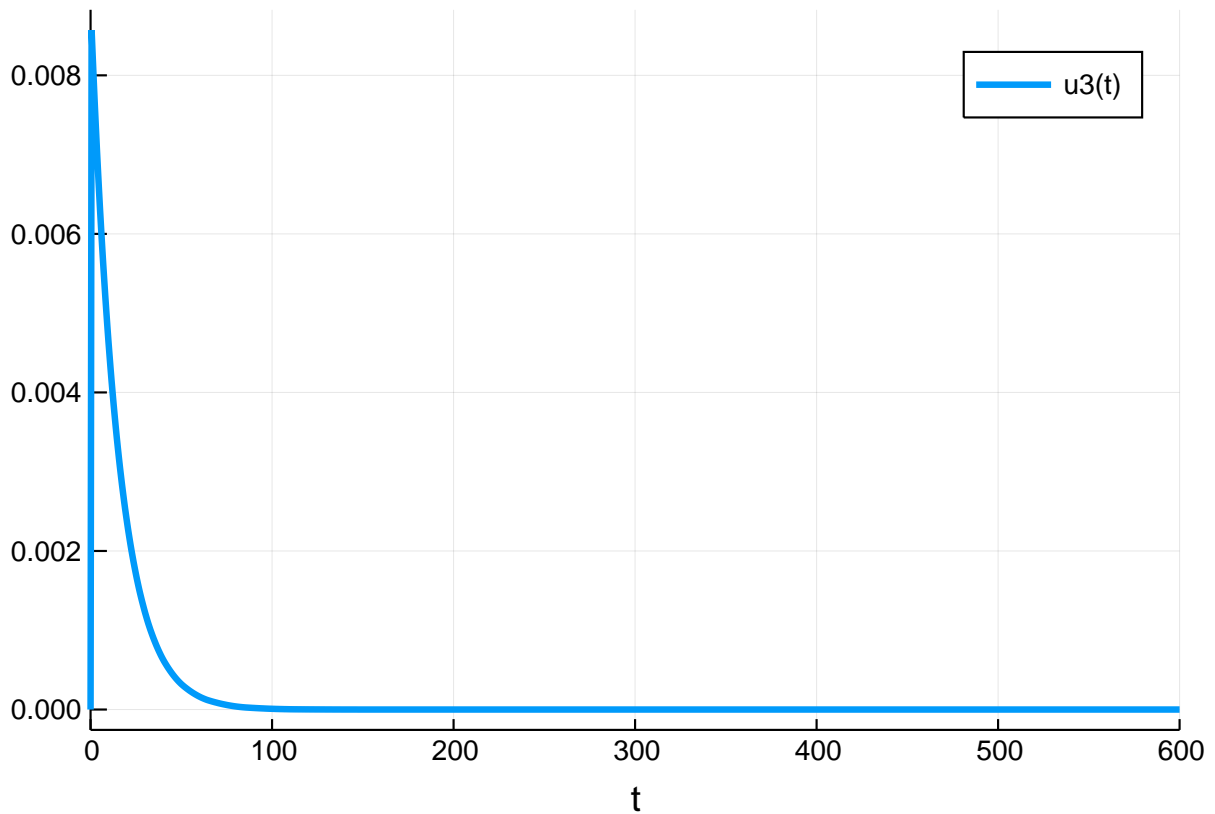
subject = Subject(evs = DosageRegimen(250,cmt=[1],time=[0.0]))
param = (GER = 0.066,ρ = 5e-6,r = 1,T = 3e-5,d = 1e-4,SST = 5.5,kilST = 0.5,kaST =
14040.00076,kaGU = 14040.000063,kt = 0.035,SGU1 = 5.5,SGU2 = 5.5,SGU3 = 5.5,SGU4 =
5.5,SGU5 = 5.5,SGU6 = 5.5,SGU7 = 5.5,kilGU1 = 0.0 ,kilGU2 = 0.0,kilGU3 = 0.0,kilGU4
= 0.0,kilGU5 = 0.0,kilGU6 = 0.0,kilGU7 = 0.0,EHR = 0 ,
kbil = 0.0,VLI = 1690,Kp = 1.3,ktCO = 0.0007,SCO = 5.5,VCO = 700,kilCO =
0.0007,kaCO = 14040.0000542,CP = 0,QLU = 5233,VLU = 1172,VST1 = 50,VST2 = 154,VGU =
1650,VAR = 1698,AIR = 0.0,VVE = 3396,VIR = 0.0,QBR = 700,VBR = 1450,QLI = 1650,QKI =
1100,QHR = 150,VHR = 310,QMU = 750,VMU = 35000,QAD = 260,
VAD = 10000,QSK = 300,VSK = 7800,QBO = 250,VBO = 4579,QTH = 80,VTH = 29,QST =
38,QGU = 1100,Ker = 10.0,QPA = 133,VPA = 77,QSP = 77,VSP = 192,CLint = 0.315,QHA =
302,VKI = 280,R = 1)

y0 = (η = [0.0,0.0])

sol_diffeq = solve(pbpkmodel,subject,param,y0,tspan=(0.0,600.0),progress=true)

using Plots
plot(sol_diffeq,vars=3)

```



### 3 Global Sensitivity Analysis

```
function sensivity_func(pars)
    y0 = ( $\eta$  = [0.0,0.0])
    sim = solve(pbpkmodel,subject,pars,y0,tspan=(0.0,600.0))
    f = t -> -sim(t;idxs=3)
    res = optimize(f,0.0,600.0,Brent())
    i,e = quadgk(f,0.0,600.0)
    [-Optim.minimum(res),-250/i]
end

a = []
for i in param
    if i != 0
        push!(a,[i-0.05*i,i+ 0.05*i])
    else
        push!(a,[0.0,1e-4])
    end
end

using Random
Random.seed!(5)
m = DiffEqSensitivity.morris_sensitivity(
    sensivity_func,a,[10 for i in 1:70];
    relative_scale=false,len_trajectory=75,
    total_num_trajectory=50,num_trajectory=20)
```