

Model code

Model S1: Gunn Rat KroneckerBio Model File

```
## UGT1A1 Model ##

#####

% Compartments UGT1A1 Model

Plasma 3 0.0078 # (L) Volume of the central compartment

#####

#####

% States Plasma

#Name      SeedName(=Multiplier)
LNP        LNP_0=0.0078
LNPP       LNPP_0=0.0078
LNPa       LNPa_0=0.0078
LNPe       LNPe_0=0.0078
mRNAC      mRNAC_0=0.0078
UGTc       UGTc_0=0.0078
Bil        Bil_0=0.0078
MGT        MGT_0=0.0078
DGT        DGT_0=0.0078
sBil       sBil_0=0.0078
Bil:UGTc   Bil:UGTc_0=0.0078

% Outputs

#PlasmaDrug      LNP
#ConjugatedBilirubin  MGT DGT
#UnconjugatedBilirubin Bil
#mRNA            mRNAC
#UGTc            UGTc
TotalBilirubin   Bil MGT DGT
```

```

PlasmaDrug      LNP
mRNA            mRNAc LNPa LNPe
Enzyme          UGTc  Bil:UGTc
cytomRNA       mRNAc

% Inputs Plasma
running         0

#####

% Parameters
kw              1e-5
k12             1e-5
k21             1e-5
ka              1e-5
ke              1e-5
de              1e-5
kl              1e-5
dmRNA          1e-5
kt              1e-5
ktbg            1e-5
dUGTc          1e-5
kcat            1e-5
kclearBil      1e-5
kclearMGT      1e-5
kclearDGT      1e-5
kelSbil        1e-5
ksyn            1e-5
ksynhigh       1e-5
kon             1e-5
koff            1e-5

#####

% Seeds
#Name          Value

```

```

LNP_0      0
LNPP_0     0
LNPa_0     0
LNPe_0     0
mRNAC_0    0
UGTc_0     0
Bil_0      0
MGT_0      0
DGT_0      0
sBil_0     1
Bil:UGTc_0 0

```

```
#####
```

```
% Reactions Plasma
```

```

LNP      0      0      0      kw      0      "(1) 1st order elimination"
LNP      0      LNPP      0      k12      k21      "(1) distribution"
LNPP      0      0      0      kw      0      "(1) 1st order elimination"
LNP      0      LNPa      0      ka      0      "(2) Attachment"
LNPa      0      LNPe      0      ke      0      "(3) endocytosis"
LNPe      0      0      0      de      0      "(4) fails to escape from endosome"
LNPe      0      mRNAC      0      kl      0      "(5) escape from endosome"
mRNAC      0      0      0      dmRNA      0      "(7) mRNA degrades"
0      0      0      UGTc      ktbg      0      "(8) endogenous translation"
mRNAC      0      mRNAC      UGTc      kt      0      "(9) translation"
UGTc      0      0      0      dUGTc      0      "(10) Cytoplasmic protein degrades"
Bil:UGTc      0      Bil      0      dUGTc      0      "(10) Cytoplasmic protein degrades"
UGTc      Bil      Bil:UGTc      0      kon      koff      "(11) Glucuronididation"
Bil:UGTc      0      UGTc      MGT      kcat      0      "(12) Gluronididation"
UGTc      MGT      UGTc      DGT      kcat      0      "(13) Gluronididation"
0      0      Bil      0      ksyn      0      "(14) Production of Bilirubin"
sBil      0      Bil      sBil      ksynhigh      0      "(15) High Production of Bilirubin"
sBil      running 0      0      kelSbil      0      "(16) Production of Bilirubin"
Bil      0      0      0      kclearBil      0      "(17) Elimination of Bilirubin"
MGT      0      0      0      kclearMGT      0      "(18) Elimination of Monglucouronide"
DGT      0      0      0      kclearDGT      0      "(19) Elimination of Diglucouronide"

```


Supplemental Model 2 CNI Human KroneckerBio Model File

```
## UGT1A1 Model ##

#####

% Compartments UGT1A1 Model
Plasma 3 3.0 # (L) Volume of the central compartment

#####

#####

% States Plasma

#Name      SeedName(=Multiplier)
LNP        LNP_0=3.0
LNPP       LNPP_0=3.0
LNPa       LNPa_0=3.0
LNPe       LNPe_0=3.0
mRNAC      mRNAC_0=3.0
UGTc       UGTc_0=3.0
Bil        Bil_0=3.0
MGT        MGT_0=3.0
DGT        DGT_0=3.0
sBil       sBil_0=3.0
Bil:UGTc   Bil:UGTc_0=3.0
ADA        ADA_0=3.0

% Outputs

#PlasmaDrug      LNP
#ConjugatedBilirubin  MGT DGT
#UnconjugatedBilirubin  Bil
#mRNA             mRNAC
#UGTc            UGTc
TotalBilirubin    Bil MGT DGT
PlasmaDrug        LNP
mRNA              mRNAC LNPa LNPe
```

```

Enzyme          UGTc  Bil:UGTc
cytomRNA        mRNAc
LNPa            LNPa

% Inputs Plasma
ksynhigh        1e-5
ksyn            1e-5
kada            0

#####

% Parameters
kw              1e-5
k12             1e-5
k21             1e-5
ka              1e-5
ke              1e-5
de              1e-5
k1              1e-5
dmRNA           1e-5
kt              1e-5
ktbg            1e-5
dUGTc           1e-5
kcat            1e-5
kclearBil       1e-5
kclearMGT       1e-5
kclearDGT       1e-5
kelSbil         1e-5
kon             1e-5
koff            1e-5
ktemp           1
ktemp2          1
ktemp3          1
kada_deg        1e-5

#####

```

```

% Seeds

#Name      Value
LNP_0      0
LNPP_0     0
LNPa_0     0
LNPe_0     0
mRNAc_0    0
UGTc_0     0
Bil_0      0
MGT_0      0
DGT_0      0
sBil_0     0
Bil:UGTc_0 0
ADA_0      0

#####

% Reactions Plasma

LNP      0      0      0      kw      0      "(1) 1st order elimination"
LNP      0      LNPP    0      k12     k21    "(1) distribution"
LNPP     0      0      0      kw      0      "(1) 1st order elimination"
LNP      0      LNPa    0      ka      0      "(2) Attachment"
LNPa     0      LNPe    0      ke      0      "(3) endocytosis"
LNPe     0      0      0      de      0      "(4) fails to escape from endosome"
LNPe     0      mRNAc   0      kl      0      "(5) escape from endosome"
mRNAc    0      0      0      dmRNA   0      "(7) mRNA degrades"
0         0      0      UGTc    ktbg    0      "(8) endogenous translation"
mRNAc    0      mRNAc   UGTc    kt      0      "(9) translation"
UGTc     0      0      0      dUGTc   0      "(10) Cytoplasmic protein degrades"
Bil:UGTc 0      Bil      0      dUGTc   0      "(10) Cytoplasmic protein degrades"
UGTc     Bil    Bil:UGTc 0      kon     koff   "(11) Glucuronididation"
Bil:UGTc 0      UGTc     MGT     kcat    0      "(12) Gluronididation"

UGTc     MGT    UGTc:MGT 0      kon     koff   "(13) Gluronididation"
UGTc:MGT 0      UGTc     DGT     kcat    0      "(13) Gluronididation"

ksyn     0      Bil      0      ktemp   0      "(14) Production of Bilirubin"
sBil     0      Bil      0      kelSbil 0      "(15) High Production of Bilirubin"

```

0	ksynhigh	sBil	0	ktemp2	0	"(15) High Production of Bilirubin"
Bil	0	0	0	kclearBil	0	"(17) Elimination of Bilirubin"
MGT	0	0	0	kclearMGT	0	"(18) Elimination of Monglucouronide"
DGT	0	0	0	kclearDGT	0	"(19) Elimination of Diglucouronide"
kada	0	ADA	0	ktemp3	0	"(20) ramping up of accelerated ... clearance (called ADA here but could be something else"
ADA	LNP	0	0	kada_deg	0	"(21) ADA binding to LNP and immediately degrading complex"