Model code

Model S1: Gunn Rat KroneckerBio Model File

```
## UGTA1A Model ##


#############################################################################

% Compartments UGTA1A Model

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


#############################################################################



#############################################################################

% States Plasma

#Name       SeedName(=Multiplyer)

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 CN1 Human KroneckerBio Model File

```
## UGTA1A Model ##


################################################################################
% Compartments UGTA1A Model
Plasma  3   3.0 # (L) Volume of the central compartment


################################################################################



################################################################################
% States Plasma
#Name       SeedName(=Multiplyer)
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

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

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"
```