Model equations for metformin

Central plasma compartment

$V_{plasma} * dC_{plasma}/dt = Q_{h,p}*C_{EH,p,,5}+Q_{r,p,6}*C_{CD,p}+k_{out}*V_{erythro}*C_{erythro} - Q_{h,p}*C_{plasma} - Q_{r,p}*C_{plasma} -$

$Q_{muscle,p}*(C_{plasma} - C_{muscle,p}/K_{p,muscle}) -$

$Q_{skin,p}*(C_{plasma}-C_{skin,p}/K_{p,skin})-Q_{adipose,p}*(C_{plasma}-C_{adipose,p}/K_{p,adipose})-k_{in}*V_{plasma}*C_{plasma})$

Central erythrocyte compartment

$V_{erythro} * dC_{erythro}/dt$

$=Q_{h,e}*C_{EH,e,5}+Q_{r,e,6}*C_{CD,e}+k_{in}*V_{plasma}*C_{plasma}-Q_{h,e}*C_{EH,e,1}-Q_{re}*C_{erythro}-Q_{muscle,e}*(C_{erythro}-C_{muscle,e})$

$-Q_{skin,e}*(C_{plasma}-C_{skin,e})-Q_{adipose,e}*(C_{plasma}-C_{adipose,e})-k_{out}*V_{erythro}*C_{erythro})$

Distribution compartments

$V_{muscle,p} * dtC_{muscle,p}/dt = (Q_{muscle,p}*C_{plasma} + k_{out}*V_{muscle,e}*C_{muscle,e} - k_{in}*V_{musle,p}*C_{muscle,p}/K_{p,muscle}$

$– Q_{muscle,p}*C_{muscle,p}/K_{p,muscle})$

$V_{muscle,e} * dtC_{muscle,e}/dt = (Q_{muscle,e}*C_{erythro} + k_{in}*V_{muscle,p}*C_{muscle,p}/K_{p,muscle} – k_{out}*V_{musle,e}*C_{muscle,e}$

$- Q_{muscle,e}*C_{muscle,e})$

$V_{skin,p} * dtC_{skin,p}/dt = (Q_{skin,p}*C_{plasma} + k_{out}*V_{skin,e}*C_{skin,e} - k_{in}*V_{skin,p}*C_{skin,p}/K_{p,skin} -$

$Q_{skin,p}*C_{skin,p}/K_{p,skin})$

$V_{skin,e} * dtC_{skin,e}/dt = (Q_{skin,e}*C_{erythro} + k_{in}*V_{skin,p}*C_{skin,p}/K_{p,skin} - k_{out}*V_{skin,e}*C_{skin,e} - Q_{skin,e}*C_{skin,e})$

$V_{adipose,p} * dtC_{adipose,p}/dt = (Q_{adipose,p}*C_{plasma} + k_{out}*V_{adipose,e}*C_{adipose,e} -$

$k_{in}*V_{adipose,p}*C_{adipose,p}/K_{p,adipose} - Q_{adipose,p}*C_{adipose,p}/K_{p,adipose})$

$V_{adipose,e} * dtC_{adipose,e}/dt = (Q_{adipose,e}*C_{erythro} + k_{in}*V_{adipose,p}*C_{adipose,p}/K_{p,adipose} -$

$k_{out}*V_{adipose,e}*C_{adipose,e} - Q_{adipose,e}*C_{adipose,e})$

Intestinal compartments (i=1~3)

$dX_{intestine,1} / dt = k_{trans} * X_{transit} - ka*X_{intestine,1} - ka*(1-FaFg)^{1/3}/(1-(1-FaFg)^{1/3})*X_{intestine,1}$

$dX_{intestine,2} / dt = ka*(1-FaFg)^{1/3}/(1-(1-FaFg)^{1/3})*X_{intestine,1} - ka*X_{intestine,2} -$

$ka*(1-FaFg)^{1/3}/(1-(1-FaFg)^{1/3})*X_{intestine,2}$

$dX_{intestine,3} / dt = ka*(1-FaFg)^{1/3}/(1-(1-FaFg)^{1/3})*X_{intestine,2} - ka*X_{intestine,3} -$

$ka*(1-FaFg)^{1/3}/(1-(1-FaFg)^{1/3})*X_{intestine,3}$

Transit compartment

$$dX_{transit} / dt = - k_{trans} * X_{transit}$$

Extracellular hepatic compartments of metformin without the coadministration of inhibitors (i = 1~5)

$$(V_{EH,p} /5) * dC_{EH,p,i} / dt = ka * (X_{intestine,1}+ X_{intestine,2}+ X_{intestine,3}) + Q_{h,p} * (C_{plasma} - C_{EH,p,i}) + k_{out}*(V_{EH,e}/5)*C_{EH,e,I} + fh * (PS_{dif,eff} /5) * C_{HC,i} - (V_{max\_met\_OCT1}*(C_{EH,p,i}/(K_{m\_met\_OCT1} + C_{EH,p,i}) – C_{HC,i} *e^{Nh}/R_{OCT1,inf/eff}/(K_{m\_met\_OCT1}+ C_{HC,i}))/5 – fu*(PS_{dif,inf} /5)*C_{EH,p,i} - k_{in}*(V_{EH,p,i} /5)*C_{EH,p,i}; (i = 1)$$

$$(V_{EH,p} /5) * dC_{EH,p,i} / dt = Q_{h,p} * (C_{plasma} - C_{EH,p,i}) + k_{out}*(V_{EH,e}/5)*C_{EH,e,i} + fh * (PS_{dif,eff} / 5) * C_{HC,i} - (V_{max\_met\_OCT1}*(C_{EH,p,i}/(K_{m\_met\_OCT1} + C_{EH,p,i}) - C_{HC,i} *e^{Nh}/R_{OCT1,inf/eff}/(K_{m\_met\_OCT1}+ C_{HC,i}))/5 – fu*(PS_{dif,inf} /5) * C_{EH,p,i} - k_{in}*(V_{EH,p,i} /5)*C_{EH,p,i}; (i = 2~5)$$

$$(V_{EH,e} /5) * dC_{EH,p,i} / dt = Q_{he} * (C_{erythro} - C_{EH,e,i}) + k_{in}*(V_{EH,p,i} /5)*C_{EH,p,i} - k_{out}*(V_{EH,e}/5)*C_{EH,e,i}; (i=1~5)$$

Hepatocyte compartments of metformin without the coadministration of inhibitors (i = 1~5)

$(V_{HC,i}/5) * dC_{HC,i}/dt = (V_{max\_met\_OCT1} * (C_{EH,p,i}/(K_{m\_met\_OCT1} + C_{EH,p,i}) - C_{HC,i} * e^{Nh}/R_{OCT1,inf/eff}/(K_{m\_met\_OCT1} + C_{HC,i}))/5 + fu*(PS_{dif,inf}/5)*C_{EH,p,i} - fh*(PS_{dif,eff}/5)*C_{HC,i} - fh*CL_{int,met}*C_{HC,i}$; (i=1~5)

Extra glomerulus compartment

$V_{G,p}*dC_{G,p}/dt = Q_{r,p}*C_{plasma} + k_{out}*V_{G,e}*C_{G,e} - Q_{r,p,1}*C_{G,p} - Q_{u1}*C_{G,p} - k_{in}*V_{G,p}*C_{G,p}$

$V_{G,e}*dC_{G,e/}dt = Q_{r,e}*C_{erythro} + k_{in}*V_{G,p}*C_{G,p} - Q_{r,e,1}*C_{G,e} - k_{out}*V_{G,e}*C_{G,e}$

Glomerulus compartment

$V_{G,u}*dC_{G,u}/dt = Q_{GFR}*(fu*C_{G,p} - C_{G,u}))$

Kidney: Proximal tubule <u>(i=1~3)</u>

$$(V_{PT,p}/3)^* dC_{PT,p,1}/dt = Q_{r,p,1}*C_{G,p} + fc*1/3*PS_{r,PT,difeff}*C_{PT,cell,1} + k_{out}*(V_{PT,e}/3)*C_{PT,e,1} - fb*1/3*V_{max\_OCT2}*(C_{PT,p,1}/(K_{m\_OCT2} + C_{PT,p,1}) – C_{PT,cell,1}*exp(Nvpt)/R_{OCT2,inf/eff}/(K_{m\_OCT2} + C_{PT,cell,1})) - fb*1/3*PS_{r,PT,difinf}*C_{PT,r,1} – Q_{r,p,2}*C_{PT,p,r,1} - k_{in}*(V_{PT,p}/3)*C_{PT,p,1}$$

$$(V_{PT,e}/3)*dC_{PT,e,1}/dt = Q_{r,e,1}*C_{G,e} + k_{in}*(V_{PT,p}/3)*C_{PT,p,1} – Q_{,r,e,2}*C_{PT,e,1} – k_{out}*(V_{PT,e}/3)*C_{PT,e,1}$$

$$(V_{PT,c}/3)*dC_{PT,cell,1}/dt = fb*1/3*V_{max\_OCT2}*(C_{PT,p,1}/(K_{m\_OCT2} + C_{PT,p,1}) – C_{PT,cell,1}*exp(Nvpt)/R_{OCT2,inf/eff}/(K_{m\_OCT2} + C_{PT,cell,1})) + fb*1/3*PS_{r,PT,difinf}*C_{PT,p,1} + fu*1/3*PS_{u,PT,difinf}*C_{PT,u,1} - fc*1/3*PS_{r,PT,difeff}*C_{PT,cell,1} - fc*1/3*(V_{max,MATE}/(K_{m,MATE} +C_{PT,cell,1}) + PS_{u,PT,difeff})*C_{PT,cell,1}$$

$$(V_{PT,u}/3)*dC_{PT,u,1}/dt = Q_{u1}*C_{PT,cell,1} + fc*1/3*(V_{max,MATE}/(K_{m,MATE} + C_{PT,cell,1}) + PS_{u,PT,difeff})*C_{PT,cell,1} - fu*1/3*PS_{u,PT,difinf}*C_{PT,u,1} - Q_{u2}*C_{PT,u,1}$$

(i=1)

$$(V_{PT,p}/3)*dC_{PT,p,i}/dt = Q_{r,p,i}*C_{PT,p,(i-1)} + fc*1/3*PS_{r,PT,difeff}*C_{PT,cell,i} + k_{out}*(V_{PT,e}/3)*C_{PT,e,i} - fb*1/3*V_{max\_OCT2}*(C_{PT,p,i}/(K_{m\_OCT2} + C_{PT,p,i}) – C_{PT,cell,i}*exp(Nvpt)/R_{OCT2,inf/eff}/(K_{m\_OCT2} + C_{PT,cell,i})) - fb*1/3*PS_{r,PT,difinf}*C_{PT,p,i} – Q_{r,p,(i+1)}*C_{PT,p,i} - k_{in}*(V_{PT,p}/3)*C_{PT,p,i}$$

$$(V_{PT,e}/3)*dC_{PT,e,i}/dt = Q_{,r,e,i}*C_{PT,e,(i-1)} + k_{in}*(V_{PT,p}/3)*C_{PT,p,i} – Q_{,r,e,2}*C_{PT,e,i} – k_{out}*(V_{PT,e}/3)*C_{PT,e,i}$$

$$(V_{PT,c}/3)*dC_{PT,cell,i}/dt = fb*1/3*V_{max\_OCT2}*(C_{PT,p,i}/(K_{m\_OCT2} + C_{PT,p,i}) - C_{PT,cell,i}*\exp(Nvpt)/R_{OCT2,inf/eff}/(K_{m\_OCT2} + C_{PT,cell,i})) + fb*1/3*PS_{r,PT,difinf}*C_{PT,p,i} + fu*1/3*PS_{u,PT,difinf}*C_{PT,u,i} - fc*1/3*PS_{r,PT,difeff}*C_{PT,cell,i} - fc*1/3*(V_{max,MATE}/(K_{m,MATE} +C_{PT,cell,i}) + PS_{u,PT,difeff})*C_{PT,cell,i}$$

$$(V_{PT,u}/3)*dC_{PT,u,i}/dt = Q_{u1}* C_{PT,cell,i} + fc*1/3*(V_{max,MATE}/(K_{m,MATE} + C_{PT,cell,i}) + PS_{u,PT,difeff})*C_{PT,cell,i} - fu*1/3*PS_{u,PT,difinf}*C_{PT,u,i} - Q_{u2}*C_{PT,u,i}$$

(i=2, 3)

Distal tubule compartment

$$V_{DT,p}*dC_{DT,p}/dt = Q_{r,p,4}*C_{PT,p,3} + fc*PS_{r,dt,difeff}*C_{DT,cell} + k_{out}*V_{DT,e}*C_{DT,e} - fb*PS_{r,DT,difinf}*C_{DT,p} - Q_{r,p,5}*C_{DT,p} - k_{in}*V_{DT,p}*C_{DT,p}$$

$$V_{DT,e}*dC_{DT,e}/dt = Q_{r,e,4}*C_{PT,e,3} + k_{in}*V_{DT,p}*C_{DT,p} – Q_{,r,e,5}*C_{DT,e} – k_{out}*V_{DT,e}*C_{DT,e}$$

$$V_{DT,cell}*dC_{DT,cell}/dt = fb*PS_{r,DT,difinf}*C_{dt,p} + fu*PS_{u,DT,difinf}*C_{DT,u} - fc*PS_{r,DT,difeff}*C_{DTt,cell} - fc*PS_{u,DTt,difeff}*C_{DT,cell}$$

$$V_{DT,u}*dC_{DT,u}/dt = Q_{u,4}*C_{PT,u,3} + fc*PS_{u,DT,difeff}*C_{DT,cell} - fu*PS_{u,DT,difinf}*C_{DT,u} - Q_{u,5}*C_{DT,u}$$

Collecting duct compartment

$V_{CD,p}*dC_{CD,p}/dt = Q_{r,p,5}*C_{dt,p} + fc*PS_{r,CD,difeff}*C_{CD,cell} + k_{out}*V_{CD,e}*C_{CD,e} - fb*PS_{r,CD,difinf}*C_{CD,p} -$

$Q_{r,p,6}*C_{CD,p} - k_{in}*V_{CD,p}*C_{CD,p}$

$M_{СВбу}*вC_{СВбу}.ве = Йб_{кбуб5}*C_{ВЕбу} + л_{шт}*M_{СВбз}*C_{СВбз} – Йб_{кбуб6}*C_{СВбу} – л_{щге}*M_{СВбу}*C_{СВбу}$

$V_{CD,cell}*dC_{CD,cell}/dt = fb*PS_{r,CD,difinf}*C_{CD,p} + fu*PS_{u,CD,difinf}*C_{CD,u} - fc*PS_{r,CD,difeff}*C_{CD,cell} -$

$fc*PS_{u,CD,difeff}*C_{CD,cell}$

$V_{CD,u}*dC_{CD,u}/dt = Q_{u,5}*C_{DT,u} + fc*PS_{u,CD,difeff}*C_{CD,cell} - fu*PS_{u,CD,difinf}*C_{CD,cell} - Q_{u,6}*C_{CD,u}$

Urine compartment

$dX_{urine}/dt = Q_{u,6}*C_{CD,u}$

Other equations

Plasma and erythrocyte flow in each compartment (t: compartment name)

$Q_{t,p} = Q_t*(1-He)$

$Q_{t,e} =Q_t*He$

$Q_{r,1} = Q_r - Q_{GFR}$

$Q_{r,2} = Q_{r,1} + (Q_{u,1}-Q_{u,2})$,

$Q_{r,3} = Q_{r,2} + (Q_{u,2}-Q_{u,3})$,

$Q_{r,4} = Q_{r,3} + (Q_{u,3}-Q_{u,4})$,

$Q_{r,5} = Q_{r,4} + (Q_{u,4}-Q_{u,5})$,

$Q_{r,6} = Q_r - Q_{u,6,}$

$V_{plasma} = (1-He)*V_{blood}$,

$V_{erythro} = He*V_{blood}$,

$V_{EH,p} = (1-He)*V_{EH}$,

$V_{EH,e} = He*V_{EH}$,

$V_{muscle,p} = (1-He)*(0.026+0.12)*V_{muscle} + 0.854*V_{muscle}$,

$V_{muscle,e} = He*(0.026+0.12)*V_{muscle}$,

$V_{skin,p} = (1-He)*(0.019+0.302)V_{skin}+0.679*V_{skin}$,

$V_{skin,e} = He*(0.019+0.302)*V_{skin}$,

$V_{adipose,p} = (1-He)*(0.01+0.135)*V_{adipose}+0.855*V_{adipose}$,

$V_{adipose,e} = He*(0.01+0.135)*V_{adipose}$,

$V_{r,p} = 0.30*(1-He)*V_{renal}$,

$V_{r,e} = 0.30*He*V_{renal}$

$V_{r,cell} = 0.24*Venal_r$,

$V_{r,urine} = 0.46*V_{renal}$,

$V_{G,p} = 5/129*V_{r,p}$,

$V_{PT,p} = 17/129*V_{r,p}$,

$V_{DT,p} = 11/129*V_{r,p}$,

$V_{CD,p} = 62/129*V_{r,p}$,

$V_{G,u} = 5/129*Vr_{,urine}$

$V_{PT,u} = 17/129*V_{r,urine}$

$V_{DT,u} = 11/129*V_{r,urine}$

$V_{CD,u} = 62/129*V_{r,urine}$

$V_{PT,cell} = 17/124*V_{r,cell}$,

$V_{DT,cell} = 11/124*V_{r,cell}$,

$V_{CD,cell} = 62/124*V_{r,cell}$,

$V_{G,e} = 5/129*V_{r,e}$,

$V_{PT,e} = 17/129*V_{r,e}$,

$V_{DT,e} = 11/129*V_{r,e}$,

$V_{CD,e}$ = 62/129*$V_{r,e}$,

Nh = z*Volt_h*F/(R*T),

ENh = exp(Nh),

Nupt=z*Volt_upt*F/(R*T),

ENupt = exp(Nupt),

Nudt=z*Volt_udt*F/(R*T),

ENudt = exp(Nudt),

Nucd=z*Volt_ucd*F/(R*T),

ENucd = exp(Nucd),

Nvpt=z*Volt_vpt*F/(R*T),

ENvpt = exp(Nvpt),

Nvdt=z*Volt_vdt*F/(R*T),

ENvdt = exp(Nvdt),

Nvcd=z*Volt_vcd*F/(R*T),

ENvcd = exp(Nvcd),

Km_met_OCT1 = Km_met_OCT1_uM*MW,

$K_{m\_met\_OCT2} = K_{m\_met\_OCT2\_uM}*MW$,

$K_{m\_met\_MATE} = K_{m\_met\_MATE\_uM}*MW$,

$PS_{h,act} = 1/(1+ R_{dif})*CL_{intall}/\beta_{liver}$,

$PS_{h,difin} = PS_{h,act}*R_{dif}$,

$PS_{h,difout}=PS_{h,difin}/\gamma_h$,

$CL_{met} = CL_{intall}/(1- \beta_{liver} *Rdif/(1+ R_{dif})/ \gamma_h$,

$V_{max\_met\_OCT1} = PS_{h,act}*K_{m\_met\_OCT1}$,

$PS_{r,PT,difinf} = Pd*SA_{r,PT}*1000*Nvpt/(ENvpt-1)$,

$PS_{u,PT,difinf} = Pd*SA_{u,PT}*1000*Nupt/(ENupt-1)$,

$PS_{u,PT,difeff} = PS_{u,PT,difinf}/\gamma_{u,PT}$,

$PS_{r,PT,difeff} = PS_{r,PT,difinf} / \gamma_{r,PT}$,

$PS_{MATE} = PS_{u,PT,difeff}*R_{MATE/dif}$,

$V_{max,MATE} = PS_{MATE}*K_{m,MATE}$

$PS_{OCT2} = ((R_{MATE/dif} + 1)*PS_{u,PT,difeff} *(1-\beta_{kidney})/\beta_{kidney} – PS_{r,PT,difeff})*R_{OCT2,inf/eff}/ENvpt$,

$V_{max,OCT2} = PS_{OCT2}*K_{m,OCT2}$

$PS_{r,DT,difinf} = Pd*SA_{r,DT}*1000*Nvdt/(ENvdt-1)$,

$PS_{r,CD,difinf} = Pd*SA_{r,CD}*1000*Nvcd/(ENvcd-1)$,

$PS_{u,CD,difinf} = Pd*SA_{u,DT}*1000*Nudt/(ENudt-1)$,

$PS_{u,CD,difinf} = Pd*SA_{u,CD}*1000*Nucd/(ENucd-1)$,

$PS_{r,DT,difeff} = PS_{r,DT,difinf} / \gamma_{r,DT}$,

$PS_{u,CD,difeff} = PS_{u,DT,difinf} / \gamma_{u,DT}$,

$PS_{r,CD,difeff} = PS_{r,CD,difinf} / \gamma_{r,CD}$,

$PS_{u,CD,difeff} = PS_{u,CD,difinf} / \gamma_{u,CD}$,

Model equations for cimetidine

Central plasma compartment

$$V_{blood}*dC_{blood}/dt = Q_h*C_{EH}+Q_{r6}*C_{r6} - Q_h*C_{blod} - Q_{r,p}*C_{plasma} - Q_{muscle}*(C_{blood} - C_{muscle}/K_{p,muscle}) -$$

$$Q_{skin}*(C_{blood} -C_{skin}/K_{p,skin})-Q_{adipose}*(C_{blood} -C_{adipose}/K_{p,adipose})$$

Distribution compartments

$$V_{muscle}*dtC_{muscle}/dt = (Q_{muscle}*C_{blood}– Q_{muscle}*C_{muscle}/K_{p,muscle})$$

$$V_{skin}*dtC_{skin}/dt = (Q_{skin}*C_{blood}– Q_{skin}*C_{skin}/K_{p,skin})$$

$$V_{adipose}*dtC_{adipose}/dt = (Q_{adipose}*C_{blood} – Q_{adipose}*C_{adipose}/K_{p,adipose})$$

Intestinal compartments

$$dX_{intestine} / dt = – ka/FaFg*X_{intestine}$$

Extracellular hepatic compartments

$$V_{EH}*dC_{EH} / dt = ka*X_{intestine} + Q_h*(C_{blood} - C_{EH}) + fh*PS_{dif,eff}*C_{HC} -$$

$$(V_{max\_met\_OCT1}*(C_{EH,p,i}/(K_{m\_met\_OCT1} + C_{EH,p,i}) – C_{HC,i}*e^{Nh}/R_{OCT1,inf/eff}/(K_{m\_met\_OCT1}+ C_{HC,i}))/5 –$$

$$fu*(PS_{dif,inf}+PS_{act\_inf})*C_{EH}/Rb$$

Hepatocyte compartments

$V_{HC}*dC_{HC}/dt = fu*(PS_{dif,inf}+PS_{act\_inf})*C_{EH}/Rb - fh*PS_{dif,eff}*C_{HC} - fh*CL_{int,met}*C_{HC}$; (i=1~5)

Extracellular glomerulus compartment

$V_{r,1}*dC_{r1}/dt = Q_r*C_{blood} - Q_{r1}*C_{r1} - fu*Q_{u1}*C_{r,1}/Rb$

Glomerulus compartment

$V_G*dC_G/dt = Q_{GFR}*(fu*C_{r,1}/Rb - C_G))$

Kidney: Proximal tubule <u>(i=1~3)</u>

$(V_{PT,r}/3)*dC_{PT,r,i}/dt = Q_{r,i}*C_{r,i} + fc*1/3*PS_{r,PT,difeff}*C_{PT,cell,i} - 1/3*V_{max\_OCT2}*((fu*f_{PT,ion\_b}$

$*C_{PT,r,i}/Rb)/(K_{m\_OCT2} + (fu*f_{ion\_b}*C_{PT,r,i}/Rb)) - fc*f_{ion\_c}*C_{PT,cell,i}*exp(Nvpt)/R_{OCT2,inf/eff}/(K_{m\_OCT2} +$

$fc*f_{ion\_c}*C_{PT,cell,i})) - 1/3*V_{max\_OAT3}*((fu*f_{ion\_b}*C_{PT,r,i}/Rb)/(K_{m\_OAT3} + (fu*f_{ion\_b}*C_{PT,r,i}/Rb))-$

$1/3*PS_{r,PT,difinf}*fu*C_{PT,r,i}/Rb - Q_{r(i+1)}*C_{PT,r,i}$,

$$(V_{PT,c}/3)*dC_{PT,cell,i}/dt = fb*1/3*V_{max\_OCT2}*(fu*f_{ion\_b}*C_{PT,r,i}/Rb)/(K_{m\_OCT2} + fu*f_{ion\_b}*C_{PT,r,i}/Rb) –$$

$$fc*f_{PT,ion\_c}\ C_{PT,cell,i}*exp(Nvpt)/R_{OCT2,inf/eff}/(K_{m\_OCT2} + fc*f_{ion\_c}*C_{PT,cell,i})) + 1/3*V_{max\_OAT3}*$$

$$((fu*f_{ion\_b}*C_{PT,r,i}/Rb)/(K_{m\_OAT3} + (fu*f_{ion\_b}*C_{PT,r,i}/Rb)) + 1/3*PS_{r,PT,difinf}* fu*C_{PT,r,i}/Rb +$$

$$fu*1/3*PS_{u,PT,difinf}*C_{PT,u,i} - fc*1/3*PS_{r,PT,difeff}*C_{PT,cell,i} - fc*1/3*(f_{ion\_u}*V_{max,MATE}/(K_{m,MATE} + fc$$

$$*f_{PT,ion\_u}*C_{PT,cell,i}) + PS_{u,PT,difeff})*C_{PT,cell,i}$$

$$(V_{PT,u}/3)*dC_{PT,u,i}/dt = Q_{u1}*C_{PT,cell,i} + fc*1/3*(f_{PT,ion\_u} * V_{max,MATE}/(K_{m,MATE} + fc *f_{PT,ion\_u} *C_{PT,cell,i})$$

$$+ PS_{u,PT,difeff})*C_{PT,cell,i} - fu*1/3*PS_{u,PT,difinf}*C_{PT,u,i} - Q_{u2}*C_{PT,u,i}$$

Distal tubule compartment

$$V_{DT,r}*dC_{DT}/dt = Q_{r4}*C_{PT,3} + fc*PS_{r,dt,difeff}*C_{DT,cell} - fu*PS_{r,DT,difinf}*C_{DT}/Rb - Q_{r5}*C_{DT}$$

$$V_{DT,cell}*dC_{DT,cell}/dt = fu*PS_{r,DT,difinf}*C_{DT}/Rb + fu*PS_{u,DT,difinf}*C_{DT,u} - fc*PS_{r,DT,difeff}*C_{DT,cell} -$$

$$fc*PS_{u,DTt,difeff}*C_{DT,cell}$$

$$V_{DT,u}*dC_{DT,u}/dt = Q_{u4}*C_{PT,u,3} + fc*PS_{u,DT,difeff}*C_{DT,cell} - fu*PS_{u,DT,difinf}*C_{DT,u} - Q_{u5}*C_{DT,u}$$

Collecting duct compartment

$$V_{CD,r}*dC_{CD}/dt = Q_{r5}*C_{dt,p} + fc*PS_{r,CD,difeff}*C_{CD,cell} - fu*PS_{r,CD,difinf}*C_{CD}/Rb - Q_{r6}*C_{CD,p}$$

$V_{CD,cell}*dC_{CD,cell}/dt = fu*PS_{r,CD,difinf}*C_{CD}/Rb + fu*PS_{u,CD,difinf}*C_{CD,u} - fc*PS_{r,CD,difeff}*C_{CD,cell} -$

$fc*PS_{u,CD,difeff}*C_{CD,cell}$

$V_{CD,u}*dC_{CD,u}/dt = Q_{u5}*C_{DT,u} + fc*PS_{u,CD,difeff}*C_{CD,cell} - fu*PS_{u,CD,difinf}*C_{CD,cell} - Q_{u6}*C_{CD,u}$

Urine compartment

$dX_{urine}/dt = Q_{u6}*C_{CD,u}$

Other calculations

$Q_{r1} = Q_r-Q_{u1}$,

$Q_{r2} = Q_{r1} + ((Q_{u1}-Q_{u6})/5)$,

$Q_{r3} = Q_{r2} + ((Q_{u1}-Q_{u6})/5)$,

$Q_{r4} = Q_{r3} + ((Q_{u1}-Q_{u6})/5)$,

$Q_{r5} = Q_{r4} + ((Q_{u1}-Q_{u6})/5)$,

$Q_{r6} = Q_r-Q_{u6}$,

$V_{r,blood} = 0.30*V_{renal}$,

$V_{r,cell} = 0.24*V_{renal}$,

$V_{r,urine} = 0.46*V_{renal}$,

$V_G = 5/129*V_{r,blood}$,

$V_{PT} = 17/129*V_{r,blood}$,

$V_{DT} = 11/129*V_{r,blood}$,

$V_{CD} = 62/129*V_{r,blood}$,

$V_{G,u} = 5/129*V_{r,urine}$

$V_{PT,u} = 17/129*V_{r,urine}$

$V_{DT,u} = 11/129*V_{r,urine}$

$V_{CD,u} = 62/129*V_{r,urine}$

$V_{PT,cell} = 17/124*V_{r,cell}$,

$V_{DT,cell} = 11/124*V_{r,cell}$,

$V_{CD,cell} = 62/124*V_{r,cell}$,

$PS_{dif\_inf} = Rdif*PS_{act\_inf}$,

$PS_{dif\_eff} = PS_{dif\_inf}/\gamma_h$,

$f_{r,ion} = 1/(1+10^{(pH_b - pKa_{cim})})$,

$f_{r,union} = f_{r,ion}*10^{(pH_b - pKa_{cim})}$,

$f_{c,ion} = 1/(1+10^{(pH_c - pKa_{cim})})$,

$f_{c,union} = f_{c,ion}*10^{(pH_c - pKa_{cim})}$,

$f_{u,ion,PT} = 1/(1+10^{(pH_{PT,u} - pKa_{cim})})$,

$f_{u,union,PT} = f_{u,ion,PT}*10^{(pH_{PT,u} - pKa\_cim)}$,

$f_{u,ion,DT} = 1/(1+10^{(pH_{DT,u} - pKa\_cim)})$,

$f_{u,union,DT} = f_{u,ion,DT}*10^{(pH_{DT,u} - pKa\_cim)}$,

$f_{u,ion,CD} = 1/(1+10^{(pH_{CD,u} - pKa\_cim)})$,

$f_{u,union,CD} = f_{u,ion,CD}*10^{(pH_{CD,u} - pKa\_cim)}$,

$N_{u,PT}=z*Volt_{u,PT}*F/(R*T)$,

$N_{u,DT}=z*Volt_{u,DT}*F/(R*T)$,

$N_{u,CD}=z*Volt_{u,CD}*F/(R*T)$,

$N_{r,PT}=z*Volt_{r,PT}*F/(R*T)$,

$N_{r,DT}=z*Volt_{r,DT}*F/(R*T)$,

$N_{r,CD}=z*Volt_{r,CD}*F/(R*T)$,

$Pd_{union} = Pd/(f_{r,ion}*\lambda + f_{r,union})$,

$Pd_{ion} = Pd_{union}*\lambda$,

$PS_{r,PT,difinf,union} = Pd_{union}*SA_{r,PT}*1000$,

$$PS_{r,PT,difinf,ion} = Pd_{ion}*SA_{r,PT}*1000*N_{r,PT}/(\exp(N_{r,PT})-1),$$

$$PS_{r,PT,difinf} = PS_{r,PT,difinf,union} *f_{r,union} + PS_{r,PT,difinf,ion} *f_{r,ion},$$

$$\gamma_{r,1} = (\lambda* f_{r,ion} + f_{r,union})/(\exp(N_{r,PT})*\lambda*f_{c,ion} + f_{c,union}),$$

$$PS_{r,PT,difeff} = PS_{r,PT,difinf} / \gamma_{r,1},$$

$$PS_{u,PT,difinf,union} = Pd_{union}*SA_{u,PT}*1000,$$

$$PS_{u,PT,difinf,ion} = Pd_{ion}*SA_{u,PT}*1000*N_{u,PT}/(\exp(N_{u,PT})-1),$$

$$PS_{u,PT,difinf} = PS_{u,PT,difinf,union} *f_{u,union} + PS_{u,PT,difinf,ion} *f_{u,ion},$$

$$\gamma_{u,1} = (\lambda*f_{u,ion} + f_{u,union})/(\exp(N_{u,PT})*\lambda*f_{c,ion} + f_{c,union}),$$

$$PS_{u,PT,difeff} = PS_{u,PT,difinf} / \gamma_{u,1},$$

$$PS_{r,DT,difinf,union} = Pd_{union}*SA_{r,DT}*1000,$$

$$PS_{r,DT,difinf,ion} = Pd_{ion}*SA_{r,DT}*1000*N_{r,DT}/(\exp(N_{r,DT})-1),$$

$$PS_{r,DT,difinf} = PS_{r,DT,difinf,union} *f_{r,union} + PS_{r,DT,difinf,ion} *f_{r,ion},$$

$$\gamma_{r,2} = (\lambda*f_{r,ion} + f_{r,union})/(\exp(N_{r,DT})*\lambda*f_{c,ion} + f_{c,union}),$$

$$PS_{r,DT,difeff} = PS_{r,DT,difinf} / \gamma_{r,2},$$

$$PS_{u,DT,difinf,union} = Pd_{union}*SA_{u,DT}*1000,$$

$$PS_{u,DT,difinf,ion} = Pd_{ion}*SA_{u,DT}*1000*N_{u,DT}/(\exp(N_{u,DT})-1),$$

$$PS_{u,DT,difinf} = PS_{u,DT,difinf,union}*f_{u,union} + PS_{u,DT,difinf,ion}*f_{u,ion},$$

$$\gamma_{u,2} = (\lambda*f_{u,ion} + f_{u,union})/(\exp(N_{u,DT})*\lambda*f_{c,ion} + f_{c,union}),$$

$$PS_{u,DT,difeff} = PS_{u,DT,difinf} / \gamma_{u,2},$$

$$PS_{r,CD,difinf,union} = Pd_{union}*SA_{r,CD}*1000,$$

$$PS_{r,CD,difinf,ion} = Pd_{ion}*SA_{r,CD}*1000*N_{r,CD}/(\exp(N_{r,CD})-1),$$

$$PS_{r,CD,difinf} = PS_{r,CD,difinf,union}*f_{r,union} + PS_{r,CD,difinf,ion}*f_{r,ion},$$

$$\gamma_{r,3} = (\lambda*f_{r,ion} + f_{r,union})/(\exp(N_{r,CD})*\lambda*f_{c,ion} + f_{c,union}),$$

$$PS_{r,CD,difeff} = PS_{r,CD,difinf} / \gamma_{r,3},$$

$$PS_{u,CD,difinf,union} = Pd_{union}*SA_{u,CD}*1000,$$

$$PS_{u,CD,difinf,ion} = Pd_{ion}*SA_{u,CD}*1000*N_{u,CD}/(\exp(N_{u,CD})-1),$$

$$PS_{u,CD,difinf} = PS_{u,CD,difinf,union}*f_{u,union} + PS_{u,CD,difinf,ion}*f_{u,ion},$$

$$\gamma_{u,3} = (\lambda*f_{u,ion} + f_{u,union})/(\exp(N_{u,CD})*\lambda*f_{c,ion} + f_{c,union}),$$

$$PS_{u,CD,difeff} = PS_{u,CD,difinf} / \gamma_{u,3},$$

$$K_{m,OCT2} = K_{m,OCT2,uM}*MW*fu*f_{r,ion},$$

$V_{max,OCT2} = V_{max,OCT2,uM}*MW*fu*f_{r,ion}$,

$K_{m,OAT3} = K_{m,OAT3,uM}*MW*fu*f_{r,ion}$,

$V_{max,OAT3} = V_{max,OAT3,uM}*MW*fu*f_{r,ion}$,

$K_{m,MATE} = K_{m,MATE,uM}*MW*fc*f_{c,ion}$,

$V_{max,MATE} = V_{max,MATE,uM}*MW*fc*f_{c,ion}$,