The Detailed Mathematical Model

Model Input- Plasma macronutrients

$b_{Gpi} = 5; Ca_{Ala0} = 0.25;$
$if\ (Gpi < 5);$
$Ca_{Glu} = 5 - (5 - Gpi) * \left(1 - exp\left(-\frac{t-0}{30}\right)\right); else$
$if\ (Gpi > 5); Ca_{Glu} = 5 + (Gpi - 5) * \left(1 - exp\left(-\frac{t-0}{30}\right)\right); else\ Ca\_Glu = 5 * 1;$
end
end
$\%Ca_{Glu} = \left(\frac{Ca_{Glup}}{1.88}\right) * \frac{10}{180}; \%$

$if\ (FF < 0.68)$
$Ca_{FFA} = 0.68 - (0.68 - FF) * \left(1 - exp\left(-\frac{t-0}{30}\right)\right); else$
$if\ (FF > 0.68);;$
$Ca_{FFA} = 0.68 + (FF - 0.68) * \left(1 - exp\left(-\frac{t-0}{30}\right)\right); else\ Ca\_FFA = 0.68;$
end
end

$if\ AAm < 0.25;$
$Ca_{Ala} = 0.25 - (0.25 - AAm) * \left(1 - exp\left(-\frac{t-0}{30}\right)\right); else$
$if\ (AAm > 0.25);$
$Ca_{Ala} = 0.25 + (AAm - 0.25) * \left(1 - exp\left(-\frac{t-0}{30}\right)\right); else\ Ca\_Ala = 0.25;$
end
end

Metabolic Controllers and regulations

$\%Redox\ controllers$
$K_{NAD_L} = 0.45;$
$K_{NADH_L} = 0.05;$
$K_{Rdxp} = \frac{K_{NADH_L}}{K_{NAD_L}};$
$K_{Rdx_N} = \frac{1}{K_{Rdxp}};$
$Rdx_P = \frac{NADH_L}{NAD_L};$
$Rdx_N = \frac{1}{Rdx_P};$

$RDX_{Ptv} = \frac{Rdx_P}{Rdx_P + K_{Rdx_P}};$
$RDX_{Ntv} = \frac{Rdx_N}{Rdx_N + K_{Rdx_N}};$

$\%GTP - GDP\ Controller$
$K_{GTP_L} = 0.29;$
$K_{GDP_L} = 0.1;$
$Gtp = \frac{GTP_L}{GDP_L};$
$Gdp = \frac{1}{Gtp};$

$$K_{Gtp} = \frac{K_{GTP_L}}{K_{GDP_L}};$$

$$K_{Gdp} = \frac{1}{K_{Gtp}};$$

$$GTP_{Ptv} = \frac{Gtp}{Gtp + K_{Gtp}};$$

$$GTP_{Ntv} = \frac{Gdp}{Gdp + K_{Gdp}};$$

%ATP − ADP Controller

$$K_{ATP_L} = 2.8;$$

$$K_{ADP_L} = 0.8;$$

$$Atp = \frac{ATP_L}{ADP_L};$$

$$Adp = \frac{1}{Atp};$$

$$K_{Atp} = \frac{K_{ATP_L}}{K_{ADP_L}};$$

$$K_{Adp} = \frac{1}{K_{Atp}};$$

$$ATP_{Ptv} = \frac{Atp}{Atp + K_{Atp}};$$

$$ATP_{Ntv} = \frac{Adp}{Adp + K_{Adp}};$$

$$ATP_{Ntv2} = 2 * \left(\frac{2.8^2}{2.8^2 + ATP_L^2}\right);$$

%Glucagon Activated Calcium Cascade

$$GPRT = 26.* \left(\frac{LRS.}{95000 + LRS}\right);$$

$$PLCi = 233.* \left(.\frac{GPRT.^2}{32.^2 + GPRT.^2}\right);$$

$$IP3i = 16.3.* \left(.\frac{PLCi.^4}{42.^4 + PLCi.^4}\right);$$

$$Cal = 35.* \left(\frac{IP3i.^{1.8}}{9.^{1.8} + IP3i.^{1.8}}\right);$$

%AMPK

$$AMPK_{Eff} = AMPK;$$

$$PKA_L = \frac{C}{9.0e} - 6;$$

%Common Function of Insulin Effect

$$Insu_{Ptv_{Eff}} = 0.5 * \left(1 + \left(5 * \left(\frac{x17^2}{x17^2 + 2.3^2}\right)\right)\right);$$

$$Insu_{Ntv_{Eff}} = 1.25 * \left(\frac{2.3^2}{2.3^2 + x17^2}\right);$$

%Common Function of Glucgon effect

$$Glcn_{Ptv_{Eff}} = 0.5 * \left(1 + 10 * \left(\frac{PKA_L^2}{PKA_L^2 + 3^2}\right)\right);$$

$$Glcn_{Ntv_{Eff}} = 1.25 * \left(\frac{2^2}{2^2 + PKA_L^2}\right);$$

%GLycolysis Regulation

$$AKt_{Ptv_{glysis}} = 5 * \left(\frac{x17^2}{x17^2 + 2.25^2}\right);$$

$$SREBP_{Ptv_{glysis}} = 5 * \left(\frac{SREBP^2}{SREBP^{+2.2^2}}\right);$$

$$CHREBp_{Ptv_{glysis}} = 5 * \left(\frac{CHREBp^2}{CHREBp^2 + 2^2}\right);$$

$$AMPK_{Eff_{glysis}} = 5 * \left(\frac{AMPK_{Eff}^2}{AMPK_{Eff}^2 + 0.55^2}\right);$$

$$FOXO_{Ntv} = 1.25 * \frac{0.4^2}{0.4^2 + FOXO^2};$$

$$Reg_{Glysis} = (0.20) * \left(1 + AKt_{Ptv_{glysis}} + SREBP_{Ptv_{glysis}} + AMPK_{Eff_{glysis}} + CHREBp_{Ptv_{glysis}}\right) * FOXO_{Ntv};$$

%GLycolysis Regulation I

$$AKt_{Ptv_{glysis}} = 16 * \left(\frac{x17^4}{x17^4 + 2.25^4}\right);$$

$$SREBP_{Ptv_{glysis}} = 5 * \left(\frac{SREBP^2}{SREBP^2 + 2.2^2}\right);$$

$$CHREBp_{Ptv_{glysis}} = 5 * \left(\frac{CHREBp^2}{CHREBp^2 + 2^2}\right);$$

$$AMPK_{Eff_{glysis}} = 5 * \left(\frac{AMPK_{Eff}^2}{AMPK_{Eff}^2 + 0.55^2}\right);$$

$$FOXO_{Ntv} = 1.25 * \frac{0.4^2}{0.4^2 + FOXO^2};$$

$$Reg_{Glu_{G6p_L}} = (0.20) * \left(1 + AKt_{Ptv_{glysis}} + SREBP_{Ptv_{glysis}} + AMPK_{Eff_{glysis}} + CHREBp_{Ptv_{glysis}}\right) * FOXO_{Ntv};$$

%GLycolysis Regulation II − Pyruvate kinase

$$cAMP_{rt} = \frac{cAMP}{3.2e} - 6;$$

$$cAMP_{Ntv_{PEP_{Pyr}}} = \frac{2.5^2}{2.5^2 + cAMP_{rt}^2};$$

$$Glu_{PEP_{Pyr_{Ptv}}} = 2 * \left(1 - \left(\frac{5^3}{5^3 + Glu_L^3}\right)\right);$$

$$Reg_{PEP_{Pyr}} = 1.16 * Reg_{Glysis} * cAMP_{Ntv_{PEP_{Pyr}}} * Glu_{PEP_{Pyr_{Ptv}}};$$

%Gluconeogenesis I

$$CREB_{Ptv_{Glunsis}} = 10 * \left(\frac{CREB^2}{CREB^2 + 0.66^2}\right);$$

$$CEBPa_{Ptv_{Glunsis}} = 3 * \left(\frac{CEBPa^1}{CEBPa^1 + 2^1}\right);$$

$$FOXO_{Ptv_{Glunsis}} = 3 * \left(\frac{FOXO^1}{FOXO^1 + 0.2^1}\right);$$

$$PGC1_{Eff_{Glnsis}} = 5 * \left(\frac{PGC1^2}{PGC1^2 + 2^2}\right);$$

$$AMPK_{Ntv_{Glunsis}} = 1.216 * \left(\frac{0.6^2}{0.6^2 + AMPK_{Eff}^2}\right);$$

$$Reg_{Glunsis} = 0.2 * \left(1 + CREB_{Ptv_{Glunsis}} + FOXO_{Ptv_{Glunsis}} + CEBPa_{Ptv_{Glunsis}} + PGC1_{Eff_{Glnsis}}\right) * AMPK_{Ntv_{Glunsis}};$$

%Gluconeogenesis II

$$CREB_{Ptv_{G6p_{Glu}}} = 28 * \left(\frac{CREB^3}{CREB^3 + 0.66^3}\right);$$

$$CEBPa_{Ptv_{Glunsis}} = 3 * \left(\frac{CEBPa^1}{CEBPa^1 + 2^1}\right);$$

$$FOXO_{Ptv_{Glunsis}} = 9 * \left(\frac{FOXO^3}{FOXO^3 + 0.4^3}\right);$$

$$PGC1_{Eff_{Glnsis}} = 5 * \left(\frac{PGC1^2}{PGC1^2 + 2^2}\right);$$

$$AMPK_{Ntv_{Glunsis}} = 1.216 * \left(\frac{0.6^2}{0.6^2 + AMPK_{Eff}^2}\right);$$

$$AKT_{Ntv_{G6p_{Glu}}} = 1.25 * \left(\frac{2.25^2}{x17.^2 + 2.3^2}\right);$$

$$Reg_{G6p_{Glu}} = 0.2 * \left(1 + CREB_{Ptv_{G6p_{Glu}}} + FOXO_{Ptv_{Glunsis}} + CEBPa_{Ptv_{Glunsis}} + PGC1_{Eff_{Glnsis}}\right) * AMPK_{Ntv_{Glunsis}} * AKT_{Ntv_{G6p_{Glu}}};$$

%Gluconeogenesis III

$$CREB_{Ptv_{OAA_{PEP}}} = 28 * \left(\frac{CREB^{3.0}}{CREB^{3.0} + 0.66^3}\right);$$

$$CEBPa_{Ptv_{Glunsis}} = 9 * \left(\frac{CEBPa^3}{CEBPa^3 + 2^3}\right);$$

$$FOXO_{Ptv_{Glunsis}} = 9 * \left(\frac{FOXO^3}{FOXO^3 + 0.4^3}\right);$$

$$PGC1_{Eff_{Glnsis}} = 5 * \left(\frac{PGC1^2}{PGC1^2 + 2^2}\right);$$

$$AMPK_{Ntv_{Glunsis}} = 1.216 * \left(\frac{0.6^2}{0.6^2 + AMPK_{Eff}^2}\right);$$

$$Reg_{OAA_{PEP}} = 0.2 * \left(1 + CREB_{Ptv_{OAA_{PEP}}} + FOXO_{Ptv_{Glunsis}} + CEBPa_{Ptv_{Glunsis}} + PGC1_{Eff_{Glnsis}}\right) * AMPK_{Ntv_{Glunsis}};$$

%

%FFA Synthesis

$$SREBP_{Ptv_{FAsynt}} = 5 * \left(\frac{SREBP^2}{SREBP^2 + 2.0^2}\right);$$

$$CHREBp_{Ptv_{FAsynt}} = 10 * \left(\frac{CHREBp^2}{CHREBp^2 + 3^2}\right);$$

$$PPARg_{Ptv_{FAsynt}} = 3.* \left(.\frac{PPARg.^1}{PPARg.^1 + 2.^1}\right);$$

$$Glsmn_{Ptv_{FAsynt}} = 5 * \left(\frac{Glsmn_L^2}{Glsmn_L^2 + 0.2^2}\right);$$

$$AMPK_{Ntv_{FAsynt}} = 1.11 * \left(\frac{0.6^2}{0.6^2 + AMPK_{Eff}^2}\right);$$

$$TRB_{Ntv_{FAsynt}} = 1.25 * \left(\frac{2^2}{TRB3^2 + 2^2}\right);$$

$$Reg_{FAsynt} = 0.2 * \left(1 + SREBP_{Ptv_{FAsynt}} + CHREBp_{Ptv_{FAsynt}} + PPARg_{Ptv_{FAsynt}} + Glsmn_{Ptv_{FAsynt}}\right) * AMPK_{Ntv_{FAsynt}} * TRB_{Ntv_{FAsynt}};$$

%FFA Breakdown

$$PKA_L = \frac{C}{8.0e} - 6;$$

$$PKA_{Ptv_{FABrk}} = 5 * \left(\frac{PKA_L^2}{PKA_L^2 + 2^2}\right);$$

$$PPARab_{Ptv_{FABrk}} = 3 * \left(\frac{PPARab^1}{PPARab^1 + 2.0^1}\right);$$

$$SREBP_{Ntv_{FABrk}} = 1.25 * \left(\frac{2.0^2}{SREBP^2 + 2.0^2}\right);$$

$$FOXO_{Ptv_{FABrk}} = 2.* \left(FOXO.^1 .\frac{}{FOXO.^1 + 0.20^1}\right);$$

$$TRB3_{Ptv_{FABrk}} = 2 * \left(\frac{TRB3}{TRB3 + 1}\right);$$

$$Reg_{FABrk} = 0.2 * (1 + PKA_{Ptv_{FABrk}} + PPARab_{Ptv_{FABrk}} + FOXO_{Ptv_{FABrk}} + TRB3_{Ptv_{FABrk}}) * SREBP_{Ntv_{FABrk}};$$

%TG Synthesis

$$SREBP_{Ptv_{TGsynt}} = 9 * \left(\frac{SREBP^3}{SREBP^3 + 2.0^3}\right);$$

$$AKT_{Ptv_{TGsynt}} = 5 * \left(\frac{x17^2}{x17^2 + 2.25^2}\right);$$

$$PPARg_{Ptv_{TGsynt}} = 10 * \left(\frac{PPARg^2}{PPARg^2 + 3^2}\right);$$

$$Reg_{TGsynt} = 0.25 * \left(1 + SREBP_{Ptv_{TGsynt}} + AKT_{Ptv_{TGsynt}} + PPARg_{Ptv_{TGsynt}}\right);$$

%TG Breakdown

$$PKA_L = \frac{C}{9.0e} - 6;$$

$$PKA_{Ptv_{TGBrk}} = 5 * \left(\frac{PKA_L^2}{PKA_L^2 + 2^2}\right);$$

$$AKT_{Ntv_{TGBrk}} = 1.25 * \left(\frac{2.25^2}{x17^2 + 2.25^2}\right);$$

$$FOXO_{Ptv_{TGBrk}} = 3.* \left(.\frac{FOXO.^1}{FOXO.^1 + 0.40^1}\right);$$

$$Reg_{TGBrk} = 0.33 * (1 + PKA_{Ptv_{TGBrk}} + FOXO_{Ptv_{TGBrk}}) * AKT_{Ntv_{TGBrk}};$$

%Protein Synthesis

$$S6K_{Ptv_{Prosynt}} = 5.0.* \left(.\frac{S6K1p_L.^1}{S6K1p_L.^1 + 4^1}\right);$$

$$AKt_{Ptv_{Prosynt}} = 2.0 * \left(\frac{x17^1}{x17.^1 + 1.0^1}\right);$$

$$Reg_{Prosynt} = 0.33 * \left(1 + S6K_{Ptv_{Prosynt}} + AKt_{Ptv_{Prosynt}}\right);$$

%Protein Breakdown

$$PKA_{Ptv_{ProBrk}} = 2.* \left(.\frac{PKA_L.^1}{PKA_L.^1 + 1.^1}\right);$$

$$AKT_{Ntv_{ProBrk}} = 1.25 * \left(.\frac{2.25.^2}{x17.^2 + 2.25.^2}\right);$$

$$AA_{Ntv} = 1;$$

$$Reg_{ProBrk} = 0.5.* (1 + PKA_{Ptv_{ProBrk}}). * AKT_{Ntv_{ProBrk}};$$

%Glycogen Synthasis

$$Gsk3_b = 3 * \left(\frac{10}{90}\right);$$

$$Gsk3_{act} = \frac{x23}{x22};$$

$$Reg_{Glysynt} = 12 * \left(\frac{Gsk3_{act}^2}{Gsk3_{act}^2 + Gsk3_b^2}\right);$$

%Glycogen Breakdown

$$GPa_K = 0.025;$$

$$GPa_{Eff} = 10 * \left(\frac{GPa}{GPa + GPa_K}\right);$$

$$Cal_{eff_{GlyBrk}} = 2 * \left(\frac{Cal^1}{Cal^1 + 3.0^1}\right);$$

$$AMP_{GlyBrk} = 0 * \left(\frac{AMP_L}{1.6 + AMP_L}\right);$$

$$Reg_{GlyBrk} = (0.33) * \left(1 + GPa_{Eff} + Cal_{eff_{GlyBrk}} + AMP_{GlyBrk}\right);$$

%TCA cycle

%Pyruvate dehydrogenase

$$AKt_{Ptv_{PDH}} = 17.* \left(.\frac{x17.^4}{x17.^4 + 2.25^4}\right);$$

$$CHREBp_{Ptv_{PDH}} = 10 * \left(\frac{CHREBp^2}{CHREBp^2 + 3^2}\right);$$

$$Cal_{Ptv_{PDH}} = 9.* \left(\frac{Cal.^2}{Cal.^2 + 7.0^2}\right);$$

$\%ATP_{Ntv_{PDH}} =$

$$Reg_{PDH} = (0.25 * 1.135) * (1 + AKt_{Ptv_{PDH}} + Cal_{Ptv_{PDH}} + CHREBp_{Ptv_{PDH}});$$

%Citrate synthase

$$AKt_{Ptv_{CS}} = 17.* \left(.\frac{x17.^4}{x17.^4 + 2.25^4}\right);$$

$$CHREBp_{Ptv_{CS}} = 10 * \left(\frac{CHREBp^2}{CHREBp^2 + 3^2}\right);$$

$$Cal_{Ptv_{CS}} = 9.*\left(\frac{Cal.^2}{Cal.^2 + 7.0^2}\right);$$

$$Reg_{CS} = (0.25 * 1.135) * (1 + AKt_{Ptv_{CS}} + Cal_{Ptv_{CS}} + CHREBp_{Ptv_{CS}});$$

%Isocitrate dehydrogenase

$$Cal_{Ptv_{ISD}} = 4.5.*\left(.\frac{Cal.^{1.5}}{Cal.^{1.5} + 4.5.^{1.5}}\right);$$

$$Reg_{ISD} = 0.5 * (1 + Cal_{Ptv_{ISD}});$$

%alpa Ketoglutarate

$$Reg_{AKG} = 1;$$

%Oxidative phosphorylation

$$PKA_L = \frac{C.}{8.0e - 6};$$

$$PKA_{Ptv_{Oxphos}} = 10.*\left(\frac{{PKA_L}^2}{PKA_L.^2 + 3.^2}\right);$$

$$Cal_{Ptv_{Oxphos}} = 5 * \left(\frac{Cal^2}{Cal^2 + 6.0^2}\right);$$

$$Reg_{Oxphos} = 0.33. * \left(1 + PKA_{Ptv_{Oxphos}} + Cal_{Ptv_{Oxphos}}\right);$$

%ATP Hydrolysis

$$Cal_{eff_{ATPlysis}} = 4 * \left(\frac{Cal.^1}{Cal^1 + 5.5^1}\right);$$

$$Reg_{ATPlysis} = 0.5.* \left(1 + Cal_{eff_{ATPlysis}}\right);$$

%Urea Cycle

$$CEBPa_{Ptv_{URC}} = 17 * \left(\frac{CEBPa^4}{CEBPa^4 + 2^4}\right);$$

$$PPARab_{Ntv_{URC}} = 1.25 * \left(\frac{3.0^2}{PPARab^2 + 3.0^2}\right);$$

$$cAMP_{rt} = \frac{cAMP}{3.2e} - 6;$$

$$cAMP_{Ptv_{URC}} = 10 * \left(\frac{cAMP_{rt}^2}{cAMP_{rt}^2 + 3^2}\right);$$

$$AA_{Ptv} = 3.5 * \left(\frac{Ala_L^1}{0.4^1 + Ala_L^1}\right);$$

$$Reg_{URC} = 0.25 * (1 + CEBPa_{Ptv_{URC}} + cAMP_{Ptv_{URC}} + AA_{Ptv}) * PPARab_{Ntv_{URC}};$$

%Glucose uptake

$$SREBP_{Ptv_{Gluup}} = 9 * \left(\frac{SREBP^3}{SREBP^3 + 2.2^3}\right);$$

$$Reg_{Glu_{up}} = 0.33 * \left(1 + Insu_{Ptv_{Eff}} + SREBP_{Ptv_{Gluup}}\right);$$

%FFA uptake

$$PPARab_{Ptv_{Fatup}} = 5 * \left(\frac{PPARab^2}{PPARab^2 + 2.0^2}\right);$$

$$Reg_{Fat_{up}} = 0.33 * 0.85 * \left(1 + Insu_{Ptv_{Eff}} + PPARab_{Ptv_{Fatup}}\right);$$

%Amino Acid uptake

$$cAMP_{rt} = \frac{cAMP}{3.2e} - 6;$$

$$cAMP_{Ptv_{AA_{up}}} = 10 * \left(\frac{cAMP_{rt}^2}{3.5^2 + cAMP_{rt}^2}\right);$$

$$mTOR_{Ptv} = 5 * \left(\frac{mTOR_{Raptor_L^2}}{mTOR_{Raptor_L^2} + 1.5^2}\right);$$

$$Reg_{AA_{up}} = 0.25 * \left(1 + Insu_{Ptv_{Eff}} + mTOR_{Ptv} + cAMP_{Ptv_{AA_{up}}}\right);$$

%Cholesterol synthesis regulation

$$SREBP_{Ptv_{Chol}} = 9 * \left(\frac{SREBP^3}{SREBP^3 + 2.0^3}\right);$$

$$AMPK_{Ntv_{Chol}} = 1.25 * \left(\frac{0.6^2}{0.6^2 + AMPK_{Eff}^2}\right);$$

$$PKA_{Ntv_{Chol}} = 1.25 * \left(\frac{2^2}{2^2 + PKA_L^2}\right);$$

$$Reg_{Chol_{Synt}} = 0.5 * (1 + SREBP_{Ptv_{Chol}}) * AMPK_{Ntv_{Chol}} * PKA_{Ntv_{Chol}};$$

Metabolic Fluxes

$\%Glycolysis - I$
$\%Glu + ATP - -- \rightarrow \; G6p + \; ADP$
$V_{Glu_{G6p_L}} = 7.48 * 2.2 * Reg_{Glu_{G6p_L}};$
$K_{glu_L} = 7.5;$
$K_{gkrp_{F6p_L}} = 0.01; \%;$
$b_{gkrp} = 0.7;$
$n_{gkrp} = 2;$
$K_{gkrp_{Glu_L}} = 15;$
$K_{ATP_L} = 0.28;$
$n_{glu} = 1.6;$

$$F6p_f = \left(1 - \left(\frac{b_{gkrp} * F6p_L}{F6p_L + K_{gkrp_{F6p_L}}}\right)\right);$$

$$Gkf = \left(\frac{Glu_{L^n_{gkrp}}}{\left(Glu_{L^n_{gkrp}}\right) + \left(K_{gkrp_{Glu_{L^n_{gkrp}}}}\right)}\right);$$

$$F_{Glu_{G6p_L}} = \left(V_{Glu_{G6p_L}}\right) * \left(\frac{Glu_L\ n_{glu}}{K_{glu_L\ n_{glu}} + Glu_L\ n_{glu}}\right) * \left(\frac{ATP_L}{K_{ATP_L} + ATP_L}\right) * F6p_f * Gkf; \% * ATP_{Ptv}$$

$$\% \frac{Glucokinase}{Hexokinase} \%$$

$\%Gluconeogenesis - III$
$\%G6p - - - - - - - - - - - - \rightarrow Glu + Ppi$
$V_{G6p_{Glu_L}} = 1.84 * 2.5 * 1.25 * Reg_{G6p_{Glu}};$
$K_{G6p_L} = 0.2 * 3;$

$$F_{G6p_{Glu_L}} = \left(V_{G6p_{Glu_L}}\right) * \left(\frac{G6p_L}{K_{G6p_L} + G6p_L}\right);$$

$\%Glycolysis\ II$
$V_{G6p_{F6p_L}} = 0.264 * 1.0 * Reg_{Glysis};$
$K_{G6p_L} = 0.4;$

$$Reg_{Cit_{PFK}} = 1.25 * \left(\frac{1}{1 + Cit_{Lc}}\right);$$

$$F_{G6p_{F6p_L}} = V_{G6p_{F6p_L}} * \left(\frac{G6p_L}{G6p_L + K_{G6p_L}}\right) * Reg_{Cit_{PFK}};$$

$V_{F6p_{G6p_L}} = 1.05 * Reg_{Glunsis};$
$K_{F6p_L} = 0.05;$

$$F_{F6p_{G6p_L}} = V_{F6p_{G6p_L}} * \left(\frac{F6p_L}{F6p_L + K_{F6p_L}}\right);$$

$\%Pentose\ Phosphate\ shunt1$
$\%G6p + 2NADP - --\rightarrow R5p + 2NADPH + Co2$

$$rsnp_L = \frac{NADP_L}{NADPH_L};$$

$$vnp_L = \frac{0.93}{7.1};$$

$$V_{G6p_{R5p_L}} = 0.28 * 1.5 * Reg_{FAsynt}; \%$$

$$K_{G6p_{R5p_L}} = 0.4;$$

$$F_{G6p_{R5p_L}} = V_{G6p_{R5p_L}} * \left(\frac{rsnp_L}{vnp_L + rsnp_L}\right) * \left(\frac{G6p_L}{K_{G6p_{R5p_L}} + G6p_L}\right);$$

$\%Pentose\ Phosphate\ shunt1I$
$\%3R5P - --\rightarrow 2F6p + GAP1$

$$V_{R5p_{F6p_{Gap_L}}} = 0.14 * 0.8 * Reg_{FAsynt};$$

$$K_{R5p_{F6p_{Gap_L}}} = 0.004;$$

$$F_{R5p_{F6p_{Gap_L}}} = V_{R5p_{F6p_{Gap_L}}} * \left(\frac{R5p_L}{K_{R5p_{F6p_{Gap_L}}} + R5p_L}\right);$$

$\%Glycogenesis$
$\%G6p + ATP - - - - --\rightarrow Gly + ADP + 2Ppi$

$$V_{G6p_{Gly_L}} = 0.4 * Reg_{Glysynt};$$

$$K_{G6p_L} = 0.2;$$

$$K_{UTP_L} = 0.27;$$

$$F_{G6p_{Gly_L}} = \left(V_{G6p_{Gly_L}}\right) * \left(\frac{UTP_L}{K_{UTP_L} + UTP_L}\right) * \left(\frac{G6p_L}{K_{G6p_L} + G6p_L}\right);$$

$\%Glycogenolysis$
$\%Gly + Ppi - - - -\rightarrow G6p$

$$C_{Gly} = 500;$$

$$K1_{max} = 0.2; i_{Glu} = 8;$$

$$K_{AMP_L} = 0.16;$$

$$K_{ATP_L} = 2.8;$$

$$Fmax_{Gly_{G6p_L}} = (1 + K1_{max}) * \left(\frac{Gly_L}{Gly_L + K1_{max} * C_{Gly}}\right); \_Gly\_Eff = Fmax\_Gly\_G6p\_L * exp(-(0.693 * Glu\_L/Ki\_Glu));$$

$$AMP_{eff_{GlyBrk}} = 3.* \left(\frac{\frac{AMP_L}{ATP_L}}{\left(\frac{AMP_L}{ATP_L}\right) + \left(2 * \left(\frac{K_{AMP_L}}{K_{ATP_L}}\right)\right)}\right);$$

$$V_{Gly_{G6p_L}} = 3.84 * 1.0 * Reg_{GlyBrk} * Glu_{Gly_{Eff}};$$

$$K_{Gly_L} = 500;$$

$$K_{Ppi_L} = 4.6;$$

$$F\_Gly\_G6p\_L = (V\_Gly\_G6p\_L) * AMP\_eff\_GlyBrk * (((Gly\_L * Ppi\_L)/(K\_Gly\_L * K\_Ppi\_L))/(1 + (Gly\_L/K\_Gly\_L) \ldots$$
$$+(Ppi\_L/K\_Ppi\_L) + ((Gly\_L * Ppi\_L)/(K\_Gly\_L * K\_Ppi\_L))));$$

$\%Glycolysis\ III - PFK$
$V_{F6p_{F16bp_L}} = 0.5384 * 0.5 * Reg_{Glysis};$
$K_{F6p_L} = 0.05;$
$K_{AMP_L} = 0.16;$
$K_{ATP_L} = 2.8;$

$$AMP_{Act} = 2 * \left(\frac{\frac{AMP_L}{ATP_L}}{\left(\frac{K_{AMP_L}}{K_{ATP_L}}\right) + \left(\frac{AMP_L}{ATP_L}\right)} \right);$$

$$Reg_{Cit_{PFK}} = 1.25 * \left(\frac{1}{1 + Cit_{Lc}}\right);$$

$$F_{F6p_{F16bp_L}} = V_{F6p_{F16bp_L}} * \left(\frac{F6p_L}{K_{F6p_L} + F6p_L}\right) * AMP_{Act} * Reg_{Cit_{PFK}};$$

$\%Gluconeogenesis$
$V_{F16bp_{F6p_L}} = 1.056 * Reg_{Glunsis};$
$K_{F16bp_L} = 0.02;$

$$F_{F16bp_{F6p_L}} = V_{F16bp_{F6p_L}} * \left(\frac{F16bp_L}{K_{F16bp_L} + F16bp_L}\right);$$

$\%\%Aldolase$
$\%F16bp < - - - - \rightarrow DHAP + GRP$
$\%\%G6P + ATP - - - \rightarrow 2GA3p + ADP$
$V_{F16bp_{Gap_L}} = 0.269 * 1.5 * Reg_{Glysis};$
$K_{F16bp_L} = 0.04;$

$$F_{F16bp_{Gap_L}} = \left(V_{F16bp_{Gap_L}}\right) * \left(\frac{F16bp_L}{K_{F16bp_L} + F16bp_L}\right);$$

$\%\%Gluconeogenesis - II$
$\%2GAP - - - \rightarrow G6p + Ppi$
$V_{Gap_{F16bp_L}} = 2.112 * 2 * Reg_{Glunsis};$
$K_{Gap_L} = 0.11 * 3;$

$$F_{Gap_{F16bp_L}} = \left(V_{Gap_{F16bp_L}}\right) * \left(\frac{Gap_L}{K_{Gap_L} + Gap_L}\right);$$

$\%Glycolysis\ - III$
$\%Gap + Ppi + NAD + ADP - - - - \rightarrow PEP + NADH + ATP$

$$Glu_{Ntv_{GDH}} = \left(\frac{12^{2.5}}{12^{2.5} + Glu_L^{2.5}}\right);$$

$V_{Gap_{PEP_L}} = 5.22 * 1 * Reg_{Glysis} * Glu_{Ntv_{GDH}};\ \%$
$K_{Gap_L} = 0.11;$
$K_{Ppi_L} = 4.6 * 1;$
$F_{Gap_{PEP_L}} = \left(V_{Gap_{PEP_L}}\right) * \ ATP_{Ntv} * \ RDX_{Ntv} * \ldots$
$(((Gap\_L * Ppi\_L)/(K\_Gap\_L * K\_Ppi\_L))/(1 + (Gap\_L/K\_Gap\_L) + (Ppi\_L/K\_Ppi\_L) \ldots$

$+((Gap\_L * Ppi\_L)/(K\_Gap\_L * K\_Ppi\_L))));$

$\%Gluconeogenesis - I$
$\%PEP + 2ATP + NADH ---\rightarrow GAP + 2ADP + NAD + 2Ppi$
$V_{PEP_{Gap_L}} = 7.83 * 2.0 * 1 * Reg_{OAA_{PEP}};\%$
$K_{PEP_L} = 0.15 * 3;$

$$AMP_{Act} = 5 * \left(\frac{\left(\frac{AMP_L}{ATP_L}\right)^2}{\left(2 * \left(\frac{K_{AMP_L}}{K_{ATP_L}}\right)\right)^2 + \left(\frac{AMP_L}{ATP_L}\right)^2} \right);$$

$$F_{PEP_{Gap_L}} = \left(V_{PEP_{Gap_L}}\right) * ATP_{Ptv} * RDX_{Ptv} * \left(\frac{PEP_L}{K_{PEP_L} + PEP_L}\right) * AMP_{Act};$$

$\%Glycerol\ 3 - P\ Oxidation$
$\%GRP + NAD ----\rightarrow GAP + NADH$
$V_{Grp_{Gap_L}} = 0.444 * Reg_{Glunsis};$
$K_{Grp_L} = 0.24;$

$$F_{Grp_{Gap_L}} = \left(V_{Grp_{Gap_L}}\right) * RDX_{Ntv} * \left(\frac{Grp_L}{K_{Grp_L} + Grp_L}\right);$$

$\%Gluconeogenesis\ IV$
$\%\ \%Oxaloacetae\ to\ PEP$

$V_{OAA_{PEP_L}} = 3.6348 * 1.5 * Reg_{OAA_{PEP}};$
$K_{OAA_{PEP_L}} = 0.002 * 2;$

$$F_{OAA_{PEP_L}} = \left(V_{OAA_{PEP_L}}\right) * \left(\frac{OAA_{cyt_L}}{OAA_{cyt_L} + K_{OAA_{PEP_L}}}\right) * GTP_{Ptv};$$

$\%Glycolysis\ - IV$
$\%PEP + ADP ----\rightarrow Pyr + ATP$
$V_{PEP_{Pyr_L}} = 2.285 * 2.0 * Reg_{PEP_{Pyr}};$
$K_{PEP_{Pyr_L}} = 0.15 * 3;$
$K_{Ala_L} = 0.8;$
$K_{F16bp_L} = 0.02;$

$$Ala_{Ntv_{Reg}} = 1.25 * \left(\frac{K_{Ala_L}}{K_{Ala_L} + Ala_L}\right);$$

$$F16bp_{Ptv_{Reg}} = \left(\frac{F16bp_L}{K_{F16bp_L} + F16bp_L}\right);$$

$$F_{PEP_{Pyr_L}} = \left(V_{PEP_{Pyr_L}} * \left(\frac{PEP_L}{K_{PEP_{Pyr_L}} + PEP_L}\right)\right) * ATP_{Ntv} * F16bp_{Ptv_{Reg}} * Ala_{Ntv_{Reg}};$$

$\%Pyruvate\ Reduction$
$\%Pyr + NADH ------\rightarrow LAC + NAD$
$V_{Pyr_{Lac_L}} = 0.84;$

$K_{Pyr_L} = 0.35;$

$$F_{Pyr_{Lac_L}} = \left(V_{Pyr_{Lac_L}}\right) * RDX_{Ptv} * \left(\frac{Pyr_{Cyt_L}}{K_{Pyr_L} + Pyr_{Cyt_L}}\right);$$

$\%Lactate\ Oxidation$
$\%LAC + NAD - - - - -\rightarrow\ Pyr + NADH$
$V_{Lac_{Pyr_L}} = 1.92 * Reg_{Glunsis};$
$K_{Lac_L} = 0.82;$

$$F_{Lac_{Pyr_L}} = \left(V_{Lac_{Pyr_L}}\right) * \left(\frac{Lac_L}{K_{Lac_L} + Lac_L}\right) * RDX_{Ntv};\ \%$$

$\%Mal - --\rightarrow Pyr$

$$rsnp_L = \frac{NADP_L}{NADPH_L};$$

$$vnp_L = \frac{0.93}{7.1};$$

$V_{Mal_{Pyr_L}} = 0.28 * 2 * Reg_{FAsynt};\ \%$
$K_{Mal_L} = 0.5 * 3;$

$$F_{Mal_{Pyr_L}} = V_{Mal_{Pyr_L}} * \left(\frac{rsnp_L}{rsnp_L + vnp_L}\right) * \left(\frac{Mal_{Lc}}{K_{Mal_L}} + Mal_{Lc}\right);\ \%$$

$\%Pyr_{Transport} to\ mitocondria$
$V_{Pyr_{trans}} = 6.4309 * Reg_{Glunsis};$
$K_{Pyr_{trans}} = 0.1;$

$$F_{Pyr_{trans}} = \left(\frac{V_{Pyr_{trans}}}{K_{Pyr_{trans}}}\right) * \frac{Pyr_{Cyt_L} - Pyr_{mit_L}}{1 + \frac{Pyr_{Cyt_L} + Pyr_{mit_L}}{K_{Pyr_{trans}}}};$$

$\%Gluconeogenesis\ V$
$\%Pyruate\ Carboxylase$
$\%Pyr + ATP + Co2 - - - - -\rightarrow OAA + ADP + P$
$V_{Pyr_{OAA_L}} = 13.0992 * 1.5 * Reg_{Glunsis}; K_{Pyr_{Ln}} = 0.25 * 2;$
$K_{Co2_{L2}} = 15.43;$
$K_{ATP_{L1}} = 2.8;$
$na = 2.5;$
$K_{Acoa_L} = 0.04;$
$AMP_{eff_{Pyr_{OAA}}} = 1;$

$$F_{Pyr_{OAA_L}} = V_{Pyr_{OAA_L}} * \left(\frac{Pyr_{mit_L}}{Pyr_{mit_L} + K_{Pyr_{Ln}}}\right) * \left(\frac{ATP_L}{ATP_L + K_{ATP_{L1}}}\right) * \dots$$
$$\left(\frac{Co2_L}{Co2_L + K_{Co2_{L2}}}\right) * \left(\frac{Acoa_{mit_L^{na}}}{\left(Acoa_{mit_L^{na}}\right) + \left(K_{Acoa_L^{na}}\right)}\right) * AMP_{eff_{Pyr_{OAA}}};\ \%$$

$\%Pyruvate\ Dehydrogenase$

$\%Pyr + Coa + NAD - - - - \rightarrow Acoa + Co2 + NADH + H$

$V_{Pyr_{Acoa_L}} = 1.8 * 1.5 * Reg_{PDH}; \% * ATP_{Ntv2}; \%$

$K_{Pyr_{La}} = 0.25 * 2; \% \frac{0.25}{4};$

$K_{NAD_{La}} = 0.45; \% \frac{0.450}{10};$

$Ki_{NADH_L} = 0.05;$

$K_{Coa_{La}} = 0.14; \% \frac{0.14}{4};$

$Ki_{Acoa_L} = 0.04;$

$$F\_Pyr\_Acoa\_L = (V\_Pyr\_Acoa\_L * (Pyr\_mit\_L/(K\_Pyr\_La + Pyr\_mit\_L)) \ldots$$
$$* \left(\frac{NAD_L}{NAD_L + \left(K_{NAD_{La}} * \left(1 + \left(\frac{NADH_L}{Ki_{NADH_L}} \right) \right) \right)} \right) \ldots$$
$$* (Coa\_L/(Coa\_L + (K\_Coa\_La * (1 + (Acoa\_mit\_L/Ki\_Acoa\_L))))));$$

$\%TCA\ Cycle - I$

$\%OAA + Acoa - - \rightarrow Cit$

$V_{OAA_{Acoa_{Cit_{Lm}}}} = 4.752 * 1.5 * Reg_{CS}; \% * ATP_{Ntv2};$

$K_{OAA_{mit_L}} = 0.003;$

$K_{Acoa_{mit_L}} = 0.08; \%$

$$AMP_{Ptv_{Cit}} = 5.* \left(\frac{\left(\frac{AMP_L}{ATP_L}\right)^2}{\left(\frac{AMP_L}{ATP_L}\right)^2 + \left(2 * \left(\frac{K_{AMP_L}}{K_{ATP_L}}\right)\right)^2} \right);$$

$$F_{OAA_{Acoa_{Cit_{Lm}}}} = V_{OAA_{Acoa_{Cit_{Lm}}}} * \frac{\frac{OAA_{mit_L} * Acoa_{mit_L}}{K_{OAA_{mit_L}} * K_{Acoa_{mit_L}}}}{\ldots \left(1 + \left(\frac{OAA_{mit_L}}{K_{OAA_{mit_L}}} \right) + \left(\frac{Acoa_{mit_L}}{K_{Acoa_{mit_L}}} \right) + \left(\frac{OAA_{mit_L} * Acoa_{mit_L}}{K_{OAA_{mit_L}} * K_{Acoa_{mit_L}}} \right) \right)} * AMP_{Ptv_{Cit}};$$

$\%TCA\ Cycle - III$

$\%Cit - - - \rightarrow AKG$

$V_{Cit_{AKG_L}} = 5.34 * Reg_{ISD} * ATP_{Ntv2};$

$K_{Cit_{Lm}} = 1;$

$Ki_{Scoa} = 3;$

$SucoA_{Ntv_{CS}} = 1 + \left(\frac{Scoa_L}{Ki_{Scoa}} \right);$

$$F_{Cit_{AKG_L}} = V_{Cit_{AKG_L}} * \left(\frac{Cit_{Lm}}{Cit_{Lm} + K_{Cit_{Lm}} * SucoA_{Ntv_{CS}}} \right) * RDX_{Ntv}; \%$$

$\%TCA\ Cycle - IV$

$\%AKG - - \rightarrow SucoA$

$V_{AKG_{Sucoa_L}} = 11.96 * Reg_{AKG} * 2.0;$
$K_{AKG_L} = 0.15 * 3;$
$K_{Coa_L} = 0.14;$
$Ki_{Scoa} = 3;$
$SucoA_{Ntv_{AKG}} = 1 + \left(\frac{Scoa_L}{Ki_{Scoa}}\right);$
$K_{AMP_L} = 0.16;$
$K_{ATP_L} = 2.8;$

$$AMP_{Ptv_{AKG}} = 3.* \left(\frac{\frac{AMP_L}{ATP_L}}{\left(\frac{AMP_L}{ATP_L}\right) + 2 * \left(\frac{K_{AMP_L}}{K_{ATP_L}}\right)}\right);$$

$$F_{AKG_{Scoa_L}} = V_{AKG_{Sucoa_L}} * \left(\frac{AKG_L}{AKG_L + K_{AKG_L}}\right) * \left(\frac{Coa_L}{Coa_L + K_{Coa_L} * SucoA_{Ntv_{AKG}}}\right) * RDX_{Ntv} * AMP_{Ptv_{AKG}};$$

$\%SucCoA - -\!-\!\rightarrow SuC$

$V_{Scoa_{Suc_L}} = 19.136 * 1 * Glcn_{Ptv_{Eff}};$ %;
$K_{Scoa_L} = 1.5;$
$K_{Ppi_L} = 4.6;$

$$F_{Scoa_{Suc_L}} = V_{Scoa_{Suc_L}} * \left(\frac{Scoa_L * \frac{Ppi_L}{K_{Scoa_L} * K_{Ppi_L}}}{1 + \left(\frac{Scoa_L}{K_{Scoa_L}}\right) + \left(\frac{Ppi_L}{K_{Ppi_L}}\right) + \left(Scoa_L * \frac{Ppi_L}{K_{Scoa_L} * K_{Ppi_L}}\right)}\right) * GTP_{Ntv};$$

$\%Suc - -\!-\!\rightarrow Scoa$
$V_{Suc_{Scoa_L}} = 9.568;$
$K_{Suc_L} = 1;$
$K_{Coa_L} = 0.14;$

$$F_{Suc_{Scoa_L}} = V_{Suc_{Scoa_L}} * \left(\frac{Suc_L * \frac{Coa_L}{K_{Suc_L} * K_{Coa_L}}}{1 + \left(\frac{Suc_L}{K_{Suc_L}}\right) + \left(\frac{Coa_L}{K_{Coa_L}}\right) + \left(Suc_L * \frac{Coa_L}{K_{Suc_L} * K_{Coa_L}}\right)}\right) * GTP_{Ptv};$$

$\%TCA\ Cycle - V$
$\%Succinate - -\!\rightarrow Malate$
$V_{Suc_{Mal_L}} = 4.784 * Glcn_{Ptv_{Eff}};$
$K_{Suc_L} = 1;$
$K_{FAD_L} = 2;$
$K_{FADH_L} = 0.24;$

$$FAD_{Ptv} = \frac{\frac{FAD_L}{FADH_L}}{\left(\frac{K_{FAD_L}}{K_{FADH_L}}\right) + \left(\frac{FAD_L}{FADH_L}\right)};$$

$$F_{Suc_{Mal_L}} = V_{Suc_{Mal_L}} * \left(\frac{Suc_L}{K_{Suc_L} + Suc_L}\right) * FAD_{Ptv};$$

%TCA Cycle − VII
%Mal − − − −OAA
$V_{Mal_{OAA_{Lm}}} = 5.424;$
$K_{Mal_{Lm}} = 1;$
$$F_{Mal_{OAA_{Lm}}} = V_{Mal_{OAA_{Lm}}} * \left(\frac{Mal_{Lm}}{K_{Mal_{Lm}} + Mal_{Lm}}\right) * RDX_{Ntv};$$

%TCA Cycle − VI
%OAA − −−→ Mal
$V_{OAA_{Mal_{Lm}}} = 3.9468 * Glcn_{Ptv_{Eff}} * 1.5;$ %;
$K_{OAA_{mit_{Lm}}} = 0.003 * 2;$
$$F_{OAA_{Mal_{Lm}}} = V_{OAA_{Mal_{Lm}}} * \left(\frac{OAA_{mit_L}}{K_{OAA_{mit_{Lm}}} + OAA_{mit_L}}\right) * RDX_{Ptv};$$

%Malate Shuttle
$V_{Mal_{Shtl_L}} = 1.9734 * Glcn_{Ptv_{Eff}} * 1.563;$
$K_{Mal_{Lm}} = 1;$
$$F_{Mal_{Shtl_L}} = V_{Mal_{Shtl_L}} * \left(\frac{Mal_{Lm}}{K_{Mal_{Lm}} + Mal_{Lm}}\right);$$

%Mal − −→ OAA in cytosol
$V_{Mal_{OAA_{Lc}}} = 5.5 * 1.5 * Glcn_{Ptv_{Eff}} * 1.563; K_{Mal_{Lc}} = 0.5 * 2;$
$$F_{Mal_{OAA_{Lc}}} = V_{Mal_{OAA_{Lc}}} * \left(\frac{Mal_{Lc}}{K_{Mal_{Lc}} + Mal_{Lc}}\right) * RDX_{Ntv};$$

%%OAA − −−→ Malin cyosol
$V_{OAA_{Mal_{Lc}}} = 1.8332 * 1.0;$
$K_{OAA_{cyt_{Lc}}} = 0.002;$
$$F_{OAA_{Mal_{Lc}}} = V_{OAA_{Mal_{Lc}}} * \left(\frac{OAA_{cyt_L}}{K_{OAA_{cyt_{Lc}}} + OAA_{cyt_L}}\right) * RDX_{Ptv};$$

%%%%%% − − − −Fatty Acid Metabolism − − − − − −%%

%Citrate Shuttle
$V_{Cit_{Shtl}} = 0.3636 * Reg_{FAsynt};$
$K_{Palcoa_{Li}} = 0.02;$
$$Placoa_{Cit_{Ntv}} = 1 + \left(\frac{Palcoa_{Lm}}{K_{Palcoa_{Li}}}\right);$$
$K_{Cit_{Shtl}} = 1;$
$$F_{Cit_{Shtl}} = V_{Cit_{Shtl}} * \left(\frac{Cit_{Lm}}{Cit_{Lm} + K_{Cit_{Shtl}} * Placoa_{Cit_{Ntv}}}\right);$$ %

%Cit + Coa + ATP − −−→ OAA + Acoa + ADP + Pi
$V_{Cit_{OAA_{Acoa_{Lc}}}} = 1.2 * 1.5 * Reg_{FAsynt};$
$K_{Cit_{Lc}} = 0.5;$
$K_{Coa_L} = 0.14 * 2;$

$K_{Palcoa_{Li}} = 0.06;$

$Placoa_{Acoa_{Ntv}} = 1 + \left(\frac{Palcoa_{Lm}}{K_{Palcoa_{Li}}}\right);$

$F_{Cit_{OAA_{Acoa_{Lc}}}} = V_{Cit_{OAA_{Acoa_{Lc}}}} * \left(\frac{Cit_{Lc}}{Cit_{Lc} + K_{Cit_{Lc}} * Placoa_{Acoa_{Ntv}}}\right) * \left(\frac{Coa_L}{Coa_L + K_{Coa_L}}\right) * ATP_{Ptv};$

$\%Acoa + ATP + Co2 --\rightarrow Malcoa + ADP + Pi$

$V_{Acoa_{Malcoa_L}} = 0.6 * 1.228 * Reg_{FAsynt};$

$K_{Acoa_{Lc}} = 0.03 * 1;$

$K_{Cit_{Lc}} = 0.5 * 2;$

$K_{Palcoa_{Li}} = 0.03;$

$K_{Co2_L} = 15.43;$

$Palcoa_{Malcoa_{Ntv}} = \left(1 + \left(\frac{Palcoa_{Lc}}{K_{Palcoa_{Li}}}\right)\right);$

$F_{Acoa_{Malcoa_L}} = V_{Acoa_{Malcoa_L}} * \left(\frac{Acoa_{cyt_L}}{Acoa_{cyt_L} + K_{Acoa_{Lc}} * \ Palcoa_{Malcoa_{Ntv}}}\right) * \left(1 + \left(\frac{Cit_{Lc}}{K_{Cit_{Lc}} + Cit_{Lc}}\right)\right) \dots$

$* \left(\frac{Co2_L}{K_{Co2_L} + Co2_L}\right) * ATP_{Ptv};$

$\%Acoa + 7Malcoa + NADPH ---\rightarrow FFA + 8CoA + 14NADP + Co2$

$V_{Malcoa_{FFA_L}} = 0.12 * 1.5 * 1.5 * Reg_{FAsynt};$

$K_{Acoa_{Lc}} = 0.06;$

$K_{Malcoa_L} = 0.06;$

$rsnpp_L = \frac{NADPH_L}{NADP_L};$

$vnpp_L = \frac{7.1}{0.93};$

$F_{Malcoa_{FFA_L}} = V_{Malcoa_{FFA_L}} * \left(\frac{rsnpp_L}{rsnpp_L + vnpp_L}\right) * \left(\frac{Acoa_{cyt_L}}{K_{Acoa_{Lc}} + Acoa_{cyt_L}}\right) * \left(\frac{Malcoa_L}{K_{Malcoa_L} + Malcoa_L}\right);$

$\%FFA + ATP + CoA ---\rightarrow PalcoA + AMP + 2Pi$

$V_{FFA_{Palcoa_L}} = 2.992 * Reg_{FABrk};$

$K_{FFA_L} = 0.57;$

$K_{Coa_L} = 0.14 * 3;$

$K_{Malcoa_{Li}} = 0.06;$

$Malcoa_{Palcoa_{Ntv}} = \left(1 + \left(\frac{Malcoa_L}{K_{Malcoa_{Li}}}\right)\right);$

$F_{FFA_{Palcoa_L}} = V_{FFA_{Palcoa_L}} * \left(\frac{FFA_L}{FFA_L + K_{FFA_L}}\right) * \left(\frac{Coa_L}{Coa_L + K_{Coa_L} * Malcoa_{Palcoa_{Ntv}}}\right) * ATP_{Ptv};$

$\%Beta\ Oxidation$

$\%Palcoa + 7CoA + 14NAD --\rightarrow 8ACoA + 14NADH$

$V_{Palcoa_{Acoa_L}} = 1.36 * 1.2 * Reg_{FABrk} * ATP_{Ntv2};$

$K_{Palcoa_{Lm}} = 0.02 * 1;$

$K_{Coa_L} = 0.14;$
$K_{Acoa_{Lm}} = 0.04;$

$$Acoa_{Palcoa_{Ntv}} = \left(1 + \left(\frac{Acoa_{mit_L^4}}{K_{Acoa_{Lm}^4}}\right)\right);$$

$$F_{Palcoa_{Acoa_L}} = V_{Palcoa_{Acoa_L}} * \left(\frac{Palcoa_{Lm}}{Palcoa_{Lm} + K_{Palcoa_{Lm}} * Acoa_{Palcoa_{Ntv}}}\right) * \left(\frac{Coa_L}{Coa_L + K_{Coa_L}}\right) * RDX_{Ntv};$$

%Carnitine Shttule
$V_{Carn_{Shtl}} = 0.544 * Reg_{FABrk};$
$K_{Palcoa_L} = 0.03;$
$K_{Malcoa_{Li}} = 0.03;$

$$F_{Carn_{Shtl}} = V_{Carn_{Shtl}} * \left(\frac{Palcoa_{Lc}}{Palcoa_{Lc} + K_{Palcoa_L}}\right) * \left(\frac{K_{Malcoa_{Li}}}{K_{Malcoa_{Li}} + Malcoa_L}\right);$$

%Glycerol Phosphorylation
%GLR + ATP − − − −→ GRP + ADP
$V_{Glr_{Grp_L}} = 0.576 * 0.5 * Reg_{FAsynt} * (1 + Reg_{Glunsis});$ %
$K_{Glr_L} = 0.07;$

$$F_{Glr_{Grp_L}} = \left(V_{Glr_{Grp_L}}\right) * \left(\frac{Glr_L}{K_{Glr_L} + Glr_L}\right) * ATP_{Ptv};$$

%Lypolysis
%TG − − − −→ GLR + 3FA
$V_{TG_{FFA_{Glr_L}}} = 0.008 * Reg_{TGBrk};$
$K_{TG_L} = 3;$

$$F_{TG_{FFA_{Glr_L}}} = \left(V_{TG_{FFA_{Glr_L}}}\right) * \left(\frac{TG_L}{K_{TG_L} + TG_L}\right);$$

%Triglyceride Synthesis
%GRP + 3FA + 6ATP − − − − − − − − −→ TG + 6ADP + 7Ppi
$V_{FFA_{Grp_{TG_L}}} = 0.8 * 1.0 * Reg_{TGsynt};$
$K_{FFA_L} = 0.57;$
$K_{Grp_L} = 0.24;$

```
F_FFA_Grp_TG_L = (V_FFA_Grp_TG_L) * ATP_Ptv * (((FFA_L * Grp_L)/(K_FFA_L * K_Grp_L)) ...
  /(1 + (FFA_L/K_FFA_L) + (Grp_L/K_Grp_L) + ((FFA_L * Grp_L)/(K_FFA_L * K_Grp_L))));
```

%TCA Cycle − VII
%Acoa − −−→ Ket
$V_{Acoa_{Ket_L}} = 0.1 * Insu_{Ntv_{Eff}};$
$K_{camp} = 10^{-5.5};$
$ep = 2;$

$$F_{Acoa_{Ket_L}} = V_{Acoa_{Ket_L}} * \left(Acoa_{mit_L^2}\right) * \left(1 + \left(\frac{cAMP^{ep}}{(K_{camp}^{ep}) + (cAMP^{ep})}\right)\right);$$

%Ketone transport

$Vt_{Ket_L} = 0.1;$

$T_{Ket_L} = Vt_{Ket_L} * Ket_L;$

%Oxidative Phosphorylation

%O2 + 6ADP + 6Ppi + 2NADH – – – – –→ 2H2O + 6ATP + 2NAD

$V_{O2_{H2O_{Ln}}} = 40.076 * 0.8 * Reg_{Oxphos};$

$K_{o2_L} = 0.027;$

$K_{Rdxp} = 0.11;$

$K_{Ppi_L} = 4.6;$

$$F_{O2_{H2O_{Ln}}} = \left(V_{O2_{H2O_{Ln}}}\right) * ATP_{Ntv} * \left(\frac{Rdx_P}{K_{Rdxp} + Rdx_P}\right) * (((O2\_L * Ppi\_L)/(K\_o2\_L * K\_Ppi\_L))/((1 + (O2\_L/K\_o2\_L) + (Ppi\_L/K\_Ppi\_L) + ((O2\_L * Ppi\_L)/(K\_o2\_L * K\_Ppi\_L)))));$$

%O2 + 4ADP + 4Ppi + 2FADH – – – – –→ 2H2O + 4ATP + 2FAD

$V_{O2_{H2O_{Lf}}} = 16.16 * 0.9 * Reg_{Oxphos};$

$K_{o2_L} = 0.027;$

$K_{Ppi_L} = 4.6;$

$K_{FADH_L} = 0.24;$

$K_{FAD_L} = 2;$

$$FADH_{Ptv} = \frac{\frac{FADH_L}{FAD_L}}{\left(\frac{K_{FADH_L}}{K_{FAD_L}}\right) + \left(\frac{FADH_L}{FAD_L}\right)};$$

$$F_{O2_{H2O_{Lf}}} = \left(V_{O2_{H2O_{Lf}}}\right) * ATP_{Ntv} * FADH_{Ptv} * (((O2\_L * Ppi\_L)/(K\_o2\_L * K\_Ppi\_L))/((1 + (O2\_L/K\_o2\_L) + (Ppi\_L/K\_Ppi\_L) + ((O2\_L * Ppi\_L)/(K\_o2\_L * K\_Ppi\_L)))));$$

%ATP Hydrolysis

%ATP – – – –→ ADP + Ppi

$V_{ATP_{ADP_L}} = 33.4004 * 0.70 * Reg_{ATPlysis};$

$K_{ATP_L} = 2.8;$

$$F_{ATP_{ADP_L}} = \left(V_{ATP_{ADP_L}}\right) * \left(\frac{ATP_L}{K_{ATP_L} + ATP_L}\right);$$

%Alanine Transport

%ATP–→ GTP

$V_{ATP_{GTP_{Lm}}} = 87.5;$

$Keq_{ATP_{GTP_L}} = 0.8464;$

$K_{ATP_{Lm}} = 2.8;$ %1.33;

$K_{GDP_{Lm}} = 0.1;$ %0.031;

$K_{ADP_{Lm}} = 0.8;$ %0.042;

$K_{GTP_{Lm}} = 0.3;$ %0.15;

$$F\_ATP\_GTP\_L = (((V\_(ATP\_(GTP\_Lm))/(K\_(ATP\_Lm) * K\_(GDP\_Lm))) * ((ATP\_L * GDP\_L) - ((ADP\_L * (GTP\_L)/(Keq\_(ATP\_(GTP\_L))))))) / ((1 + (ATP\_L/K\_ATP\_Lm)) * (1 + (GDP_L/K\_GDP\_Lm)) + ((1 + (ADP\_L/K\_ADP\_Lm)) * (1 + (GTP\_L/K\_GTP\_Lm))) - 1));$$

%Adenylate Kinase
%ATP + AMP < − − − −→ 2ADP
$V_{ATP_{AMP_{ADP_L}}} = 25;$
$Keq_{ATP_{AMP_{ADP_L}}} = 1.43;$
$K_{ATP_{L4}} = 2.8;$ %0.09;
$K_{AMP_{L2}} = 0.16;$ %0.08;
$K_{ADP_{L2}} = 0.8;$ %0.11;

$$F_{ATP_{AMP_{ADP_L}}} = \frac{\left(\frac{V_{ATP_{AMP_{ADP_L}}}}{K_{ATP_{L4}} * K_{AMP_{L2}}}\right) * \left((ATP_L * AMP_L) - \left(\frac{ADP_L^2}{Keq_{ATP_{AMP_{ADP_L}}}}\right)\right)}{\left(\left(1 + \left(\frac{ATP_L}{K_{ATP_{L4}}}\right)\right) * \left(1 + \left(\frac{AMP_L}{K_{AMP_{L2}}}\right)\right) + \left(2 * \frac{ADP_L}{K_{ADP_{L2}}}\right) + \left(\frac{ADP_L^2}{K_{ADP_{L2}}^2}\right)\right)};$$

%ATP + UDP < − −−→ ADP + UTP
$V_{ATP_{UTP_L}} = 87.5 * 0.10;$ % $* Insu_{Ptv_{Eff}}$;
$Keq_{ATP_{UTP_L}} = 1;$
%$K_{GDP_L} = 0.031;$
$K_{ATP_{L3}} = 2.8;$
$K_{ADP_{L1}} = 0.8;$
%$K_{GTP_L} = 0.15;$
$K_{UDP_L} = 0.19;$
$K_{UTP_L} = 16;$

$$F_{ATP_{UTP_L}} = \frac{\left(\frac{V_{ATP_{UTP_L}}}{K_{ATP_{L3}} * K_{UDP_L}}\right) * (ATP_L * UDP_L) - \left(\frac{ADP_L * UTP_L}{Keq_{ATP_{UTP_L}}}\right)}{\left(\left(1 + \left(\frac{ATP_L}{K_{ATP_{L3}}}\right)\right) * \left(1 + \left(\frac{UDP_L}{K_{UDP_L}}\right)\right) + \left(1 + \left(\frac{ADP_L}{K_{ADP_{L1}}}\right)\right) * \left(1 + \left(\frac{UTP_L}{K_{UTP_L}}\right)\right) - 1\right)}$$

%%%%%% − − − −Amino Acid Metabolism − − − − − − − −

%Pyruvate formation from Amino Acids
%Ala + AKG − −−→ pyr + Gmt
$V_{Ala_{Pyr_L}} = 0.96 * Reg_{ProBrk};$ % $* Reg_{Glunsis1} Insu_{Eff1_{Ntv}} * \left(1 + Glcgn_{Eff_{Ptv}}\right) * 1.33;$ % $* 120;$
$K_{Ala_L} = 0.20;$
$K_{AKG_L} = 0.15;$
$$F_{Ala_{Pyr_L}} = V_{Ala_{Pyr_L}} * \left(\frac{Ala_L}{Ala_L + K_{Ala_L}}\right) * \left(\frac{AKG_L}{AKG_L + K_{AKG_L}}\right);$$

%Protein sunthesis
%Pyr + Gmt − −−→ AKG + Ala
$V_{Pyr_{Ala_L}} = 0.32 * Reg_{Prosynt};$
$K_{Pyr_L} = 0.25;$
$K_{Gmt_L} = 0.3;$ % 4.3;

$$F_{Pyr_{Ala_L}} = V_{Pyr_{Ala_L}} * \left(\frac{Pyr_{mit_L}}{Pyr_{mit_L} + K_{Pyr_L}}\right) * \left(\frac{Gmt_L}{Gmt_L + K_{Gmt_L}}\right);$$

%*Aspartate formation*
%*OAA* + *Gmt* − −−→ *AKG* + *Asprt*

$V_{OAA_{Asprt_L}} = 0.768 * 0.5625;$

$K_{OAA_{Lc}} = 0.002 * 0.5;$

$K_{Gmt_L} = 0.3 * 0.5;$

$$F_{OAA_{Asprt_L}} = V_{OAA_{Asprt_L}} * \left(\frac{OAA_{cyt_L}}{OAA_{cyt_L} + K_{OAA_{Lc}}}\right) * \left(\frac{Gmt_L}{Gmt_L + K_{Gmt_L}}\right);$$

%*Aspartate to OAA*
%*Asprt* + *AKG* − −−→ *Gmt* + *OAA*

$V_{Asprt_{OAA_L}} = 0.256 * 1.5 * Reg_{ProBrk};$

$K_{Asprt_L} = 0.6 * 2;$

$K_{AKG_L} = 0.15;$

$$F_{Asprt_{OAA_L}} = V_{Asprt_{OAA_L}} * \left(\frac{Asprt_L}{Asprt_L + K_{Asprt_L}}\right) * \left(\frac{AKG_L}{AKG_L + K_{AKG_L}}\right);$$

%*Protein synthesis*
%*Ala* − −→ *Prot*

$V_{Ala_{Prot}} = 0.1 * 1.5 * Reg_{Prosynt};$

$K_{Ala_L} = 0.25 * 2;$

$$F_{Ala_{Prot_L}} = V_{Ala_{Prot}} * \left(\frac{Ala_L}{Ala_L + K_{Ala_L}}\right);$$

%*Asprt* − −→ *Prot*

$V_{Asprt_{Prot_L}} = 0.1 * 2.5 * Reg_{Prosynt};$

$K_{Asprt_L} = 0.6 * 4;$

$$F_{Asprt_{Prot_L}} = V_{Asprt_{Prot_L}} * \left(\frac{Asprt_L}{Asprt_L + K_{Asprt_L}}\right);$$

%*Gmt* − −−→ *Prot*

$V_{Gltm_{Prot_L}} = 0.1 * 1.5 * Reg_{Prosynt};$

$K_{Gltm_L} = 0.5 * 2;$

$$F_{Gltm_{Prot_L}} = V_{Gltm_{Prot_L}} * \left(\frac{Gltm_L}{Gltm_L + K_{Gltm_L}}\right);$$

%*Prot break down*
%$Prot_{AA}$

$V_{Prot_{Ala_L}} = 0.1 * Reg_{ProBrk};$

$K_{Prot_L} = 250;$

$$F_{Prot_{Ala_L}} = V_{Prot_{Ala_L}} * \left(\frac{Prot_L}{Prot_L + K_{Prot_L}}\right);$$

$\%Prot_{Asprt}$
$V_{Prot_{Asprt_L}} = 0.1 * 0.75 * Reg_{ProBrk};$
$K_{Prot_L} = 250 * 0.5;$
$AMP_{Ptv} = 1;$

$$F_{Prot_{Asprt_L}} = V_{Prot_{Asprt_L}} * \left(\frac{Prot_L}{Prot_L + K_{Prot_L}}\right) * AMP_{Ptv};$$

$\%Prot_{Gmt}$
$\%Prot_{Glmtt}$
$V_{Prot_{Gltm_L}} = 0.1 * Reg_{ProBrk};$
$K_{Prot_L} = 250;$
$$F_{Prot_{Gltm_L}} = V_{Prot_{Gltm_L}} * \left(\frac{Prot_L}{Prot_L + K_{Prot_L}}\right);$$

$\%Urea\ cycle$

$\%UC - I$
$\%Gmt + NADP <-----\rightarrow AKG + NH4 + NADPH$
$V_{Gmt_{AKG_L}} = 0.96 * 1 * 2.5 * Reg_{ProBrk};$
$K_{Gmt_L} = 0.3 * 4;$
$$FFA_{Ntv_{GDH}} = 1.0 * \left(\frac{2.5^2}{2.5^2 + FFA_L^2}\right);$$
$$F_{Gmt_{AKG_L}} = V_{Gmt_{AKG_L}} * \left(\frac{Gmt_L}{Gmt_L + K_{Gmt_L}}\right) * RDX_{Ntv} * FFA_{Ntv_{GDH}}; \%$$

$\%AKG + NH4 + NADPH <----\rightarrow Gmt + NADP$
$V_{AKG_{Gmt_L}} = 0.64 * Reg_{Prosynt};$
$K_{AKG_L} = 0.15 * 1;$
$K_{NH4_L} = 0.086;$
$$F_{AKG_{Gmt_L}} = V_{AKG_{Gmt_L}} * \left(\frac{AKG_L}{AKG_L + K_{AKG_L}}\right) * \left(\frac{NH4_L}{NH4_L + K_{NH4_L}}\right) * RDX_{Ptv};$$

$\%UC - II$
$\%N - Acytyl\ glutamate\ formation$
$\%Acoa_{Gmt} <--\rightarrow Coa + NAG$
$V_{Acoa_{Gmt_{NAG_L}}} = 0.2 * 1;$
$K_{Gmt_L} = 0.3;$
$K_{Acoa_{Lm}} = 0.04 * 0.5;$
$K_{Arg_L} = 0.07 * 1;$
$$Reg_{Arg_{NAG}} = 1 + \left(\frac{Arg_L}{Arg_L + K_{Arg_L}}\right);$$
$$F_{Acoa_{Gmt_{NAG_L}}} = V_{Acoa_{Gmt_{NAG_L}}} * \left(\frac{Acoa_{mit_L}}{Acoa_{mit_L} + K_{Acoa_{Lm}}}\right) * \left(\frac{Gmt_L}{Gmt_L + K_{Gmt_L}}\right) * Reg_{Arg_{NAG}};$$

$\%NAG + Coa <---\rightarrow Acoa + Gmt$
$V_{NAG_{Acoa_{Gmt_L}}} = 0.4 * 2.0;$
$K_{Coa_L} = 0.14;$

$K_{NAG_L} = 0.02 * 3;$

$$F_{NAG_{Acoa_{Gmt_L}}} = V_{NAG_{Acoa_{Gmt_L}}} * \left(\frac{NAG_L}{NAG_L + K_{NAG_L}}\right) * \left(\frac{Coa_L}{Coa_L + K_{Coa_L}}\right);$$

%UC − III
%Carbomyl phosphate formation
%NH4 + Co2 + 2ATP −−−−−−−−→ Crbphos + 2ADP + 2pi

$V_{NH4_{Crbphos_L}} = 1.6 * 3.1 * 1 * \; Reg_{URC} * 1.563;$

$K_{NH4_L} = 0.086 * 5;$

$K_{Co2_L} = 15.43 * 1;$

$K_{NAG_L} = 0.02 * 1;$

$$Reg_{NAG_{CPS}} = \left(\frac{NAG_L}{NAG_L + K_{NAG_L}}\right);$$

$$FFA_{Ntv_{CPS}} = 1.0 * \left(\frac{1.8^2}{1.8^2 + FFA_L^2}\right);$$

$AMP_{Ptv_{Crb}} = 1;$

$$F_{NH4_{Crbphos_L}} = V_{NH4_{Crbphos_L}} * \left(\frac{NH4_L}{NH4_L + K_{NH4_L}}\right) * \left(\frac{Co2_L}{Co2_L + K_{Co2_L}}\right) * Reg_{NAG_{CPS}} * ATP_{Ptv} * FFA_{Ntv_{CPS}} * AMP_{Ptv_{Crb}};$$

%UC − IV
%Citrullin formation
%Crbphos + Ornitine −−−−−→ Citrullin + Pi

$V_{Crbphos_{Ornit_{Citrin_L}}} = 0.64 * 3.0 * 1.75 * \; Reg_{URC} * 1.563;$

$K_{Crbphos_L} = 0.05 * 4.0;$

$K_{Ornit_L} = 0.052 * 2;$

$$F_{Crbphos_{Ornit_{Citrin_L}}} = V_{Crbphos_{Ornit_{Citrin_L}}} * \left(\frac{Crbphos_L}{Crbphos_L + K_{Crbphos_L}}\right) * \left(\frac{Ornit_L}{Ornit_L + K_{Ornit_L}}\right);$$

%UC − V
%Citrulin + Aspartate + ATP −−−−→ Succinate + Arginine + ADP + Pi

$V_{Citrin_{Asprt_{Arg_L}}} = 2.5 * 1.28 * 2 * \; Reg_{URC} * 1.563;$

$K_{Citrin_L} = 0.03 * 5;$

$K_{Asprt_L} = 0.6;$

$$AMP_{Ptv_{Citrin}} = 12 * \left(\frac{\left(\frac{AMP_L}{ATP_L}\right)^2}{\left(\frac{AMP_L}{ATP_L}\right)^2 + \left(3 * \left(\frac{K_{AMP_L}}{K_{ATP_L}}\right)\right)^2}\right);$$

$$F_{Citrin_{Asprt_{Arg_L}}} = V_{Citrin_{Asprt_{Arg_L}}} * \left(\frac{Citrin_L}{Citrin_L + K_{Citrin_L}}\right) * \left(\frac{Asprt_L}{Asprt_L + K_{Asprt_L}}\right) * ATP_{Ptv} * AMP_{Ptv_{Citrin}};$$

%UC − VI
%Arg −−−−→ Urea + Ornitine

$V_{Arg_{Ornit_{Urea_L}}} = 0.32 * 1 * 2 * \; Reg_{URC} * 1.563 * 1.25;$

$K_{Arg_L} = 0.07 * 3;$

$$F_{Arg_{Ornit_{Urea_L}}} = V_{Arg_{Ornit_{Urea_L}}} * \left(\frac{Arg_L}{Arg_L + K_{Arg_L}}\right);$$

$\%Glutamine\ deamination$
$V_{Gltm_{Gmt_L}} = 0.256 * 1.5 * Reg_{ProBrk};$
$K_{Gltm} = 0.5 * 2;$
$F_{Gltm_{Gmt_L}} = V_{Gltm_{Gmt_L}} * \left(\frac{Gltm_L}{Gltm_L + K_{Gltm}}\right);$

$\%\%\%\% - - - - - - - Hexoseamine\ Pathway - - - - - - - - - - \%\%\%\%\%$
$\% - Glucosamoine\ formation$
$\%F6p + Glutamine - - -\rightarrow Glucosamine$
$V_{F6p_{Glsmn_L}} = 0.6 * 0.062 * 2.23 * 0.1 * 0.5; \%e - 1$
$K_{F6p_L} = 0.1; \% - - - - - -$
$K_{Gltm} = 0.5 * 2;$
$Ki_{GlNAc} = 0.015 * 3;$
$FFA_{Ptv_{HSP}} = 4 * \left(\frac{FFA_L}{FFA_L + 1.7}\right);$
$GlNAc_{Ntv_{HSP}} = 1 + \left(\frac{GlNAc_L}{Ki_{GlNAc}}\right);$
$F_{F6p_{Glsmn_L}} = V_{F6p_{Glsmn_L}} * \left(\frac{F6p_L}{F6p_L + K_{F6p_L}}\right) * \left(\frac{Gltm_L}{Gltm_L + K_{Gltm} * GlNAc_{Ntv_{HSP}}}\right) * FFA_{Ptv_{HSP}} * Glu_{Ptv_{HSP}};$

$\%N - acetylglucosamine\ Formation$
$\%Glucosamine + Acoa + UTP - - - - - - -\rightarrow UDP_N - AcetylGlucosamine + Coa + Ppi$
$V_{Glsmn_{GlNAc_L}} = 0.05 * 1.43 * 2 * 0.1 * 0.5 * 0.5; \%e - 1$
$K_{Glsmn} = 0.26;$
$K_{Acoa_{cyt_L}} = 0.03;$
$K_{UTP_L} = 0.27;$
$Glu_{Ptv_{HSP}} = \left(3 * \left(\frac{Glu_L}{Glu_L + 12}\right)\right);$

$F_{Glsmn_{GlNAc_L}} = V_{Glsmn_{GlNAc_L}} * \left(\frac{Glsmn_L}{Glsmn_L + K_{Glsmn}}\right) * \left(\frac{Acoa_{cyt_L}}{Acoa_{cyt_L} + K_{Acoa_{cyt_L}}}\right) * \left(\frac{UTP_L}{UTP_L + K_{UTP_L}}\right) * Glu_{Ptv_{HSP}};$

$\%N_{Acetylglucosamine} decay$
$kd_{glnac} = 0.01 * 2 * 0.5 * 0.11; \%e - 1$
$Km_{GlNAc} = 0.015 * 3;$
$GlNAc_{decay} = kd_{glnac} * \left(\frac{GlNAc_L}{GlNAc_L + Km_{GlNAc}}\right);$

$\%\%\%\%\% - Cholesterol\ biosynthesis\ Pathway - - - -$
$- - - - - \%\%\%\%\%$

$rsnpp_L = \frac{NADPH_L}{NADP_L}; \%0.015; \%$
$vnpp_L = \frac{7.1}{0.93};$

%HMGCoa Synthesis
%3Acoa ----→ HMGCoa + 2Coa ---–HMGCoA synthase

$V_{Acoa_{HMGCoa_L}} = (1.5 * 8e-4) * Reg_{Chol_{Synt}};$

$K_{Acoa_L} = 0.03;$

$Ki_{Chol_L} = 12;$

$$F_{Acoa_{HMGCoa_L}} = V_{Acoa_{HMGCoa_L}} * \left(\frac{Acoa_{cyt_L}}{Acoa_{cyt_L} + K_{Acoa_L}}\right) * \left(\frac{Ki_{Chol_L^2}}{Ki_{Chol_L^2} + Chol_L^2}\right);$$

%Mevelonate synthesis --HMGCoA Reductase
%HMGCoa + 2NADPH ----→ Mevl + 2NADP

$V_{HMGCoa_{Mevl_L}} = (1.5 * 20e-4) * Reg_{Chol_{Synt}};$

$K_{HMGCoa_L} = 0.03;$

$Ki_{Mevl} = 0.4;$

$$Mevl_{Ntv} = \left(1 + \left(\frac{Mevl_L}{Ki_{Mevl}}\right)\right);$$

$$F_{HMGCoa_{Mevl_L}} = V_{HMGCoa_{Mevl_L}} * \left(\frac{HMGCoa_L}{HMGCoa_L + K_{HMGCoa_L} * Mevl_{Ntv}}\right) * \left(\frac{rsnpp_L}{rsnpp_L + vnpp_L}\right) * \left(\frac{Ki_{Chol_L^2}}{Ki_{Chol_L^2} + Chol_L^2}\right) * ATP_{Ntv2};$$

%Squalene synthesis
%Mevl + NADPH + 3ATP ---→ Squl + NADP + 3ADP + 3Pi + Co2;

$V_{Mevl_{Squl_L}} = (32 * 1e-4) * Reg_{Chol_{Synt}};$

$K_{Mevl_L} = 0.2;$

$$F_{Mevl_{Squl_L}} = V_{Mevl_{Squl_L}} * \left(\frac{Mevl_L}{Mevl_L + K_{Mevl_L}}\right) * \left(\frac{rsnpp_L}{rsnpp_L + vnpp_L}\right) * ATP_{Ptv};$$

%Cholesterol synthesis
%Squl + 2o2 + NADPH ---→ Chol + NADP + 2Co2;

$V_{Squl_{Chol_L}} = (16 * 1e-4) * Reg_{Chol_{Synt}};$

$K_{Squl_L} = 0.18;$

$$F_{Squl_{Chol_L}} = V_{Squl_{Chol_L}} * \left(\frac{Squl_L}{Squl_L + K_{Squl_L}}\right) * \left(\frac{rsnpp_L}{rsnpp_L + vnpp_L}\right);$$

%Bile Acid Synthesis

$V_{Chol_{Bile_L}} = (5.5 * 1e-5) * Reg_{Chol_{Synt}};$

$K_{Chol_L} = 6;$

$$F_{Chol_{Bile_L}} = V_{Chol_{Bile_L}} * \left(\frac{Chol_L}{Chol_L + K_{Chol_L}}\right) * \left(\frac{rsnpp_L}{rsnpp_L + vnpp_L}\right);$$

%%%%%%Plasma uptake and release of Metabolites %%%%%

%Glu_{up}

%$Glu_{up_L} = -0.731;$

$Tb_{Glu_{cyt}} = 40;$ %37.5;

$Mb_{Glu_L} = 12;$

$$Glu_{up_L} = Reg_{Glu_{up}} * Tb_{Glu_{cyt}} * \left(\left(\frac{Cb_{Glu_L}}{Mb_{Glu_L} + Cb_{Glu_L}}\right) - \left(\frac{Glu_L}{Mb_{Glu_L} + Glu_L}\right)\right);$$

$\%Pyr_{up}$
$Tb_{Pyr_L} = 1.12;$
$Mb_{Pyr_L} = 0.068;$
$Mb_{Pyr_{Cyt_L}} = 1;$

$$Pyr_{up_L} = Tb_{Pyr_L} * \left(\left(\frac{Cb_{Pyr_L}}{Mb_{Pyr_L} + Cb_{Pyr_L}}\right) - \left(1.02 * \frac{Pyr_{Cyt_L}}{Mb_{Pyr_L} + Mb_{Pyr_{Cyt_L}}}\right)\right);$$

$\%Lac_{up}$
$Tb_{Lac_L} = 2.816;$
$Mb_{Lac_L} = 0.6;$

$$Lac_{up_L} = Tb_{Lac_L} * \left(\left(\frac{Cb_{Lac_L}}{Mb_{Lac_L} + Cb_{Lac_L}}\right) - \left(\frac{Lac_L}{Mb_{Lac_L} + Lac_L}\right)\right);$$

$\%Ala\ pool\ (release)$
$Tb_{Ala_L} = 1.5 * 0.750;$
$Mb_{Ala_L} = 0.25;$
$Mb_{Ala_{Lt}} = 0.5;$

$$Ala_{up_L} = Reg_{AA_{up}} * Tb_{Ala_L} * \left(\left(\frac{Cb_{Ala_L}}{Mb_{Ala_L} + Cb_{Ala_L}}\right) - \left(\frac{Ala_L}{Mb_{Ala_{Lt}} + Ala_L}\right)\right);$$

$\%Gltm - Glutamine\ pool$
$Tb_{Glmt_L} = 1.5 * 0.750;$
$Mb_{Gltm_L} = 0.25;$
$Mb_{Gltm_{Lt}} = 1;$

$$Gltm_{up_L} = Reg_{AA_{up}} * Tb_{Glmt_L} * \left(\left(\frac{Cb_{Ala_L}}{Mb_{Gltm_L} + Cb_{Ala_L}}\right) - \left(\frac{Gltm_L}{Mb_{Gltm_{Lt}} + Gltm_L}\right)\right);$$

$\%Asprt - Aspartate\ pool$
$Tb_{Asprt_L} = 0.25 * 1.5 * 0.750;$
$Mb_{Asprt_L} = 0.25;$
$Mb_{Asprt_{Lt}} = 1;$

$$Asprt_{up_L} = Reg_{AA_{up}} * Tb_{Asprt_L} * \left(\left(\frac{Cb_{Ala_L}}{Mb_{Asprt_L} + Cb_{Ala_L}}\right) - \left(\frac{Asprt_L}{Mb_{Asprt_{Lt}} + Asprt_L}\right)\right);$$

$AA_{up_L} = Ala_{up_L} + Gltm_{up_L} + Asprt_{up_L};$

$\%Free\ Fatty\ Acids(uptake)$
$Mb_{FFA_L} = 0.57;$
$Tb_{FFA_L} = 4.77;$
$lam_{FFA_L} = 1.9;$

$$FFA_{up_L} = Reg_{Fat_{up}} * Tb_{FFA_L} * \left(\left(\frac{Cb_{FFA_L}}{Mb_{FFA_L} + Cb_{FFA_L}}\right) - \left(\frac{FFA_L}{Mb_{FFA_L} + FFA_L}\right)\right);$$

$\%Glycerol(uptake)$
$lam_{Glr_L} = 32;$
$Glr_{up_L} = lam_{Glr_L} * (Cb_{Glr_L} - Glr_L);$

$\%Triglycerides\ (Uptake)$
$lam_{TG_L} = 0.01450;$
$TG_{rel_L} = lam_{TG_L} * \left(\left(Cb_{TG_L} - TG_L\right)\right);$

$\%Carbon\ dioxide\ production\ @\ 0.8\ RQ$

$lam_{Co2_L} = 0.140;$
$Co2_{rel_L} = lam_{Co2_L} * \left(Cb_{Co2_L} - 1 * Co2_L\right);$

$\%Oxygen\ uptake\ @\ 0.8\ RQ$

$lam_{O2_L} = 0.86 * 51;$
$O2_{up_L} = lam_{O2_L} * \left(Cb_{O2_L} - O2_L\right);$

$\%Urea\ Transport$
$V_{Urea_{Bld}} = 0.32 * 1.563;$
$Ca_{Urea_L} = 8;$
$F_{Urea_{Bld}} = V_{Urea_{Bld}} * \left(Urea_L - 0.55 * Ca_{Urea_L}\right);$

$\%Ammonia\ Transport$
$V_{NH4_{Bld}} = 1.367;$
$Ca_{NH4} = 0.09;$
$F_{NH4_{Bld}} = V_{NH4_{Bld}} * (NH4_L - 0.58 * Ca_{NH4});$

$Vol_{tis_L} = 1.5; \%lit$
$Vol_{bld} = 1.5; \%lit5; \%$
$Vol_{celf} = 0.80 * Vol_{tis_L}; \% * .03; \%$
$Vol_{cytl} = 0.75 * Vol_{celf};$
$Vol_{mitl} = 0.25 * Vol_{celf};$
$Vol_{bldf} = \frac{Vol_{bld}}{Vol_{tis_L}};$
$Vglu_L = Vol_{cytl}; \%1.397968; \%$
$Vpyr_L = Vol_{cytl}; \%1.3484084; \%$
$Vpyr_{Lm} = Vol_{mitl}; \%Vpyr_L; \%0.05 * Vpyr_L; \%$
$Vlac_L = Vol_{cytl}; \%1.3933634; \%$
$Vala_L = Vol_{cytl}; \%1.3461162; \%$
$Vglr_L = Vol_{cytl}; \%1.33471481; \%$
$Vffa_L = Vol_{cytl}; \%1.4353053; \%$
$Vtg_L = Vol_{cytl}; \%1.3642343; \%$
$Veff_L = Vol_{cytl}; \%1.144; \%$
$Veff_{Lm} = Vol_{mitl}; \%Veff_L; \%0.05 * 1.43; \%$
$Vo2_L = Vol_{mitl}; \%23.18173; \%$

ODE Equations − Mass Balance

%Glucose Balance
%Gluprime
$dP(1) = ((F\_G6p\_Glu\_L) - (F\_Glu\_G6p\_L) + (Glu\_up\_L))/Vglu\_L;$

%Glucose 6 − Phosphate balance
%G6pprime
$dP(2) = ((F\_Glu\_G6p\_L) + (F\_Gly\_G6p\_L) - (F\_G6p\_Glu\_L) - (F\_G6p\_Gly\_L) - (F\_G6p\_F6p\_L) + (F\_F6p\_G6p\_L) - (F\_G6p\_R5p\_L))/Veff\_L;$

%Glycogen Balance
%Glyprime
$dP(3) = (((F\_G6p\_Gly\_L) - (F\_Gly\_G6p\_L)))/Veff\_L;$

%Glyceraldehyde Phosphate(GAP) Balance
%Gapprime
$dP(4) = ((2 * (F\_F16bp\_Gap\_L)) + (F\_PEP\_Gap\_L) + (F\_Grp\_Gap\_L) - (F\_Gap\_F16bp\_L) - (F\_Gap\_PEP\_L) + ((1/3) * F\_R5p\_F6p\_Gap\_L))/Veff\_L;$

%PEP_cyt
$dP(5) = (F\_Gap\_PEP\_L - F\_PEP\_Gap\_L - (F\_PEP\_Pyr\_L) + (F\_OAA\_PEP\_L))/Veff\_L;$

%Pyruvate Balance
%Pyrprime =
$dP(6) = ((F\_PEP\_Pyr\_L) + (F\_Lac\_Pyr\_L) - (F\_Pyr\_Lac\_L) + (F\_Ala\_Pyr\_L) - (F\_Pyr\_Ala\_L) + F\_Mal\_Pyr\_L - F\_Pyr\_trans + Pyr\_up\_L)/Vpyr\_L;$

%Pyr_mit_L
$dP(129) = (F\_Pyr\_trans - F\_Pyr\_OAA\_L - F\_Pyr\_Acoa\_L)/Vpyr\_Lm;$

%Lactate Balance
%Lacprime
$dP(7) = ((F\_Pyr\_Lac\_L) - (F\_Lac\_Pyr\_L) + (Lac\_up\_L))/Vlac\_L;$

%Alanine Balance
%Alaprime
$dP(8) = (F\_Pyr\_Ala\_L - (F\_Ala\_Pyr\_L) - (F\_Ala\_Prot\_L) + (F\_Prot\_Ala\_L) + (Ala\_up\_L))/Vala\_L;$

%Glycerol Balance
%Glrprime
$dP(9) = ((F\_TG\_FFA\_Glr\_L) - (F\_Glr\_Grp\_L) + (Glr\_up\_L))/Vglr\_L;$

%Free Fatty Acid Balance
%FFAprime
$dP(10) = ((3 * (F\_TG\_FFA\_Glr\_L)) + (F\_Malcoa\_FFA\_L) - (F\_FFA\_Grp\_TG\_L) - (F\_FFA\_Palcoa\_L) + (FFA\_up\_L))/Vffa\_L;$

%Glycerol 3 Phosphate(GRP)Balance
%Grpprime
$dP(11) = ((F\_Glr\_Grp\_L) - (F\_Grp\_Gap\_L) - ((F\_FFA\_Grp\_TG\_L)/3))/Veff\_L;$

%Triglyceride Balance
%TGprime
$dP(12) = (((F\_FFA\_Grp\_TG\_L)/3) - (F\_TG\_FFA\_Glr\_L) + (TG\_rel\_L))/Vtg\_L;$

%Oxygen Balance
%O2prime
$dP(13) = (((-F\_O2\_H2O\_Ln) - (F\_O2\_H2O\_Lf)) + (O2\_up\_L))/Vo2\_L;$

%Carbon Dioxide Balance
%Co2prime
$H\_ion\_cel = 7.94e - 5;$
$K\_Co2\_hyd = 7.95e - 4;$
$Vol\_cel\_Co2\_L = Veff\_L * (1 + (K\_Co2\_hyd/H\_ion\_cel));$
$$dP(14) = (F\_OAA\_PEP\_L + (7 * F\_Malcoa\_FFA\_L) + F\_Pyr\_Acoa\_L + F\_Cit\_AKG\_L + F\_AKG\_Scoa\_L + F\_G6p\_R5p\_L + F\_Mal\_Pyr\_L - F\_NH4\_Crbphos\_L - F\_Pyr\_OAA\_L - F\_Acoa\_Malcoa\_L + Co2\_rel\_L)/Vol\_cel\_Co2\_L;$$

%Oxaloacetate Balance

%Oxa − Acetate − Cyt
$$dP(15) = (F\_Mal\_OAA\_Lc - F\_OAA\_Mal\_Lc - F\_OAA\_PEP\_L + F\_Cit\_OAA\_Acoa\_Lc - F\_OAA\_Asprt\_L + F\_Asprt\_OAA\_L)/Veff\_L;$$

%Oxa − Acetate − mit
$$dP(16) = (F\_Pyr\_OAA\_L - F\_OAA\_Acoa\_Cit\_Lm - F\_OAA\_Mal\_Lm + F\_Mal\_OAA\_Lm)/Veff\_Lm;$$ %

%Acetyl Coenzyme A (ACoA) BAlabce
%Acoa_cyt
$$dP(17) = ((F\_Cit\_OAA\_Acoa\_Lc) - (F\_Acoa\_Malcoa\_L) - (F\_Malcoa\_FFA\_L) - (F\_Glsmn\_GlNAc\_L) - (3 * F\_Acoa\_HMGCoa\_L))/Veff\_L;$$

%Acoa_mit
$$dP(18) = (F\_Pyr\_Acoa\_L - F\_OAA\_Acoa\_Cit\_Lm + (8 * F\_Palcoa\_Acoa\_L) - F\_Acoa\_Gmt\_NAG\_L + F\_NAG\_Acoa\_Gmt\_L)/Veff\_Lm;$$

%Citrate_mit
$$dP(19) = ((F\_OAA\_Acoa\_Cit\_Lm) - (F\_Cit\_AKG\_L) - F\_Cit\_Shtl)/Veff\_Lm;$$

%Citrate cyt
$$dP(130) = (F\_Cit\_Shtl - (F\_Cit\_OAA\_Acoa\_Lc))/Veff\_L;$$

%AKG
$$dP(20) = ((F\_Cit\_AKG\_L) - F\_AKG\_Scoa\_L + F\_Gmt\_AKG\_L - F\_AKG\_Gmt\_L + F\_Pyr\_Ala\_L - F\_Ala\_Pyr\_L - F\_Asprt\_OAA\_L + F\_OAA\_Asprt\_L)/Veff\_Lm;$$

%Succinate
$$dP(21) = (F\_Scoa\_Suc\_L - F\_Suc\_Scoa\_L - F\_Suc\_Mal\_L)/Veff\_Lm;$$

%SCoa_L
$$dP(127) = (F\_AKG\_Scoa\_L - F\_Scoa\_Suc\_L + F\_Suc\_Scoa\_L)/Veff\_Lm;$$

%Malate_mit

$$dP(22) = (F\_Suc\_Mal\_L + F\_OAA\_Mal\_Lm - F\_Mal\_OAA\_Lm - F\_Mal\_Shtl\_L + F\_Citrin\_Asprt\_Arg\_L)/Veff\_Lm;$$

%Malate_cyt

$$dP(23) = (F\_Mal\_Shtl\_L + F\_OAA\_Mal\_Lc - F\_Mal\_OAA\_Lc - F\_Mal\_Pyr\_L)/Veff\_L;$$

%Ketone

$$dP(24) = (F\_Acoa\_Ket\_L - T\_Ket\_L)/Veff\_Lm;$$

%Glutamate

$$dP(25) = (F\_AKG\_Gmt\_L - F\_Gmt\_AKG\_L - F\_Pyr\_Ala\_L + F\_Ala\_Pyr\_L + F\_Asprt\_OAA\_L - F\_OAA\_Asprt\_L + F\_Gltm\_Gmt\_L - F\_Acoa\_Gmt\_NAG\_L + F\_NAG\_Acoa\_Gmt\_L + F\_F6p\_Glsmn\_L)/Veff\_Lm;$$

%Coenzyme A (CoA)Balance

%Coa

$$dP(26) = ((-F\_Pyr\_Acoa\_L) + (F\_OAA\_Acoa\_Cit\_Lm) - (F\_Cit\_OAA\_Acoa\_Lc) - (F\_FFA\_Palcoa\_L) - (7 * F\_Palcoa\_Acoa\_L) + (8 * F\_Malcoa\_FFA\_L) - (F\_AKG\_Scoa\_L) - (F\_Suc\_Scoa\_L) + (F\_Scoa\_Suc\_L) + (F\_Acoa\_Gmt\_NAG\_L) - (F\_NAG\_Acoa\_Gmt\_L) + (F\_Glsmn\_GlNAc\_L) + (2 * F\_Acoa\_HMGCoa\_L) + (F\_HMGCoa\_Mevl\_L))/Veff\_L;$$

%NAD + Balance

$$dP(27) = ((F\_PEP\_Gap\_L) + (F\_Pyr\_Lac\_L) + (2 * (F\_O2\_H2O\_Ln)) - (F\_Gap\_PEP\_L) - (F\_Pyr\_Acoa\_L) - (F\_Lac\_Pyr\_L) - (F\_Grp\_Gap\_L) - F\_Cit\_AKG\_L + F\_AKG\_Gmt\_L - F\_Gmt\_AKG\_L \ldots - (F\_AKG\_Scoa\_L) - (F\_Mal\_OAA\_Lm) + (F\_OAA\_Mal\_Lm) - (F\_Mal\_OAA\_Lc) + (F\_OAA\_Mal\_Lc) - (7 * (F\_Palcoa\_Acoa\_L)))/Veff\_L;$$

%NADH Balance

$$dP(28) = (-(F\_PEP\_Gap\_L) - (F\_Pyr\_Lac\_L) - (2 * (F\_O2\_H2O\_Ln)) + (F\_Gap\_PEP\_L) + (F\_Pyr\_Acoa\_L) + (F\_Lac\_Pyr\_L) + (F\_Grp\_Gap\_L) + F\_Cit\_AKG\_L - F\_AKG\_Gmt\_L + F\_Gmt\_AKG\_L + (F\_AKG\_Scoa\_L) + (F\_Mal\_OAA\_Lm) - (F\_OAA\_Mal\_Lm) + (F\_Mal\_OAA\_Lc) - (F\_OAA\_Mal\_Lc) + (7 * (F\_Palcoa\_Acoa\_L)))/Veff\_L;$$

%ATP Balance

%ATPprime

$$dP(29) = ((F\_Gap\_PEP\_L) + (F\_PEP\_Pyr\_L) + (6 * (F\_O2\_H2O\_Ln)) + (4 * (F\_O2\_H2O\_Lf)) - (F\_Glu\_G6p\_L) - (F\_Cit\_OAA\_Acoa\_Lc) - (F\_F6p\_F16bp\_L) - (F\_PEP\_Gap\_L) - (F\_Pyr\_OAA\_L) - (F\_Glr\_Grp\_L) - (F\_ATP\_GTP\_L) - (F\_ATP\_UTP\_L) - (2 * F\_NH4\_Crbphos\_L) - (F\_Citrin\_Asprt\_Arg\_L) - (2 * (F\_FFA\_Palcoa\_L)) - (2 * (F\_FFA\_Grp\_TG\_L)) - ((F\_Acoa\_Malcoa\_L)) - (F\_ATP\_ADP\_L) - (F\_ATP\_AMP\_ADP\_L) - (3 * F\_Mevl\_Squl\_L))/Veff\_L;$$

%ADP Balance

%ADPprime

$$dP(30) = (-(F\_Gap\_PEP\_L) - (F\_PEP\_Pyr\_L) - (6*(F\_O2\_H2O\_Ln)) - (4*(F\_O2\_H2O\_Lf)) + (F\_Glu\_G6p\_L) + (F\_Cit\_OAA\_Acoa\_Lc) + (F\_F6p\_F16bp\_L) + (F\_PEP\_Gap\_L) + (F\_Pyr\_OAA\_L) + (F\_Glr\_Grp\_L) + (F\_ATP\_GTP\_L) + (F\_ATP\_UTP\_L) + (2*F\_NH4\_Crbphos\_L) + (F\_Citrin\_Asprt\_Arg\_L) + (2*(F\_FFA\_Palcoa\_L)) + (2*(F\_FFA\_Grp\_TG\_L)) + ((F\_Acoa\_Malcoa\_L)) + (F\_ATP\_ADP\_L) + (2*F\_ATP\_AMP\_ADP\_L) + (3*F\_Mevl\_Squl\_L))/Veff\_L; \%$$

$\%GTP -$

$$dP(31) = ((F\_ATP\_GTP\_L) - (F\_OAA\_PEP\_L) + F\_Scoa\_Suc\_L - F\_Suc\_Scoa\_L)/Veff\_L;$$

$\%GDP$

$$dP(32) = (-(F\_ATP\_GTP\_L) + (F\_OAA\_PEP\_L) - F\_Scoa\_Suc\_L + F\_Suc\_Scoa\_L)/Veff\_L;$$

$\%Phosphate(Ppi)\ Balance$

$\%Ppiprime$

$$dP(33) = ((F\_PEP\_Gap\_L) + (F\_Pyr\_OAA\_L) + ((F\_F16bp\_F6p\_L)) + (F\_G6p\_Glu\_L) + (2*(F\_G6p\_Gly\_L)) + (2*(F\_FFA\_Palcoa\_L)) + (1*F\_NH4\_Crbphos\_L) + (F\_Citrin\_Asprt\_Arg\_L) + (F\_Crbphos\_Ornit\_Citrin\_L) + ((F\_Acoa\_Malcoa\_L)) + ((7/3)*(F\_FFA\_Grp\_TG\_L)) + (F\_ATP\_ADP\_L) + (F\_Cit\_OAA\_Acoa\_Lc) - (F\_Gap\_PEP\_L) - (F\_Gly\_G6p\_L) - (F\_Scoa\_Suc\_L) + (F\_Suc\_Scoa\_L) - (6*(F\_O2\_H2O\_Ln)) - (4*(F\_O2\_H2O\_Lf)) + (F\_Glsmn\_GlNAc\_L) + (3*F\_Mevl\_Squl\_L))Veff\_L;$$

$\%AMP$

$$dP(34) = (-F\_ATP\_AMP\_ADP\_L)/Veff\_L;$$

$\%Prot\_L$

$$dP(35) = (F\_Ala\_Prot\_L - F\_Prot\_Ala\_L + F\_Asprt\_Prot\_L - F\_Prot\_Asprt\_L + F\_Gltm\_Prot\_L - F\_Prot\_Gltm\_L)/Veff\_L;$$

$\%F6p$

$$dP(123) = ((F\_G6p\_F6p\_L) - (F\_F6p\_G6p\_L) - (F\_F6p\_F16bp\_L) + (F\_F16bp\_F6p\_L) + ((2/3)*F\_R5p\_F6p\_Gap\_L) - F\_F6p\_Glsmn\_L)/Veff\_L;$$

$\%F16bp$

$$dP(131) = ((F\_F6p\_F16bp\_L) - (F\_F16bp\_F6p\_L) - (F\_F16bp\_Gap\_L) + ((1/2)*F\_Gap\_F16bp\_L))/Veff\_L;$$

$\%R5p$

$$dP(124) = ((F\_G6p\_R5p\_L) - (F\_R5p\_F6p\_Gap\_L))/Veff\_L;$$

$\%NADPH$

$$dP(125) = (2*(F\_G6p\_R5p\_L) + (F\_Mal\_Pyr\_L) - (14*F\_Malcoa\_FFA\_L) - (2*F\_HMGCoa\_Mevl\_L) - (F\_Mevl\_Squl\_L) - (F\_Squl\_Chol\_L) - (F\_Chol\_Bile\_L))/Veff\_L;$$

$\%NADP$

$$dP(126) = (-(2*F\_G6p\_R5p\_L) - (F\_Mal\_Pyr\_L) + (14*F\_Malcoa\_FFA\_L) + (2*F\_HMGCoa\_Mevl\_L) + (F\_Mevl\_Squl\_L) + (F\_Squl\_Chol\_L) + (F\_Chol\_Bile\_L))/Veff\_L;$$

$\%Malcoa$

$$dP(132) = (F\_Acoa\_Malcoa\_L - (7*F\_Malcoa\_FFA\_L))/Veff\_L;$$

$\%Palcoa\_cyt$

$$dP(133) = (F\_FFA\_Palcoa\_L - F\_Carn\_Shtl)/Veff\_L;$$

$\%Palcoa\_mit$

$$dP(134) = (F\_Carn\_Shtl - F\_Palcoa\_Acoa\_L)/Veff\_Lm;$$

%UTP
dP(135) = (−F_G6p_Gly_L + F_ATP_UTP_L − F_Glsmn_GlNAc_L)/Veff_L;

%UDP
dP(136) = (F_G6p_Gly_L − F_ATP_UTP_L + GlNAc_decay)/Veff_L;

%FADH
dP(137) = (F_Suc_Mal_L + (7 ∗ F_Palcoa_Acoa_L) − (2 ∗ (F_O2_H2O_Lf)))/Veff_Lm;

%FAD
dP(138) = (−F_Suc_Mal_L − (7 ∗ F_Palcoa_Acoa_L) + (2 ∗ (F_O2_H2O_Lf)))/Veff_Lm;

%Asprartate
dP(140) = (F_OAA_Asprt_L − F_Asprt_OAA_L − F_Asprt_Prot_L + F_Prot_Asprt_L
− F_Citrin_Asprt_Arg_L + Asprt_up_L)/Veff_L;

%Ammonia − NH4
dP(141) = (F_Gmt_AKG_L − F_AKG_Gmt_L − F_NH4_Crbphos_L + F_Gltm_Gmt_L
− F_NH4_Bld)/Veff_Lm;

%Carbomyl phosphate
dP(142) = (F_NH4_Crbphos_L − F_Crbphos_Ornit_Citrin_L)/Veff_Lm;

%Citrullin
dP(143) = (F_Crbphos_Ornit_Citrin_L − F_Citrin_Asprt_Arg_L)/Veff_L;

%Arginine
dP(144) = (F_Citrin_Asprt_Arg_L − F_Arg_Ornit_Urea_L)/Veff_L;

%Ornitine
dP(145) = (F_Arg_Ornit_Urea_L − F_Crbphos_Ornit_Citrin_L)/Veff_L;

%Urea
dP(146) = (F_Arg_Ornit_Urea_L − F_Urea_Bld)/Veff_L;

%N − acetylglutamate
dP(147) = (F_Acoa_Gmt_NAG_L − F_NAG_Acoa_Gmt_L)/Veff_Lm;

%Glutamine
dP(150) = (−F_F6p_Glsmn_L + F_Prot_Gltm_L − F_Gltm_Prot_L − F_Gltm_Gmt_L + Gltm_up_L)/Veff_L;

%Glucosamine
dP(151) = (F_F6p_Glsmn_L − F_Glsmn_GlNAc_L)/Veff_L;

%N − Acetylglucosamine
dP(152) = (F_Glsmn_GlNAc_L − GlNAc_decay)/Veff_L;

%HMGCoA
dP(160) = (F_Acoa_HMGCoa_L − F_HMGCoa_Mevl_L)/Veff_L;

%Mevelonate
dP(161) = (F_HMGCoa_Mevl_L − F_Mevl_Squl_L)/Veff_L;

$\%Squalene$
$dP(162) = (F\_Mevl\_Squl\_L - F\_Squl\_Chol\_L)/Veff\_L;$

$\%Cholesterol$
$Chol\_decay = 7.5e-5 * Chol\_L;$
$dP(163) = (F\_Squl\_Chol\_L - F\_Chol\_Bile\_L - Chol\_decay)/Veff\_L;$

$\%Bile$
$Bile\_decay = 1.5e-5 * Bile\_L;$
$dP(164) = (F\_Chol\_Bile\_L - Bile\_decay)/Veff\_L;$

Signaling and Meal Simulation

$\% - - - - - - - - Insulin\ signalling\ Modellling - \%$

$\%Molecular\ model\ for\ Glucose\ mobilization\ and\ uptake$
$\%Om\ shri\ Ram\ Jairam\ Jai\ Jai\ Ram\%\%Om\ Shri\ Balkrushnai\ Namaha\%$
$\%Om\ Shri\ Ganeshaya\ Namaha\%\%On\ Shri\ PanduRangAya\ Namaha\%$
$\%Om\ Shri\ Saraswataye\ Namaha\%\%Omshri\ mauli\ Samarth\%OmshriRam$

$PTEN = 1;$
$SHIP = 1;$
$IRp = 8.97e-13; \%M$
$APequil = 100/11; \%9.090909;$
$k1 = 6e7; \%/M/min$
$k2 = 6e7; \%/M/min$
$k3 = 2500; \%/min$
$k4 = 0.003/9; \%3.3333e-4; \%/min$
$k6 = 0.461; \%\ /min$
$k7 = 4.16; \%\ /min$
$k8 = 0.7065e12; \%/min$
$k10 = \left(\frac{3.1}{2.9}\right) * 2.77;$
$k13 = (4/96) * 0.167; \%/\ min\%6.958333e-3;$
$k14 = 96 * 0.001155; \%\ /min\%0.11088;$
$k15 = 0.2; \%\ /min$
$k16 = 20; \%\ /min$
$k17 = 0.2; \%\ /min$
$k18 = 0.003; \%\ /min$
$k19 = 2.1e-3; \%\ /min$
$k20 = 2.1e-4; \%\ /min$
$k21 = 1.67e-18; \%\ /min$
$k22 = (2.5/7.45) * 4.16; \%\ /min\%1.395973;$
$k23 = 10; \%\ /min$
$k25 = 2.77; \%\ /min$
$k26 = 6.9314; \%10 * log(2); \%\ /min$
$k27 = 6.9314; \%10 * log(2); \%\ /min$
$k28 = 0.167; \%\ /min$
$k29 = 0.001155; \%\%\ /min$
$k31 = 0.346574; \%(log(2))/2; \%min$
$k30 = k31 * (((2.5/7.45) * (3.70e-13))/((6.27e-13) - ((2.5/7.45) * (3.7e-13)))); \%0.085576;$

```
k32 = 0.346574; %(ln2/2)
k33 = 0.23105; %(ln2/3)
 R1 = 9e - 13; %M
a1 = 0.12;  % /min
a2 = 0.3;  %/min
a3 = 0.01;  % /min
a4 = 6e7;  % /M/min
a5 = 0.2; % /min
b1 = 0.0151; % /min
b2 = 0.002; % /min
b3 = 0.01; % /min
V = 11; % L
Vp = 3; %L

Rm = 4.44e - 12;  % M/min
c1 = 1162;  % mg/l
p1 = 0.005 * 180;  %mmol/l; %/mg/l
p2 = 0.01594; %/mg/l
q1 = 10;
q2 = 1.85;

% - - - - - - - -new calcium model - - - - - - - - - -
n1 = 0.1; % * 60
n2 = 1.5 * 2; %1.5
n3 = 0.64; % * 60
n4 = 0.19; % -* 60 - - - - - -
n5 = 4.88; % * 60
n6 = 1.18; % -* 60 - - - - - - - - - - - -
n7 = 2.08; % * 70
n8 = 32.24; % * 60
n9 = 29.09; % * 60 - - - - - - - -
n10 = 5; % * 60
n11 = 2.67; % * 60 - - - - - - - - - - -
n12 = 0.7; % * 60
n13 = 13.58; % * 60
n14 = 153; % * 60
n15 = 0.16; % -* 60 - - - - - - - - - - - - -
n16 = 4.85; % * 60
n17 = 0.05; % - - * 60 - - - - - - - - - - - - - - - -

% - - - - - - - - - - - - - -Glucagon Receptror Model

% - - - - -Parameters
C1 = 10 * 60;  %/sec
c2 = 100 * 60; %micro Mol/sec
c3a = 5.2 * 60e - 3; %/sec
c4 = 4 * 60e - 3; %/sec
c5 = 5.2 * 60e - 3; %/sec
G23 = 1 * 60e - 7; %/sec
c6 = 0.2 * 60; % /sec
kcal1 = 1.47 * 60e3; %micro mol/sec
kcal2 = 35.4;
kplc1 = 2.19 * 60e3; %micro mol/sec
kplc2 = 5.7;
c7 = 6.5 * 60e4; %6.4e4/sec - - - - -Scaled
```

```
c8 = 650 * 60; %/sec ---------- Scaled - Desensitization constant
A0 = 3;
B1 = 100 ; %100 ------------ Value scaled
B2 = 1e6;
kpc = 6.06 * 60e - 4; %/sec
kpc1 = 0.282;
kpc2 = 0.255;
R0 = 126500;
G0 = 100000;

% ---------------Meal simulation --------------------

conf = 5.31915; % --conversion factor from mg/kg/min to mg/l/min for glucose appearance
%ie - by using distribution volm of glucose = 1.88 dl/Kg
Kmaxi = 0.0558; %0.054; %/min
Kmini = 0.0080; %0.006; %/min
 Kg_abs = 0.057; % * ((1 - exp(-((t - 100)./90)))); %0.057; %0.071; %0.057; %/min0.012 ----
                        --Glu absorption rate connst.
 Kp_abs = 0.01; %097; %/min ---------- Protein absn.rate
Kft_abs = 0.015;
Kf_abs = 0.015; % .* ((1 - exp(-((t - 100)./180)))); %/min ------------Fat absn.rate
Kgri = 0.0558; %/min
F = 0.90; %dimensionless
a = 0.00013; %/mg
b = 0.7; %0.82; %dim
c = 0.00236 * 180; %0.00236; %/mg
d = 0 * 0.10; %dim
%  CHO = 0 * 70000;
% Pro = 0 * 20000; %mg
%  Fat = 0 * 20000; %mg --- mmol20000;
TF1 = CHO + Pro + Fat; %108000/180;
BW = 75; %Kg
KexA = 0.0005; %/min
KexB = 10; %mmol/l
b_Qst  = 0;
b_Qst1 = 0;
b_Qst2 = 0;
b_Qgut = 0;
b_Glu_gut = 0;
b_Pro_gut = 0;
b_Fat_gut = 0;
% -------------Glucose/Protein/Fat Rate of appearance -------
TF2 = 1; %108000;
CHO2 = 1; %70000;
TF3 = 1; %108000;
CHO3 = 1; %70000;
       TF = TF1;


if t == 0 && t <= 100;
   P1 = 0;
   TF = TF1;
else
 if  t > 100 && t ≤ 100 + (0.0002 * TF);
   P1 = d;
```

```
    TF = TF1;
  else
    P1 = 0;
    TF = TF1;
end
end

%TF = TF1;
Qst = Qst1 + Qst2;
 alpha = (2.5/(TF * (1 - b)));
  beta = (2.5/(TF * c));

if P1 > 0;
 Kempt = Kmini + (((Kmaxi - Kmini)/2) * ((tanh(alpha * (Qst - (b * TF)))) + 1));

else
  Kempt = 0 ;
 end


%Qst1
dP(102) = -(Kgri * Qst1) + TF * P1;

%Qst2
dP(103) = -(Kempt * Qst2) + (Kgri * Qst1);

glf = (CHO/TF); %(CHO/TF)
dP(104) = (Qst2 * glf * Kempt) - (Kg_abs * Glu_gut);

%Rate Glucose appearance
Ra_Glu = ((F * Kg_abs * Glu_gut)); % ----- converted from mg/min to mmol/min



%Amount of Protein in Gut - Pro_gut
prf = (Pro/TF);
dP(105) = (Qst2 * prf * Kempt) - (Kp_abs * Pro_gut);

Kpt_abs = 0.01;
dP(165) = (Kp_abs * Pro_gut) - (Kpt_abs * Pro_Int);


%Amount of Fat in Gut Fat_gut
ftf = (Fat/TF);
dP(106) = (Qst2 * ftf * Kempt) - (Kft_abs * Fat_gut);

%Rate of appearance of protein -
Ra_Pro = ((F * Kpt_abs * Pro_Int)/130);


%Amount of Fat in Gut Fat_gut
%ftf = (Fat/TF);

dP(107) = (Kft_abs * Fat_gut) - (Kf_abs * Fat_Int);
```

```
%Rate of appearance of Fat -
Ra_Fat = ((F * Kf_abs * Fat_Int)/290); % ----- converted from mg/min to mmol/min

% ----------------- Insulin Kinetic ---------------------


dP(166) = 0; % - (b1 + b2) * Ins_P + Ins_sec;

%%%%%%%% Blood Glucose %%%%%%
Uii = 1 * (Ca_Glup^4/(Ca_Glup^4 + 2^4)); % - mg/kg/min0.4166; %mmol/min -----
kx1 = 0.0005;
if Ca_Glup > 339;
K_ex = kx1 * (Ca_Glup - 339);
else
  K_ex = 0;
end

kgp1 = 0.065; %0.065
kgp2 = 0.079; %0.079

Vm0 = 2.50 * 1; % ----- mg/kg/min1.04167; %mmol/min% -----
Vmx = 0.047 * 0.1; % --- mg/kg/min --/pmol/l0.0196;
Km0 = 225.6; % ---- mg/kg7.55;
Kmx = 0;
Vi = 0.05;
Ins_P = (InsP/Vi);

Vm_X = Vm0 + Vmx * 0.27 * Ins_P; %Ins_Int;
Km_X = Km0 + Kmx * 0.27 * Ins_P; %Ins_Int;

Uid_g = (Vm_X * Ca_Glu_OT/(Km_X + Ca_Glu_OT));

Glu_up_L1 = -Glu_up_L * 180/75;

Ra_Glu1 = Ra_Glu/75;

%Plasma Glucose
dP(154) = 0; %(Glu_up_L1 + Ra_Glu1 - Uii - K_ex - kgp1 * Ca_Glup + kgp2 * Ca_Glu_OT)/5.0;

%Glucose in Other tissues
dP(155) = 0; %(-Uid_g + kgp1 * Ca_Glup - kgp2 * Ca_Glu_OT);

kap1 = 0.1 * (11 * Ca_Alap^2.5/(Ca_Alap^2.5 + 0.65^2.5));
kap2 = 0.9 * (50^2/(Ins_P^2 + 50^2));

Vma0 = 0.025;
Vmxa = 0.01 * 0.27 * 50 * 2.25 * (16.5 * (Ins_P^2.5/(Ins_P^2.5 + 150^2.5)));
Kma0 = 0.65;

Vm_A = Vma0 + Vmxa;
Km_A = Kma0;

Uid_p = (Vm_A * Ca_Alap^3/(Km_A^3 + Ca_Alap^3));

%Plasma Amino Acids
```

```
dP(156) = 0 * (-AA_up_L + Ra_Pro - kap1  + kap2 - Uid_p)/5;

%AA in Other tissues
dP(157) = 0 * -Uid_p +  kap1  - kap2;
kfp1 = 0.07 * (11 * Ca_FFAp^2.5/(Ca_FFAp^2.5 + 1.7^2.5));
kfp2 = 0.6 * (50^2/(Ins_P^2 + 50^2));

Vmf0 = 0.025;
Vmxf = 0.01 * 0.27 * 50 * 1.5 * (16.5 * (Ins_P^3.0/(Ins_P^3.0 + 125^3.0)));
Kmf0 = 1.7;

Vm_F = Vmf0 + Vmxf;
Km_F = Kmf0;

Uid_F = (Vm_F * Ca_FFAp^3/(Km_F^3 + Ca_FFAp^3));


%Plasma FF Acids
dP(158) = 0 * (-FFA_up_L + Ra_Fat - kfp1  + kfp2 - Uid_F)/5;

%FF in Other tissues
dP(159) = 0 * -Uid_F +  kfp1  - kfp2;
Ca_Co2_F = 1.22;
Ca_Co2_T_L = 22.2;
Ca_O2_F = 0.135;
Ca_O2_T_L = 9.235;
Ca_TG = 1;
Ca_Pyr = 0.068;
Ca_Lac = 0.7; %0.5;
Ca_Glr = 0.07; %0.07;


dP(36) =  0;
 % - - - Insulin kinetics Parameters - - - - - - - -
Vi = 0.05; %L/kg
m1 = 0.190; %/min
m2 = 0.484; %/min

m4 = 0.194; %/min
m5 = 0.0304 * Vi; %1.52e - 3; %%1.52e9; %0.0304e - 12; %0.608; %; % min/M - -
                  - 0.0304; % min. Kg/pmol
m6 = 0.6471; % dimensionless
gamma = 0.5; %min

%Insulin secretion
K_AA = 0.5;
K_FF = 1.8;
na = 5.8;
nf = 4.8;
n = 4.65;
K_Glu = 8.9;
V_Glu = 48e - 12; %
V_Ala = 17e - 12;
V_FFA = 21e - 12;
Ins_sec = V_Glu.* (Ca_Glu.^n./(Ca_Glu.^n + K_Glu.^n))...
```

```
    +(V_Ala.* ((Ca_Ala^na)./(((Ca_Ala^na) + K_AA.^na))))...
    +(V_FFA.* (Ca_FFA.^nf)./((Ca_FFA.^nf) + K_FF.^nf));
ISR = (Ins_sec/1e − 12);


dP(37) = −(gamma * InsV) + ISR;

 InSec = gamma * InsV;

 %HE − Hepatic Extraction
HE = (−m5 * InSec) + m6;

m3 = ((HE * m1)/(1 − HE));
%InsL


dP(38) = (−(m1 + m3) * InsL) + (m2 * InsP) + InSec; %Insu_seci

INSLIV = (InsL/Vi) * 1e − 12;

%InsP
dP(39) = (−(m2 + m4) * InsP) + (m1 * InsL); % * 10^ − 10;

%INS = (InsP/Vi) * 1e − 12;


%Insulin in interstetial fluid − Ins_Int − − − Cobeli model − 1982
p2u = 0.0331;
p2v = 12e − 6;
b_InsP = 2.5/Vi; %50.35e − 12;
dP(40) = 0; % − (p2u * Ins_Int) + p2u * (INS − b_InsP);

%Insu_F − − − − − −Insulin concentration in Inerstetial fluid − −Cobelli model − 2007

m13 = 0.02;
m31 = 0.042;
V_Insu_F = 0.106 * 75;
InsPi = (InsP);
dP(41) = 0; %(−(m13 * Insu_F) + (m31 * InsPi))/V_Insu_F;


% − − − − − − − − − − − − − − −Insulin signalling pathway − − − − − − − − − − − − −

%x1 =  cellular insulin,
b1 = 0.0151 * 10;
b3 = 0.010 * 10; %0.002
dP(42) = (−k1 * x1 * x2) − (b3 * x1) + (b1 * Vp * INSLIV/V);
if x17 ≤ (400/11);
  PTP = 1 * (1 − (0.25 * (x17/(100/11))));
else
  PTP = 0;
end

   x1a = x1;
```

```
%x2 = concentration of unbound surface insulin receptor
dP(43) = (k15 * x3) + (k17 * PTP * x5) - (k1 * x1a * x2) + (k18 * x6) - (k4 * x2);

%x3 =  concentration of unphosphorylated once - bound surface receptors,
dP(44) = (k1 * x1a * x2) - (k15 * x3) - (k3 * x3);

%x4 =  concentration of phosphorylated twice - bound surface receptors,
dP(45) = (k2 * x1a * x5) - (k16 * x4) + (k20 * x7) - (k19 * x4);

%x5 =  concentration of phosphorylated once - bound surface receptors,
dP(46) = (k3 * x3) + (k16 * x4) - (k2 * x1a * x5) - (k17 * PTP * x5) + (k20 * x8) - (k19 * x5);

%x6 = concentration of unbound unphosphorylated intracellular receptors,
%k21 = 1.67e - 18; % /min
if (x6 + x7 + x8) > 1e - 13;
  k5 = k21 * 10e - 2; %1.67e - 17;
else    k5 = 60 * k21; %1.002e - 16;

end

dP(47) = k5 - (k21 * x6) + (k6 * PTP * (x7 + x8)) + (k4 * x2) - (k18 * x6);

%x7 = concentration of phosphorylated twice - bound intracellular receptors,
dP(48) = (k19 * x4) - (k20 * x7) - (k6 * PTP * x7);

%x8 = concentration of phosphorylated once - bound intracellular receptors,
dP(49) = (k19 * x5) - (k20 * x8) - (k6 * PTP * x8);

%x9 = concentration of unphosphorylated IRS - 1,


S6K_Ntv = 9 * (S6K1p_L^4)/((8^4.0 + S6K1p_L^4.0)); %7^1.3y10/25); %

PKC = 20 * ((x19^4)/((12^4) + (x19^4))); %(x19^1.8)/((17));

%AKTmax = 20;
%FOXO_Ptv_IRS = 3.* (FOXO.^1./(FOXO.^1 + 0.50^1));
k34 = 0.1;
dP(50) = (k22 * PTP * x10) - ((k7 * x9 * (x4 + x5)/IRp)) + (k30 * x10a) - ((k31 * PKC * x9)) - (k34
                     * S6K_Ntv * x9);

%x10 = concentration of tyrosine - phosphorylated IRS - 1,
dP(51) = (((k7 * x9 * (x4 + x5)/IRp)) + (k23 * x12) - (((k22 * PTP) + (k8 * x11)) * x10)); % * S6K;

%x10a = concentration of serine - phosphorylated IRS - 1,
dP(52) = ((k31 * PKC * x9) - (k30 * x10a) + (k34 * S6K_Ntv * x9));

%x11 = concentration of unactivated PI3 - kinase,

dP(53) = (k23 * x12) - (k8 * x11 * x10);

%x12 = concentration of tyrosine - phosphorylated IRS - 1/activated PI3 - kinase complex,
dP(54) = (k8 * x11 * x10) - (k23 * x12);
```

```
%x13 = percentage of PI(3,4,5)P3 out of the total lipid population,
k9sim = 1.39; %/min
k9bas = (0.31/99.4) * (94/3.1) * k9sim;
PI3K = (k8 * (3.7e − 13) * (1e − 13))/(k8 * (3.7e − 13) + k23); %2.54e − 15;
k9 = ((k9sim − k9bas) * (x12/PI3K)) + k9bas;
k24 = (94/3.1) * k9sim; %42.1484;
dP(55) = (k9 * x14) + (k10 * x15) − (((k24 * PTEN) + (k25 * SHIP)) * x13);

%x14 = percentage of PI(4,5)P2 out of the total lipid population,
dP(56) = (k24 * PTEN * x13) − (k9 * x14);

%x15 = percentage of PI(3,4)P2 out of the total lipid population,
dP(57) = (k25 * SHIP * x13) − (k10 * x15);

%x16 = percentage of inactivated PKB/AKT,
FOXO_Ptv_Akt = 1 * (FOXO^4/(FOXO^4 + 0.75^4));
mTORC2_act_AKT = 4 * (mTOR_Rictor_L^2/(mTOR_Rictor_L^2 + 40^2));
kmr = 0.01 * mTORC2_act_AKT;

GlNAc_inact_Akt = 1 * (0.045^2/(0.045^2 + GlNAc_L^2));
TRB3_Ntv_AKT = 1 * (3^2/(TRB3^2 + 3^2));

if x13 > 0.31;
PI3K_Act_fn = ((x13 − 0.31)/(3.1 − 0.31));
else
  PI3K_Act_fn = 0; %2e − 4;

end

%global k11i
k11 = (0.1 * k26 * 0.7) * PI3K_Act_fn * GlNAc_inact_Akt * TRB3_Ntv_AKT; % * (1.0 + FOXO_Ptv_Akt);

dP(58) = (k26 * x17) − (k11 * x16) − (kmr * x16);

%x17 = percentage of activated PKB/AKT,
dP(59) = (k11 * x16) − (k26 * x17) + (kmr * x16);

%x18 = percentage of inactivated PKC − f,
GlNAc_act_PKC = 3 * (GlNAc_L/(GlNAc_L + 0.045));
FFA_Ptv_PKC = 1 + 9 * (FFA_L^3/(FFA_L^3 + 1.4^3));
DAG_Ptv_PKC = 1 + 5 * (DAG^3/(6^3 + DAG^3));

k12 = (0.1 * k27) * PI3K_Act_fn * FFA_Ptv_PKC * GlNAc_act_PKC * DAG_Ptv_PKC; % * FFA_Ntv_PKC
                    * ((x13 − 0.31)/(3.1 − 0.31))

%Cal_pkc_rgl = 0; %2 * (Ccal^2/(5^2 + Ccal^2));
dP(60) = (k27 * x19) − (k12 * x18);

%x19 = percentage of activated PKC − f.

dP(61) = (k12 * x18) − (k27 * x19);

%Glucose uptake
%x20 − Percentage of intracellular GLUT4
```

```
Vng = 6;
ng = 8;
Kng = 8;
eff = ((0.2 * x17) + (0.8 * x19))/APequil;
Ig4 = ((2/3) - (4/96)) * k28 * eff;
k14e = k14;
dP(62) = (k28 * x21) - ((k13 + Ig4) * x20);

%x21 - Percentage of cell Surface GLUT4
dP(63) = (((k13 + Ig4) * x20) - (k28 * x21));

%x22 - Percentage of GSK3 activated - - - - - - - dephosphorylation

PKA_Li = (C/7.7e - 6) + (PKa/1.3e - 4);

FFA_Ntv_GSK3 = 1.11 * (1.5^2)/((1.5^2) + FFA_L^2);
GlNAc_inact_GSK3 = 1.11 * (0.03^3/(0.03^3 + GlNAc_L^3));
PP1_reg_Gsk3 = 3 * (PP1/(PP1 + (2 * 1.250e - 4)));

G6p_act_Gsk3 = 5 * ((G6p_L^2)/((G6p_L^2) + 0.4^2));
Cal_Ntv_Glysynt = (6.7^2/(6.7^2 + Cal^2));

k32L = k32 * (x17/(100/11)) * 0.416 * (1 + G6p_act_Gsk3 + PP1_reg_Gsk3) * Cal_Ntv_Glysynt
        * FFA_Ntv_GSK3 * GlNAc_inact_GSK3; % * PKA_gsk3_rgl_L; %

G6p_inact_Gsk3p = ((0.4^2)/(0.4^2 + G6p_L^2));
PKA_act_GSK3p = 0.625 * (1 + (5 * (PKA_Li^2/((PKA_Li^2) + (4)^2))));
k33L = k33 * PKA_act_GSK3p * G6p_inact_Gsk3p;

dP(64) = k33L * x23 - k32L * x22;

%x23 - percentage of inactivated GSK3 - - - -phosphorylated - -This activates
%Glycogen synthasis
dP(65) = k32L * x22 - k33L * x23;

dP(153) = 0; %(kg8i * G6p_act_Gsk3i * PP1_reg_Gsk3i * GSK3_eff) - (kg7i * PKA_act_GSK3p1
        * G6p_inact_Gsk3pi * Glysy);


%%%%%%%%%%%%%%%%%%%%% Glucagon Secretion and kinetics%%%%%%%%%%%%%

%Gucagon balance - -Glcgn
Gm = 2.0e - 10; %2.23e - 10; % M/min
%u1 - Glucagon Infusion rate
%Am_Glcn = (Ca_Ala - 0.25);
if (Ca_Ala - 0.25) >= 0;
  Am_Glcn = (Ca_Ala - 0.25);
else
   Am_Glcn = 0;
end
AA_Glcn_Eff = 125e - 12 * ((Am_Glcn^4.5)/(Am_Glcn^4.5 + 0.7^4.5));
Glcn_Sec = (Gm/(1 + (q1 * exp(p1 * (Ca_Glu - 5))))) + AA_Glcn_Eff;
% %Gsec = (a71 * (Ieff * Geff) * 2.857e - 3);
```

```
% Gsec = (a71 * (Ieff * Geff) * 2.857e - 11);

%Plasma Glucagon conc.
%Gnp = -(a1 + a2) * Gnp + u1;
%Glsec = ((Gsec/Gln_mol) * 1000);
a1 = 0.12; % /min
a2 = 0.3; %/min
a3 = 0.01; % /min

dP(66) = (-(a1 + a2) * Gnp) + Glcn_Sec; %Glsec;


%%%%%%%%%%%%%%%%%%%% - -Glucagon Calcium Signalling - - - - - - - - - - - - -

alf = 10000;
% - - - - - - - - - - - - - - - - - Glucagon receptor model - - - - - - - - - - - - - - - - -
%Glucagaon Signalling Pathway
%Hg - Cellular Glucagon Concentration
%GLCN = Gnp; %Glcn_Pl
Gln_recp = 9e - 13; %Mol
%c2a = c2 * 1e6; %((126500 - LRS)/126500) * (a4 * Glcn_F * Gln_recp)
a4 = 6e7; % /M/min
a1 = 0.12; % - - - - - - - - adjusted from 0.12 to 0.012;
a3 = 0.1;
Rt = 126500;
dP(67) = (a1 * Vp * Gnp/V) - (a3 * Glcn_F) - ((a4) * Glcn_F * (FR/Rt) * Gln_recp); % + (alf * c2
                    * Glcn_F * RS); %; %  +

GCN = Gnp * 1e6; %Glcn_PlGlcn_F
c3 = c3a * (2 * (GCN)/(((50.0e - 6)) + GCN));
%dp(26) - FR - free receptor
dP(68) =  (C1 * LR) - (c2 * GCN * FR) - (c3 * FR) + (c4 * RS);


%dP(26) - RS - Sequesterd receptor
dP(69) = (C1 * LRS) - (alf * c2 * GCN * RS) + (c3 * FR) - (c4 * RS);

%dP(27) - LR - Ligand bound receptor
dP(70) = (c2 * GCN * FR) - (C1 * LR) + ((c4/alf) * LRS) - (c3 * LR) +  (c5 * LRP);


GPRT = 26.* (LRS./(95000 + LRS));
PLCi = 233.* (GPRT.^2./(32.^2 + GPRT.^2));
IP3i = 16.3.* (PLCi.^4./(42.^4 + PLCi.^4));
Cal = 35.* (IP3i.^1.8)./(9.^1.8 + IP3i.^1.8);

%dP(28) - LRS - ligand bound sequestered receptor
%GPRT; % = Gprt;
dP(71) = (c3 * LR) - ((c4/alf) * LRS) + (alf * c2 * GCN * RS) - (C1 * LRS) - (c8 * (1 + ((A0
                    * (GPRT))/(B1 + (GPRT)))) * (LRS/(B2 + LRS)));

%dP(31) - LRP
dP(72) = (c8 * (1 + ((A0 * (GPRT))/(B1 + (GPRT)))) * (LRS/(B2 + LRS))) -  (c5 * LRP);
```

```
%Ccal = 0.0072.*(PLC.^3) - 0.5418.*(PLC.^2) + 14.006.*PLC - 119.93;

% ----------- Another Calcium model -------------------------
%Cal = 35*(IP3^1.8)/(9^1.8 + IP3^1.8);
%Ccal = Cal;
% IGprti = 10 - (Gprt);
% %dP(21) - Gprt
dP(73) = 0; %n1 + (Gprt*n2*(((LRS + LR)/Rt)^0.8)) - (Gprt*((n3*(PLC/(Gprt + n4))) + (n5
       *Ccal/((Gprt + n6))))); %(Lig_bnd + Rcp_Seq)(1 + (((LRS + RS))/Rt)

% %dP(22) - PLC
dP(74) = 0; %n7*Gprt - (n8*PLC/(PLC + n9));


%IP30; %
bi = 2*60; %/s
vi = 2*60;
ks = 0.02;
kc1 = 1;
csi = -1;
Kc1p = kc1 + csi*(C/(ks + C))^4;
%Cal_cti = Ccal;
dP(75) = 0; %vi*((0.1*Ccal*0.1*PLC)/(Kc1p + 0.1*Ccal)) - bi*(IP3);



% %dP(23) - Ccal
dP(76) = 0; %(n10*Ccal*IP3*Ecal/(Ecal + n11)) + (n12*IP3) + (n13*Gprt) - (n14*Ccal/(Ccal
       + n15)) - (n16*Ccal/(Ccal + n17));
%
% %dP(24) - Ecal
dP(77) = 0; %(n16*Ccal/(Ccal + n17)) - (n10*Ccal*PLC*Ecal/(Ecal + n11));


%PKC
PKCt = 1;
PKCa = PKCt - PKCi;
vp1 = 1*60;
vp2 = 0.7*60;
kdc = 0.2*10;
dP(78) = 0; %vp1*(DAG*0.1*Ccal/(kdc + DAG))*PKCa - vp2*(PKCi/(kdc + DAG));

%DAG
vi = 2*60;
vf = 1.5*60;
bd = 0.50*60; %/sec
K_FFA_L = 1.35;
dP(79) = vi*((0.1*Cal*0.1*PLCi)/(Kc1p + 0.1*Cal)) + vf*(FFA_L) - bd*DAG; % - dP(78);

% %%%%%%%%%%%%%% Glucagon Signaling Model%%%%%%%%%%%%%%%%%%%%%%%%%%%%

% ----------- Rates for Glycogen Signalling in Liver ----------------
%function par = par_glycogen()

kg1 = 1.4 *60; % min - 1 rate constant for phosphorylation of inhibitor [48]
```

```
kg2  = 0.001  * 60; % 0.01 min − 1 rate constant for dephosphorylation of inhibitor [assumed]
kg3  =  20  * 60; % min − 1 rate constant for phosphorylation of phosphorylase kinase [assumed]
kg4  =  5  * 60; % min − 1 rate constant for dephosphorylation of phosphorylase kinase [assumed]
kg5  =  20  * 60; % min − 1 rate constant for phosphorylation of Phosphorylase [42]
kg6  =  5  * 60; % min − 1 rate constant for dephosphorylation of Phosphorylase [49]
kg7  =  20  * 60; % min − 1 rate constant for phosphorylation of glycogen synthase [assumed]
kg8  =  0.05  * 60; % min − 1 rate constant for dephosphorylation of glycogen synthase [assumed]
%k8g  =  5 * 60;

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
% Michaelis − Menten constants
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
kmg1  =  5 /1000; % mM for inhibitor phosphorylation [48]
kmg2  =  0.7 /1000; % mM for dephosphorylation of Inhibitor [52]
kmg3  =  0.4 /1000; % mM for Phosphorylation of phosphorylase kinase [assumed]
kmg4  =  1.1 /1000; % mM for dephosphorylation of phosphorylase kinase [52]
kmg5  =  10 /1000; % mM for phosphorylation of phosphorylase [25]
kmg6  =  5 /1000; % mM for dephosphorylation of phosphorylase [47]
kmg7  =  15 /1000; % mM for phosphorylation of glycogen synthase [assumed]
kmg8  =  0.12 /1000; % mM for dephosphorylation of glycogen synthase [50]
kd1  = 0.002/1000; %;

capkt  =  0.25 /1000; % mM total R2C2 ie. cAMP dependent protein kinase, CAPK [3]
It  =  1.8 /1000; % mM total Inhibitor concentration [3]
kt  =  2.5 /1000; % mM total Phosphorylase kinase [35]
pt  =  70 /1000; % mM total Glycogen Phosphorylase [3]
%pt  =  80 /1000; % mM total Glycogen Phosphorylase [3]
st  =  3 /1000; % mM total Glycogen synthase [3]
PP1t  =  0.25 /1000; % mM PTPase 1 [33]
PP2A  =  0.025 /1000; % 0.025

%kg11  =  0.043 /1000; % mM Dissociation constant of cAMP [35]
%kg22  =  0.7 /1000; % mM Dissociation constant of cAMP [35]
ki  =  100 /1000; % mM cAMP inhibition constant
campt  =  10 /1000; % mM maximum cAMP [3]
kg2j  =  349500 /1000; % mM activation constant of glucose − 6 − phosphate for synthase PP1
g6pt  =  700 /1000; % mM maximum glucose − 6 − Phosphate [33]
kgi  =  10000 /1000; % mM activation constant of glucose for phosphorylase phosphatase
s1i  =  100; % a multiplicative factor for glucose − 6
                − phosphate effect on glycogen synthase dephosphorylation
kg2i  =  500 /1000; % mM inhibition due to glucose − 6 − phosphate  =  0.05 mM
s2i  =  0.001; % a multiplicative factor for glucose effect on phosphorylase phosphatase

kgg1 = 1.50 * 60e − 7;  %0.00031 *  min
                − 1 rate constant for phosphorylation of PP1 by AKT [assumed]
kmgg1 = 0.4/1000; % mM for Phosphorylation of PP1 [assumed]

GLN = Gnp; %Glcn_F; %Gnp; %0.30e − 6; %0.033 * Gln_Sec;
INS = x1a;
 %kd is regulated by glycogen

Gly_L = 470; %
Gly_M = 95;
  c0_L  =  5.0; %210;
  c0_M  = 5; %47.5; %47.5;
```

$ex = 5;$
$kdmax = 3.2/1000;$
$kdmin = 2/1000;$

$$kd_L = \left((kdmax - kdmin) * \left(\frac{c0_L^{ex}}{c0_L^{ex} + Gly_L^{ex}}\right) + kdmin\right);$$

$kd\_M = (kdmax - kdmin) * (c0\_M \wedge ex/(c0\_M \wedge ex + Gly\_M \wedge ex)) + kdmin;$
$k\_al = .001 * 60 * 1000;$ % min − 1 mM − 1 dissociation rate constant for PP1_GPa
$kal = k\_al/kd\_L;$ % min − 1 association rate constant for PP1_GPa
$k\_am = .001 * 60 * 1000;$ % min − 1 mM − 1 dissociation rate constant for PP1_Ip
$kam = k\_am/kd\_M;$ % min − 1 association rate constant for PP1_Ip

%kgc_1 = 1000 * 60 * 1000^2; % dissociation rate constant for [R2C(cAMP)2] + [C]
$k11a = 0.043/1000;$ % mM Dissociation constant of cAMP [35](R2C2 * (cAMP^2))/(R2_C_cAMP2 * C);
$k22a = 0.7/1000;$ % mM Dissociation constant of cAMP [35](R2_C_cAMP2 * (cAMP^2))/(R2_cAMP4 * C); %
$kgc\_1 = 60 * 1000;$ %1.3953e15;
$kgc1 = kgc\_1/k11a;$ % association rate constant for [R2C(cAMP)2] + [C]
%kgc_2 = 1000 * 60 * 1000^2; % dissociation rate constant for [R2(cAMP)4] + [C]
$kgc\_2 = 1000 * 60;$ %8.5714e13;
$kgc2 = kgc\_2/k22a;$ % assoc
$campt = 10/1000;$ %

$Phk = PKa;$
$PKA = C;$
$CAMPK = R2C2;$
$CAMPK\_cAMP2 = R2\_C\_cAMP2;$
$CAMPK\_cAMP4 = R2\_cAMP4;$

$Epn = 0;$
$K\_epn = 250e - 12;$

$gsk\_eff = x23/x22;$
$GSK3\_rgl = 3.6 * (gsk\_eff/(0.3 + gsk\_eff));$
$gluc = Glu\_L;$
$g6p = G6p\_L;$

$kmg5s = kmg5.* (1 + (s1i * g6p./kg2i));$ % * GSK3_rgl; % − − − G6p Effect on Gly phos
$kmg6s = kmg6./(1 + (s2i * gluc./kgi));$ % − − − Glucose effect on Glycogen Phosphorylation
$kmg7s = kmg7.* (1 + (s1i * g6p./kg2i));$ % * GSK3_rgl; % − − − Inhibitory G6p Effect on Gly Synth
$kmg8s = kmg8./(1 + (s1i * g6p./kg2i));$ % * GSK3_rgl; % − − − activation G6p Effect on Gly Synth

%Calcium regulation of Phk
$Cal\_max = 20;$
$Cal = 0.1 * Ccal;$ %mMol
$Cal\_rgl = 4 * ((Cal)/(Cal\_max));$
%AKT regulation

$$Aktmax = 100/11;$$
$$Akt\_act = 1; \%4 * (x17/Aktmax);$$

$$\%GSk3\_Amax = 60; \%\%15\ in\ Muscle$$
$$GSK3\_act\_rgl = 2 * (x23/(25 + x23));$$

$$GSK3\_Inmax = 74; \% --- 85\ in\ muscle$$
$$GSK3\_inact\_rgl = 2 * (x22/(GSK3\_Inmax + x22));$$
$$inh = 2 * (GSK3\_Inmax/(GSK3\_Inmax + x22));$$

$$gsk\_eff = x23/x22;$$
$$GSK3\_rgl = 3.6 * (gsk\_eff/(0.3 + gsk\_eff));$$

$$cqi = 2.5;$$
$$kq = 0.003;$$
$$Kck = 1 + (cqi * (Cal\verb|^|3.0/(9\verb|^|3.0 + Cal\verb|^|3.0))); \%Effect\ of\ PKC\ on\ cAMP\ activation$$

$$Jg3 = (kg3 * (PKA) * (kt - Phk) / (kmg3 + (kt - Phk))); --\ Activation\ of\ Phk\ by\ PKA$$
$$Jg4 = (kg4 * (PP1 + PP1\_GPa) * Phk / (kmg4 + Phk)); \%; --- Deactivation\ of\ Phk\ by\ PP1$$
$$Jg5 = (kg5 * Phk * (pt - GPa) / (kmg5s + (pt - GPa))); \% ---\ Activation\ of\ Gly\ Phos\ by\ Phk$$
$$Jg6 = (kg6 * (PP1 + PP1\_GPa) * GPa / (kmg6s + GPa)); --- Deactvation\ Glyphos\ by\ PP1$$

$$Jg7 = \left(kg7 * (Phk + PKA) * \frac{GSa}{(kmg7s + GSa)}\right);$$
$$Jg8 = (kg8 * (PP1) * (st - GSa) / (kmg8s + (st - GSa)));$$

$$Jg9 = kal * PP1 * GPa - k\_al * PP1\_GPa;$$
$$Jg10 = kgc1 * CAMPK * (cAMP\verb|^|2) - kgc\_1 * CAMPK\_cAMP2 * PKA;$$
$$Jg11 = kgc2 * CAMPK\_cAMP2 * (cAMP\verb|^|2) - kgc\_2 * CAMPK\_cAMP4 * PKA;$$

$$\%dPKA$$
$$dP(86) = Jg10 + Jg11;$$

$$kc1 = 10\verb|^|(-5.5);$$
$$kcm1 = 16.33e - 12;$$
$$kc2 = 1 * 1.25;$$
$$kcm2 = 1;$$
$$pn = 2.0;$$
$$pe = 4;$$

$$Jg12 = \left(\left(Kck * kc1 * \left(\frac{GLN^{pe}}{kcm1^{pe} + GLN^{pe}}\right)\right) - \left(\left(kc2 * \left(\frac{PDE3a^{pn}}{kcm2^{pn} + PDE3a^{pn}}\right)\right) * cAMP\right)\right);$$
$$Va1 = 1.5 * 1.8e18;$$
$$Va2 = 1.5 * 2.5e9;$$
$$kcamp1 = 2 * 3.2e - 6;$$
$$kcamp2 = 2 * 3.2e - 6;$$
$$PKAt = 0.6e - 3;$$

$$Jg13 = (Va1 * ((cAMP\verb|^|2)/(kcamp1 + cAMP)) * (PKAt - PKA)) - (Va2 * PKA/(kcamp2 + cAMP));$$

```
% GLYCOGEN ode eqns:

%dPP1
dP(80) = -Jg9;

%dPP1_GPa
dP(81) = Jg9;

%dPhk
dP(82) = Jg3  - Jg4;

%dGPa
dP(83) = Jg5 - Jg6  - Jg9;

%dGSa
dP(84) = Jg8 - Jg7;

%dCAMPK
dP(85) = - Jg10;

%dPKA
dP(86) = (Jg10 + Jg11);

%dCAMPK_cAMP2
dP(87) = Jg10 - Jg11;

dP(88) = Jg11;

%dcAMP
dP(89) = Jg12 - 2 * (Jg10 + Jg11) ;

%PDE3 Activation by AKt

%PDE3a
kakt = 0.125;
kpde = 0.300;
PDE3t = 5; %30e - 12;
PKA_L = C/8.0e - 6;
K1_PDE3a = 7e - 12;
K2_PDE3a = 10e - 12;
K_bpde3 = 0.01;
dP(90) = K_bpde3 + ((kakt * (x17^1.5/(3.6^1.5 + x17^1.5))) * (PDE3t - PDE3a)) -  (kpde
           * ((PKA_L^1)/(5^1 + (PKA_L^1))) * PDE3a);

%%%%%%%%%% - - - - - - - - - - - - - - - - - - - - -mTOR signaling in Muscle - - - - - -
           - -%%%%%%
% - - - - - Total Concntrations - - - - - - - -
%In = 0.1;

RaptorT  =  50;
RictorT  =  50;
mTORT  =  100;
FKBP38T  =  50; %50
```

$S6K1T\ =\ 50;$
$PRAS40T\ =\ 50;$
$RhebT = 100;$
$GEF = 0.2;$

% − − − −Parameters − − − − − − − −
$f1 = 1;$
$f2 = 5;$
$f3 = 1;$
$f4 = 1;$
$f5 = 5;$
$f6 = 1 * 0.4;$

$f7 = 1.3e - 1;$
$f8 = 1.5e - 2;$
$f9 = 324;$
$f10 = 300;$
$f11 = 6.6e - 3;$
$f12 = 1.38e - 1;$

$f13 = 10;$
$f14 = 10;$
$f15 = 1;$
$f16 = 1;$
$f17 = 1;$
$f18 = 1;$
$f19 = 15;$
$f20 = 1.50e - 3;$
$f21 = 0.5e - 3;$
$f22 = 1.0;$
$f23 = 1;$
$f24 = 1;$
$f25 = 2.0;$
$f26 = 1.5;$

$ft_M = 1;$
$ft\_L = 0.6 * 1.0;$
$fm1 = 700;$
$fm2 = 20;$
$fad\_M = 1.3;$
$fad\_L = 0.2 * 3;$

$faa\_M = 4 * 5;$
$faa\_L = 4 * 0.2;$
$fpp = 6;$
$fnr = 200;$
$fto = 2;$
$na = 0.8;$
$np = 1.2;$
$nt = 4;$
$nr = 2;$
$ns = 4.20;$
$nb = 1.0;$
%%% − − − − − −Regulations − − − − −
$AA\_L = (0.5 * Ala\_L + 0.4 * Gltm\_L + 0.1 * Asprt\_L);$

```
GTP_l = GTP_L * 1e3;
GDP_l = GDP_L * 1e3;

%TSC
%q = AKT/AKTt;
AKTmax = 10;
Ins_act_L = ((x17)/AKTmax);
AMPK_Ntv_TSC = ((0.75^2)/(0.75^2 + AMPK_Eff^2));
TSC_L = 0.02 + (0.03 * (1 - Ins_act_L * AMPK_Ntv_TSC)); %

PDK1_L = 5 * (x15/(2.5 + x15)); %2


m_L = (0.1 + (10 * AA_L^2/(0.2^2 + AA_L^2)));
%m = 10;

%AA influence on RhebGTP translocation and effect of Rheb overexpression

ktf_L = ft_L * (((AA_L^nb)/(AA_L^nb + fad_L^nb)) + ((RhebGTP_L^nr)/(RhebGTP_L^nr
          + fnr ^nr)));

%Translocated RhebGTP
RhebaT = ktf_L * RhebGTP_L;

Rheba_L = RhebaT - (FKBP38_RhebGTP_L + mTOR_Raptor_FKBP38_RhebGTP_L);

%Rheba = (y5 * S8o) - (y3 + y8);
% AA influence on binding of RhebGTP tp mTOR_Raptor_FKBP38;

K4r_L = f4 * ((AA_L^na)/(AA_L^na + fad_L^na));

%mTOR regulation of phosphatase of S6K1
PP2Amax = 5;
PP2A_L = PP2Amax * (fpp^np/(fpp^np + mTOR_Raptor_L^np));

%PP2A regulation of mTOR raptor

df1_L = ((fto^nt)/(fto^nt + PP2A_L^nt));

%AA and insulin influence on phosphorylation of PRAS40

K14r_L = f14 * ((AA_L^na)/(AA_L^na + fad_L^na)) * Ins_act_L;

% %mTOR_Raptor activation by AA in absence of insulin

K19r_L = f19 * ((AA_L^ns)/(AA_L^ns + faa_L^ns));

%Flooding by RhebGTP overexpression

K22r_L = f22 * (Rheba_L^2)/(10^2 + Rheba_L^2); %


% --------mass balance -----------
Rheb_L = RhebT - (RhebGTP_L + Rheba_L + RhebGDP_L + FKBP38_RhebGTP_L
          + mTOR_Raptor_FKBP38_RhebGTP_L);
```

$$PRAS40\_L = PRAS40T - (PRAS40p\_L + mTOR\_Raptor\_PRAS40\_L + mTOR\_Raptor\_FKBP38\_PRAS40\_L);$$

$$mTOR\_L = mTORT - (mTOR\_Raptor\_L + mTOR\_Rictor\_L + mTOR\_Raptor\_FKBP38\_L + mTOR\_Raptor\_PRAS40\_L + mTOR\_Raptor\_FKBP38\_PRAS40\_L + mTOR\_Raptor\_FKBP38\_RhebGTP\_L);$$

$$Raptor\_L = RaptorT - (mTOR\_Raptor\_L + mTOR\_Raptor\_FKBP38\_L + mTOR\_Raptor\_PRAS40\_L + mTOR\_Raptor\_FKBP38\_PRAS40\_L + mTOR\_Raptor\_FKBP38\_RhebGTP\_L);$$

$$Rictor\_L = RictorT - mTOR\_Rictor\_L;$$

$$FKBP38\_L = FKBP38T - (FKBP38\_RhebGTP\_L + mTOR\_Raptor\_FKBP38\_L + mTOR\_Raptor\_FKBP38\_RhebGTP\_L + mTOR\_Raptor\_FKBP38\_PRAS40\_L);$$

$$S6K1\_L = S6K1T - S6K1p\_L;$$

%%%%% – – – – – – – – – Reaction rates – – – – – – – – –

$$F1\_L = f1 * mTOR\_L * Raptor\_L;$$

$$F2\_L = f2 * (mTOR\_Raptor\_L);$$

$$F3\_L = f3 * (mTOR\_Raptor\_L) * FKBP38\_L;$$

$$F4\_L = K4r\_L * (mTOR\_Raptor\_FKBP38\_L) * RhebGTP\_L;$$

$$F5\_L = f5 * (mTOR\_Raptor\_FKBP38\_RhebGTP\_L);$$

$$F6\_L = f6 * (FKBP38\_RhebGTP\_L);$$

$$F7\_L = f7 * GTP\_l * Rheb\_L;$$

$$F8\_L = f8 * (RhebGTP\_L);$$

$$F9\_L = f9 * TSC\_L * (RhebGTP\_L/(fm2 + RhebGTP\_L));$$

$$F10\_L = f10 * GEF * (RhebGDP\_L/(fm1 + RhebGDP\_L));$$

$$F11\_L = f11 * RhebGDP\_L;$$

$$F12\_L = f12 * GDP\_l * Rheb\_L;$$

$$F13\_L = f13 * (mTOR\_Raptor\_L) * (PRAS40\_L);$$

$$F14\_L = K14r\_L * (mTOR\_Raptor\_PRAS40\_L);$$

$$F15\_L = f15 * (mTOR\_Raptor\_PRAS40\_L) * FKBP38\_L;$$

$$F16\_L = f16 * (mTOR\_Raptor\_FKBP38\_L) * PRAS40\_L;$$

$$F17\_L = f17 * (mTOR\_Raptor\_FKBP38\_PRAS40\_L) * RhebGTP\_L;$$

$$F18\_L = f18 * PRAS40p\_L;$$

$F19\_L = K19r\_L * (mTOR\_Raptor\_FKBP38\_PRAS40\_L);$

$F20\_L = f20 * PDK1\_L * (mTOR\_Raptor\_L) * df1\_L * (S6K1\_L);$

$F21\_L = f21 * S6K1p\_L * PP2A\_L;$

$F22\_L = K22r\_L * Rheba\_L * mTOR\_Raptor\_PRAS40\_L;$

$F23\_L = f23 * m\_L * mTOR\_Raptor\_FKBP38\_L * Rheba\_L;$

$F24\_L = f24 * m\_L * mTOR\_Raptor\_FKBP38\_PRAS40\_L * Rheba\_L;$

$\%\%\%\%\%\% - - - - - ODE - - - - - \%\%\%\%\%\%$
$\%mTPR\_raptor$
$dP(91) = F1\_L - F2\_L - F3\_L + F5\_L - F13\_L + F14\_L + F19\_L + F22\_L;$

$\%(mTOR\_Raptor\_FKBP38)$
$dP(92) = F3\_L + F5\_L - F16\_L - F23\_L;$

$\%(FKBP38\_RhebGTP)$
$dP(93) = F5\_L - F6\_L + F24\_L; \% + F17\_L;$

$\%(mTOR\_Raptor\_PRAS40)$
$dP(94) = F13\_L - F14\_L - F15\_L - F22\_L + F24\_L; \% + F17\_L;$

$\%(mTOR\_Raptor\_FKBP38\_PRAS40)$
$dP(95) = F16\_L + F15\_L - F19\_L - F24\_L; \% - F17\_L;$

$\%S6K1p$
$AMPK\_Ntv\_S6K = ((0.75^\wedge 2.0)/(0.75^\wedge 2.0 + AMPK\_Eff^\wedge 2.0));$
$dP(96) = F20\_L * AMPK\_Ntv\_S6K - F21\_L;$

$\%(mTOR\_Raptor\_FKBP38\_RhebGTP)$
$dP(97) = F23\_L - F5\_L; \% + F4\_L;$

$\%PRAS40p$
$dP(98) = F14\_L - F18\_L;$

$\%RhebGTP$
$dP(99) = F7\_L - F8\_L - F9\_L + F10\_L + F6\_L;$

$\%RhebGDP$
$dP(100) = F9\_L - F10\_L - F11\_L + F12\_L;$

$\%mTOR\_Rictor$
$S6K\_inact\_mTORC2 = 2 * (S6K1p\_L^\wedge 1/(10^\wedge 1 + S6K1p\_L^\wedge 1));$
$AA\_act\_mTORC2 = 5 * (AA\_L^\wedge 2/(AA\_L^\wedge 2 + 0.5^\wedge 2));$
$$dP(101) = f25 * mTOR\_L * Rictor\_L * PI3K\_Act\_fn * AA\_act\_mTORC2 - f26 * mTOR\_Rictor\_L * (1 + S6K\_inact\_mTORC2);$$

```
% − − − − − − − − − − − − − − − − −Oxygen and Corbon dioxide distribution volums − − −
% − − − − − − − − − − O2 − Co2 transport parameters − − − − − −

%C_art_O2_F = 0.135; % − − − @100 mmHg
%C_bld_O2_F = 0.0491; % − − − @36.37 mmHg
H_rbc = 0.45;
C_rbc = 5.2; % − − − mM
K_Hb_O2 = 7800.7; % − −/2.7mM
eta = 2.7;
HC_mit_Mb = 0.5; % − − − mM
C_mit_Mb = 5; %
K_Mb_O2 = 308.64; % − − − mM
K_Hb_Co2 = 0.1237; % − − −/mM
K_Co2_hyd = 7.95e − 4; % − −mM

 Vol_bld_L = Vol_bldf; %1.5; %lit5; %

% − − − − − − − − − − − − − − − − −Oxygen and Corbon dioxide distribution volums − − −

Cb_O2_T_L = Cb_O2_L + ((4 ∗ H_rbc ∗ C_rbc ∗ K_Hb_O2 ∗ ((Cb_O2_L)^eta))/(1 + (K_Hb_O2
            ∗ ((Cb_O2_L)^eta))));

Vol_bld_O2_L = Vol_bld_L ∗ (1 + ((4 ∗ eta ∗ H_rbc ∗ C_rbc ∗ K_Hb_O2 ∗ ((Cb_O2_L)^(eta − 1)))/((1
            + K_Hb_O2 ∗ ((Cb_O2_L)^eta))^2)));

pH_rbc = 7.24;
pH_plasm = 7.4;
C_pl_H = 10^(−pH_plasm + 3); % − −mM
C_rbc_H = 10^(−pH_rbc + 3); % − −mM

Vol_bld_Co2_L = Vol_bld_L ∗ (1 + ((4 ∗ H_rbc ∗ C_rbc ∗ K_Hb_Co2)/((1 + K_Hb_Co2 ∗ Cb_Co2_L)^2))
            + ((((1 − H_rbc)/C_pl_H) + (H_rbc/C_rbc_H)) ∗ K_Co2_hyd));


Cb_Co2_T_L = Cb_Co2_L + ((4 ∗ H_rbc ∗ C_rbc ∗ K_Hb_Co2 ∗ Cb_Co2_L)/((1 + K_Hb_Co2 ∗ Cb_Co2_L)))
            + ((((1 − H_rbc)/C_pl_H) + (H_rbc/C_rbc_H)) ∗ K_Co2_hyd ∗ Cb_Co2_L);



Ql = 1.5;
INSLIV = InsL/Vi;
INS_b = 180e − 12;
Meal_bld_Eff = 1 + (2.5 ∗ ((INSLIV^4)/((INSLIV^4) + (3 ∗ INS_b)^4)));
Qlt = Ql ∗ Meal_bld_Eff;
% − − − − − −Blood metabolite balance − − − − − − − − − −
%Blood glucose − Cb_Glu
dP(108) = (Qlt ∗ (Ca_Glu − Cb_Glu_L) − Glu_up_L)/Vol_bld_L;

%Blood Pyruvate balance − Cb_Pyr
dP(109) = (Qlt ∗ (Ca_Pyr − Cb_Pyr_L) − Pyr_up_L)/Vol_bld_L;

%Blood Lactate balance − Cb_Lac,
dP(110) = (Qlt ∗ (Ca_Lac − Cb_Lac_L) − Lac_up_L)/Vol_bld_L;
```

```
%Blood alanine balance - Cb_Ala
AA_up_L = Ala_up_L + Gltm_up_L + Asprt_up_L;
dP(111) = (Qlt * (Ca_Ala - Cb_Ala_L) - AA_up_L)/Vol_bld_L;

%Blood Glycerol balance - Cb_Glr
dP(112) = (Qlt * (Ca_Glr - Cb_Glr_L) - Glr_up_L)/Vol_bld_L;

%Blood FFA balance - Cb_FFA
dP(113) = (Qlt * (Ca_FFA - Cb_FFA_L) - FFA_up_L)/Vol_bld_L;

%Blood TG balance
dP(114) = (Qlt * (Ca_TG - Cb_TG_L) - TG_rel_L)/(Vol_bld_L);

%Blood Co2 balance - Cb_Co2_F
dP(115) = (Qlt * (Ca_Co2_T_L - Cb_Co2_T_L) - Co2_rel_L)/Vol_bld_Co2_L;

%Blood O2 balance - Cb_O2_Fr
dP(116) = (Qlt * (Ca_O2_T_L - Cb_O2_T_L) - O2_up_L)/Vol_bld_O2_L;


%%%%%% ----------Transcriptional Regulation ----%%%%%%%

%SREBP1c
ksr1 = 0.005;
ksr2 = 0.005;
ksr0 = 0.0040;
Inseff = (x17 + x19)/3;
S6k_Ptv = 0.5 * (S6K1p_L^2/(S6K1p_L^2 + 1^2));
cAMP_Ntv = 2 * ((3.2e - 6)^2/((3.2e - 6)^2 + cAMP^2));
AMPK_Ntv = 1.25 * ((0.5^2)/(0.5^2 + AMPK_Eff^2));
FOX_Ntv_SREBP = (0.5^2/(FOXO^2 + (0.5^2)));
AKT_PKC_Ptv_SREBP = 5 * (Inseff^2/(Inseff^2 + 2^2));
dP(117) = ksr0 + (ksr1 * S6k_Ptv * cAMP_Ntv * AMPK_Ntv * FOX_Ntv_SREBP * AKT_PKC_Ptv_SREBP)
          - ksr2 * (SREBP);

%PPARg
kprg1 = 0.015;
kprg2 = 0.02;
kprg0 = 0.015;
kprg3 = 0.005;
FFA_Ptv = 12.5 * (FFA_L^3.5/(FFA_L^3.5 + 1.71^3.5));
AKT_Ptv_PPARg = 5 * (x17^2/(x17^2 + 2^2));
FOX_Ntv_PPARg = 1.25 * (0.5^2/(FOXO^2 + (0.5^2)));
dP(118) = kprg0 + (kprg1 * AKT_Ptv_PPARg * S6k_Ptv * FOX_Ntv_PPARg) + (kprg3 * FFA_Ptv)
          - kprg2 * (PPARg);

%PPARab
kpra1 = 0.02 * 0.25;
kpra2 = 0.02;
kpra0 = 0.017;
PKA_Ptv_PPARa = 3 * (PKA_L^1.0/(PKA_L^1.0 + 2^1.0));
FFA_Ptv = 5 * (FFA_L^2/(FFA_L^2 + 1.15^2));
PGC_Ptv_PPARab = 5 * (PGC1^2/(PGC1^2 + 2^2)); % * S6k_Ptv
dP(119) = kpra0 + (kpra1 * PKA_Ptv_PPARa * FFA_Ptv * PGC_Ptv_PPARab) - kpra2 * (PPARab); %
```

```
%CREB
kcr1 = 0.1;
kcr2 = 0.3;
CREBt = 1;
PKA_Ptv_CREB = 5 * (PKA_L^2/(PKA_L^2 + 2^2));
AKT_Ntv_CREB = 1.5 * (2/(2 + x17^2));
dP(120) = (kcr1 * PKA_Ptv_CREB * (CREBt − CREB) * AKT_Ntv_CREB) − kcr2 * (CREB);

%CHREBp
khr1 = 0.02;
khr2 = 0.02;
khr0 = 0.0025;
Glu_Ptv = 1 + 5 * (Glu_L^5/(Glu_L^5 + 10^5));
PKA_L = C/8.0e − 6;
PKA_Ntv = 1 * (3^2/(3^2 + PKA_L^2));
AMPK_Ntv = 1.4 * ((0.4^2)/(0.4^2 + AMPK_Eff^2));
dP(121) = khr0 + (khr1 * Glu_Ptv * PKA_Ntv * AMPK_Ntv) − khr2 * (CHREBp);


%FOXO
kfr11 = 2.5346e − 3;
kfr0 = 2.43e − 3;
kfr2 = 0.0216;
GlNAc_Ptv_FOXO = 9 * (GlNAc_L^3/(GlNAc_L^3 + 0.03^3));
AMPK_Ntv = 1.25 * ((0.50^2)/(0.5^2 + AMPK_Eff^2));
```

$$AKT_{Ntv_{FOXO}} = 3 * \left(\frac{x17^1}{x17^1 + 2.25^1}\right);$$

```
PPARg_Ntv_FOXO =  (2^2/(PPARg^2 + 2^2));
dP(122) = kfr0 + ((kfr11 * AMPK_Ntv * PPARg_Ntv_FOXO * GlNAc_Ptv_FOXO)) − kfr2 * (FOXO
          * AKT_Ntv_FOXO);

%AMPK
K_AMP_L = 0.16;
K_ATP_L = 2.8;
AMP_ATP_AMPK = 2 * ((AMP_L/ATP_L)/((K_AMP_L/K_ATP_L) + (AMP_L/ATP_L)));
AKT_Ntv_AMPK = 5 * (x17^2/(x17^2 + 2.26^2));
PKA_Ntv_AMPK = (3^2/(3^2 + PKA_L^2));
AMPKt = 1;
kam1 = 1;
Kam2 = 2.25;

dP(128) = (kam1 * AMP_ATP_AMPK * (PKA_Ntv_AMPK) * (AMPKt − AMPK)) − Kam2 * (AMPK)
          * AKT_Ntv_AMPK;

%CEBPa
kcb1 = 0.02 * 0.25;
kcb2 = 0.02;
kcb0 = 0.016;
PKC_Ntv_CEBPa = 1 * (3^2/(3^2 + x19^2));
cAMP_rt = cAMP/3.2e − 6;
cAMP_Ptv_CEBPa = 9 * (cAMP_rt^2/(cAMP_rt^2 + 3^2));
dP(139) = kcb0 + ((kcb1 * PKC_Ntv_CEBPa * cAMP_Ptv_CEBPa)) − kcb2 * (CEBPa);

%PGC1
```

```
kpc1 = 0.02 * 0.25;
kpc2 = 0.02;
kpc0 = 0.016;
FOXO_Ptv_PGC = 3 * (FOXO/(FOXO + 0.4));
AKT_Ntv_PGC = 1.25 * (2^2/(x17^2 + 2.2^2));
CREB_Ptv_PGC = 9 * (CREB^3/(CREB^3 + 0.5^3));
dP(148) = kpc0 + ((kpc1 * CREB_Ptv_PGC * FOXO_Ptv_PGC * AKT_Ntv_PGC)) − kpc2 * (PGC1);


%TRB3
ktr1 = 0.02 * 0.25;
ktr2 = 0.02;
ktr0 = 0.014;
PI3K_Ptv_TRB = 3.8 * (x13^1.5/(x13^1.5 + 1.25^1.5));
PKC_Ptv_TRB = 1.5 * (x19^1/(x19^1 + 0.5^1));
PPAR_Ptv_TRB3 = 10 * ((PPARab^2)/((PPARab^2) + 3^2));
PGC_Ptv_PPARab = 5 * (PGC1^2/(PGC1^2 + 2^2));
dP(149) = ktr0 + (ktr1 * PPAR_Ptv_TRB3 * PI3K_Ptv_TRB * PGC_Ptv_PPARab * PKC_Ptv_TRB) − (ktr2
        * TRB3);
```