**Data Supplement: Mathematical Model for Metabolic and Signaling regulatory network**

**Metabolic rate equations**

*%Glucose*

*dP(1)= ((F\_G6p\_Glu\_L)-(F\_Glu\_G6p\_L)+(Glu\_up\_L))/Vglu\_L;*

*%Glucose 6-Phosphate*

*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 (held constant for MCA)*

*dP(3)=((F\_G6p\_Gly\_L)-(F\_Gly\_G6p\_L))/Veff\_L;*

*%F6p*

*dP(4)=((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;*

*%R5p*

*dP(5)=((F\_G6p\_R5p\_L)-(F\_R5p\_F6p\_Gap\_L))/Veff\_L;*

*%F16bp*

*dP(6)=((F\_F6p\_F16bp\_L)-(F\_F16bp\_F6p\_L)-(F\_F16bp\_Gap\_L)+((1/2)\*F\_Gap\_F16bp\_L))/Veff\_L;*

*%Glyceraldehyde Phosphate(GAP)*

*dP(7)= ((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;*

*%Phospoenoyl Pyruvate*

*dP(8)=(F\_Gap\_PEP\_L- F\_PEP\_Gap\_L -(F\_PEP\_Pyr\_L)+(F\_OAA\_PEP\_L))/Veff\_L;*

*%Pyruvate (cytosol)*

*dP(9)= ((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;*

*% Pyruvate (mitochondria)*

*dP(10)=(F\_Pyr\_trans - F\_Pyr\_OAA\_L- F\_Pyr\_Acoa\_L )/Vpyr\_Lm;*

*%Lactate*

*dP(11)= ((F\_Pyr\_Lac\_L)-(F\_Lac\_Pyr\_L)+(Lac\_up\_L))/Vlac\_L;*

*%Alanine*

*dP(12) = (F\_Pyr\_Ala\_L-(F\_Ala\_Pyr\_L)-(F\_Ala\_Prot\_L)+(F\_Prot\_Ala\_L)+(Ala\_up\_L))/Vala\_L;*

*%Asprartate*

*dP(13)=(F\_OAA\_Asprt\_L-F\_Asprt\_OAA\_L-F\_Asprt\_Prot\_L+F\_Prot\_Asprt\_L- F\_Citrin\_Asprt\_Arg\_L+*

*F\_OAA\_Asprt\_Lm+ Asprt\_up\_L)/Veff\_L;%*

*%Glutamate*

*dP(14)= (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\_OAA\_Asprt\_Lm -F\_Acoa\_Gmt\_NAG\_L+F\_NAG\_Acoa\_Gmt\_L + F\_F6p\_Glsmn\_L)/Veff\_Lm;*

*%Glutamine*

*dP(15)=(-F\_F6p\_Glsmn\_L+F\_Prot\_Gltm\_L-F\_Gltm\_Prot\_L-F\_Gltm\_Gmt\_L+Gltm\_up\_L)/Veff\_L;*

*%Protien*

*dP(16)= (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;*

*%Glycerol*

*dP(17) = ((F\_TG\_FFA\_Glr\_L)-(F\_Glr\_Grp\_L)+(Glr\_up\_L))/Vglr\_L;*

*%Free Fatty Acid*

*dP(18)=((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)*

*dP(19)= ((F\_Glr\_Grp\_L)-(F\_Grp\_Gap\_L)-((F\_FFA\_Grp\_TG\_L)/3))/Veff\_L;*

*%Triglyceride*

*dP(20)= (((F\_FFA\_Grp\_TG\_L)/3)-(F\_TG\_FFA\_Glr\_L)+(TG\_rel\_L))/Vtg\_L;*

*%Malcoa*

*dP(21)=(F\_Acoa\_Malcoa\_L-(7\*F\_Malcoa\_FFA\_L))/Veff\_L;*

*%Palcoa\_cyt*

*dP(22)=(F\_FFA\_Palcoa\_L-F\_Carn\_Shtl)/Veff\_L;*

*%Palcoa\_mit*

*dP(23)=(F\_Carn\_Shtl-F\_Palcoa\_Acoa\_L)/Veff\_Lm;*

*%Oxygen*

*dP(24)= (((-F\_O2\_H2O\_Ln)-(F\_O2\_H2O\_Lf))+(O2\_up\_L))/Vo2\_L;*

*%Carbon dioxide*

*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(25)=(F\_OAA\_PEP\_L+(7\*F\_Malcoa\_FFA\_L)+ F\_Pyr\_Acoa\_L + F\_Cit\_AKG\_L + \_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 (cytosol)*

*dP(26)= ( - F\_OAA\_PEP\_L + F\_Cit\_OAA\_Acoa\_Lc- F\_OAA\_Asprt\_L+ F\_Asprt\_OAA\_L)/Veff\_L;*

*%Oxaloacetate (mitochondria)*

*dP(27)= (F\_Pyr\_OAA\_L - F\_OAA\_Acoa\_Cit\_Lm + F\_Mal\_OAA\_Lm - F\_OAA\_Asprt\_Lm)/Veff\_Lm;*

*%Acetyl Coenzyme A (cytosol)*

*dP(28)=((F\_Cit\_OAA\_Acoa\_Lc)- (F\_Acoa\_Malcoa\_L)-(F\_Malcoa\_FFA\_L)-(F\_Glsmn\_GlNAc\_L)-*

*3\*F\_Acoa\_HMGCoa\_L))/Veff\_L;*

*% Acetyl Coenzyme A (mitochondria)*

*dP(29)= (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 cytosol*

*dP(30)=(F\_Cit\_Shtl-(F\_Cit\_OAA\_Acoa\_Lc))/Veff\_L;*

*%Citrate mitochondria*

*dP(31)= ((F\_OAA\_Acoa\_Cit\_Lm)- (F\_Cit\_AKG\_L)-F\_Cit\_Shtl)/Veff\_Lm;*

*%Alphaketoglutarate*

*dP(32)= ((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\_Lm+F\_OAA\_Asprt\_L)/Veff\_Lm;*

*%Succinate*

*dP(33)=(F\_Scoa\_Suc\_L-F\_Suc\_Scoa\_L- F\_Suc\_Mal\_L)/Veff\_Lm;*

*%Succinyl CoA*

*dP(34)=(F\_AKG\_Scoa\_L- F\_Scoa\_Suc\_L + F\_Suc\_Scoa\_L)/Veff\_Lm;*

*%Malate*

*dP(35)= (F\_Suc\_Mal\_L - F\_Mal\_OAA\_Lm - F\_Mal\_Pyr\_L + F\_Citrin\_Asprt\_Arg\_L)/Veff\_Lm;*

*%Ketone*

*dP(36)= (F\_Acoa\_Ket\_L - T\_Ket\_L)/Veff\_Lm;*

*%Coenzyme A (CoA)*

*dP(37)=((-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*

*dP(38)= ((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) -(7\*(F\_Palcoa\_Acoa\_L)))/Veff\_L;*

*%NADH*

*dP(39)= (-(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) +(7\*(F\_Palcoa\_Acoa\_L)))/Veff\_L;*

*%ATP Balance*

*dP(40)= ((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*

*dP(41)= (-(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(42)= ((F\_ATP\_GTP\_L)- (F\_OAA\_PEP\_L)+ F\_Scoa\_Suc\_L- F\_Suc\_Scoa\_L )/Veff\_L;*

*%GDP*

*dP(43)=(-(F\_ATP\_GTP\_L)+ (F\_OAA\_PEP\_L) - F\_Scoa\_Suc\_L+ F\_Suc\_Scoa\_L)/Veff\_L ;*

*%Phosphate(Ppi)*

*dP(44)= ((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(45)=(-F\_ATP\_AMP\_ADP\_L)/Veff\_L;*

*%NADPH*

*dP(46)=(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(47)=(-(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;*

*%UTP*

*dP(48)=(-F\_G6p\_Gly\_L+ F\_ATP\_UTP\_L)/Veff\_L;*

*%UDP*

*dP(49)=(F\_G6p\_Gly\_L-F\_ATP\_UTP\_L)/Veff\_L;*

*%FADH*

*dP(50)=(F\_Suc\_Mal\_L+(7\*F\_Palcoa\_Acoa\_L)-(2\*(F\_O2\_H2O\_Lf)))/Veff\_Lm;*

*%FAD*

*dP(51)=(-F\_Suc\_Mal\_L-(7\*F\_Palcoa\_Acoa\_L)+(2\*(F\_O2\_H2O\_Lf)))/Veff\_Lm;*

*%Ammonia-NH4*

*dP(52)=(F\_Gmt\_AKG\_L-F\_AKG\_Gmt\_L-F\_NH4\_Crbphos\_L+F\_Gltm\_Gmt\_L-F\_NH4\_Bld)/Veff\_Lm;*

*%Carbomyl phosphate*

*dP(53)=(F\_NH4\_Crbphos\_L - F\_Crbphos\_Ornit\_Citrin\_L)/Veff\_Lm;*

*%Citrullin*

*dP(54)=(F\_Crbphos\_Ornit\_Citrin\_L-F\_Citrin\_Asprt\_Arg\_L)/Veff\_L;*

*%Arginine*

*dP(55)=(F\_Citrin\_Asprt\_Arg\_L-F\_Arg\_Ornit\_Urea\_L)/Veff\_L;*

*%Ornitine*

*dP(56)=(F\_Arg\_Ornit\_Urea\_L-F\_Crbphos\_Ornit\_Citrin\_L)/Veff\_L;*

*%Urea*

*dP(57)=(F\_Arg\_Ornit\_Urea\_L-F\_Urea\_Bld)/Veff\_L;*

*%N-acetylglutamate*

*dP(58)=(F\_Acoa\_Gmt\_NAG\_L-F\_NAG\_Acoa\_Gmt\_L)/Veff\_Lm;*

*%Glucosamine*

*dP(59)=(F\_F6p\_Glsmn\_L-F\_Glsmn\_GlNAc\_L)/Veff\_L;*

*%N-Acetylglucosamine*

*dP(60)= (F\_Glsmn\_GlNAc\_L-GlNAc\_decay)/Veff\_L;*

*%HMGCoA*

*dP(61)=(F\_Acoa\_HMGCoa\_L-F\_HMGCoa\_Mevl\_L)/Veff\_L;*

*%Mevelonate*

*dP(62)= (F\_HMGCoa\_Mevl\_L- F\_Mevl\_Squl\_L)/Veff\_L;*

*%Squalene*

*dP(63)= (F\_Mevl\_Squl\_L- F\_Squl\_Chol\_L)/Veff\_L;*

*%Cholesterol*

*Chol\_decay=7.5e-5\*Chol\_L;*

*dP(64)= (F\_Squl\_Chol\_L- F\_Chol\_Bile\_L-Chol\_decay)/Veff\_L;*

*%Bile*

*Bile\_decay=1.0e-5\*Bile\_L;*

*dP(65)= (F\_Chol\_Bile\_L- Bile\_decay)/Veff\_L;*

*%Blood glucose-Cb\_Glu*

*dP(73)=(Qlt\*(Ca\_Glu-Cb\_Glu\_L)-Glu\_up\_L)/Vol\_bld\_L;*

*%Blood Pyruvate balance-Cb\_Pyr*

*dP(74)=(Qlt\*(Ca\_Pyr-Cb\_Pyr\_L)-Pyr\_up\_L)/Vol\_bld\_L;*

*%Blood Lactate balance-Cb\_Lac,*

*dP(75)=(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(76)=(Qlt\*(Ca\_Ala-Cb\_Ala\_L)-AA\_up\_L)/Vol\_bld\_L;*

*%Blood Glycerol balance-Cb\_Glr*

*dP(77)=(Qlt\*(Ca\_Glr-Cb\_Glr\_L)-Glr\_up\_L)/Vol\_bld\_L;*

*%Blood FFA balance-Cb\_FFA*

*dP(78)=(Qlt\*(Ca\_FFA-Cb\_FFA\_L)-FFA\_up\_L)/Vol\_bld\_L;*

*%Blood TG balance*

*dP(79)=(Qlt\*(Ca\_TG-Cb\_TG\_L)-TG\_rel\_L)/(Vol\_bld\_L);*

*%Blood Co2 balance-Cb\_Co2\_F*

*dP(80)=(Qlt\*(Ca\_Co2\_T\_L-Cb\_Co2\_T\_L)-Co2\_rel\_L)/Vol\_bld\_Co2\_L;*

*%Blood O2 balance-Cb\_O2\_Fr*

*dP(81)=(Qlt\*(Ca\_O2\_T\_L-Cb\_O2\_T\_L)-O2\_up\_L)/Vol\_bld\_O2\_L;*

**Regulatory effects by signaling and transcription network on metabolic pathways**