

Supplementary Information

Supplementary Table S1. List of biochemical reactions considered in insect High Five cells metabolic model.

Reversible	Reaction	Enzyme(s)	Acronym
Glycolysis			
0	Glc + ATP <-> G6P + ADP	Hexokinase	HK
0	G6P <-> F6P	Phosphoglucose isomerase	PGI
0	F6P + ATP <-> 2 GAP + ADP	Phosphofructokinase, aldolase, Triose Phosphate isomerase	ALD
0	GAP + NAD + ADP <-> PEP + NADH + ATP	GAP dehydrogenase, Phosphoglycerate kinase, Phosphoglycerate mutase, enolase	GAPDH
-1	PEP + ADP -> Pyr + ATP	Pyruvate kinase	PK
Pentose Phosphate Pathway			
-1	G6P + 2 NADP -> R5P + CO ₂ + 2 NADPH	Glucose-6-P dehydrogenase	PPPox
Tricarboxylic Acid Cycle			
-1	ACoA + OAA -> Cit	Citrate synthase	CS
0	Cit + NAD <-> aKG + CO ₂ + NADH	Acotinase, Isocitrate dehydrogenase	IDH
-1	aKG + NAD -> SuCoA + CO ₂ + NADH	α -ketoglutarate dehydrogenase	ADH
0	SuCoA + ADP <-> Suc + ATP	SuCoA synthetase	SS
0	Suc + FAD <-> Fum + FADH ₂	Succinil dehydrogenase	SDH
0	Fum <-> Mal	Fumarase	Fum
0	Mal + NAD <-> OAA + NADH	Malate dehydrogenase	MDH
Pyruvate Node			
-1	Pyr + NAD -> ACoA + CO ₂ + NADH	Pyruvate dehydrogenase	PDH
0	Pyr + NADH <-> Lac + NAD	Lactate dehydrogenase	LDH
0	Pyr + Glu <-> Ala + aKG	Alanine aminotransferase	AlaAT
Anaplerotic and Cataplerotic			
0	Mal + NADP <-> Pyr + CO ₂ + NADPH	Malic Enzyme	ME
Oxidative Phosphorilation			
-1	NADH + 0.5 O ₂ + 2.5 ADP -> NAD + 2.5 ATP		
-1	FADH ₂ + 0.5 O ₂ + 1.5 ADP -> FAD + 1.5 ATP		
Amino acid Degradation			
-1	Gln -> Glu + NH ₄ ⁺	Gln dehydrogenase	GlnDeg
-1	Glu + NAD <-> aKG + NADH + NH ₄ ⁺	Glu dehydrogenase	GDH
-1	Glu + NADPH -> Pro + NADP	Pro dehydrogenase	ProDH
-1	Arg + aKG + NAD -> 2 Glu + NADH + urea	Arginase	ArgDeg
-1	His -> Glu + CO ₂ + 2 NH ₄ ⁺	His NH ₄ ⁺ lyase;	HisDeg
-1	Val + aKG + 3 NAD + FAD + ATP -> SuCoA + Glu + CO ₂ + 3 NADH + FADH ₂ + ADP	Val dehydrogenase	ValDeg
-1	Ile + aKG + ATP + 2 NAD -> SuCoA + ACoA + Glu + CO ₂ + ADP + 2 NADH	Ile aminotransferase	IleAT
-1	Met + Ser + NAD + 2 ATP -> SuCoA + Cys + C1 + NH ₄ ⁺ + NADH + 2 ADP	Met oxidase	MetDeg
-1	Asn -> Asp + NH ₄ ⁺	Asparaginase	AsnDeg

-1	Asp + aKG <-> OAA + Glu	Asp aminotransferase	AspAT
-1	Phe + NADH + O ₂ -> Tyr + NAD	Phe hydroxylase	PheDeg
-1	Tyr + aKG + 2 O ₂ -> Fum + 2 ACoA + CO ₂ + Glu	Tyr aminotransferase	TyrDeg
-1	Cys -> Pyr + NH ₄ ⁺	Cys lyase	CysDeg
-1	Ser <-> Pyr + Gly + NH ₄ ⁺	Ser deaminase	SerDA
-1	2 Gly + NAD -> Ser + CO ₂ + NH ₄ ⁺ + NADH	Gly hydroxitransferase	GlyDeg
-1	Thr + NAD -> Gly + ACoA + NADH	Thr aldolase	ThrAD
-1	Leu + aKG + NAD + ATP -> 3 ACoA + Glu + NADH + ADP	Leu dehydrogenase	LeuDH
-1	Lys + 2 aKG + 4 NAD + NADPH -> 2 ACoA + 2 CO ₂ + 2 Glu + 4 NADH + NADP	Lysine 2-monooxidase	LysDeg
Transport			
	Glc.ext -> Glc		
	Lac -> Lac.ext		
	NH ₄ ⁺ -> NH ₄ ⁺ .ext		
	Ala <-> Ala.ext		
	CO ₂ -> CO ₂ .ext		
	Glu.ext + 1 ATP -> Glu + 1 ADP		
	Asp.ext + 1 ATP -> Asp + 1 ADP		
	Gln.ext + 0.33 ATP -> Gln + 0.33 ADP		
	Asn.ext + 0.33 ATP -> Asn + 0.33 ADP		
	Arg.ext + 0.33 ATP -> Arg + 0.33 ADP		
	Gly.ext + 0.33 ATP -> Gly + 0.33 ADP		
	His.ext + 0.33 ATP -> His + 0.33 ADP		
	Ile.ext + 0.33 ATP -> Ile + 0.33 ADP		
	Leu.ext + 0.33 ATP -> Leu + 0.33 ADP		
	Lys.ext + 0.33 ATP -> Lys + 0.33 ADP		
	Met.ext + 0.33 ATP -> Met + 0.33 ADP		
	Phe.ext + 0.33 ATP -> Phe + 0.33 ADP		
	Ser.ext + 0.33 ATP -> Ser + 0.33 ADP		
	Thr.ext + 0.33 ATP -> Thr + 0.33 ADP		
	Tyr.ext + 0.33 ATP -> Tyr + 0.33 ADP		
	Val.ext + 0.33 ATP -> Val + 0.33 ADP		
Biomass & Macromolecules Synthesis			
-1	0.758 Ala + 0.276 Glu + 0.347 Gln + 0.931 Gly + 0.537 Ser + 0.38 Lys + 0.506 Leu + 0.263 Ile + 0.279 Arg + 0.289 Asp + 0.394 Thr + 0.421 Val + 0.119 Met + 0.158 Phe + 0.117 Tyr + 0.114 His + 0.374 Pro + 0.273 Asn + 0.189 Cys + 10.014 ATP -> 1 Protein + 10.014 ADP		Prot
-1	0.5 CO ₂ + R5P + 1.9 Gln + 1.3 Ser + 1.3 Asp + 0.7 NAD + NADPH + 9 ATP -> 1.9 Glu + 0.8 Fum + 0.8 Gly + DNA + 0.7 NADH + NADP + 9 ADP		DNA
-1	CO ₂ + R5P + 1.9 Gln + Ser + 1.3 Asp + NAD + ATP -> Glu + 0.8 Fum + 0.5 Gly + RNA + NADH + ADP		RNA
-1	9 ACoA + 7 NADPH + 26 ATP + 10 NADH + 1 O ₂ -> 1 FA + 7 NADP + 26 ADP + 10 NAD		FA
-1	1000 Protein + 219.8 FA + 177.3 DNA + 445 RNA -> 1 Biomass		Biom

Table footnote: Reaction Reversibility: 0 – reversible / -1 – irreversible. Acronym codes: aKG – alpha-ketoglutarate; ACoA – Acetyl-CoA; ADP – Adenosine diphosphate; Ala – Alanine; Arg – Arginine; Asn – Asparagine; Asp – Aspartic acid; ATP – Adenosine triphosphate; Cit – Citrate; CO₂ – Carbon dioxide; Cys – Cysteine; DNA – Deoxyribonucleic acid; F6P – Fructose 6-phosphate; FA – Fatty acid; FAD/FADH₂ – Flavin adenine dinucleotide; Fum – Fumarate; G6P – Glucose 6-phosphate; GAP – Glycerol aldehyde phosphate; Glc – Glucose; Gln – Glutamine; Glu – Glutamic acid; Gly – Glycine; His – Histidine; Ile – Isoleucine; Leu – Leucine; Lys – Lysine; Mal – Malate; Met – Methionine; NAD/NADH - Nicotinamide adenine dinucleotide; NADPNADPH – Nicotinamide adenine dinucleotide phosphate; NH₄⁺ - Ammonium; O₂ – oxygen; OAA – Oxaloacetic acid; PEP – Phosphoenol pyruvate; Phe – Phenylalanine; Pyr – Pyruvate; R5P – Ribose-5-phosphate; RNA – Ribonucleic acid; Ser – Serine; Suc – Succinate; SuCoA – Succinate-CoA; Thr – Threonine; Tyr – Tyrosine; Val – Valine

Supplementary Table S2. Biochemical reactions rates assessed by MFA analysis.

	Acronym	Reaction	Cell Growth Phase	Infection Phase							
				Group 1				Group 2			
				Monovalent		Multivalent		Monovalent		Multivalent	
				Rate ± SD	Rate ± SD	Rate ± SD	Rate ± SD	Rate ± SD	Rate ± SD	Rate ± SD	Rate ± SD
Glycolysis	HK	Glc + ATP = G6P + ADP	120.7 ± 33.2	109.1 ± N/D	189.2 ± N/D	191.9 ± N/D	202.5 ± N/D				
	PGI	G6P = F6P	110.8 ± 34.5	101.7 ± N/D	181.0 ± N/D	183.9 ± N/D	194.4 ± N/D				
	ALD	F6P + ATP = 2 GAP + ADP	110.8 ± 34.5	101.7 ± N/D	180.9 ± N/D	183.9 ± N/D	194.4 ± N/D				
	GAPDH	GAP + NAD + ADP = PEP + NADH + ATP	221.5 ± 70.0	203.5 ± N/D	362.0 ± N/D	367.7 ± N/D	388.9 ± N/D				
	PK	PEP + ADP = Pyr + ATP	221.5 ± 70.0	203.5 ± N/D	362.0 ± N/D	367.7 ± N/D	388.9 ± N/D				
PPP	PPPoX	G6P + 2 NADP = R5P + CO ₂ + 2 NADPH	9.9 ± 2.5	7.4 ± N/D	8.2 ± N/D	8.0 ± N/D	8.1 ± N/D				
Pyruvate node	LDH	Pyr + NADH = Lac + NAD	18.7 ± 6.2	4.2 ± N/D	-8.3 ± N/D	3.1 ± N/D	6.5 ± N/D				
	PDH	Pyr + NAD = ACoA + CO ₂ + NADH	77.5 ± 7.2	38.6 ± N/D	34.9 ± N/D	48.4 ± N/D	43.3 ± N/D				
	AlaAT	Pyr + Glu = Ala + αKG	185.4 ± 64.5	184.9 ± N/D	342.3 ± N/D	342.8 ± N/D	363.6 ± N/D				
TCA & Anaplerotic and Cataplerotic	CS	ACoA + OAA = Cit	138.5 ± 66.5	178.5 ± N/D	319.7 ± N/D	305.1 ± N/D	343.5 ± N/D				
	IDH	Cit + NAD = αKG + CO ₂ + NADH	147.8 ± 55.0	131.5 ± N/D	342.6 ± N/D	359.2 ± N/D	341.7 ± N/D				
	ADH	αKG + NAD = CO ₂ + SuCoA + NADH	158.4 ± 66.9	207.5 ± N/D	377.6 ± N/D	334.2 ± N/D	366.0 ± N/D				
	SS	SuCoA + ADP = Suc + ATP	156.1 ± 64.9	211.8 ± N/D	344.7 ± N/D	332.6 ± N/D	369.0 ± N/D				
	SDH	Suc + FAD = Fum + FADH ₂	156.1 ± 64.9	211.8 ± N/D	344.7 ± N/D	332.6 ± N/D	369.0 ± N/D				
	Fum	Fum = Mal	165.1 ± 63.7	220.9 ± N/D	353.7 ± N/D	335.9 ± N/D	378.0 ± N/D				
	MDH	Mal + NAD = OAA + NADH	87.1 ± 57.4	182.5 ± N/D	315.2 ± N/D	292.0 ± N/D	335.5 ± N/D				
	ME	Mal + NADP = Pyr + CO ₂ + NADPH	78.0 ± 8.3	38.4 ± N/D	38.5 ± N/D	43.9 ± N/D	42.5 ± N/D				
Amino Acid Metabolism	AspAT	αKG + Asp = Glu + OAA	77.5 ± 7.2	38.6 ± N/D	34.9 ± N/D	48.4 ± N/D	43.3 ± N/D				
	AsnDeg	Asn = Asp + NH ₄ ⁺	51.4 ± 11.7	-4.0 ± N/D	4.5 ± N/D	13.1 ± N/D	8.0 ± N/D				
	CysDeg	Cys = Pyr + NH ₄ ⁺	63.4 ± 3.4	6.9 ± N/D	15.3 ± N/D	25.0 ± N/D	21.7 ± N/D				
	GlnDeg	Gln = Glu + NH ₄ ⁺	3.1 ± 1.1	2.6 ± N/D	3.3 ± N/D	1.2 ± N/D	0.3 ± N/D				
	GDH	Glu + NAD = αKG + NH ₄ ⁺ + NADH	3.8 ± 4.5	17.1 ± N/D	10.8 ± N/D	18.1 ± N/D	11.1 ± N/D				
	GlyDeg	2 Gly + NAD = Ser + CO ₂ + NH ₄ ⁺ + NADH	-16.0 ± 3.9	-0.3 ± N/D	-2.7 ± N/D	-12.2 ± N/D	-6.3 ± N/D				
	LeuDH	Leu + αKG + NAD + ATP = 3 ACoA + Glu + NADH + ADP	-3.3 ± 1.7	-2.4 ± N/D	-3.3 ± N/D	-3.4 ± N/D	-3.2 ± N/D				
	SerDA	Ser = Pyr + NH ₄ ⁺ + Gly	-3.1 ± 0.6	2.0 ± N/D	-0.6 ± N/D	-1.0 ± N/D	-0.4 ± N/D				
Macromol. synthesis	Prot	Protein synthesis	-20.9 ± 1.5	-16.9 ± N/D	-18.3 ± N/D	-18.5 ± N/D	-18.2 ± N/D				
	DNA	DNA synthesis	15.9 ± 4.1	11.7 ± N/D	13.2 ± N/D	12.9 ± N/D	12.9 ± N/D				
	RNA	RNA synthesis	2.8 ± 0.7	2.1 ± N/D	2.4 ± N/D	2.3 ± N/D	2.3 ± N/D				
	FA	Fatty Acid synthesis	7.1 ± 1.8	5.3 ± N/D	5.9 ± N/D	5.7 ± N/D	5.8 ± N/D				
	Biomass	Biomass synthesis	3.5 ± 0.9	2.6 ± N/D	2.9 ± N/D	2.8 ± N/D	2.8 ± N/D				
	HK	Glc + ATP = G6P + ADP	0.015 ± 0.00	0.012 ± N/D	0.013 ± N/D	0.013 ± N/D	0.013 ± N/D				

Table footnote: For cell growth phase, data is expressed as mean ± standard deviation (SD) of four biological replicates (n=4); for infection phase, data is relative to one biological replicate (n=1), N/D - Not Determined.