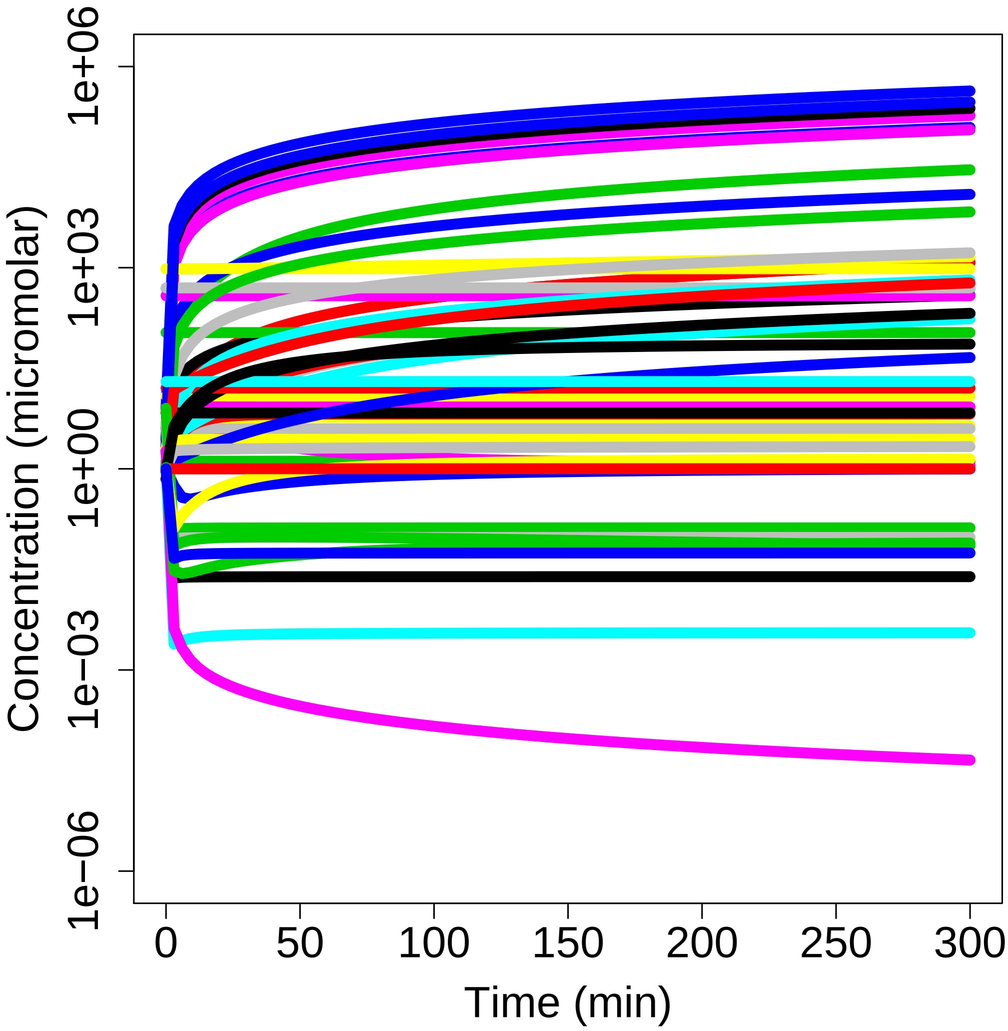

Figure S1. A whole model view of the metabolites included in this model of folate biosynthesis and utilisation pathways reaching steady state levels. Some of these substrates and products are illustrated and discussed in the main text and figures.

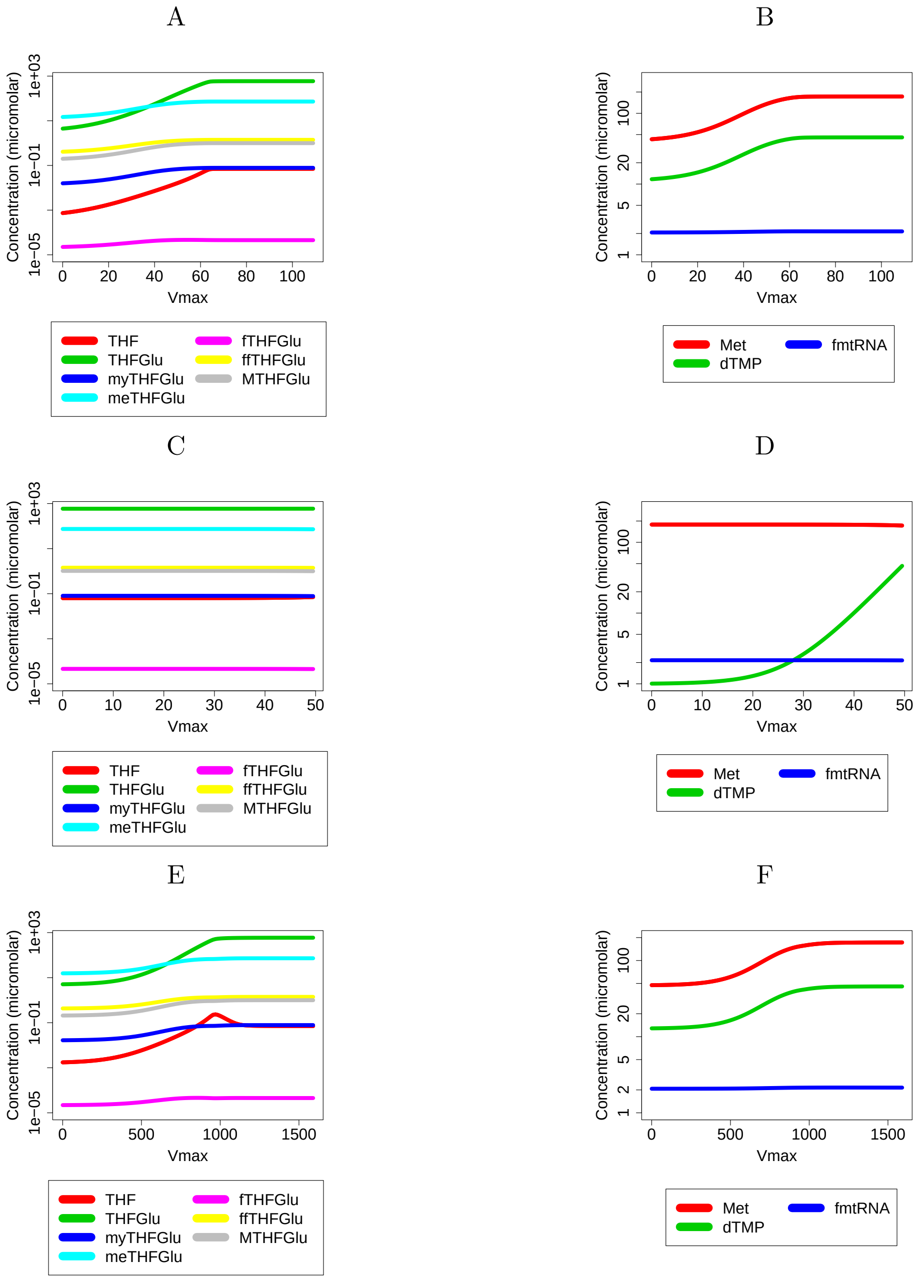

Figure S2. Effect of decreasing the V_{max} of enzyme targets for current antifolates on the steady-state levels of folate metabolites and products. (A and B) DHPS, (C and D) TS, and (E and F) PSCVT. Abbreviations as in Table S1 for enzymes and Table S2 for metabolites. V_{max} values in micromoles per litre per time unit in minutes (micromoles $(\text{Litre})^{-1}(\text{min})^{-1}$). The V_{max} values for each enzyme corresponds to the values entered for the corresponding reaction (Table S4).

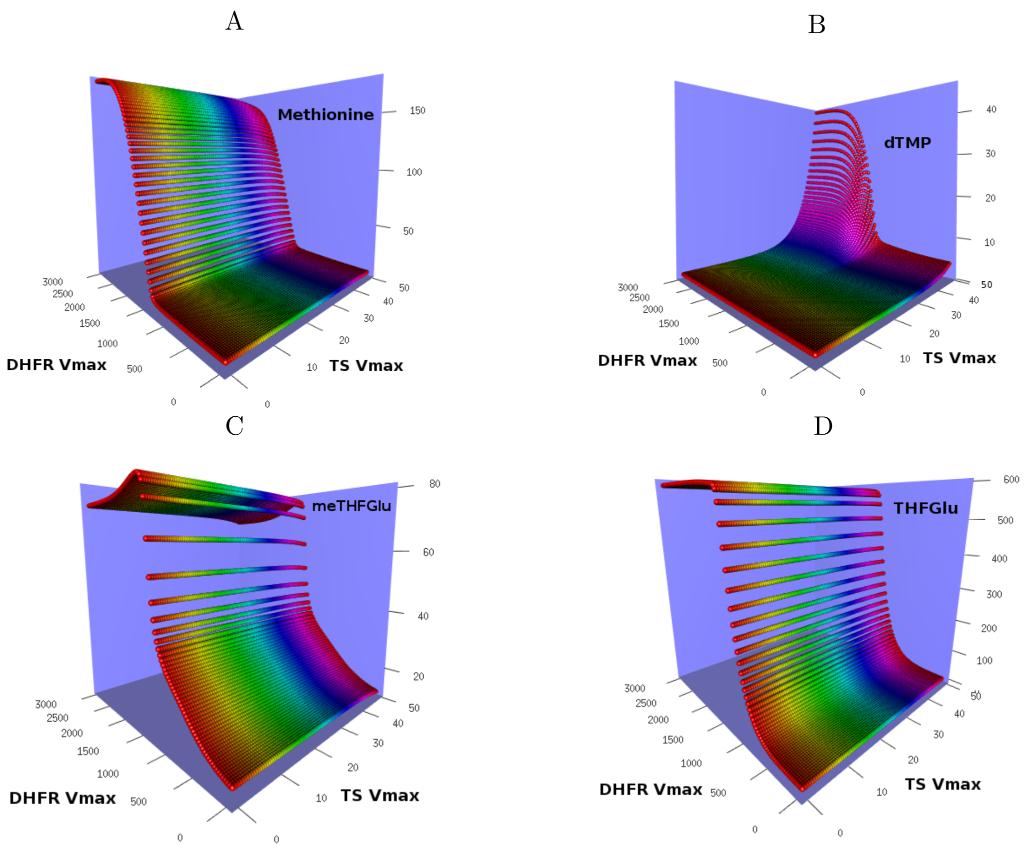

Figure S3. Modelling current antifolate combination therapies: DHFR and TS inhibitors. The different V_{max} values span from 0.1 up to the values entered for each reaction in this model (Table S4). The levels of four metabolites (A) Met, (B) dTMP, (C) meTHFGLu, and (D) THFGlu) plotted to illustrate the effects of this dual inhibition on the folate intermediates and products considered more important in the model. Abbreviations as in Table S2.

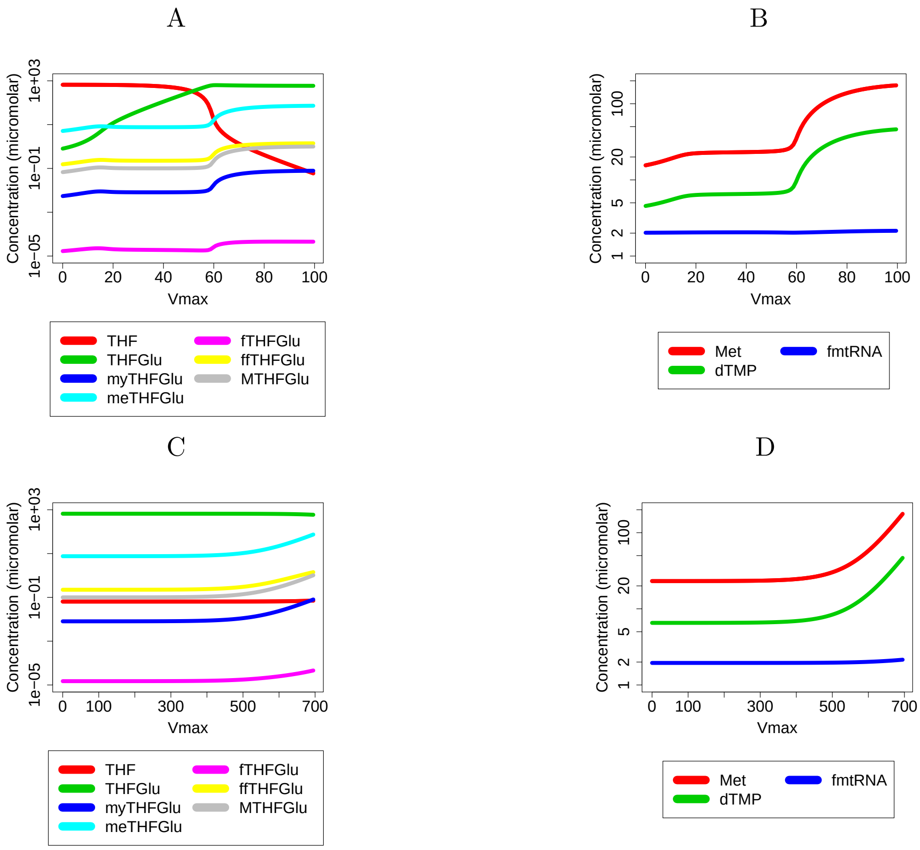

Figure S4. Effect of V_{max} decrease of potentially new antifolate targets on steady-state levels of folate cycle metabolites and products. FPGS (a-b) and SHMT (c-d) were chosen since inhibitors have been described for these two enzymes [1] and [2], respectively.

References

[1] P. Wang, Q. Wang, Y. Yang, J. K. Coward, A. Nzila, P. F. G. Sims, and J. E. Hyde. "Characterisation of the bifunctional dihydrofolate synthase-folylpolyglutamate synthase from \emph{Plasmodium falciparum}; a potential novel target for antimalarial antifolate inhibition." In: *Molecular and biochemical parasitology* 172.1 (2010), pp. 41–51.

[2] K. Sopitthummakhun, C. Thongpanchang, T. Vilaivan, Y. Yuthavong, P. Chaiyen, and U. Leartsakulpanich. "\emph{Plasmodium} serine hydroxymethyltransferase as a potential anti-malarial target: inhibition studies using improved methods for enzyme production and assay." In: *Malaria journal* 11.1 (2012), p. 194.

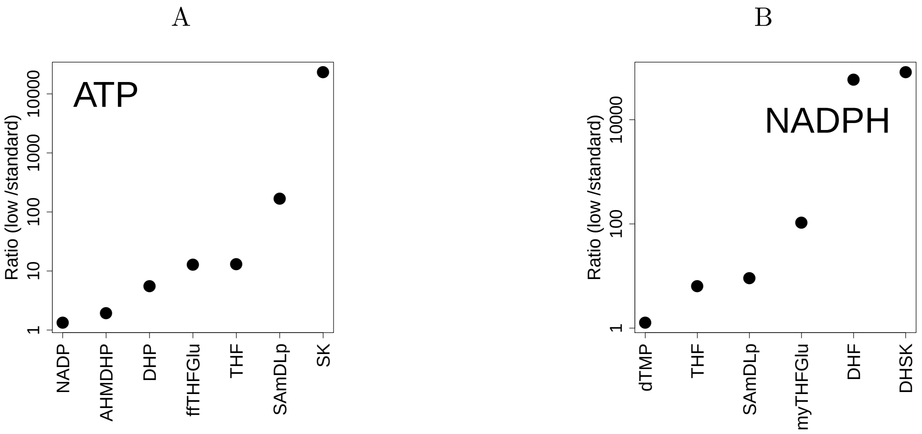

Figure S5. Folate biosynthesis metabolites with increased concentration when the model was simulated at low concentrations of (A) ATP or (B) NADPH. Abbreviations for metabolites as in Table S2.

Table S1: Enzyme reactions as found in KEGG (accessed July 2015)

Number	Enzyme Name (KEGG)	Abbreviation	KEGG	EC	Reaction
1	3-Deoxy-7-phosphoheptulonate synthase	DAHPS	R01826	2.5.1.54	Phosphoenolpyruvate + D-Erythrose 4-phosphate + H_2O = 2-Dehydro-3-deoxy-D-arabino-heptonate 7-phosphate + Orthophosphate
2	2-Dehydro-3-deoxy-D-arabino-heptonate 7-phosphate phosphate-lyase (3-Dehydroquinate synthase)	DHQS	R03083	4.2.3.4	2-Dehydro-3-deoxy-D-arabino-heptonate 7-phosphate = 3-Dehydroquinate + Orthophosphate
3	3-Dehydroquinate hydro-lyase (3-Dehydroquinate dehydratase)	DHQD	R03084	4.2.1.10	3-Dehydroquinate = 3-Dehydroshikimate + H_2O
4	Shikimate:$NADP^+$ 3-oxidoreductase (Shikimate 5-dehydrogenase)	SKDH	R02413	1.1.1.25	Shikimate + $NADP^+$ = 3-Dehydroshikimate + NADPH + H^+
5	ATP:Shikimate 3-phosphotransferase (Shikimate kinase)	SK	R02412	2.7.1.71	ATP + Shikimate = ADP + Shikimate 3-phosphate
6	Phosphoenolpyruvate:3-phosphoshikimate 5-O-(1-carboxyvinyl)-transferase	PSCVT	R03460	2.5.1.19	Phosphoenolpyruvate + Shikimate 3-phosphate = Orthophosphate + 5-O-(1-Carboxyvinyl)-3-phosphoshikimate
7	5-O-(1-Carboxyvinyl)-3-phosphoshikimate phosphate-lyase (chorismate synthase)	CS	R01714	4.2.3.5	5-O-(1-Carboxyvinyl)-3-phosphoshikimate = Chorismate + Orthophosphate
8	Aminodeoxychorismate synthase	ADCS	R01716	2.6.1.85	Chorismate + L-Glutamine = 4-Amino-4-deoxychorismate + L-Glutamate
9	Aminodeoxychorismate lyase	ADCL	R05553	4.1.3.38	4-Amino-4-deoxychorismate = 4-Aminobenzoate + Pyruvate
10	GTP 7,8,9-dihydrolase (GTP cyclohydrolase I)	GTPCHI	R00424	3.5.4.16	GTP + H_2O = 7,8-Dihydroneopterin 3'-triphosphate + Formate
11	Dihydroneopterin aldolase	DHNA	R03504	4.1.2.25	2-Amino-4-hydroxy-6-(D-erythro-1,2,3-trihydroxypropyl)-7,8-dihydropteridine = Glycolaldehyde + 2-Amino-4-hydroxy-6-hydroxymethyl-7,8-dihydropteridine + Triphosphate
12	2-Amino-4-hydroxy-6-hydroxymethyldihydropteridine pyrophosphokinase	PPPK	R03503	2.7.6.3	ATP + 2-Amino-4-hydroxy-6-hydroxymethyl-7,8-dihydropteridine = AMP + 2-Amino-7,8-dihydro-4-hydroxy-6-(diphosphooxymethyl)pteridine
13	Dihydropteroate synthase	DHPS	R03067	2.5.1.15	2-Amino-7,8-dihydro-4-hydroxy-6-(diphosphooxymethyl)pteridine + 4-Aminobenzoate = Diphosphate + Dihydropteroate
14	7,8-Dihydrofolate synthase	DHFS	R02237	6.3.2.12	ATP + Dihydropteroate + L-Glutamate = ADP + Orthophosphate + Dihydrofolate
15	Dihydrofolate reductase	DHFR	R00939	1.5.1.3	Dihydrofolate + NADPH + H^+ = Tetrahydrofolate + $NADP^+$
16	Folylpoly-gamma-glutamate synthase	FPGS	R04241	6.3.2.17	ATP + THF-polyglutamate(n) + L-Glutamate = ADP + Orthophosphate + THF-polyglutamate(n+1)
17	Serine hydroxymethyltransferase	SHMT	R00945	2.1.2.1	THF-polyglutamate(n) + L-Serine = 5,10-Methylenetetrahydrofolate + Glycine
18a	Dihydrolipoamide dehydrogenase	DLDH	R03815	1.8.1.4	Lipoylprotein + NADH + H^+ = Dihydrolipoylprotein + NAD^+
18b	Glycine decarboxylase (P protein)	GCV.P	R03425	1.4.4.2	Glycine + Dihydrolipoylprotein = S-Aminomethyldihydrolipoylprotein + CO_2
18c	S-Aminomethyldihydrolipoylprotein:tetrahydrofolate aminomethyltransferase (T protein)	GCV.T	R04125	2.1.2.10	S-Aminomethyldihydrolipoylprotein + Tetrahydrofolate = Lipoylprotein + 5,10-Methylenetetrahydrofolate + Ammonia
19	5,10-Methylenetetrahydrofolate reductase	MTHFR	R01224	1.5.1.20	5,10-Methylenetetrahydrofolate + NADPH + H^+ = 5-Methyltetrahydrofolate + $NADP^+$
20	Methionine synthase	MS	R00946	2.1.1.13	5-Methyltetrahydrofolate + L-Homocysteine = Tetrahydrofolate + L-Methionine
21	Thymidylate synthase	TS	R02101	2.1.1.45	dUMP + 5,10-Methylenetetrahydrofolate = Dihydrofolate + dTMP
22	5,10-Methylenetetrahydrofolate dehydrogenase	MTHFD	R01220	1.5.1.5	5,10-Methylenetetrahydrofolate + $NADP^+$ = 5,10-Methenyltetrahydrofolate + NADPH
23	5,10-Methenyltetrahydrofolate cyclohydrolase	MTHFC	R01655	3.5.4.9	5,10-Methenyltetrahydrofolate + H_2O = 10-Formyltetrahydrofolate + H^+
24	10-Formyltetrahydrofolate synthetase	MTHFS	R00943	6.3.4.3	ADP + Orthophosphate + 10-Formyltetrahydrofolate = Tetrahydrofolate + Formate + ATP
25	Methionyl-tRNA formyltransferase	MTFMT	R03940	2.1.2.9	L-Methionyl-tRNA + 10-Formyltetrahydrofolate = Tetrahydrofolate + N-Formylmethionyl-tRNA
26	10-Formyltetrahydrofolate dehydrogenase	FTHFD	R00941	1.5.1.6	10-Formyltetrahydrofolate + $NADP^+$ + H_2O = Tetrahydrofolate + CO_2 + NADPH + H^+
27	6-Pyruvoyltetrahydropterin synthase	PTPS	R04286	4.2.3.12	7,8-Dihydroneopterin 3'-triphosphate = 6-Pyruvoyltetrahydropterin + Triphosphate
28	S-Aminomethyldihydrolipoylprotein:tetrahydrofolate aminomethyltransferase (T protein)	GCV.T	R02300	2.1.2.10	5,10-Methenyltetrahydrofolate = Folinic acid
29	5-formyltetrahydrofolate cyclo-ligase	FCL	R02301	6.3.3.2	ATP + Folinic acid + H^+ = ADP + Orthophosphate + 5,10-Methenyltetrahydrofolate

Table S2: List of metabolite abbreviations as included in the model

Abbreviation	Name (KEGG)	Formula	KEGG
ADC	4-Amino-4-deoxychorismate	C10H11NO5	C11355
ADP	ADP	C10H15N5O10P2	C00008
AHMDHP	2-Amino-4-hydroxy-6-hydroxymethyl-7,8-dihydropteridine	C7H9N5O2	C01300
AHMDPP	2-Amino-4-hydroxy-6-hydroxymethyl-7,8-dihydropteridine diphosphate	C7H11N5O8P2	C04807
AMP	AMP	C10H14N5O7P	C00020
ATP	ATP	C10H16N5O13P3	C00002
CM	Chorismate	C10H10O6	C00251
CVPSK	5-O-(1-Carboxyvinyl)-3-phosphoshikimate	C10H13O10P	C01269
DAHP	2-Dehydro-3-deoxy-D-arabino-heptonate 7-phosphate	C7H13O10P	C04691
DHF	Dihydrofolate	C19H21N7O6	C00415
DHNTP	7,8-Dihydroneopterin 3'-triphosphate	C9H16N5O13P3	C04895
DHP	7,8-Dihydropteroate	C14H14N6O3	C00921
DHQ	3-Dehydroquinate	C7H10O6	C00944
DHSK	3-Dehydroshikimate	C7H8O5	C02637
DLp	Dihydrolipoylprotein ([H Protein]-dihydrolipoyllysine)	C8H16NOS2R	C02972
dTMP	Deoxythymidine 5'-phosphate	C10H15N2O8P	C00364
dUMP	Deoxyuridine 5'-phosphate	C9H13N2O8P	C00365
E4P	D-Erythrose 4-phosphate	C4H9O7P	C00279
ffTHFGlu	5-formyltetrahydrofolate	C20H23N7O7	C03479
formyl	Formate	CH2O2	C00058
formylmtRNA	N-Formylmethionyl-tRNA	C21H30N6O12PSR(C5H8O6PR)n	C03294
fTHFGlu	10-Formyltetrahydrofolate	C20H23N7O7	C00234
Gln	L-Glutamine	C5H10N2O3	C00064
Glu	L-Glutamate	C5H9NO4	C00025
Gly	Glycine	C2H5NO2	C00037
GTP	Guanosine 5'-triphosphate	C10H16N5O14P3	C00044
HAD	Hydroxyacetaldehyde (Glycolaldehyde)	C2H4O2	C00266
Hcy	L-Homocysteine	C4H9NO2S	C00155
Lp	Lipoylprotein ([H Protein]-lipoyllysine)	C8H14NOS2R	C02051
Met	L-Methionine	C5H11NO2S	C00073
meTHFGlu	5,10-Methenyltetrahydrofolate	C20H22N7O6	C00445
MTHFGlu	5-Methyltetrahydrofolate	C20H25N7O6	C00440
mtRNA	L-Methionyl-tRNA	C20H30N6O11PSR(C5H8O6PR)n	C02430
myTHFGlu	5,10-Methylenetetrahydrofolate	C20H23N7O6	C00143
NAD	NAD^+	C21H28N7O14P2	C00003
NADH	$NADH + H^+$	C21H29N7O14P2	C00004
NADP	$NADP^+$	C21H29N7O17P3	C00006
NADPH	$NADPH + H^+$	C21H30N7O17P3	C00005
NH3	Ammonia	NH3	C00014
pABA	4-Aminobenzoate (p-Aminobenzoate)	C7H7NO2	C00568
PEP	Phosphoenolpyruvate	C3H5O6P	C00074
Pi	Orthophosphate	H3PO4	C00009
PTHP	6-Pyruvoyltetrahydropterin	C9H11N5O3	C03684
Pyr	Pyruvate	C3H4O3	C00022
SAmDLp	S-Aminomethyldihydrolipoylprotein (H-Protein-S-aminomethyldihydrolipoyllysine)	C9H19N2OS2R	C01242
Ser	L-Serine	C3H7NO3	C00065
SK	Shikimate	C7H10O5	C00493
SKP	Shikimate 3-phosphate	C7H11O8P	C03175
THF	Tetrahydrofolate	C19H23N7O6	C00101
THFGlu	THF-polyglutamate(n)	C24H30N8O9(C5H7NO3)n-2	C03541

Table S3: k_m values compiled from BRENDA (accessed July 2015). Each enzyme plus substrate combination is denoted by the enzyme abbreviation followed by a dot and the abbreviation for the substrate. For this model the median values for each combination were drawn from a number of entries as noted at the bottom of the data for each ”enzyme.substrate” combination. Values in millimolar. All abbreviations as detailed in Tables S1 and S2.

DAHPS.E4P	**DAHPS.PEP**	**DHQS.DAHP**	**DHQD.DHQ**	**SKDH.DHSK**	**SKDH.NADPH**	**SK.ATP**	**SK.Shi**	**PSCVT.SK3P**	**PSCVT.PEP**	**CS.CVPSK**
Min. :0.00260	Min. :0.0032	Min. :0.00055	Min. :0.01500	Min. :0.02900	Min. :0.0100	Min. :0.0480	Min. : 0.0390	Min. :0.00025	Min. : 0.00180	Min. :0.00130
1st Qu.:0.08255	1st Qu.:0.0130	1st Qu.:0.00205	1st Qu.:0.03075	1st Qu.:0.02900	1st Qu.:0.0110	1st Qu.:0.1032	1st Qu.: 0.1050	1st Qu.:0.01450	1st Qu.: 0.02725	1st Qu.:0.01002
Median :0.28500	Median :0.0360	Median :0.00470	Median :0.05800	Median :0.03000	Median :0.0110	Median :0.1515	Median : 0.2000	Median :0.08000	Median : 0.09310	Median :0.01270
Mean :0.87231	Mean :0.3180	Mean :0.02569	Mean :0.15528	Mean :0.03325	Mean :0.0192	Mean :0.2054	Mean : 1.8409	Mean :0.23876	Mean : 1.13585	Mean :0.02699
3rd Qu.:1.07500	3rd Qu.:0.1600	3rd Qu.:0.02700	3rd Qu.:0.16500	3rd Qu.:0.03425	3rd Qu.:0.0300	3rd Qu.:0.2132	3rd Qu.: 0.3505	3rd Qu.:0.19150	3rd Qu.: 0.29050	3rd Qu.:0.04200
Max. :6.80000	Max. :3.5000	Max. :0.22800	Max. :0.65000	Max. :0.04400	Max. :0.0340	Max. :0.6200	Max. :20.0000	Max. :2.50000	Max. :43.60000	Max. :0.08000
46	45	18	28	4	5	10	15	63	84	14
ADCS.Cho	**ADCS.Gln**	**ADCL**	**GTPCH.I.GTP**	**DHNA.DHNTP**	**PTPS.DHNTP**	**PPPK.AHMDHP**	**PPPK.ATP**	**DHPS.AHMDPP**	**DHPS.pABA**	**DHFS.DHP**
Min. :0.00150	Min. :0.60	Mode:logical	Min. :0.00400	Min. :0.00076	Min. :0.00050	Min. :0.00039	Min. :0.01100	Min. :0.00040	Min. :0.00037	Min. :0.00025
1st Qu.:0.00420	1st Qu.:0.85	NA's:148	1st Qu.:0.00915	1st Qu.:0.00390	1st Qu.:0.00800	1st Qu.:0.00160	1st Qu.:0.01200	1st Qu.:0.00152	1st Qu.:0.00085	1st Qu.:0.00074
Median :0.01300	Median :1.10	NA	Median :0.01760	Median :0.00740	Median :0.01000	Median :0.00360	Median :0.01500	Median :0.00315	Median :0.00260	Median :0.00100
Mean :0.03474	Mean :1.10	NA	Mean :0.03055	Mean :0.01717	Mean :0.01736	Mean :0.00651	Mean :0.02317	Mean :0.01137	Mean :0.25597	Mean :0.00575
3rd Qu.:0.05800	3rd Qu.:1.35	NA	3rd Qu.:0.04950	3rd Qu.:0.02100	3rd Qu.:0.01270	3rd Qu.:0.01000	3rd Qu.:0.01650	3rd Qu.:0.01268	3rd Qu.:0.00708	3rd Qu.:0.00125
Max. :0.09700	Max. :1.60	NA	Max. :0.08000	Max. :0.06400	Max. :0.10000	Max. :0.01500	Max. :0.07000	Max. :0.05140	Max. :4.02000	Max. :0.03500
5	2	0	12	21	26	9	6	10	21	7
DHFS.Glu	**DHFS.ATP**	**DHFR.DHF**	**DHFR.NADPH**	**TS.myTHF**	**TS.dUMP**	**FPGS.THF**	**FPGS.Glu**	**FPGS.ATP**	**SHMT.Ser**	**SHMT.THF**
Min. :0.00597	Min. :0.0069	Min. : 0.000040	Min. :0.000430	Min. :0.00074	Min. :0.00070	Min. :0.00081	Min. : 0.053	Min. :0.00460	Min. : 0.130	Min. :0.0037
1st Qu.:0.25000	1st Qu.:0.0228	1st Qu.: 0.001300	1st Qu.:0.002925	1st Qu.:0.00845	1st Qu.:0.00259	1st Qu.:0.00470	1st Qu.: 0.316	1st Qu.:0.04375	1st Qu.: 0.165	1st Qu.:0.0131
Median :1.38000	Median :0.1000	Median : 0.003000	Median :0.006125	Median :0.01700	Median :0.00540	Median :0.02600	Median : 0.740	Median :0.12800	Median : 0.700	Median :0.0400
Mean :2.25466	Mean :0.1279	Mean : 0.400859	Mean :0.023051	Mean :0.04648	Mean :0.01626	Mean :0.19810	Mean : 18.637	Mean :1.06353	Mean : 2.779	Mean :0.4169
3rd Qu.:3.50000	3rd Qu.:0.2200	3rd Qu.: 0.008825	3rd Qu.:0.013250	3rd Qu.:0.04270	3rd Qu.:0.01500	3rd Qu.:0.11975	3rd Qu.: 2.175	3rd Qu.:1.22750	3rd Qu.: 1.315	3rd Qu.:0.2765
Max. :9.10000	Max. :0.2900	Max. :21.700000	Max. :0.415000	Max. :0.31250	Max. :0.17900	Max. :6.80000	Max. :350.000	Max. :5.70000	Max. :65.300	Max. :3.4000
9	5	148	120	64	81	140	43	36	55	35
MTHFR.myTHF	**MTHFR.NADPH**	**MS.MTHF**	**MS.Hcy**	**GCV.T.myTHF**	**GCV.P.Gly**	**GCV.L.DHL**	**GCV.L.LPA**	**MTHFD.myTHF**	**MTHFD.NADP**	**MTHFC.FTHF**
Min. : 0.0004	Min. :0.00730	Min. :0.0040	Min. :0.00260	Min. :0.00920	Min. : 2.840	Min. :0.0170	Min. : 0.050	Min. :0.00110	Min. :0.0004	Min. :0.00900
1st Qu.: 0.0145	1st Qu.:0.01600	1st Qu.:0.0244	1st Qu.:0.01100	1st Qu.:0.01080	1st Qu.: 3.020	1st Qu.:0.0900	1st Qu.: 0.485	1st Qu.:0.01050	1st Qu.:0.0110	1st Qu.:0.02200
Median : 0.0330	Median :0.01900	Median :0.0300	Median :0.01700	Median :0.06770	Median : 4.505	Median :0.2900	Median : 1.280	Median :0.02500	Median :0.0220	Median :0.03100
Mean : 0.3807	Mean :0.02246	Mean :0.2283	Mean :0.08137	Mean :0.05878	Mean :10.707	Mean :0.3461	Mean : 2.754	Mean :0.10631	Mean :0.0816	Mean :0.07873
3rd Qu.: 0.1060	3rd Qu.:0.02950	3rd Qu.:0.0731	3rd Qu.:0.04900	3rd Qu.:0.08750	3rd Qu.: 9.950	3rd Qu.:0.5875	3rd Qu.: 3.620	3rd Qu.:0.03875	3rd Qu.:0.0910	3rd Qu.:0.07000
Max. :11.1000	Max. :0.04900	Max. :2.4000	Max. :0.43000	Max. :0.15100	Max. :40.000	Max. :0.8800	Max. :16.000	Max. :1.60000	Max. :0.6900	Max. :0.47000
35	10	13	7	9	12	26	22	22	19	35
MTHFC.meTHF	**MTHFS.formate**	**MTHFS.THF**	**MTHFS.ATP**	**FTHFD.10fTHF**	**FTHFD.NADP**	**MTFMT.10fTHF**	**MTFMT.tRNAfMet**	**5FCL.ffTHF**	**5FCL.ATP**	
Min. :0.0090	Min. : 0.035	Min. :0.00010	Min. :0.0120	Min. :0.00320	Min. :0.00040	Min. :0.00600	Min. :0.00010	Min. :0.00020	Min. :0.00021	
1st Qu.:0.0400	1st Qu.: 0.364	1st Qu.:0.01825	1st Qu.:0.0298	1st Qu.:0.00525	1st Qu.:0.00080	1st Qu.:0.00975	1st Qu.:0.00051	1st Qu.:0.00170	1st Qu.:0.00655	
Median :0.0800	Median : 3.190	Median :0.13500	Median :0.0745	Median :0.00785	Median :0.00090	Median :0.01215	Median :0.00107	Median :0.00485	Median :0.06300	
Mean :0.2847	Mean : 7.584	Mean :0.36172	Mean :0.0874	Mean :0.00988	Mean :0.00114	Mean :0.01095	Mean :0.00260	Mean :0.16480	Mean :0.39370	
3rd Qu.:0.2500	3rd Qu.:11.875	3rd Qu.:0.43600	3rd Qu.:0.1105	3rd Qu.:0.01365	3rd Qu.:0.00100	3rd Qu.:0.01335	3rd Qu.:0.00306	3rd Qu.:0.01575	3rd Qu.:0.41250	
Max. :2.3600	Max. :38.000	Max. :2.30000	Max. :0.2200	Max. :0.02000	Max. :0.00350	Max. :0.01350	Max. :0.01000	Max. :2.50000	Max. :5.00000	
35	20	22	12	12	8	4	32	24	32	

Table S4: Enzyme specific activities (from BRENDA, accessed July 2015) are here extrapolated to V_{max}. The median values for specific activities were taken for most enzymes to extrapolate V_{max} values (at the bottom of the data for each enzyme). In some cases the third quartile or the mean were used instead. The number of entries for each enzyme are noted at the top of the data for each enzyme. All abbreviations as detailed in Table S1. V_{max} values were calculated by extrapolating the mass of protein in milligrams to volume in Litres using the parameters typical of a bacterial such as *E. coli* (proteins constitute about 55% of the dry cell weight and the cytoplasm has a density of 1.1 with 70% water) [1]: one milligram of protein (specific activities are expressed per milligram of purified protein) represents 1.818 (1 divided by 0.55) milligrams of total cell dry weight; at a density of 1.1 this mass corresponds to 1.65 (1.818 divided by 1.65 equals 1.1) millilitres of protein volume. Which is 30% of cell volume. Total cell volume (plus water) is 5.5 millilitres (1.65 divided by 0.3). Finally, 5.5 millilitres represent $1/182^{th}$ of a litre. Thus, the one milligram of protein against which every specfic activity is reported represents $1/182^{th}$ of total cell volume in litres. To express specific activities per litre (V_{max}) the values compiled here are simply multiplied by 182.

DAHPS	**DHQS**	**DHQD**	**SKDH**	**SK**	**PSCVT**	**CS**	**ADCS**	**ADCL**	**GTPCH.I**
50	22	20	13	6	61	5	0	0	10
Min. : 0.005	Min. : 0.00900	Min. : 0.0002	Min. : 0.28	Min. : 0.0572	Min. : 0.0058	Min. : 0.004	Mode:logical	Mode:logical	Min. : 0.00000
1st Qu.: 0.835	1st Qu.: 0.01825	1st Qu.: 0.0898	1st Qu.: 3.90	1st Qu.: 31.2925	1st Qu.: 1.4000	1st Qu.: 0.920	NA's:91	NA's:91	1st Qu.: 0.00042
Median : 3.180	**Median : 0.04100**	**Median : 0.6400**	**Median : 95.00**	**Median :100.0000**	**Median : 8.5000**	**Median : 4.000**	NA	NA	Median : 0.08950
Mean : 15.588	Mean : 4.57891	Mean : 182.7259	Mean : 356.26	Mean :120.0579	Mean :15.8400	Mean :10.365	NA	NA	Mean : 25.52802
3rd Qu.: 10.953	3rd Qu.: 1.10750	3rd Qu.: 73.2250	3rd Qu.: 732.00	3rd Qu.:101.4250	3rd Qu.:21.1000	3rd Qu.:14.800	NA	NA	**3rd Qu.: 8.32500**
Max. :160.000	Max. :44.00000	Max. :1710.0000	Max. :1479.00	Max. :410.0000	Max. :94.7000	Max. :32.100	NA	NA	Max. :173.00000
578.76	7.462	116.48	17290	18200	1547	728			1515.15
DHNA	**PTPS**	**PPPK**	**DHPS**	**DHFS**	**DHFR**	**TS**	**FPGS**	**SHMT**	**GCV.T**
2	27	1	13	3	81	47	49	36	1
Min. :0.0039	Min. : 0.00023	Min. :2.1	Min. : 0.00005	Min. :0.00700	Min. : 0.0025	Min. : 0.0001	Min. : 0.0000	Min. : 0.012	Min. :1.08
1st Qu.:2.1779	1st Qu.: 0.00502	1st Qu.:2.1	1st Qu.: 0.17400	1st Qu.:0.01125	1st Qu.: 8.0000	1st Qu.: 0.0023	1st Qu.: 0.0003	1st Qu.: 0.580	1st Qu.:1.08
Median :4.3520	Median : 0.07400	**Median :2.1**	**Median : 0.57700**	**Median :0.01550**	**Median : 19.1000**	**Median : 0.2700**	Median : 0.1380	**Median : 3.750**	**Median :1.08**
Mean :4.3520	Mean : 3.85610	Mean :2.1	Mean : 4.13905	Mean :0.18583	Mean : 51.7940	Mean : 19.5075	Mean : 1.8333	Mean : 5.104	Mean :1.08
3rd Qu.:6.5260	**3rd Qu.: 0.12450**	3rd Qu.:2.1	3rd Qu.: 1.25000	3rd Qu.:0.27525	3rd Qu.: 46.0000	3rd Qu.: 2.7500	**3rd Qu.: 0.4650**	3rd Qu.: 7.343	3rd Qu.:1.08
Max. :8.7000	Max. :57.40000	Max. :2.1	Max. :30.00000	Max. :0.53500	Max. :321.0000	Max. :414.0000	Max. :45.6000	Max. :32.400	Max. :1.08
792.064	22.659	382.2	105.014	2.821	3476.2	49.14	84.63	682.5	196.56
GCV.P	**GCV.L**	**MTHFR**	**MS**	**MTHFD**	**MTHFC**	**MTHFS**	**FTHFD**	**MTFMT**	**5-FCL**
7	56	23	12	26	91	8	12	5	11
Min. :0.0200	Min. : 0.002	Min. : 0.00004	Min. :0.00017	Min. : 0.009	Min. : 0.0002	Min. : 23.00	Min. :0.00278	Min. :0.0130	Min. :0.00006
1st Qu.:0.1515	1st Qu.: 2.482	1st Qu.: 0.00086	1st Qu.:0.00185	1st Qu.: 0.110	1st Qu.: 0.4370	1st Qu.: 35.95	1st Qu.:0.13150	1st Qu.:0.5300	1st Qu.:0.00034
Median :1.0450	**Median : 29.850**	Median : 0.00890	Median :0.02000	**Median : 10.400**	**Median : 2.4000**	**Median : 84.15**	**Median :0.32600**	**Median :0.6400**	Median :0.00150
Mean :1.2411	Mean : 99.055	Mean : 17.86266	Mean :1.59637	Mean : 81.656	Mean : 33.7917	Mean :179.64	Mean :0.41896	Mean :0.7106	**Mean :2.62000**
3rd Qu.:1.5950	3rd Qu.:127.000	**3rd Qu.: 4.06000**	**3rd Qu.:2.08750**	3rd Qu.: 53.875	3rd Qu.: 22.6000	3rd Qu.:200.50	3rd Qu.:0.65500	3rd Qu.:1.1400	3rd Qu.:3.30000
Max. :4.1300	Max. :843.000	Max. :153.00000	Max. :9.30000	Max. :720.000	Max. :470.0000	Max. :780.00	Max. :1.04000	Max. :1.2300	Max. :13.00000
751.66	5432.7	738.92	379.925	1892.8	436.8	15315.3	59.332	116.48	476.84

References

[1] O. Demin, G. Lebedeva, A. Kolupaev, E. Zobova, T. Plyusnina, A. Lavrova, A. Dubinsky, E. Goryacheva, F. Tobin, and I. Goryanin. "Kinetic modelling as a modern technology to explore and modify living cells". In: *Modelling in Molecular Biology*. Ed. by G Ciobanu and G Rozenberg. Springer-Verlag, 2004, pp. 59–124.

Table S5. Initial and steady state concentrations. Metabolites abbreviations as in Table S2. Concentrations in micromolar and rates in micromoles $(\text{Litre})^{-1}(\text{min})^{-1}$. Fixed initial concentrations in bold.

Number	Metabolite	Initial	Steady state	Rate
1	DAHP	0.980	12407.571	4.13E+001
2	PEP	**16.010**	16.010	0
3	Pi	2.726	295149.675	9.98E+002
4	DHQ	0.999	3.968	5.37E-006
5	EP	**107.502**	107.502	0
6	DHSK	1.928	0.025	3.12E-008
7	SK	5.068	0.095	1.20E-007
8	SKP	2.000	2.769	3.62E-006
9	CVPSK	0.917	0.131	1.69E-007
10	CM	1.009	388.993	9.87E-001
11	Gln	**381.001**	381.001	0
12	Glu	960.000	1451.181	1.89E+000
13	ADC	0.991	1195.091	4.27E+000
14	Pyr	1.000	655.033	2.20E+000
15	pABA	1.004	0.056	1.81E-007
16	DHNTP	4.000	186178.130	6.25E+002
17	GTP	**487.487**	487.487	0
18	AHMDHP	2.019	123394.921	4.11E+002
19	HAD	2.002	237496.305	7.92E+002
20	PTHP	1.002	6794.104	2.27E+001
21	AHMDPP	0.987	113447.407	3.79E+002
22	DHP	0.996	4.382	5.28E-003
23	DHF	1.143	0.004	6.95E-008
24	THF	8.000	0.071	8.49E-005
25	THFGlu	1.000	592.532	2.18E+000
26	Gly	**499.997**	499.997	0
27	Ser	**6.804**	6.804	0
28	myTHFGlu	1.044	0.078	2.27E-005
29	MTHFGlu	1.000	0.997	3.02E-004
30	Hcy	**1.000**	1.000	0.00E+000
31	Met	1.000	172.686	6.79E-001
32	dTMP	0.997	45.690	1.77E-001
33	dUMP	**20.003**	20.003	0
34	meTHFGlu	0.908	72.443	2.61E-002
35	fTHFGlu	1.833	0.000	1.82E-007
36	fmtRNA	0.997	2.144	2.10E-004
37	mtRNA	**1.003**	1.003	0
38	COTwo	0.989	204.551	6.93E-001
39	ADP	2.828	28864.964	1.10E+002
40	ATP	**963.019**	963.019	0
41	NADP	2.000	1665.157	4.70E+000
42	NADPH	**12.198**	12.198	0
43	AMP	0.984	114102.384	3.81E+002
44	DLp	0.702	6.569	1.20E-014
45	SAmDLp	1.000	1.144	4.38E-004
46	Lp	**1.298**	1.298	0
47	NAD	0.702	208.517	6.93E-001
48	NADH	**8.350**	8.350	0
49	Ammonia	0.990	202.793	6.93E-001
50	Formyl	8.000	431832.140	1.45E+003
51	ffTHFGlu	1.000	1.399	3.10E-004

$$\frac{d([DAHP]\cdot V_{compartment})}{dt} = +V_{compartment}\cdot\left(\frac{578.76\cdot[EP]\cdot[PEP]}{36\cdot 285+36\cdot[EP]+285\cdot[PEP]+[EP]\cdot[PEP]}\right) - V_{compartment}\cdot\left(\frac{7.462\cdot[DAHP]}{4.7+[DAHP]}\right)$$

$$\frac{d([Pi]\cdot V_{compartment})}{dt} = +V_{compartment}\cdot\left(\frac{578.76\cdot[EP]\cdot[PEP]}{36\cdot 285+36\cdot[EP]+285\cdot[PEP]+[EP]\cdot[PEP]}\right) + V_{compartment}\cdot\left(\frac{7.462\cdot[DAHP]}{4.7+[DAHP]}\right) + V_{compartment}\cdot\left(\frac{792.064\cdot[DHNTP]}{7.4+[DHNTP]}\right) + V_{compartment}\cdot\left(\frac{22.659\cdot[DHNTP]}{10+[DHNTP]}\right) + V_{compartment}\cdot\left(\frac{2.821\cdot[DHP]\cdot[Glu]\cdot[ATP]}{1\cdot 1380\cdot 100+1\cdot([Glu]+[ATP])+1380\cdot([DHP]+[ATP])+100\cdot([Glu]+[ATP])+[DHP]\cdot[Glu]\cdot[ATP]}\right) + V_{compartment}\cdot\left(\frac{84.63\cdot[THF]\cdot[Glu]\cdot[ATP]}{26\cdot\left(1+\frac{[DHF]}{3.1}\right)\cdot 740\cdot 128+26\cdot([Glu]+[ATP])+740\cdot([THF]+[ATP])+128\cdot([THF]+[Glu])+[THF]\cdot[Glu]\cdot[ATP]}\right) + V_{compartment}\cdot\left(\frac{105.014\cdot[AHMDPP]\cdot[pABA]}{3.15\cdot 2.6+2.6\cdot[AHMDPP]+3.15\cdot[pABA]+[AHMDPP]\cdot[pABA]}\right) - V_{compartment}\cdot\left(\frac{15315.3\cdot[fTHFGlu]\cdot[ADP]\cdot[Pi]}{134\cdot 3190\cdot 74.5+134\cdot([ADP]+[Pi])+3190\cdot([fTHFGlu]+[Pi])+74.5\cdot([ADP]+[fTHFGlu])+[fTHFGlu]\cdot[ADP]\cdot[Pi]}\right) + V_{compartment}\cdot\left(\frac{500\cdot[ATP]\cdot[ffTHFGlu]}{50\cdot 5+50\cdot[ffTHFGlu]+5\cdot[ATP]+[ATP]\cdot[ffTHFGlu]}\right) + V_{compartment}\cdot\left(\frac{18200\cdot[SK]\cdot[ATP]}{200\cdot 151.5+200\cdot[ATP]+151.5\cdot[SK]+[SK]\cdot[ATP]}\right) + V_{compartment}\cdot\left(\frac{1547\cdot[SKP]\cdot[PEP]}{93\cdot 80+93\cdot[PEP]+80\cdot[SKP]+[PEP]\cdot[SKP]}\right) + V_{compartment}\cdot\left(\frac{728\cdot[CVPSK]}{12.7+[CVPSK]}\right)$$

$$\frac{d([DHQ]\cdot V_{compartment})}{dt} = +V_{compartment}\cdot\left(\frac{7.462\cdot[DAHP]}{4.7+[DAHP]}\right) - V_{compartment}\cdot\left(\frac{116.48\cdot[DHQ]}{58+[DHQ]}\right)$$

$$\frac{d([DHSK]\cdot V_{compartment})}{dt} = +V_{compartment}\cdot\left(\frac{116.48\cdot[DHQ]}{58+[DHQ]}\right) - V_{compartment}\cdot\left(\frac{17290\cdot[DHSK]\cdot[NADPH]}{30\cdot 11+30\cdot[NADPH]+11\cdot[DHSK]+[DHSK]\cdot[NADPH]}\right)$$

$$\frac{d([SK]\cdot V_{compartment})}{dt} = +V_{compartment}\cdot\left(\frac{17290\cdot[DHSK]\cdot[NADPH]}{30\cdot 11+30\cdot[NADPH]+11\cdot[DHSK]+[DHSK]\cdot[NADPH]}\right) - V_{compartment}\cdot\left(\frac{18200\cdot[SK]\cdot[ATP]}{200\cdot 151.5+200\cdot[ATP]+151.5\cdot[SK]+[SK]\cdot[ATP]}\right)$$

$$\frac{d([SKP]\cdot V_{compartment})}{dt} = +V_{compartment}\cdot\left(\frac{18200\cdot[SK]\cdot[ATP]}{200\cdot 151.5+200\cdot[ATP]+151.5\cdot[SK]+[SK]\cdot[ATP]}\right) - V_{compartment}\cdot\left(\frac{1547\cdot[SKP]\cdot[PEP]}{93\cdot 80+93\cdot[PEP]+80\cdot[SKP]+[PEP]\cdot[SKP]}\right)$$

$$\frac{d([CVPSK]\cdot V_{compartment})}{dt} = +V_{compartment}\cdot\left(\frac{1547\cdot[SKP]\cdot[PEP]}{93\cdot 80+93\cdot[PEP]+80\cdot[SKP]+[PEP]\cdot[SKP]}\right) - V_{compartment}\cdot\left(\frac{728\cdot[CVPSK]}{12.7+[CVPSK]}\right)$$

$$\frac{d([CM]\cdot V_{compartment})}{dt} = +V_{compartment}\cdot\left(\frac{728\cdot[CVPSK]}{12.7+[CVPSK]}\right) - V_{compartment}\cdot\left(\frac{26\cdot[CM]\cdot[Gln]}{13\cdot 1100+13\cdot[Gln]+1100\cdot[CM]+[CM]\cdot[Gln]}\right)$$

$$\frac{d([Glu]\cdot V_{compartment})}{dt} = -V_{compartment}\cdot\left(\frac{2.821\cdot[DHP]\cdot[Glu]\cdot[ATP]}{1\cdot 1380\cdot 100+1\cdot([Glu]+[ATP])+1380\cdot([DHP]+[ATP])+100\cdot([Glu]+[ATP])+[DHP]\cdot[Glu]\cdot[ATP]}\right) - V_{compartment}\cdot\left(\frac{84.63\cdot[THF]\cdot[Glu]\cdot[ATP]}{26\cdot\left(1+\frac{[DHF]}{3.1}\right)\cdot 740\cdot 128+26\cdot([Glu]+[ATP])+740\cdot([THF]+[ATP])+128\cdot([THF]+[Glu])+[THF]\cdot[Glu]\cdot[ATP]}\right) + V_{compartment}\cdot\left(\frac{26\cdot[CM]\cdot[Gln]}{13\cdot 1100+13\cdot[Gln]+1100\cdot[CM]+[CM]\cdot[Gln]}\right)$$

$$\frac{d([ADC]\cdot V_{compartment})}{dt} = +V_{compartment}\cdot\left(\frac{26\cdot[CM]\cdot[Gln]}{13\cdot 1100+13\cdot[Gln]+1100\cdot[CM]+[CM]\cdot[Gln]}\right) - V_{compartment}\cdot\left(\frac{2.2\cdot[ADC]}{1.1+[ADC]}\right)$$

$$\frac{d([Pyr]\cdot V_{compartment})}{dt} = +V_{compartment}\cdot\left(\frac{2.2\cdot[ADC]}{1.1+[ADC]}\right)$$

$$\frac{d([pABA]\cdot V_{compartment})}{dt} = -V_{compartment}\cdot\left(\frac{105.014\cdot[AHMDPP]\cdot[pABA]}{3.15\cdot 2.6+2.6\cdot[AHMDPP]+3.15\cdot[pABA]+[AHMDPP]\cdot[pABA]}\right) + V_{compartment}\cdot\left(\frac{2.2\cdot[ADC]}{1.1+[ADC]}\right)$$

$$\frac{d([DHNTP]\cdot V_{compartment})}{dt} = -V_{compartment}\cdot\left(\frac{792.064\cdot[DHNTP]}{7.4+[DHNTP]}\right) - V_{compartment}\cdot\left(\frac{22.659\cdot[DHNTP]}{10+[DHNTP]}\right) + V_{compartment}\cdot\left(\frac{1515.15\cdot[GTP]}{17.6\cdot\left(1+\frac{[THF]}{0.157}\right)+[GTP]}\right)$$

$$\frac{d([AHMDHP]\cdot V_{compartment})}{dt} = +V_{compartment}\cdot\left(\frac{792.064\cdot[DHNTP]}{7.4+[DHNTP]}\right) - V_{compartment}\cdot\left(\frac{382.2\cdot[ATP]\cdot[AHMDHP]}{3.6\cdot 15+15\cdot[ATP]+3.6\cdot[AHMDHP]+[ATP]\cdot[AHMDHP]}\right)$$

$$\frac{d([HAD]\cdot V_{compartment})}{dt} = +V_{compartment}\cdot\left(\frac{792.064\cdot[DHNTP]}{7.4+[DHNTP]}\right)$$

$$\frac{d([PTHP]\cdot V_{compartment})}{dt} = +V_{compartment}\cdot\left(\frac{22.659\cdot[DHNTP]}{10+[DHNTP]}\right)$$

$$\frac{d([AHMDPP]\cdot V_{compartment})}{dt} = +V_{compartment}\cdot\left(\frac{382.2\cdot[ATP]\cdot[AHMDHP]}{3.6\cdot 15+15\cdot[ATP]+3.6\cdot[AHMDHP]+[ATP]\cdot[AHMDHP]}\right) - V_{compartment}\cdot\left(\frac{105.014\cdot[AHMDPP]\cdot[pABA]}{3.15\cdot 2.6+2.6\cdot[AHMDPP]+3.15\cdot[pABA]+[AHMDPP]\cdot[pABA]}\right)$$

$$\frac{d([DHP]\cdot V_{compartment})}{dt} = -V_{compartment}\cdot\left(\frac{2.821\cdot[DHP]\cdot[Glu]\cdot[ATP]}{1\cdot 1380\cdot 100+1\cdot([Glu]+[ATP])+1380\cdot([DHP]+[ATP])+100\cdot([Glu]+[ATP])+[DHP]\cdot[Glu]\cdot[ATP]}\right) + V_{compartment}\cdot\left(\frac{105.014\cdot[AHMDPP]\cdot[pABA]}{3.15\cdot 2.6+2.6\cdot[AHMDPP]+3.15\cdot[pABA]+[AHMDPP]\cdot[pABA]}\right)$$

$$\frac{d([DHF]\cdot V_{compartment})}{dt} = +V_{compartment}\cdot\left(\frac{2.821\cdot[DHP]\cdot[Glu]\cdot[ATP]}{1\cdot1380\cdot100+1\cdot([Glu]+[ATP])+1380\cdot([DHP]+[ATP])+100\cdot([Glu]+[ATP])+[DHP]\cdot[Glu]\cdot[ATP]}\right)$$

$$-V_{compartment}\cdot\left(\frac{3000\cdot[DHF]\cdot[NADPH]}{3\cdot6.12+3\cdot[NADPH]+6.12\cdot[DHF]+[DHF]\cdot[NADPH]}\right)$$

$$+V_{compartment}\cdot\left(\frac{49.14\cdot[myTHFGlu]\cdot[dUMP]}{17\cdot\left(1+\frac{[DHF]}{0.428}\right)\cdot5.4+17\cdot[dUMP]+5.4\cdot[myTHFGlu]+[myTHFGlu]\cdot[dUMP]}\right)$$

$$\frac{d([THF]\cdot V_{compartment})}{dt} = +V_{compartment}\cdot\left(\frac{3000\cdot[DHF]\cdot[NADPH]}{3\cdot6.12+3\cdot[NADPH]+6.12\cdot[DHF]+[DHF]\cdot[NADPH]}\right)$$

$$-V_{compartment}\cdot\left(\frac{84.63\cdot[THF]\cdot[Glu]\cdot[ATP]}{26\cdot\left(1+\frac{[DHF]}{3.1}\right)\cdot740\cdot128+26\cdot([Glu]+[ATP])+740\cdot([THF]+[ATP])+128\cdot([THF]+[Glu])+[THF]\cdot[Glu]\cdot[ATP]}\right)$$

$$\frac{d([THFGlu]\cdot V_{compartment})}{dt} = +V_{compartment}\cdot\left(\frac{84.63\cdot[THF]\cdot[Glu]\cdot[ATP]}{26\cdot\left(1+\frac{[DHF]}{3.1}\right)\cdot740\cdot128+26\cdot([Glu]+[ATP])+740\cdot([THF]+[ATP])+128\cdot([THF]+[Glu])+[THF]\cdot[Glu]\cdot[ATP]}\right)$$

$$-V_{compartment}\cdot\left(\frac{682.5\cdot[THFGlu]\cdot[Ser]}{40\cdot\left(1+\frac{[THF]}{0.157}\right)\cdot700+40\cdot[Ser]+700\cdot[THFGlu]+[THFGlu]\cdot[Ser]}\right)$$

$$+V_{compartment}\cdot\left(\frac{379.925\cdot[MTHFGlu]\cdot[Hcy]}{30\cdot17+30\cdot[Hcy]+17\cdot[MTHFGlu]+[MTHFGlu]\cdot[Hcy]}\right)$$

$$+V_{compartment}\cdot\left(\frac{116.48\cdot[fTHFGlu]\cdot[mtRNA]}{12.15\cdot1.07+12.15\cdot[mtRNA]+1.07\cdot[fTHFGlu]+[fTHFGlu]\cdot[mtRNA]}\right)$$

$$+V_{compartment}\cdot\left(\frac{59.332\cdot[fTHFGlu]\cdot[NADP]}{7.85\cdot0.9+7.85\cdot[NADP]+0.9\cdot[fTHFGlu]+[fTHFGlu]\cdot[NADP]}\right)$$

$$-V_{compartment}\cdot\left(\frac{196.56\cdot[THFGlu]\cdot[SAmDLp]}{67.7\cdot290+67.7\cdot[SAmDLp]+290\cdot[THFGlu]+[THFGlu]\cdot[SAmDLp]}\right)$$

$$+V_{compartment}\cdot\left(\frac{15315.3\cdot[fTHFGlu]\cdot[ADP]\cdot[Pi]}{134\cdot3190\cdot74.5+134\cdot([ADP]+[Pi])+3190\cdot([fTHFGlu]+[Pi])+74.5\cdot([ADP]+[fTHFGlu])+[fTHFGlu]\cdot[ADP]\cdot[Pi]}\right)$$

$$\frac{d([myTHFGlu]\cdot V_{compartment})}{dt} = +V_{compartment}\cdot\left(\frac{682.5\cdot[THFGlu]\cdot[Ser]}{40\cdot\left(1+\frac{[THF]}{0.157}\right)\cdot700+40\cdot[Ser]+700\cdot[THFGlu]+[THFGlu]\cdot[Ser]}\right)$$

$$-V_{compartment}\cdot\left(\frac{738.92\cdot[myTHFGlu]\cdot[NADPH]}{33\cdot\left(1+\frac{[DHF]}{0.428}\right)\cdot19+33\cdot[NADPH]+19\cdot[myTHFGlu]+[myTHFGlu]\cdot[NADPH]}\right)$$

$$-V_{compartment}\cdot\left(\frac{49.14\cdot[myTHFGlu]\cdot[dUMP]}{17\cdot\left(1+\frac{[DHF]}{0.428}\right)\cdot5.4+17\cdot[dUMP]+5.4\cdot[myTHFGlu]+[myTHFGlu]\cdot[dUMP]}\right)$$

$$-V_{compartment}\cdot\left(\frac{1892.8\cdot[myTHFGlu]\cdot[NADP]}{25\cdot\left(1+\frac{[DHF]}{0.428}\right)\cdot22+25\cdot[NADP]+22\cdot[myTHFGlu]+[myTHFGlu]\cdot[NADP]}\right)$$

$$+V_{compartment}\cdot\left(\frac{196.56\cdot[THFGlu]\cdot[SAmDLp]}{67.7\cdot290+67.7\cdot[SAmDLp]+290\cdot[THFGlu]+[THFGlu]\cdot[SAmDLp]}\right)$$

$$\frac{d([MTHFGlu]\cdot V_{compartment})}{dt} = +V_{compartment}\cdot\left(\frac{738.92\cdot[myTHFGlu]\cdot[NADPH]}{33\cdot\left(1+\frac{[DHF]}{0.428}\right)\cdot19+33\cdot[NADPH]+19\cdot[myTHFGlu]+[myTHFGlu]\cdot[NADPH]}\right)$$

$$-V_{compartment}\cdot\left(\frac{379.925\cdot[MTHFGlu]\cdot[Hcy]}{30\cdot17+30\cdot[Hcy]+17\cdot[MTHFGlu]+[MTHFGlu]\cdot[Hcy]}\right)$$

$$\frac{d([Met]\cdot V_{compartment})}{dt} = +V_{compartment}\cdot\left(\frac{379.925\cdot[MTHFGlu]\cdot[Hcy]}{30\cdot17+30\cdot[Hcy]+17\cdot[MTHFGlu]+[MTHFGlu]\cdot[Hcy]}\right)$$

$$\frac{d([dTMP]\cdot V_{compartment})}{dt} = +V_{compartment}\cdot\left(\frac{49.14\cdot[myTHFGlu]\cdot[dUMP]}{17\cdot\left(1+\frac{[DHF]}{0.428}\right)\cdot5.4+17\cdot[dUMP]+5.4\cdot[myTHFGlu]+[myTHFGlu]\cdot[dUMP]}\right)$$

$$\frac{d([meTHFGlu]\cdot V_{compartment})}{dt} = +V_{compartment}\cdot\left(\frac{1892.8\cdot[myTHFGlu]\cdot[NADP]}{25\cdot\left(1+\frac{[DHF]}{0.428}\right)\cdot22+25\cdot[NADP]+22\cdot[myTHFGlu]+[myTHFGlu]\cdot[NADP]}\right)$$

$$-V_{compartment}\cdot((0.08\cdot[meTHFGlu]-0.031\cdot[fTHFGlu]))$$

$$-V_{compartment}\cdot\left(\frac{200\cdot[meTHFGlu]}{67+[meTHFGlu]}\right)$$

$$+V_{compartment}\cdot\left(\frac{500\cdot[ATP]\cdot[ffTHFGlu]}{50\cdot5+50\cdot[ffTHFGlu]+5\cdot[ATP]+[ATP]\cdot[ffTHFGlu]}\right)$$

$$\frac{d([fTHFGlu]\cdot V_{compartment})}{dt} = -V_{compartment}\cdot\left(\frac{116.48\cdot[fTHFGlu]\cdot[mtRNA]}{12.15\cdot1.07+12.15\cdot[mtRNA]+1.07\cdot[fTHFGlu]+[fTHFGlu]\cdot[mtRNA]}\right)$$

$$-V_{compartment}\cdot\left(\frac{59.332\cdot[fTHFGlu]\cdot[NADP]}{7.85\cdot0.9+7.85\cdot[NADP]+0.9\cdot[fTHFGlu]+[fTHFGlu]\cdot[NADP]}\right)$$

$$-V_{compartment}\cdot\left(\frac{15315.3\cdot[fTHFGlu]\cdot[ADP]\cdot[Pi]}{134\cdot3190\cdot74.5+134\cdot([ADP]+[Pi])+3190\cdot([fTHFGlu]+[Pi])+74.5\cdot([ADP]+[fTHFGlu])+[fTHFGlu]\cdot[ADP]\cdot[Pi]}\right)$$

$$+V_{compartment}\cdot((0.08\cdot[meTHFGlu]-0.031\cdot[fTHFGlu]))$$

$$\frac{d([fmtRNA]\cdot V_{compartment})}{dt} = +V_{compartment}\cdot\left(\frac{116.48\cdot[fTHFGlu]\cdot[mtRNA]}{12.15\cdot1.07+12.15\cdot[mtRNA]+1.07\cdot[fTHFGlu]+[fTHFGlu]\cdot[mtRNA]}\right)$$

$$\frac{d([COTwo]\cdot V_{compartment})}{dt} = +V_{compartment}\cdot\left(\frac{751.66\cdot[DLp]\cdot[Gly]}{4505\cdot290+4505\cdot[Gly]+290\cdot[DLp]+[DLp]\cdot[Gly]}\right)$$

$$+V_{compartment}\cdot\left(\frac{59.332\cdot[fTHFGlu]\cdot[NADP]}{7.85\cdot0.9+7.85\cdot[NADP]+0.9\cdot[fTHFGlu]+[fTHFGlu]\cdot[NADP]}\right)$$

$$\frac{d([ADP]\cdot V_{compartment})}{dt} = +V_{compartment}\cdot\left(\frac{2.821\cdot[DHP]\cdot[Glu]\cdot[ATP]}{1\cdot1380\cdot100+1\cdot([Glu]+[ATP])+1380\cdot([DHP]+[ATP])+100\cdot([Glu]+[ATP])+[DHP]\cdot[Glu]\cdot[ATP]}\right)$$

$$+V_{compartment}\cdot\left(\frac{84.63\cdot[THF]\cdot[Glu]\cdot[ATP]}{26\cdot\left(1+\frac{[DHF]}{3.1}\right)\cdot740\cdot128+26\cdot([Glu]+[ATP])+740\cdot([THF]+[ATP])+128\cdot([THF]+[Glu])+[THF]\cdot[Glu]\cdot[ATP]}\right)$$

$$-V_{compartment}\cdot\left(\frac{15315.3\cdot[fTHFGlu]\cdot[ADP]\cdot[Pi]}{134\cdot3190\cdot74.5+134\cdot([ADP]+[Pi])+3190\cdot([fTHFGlu]+[Pi])+74.5\cdot([ADP]+[fTHFGlu])+[fTHFGlu]\cdot[ADP]\cdot[Pi]}\right)$$

$$+V_{compartment}\cdot\left(\frac{500\cdot[ATP]\cdot[ffTHFGlu]}{50\cdot5+50\cdot[ffTHFGlu]+5\cdot[ATP]+[ATP]\cdot[ffTHFGlu]}\right)$$

$$+V_{compartment}\cdot\left(\frac{18200\cdot[SK]\cdot[ATP]}{200\cdot151.5+200\cdot[ATP]+151.5\cdot[SK]+[SK]\cdot[ATP]}\right)$$

$$\frac{d([NADP]\cdot V_{compartment})}{dt} = +V_{compartment}\cdot\left(\frac{3000\cdot[DHF]\cdot[NADPH]}{3\cdot6.12+3\cdot[NADPH]+6.12\cdot[DHF]+[DHF]\cdot[NADPH]}\right)$$

$$+V_{compartment}\cdot\left(\frac{738.92\cdot[myTHFGlu]\cdot[NADPH]}{33\cdot\left(1+\frac{[DHF]}{0.428}\right)\cdot19+33\cdot[NADPH]+19\cdot[myTHFGlu]+[myTHFGlu]\cdot[NADPH]}\right)$$

$$-V_{compartment}\cdot\left(\frac{1892.8\cdot[myTHFGlu]\cdot[NADP]}{25\cdot\left(1+\frac{[DHF]}{0.428}\right)\cdot22+25\cdot[NADP]+22\cdot[myTHFGlu]+[myTHFGlu]\cdot[NADP]}\right)$$

$$- V_{compartment} \cdot \left(\frac{59.332 \cdot [fTHFGlu] \cdot [NADP]}{7.85 \cdot 0.9 + 7.85 \cdot [NADP] + 0.9 \cdot [fTHFGlu] + [fTHFGlu] \cdot [NADP]} \right)$$

$$+ V_{compartment} \cdot \left(\frac{17290 \cdot [DHSK] \cdot [NADPH]}{30 \cdot 11 + 30 \cdot [NADPH] + 11 \cdot [DHSK] + [DHSK] \cdot [NADPH]} \right)$$

$$\frac{d([AMP] \cdot V_{compartment})}{d\,t} = + V_{compartment} \cdot \left(\frac{382.2 \cdot [ATP] \cdot [AHMDHP]}{3.6 \cdot 15 + 15 \cdot [ATP] + 3.6 \cdot [AHMDHP] + [ATP] \cdot [AHMDHP]} \right)$$

$$\frac{d([DLp] \cdot V_{compartment})}{d\,t} = - V_{compartment} \cdot \left(\frac{751.66 \cdot [DLp] \cdot [Gly]}{4505 \cdot 290 + 4505 \cdot [Gly] + 290 \cdot [DLp] + [DLp] \cdot [Gly]} \right)$$

$$+ V_{compartment} \cdot \left(\frac{5432.7 \cdot [NADH] \cdot [Lp]}{58 \cdot 1280 + 58 \cdot [Lp] + 1280 \cdot [NADH] + [NADH] \cdot [Lp]} \right)$$

$$\frac{d([SAmDLp] \cdot V_{compartment})}{d\,t} = + V_{compartment} \cdot \left(\frac{751.66 \cdot [DLp] \cdot [Gly]}{4505 \cdot 290 + 4505 \cdot [Gly] + 290 \cdot [DLp] + [DLp] \cdot [Gly]} \right)$$

$$- V_{compartment} \cdot \left(\frac{196.56 \cdot [THFGlu] \cdot [SAmDLp]}{67.7 \cdot 290 + 67.7 \cdot [SAmDLp] + 290 \cdot [THFGlu] + [THFGlu] \cdot [SAmDLp]} \right)$$

$$\frac{d([NAD] \cdot V_{compartment})}{d\,t} = + V_{compartment} \cdot \left(\frac{5432.7 \cdot [NADH] \cdot [Lp]}{58 \cdot 1280 + 58 \cdot [Lp] + 1280 \cdot [NADH] + [NADH] \cdot [Lp]} \right)$$

$$\frac{d([Ammonia] \cdot V_{compartment})}{d\,t} = + V_{compartment} \cdot \left(\frac{196.56 \cdot [THFGlu] \cdot [SAmDLp]}{67.7 \cdot 290 + 67.7 \cdot [SAmDLp] + 290 \cdot [THFGlu] + [THFGlu] \cdot [SAmDLp]} \right)$$

$$\frac{d([Formyl] \cdot V_{compartment})}{d\,t} = + V_{compartment} \cdot \left(\frac{15315.3 \cdot [fTHFGlu] \cdot [ADP] \cdot [Pi]}{134 \cdot 3190 \cdot 74.5 + 134 \cdot ([ADP] + [Pi]) + 3190 \cdot ([fTHFGlu] + [Pi]) + 74.5 \cdot ([ADP] + [fTHFGlu]) + [fTHFGlu] \cdot [ADP] \cdot [Pi]} \right)$$

$$+ V_{compartment} \cdot \left(\frac{1515.15 \cdot [GTP]}{17.6 \cdot \left(1 + \frac{[THF]}{0.157}\right) + [GTP]} \right)$$

$$\frac{d([ffTHFGlu] \cdot V_{compartment})}{d\,t} = + V_{compartment} \cdot \left(\frac{200 \cdot [meTHFGlu]}{67 + [meTHFGlu]} \right)$$

$$- V_{compartment} \cdot \left(\frac{500 \cdot [ATP] \cdot [ffTHFGlu]}{50 \cdot 5 + 50 \cdot [ffTHFGlu] + 5 \cdot [ATP] + [ATP] \cdot [ffTHFGlu]} \right)$$