Supplementary Material for the article "Mathematical Analysis of the Influence of Brain Metabolism on the BOLD signal in Alzheimer's Disease"

Supplementary Tables

Table 1: Values from databases and publications used to provide an initial guess for the parameter balancing routine described in the *Material & Methods* section.

Quantity Type	Reaction ID	Species	Value	Reference
equilibrium constant	R01056		0.457	eQuilibrator
equilibrium constant	R01528		170	Joshi & Palsson [?]
equilibrium constant	R01529		3.91	eQuilibrator
equilibrium constant	R01641		0.216	eQuilibrator
equilibrium constant	R01827		1.34	eQuilibrator
equilibrium constant	R01830		0.01777	eQuilibrator
equilibrium constant	R02035		4.7e+03	eQuilibrator
equilibrium constant	R02736		2.56	eQuilibrator
concentration		G6L	0.45366	sampled from glycolytic species
concentration		G6P	0.1	from glycolysis model
concentration		NADP	0.45366	sampled from glycolytic species
concentration		NADPH	0.45366	sampled from glycolytic species
concentration		P6G	0.45366	sampled from glycolytic species
concentration		Ru5P	0.45366	sampled from glycolytic species
concentration		X5P	0.45366	sampled from glycolytic species
concentration		R5P	0.45366	sampled from glycolytic species
concentration		GAP	0.0056	from glycolysis model
concentration		S7P	0.45366	sampled from glycolytic species
concentration		E4P	0.45366	sampled from glycolytic species
concentration		F6P	0.1091	from glycolysis model
Michaelis constant	R02736	NADP	3.0e-05	SabioRK
Michaelis constant	R02736	G6P	6.9e-05	SabioRK
Michaelis constant	R02736	NADP	1.2e-05	SabioRK
Michaelis constant	R01528	P6G	3.0e-05	SabioRK
Michaelis constant	R01528	P6G	4.0e-05	SabioRK
Michaelis constant	R01641	X5P	1.5e-04	SabioRK
Michaelis constant	R01641	R5P	0.0017	SabioRK

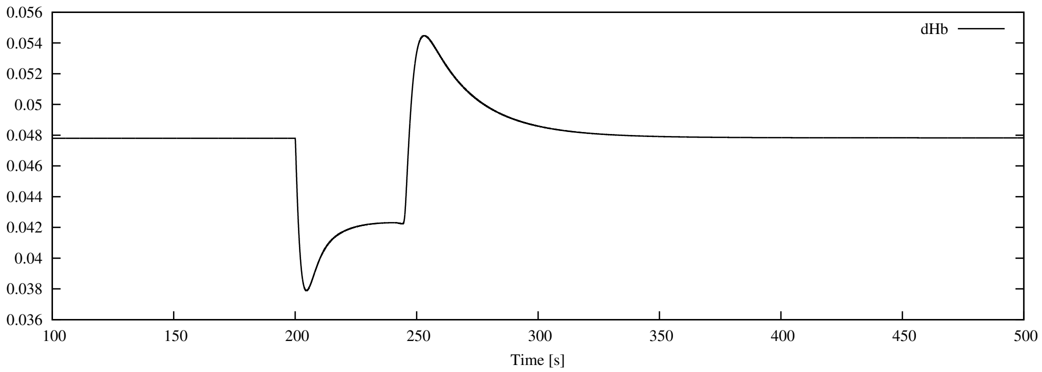

Figure 1: Time course of dHb concentration.

Table 2: Metabolic reactions and parameter values for astrocytes. For a detailled description of the equations for glycolysis and mitochondrial respiration see [?]. Parameters for glycolytic reactions have been adjusted to guarantee a physiological meaningful flux distribution using enzyme rescaling. Equations and parameter values for the pentose-phosphate pathway were determined as described in the *Materials & Methods* section.

Glycolysis and mitochondrial respiration

Equation	Parameter	Value
Hexokinase		
$v^g_{\mathrm{HK}} = k_{HK} \cdot \mathrm{ATP}^g \left(1 + \frac{\mathrm{G6P}^g}{K_{I,G6P}}\right)^{-1}$	k_{HK}	0.01
	$K_{I,\mathrm{GLC}}$	0.02
PGI		
$v^g_{PGI} = k_1 \cdot \mathrm{G6P}^g - k_2 \cdot \mathrm{F6P}^g$	k_1	931.69
	k_2	2273.32
PFK		
$v^g_{PFK} = k_{PFK} \cdot \mathrm{ATP}^g \cdot \left(1 + \left(\frac{\mathrm{ATP}^g}{K_{I,\mathrm{ATP}}}\right)^{nH}\right)^{-1} \cdot \frac{\mathrm{F6P}^g}{\mathrm{F6P}^g + K_{m,\mathrm{F6P}}}$	k_{PFK}	0.2
	$K_{I,\mathrm{ATP}}$	1.0
	nH	4
	$K_{m,\mathrm{F6P}}$	0.18
PGK		
$v^g_{PGK} = k_{PGK} \cdot \mathrm{GAP}^g \cdot \mathrm{ADP}^g \cdot \frac{\mathrm{NAD}^g}{\mathrm{NADH}^g}$	k_{PGK}	3.0
PK		
$v^g_{PK} = k_{PK} \cdot \mathrm{PEP}^g \cdot \mathrm{ADP}^g$	k_{PK}	20
LDH		
$v^g_{LDH} = k_1 \cdot \mathrm{PYR}^g \cdot \mathrm{NADH}^g - k_2 \cdot \mathrm{LAC}^g \cdot \mathrm{NAD}^g$	k_1	780
	k_2	32
mitochondrial respiration		
$v^g_{MITO} = V_{\max} \cdot \frac{\mathrm{PYR}^g}{\mathrm{PYR}^g + K_{m,\mathrm{PYR}}} \cdot \frac{\mathrm{ADP}^g}{\mathrm{ADP}^g + K_{m,\mathrm{ADP}}} \cdot \frac{\mathrm{O_2}^g}{\mathrm{O_2}^g + K_{m,\mathrm{O_2}}}$	$V_{\max}$	0.01
	$K_{m,\mathrm{PYR}}$	0.0632
$\cdot \left(1 - \frac{1}{1 + e^{-5 \cdot \left(\frac{\mathrm{ATP}^g}{\mathrm{ADP}^g} - 20\right)}}\right)$	$K_{m,\mathrm{ADP}}$	0.00107
	$K_{m,\mathrm{O_2}}$	0.0029658

Pentose-phosphate pathway

Equation	Parameter	Value
R02736: ZWF		
	$V_{\max}$	0.29057
	K_{eq}	22906
$v^g_{ZWF} = V_{\max} \cdot \frac{1}{K_{\mathrm{G6P}} \cdot K_{\mathrm{NADP}}} \cdot \frac{\mathrm{G6P}^g \cdot \mathrm{NADP}^g - \frac{\mathrm{G6L}^g \cdot \mathrm{NADPH}^g}{K_{\mathrm{eq}}}}{\left(1 + \frac{\mathrm{G6P}^g}{K_{\mathrm{G6P}}}\right) \cdot \left(1 + \frac{\mathrm{NADP}^g}{K_{\mathrm{NADP}}}\right) + \left(1 + \frac{\mathrm{G6L}^g}{K_{\mathrm{G6L}}}\right) \cdot \left(1 + \frac{\mathrm{NADPH}^g}{K_{\mathrm{NADPH}}}\right) - 1}$	K_{G6P}	6.91392e-05
	K_{NADP}	1.31616e-05
	K_{G6L}	0.0180932
	K_{NADPH}	0.00050314
R02035: SOL		
	$V_{\max}$	0.184701
$v^g_{SOL} = V_{\max} \cdot \frac{1}{K_{\mathrm{G6L}}} \cdot \frac{\mathrm{G6L}^g - \frac{\mathrm{P6G}^g}{K_{\mathrm{eq}}}}{\left(1 + \frac{\mathrm{G6L}^g}{K_{\mathrm{G6L}}}\right) + \left(1 + \frac{\mathrm{P6G}^g}{K_{\mathrm{P6G}}}\right) - 1}$	K_{eq}	531174
	K_{G6L}	0.0180932
	K_{P6G}	2.28618
R01528: GND		

Table 2: continued

Equation	Parameter	Value
	$V_{\max}$	1.31377
	K_{eq}	4.0852e+07
$v^g_{GND} = V_{\max} \cdot \frac{1}{K_{\mathrm{P6G}} \cdot K_{\mathrm{NADP}}} \cdot \frac{\mathrm{P6G}^g \cdot \mathrm{NADP}^g - \frac{\mathrm{Ru5P}^g \cdot \mathrm{NADPH}^g}{K_{\mathrm{eq}}}}{\left(1+\frac{\mathrm{P6G}^g}{K_{\mathrm{P6G}}}\right) \cdot \left(1+\frac{\mathrm{NADP}^g}{K_{\mathrm{NADP}}}\right) + \left(1+\frac{\mathrm{Ru5P}^g}{K_{\mathrm{Ru5P}}}\right) \cdot \left(1+\frac{\mathrm{NADPH}^g}{K_{\mathrm{NADPH}}}\right) - 1}$	K_{P6G}	3.23421e-05
	K_{NADP}	3.11043e-06
	K_{Ru5P}	0.0537179
	K_{NADPH}	0.00050314
R01056: RKI		
	$V_{\max}$	0.000821984
$v^g_{RKI} = V_{\max} \cdot \frac{1}{K_{\mathrm{Ru5P}}} \cdot \frac{\mathrm{Ru5P}^g - \frac{\mathrm{R5P}^g}{K_{\mathrm{eq}}}}{\left(1+\frac{\mathrm{Ru5P}^g}{K_{\mathrm{Ru5P}}}\right) + \left(1+\frac{\mathrm{R5P}^g}{K_{\mathrm{R5P}}}\right) - 1}$	K_{eq}	0.0282061
	K_{Ru5P}	0.0537179
	K_{R5P}	0.778461
R01529: RPE		
	$V_{\max}$	0.00775925
$v^g_{RPE} = V_{\max} \cdot \frac{1}{K_{\mathrm{Ru5P}}} \cdot \frac{\mathrm{Ru5P}^g - \frac{\mathrm{X5P}^g}{K_{\mathrm{eq}}}}{\left(1+\frac{\mathrm{Ru5P}^g}{K_{\mathrm{Ru5P}}}\right) + \left(1+\frac{\mathrm{X5P}^g}{K_{\mathrm{X5P}}}\right) - 1}$	K_{eq}	39.2574
	K_{Ru5P}	0.0537179
	K_{X5P}	0.603002
R5P sink		
$v^g_{R5P} = k \cdot \mathrm{R5P}^g$	k	0
R01641: TKL-1		
	$V_{\max}$	0.000244278
	K_{eq}	1.65287e+06
$v^g_{TKL-1} = V_{\max} \cdot \frac{1}{K_{\mathrm{X5P}} \cdot K_{\mathrm{R5P}}} \cdot \frac{\mathrm{X5P}^g \cdot \mathrm{R5P}^g - \frac{\mathrm{GAP}^g \cdot \mathrm{S7P}^g}{K_{\mathrm{eq}}}}{\left(1+\frac{\mathrm{X5P}^g}{K_{\mathrm{X5P}}}\right) \cdot \left(1+\frac{\mathrm{R5P}^g}{K_{\mathrm{R5P}}}\right) + \left(1+\frac{\mathrm{GAP}^g}{K_{\mathrm{GAP}}}\right) \cdot \left(1+\frac{\mathrm{S7P}^g}{K_{\mathrm{S7P}}}\right) - 1}$	K_{X5P}	0.000173625
	K_{R5P}	0.000585387
	K_{GAP}	0.168333
	K_{S7P}	0.192807
R01830: TKL-2		
	$V_{\max}$	0.000137124
	K_{eq}	0.0777764
$v^g_{TKL-2} = V_{\max} \cdot \frac{1}{K_{\mathrm{F6P}} \cdot K_{\mathrm{GAP}}} \cdot \frac{\mathrm{F6P}^g \cdot \mathrm{GAP}^g - \frac{\mathrm{X5P}^g \cdot \mathrm{E4P}^g}{K_{\mathrm{eq}}}}{\left(1+\frac{\mathrm{F6P}^g}{K_{\mathrm{F6P}}}\right) \cdot \left(1+\frac{\mathrm{GAP}^g}{K_{\mathrm{GAP}}}\right) + \left(1+\frac{\mathrm{X5P}^g}{K_{\mathrm{X5P}}}\right) \cdot \left(1+\frac{\mathrm{E4P}^g}{K_{\mathrm{E4P}}}\right) - 1}$	K_{F6P}	0.0799745
	K_{GAP}	0.168333
	K_{X5P}	0.603002
	K_{E4P}	0.109681
R01827: TAL		
	$V_{\max}$	0.0080394
	K_{eq}	0.323922
$v^g_{TAL} = V_{\max} \cdot \frac{1}{K_{\mathrm{GAP}} \cdot K_{\mathrm{S7P}}} \cdot \frac{\mathrm{GAP}^g \cdot \mathrm{S7P}^g - \frac{\mathrm{F6P}^g \cdot \mathrm{E4P}^g}{K_{\mathrm{eq}}}}{\left(1+\frac{\mathrm{GAP}^g}{K_{\mathrm{GAP}}}\right) \cdot \left(1+\frac{\mathrm{S7P}^g}{K_{\mathrm{S7P}}}\right) + \left(1+\frac{\mathrm{F6P}^g}{K_{\mathrm{F6P}}}\right) \cdot \left(1+\frac{\mathrm{E4P}^g}{K_{\mathrm{E4P}}}\right) - 1}$	K_{GAP}	0.168333
	K_{S7P}	0.192807
	K_{F6P}	0.0799745
	K_{E4P}	0.109681
Housekeeping reactions astrocytes		
AK		
$v^g_{AK} = k_1 \cdot ADP^g \cdot ADP^g - k_2 \cdot ATP^g \cdot AMP^g$	k_1	1000

Table 2: continued

Equation	Parameter	Value
	k_2	920
ATPase		
$v^g_{ATPase} = V_{\max,ATPase} \cdot \frac{\mathrm{ATP}}{\mathrm{ATP}+K_{m,\mathrm{ATP}}}$	$V_{\max,ATPase}$	0.035
	$K_{m,\mathrm{ATP}}$	0.001
Creatine kinase		
$v^g_{CK,f} = k_{CK,f} \cdot \mathrm{ADP}^g \cdot \mathrm{PCr}^g - k_{CK,r} \cdot \mathrm{ATP}^g \cdot \mathrm{Cr}^g$	$k_{CK,f}$	0.5
	$k_{CK,r}$	0.01
NADPH oxidase astrocytes		
$v^g_{NADPH} = k_1 \cdot \mathrm{NADPH}^g$	k_1	0.000209722

Table 3: Metabolic reactions and parameter values for neurons. For a detailled description of the equations for glycolysis and mitochondrial respiration see [?]. Parameters for glycolytic reactions have been adjusted to guarantee a physiological meaningful flux distribution using enzyme rescaling. Equations and parameter values for the pentose-phosphate pathway were determined as described in the *Materials & Methods* section.

Equation	Parameter	Value
Glycolysis and mitochondrial respiration		
Hexokinase		
$v^n_{\mathrm{HK}} = k_{HK} \cdot \mathrm{ATP}^n \left(1 + \frac{\mathrm{G6P}^n}{K_{I,G6P}}\right)^{-1}$	k_{HK}	0.022
	$K_{I,\mathrm{GLC}}$	0.02
PGI forward		
$v^g_{PGI} = k_1 \cdot \mathrm{G6P}^n - k_2 \cdot \mathrm{F6P}^n$	k_1	931.69
	k_2	2273.32
PFK		
$v^n_{PFK} = k_{PFK} \cdot \mathrm{ATP}^n \cdot \left(1 + \left(\frac{\mathrm{ATP}^n}{K_{I,\mathrm{ATP}}}\right)^{nH}\right)^{-1} \cdot \frac{\mathrm{F6P}^n}{\mathrm{F6P}^n + K_{m,\mathrm{F6P}}}$	k_{PFK}	0.44
	$K_{I,\mathrm{ATP}}$	1.0
	nH	4
	$K_{m,\mathrm{F6P}}$	0.18
PGK		
$v^n_{PGK} = k_{PGK} \cdot \mathrm{GAP}^n \cdot \mathrm{ADP}^n \cdot \frac{\mathrm{NAD}^n}{\mathrm{NADH}^n}$	k_{PGK}	10
PK		
$v^n_{PK} = k_{PK} \cdot \mathrm{PEP}^n \cdot \mathrm{ADP}^n$	k_{PK}	44
LDH		
$v^n_{LDH} = k_1 \cdot \mathrm{PYR}^n \cdot \mathrm{NADH}^n - k_2 \cdot \mathrm{LAC}^n \cdot \mathrm{NAD}^n$	k_1	2000
	k_2	15
mitochondrial respiration		
$v^n_{MITO} = V_{\max} \cdot \frac{\mathrm{PYR}^n}{\mathrm{PYR}^n + K_{m,\mathrm{PYR}}} \cdot \frac{\mathrm{ADP}^n}{\mathrm{ADP}^n + K_{m,\mathrm{ADP}}} \cdot \frac{\mathrm{O_2}^n}{\mathrm{O_2}^n + K_{m,\mathrm{O_2}}}$	$V_{\max}$	0.1
	$K_{m,\mathrm{PYR}}$	0.0632
$\cdot \left(1 - \frac{1}{1 + e^{-5 \cdot \left(\frac{\mathrm{ATP}^n}{\mathrm{ADP}^n} - 20\right)}}\right)$	$K_{m,\mathrm{ADP}}$	0.00107
	$K_{m,\mathrm{O_2}}$	0.0029658
Pentose-phosphate pathway		
ZWF		
	$V_{\max}$	0.586458
	K_{eq}	22906
$v^n_{ZWF} = V_{\max} \cdot \frac{1}{K_{\mathrm{G6P}} \cdot K_{\mathrm{NADP}}} \cdot \frac{\mathrm{G6P}^n \cdot \mathrm{NADP}^n - \frac{\mathrm{G6L}^n \cdot \mathrm{NADPH}^n}{K_{\mathrm{eq}}}}{\left(1 + \frac{\mathrm{G6P}^n}{K_{\mathrm{G6P}}}\right) \cdot \left(1 + \frac{\mathrm{NADP}^n}{K_{\mathrm{NADP}}}\right) + \left(1 + \frac{\mathrm{G6L}^n}{K_{\mathrm{G6L}}}\right) \cdot \left(1 + \frac{\mathrm{NADPH}^n}{K_{\mathrm{NADPH}}}\right) - 1}$	K_{G6P}	6.91392e-05
	K_{NADP}	1.31616e-05
	K_{G6L}	0.0180932
	K_{NADPH}	0.00050314
SOL		
	$V_{\max}$	0.373782
$v^n_{SOL} = V_{\max} \cdot \frac{1}{K_{\mathrm{G6L}}} \cdot \frac{\mathrm{G6L}^n - \frac{\mathrm{P6G}^n}{K_{\mathrm{eq}}}}{\left(1 + \frac{\mathrm{G6L}^n}{K_{\mathrm{G6L}}}\right) + \left(1 + \frac{\mathrm{P6G}^n}{K_{\mathrm{P6G}}}\right) - 1}$	K_{eq}	531174
	K_{G6L}	0.0180932
	K_{P6G}	2.28618
GND		

Table 3: continued

Equation	Parameter	Value
$v^n_{GND} = V_{\max} \cdot \frac{1}{K_{\mathrm{P6G}} \cdot K_{\mathrm{NADP}}} \cdot \frac{\mathrm{P6G}^n \cdot \mathrm{NADP}^n - \frac{\mathrm{Ru5P}^n \cdot \mathrm{NADPH}^n}{K_{\mathrm{eq}}}}{\left(1+\frac{\mathrm{P6G}^n}{K_{\mathrm{P6G}}}\right) \cdot \left(1+\frac{\mathrm{NADP}^n}{K_{\mathrm{NADP}}}\right) + \left(1+\frac{\mathrm{Ru5P}^n}{K_{\mathrm{Ru5P}}}\right) \cdot \left(1+\frac{\mathrm{NADPH}^n}{K_{\mathrm{NADPH}}}\right) - 1}$	$V_{\max}$	2.6574
	K_{eq}	4.0852e+07
	K_{P6G}	3.23421e-05
	K_{NADP}	3.11043e-06
	K_{Ru5P}	0.0537179
	K_{NADPH}	0.00050314
RKI		
$v^n_{RKI} = V_{\max} \cdot \frac{1}{K_{\mathrm{Ru5P}}} \cdot \frac{\mathrm{Ru5P}^n - \frac{\mathrm{R5P}^n}{K_{\mathrm{eq}}}}{\left(1+\frac{\mathrm{Ru5P}^n}{K_{\mathrm{Ru5P}}}\right) + \left(1+\frac{\mathrm{R5P}^n}{K_{\mathrm{R5P}}}\right) - 1}$	$V_{\max}$	0.00165901
	K_{eq}	0.0282061
	K_{Ru5P}	0.0537179
	K_{R5P}	0.778461
RPE		
$v^n_{RPE} = V_{\max} \cdot \frac{1}{K_{\mathrm{Ru5P}}} \cdot \frac{\mathrm{Ru5P}^n - \frac{\mathrm{X5P}^n}{K_{\mathrm{eq}}}}{\left(1+\frac{\mathrm{Ru5P}^n}{K_{\mathrm{Ru5P}}}\right) + \left(1+\frac{\mathrm{X5P}^n}{K_{\mathrm{X5P}}}\right) - 1}$	$V_{\max}$	0.0156605
	K_{eq}	39.2574
	K_{Ru5P}	0.0537179
	K_{X5P}	0.603002
R5P sink		
$v^n_{R5P} = k \cdot \mathrm{R5P}^n$	k	0
TKL-1		
$v^n_{TKL-1} = V_{\max} \cdot \frac{1}{K_{\mathrm{X5P}} \cdot K_{\mathrm{R5P}}} \cdot \frac{\mathrm{X5P}^n \cdot \mathrm{R5P}^n - \frac{\mathrm{GAP}^n \cdot \mathrm{S7P}^n}{K_{\mathrm{eq}}}}{\left(1+\frac{\mathrm{X5P}^n}{K_{\mathrm{X5P}}}\right) \cdot \left(1+\frac{\mathrm{R5P}^n}{K_{\mathrm{R5P}}}\right) + \left(1+\frac{\mathrm{GAP}^n}{K_{\mathrm{GAP}}}\right) \cdot \left(1+\frac{\mathrm{S7P}^n}{K_{\mathrm{S7P}}}\right) - 1}$	$V_{\max}$	0.000493027
	K_{eq}	1.65287e+06
	K_{X5P}	0.000173625
	K_{R5P}	0.000585387
	K_{GAP}	0.168333
	K_{S7P}	0.192807
TKL-2		
$v^n_{TKL-2} = V_{\max} \cdot \frac{1}{K_{\mathrm{F6P}} \cdot K_{\mathrm{GAP}}} \cdot \frac{\mathrm{F6P}^n \cdot \mathrm{GAP}^n - \frac{\mathrm{X5P}^n \cdot \mathrm{E4P}^n}{K_{\mathrm{eq}}}}{\left(1+\frac{\mathrm{F6P}^n}{K_{\mathrm{F6P}}}\right) \cdot \left(1+\frac{\mathrm{GAP}^n}{K_{\mathrm{GAP}}}\right) + \left(1+\frac{\mathrm{X5P}^n}{K_{\mathrm{X5P}}}\right) \cdot \left(1+\frac{\mathrm{E4P}^n}{K_{\mathrm{E4P}}}\right) - 1}$	$V_{\max}$	0.000276758
	K_{eq}	0.0777764
	K_{F6P}	0.0799745
	K_{GAP}	0.168333
	K_{X5P}	0.603002
	K_{E4P}	0.109681
TAL		
$v^n_{TAL} = V_{\max} \cdot \frac{1}{K_{\mathrm{GAP}} \cdot K_{\mathrm{S7P}}} \cdot \frac{\mathrm{GAP}^n \cdot \mathrm{S7P}^n - \frac{\mathrm{F6P}^n \cdot \mathrm{E4P}^n}{K_{\mathrm{eq}}}}{\left(1+\frac{\mathrm{GAP}^n}{K_{\mathrm{GAP}}}\right) \cdot \left(1+\frac{\mathrm{S7P}^n}{K_{\mathrm{S7P}}}\right) + \left(1+\frac{\mathrm{F6P}^n}{K_{\mathrm{F6P}}}\right) \cdot \left(1+\frac{\mathrm{E4P}^n}{K_{\mathrm{E4P}}}\right) - 1}$	$V_{\max}$	0.0162259
	K_{eq}	0.323922
	K_{GAP}	0.168333
	K_{S7P}	0.192807
	K_{F6P}	0.0799745
	K_{E4P}	0.109681
Housekeeping reactions neurons		
AK		
$v^n_{AK} = k_1 \cdot ADP^n \cdot ADP^n - k_2 \cdot ATP^n \cdot AMP^n$	k_1	1000

Table 3: continued

Equation	Parameter	Value
	k_2	920
ATPase		
$v^n_{ATPase} = V_{\max,ATPase} \cdot \frac{\text{ATP}^n}{\text{ATP}^n + K_{m,\text{ATP}}}$	$V_{\max,ATPase}$	0.07
	$K_{m,\text{ATP}}$	0.001
Creatine kinase		
$v^n_{CK,f} = k_{CK,f} \cdot \text{ADP}^n \cdot \text{PCr}^n - k_{CK,r} \cdot \text{ATP}^n \cdot \text{Cr}^n$	$k_{CK,f}$	0.5
	$k_{CK,r}$	0.01
NADPH oxidase astrocytes		
$v^n_{NADPH} = k_1 \cdot \text{NADPH}^n$	k_1	0.00281384

Table 4: Rate laws, algebraic equations and values at rest for species with a variable concentration in the model. Arterial concentration is fix for glucose (Glu^a) at 4.8 mmol/ml, carbon dioxide ($\mathrm{CO2}^a$) at 1.2 mmol/ml, oxygen ($\mathrm{O2}^a$) at 8.34 mmol/ml and lactate (LAC^a) at 0.313 mmol/ml.

Species	Value at rest	Equation	
			Astrocytes
ATP	2.26	$\frac{\mathrm{dATP}^g}{\mathrm{dt}}$	$= -v^g_{HK} - v^g_{PFK} + v^g_{PGK} + v^g_{PK} + 15 \cdot v^g_{Mito} + v^g_{CK}$
			$- v^{gn}_{\mathrm{GLU}} - v^g_{pump} + v^g_{AK} - v^g_{ATPase}$
ADP	0.12	$\frac{\mathrm{dADP}^g}{\mathrm{dt}}$	$= v^g_{HK} + v^g_{PFK} - v^g_{PGK} - v^g_{PK} - 15 \cdot v^g_{Mito} - v^g_{CK}$
			$+ v^{gn}_{\mathrm{GLU}} + v^g_{pump} - 2 \cdot v^g_{AK} + v^g_{ATPase}$
AMP	0.006	AMP^g	$= \mathrm{ANP}^g - \mathrm{ADP}^g - \mathrm{ATP}^g$ ($\mathrm{ANP}^g = 2.379$)
GLC	1.14	$\frac{\mathrm{dGLC}^g}{dt}$	$= v^{eg}_{\mathrm{GLC}} + v^{cg}_{\mathrm{GLC}} - v^g_{\mathrm{HK}}$
G6P	0.07	$\frac{\mathrm{dG6P}^g}{\mathrm{dt}}$	$= v^g_{\mathrm{HK}} - v^g_{PGI} - v^g_{ZWF}$
F6P	0.0.046	$\frac{\mathrm{dF6P}^g}{\mathrm{dt}}$	$= v^g_{PGI} - v^g_{PFK} - v^g_{TKL-2} + v^g_{TAL}$
GAP	0.0.002	$\frac{\mathrm{dGAP}^g}{\mathrm{dt}}$	$= 2 \cdot v^g_{PFK} - v^g_{PGK} + v^g_{TKL-1} - v^g_{TKL-2} - v^g_{TAL}$
G6L	2.9e-06	$\frac{\mathrm{dG6L}^g}{\mathrm{dt}}$	$= v^g_{ZWF} - v^g_{SOL}$
P6G	0.0018	$\frac{\mathrm{dP6G}^g}{\mathrm{dt}}$	$= v^g_{SOL} - v^g_{GND}$
Ru5P	0.0006	$\frac{\mathrm{dRu5P}^g}{\mathrm{dt}}$	$= v^g_{GND} - v^g_{RPE} - v^g_{RKI}$
R5P	2.6e-05	$\frac{\mathrm{dR5P}^g}{\mathrm{dt}}$	$= v^g_{RKI} - v^g_{TKL-1} - v^g_{R5P}$
X5P	0.02	$\frac{\mathrm{dX5P}^g}{\mathrm{dt}}$	$= v^g_{RPE} - v^g_{TKL-1} + v^g_{TKL-2}$
S7P	0.277	$\frac{\mathrm{dS7P}^g}{\mathrm{dt}}$	$= v^g_{TKL-1} - v^g_{TAL}$
E4P	0.0056	$\frac{\mathrm{dE4P}^g}{\mathrm{dt}}$	$= v^g_{TAL} + v^g_{TKL-2}$
PEP	0.03	$\frac{\mathrm{dPEP}^g}{\mathrm{dt}}$	$= v^g_{PGK} - v^g_{PK}$
PYR	0.16	$\frac{\mathrm{dPYR}^g}{\mathrm{dt}}$	$= v^g_{PK} - v^g_{Mito} - v^g_{LDH}$
LAC	1.36	$\frac{\mathrm{dLAC}^g}{\mathrm{dt}}$	$= v^g_{LDH} - v^{ge}_{LAC} - v^{gc}_{LAC}$
O2	0.04	$\frac{\mathrm{dO2}^g}{\mathrm{dt}}$	$= v^{cg}_{\mathrm{O2}} - 3 \cdot v^g_{Mito}$
Cr	4.6	$\frac{\mathrm{dCr}^g}{\mathrm{dt}}$	$= v^g_{CK}$
PCr	0.4	$\frac{\mathrm{dPCr}^g}{\mathrm{dt}}$	$= -v^g_{CK}$
NADH	0.057	$\frac{\mathrm{dNADH}^g}{\mathrm{dt}}$	$= v^g_{PGK} - v^g_{Mito} - v^g_{LDH}$
NAD	0.163	$\frac{\mathrm{dNAD}^g}{\mathrm{dt}}$	$=$ - $v^g_{PGK} + v^g_{Mito} + v^g_{LDH}$
NADPH	0.29123	$\frac{\mathrm{dNADPH}^g}{\mathrm{dt}}$	$= v^g_{ZWF} + v^g_{GND} - v^g_{NADPH}$
NADP	1.5e-09	$\frac{\mathrm{dNADP}^g}{\mathrm{dt}}$	$= v^g_{NADPH} - v^g_{ZWF} - v^g_{GND}$
Na+	15.5	$\frac{\mathrm{dNa+}^g}{\mathrm{dt}}$	$= v^g_{Leak} + v^{eg}_{GLU} - 3 \cdot v^g_{pump}$
GLU	0	$\frac{\mathrm{dGLU}^g}{\mathrm{dt}}$	$= v^{eg}_{GLU} - v^{gn}_{GLU}$
			Neurons
ATP	2.26	$\frac{\mathrm{dATP}^n}{\mathrm{dt}}$	$= -v^n_{HK} - v^n_{PFK} + v^n_{PGK} + v^n_{PK} + 15 \cdot v^n_{Mito} + v^n_{CK}$
			$- v^{nn}_{\mathrm{GLU}} - v^n_{pump} + v^n_{AK} - v^n_{ATPase}$
ADP	0.12	$\frac{\mathrm{dADP}^n}{\mathrm{dt}}$	$= v^n_{HK} + v^n_{PFK} - v^n_{PGK} - v^n_{PK} - 15 \cdot v^n_{Mito} - v^n_{CK}$
			$+ v^{nn}_{\mathrm{GLU}} + v^n_{pump} - 2 \cdot v^n_{AK} + v^n_{ATPase}$
AMP	0.006	AMP^n	$= \mathrm{ANP}^n - \mathrm{ADP}^n - \mathrm{ATP}^n$ ($\mathrm{ANP}^n = 2.379$)
GLC	1.14	$\frac{\mathrm{dGLC}^n}{dt}$	$= v^{en}_{\mathrm{GLC}} + v^{cn}_{\mathrm{GLC}} - v^n_{\mathrm{HK}}$
G6P	0.11	$\frac{\mathrm{dG6P}^n}{\mathrm{dt}}$	$= v^n_{\mathrm{HK}} - v^n_{PGI} - v^n_{ZWF}$
F6P	0.45	$\frac{\mathrm{dF6P}^n}{\mathrm{dt}}$	$= v^n_{PGI} - v^n_{PFK} - v^n_{TKL-2} + v^n_{TAL}$
GAP	0.001	$\frac{\mathrm{dGAP}^n}{\mathrm{dt}}$	$= 2 \cdot v^n_{PFK} - v^n_{PGK} + v^n_{TKL-1} - v^n_{TKL-2} - v^n_{TAL}$
G6L	3.0e-06	$\frac{\mathrm{dG6L}^n}{\mathrm{dt}}$	$= v^n_{ZWF} - v^n_{SOL}$

P6G	0.0029	$\frac{\mathrm{dP6G}^n}{\mathrm{dt}} = v^n_{SOL} - v^n_{GND}$
Ru5P	0.00067	$\frac{\mathrm{dRu5P}^n}{\mathrm{dt}} = v^n_{GND} - v^n_{RPE} - v^n_{RKI}$
R5P	2.7e-05	$\frac{\mathrm{dR5P}^n}{\mathrm{dt}} = v^n_{RKI} - v^n_{TKL-1} - v^n_{R5P}$
X5P	0.02	$\frac{\mathrm{dX5P}^n}{\mathrm{dt}} = v^n_{RPE} - v^n_{TKL-1} + v^n_{TKL-2}$
S7P	0.2	$\frac{\mathrm{dS7P}^n}{\mathrm{dt}} = v^n_{TKL-1} - v^n_{TAL}$
E4P	0.006	$\frac{\mathrm{dE4P}^n}{\mathrm{dt}} = v^n_{TAL} + v^n_{TKL-2}$
PEP	0.003	$\frac{\mathrm{dPEP}^n}{\mathrm{dt}} = v^n_{PGK} - v^n_{PK}$
PYR	0.13	$\frac{\mathrm{dPYR}^n}{\mathrm{dt}} = v^n_{PK} - v^n_{Mito} - v^n_{LDH}$
LAC	1.36	$\frac{\mathrm{dLAC}^n}{\mathrm{dt}} = v^n_{LDH} - v^{ne}_{LAC} - v^{nc}_{LAC}$
O2	0.03	$\frac{\mathrm{dO2}^n}{\mathrm{dt}} = v^{cn}_{O2} - 3 \cdot v^n_{Mito}$
Cr	3.5	$\frac{\mathrm{dCr}^n}{\mathrm{dt}} = -v^n_{CK}$
PCr	1.5	$\frac{\mathrm{dPCr}^n}{\mathrm{dt}} = v^n_{CK}$
NADH	0.016	$\frac{\mathrm{dNADH}^n}{\mathrm{dt}} = v^n_{PGK} - v^n_{Mito} - v^n_{LDH}$
NAD	0.204	$\frac{\mathrm{dNAD}^n}{\mathrm{dt}} = \text{-}\ v^n_{PGK} + v^n_{Mito} + v^n_{LDH}$
NADPH	0.29123	$\frac{\mathrm{dNADPH}^n}{\mathrm{dt}} = v^n_{ZWF} + v^n_{GND} - v^n_{NADPH}$
NADP	2.2e-09	$\frac{\mathrm{dNADP}^n}{\mathrm{dt}} = v^n_{NADPH} - v^n_{ZWF} - v^n_{GND}$
Na+	15.53	$\frac{\mathrm{dNa+}^n}{\mathrm{dt}} = v^n_{Leak} + v^{en}_{GLU} - 3 \cdot v^n_{pump}$
GLU	3	$\frac{\mathrm{dGLU}^n}{\mathrm{dt}} = v^{en}_{GLU} - v^{nn}_{GLU}$
	extracellular space	
GLC	1.14	$\frac{\mathrm{dGLC}^e}{\mathrm{dt}} = v^{ce}_{GLC} - v^{en}_{GLC} - v^{eg}_{GLC}$
LAC	1.3	$\frac{\mathrm{dLAC}^e}{\mathrm{dt}} = v^{ge}_{LAC} - v^{ec}_{LAC} - v^{en}_{LAC}$
GLU	0	$\frac{\mathrm{dGLU}^e}{\mathrm{dt}} = v^{ne}_{GLU} - v^{eg}_{GLU}$
Na+	150 (fixed)	
	capillaries	
GLC	4.6	$\frac{\mathrm{dGLC}^c}{\mathrm{dt}} = v^{ac}_{GLC} - v^{ce}_{GLC} - v^{cg}_{GLC}$
O2	7.3	$\frac{\mathrm{dO2}^c}{\mathrm{dt}} = v^{ac}_{O2} - v^{cn}_{O2} - v^{cg}_{O2}$
LAC	0.34	$\frac{\mathrm{dLAC}^c}{\mathrm{dt}} = v^{gc}_{LAC} - v^{ca}_{LAC} + v^{ec}_{LAC}$
CO2	2.2	$\frac{\mathrm{dCO2}^c}{\mathrm{dt}} = 3 \cdot v^n_{Mito} + 3 \cdot v^g_{Mito} - v^{ca}_{CO2}$
dHb	0.047	$\frac{\mathrm{dHb}^c}{\mathrm{dt}} = v_{dHb,in} - v_{dHb,out}$

Metabolic Control Analysis:
Metabolic control analysis was performed for the model at steady state using an improved version of the Reder algorithm [?] implemented in Copasi V4.16 [?]. To analyse the impact of these changes on the flux distribution between the main glycolytic branch and the PPP branch, we calculated the flux control coefficients for the first reaction in the PPP (ZWF in astrocytes and neurons). To calculate the coefficients, we used a version of our model operating at steady state, which is not subject to stimulation. The concentration of NADP and NADPH in neurons and astrocytes was fixed, to prevent the NADPH oxidase to influence the results. This is necessary to account for the fact that the rate constant for NADPH oxidase is not based on experimental data. According to the summation theorem for flux control coefficients the sum of all coeffecients for a single reaction should add up to zero [?]. The calculated coefficients were summed up and are sufficiently close to zero.
Changes in enzyme expression lead to changes in the reaction rate of the corresponding reactions. While the calculated flux control coefficients for flux J_{ZWF} and reaction rate v_i, F^i_{ZWF} are unequal to zero for nearly all metabolic reactions, we restrict the following discussion to cases where $|F^i_{ZWF}| > 0.002$.
The metabolic reaction with non-zero flux control coefficients are listed in Figure 2. Most control is exerted by Hexokinase, ZWF, SOL, and ATPase in both neurons and astrocytes and by the mitochondrial respiration in astrocytes only.

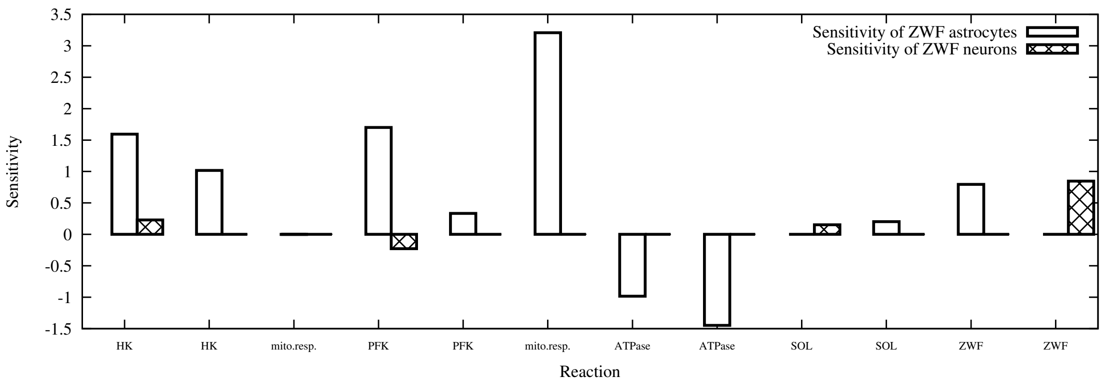

Figure 2: Selected flux control coefficients for ZWF in neurons and astrocytes. Shown are metabolic reactions where $|F^i_{ZWF}| > 0.002$. The necessary condition for the steady state analysis of the model is the absence of time-dependent reactions (i.e. constant venous volume, absence of neuronal stimulation, constant cerebral blood flow and constant glycogen breakdown).

The results of the metabolic control analysis indicate that hexokinase as well as the first two reactions of the pentose-phosphate pathway are decisive in the control of the flux distribution between the main glycolytic branch and the PPP. This finding supports the hypothesis by [?], who speculated that an increase in glucose 6 phosphate dehydrogenase induces an increased activity in the PPP.

Table 5: Exchange reactions used in the model. Superscripts indicate the location of the species (a = arteries, c = capillaries, e = extracellular space, g = astrocytes (glia cells), n = neurons)

Glucose and lactate exchange:		
$\mathrm{Glc}^a \leftrightarrow \mathrm{Glc}^c$	$\frac{2 \cdot F_{in}}{V_c} (\mathrm{Glc}^a - \mathrm{Glc}^c)$	
$\mathrm{Glc}^c \leftrightarrow \mathrm{Glc}^e$	$V_{max} \cdot \left(\frac{\mathrm{Glc}^c}{\mathrm{Glc}^c + K} - \frac{\mathrm{Glc}^e}{\mathrm{Glc}^e + K} \right)$	$V_{max} = 3.22$ $K = 9$
$\mathrm{Glc}^c \leftrightarrow \mathrm{Glc}^g$	$V_{max} \cdot \left(\frac{\mathrm{Glc}^c}{\mathrm{Glc}^c + K} - \frac{\mathrm{Glc}^g}{\mathrm{Glc}^g + K} \right)$	$V_{max} = 0.32$ $K = 9$
$\mathrm{Glc}^e \leftrightarrow \mathrm{Glc}^n$	$V_{max} \cdot \left(\frac{\mathrm{Glc}^e}{\mathrm{Glc}^e + K} - \frac{\mathrm{Glc}^n}{\mathrm{Glc}^n + K} \right)$	$V_{max} = 8826$ $K = 9$
$\mathrm{Glc}^e \leftrightarrow \mathrm{Glc}^g$	$V_{max} \cdot \left(\frac{\mathrm{Glc}^e}{\mathrm{Glc}^e + K} - \frac{\mathrm{Glc}^c}{\mathrm{Glc}^c + K} \right)$	$V_{max} = 956$ $K = 9$
$\mathrm{Lac}^c \leftrightarrow \mathrm{Lac}^a$	$\frac{2 \cdot F_{in}}{V_c} (\mathrm{Lac}^a - \mathrm{Lac}^c)$	
$\mathrm{Lac}^e \leftrightarrow \mathrm{Lac}^c$	$V_{max} \cdot \left(\frac{\mathrm{Lac}^e}{\mathrm{Lac}^e + K} - \frac{\mathrm{Lac}^c}{\mathrm{Lac}^c + K} \right)$	$V_{max} = 0.00587$ $K = 0.5$
$\mathrm{Lac}^g \leftrightarrow \mathrm{Lac}^c$	$V_{max} \cdot \left(\frac{\mathrm{Lac}^g}{\mathrm{Lac}^g + K} - \frac{\mathrm{Lac}^c}{\mathrm{Lac}^c + K} \right)$	$V_{max} = 0.00435$ $K = 0.5$
$\mathrm{Lac}^n \leftrightarrow \mathrm{Lac}^e$	$V_{max} \cdot \left(\frac{\mathrm{Lac}^n}{\mathrm{Lac}^n + K} - \frac{\mathrm{Lac}^e}{\mathrm{Lac}^e + K} \right)$	$V_{max} = 0.2175$ $K = 0.5$
$\mathrm{Lac}^g \leftrightarrow \mathrm{Lac}^e$	$V_{max} \cdot \left(\frac{\mathrm{Lac}^g}{\mathrm{Lac}^g + K} - \frac{\mathrm{Lac}^e}{\mathrm{Lac}^e + K} \right)$	$V_{max} = 0.057$ $K = 0.5$
Oxygen and carbon-dioxide exchange reactions:		
$\mathrm{O2}^a \leftrightarrow \mathrm{O2}^c$	$\frac{2 \cdot F_{in}}{V_c} (\mathrm{O2}^a - \mathrm{O2}^c)$	
$\mathrm{O2}^c \rightarrow \mathrm{O2}^g$	$\frac{PS_{cap}}{V_g} \cdot \left(K_{O2} \left(\frac{HbOP}{\mathrm{O2}^c} - 1 \right)^{\frac{-1}{nh}} - \mathrm{O2}^g \right)$	$PS_{cap} = 10.0$ $K_{O2} = 0.0361$ $HbOP = 8.6$ $nh = 2.73$
$\mathrm{O2}^c \rightarrow \mathrm{O2}^n$	$\frac{PS_{cap}}{V_n} \cdot \left(K_{O2} \left(\frac{HbOP}{\mathrm{O2}^c} - 1 \right)^{\frac{-1}{nh}} - \mathrm{O2}^n \right)$	$PS_{cap} = 40.5$ $K_{O2} = 0.0361$ $HbOP = 8.6$ $nh = 2.73$
$\mathrm{CO2}^c \leftrightarrow \mathrm{CO2}^a$	$\frac{2 \cdot F_{in}}{V_c} (\mathrm{CO2}^a - \mathrm{CO2}^c)$	
Neurotransmitter cycling:		
$\mathrm{GLU}^g \rightarrow \mathrm{GLU}^n$	$v_{GLU}^{gn} = V_{max} \cdot \frac{\mathrm{GLU}^g}{\mathrm{GLU}^g + K_{GLU}} \cdot \frac{\mathrm{ATP}^g}{\mathrm{ATP}^g + K_{ATP}}$	$V_{max} = 0.3$ $K_{GLU} = 0.05$ $K_{ATP} = 0.01532$
$\mathrm{GLU}^e \rightarrow \mathrm{GLU}^g$	$v_{GLU}^{eg} = V_{max} \frac{\mathrm{GLU}^e}{\mathrm{GLU}^e + K_{GLU}}$	$V_{max} = 0.026$ $K_{GLU} = 0.05$
$\mathrm{GLU}^n \rightarrow \mathrm{GLU}^e$	$v_{GLU}^{ne} = v_{stim} \cdot r_{Na,GLU} \cdot \frac{\mathrm{GLU}^n}{\mathrm{GLU}^n + K_{GLU}}$	$r_{Na,GLU} = 0.075$ $K_{GLU} = 0.05$

References

1. Joshi A and Palsson Bo. Metabolic dynamics in the human red cell: Part I A comprehensive kinetic model. *Journal of Theoretical Biology* 1989; 141(4): 515:528

2. Cloutier M, Bolger FB, Lowry JP et al. An integrative dynamic model of brain energy metabolism using in vivo neurochemical measurements. *Journal of Computational Neuroscience* 2009; 27(3): 391-414.

3. Smallbone K. Metabolic Control Analysis: Rereading Reder. *arXiv:13056449 [qbio]* 2013;

4. Hoops S, Sahle S, Gauges R et al. COPASI COmplex PAthway SImulator. *Bioinformatics* 2006; 22(24): 3067-307

5. Cornish-Bowden A. *Fundamentals of Enzyme Kinetics*. 4th ed. Viley-VCH, 2012.

6. Palmer AM. The activity of the pentose-phosphate pathway is increased in response to oxidative stress in Alzheimer's disease. *Journal of Neural Transmission* 1999; 106(3-4): 317-328.