Supplementary Table 2: Employed objective functions with corresponding reasonings

objective function	**Reasoning**	**Literature application**	**Deficits in the Simulation Results**
minimization of squared sum of total fluxes (Euclidean norm)	Cells try to minimize the load on their enzymes, trying to perform its duties by spending its sources (enzymes) in minimum amount.	(Bonarius *et al.*, 1996 ; Holzhutter, 2004)	- zero Lactate release flux - zero flux for Glutamate transfer from neurons to astrocytes (r_{76})
minimization of redox potential	This can be interpreted as maximization of energy efficiency. By minimizing the oxidation, energy is conserved.	(Knorr *et al.*, 2007 ; Savinell & Palsson, 1992)	- low Lactate release flux (1% of glucose) - zero flux for glutamate/ glutamine/ GABA cycles (r_{76},r_{79},r_{82}) - zero BCAA shuttle fluxes
minimization of ATP production	This implies efficient use of energy. Cell is forced to perform its functions with minimal energy need, leading ATP conservation.	(Knorr *et al.*, 2007)	- zero Lactate release flux - zero flux for Glutamate transfer from neurons to astrocytes - inactive astrocytic PPP flux (r_{14})
maximization of ATP production	Production of energy is aimed for other processes not considered in the model	(Beasley & Planes, 2007 ; Ramakrishna *et al.*, 2001)	- low Lactate release flux (1.5 % of glucose) - inactive neuronal PPP flux (r_{51}) - zero flux for glutamate/ glutamine/ GABA cycles (r_{76},r_{79},r_{82})
Maximization of transfer fluxes from astrocytes to neurons	Astrocytes are support cells for neurons. This objective ensures highest support by astrocytes to neurons.	intuition	- zero Lactate release flux - zero flux for glutamate/ glutamine/ GABA cycles (r_{76},r_{79},r_{82}) - very high neuronal oxidative metabolism (7-fold higher than astrocytic one)

ATP maximization for neurons, ATP minimization for astrocytes	Each cell type is assumed to have different, but interrelated, objectives. Neurons are known to have high oxidative metabolism whereas this is not the case for astrocytes.	intuition	- zero Lactate release flux - zero flux for glutamate/ glutamine/ GABA cycles (r_{76},r_{79},r_{82}) - inactive neuronal PPP flux (r_{51})
Maximization of NADPH producing reactions	Cells need NADPH for protection from oxidative stress and for lipid synthesis	(Fell & Small, 1986)	- zero Lactate release flux - zero flux for Glutamate transfer from neurons to astrocytes - very low flux for return part of the glutamate-glutamine cycle (r_{79}) and GABA cycle
maximization of malate shuttle in neurons	Support of oxidative metabolism of neurons is aimed by transferring optimum amount of NADH from cytosol to mitochondria.	intuition	- zero Lactate release flux - zero flux for Glutamate transfer from neurons to astrocytes - low flux for return part of the glutamate-glutamine cycle (r79) and GABA cycle - zero flux of BCAA cycling
maximization of glutamine transfer from astrocytes to neurons	Astrocytes are considered as glutamate producers for neurons	intuition	- inactive astrocytic PPP flux (r_{14})
Maximization of glutamate-glutamine-GABA exchange between astrocytes and neurons	**glutamate, glutamine and GABA constitute the most important trafficking between astrocytes and neurons**	**intuition**	

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