SUPPLEMENTARY INFORMATION

THE STABILITY AND ROBUSTNESS OF METABOLIC STATES: IDENTIFYING STABILIZING SITES IN METABOLIC NETWORKS

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Modelling details

Parameter intervals and allosteric regulation

In total, 10 different target sites of allosteric regulation are included into the model. They are listed in the upper part of Table I together with their intervals the sampling under different preconditions ($\mathbf{C_{reg}}$ and $\mathbf{C_{noreg}}$). All nonzero saturation parameters θ^{μ}_{S}, that are not mentioned explicitly in Table I, lie within the interval of $[0, 1]$ if the metabolite S is a substrate and $[-1, 0]$ if S is a product of the reaction $\nu(S)$, respectively.

with regulation ($\mathbf{C_{reg}}$)			without regulation ($\mathbf{C_{noreg}}$)
saturation parameter	regulation	interval	interval
$\theta^{PK}_{Fru16P2}$	activation	$[0 \dots 4]$	0
$\theta^{HK}_{23P2Gri}$	inhibition	$[-1 \dots 0]$	0
$\theta^{G6PD}_{23P2Gri}$	inhibition	$[-1 \dots 0]$	0
$\theta^{6PGD}_{23P2Gri}$	inhibition	$[-1 \dots 0]$	0
θ^{6PGD}_{ATP}	inhibition	$[-1 \dots 0]$	0
θ^{PFK}_{AMP}	activation	$[0 \dots 4]$	0
θ^{PFK}_{ATP}	inhibition	$[-4 \dots 1]$	$[0 \dots 1]$
θ^{PK}_{ATP}	inhibition	$[-4 \dots 0]$	$[-1 \dots 0]$
$\theta^{PFK}_{23P2Gri}$	inhibition	$[-1 \dots 0]$	0
θ^{G6PD}_{ATP}	inhibition	$[-1 \dots 0]$	0
θ^{AK}_{ADP}	$[0 \dots 2]$		
θ^{GSSGR}_{GSH}	$[-2 \dots 0]$		

Table I: All saturation parameters associated with allosteric regulation as well as all non-standard intervals for saturation parameters are shown here.

Matrix of saturation parameters

The matrix θ, which contains all saturation parameters, is shown in Table II. For clarity, the saturation parameters are denoted as $t(1)$ to $t(44)$ in case of substrate activation and $p(1)$ to $p(43)$ in case of product inhibition. The parameters describing the allosteric regulation are abbreviated as $r(1)$ to $r(10)$. In total, there are 97 saturation parameters.

Glcin	Glc6P	Fru6P	Fru16P2	GraP	DHAP	13P2Gri	23P2Gri	3PGri	2PGri	PEP	6PGlcA	Rul5P	Xul5P	Rib5P	Sed7P	E4P	ATP	AMP	NAD	NADP	GSH	Pyr	Lac	P	PRPP	ADP	GSSG	NADH	NADPH	
-p(1)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	GlcT +
1-p(1)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	GlcT -
t(1)	-p(2)	0	0	0	0	0	-r(2)	0	0	0	0	0	0	0	0	0	t(24)	0	0	0	0	0	0	0	0	-p(39)	0	0	0	HK +
t(1)-1	1-p(2)	0	0	0	0	0	-r(2)	0	0	0	0	0	0	0	0	0	t(24)-1	0	0	0	0	0	0	0	0	1-p(39)	0	0	0	HK -
0	t(2)	-p(3)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	GPI +
0	t(2)-1	1-p(3)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	GPI -
0	0	t(4)	-p(6)	0	0	0	-r(9)	0	0	0	0	0	0	0	0	0	1-r(7)	r(6)	0	0	0	0	0	0	0	-p(40)	0	0	0	PFK +
0	0	t(4)-1	1-p(6)	0	0	0	-r(9)	0	0	0	0	0	0	0	0	0	-r(7)	r(6)	0	0	0	0	0	0	0	1-p(40)	0	0	0	PFK -
0	0	0	t(5)	-p(7)	-p(11)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	ALD +
0	0	0	t(5)-1	1-p(7)	1-p(11)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	ALD -
0	0	0	0	-p(8)	t(8)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	TPI +
0	0	0	0	1-p(8)	t(8)-1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	TPI -
0	0	0	0	t(6)	0	-p(12)	0	0	0	0	0	0	0	0	0	0	0	0	t(28)	0	0	0	0	t(36)	0	0	0	-p(41)	0	GAPD +
0	0	0	0	t(6)-1	0	1-p(12)	0	0	0	0	0	0	0	0	0	0	0	0	t(28)-1	0	0	0	0	t(36)-1	0	0	0	1-p(41)	0	GAPD -
0	0	0	0	0	0	t(9)	0	-p(14)	0	0	0	0	0	0	0	0	-p(25)	0	0	0	0	0	0	0	0	t(38)	0	0	0	PGK +
0	0	0	0	0	0	t(9)-1	0	1-p(14)	0	0	0	0	0	0	0	0	1-p(25)	0	0	0	0	0	0	0	0	t(38)-1	0	0	0	PGK -
0	0	0	0	0	0	t(10)	-p(13)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	DPGM +
0	0	0	0	0	0	t(10)-1	1-p(13)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	DPGM -
0	0	0	0	0	0	0	t(11)	-p(15)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-p(38)	0	0	0	0	0	DPGase +
0	0	0	0	0	0	0	t(11)-1	1-p(15)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1-p(38)	0	0	0	0	0	DPGase -
0	0	0	0	0	0	0	0	t(12)	-p(16)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	PGM +
0	0	0	0	0	0	0	0	t(12)-1	1-p(16)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	PGM -
0	0	0	0	0	0	0	0	0	t(13)	-p(17)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	EN +
0	0	0	0	0	0	0	0	0	t(13)-1	1-p(17)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	EN -
0	0	0	r(1)	0	0	0	0	0	0	t(14)	0	0	0	0	0	0	-r(8)	0	0	0	0	-p(33)	0	0	0	t(39)	0	0	0	PK +
0	0	0	r(1)	0	0	0	0	0	0	t(14)-1	0	0	0	0	0	0	1-r(8)	0	0	0	0	1-p(33)	0	0	0	t(39)-1	0	0	0	PK -
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-p(29)	0	0	t(32)	-p(34)	0	0	0	0	t(42)	0	LDH +
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1-p(29)	0	0	t(32)-1	1-p(34)	0	0	0	0	t(42)-1	0	LDH -
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-p(30)	0	t(33)	-p(35)	0	0	0	0	0	t(43)	LDHP +
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1-p(30)	0	t(33)-1	1-p(35)	0	0	0	0	0	t(43)-1	LDHP -
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	t(25)	0	0	0	0	0	0	0	0	0	0	0	0	ATPase
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-p(27)	-p(28)	0	0	0	0	0	0	0	t(40)	0	0	0	AK +
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1-p(27)	1-p(28)	0	0	0	0	0	0	0	t(40)-2	0	0	0	AK -
0	t(3)	0	0	0	0	0	-r(3)	0	0	0	-p(18)	0	0	0	0	0	-r(10)	0	0	t(29)	0	0	0	0	0	0	0	0	-p(42)	G6PD +
0	t(3)-1	0	0	0	0	0	-r(3)	0	0	0	1-p(18)	0	0	0	0	0	-r(10)	0	0	t(29)-1	0	0	0	0	0	0	0	0	1-p(42)	G6PD -
0	0	0	0	0	0	0	-r(4)	0	0	0	t(15)	-p(19)	0	0	0	0	-r(5)	0	0	t(30)	0	0	0	0	0	0	0	0	-p(43)	6PGD +
0	0	0	0	0	0	0	-r(4)	0	0	0	t(15)-1	1-p(19)	0	0	0	0	-r(5)	0	0	t(30)-1	0	0	0	0	0	0	0	0	1-p(43)	6PGD -
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-p(31)	-p(32)	0	0	0	0	0	t(41)	0	t(44)	GSSGR +
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1-p(31)	2-p(32)	0	0	0	0	0	t(41)-1	0	t(44)-1	GSSGR -
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	t(31)	0	0	0	0	0	0	0	0	GSHox
0	0	0	0	0	0	0	0	0	0	0	0	t(16)	-p(20)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	EP +
0	0	0	0	0	0	0	0	0	0	0	0	t(16)-1	1-p(20)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	EP -
0	0	0	0	0	0	0	0	0	0	0	0	t(17)	0	-p(21)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	KI +
0	0	0	0	0	0	0	0	0	0	0	0	t(17)-1	0	1-p(21)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	KI -
0	0	0	0	-p(9)	0	0	0	0	0	0	0	0	t(18)	t(20)	-p(22)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	TK1 +
0	0	0	0	1-p(9)	0	0	0	0	0	0	0	0	t(18)-1	t(20)-1	1-p(22)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	TK1 -
0	0	-p(4)	0	t(7)	0	0	0	0	0	0	0	0	0	0	t(22)	-p(23)	0	0	0	0	0	0	0	0	0	0	0	0	0	TA +
0	0	1-p(4)	0	t(7)-1	0	0	0	0	0	0	0	0	0	0	t(22)-1	1-p(23)	0	0	0	0	0	0	0	0	0	0	0	0	0	TA -
0	0	0	0	0	0	0	0	0	0	0	0	0	0	t(21)	0	0	t(26)	-t(27)	0	0	0	0	0	0	-p(37)	0	0	0	0	PRPPS +
0	0	0	0	0	0	0	0	0	0	0	0	0	0	t(21)-1	0	0	t(26)-1	1-t(27)	0	0	0	0	0	0	1-p(37)	0	0	0	0	PRPPS -
0	0	-p(5)	0	-p(10)	0	0	0	0	0	0	0	0	t(19)	0	0	t(23)	0	0	0	0	0	0	0	0	0	0	0	0	0	TK2 +
0	0	1-p(5)	0	1-p(10)	0	0	0	0	0	0	0	0	t(19)-1	0	0	t(23)-1	0	0	0	0	0	0	0	0	0	0	0	0	0	TK2 -
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-p(36)	0	0	0	0	0	PT +
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1-p(36)	0	0	0	0	0	PT -
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	t(35)	0	0	0	0	0	0	LacT +
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	t(35)-1	0	0	0	0	0	0	LacT -
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	t(34)	0	0	0	0	0	0	0	PyrT +
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	t(34)-1	0	0	0	0	0	0	0	PyrT -
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	t(37)	0	0	0	0	PRPPT

Table II: Matrix θ of saturation parameters. The saturation parameters are denoted as t (substrate activation), p (product inhibition) and r (allosteric regulation). '+' and '-' indicate forward and backward in the case of a reversible reaction.

Steady state concentrations

metabolite	concentration S_1^0	concentration S_2^0
Glcin	4.569	4.3982
Glc6P	0.0405	0.0032
Fru6P	0.0157	0.0011
Fru16P2	0.0097	0.0018
GraP	0.0061	0.0019
DHAP	0.149	0.0483
13P2G	0.0005	0.0001
23P2G	2.6222	0.8914
3PG	0.0656	0.1663
2PG	0.0084	0.0223
PEP	0.0109	0.0321
6PG	0.0255	0.0018
Ru5P	0.0048	0.0024
X5P	0.0129	0.0063
R5P	0.0141	0.007
S7P	0.016	0.0005
E4P	0.0064	0.0005
ATP	1.606	0.5363
AMP	0.0731	0.8153
NAD	0.0654	0.0654
NADP	0.002	0.0088
GSH	3.1136	3.1136
Pyr	0.084	0.084
Lac	1.6803	1.6805
P	0.9992	1.0045
PRPP	1	1
ADP	0.3209	0.6484
GSSG	0.0002	0.002
NADH	0.0002	0.002
NADPH	0.05	0.0432

Table III: Metabolic concentrations (in mMol) at steady states S_1^0 (normal conditions; $k_{ATPase} = 1.68h^{-1}$) and S_2^0 (increased energy demand; $k_{ATPase} = 10h^{-1}$).

Fluxes at different steady states

The net fluxes at steady state S_1^0 (normal condition; $k_{ATPase} = 1.68h^{-1}$) and at S_2^0 (increased energy demand; $k_{ATPase} = 10h^{-1}$) are shown in Table IV. The net flux for a reversible reaction is calculated as the difference between the forward and the backward flux.

reaction	net flux under S_1^0 $\left[\frac{\text{mM}}{\text{h}}\right]$	net flux under S_2^0 $\left[\frac{\text{mM}}{\text{h}}\right]$
GlcT	1.5062	2.1275
HK	1.5062	2.1354
GPI	1.4096	2.0900
PFK	1.4567	2.2911
ALD	1.4568	2.3314
TPI	1.4568	2.3524
GAPD	2.9371	4.7681
PGK	2.4696	4.6493
DPGM	0.4677	0.1397
DPGase	0.4668	0.1587
PGM	2.9371	4.8196
EN	2.9371	4.8310
PK	2.9371	4.8420
LDH	2.9372	4.7679
LDHP	0.1000	0.0933
ATPase	2.3947	5.1008
AK	-0.0267	0.0039
G6PD	0.0967	0.0783
6PGD	0.0967	0.1058
GSSGR	0.0934	0.0929
GSHox	0.0934	0.0934
EP	0.0471	0.1082
KI	0.0496	0.0223
TK1	0.0236	0.0343
TA	0.0236	0.0698
PRPPS	0.0261	0.0126
TK2	0.0236	0.0987
PT	0.0781	-0.4493
LacT	3.0372	4.8612
PyrT	-0.1001	-0.0192
PRPPT	0.0261	0.0261

Table IV: Net fluxes at different steady states.

Stoichiometry

The stoichiometry of the considered metabolic network is shown in Table V. All reversible reactions are split into a forward (+) and a backward (-) reaction.
Mass conservation of any metabolite will lead to linear dependencies of the concentrations. This results in a rank deficiency of $\mathbf{N}$. Because the reverse also holds, mass conservation can be detected by calculating the rank of $\mathbf{N}$. The rank of $\mathbf{N}$ shows a deficiency of 4. This is in accordance with mass conservation constraints for following pools of metabolites : AMP/ADP/ATP , GSH/GSSG , NAD/NADH and NADP/NADPH. The null space reveals 33 independent fluxes at steady state, 28 of them representing cycling fluxes.

Glct		HK		GPI		PFK		ALD		TPI		GAPDH		PGK		DPGM		DPGase		PGM		EN		PK		LDH		LDH(P)		met.
+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	
1	-1	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Glcin
0	0	1	-1	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Glc6P
0	0	0	0	1	-1	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Fru6P
0	0	0	0	0	0	1	-1	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Fru16P2
0	0	0	0	0	0	0	0	1	-1	1	-1	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	GraP
0	0	0	0	0	0	0	0	1	-1	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	DHAP
0	0	0	0	0	0	0	0	0	0	0	0	1	-1	-1	1	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	13P2Gri
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	-1	-1	1	0	0	0	0	0	0	0	0	0	0	23P2Gri
0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	-1	0	0	1	-1	-1	1	0	0	0	0	0	0	0	0	3PGri
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	-1	-1	1	0	0	0	0	0	0	2PGri
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	-1	-1	1	0	0	0	0	PEP
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6PGlcA
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Rul5P
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Xul5P
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Rib5P
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Sed7P
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	E4P
0	0	-1	1	0	0	-1	1	0	0	0	0	0	0	1	-1	0	0	0	0	0	0	0	0	1	-1	0	0	0	0	ATP
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	AMP
0	0	0	0	0	0	0	0	0	0	0	0	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	-1	0	0	NAD
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	-1	NADP
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	GSH
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	-1	-1	1	-1	1	Pyr
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	-1	1	-1	Lac
0	0	0	0	0	0	0	0	0	0	0	0	-1	1	0	0	0	0	1	-1	0	0	0	0	0	0	0	0	0	0	Pi
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	PRPP
0	0	1	-1	0	0	1	-1	0	0	0	0	0	0	-1	1	0	0	0	0	0	0	0	0	-1	1	0	0	0	0	ADP
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	GSSG
0	0	0	0	0	0	0	0	0	0	0	0	1	-1	0	0	0	0	0	0	0	0	0	0	0	0	-1	1	0	0	NADH
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	1	NADPH

ATPase	AK		G6PD		6PGD		GSSGR		GSHox	EP		KI		TK1		TA		PRPPS		TK2		Pt		Lact		Pyrt		PRPPT	met.
	+	-	+	-	+	-	+	-		+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-		
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Glcin
0	0	0	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Glc6P
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	-1	0	0	1	-1	0	0	0	0	0	0	0	Fru6P
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Fru16P2
0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	-1	-1	1	0	0	1	-1	0	0	0	0	0	0	0	GraP
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	DHAP
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	13P2Gri
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	23P2Gri
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3PGri
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2PGri
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	PEP
0	0	0	1	-1	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6PGlcA
0	0	0	0	0	1	-1	0	0	0	-1	1	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Rul5P
0	0	0	0	0	0	0	0	0	0	1	-1	0	0	-1	1	0	0	0	0	-1	1	0	0	0	0	0	0	0	Xul5P
0	0	0	0	0	0	0	0	0	0	0	0	1	-1	-1	1	0	0	-1	1	0	0	0	0	0	0	0	0	0	Rib5P
0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	-1	-1	1	0	0	0	0	0	0	0	0	0	0	0	Sed7P
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	-1	0	0	-1	1	0	0	0	0	0	0	0	E4P
-1	1	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	1	0	0	0	0	0	0	0	0	0	ATP
0	1	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	-1	0	0	0	0	0	0	0	0	0	AMP
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	NAD
0	0	0	-1	1	-1	1	1	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	NADP
0	0	0	0	0	0	0	2	-2	-2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	GSH
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	1	0	Pyr
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	1	0	0	0	Lac
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	-1	0	0	0	0	0	Pi
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	-1	0	0	0	0	0	0	0	0	-1	PRPP
1	-2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	ADP
0	0	0	0	0	0	0	-1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	GSSG
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	NADH
0	0	0	1	-1	1	-1	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	NADPH

Table V: Stoichiometry of energy and redox metabolism of the erythrocyte. '+' and '-' indicate forward and backward in the case of a reversible reaction.

Supplemental results

Analyzing individual regulation parameters

The role of each regulation parameter (i.e. a saturation parameter corresponding to allosteric regulation) in the absence of any other regulation parameter is elucidated. Therefore all saturation parameters are chosen randomly and all but one regulation parameters are set to zero. This non-zero regulation parameter is increased stepwise and $\lambda_{Re}^{\max}$ is calculated at each step. Subsequently, the monotony of $\lambda_{Re}^{\max}$ (with respect to the stepwise increased regulation parameter) is determined. The results for a set of 1000 samples are shown in Table VI.

regulation parameter	$\lambda_{Re}^{\max}$ monotonically increasing	$\lambda_{Re}^{\max}$ monotonically decreasing	$\lambda_{Re}^{\max}$ not monotone
$\theta_{Fru16P2}^{PK}$	878	94	28
$\theta_{23P2Gri}^{HK}$	16	987	7
$\theta_{23P2Gri}^{G6PD}$	147	853	0
$\theta_{23P2Gri}^{6PGD}$	188	812	0
θ_{ATP}^{6PGD}	166	834	0
θ_{AMP}^{PFK}	19	966	15
θ_{ATP}^{PFK}	14	986	0
θ_{ATP}^{PK}	130	870	0
$\theta_{23P2Gri}^{PFK}$	30	970	0
θ_{ATP}^{G6PD}	154	846	0

Table VI: One regulation parameter (first column) is increased stepwise while all other regulation parameters are set to zero. This is done for 1000 different samples of saturation parameters. Columns 2 to 4 show how often (out of the 1000 samples) $\lambda_{Re}^{\max}$ is monotonically increasing, monotonically decreasing or not monotone at all, respectively.

Extended ranking

The extended rankings for the saturation parameters are shown in Tables VI to XI. For clarity, each saturation parameter $\theta^{\text{reaction}}_{\text{metabolite}}$ is denoted by the metabolite and the reaction which is saturated by this metabolite.

parameter		correlation coefficient
Fru16P2	PFK	0.37
PEP	PK	0.17
ADP	HK	-0.16
Glc6P	HK	0.16
13P2G	DPGM	-0.16
ADP	PFK	-0.11
Fru6P	PFK	0.11
ATP	ATPase	-0.1
ADP	PK	-0.09
PRPP	PRPPT	-0.07
23P2G	DPGM	-0.07
ATP	HK	0.05
PRPP	PRPPS	0.05
ATP	PFK	-0.04
ATP	PK	0.03
23P2G	DPGase	-0.03
Fru16P2	ALD	0.02
2PG	EN	0.02
PEP	EN	0.02
AMP	PRPPS	-0.02
R5P	PRPPS	-0.01

Table VII: Correlation coefficients for the saturation parameters of $\mathbf{C_{noreg}}$. All parameters that are not listed here are not significant.

parameter		mutual information
PRPP	PRPPT	0.16
Fru16P2	PFK	0.145
PRPP	PRPPS	0.069
Glc6P	HK	0.045
PEP	PK	0.019
ADP	HK	0.016
13P2G	DPGM	0.012
Fru6P	PFK	0.011
23P2G	DPGase	0.005
ADP	PFK	0.005
ATP	ATPase	0.003
23P2G	DPGM	0.002
ADP	PK	0.002
3PG	DPGase	$< 10^{-3}$

Table VIII: Mutual information for the saturation parameters of $\mathbf{C_{noreg}}$. All parameters that are not listed here are not sgnificant.

parameter		p-value
Fru16P2	PFK	$< 10^{-6}$
Glc6P	HK	$< 10^{-6}$
ADP	HK	$< 10^{-6}$
Fru6P	PFK	$< 10^{-6}$
PEP	PK	$< 10^{-6}$
ADP	PFK	$< 10^{-6}$
23P2G	DPGase	$< 10^{-6}$
ATP	ATPase	$< 10^{-6}$
13P2G	DPGM	$< 10^{-6}$
ADP	PK	$< 10^{-6}$
23P2G	DPGM	$< 10^{-6}$
3PG	DPGase	$< 10^{-5}$
ATP	HK	$< 10^{-4}$

Table IX: P-value of the KS-test for the saturation parameters of $\mathbf{C_{noreg}}$. All parameters that are not listed here are not significant.

Detailed rankings for suppressed allosteric regulation ($\mathbf{C_{noreg}}$). From a total amount of 87 only the significant parameters are listed.

parameter		correlation coefficient
AMP	PFK [a]	-0.25
Glc6P	HK	0.17
ADP	HK	-0.13
Fru6P	PFK	0.12
Fru16P2	PK [a]	0.12
ATP	PFK [a]	0.09
ADP	PFK	-0.07
ATP	ATPase	-0.05
Fru16P2	PFK	0.05
3PG	DPGase	-0.05
ATP	HK	0.04
PRPP	PRPPT	-0.04
ATP	PK [a]	0.03
PEP	PK	-0.03
ADP	PK	0.03
NADP	LDHP	0.03
PRPP	PRPPS	0.03
13P2G	DPGM	-0.03
R5P	PRPPS	-0.01
23P2G	DPGM	0.01
23P2G	HK [a]	-0.01

Table X: Correlation coefficients for the saturation parameters of $\mathbf{C_{reg}}$. All parameters that are not listed here are not significant.

parameter		mutual information
Glc6P	HK	0.047
AMP	PFK [a]	0.046
Fru6P	PFK	0.011
Fru16P2	PK [a]	0.01
ADP	HK	0.008
ATP	PFK [a]	0.002

Table XI: Mutual information for the saturation parameters of $\mathbf{C_{reg}}$. All parameters that are not listed here are not significant.

parameter		p-value
Glc6P	HK	$< 10^{-6}$
AMP	PFK [a]	$< 10^{-6}$
Fru6P	PFK	$< 10^{-6}$
Fru16P2	PK [a]	$< 10^{-6}$
ADP	HK	$< 10^{-6}$
ATP	PFK [a]	$< 10^{-4}$
3PG	DPGase	$< 10^{-4}$
ATP	ATPase	0.01
ADP	PFK	0.013

Table XII: P-value of the KS-test for the saturation parameters of $\mathbf{C_{reg}}$. All parameters that are not listed here are not significant.

Detailed rankings for allowed allosteric regulation ($\mathbf{C_{reg}}$). Those parameters marked with [a] correspond to allosteric regulation. From a total of 97only the significant parameters are listed.

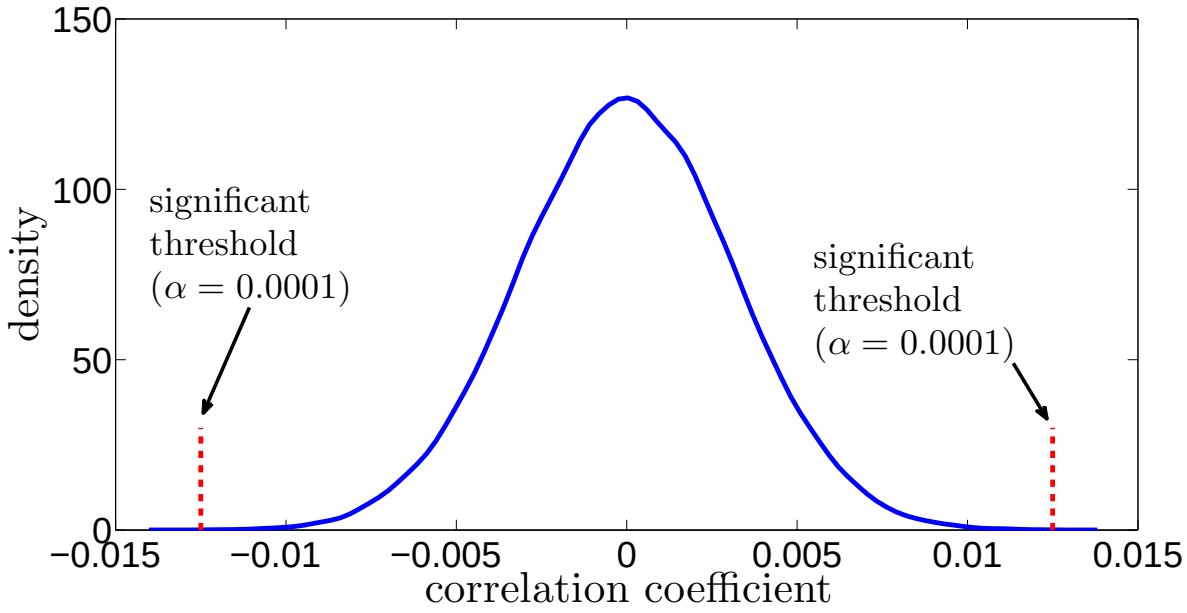

Figure 1: Correlation coefficient between saturation parameters and shuffled eigenvalues. The dotted red line marks the threshold for $\alpha = 0.0001$. All saturation parameters with a higher (absolute) correlation coefficient than 0.0012 are considered to be significant.

Significant parameters

We used a shuffling approach to calculate a threshold for the significant parameters. Therefore we permuted the values of $\lambda_{Re}^{\max}$, leading to a totally random relation between the saturation parameters and $\lambda_{Re}^{\max}$. The resulting probability density function for the correlation coefficients 0f 1000 permutations can be seen in Figure 1 (similar results for mutual information). The threshold of 0.0012 was chosen in such a way that only 0.01% (significance level $\alpha = 0.0001$) of the calculated correlation are above the threshold (considering absolute values).

Comparison of measures

We compared the rankings according to three different measures (correlation coefficients, mutual information, Kolmogorov-Smirnov-test). The rankings for the significant parameters are in good accordance to each other (see Figure 2), justifying our decision to restrict the further analysis on the ranking obtained by correlation coefficients.

The measures used so far are dependent on the relation between the saturation parameters and $\lambda_{Re}^{\max}$. One could argue that these measures are not suitable to analyse the influence of the saturation parameters on stability because stability is not determined by the exact *value* of $\lambda_{Re}^{\max}$ but by its *sign*. We therefore calculated a forth measure, defined as the mutual information between the saturation parameters and the frequency of stable models. This forth measure is in good accordance with the ranking according to correlation coefficients (see Figure 3), underlying once again the relevance and usefulness of the correlation coefficients.

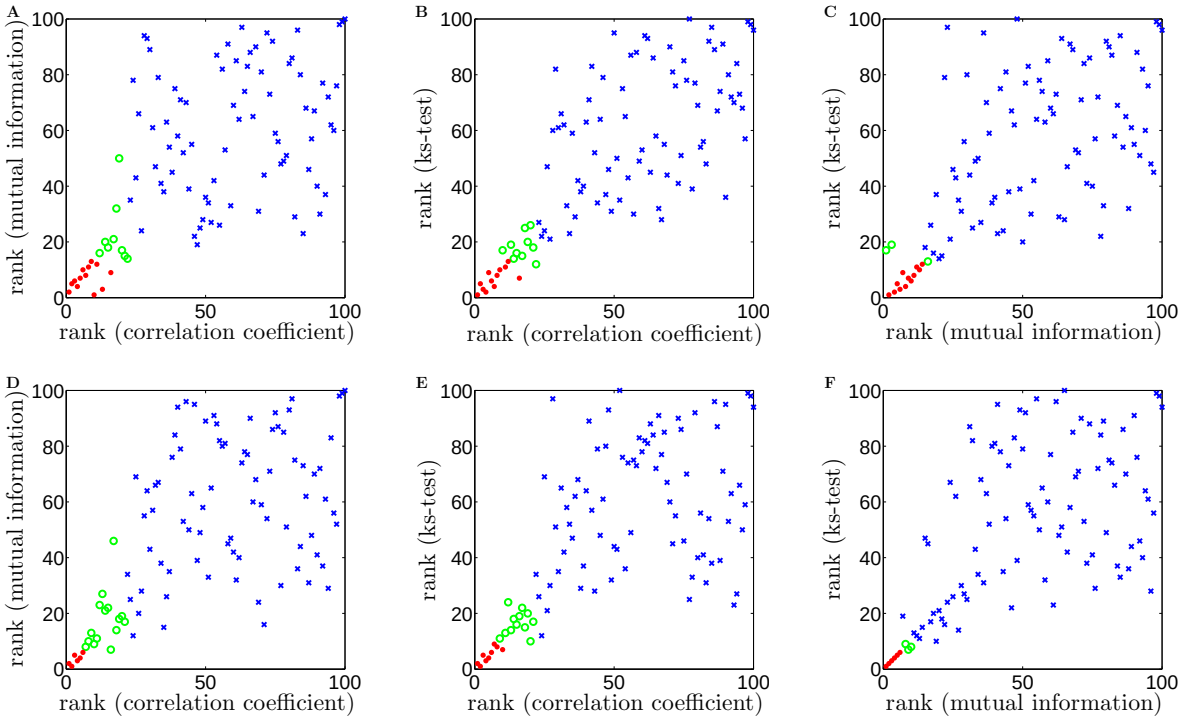

Figure 2: Comparison of the different measures for $\mathbf{C_{noreg}}$ (**A - C**) and $\mathbf{C_{reg}}$ (**D - F**). The red dots are significant in both measures, the green circles only in one and the blue crosses are not significant at all. Clearly, the different rankings are consistent with each other and show similar results, especially for the significant parameters.

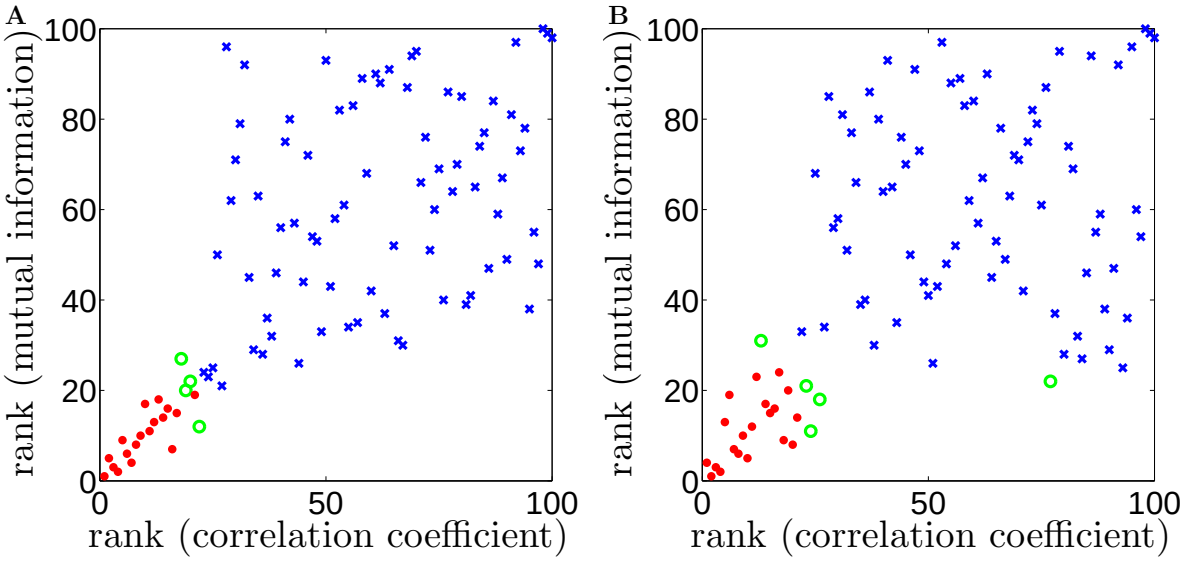

Figure 3: Comparison of the ranking according to correlation coefficients between the saturation parameters and $\lambda_{Re}^{\max}$ and the mutual information between the saturation parameters and the frequency of stable models (**A** for $\mathbf{C_{noreg}}$ and **B** for $\mathbf{C_{reg}}$). The red dots are significant in both measures, the green circles only in one and the blue crosses are not significant at all.