

**Supplementary Table 3. Metabolic flux distributions of parental, Ras, Akt cells in normoxia and parental iBMK cells in hypoxia.** Fluxes are obtained as described in the Methods. The table shows the best estimate and standard deviation. Fluxes are in units of nmole/ (h \*  $\mu$ l cells).

Reaction	Reaction description	Atom mapping	Constrained	Fluxes				Fluxes STD			
				Parental	Ras	Akt	Parental - hypoxia	Parental	Ras	Akt	Parental - hypoxia
F1	1/2 glucose.ext -> pyruvate	abc->abc	1	172.6	349.7	320.2	309.7	7.8	25.2	32.7	0.1
F2	pyruvate + NAD <sup>+</sup> -> acetyl-CoA (m) + CO <sub>2</sub> + NADH	abc->bc + a	0	20.5	10.8	24.5	4.7	<0.1	0.5	0.1	0.2
F3	acetyl-CoA (m) + malate + NAD <sup>+</sup> -> citrate + NADH	abcd+ef->dcbfca	0	26.4	11.3	30.4	8.4	<0.1	0.5	0.1	0.5
F4	citrate + NAD <sup>+</sup> -> alpha-ketoglutarate + CO <sub>2</sub> + NADH	abcdef->abcde+f	0	30.0	14.8	32.6	35.2	0.1	0.9	0.1	1.1
F5	alpha-ketoglutarate + CO <sub>2</sub> + NADH -> citrate + NAD <sup>+</sup>	abcde+f->abcdef	0	5.3	4.9	5.0	20.1	0.6	0.4	0.7	1.3
F6	alpha-ketoglutarate + NAD <sup>+</sup> + FAD -> fumarate + CO <sub>2</sub> + NADH + FADH <sub>2</sub>	abcde->1/2 bcde + 1/2 edcb	0	77.2	64.6	84.6	57.1	<0.1	1.7	<0.1	<0.1
F7	malate/OAA + NAD <sup>+</sup> -> pyruvate + CO <sub>2</sub> + NADH	abcd -> abc	0	7.2	12.0	<0.1	<0.1	3.8	8.0	<0.1	<0.1
F8	pyruvate + CO <sub>2</sub> + NADH -> malate/OAA + NAD <sup>+</sup>	abc + d -> abcd	0	8.5	5.4	7.2	8.0	1.2	1.0	1.3	0.6
F9	citrate -> malate + acetyl-CoA (c).ext	abcdef -> fcba + ed	0	2.1	1.5	4.3	0.2	0.2	0.2	0.4	0.1
F10	other sources (e.g. fatty acid) -> acetyl-CoA (m)	ab -> ab	0	5.9	0.5	5.9	3.7	0.8	0.7	0.9	0.7
F11	glutamine -> alpha-ketoglutarate	abcde -> abcde	1	52.5	54.7	57.0	42.0	<0.1	1.6	<0.1	1.0
F12	pyruvate + NADH -> lactate.ext + NAD <sup>+</sup>	abc -> abc	1	150.8	345.6	288.5	297.0	8.8	26.5	33.2	0.3
F13	malate + NAD <sup>+</sup> -> OAA + NADH	abcd -> abcd	0	54.2	48.1	65.8	56.9	1.0	3.7	1.6	0.7
F14	acetyl-CoA (c) -> biomass		1	2.1	1.5	4.3	0.2	0.2	0.1	0.4	0.1
F15	citrate.ext -> citrate	abcdef -> abcdef	0	0.4	0.1	1.6	6.9	0.8	0.2	1.0	0.5
F16	fumarate <-> malate/OAA	abcd -> 1/2 abcd + 1/2 dcba	0	77.2	64.6	84.6	57.1	<0.1	1.7	<0.1	<0.1
F17	1/2 glucose + NAD -> serine + NADH		1	5.6	4.0	9.6	0.4	0.6	1.2	2.3	<0.1
F18	pyruvate -> pyruvate.ext	abc -> abc	1	17.0	16.0	20.0	12.0	6.1	8.8	7.7	4.6
F19	NADH + 1/2 O <sub>2</sub> => NAD	abc -> abc	1	306.2	224.1	351.5	204.5	0.0	6.3	0.0	0.0