Supplementary tables

Supplementary table 1: Maximum yields on glucose feed

Comparison of maximum product yields of the wild type networks for the five pathways in *S. cerevisiae* and *E. coli*. Yields are the fraction of carbons in the substrate glucose (single carbon source) that end up in the product ccMA.

S. cerevisiae:

Pathway branch	EFM count	Max. yield [%]	Max. yield with biomass [%]
DHS-pathway	29,836,123	85.7	84.8
ANTH-pathway	29,567,053	70.4	65.8
DHBA-pathway	31,739,546	80	77.3
SA-pathway	29,704,354	72.3	69.8
pHBA-pathway	29,953,182	72	66.1

E. coli:

Pathway branch	EFM count	Max. yield [%]	Max. yield with biomass [%]
DHS-pathway	468,715	85.7	79.45
ANTH-pathway	493,917	68.8	64.7
DHBA-pathway	482,135	79.4	75.3
SA-pathway	484,284	71.05	65.4
pHBA-pathway	506,231	70.6	67.8

Supplementary table 2: Maximum yields on glucose + glycerol co-feed

Comparison of maximum product yields of the wild type networks for the five pathways in *E. coli*. Yields are the fraction of carbons in the substrates glucose and glycerol (mixed carbon source, variable ratio) that end up in the product ccMA.

Pathway branch	EFM count	Max. yield [%]	Max. yield with biomass [%]
DHS-pathway	876,044	89.7	84.8
ANTH-pathway	938,621	70.4	65.8
DHBA-pathway	913,663	84.5	77.7
SA-pathway	926,636	75.65	69.7
pHBA-pathway	963,577	75.2	69.96

Supplementary tables

Supplementary table 3: Maximum and minimum yields of *S. cerevisiae* knock-out networks

Comparison of maximum and minimum product yields of the knock-out strategies for the five pathways in *S. cerevisiae*. For the DHS-pathway only a two-target knock-out strategy that minimizes the number of low-yield-modes is shown. For the other pathways, which allow the rewiring of pyruvate metabolism, a second knock-out that can further increase the minimum yield is included. Yields are percentage carbon yields of the product in respect to the substrate glucose.

Pathway branch	Knock-out targets	Max. yield without biomass [%]	Max. yield with biomass [%]	Min. yield without biomass [%]	Min. yield with biomass [%]
DHS-pathway	G6PD GPDH	85.7	84.8	0	0
ANTH-pathway	PYK	70.4	65.8	28.4	29.5
	PYK GPDH			54.5	46.9
DHBA-pathway	PYK	80	77.3	25.3	26.2
	PYK GPDH			57.1	46.9
SA-pathway	PYK	72.3	69.8	31.6	32.9
	PYK GPDH			57.1	49.6
pHBA-pathway	PYK	72	66.1	27.5	29
	PYK GPDH			54.5	46.4

Supplementary tables

Supplementary table 4: Maximum and minimum yields of *E. coli* knock-out networks

Comparison of maximum product yields of the knock-out strategies for the five pathways in *E. coli*. For the ANTH-pathway two alternate knock-out strategies are shown, while for the DHBA-, SA- and pHBA-pathways only the more rational strategy based on rewiring pyruvate metabolism is shown. Yields are percentage carbon yields of the product in respect to the substrate glucose.

Pathway branch	Knock-out targets	Max. yield without biomass [%]	Max. yield with biomass [%]	Min. yield without biomass [%]	Min. yield with biomass [%]
DHS-pathway	GPI PGD PGM/PGH GPI PGD GAP/PGK	75	74.9 74.97	75	71.6 73.3
ANTH-pathway	GPI TAL PGM/PGH GPI TAL GAP/PGK	50	49.8 49.9	50	44.9 47.5
	PTS PYK EDA MAE PTS PYK EDA MAE FRD	68.3	64.7	8.8 25	5.2 25.8
DHBA-pathway	PTS PYK EDA MAE PTS PYK EDA MAE FRD	78.1	75.3	9.1 25	6.3 25.8
SA-pathway	PTS PYK EDA MAE PTS PYK EDA MAE FRD	70.4	61.6	9.1 25	5.5 25.8
pHBA-pathway	PTS PYK EDA MAE PTS PYK EDA MAE FRD	69.9	62.2	9.1 25	5.5 25.8

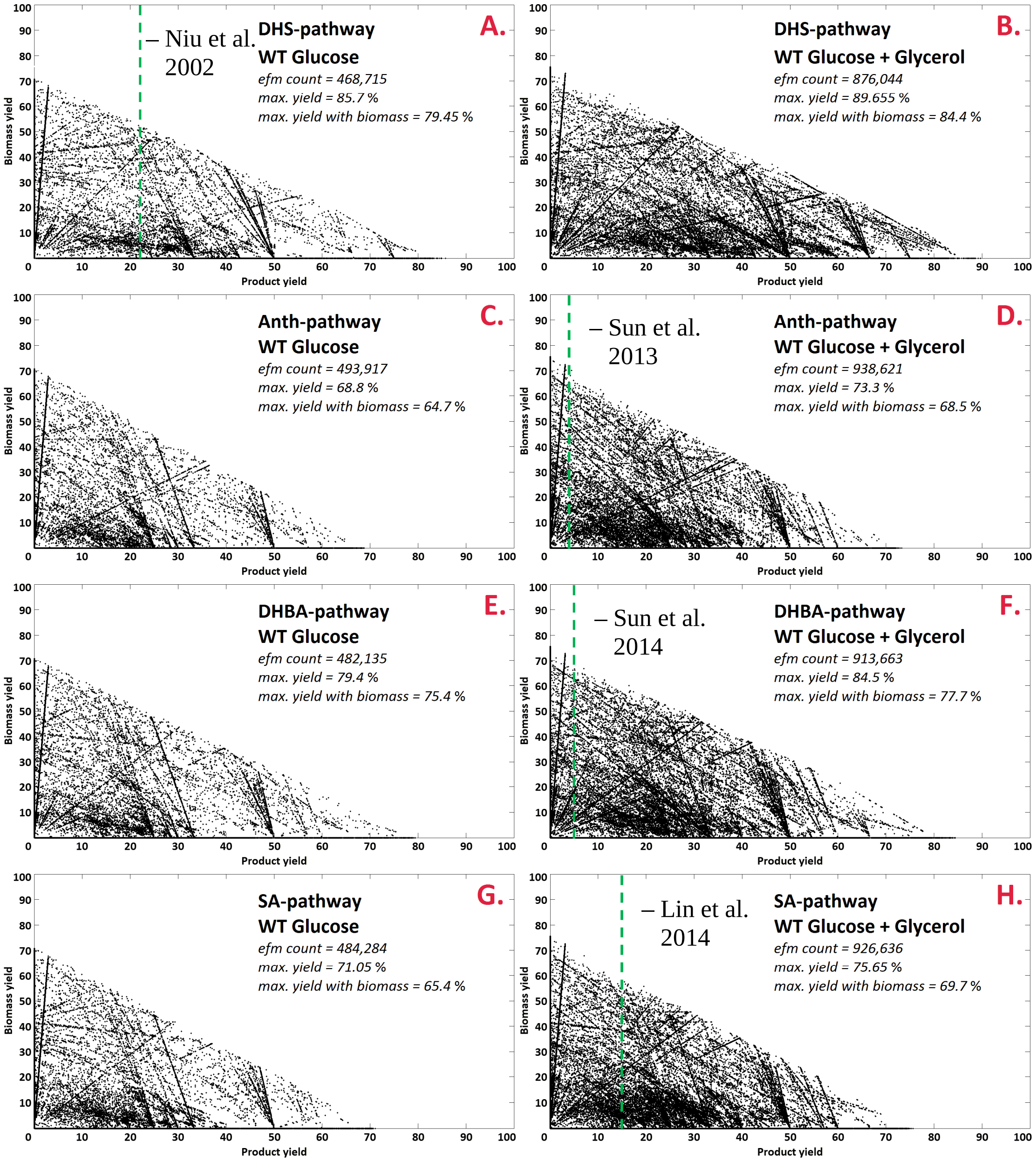
Supplementary tables

Supplementary table 5: Comparison of knock-out targets

Corresponding enzymes and coding genes for each knock-out target and organism are stated in the table below. This is meant to serve a better understanding of the manuscript as a knock-out target determined in the analysis is always a specific function / reaction, rather than a single gene. This may also aid in determining the experimental effort when comparing the knock-out strategies.

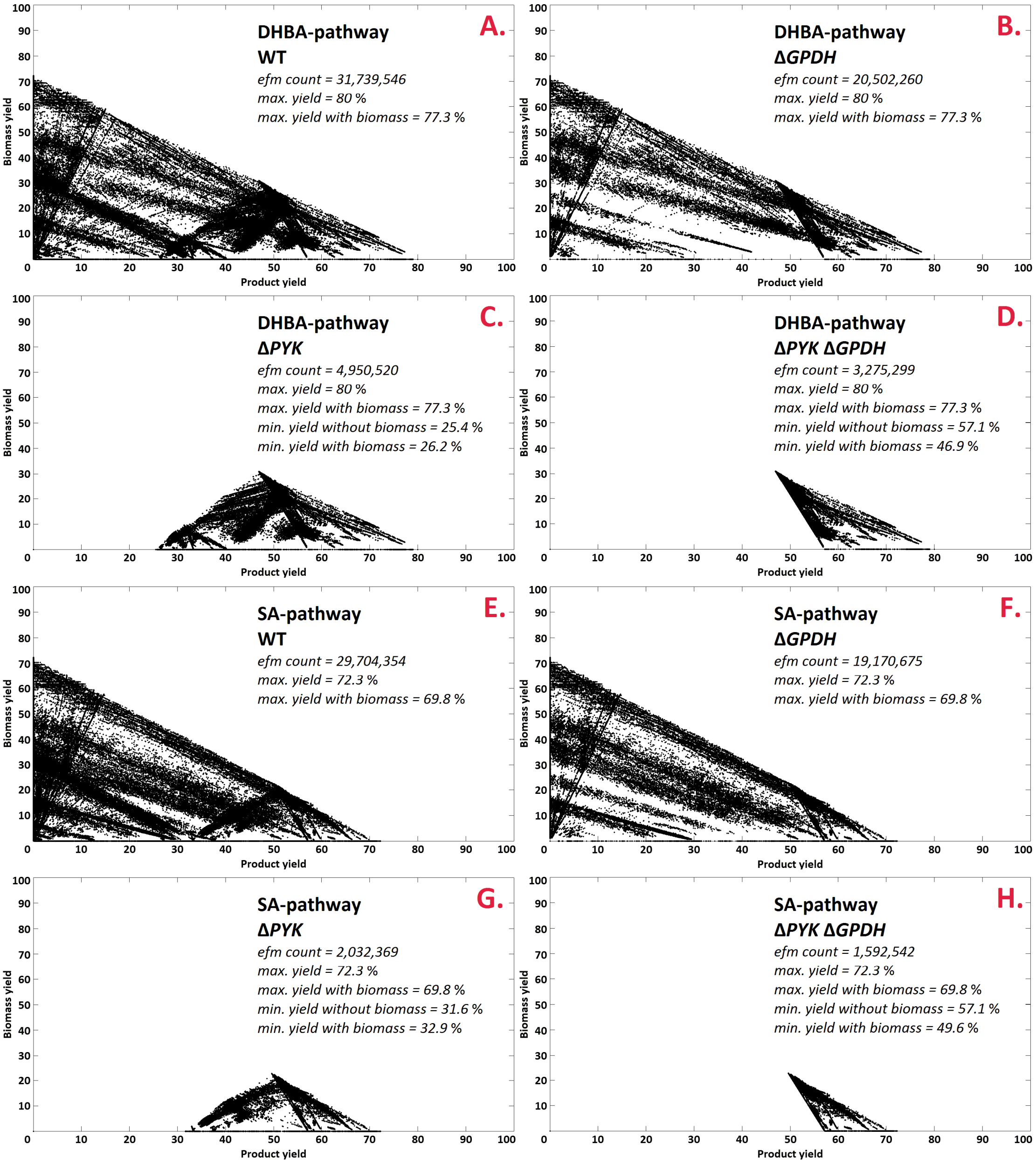
S. cerevisiae knock-out target		Gene(s)	*E. coli* knock-out target		Gene(s)
GPDH	glycerol-3-phosphate dehydrogenase (two isozymes)	*GPD1/GPD2*	PTS	phosphotransferase system (multi-component system)	npr/ptsO/rpoR/yhbK ptsH/hpr/Hpr/ctr ptsI/ctr ptsP/ygdF/ygdO
PYK	pyruvate kinase (two isozymes)	*CDC19/PYK2*	PYK	pyruvate kinase (two isozymes)	pykA pykF
G6PD	glucose-6-phosphate 1-dehydrogenase	*ZWF1*	FRD	fumarate reductase (four separately expressed subunits)	frdA, frdB, frdC, frdD
			EDA	2-dehydro-3-deoxy-phosphogluconate aldolase	eda/hga/kdgA/kga
			MAE	malic enzyme (NADP & NAD dependent enzymes)	maeB/ypfF sfcA/maeA/mae
			GPI	glucose-6-phosphate isomerase	pgi
			PGD	phosphogluconate dehydrogenase	gnd
			TAL	transaldolase	talB
			PGM	phosphoglycerate mutase (two enzymes)	gpmA/gpmM
			ENO	phosphopyruvate hydratase	eno
			GAPDH	glyceraldehyde-3-phosphate dehydrogenase	gapA
			PGK	phosphoglycerate kinase	pgk

Supplementary figures



Supplementary figure 5 – EM distribution *E. coli* Glucose + Glycerol co-feed
Product vs. biomass yield plots of the EFM distribution of *E. coli* WT networks. This figure is supposed to serve a better comparability of the different yields achieved by the two groups that derived ccMA from the two different branches of shikimate pathway in *E. coli* on different carbon sources. Key data is indicated on the charts. Each point in a chart corresponds to the specific product and biomass yield of the respective elementary flux mode. Yields are carbon yields in %. A green dashed vertical line indicates currently achieved product yields in the respective approaches.

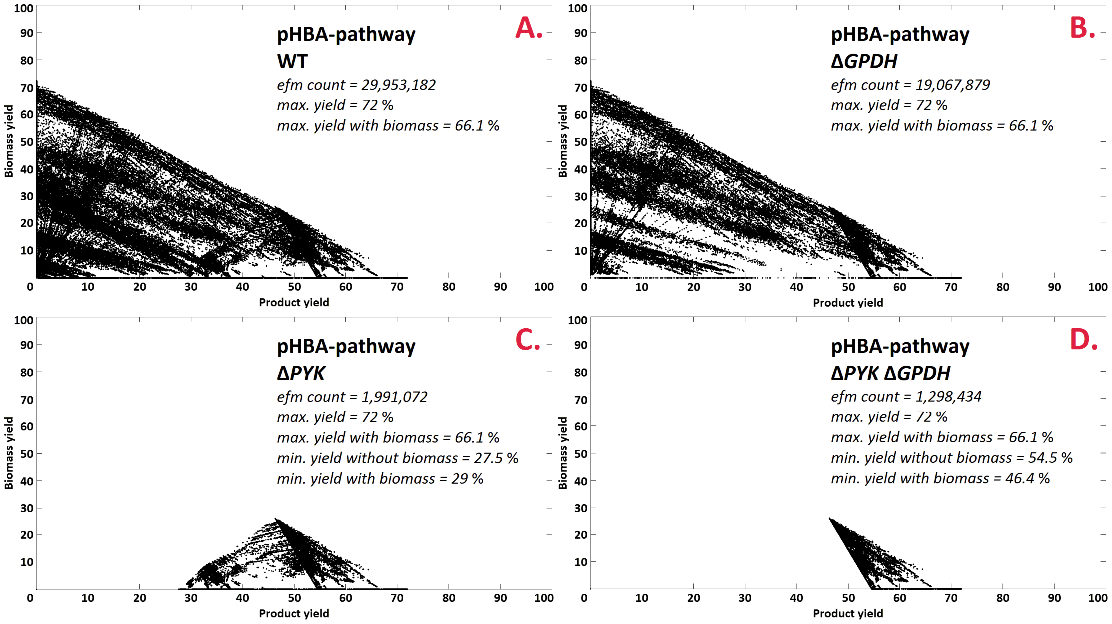
Supplementary figures



Supplementary figure 6 – Yield vs. biomass plots of knock-out strategies for *S. cerevisiae*

Product vs. biomass yield plots of the EFM distribution of isochorismate derived routes in *S. cerevisiae* networks. For each pathway four scenarios are shown, comparing the wild type with the determined knock-out metabolism. Key data as well as respective knock-outs are indicated on the charts. Each point in a chart corresponds to the specific product and biomass yield of the respective elementary flux mode. Yields are carbon yields in %.

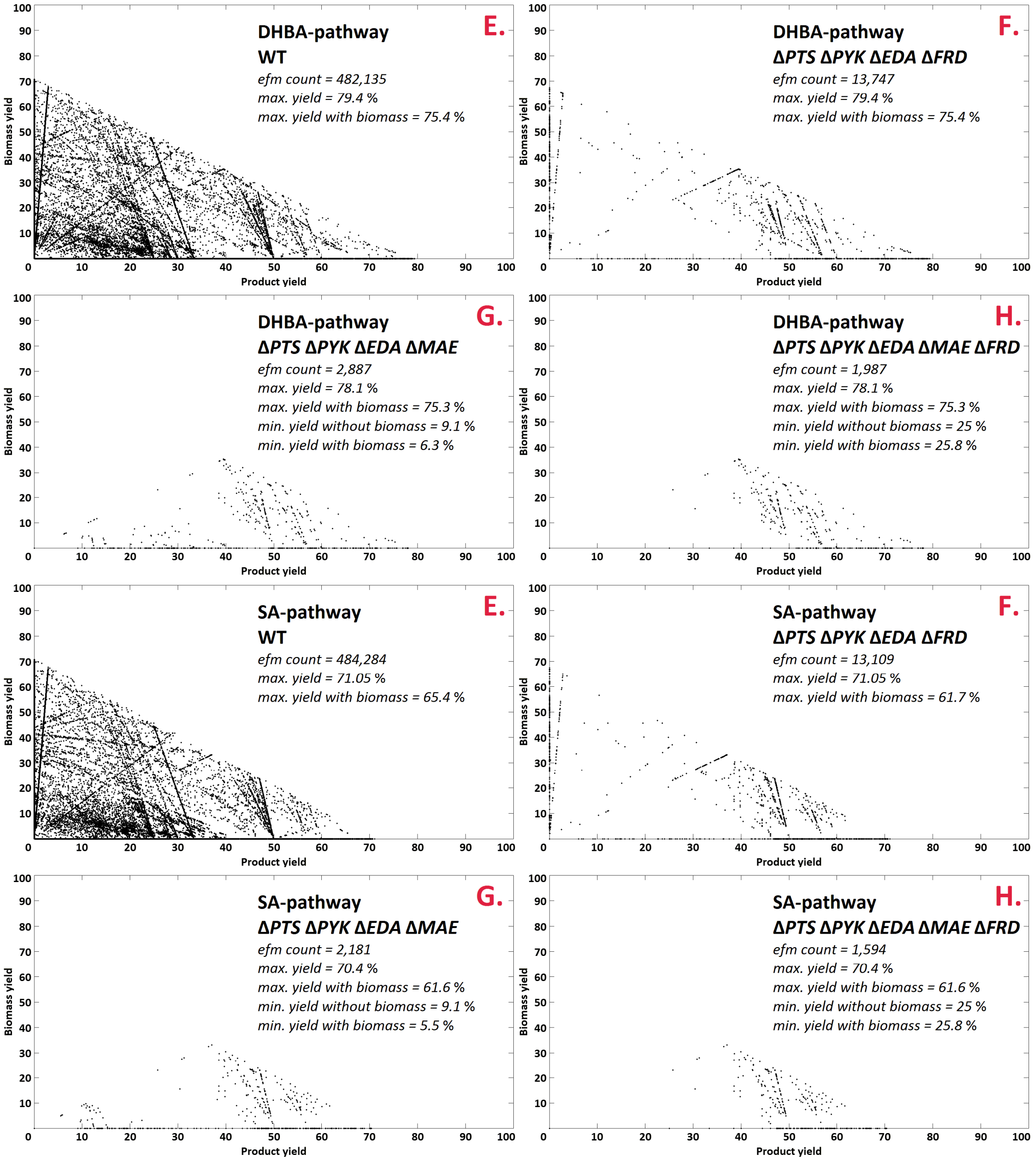
Supplementary figures



Supplementary figure 7 – Yield vs. biomass plots of knock-out strategies for *S. cerevisiae*

Product vs. biomass yield plots of the EFM distribution of the pHBA-pathway in *S. cerevisiae* networks. For each pathway four scenarios are shown, comparing the wild type with the determined knock-out metabolism. Key data as well as respective knock-outs are indicated on the charts. Each point in a chart corresponds to the specific product and biomass yield of the respective elementary flux mode. Yields are carbon yields in %.

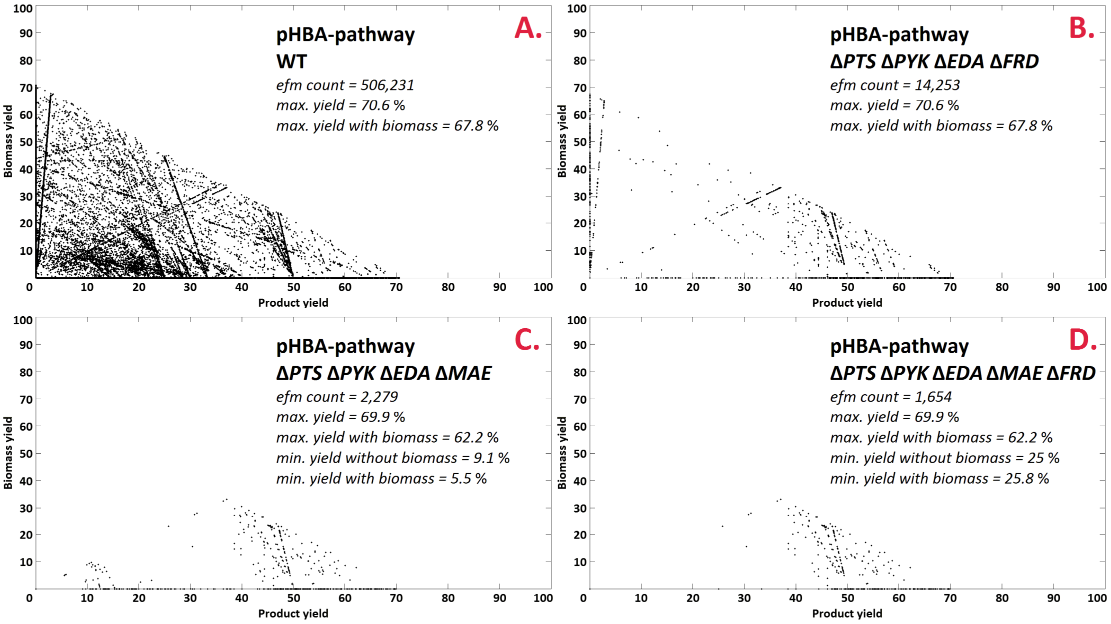
Supplementary figures



Supplementary figure 8 – Yield vs. biomass plots of alternative knock-out strategy for *E. coli*

Product vs. biomass yield plots of the EFM distribution of isochorismate derived routes in *E. coli* networks. Four scenarios are shown, comparing the wild type with the determined knock-out metabolism. Key data as well as respective knock-outs are indicated on the charts. Each point in a chart corresponds to the specific product and biomass yield of the respective elementary flux mode. Yields are carbon yields in %.

Supplementary figures



Supplementary figure 9 – Yield vs. biomass plots of alternative knock-out strategy for *E. coli*

Product vs. biomass yield plots of the EFM distribution of the pHBA-pathway in *E. coli* networks. Four scenarios are shown, comparing the wild type with the determined knock-out metabolism. Key data as well as respective knock-outs are indicated on the charts. Each point in a chart corresponds to the specific product and biomass yield of the respective elementary flux mode. Yields are carbon yields in %.