Supplemental material for Heinken, A. and Thiele, I.

Supplemental Results

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Supplemental Results

Correlation between metabolic distances between microbes and microbe-microbe interactions

Under the expectation that metabolic distance would correlate with giver/consumer interactions and inversely correlate with competitive interactions, we plotted the Jaccard reaction and metabolite distance scores (determined in Ref. [1]) against the percentage of interactions for each pair (Figure S2). However, we found that reaction and metabolite distance could only poorly explain the giver/consumer, mutualistic, or competitive interaction displayed per pair (Figure S2). The correlations between the reaction and metabolite distances and the percentages of giver/consumer relationships were 36% and 32%, respectively (Figure S2a-b). For competitive relationships, the correlation was 35% for the reaction distance and 31% for the metabolite distance (Figure S2c-d). Accordingly, we found differences in the predicted behavior between the *E. coli* MG1655 and the *E. coli* O157:H7 strains despite reaction and metabolite distance scores of 0.03 or less between the three *E. coli* strains (Figure 1c, Figure S2). We conclude that metabolic proximity does not provide an adequate explanation for the capability of certain pairs to engage in commensal, mutualistic, or competitive interactions. The more likely explanation for the observed species-specific differences in interaction type is the metabolic functions encoded in the bacterial genomes. It should be noted, however, that the observed low metabolic proximity between most of the 11 microbes is partly due to reconstruction bias, which leads to the inclusion or omission of certain pathways.

Supplemental Tables

Table S1: Description of the included reconstructions and the reconstructed species. Modifications to the reconstructions are described in Ref. [1].

Reconstructed Organism	Type	NCBI Taxonomy ID	Reconstruction Version	Reactions	Metabo-lites	Genes	Ref.
Bacteroides thetaiotaomicron VPI-5482	Commensal	226186	iAH991	1528	1176	993	[2]
Faecalibacterium prausnitzii A2-165	Commensal	411483	iFpraus_v1.0	1030	833	602	[3]
Escherichia coli str. K-12 substr. MG1655	Commensal	511145	iEco1339_Mg1655	2428	1705	1338	[4]
Lactobacillus plantarum WCFS1	Probiotic	220668	Unnamed	777	662	724	[5]
Lactococcus lactis subsp. cremoris MG1363	Probiotic	416870	Unnamed	751	650	518	[6]
Streptococcus thermophilus LMG 18311	Probiotic	264199	Unnamed	556	549	422*	[7]
Helicobacter pylori 26695	Opportunistic Pathogen	85962	iIT341	555	485	339	[8]
Klebsiella pneumoniae MGH 78578	Opportunistic Pathogen	1328388	iYL1228	2262	1658	1229	[9]
Salmonella enterica subsp. typhimurium LT2	Pathogen	99287	STM_v1.0	2623	1864	1288	[10]
Escherichia coli O157:H7 strain Sakai	Pathogen	386585	iEco1345_Sakai	2372	1688	1345	[4]
Escherichia coli O157:H7 strain EDL933	Pathogen	155864	iEco1344_EDL933	2376	1686	1344	[4]
Homo sapiens (small intestinal enterocyte)	Host	9606	hs_sIEC611	1282	844	611	[11]

Table S3: Uptake constraints on external exchanges in the framework implemented to simulate the three *in silico* dietary regimes (Figure 2b).

Metabolite type/ BiGG ID	**Metabolite**	**Uptake rate (mmol*gDW^{-1} * hr^{-1})**		
		Adjusted to carbons per molecule		
Simple sugars and starch		**Western diet**	**High fiber diet**	**Protein diet**
fru	Fructose	0.29486781	0.0625	0.15625
glc	Glucose	0.29486781	0.0625	0.15625
gal	Galactose	0.29486781	0.0625	0.15625
man	Mannose	0.29486781	0.0625	0.15625
lcts	Lactose	0.14743391	0.03125	0.078125
malt	Maltose	0.14743391	0.03125	0.078125
sucr	Sucrose	0.14743391	0.03125	0.078125
melib	Melibiose	0.14743391	0.03125	0.078125
strch1	Soluble starch	0.21444932	0.04545455	0.11363636
Fiber		**Western diet**	**High fiber diet**	**Protein diet**
inulin	Inulin	0.00078365	0.01527778	0.00694444
levan1000	Levan	2.351E-05	0.00045833	0.00020833
starch1200	Insoluble starch	1.9591E-05	0.00038194	0.00017361
arabinogal	Arabinogalactan	3.6528E-05	0.00071214	0.0003237
pect	Pectins	5.5644E-05	0.00108481	0.0004931
pullulan1200	Pullulan	1.9591E-05	0.00038194	0.00017361
amylose300	Amylose	7.8365E-05	0.00152778	0.00069444
lmn30	Laminarin	0.00078365	0.01527778	0.00694444
raffin	Raffinose	0.00783653	0.15277778	0.06944444
stys	Stachyose	0.0058774	0.11458333	0.05208333
oligofru4	Oligofructose	0.0058774	0.11458333	0.05208333
dextran40	Dextran	0.00029387	0.00572917	0.00260417
Fat		**Western diet**	**High fiber diet**	**Protein diet**
arachd	Arachidonic acid	0.00386729	0.00220988	0.00220988
chsterol	Cholesterol	0.00575975	0.00329129	0.00329129
glyc	Glycerol	2.09119895	1.19497083	1.19497083
hdca	Hexadecanoic acid	0.46058299	0.26319028	0.26319028
hdcea	Hexadecenoic acid	0.04243272	0.02424727	0.02424727
lnlc	linoleic acid (all cis C18:2) n-6	0.41728993	0.23845139	0.23845139

lnlnca	alpha-Linolenic acid, C18:3, n-3	0.02041092	0.01166338	0.01166338
lnlncg	gamma-linolenic acid	0.02041092	0.01166338	0.01166338
ocdca	octadecanoate (n-C18:0)	0.19670876	0.112405	0.112405
ocdcea	octadecenoate (n-C18:1)	0.79184823	0.4524847	0.4524847
octa	octanoate (n-C8:0)	0.01503944	0.00859397	0.00859397
ttdca	tetradecanoate (n-C14:0)	0.07979793	0.04559882	0.04559882
Protein		**Western diet**	**High fiber diet**	**Protein diet**
ala-L	L-alanine	0.3	0.3	0.6
arg-L	L-arginine	0.15	0.15	0.3
glu-L	L-glutamate	0.18	0.18	0.36
gly	Glycine	0.45	0.45	0.9
ile-L	L-isoleucine	0.15	0.15	0.3
leu-L	L-leucine	0.15	0.15	0.3
lys-L	L-lysine	0.15	0.15	0.3
met-L	L-methionine	0.18	0.18	0.36
pro-L	L-proline	0.18	0.18	0.36
asn-L	L-asparagine	0.225	0.225	0.45
asp-L	L-aspartate	0.225	0.225	0.45
his-L	L-histidine	0.15	0.15	0.3
phe-L	L-phenylalanine	0.099	0.099	0.198
ser-L	L-serine	0.3	0.3	0.6
thr-L	L-threonine	0.225	0.225	0.45
trp-L	L-tryptophan	0.081	0.081	0.162
tyr-L	L-tyrosine	0.099	0.099	0.198
gln-L	L-glutamine	0.18	0.18	0.36
val-L	L-valine	0.18	0.18	0.36
cys-L	L-cysteine	0.3	0.3	0.6
Vitamins/ minerals/ other		**Western diet**	**High fiber diet**	**Protein diet**
adocbl	Adenosylcobalamin	1	1	1
avite1	alpha-Tocopherol	1	1	1
ca2	Calcium	1	1	1
cbl1	Cob(I)alamin	1	1	1
chol	Choline	1	1	1

cl	Chloride	1	1	1
cobalt2	Co2+	1	1	1
cu2	Cu2+	1	1	1
fe2	Fe2+	1	1	1
fe3	Fe3+	1	1	1
fe3dcit	Fe(III)dicitrate	1	1	1
fol	Folate	1	1	1
h2s	Hydrogen sulfide	1	1	1
k	potassium	1	1	1
mg2	magnesium	1	1	1
mn2	Mn2+	1	1	1
mobd	Molybdate	1	1	1
mqn8	Menaquinone 8	1	1	1
na1	Sodium	1	1	1
nac	Nicotinate	1	1	1
orot	Orotate	1	1	1
pheme	Protoheme	1	1	1
phyQ	Phylloquinone	1	1	1
pime	Pimelate	1	1	1
pnto-R	(R)-Pantothenate	1	1	1
pydam	Pyridoxamine	1	1	1
pydx	Pyridoxal	1	1	1
pydxn	Pyridoxine	1	1	1
retinol	Retinol	1	1	1
ribflv	Riboflavin	1	1	1
sel	Selenate	1	1	1
so4	Sulfate	1	1	1
spmd	Spermidine	1	1	1
thf	5,6,7,8-Tetrahydrofolate	1	1	1
thm	Thiamin	1	1	1
vitd3	Vitamin D3	1	1	1
zn2	Zinc	1	1	1

Table S4: Pareto frontiers for 55 pairs on 12 scenarios grouped into four types (total n = 600). Type 1: Microbes benefit the other microbe at low growth rates but compete at higher growth rates; Type 2: Microbe benefit each other even at highest possible growth rates; Type 3: Only one microbe benefits the other at low growth rates but competes at high growth rates; Type 4: The microbes compete at every possible growth tradeoff. Examples for the four types are shown in Figure 2. WD = Western diet, HFD = high fiber diet, PD = protein diet, sIEC = small intestinal enterocyte.

Scenario			Type 1	Type 2	Type 3	Type 4	Total
- O_2	- sIEC	WD	16	5	16	8	45
		HFD	9	5	21	10	45
		PD	18	5	13	9	45
	+ sIEC	WD	18	0	10	17	45
		HFD	8	5	20	12	45
		PD	14	5	12	14	45
+ O_2	- sIEC	WD	6	0	34	15	55
		HFD	8	0	38	9	55
		PD	24	0	27	4	55
	+ sIEC	WD	5	0	34	16	55
		HFD	6	0	34	15	55
		PD	12	0	32	11	55
Western diet total			45	5	94	56	200
High fiber diet total			31	10	113	46	200
Protein diet total			68	10	84	38	200
Without oxygen total			83	25	92	70	270
With oxygen total			61	0	199	70	330
Without sIEC total			81	15	149	55	300
With sIEC total			63	10	142	85	300
Total			144	25	291	140	600

Table S5: Growth rates achieved when each microbe is grown alone and linked with enterocyte, as well as simultaneously optimized growth of each microbe-microbe pair with and without the enterocyte.

Scenario	BT	FP	LP	LL	ST	HP	KP	STy	EC	ECs	ECe
Western diet, no oxygen											
Single	0.22	0.13	0.13	0.11	0.07	N/A	0.11	0.10	0.16	0.14	0.14
With IEC	0.26	0.18	0.29	0.21	0.26	N/A	0.22	0.22	0.28	0.26	0.26
With BT	N/A	0.04	0.58	0.19	0.19	N/A	0.08	0.14	0.03	0.03	0.03
With FP	0.31	N/A	0.29	0.19	0.14	N/A	0.21	0.35	0.46	0.42	0.42
With LP	0.18	0.04	N/A	0.01	0.14	N/A	0.22	0.23	0.32	0.28	0.28
With LL	0.10	0.03	0.14	N/A	0.10	N/A	0.09	0.12	0.15	0.13	0.13
With ST	0.09	0.08	0.01	0.04	N/A	N/A	0.01	0.01	0.02	0.04	0.04
With KP	0.21	0.05	0.22	0.09	0.17	N/A	N/A	0.12	0.14	0.12	0.12
With STy	0.18	0.07	0.23	0.02	0.15	N/A	0.01	N/A	0.16	0.13	0.13
With EC	0.34	0.03	0.32	0.02	0.29	N/A	0.001	0.004	N/A	0.01	0.03
With ECs	0.32	0.05	0.28	0.02	0.15	N/A	0.01	0.01	0.14	N/A	0.06
With ECe	0.32	0.05	0.28	0.02	0.15	N/A	0.01	0.01	0.14	0.07	N/A
With BT/ IEC	N/A	0.05	0.59	0.20	0.25	N/A	0.07	0.13	0.02	0.03	0.03
With FP/ IEC	0.37	N/A	0.37	0.24	0.31	N/A	0.18	0.44	0.55	0.48	0.48
With LP/ IEC	0.17	0.05	N/A	0.003	0.21	N/A	0.35	0.37	0.35	0.28	0.28
With LL/ IEC	0.15	0.03	0.30	N/A	0.25	N/A	0.18	0.24	0.27	0.25	0.25
With ST/ IEC	0.11	0.04	0.11	0.05	N/A	N/A	0.04	0.01	0.08	0.07	0.07
With KP/ IEC	0.28	0.14	0.38	0.16	0.29	N/A	N/A	0.22	0.27	0.25	0.25
With STy/ IEC	0.23	0.08	0.39	0.04	0.31	N/A	0.02	N/A	0.28	0.25	0.25
With EC/ IEC	0.39	0.05	0.45	0.04	0.29	N/A	0.001	0.004	N/A	0.01	0.03
With ECs/ IEC	0.36	0.04	0.44	0.04	0.27	N/A	0.001	0.001	0.27	N/A	0.13
With ECe/ IEC	0.36	0.04	0.44	0.04	0.27	N/A	0.001	0.001	0.25	0.13	N/A
Scenario	**BT**	**FP**	**LP**	**LL**	**ST**	**HP**	**KP**	**STy**	**EC**	**ECs**	**ECe**
High fiber diet, no oxygen											
Single	0.44	0.07	0.04	0.04	0.02	N/A	0.04	0.04	0.06	0.05	0.05
With IEC	0.45	0.11	0.10	0.09	0.11	N/A	0.08	0.09	0.12	0.10	0.10
With BT	N/A	0.38	0.71	0.28	0.35	N/A	0.13	0.19	0.44	0.42	0.42
With FP	0.12	N/A	0.13	0.06	0.06	N/A	0.06	0.19	0.41	0.21	0.21
With LP	0.11	0.02	N/A	0.01	0.04	N/A	0.08	0.10	0.14	0.10	0.10
With LL	0.23	0.05	0.04	N/A	0.05	N/A	0.03	0.05	0.06	0.05	0.05
With ST	0.20	0.04	0.01	0.01	N/A	N/A	0.01	0.01	0.02	0.01	0.01
With KP	0.38	0.06	0.08	0.03	0.05	N/A	N/A	0.04	0.05	0.03	0.03
With STy	0.31	0.02	0.10	0.01	0.06	N/A	0.01	N/A	0.06	0.04	0.04
With EC	0.08	0.07	0.14	0.01	0.17	N/A	0.001	0.01	N/A	0.01	0.001
With ECs	0.10	0.03	0.10	0.01	0.06	N/A	0.01	0.01	0.05	N/A	0.02
With ECe	0.10	0.03	0.10	0.01	0.06	N/A	0.01	0.01	0.05	0.02	N/A

Scenario	BT	FP	LP	LL	ST	HP	KP	STy	EC	ECs	ECe
With BT/ IEC	N/A	0.27	0.73	0.31	0.39	N/A	0.10	0.16	0.24	0.05	0.05
With FP/ IEC	0.30	N/A	0.18	0.09	0.17	N/A	0.09	0.28	0.50	0.28	0.28
With LP/ IEC	0.10	0.03	N/A	0.004	0.11	N/A	0.18	0.21	0.27	0.22	0.22
With LL/ IEC	0.24	0.06	0.11	N/A	0.12	N/A	0.07	0.10	0.12	0.10	0.10
With ST/ IEC	0.21	0.03	0.01	0.003	N/A	N/A	0.01	0.01	0.01	0.01	0.01
With KP/ IEC	0.43	0.08	0.18	0.06	0.13	N/A	N/A	0.09	0.12	0.10	0.10
With STy/ IEC	0.40	0.05	0.21	0.01	0.13	N/A	0.01	N/A	0.12	0.10	0.10
With EC/ IEC	0.34	0.09	0.27	0.01	0.17	N/A	0.001	0.01	N/A	0.01	0.001
With ECs/ IEC	0.51	0.04	0.22	0.01	0.13	N/A	0.001	0.001	0.11	N/A	0.09
With ECe/ IEC	0.51	0.04	0.22	0.01	0.13	N/A	0.001	0.001	0.12	0.01	N/A
Scenario	**BT**	**FP**	**LP**	**LL**	**ST**	**HP**	**KP**	**STy**	**EC**	**ECs**	**ECe**
Protein diet, no oxygen											
Single	0.24	0.10	0.08	0.07	0.05	N/A	0.07	0.07	0.10	0.09	0.09
With IEC	0.29	0.14	0.18	0.14	0.19	N/A	0.14	0.15	0.19	0.17	0.17
With BT	N/A	0.03	0.88	0.11	0.24	N/A	0.03	0.04	0.03	0.02	0.02
With FP	0.33	N/A	0.19	0.09	0.12	N/A	0.08	0.28	0.77	0.31	0.31
With LP	0.50	0.03	N/A	0.01	0.09	N/A	0.15	0.18	0.22	0.19	0.19
With LL	0.17	0.07	0.09	N/A	0.10	N/A	0.06	0.09	0.10	0.09	0.09
With ST	0.06	0.05	0.01	0.01	N/A	N/A	0.01	0.05	0.02	0.01	0.01
With KP	0.27	0.10	0.15	0.06	0.10	N/A	N/A	0.08	0.08	0.07	0.07
With STy	0.28	0.02	0.18	0.02	0.06	N/A	0.01	N/A	0.11	0.08	0.08
With EC	0.33	0.20	0.22	0.02	0.27	N/A	0.001	0.01	N/A	0.02	0.001
With ECs	0.31	0.04	0.19	0.02	0.12	N/A	0.01	0.01	0.08	N/A	0.01
With ECe	0.31	0.04	0.19	0.02	0.12	N/A	0.01	0.01	0.09	0.07	N/A
With BT/ IEC	N/A	0.05	0.95	0.11	0.25	N/A	0.03	0.03	0.03	0.03	0.03
With FP/ IEC	0.40	N/A	0.26	0.14	0.25	N/A	0.12	0.38	0.88	0.37	0.37
With LP/ IEC	0.46	0.05	N/A	0.01	0.21	N/A	0.30	0.37	0.42	0.38	0.38
With LL/ IEC	0.22	0.07	0.19	N/A	0.21	N/A	0.12	0.17	0.19	0.17	0.17
With ST/ IEC	0.12	0.03	0.01	0.01	N/A	N/A	0.01	0.02	0.01	0.01	0.01
With KP/ IEC	0.32	0.13	0.30	0.11	0.22	N/A	N/A	0.15	0.19	0.16	0.16
With STy/ IEC	0.34	0.07	0.37	0.02	0.21	N/A	0.01	N/A	0.20	0.17	0.17
With EC/ IEC	0.38	0.22	0.42	0.02	0.27	N/A	0.001	0.01	N/A	0.02	0.001
With ECs/ IEC	0.36	0.05	0.38	0.02	0.23	N/A	0.001	0.004	0.17	N/A	0.16
With ECe/ IEC	0.36	0.05	0.38	0.02	0.23	N/A	0.001	0.004	0.19	0.001	N/A
Scenario	**BT**	**FP**	**LP**	**LL**	**ST**	**HP**	**KP**	**STy**	**EC**	**ECs**	**ECe**
Western diet, with oxygen											
Single	0.44	0.17	0.47	0.11	0.09	0.20	0.51	0.43	0.49	0.49	0.49
With IEC	0.45	0.25	0.70	0.21	0.39	0.34	0.51	0.55	0.60	0.51	0.51
With BT	N/A	0.22	0.79	0.33	0.24	0.46	0.57	0.19	0.52	0.52	0.52
With FP	0.28	N/A	0.66	0.12	0.15	0.25	0.53	0.16	0.48	0.48	0.48

Scenario	BT	FP	LP	LL	ST	HP	KP	STy	EC	ECs	ECe
With LP	0.08	0.04	N/A	0.01	0.26	0.13	0.17	0.17	0.08	0.08	0.08
With LL	0.24	0.14	0.52	N/A	0.22	0.07	0.10	0.22	0.09	0.11	0.11
With ST	0.35	0.09	0.27	0.02	N/A	0.31	0.44	0.31	0.28	0.29	0.29
With HP	0.04	0.18	0.50	0.32	0.09	N/A	0.53	0.01	0.48	0.48	0.48
With KP	0.01	0.01	0.70	0.55	0.17	0.01	N/A	0.01	0.01	0.01	0.01
With STy	0.31	0.30	0.60	0.33	0.22	0.45	0.56	N/A	0.48	0.48	0.48
With EC	0.01	0.01	0.79	0.52	0.36	0.01	0.57	0.01	N/A	0.05	0.24
With ECs	0.01	0.01	0.78	0.49	0.34	0.01	0.57	0.01	0.43	N/A	0.24
With ECe	0.01	0.01	0.78	0.49	0.34	0.01	0.57	0.01	0.25	0.25	N/A
With BT/ IEC	N/A	0.12	0.84	0.43	0.36	0.46	0.66	0.29	0.60	0.60	0.60
With FP/ IEC	0.44	N/A	0.74	0.16	0.45	0.21	0.55	0.22	0.60	0.51	0.51
With LP/ IEC	0.05	0.05	N/A	0.002	0.51	0.02	0.06	0.11	0.08	0.04	0.04
With LL/ IEC	0.15	0.15	0.72	N/A	0.45	0.02	0.07	0.22	0.11	0.07	0.07
With ST/ IEC	0.27	0.03	0.29	0.02	N/A	0.20	0.24	0.36	0.31	0.18	0.18
With HP/ IEC	0.02	0.25	0.72	0.36	0.46	N/A	0.54	0.05	0.60	0.51	0.51
With KP/ IEC	0.002	0.001	0.84	0.57	0.49	0.001	N/A	0.001	0.001	0.001	0.001
With STy/ IEC	0.28	0.35	0.88	0.45	0.34	0.52	0.65	N/A	0.60	0.60	0.60
With EC/ IEC	0.001	0.001	0.94	0.63	0.53	0.001	0.65	0.001	N/A	0.27	0.30
With ECs/ IEC	0.002	0.001	0.86	0.56	0.59	0.001	0.57	0.001	0.33	N/A	0.26
With ECe/ IEC	0.002	0.001	0.86	0.56	0.59	0.001	0.57	0.001	0.30	0.26	N/A
Scenario	**BT**	**FP**	**LP**	**LL**	**ST**	**HP**	**KP**	**STy**	**EC**	**ECs**	**ECe**
High fiber diet, with oxygen											
Single	0.44	0.08	0.26	0.04	0.02	0.13	0.44	0.33	0.49	0.49	0.49
With IEC	0.45	0.14	0.46	0.09	0.15	0.34	0.51	0.53	0.60	0.51	0.51
With BT	N/A	0.49	0.93	0.60	0.76	0.46	0.57	0.19	0.52	0.52	0.52
With FP	0.01	N/A	0.44	0.05	0.06	0.37	0.53	0.32	0.48	0.48	0.48
With LP	0.01	0.03	N/A	0.01	0.13	0.21	0.33	0.26	0.12	0.13	0.13
With LL	0.05	0.08	0.29	N/A	0.08	0.19	0.29	0.35	0.23	0.32	0.32
With ST	0.09	0.04	0.15	0.01	N/A	0.16	0.42	0.33	0.44	0.44	0.44
With HP	0.04	0.01	0.21	0.19	0.04	N/A	0.07	0.21	0.48	0.48	0.48
With KP	0.01	0.01	0.45	0.29	0.04	0.40	N/A	0.40	0.01	0.05	0.05
With STy	0.31	0.13	0.26	0.01	0.01	0.24	0.07	N/A	0.48	0.48	0.48
With EC	0.01	0.01	0.71	0.34	0.08	0.01	0.57	0.01	N/A	0.24	0.24
With ECs	0.01	0.01	0.69	0.23	0.08	0.01	0.53	0.01	0.25		0.24
With ECe	0.01	0.01	0.69	0.23	0.08	0.01	0.53	0.01	0.25	0.24	
With BT/ IEC	N/A	0.53	0.93	0.60	0.85	0.46	0.66	0.29	0.60	0.60	0.60
With FP/ IEC	0.04	N/A	0.56	0.10	0.22	0.35	0.55	0.40	0.60	0.51	0.51
With LP/ IEC	0.01	0.02		0.003	0.22	0.13	0.18	0.28	0.18	0.10	0.10
With LL/ IEC	0.04	0.08	0.48	N/A	0.20	0.07	0.10	0.48	0.45	0.16	0.16
With ST/ IEC	0.03	0.02	0.28	0.01	N/A	0.38	0.46	0.46	0.49	0.37	0.37

Scenario	BT	FP	LP	LL	ST	HP	KP	STy	EC	ECs	ECe
With HP/ IEC	0.02	0.12	0.47	0.31	0.14	N/A	0.54	0.09	0.60	0.51	0.51
With KP/ IEC	0.002	0.001	0.65	0.53	0.13	0.001	N/A	0.22	0.08	0.001	0.001
With STy/ IEC	0.28	0.17	0.50	0.06	0.10	0.48	0.36	N/A	0.60	0.60	0.60
With EC/ IEC	0.001	0.001	0.77	0.19	0.18	0.001	0.56	0.001	N/A	0.30	0.26
With ECs/ IEC	0.002	0.001	0.75	0.45	0.25	0.001	0.57	0.002	0.30	N/A	0.26
With ECe/ IEC	0.002	0.001	0.75	0.45	0.25	0.001	0.57	0.002	0.33	0.26	N/A
Scenario	**BT**	**FP**	**LP**	**LL**	**ST**	**HP**	**KP**	**STy**	**EC**	**ECs**	**ECe**
Protein diet, with oxygen											
Single	0.58	0.12	0.42	0.07	0.06	0.26	0.55	0.53	0.69	0.67	0.67
With IEC	0.63	0.19	0.62	0.14	0.26	0.61	0.69	0.71	0.82	0.79	0.79
With BT	N/A	0.04	0.89	0.25	0.25	0.93	0.56	0.71	0.58	0.69	0.69
With FP	0.59	N/A	0.58	0.09	0.12	0.60	0.62	0.66	0.93	0.80	0.80
With LP	0.50	0.03	N/A	0.01	0.28	0.39	0.63	0.48	0.53	0.55	0.55
With LL	0.40	0.10	0.46	N/A	0.15	0.34	0.40	0.55	0.69	0.67	0.67
With ST	0.40	0.06	0.19	0.01	N/A	0.36	0.50	0.49	0.64	0.62	0.62
With HP	0.07	0.02	0.39	0.34	0.09	N/A	0.08	0.41	0.05	0.05	0.05
With KP	0.21	0.03	0.63	0.40	0.08	0.56	N/A	0.53	0.65	0.63	0.63
With STy	0.10	0.03	0.48	0.02	0.06	0.41	0.08	N/A	0.70	0.67	0.67
With EC	0.32	0.04	0.89	0.02	0.07	0.76	0.09	0.01	N/A	0.01	0.08
With ECs	0.18	0.02	0.85	0.02	0.07	0.73	0.09	0.01	0.68	N/A	0.22
With ECe	0.18	0.02	0.85	0.02	0.07	0.73	0.09	0.01	0.61	0.45	N/A
With BT/ IEC	N/A	0.04	1.08	0.31	0.30	0.93	0.68	0.75	0.51	0.70	0.70
With FP/ IEC	0.69	N/A	0.67	0.13	0.33	0.73	0.68	0.77	1.04	0.88	0.88
With LP/ IEC	0.40	0.03	N/A	0.01	0.46	0.39	0.68	0.64	0.57	0.51	0.51
With LL/ IEC	0.42	0.12	0.62	N/A	0.33	0.28	0.50	0.69	0.81	0.79	0.79
With ST/ IEC	0.42	0.03	0.24	0.02	N/A	0.76	0.57	0.61	0.70	0.68	0.68
With HP/ IEC	0.06	0.01	0.67	0.47	0.23	N/A	0.09	0.31	0.05	0.05	0.05
With KP/ IEC	0.15	0.06	0.82	0.50	0.18	0.73	N/A	0.66	0.77	0.75	0.75
With STy/ IEC	0.13	0.05	0.79	0.03	0.14	0.72	0.10	N/A	0.83	0.80	0.80
With EC/ IEC	0.46	0.07	1.00	0.04	0.17	0.90	0.09	0.01	N/A	0.02	0.001
With ECs/ IEC	0.23	0.03	0.98	0.03	0.16	0.87	0.09	0.002	0.80	N/A	0.26
With ECe/ IEC	0.23	0.03	0.98	0.03	0.16	0.87	0.09	0.002	0.82	0.53	N/A

Table S6: Description of the ten recurring metabolite exchanges between pairs predicted for the microbe-microbe pairs, and occurance by pair. Pairs that did not display any reoccuring exchanges are not shown.

i) pyruvate/ D-lactate shuttling coupled to NAD^+/NADH interconversion
ii) ethanol/ acetaldehyde shuttling coupled to NAD^+/NADH interconversion
iii) L-alanine/ L-lactate exchange with pyruvate as an intermediate
iv) fumarate/ succinate exchange depending on quinol and NAD^+/NADH
v) succinate/ malate exchange depending on quinol and FAD/ FADH2 or NAD^+/NADH
vi) glutamate/ citrate exchange depending on transamination
vii) acetate/ butyrate exchange depending on acetyl-CoA and butyryl-CoA
viii) acetate/ dihydroxyacetone exchange via pyruvate and acetyl-CoA as intermediates
ix) threonine/ glycine interconversion via acetaldehyde
x) 2,3-butandiol/ diacetyl interconversion via R-acetoin

	# scenarios containing crossfeeding exchanges per pair										
Pair	**(i) Pyruvate/ D-lactate**	**(ii) Acetaldehyde/ Ethanol**	**(iii) L-alanine/ L-lactate**	**(iv) Fumarate/ Succinate**	**(v) Malate/ Succinate**	**(vi) Citrate/ Glutamate**	**(vii) Acetate/ Butyrate**	**(viii) Acetate/ Dihydroxyacetone**	**(ix) Glycine/ Threonine**	**(x) 2,3-butandiol/ Diacetyl**	**Total # of scenarios**
BTFP				8					7		**12**
BTLP	8		8						4		**12**
BTLL			1						1		**12**
BTST			1								**12**
BTSTy	5										**12**
BTEC	1			2							**12**
BTECs	1			2							**12**
BTECe	1			2							**12**
FPLP					12				9		**12**
FPLL									1		**12**
FPST						12					**12**
FPKP					2	1					**12**
FPSTy				6		7					**12**
FPEC				8		8	7				**12**
FPECs				8		8					**12**

FPECe				8		8					**12**
LPST			1					8			**12**
LPHP		6									**6**
LPKP	12	10									**12**
LPSTy	12	11									**12**
LPEC	12	8									**12**
LPECs	12	8									**12**
LPECe	12	8									**12**
LLST			2								**12**
LLHP		6			4						**6**
LLKP		12								12	**12**
LLSTy		11									**12**
LLEC		12									**12**
LLECs		11									**12**
LLECe		11									**12**
STSTy						5		3			**12**
STEC						6					**12**
STECs						5					**12**
STECe						5					**12**
HPKP		2									**6**
HPSTy		2		5							**6**
HPEC		2		2							**6**
HPECs		2		2							**6**
HPECe		2		2							**6**
KPSTy		2									**12**
KPEC		2									**12**
KPECs		2									**12**
KPECe		2									**12**

Table S7: Co-occurances of the ten metabolite exchanges described in Table S6 in all 600 pairs grouped by type of interaction. Co-occuring exchanges that were not computed in any pairs are not shown.

Exchange co-occurances summed up for predicted interactions	Parasitism (n=299)	Commensalism (n=22)	Neutralism (n=1)	Amensalism (n=175)	Competition (n=66)	Mutualism (n=37)
Average # of exchange co-occurances/ pair	0.29	0.38	0	0.03	0.09	1.05
Pyruvate/ D-lactate + Acetaldehyde/ Ethanol	10	4		2		29
Pyruvate/ D-lactate + L-alanine/ L-lactate	6					1
Pyruvate/ D-lactate + Fumarate/ Succinate	2					
Pyruvate/ D-lactate + Glycine/ Threonine	2					1
Acetaldehyde/ Ethanol + Fumarate/ Succinate	8					
Acetaldehyde/ Ethanol + Malate/ Succinate	3					1
Acetaldehyde/ Ethanol + 2,3-butandiol/ Diacetyl	6				6	
L-alanine/ L-lactate + Acetate/ Dihydroxyacetone	1					
L-alanine/ L-lactate + Glycine/ Threonine	3					1
Fumarate/ Succinate + Citrate/ Glutamate	26	1				2
Fumarate/ Succinate + Acetate/ Butyrate	4	1				2
Fumarate/ Succinate + Glycine/ Threonine	4	1				
Malate/ Succinate + Glycine/ Threonine	7			2		
Citrate/ Glutamate + Acetate/ Butyrate	4	1				2
Citrate/ Glutamate + Acetate/ Dihydroxyacetone	1			1		

Supplemental Figures

Figure S1: Pareto optimality analysis of all possible pairs in every scenario.

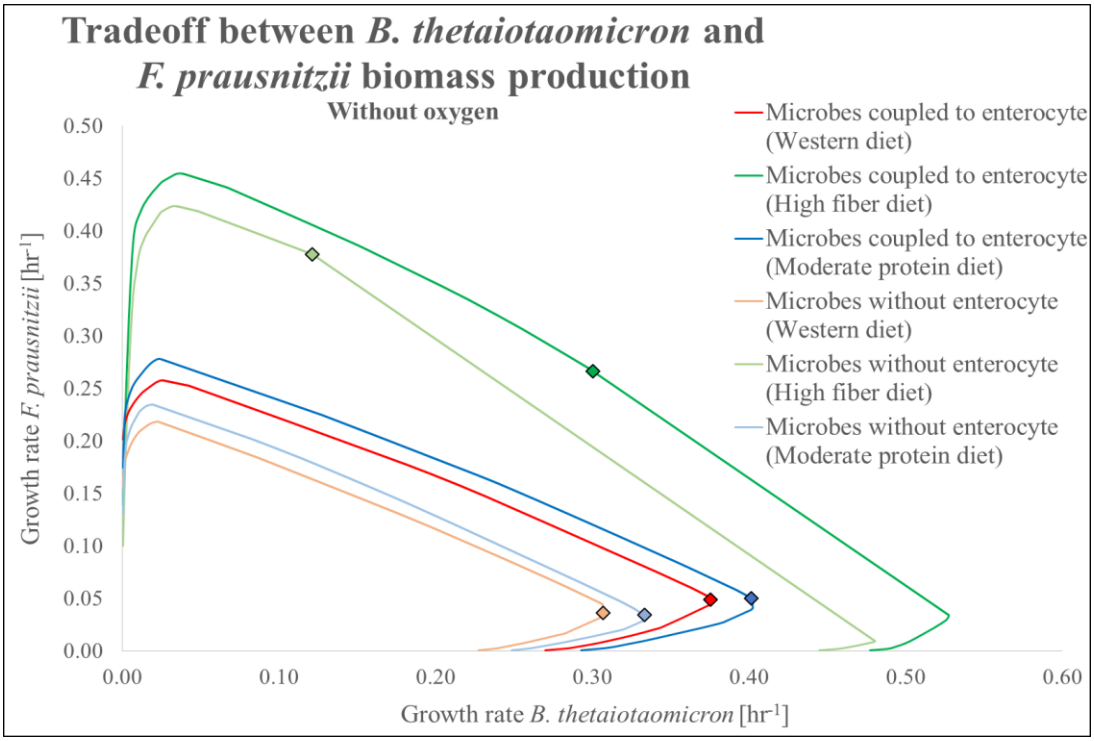


Figure S1.1

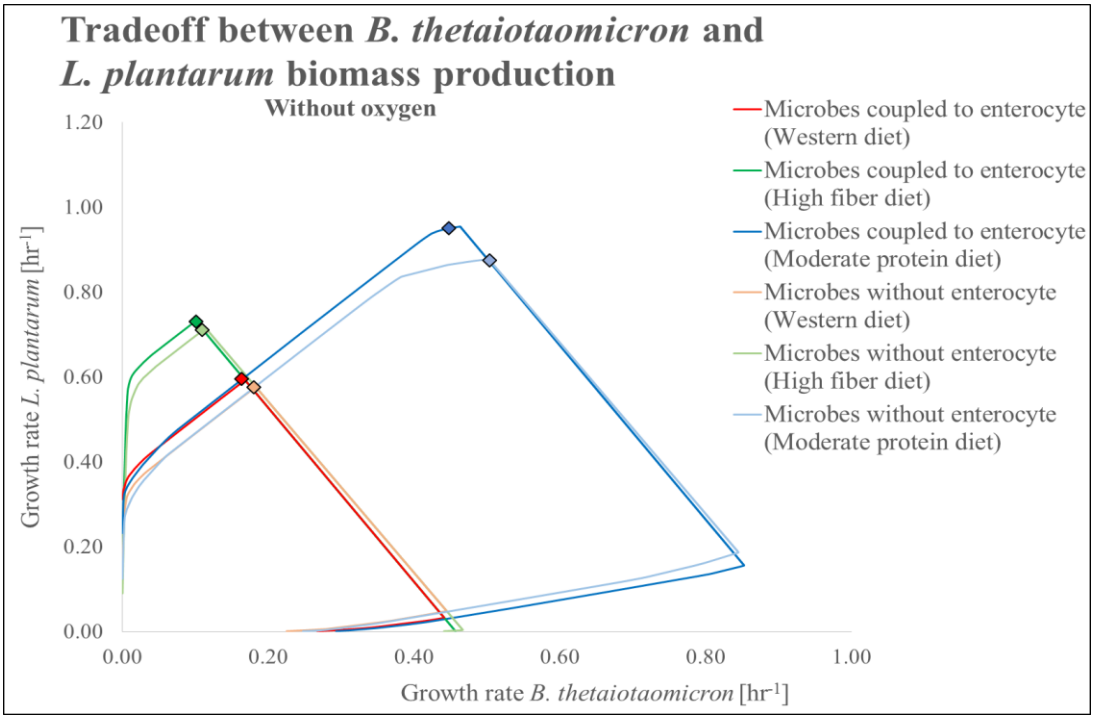


Figure S1.2

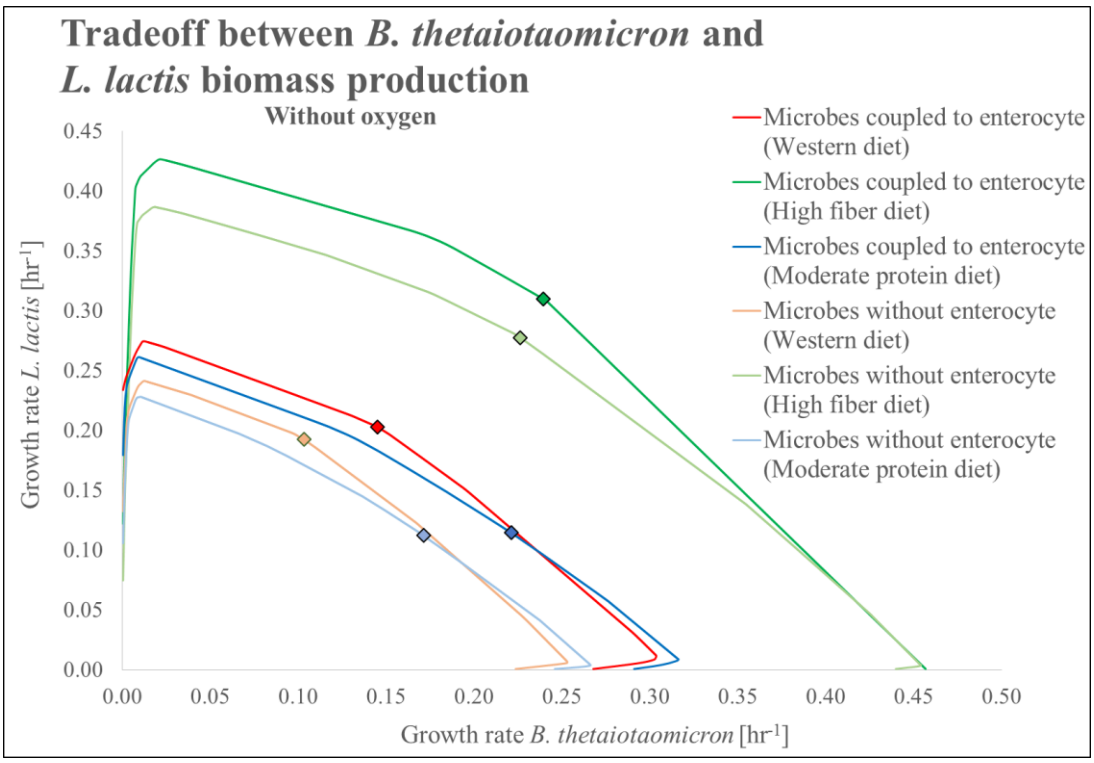


Figure S1.3

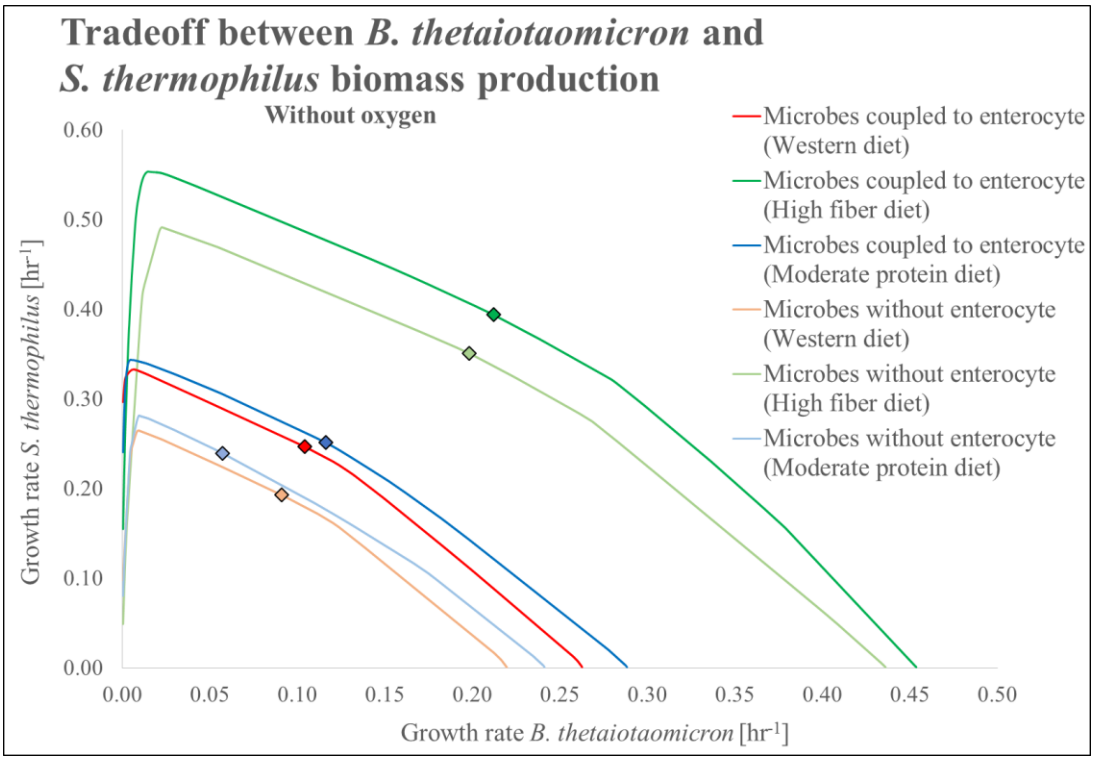


Figure S1.4

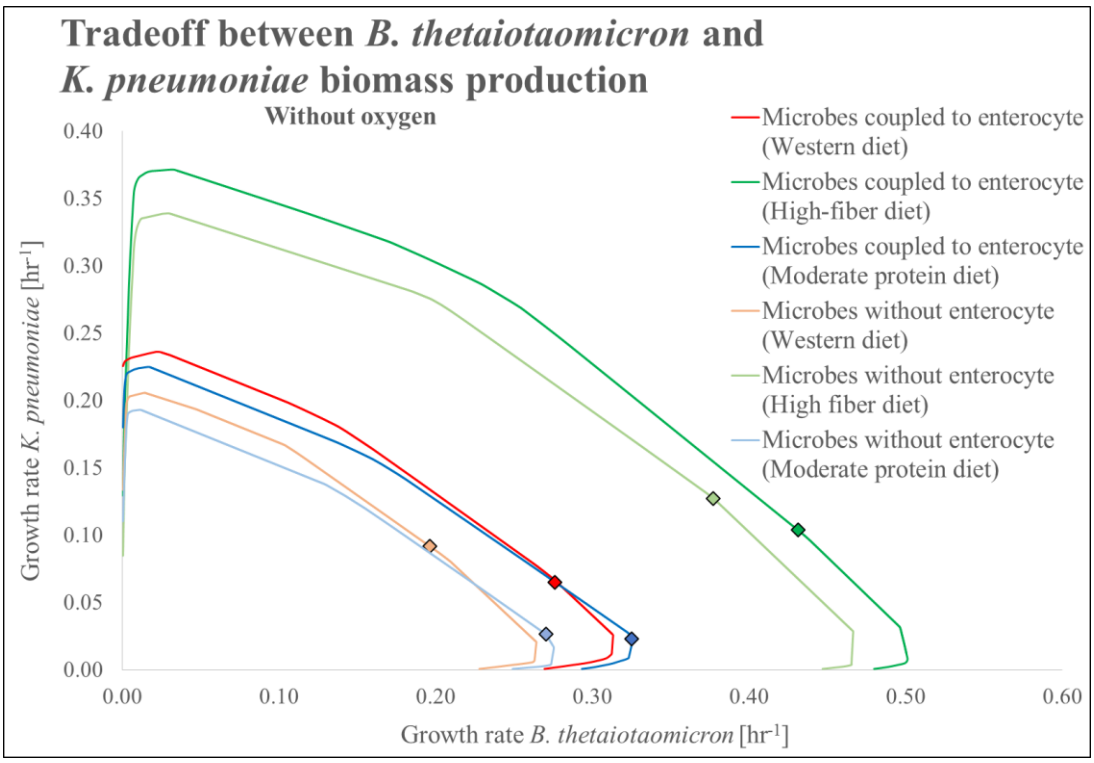


Figure S1.5

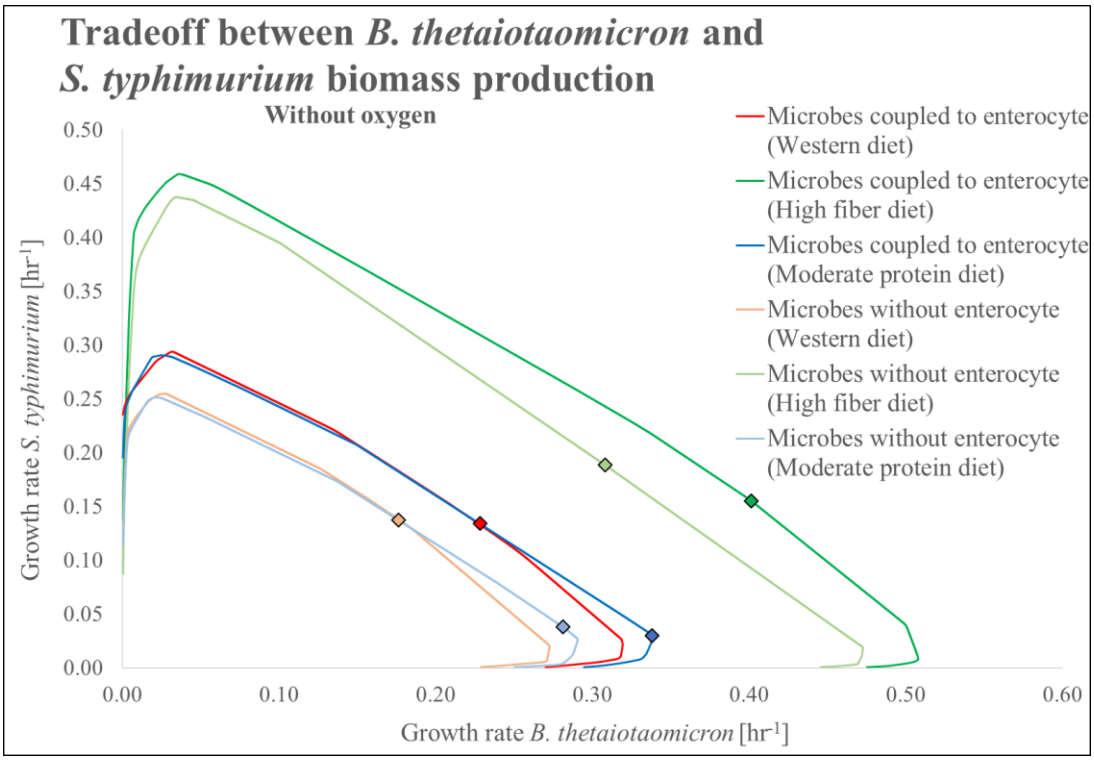


Figure S1.6

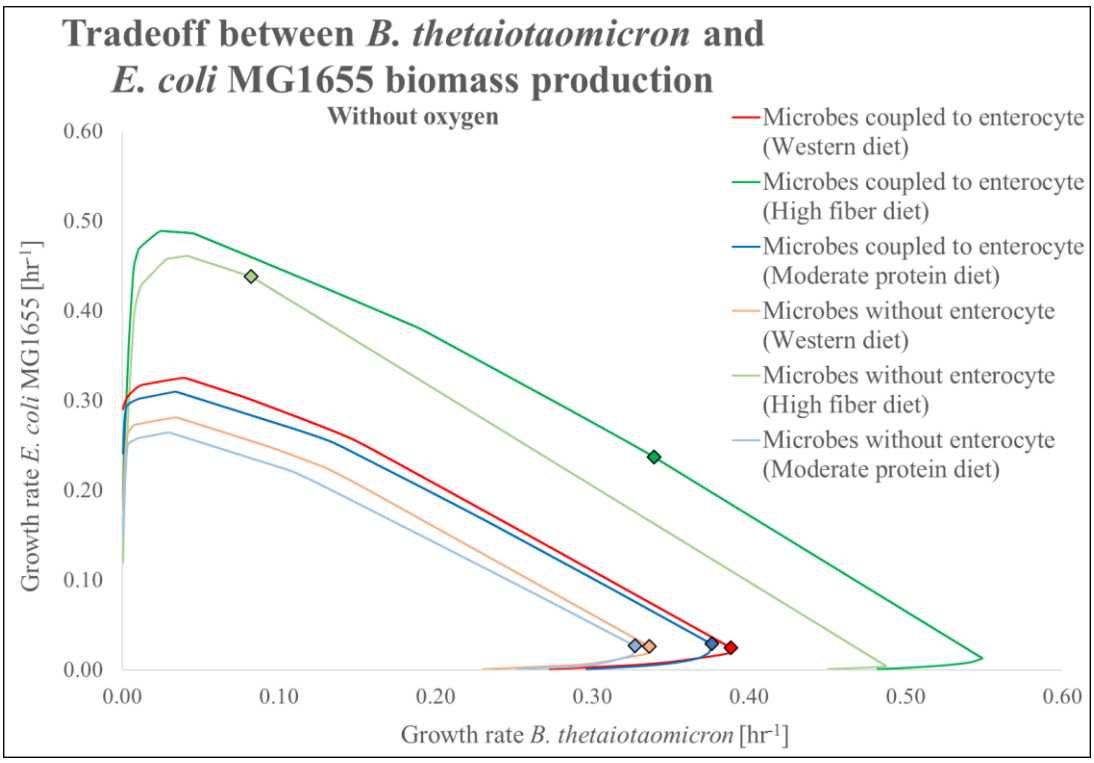


Figure S1.7

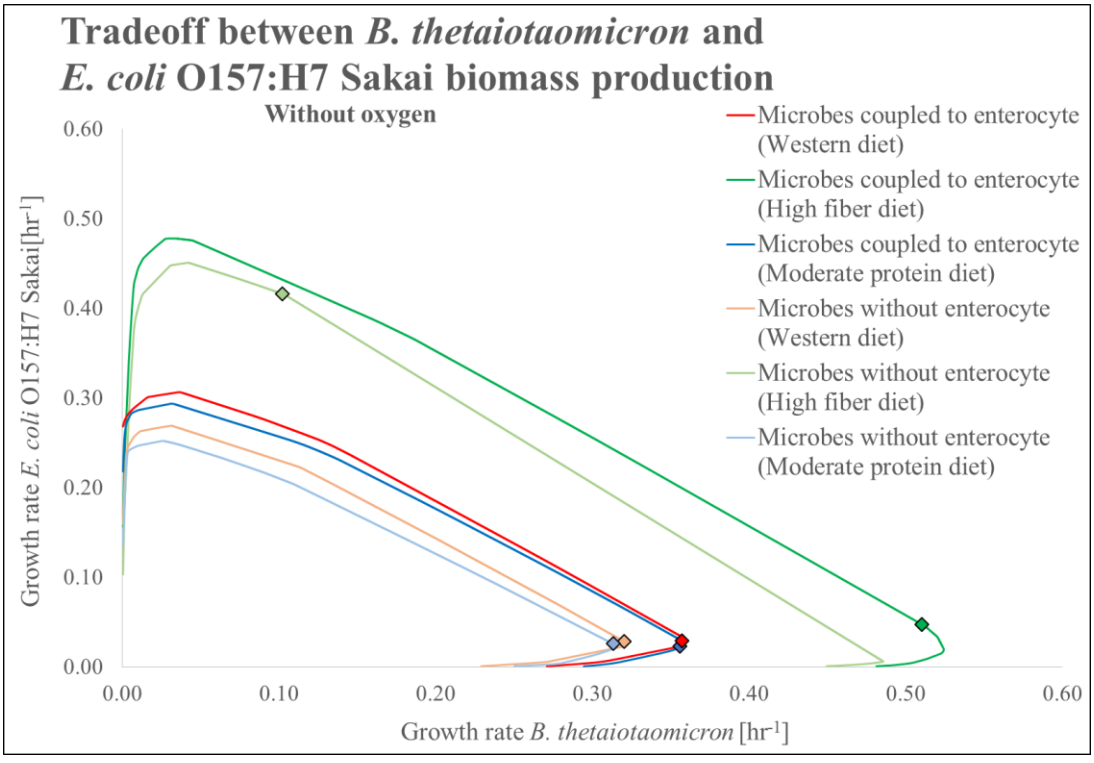


Figure S1.8

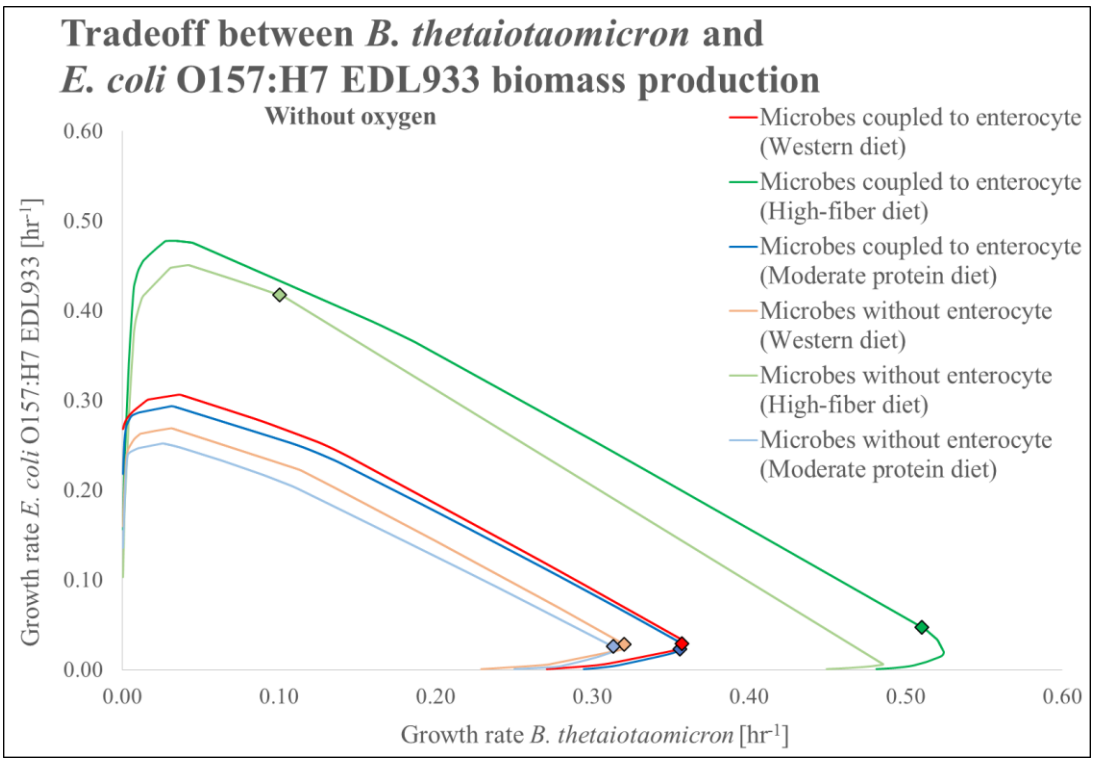


Figure S1.9

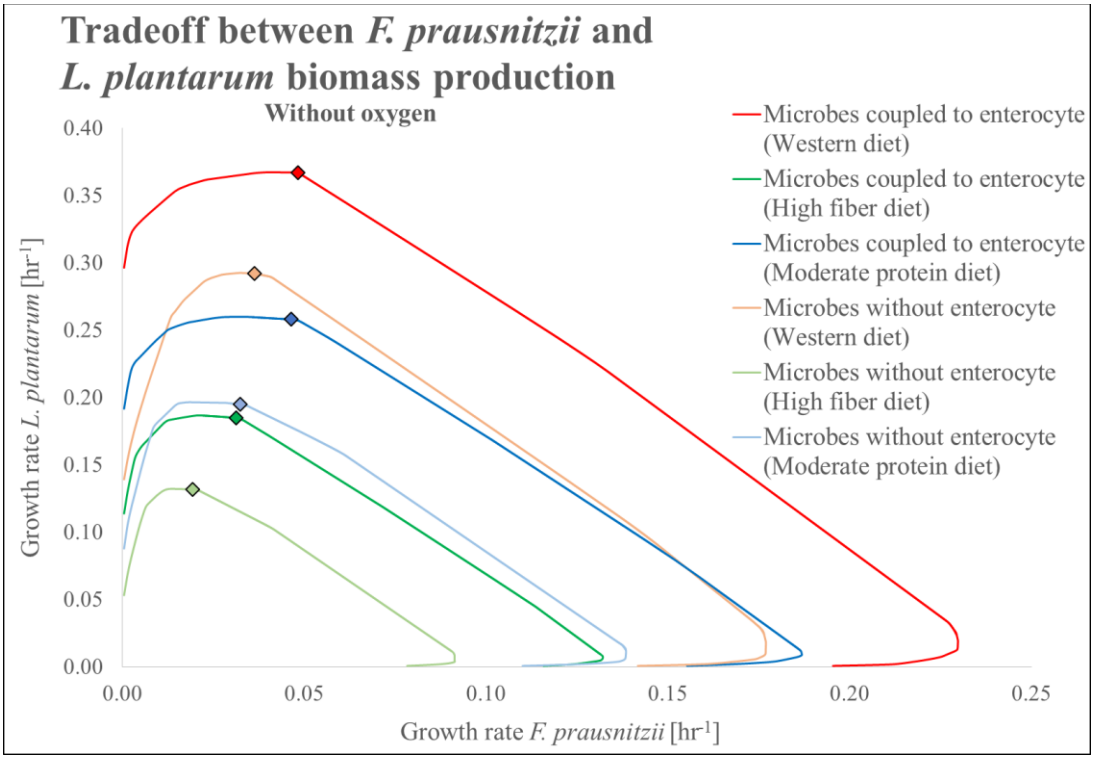


Figure S1.10

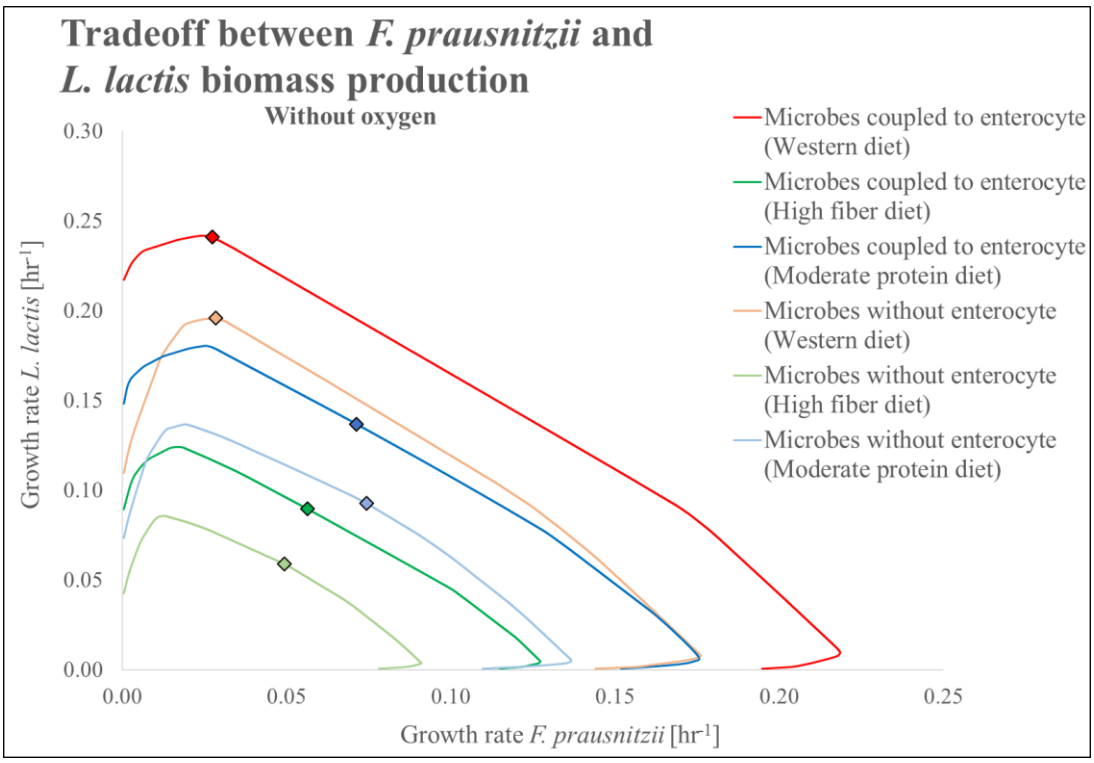


Figure S1.11

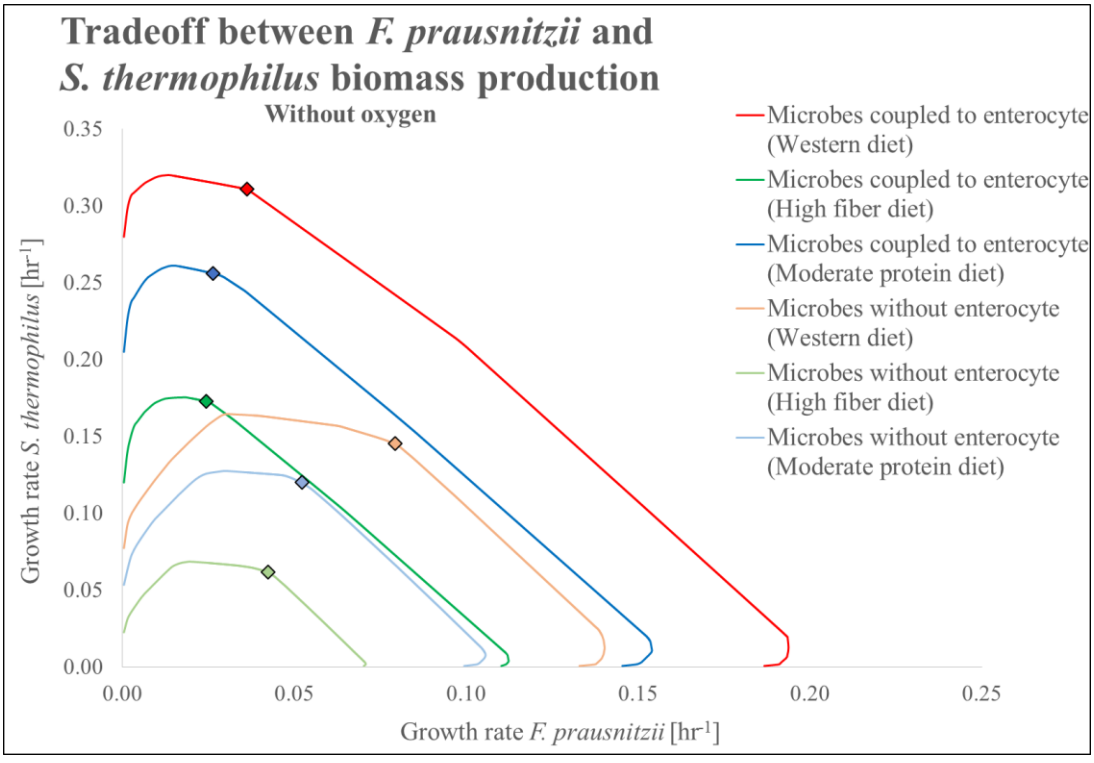


Figure S1.12

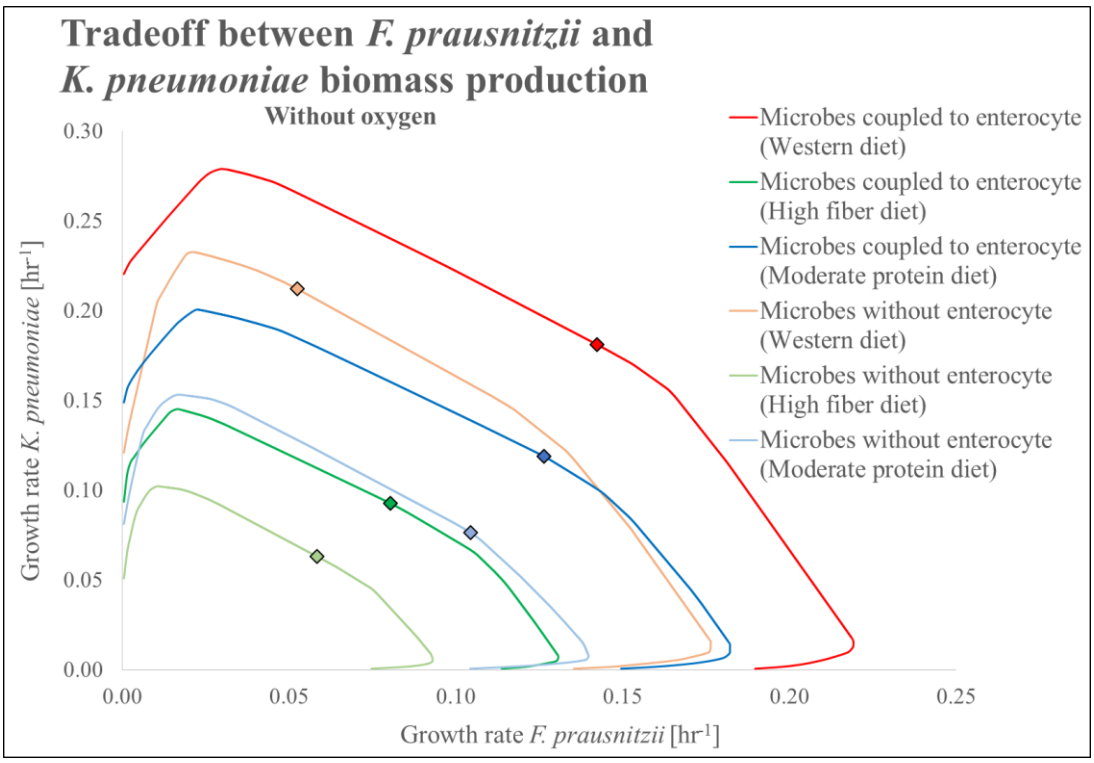


Figure S1.13

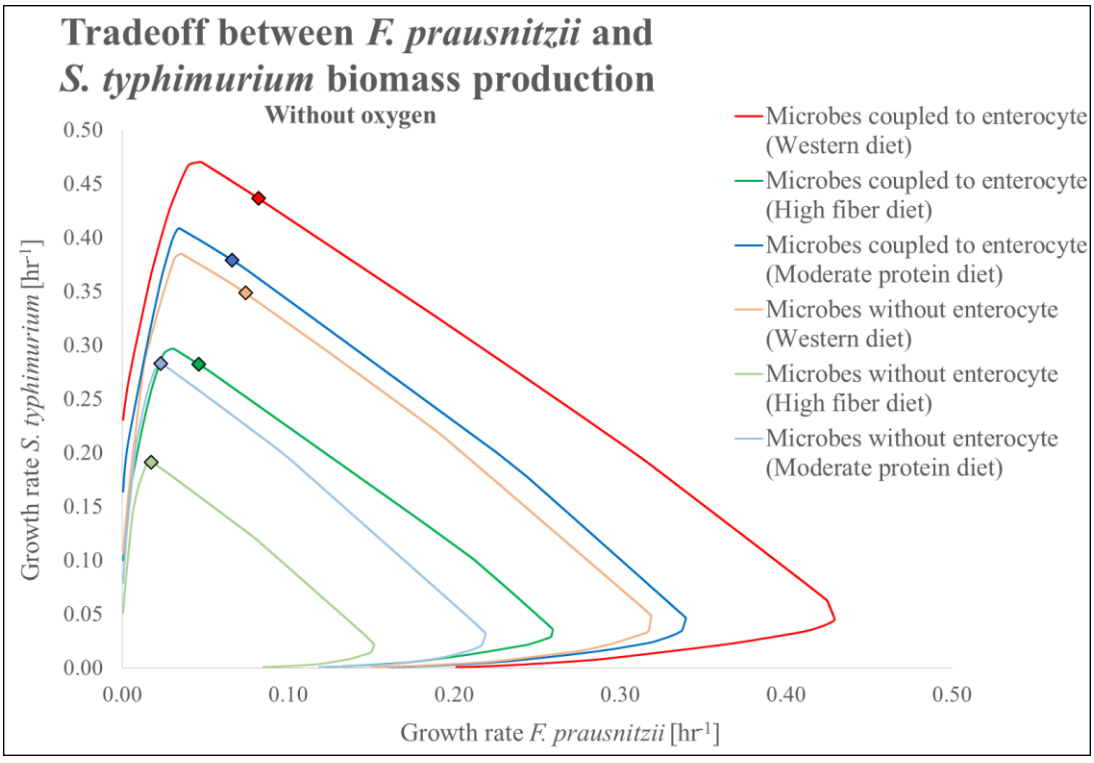


Figure S1.14

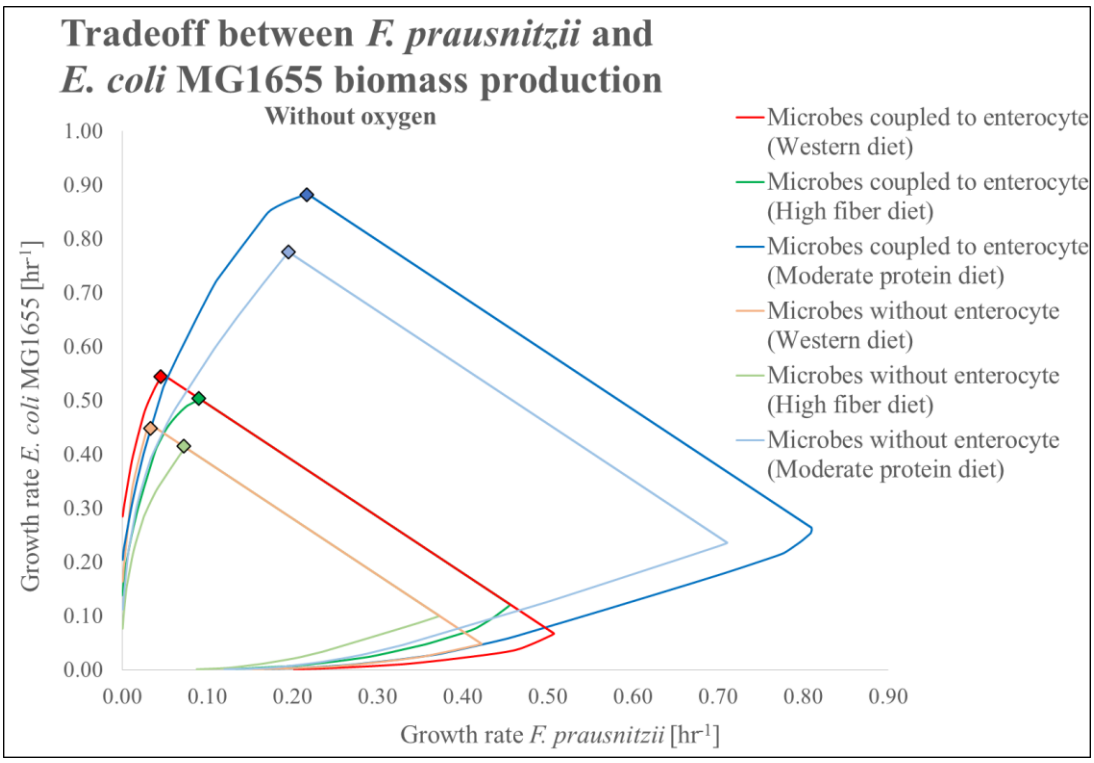


Figure S1.15

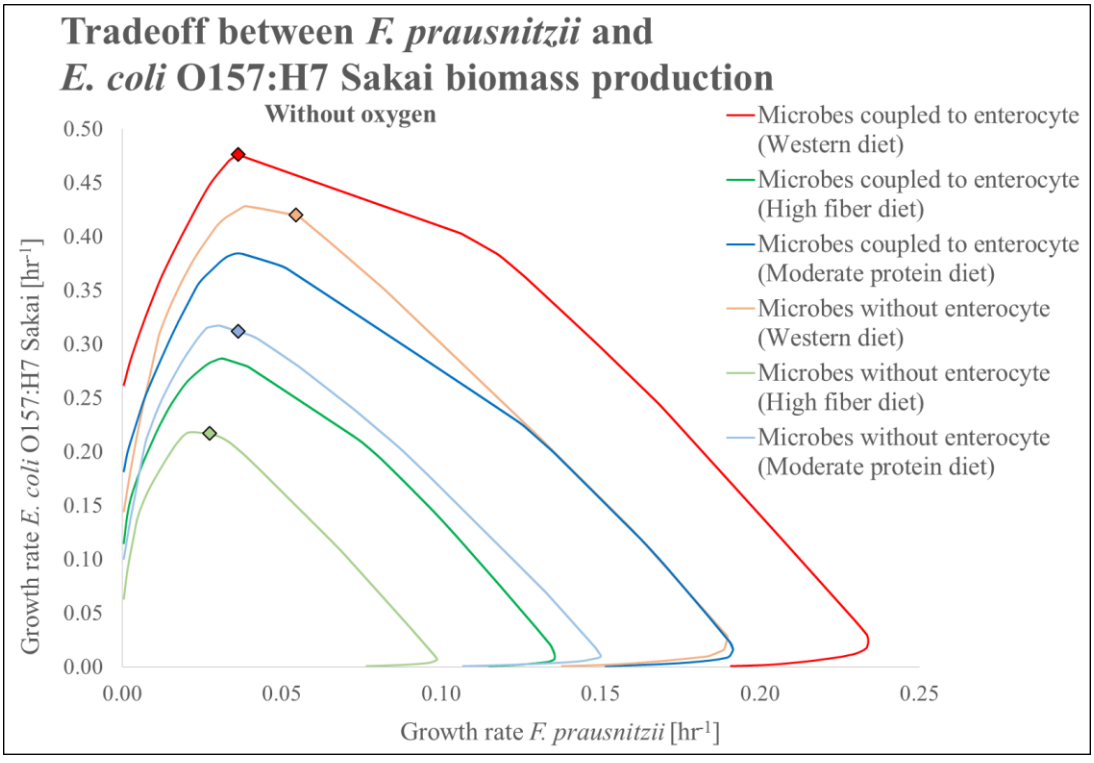


Figure S1.16

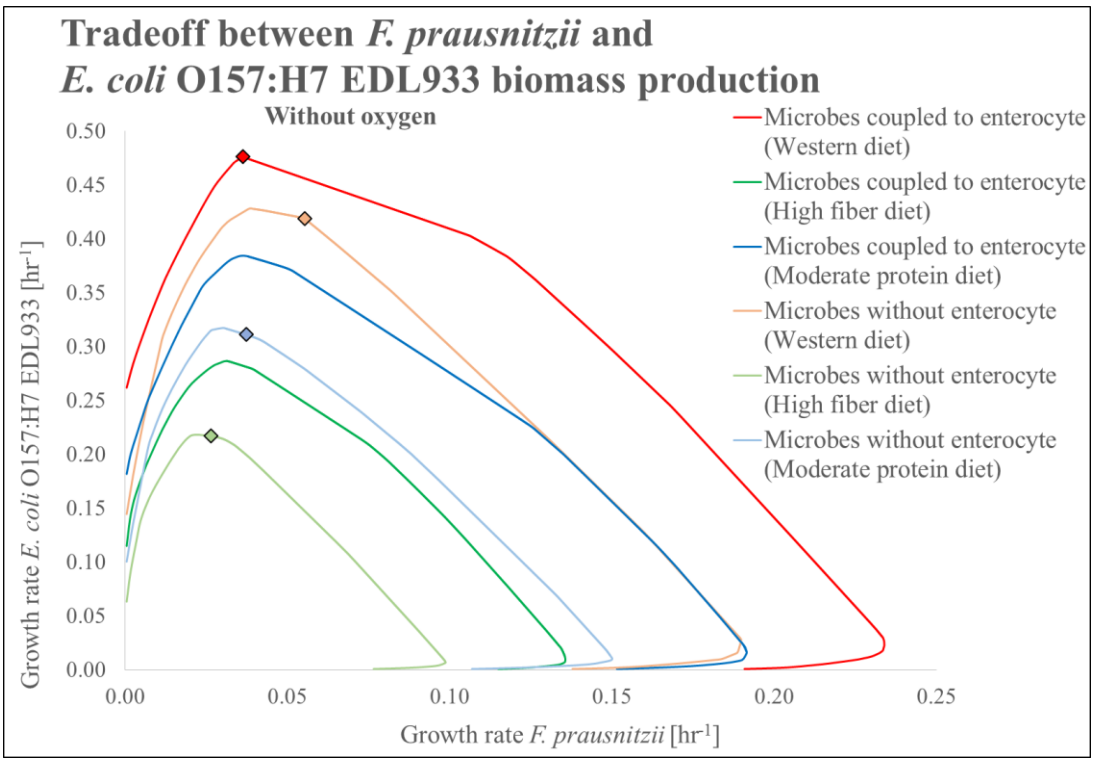


Figure S1.17

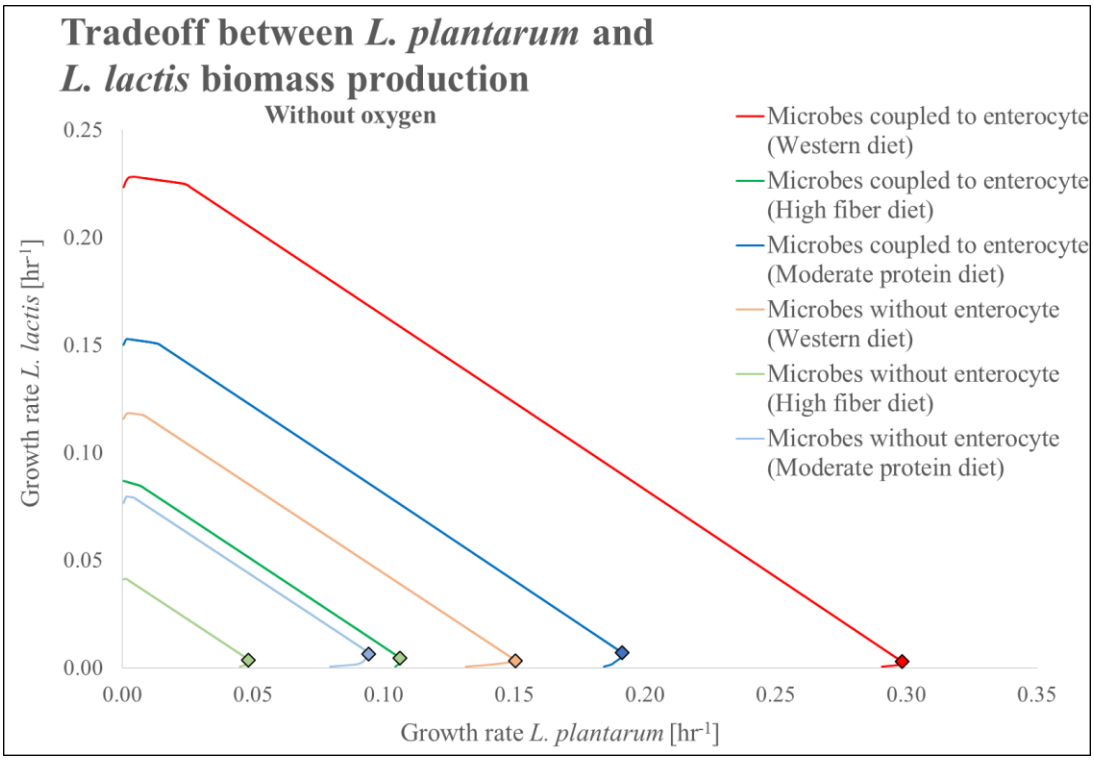


Figure S1.18

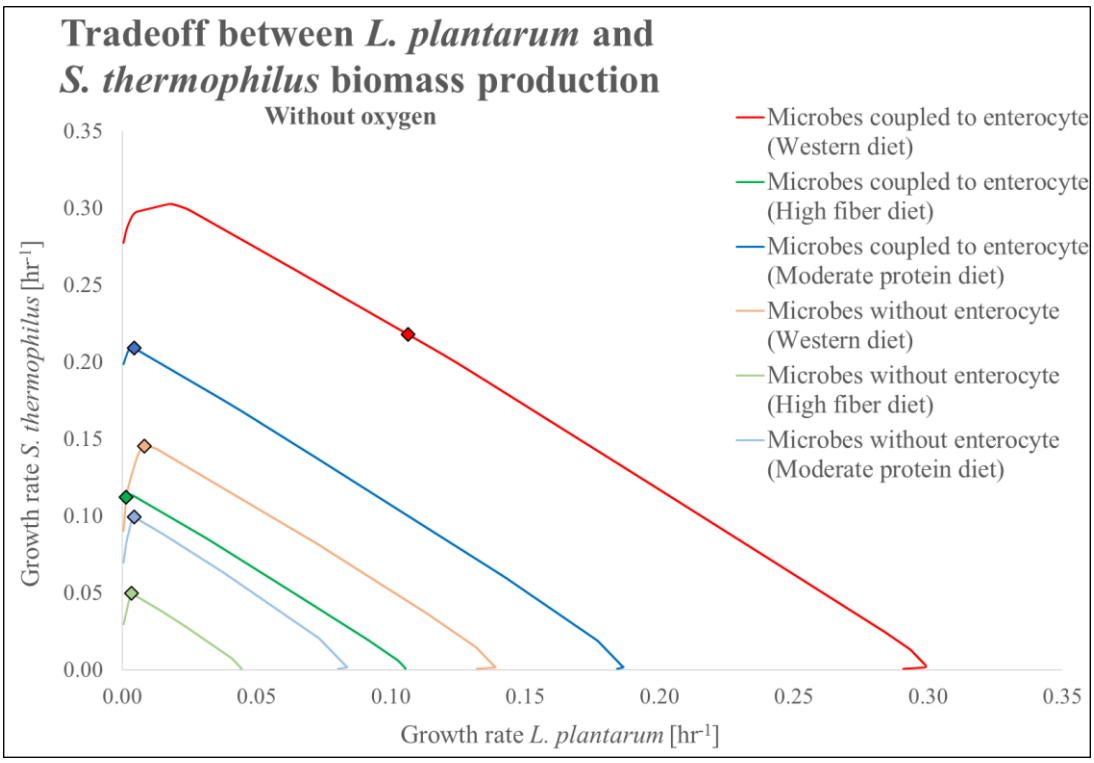


Figure S1.19

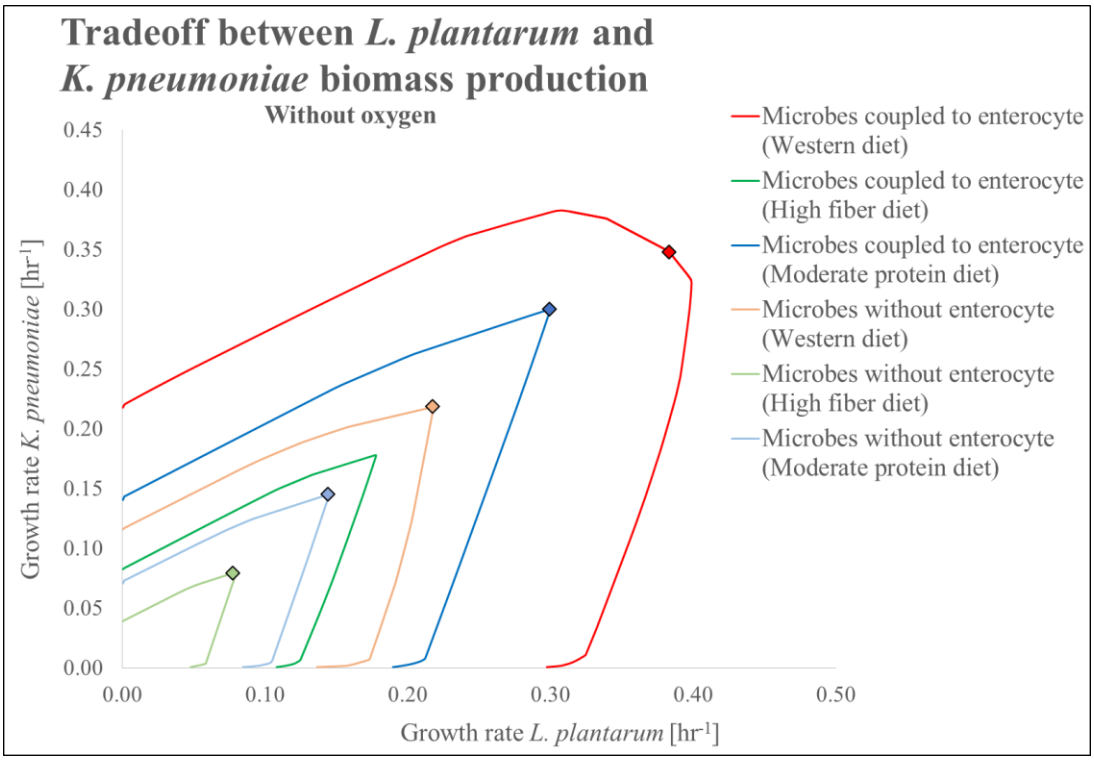


Figure S1.20

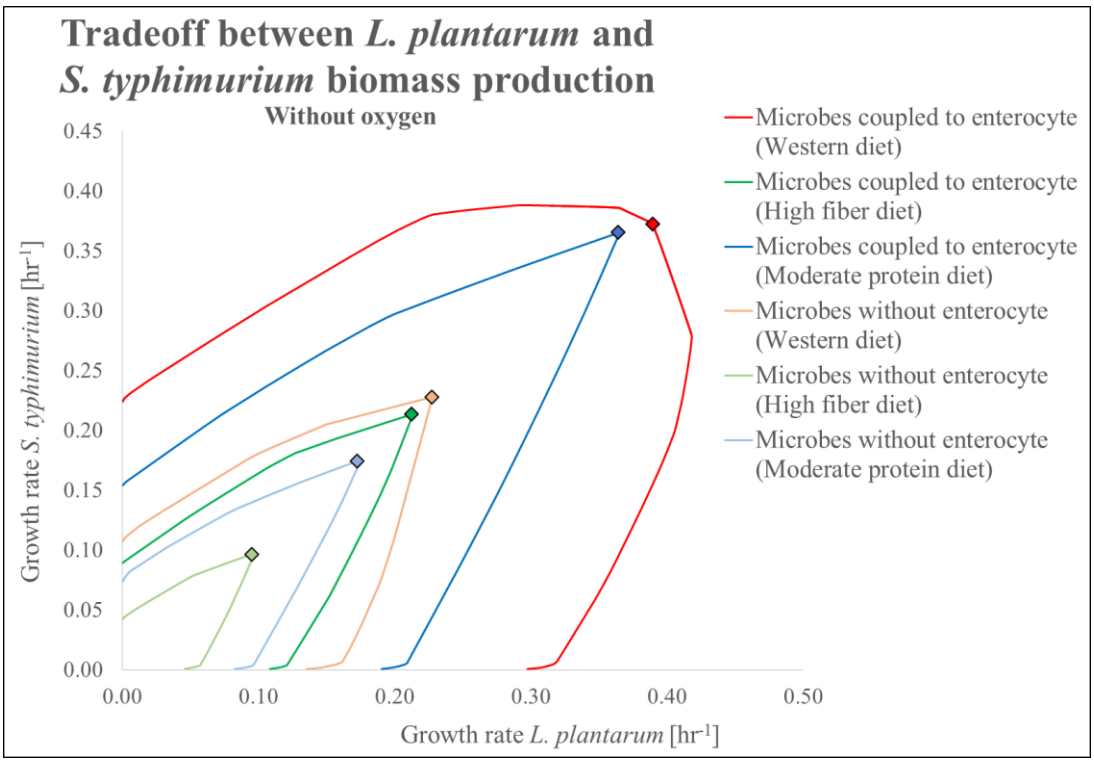


Figure S1.21

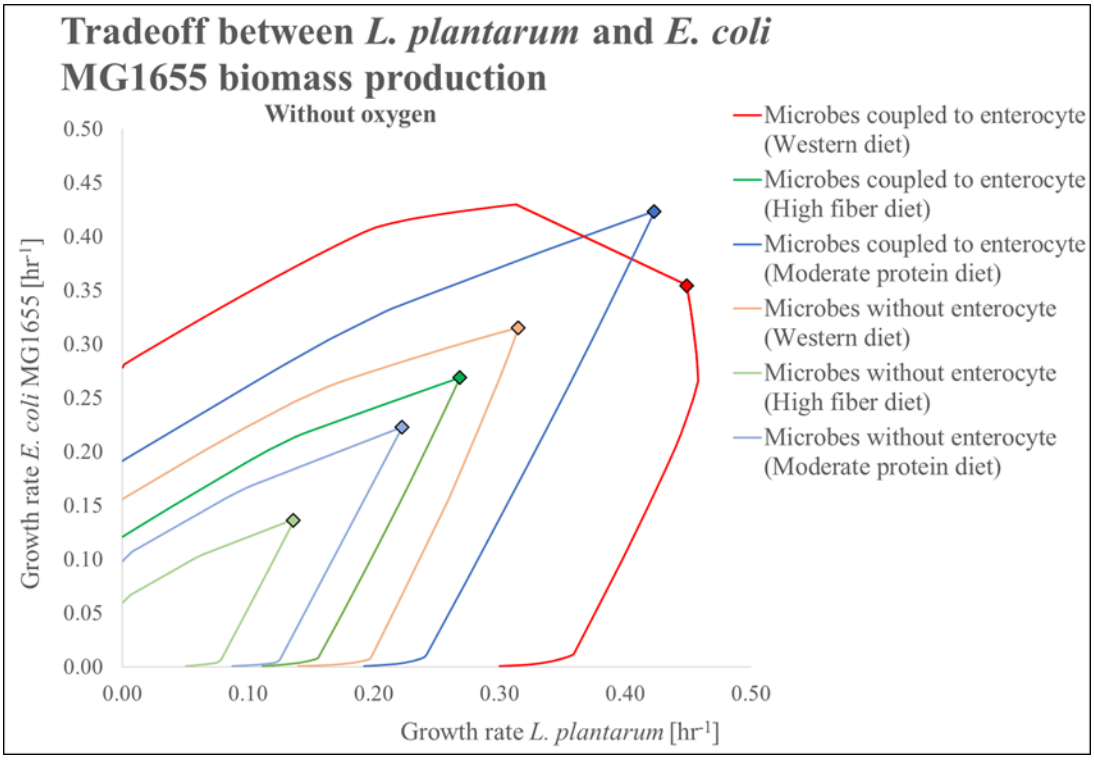


Figure S1.22

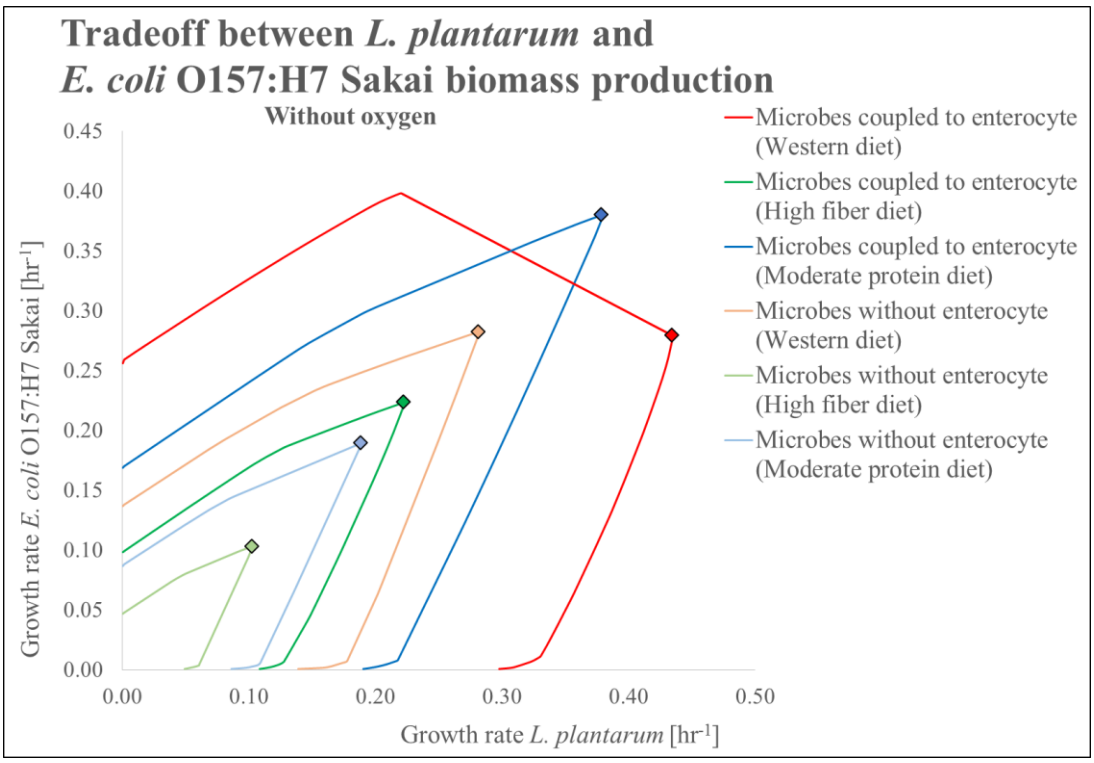


Figure S1.23

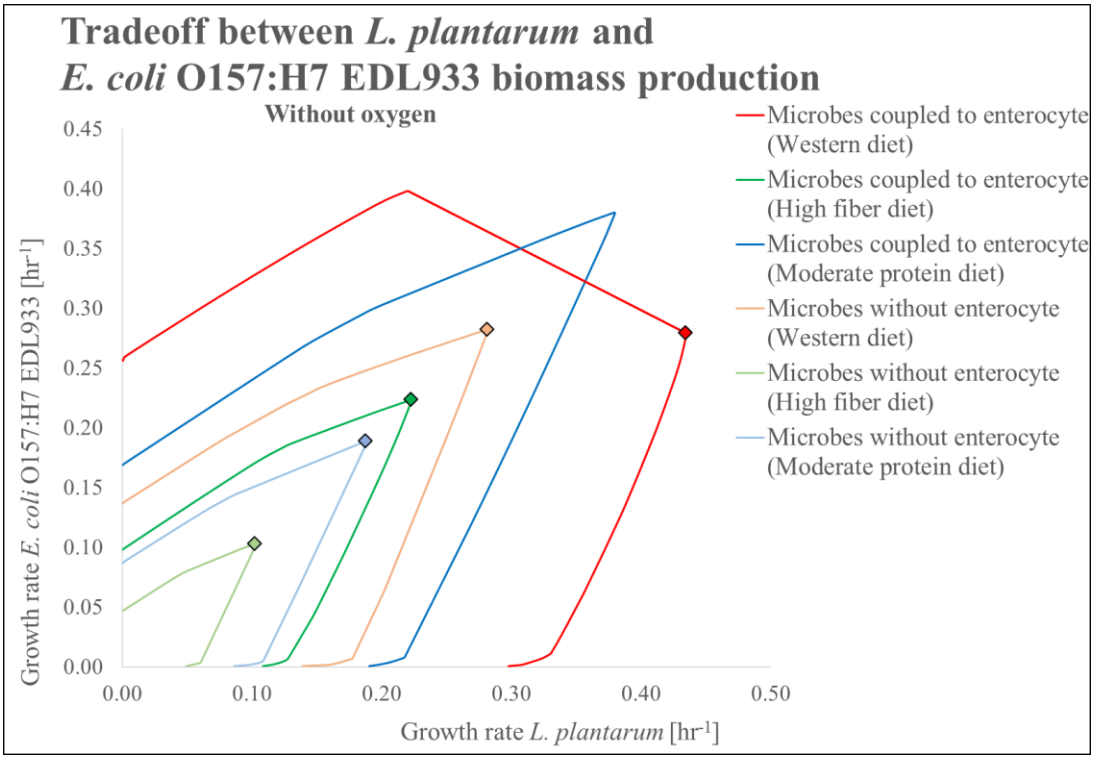


Figure S1.24

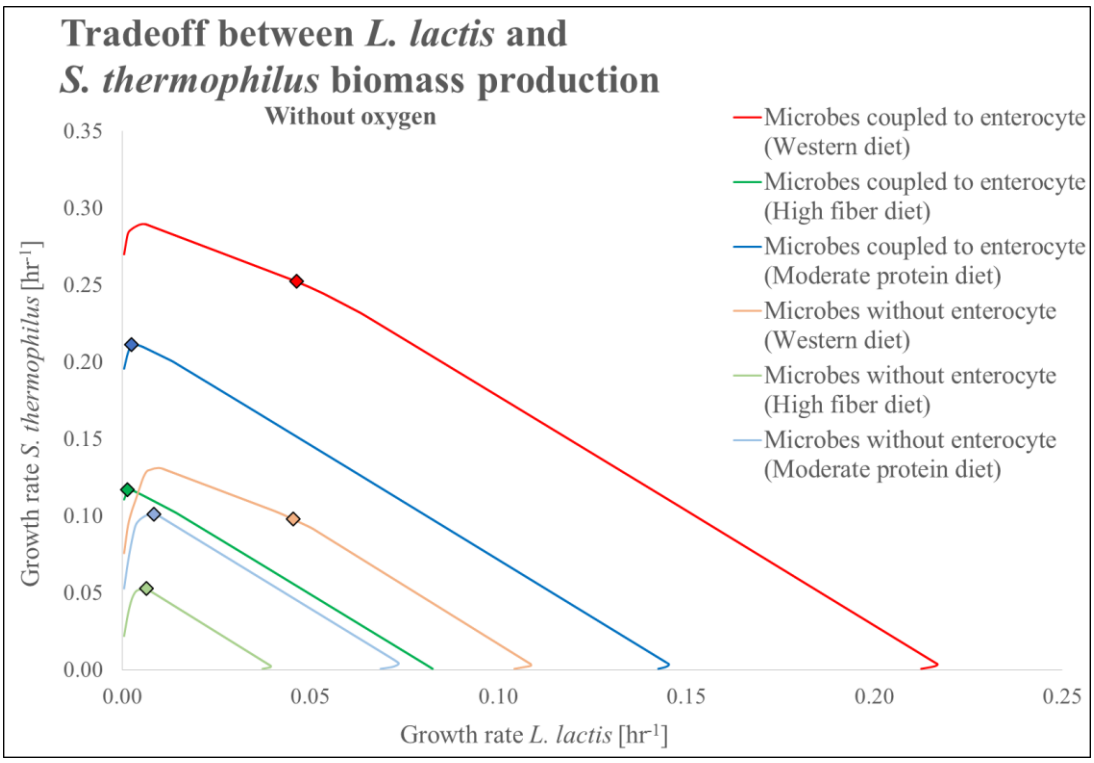


Figure S1.25

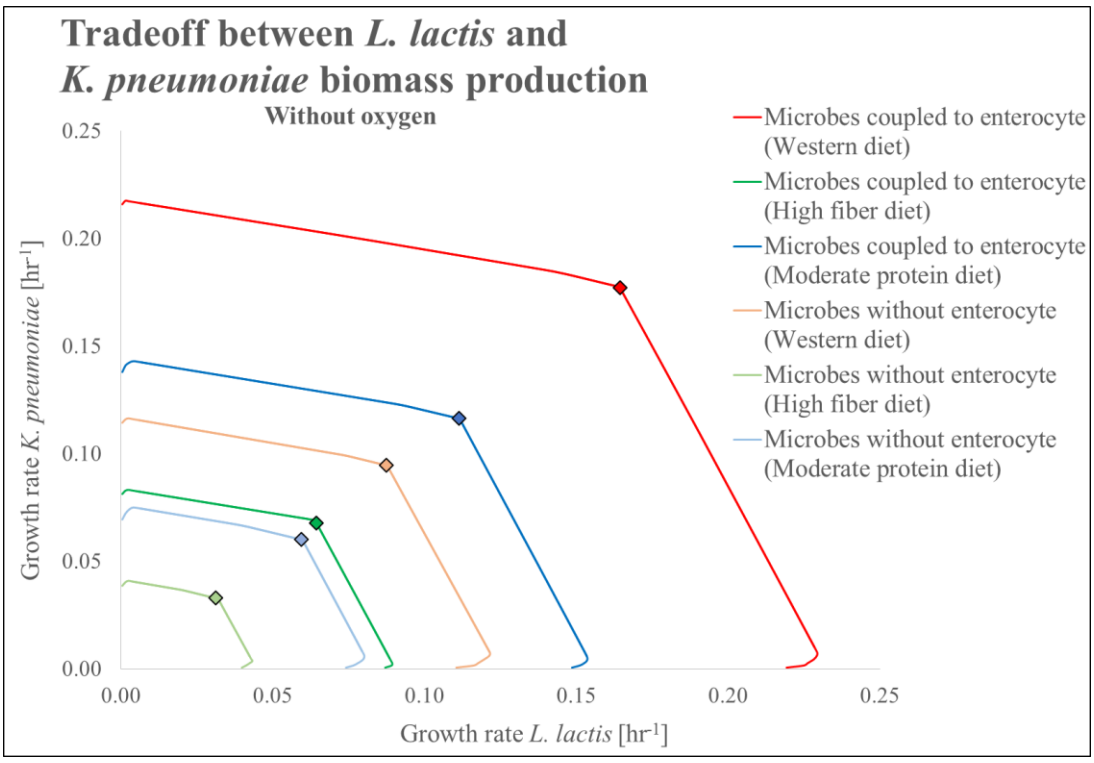


Figure S1.26

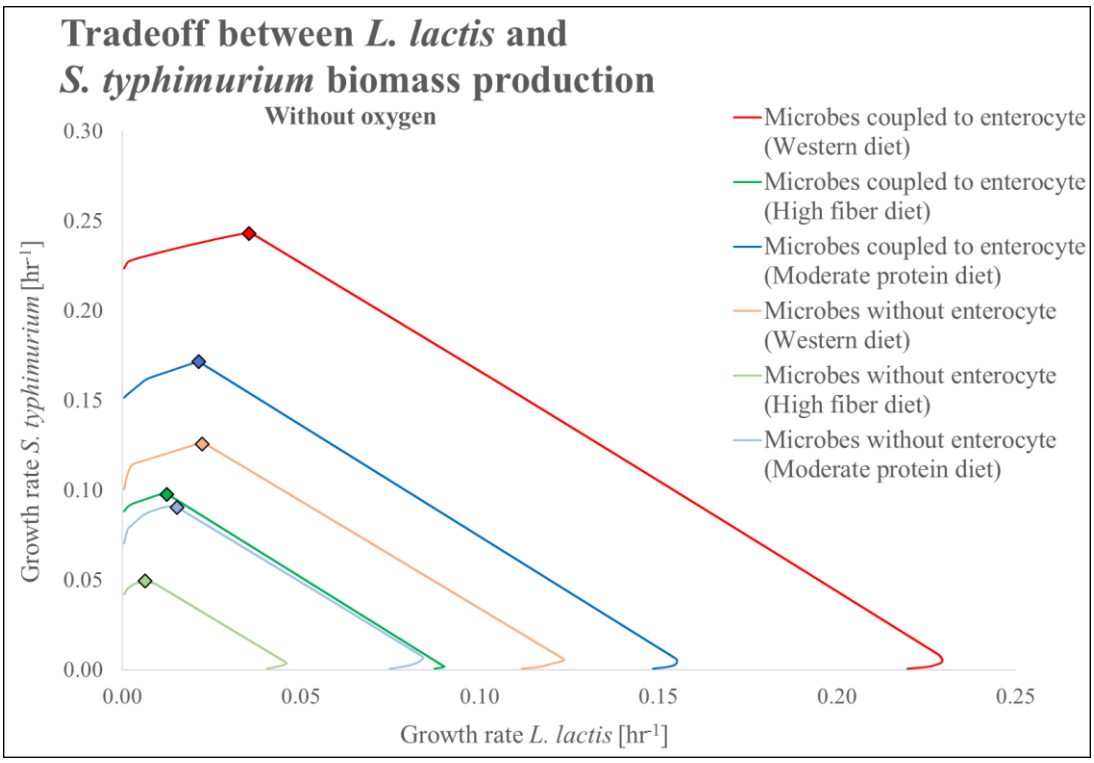


Figure S1.27

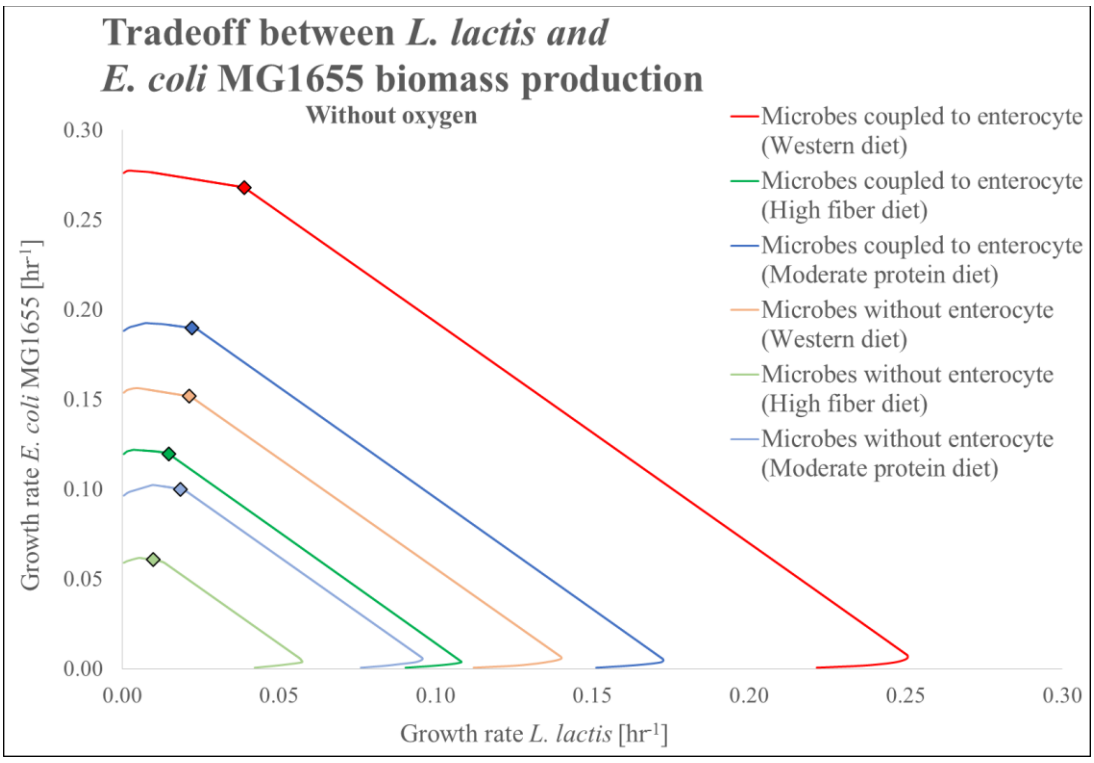
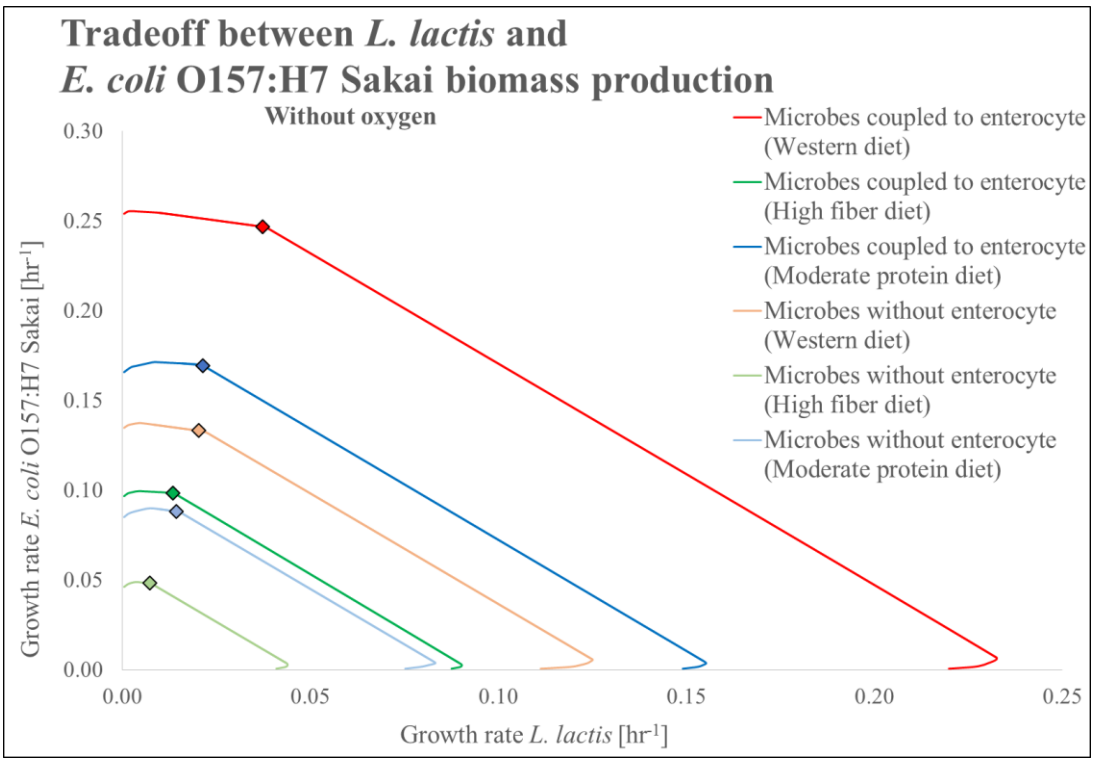


Figure S1.28



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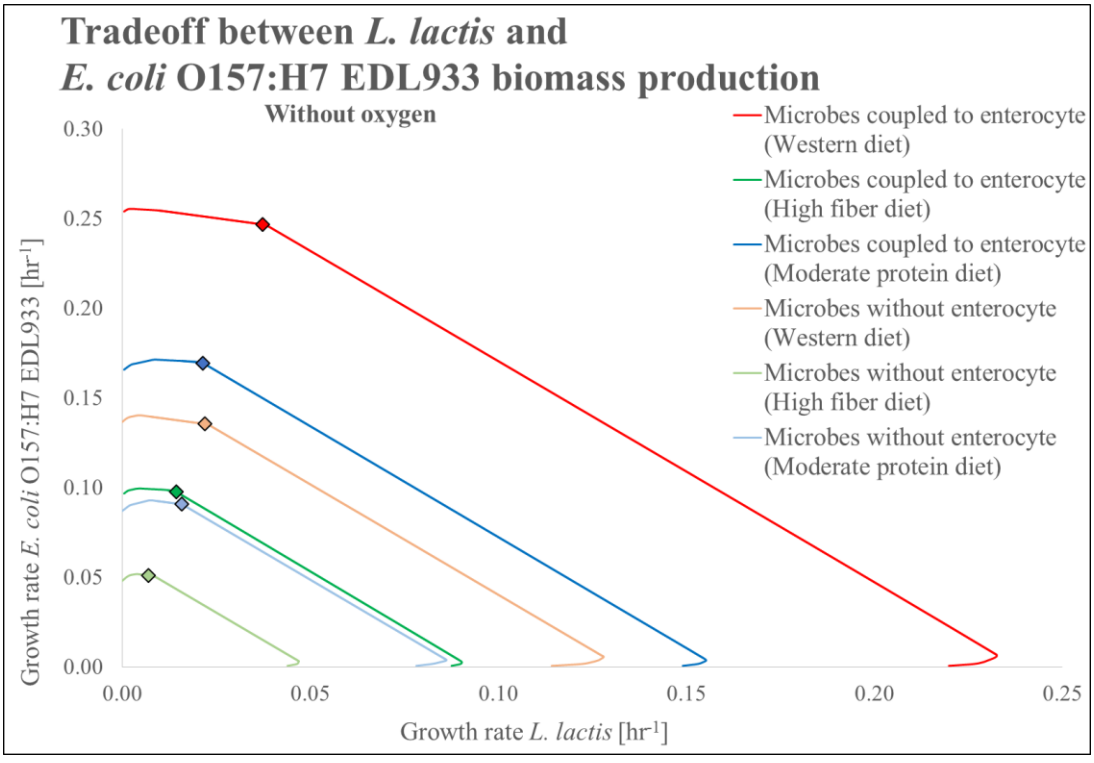

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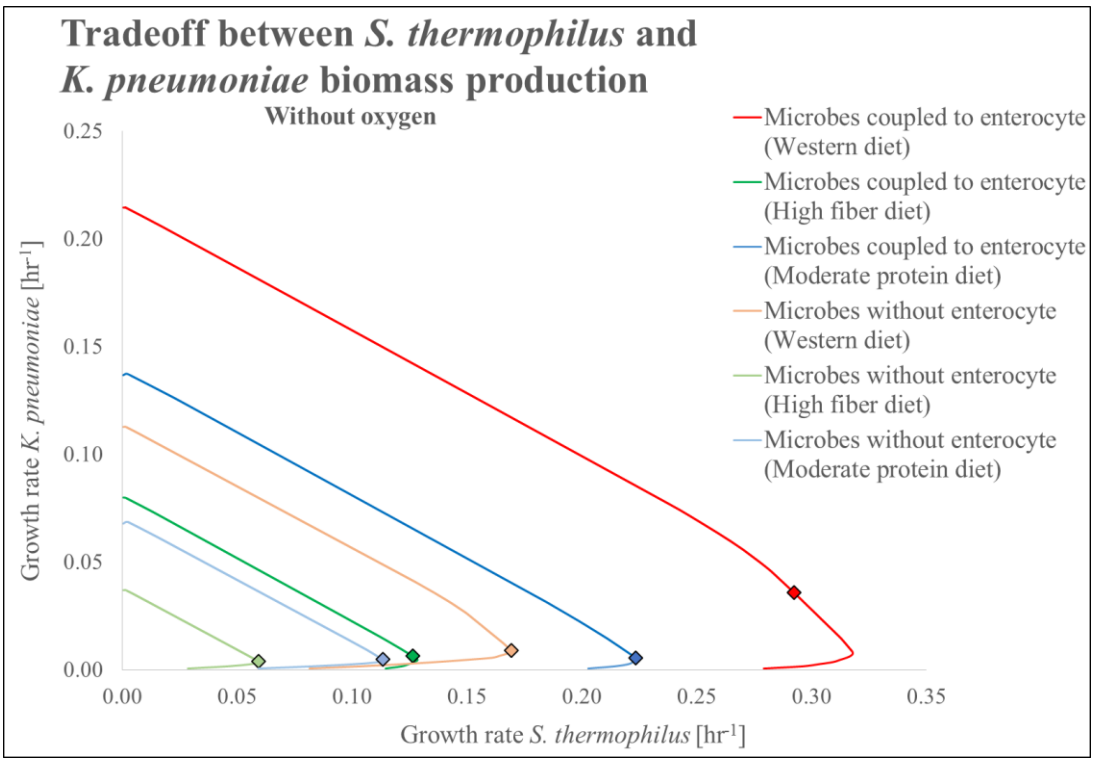

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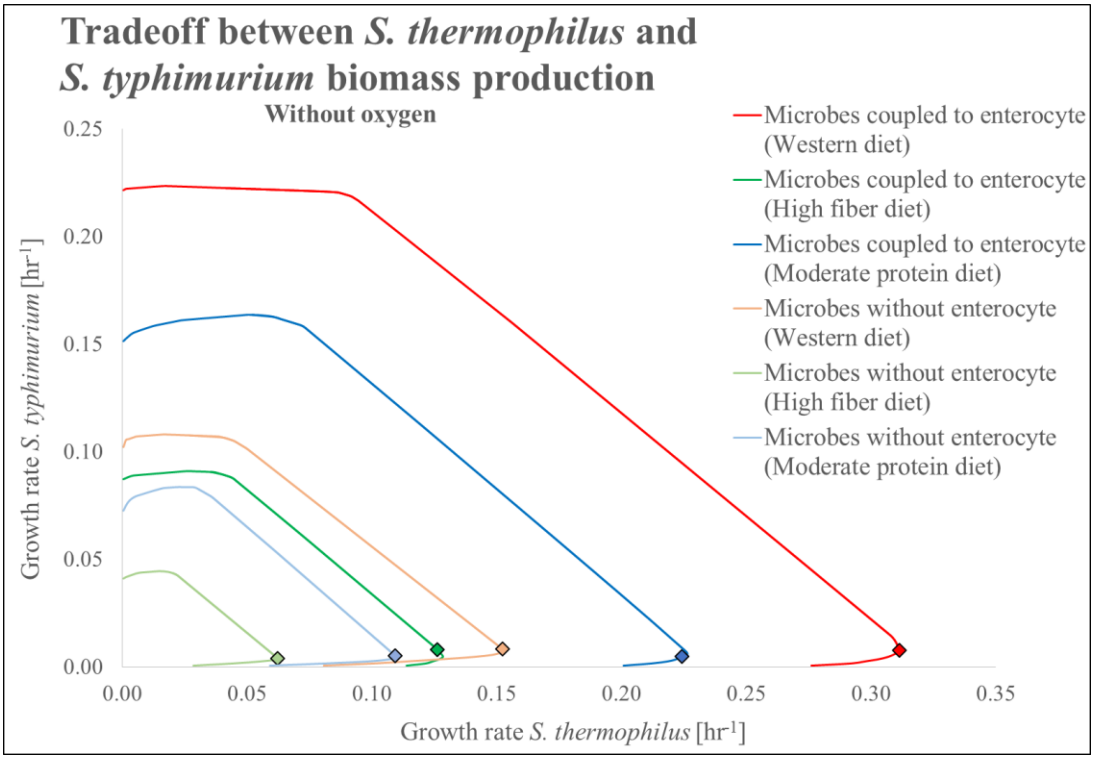

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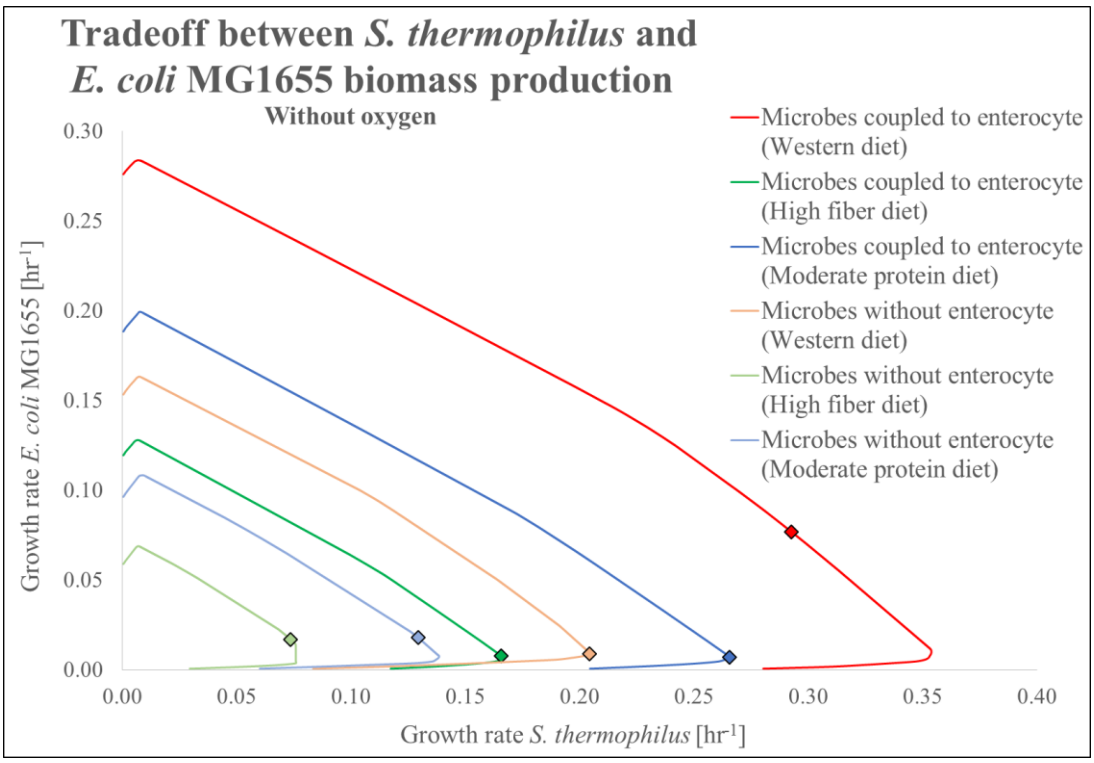

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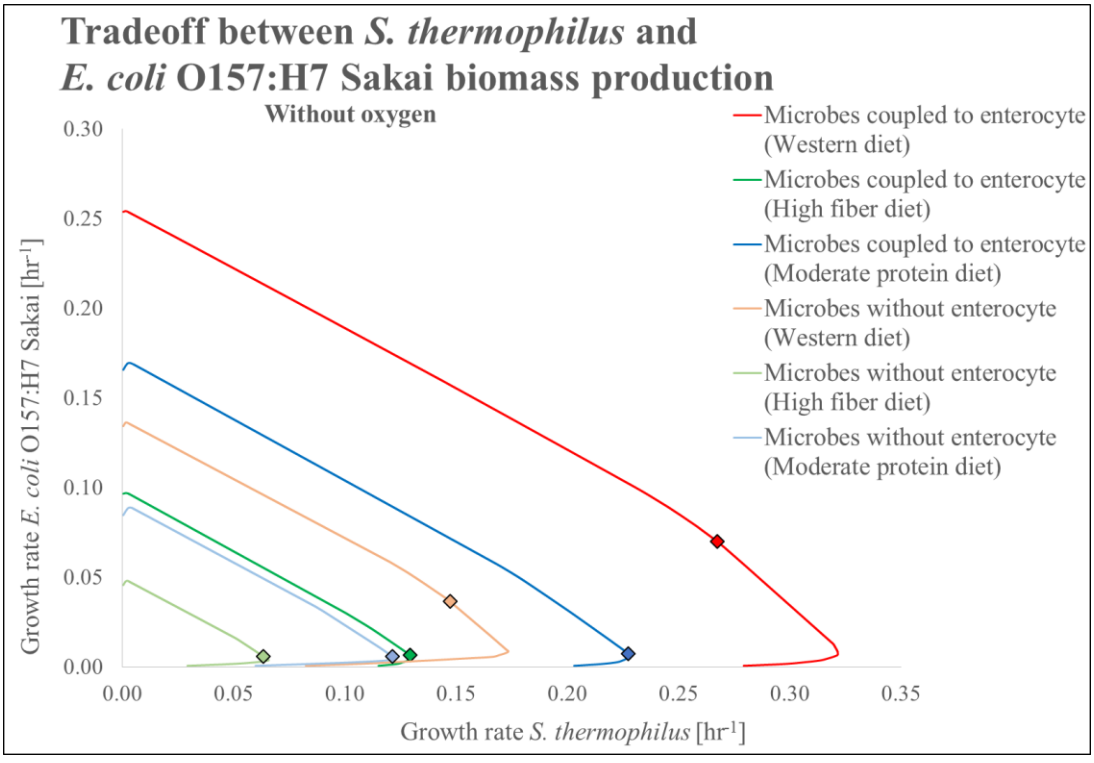

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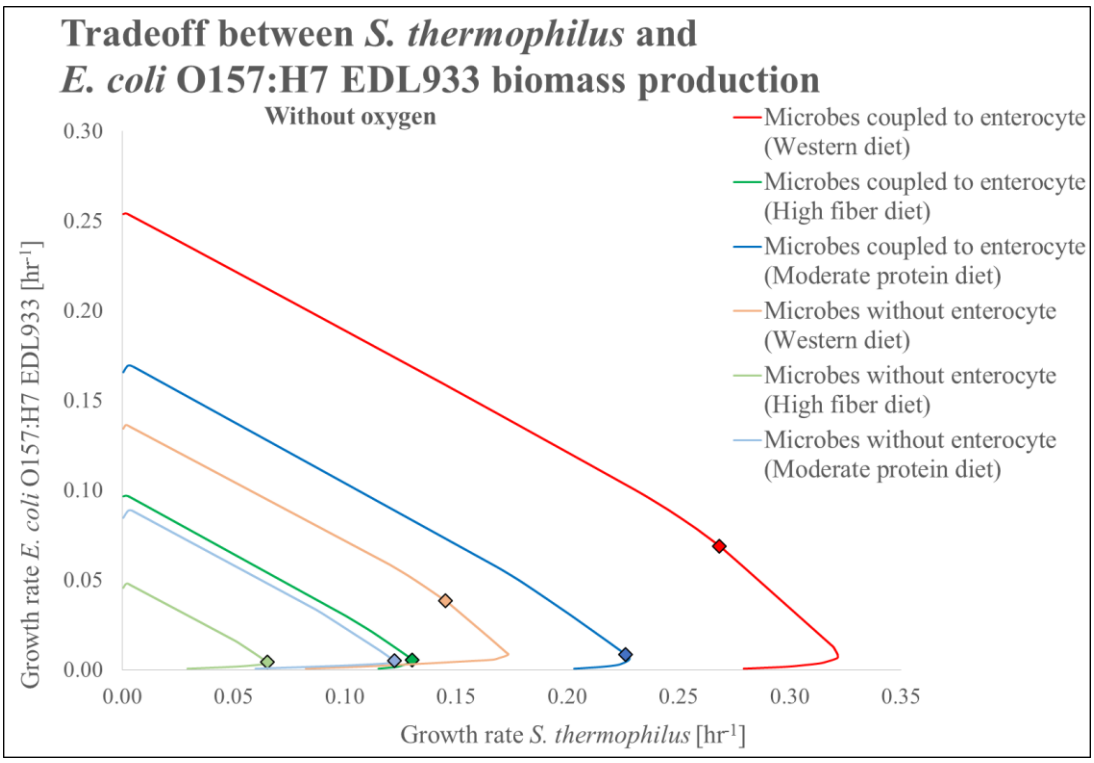

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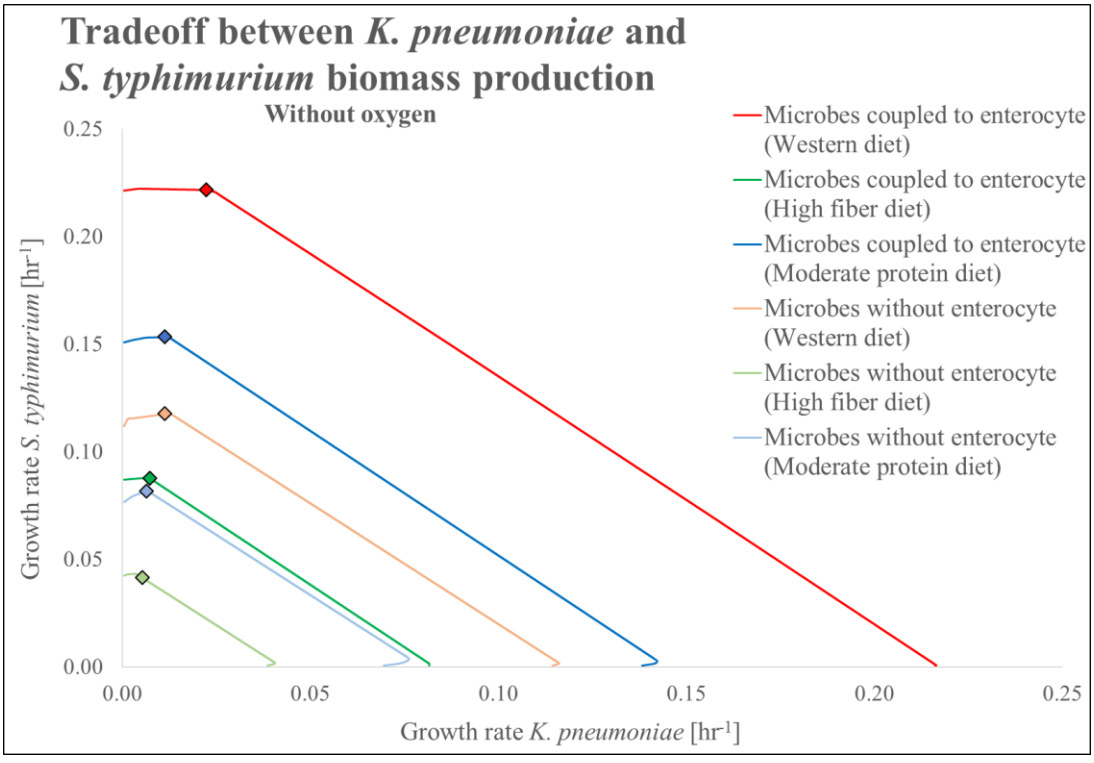

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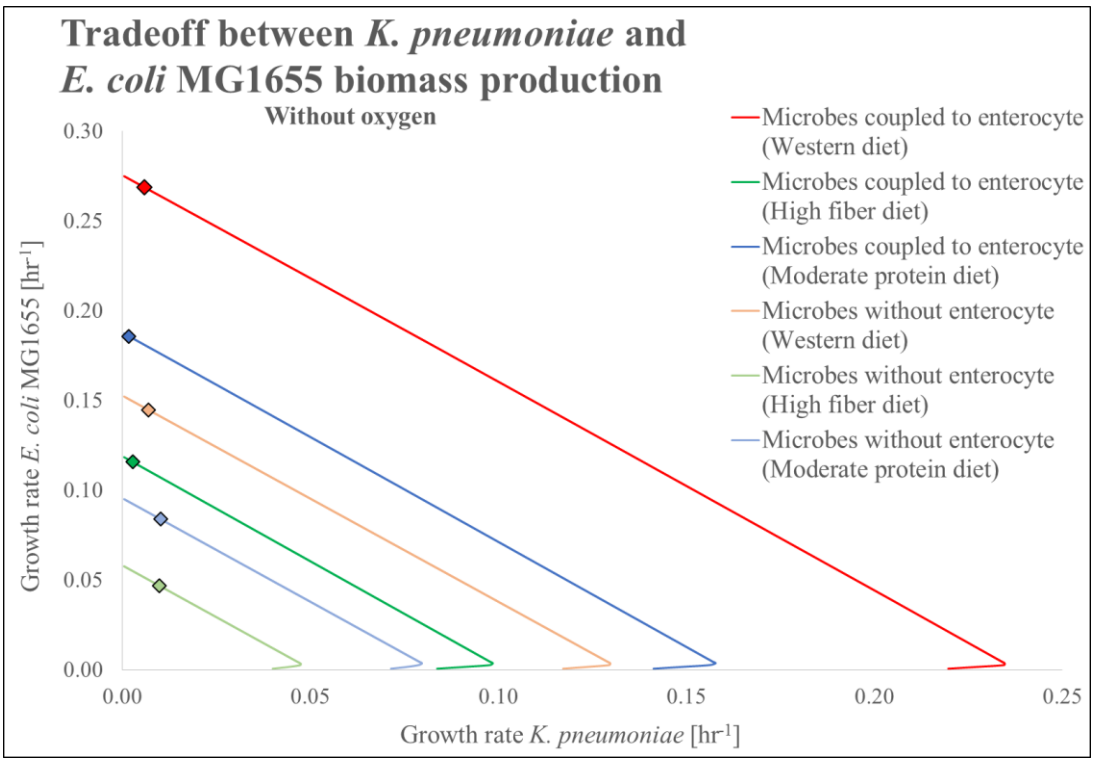

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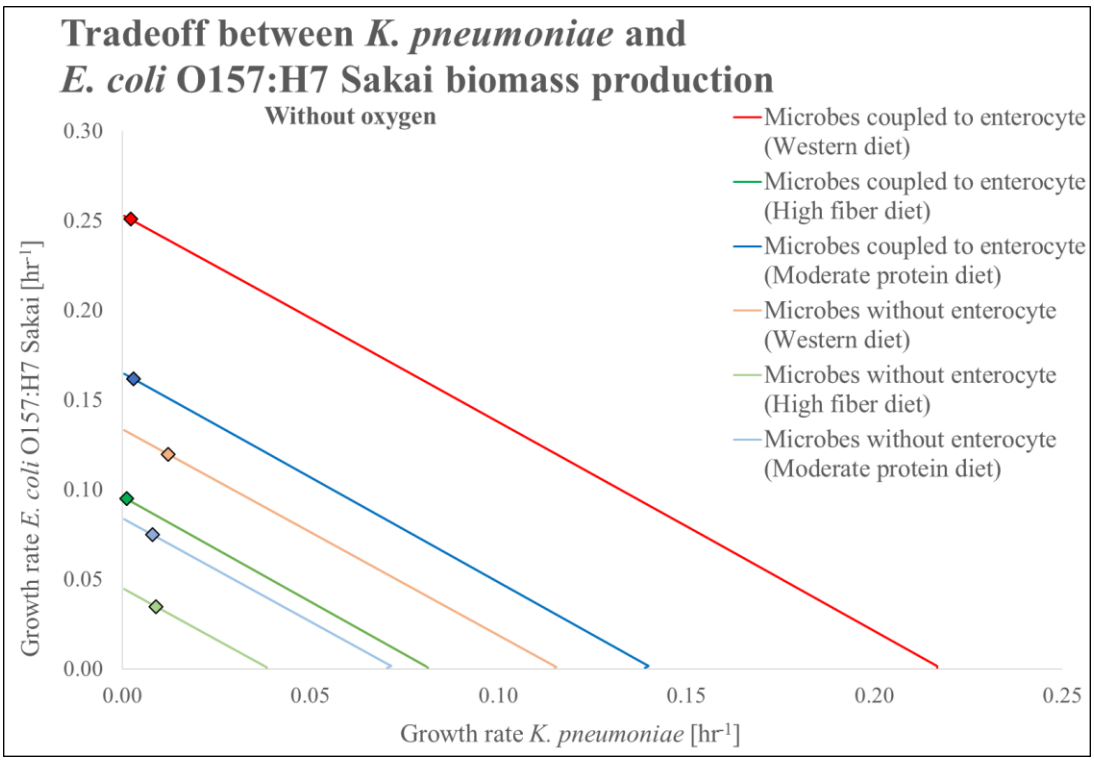

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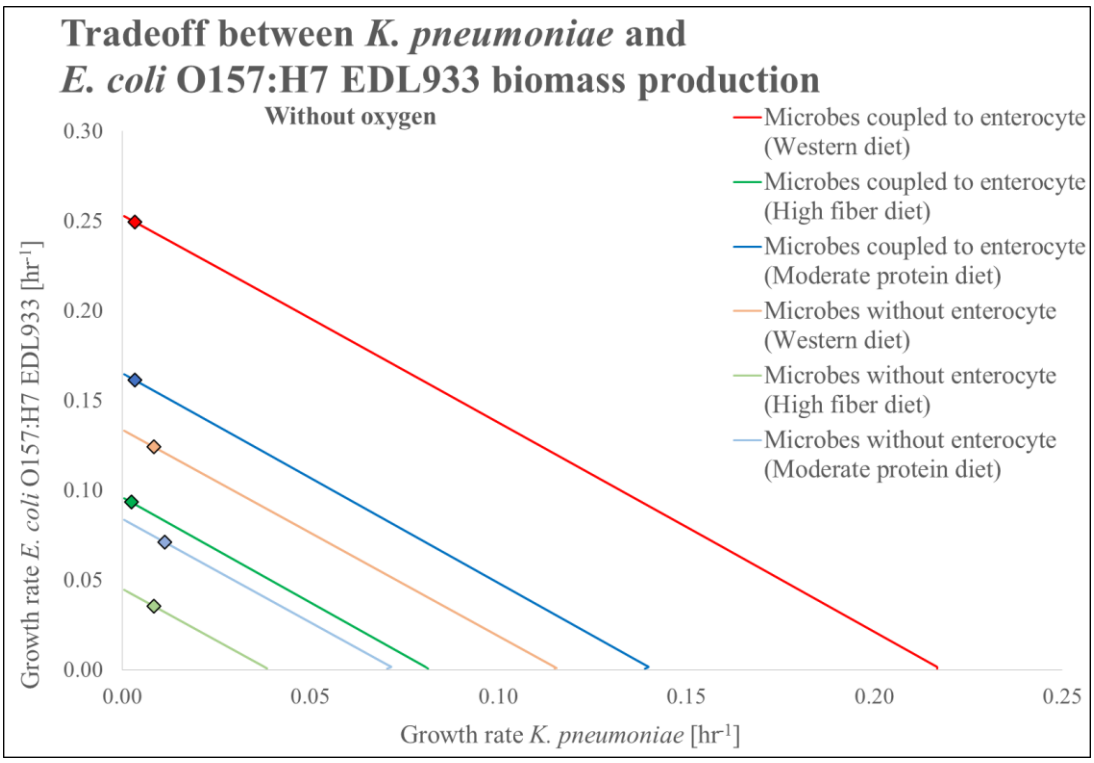

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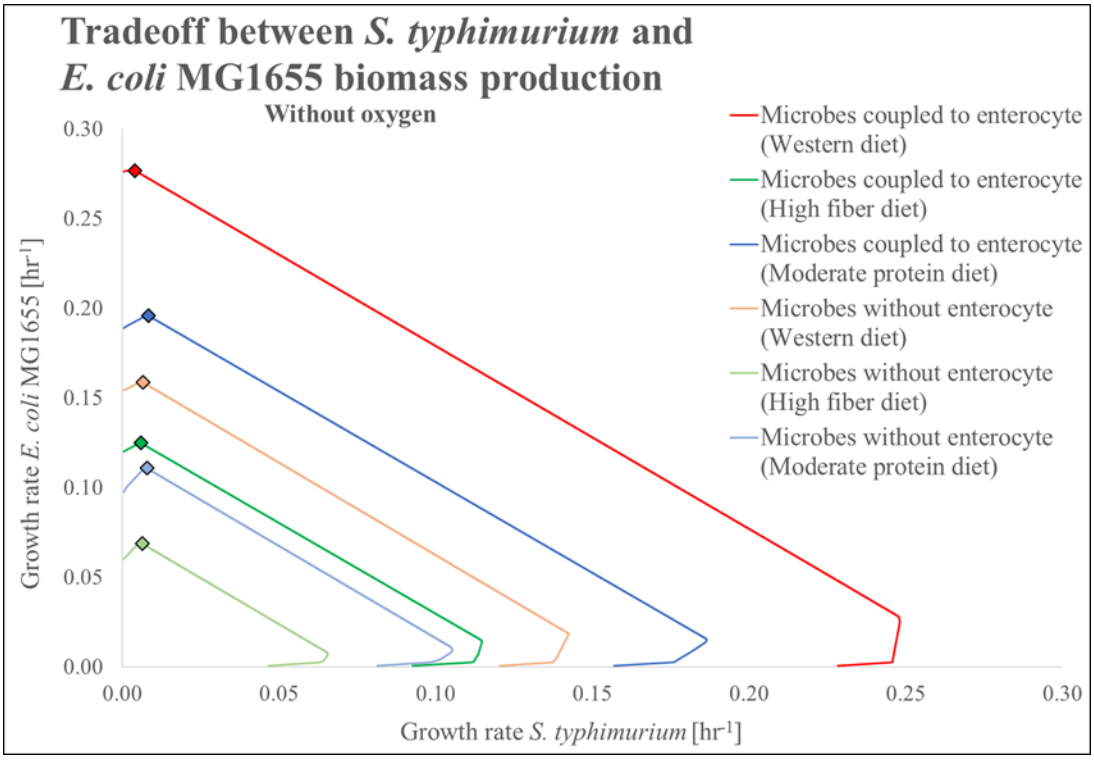

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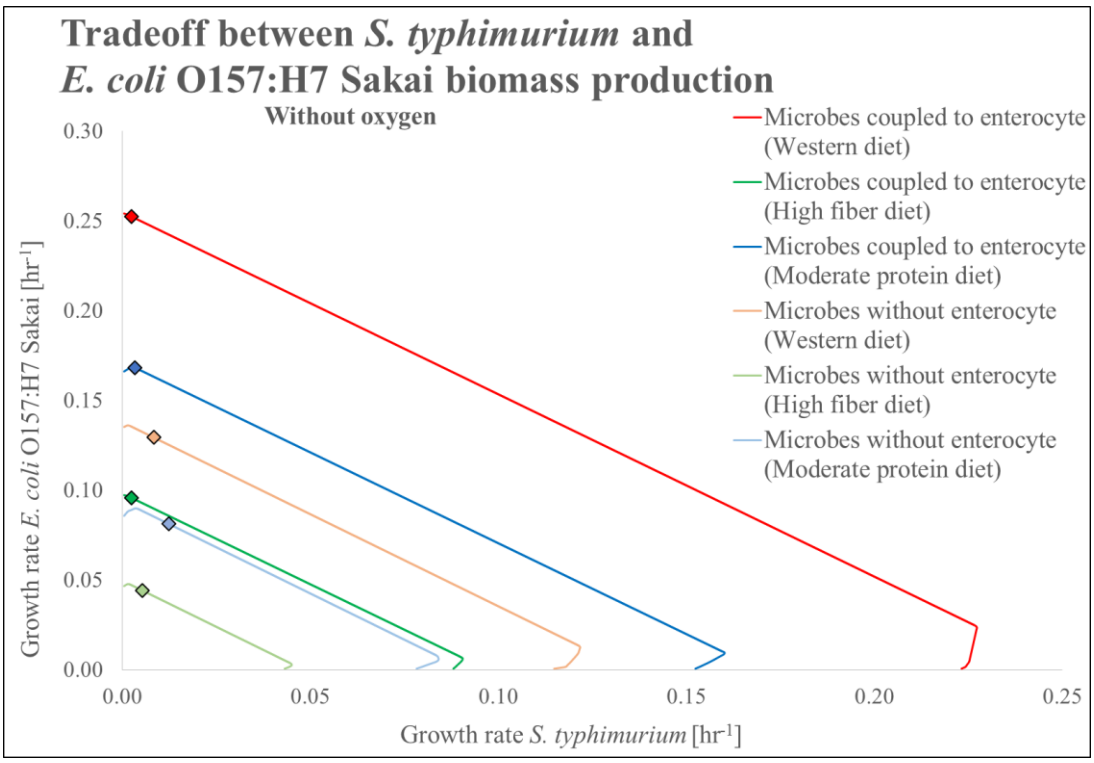

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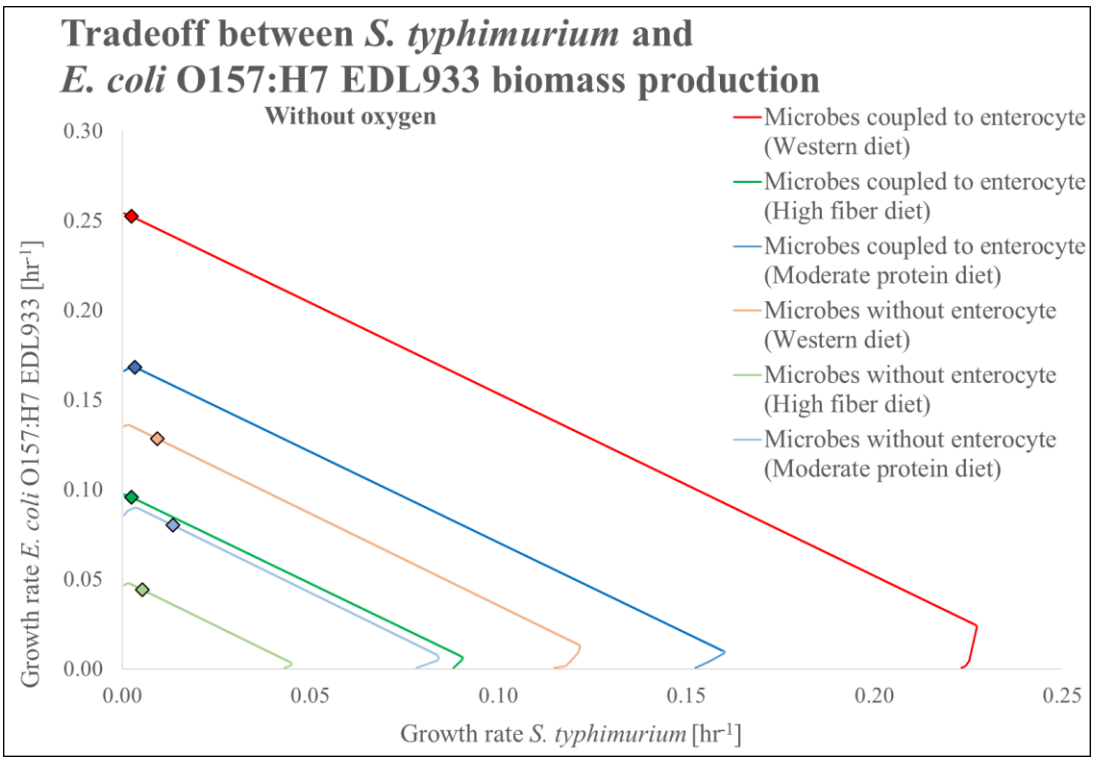

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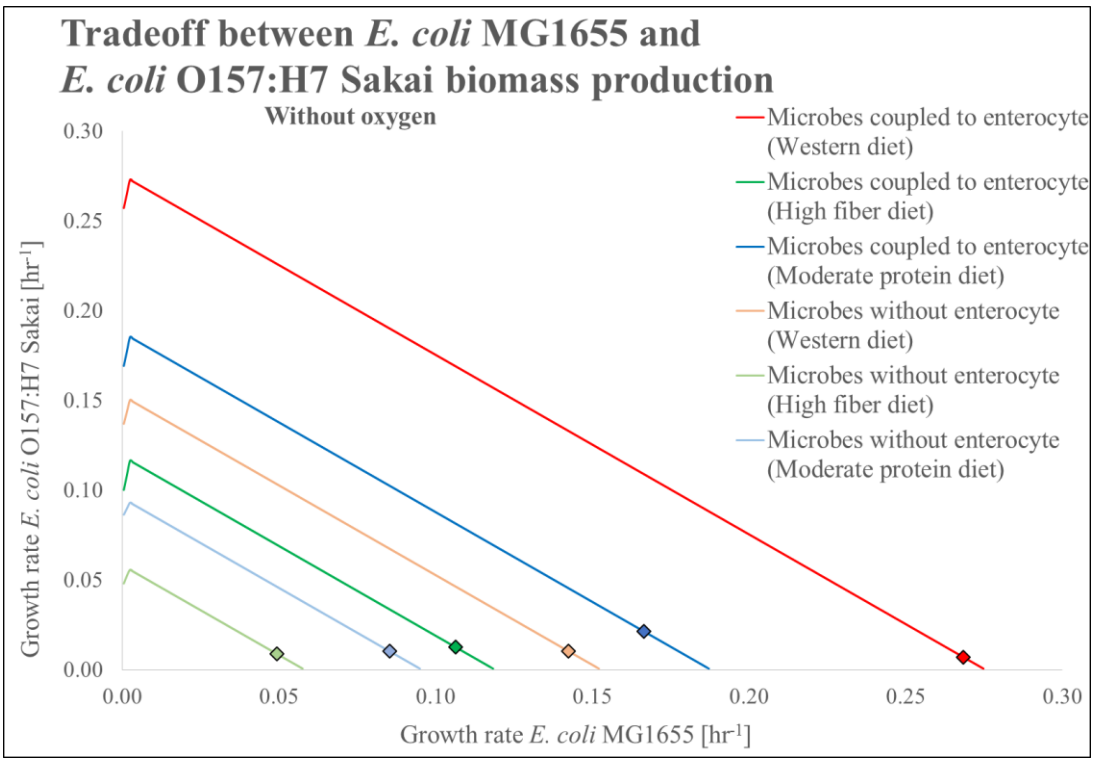

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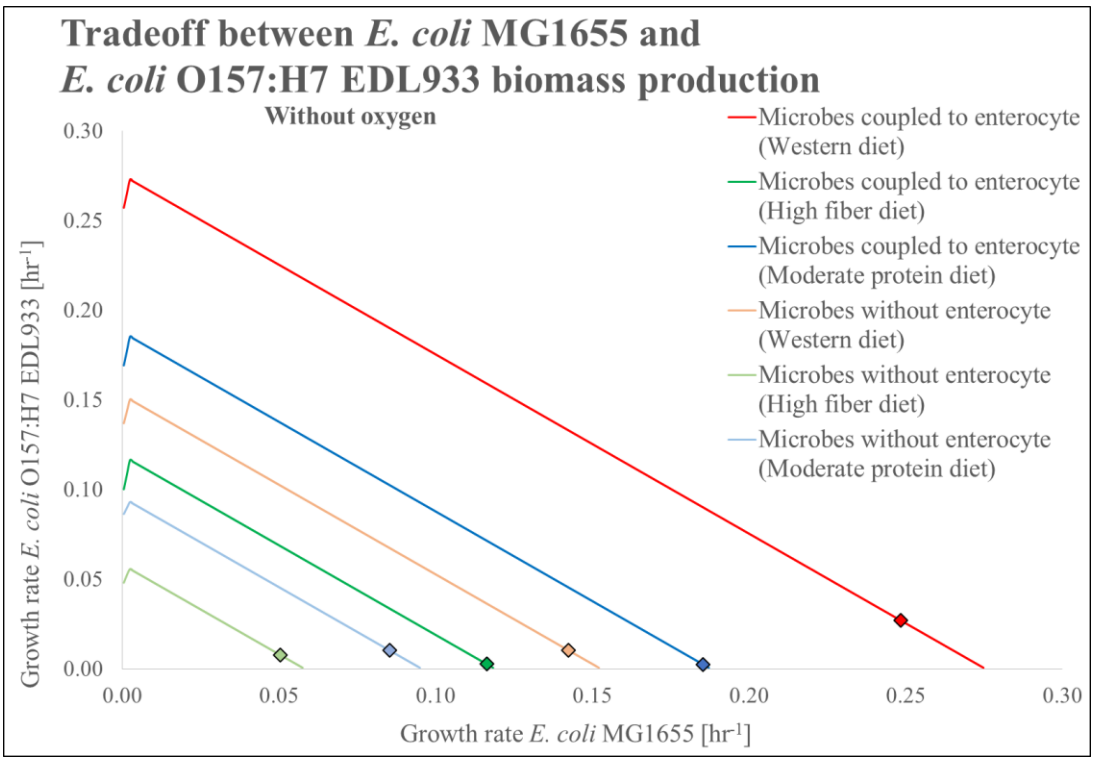

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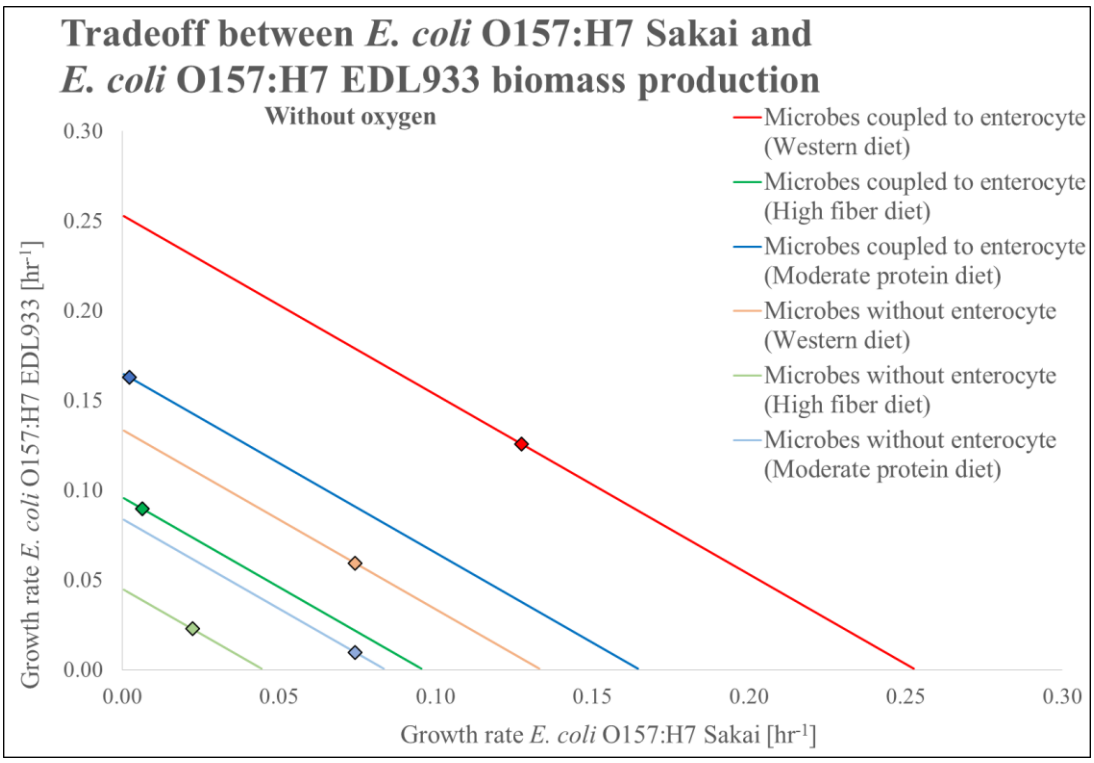

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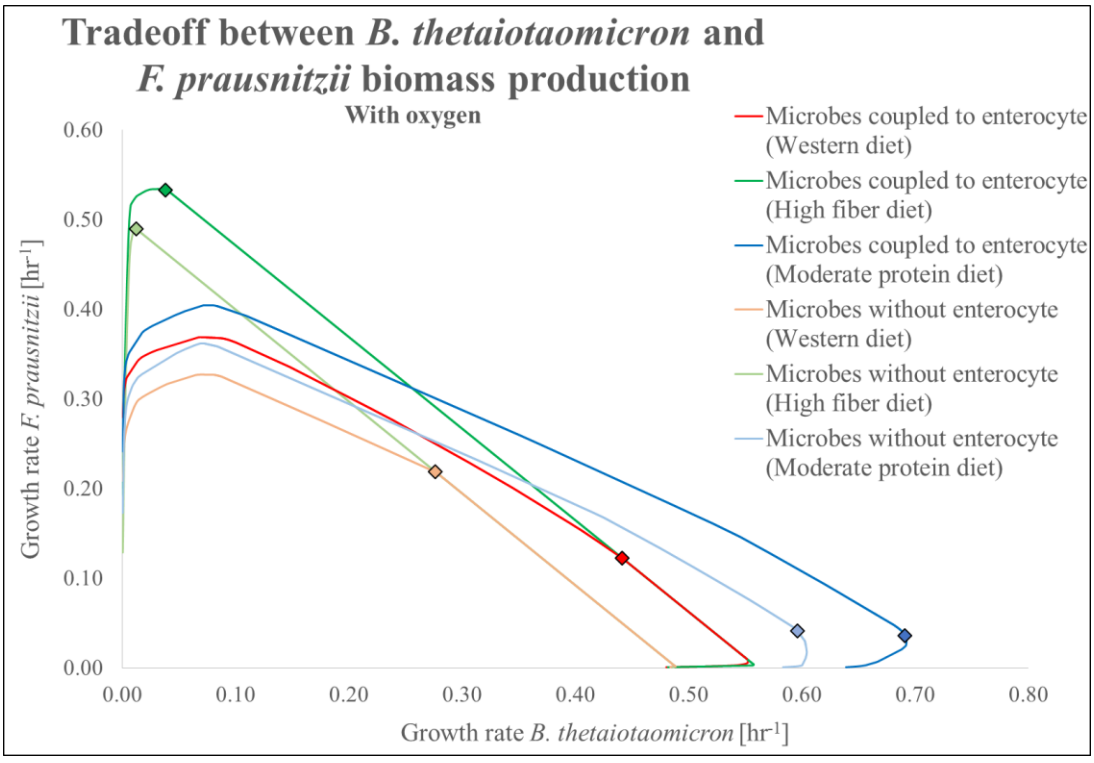

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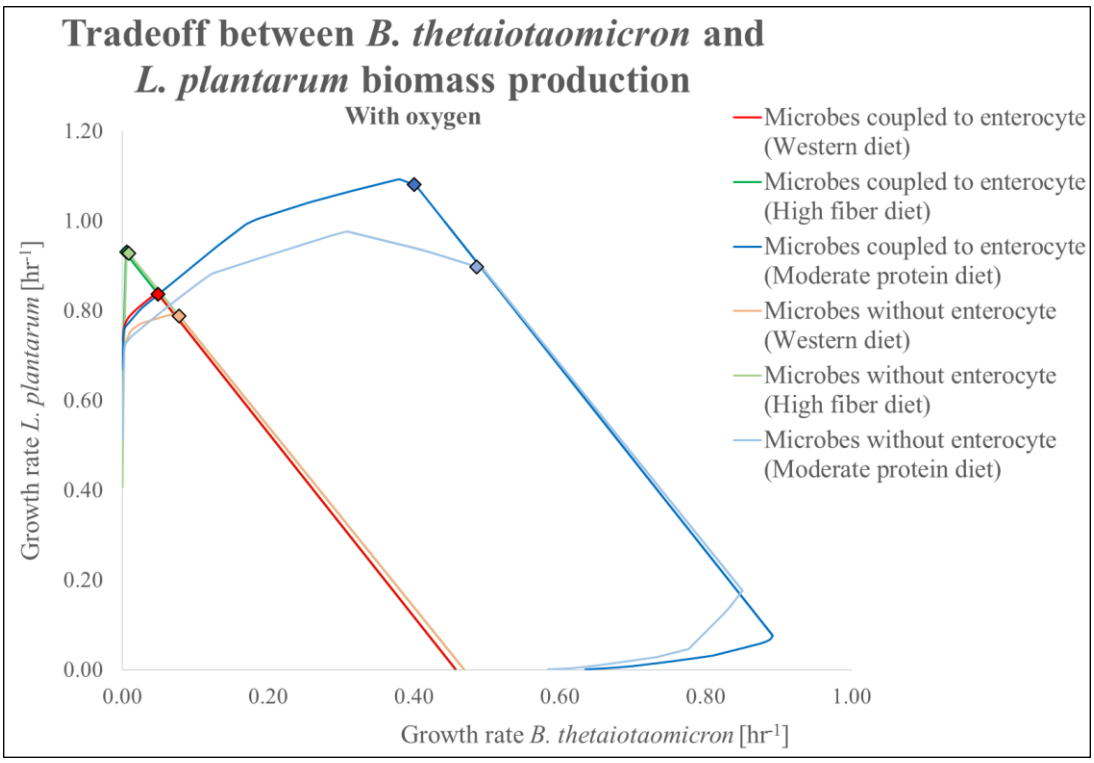

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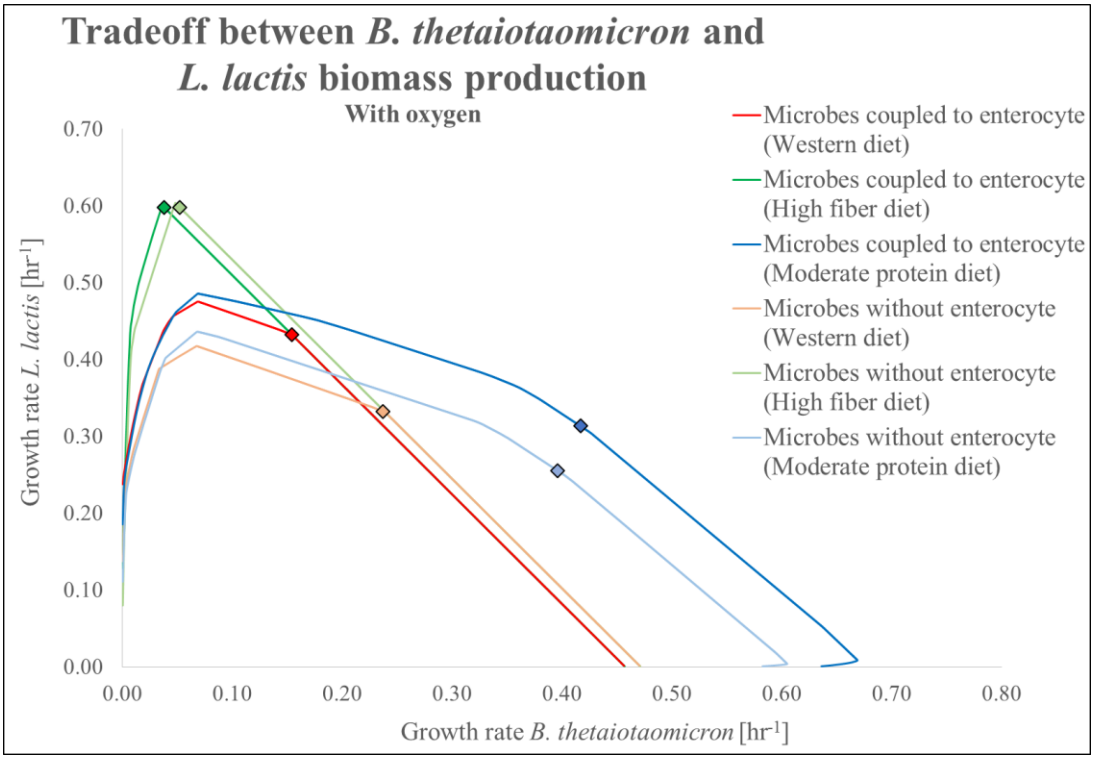

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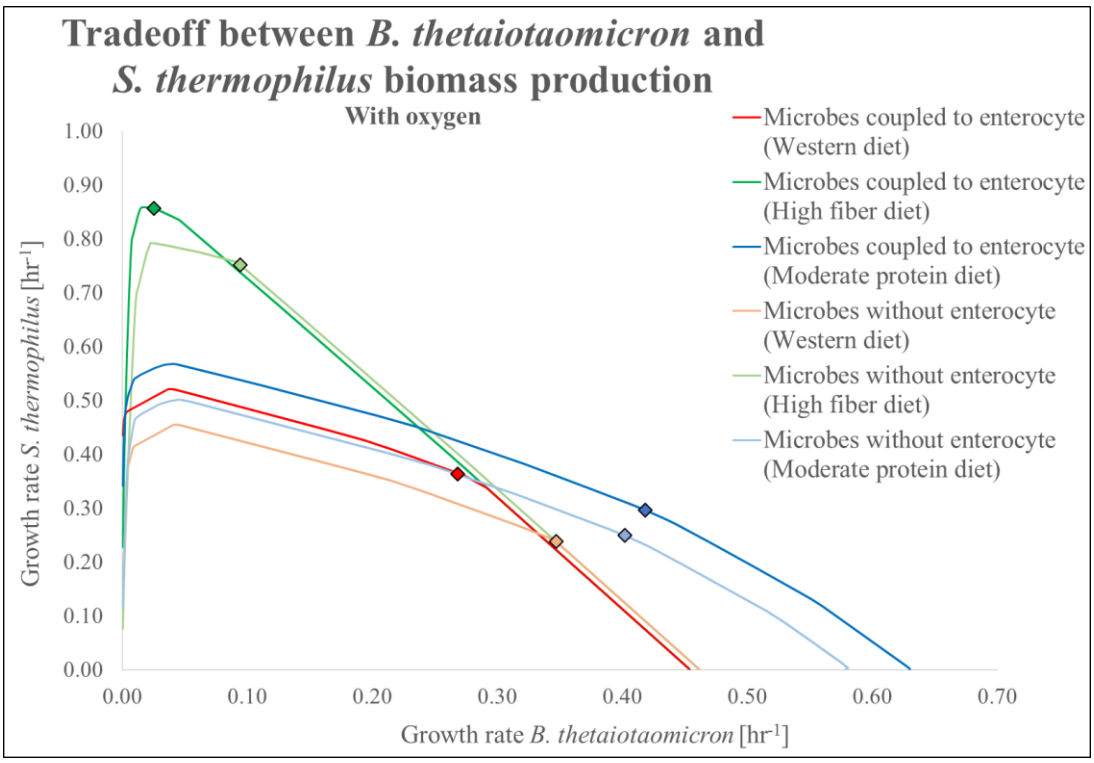

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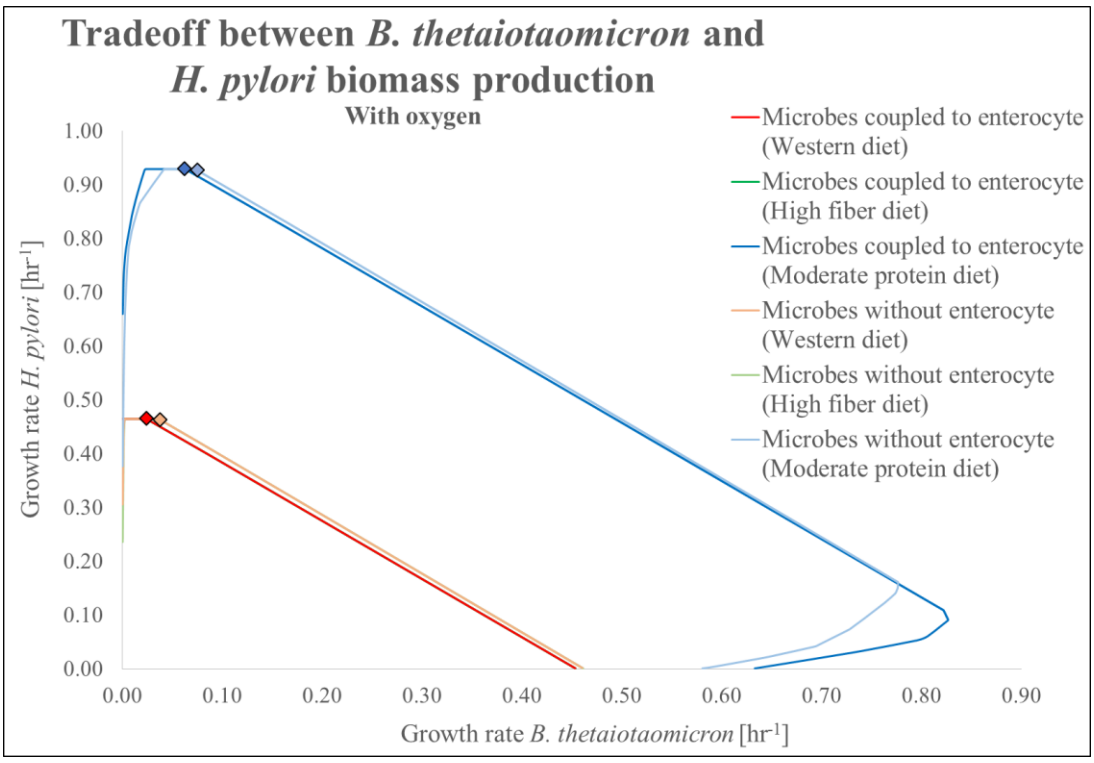

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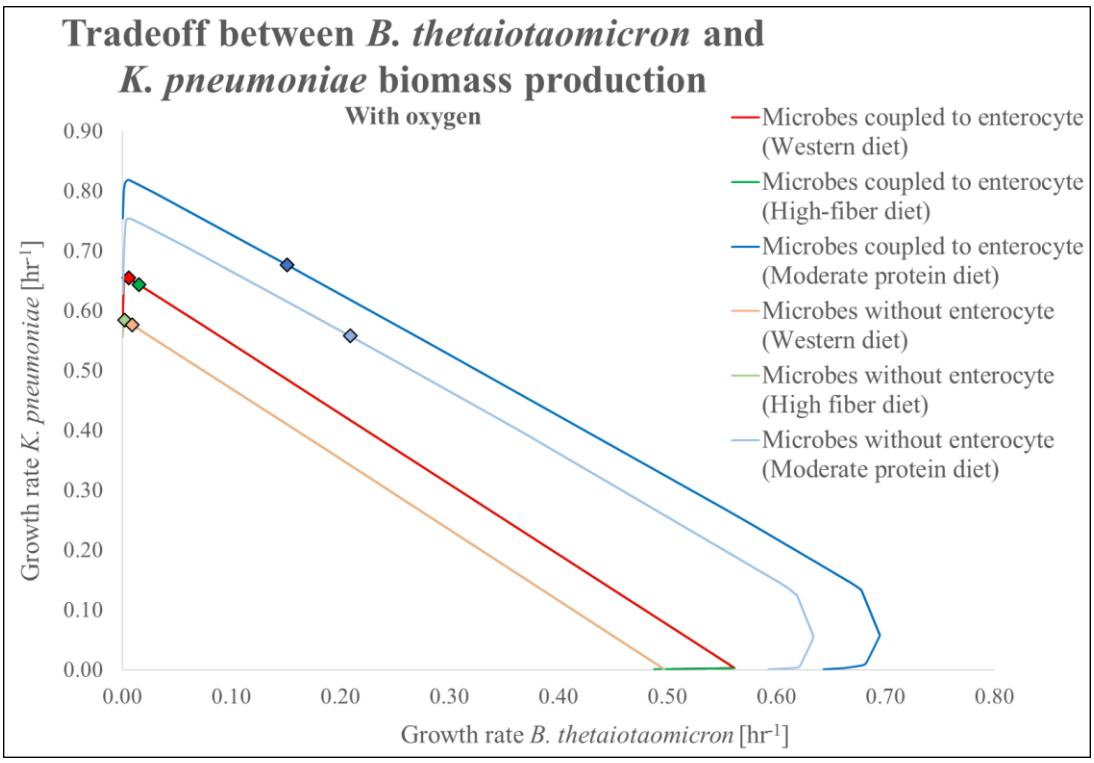

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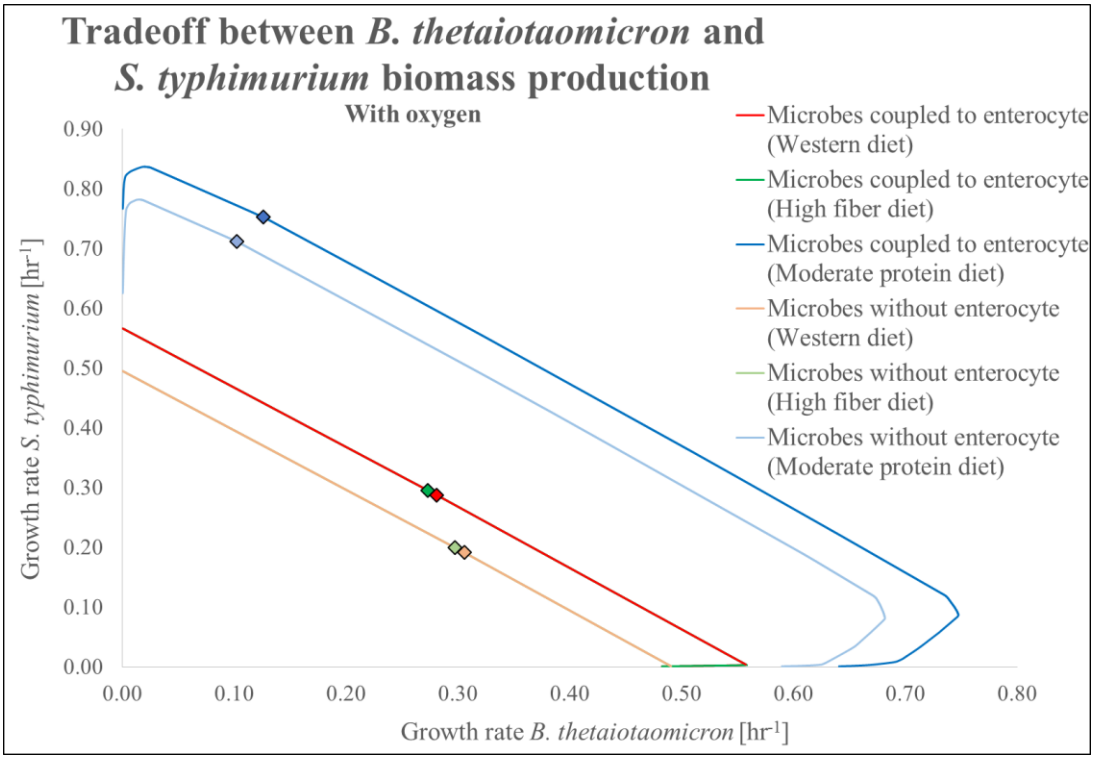

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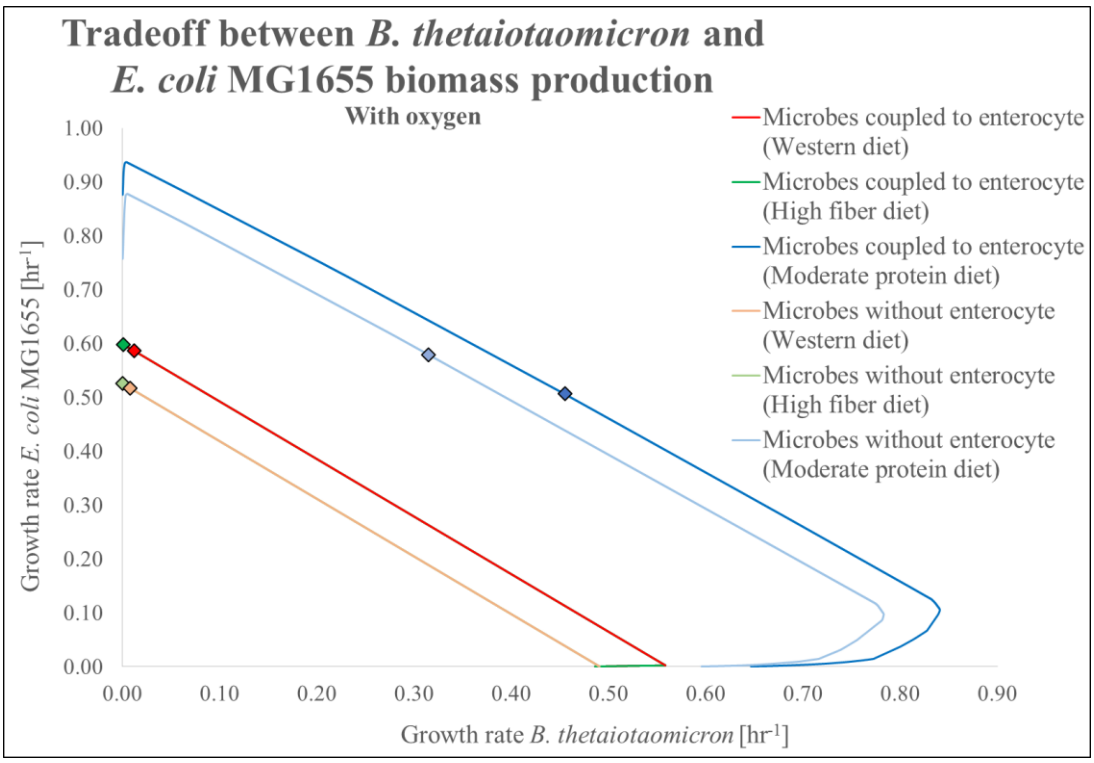

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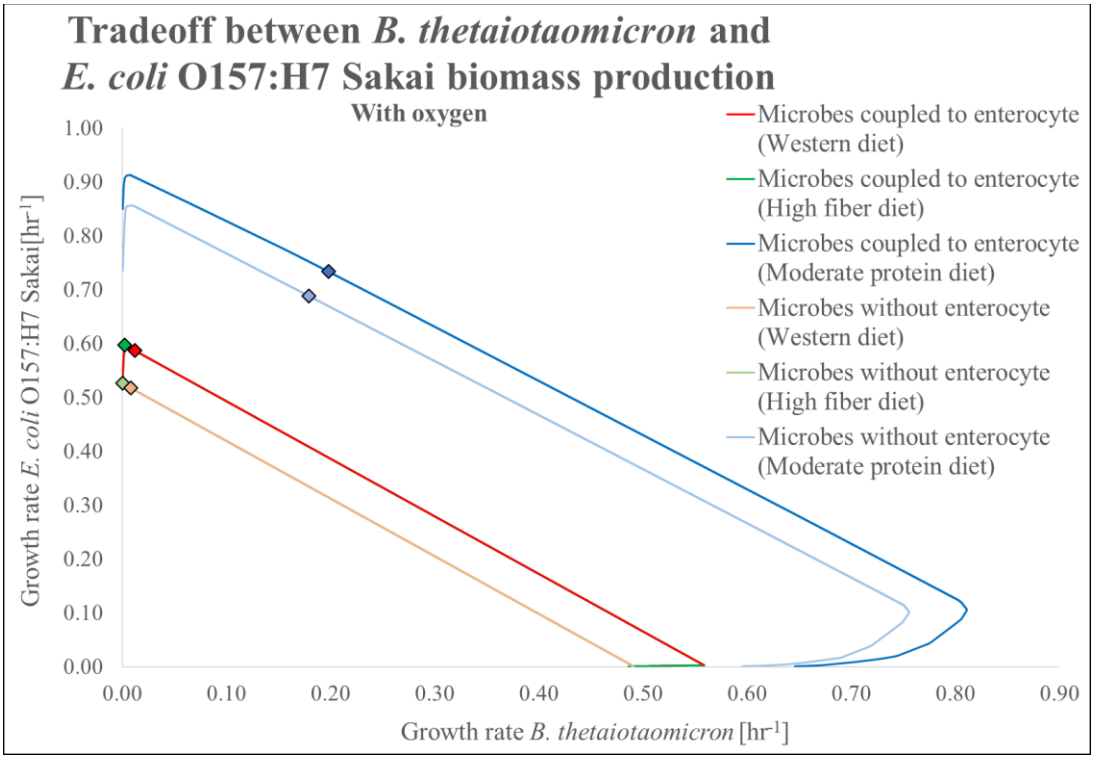

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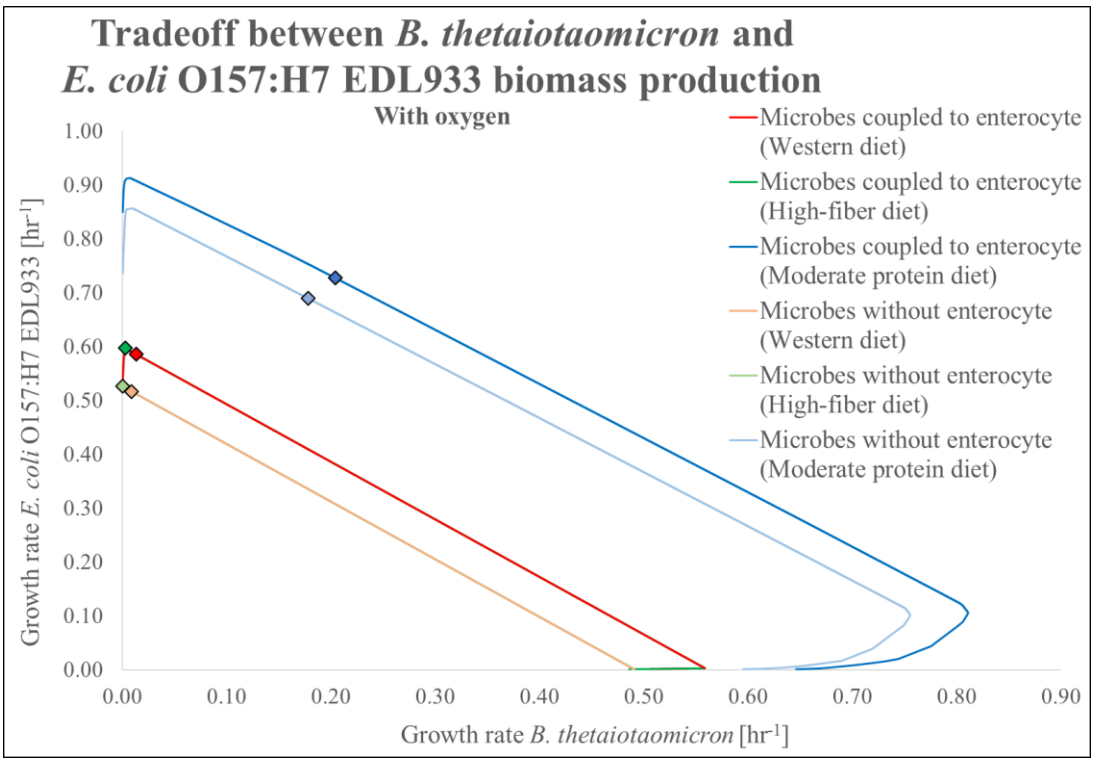

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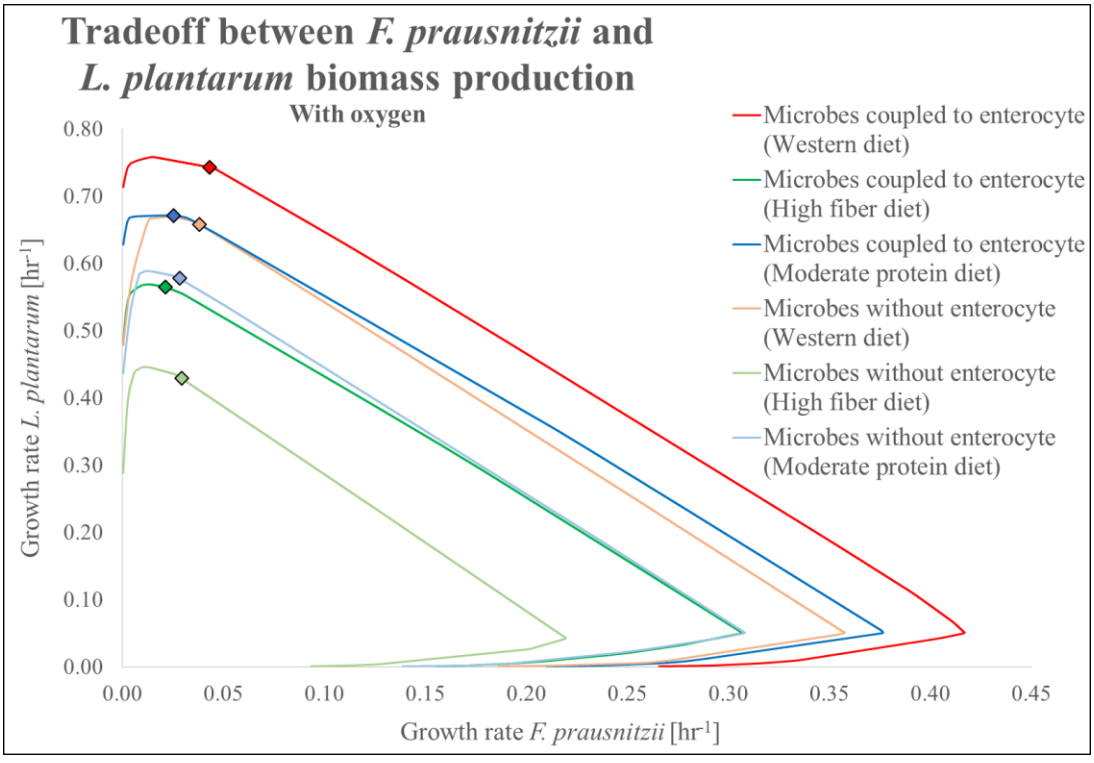

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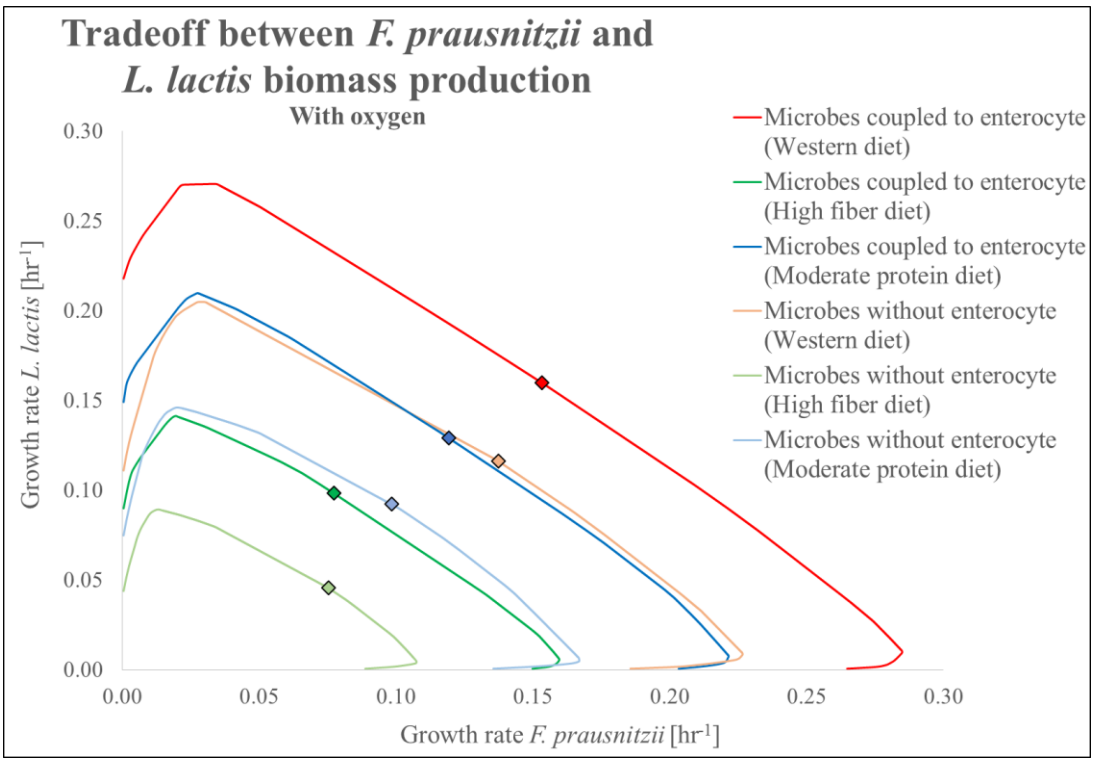

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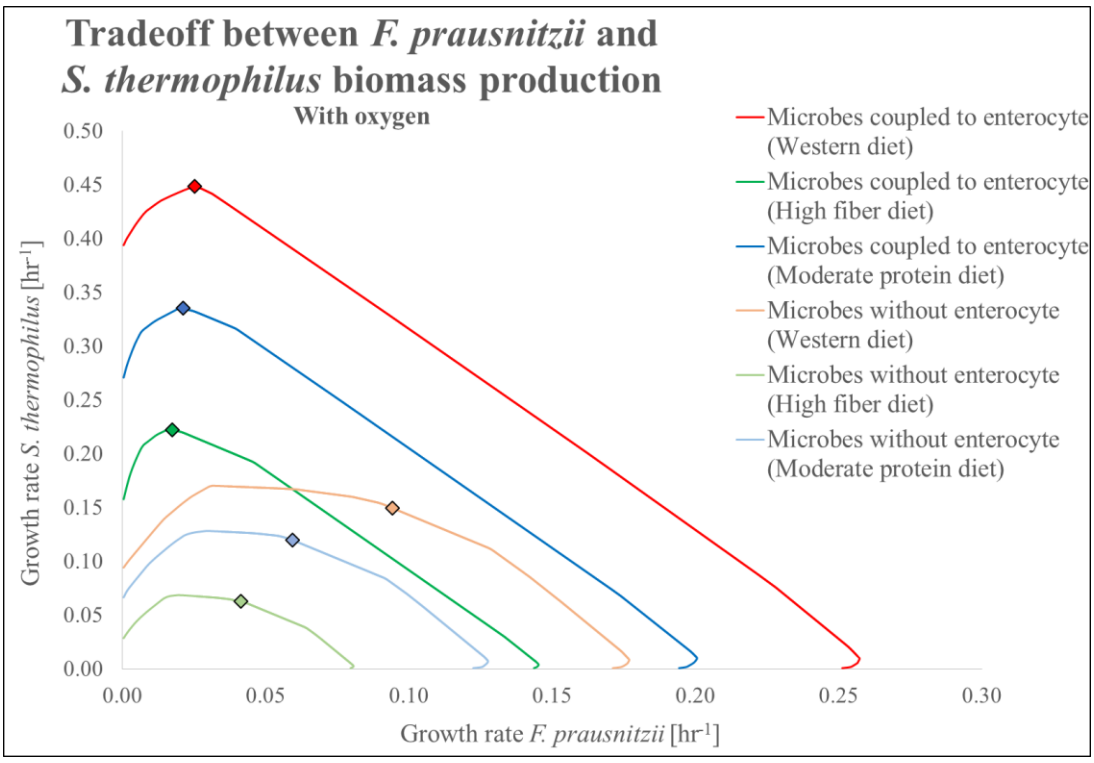

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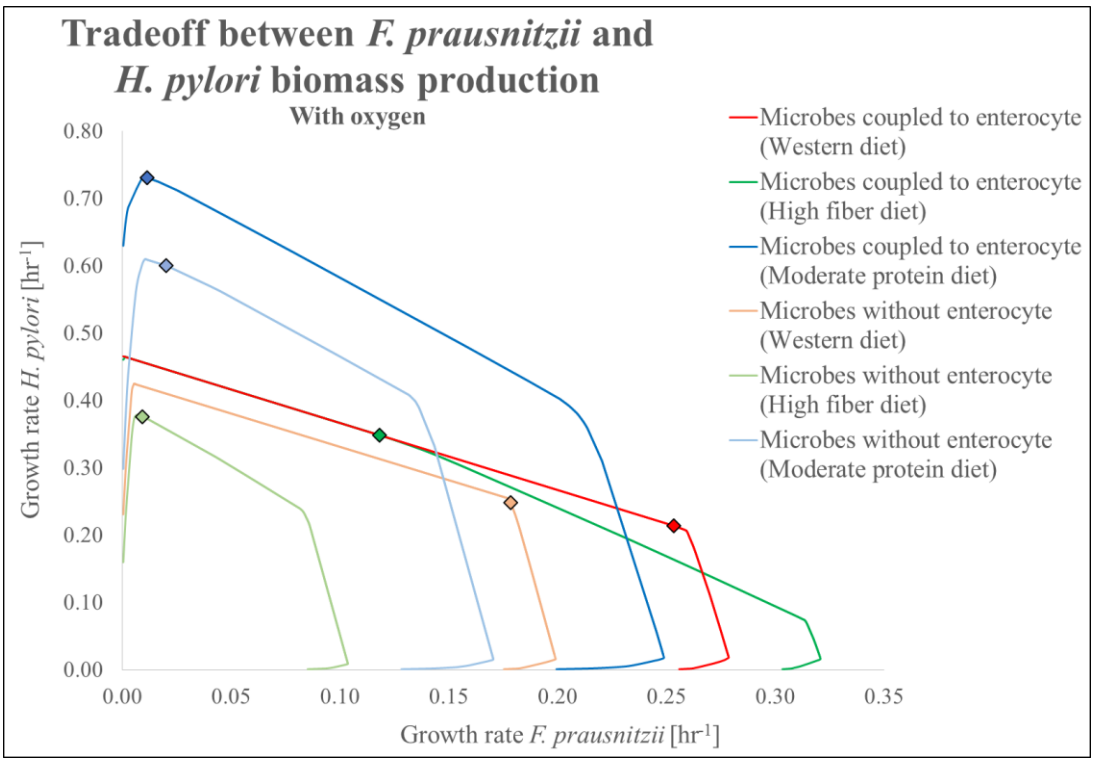

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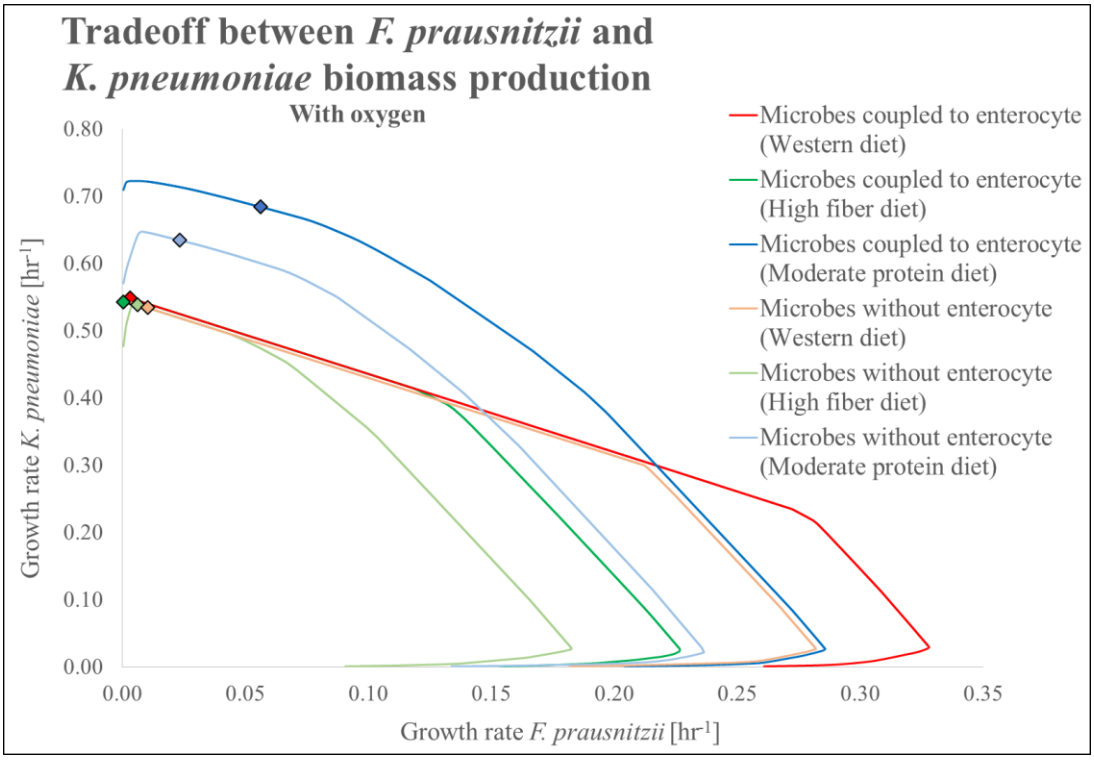

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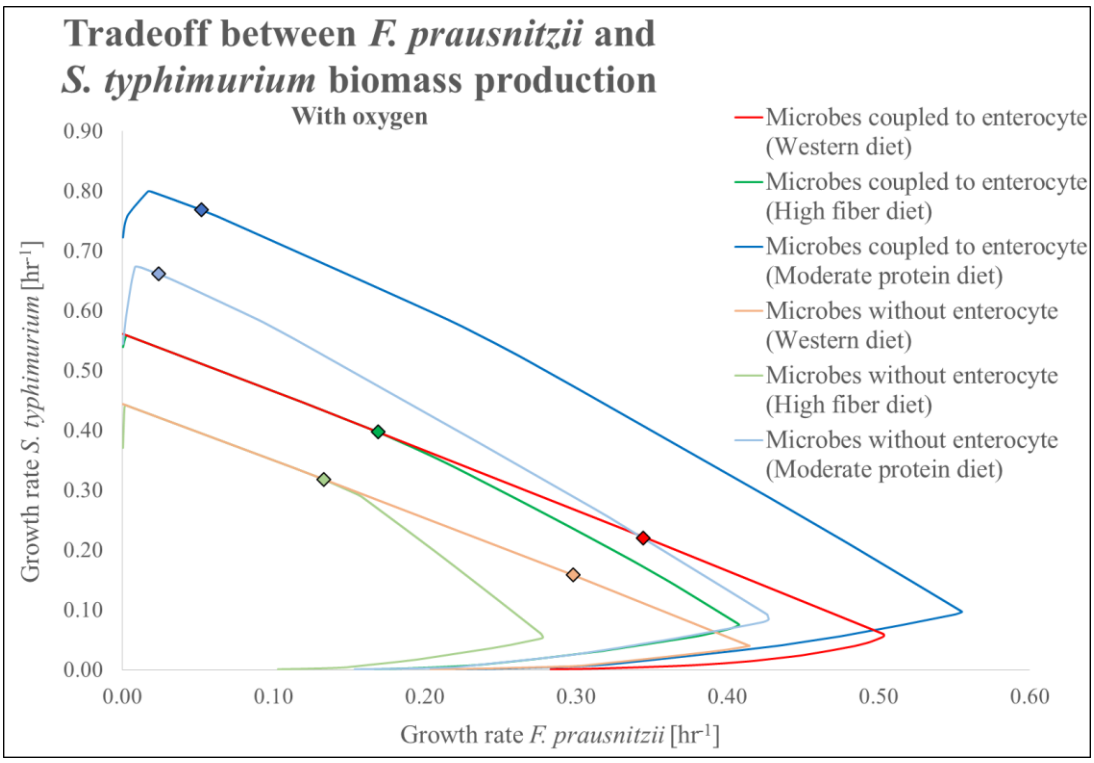

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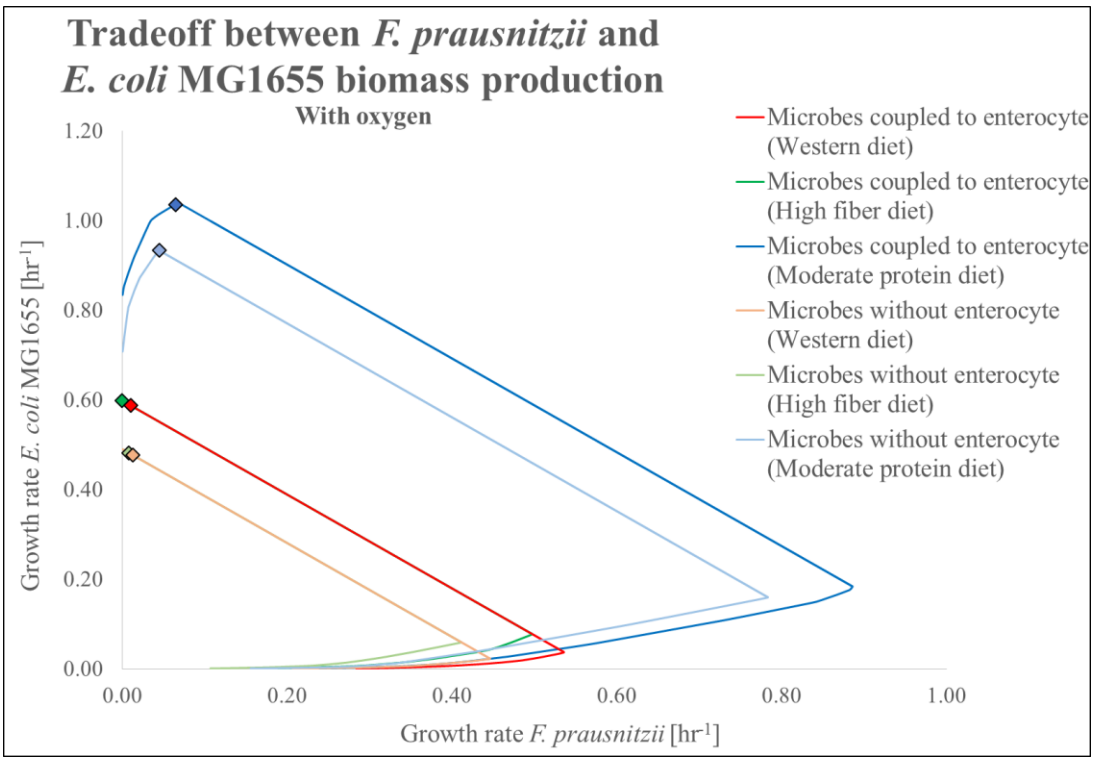

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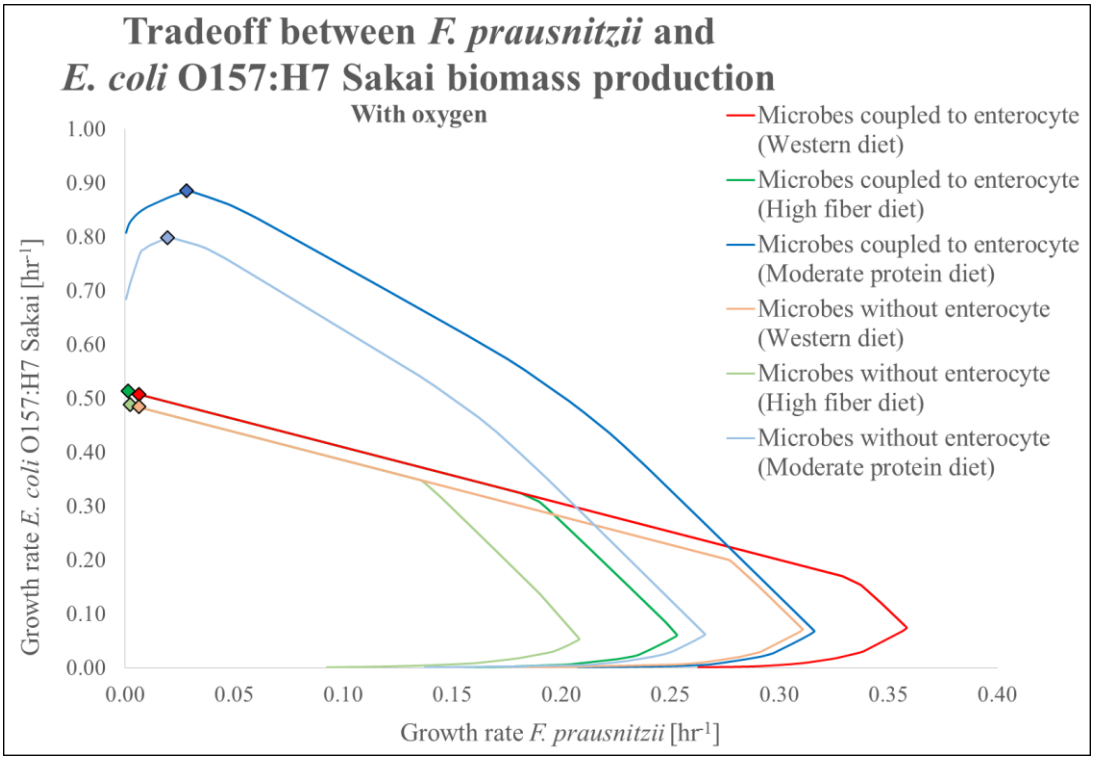

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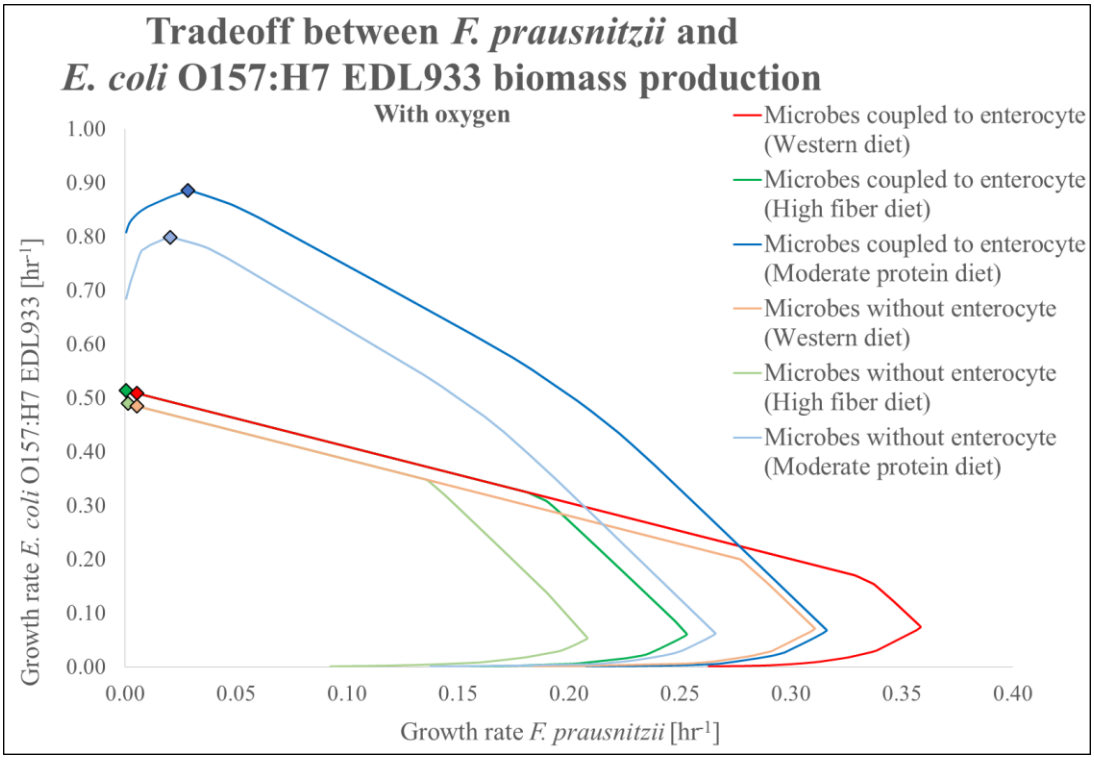

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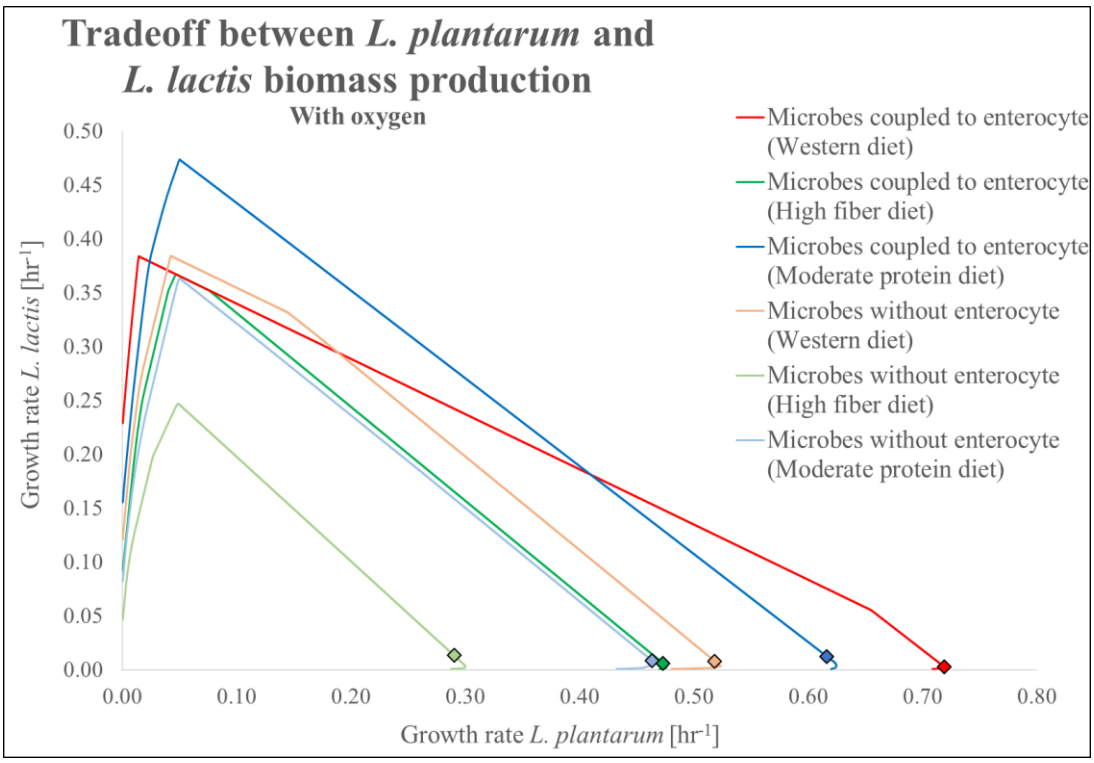

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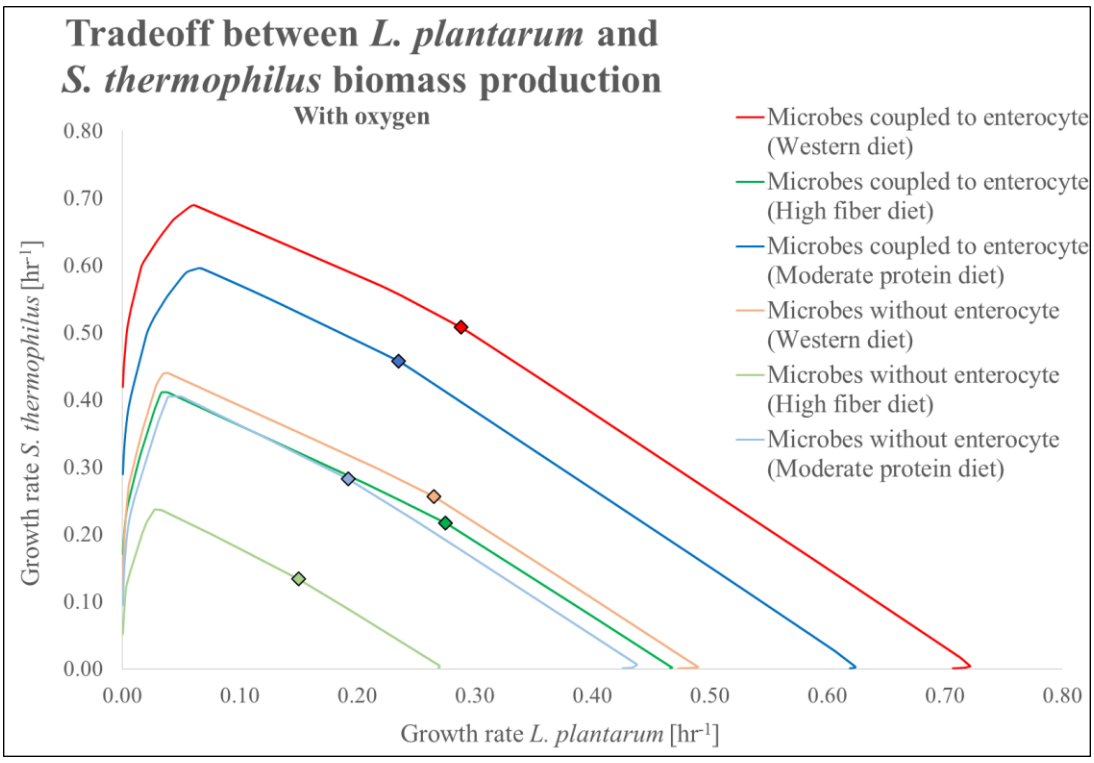

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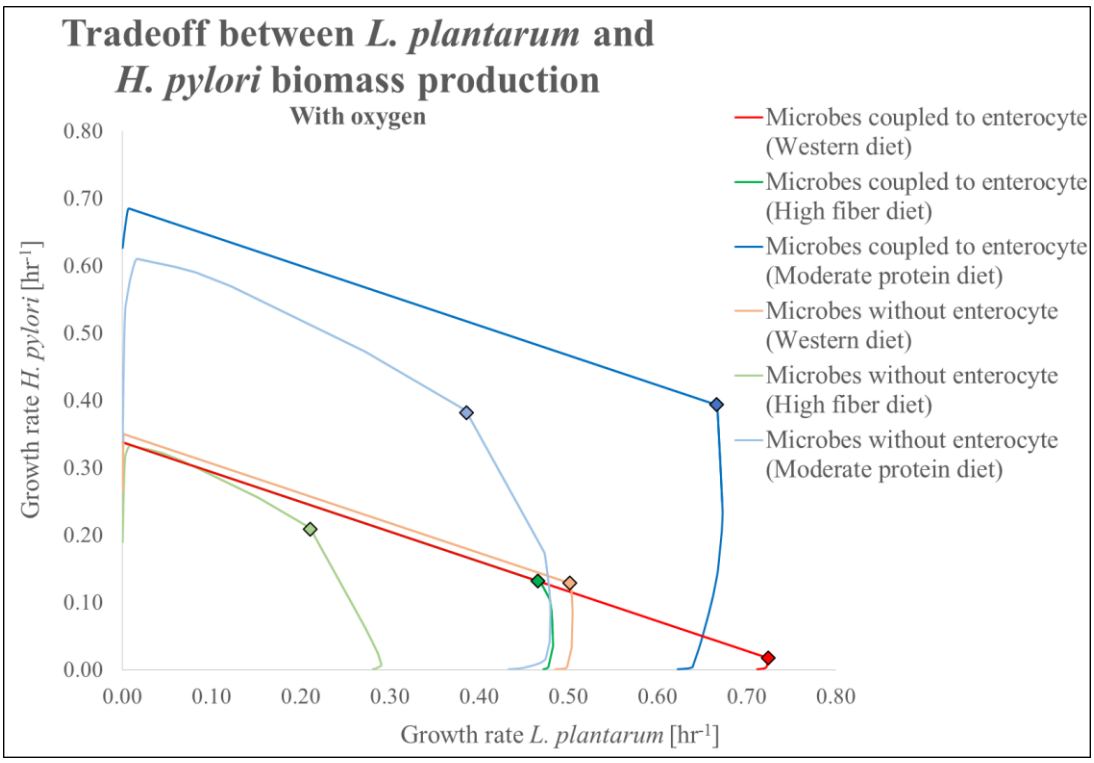

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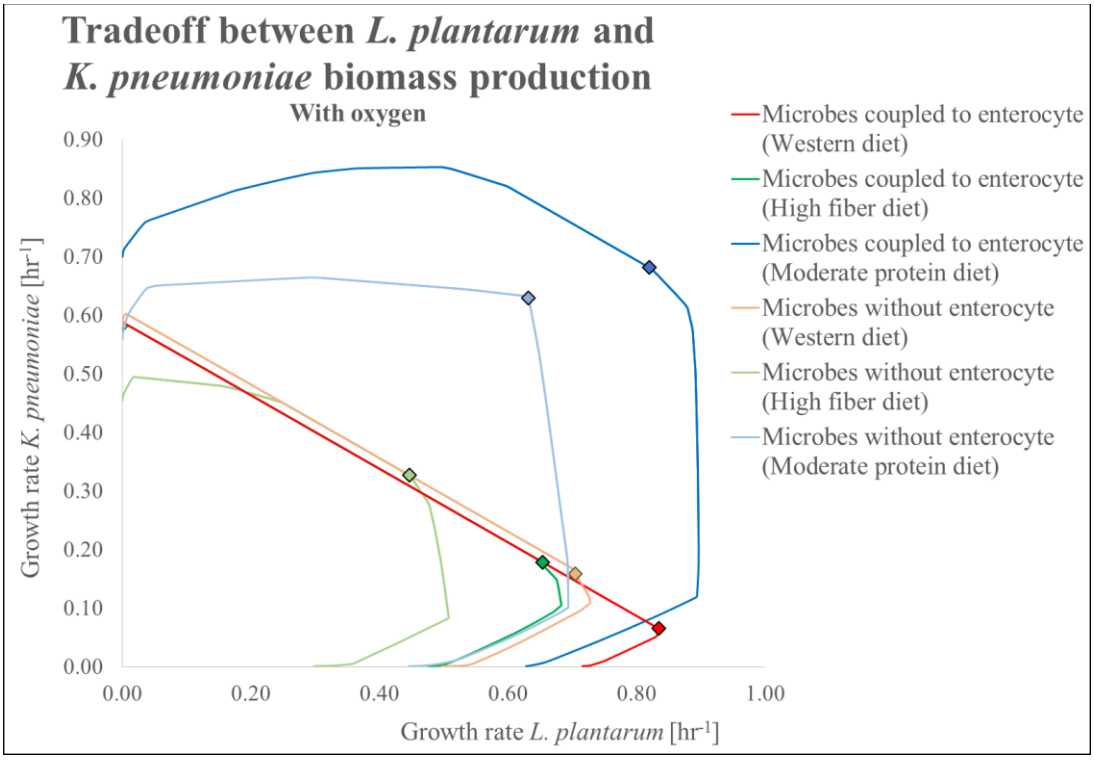

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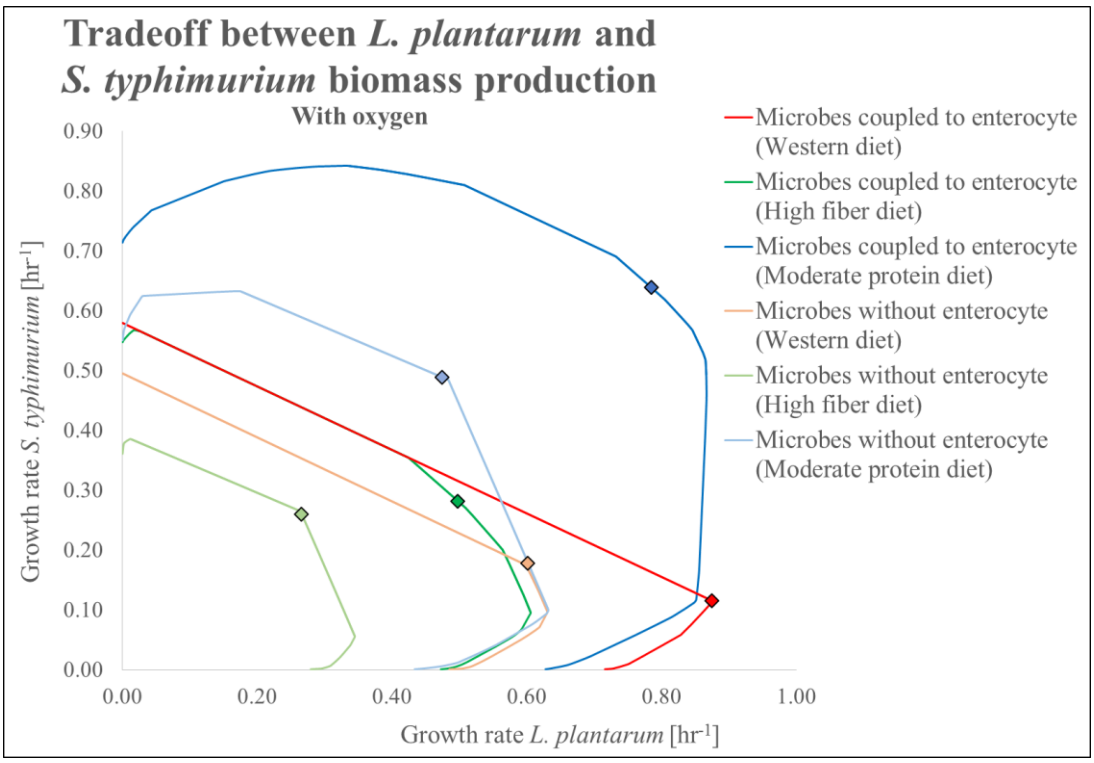

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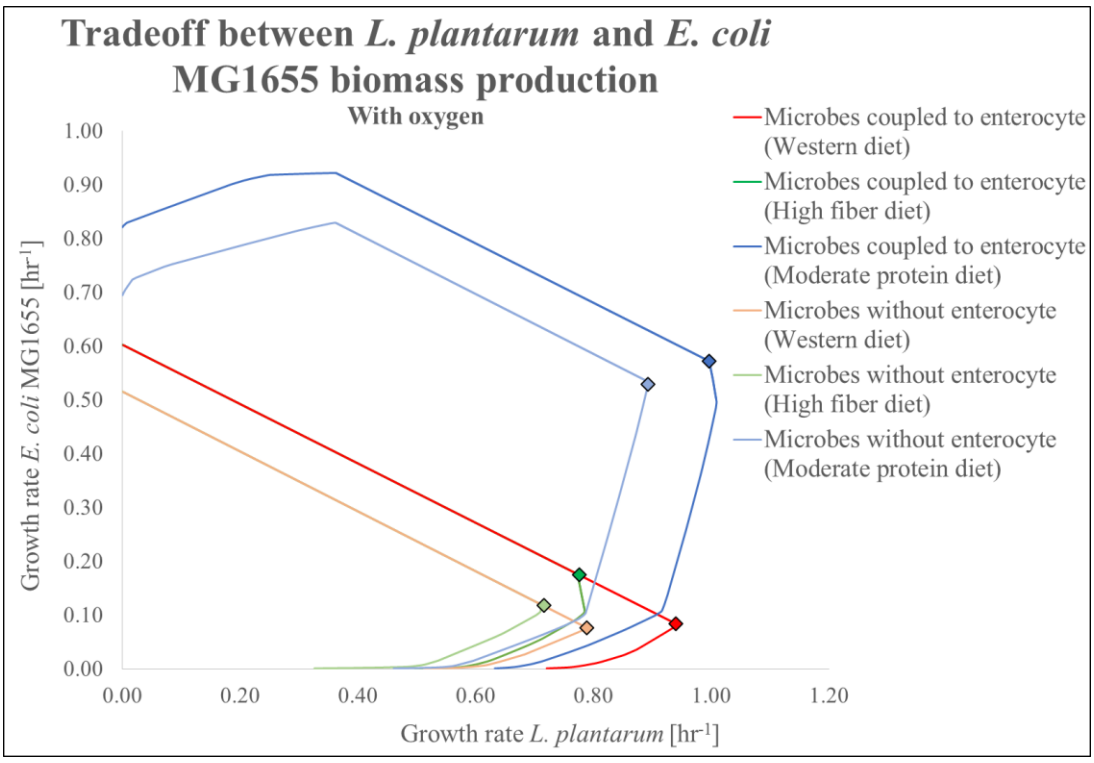

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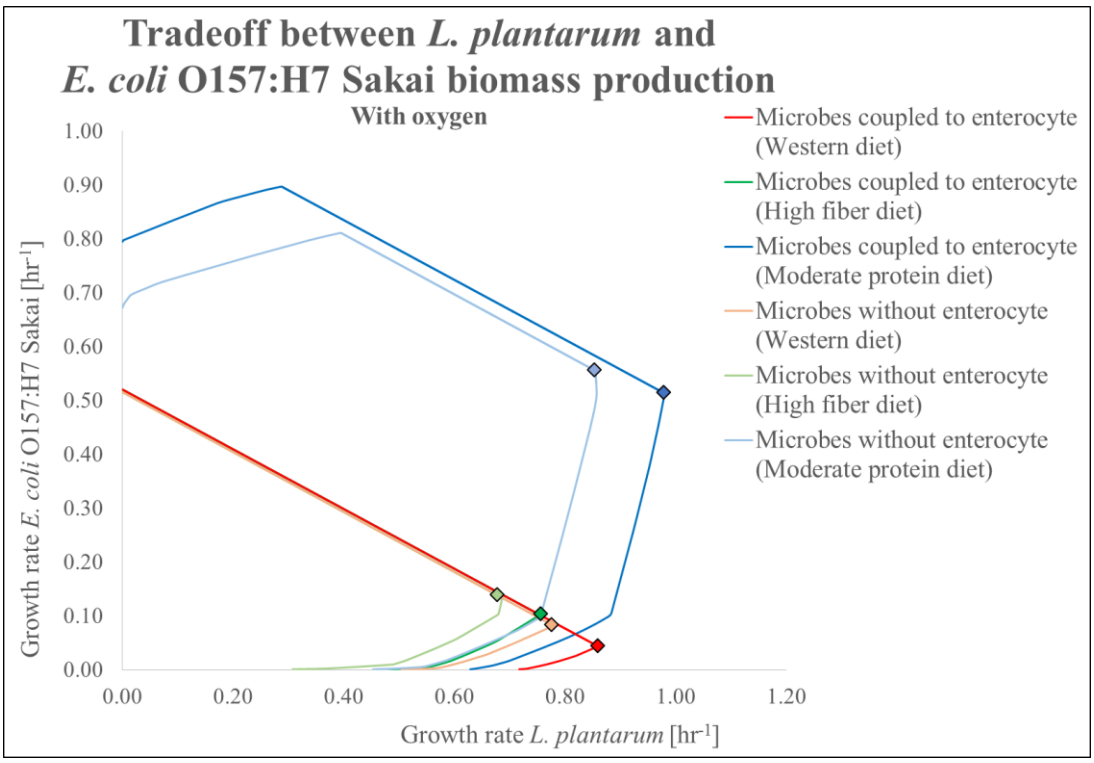

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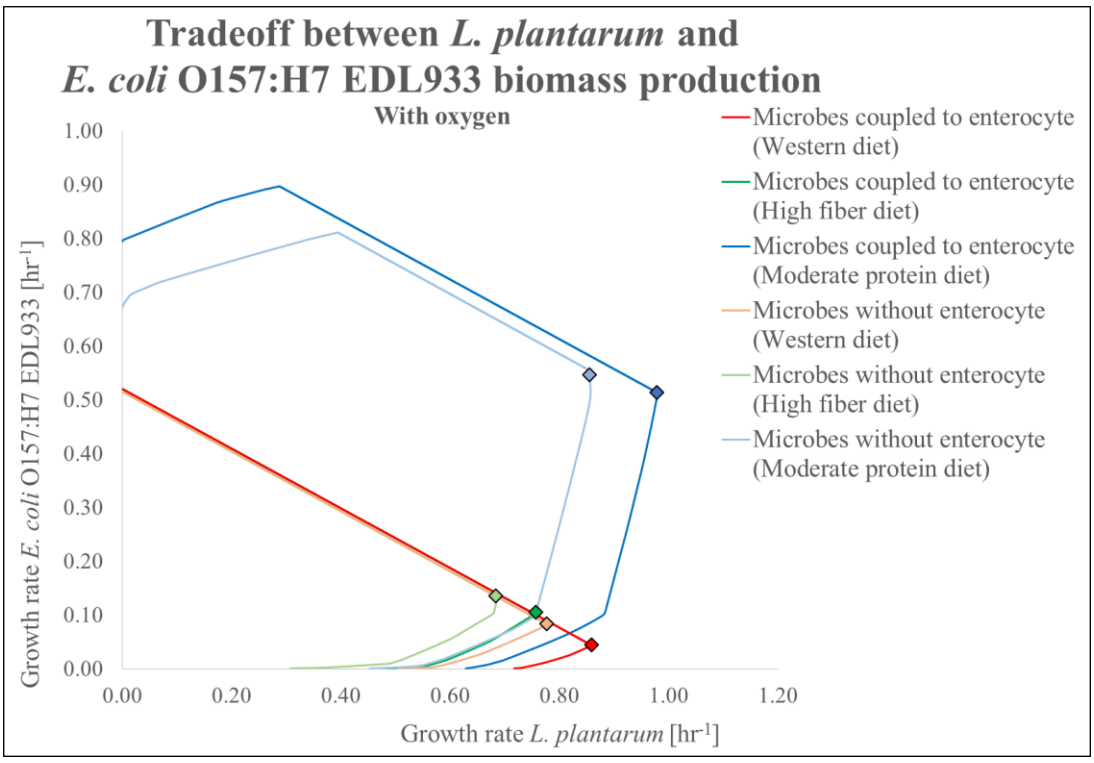

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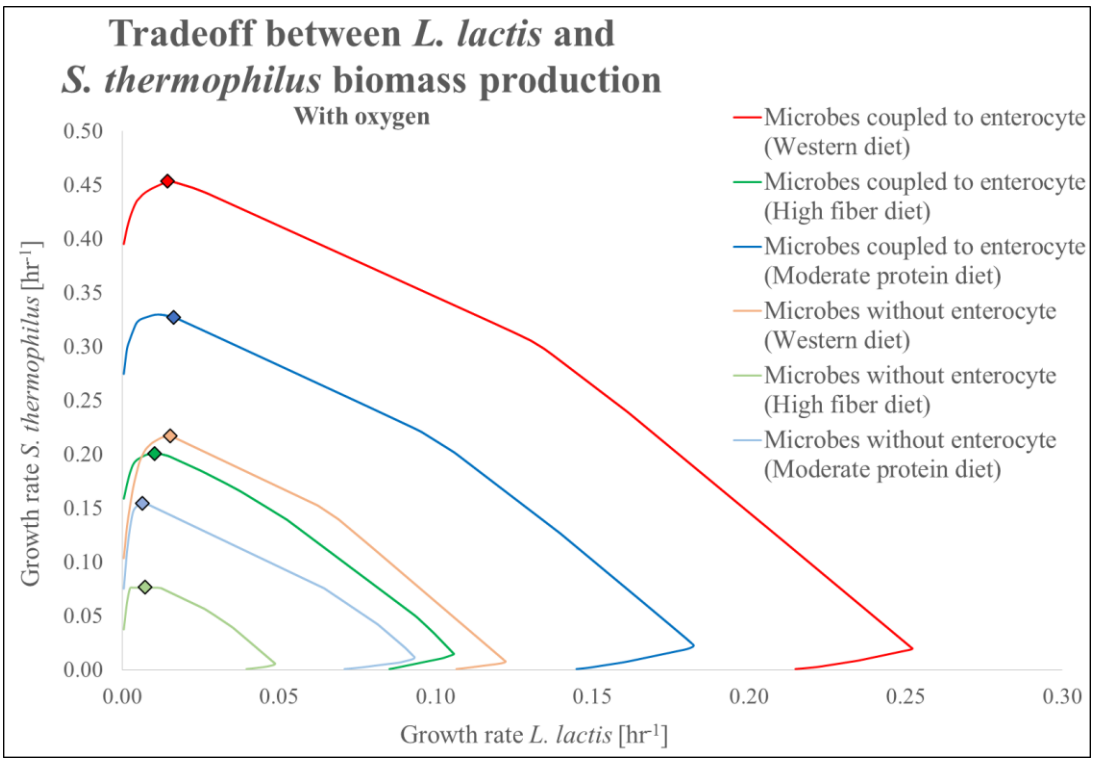

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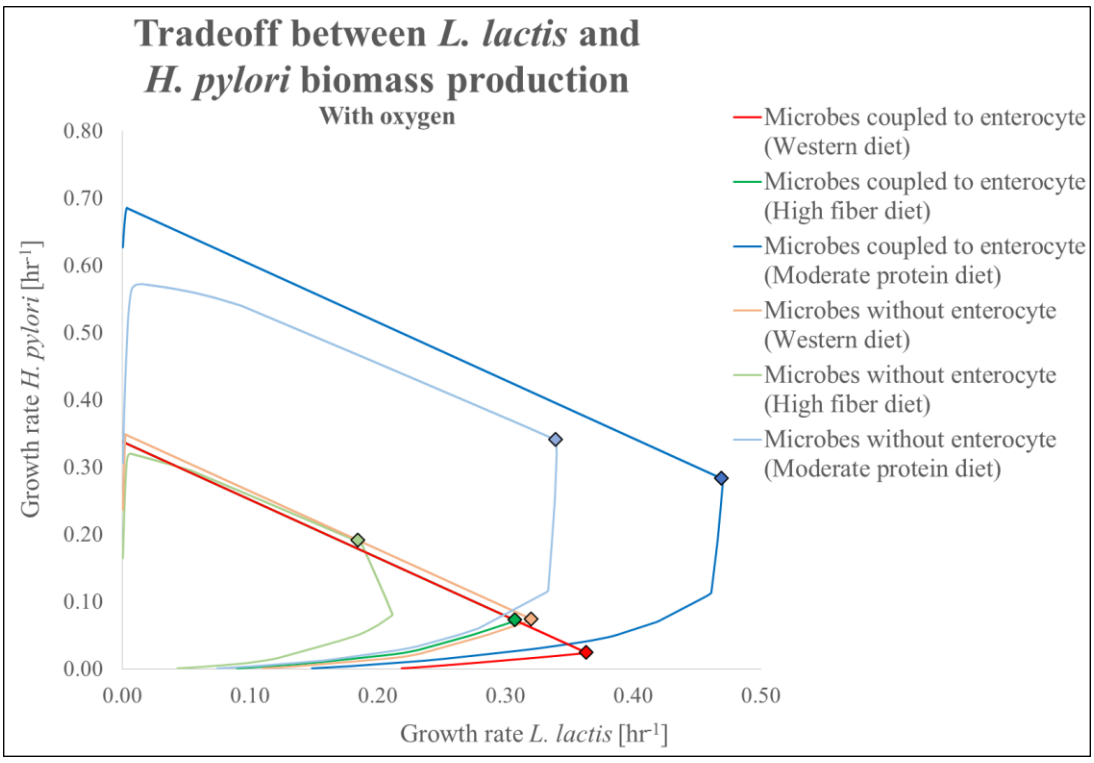

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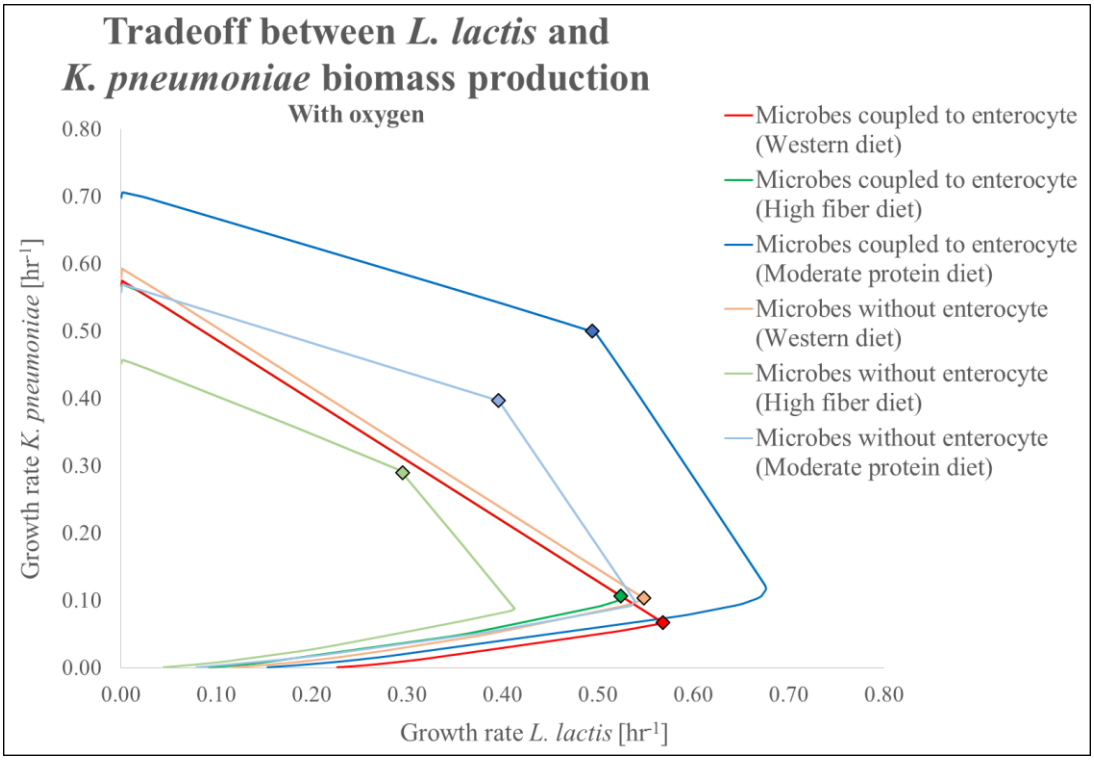

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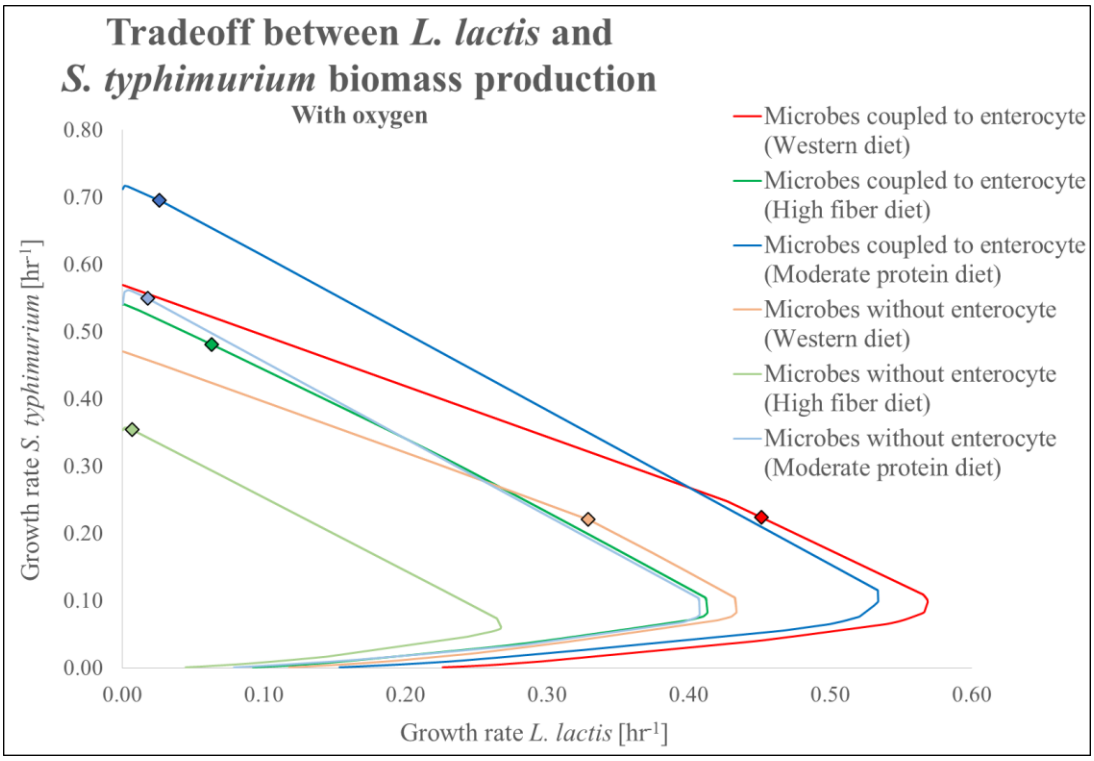

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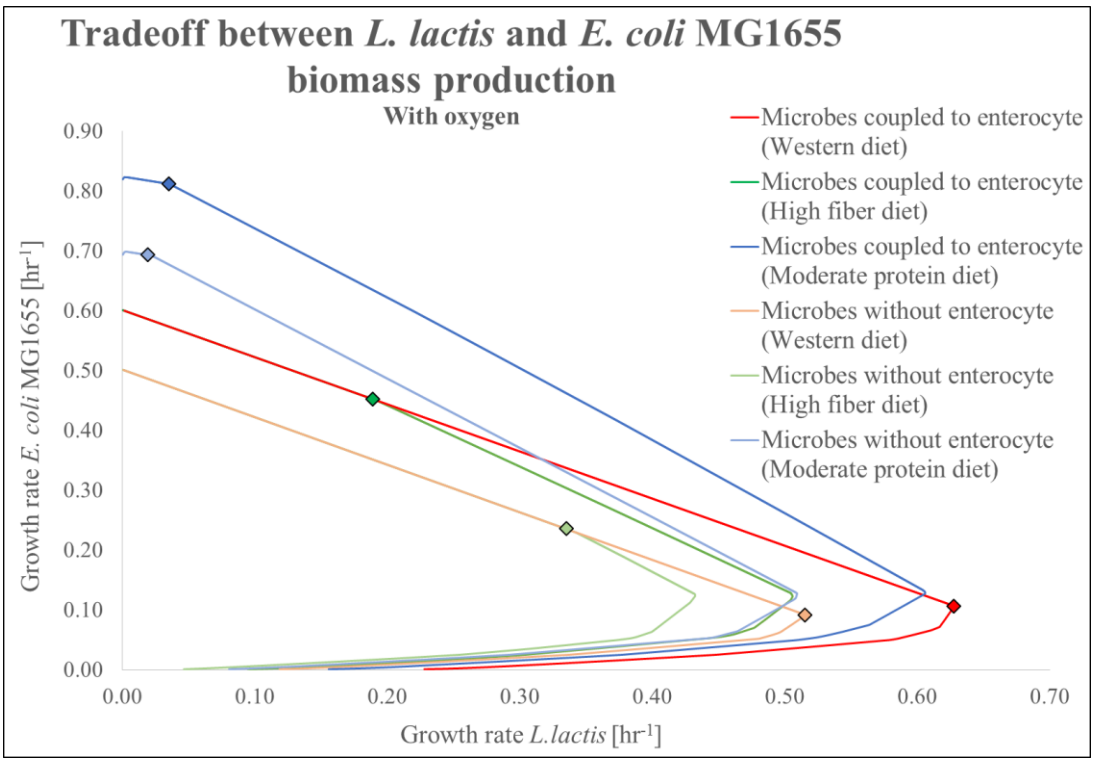

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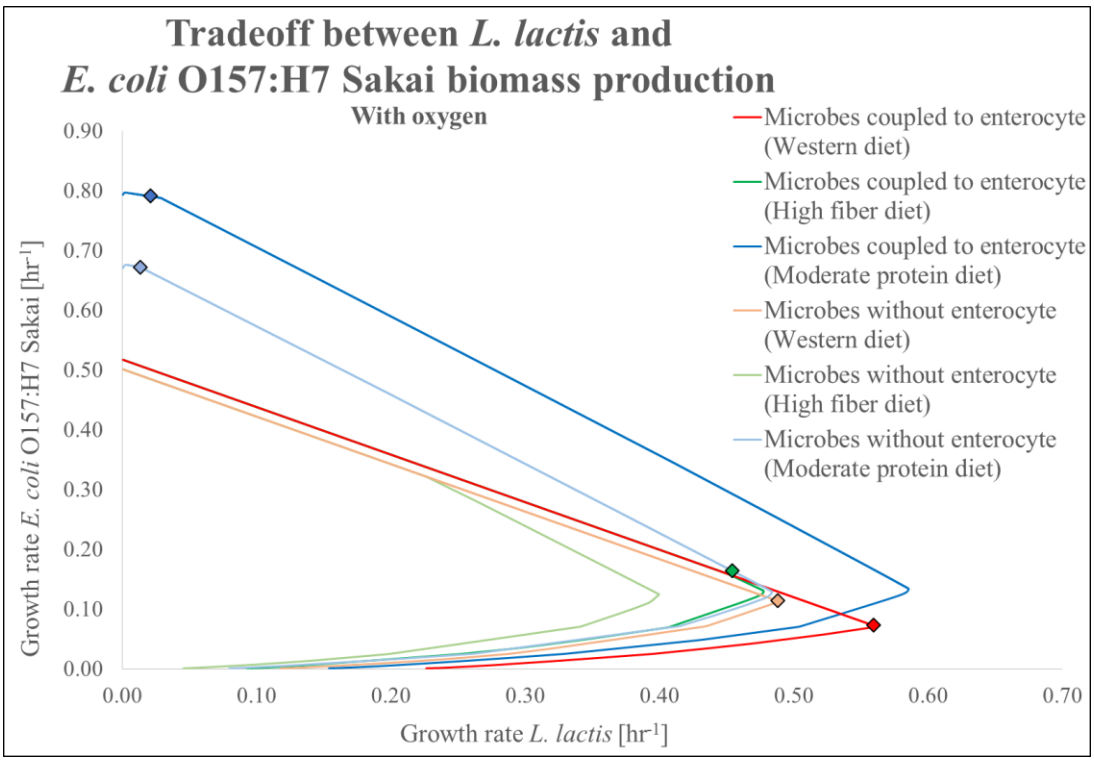

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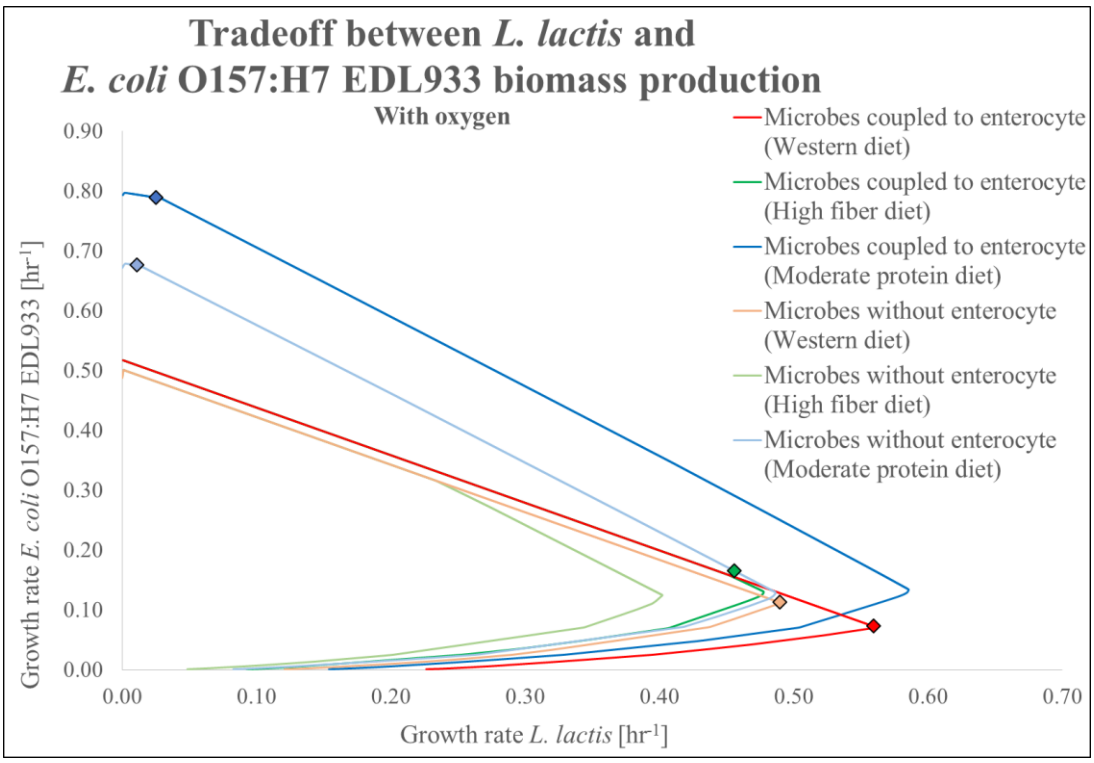

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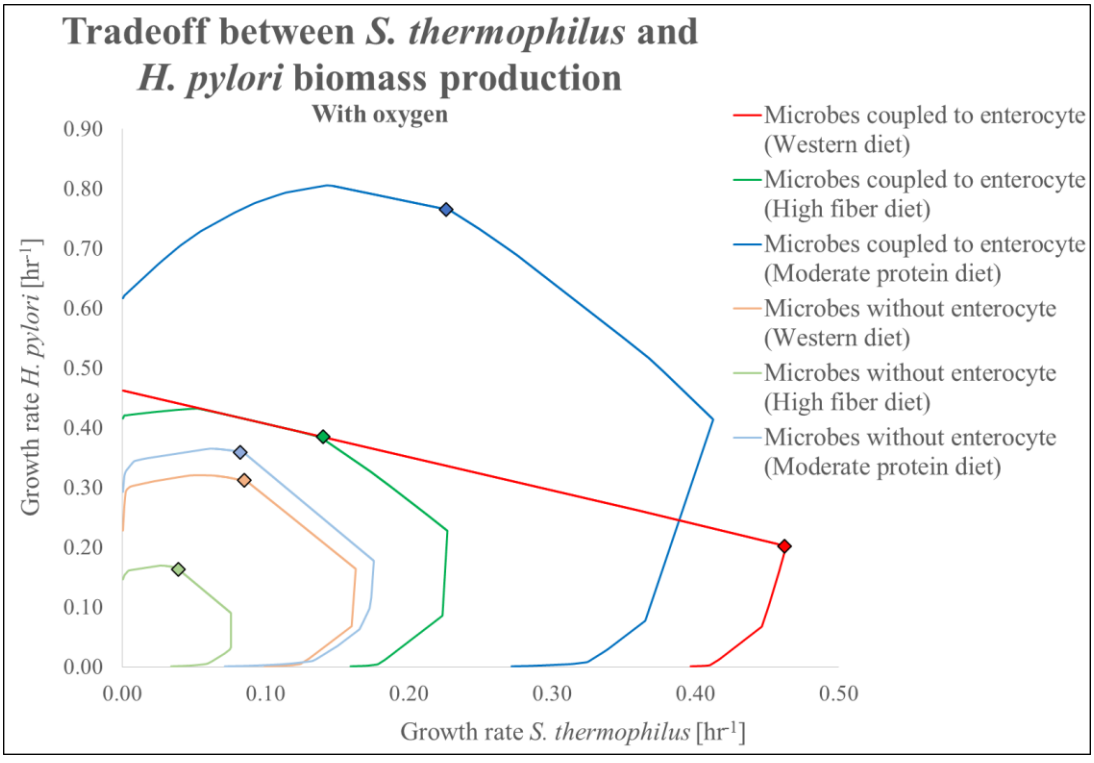

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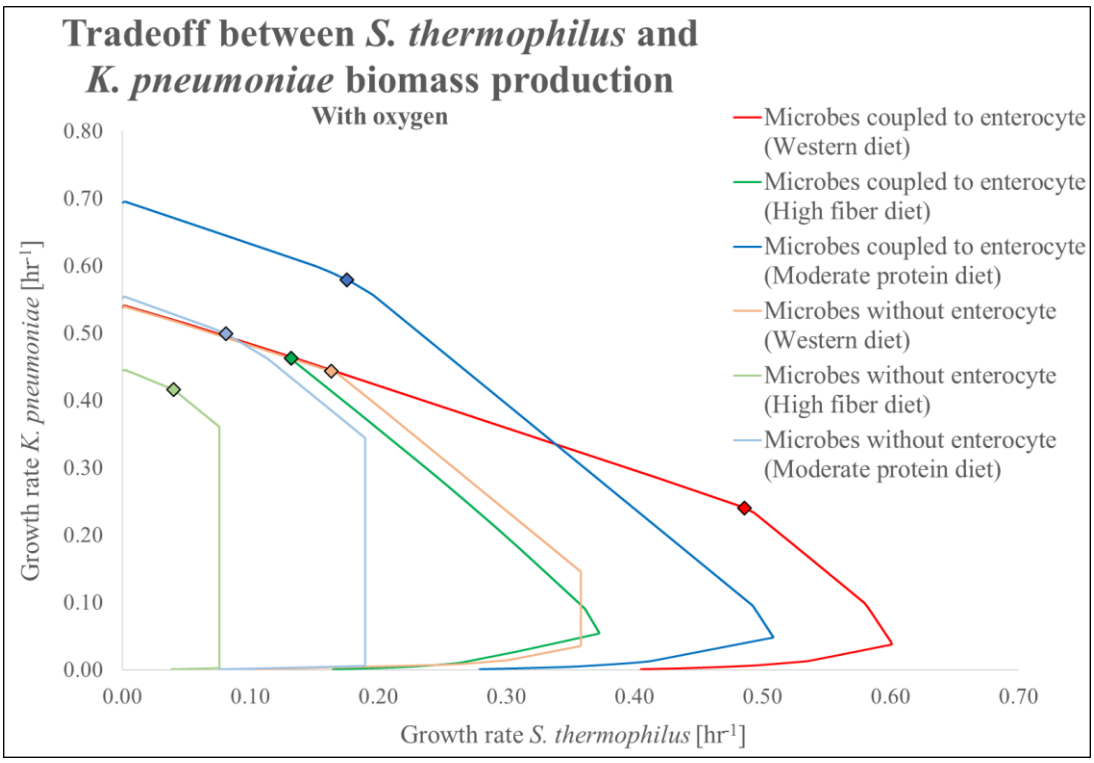

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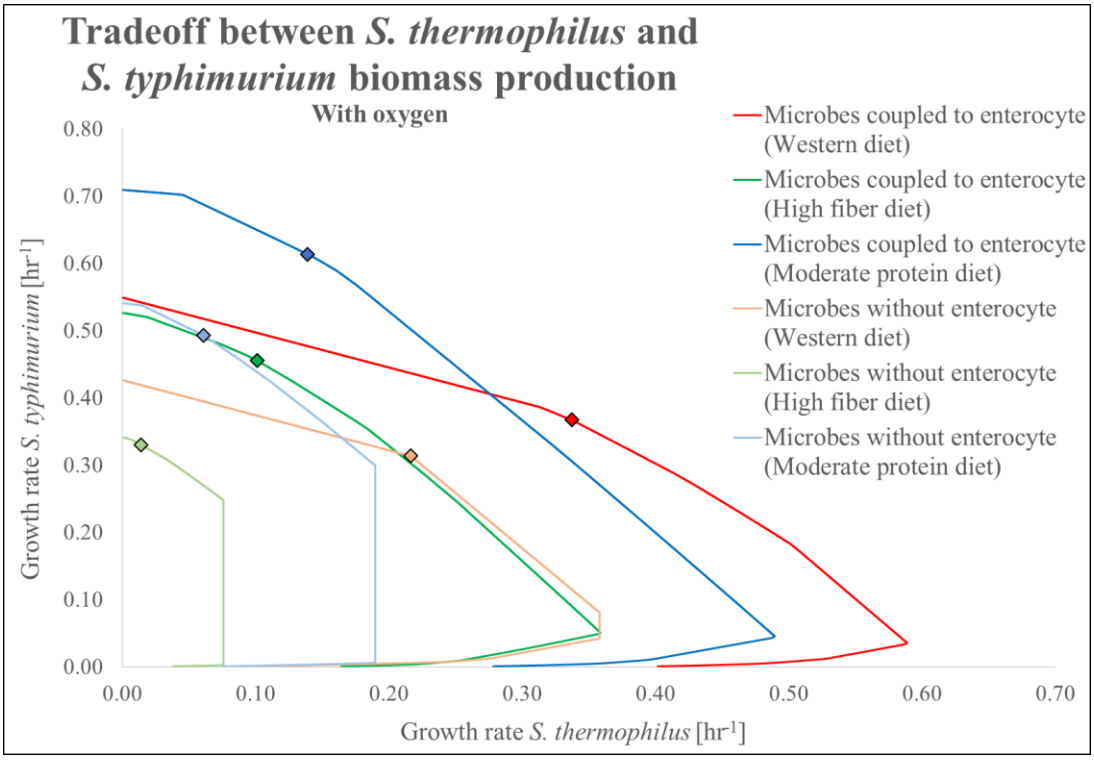

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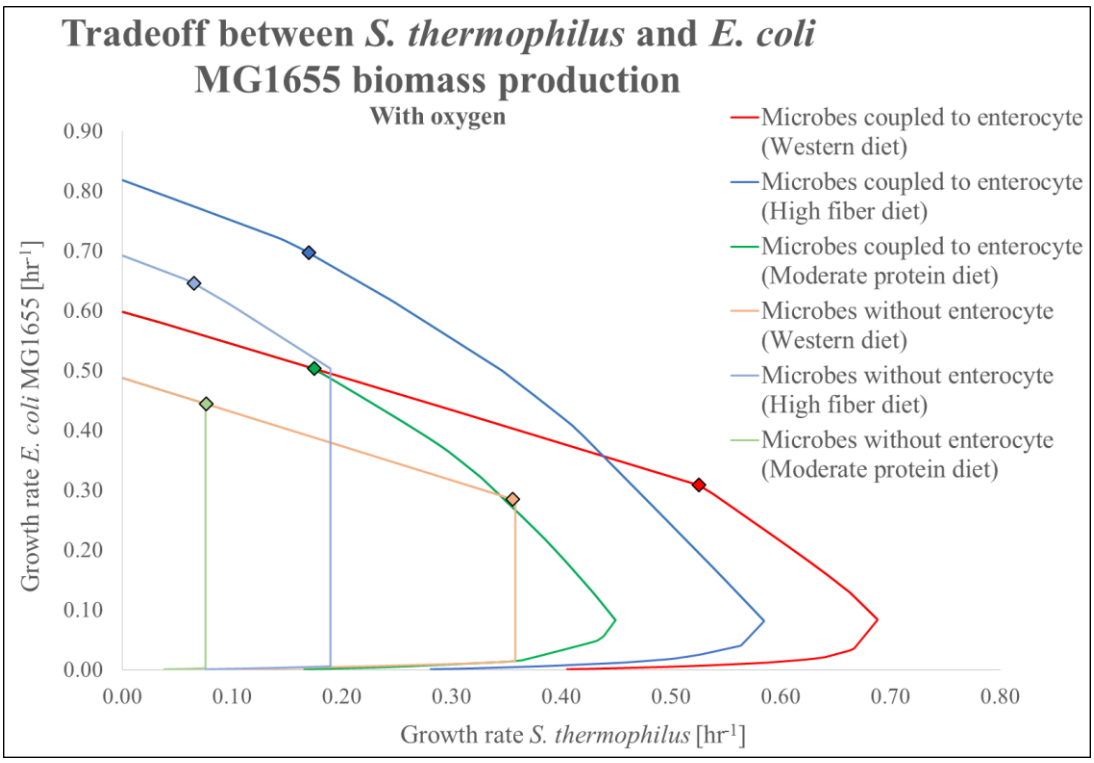

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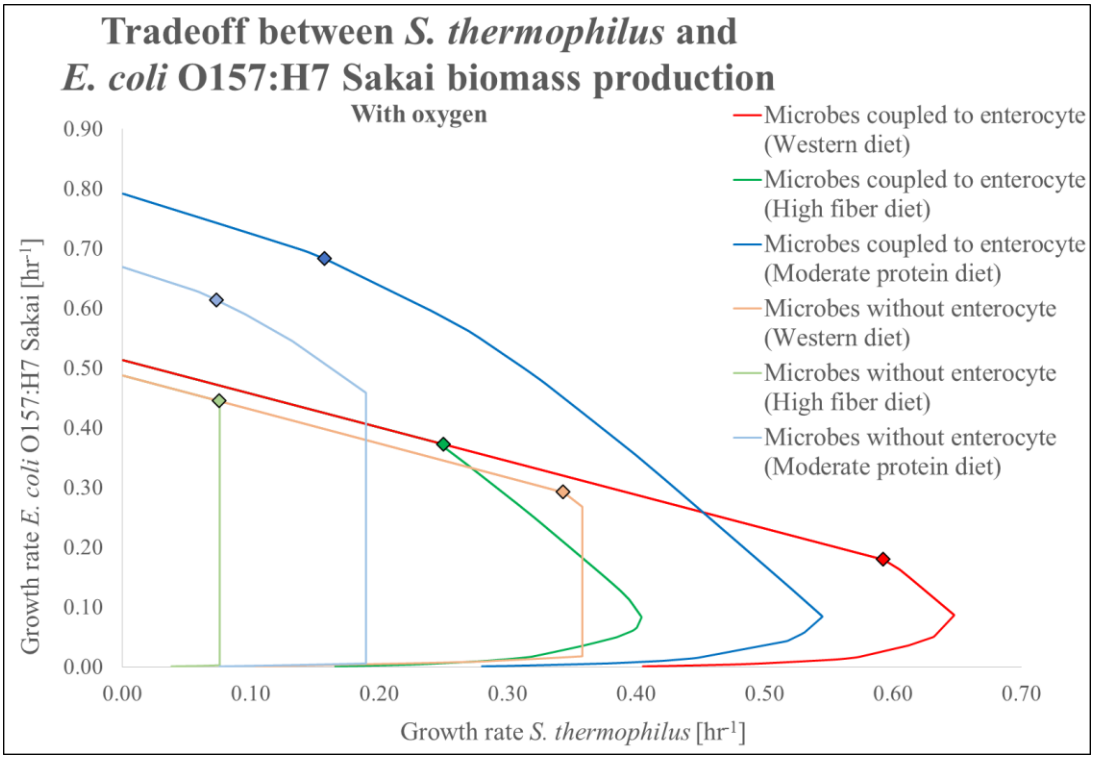

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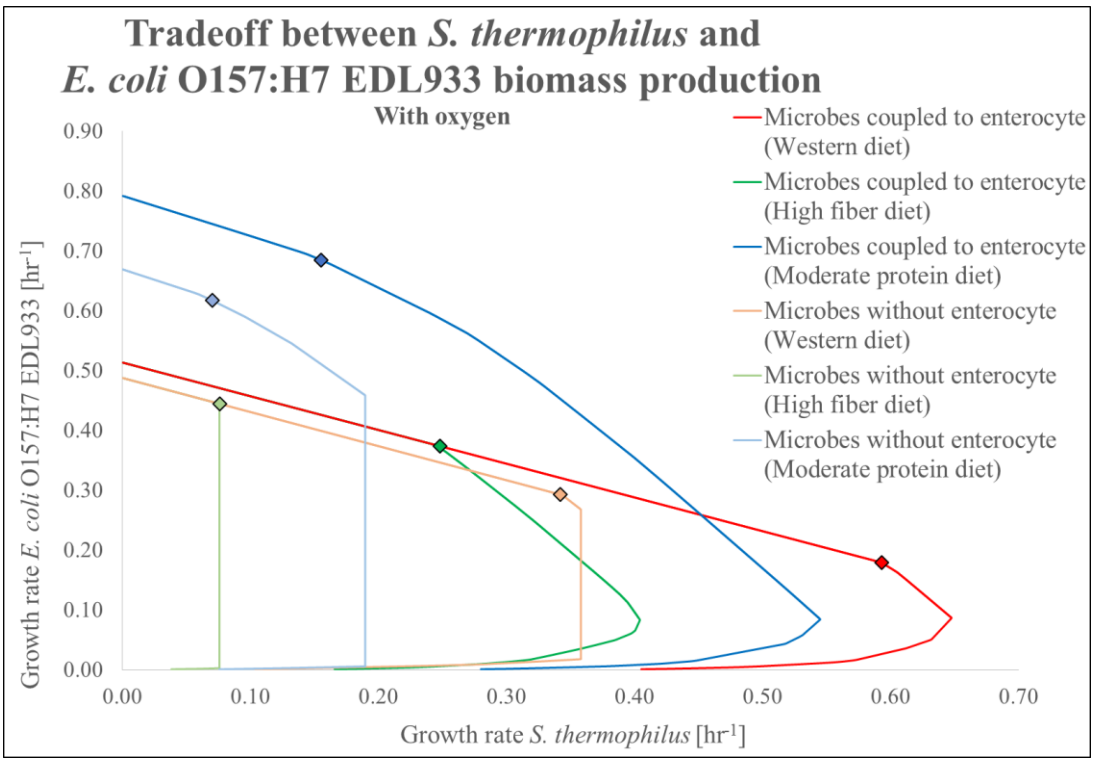
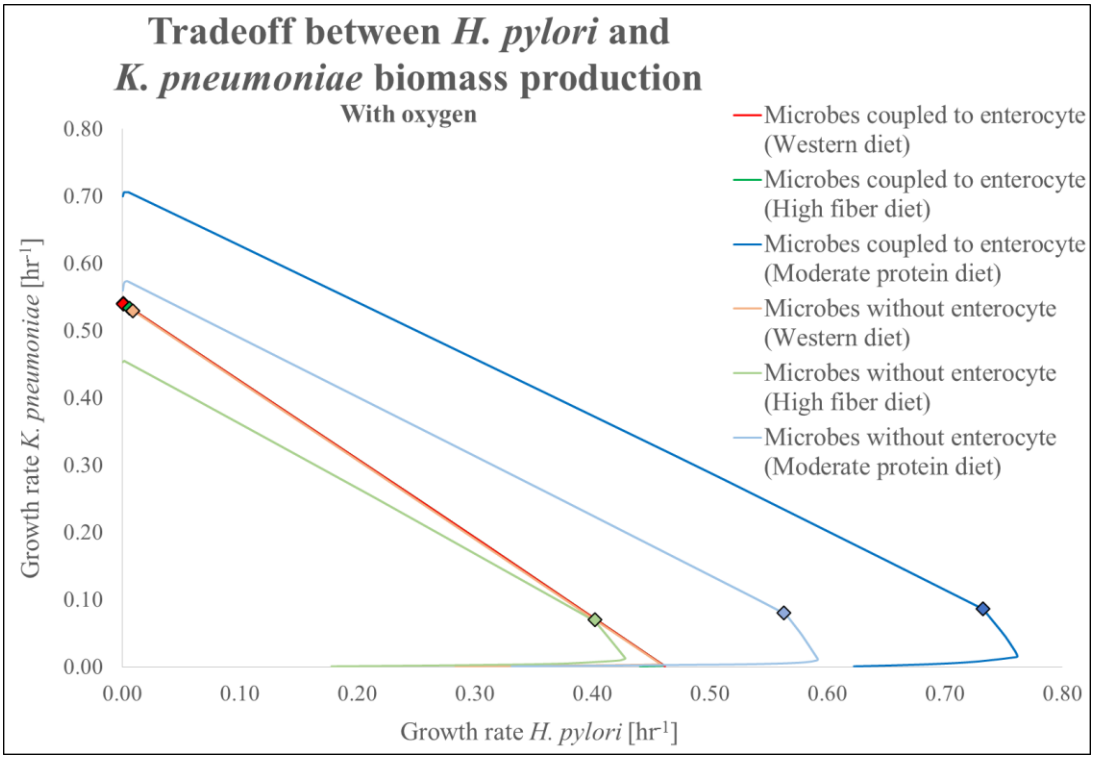


Figure S1.85



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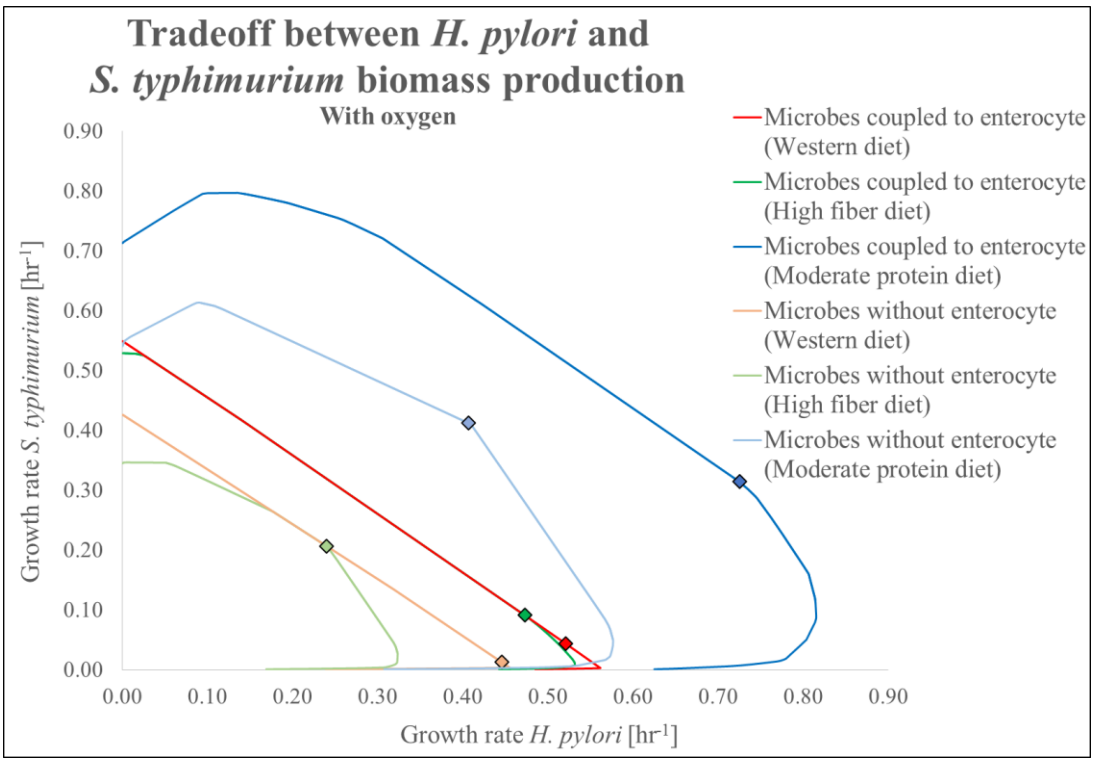

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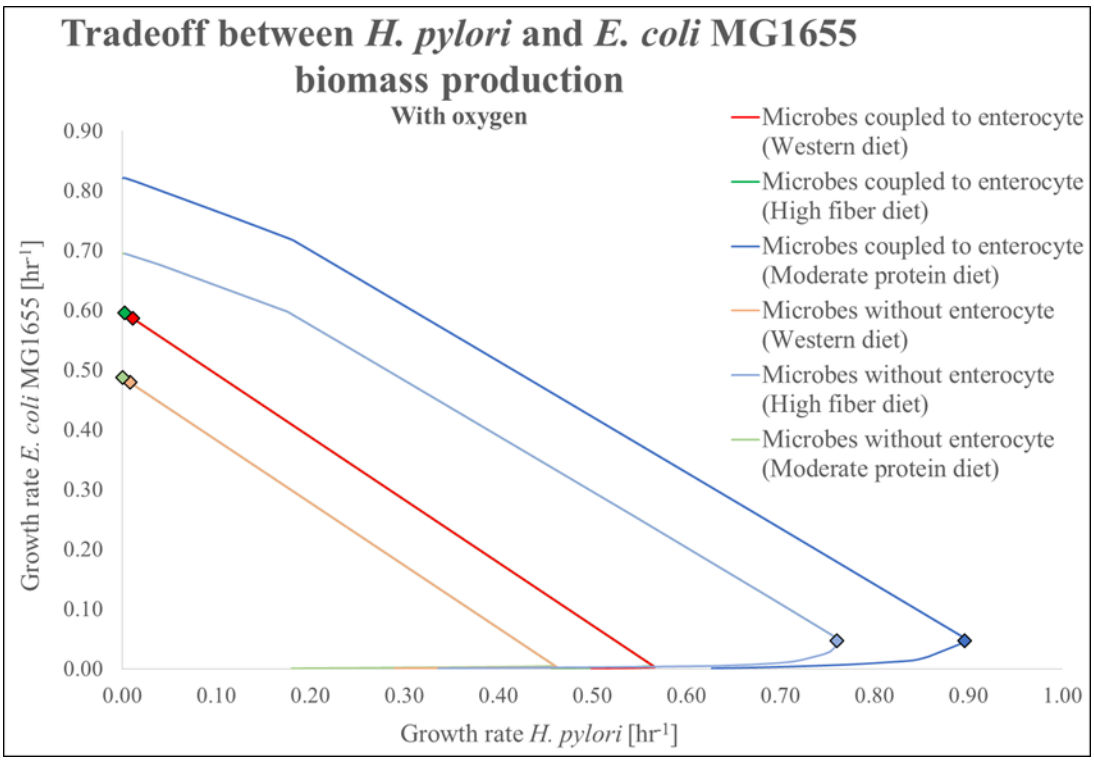

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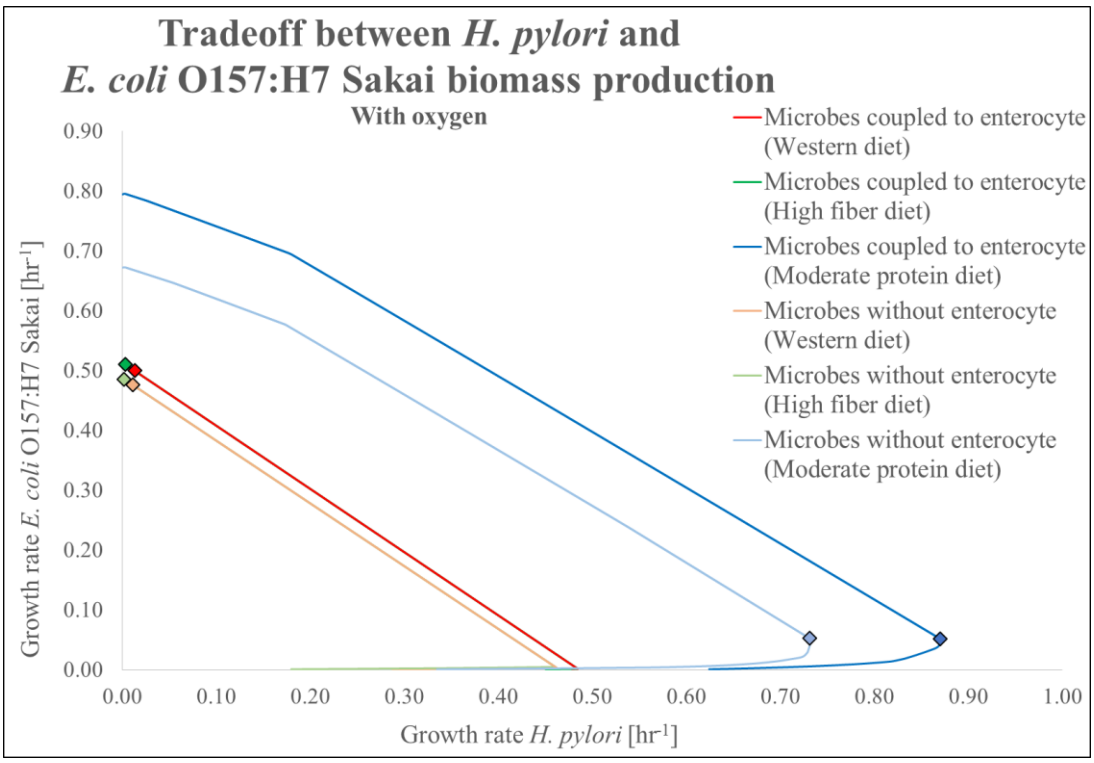

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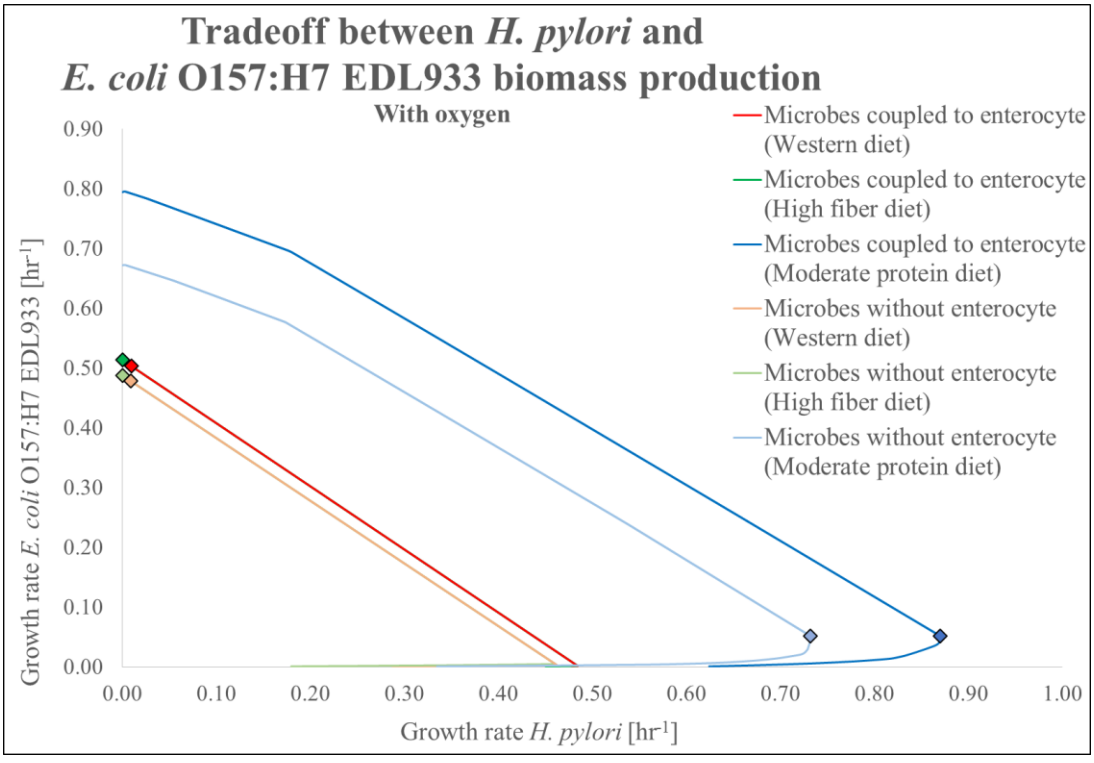

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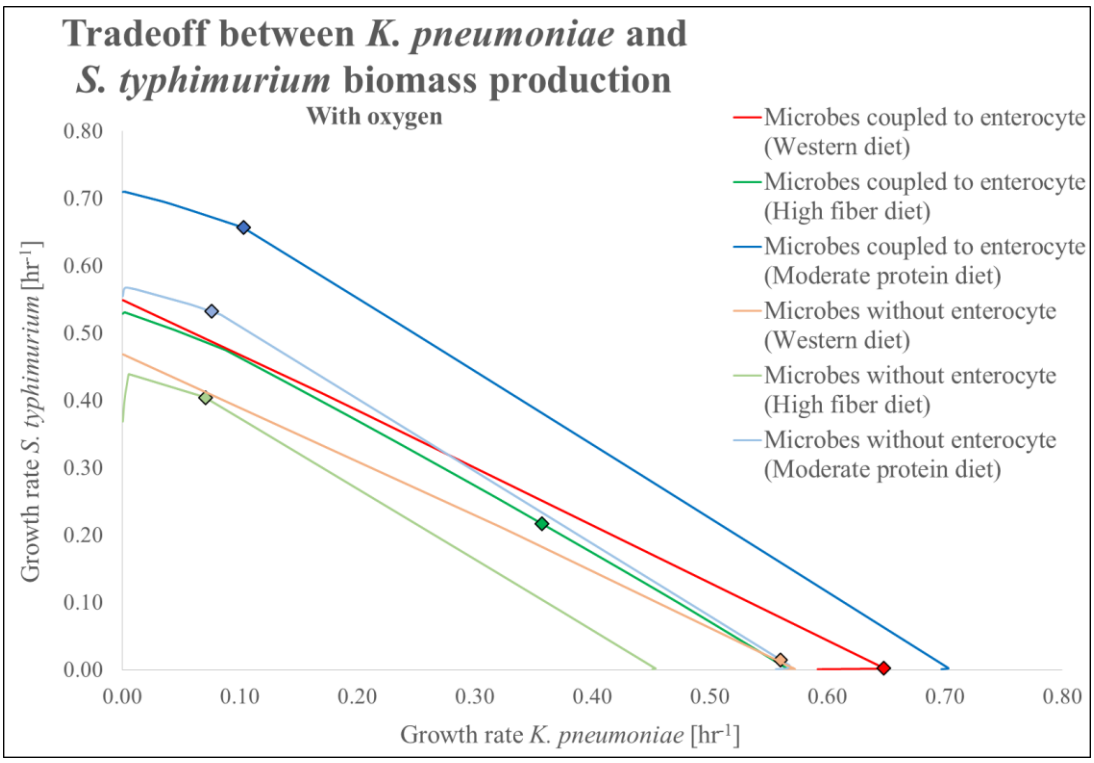

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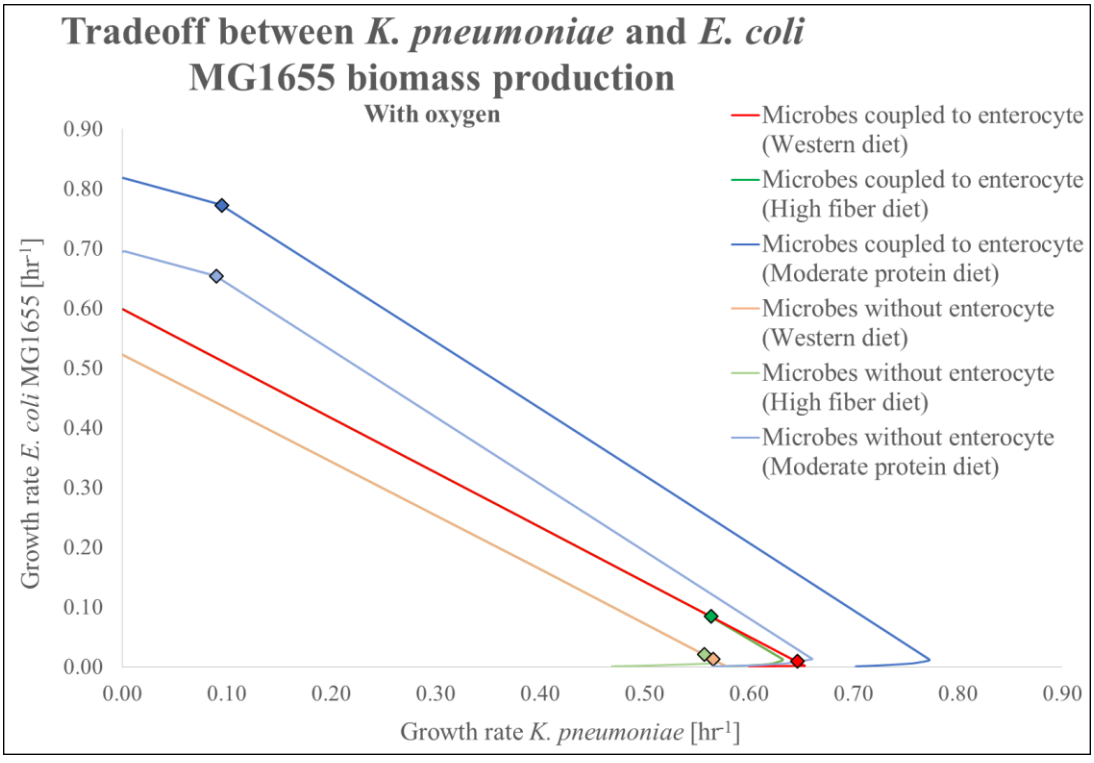

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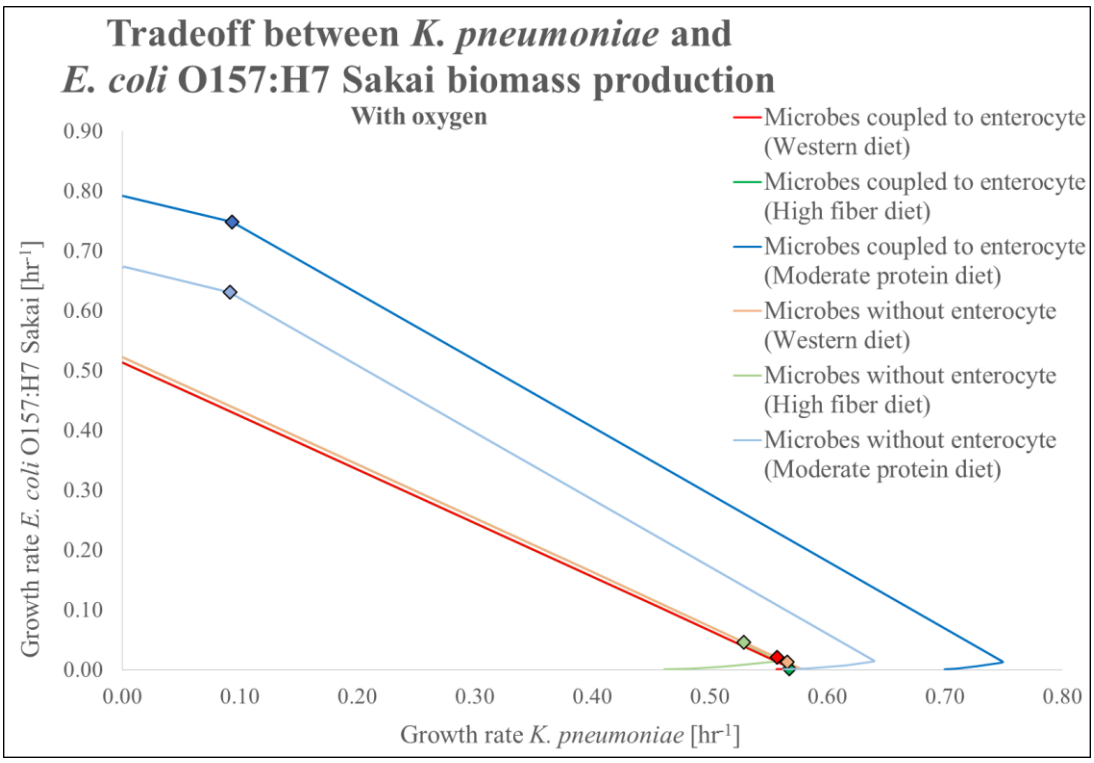

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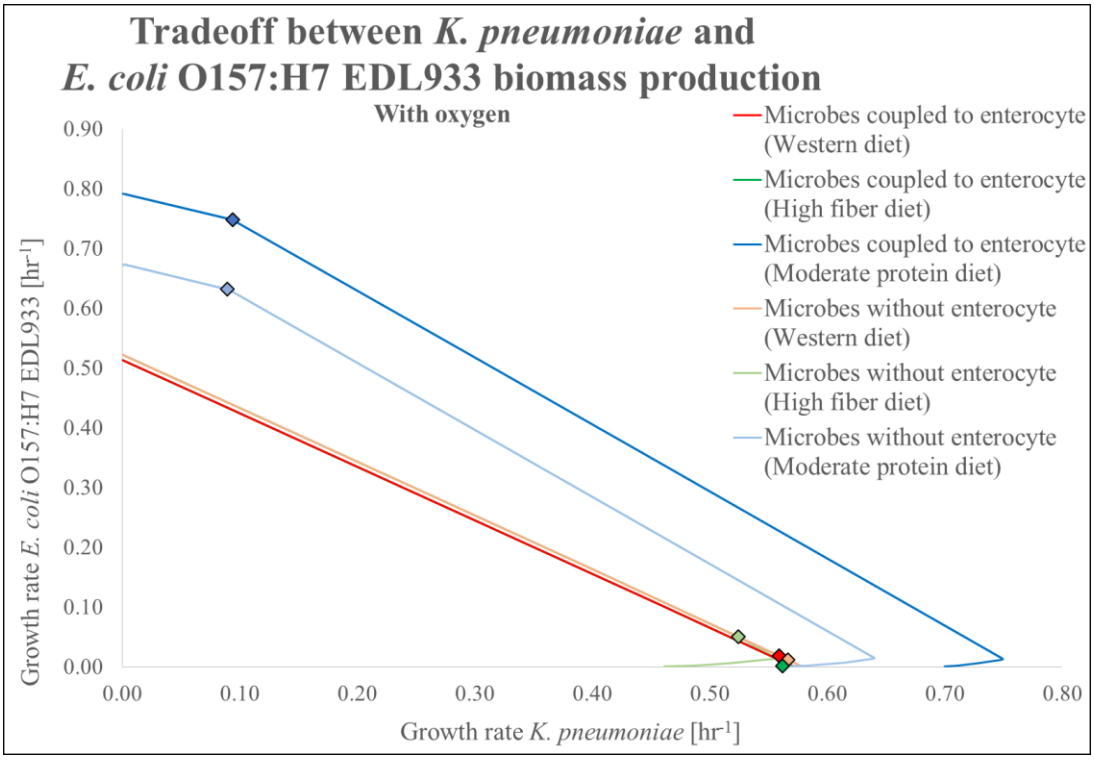

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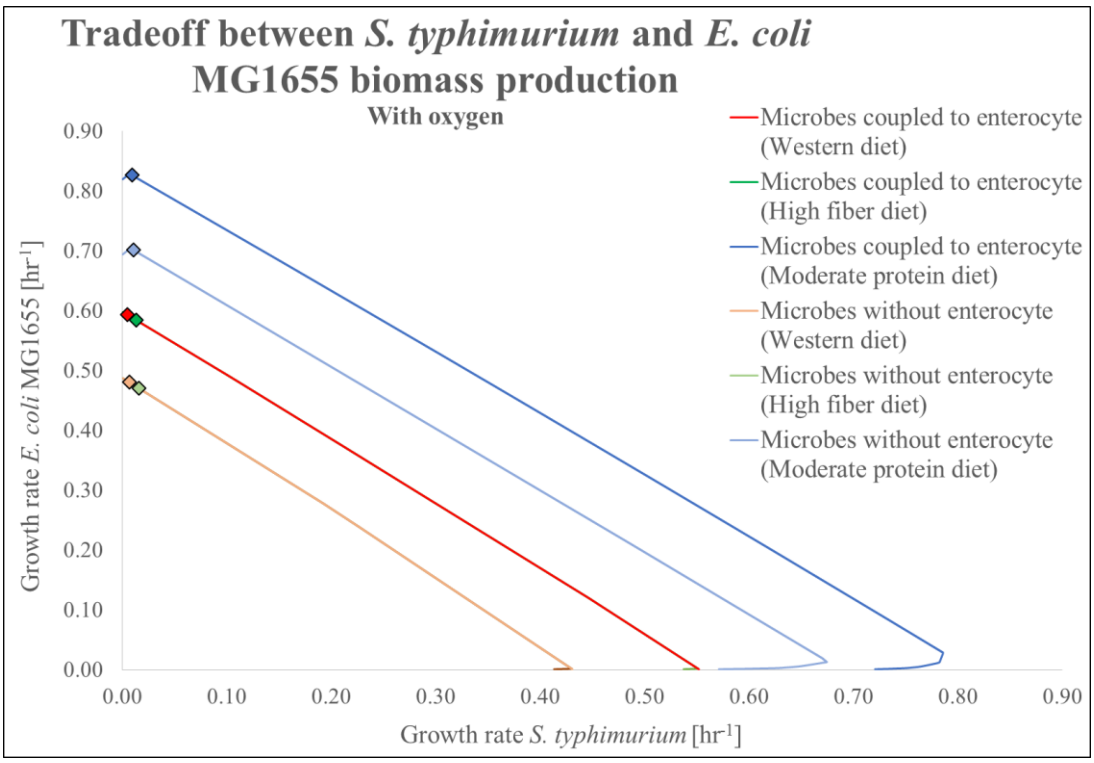

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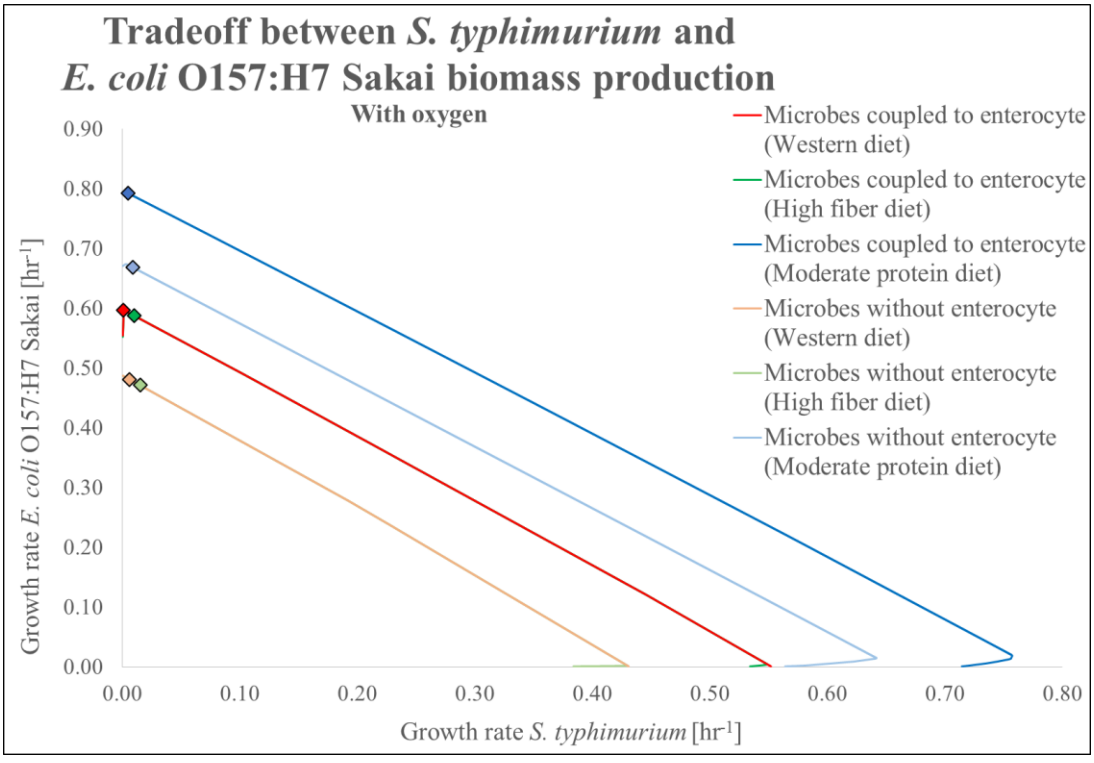

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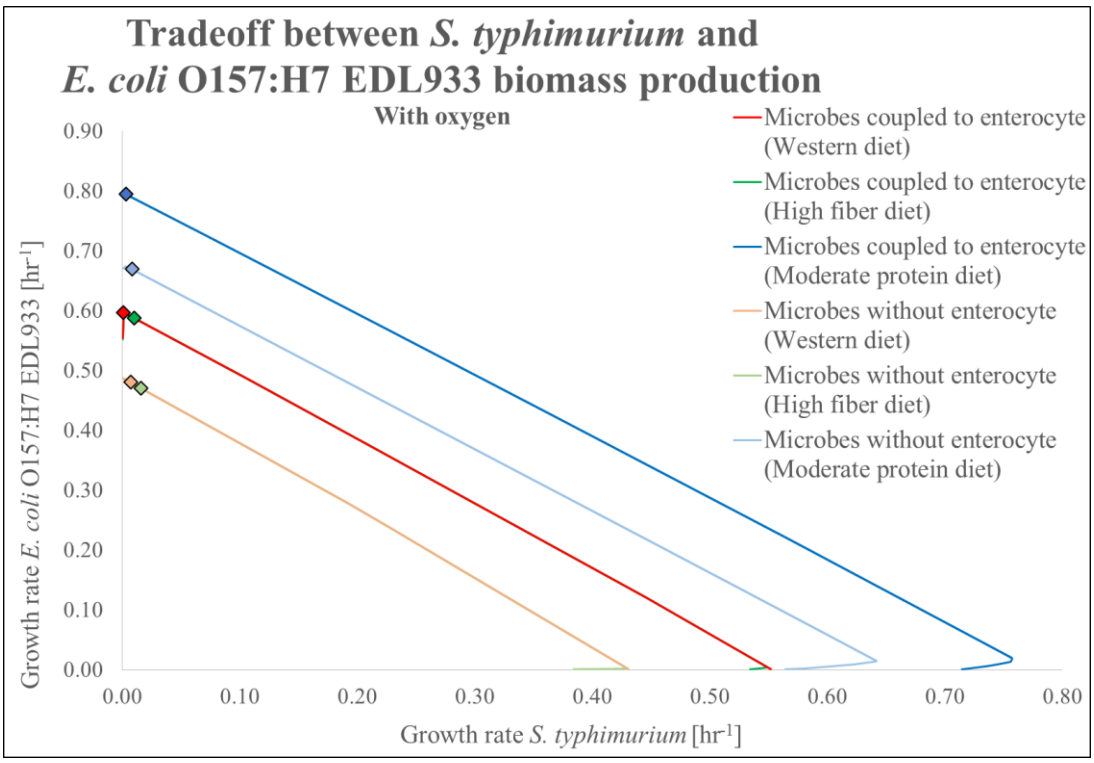

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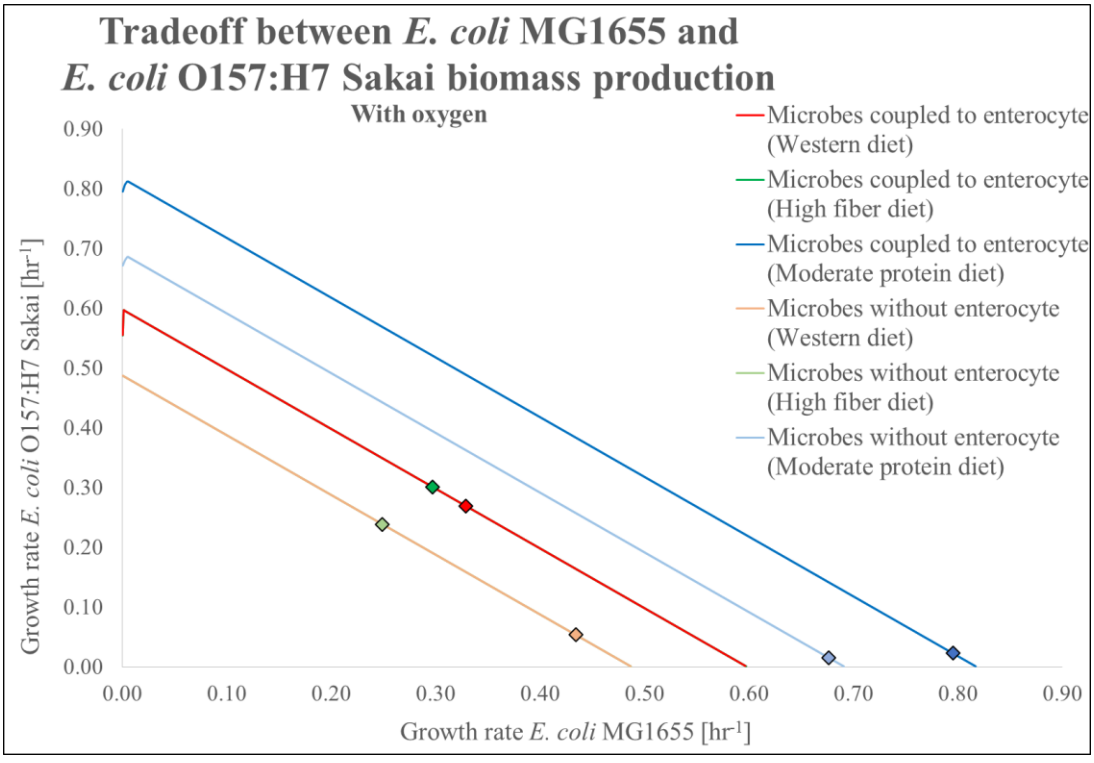

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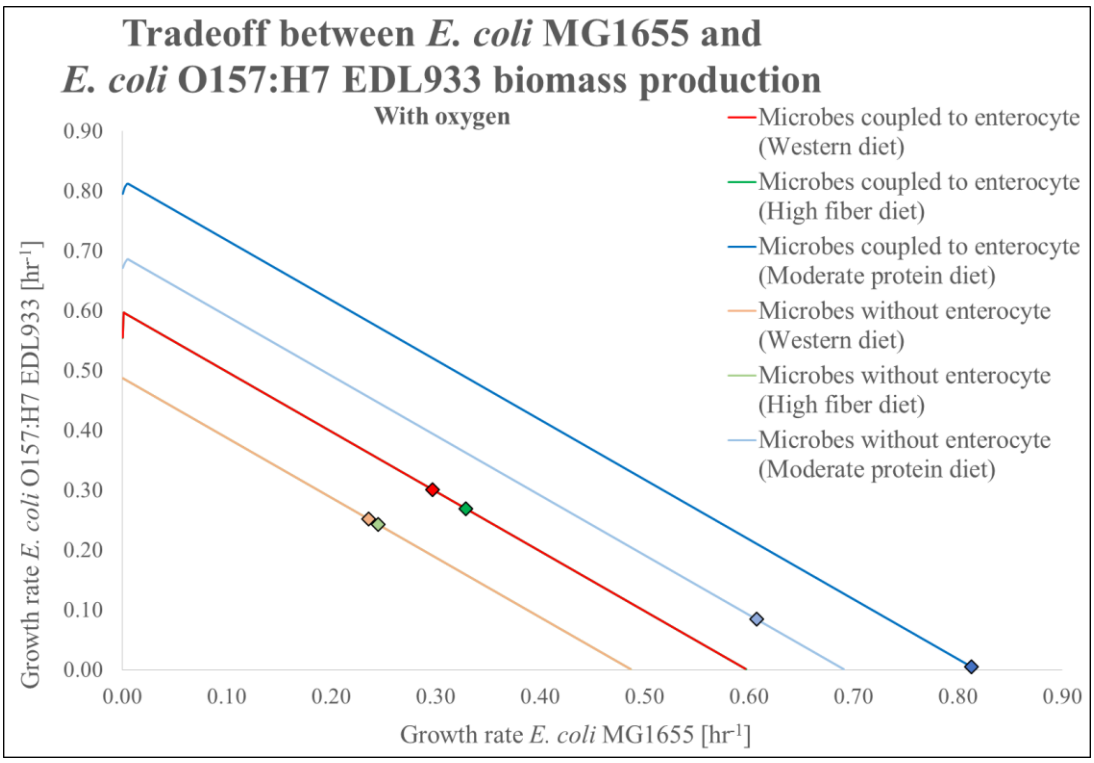

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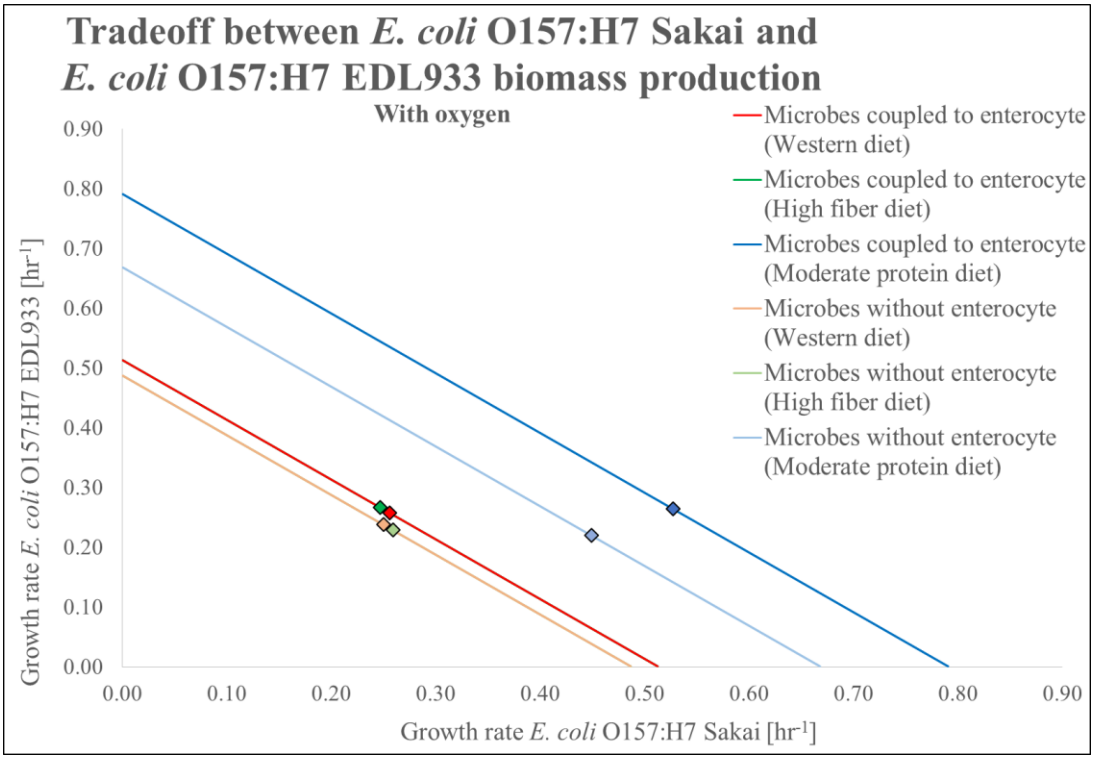

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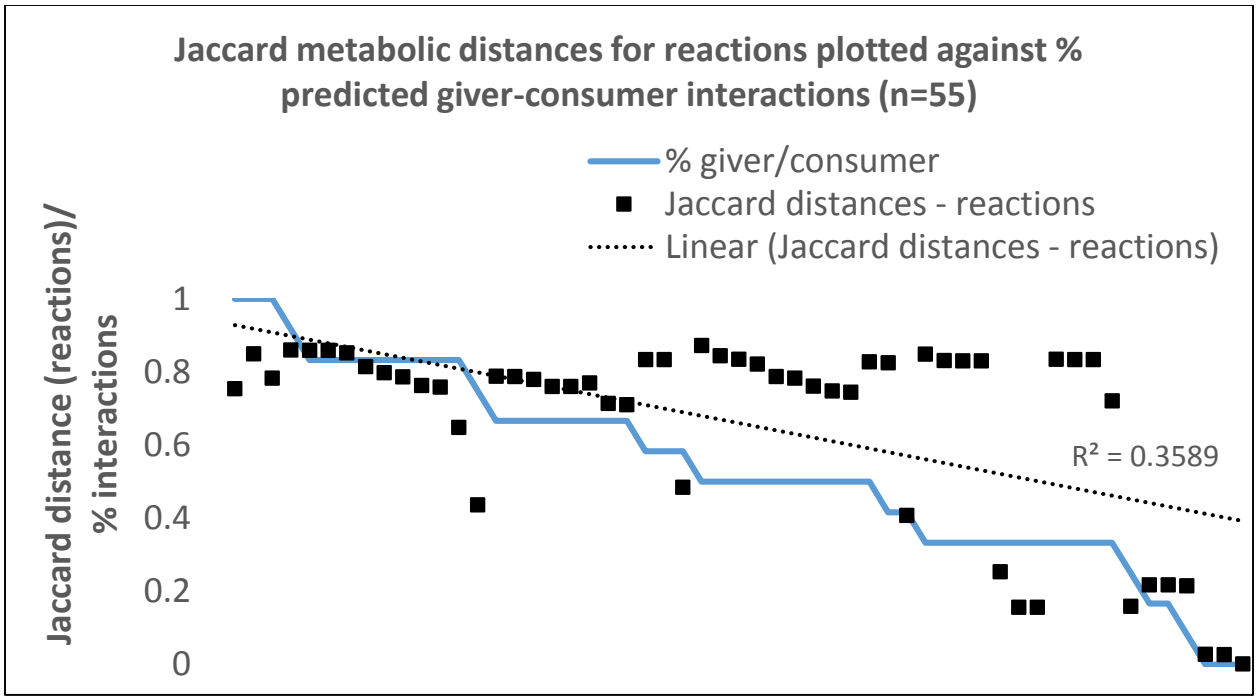


Figure S2a): Jaccard metabolic distances for each pair (reactions) plotted against percentage of giver/ consumer interactions for each pair, and display of R-squared value for the correlation between Jaccard distance and giver/ consumer interactions.

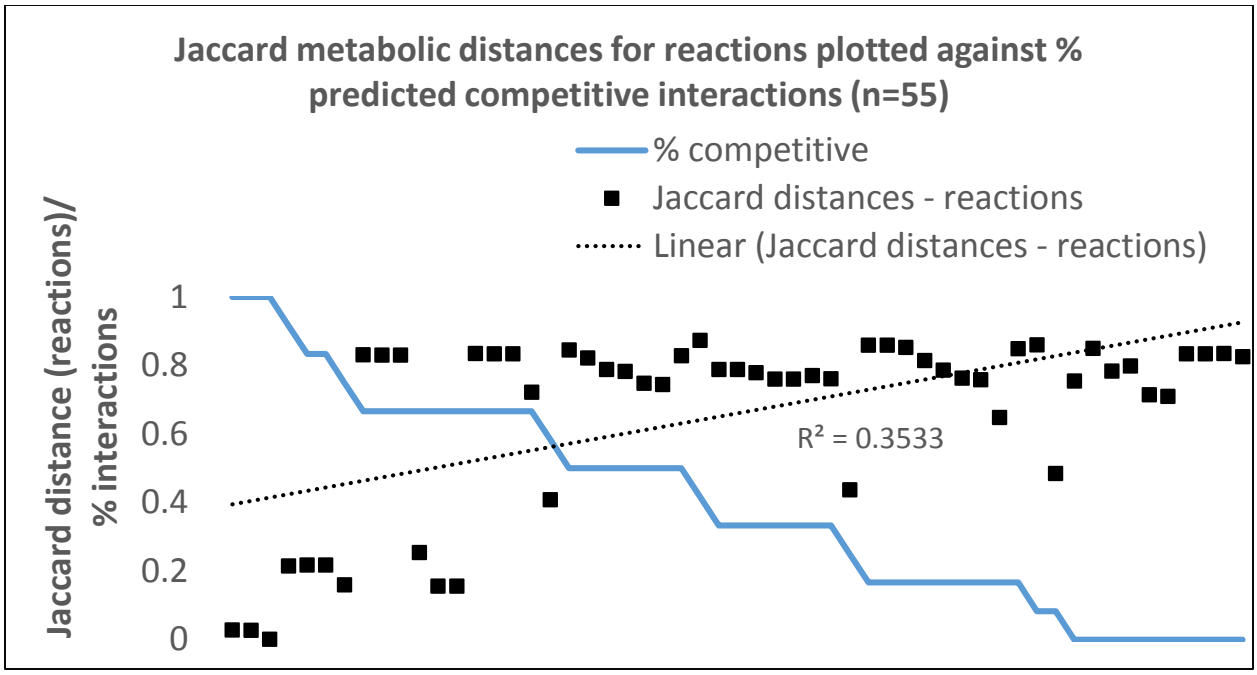


Figure S2b): Jaccard metabolic distances for each pair (reactions) plotted against percentage of competitive interactions for each pair, and display of R-squared value for the correlation between Jaccard distance and competitive interactions.

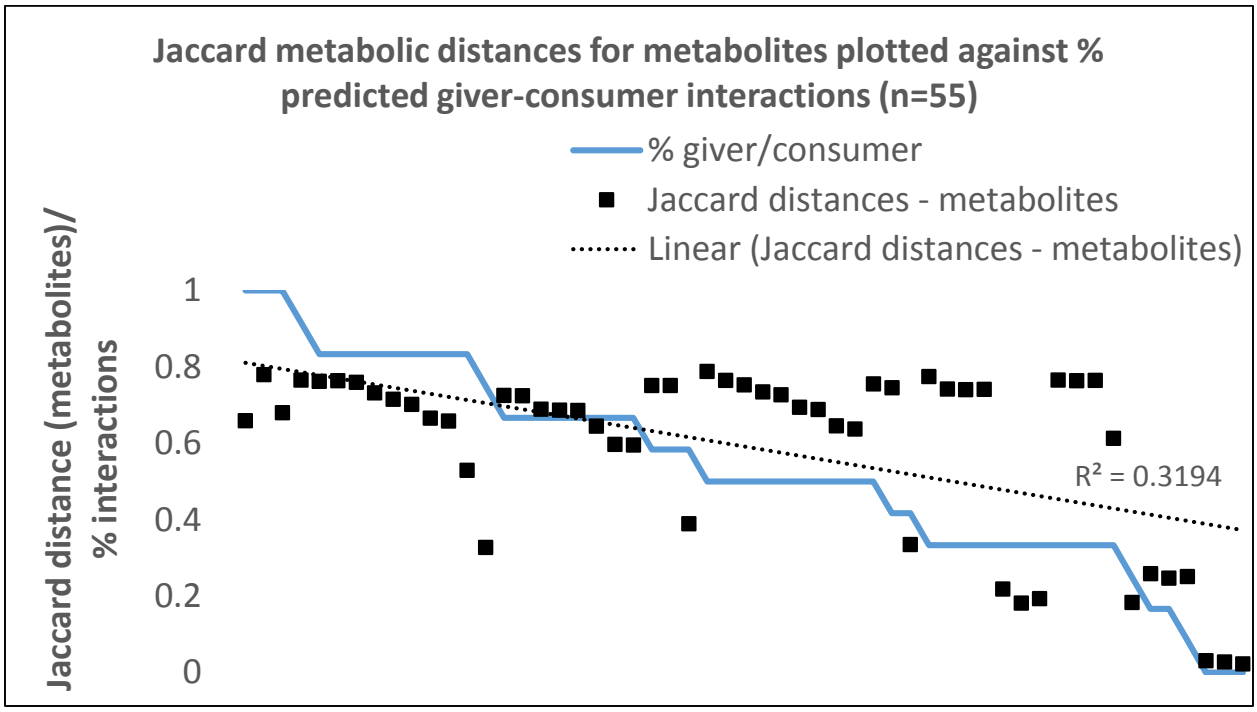


Figure S2c): Jaccard metabolic distances for each pair (metabolites) plotted against percentage of giver/ consumer interactions for each pair, and display of R-squared value for the correlation between Jaccard distance and giver/ consumer interactions.

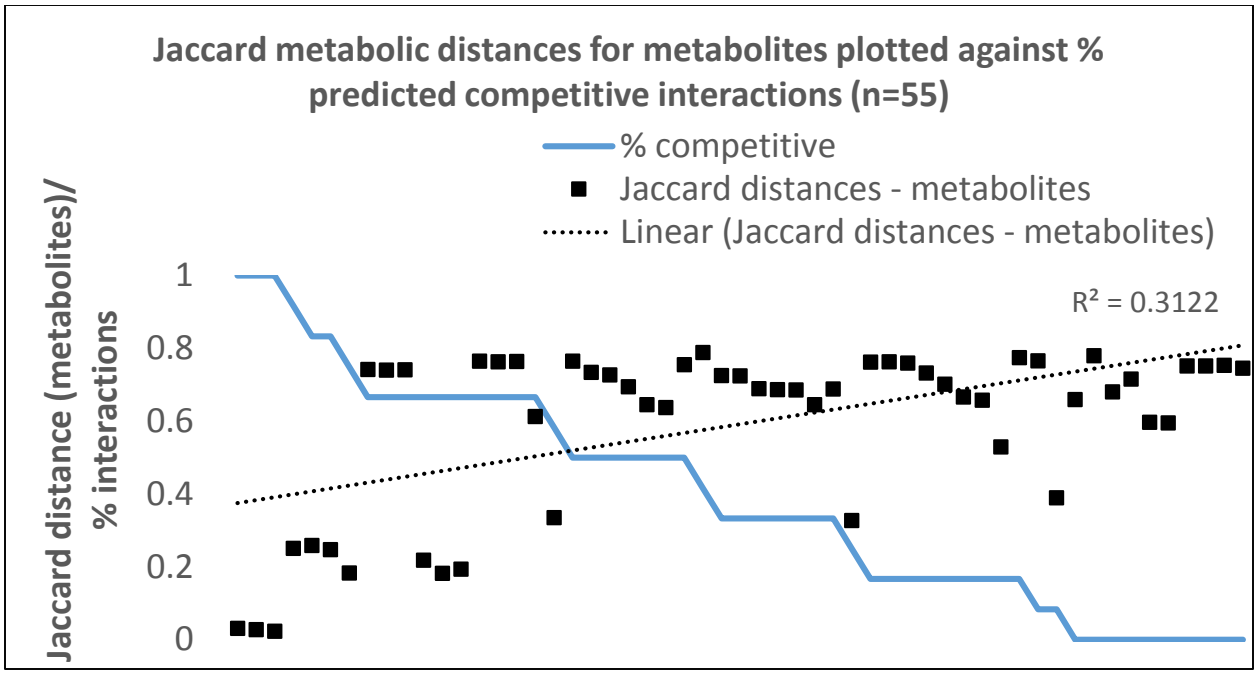


Figure S2d): Jaccard metabolic distances for each pair (metabolites) plotted against percentage of competitive interactions for each pair, and display of R-squared value for the correlation between Jaccard distance and competitive interactions.

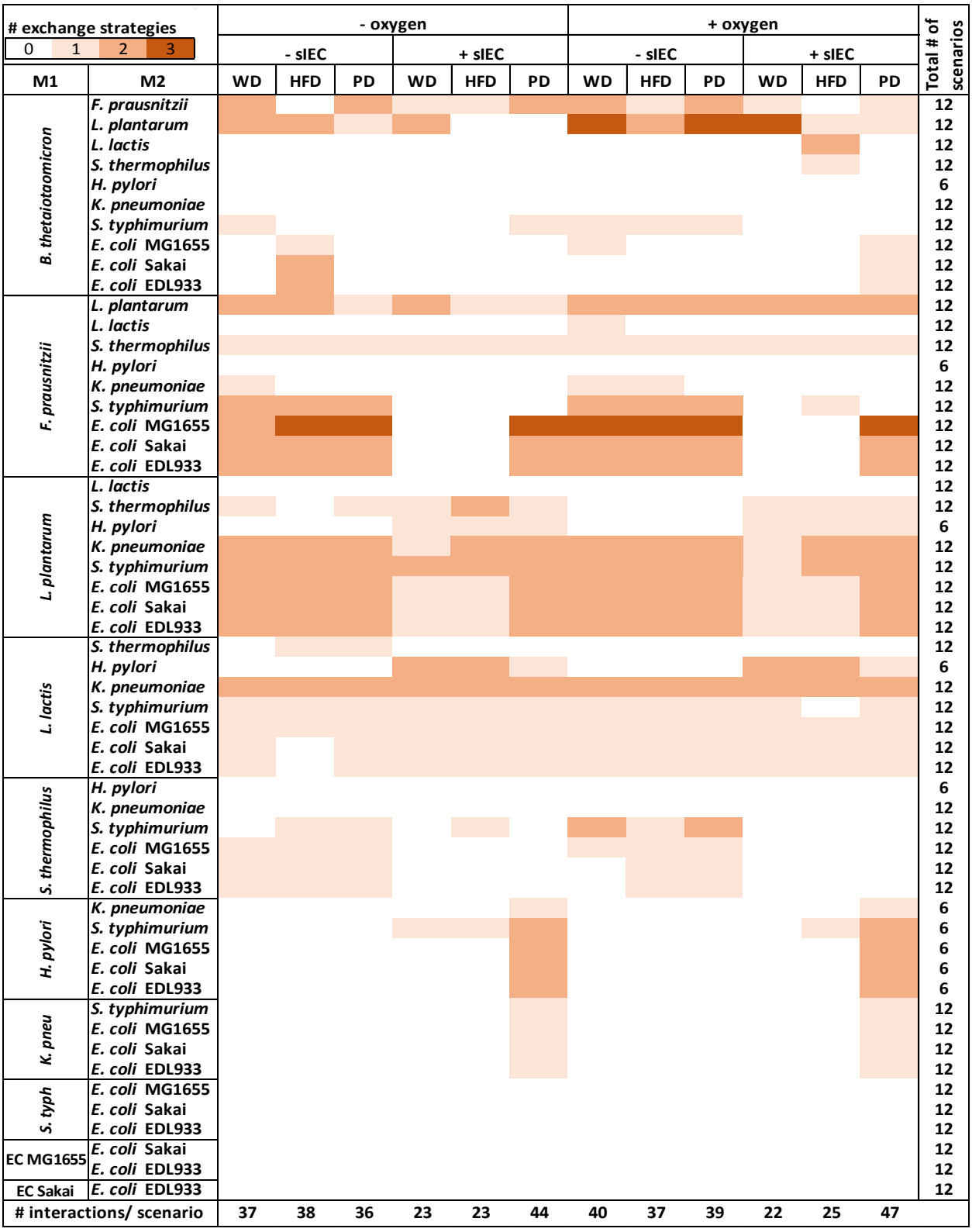
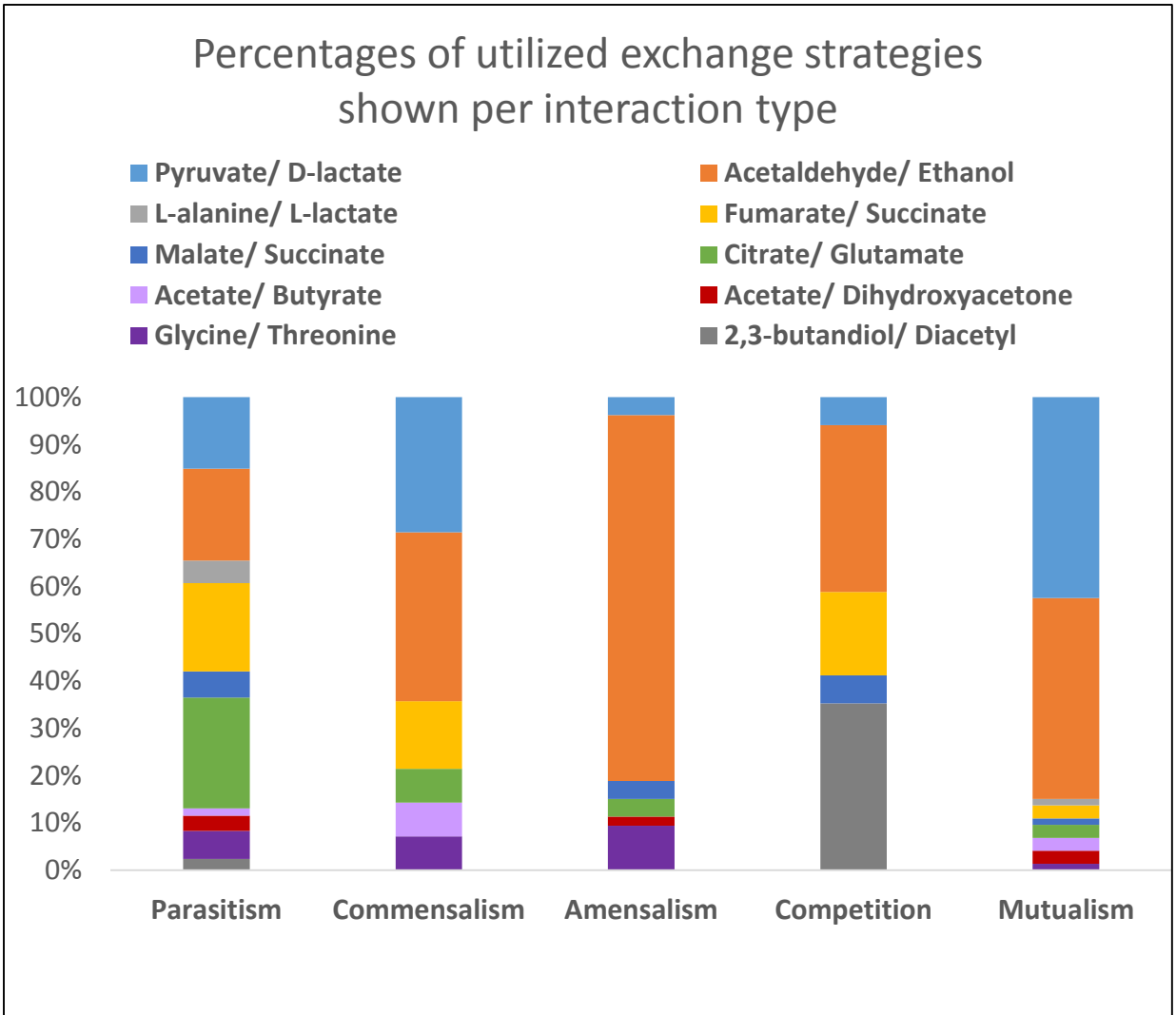


Figure S3: Number of metabolic exchange strategies (defined in Table S6) displayed per pair in the 12 scenarios. WD = Western diet, HFD = high fiber diet, PD = protein diet, sIEc = small intestinal enterocyte.



	Total exchange strategies #	Pairs #	Exchanges/pair
Parasitism	252	299	0.84
Commensalism	14	21	0.67
Neutralism	0	1	0.00
Amensalism	53	175	0.30
Competition	17	67	0.25
Mutualism	73	37	1.97

Figure S4: Number of metabolite exchange strategies (defined in Table S6) computed per interaction type and pair, and percentage of exchange strategies computed for each interaction type.

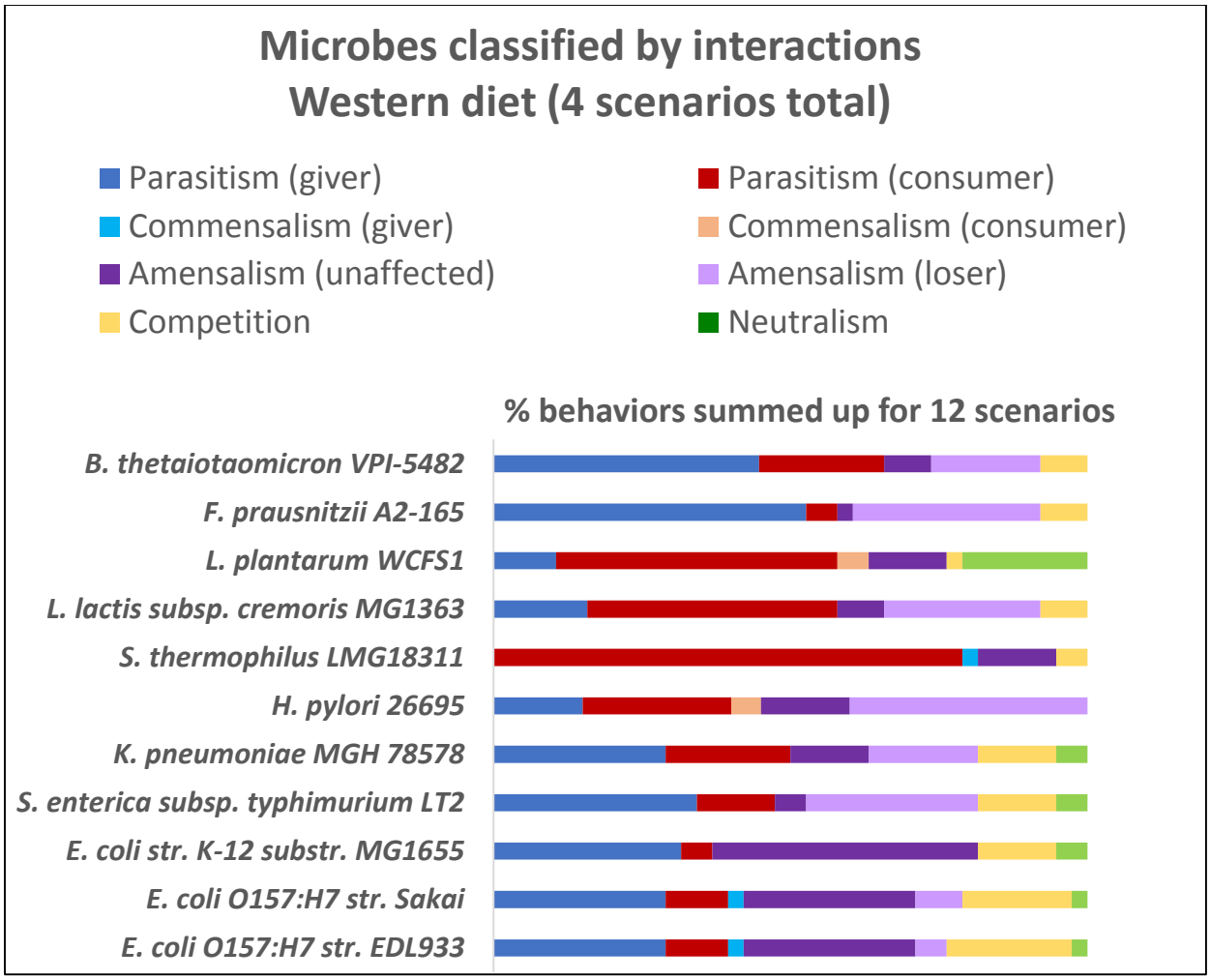


Figure S5a: Microbes classified by % interactions participated in on Western diet. The plot sums up 40 interactions per microbe in four scenarios (Figure 2c), with the exception of *H. pylori* for which only 20 interactions were calculated as no growth was predicted without oxygen. In total, 400 interactions were predicted on Western diet (200 pairs).

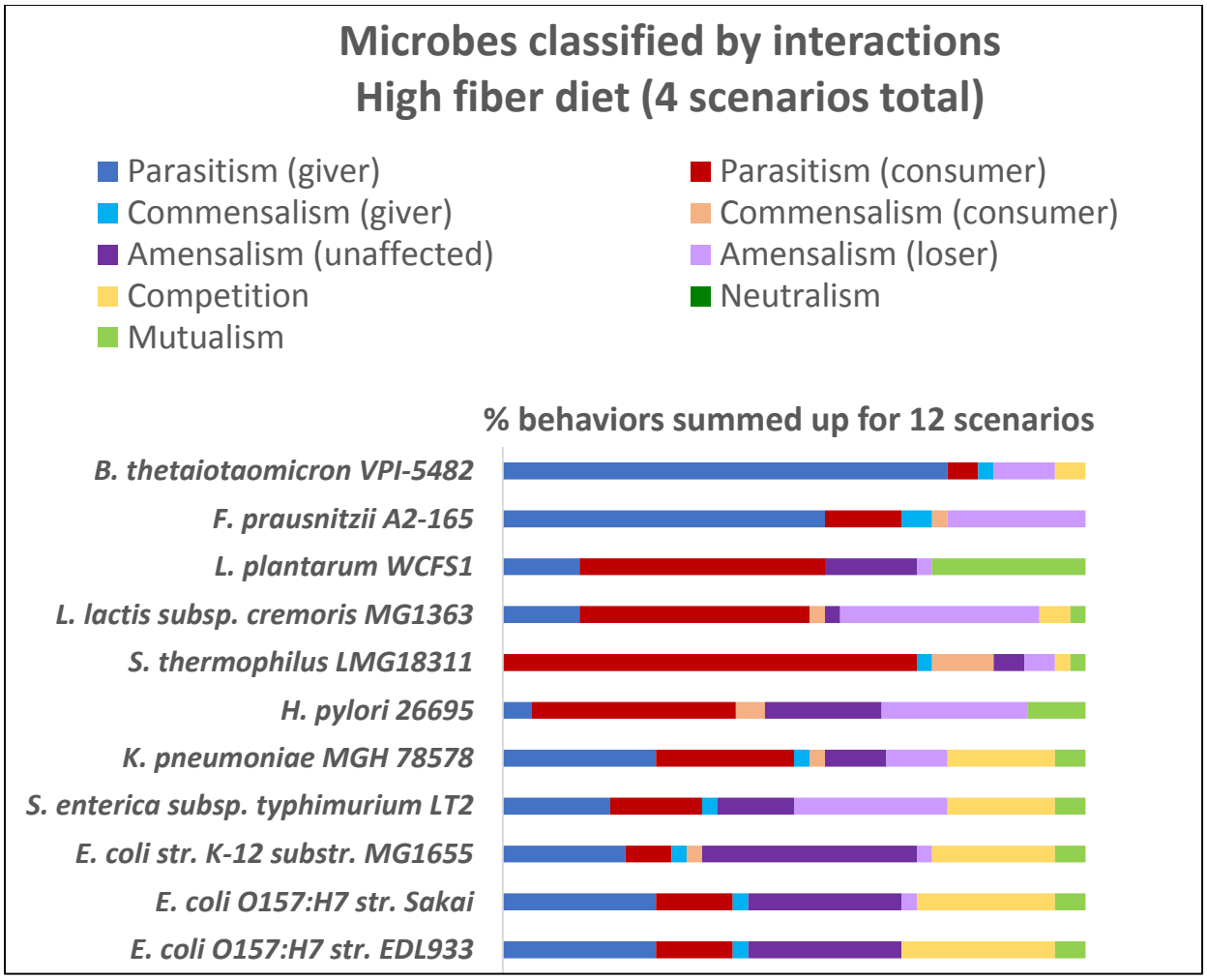


Figure S5b: Microbes classified by % interactions participated in on High fiber diet. The plot sums up 40 interactions per microbe in four scenarios (Figure 2c), with the exception of *H. pylori* for which only 20 interactions were calculated as no growth was predicted without oxygen. In total, 400 interactions were predicted on High fiber diet (200 pairs).

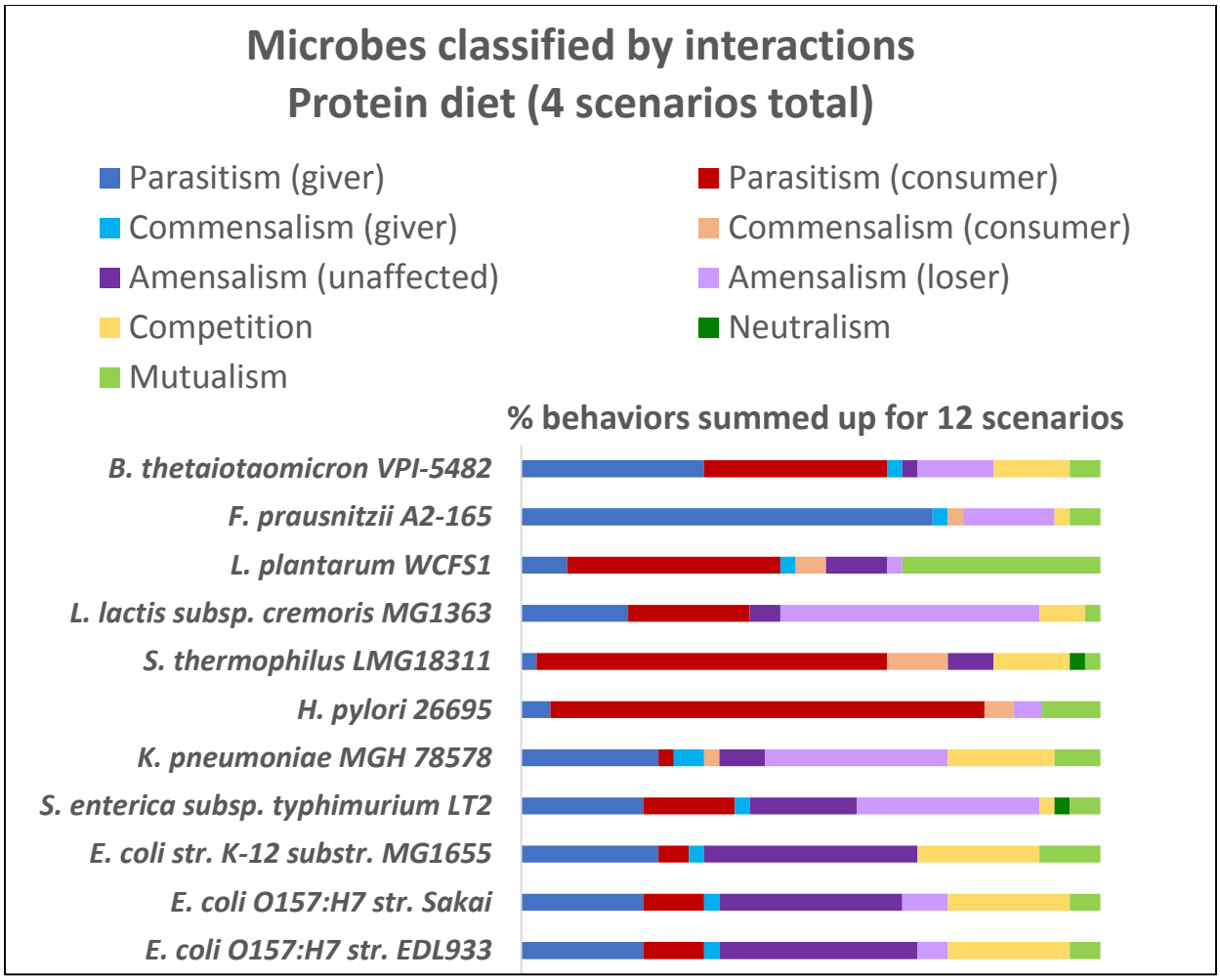


Figure S5c: Microbes classified by % interactions participated in on Protein diet. The plot sums up 40 interactions per microbe in four scenarios (Figure 2c), with the exception of *H. pylori* for which only 20 interactions were calculated as no growth was predicted without oxygen. In total, 400 interactions were predicted on Protein diet (200 pairs).

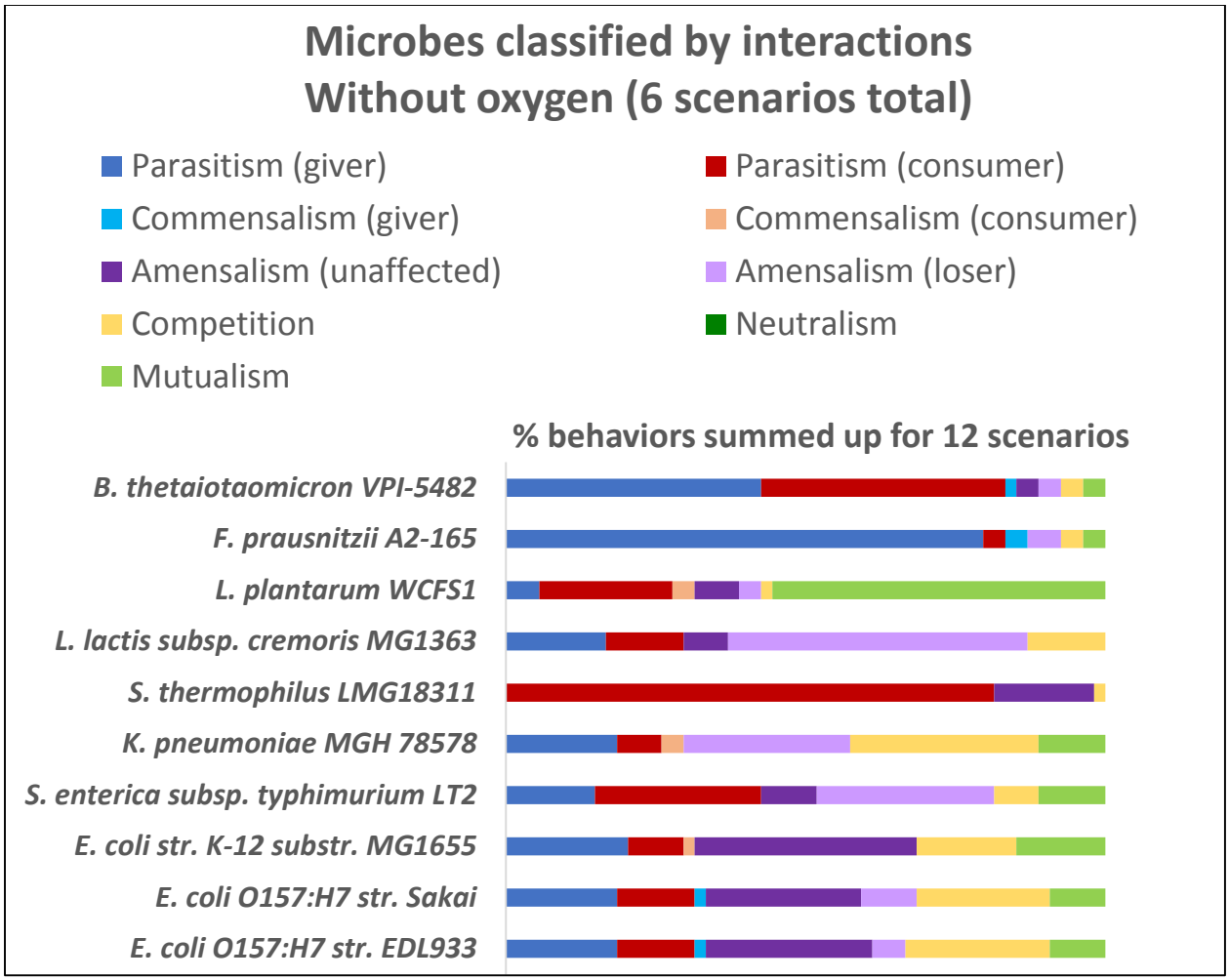


Figure S6a: Microbes classified by % interactions participated in on scenarios without oxygen (six in total, Figure 2c). The plot sums up 54 interactions per microbe. In total, 540 interactions were predicted on scenarios without oxygen (270 pairs).

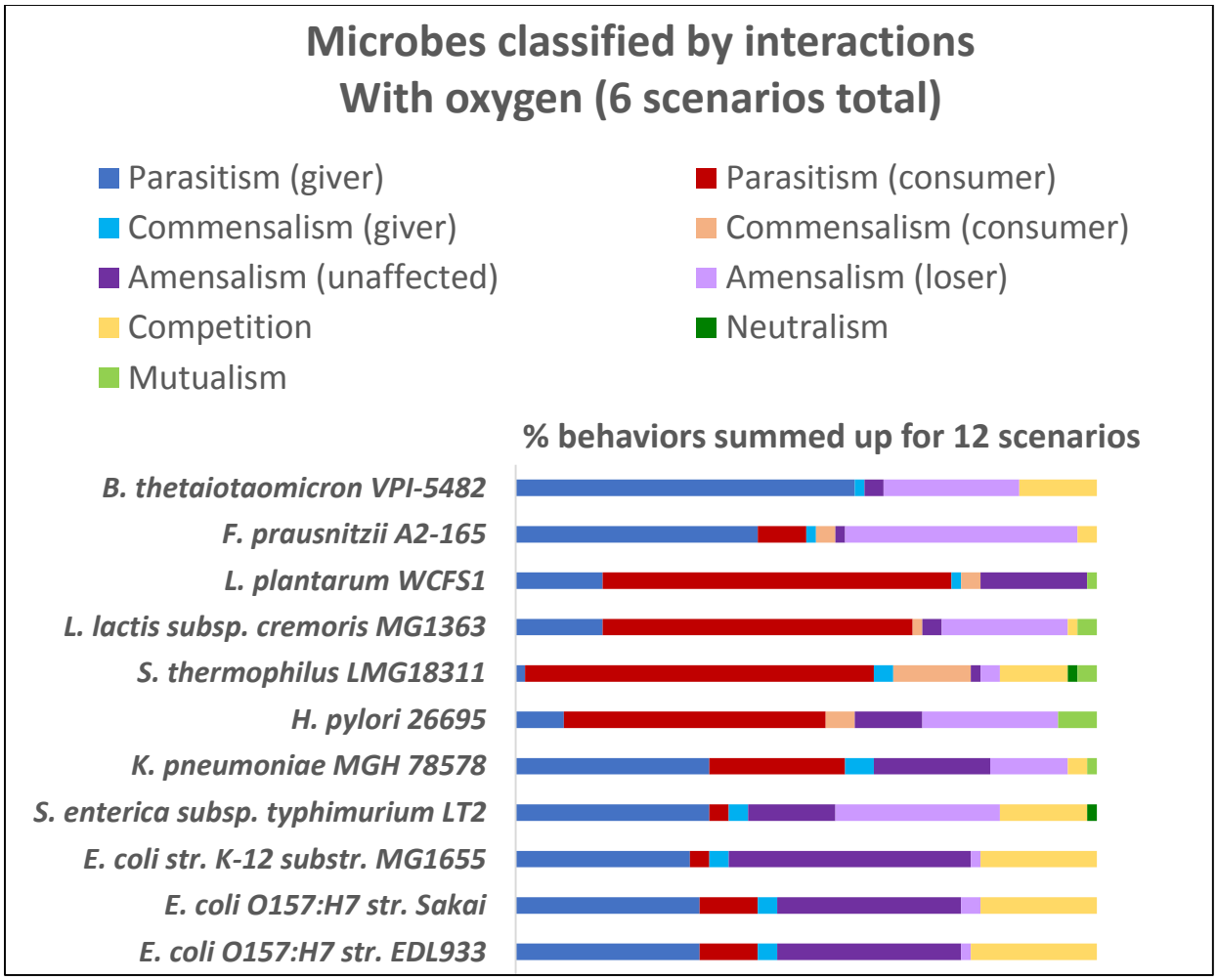


Figure S6b: Microbes classified by % interactions participated in on scenarios with oxygen (six in total, Figure 2c). The plot sums up 60 interactions per microbe. In total, 660 interactions were predicted on scenarios without oxygen (330 pairs).

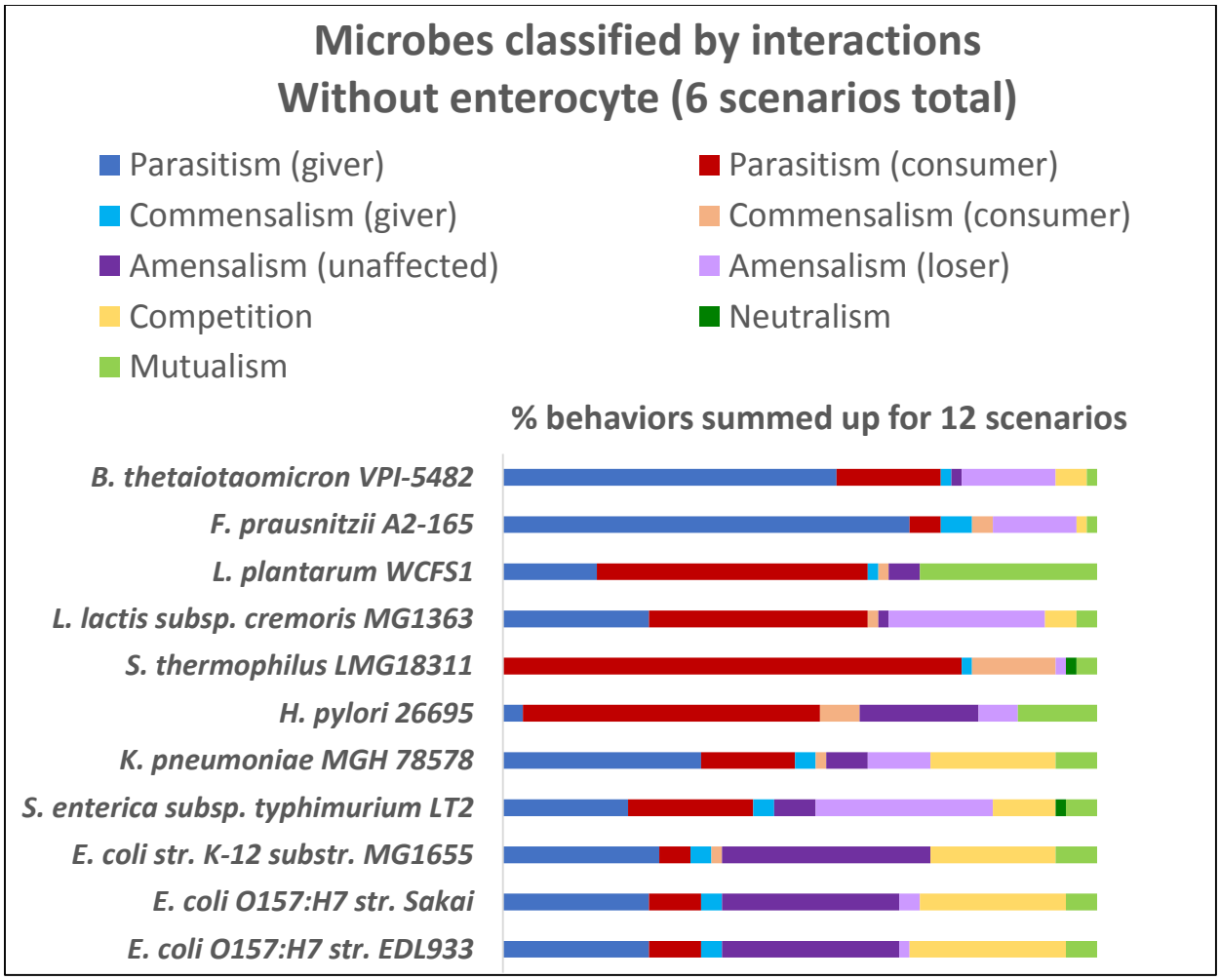


Figure S7a: Microbes classified by % interactions participated in on scenarios without enterocyte. The plot sums up 60 interactions per microbe in six scenarios (Figure 2c), with the exception of *H. pylori* for which only 30 interactions were calculated as no growth was predicted without oxygen. In total, 600 interactions were predicted on scenarios without enterocyte (300 pairs).

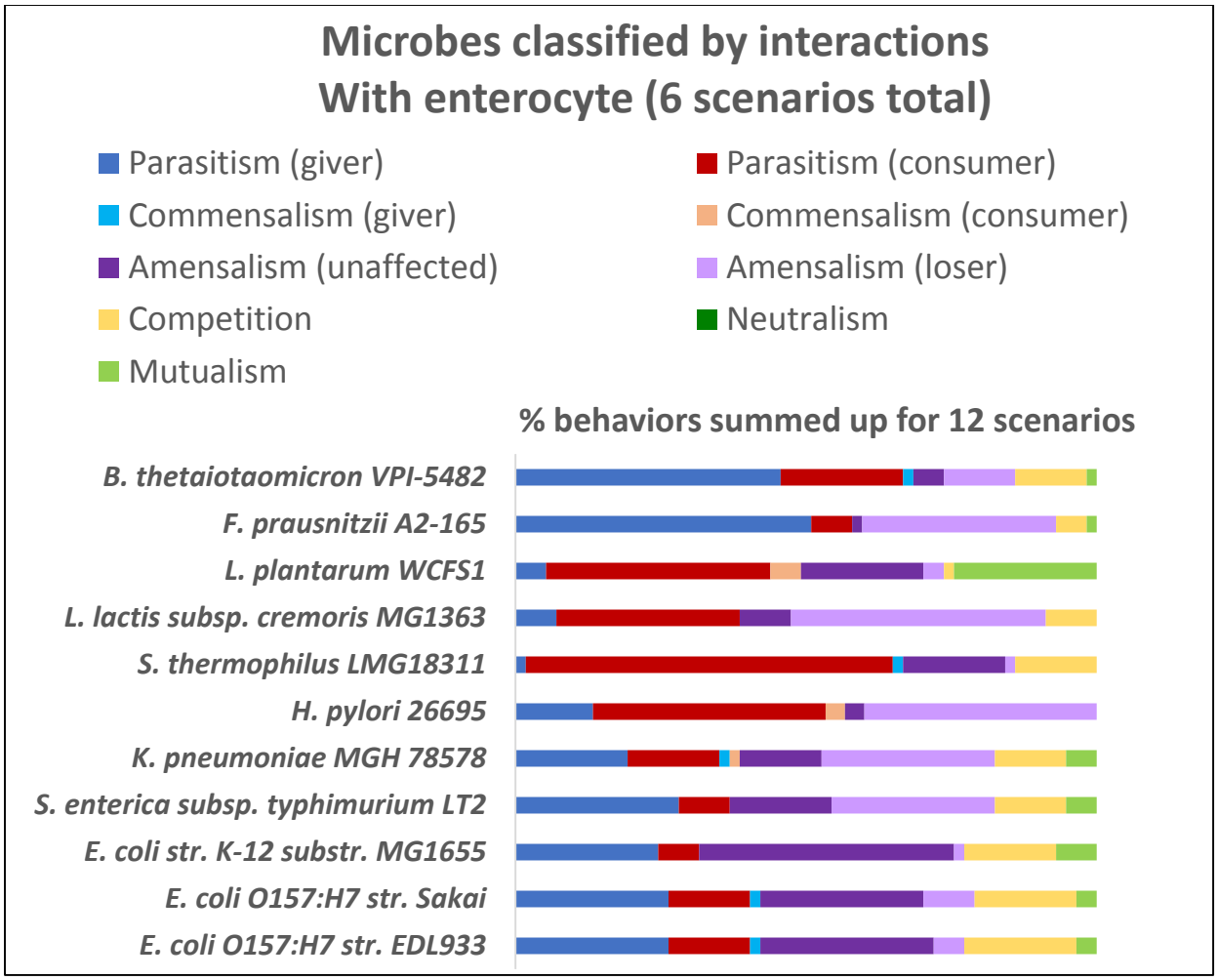


Figure S7b: Microbes classified by % interactions participated in on scenarios with enterocyte. The plot sums up 60 interactions per microbe in six scenarios (Figure 2c), with the exception of *H. pylori* for which only 30 interactions were calculated as no growth was predicted without oxygen. In total, 600 interactions were predicted on scenarios with enterocyte (300 pairs).

Supplemental References

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