

SM 1 Regression analysis and ANOVA of Cell Concentration (cells/mL) and lactic acid (LA) concentration for the 2² factorial design.

Regression Analysis Cell Concentration (cell/mL)

Name	Coefficient	Standard Error	calculated t	p-value
Mean	10.64	0.14	77.70	0.0000
x ₁	-0.03	0.14	-0.26	0.8109
x ₂	-0.81	0.14	-5.93	0.0040
x ₁ · x ₂	-0.67	0.14	-4.86	0.0083

ANOVA Cell Concentration (cell/mL)

Variation Source	Sum of Squares	Degrees of Freedom	Mean Square	F _{calc}	p-value
Regression	8.8	3	2.9	19.6	0.00744
Residuals	0.6	4	0.2		
Lack of Fit	0.0	0	Infinity	Infinity	NaN
Pure Error	0.6	4	0.2		
Total	9.4	7			

R²=93.63%

Regression LA Concentration (g/L)

Name	Coefficient	Standard Error	calculated t	p-value
Mean	7.70	0.31	24.82	0.0000
x ₁	1.31	0.31	4.21	0.0136
x ₂	-5.82	0.31	-18.77	0.0000
x ₁ · x ₂	-1.27	0.31	-4.11	0.0148

ANOVA LA Concentration (g/L)

Variation Source	Sum of Squares	Degrees of Freedom	Mean Square	F _{calc}	p-value
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Variation Source	Sum of Squares	Degrees of Freedom	Mean Square	F_{calc}	p-value
Regression	297.5	3	99.2	128.9	0.00020
Residuals	3.1	4	0.8		
Lack of Fit	0.0	0	Infinity	Infinity	NaN
Pure Error	3.1	4	0.8		
Total	300.6	7			

$R^2 = 98.98\%$

SM2. LA chromatograms from the MD experiments

SAMPLE 1

100% YE	Name	Retention Time	Area	% Area	Height
	1	6,029	937201	17,02	58194
	2	6,539	82989	1,51	4750
	3	7,113	145446	2,64	5845
	4	7,758	99773	1,81	5517
	5	8,182	396622	7,2	23142
	6	8,673	1608928	29,21	64011
	7	9,317	1598569	29,02	57342
	8	12,202	581504	10,56	30783
	9	14,436	35237	0,64	1942
	10	16,523	21312	0,39	1070

SAMPLE 2

100% CSL	Name	Retention Time	Area	% Area	Height
	1	6,03	942151	16,91	60535
	2	6,548	88622	1,59	4883
	3	7,117	139613	2,51	5732
	4	7,758	96425	1,73	5295
	5	8,175	362887	6,51	21945
	6	8,674	1610343	28,9	63606
	7	9,366	1875019	33,65	66969
	8	12,202	364835	6,55	19303
	9	14,437	58117	1,04	3103
	10	16,603	34561	0,62	1020

SAMPLE 3

100%HSP	Name	Retention Time	Area	% Area	Height
	1	6,065	1275374	25,02	89933
	2	6,566	80792	1,58	4756
	3	7,124	132217	2,59	4643
	4	7,867	63060	1,24	3952
	5	8,141	205679	4,03	13692
	6	8,676	1403877	27,54	54163
	7	9,38	1724414	33,82	63539
	8	12,203	199119	3,91	10989
	9	14,442	13649	0,27	866

SAMPLE 4

50%YE- 50%CSL	Name	Retention Time	Area	% Area	Height
	1	0,418	25539	0,48	1217
	2	6,031	901751	16,91	57648

3	6,542	79418	1,49	4391
4	7,115	139148	2,61	5701
5	7,765	104365	1,96	5256
6	8,179	371279	6,96	22239
7	8,676	1535063	28,79	61259
8	9,323	1547908	29,03	55247
9	12,205	575754	10,8	30552
10	14,441	34404	0,65	1895
11	16,552	17464	0,33	873

SAMPLE 5

50%YE-
50%HSP

Name	Retention Time	Area	% Area	Height
1	0,133	72925	1,42	477
2	6,057	1115706	21,76	76039
3	6,558	81223	1,58	4539
4	7,123	140638	2,74	5137
5	7,769	78738	1,54	4627
6	8,169	306716	5,98	19056
7	8,678	1394533	27,2	55168
8	9,341	1465309	28,58	52215
9	12,207	427249	8,33	22764
10	14,442	27289	0,53	1562
11	16,526	17427	0,34	739

SAMPLE 6

50%CSL-
50%HSP

Name	Retention Time	Area	% Area	Height
1	6,056	1081719	22,13	74455
2	6,563	86435	1,77	4906
3	7,122	115329	2,36	4744
4	7,767	89286	1,83	4437
5	8,157	265370	5,43	16792
6	8,679	1358959	27,8	53238
7	9,377	1604500	32,82	57870
8	12,207	262717	5,37	14181
9	14,444	24345	0,5	1421

SAMPLE 7

33%YE-
33%CSL-
33%HSP

Name	Retention Time	Area	% Area	Height
1	0,419	22548	0,39	1081
2	6,055	1181585	20,39	79117
3	6,56	85917	1,48	4836
4	7,125	143964	2,48	5970

5	7,768	97735	1,69	5392
6	8,191	381110	6,58	23060
7	8,681	1599731	27,61	63889
8	9,341	1685904	29,1	59744
9	12,211	557340	9,62	29586
10	14,447	21532	0,37	1252
11	16,551	16893	0,29	838

SAMPLE 8

33%YE-
33%CSL-
33%HSP

Name	Retention Time	Area	% Area	Height
1	0,133	64914	1,09	432
2	6,054	1217473	20,51	80726
3	6,559	91379	1,54	5065
4	7,127	154611	2,6	6123
5	7,769	97865	1,65	5566
6	8,191	385399	6,49	23159
7	8,681	1629251	27,45	65144
8	9,339	1705263	28,73	60486
9	12,211	542075	9,13	28813
10	14,446	32354	0,55	1822
11	16,55	15082	0,25	783

SAMPLE 9

33%YE-
33%CSL-
33%HSP

Name	Retention Time	Area	% Area	Height
1	6,055	1253467	20,91	82586
2	6,56	90012	1,5	5212
3	7,129	158321	2,64	6272
4	7,769	99552	1,66	5663
5	8,195	391404	6,53	23663
6	8,683	1671427	27,88	66726
7	9,338	1733976	28,92	61376
8	12,211	547014	9,12	29059
9	14,446	35542	0,59	1995
10	16,547	15096	0,25	783

SAMPLE 10

33%YE-
33%CSL-
33%HSP

Name	Retention Time	Area	% Area	Height
1	6,057	1191982	21,26	79640
2	6,562	83383	1,49	4838
3	7,129	154008	2,75	5765

4	7,769	80700	1,44	5132
5	8,19	356079	6,35	21561
6	8,686	1546313	27,58	61653
7	9,349	1651687	29,46	57841
8	12,215	484988	8,65	25816
9	14,449	34568	0,62	1945
10	16,558	22660	0,4	858

The retention time of LA is 12.2 minutes. The LA concentration for each sample is:

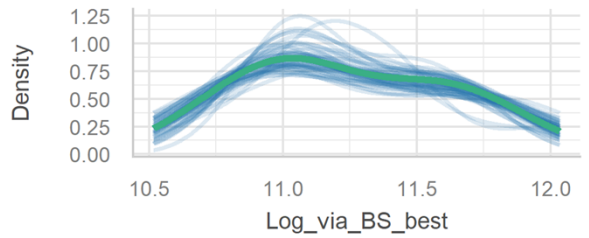
	Área-Lactic acid	Lactic acid (g/L)
#1	581504	18,32
#2	364835	11,82
#3	199119	6,85
#4	575754	18,15
#5	427249	13,69
#6	262717	8,76
#7	557340	17,60
#8	542075	17,14
#9	547014	17,29
#10	484988	15,43

SM3 Models Validation

Model 9. Viability biomass (log/gDB)

Posterior Predictive Check

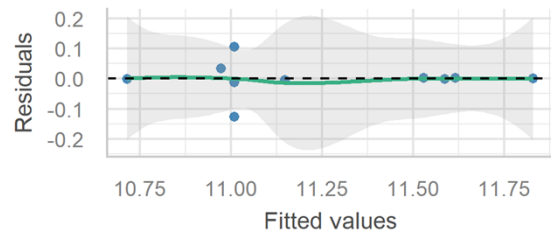
Model-predicted lines should resemble observed data line



— Observed data — Model-predicted data

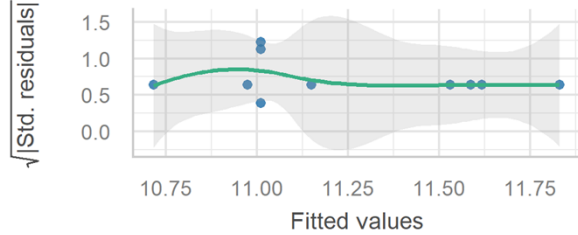
Linearity

Reference line should be flat and horizontal



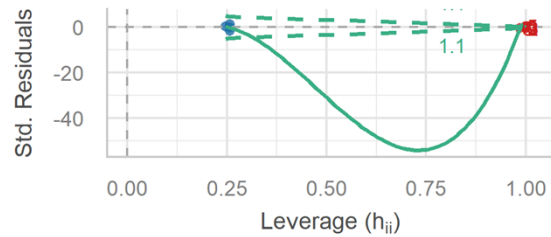
Homogeneity of Variance

Reference line should be flat and horizontal



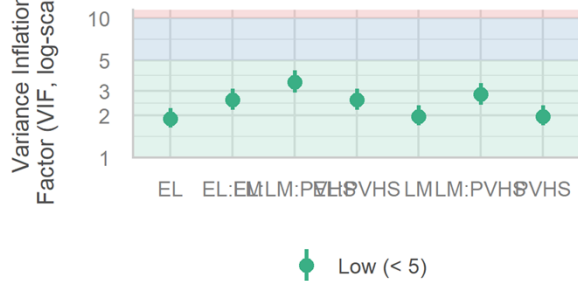
Influential Observations

Points should be inside the contour lines



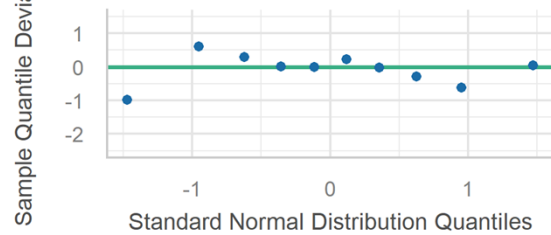
Collinearity

High collinearity (VIF) may inflate parameter uncertainty



Normality of Residuals

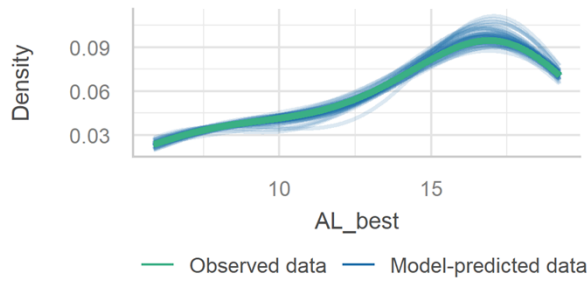
Dots should fall along the line



Model 10. LA concentration (g/L)

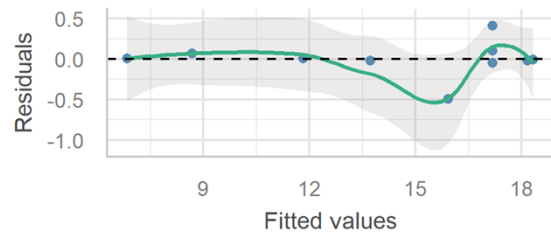
Posterior Predictive Check

Model-predicted lines should resemble observed data line



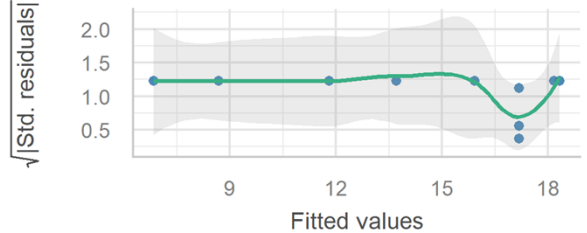
Linearity

Reference line should be flat and horizontal



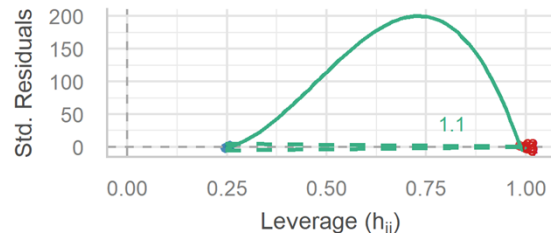
Homogeneity of Variance

Reference line should be flat and horizontal



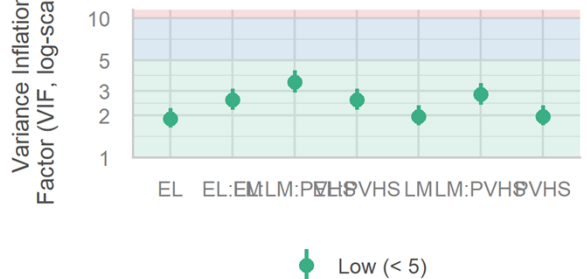
Influential Observations

Points should be inside the contour lines



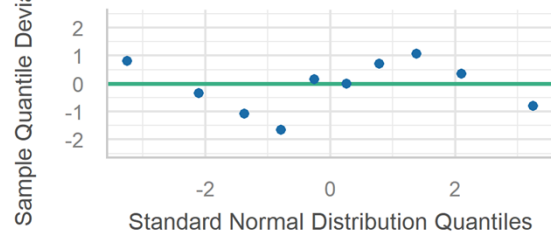
Collinearity

High collinearity (VIF) may inflate parameter uncertainty



Normality of Residuals

Dots should fall along the line



SM 4. Results for the global desirability in the experimental mixture design (EMD)

YE	CSL	HSP	Cell viability (log CFU/g DB)	LA (g/L)	Medium Cost (USD/L)	Global desirability
0.52	0.48	0.00	11.63	18.30	0.51	0.78
0.77	0.00	0.23	11.77	17.79	0.54	0.77
0.58	0.42	0.00	11.64	18.84	0.52	0.77
0.69	0.00	0.31	11.72	16.81	0.51	0.76
0.85	0.00	0.15	11.80	18.37	0.57	0.75
0.39	0.61	0.00	11.60	16.93	0.48	0.75
0.76	0.04	0.20	11.66	18.87	0.54	0.75
0.43	0.54	0.04	11.45	18.23	0.48	0.73
0.59	0.37	0.04	11.50	20.01	0.52	0.72

0.69	0.08	0.23	11.49	19.48	0.52	0.71
0.62	0.07	0.32	11.43	18.08	0.49	0.71
0.57	0.00	0.43	11.61	14.93	0.47	0.69
0.22	0.78	0.00	11.58	14.64	0.43	0.69
0.31	0.66	0.04	11.44	16.39	0.45	0.69
0.40	0.53	0.07	11.33	18.49	0.47	0.68
0.62	0.10	0.28	11.36	19.20	0.50	0.68
0.38	0.54	0.08	11.28	18.32	0.46	0.66
0.64	0.26	0.10	11.37	21.54	0.52	0.66
0.94	0.02	0.04	11.80	18.77	0.60	0.65
0.19	0.78	0.04	11.46	14.41	0.42	0.65
0.52	0.03	0.45	11.46	14.89	0.45	0.65
0.28	0.63	0.09	11.26	16.57	0.44	0.62
0.51	0.08	0.41	11.28	16.37	0.46	0.62
0.47	0.42	0.11	11.20	20.37	0.48	0.61
0.55	0.13	0.32	11.19	18.95	0.48	0.61
0.48	0.06	0.47	11.30	14.97	0.44	0.59
0.45	0.00	0.55	11.48	12.87	0.43	0.59
0.16	0.76	0.09	11.34	14.00	0.41	0.59
0.33	0.54	0.14	11.11	17.94	0.44	0.57
0.04	0.88	0.08	11.47	11.92	0.38	0.56
