Supporting Information for

HIPPO: An iterative reparametrization method for identification and calibration of dynamic bioreactor models of complex processes

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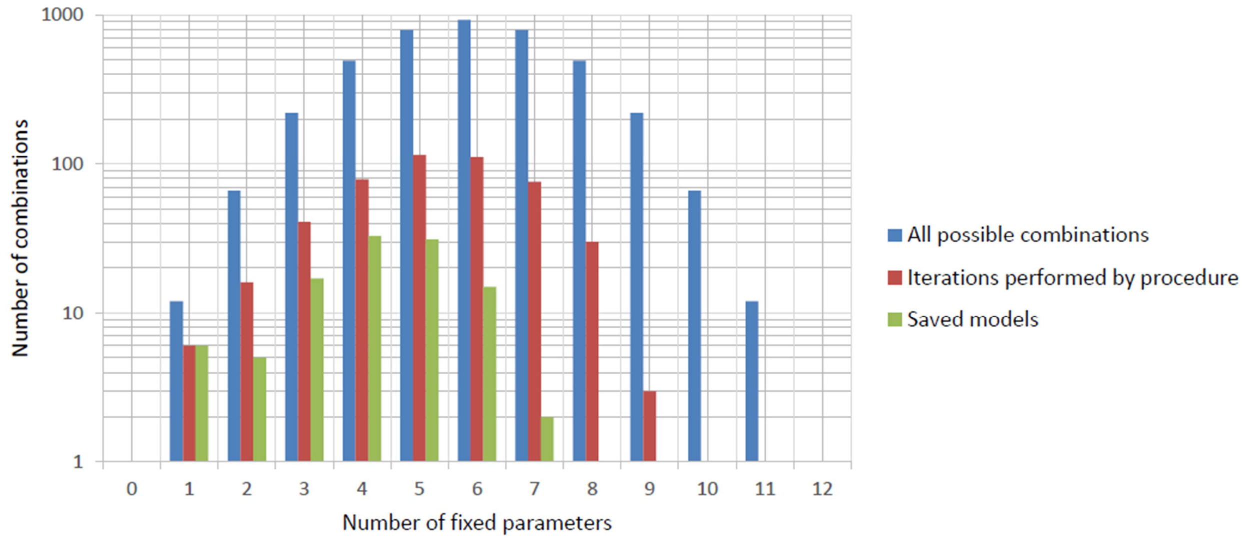
SUPPLEMENTARY FIGURES AND TABLES

(a)



(b)

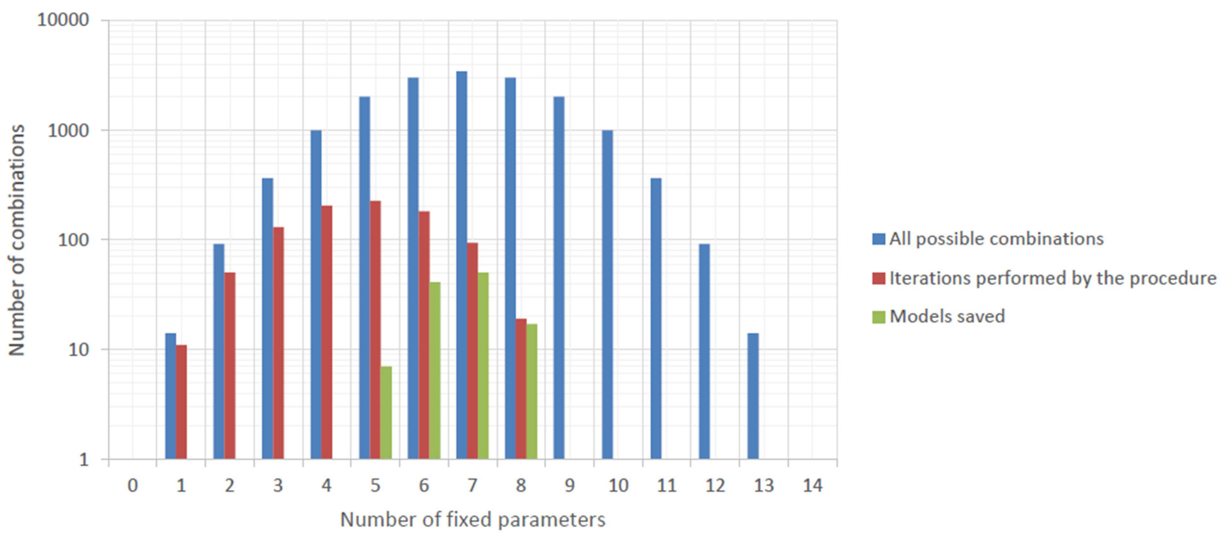


Figure S1. The number of iterations as a function of number of fixed parameters performed with our procedure (red bars) is shown in comparison to the total possible combinations (blue bars) and the total number of reparametrization found with no problems (green bars), for (a) the MFB model and (b) the SSF model.

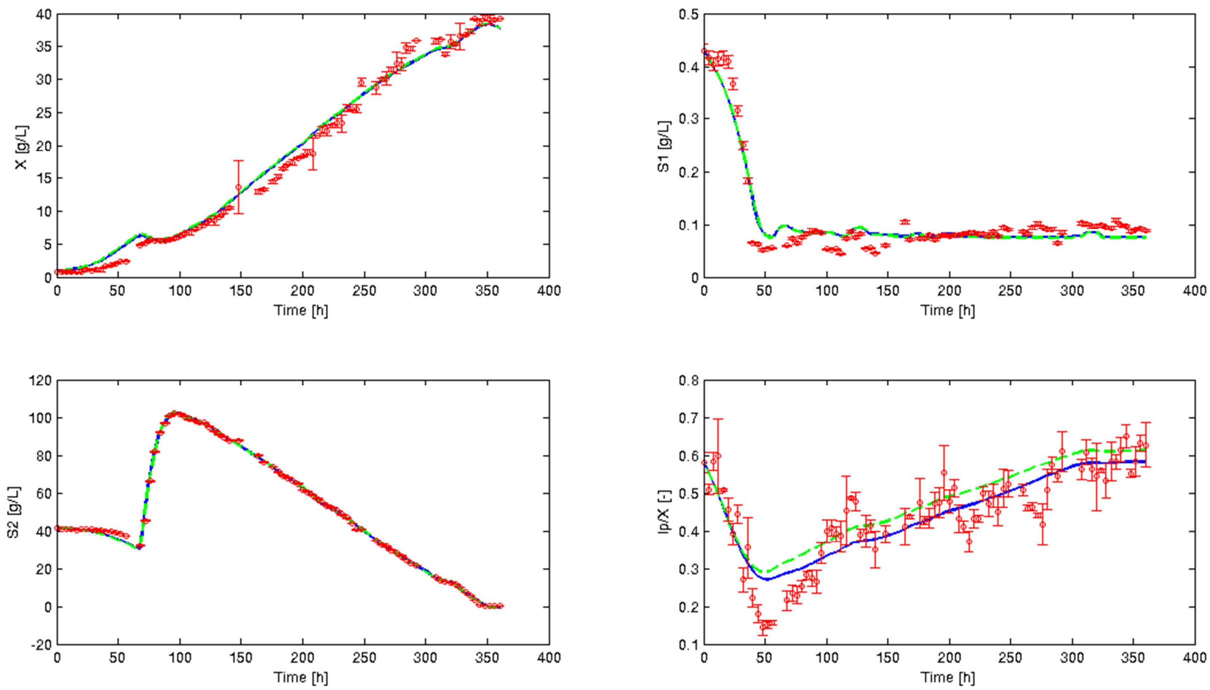


Figure S2: The values of the fixed parameters do not affect the fitting performance for the MFB model. Optimal 4-parameter model (continuous blue line), 4-parameter model with fixed values taken from Surisetty et al. (2010) [1] (segmented green line), experimental data (red circles with error bars).

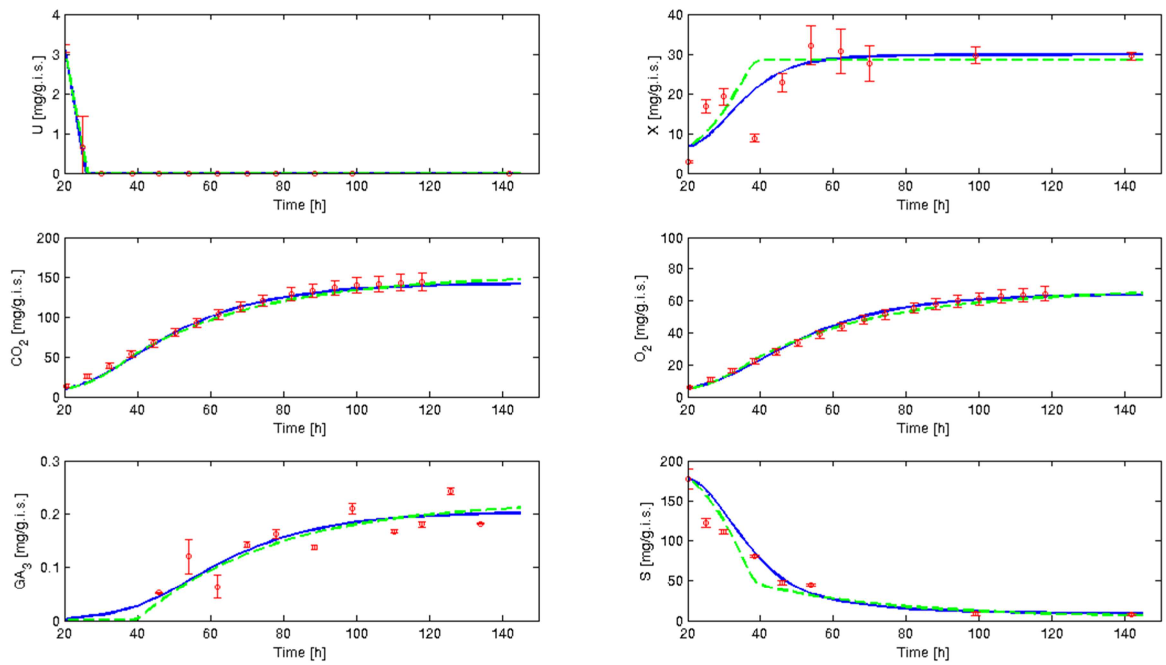


Figure S3: The values of the fixed parameters do not affect the fitting performance for the SSF model. Optimal 6-parameter model (continuous blue line), 6-parameter model with fixed values taken from Sacher et al. (2011) [2] (segmented green line), experimental data (red circles with error bars).

Table S1. Comparison for all the non-problem solutions generated by the procedure for the MFB model. The score for model comparison was calculated as follows:

$$\text{Score} = \frac{\{\text{AICc}\}_i}{|\sum_i \{\text{AICc}\}_i|} + \frac{\{\text{mean(CC)}\}_i}{|\sum_i \{\text{mean(CC)}\}_i|} \qquad \text{[Equation 9]}$$

	Fixed Parameters												F_1	AICc	mean(CC)	Score
1	1	2		4							11	12	9.57E+03	397.2	1.11E-01	1.18E-01
2	1			4			7	8	9	10			9.81E+03	397.3	6.00E-02	6.78E-02
3	1			4			7					12	9.73E+03	403.8	5.40E-02	6.20E-02
4			3				7	8	9		11	12	1.06E+04	444.1	5.06E-02	5.96E-02
5	1		3							10		12	9.68E+03	404.6	5.10E-02	5.90E-02
6	1					6		8	9	10		12	9.46E+03	396.5	4.81E-02	5.60E-02
7	1		3			6						12	9.56E+03	404.3	4.25E-02	5.07E-02
8		2	3						9	10		12	9.91E+03	401.4	2.53E-02	3.38E-02
9		2	3		5	6	7			10			1.08E+04	406.5	2.50E-02	3.36E-02
10	1			4							11		1.18E+04	456.3	2.10E-02	3.08E-02
11	1		3				7		9			12	9.37E+03	405.9	2.06E-02	2.92E-02
12		2	3		5		7		9			12	9.84E+03	396.8	1.97E-02	2.81E-02
13			3				7		9				1.44E+04	449.1	1.75E-02	2.72E-02
14			3		5							12	1.89E+04	461.5	1.69E-02	2.69E-02
15	1		3	4	5		7		9				1.11E+04	415.0	1.71E-02	2.60E-02
16					5			8					1.54E+04	452.4	1.62E-02	2.60E-02
17	1			4	5							12	1.03E+04	422.4	1.52E-02	2.44E-02
18			3	4			7						1.23E+04	427.5	1.48E-02	2.40E-02
19	1			4	5					10		12	9.59E+03	400.8	1.46E-02	2.32E-02
20	1			4			7	8	9				1.69E+04	466.7	1.22E-02	2.24E-02
21			3	4			7	8	9	10		12	1.01E+04	400.9	1.17E-02	2.04E-02
22	1		3		5			8	9		11	12	9.47E+03	393.4	1.15E-02	2.00E-02
23	1		3				7					12	9.86E+03	408.0	1.10E-02	1.99E-02
24	1		3	4						10		12	9.56E+03	400.0	1.01E-02	1.88E-02
25	1							8		10			1.37E+04	451.9	8.71E-03	1.86E-02
26	1		3	4	5				9	10			9.69E+03	401.0	9.67E-03	1.84E-02
27	1	2					7			10		12	9.57E+03	422.2	8.98E-03	1.82E-02
28	1				5		7			10		12	9.71E+03	399.5	8.69E-03	1.74E-02
29	1	2		4	5		7		9	10			1.05E+04	398.7	8.29E-03	1.70E-02
30	1		3			6	7					12	9.94E+03	400.6	8.19E-03	1.70E-02
31	1			4				8	9	10		12	9.55E+03	395.2	7.54E-03	1.62E-02
32	1		3		5		7		9		11		1.13E+04	436.4	6.39E-03	1.60E-02
33	1		3				7		9		11	12	1.02E+04	403.4	7.02E-03	1.59E-02
34		2	3	4	5			8	9			12	9.53E+03	411.2	6.80E-03	1.58E-02
35	1					6				10			1.17E+04	429.6	6.19E-03	1.56E-02
36			3	4	5		7	8	9			12	9.61E+03	393.5	6.86E-03	1.55E-02
37	1		3	4			7				11	12	9.66E+03	403.1	6.49E-03	1.53E-02
38	1	2		4			7					12	9.94E+03	402.4	6.38E-03	1.52E-02
39	1	2	3	4			7						1.20E+04	418.2	5.98E-03	1.52E-02
40	1	2	3				7	8	9			12	9.60E+03	405.0	6.19E-03	1.51E-02
41	1	2		4			7		9	10		12	9.43E+03	392.5	6.45E-03	1.51E-02
42		2	3			6			9			12	1.09E+04	455.5	5.00E-03	1.50E-02

	Fixed Parameters												F_1	AICc	mean(CC)	Score
43	1	2		4				8	9		11	12	9.30E+03	394.3	6.36E-03	1.50E-02
44	1	2	3	4					9			12	9.68E+03	408.8	5.72E-03	1.47E-02
45	1		3		5		7	8	9			12	9.64E+03	403.6	5.63E-03	1.45E-02
46	1	2					7	8		10		12	9.57E+03	403.0	5.64E-03	1.45E-02
47	1	2	3			6	7					12	9.58E+03	421.1	5.21E-03	1.45E-02
48	1		3	4	5		7				11	12	9.61E+03	405.4	5.56E-03	1.45E-02
49		2	3	4	5		7						1.11E+04	449.5	4.54E-03	1.45E-02
50	1	2		4	5		7	8				12	9.71E+03	408.9	5.24E-03	1.42E-02
51	1		3	4	5			8	9		11	12	9.70E+03	394.7	5.51E-03	1.42E-02
52	1	2					7		9	10		12	9.78E+03	396.9	5.45E-03	1.42E-02
53	1				5		7	8			11	12	1.07E+04	406.6	5.12E-03	1.41E-02
54	1	2			5		7	8				12	1.03E+04	413.5	4.78E-03	1.39E-02
55	1	2	3	4			7	8	9	10			9.74E+03	390.9	5.03E-03	1.36E-02
56	1	2		4					9	10		12	9.57E+03	399.1	4.83E-03	1.36E-02
57	1	2		4	5		7	8		10			1.36E+04	438.2	3.68E-03	1.34E-02
58			3	4	5		7		9	10			9.99E+03	401.0	4.51E-03	1.34E-02
59	1		3		5	6			9	10		12	9.38E+03	399.1	4.30E-03	1.31E-02
60	1	2			5		7		9			12	9.90E+03	417.8	3.84E-03	1.31E-02
61		2	3		5		7	8	9		11	12	9.45E+03	392.7	4.33E-03	1.30E-02
62	1	2		4					9		11		1.20E+04	430.5	3.29E-03	1.28E-02
63	1	2		4			7		9		11	12	9.60E+03	398.4	4.01E-03	1.28E-02
64		2	3	4			7	8	9		11	12	9.71E+03	392.5	4.12E-03	1.28E-02
65	1	2		4			7		9				9.67E+03	400.0	3.93E-03	1.28E-02
66	1	2	3	4						10			1.02E+04	406.1	3.77E-03	1.27E-02
67	1	2					7	8	9	10		12	9.45E+03	400.0	3.75E-03	1.26E-02
68	1	2	3	4			7			10		12	9.71E+03	397.6	3.78E-03	1.26E-02
69	1	2	3				7	8		10			1.07E+04	412.9	3.26E-03	1.24E-02
70	1	2	3				7	8		10		12	9.45E+03	399.7	3.48E-03	1.23E-02
71			3		5	6	7		9			12	1.04E+04	461.3	1.91E-03	1.21E-02
72			3	4	5				9		11	12	1.03E+04	403.8	3.05E-03	1.20E-02
73	1	2		4	5			8		10		12	9.68E+03	396.0	3.07E-03	1.18E-02
74	1	2			5			8		10		12	9.61E+03	395.1	3.07E-03	1.18E-02
75	1	2				6	7			10		12	9.47E+03	411.1	2.66E-03	1.18E-02
76	1	2				6		8	9			12	9.65E+03	403.7	2.69E-03	1.16E-02
77	1	2	3	4			7		9		11	12	9.47E+03	393.1	2.91E-03	1.16E-02
78	1		3		5	6	7	8				12	9.48E+03	397.8	2.74E-03	1.15E-02
79	1	2		4	5		7	8	9				9.84E+03	409.7	2.37E-03	1.14E-02
80			3		5		7	8	9		11	12	9.48E+03	392.2	2.70E-03	1.14E-02
81	1	2		4			7	8		10		12	9.48E+03	404.8	2.38E-03	1.13E-02
82	1	2		4	5		7		9		11		1.04E+04	420.8	1.97E-03	1.13E-02
83			3		5	6		8	9	10		12	9.65E+03	396.4	2.28E-03	1.11E-02
84	1	2			5		7	8	9		11	12	9.60E+03	392.2	2.34E-03	1.10E-02
85		2	3	4	5				9	10			9.76E+03	409.3	1.81E-03	1.09E-02
86	1		3	4	5		7	8			11	12	9.59E+03	391.0	2.19E-03	1.09E-02
87	1	2			5	6	7			10			9.67E+03	410.4	1.65E-03	1.07E-02
88	1	2	3			6		8				12	9.74E+03	415.9	1.38E-03	1.06E-02
89	1	2	3					8			11	12	9.83E+03	408.7	1.49E-03	1.06E-02

	Fixed Parameters												F_1	AICc	mean(CC)	Score
90	1	2	3			6					11	12	9.55E+03	403.1	1.62E-03	1.06E-02
91		2	3	4	5				9		11	12	9.65E+03	415.0	1.26E-03	1.05E-02
92	1	2		4	5				9			12	9.82E+03	398.8	1.58E-03	1.04E-02
93		2	3	4	5		7		9			12	1.02E+04	401.7	1.50E-03	1.04E-02
94		2	3			6		8				12	1.06E+04	420.3	8.70E-04	1.02E-02
95		2	3	4	5		7	8		10		12	9.38E+03	397.0	1.35E-03	1.02E-02
96		2	3		5		7	8	9	10		12	9.58E+03	394.5	1.28E-03	1.00E-02
97	1	2	3	4			7		9	10			9.54E+03	398.4	1.10E-03	9.95E-03
98	1		3	4	5		7	8	9		11		9.89E+03	412.6	7.70E-04	9.93E-03
99		2	3		5	6	7	8	9	10		12	9.44E+03	390.0	1.18E-03	9.84E-03
100	1		3			6	7	8	9	10			1.02E+04	399.1	9.08E-04	9.77E-03
101	1	2	3	4			7	8	9		11	12	9.56E+03	388.9	1.13E-03	9.76E-03
102	1		3		5	6		8	9		11		1.03E+04	410.5	5.00E-04	9.62E-03
103		2	3			6	7		9			12	1.15E+04	410.9	4.37E-04	9.57E-03
104		2	3		5	6	7			10		12	9.75E+03	396.7	6.78E-04	9.49E-03
105	1	2	3			6	7		9	10			1.07E+04	402.6	4.10E-04	9.36E-03
106	1		3		5	6	7		9		11	12	9.57E+03	410.1	2.24E-04	9.34E-03
107		2	3		5	6	7	8			11	12	9.62E+03	400.0	1.38E-04	9.03E-03
108	1	2				6	7	8	9		11	12	9.64E+03	390.8	2.33E-04	8.92E-03
109		2	3		5	6		8	9		11	12	9.47E+03	390.5	1.67E-04	8.85E-03
110		2	3		5	6	7		9		11	12	9.46E+03	390.7	4.61E-05	8.74E-03

Table S2. Comparison for all the non-problem solutions generated by the procedure for the SSF model. The score is calculated with equation 9.

	Fixed Parameters														F_2	AICc	mean(CC)	Score
1	1				5				9		11		13		0.1831	-94.18	0.8030	2.67E-02
2				4	5			8			11		13		0.1889	-93.37	0.7308	2.37E-02
3	1			4	5		7				11		13		0.1911	-98.49	0.6973	2.18E-02
4	1			4	5		7				11			14	0.1696	-101.59	0.6627	2.01E-02
5	1				5		7		9	10	11				0.3234	-84.81	0.4693	1.31E-02
6				4				8		10	11		13		0.2158	-89.91	0.4666	1.26E-02
7	1			4						10	11			14	0.2321	-88.02	0.4437	1.18E-02
8								8	9	10	11		13		0.2252	-88.81	0.4441	1.17E-02
9	1								9	10	11			14	0.2202	-89.39	0.4410	1.15E-02
10								8	9	10	11			14	0.2197	-89.45	0.4245	1.08E-02
11				4	5	6		8				12		14	0.1559	-103.78	0.4451	1.05E-02
12	1			4	5	6					11		13		0.1644	-102.41	0.4111	9.17E-03
13					5	6		8	9			12	13		0.1643	-102.42	0.4077	9.03E-03
14	1			4	5	6					11			14	0.1640	-102.46	0.4031	8.83E-03
15				4	5	6		8			11			14	0.1645	-102.38	0.3818	7.92E-03
16					5			8	9	10	11		13		0.1734	-101.01	0.3780	7.87E-03
17	1			4	5	6						12	13		0.1658	-102.18	0.3776	7.76E-03
18	1			4	5	6	7					12	13		0.1642	-107.21	0.3847	7.64E-03
19							7	8	9	10	11			14	0.2255	-94.19	0.3588	7.61E-03
20	1				5	6			9		11			14	0.1642	-102.43	0.3620	7.06E-03
21				4	5	6	7	8				12	13		0.1588	-108.07	0.3662	6.77E-03
22	1			4	5	6	7					12		14	0.1643	-107.20	0.3641	6.76E-03
23					5	6		8	9			12		14	0.1645	-102.38	0.3533	6.69E-03
24	1			4			7			10		12		14	0.1856	-99.25	0.3423	6.48E-03
25	1				5	6			9		11		13		0.1641	-102.44	0.3437	6.27E-03
26	1			4	5	6						12		14	0.1646	-102.37	0.3370	6.00E-03
27	1				5	6			9			12	13		0.1580	-103.43	0.3312	5.66E-03
28				4	5	6		8			11		13		0.1575	-103.51	0.3293	5.57E-03
29					5	6		8	9		11		13		0.1578	-103.47	0.3261	5.43E-03
30	1				5	6	7		9			12	13		0.1643	-107.19	0.3319	5.37E-03
31					5	6		8	9		11			14	0.1641	-102.46	0.3211	5.30E-03
32	1			4	5					10	11			14	0.2757	-88.96	0.2738	4.39E-03
33				4	5			8		10	11			14	0.2810	-88.46	0.2724	4.37E-03
34					5	6	7	8	9		11		13		0.1642	-107.22	0.3036	4.16E-03
35	1			4	5					10	11		13		0.2244	-94.31	0.2705	3.81E-03
36					5			8	9	10	11			14	0.2845	-88.14	0.2442	3.19E-03
37				4	5			8		10	11		13		0.2064	-96.49	0.2455	2.55E-03
38	1				5		7		9	10	11		13		0.2985	-91.67	0.2345	2.48E-03
39	1				5				9	10	11			14	0.2422	-92.33	0.2319	2.31E-03
40	1			4	5	6	7				11			14	0.1615	-107.65	0.2600	2.25E-03
41	1				5	6	7		9		11		13		0.1642	-107.21	0.2576	2.18E-03
42	1			4	5	6	7				11		13		0.1644	-107.19	0.2560	2.11E-03
43	1			4		6				10		12	13		0.1668	-102.02	0.2391	1.82E-03
44	1	2			5				9	10	11			14	0.3127	-90.46	0.2043	1.28E-03
45					5		7	8	9	10	11			14	0.3157	-90.21	0.2031	1.25E-03
46					5	6	7	8	9		11			14	0.1646	-107.15	0.2168	4.32E-04
47	1			4	5		7			10	11			14	0.1745	-105.63	0.2051	5.59E-05

	Fixed Parameters														F_2	AICc	mean(CC)	Score
48	1			4		6				10	11			14	0.1708	-101.41	0.1950	-2.63E-05
49	1	2		4	5					10	11			14	0.2048	-101.46	0.1924	-1.44E-04
50				4		6		8		10		12		14	0.1644	-102.41	0.1805	-7.33E-04
51	1			4		6				10		12		14	0.1644	-102.40	0.1798	-7.61E-04
52	1				5	6	7		9		11			14	0.1608	-107.76	0.1886	-8.29E-04
53	1				5		7		9	10	11			14	0.1664	-106.87	0.1863	-8.54E-04
54				4		6	7	8		10		12	13		0.1642	-107.21	0.1807	-1.12E-03
55	1	2			5				9	10	11		13		0.1863	-103.93	0.1729	-1.19E-03
56	1			4		6				10	11		13		0.1642	-102.43	0.1586	-1.67E-03
57				4		6		8		10	11		13		0.1642	-102.43	0.1560	-1.79E-03
58				4		6		8		10	11			14	0.1671	-101.98	0.1400	-2.44E-03
59	1					6	7		9	10		12	13		0.1643	-107.20	0.1492	-2.47E-03
60	1				5	6			9	10		12		14	0.1642	-107.21	0.1430	-2.74E-03
61	1			4		6	7			10		12	13		0.1655	-107.00	0.1329	-3.16E-03
62	1			4		6	7			10	11		13		0.1639	-107.26	0.1238	-3.57E-03
63	1			4		6	7			10		12		14	0.1643	-107.20	0.1219	-3.65E-03
64	1				5	6	7		9	10		12	13		0.1642	-111.46	0.1284	-3.72E-03
65	1					6			9	10		12	13		0.1641	-102.46	0.1093	-3.80E-03
66						6		8	9	10		12	13		0.1656	-102.22	0.1078	-3.84E-03
67						6		8	9	10	11		13		0.1717	-101.27	0.1039	-3.93E-03
68				4		6		8		10		12	13		0.1567	-103.65	0.1081	-3.95E-03
69				4	5	6		8		10	11			14	0.1649	-107.11	0.1125	-4.04E-03
70	1			4		6	7			10	11			14	0.1638	-107.28	0.1124	-4.06E-03
71				4		6	7	8		10		12		14	0.1577	-108.27	0.1142	-4.07E-03
72	1					6			9	10		12		14	0.1645	-102.39	0.0960	-4.36E-03
73						6		8	9	10		12		14	0.1654	-102.25	0.0948	-4.40E-03
74	1					6			9	10	11			14	0.1648	-102.33	0.0858	-4.80E-03
75	1			4	5	6				10	11		13		0.1640	-107.24	0.0942	-4.84E-03
76						6		8	9	10	11			14	0.1642	-102.44	0.0840	-4.88E-03
77				4	5	6		8		10	11		13		0.1642	-107.22	0.0918	-4.94E-03
78	1			4	5	6				10		12	13		0.1642	-107.21	0.0833	-5.31E-03
79						6	7	8	9	10		12	13		0.1649	-107.10	0.0803	-5.43E-03
80	1			4	5	6				10	11			14	0.1640	-107.25	0.0804	-5.44E-03
81						6	7	8	9	10	11		13		0.1644	-107.18	0.0760	-5.62E-03
82				4	5	6		8		10		12	13		0.1559	-108.57	0.0784	-5.63E-03
83	1					6	7		9	10		12		14	0.1645	-107.16	0.0696	-5.89E-03
84						6	7	8	9	10		12		14	0.1644	-107.18	0.0691	-5.91E-03
85				4	5	6		8		10		12		14	0.1640	-107.24	0.0678	-5.97E-03
86	1					6	7		9	10	11			14	0.1645	-107.16	0.0671	-6.00E-03
87	1			4	5	6	7			10	11		13		0.1641	-111.47	0.0736	-6.08E-03
88						6	7	8	9	10	11			14	0.1641	-107.23	0.0645	-6.12E-03
89	1			4	5	6				10		12		14	0.1573	-108.33	0.0664	-6.13E-03
90	1				5	6			9	10	11		13		0.1641	-107.22	0.0628	-6.19E-03
91	1			4	5	6	7			10		12	13		0.1643	-111.44	0.0657	-6.41E-03
92	1			4	5	6	7			10	11			14	0.1640	-111.49	0.0640	-6.49E-03
93					5	6		8	9	10	11		13		0.1579	-108.24	0.0564	-6.55E-03
94	1	2		4	5	6				10		12	13		0.1640	-111.49	0.0625	-6.56E-03
95	1	2		4	5	6				10	11			14	0.1640	-111.50	0.0596	-6.68E-03
96	1				5	6			9	10		12	13		0.1643	-107.19	0.0504	-6.72E-03

	Fixed Parameters														F_2	AICc	mean(CC)	Score
97	1				5	6			9	10	11			14	0.1649	-107.11	0.0474	-6.84E-03
98				4		6		8	9	10	11			14	0.1641	-107.23	0.0451	-6.95E-03
99					5	6		8	9	10	11			14	0.1643	-107.19	0.0447	-6.97E-03
100	1	2		4	5	6				10		12		14	0.1641	-111.48	0.0512	-7.04E-03
101	1			4	5	6	7			10		12		14	0.1596	-112.20	0.0515	-7.09E-03
102				4		6		8	9	10		12	13		0.1557	-108.59	0.0441	-7.11E-03
103					5	6		8	9	10		12	13		0.1558	-108.58	0.0437	-7.12E-03
104	1	2		4	5	6	7			10	11		13		0.1640	-115.29	0.0565	-7.13E-03
105	1				5	6	7		9	10	11		13		0.1640	-111.49	0.0459	-7.27E-03
106	1	2			5	6			9	10	11		13		0.1598	-112.18	0.0420	-7.49E-03
107					5	6	7	8	9	10	11		13		0.1599	-112.15	0.0409	-7.54E-03
108	1	2			5	6			9	10		12	13		0.1641	-111.48	0.0370	-7.65E-03
109	1				5	6	7		9	10	11			14	0.1640	-111.49	0.0362	-7.69E-03
110					5	6		8	9	10		12		14	0.1558	-108.58	0.0299	-7.71E-03
111	1	2			5	6			9	10	11			14	0.1639	-111.50	0.0341	-7.78E-03
112				4		6		8	9	10		12		14	0.1557	-108.60	0.0280	-7.80E-03
113	1				5	6	7		9	10		12		14	0.1643	-111.45	0.0269	-8.08E-03
114	1	2			5	6			9	10		12		14	0.1641	-111.48	0.0253	-8.15E-03
115					5	6	7	8	9	10		12		14	0.1578	-112.49	0.0214	-8.40E-03
116					5	6		8	9	10		12	13	14	0.1557	-112.85	0.0219	-8.41E-03

Table S3. Estimated parameters in the SSF 6-parameter model validation.

Parameter	Value	CI	CC
μ_m [1/h]	4.55E-01	±2.56E-02	1.13E-01
k_d [g/g]	2.99E-02	±2.74E-03	1.83E-01
k_U [g/mL]	1.38E-04	±6.77E-06	9.85E-02
m_{CO_2} [1/h]	2.17E-01	±1.46E-02	1.34E-01
m_{O_2} [g/mL]	8.93E-02	-	-
k_p [g/mL]	9.44E-05	-	-
Y_{NX} [g/g]	1.57E+01	±9.07E-01	1.15E-01
k_N [1/h]	2.81E-03	-	-
Y_{CO_2X} [g/g]	2.22E+00	-	-
Y_{O_2x} [1/h]	1.83E+01	-	-
β_m [g/mL]	5.23E-04	±4.88E-05	1.87E-01
k_i [g/g]	4.16E04	-	-
Y_{SX} [g/g]	1.70E-01	-	-
m_S [g/g•h]	5.00E-02	-	-

CASE STUDY MODELS

Algal bioreactor model

Dynamic Model

The model used in this work was proposed by Surisetty et al. [3], and contains 6 ordinary differential equations (ODE) and 12 fitting parameters (Table S4). The state variables of the model are:

(1) x: Functionally active biomass concentration [g/mL]

(2) S_1: Nitrogen source concentration in culture media [g/mL]

(3) S_2: Carbon source concentration in culture media [g/mL]

(4) Q: Total nitrogen cellular quota [g/mL]

(5) I_p: Total algal oil stored in cells [g/mL]

(6) V: Total reactor volume [mL]

Table S4. Model parameters for the MFB model [3].

Parameter	Name
μ_m	Maximum growth rate [1/h]
q_{min}	Minimum cell quota for supporting growth [g/g]
k_q	Half saturation constant of nitrogen quota for growth [g/mL]
ρ_m	Maximum uptake rate [1/h]
k_s	Half saturation constant of carbon source for growth [g/mL]
s_0	Threshold nitrogen source concentration [g/mL]
Y_{SX}	Substrate to biomass yield [g/g]
k_m	Maintenance constant [1/h]
Y_{SP}	Substrate to product yield [g/g]
π_m	Maximum oil production rate [1/h]
k_π	Half saturation constant for oil production [g/mL]
Y_{qX}	Substrate quota to biomass [g/g]

The dynamics of the fed-batch bioreactor system for microalgal growth and oil production are described by the following ODE set:

$$\frac{dx}{dt} = \mu x - x\frac{f_0}{V} - x\left(f_1^i + f_2^i - f_0\right)\frac{1}{V} \quad \text{[Equation 10]}$$

$$\frac{dS_1}{dt} = -\rho x + S_1^i\frac{f_1^i}{V} - S_1\frac{f_0}{V} - S_1\left(f_1^i + f_2^i - f_0\right)\frac{1}{V} \quad \text{[Equation 11]}$$

$$\frac{dS_2}{dt} = -\frac{1}{Y_{SX}}\mu x + S_2^i\frac{f_2^i}{V} - S_2\frac{f_0}{V} - k_m x - \frac{1}{Y_{SP}}\pi x - S_2\left(f_1^i + f_2^i - f_0\right)\frac{1}{V} \quad \text{[Equation 12]}$$

$$\frac{dQ}{dt} = \rho x - \frac{1}{Y_{qX}}\mu x - Q\frac{f_0}{V} - Q\left(f_1^i + f_2^i - f_0\right)\frac{1}{V} \quad \text{[Equation 13]}$$

$$\frac{dI_p}{dt} = \pi x - I_p\frac{f_0}{V} - I_p\left(f_1^i + f_2^i - f_0\right)\frac{1}{V} \quad \text{[Equation 14]}$$

$$\frac{dV}{dt} = f_1^i + f_2^i - f_0 \quad \text{[Equation 15]}$$

The values f_1^i, f_2^i and f_0 are the flowrates of the model. f_1^i is the input flowrate of nitrogen rich feed, f_2^i the input flowrate of carbon rich feed, and f_0 the outflow from the reactor due to sampling (5.5 mL each 4 hours). Finally, S_1^i and S_2^i are the nitrogen and carbon feed concentrations, respectively.

The model also includes a set of constitutive algebraic equations which define the production and consumption rates. The biomass growth rate is described by the product between carbon and nitrogen Monod type kinetics. Here, the carbon source is the carbon concentration in the culture media. In turn, the nitrogen source corresponds to the specific intracellular nitrogen quota (q=Q/X) that has a minimum threshold above which microalgal growth (q_{min}) is possible (when q is below q_{min}, the biomass growth rate is zero). Therefore, the biomass growth rate can be written as:

$$\mu = \mu_m \left(\frac{q - q_{min}}{k_q + q}\right)\left(\frac{S_2}{k_s + S_2}\right) \qquad \text{[Equation 16]}$$

The model proposed by Caperon and Meyer [4] was used for the nitrogen uptake rate, where the concentration of nitrogen in the culture media and the maximum uptake rate ρ_m define the value of the uptake rate. This can be written as:

$$\rho = \rho_m \left(1 - \frac{S_0}{S_1}\right) \qquad \text{[Equation 17]}$$

Where s_o is the minimum nitrogen concentration at which absorption occurs. For the oil production rate, a Michaelis-Menten relation was used, which includes a saturation term that considers a reduction in oil production when the cell is oil saturated. The expression for the oil production rate is the following:

$$\pi = \pi_m \frac{S_2}{k_\pi + S_2}\left(1 - \frac{I_p}{X}\right) \qquad \text{[Equation 18]}$$

In this model, the measured variables were the concentrations of carbon (S_2) and nitrogen (S_1) sources in the culture media, the oil mass fraction stored in the cells (I_p/X), and the measured biomass concentration ($X = x + I_p + Q$).

Parameter Estimation

For parameter estimation we used as initial values those obtained by Surisetty et al. [1]. The definition of upper and lower limits for the parameter estimation were also those of Surisetty et al. [1], except for the boundaries of s_o. This exception was made because the optimization method did not succeed with the original set of lower and upper limits (certain combinations of parameters resulted in unfeasible integrations). Therefore, a narrower interval was used; an upper limit of 1e-4 instead of 7e-4. This new bound includes the optimized value reported by Surisetty et al. [1]. Lastly, for the construction of the objective function, the measured data and the associated variances were directly facilitated by Surisetty et al. [1]. The experimental data was measured from 0 to 360 h of cultivation, every 4 h, and is available in Table S5.

Table S5. Experimental data used for calibration of the MFB model. e(Var) refers to the measurement error of the variable Var.

Time [h]	X [g/mL]	e(X) [g/mL]	S_1 [g/mL]	e(S_1) [g/mL]	S_2 [g/mL]	e(S_2) [g/mL]	I_p/X [-]	e(I_p/X) [-]
0	8.57E-04	1.43E-04	4.30E-04	1.25E-05	4.15E-02	1.37E-04	5.80E-01	2.70E-02
4	8.57E-04	1.43E-04	4.16E-04	1.25E-05	4.08E-02	1.35E-04	5.09E-01	1.35E-02
8	7.86E-04	1.43E-04	4.04E-04	1.21E-05	4.09E-02	1.35E-04	5.83E-01	2.42E-02
12	8.57E-04	1.43E-04	4.14E-04	1.24E-05	4.07E-02	1.34E-04	5.97E-01	9.79E-02
16	7.50E-04	7.14E-05	4.16E-04	1.25E-05	4.05E-02	1.34E-04	5.08E-01	2.06E-03
20	8.57E-04	0.00E+00	4.09E-04	1.23E-05	4.08E-02	1.35E-04	4.56E-01	3.02E-02
24	1.14E-03	1.43E-04	3.65E-04	1.10E-05	4.08E-02	1.35E-04	3.92E-01	2.84E-02
28	1.04E-03	7.14E-05	3.16E-04	9.50E-06	4.07E-02	1.34E-04	4.44E-01	2.29E-02
32	1.14E-03	1.43E-04	2.51E-04	7.50E-06	4.06E-02	1.34E-04	2.70E-01	3.16E-02
36	1.07E-03	2.86E-04	1.82E-04	5.50E-06	4.01E-02	1.32E-04	3.55E-01	8.05E-02
40	1.61E-03	7.14E-05	6.52E-05	2.00E-06	3.99E-02	1.32E-04	2.24E-01	2.42E-02
44	1.75E-03	7.14E-05	6.26E-05	1.90E-06	3.97E-02	1.31E-04	1.80E-01	2.46E-02
48	2.04E-03	7.14E-05	5.09E-05	1.50E-06	3.91E-02	1.29E-04	1.43E-01	1.88E-02
52	2.29E-03	0.00E+00	5.43E-05	1.60E-06	3.84E-02	1.27E-04	1.50E-01	8.34E-03
56	2.43E-03	1.43E-04	5.48E-05	1.60E-06	3.73E-02	1.23E-04	1.56E-01	7.06E-03
68	4.82E-03	7.14E-05	5.89E-05	1.80E-06	3.21E-02	1.06E-04	2.16E-01	2.61E-02
72	5.18E-03	7.14E-05	7.21E-05	2.20E-06	4.54E-02	1.50E-04	2.35E-01	2.21E-02
76	5.61E-03	7.14E-05	6.45E-05	1.90E-06	6.62E-02	2.19E-04	2.30E-01	2.28E-02
80	5.43E-03	0.00E+00	7.41E-05	2.20E-06	8.19E-02	2.70E-04	2.52E-01	1.53E-02
84	5.53E-03	2.35E-04	8.22E-05	2.50E-06	9.19E-02	3.03E-04	2.82E-01	1.07E-02
88	5.50E-03	1.43E-04	8.90E-05	2.70E-06	9.68E-02	3.20E-04	2.74E-01	2.04E-02
92	5.68E-03	2.14E-04	8.49E-05	2.50E-06	1.01E-01	3.32E-04	2.66E-01	3.01E-02
96	5.86E-03	1.43E-04	8.41E-05	2.50E-06	1.02E-01	3.36E-04	3.41E-01	2.81E-02
100	6.18E-03	2.14E-04	5.27E-05	1.60E-06	1.02E-01	3.35E-04	3.99E-01	3.06E-02
104	6.49E-03	1.55E-04	5.18E-05	1.60E-06	1.00E-01	3.32E-04	4.08E-01	2.17E-02
108	6.67E-03	3.46E-04	5.24E-05	1.60E-06	9.89E-02	3.26E-04	3.92E-01	1.98E-02
112	7.18E-03	7.14E-05	4.35E-05	1.30E-06	9.84E-02	3.25E-04	3.85E-01	4.21E-02
116	7.64E-03	0.00E+00	7.18E-05	2.20E-06	9.72E-02	3.21E-04	4.54E-01	9.08E-02
120	7.96E-03	7.14E-05	8.56E-05	2.60E-06	9.70E-02	3.20E-04	4.86E-01	4.04E-03
124	8.64E-03	1.43E-04	7.46E-05	2.20E-06	9.51E-02	3.14E-04	4.77E-01	2.41E-02
128	8.58E-03	6.98E-04	8.13E-05	2.40E-06	9.29E-02	3.07E-04	3.89E-01	1.54E-02
132	9.18E-03	7.14E-05	5.42E-05	1.60E-06	9.10E-02	3.00E-04	3.99E-01	4.26E-02
136	9.89E-03	2.14E-04	5.49E-05	1.60E-06	8.97E-02	2.96E-04	4.13E-01	1.72E-02
140	1.06E-02	1.43E-04	4.53E-05	1.40E-06	8.78E-02	2.90E-04	3.50E-01	4.74E-02
148	1.37E-02	4.00E-03	6.04E-05	1.80E-06	8.77E-02	2.89E-04	3.91E-01	2.15E-02
164	1.29E-02	3.57E-04	1.05E-04	3.10E-06	7.98E-02	2.63E-04	4.10E-01	4.78E-02
168	1.33E-02	1.43E-04	7.03E-05	2.10E-06	7.62E-02	2.52E-04	4.37E-01	3.70E-03
176	1.45E-02	2.14E-04	7.35E-05	2.20E-06	7.36E-02	2.43E-04	4.73E-01	6.49E-02

180	1.53E-02	2.86E-04	7.29E-05	2.20E-06	7.10E-02	2.34E-04	4.26E-01	1.04E-02
184	1.64E-02	1.23E-04	7.92E-05	2.40E-06	6.90E-02	2.28E-04	4.33E-01	2.62E-02
188	1.71E-02	7.14E-05	7.08E-05	2.10E-06	6.77E-02	2.23E-04	4.70E-01	3.10E-02
192	1.74E-02	4.29E-04	7.69E-05	2.30E-06	6.63E-02	2.19E-04	4.73E-01	3.96E-02
196	1.80E-02	7.14E-05	7.97E-05	2.40E-06	6.47E-02	2.13E-04	5.54E-01	7.28E-02
200	1.83E-02	1.07E-04	7.78E-05	2.30E-06	6.14E-02	2.03E-04	4.77E-01	2.97E-02
204	1.90E-02	4.94E-04	7.88E-05	2.40E-06	6.04E-02	1.99E-04	5.13E-01	2.29E-02
208	1.86E-02	2.43E-03	7.97E-05	2.40E-06	5.87E-02	1.94E-04	4.32E-01	3.74E-02
212	2.15E-02	7.14E-05	8.21E-05	2.50E-06	5.68E-02	1.87E-04	4.12E-01	1.51E-02
216	2.23E-02	5.00E-04	8.42E-05	2.50E-06	5.49E-02	1.81E-04	3.72E-01	2.71E-02
220	2.22E-02	7.86E-04	8.33E-05	2.50E-06	5.32E-02	1.76E-04	4.32E-01	2.54E-02
224	2.30E-02	2.34E-04	8.20E-05	2.50E-06	5.21E-02	1.72E-04	4.32E-01	9.63E-03
228	2.34E-02	7.42E-04	8.10E-05	2.40E-06	5.06E-02	1.67E-04	4.98E-01	1.91E-02
232	2.34E-02	1.29E-03	7.80E-05	2.30E-06	4.85E-02	1.60E-04	4.72E-01	3.31E-02
236	2.56E-02	5.00E-04	8.57E-05	2.60E-06	4.68E-02	1.55E-04	4.92E-01	3.04E-02
240	2.54E-02	7.14E-05	7.68E-05	2.30E-06	4.40E-02	1.45E-04	4.51E-01	3.85E-02
244	2.55E-02	6.43E-04	9.37E-05	2.80E-06	4.06E-02	1.34E-04	5.12E-01	4.92E-02
248	2.95E-02	5.95E-04	8.97E-05	2.70E-06	4.10E-02	1.35E-04	5.24E-01	3.39E-02
260	2.88E-02	9.29E-04	8.65E-05	2.60E-06	3.48E-02	1.15E-04	5.08E-01	1.61E-02
264	2.99E-02	2.86E-04	8.20E-05	2.50E-06	3.27E-02	1.08E-04	4.60E-01	8.08E-03
268	3.01E-02	1.00E-03	9.39E-05	2.80E-06	3.15E-02	1.04E-04	4.63E-01	1.13E-02
272	3.16E-02	2.98E-04	1.02E-04	3.00E-06	2.96E-02	9.78E-05	4.41E-01	6.94E-03
276	3.25E-02	1.67E-03	9.45E-05	2.80E-06	2.81E-02	9.28E-05	4.17E-01	5.35E-02
280	3.23E-02	1.00E-03	9.02E-05	2.70E-06	2.66E-02	8.78E-05	5.08E-01	5.29E-02
284	3.48E-02	7.86E-04	9.13E-05	2.70E-06	2.47E-02	8.14E-05	5.75E-01	2.13E-02
288	3.47E-02	3.57E-04	6.41E-05	1.90E-06	2.29E-02	7.56E-05	5.45E-01	1.67E-02
292	3.58E-02	0.00E+00	8.45E-05	2.50E-06	2.17E-02	7.15E-05	6.10E-01	5.28E-02
308	3.58E-02	3.57E-04	1.03E-04	3.10E-06	1.54E-02	5.07E-05	5.62E-01	2.62E-02
312	3.61E-02	0.00E+00	1.01E-04	3.00E-06	1.35E-02	4.47E-05	6.08E-01	3.43E-02
316	3.39E-02	2.14E-04	9.61E-05	2.90E-06	1.31E-02	4.34E-05	5.61E-01	3.04E-02
320	3.57E-02	9.81E-04	9.69E-05	2.90E-06	1.25E-02	4.11E-05	5.43E-01	8.92E-02
324	3.54E-02	1.54E-04	9.82E-05	2.90E-06	1.18E-02	3.89E-05	5.58E-01	5.50E-03
328	3.66E-02	2.00E-03	9.46E-05	2.80E-06	9.78E-03	5.67E-05	5.32E-01	4.62E-02
332	3.68E-02	7.14E-05	9.32E-05	2.80E-06	7.65E-03	4.44E-05	5.83E-01	5.18E-02
336	3.73E-02	3.57E-04	1.08E-04	3.20E-06	5.55E-03	3.22E-05	5.82E-01	1.93E-02
340	3.91E-02	1.43E-04	9.90E-05	3.00E-06	3.39E-03	1.96E-05	6.15E-01	3.05E-02
344	3.88E-02	5.00E-04	9.70E-05	2.90E-06	1.14E-03	6.60E-06	6.51E-01	2.99E-02
348	3.94E-02	4.29E-04	8.69E-05	2.60E-06	1.67E-05	1.00E-07	5.51E-01	9.62E-03
352	3.90E-02	7.14E-04	9.00E-05	2.70E-06	1.29E-05	1.00E-07	5.83E-01	3.90E-02
356	3.90E-02	1.43E-04	9.22E-05	2.80E-06	5.70E-06	0.00E+00	6.32E-01	2.01E-02
360	3.92E-02	0.00E+00	8.74E-05	2.60E-06	1.55E-05	1.00E-07	6.27E-01	5.84E-02

Model-Specific Criteria in Reparametrization Procedure

As indicated in the Methods section (Iterative heuristic procedure), the parameter groups that cannot be fixed simultaneously, as part of the TCI, are:

I. μ_m, q_m, K_q and K_s (otherwise eq. 10 would have fixed all of its associated parameters).

II. ρ_m and s_0 (id. eq. 11).

III. π_m and K_π (id. eq. 14).

Equations 12 and 13 have combinations of the aforementioned parameter groups, and equation 15 has no parameters associated; therefore no further criteria are required. Finally, the factor used for TCIII is 1.2, because initial trials displayed several identifiability problems when fixing some parameters. The threshold 1.2 should therefore be used in models with several initial identifiability problems.

Solid substrate fermentation model

Dynamic Model

The solid substrate fermentation model proposed by Gelmi et al. [5] describes the changes in the biomass of *G. fujikuroi* growing with inert support. The model does not incorporate the lag phase and includes the following assumptions: (i) oxygen transfer resistance is low, (ii) available nitrogen is the limiting substrate (carbon source is not limiting) and (iii) both temperature and water activity remain constant during fermentation at 25°C and 0.999, respectively.

The model consists of eight coupled ordinary differential equations with 14 unknown parameters (Table S6). The state variables expressed per grams of inert support (g.i.s.) are:

(1) X: active biomass [g/g.i.s.] (not measured)

(2) U: urea [g/g.i.s.]

(3) N_I: intermediary nitrogen [g/g.i.s.] (not measured)

(4) X_m: measured biomass (active and inactive) [g/g.i.s.]

(5) CO_2: carbon dioxide [g/g.i.s.]

(6) O_2: oxygen [g/g.i.s.]

(7) GA_3: gibberellic acid [g/g.i.s.]

(8) S: starch [g/g.i.s.]

Table S6. Model parameters for the SSF model [5].

Parameter	Name
μ_m	Maximum growth rate [1/h]
k_d	Death rate [1/h]
k_U	Conversion rate from urea to available nitrogen [g/g.i.s.•h]
m_{CO_2}	CO_2 maintenance coefficient [g/g•h]
m_{O_2}	O_2 maintenance coefficient [g/g•h]
k_p	GA_3 degradation rate [1/h]
Y_{NX}	Nitrogen to biomass yield [g/g]
k_N	Half saturation constant of nitrogen source for growth [g/g.i.s]
Y_{CO_2X}	CO_2 to biomass yield [g/g]
Y_{O_2X}	Oxygen to biomass yield [g/g]
β_m	Maximum specific GA_3 production rate [1/h]
k_i	Substrate inhibition constant [1/(g/g.i.s.)]
Y_{SX}	Substrate to biomass yield [g/g]
m_S	Substrate maintenance coefficient [g/g•h]

The solid substrate fermentation process is described by the following set of ordinary differential equations:

$$\frac{dX}{dt} = \mu X - k_d X \qquad \text{[Equation 19]}$$

$$\frac{dU}{dt} = -k_u \qquad \text{[Equation 20]}$$

$$\frac{dN_I}{dt} = 0.47\, k_u - \mu \frac{X}{Y_{NX}} \qquad \text{[Equation 21]}$$

$$\frac{dX_m}{dt} = \mu X \qquad \text{[Equation 22]}$$

$$\frac{dCO_2}{dt} = \mu \frac{X}{Y_{CO_2X}} + m_{CO_2} X \qquad \text{[Equation 23]}$$

$$\frac{dO_2}{dt} = \mu \frac{X}{Y_{O_2X}} + m_{O_2} X \qquad \text{[Equation 24]}$$

$$\frac{dGA_3}{dt} = \beta X - k_p GA_3 \qquad \text{[Equation 25]}$$

$$\frac{dS}{dt} = -\mu \frac{X}{Y_{SX}} - m_s X \qquad \text{[Equation 26]}$$

Also, the model includes two algebraic equations describing the specific growth rate of the *G. fujikuroi* (μ) and production rate of GA_3 (β). The specific growth rate has a standard Monod kinetic and the GA_3 production a substrate inhibition kinetic.

$$\mu = \frac{\mu_m N}{N + k_N} \quad \text{[Equation 27]}$$

$$\beta = \frac{\beta_m}{1 + k_i N} \quad \text{[Equation 28]}$$

Parameter Estimation

The initial point for parameter estimation was a solution obtained from a previously performed SSm optimization that achieved a relatively good fitting. The lower and upper bounds in our procedure were the same used by Sacher et al. [2]. The experimental data measured was directly facilitated by Gelmi et al. [6]; briefly, the fermentation process was done in 46 inoculated columns and samples were obtained over a 142 h cultivation period. The sampling was performed in duplicate for gases (O_2 and CO_2) and in quadruplicate for biomass (X_m), urea (U), starch (S) and gibberellic acid (GA_3). Finally, for calibration purposes, the data was smoothed and interpolated to achieve equal amounts of measurements for each variable, as seen in Table S7.

Table S7. Experimental data used for calibration of the SSF model.

Time [h]	U [g/g.i.s.]	X_{measu} [g/g.i.s.]	CO_2 [g/g.i.s.]	O_2 [g/g.i.s.]	GA_3 [g/g.i.s.]	S [g/g.i.s.]
20	3.15E-03	6.88E-03	8.85E-03	4.67E-03	0.00E+00	1.77E-01
25	6.58E-04	1.04E-02	1.90E-02	9.17E-03	0.00E+00	1.31E-01
30	2.00E-06	1.41E-02	2.98E-02	1.41E-02	0.00E+00	1.04E-01
35	0.00E+00	1.76E-02	4.17E-02	1.93E-02	0.00E+00	8.47E-02
40	0.00E+00	2.06E-02	5.42E-02	2.45E-02	1.70E-05	6.95E-02
45	0.00E+00	2.31E-02	6.69E-02	2.94E-02	4.40E-05	5.74E-02
50	0.00E+00	2.52E-02	7.89E-02	3.40E-02	6.70E-05	4.78E-02
55	0.00E+00	2.68E-02	8.98E-02	3.83E-02	8.70E-05	4.00E-02
60	0.00E+00	2.81E-02	9.94E-02	4.21E-02	1.04E-04	3.37E-02
65	0.00E+00	2.90E-02	1.08E-01	4.56E-02	1.19E-04	2.85E-02
70	0.00E+00	2.98E-02	1.14E-01	4.87E-02	1.32E-04	2.43E-02
75	0.00E+00	3.03E-02	1.20E-01	5.14E-02	1.43E-04	2.09E-02
80	0.00E+00	3.06E-02	1.24E-01	5.39E-02	1.53E-04	1.81E-02
85	0.00E+00	3.09E-02	1.28E-01	5.60E-02	1.61E-04	1.57E-02
90	0.00E+00	3.10E-02	1.31E-01	5.78E-02	1.68E-04	1.38E-02
95	0.00E+00	3.10E-02	1.33E-01	5.94E-02	1.75E-04	1.23E-02
100	0.00E+00	3.09E-02	1.35E-01	6.07E-02	1.80E-04	1.10E-02
105	0.00E+00	3.08E-02	1.36E-01	6.19E-02	1.85E-04	9.91E-03
110	0.00E+00	3.06E-02	1.37E-01	6.28E-02	1.89E-04	9.03E-03
115	0.00E+00	3.04E-02	1.38E-01	6.35E-02	1.92E-04	8.31E-03
120	0.00E+00	3.02E-02	1.39E-01	6.41E-02	1.95E-04	7.71E-03
125	0.00E+00	2.99E-02	1.39E-01	6.45E-02	1.98E-04	7.22E-03
130	0.00E+00	2.97E-02	1.40E-01	6.47E-02	2.00E-04	6.82E-03
135	0.00E+00	2.94E-02	1.40E-01	6.48E-02	2.02E-04	6.48E-03
140	0.00E+00	2.91E-02	1.40E-01	6.48E-02	2.04E-04	6.21E-03
145	0.00E+00	2.88E-02	1.40E-01	6.47E-02	2.05E-04	5.98E-03

Model-Specific Criteria in Reparametrization Procedure

As indicated in the Methods section (Iterative heuristic procedure), the parameter groups that cannot be fixed all at the same time, as part of the TCI, are:

I. K_U (otherwise eq. 20 would have fixed all of it associated parameters).

II. μ_N and K_N (id. eq. 22).

III. β_M, k_i and k_p (id. eq. 25).

The remaining differential equations (19, 21, 23, 24 and 26) include at least one of these parameter groups and consequently no additional criteria are needed. Finally, the factor used for the TCIII is 1.5, given that few iterations were generated in the initial testing of the procedure, due to relatively few identifiability issues. The threshold of 1.5 should therefore be used in models with few initial identifiability problems.

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