Supplementary Table 1: the inventory of different objective functions. Each objective function is categorized based on the mathematical formulation of the objective, type of the problem, goal of the study and the need of reformulation.

The following abbreviations are used in the table: Lin: Linear, Quad: Quadratic, Lin Frac: Linear Fractional, Quad Frac: Quadratic Fractional, NonLin: Nonlinear, LP: Linear Programming, MILP: Mixed Integer Linear Programming, QP: Quadratic Programming, MIQP: Mixed Integer Quadratic Programming, MIQCP, Mixed Integer Quadratically Constrained Programming, FLP: Fractional Linear Programming, MIFLP: Mixed Integer Fractional Linear Programming, QFP: Quadratic Fractional Programming, MO: Multi-Objective Optimization, BL: Bi-Level Optimization, Phys: Physiology, App: Application, DI: Data Integration, C: Consistent, RN: Reformulation is Needed.

The meaning of the special signs: # represents the original problem before reformulation. & represents a type of problem that should be normally reformulated, but in this case, it is solved directly without reformulation. × represent the reformulations that are provided in this paper.

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
1	Max. biomass (growth rate)	*					*	*									*			*		(1-6)
2	Max. ATP yield	*					*										*			*		(3, 7)
3	Min. the overall flux		*						*	*							*			*		(8-10, 82)
4	Max. ATP per flux unit (sum of fluxes)			*			*					#					*				*	11
5	Min. redox potential	*					*										*			*		12
6	Min. ATP production	*					*										*			*		12
7	Max. ATP production	*					*	*									*			*		(12-14)

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
8	Max. the number of reactions whose activity is consistent with their expression state	*						*											*	*		15
9	Min. the inconsistency between gene expression and flux values	*					*												*	*		(16, 17)

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
10	Min. the number of reactions that carry flux and produce a specific set of metabolites	*						*											*	*		10
11	Max. the consistency between relative experimentally observed changes in gene expression and metabolite changes with the flux levels	*						*											*	*		18

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
12	Max. the correlation between gene expression and fluxes	*						*											*	*		19
13	Min. Growing Reaction Set	*						*									*			*		20
14	Max. bioengineering objective for the outer and max. biomass for the inner problem	*						*								#		*			*	21

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
15	Max. a linear combination of fluxes with penalty terms for the total number of gene deletions or over-expressions for the outer and Max. biomass for the inner problem	*						*								#		*			*	22

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
16	Min. metabolic adjustment	*	*				*		*								*			*		(23, 24)
17	Min. the number of significant flux changes after perturbation	*					*	*									*			*		25

18	Min. the sum of squared differences between flux variables and MFA estimates weighted by the reciprocal of confidence intervals, and the sum of squared enzyme contributions weighted by the reciprocal of enzyme expression values		*						*										*	*		26

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
19	Min. the relative flux changes from a reference state for reactions active in the reference state and the enzyme contribution increases for enzymes inactive in the reference state with a penalty α		*						*								*			*		26

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
20	Min. sum of squared internal fluxes		*						*								*			*		27
21	Opt. the level of pattern regulation and the level of differential gene expression	*						*											*	*		28

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
22	Min. the variance of weighted sum of squared residuals between measured and computed massisotopomer distributions		*						*										*	*		29

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
23	Min. the difference between measured and predicted metabolite uptake and secretion rates		*						*										*	*		(29, 30)
24	Min. the total metabolite concentrations and total enzyme concentrations		*						*								*			*		31

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
25	Min. the total sum of absolute fluxes	*					*										*			*		32
26	Min. the number of active reactions	*						*									*			*		33
27	Min. the sum of nutrient import costs	*					*										*			*		34

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
28	Min. number of nonnative reactions needed to meet the identified maximum yield for the outer and Max. the yield on a weight basis of a particular product for the inner[1]	*						*								#		*			×	35

[1] They solved it by solving the inner problem first and then, they added the inner problem as a constraint to the outer problem.

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
29	Min. the difference between experimentally measured absolute gene expression data and predicted internal reaction fluxes weighted by confidence level	*					*												*	*		36

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
30	Max. the agreement between fluxes and gene expression	*						*											*	*		37
31	Min. of Manhattan distance between the reference metabolite turnover and mutant metabolite turnover	*					*										*			*		38
32	Max. biomass turnover	*					*										*			*		38

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
33	Max./Min. ATP turnover per glucose uptake			*			*					#					*				*	38
34	Max./Min. NADH turnover per glucose uptake			*			*					#					*				*	38

35	Min. the sum of squared error between measured fluxes and their predicted values from the model for the outer, Max. the sum of all possible objectives for the inner and weights are chosen from the upper level problem		*							*						#			*		*	39

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
36	Min. error for the outer, Max. a linear combination of objective functions for the inner[2]	*					*									#			*		*	40

[2] They did not mention how to solve the bilevel problem.

37	Max. 3 objectives: biomass yield, weighted sum of all of the NADPH-producing reactions in the model, and the weighted sum of all NADPH-producing reactions with the exception of the trans-hydrogenase reaction[3]	*					*								#		*				*	41

[3] They used epsilon-constraint method.

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
38	Max. the extracellular biomass concentration for the outer and Max. biomass yield for the inner					*										&	*				*	42

39	Min. a flux ratio of interest subject to media changes and gene deletions for the inner problem. Min. the number of deletions such that the minimum flux ratio is positive, ensuring that coupling occurs between a measurable flux and the chosen reaction			*				*								#		*			*	43

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
40	Min. the set of possible exchanged metabolites between two organisms 1 and 2 that can grow simultaneously under a specified condition	*						*									*			*		44

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
41	Min. weighted sum of flux magnitudes (weighted by mRNA expression level)	*					*												*	*		45
42	Min. the distance between nearoptimal polytope and mutant solution space		*						*								*			*		46

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
43	Min. the number of active fluxes to achieve the maximal yield	*						*									*			*		47
44	Min. of minmax scaled metabolic adjustment		*						*								*			*		48
45	Min. the metabolic adjustment, each reaction is scaled by its reference flux		*						*								*			*		49

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
46	Min. the deviation of fluxes from experimental data for the outer and Max. of flux through a generic objective reaction for the inner		*						*							#			*		*	(50, 51)

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
47	Max. the similarity with fluxomics and metabolomics data for the outer and Min. the squared sum of fluxes for the inner[4]		*													&			*	*		52

[4] Nested Hybrid Differential Evolution was used to solve it.

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
48	Min. (1) the overall flux and (2) glucose consumption, Max. of (3) biomass,(4) ATP production and (5) NADPH production (weighted sum)	*					*								#		*				×	53

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
49	Min. sum of substrates (or light) uptake subject to an experimentally observed growth	*					*										*			*		(54, 55)

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
50	Min. the distance between dFBA growth and kinetic model growth for the outer and Min. (1) the sum of fluxes and Max. (2) growth rate for the inner		*						*						#	#	*		*		*	56
51	Max. biomass per unit flux[5]				*									*			*			*		(57-59)

[5] The objective is fractional quadratic without any proposed reformulation. The last reference solved it as an NLP.

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
52	Min. the sum of all fold-changes for all genes with increased expression in the evolved strain	*					*												*	*		58

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
53	Max. community growth (or any communitylevel objective) for the outer and Max. species growth (or any specieslevel objective) for the inner	*					*								#	#	*				*	60

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
54	Min. Euclidean or Manhattan distance between a loopless flux profile and a flux profile with loops	*	*					*		*							*			*		6
55	Min. the distance of ratios between fluxes in predicted and observed flux profiles	*					*												*	*		61

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
56	Max. ATP yield per unit of flux (sum of squared fluxes)[6]				*									*			*			*		62
57	Min. the number of reactions that can violate bounds imposed by kinetic laws (the kinetic laws were used to define reactions bounds)	*						*											*	*		63

[6] The original problem is fractional quadratic programming

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
58	Min. the number of dispensable (nonessential) reactions for the outer and Max. the weight of similarity with transcriptomics data for the inner	*						*								#			*		*	64

59	Max. bioengineering objective for the outer and Max. 2 objectives[7] for the inner problem: biomass and redirection toward producing the target compound (redirection is formulated as the effect of reaction perturbation on the production of target)	*						*							#	#		*			*	65

[7] Weighted sum is used for MO.

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
60	Max. bioengineering objective for the outer and max. 2 objectives[8] for the inner problem: biomass and the opposite of sum of fluxes (i.e. min. sum of fluxes)	*						*								#		*			*	66

[8] Weighted sum is used for MO.

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
61	Min. the metabolite turnover (i.e. the sum of absolute incoming and outcoming fluxes for a metabolite)	*					*										*			*		67

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
62	Max. the weighted sum for patterns of gene activation and inactivation to find the one that is statistically match better with transcriptomics data	*						*											*	*		68
63	Min/Max free Gibbs energy	*						*									*			*		(69, 70)

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
64	Min. metabolic adjustment and the opposite of one of these objectives: 1. Growth, 2. ATP yield, 3. Glucose uptake, 4. Ethanol yield[9]		*						*						#		*				*	71

[9] Weighted sum is used to handle MO

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
65	Min. the sum of fluxes and the opposite of one of these objectives: 1. Growth, 2. ATP yield, 3. Glucose uptake, 4. Ethanol yield[10]	*					*								#		*				*	71

[10] Weighted sum is used to handle MO

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
66	Min. the sum of fluxes of reactions to produce each metabolite	*					*										*			*		72
67	Min. the import of energy (plants)	*					*										*			*		73
68	Min. the ATP hydrolysis in maintenance reaction	*					*										*			*		73
69	Max. the production of proton (H^+)	*					*										*			*		74

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
70	Max. the sum of exchange fluxes (Max. the difference between outflux and influx as a proxy of catabolism)	*					*										*			*		74

71	Max. the ATP requirement for growth and Min. the L_1 norm of difference between production of other biomass reactants and ATP requirement (different definition of growth by disjoining biomass reactants)[11]	*					*								#		*				*	75

[11] Weighted sum is used for MO.

72	Max. the minimum product rate at the maximum cellular growth in different cellular modules for the outer[12] and Max. the minimum product rate at the maximum cellular growth in each cellular module for the inner	*						*							#	#		*			*	76

[12] Both weighted sum and goal programming were used for MO.

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
73	Max. the minimum product synthesis rate at the non-growth state ($\mu = 0$) in different cellular modules for the outer[13] and Max. the the minimum product synthesis rate at the non-growth state in each cellular module for the inner	*						*							#	#		*			*	76

[13] Both weighted sum and goal programming were used for MO.

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
74	Min. the weighted sum of absolute fluxes where the weight of each reaction is proportional to the length of its proteins (as a proxy of protein synthesis cost)	*					*										*			*		77

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
75	Max. the weighted sum of absolute fluxes where the weight of each reaction is proportional to its abundance in proteomics data	*						*											*	*		78

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
76	Max. the production of a specific metabolite (*e.g*. Mycolic acid or lactate)	*					*										*			*		(79, 80)

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
77	Min. the absolute difference between two steadystate flux profiles for two different conditions, each scaled by its corresponding vector of experimental data	*					*												*	*		81

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
78	Min. the total sum of mass flow (sum of fluxes weighted by reactant molecular weight)	*					*										*			*		83
79	Max. the rate of protein translation (the translation reaction for a protein is added to the metabolic network)	*					*										*			*		84

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
80	Min./Max. iron acquisition[14]	*					*										*			*		85
81	Min. the level of lactate dehydrogenase as an indicator of cytotoxity	*					*										*			*		85
82	Min. the reactive oxygen species (ROS)	*					*										*			*		86

[14] To study host-pathogen interaction.

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
83	Max. the biomass yield and ATP yield and Min. the sum of fluxes in a multi-objective formulation[15]	*					*								#		*				*	87
84	Max. biomass divided by a weighted sum of square of fluxes and square of ATP production				*									*			*			*		59

[15] Epsilon-constraint method was used to handle MO.

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
85	Max. the growth and Min. the deviation of system from steady state assumption (assuming uncertainty in stoichiometric network the error for Sv=0 is minimized)[16]	*					*								#		*				*	88

[16] Weighted sum was used to handle MO.

86	Min. the Euclidean distance between flux predictions and experimentally observed fluxes for the outer and Max. the weighted sum of multiple linear objectives for the inner (to find the most relevant objectives and their weights)		*						*						#	#	*		*		*	89

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
87	Min the sum of forward and backward fluxes, where the backward weighted by thermodynamic equilibrium constant as an indicator of thermodynamic effort to reverse the directionality	*					*										*			*		90

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
88	Max. the flux in different metabolic pathways (each pathway represents a metabolic function)	*					*										*			*		91

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
89	Max. the number of active reactions, supplementing unlimited substrate, to find the blocked reactions[17]	*					*											*		*		92

[17] Originally MILP, but can be relaxed to LP

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
90	Min. the number of reactions to be added to the model to rescue growth in a certain condition, where each reaction is weighted based on its biochemical and thermodynamic favorability	*						*										*	*	*		92

91	Min. the number of reactions (each reaction is weighted based on its biochemical and thermodynamic favorability) to be removed from the model to suppress growth in a certain condition for the outer, while Max. the growth in the normal condition for the inner (to maintain growth in the wildtype)	*						*								#		*	*		*	92

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
92	Min. growth for the outer and Max. the growth for the inner to find the minimal number of reaction removals to suppress growth in a specific condition (the number of reaction removals is constrained)	*						*								#		*	*		*	(93, 94)

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
93	Min. the number of reactions to be added to the model to rescue growth in a certain condition, where each reaction is weighted equally	*						*										*	*	*		93

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
94	Min. the number of reactions to be added to the model to rescue growth in a certain condition, where each reaction is weighted based on information about its metabolites and thermodynamic favorability	*						*										*	*	*		95

95	Max. the error correction for false negative growth predictions (prediction of zero growth when growth is known to occur), Min. the error introduction for false positives (prediction of growth when no growth is expected) and Min. the number of reactions to be added (gap filling reconciliation)[18]	*						*							#			*	*		*	95

[18] Weighted sum is used to handle MO.

96	Max. the chance of high scored reactions to be included and Min. the chance of low scored reactions to be removed from a generic parent model to make it organism specific (the scores are calculated by gene alignment for the genes associated to the reactions)	*						*							#			*	*		*	96

97	Min. the number of reactions to be added to the model to rescue growth in a certain condition, where each reaction is weighted based on the reverse of its similarity score (the scores are calculated by gene alignment for the genes associated to the reactions)	*						*										*	*	*		96

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
98	Max. the Min. (min mix problem) bioengineering objective for the outer and max. biomass for the inner problem	*						*								#		*			*	97
99	Max. growth and Max. production of natural byproducts[19]	*					*								#		*				*	98

[19] Epsilon-constraint method is used to handle MO.

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
100	Max. growth for the outer, Min. the violation of transcription regulatory constraints for the inner[20]	*					*									#			*		*	99
101	Max. growth, Min. the violation of transcription regulatory constraints[21]	*					*								#				*		*	100

[20] There was no method mentioned for the conversion of bilevel optimization.
[21] Weighted sum is used for MO.

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
102	Min. the number of reactions carrying flux (by assigning a cost to them) to make sure that a certain reaction carries flux	*					*										*			*		101

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
103	Max. growth and Max. production of the product and Min. the production of undesired byproducts	*						*							#			*			*	102

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
104	Min. the number of reactions to be added to the model (heterologous reactions) to satisfy a minimum yield for the production of a metabolite	*						*										*		*		103

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
105	Min. the number of active reactions between two metabolites (i.e. finding the shortest path taking steady-state feasibility into account)	*						*									*			*		104

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
106	Min. the number of active reactions between two metabolites each weighted by the number of its reactants and products (i.e. finding the lightest path)	*					*										*			*		105

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
107	Min. the number of all elemental transfers in a reaction, Min. the diversity of elemental exchanges and Max. the transfer score[22]	*						*							#		*				*	106

[22] Weighted sum is used to handle MO.

108	Max. the sum of binary variables showing the presence of a pathway between two metabolites weighted by a large number minus the length of this pathway (to find the shortest pathway, while keeping the problem always feasible)	*						*									*			*		106

109	Max. the sum of binary variables showing the presence of a pathway between two metabolites weighted by a large number minus the sum of flow variables each divided by its found flux in FBA (to find the most active pathways in FBA)	*						*									*			*		106

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
110	Max. the uptake of a specific substrate (*e.g.* ammonia or amino acids)	*					*										*			*		107
111	Max. the cardinality of the network, i.e. the number of reactions whose flux is not zero to reduce the number of blocked reactions	*					*											*		*		108

112	Min. the absolute difference between flux distribution and a set of randomly generated fluxes based on transcriptomics data (only applied to reactions whose fluxes are coupled to their gene expression by comparing fluxomics and transcriptomics data)	*					*												*	*		109

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
113	Min. the number of active reactions participating in the synthesis of a biomass building block	*						*										*		*		110

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
114	Min. two (conceptually but practically three) objectives, the absolute sum of fluxes and deviation of log concentrations of metabolites from their experimentally measured values		*							*					#				*		×	111

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
115	Min. the absolute difference between scaled measurements and fluxes multiplied by a scaling variable	*					*												*	*		112

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
116	Min. two objectives (as proxies of growth demands); the weighted sum of fluxes and biomass yield[23]	*					*								#		*				*	113

[23] Weighted Sum is used for MO.

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
117	Max. growth, Max. ATP production, Min. the total abundance of metabolic enzymes, and Min. the carbon uptake[24]	*					*								#		*				*	114

[24] Epsilon constraint is used for MO.

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
118	Max. bioengineering objective for the outer, Min. bioengineering objective for the inner	*						*								#		*			*	115

119	Max. the cellular objective including the impact of the inferred reaction for the inner, Min. the squared sum of differences between predictions and measured fluxes and Min. the number of reactants and products (sparsity) in the inferred reaction for the outer[25]		*							*						#			*		*	116

[25] KKT conditions are used for the reformulation.

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
120	Min. the uptake rate of a particular metabolite for the inner, Max. the uptake rate of the metabolite similar for the outer	*						*								#		*			*	117
121	Min. the number of open exchange reactions to specify the growth medium	*						*										*		*		(118, 119)

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
122	Max. growth, Max. demand flux for metabolites with increased concentration, Min. demand flux for metabolites with decreased concentration[26]	*					*								#				*		*	120

[26] Weighted sum is used.

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
123	Min. the number of reactions that connect an extracellular metabolite to the core	*						*										*		*		121
124	Max. production of virulence factors (definition similar to biomass)	*					*										*			*		122

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
125	Max. flux through symbiosis reaction (definition similar to biomass)	*					*										*			*		123

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
126	Max. the sum of secretion of biomass building blocks and adding reactions from a database with negative weights according to taxonomic information	*						*										*		*		124

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
127	Max. the nongrowth associated maintenance	*					*										*			*		125
128	Max. the number of active reactions each scored by the evidence for its inclusion in a specific tissue	*						*											*	*		126

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
129	Max. the number of reactions that cause metabolite accumulation	*						*									*			*		126

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
130	Min. the sum of deviation from mass action kinetics and deviation from reference fluxes due to the single nucleotide polymorphisms (SNPs)	*						*											*	*		127

131	Max. weighted sum of ATP synthesis and growth for the first inner, Min. total sum of fluxes for the second inner, and optimize fuzzy equality of the logarithmic flux changes between mutant and template (i.e. minimizing the deviation between them) for the outer[27]					*									#	&			*	*		128

[27] This is a tri-level optimization and Nested Hybrid Differential Evolution was used to solve it.

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
132	Max. weighted sum of ATP synthesis and growth for the first inner, Min. total sum of fluxes for the second inner, and Max. similarity ratio of the fluxes in mutant and template models for the outer[28]	*													#	&			*	*		128

[28] This is a tri-level optimization and Nested Hybrid Differential Evolution was used to solve it.

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
133	Min the upper bound of pyruvate kinase for the first inner, Max. growth for the second inner, and Min. flux through lactate dehydrogenase for the outer[29]	*					*									#	*				*	129

[29] This is a tri-level optimization.

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
134	Max. the production of the product for the inner and Min. the number of reaction knockouts for the outer	*						*								#		*			*	130
135	Max. the usage of reactions in host to simulate the maximum metabolic exploitation of pathogen	*					*	*									*			*		131

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
136	Min. the L1 norm of slack variables for the reaction lower and upper bounds (the bounds are calculated based on gene expression data)	*					*												*	*		132
137	Min. photon usage	*					*										*			*		133

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
138	Min. number of reaction knockouts (static) and regulated valves (dynamic) to allow switching between two distinct metabolic phenotypes	*						*										*		*		134

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
139	Min. L1-norm of fluxes and L2-norm of difference between fluxes and transcriptomics data[30]		*						*						#				*		*	135

[30] Weighted sum is used.

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
140	Min. absolute sum of fluxes and violation of reaction bounds (by assigning slack variables to each constraint) that are defined based on omics dataset[31]	*					*								#				*		*	136

[31] Weighted sum is used.

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
141	Min. the difference between upper and lowerbounds of a reaction compatible with omics dataset	*					*												*	*		136
142	Min. absolute sum of fluxes that show low expression in transcriptomics data	*					*												*	*		137

143	Min. the violation of constraints that enforce a flux in the new condition to be higher than reference state, if its gene expression is higher than the reference by assigning two slack variables to each constraint[32]	*						*											*	*		137

[32] Both the number and the sum of violations can be minimized.

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
144	Max. growth for the outer and Max. ATP maintenance for the inner	*					*									#	*				*	138
145	Min. the upper bound of Gibbs energy of all reactions in a pathway (thermodynamic driving force)	*					*	*									*			*		(139, 140)

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
146	Max. the absolute value of reaction fluxes	*						*									*			*		141
147	Max. the combination of all metabolic tasks specific to a tissue gather from the literature	*					*										*			*		142

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
148	Max. the growth of a gene knockout mutant for the inner, Max. the drop in the wildtype growth after the knockout (difference between wildtype and mutant growth) for the outer	*						*								#	*				*	143

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
149	Min. the variance of difference between flux predictions and kinetically calculated fluxes by integrating metabolomics and proteomics data		*						*										*	*		144

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
150	Min. the number of reactions modifications, i.e. knockout, up or downregulation, for the outer and Min. the production of the product for the inner	*						*								#		*			*	145

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
151	Max. the number of metabolites that can be produced in the network to distinguish the metabolites that can never be produced	*						*										*		*		146
152	Min./Max. the ratio of any two reactions			*			*					#						*			*	147

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
153	Max. the production of the product and Min. the number of genetic modifications for the outer, and Max. the growth for the inner	*						*							#	#		*			*	148

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
154	Max. the productions of the product for the outer, and Min. the metabolic adjustment for the inner	*									*					#		*			*	148
155	Weighted sum of growth rates of different microbial species	*					*								#		*				*	(149, 150)

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
156	Max. the flux through two exchange reactions between the host and the microbe[33]	*					*								#		*				*	151

[33] Epsilon-constraint method is used.

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
157	Max. growth and Min. total squared sum of fluxes for the inner (a weighted sum), and Min. absolute difference between predicted growth by FBA and kinetic model for the outer[34]	*									*					#			*		*	152

[34] First the inner problem was solved, then the outer problem.

158	Min. the weighted sum of 1) the square of difference between constrained and unconstrained fluxes with experimental data, 2) the sum of candidate biological objectives, 3) the cross-product of the weights of candidate objective to prefer only one of them, 4) the difference between the lower- and upper-bounds to find the least number of active constraints[35]		*						*						#				*		*	153

[35] Dynamic modelling

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
159	Max. the biomass concentration at the final time step[36]	*					*										*			*		154
160	Max. the total sum of biomass concentrations of different microbial species[37]	*					*									#	*				*	155

[36] Dynamic modelling
[37] Dynamic modelling

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
161	Min. the total sum of fluctuations in metabolite concentrations[38]	*					*										*			*		156
162	Min. total sum of explicit enzyme concentrations	*					*										*			*		157

[38] Dynamic modelling

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
163	Min. the sum of reaction fluxes, where each reaction is weighted by its BLAST score and DG	*					*												*	*		158

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
164	Min. the inconsistency between reaction fluxes and transcriptomics data up and downregulation in two conditions	*						*											*	*		159

165	Max. the growth in non-growing phenotypes for the inner, Min. the number of modifications, including removals or additions of the reactions, directionality changes, removals or additions of the metabolites regarding the biomass reaction, in the model to fix false growth and non-growth predictions for the outer	*						*							#	#		*			*	160

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
166	Max. the uncentered Pearson product-moment correlation between flux variables and gene transcription data[39]					*													*			161

[39] Semi-definite nonlinear optimization.

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
167	Min. the squared difference between the predicted and experimentally observed ethanol yields for the outer, Min. the weighted sum of squared fluxes and the opposite of ethanol flux for the inner[40]		*												#	&			*		*	162

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
168	Min. the difference between the measured and predicted linear combinations of the objective functions (instead of fluxes, the objective coefficients are variables)	*					*												*	*		163

[40] Bilevel problem is solved directly with an in-house algorithm.

	Objective Function	Type of Objective					Type of Problem										Goal of Study			Consistency with This Formulation		References
		Lin.	Quad.	Lin. Frac.	Quad. Frac.	NonLin.	LP	MILP	QP	MIQP	MIQCP	FLP	MIFLP	QFP	MO	BL	Phys	App	DI	C	RN	
169	Min. the L1norm of the coefficients in the objective function	*					*												*	*		163

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