GENERAL INFORMATION			FORMULATION				FEATURES						CASE STUDIES			AVAILABILITY	
METHOD	PUBLICATION URL	YEAR	FRAMEWORK	DESCRIPTION	SCALABILITY	TYPE	GPRs	DELETIONS	HETEROLOGOUS INSERTION	OVER/UNDER EXPRESSION	REGULATION	EXTRA FEATURES	ORGANISMS	MODELS	APPLICATIONS	SOFTWARE PACKAGES	DEPENDS
OptKnock	http://www.ncbi.nlm.nih.gov/pubmed/14595777	2003	BILEVEL	MIBLP - converted to single level MILP using duality theory	LOW	Exact	NO	YES	NO	NO	NO		*E. coli*	central carbon metabolism model (Edwards and Palsson, 2000)	Succinate, Lactate and 1,3-propanediol	Cobra toolbox, OptFlux	Matlab (Cobra)
OptStrain	http://www.ncbi.nlm.nih.gov/pubmed/15520298	2004	BILEVEL	MIBLP - converted to single level MILP using duality theory	LOW	Exact	NO	YES	YES	NO	NO		*E. coli* *C. acetobutylicum*	iJR904 and (Papoutsakis 1984; Desai et al, 1999)	Hydrogen and vanillin		
OptGene	http://www.ncbi.nlm.nih.gov/pubmed/16375763	2005	BILEVEL	Bi-level Heuristic. GA generates genotypes whose phenotypes are predicted by LP (FBA)	HIGH	Heuristic	NO	YES	NO	NO	NO		*S. cerevisiae*	iFF708	Vanillin, Glycerol and Succinate	Optflux, Cobra toolbox	Matlab (Cobra)
OptReg	http://www.ncbi.nlm.nih.gov/pubmed/16199194	2006	BILEVEL	MIBLP - converted to single level MILP using duality theory	LOW	Exact	NO	YES	NO	YES	NO		*E. coli*	iJR904	Ethanol		
MMF	http://www.sciencedirect.com/science/article/pii/S109671760600067X	2006	EMA	EFMs	LOW	Exact	NO	NO	NO	NO	NO		*E. coli*	core of intermediary metabolism (Carlson and Srienc, 2004)	Biomass		
EAs/SAs	http://www.ncbi.nlm.nih.gov/pubmed/19038030	2008	BILEVEL	Bi-level Heuristic. EA/SA generate genotypes whose phenotypes are predicted by LP (FBA)	HIGH	Heuristic	YES	YES	NO	NO	NO		*E. coli* *S. cerevisiae*	iJR904 iND750	Succinate and Lactate	OptFlux	
GDLS	http://www.ncbi.nlm.nih.gov/pubmed/19690565	2009	BILEVEL	MIBLP - converted to single level MILP using duality theory	MEDIUM	Heuristic	YES	YES	NO	NO	NO		*E. coli*	iAF1260	Acetate and Succinate	Cobra toolbox; author's homepage: http://crab.rutgers.edu/~dsluln/gdls/	Matlab
CiED	http://www.ncbi.nlm.nih.gov/pubmed/19633125	2009	BILEVEL	Bi-level Heuristic. Evolutionary cipher	HIGH	Heuristic	YES	YES	NO	NO	NO		*E. coli*	iJR904	Flavones		
FluxDesign	http://www.ncbi.nlm.nih.gov/pubmed/20035624	2009	EMA	EFMs	LOW	Exact	NO	YES	NO	YES	NO		*C. glutamicum* *A. niger*	(simplified models)	Lysine and Enzymes		
RobustKnock	http://www.ncbi.nlm.nih.gov/pubmed/20031969	2010	Multi-LEVEL	Max-min MIBLP - converted to single level MILP using duality theory	LOW	Exact	NO	YES	NO	NO	NO		*E. coli*	iJR904	Hydrogen, Acetate, Formate and Fumarate	Author's homepage: http://www.cs.technion.ac.il/~tomersh/methods.html	
OptORF	http://www.biomedcentral.com/1752-0509/4/53/	2010	BILEVEL	MIBLP - converted to single level MILP using duality theory	LOW	Exact	YES	YES	NO	YES	YES		*E. coli*	iMC1010 (v2)	Ethanol, isobutanol and 2-phenylethanol		
OptForce	http://www.ncbi.nlm.nih.gov/pubmed/20419153	2010		LP	LOW	Exact	NO	NO	NO	YES	NO		*E. coli*	iAF1260	Succinate	Available in the author's homepage upon request:http://maranas.che.psu.edu/submission/optforce.htm	
CASOP	http://www.ncbi.nlm.nih.gov/pubmed/20303369	2010	EMA	EFMs	LOW	Heuristic	NO	YES	NO	YES	NO		*E. coli*	central carbon metabolism model	Succinate	CellNetAnalyzer	Matlab
CASOP-GS	http://subs.emis.de/LNI/Proceedings/Proceedings173/P-173.pdf?origin=publication_detail#page=72	2010	EMA	EFMs	HIGH	Heuristic	NO	YES	NO	YES	NO		*E. coli*	iAF1260	Succinate and histidine	Available on request (including source)	
cMCS	http://www.ncbi.nlm.nih.gov/pubmed/21147248	2011	EMA	EFMs	LOW	Exact	NO	YES	NO	NO	NO		*E. coli*	(Trinh et al., 2008)	Ethanol	CellNetAnalyzer	Matlab
BiMOMA	http://www.ncbi.nlm.nih.gov/pubmed/21949695	2011	BILEVEL	MIQCP	MEDIUM	Exact	NO	YES	NO	NO	NO		*E. coli*	iJR904	Glutamate and pyruvate		
SimOptStrain	http://www.ncbi.nlm.nih.gov/pubmed/21949695	2011	BILEVEL	MILP	LOW	Exact	YES	YES	YES	NO	NO		*E. coli*	iJR904	Succinate and glycerol		
EMILIO	http://www.ncbi.nlm.nih.gov/pubmed/21414417	2011		Iterative LP (ILP)	HIGH	Exact	NO	YES	NO	YES	NO		*E. coli*	iAF1260	Succinate, glutamate and l-serine		
EAs/SAs Regulation	http://www.ncbi.nlm.nih.gov/pubmed/21144882	2011	BILEVEL	(EA/SA) rFBA/SR-FBA	HIGH	Heuristic	YES	YES	NO	NO	YES		*E. coli*	iAF1260	Ethanol	OptFlux plugin	
GDMO	http://www.ncbi.nlm.nih.gov/pubmed/23044547	2012	BILEVEL	NSGA-II based search, FBA evaluation	HIGH	Heuristic	YES	YES	NO	NO	NO		*E. coli*	iAF1260	Succinate and acetate		
GDBB	http://www.ncbi.nlm.nih.gov/pubmed/22543499	2012	BILEVEL	MIBLP converted to MILP based implementation. TBB, prevents the branch and bound algorithm from reaching optimal solution and stops at near-optimality.	HIGH	Heuristic	YES	YES	NO	YES	NO		*E. coli*	iAF1260	Succinate and acetate	Author's homepage: http://crab.rutgers.edu/~dsluln/gdbb	Matlab
EAs/SAs Over-under expression	http://online.liebertpub.com/doi/abs/10.1089/cmb.2011.0265	2012	BILEVEL	(EA/SA) FBA/MOMA/ROOM	HIGH	Heuristic	YES	YES	NO	YES	NO		*E. coli*	iJR904	Succinate and Lactate	OptFlux	

rcMCS	http://www.biomedcentral.com/1752-0509/6/103/abstract	2012	EMA	BLP(Binary Linear Programming)	LOW	Exact	YES	YES	NO	NO	YES		*E. coli*	(Trinh et al., 2008)	Ethanol		
MOMAKnock	http://www.ncbi.nlm.nih.gov/pubmed/23368729	2013	BILEVEL	MIBQP - converted to single level MILP using duality theory	LOW	Exact	YES	YES	NO	NO	NO		*E. coli*	iAF1260	Succinate		
Redirector	http://www.ncbi.nlm.nih.gov/pubmed/23341769	2013	BILEVEL	MIBLP - converted to single level MILP using duality theory	MEDIUM	Heuristic	YES	NO	NO	YES	NO		*E. coli*	iAF1260	myristoyl-CoA	Available from author's site: https://github.com//bionomicron/Redirector.git	
OptSwap	http://online.liebertpub.com/doi/abs/10.1089/ind.2013.0005	2013	MULTI-LEVEL (similar to to RobustKnock)	Max-min MIBLP - converted to single level MILP using duality theory	LOW	Exact	NO	YES	NO	NO	NO	Swapping of the cofactor specificity for oxyreductase enzymes	*E. coli*	iJO1366	production of a wide spectrum of products		
ReacKnock	http://www.ncbi.nlm.nih.gov/pubmed/24348984/	2013	BILEVEL	MIBLP - converted to single level MILP using Karush-Kuhn-Tucker for continuous inner problems.	LOW	Exact	NO	YES	NO	NO	NO		*E. coli*	iAF1260	Succinate, ethanol and threonine		
SMET	http://onlinelibrary.wiley.com/doi/10.1002/biot.201200233/abstract	2013	EMA	cMCS	LOW	Exact	NO	YES	NO	YES	NO		*E. coli*	(Rizk and Liao, 2009)	DAHP		
FastPros	http://www.ncbi.nlm.nih.gov/pubmed/24257186	2013	Multi-Step	Exaustive computation of dual mutants, LP for calculation of u-targets followed by iterative single mutant addition for best. Screening via OptKnock (MILP)	HIGH	Heuristic	NO	YES	NO	NO	NO		*E. coli*	iAF1260	production of every cytosolic metabolite	http://www-shimizu.ist.osaka-u.ac.jp/shimizu_lab/FastPros/	MatLab, COBRA
CosMos	http://onlinelibrary.wiley.com/doi/10.1002/biot.201200316/full	2013	BILEVEL	MILP	LOW	Exact	YES	YES	NO	YES	NO		*E. coli* *S. cerevisiae*	iJO1366 iMM904	Chorismate, ethanol, succinate, L-amino acids		
MCSEnumerator	http://www.ploscompbiol.org/article/info%3Adoi%2F10.1371%2Fjournal.pcbi.1003378	2014	EMA	MILP	HIGH	Exact	NO	YES	NO	NO	NO		*E. coli*	iAF1260	Fumarate and serine	CellNetAnalyzer	Matlab
k-OptForce	http://www.ploscompbiol.org/article/info%3Adoi%2F10.1371%2Fjournal.pcbi.1003487#pcbi.1003487-Curran1	2014	BILEVEL	MILP	LOW	Exact	NO	YES	NO	YES	NO	Hybrid stoichiometric and kinetic	*E. coli* *S. cerevisiae*	iAF1260 + (Chassagnole et al, 2002) iAZ900 + (van Eunen et al, 2012)	L-serine and TAL		