

MODEL-BASED ANALYSIS AND METABOLIC DESIGN OF A
CYANOBACTERIUM FOR BIO-PRODUCTS SYNTHESIS

Index

Foreword	I
Abstract	II
Resumen	IV
Resum	VI
Index	VIII
Aims, Objectives and Thesis approach	XI
Scientific contributions	XV
Chapter 1. Introduction	18
1.1 Systems Biology approach	18
1.2 The genome-scale metabolic network model	19
1.3 Metabolic network analysis	22
1.3.1 Metabolic regulation and control	22
1.3.2 Metabolic flux	23
1.3.3 Constraint-based computer simulation	25
1.3.3.1 Constraints on cellular functions	25
1.3.3.2 Methods for analyzing metabolic network states	28
1.3.3.3 Finding optimal states	29
1.4 <i>In silico</i> guided metabolic engineering for bio-products synthesis from CO ₂ and photons	34
1.4.1 Cyanobacterium model as a potential platform for metabolic engineering	36
Chapter 2. Reconstruction of cyanobacterium genome-scale metabolic network	40
2.1 Introduction	40
2.2 <i>Synechococcus elongatus</i> PCC7942 genome	41
2.3 <i>Synechococcus elongatus</i> PCC7942 metabolic model	42
2.3.1 Reconstruction procedure	42

2.3.2 Versions	46
2.3.2.1 <i>i</i> Syf646 metabolic model	46
2.3.2.2 <i>i</i> Syf715 metabolic model	47
2.3.3 Formulation of biomass equation	48
2.3.4 Network topology. Connectivity analysis	52
2.4 Conclusions	59
Chapter 3. <i>In silico</i> fluxomic behavior through constraints-based approach	62
3.1 Introduction	62
3.2 Finding optimal states	63
3.2.1 Constraints settings for system simulation	64
3.2.2 Fluxes' vector space of optimal metabolic growth. Metabolic models validation	66
3.2.3 Flux variability analysis	70
3.3 Robustness analysis of metabolic model networks	72
3.4 Conclusions	75
3.5 Methods	76
3.5.1 Cell surface area calculation	76
Chapter 4. Assessment of metabolic capabilities	81
4.1 Introduction	81
4.2 Building and enhancing chemical assignments in metabolic network	82
4.2.1 Gene essentiality analysis	83
4.2.2 Converting photons and CO ₂ into photanol	84
4.2.2.1 Ethanol	85
4.2.2.2 Higher chain alcohols	91
4.2.3 Assessing lipids synthesis for biodiesel and industrial applications.....	107
4.2.4 Assessing hydrogen evolution.....	117
4.3 Conclusions	125
4.4 Methods	126
4.4.1 Minimization of metabolic adjustment	126

4.4.2 Converting units of production rates to flux values	127
Chapter 5. Phenotypic phase plane analysis of <i>Synechococcus elongatus</i> PCC7942	130
5.1 Introduction	130
5.2 CO ₂ and light phenotype phase plane for biomass growth rate	131
5.3 CO ₂ and light phenotype phase plane for alcohols production	134
5.4 CO ₂ and light phenotype phase plane for lipids synthesis	137
5.5 CO ₂ and light phenotype phase plane for hydrogen evolution.....	139
5.6 Conclusions	140
5.7 Methods	140
5.7.1 Computing the Phase Plane	140
Chapter 6. Metabolome dynamic upon inorganic carbon acclimation... ..	143
6.1 Introduction	143
6.2 <i>iSyf715</i> as bio-molecular interaction network for integration	144
6.3 Conclusions	150
6.4 Methods	151
6.4.1 Transcriptome data analysis	151
Chapter 7. Concluding remarks	154
7.1 System biology is inherently mathematical	154
7.2 Workflow	156
Bibliography	158
Appendixes	179
Appendix 1.1	179
Appendix 1.2	220