IMPROVED DIFFERENTIAL SEARCH ALGORITHMS FOR METABOLIC NETWORK OPTIMIZATION

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DEDICATION

This thesis is dedicated to my parents, Ku Fauziah Ku Baharudin and Mohd Daud Hassan, who taught me that knowledge is the most precious things in the world.

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"Praise be to Him, the most Gracious and most Compassionate."

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ABSTRACT

The capabilities of *Escherichia coli* and *Zymomonas mobilis* to efficiently converting substrate into valuable metabolites have caught the attention of many industries. However, the production rates of these metabolites are still below the maximum threshold. Over the years, the organism strain design was improvised through the development of metabolic network that eases the process of exploiting and manipulating organism to maximize its growth rate and to maximize metabolites production. Due to the complexity of metabolic networks and multiple objectives, it is difficult to identify near-optimal knockout reactions that can maximize both objectives. This research has developed two improved modelling-optimization methods. The first method introduces a Differential Search Algorithm and Flux Balance Analysis (DSAFBA) to identify knockout reactions that maximize the production rate of desired metabolites. The latter method develops a non-dominated searching DSAFBA (ndsDSAFBA) to investigate the trade-off relationship between production rate and its growth rate by identifying knockout reactions that maximize both objectives. These methods were assessed against three metabolic networks – *E.coli* core model, iAF1260 and iEM439 for production of succinic acid, acetic acid and ethanol. The results revealed that the improved methods are superior to the other state-of-the-art methods in terms of production rate, growth rate and computation time. The study has demonstrated that the two improved modelling-optimization methods could be used to identify near-optimal knockout reactions that maximize production of desired metabolites as well as the organism's growth rate within a shorter computation time.

ABSTRAK

Keupayaan *Escherichia coli* dan *Zymomonas mobilis* untuk menukar substrat menjadi metabolit yang bernilai telah menarik perhatian banyak industri. Walau bagaimanapun, kadar penghasilan metabolit ini masih di bawah tahap maksima. Beberapa tahun kebelakangan, reka bentuk untaian organisma telah diperbaharui melalui penghasilan rangkaian metabolik yang memudahkan proses mengeksploitasi dan memanipulasi organisma untuk meningkatkan kadar pertumbuhan dan kadar penghasilan metabolit. Oleh kerana rangkaian metabolik dan pelbagai objektif yang komplek, ianya sukar untuk mengenal pasti tindak balas hampir optimal untuk disingkirkan bagi memaksimumkan dua objektif tersebut. Kajian ini telah membangunkan dua kaedah pengoptimuman-pemodelan yang lebih baik. Kaedah pertama memperkenalkan *Differential Search Algorithm and Flux Balance Analysis* (DSAFBA) untuk mengenal pasti tindak balas yang perlu disingkirkan bagi memaksimumkan kadar penghasilan metabolit yang dikehendaki. Kaedah kedua membangunkan *non-dominated sorting DSAFBA* (ndsDSAFBA) untuk menyelidik hubungan keseimbangan antara kadar penghasilan metabolit dan kadar pertumbuhan organisma dengan mengenal pasti tindak balas yang perlu disingkirkan bagi memaksimumkan kedua-dua objektif. Kaedah ini dinilai terhadap tiga rangkaian metabolik iaitu model teras *E.coli*, iAF1260 dan iEM439 untuk penghasilan asid suksinik, asid asetik dan etanol. Hasil kajian mendapati bahawa kaedah yang dicadangkan adalah lebih baik daripada kaedah lain yang kompetitif dari segi kadar penghasilan, kadar pertumbuhan dan masa pengiraan. Kajian ini menunjukkan bahawa kedua-dua kaedah pengoptimuman-pemodelan yang lebih baik ini dapat digunakan untuk mengenal pasti tindak balas penyingkiran yang paling optimal untuk memaksimumkan kadar penghasilan metabolit yang dikehendaki serta kadar pertumbuhan organism dalam masa pengiraan yang lebih pendek.

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LIST OF ABBREVIATIONS

ABC	-	Artificial Bee Colony
ACALD	-	Acetaldehyde dehydrogenase
ACKr	-	Acetate kinase
ACO	-	Ant Colony Optimization
AKGDH	-	2-Oxogluterate dehydrogenase
ATP	-	Adenosine triphosphate
BA	-	Bees Algorithm
BADE	-	Bat Algorithm based on the Differential Evolutionary Algorithm
BATFBA	-	Bat Algorithm Flux Balance Analysis
BB-BC	-	Big Bang–Big Crunch algorithm
BPCY	-	Biomass Production Couple Yield
CASOP	-	Computational Approach for Strain Optimization aiming at high Productivity
CBM	-	Constraint Based Method
CiED	-	Cipher Of Evolutionary Design
cMCSs	-	constrained Minimal Cut Sets
COBRA	-	Constraint-Based Reconstruction and Analysis Toolbox
CS	-	Cuckoo Search
CSOM	-	Computational Strain Optimization Method
DBFBA	-	Differential Bees Flux Balance Analysis
DE	-	Differential Evolution
DHORD2	-	Dihydoorotic acid dehydrogenase 2
DMOEA	-	Dynamical Multiobjective Evolutionary Algorithm
DNA	-	Deoxyribonucleic acid
DSA	-	Differential Search Algorithm
DSAFBA	-	Differential Search Algorithm Flux Balance Analysis
EDA	-	2-dehydro-3-deoxy-phosphogluconate aldolase
EDD	-	6-phosphogluconate dehydratase
EMA	-	Elementary Mode Analysis

ES	-	Evolution Strategies
F6PA	-	Fructose 6-phosphate aldolase
FBA	-	Flux Balance Analysis
FBA	-	Fructose-bisphosphate aldolase
FOCuS	-	Flower-pOllination-coupled Clonal Selection algorithm
FPA	-	Flux Pathway Analysis
FVA	-	Flux Variability Analysis
G6PDH2r	-	Glucose 6-phosphate dehydrogenase
GA	-	Genetic Algorithm
GACOFBA	-	Genetic Ant Colony Optimization Flux Balance Analysis
gDW	-	Gram dry weight
GEPSVM	-	Generalized Eigenvalue Proximal Support Vector Machine
GLUDy	-	Glutamate dehydrogenase
GLUN	-	Glutaminase
GLYCL	-	Glycine Cleavage System
GND	-	Phosphogluconate dehydrogenase
GSA	-	Gravitational Search Algorithm
HDSA	-	Hyperheuristic Differential Search Algorithm
HEX1	-	Hexokinase
hr	-	Hour
IDOND	-	L-idonate 5-dehydrogenase
JADE	-	Adaptive Differential Evolution
KEGG	-	Kyoto Encyclopedia of Genes and Genomes
LDH_D	-	D-lactate dehydrogenase
LP	-	Linear Programming
LPPFBA	-	Linear Physical Programming Flux Balance Analysis
MCs	-	Minimal Cut set
ME	-	Metabolic Engineering
ME1	-	Malic enzyme 1
ME2	-	Malic enzyme 2
MEA	-	Multi-objective Evolutionary Algorithm
Micro-GA	-	Micro Genetic Algorithm
MILP	-	Mixed integer linear programming

mmol	-	Milli mole
MOEA	-	Multiobjective Optimization Evolutionary Algorithm
MOGA	-	Multi-Objective Genetic Algorithms
MoMA	-	Minimization of Metabolic Adjustment
MOO	-	Multi-Objective Optimization
MOP	-	Multiobjective Optimization Problem
NBI	-	Normal Boundary Intersection
ndsDSAFBA	-	non-dominated sorting Differential Search Algorithm Flux Balance Analysis
NGAM	-	Non-growth ATP requirement
NISE	-	Non-Inferior Set Estimation
NPGA	-	Niched Pareto Genetic Algorithm
NSGA	-	Non-dominated Sorting Genetic Algorithm
ODE	-	Ordinary Differential Equations
PAES	-	Pareto Archived Evolution Strategy
PESA	-	Pareto Envelope-based Selection Algorithm
PFL	-	Pyruvate formate lyase
PGCD	-	Phosphoglycerate dehydrogenase
PGI	-	Glucose-6-phosphate isomerase
PSERT	-	Phosphoserine transaminase
PSO	-	Particle Swarm Optimization
PSOFBA	-	Particle Swarm Optimization Flux Balance Analysis
PSOMCS	-	Particle Swarm Optimization Constrained Minimal cut Set
PSP_L	-	Phosphoserine phosphatase
PTAr	-	Phosphotransacetylase
PYK	-	Pyruvate kinase
QP	-	Quadratic Programming
RDGA	-	Rank-Density Based Genetic Algorithm
ROOM	-	Regulatory On/Off Minimization
RWGA	-	Random Weighted Genetic Algorithm
SA	-	Simulated Annealing
SEA	-	Set-based Evolutionary Algorithm
SOO	-	Single Objective Optimization

SPEA	-	Strength Pareto Evolutionary Algorithm
SPEA2	-	Strength Pareto Evolutionary Algorithm 2
SSGA	-	Scatter Search algorithm based on the Genetic Algorithm
SUCDi	-	Succinate dehydrogenase
SUCOAS	-	Succinyl-CoA synthetase
TALA	-	Transaldolase
VEGA	-	Vector Evaluated Genetic Algorithm
WBGA	-	Weight-Based Genetic Algorithm
WBGA-MO	-	Weight-Based Genetic Algorithm for Multiobjective Optimization
XYL12	-	Xylose isomerase

LIST OF SYMBOLS

v	-	Vector of flux distributions
n, c	-	Coefficients of stoichiometric matrix
m	-	Metabolites
v_{ub}	-	Upper limits of each reaction
v_{lb}	-	Lower limits of each reaction
Z_{obj}	-	Objective function to be optimized
P	-	Amount of product produced
B	-	Grams of biomass produced
So	-	Stopover
SO	-	Superorganism
p_1, p_2	-	Control parameters
PR	-	Product rate
GR	-	Growth rate
$maxKOs$	-	Maximum number of reactions knockout
AO	-	Artificial-organism
PF	-	Pareto front
maxIter	-	Maximum iteration

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CHAPTER 1

INTRODUCTION

1.1 Overview

Ethanol, succinic acid and acetic acid are naturally synthesized in cell factories such as *Escherichia coli, Zymomonas mobilis* and *Saccharomyces cerevisiae* (Raab *et al.*, 2010). These metabolites are useful in various applications such as pharmaceuticals, food processing and biofuel as they bring more profit to the global market such as the pharmaceutical industry (Davy *et al.*, 2017). However, the productions of these metabolites are not sufficient as their production rates are theoretically below the maximum threshold. Given the intrinsic need of flexible and sustainable cell factories that can provide the maximum production of desired metabolites, these natural producers have been re-engineered and manipulated to overproduce desired metabolites.

Due to the remarkable advancements in DNA sequencing technology, hundreds of metabolic networks have been curated and constructed. The advancements have provide new information, understanding and visualization of the processes involved in the systems biology. A metabolic network consists of all enzymes and transport proteins that are associated with reactions that determine the physiological and biochemical properties of the cell. Traditional techniques such as random mutagenesis and selection have been used to decipher the available information in the model. Using traditional techniques, genetic perturbations are conducted only based on a physical characteristic (Kim *et al.*, 2015). However, it may affect the organisms' stability and feasibility. Despite the great success, however, these techniques are tedious, time-consuming, irreversible and higher error rate (Maia, Rocha and Rocha, 2016). Therefore, metabolic engineering has been introduced to engineer an efficient cell factory, considering that metabolic engineering can provide more understanding of the cell.

Metabolic engineering is an approach that exploits or improves the capabilities of organisms by manipulating enzymatic, transport and regulatory functions of the cell using recombinant DNA technology (Heirendt *et al.*, 2017). The aim of metabolic engineering is to improve the microbial strain in order to economically and industrially produces the desired metabolites. Previously, the genome sequencing has allowed the biologists to curate the biological information of an organism into the network. As time went on, huge amount of information have been generated. However little amount of information is being analysed. The assistance of *in silico* metabolic engineering has allowed a new approach of redesigning and re-engineering the organism in order to produce desirable metabolic phenotypes.

Figure 1.1 illustrates the overview of *in silico* metabolic engineering. Herein, the information pertaining to *E.coli* is represented in a metabolic network that consists of pathways, reactions, genes, and metabolites. By using the metabolic network as a template for simulating the effects of genotypic modifications, different genetic perturbation strategies can be applied. Furthermore, various methods and algorithms have been developed to optimize the metabolic network. In addition to that, the phenotypic characteristics of metabolic networks can be inferred, thus eventually produce a mutant strain with high production rate of desired metabolites and viable growth that can be applied in industrial manufacturing.

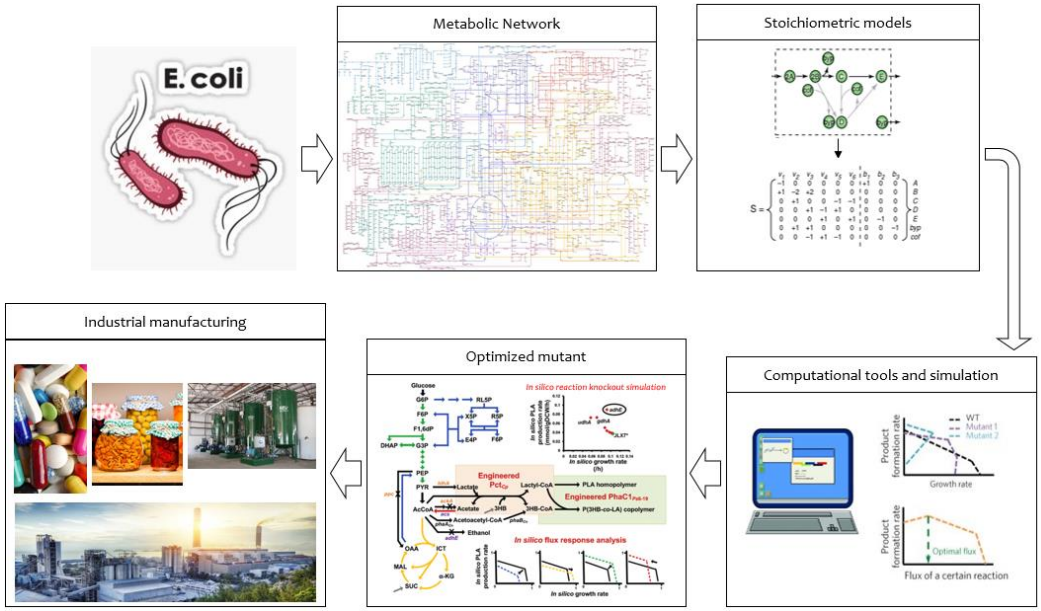

Figure 1.1 Overview of *in silico* metabolic engineering

1.2 Problem Background

Organisms have been used to manufacture commercially important products, from food additives to pharmaceuticals. These practices have begun around the year 1940s for producing biochemical such as penicillin. In recent years, the continuous growth in global population and industries has resulted in increased demand of various products such as a wide array of antibiotics. The beginning of industrial revolution has shown the usage of organisms for manufacturing substances on a large scale by designing an efficient mutant strain. Initially, the design was based on random mutagenesis and selection (traditional approaches).

However, there are several disadvantages of employing traditional approaches to improve the strains. Traditional approaches are based on intuitive design principles whereby brute force approach is being applied. This will lead to the undesired mutations that can occur elsewhere in the genome. Furthermore, the organisms usually abide to natural selection where the phenotypic and genotypic characteristics of an organism are based on population's heritable traits while maximizing the growth rate (Rocha *et al.*, 2008). Nevertheless, organism can be modify by adopting the adaptive evolution, yet the traditional approaches failed to capture these evolutions. Another disadvantages of traditional approaches include they are more prone to higher error rate, tedious and irreversible process as well as time consuming (Maia *et al.*, 2016). Thus, computational power is needed to address the issue.

Owing to the complexity of topological and regulatory metabolism of an organism, it is a pre-requisite to understand the organization and functional principles for each molecules and components in the organisms for engineering the strains. Thus, a systematic representation of the organism has been developed to view the whole metabolism processes that operates through a metabolic network. A metabolic network constitutes metabolites and reactions that are involved in generating energy and building of molecules for growth and maintenance of the cell. The metabolic network helps in rational design strategies for engineering the organisms, for example reaction/gene knockout.

However, the high connectivity in metabolic networks has caused issue in determining near-optimal set of knockout reactions. This is because, a metabolic network consists of thousands or hundreds of reactions, genes and metabolites that are interconnected among each other. This resulted in the complexity of the data. According to Hansen *et al.* (2017) and Wang *et al.* (2017), the complexity of metabolic network has resulted in the dimensions of solutions space becoming too large and exponentially increase the computational time. Furthermore, it has indirectly contributed to the combinatorial problem (Savoglidis *et al.*, 2016).

Figure 1.2 illustrates the complexity of metabolic network with different combinations of knockout reactions that can be simulated. In addition, as for an example, a metabolic network that consists of 92 reactions can have $9.3e^{10}$ combinations of 8 knockout reactions. Therefore, identifying near-optimal knockout reactions to optimize the production rate of desired metabolites and its growth rates are very challenging.

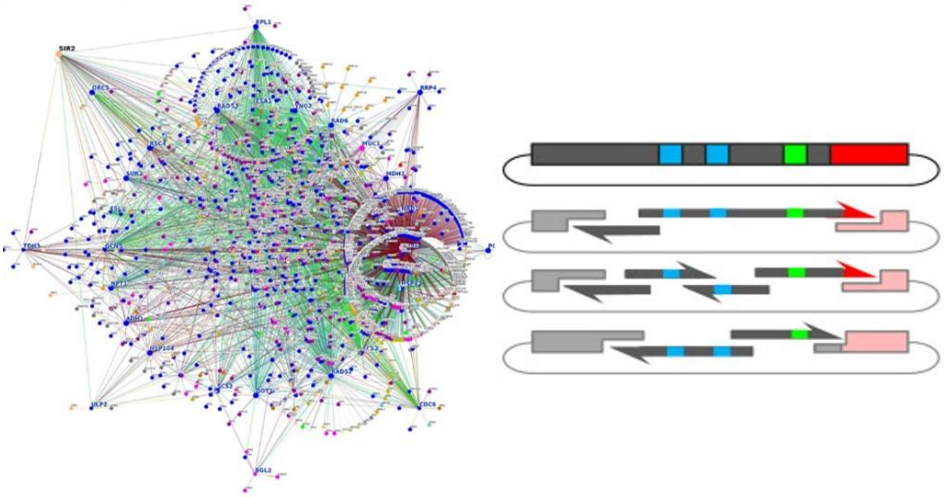

Figure 1.2 Complexity of metabolic network (left) lead to combinatorial problem (right)

Metabolic engineering has been applied to the metabolic network by identifying near-optimal knockout reactions. The aim of metabolic engineering is to improve the microbial strain in order to optimize the production of desired metabolites and its growth rates (phenotypic characteristics). Using metabolic networks, the phenotypic characteristics can be predicted using constraint-based modelling (CBM) approaches. The CBM approaches have been developed and applied to analyse the effects of genetic perturbations for the past 25 years (Bordbar *et al.*, 2014). CBM approaches such as Flux Balance Analysis (FBA), Flux Variability Analysis (FVA), Minimization of Metabolic Adjustment (MoMA) and Regulatory On/Off Minimization (ROOM) have been developed to evaluate the fluxes for each metabolite in the reactions.

Based on the literature review, discussed in Chapter 2, FBA is promising for evaluating the fluxes of metabolites in reactions, due to FBA predicts the optimal long term evolved state of the mutant while the other three approaches provide intermediate outcome of genetic manipulations. However, FBA itself could not redesign the metabolic network for maximizing the production rate of desired metabolites and its growth rate. Therefore, FBA has been improved with metaheuristic algorithms to identify a set of reactions knockout that optimize the desired objective function.

Metaheuristic algorithm is one of the most efficient optimization methods. It can be categorized into single solution and population based searches. The single solution searches operated by improving the single solution within the search space while population based searches improve a set of candidate solutions. In *in silico* metabolic engineering, single solution and population based searches have been applied to identify near-optimal knockout reactions/genes for improving the desired phenotypes. Methods such as OptGene, Set-based Evolutionary algorithm (SEA), Simulated Annealing (SA), Differential Bees Algorithm Flux Balance Analysis (DBAFBA), Genetic Ant Colony Optimization Flux Balance Analysis (GACOFBA) and others have been developed to address the issues in metabolic engineering.

However, methods such as OptGene and DBAFBA generate solutions that are over-optimistic whereby the suggested knockout genes/reactions produced high production rate of metabolites with lower growth rates (Mutturi, 2017). Therefore, population based evolutionary method such as Differential Search Algorithm (DSA) is a suitable candidate to solve the optimization problem (Civicioglu, 2013; Kurban *et al.*, 2014; Abaci and Yamacli, 2016). The main advantage of DSA is it maintains a small number of population when dealing with large problem size. Eventually, it will reduces the computation time. Another advantage of DSA is the non-sensitivity towards the control parameters (Yang *et al.*, 2013a). However, DSA has not yet been applied in identifying near-optimal knockout reactions. Furthermore, the conventional DSA only applicable for solving continuous problem whereby in this research, the problem of identifying knockout reactions are represented in binary.

Besides that, another issue is the optimization of two objectives. In real-world problems, it involves optimization of several other objectives, such as by-products, growth rates, ATP minimization and others. Figure 1.3 illustrates the production of desired product versus the biomass production (growth rate). As shown in the figure, the production of poly-3-hyrdoxybutryrate (P-3HB) at maximum rate when the biomass production is 0 (a), while the production of P-3HB at the lowest rate when the biomass production is at the highest (d). Development of most strains design has been focused on optimizing of only one objective.

Previously, the optimization techniques dealt with multiple objectives by combining them into a single objective function with individual weighted sum or treat one objective as a main objective function while the rest as constraints (Edgar *et al.*, 2001). These techniques are based on assumption that the multiple objectives will resolve at an optimal point, yet in most cases, it is unlikely to have the same optimal values for all objectives. Still, there are several disadvantages pertaining to these techniques. One of the disadvantages is no information about trade-offs among multiple competing objectives are provided. Furthermore, they provide only one near-optimal solution rather than a set of solutions. Hence, identifying near-optimal knockout reactions that provide trade-offs between production rate and its growth rate are challenging.

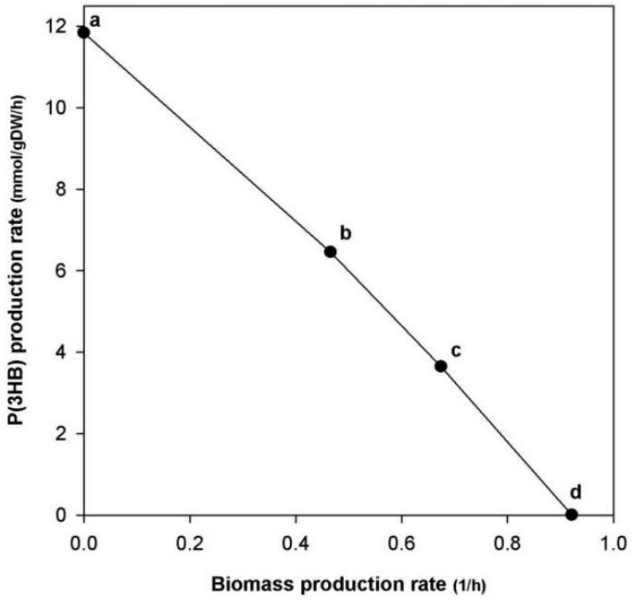

Figure 1.3 Example of optimization of two competing objectives (Oh *et al*., 2009)

FBA has issue in dealing with multiple objectives as it only deals with one single objective. Furthermore, methods such as OptGene, DBAFBA and others only focus on optimizing one single objective. Also, in multiobjective optimization problem (MOP), it is an exceptional to find a solution that simultaneously optimizes all the objective functions. Therefore, the verification of trade-offs among objectives are important for decision making of more realistic analysis. The trade-offs between production rate of metabolites and its growth rate are described by unique solutions whereby upon generation of the solution space of a given knockout reaction, the solutions that having the greatest growth rate was chosen to represent the expected phenotype of a mutant strain.

Based on the discussion in Chapter 2, non-dominated sorting (*nds*) is a promising technique for identifying Pareto solution, due to *nds* utilizes the concept of dominance in selection process. Furthermore, *nds* is able to generate an entire set of Pareto solutions in a single run and it is less susceptible to the shape of Pareto curve (Gandibleux, 2006). Hence, the classical modelling-optimization that has been developed to solve the previous problem has been improved by incorporating *nds* strategy to identify non-dominated solutions.

1.3 Problem Statement

Traditional approaches such as random mutagenesis and selection have been used for designing potential strains. However, these approaches has some limitations as they intuitively conducted based on certain physiological characteristics of the metabolism. This lead to increase experimental effort and costs. Moreover, the production rate of desired metabolites are still not satisfactorily increased (Zhao *et al.*, 2016). Since advent of omics, the information pertaining to the organism has been represented in a metabolic network. Still, due to the fact that metabolic network is consists of thousands of reactions that are interconnected among each other, one of the main concerns in improving strain design is to identify respective knockout reactions that can maximize the production rate of desired metabolites and its growth rate. This is because, only few reactions will affect the production of desired metabolites and majority of the reactions have no effect to the desired phenotype (Kim *et al.*, 2015; Mutturi, 2017).

In silico metabolic engineering problem can be depicted as an optimization problem where optimization methods is applied to find near-optimal knockout reactions to optimize the production rate of desired metabolites and its growth rates. Considering the metabolic network is usually an underdetermined system, CBM approaches are used to calculate the flux values (Park *et al.*, 2009). Although most CBM approaches including FBA, MoMA and ROOM are applied to evaluate fluxes in metabolic network, unfortunately they could not optimize and redesign the metabolic network (Shabestary and Hudson, 2016). Many of the CBM approaches have been improved with metaheuristic algorithms such as Bees Algorithm (BA), Genetic Algorithm (GA), Particle Swarm Optimization (PSO) and Ant Colony Optimization (ACO). In these methods, the metaheuristic algorithms are used to find different combination of knockout reactions while CBM approaches are used to evaluate the fitness (production rate or growth rate) of the suggested knockout reactions. For example, methods such as IdealKnock, ReacKnock, Flower-pollination coupled clonal selection algorithm (FOCuS) and others were proposed and have been used in identifying knockout reactions for maximizing the production rate of desired metabolites (Xu *et al.*, 2013; Gu *et al.*, 2016; Mutturi, 2017). Despite the good

performance shown by these methods, the production rate of desired metabolites can still be improved as the different metaheuristic algorithms have different exploration and exploitation strategies. Furthermore, these methods produce results that are over-optimistic (Patil *et al.*, 2005; Rocha *et al.*, 2008; Mutturi, 2017).

Besides, limitation also arises from the multiple conflicting objectives that provides more valuable exploration of the organism potential in strain designing. Often, when dealing with MOP, the classical modelling-optimization methods does not cope efficiently due to they only focusing on optimization of single objective. Although bi-level optimization algorithms have been formulated and developed, however they provide only one single near-optimal solution at a time to the problem. Nevertheless, in many situations, a set of different trade-offs solutions are more desirable. Furthermore, method such as OptKnock transferred the bi-level optimization into a single-level mixed integer linear programme that can exponentially increase the computation time with the increase in problem dimensions (Wang and Wu, 2015). Furthermore, the predicted flux distributions do not represent the long-term flux distributions that tend to optimize the growth rate only (Fong and Palsson, 2004; Shabestary and Hudson, 2016).

Hence, the main problem in this research is the complexity of metabolic network and existence of multiple competing objectives lead to the low production rate of desired metabolites and lack of information on the trade-off relationship between production rate and its growth rate. Thus, this research intends to address the aforementioned problems based on the following research questions:

(a) How to identify near-optimal knockout reactions in the metabolic network in order to improve the production rate of desired metabolites?

(b) How to ensure the near-optimal knockout reactions obtained can maximize the metabolites production rate and its growth rate in order to investigate the trade-off relationship between production rate and growth rate?

1.4 Research Goal and Objectives

The goal of this research is to propose improved optimization-modelling methods to efficiently identify near-optimal knockout reactions for maximizing the metabolites production rate and its growth rate.

In order to achieve the goal of this research, two objectives have been identified:

1. To propose an improved Differential Search Algorithm with Flux Balance Analysis (DSAFBA) in order to maximize the production of desired metabolites.

2. To propose non-dominated sorting algorithm on DSAFBA (ndsDSAFBA) that is able to investigate the trade-off relationship between maximization of production rate and its growth.

1.5 Scope of Study

This research is focusing on identifying combinations of reactions to be knockout from thousands and hundreds of reactions available in the genome-scale model that can enhance the production of desired metabolites and growth rate of the mutants. While there are other factors that may complicate the problem in identifying combinations of reactions to be knocked out, therefore, a list of scopes have been made in order to make this research traceable. The following are the scopes of this research:

(a) Three metabolic networks are used, namely *E.coli* core model, iAF1260, and iEM439 from *Escherichia coli* and *Zymomonas mobilis*, respectively. The type of these datasets is Systems Biology Markup Language (SBML) in XML format.

(b) The pre-processing steps are applied to the datasets by deleting essential reactions, transport reactions and peripheral reactions that are not related to the pathways of the desired metabolites.

(c) The objectives function evaluated are the production rate of desired metabolites and growth rate of mutants.

(d) Differential Search Algorithm and Flux Balance Analysis are used to identify combination of knockout reactions

(e) Succinic acid, acetic acid and ethanol are targeted for maximization as they play important roles in the industry such as food processing, pharmaceuticals and others.

1.6 The Significance of This Study

This research is considered significant in terms of computational and biological contributions. In metabolic engineering, organisms play an important role to maximize the production of desired metabolites as they serve as a natural producer or host for non-native production. With the reconstruction of the metabolic network at the genome-scale level, the simulations for genotypic perturbations has been made a success. For instance, the practice of knockout certain reactions has been made possible as scientists can select the respective reactions for knockout, thus, allow re-engineering of the organisms towards more productive hosts (Maia, Rocha and Rocha, 2016). Furthermore, with the intervention of computer simulation, the problems aroused due to the traditional techniques can be avoided, therefore, the solutions obtained via *in silico* can be used as prior knowledge for a wet lab experiment.

Secondly, the design and development of improved methods which utilizes the advantages of the searching strategy in DSA may enhance the accuracy in finding the respective reactions that can contribute to the production of desired metabolites. Furthermore, the ability of DSA to not directly go to the optimum results may overcome the premature convergence poses by previously developed methods. Thus, it can successfully find the proper respective solutions and omit solutions being trapped in local optima. On the other hand, various researches have been focusing on the development of hybrid methods such as OptForce, FPA, CSA, PSO, and BA in solving *in silico* metabolic engineering problem. However, the problems still persist and limited to maximize only a single objective, which contradicts with the real world problems that involve multiple conflicting objectives. Therefore, in this research, metaheuristic algorithm, DSA, has been improved in dealing with competing objectives by incorporating non-dominated strategy. The significance of this study is to obtain near-optimal solutions of production rate and growth rate without trapped in local optima.

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