ARTIFICIAL BEE COLONY AND DYNAMIC FLUX BALANCE ANALYSIS FOR MICROBIAL PRODUCTION

NUR FARHAH BINTI MOHD YUSOF

UNIVERSITI TEKNOLOGI MALAYSIA

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NUR FARHAH BINTI MOHD YUSOF

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To my beloved father, mother, and family.

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ABSTRACT

The ethanol and lactate productions of *Escherichia coli (E. coli)* can be optimized using metabolic engineering, which implements gene knockout techniques. The gene knockout technique is utilized inside optimization algorithms to alter the metabolism of *E. coli*. Nowadays, several hybrid optimization algorithms have been introduced to optimize the ethanol and lactate productions. However, the existing algorithms were ineffective to produce the highest production due to the huge and complex metabolic networks. Therefore, the main goal of this study is to propose a hybrid of Artificial Bee Colony and Dynamic Flux Balance Analysis (ABCDFBA) to overcome the limitation of existing algorithms. Artificial Bee Colony algorithm has advantages such as high flexibility and fast convergence. Dynamic Flux Balance Analysis algorithm can predict metabolite concentration and the dynamic of diauxic growth. Experimental results show that the ABCDFBA has performed better results in terms of Biomass-Product Coupled Yield (BPCY) of ethanol, which was 1.9505 milli-gram $(gram.glucose.hour)^{-1}$ and lactate was 6.6037 milli-gram $(gram.glucose.hour)^{-1}$ in *E. coli* performance compared to existing algorithms.

ABSTRAK

Pengeluaran etanol dan laktat oleh *Escherichia coli* (*E. coli*) boleh dioptimumkan dengan menggunakan kejuruteraan metabolik melalui teknik penyingkiran gen. Teknik penyingkiran gen ini digunakan di dalam algoritma-algoritma pengoptimuman untuk mengubah metabolisme *E. coli*. Pada masa kini, beberapa algoritma hibrid pengoptimuman telah diperkenalkan untuk mengoptimumkan pengeluaran etanol dan laktat. Walau bagaimanapun, algoritma yang sedia ada tidak berkesan untuk menghasilkan pengeluaran tertinggi disebabkan oleh rangkaian metabolik yang besar dan kompleks. Oleh itu, matlamat utama kajian ini adalah untuk mencadangkan hibrid Koloni Lebah Tiruan dan Analisa Dinamik Fluks Seimbang (ABCDFBA) untuk mengatasi kekangan algoritma-algoritma yang sedia ada. Algoritma Koloni Lebah Tiruan mempunyai kelebihan seperti kefleksibelan yang tinggi dan penumpuan cepat. Algoritma Analisa Dinamik Fluks Seimbang boleh meramalkan kepekatan metabolit dan pertumbuhan *diauxic* secara dinamik. Keputusan eksperimen menunjukkan bahawa ABCDFBA telah menghasilkan nilai Hasil Bersama Biojisim-Produk (BPCY) dalam *E. coli* yang lebih baik berbanding algoritma-algoritma sebelum ini di mana nilai etanol adalah 1.9505 miligram $(\text{gram.glukos.jam})^{-1}$ dan laktat adalah 6.6037 miligram $(\text{gram.glukos.jam})^{-1}$.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SYMBOLS

gDCW	-	gram dry cell weight
h	-	hour
mmol	-	millimole
P	-	Probability
S	-	stoichiometric matrix
S_N	-	Standard deviation
v	-	flux vector
X	-	the population of the colony size
X_n	-	individuals in the population of the colony size
Z	-	objective function

LIST OF ABBREVIATIONS

ABC	-	Artificial Bee Colony
ABCDFBA	-	A Hybrid of Artificial Bee Colony and Dynamic Flux Balance Analysis
ABCFBA	-	A Hybrid of Artificial Bee Colony and Flux Balance Analysis
ABCMOMA	-	A Hybrid of Artificial Bee Colony Algorithm and Minimization of Metabolic Adjustment
ACO	-	Ant Colony Optimization
BA	-	Bees Algorithm
BAFBA	-	A Hybrid of Bees Algorithm and Flux Balance Analysis
BAT	-	Bat Algorithm
BATFBA	-	A Hybrid of Bat Algorithm and Flux Balance Analysis
BiGG	-	Biochemical Genetic and Genomic Knowledgebase
BPCY	-	Biomass-Product Coupled Yield
CPU	-	Computer Processing Unit
DFBA	-	Dynamic Flux Balance Analysis
DOA	-	Dynamic Optimization Approach
E.coli	-	*Escherichia Coli*
FBA	-	Flux Balance Analysis
KEGG	-	Kyoto Encyclopedia of genes and genomes
LP	-	Linear Programming
MATLAB	-	Matrix Laboratory
MILP	-	Mixed Integer Linear Programming
MOMA	-	Minimization of Metabolic Adjustment
NLP	-	Non-Linear Programming
PSO	-	Particle Swarm Optimization
QP	-	Quadratic Programming

RAM	-	Random Access Memory
ROOM	-	Regulatory On/Off Metabolic
SBML	-	System Biology Markup Language
SOA	-	Static Optimization Approach

LIST OF APPENDICES

CHAPTER 1

INTRODUCTION

1.1 Overview

In this chapter, ethanol, and lactate production in *Escherichia coli* (*E. coli*), Artificial Bee Colony, and Dynamic Flux Balance Analysis are discussed. Problems background concerns on the issues and challenges faced in the ethanol and lactate production in *E. coli*. Moreover, the problem statement, goal, objectives, scopes and the significance of the research are stated respectively.

1.2 Introduction

Biofuels are one of the well-known resources to produce energy. One of the methods that produce ethanol is biomass fermentation. Biomass fermentation requires a large size of plantation area to plant corn or sugarcane in order to produce starch and sugar. Besides, rice bran is also one of the great potential material in ethanol production (Michel *et al.*, 2016). Unfortunately, the process of fermentation brought up pollution issues such as deforestation for the plantation of sugarcanes or corns. Thus, in order to avoid most of the problems to produce ethanol, metabolic engineering on microorganism was introduced to produce ethanol by using microbe. This is due to a large number of microbes is easy to be cultivated in the laboratory and it is cheap.

Recent studies show that *E. coli* is very suitable for producing bioethanol since it is a gram-negative bacterium and has the ability to convert sugar into ethanol in high yield.

Lactate has been used in a large area of processed food, cosmetics, oral and health care products and industrial applications. Besides, lactate is produced commercially by using several microorganisms (John *et al.*, 2007), such as Lactobacillus strains. In addition, simple nutritional and host production under aerobic and anaerobic conditions are one of the *E. coli* advantageous characteristics. Moreover, *E. coli* development as a host production of lactate enabled physiology of microbe with large knowledge and high established protocols for genetic manipulation (Chang *et al.*, 1999).

On the other hand, under anaerobic condition, lactate, acetate, ethanol, succinate and formate in *E. coli* are the yields of glucose mixed acid fermentation. Thus, *E. coli* is highly recommended since it is high established and an enormous knowledge explored for the physiology of *E. coli* enables it to use for genetic manipulation. In addition, gene knockout technique which made inactivation to the non-functional gene had being applied on the microorganism to boost the *E. coli* production of ethanol and lactate (Chang *et al.*, 1999).

1.2.1 Gene Knockout Technique

Organism gene that has been genetically knocked out, missing or has been deleted completely from the organism is a gene knockout technology technique. A part of a gene from the sequenced gene characteristics can be learned by researchers through the technique of gene knockout.

The term knockout refers to knock out a gene by creating a new mutant. Whereas double knockout is at the same time, two genes in an organism are knocked out. Furthermore, triple knockout and quadruple knockout is being knocked out by three or four genes.

The gene knockout technique is used to test the isolated gene function. Nevertheless, the knockout technique does not happen when repeated function of multiple genes exist. Nowadays, the gene knockout technique is frequently used in research on protein structure, biochemical production for commercial use or specific genes function.

1.2.2 Artificial Bee Colony Algorithm

Artificial Bee Colony (ABC) algorithm is an intelligent foraging behavior of honey bee swarm optimization algorithm (Karaboga, 2005). ABC discover optimization problems by measuring the speed (measurement) of artificial with good quality of solution (Karaboga and Basturk, 2007). Employed bees, unemployed bees which are onlookers and scouts respectively and food source are the main three components in ABC.

There are two different types of honey bee which are in different groups share food source information in order to achieve the food source localization task. The employed bees group is the first group that exploits a food source. Employed bees carry the precise food source information about its direction and distance from the nest, the source profitability, and the information is shared with other employed bees and scout bees (Karaboga, 2005). The second group is the unemployed bees. The unemployed bees looked for a new food source continuously. Unemployed bees are divided into scouts and onlookers. The new food source is searched by scouts around the nest. Then, employed bees shared all the information to the onlookers that wait at the nest (El-Abd, 2011). The food source is meant by the problem solution and the agent for solution finding is the bees. ABC is a population-based search algorithm used to predict the gene knockout capable of improving the production rate of targeted biochemical products.

1.2.3 Dynamic Flux Balance Analysis

Dynamic Flux Balance Analysis (DFBA) is an extension of Flux Balance Analysis (FBA) to enable the analysis of the interactions between metabolisms. DFBA allows biomass dynamic prediction, substrate and concentrations of product for growth in batch or fed-batch cultures growth (Mahadevan *et al.*, 2002). DFBA can provide the biochemical reaction pathway structured model when microorganism changes depending on the conditions of the environment. The model formulation included the expression uptake and production interaction, changes of regulatory that affected by conditions of the environment.

1.3 Problem Background

There are a lot of development in the metabolic model's simulation of the experimental data from cellular and molecular biology. However, problems occur when conducted laboratory experiments to simulate metabolic models such as large metabolic network, and low productivity.

The complexities of the metabolic network can cause data ambiguity due to difficulties in predicting the genetic modifications effects on the desirable phenotypes (Patil *et al.*, 2005; Rocha *et al.*, 2008b). Besides, the huge and complex metabolic networks that consist of numerous metabolites makes the process to obtain gene knockout challenging.

In the past, some chemical compound production such as ethanol and lactate in *E. coli* is low (Zhang *et al.*, 2011). The yield products are always far beneath their theoretical maximums. The traditional method is time-consuming and low productivity. Products with the smallest production use high computational time (Li *et al.*, 2012). The implementation of the experimental cost is high due to the lack of proper optimization tools and modeling (Srirangan *et al.*, 2012).

Thus, a hybrid of Artificial Bee Colony and Dynamic Flux Balance Analysis is proposed to optimize the production of ethanol and lactate and to solve the problems

of the large metabolic network and low productivity of ethanol and lactate. Optimization can be made in the process of a microorganism to optimize the ethanol and lactate production.

1.4 Problem Statement

Over a decade ago, genome-scale metabolic network construction becomes popular and have a lot of advantages for researchers to understand more in the perspective of genome-wide. The fitness evaluation in this study is calculated using Biomass-Product Coupled Yield (BPCY). BPCY is calculated by considering the production yield and growth rate of the desired product in order to optimize the microbial production (Patil *et al.*, 2005). Some existing algorithms have low results on BPCY due to the low production or the growth rate of the desired product is low.

The overproduction of the microbial becomes challenging as the process of the gene to be knocked out has limitations. Inside the constructed model, there are some gaps in the model due to incomplete biological information. The complex and large metabolic network caused computational time increased due to the difficulties in predicting the genetic modification effects on the desirable phenotypes and hard to obtain gene knockout (Patil *et al.*, 2005; Rocha *et al.*, 2008b). The preprocessing step should be done on the genome-scale metabolic model to reduce the search space as well to improve the computation time. As the metabolic network is large, it also leads to low productivity of the *E. coli* strains such as ethanol and lactate.

Therefore, the main problem of this research is the complex and large metabolic network and the challenging to optimize the production of the microbial strains. Thus, this research intends to address the aforementioned problems based on the following research questions:

i. How to reduce the metabolic network complexity in order to optimize the ethanol and lactate production?

ii. How to analyze the performance of the proposed hybrid algorithm in optimizing the metabolites production?

1.5 Research Goal

The goal of this research is to propose a hybrid of Artificial Bee Colony and Dynamic Flux Balance Analysis to identify a near-optimal set of gene knockout that leads to optimize the production of ethanol and lactate in *E. coli*.

1.6 Objectives

To achieve the goal, the specified objectives are as follows:

1. To develop a hybrid of Artificial Bee Colony and Dynamic Flux Balance Analysis for reducing the metabolic network complexity that leads towards optimizing ethanol and lactate production.
2. To analyze the experimental results (Biomass Coupled Yield Product, growth rate, and production yield) of each metabolite with existing algorithms and validate the list of genes deletion through biological database.

1.7 Research Scope

According to the objectives mentioned above, these research scopes are shown as follows:

i. Ethanol and lactate are the product being focused on the biomass production of *Escherichia coli*.
ii. The datasets used are *E. coli iJO1366* for ethanol production and for lactate production, which from *E. coli core* model.
iii. Format dataset is in System Biology Markup Language (SBML).

iv. COBRA Toolbox is the software used in this research which is implemented in MATLAB to perform the hybrid algorithm.

v. The research is carried out by using a hybrid of Artificial Bee Colony and Dynamic Flux Balance Analysis in order to identify a near-optimal set of gene knockout that leads to optimize the production of ethanol and lactate.

vi. The result of genes deletion is evaluated with the reactions and gene information in the biological databases.

1.8 Research Significance

The main significance of this research is to increase the metabolite production with a new hybrid algorithm. Metabolic engineering has the potential to improve the metabolite production such as ethanol and lactate. By excluding some steps under gene knockout techniques, predicting the possible changes is made and novel products by analyzing metabolic states is generated. Hence, this research is conducted with the aim of identifying the near-optimal set of gene knockout that leads to optimize the production of ethanol and lactate via a hybrid of Artificial Bee Colony and Dynamic Flux Balance Analysis. Finally, this research hopefully can improve the metabolic engineering and computer science fields.

1.9 Thesis Organization

There are five chapters in this thesis. Chapter 1 explains about the research introduction which covers the discussion of problem background, problem statement, goal, objectives, scope and research significance. Chapter 2 covers the literature review of this research which discusses the previous research and algorithms. Chapter 3 is the research methodology shows the overall research process. Chapter 4 explains the implementation of a hybrid algorithm and datasets used in this research. Chapter 5 shows the results and discussions of this research. Finally, Chapter 6 is the conclusion

of this research which covers the research contributions, limitations, and future work of this research.

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