IMPROVED PARTICLE SWARM OPTIMIZATION AND GRAVITATIONAL SEARCH ALGORITHM FOR PARAMETER ESTIMATION IN ASPARTATE PATHWAYS

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To my beloved father, mother, and family.

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ABSTRACT

One of the main issues in biological system is to characterize the dynamic behaviour of the complex biological processes. Usually, metabolic pathway models are used to describe the complex processes that involve many parameters. It is important to have an accurate and complete set of parameters that describe the characteristics of a given model. Therefore, the parameter values are estimated by fitting the model with experimental data. However, the estimation on these parameters is typically difficult and even impossible in some cases. Furthermore, the experimental data are often incomplete and also suffer from experimental noise. These shortcomings make it challenging to identify the best-fit parameters that can represent the actual biological processes involved in biological systems. Previously, a computational approach namely optimization algorithms are used to estimate the measurement of the model parameters. Most of these algorithms previously often suffered bad estimation for the biological system models, which resulted in bad fitting (error) the model with the experimental data. This research proposes a parameter estimation algorithm that can reduce the fitting error between the models and the experimental data. The proposed algorithm is an Improved Particle Swarm Optimization and Gravitational Search Algorithm (IPSOGSA) to obtain the near-optimal kinetic parameter values from experimental data. The improvement in this algorithm is a local search, which aims to increase the chances to obtain the global solution. The outcome of this research is that IPSOGSA can outperform other comparison algorithms in terms of root mean squared error (RMSE) and predictive residual error sum of squares (PRESS) for the estimated results. IPSOGSA manages to score the smallest RMSE with 12.2125 and 0.0304 for Ile and HSP metabolite respectively. The predicted results are benefits for the estimation of optimal kinetic parameters to improve the production of desired metabolites.

ABSTRAK

Salah satu isu utama dalam sistem biologi adalah untuk menggambarkan ciri dinamik proses biologi yang kompleks. Biasanya, model laluan metabolik digunakan untuk menggambarkan proses kompleks yang melibatkan banyak parameter. Ia penting untuk mempunyai satu set parameter yang tepat dan lengkap yang dapat menerangkan ciri-ciri model yang diberikan. Oleh itu, nilai-nilai parameter dianggar dengan menyesuaikan model dengan data eksperimen. Namun, anggaran pada parameter ini biasanya sukar, malahan mustahil dalam kes-kes tertentu. Tambahan pula, data eksperimen sering tidak lengkap dan juga mengalami gangguan eksperimen. Kelemahan ini menjadi cabaran untuk mendapatkan parameter terbaik yang boleh mewakili proses biologi sebenar. Sebelum ini, algoritma pengoptimuman digunakan untuk menganggarkan pengukuran parameter model. Kebanyakan algoritma sebelum ini sering mengalami anggaran yang tidak tepat bagi model sistem biologi, menyebabkan penyesuaian tidak tepat (ralat) pada model dengan data eksperimen. Penyelidikan ini mencadangkan satu algoritma anggaran parameter yang boleh mengurangkan ralat penyesuaian antara model dan data eksperimen. Algoritma yang dicadangkan adalah gabungan Kawanan Partikel Pengoptimuman yang lebih baik dan Algoritma Carian Graviti (IPSOGSA) dalam mendapatkan nilai parameter kinetik hampir optimum daripada data eksperimen. Pengubahsuaian dalam gabungan algoritma ini adalah pada carian setempat untuk meningkatkan peluang untuk mendapatkan penyelesaian global. Hasil kajian ini menunjukkan IPSOGSA dapat mengatasi algoritma perbandingan yang lain dari segi ralat punca min kuasa dua (RMSE) dan hasil kuasa dua ramalan ralat (PRESS) untuk keputusan anggaran. IPSOGSA berjaya mendapatkan nilai RMSE yang paling kecil masing-masing 12.2125 dan 0.0304 untuk metabolit Ile dan HSP. Keputusan anggaran ini bermanfaat bagi anggaran parameter kinetik optimum untuk meningkatkan pengeluaran metabolit dikehendaki.

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LIST OF SYMBOLS

$\emptyset_{ij}$	-	The random number between -1 and 1
α	-	Descending coefficient in gravitational formula
ac	-	The acceleration of an individual in population
A	-	Average error rate
c1	-	The weighting factors
c2	-	The weighting factors
D	-	The dimension of problems
$\frac{ds}{dt}$	-	Ordinary Differential Equation
gbest	-	Memory to store best solution
e	-	The generated measurement noise
F	-	The force of the individuals
fit	-	The fitness of individuals
G0	-	Descending coefficient in gravitational formula
M	-	Mass of the individual
min()	-	The minimum value
N()	-	The random numbers
n	-	Number of rows in time series data
newF	-	The fitness of new generated neighbor individuals
np	-	The number of population
p_i	-	The probability of an individual in the population
Rand	-	Random number between 0 and 1
RMSE	-	Root mean squared error
STD	-	Sample standard deviation
$s(x)$	-	The biochemical compounds with set of parameter *x*
t	-	The sampling time

v_{ij}	-	The velocity of an individual in the population
x_{ij}	-	The position of an individual in the population
y^{exp}	-	Experimental time series data
y	-	Simulated time series data

LIST OF ABBRABATIONS

*A*BC	-	Artificial Bee Colony Algorithm
A. thaliana	-	*Arabidopsis thaliana*
BA	-	Bee algorithm
E. coli	-	*Escherichia coli*
GSA	-	Gravitational Search Algorithm
HSP	-	Homoserine phosphate
IDE		Improved Differential Evolution
Ile	-	Isoleucine
IPSOGSA	-	Improved Particle Swarm Optimization and Gravitational Search Algorithm
ODE	-	Ordinary differential equations
PSO	-	Particle Swarm Optimization
PSOGSA	-	Particle Swarm Optimization and Gravitational Search Algorithm
RMSE	-	Root mean squared error
SA	-	Simulated Annealing
SBML	-	System Biology Markup Language
SD	-	Simplex Downhill
STD	-	Standard deviation

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CHAPTER 1

INTRODUCTION

1.1 Overview

This chapter was about the introduction of modeling and parameter estimation by using *in silico* optimization algorithms in biological systems. Then, the problem background and problem statement of the research are discussed and explained. Next, the objectives are determined to achieve the goal of the research. The scope also is clearly stated about the limitations, data collection, and requirements in this chapter. Finally, the last section of this chapter explains the report structure.

1.2 Introduction

Pharmaceutical and dairy food products are produced by a fermentation process which used fed-batch culture. This fed-batch culture converts substrate into desired products (metabolites), and this procedure being carried out using apparatus namely bioreactor. Aspartate metabolism can synthesize the essential amino acids which are essential to be consumed by the human. The essential amino acids which produced are Lysine, Threonine, Methionine and Isoleucine. These amino acids are the amino acid which human body unable to synthesize and required to consume from other sources. Unfortunately, the direct production of essential amino acids in the human body is unavailable to be studied and understood. The alternative ways are by understanding the living things model. The small organisms are used as a model because of the nature of these organisms able to produce both of the essential amino acid and unessential amino acid. The productions of these products are part of metabolic engineering which is the part of discipline in the biotechnology field. Microorganism such as *E. coli* and *Saccharomyces cerevisiae* are widely used as cell factory as they have a very good growth rate in production of dairy food product industries. Besides, small flowing plants especially *A. thaliana* are widely used in the production of pharmaceutical and pastries products, especially related to the amino acid derived aspartate.

Biological systems are typically complicated and not fully understandable. Most of the biologist having difficulty in facing with the enormous number of cellular components that required to be characterized based on their role in biological processes, and also their dynamic behaviors. Therefore, there are significant improvements in the research study of system biology field throughout these recent years. In system biology field, the used of the ordinary differential equation in dynamic system modeling is a popular approach (Raue *et al*., 2015). Besides, the mathematical modeling is widely used in various biological systems. Especially, it has become the fundamental in giving a better understanding of dynamic behaviors and regulation in both biological metabolism and pathways. The pathways are used to understand the complex processes that involve the relations between many parameters. Figure 1.1

gives the illustration on the pathway models. Moreover, the mathematical modeling also gives a prediction and also understanding on both biological simulation and experimental process. In mathematical modeling, there are nine operations which comprise of collect information on network structure, selection on data, simplification and assumption, framework selection, parameter estimation, model diagnostic, model validation, refine model and model application (Chou and Voit, 2009).

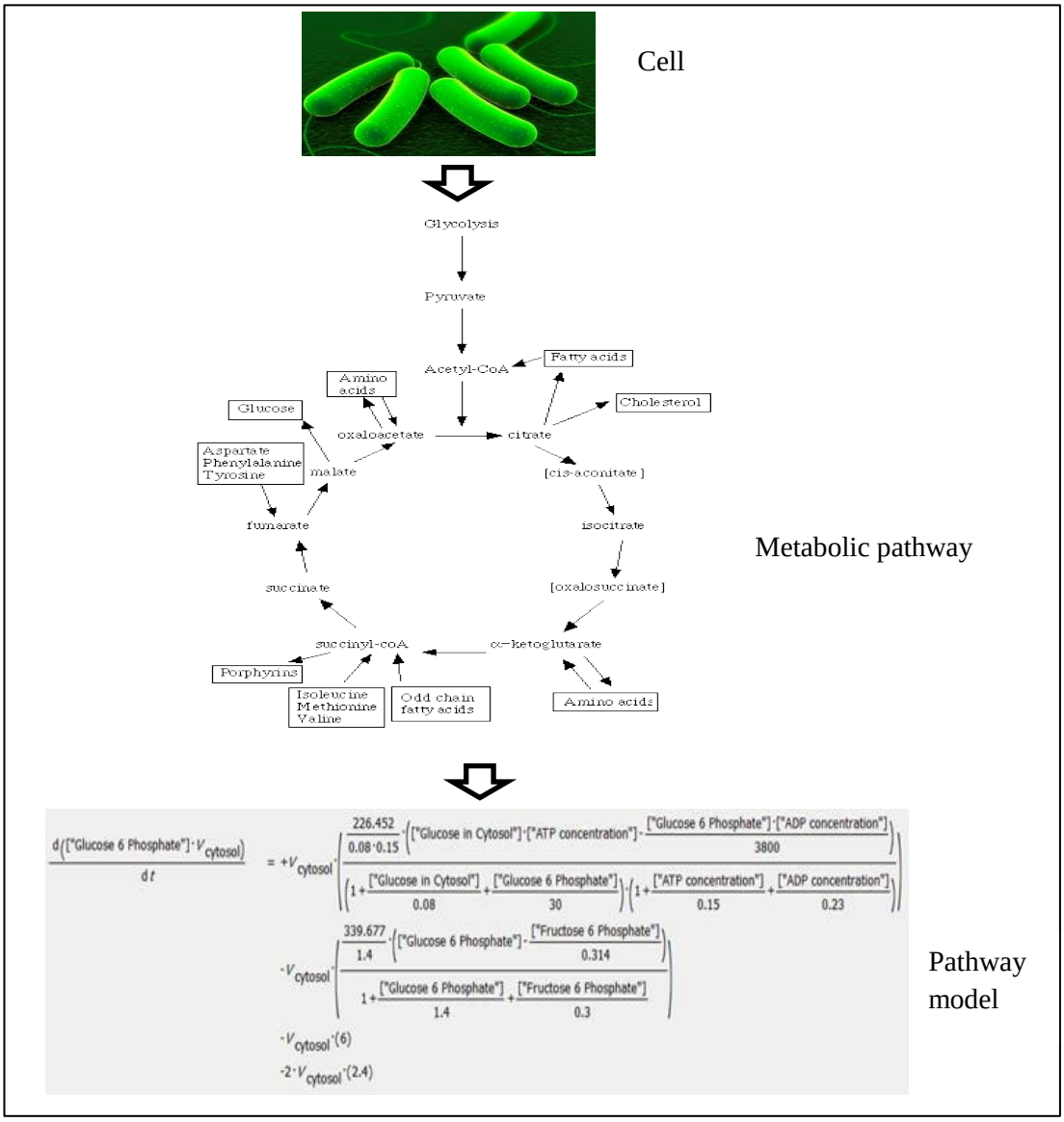

Figure 1.1. Metabolic pathway model processing

Accurate and complete set of parameters which describes the characteristic of the systems are critical and important as the system model need to be accurate. Nonetheless, the measurement of these parameters is costly and time consuming through *in vitro* experimental process. Hence, there is a requirement for fast and accurate estimation algorithms which can be used to estimate the near optimal kinetic parameter values. Parameter estimation in system biology is an optimization process. The aim is to obtain the optimum parameter values that give the best model fitting with corresponding experimental analyses. In nonlinear biological systems, meta-heuristic optimization methods are used as their capable of finding the local and global optimal efficiently.

1.3 Problem Background

Explaining the complex network biological processes that are characterized by dynamic behavior is one of the main issues in systems biology (Lillacci and Khammash, 2010; Raue *et al*., 2015). Mathematical models are commonly used to describe dynamic biological processes. These models consist of a set of parameters that describe the physical properties of a dynamic system like the rate of reactions. Measuring these parameters is usually difficult and even impossible in some cases (Fernández *et al*., 2010). The parameters are often predicted based on fitting the model output with experimental time-series data. The goal of this fitting process is to minimize the errors between these two sets of data by adjusting the parameter values of the model (Rodriguez *et al*., 2006). However, these experimental data are often incomplete and suffer from experimental noise (Villaverde *et al.*, 2015). This drawback makes it challenging to find the best-fit parameters that adequately represent the actual biological processes involved.

It is crucial that the best parameter values for the biochemical models be estimated and obtained by refining the model parameter values (Schilling *et al*., 2016). These parameter values are usually identified and measured through costly and time-consuming wet-lab experiments (Tashkova *et al*., 2011). Alternatively, these parameters can also be estimated using computational approaches. Thus, the parameters estimation turned into multimodal optimization problems, and global optimization algorithms are required to avoid local solutions (Banga, 2008; Sun, Garibaldi, and Hodgman, 2012). Currently, there are a lot of global optimization algorithms that available for estimating the model parameters in various biological systems. Nevertheless, most of the global optimization algorithms mainly Genetic Algorithm, Particle Swarm Optimization, Gravitational Search Algorithm and others often converge to the local solutions instead of the global optimum (Civicioglu and Besdok, 2013; Kang and Zhang, 2016; Sheikhalishahi *et al.*, 2013). These local solutions can lead to poorly fitting data that the model itself can potentially match accurately with a set of experimental data.

1.4 Problem Statement

The main problem of this research is the parameter estimation algorithms previously often faced bad estimation for the biological system models, which led to bad fitting (error) the model with experimental data. Figure 1.2 shows the example of model fitting with the experimental data.

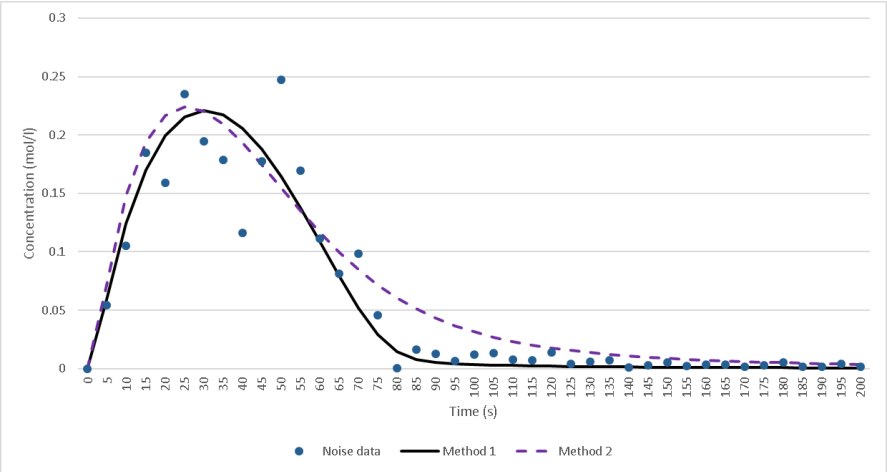

Figure 1.2: Model fitting from noisy experimental data (Note: The line graph shows good model fitting, and the dashed line shows poor model fitting)

1.5 Aim

The aim of this research is to propose a parameter estimation algorithm that can reduce the fitting error between the models estimated and experimental data.

1.6 Objectives

The specified objectives to achieve the aim of the research are as shown below

i. To design and develop Improved Particle Swarm Optimization and Gravitational Search Algorithm (IPSOGSA) in obtaining the near-optimal kinetic parameter values by minimize the fitting error of the model and experimental data.

ii. To evaluate and compare the proposed algorithm by using performance of root mean squared error and predictive residual error sum of squares.

1.7 Scopes of the Study

The scopes of this research are described as followed:

i. Case studies: Aspartate pathways of BIOMD0000000066 and BIOMD0000000212 in SBML format
ii. Data Source: BioModel database
iii. Target metabolite: Parameter estimation on the kinetic parameter values of Isoleucine and Homoserine phosphate synthesize in Aspartate pathways for *A.thaliana* and *E.coli*.
iv. Parameters estimation: Minimize the fitting error between pathway model and the experimental data.

1.8 Significant of the Study

This study intends to propose a parameter estimation algorithm for estimating the kinetic parameter values of metabolites in the biochemical pathways. Usually, the parameter estimation in the biochemical pathway is a stochastic problem, and the optimal solution cannot be guaranteed. Thus, the estimation only can achieve the near optimal condition for the estimated solutions. It is significant to determine the near-optimal parameter values in biochemical pathway model as the model itself need to be the near optimal and actual condition. Hence, the production of desired metabolites (product) can be increased and fully utilized in food and health product industries. Furthermore, there are still lacking in the modeling and simulating on the biological pathway models, especially in predicting and optimizing processes. Thus, this study intends to fill this gap, which benefits the industrial and manufacture of dairy food and health products.

1.9 Report Structure

In the first chapter, the introduction is explained briefly about the computational modeling of parameter estimation. Besides, there are also the explanation on the background of the problems, problem statement, aim, objectives and scopes covered in this research.

Chapter two gives a review on the area such as mathematical modeling on microorganisms, parameter estimation, and some optimization algorithms that available for computational parameter estimation of the biochemical pathways. Besides, the published previous works on the parameter estimation in the biological model also have been reviewed in this chapter. Besides, there are also the comparisons on different estimation algorithms which discussed in the comparison tables.

Chapter three gives an overall description of the research methodology, which included the phases and activities for each phase. Furthermore, the research framework also listed in this chapter. The description and explanation of the datasets which used in this research also mentioned. Besides, there are also performance evaluations which have being used to validate and comparison all parameter estimation algorithms. Then the last part of this chapter is about software and hardware requirements for this research.

Chapter four focuses on the implementation of proposed algorithm for parameter estimation in Aspartate metabolism pathways. The first section of this chapter is about the implementation of the proposed algorithms. Then, the following section is about the result and discussion for research outcomes. The section includes the estimated kinetic parameter values along with model output data, performance evaluation, and comparison of estimated results among the estimation algorithms. Finally, the last section explained the summary of the chapter.

Chapter five gives the conclusion of this research based on the finding throughout this research. Then, the sections of the chapter continued with the discussion on the future work, limitation, contribution and summary section of this chapter.

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