CHAPTER 1

INTRODUCTION

1.1 Introduction

Metabolic engineering has become very important in the production of a new scientific endeavor in *E. coli* (Edwards and Palsson, 1997). Metabolic engineering based on genetic engineering which is the targeted manipulation of genetic-cell information involves enzymatic, transport and regulatory gene which are the goals of direct modifications and the improvement of cellular activities (Ka et al., 1998). The classical approach of metabolic engineering requires detailed knowledge of enzyme kinetics, the system of work, intermediate pools involved and genetic manipulation (Gregory, 1999).

However, metabolic engineering is usually faced with the challenges of effectively developing and designing the cell metabolism with respect to the metabolism regulation. In order to address this, it is necessary to generate a mathematical model which can efficiently describe the dynamic behavior of the cell in response to the changes in the cultural environment and/or the specific genetic modification (Kadir et al., op cit). In fact, analysis of the sensitivity, genetic optimizing and regulatory processes are the metabolic engineering practice within cells which are done to increase the cellular production of a certain substance.

With a view to studying the dynamics of the metabolic engineering system, there is need to consider how the substrate is converted to Substrate or to a Product and which enzymes should be involved in the conversion process. The conversions in the
metabolic networks consist of a substrate and product and also between them the enzymes which can convert the substrate to product either in an irreversible or reversible way (Kadir et al., 2010). This is described in Figure 1.1. The study of the substrate, enzyme and product conversions are achieved by metabolic computational.

![Metabolic conversion](image)

**Figure 1.1:** Metabolic conversion

### 1.1.1 Metabolic Computational

Metabolic computational modeling plays a substantial role in the biological system. Every modeling has been constructed using ordinary differential equations (ODEs). The accuracy of the model output prediction would, however, depend on the behavior system physiology, which has a set of parameters such as temperature, reaction rates and kinetic constants. It had been reported that one of the powerful tools for explaining the properties of the dynamic metabolic engineering system as well as to guide experimentation is metabolic network model (Maggioa et al., 2010). Also, it was reported that to build a kinetic metabolic network model requires a large number of kinetic parameters, which has been developed to detect the concentration changes in the metabolites and reactions (Chassagnole et al., 2002). Some of the mathematical models which can describe the dynamic models have been suggested with a view to survey the behavior of the cell. Some used flux balance analysis (Reed and Palsson, 2003), (Radhakrishnanet al., 2002), (Edwards et al., 2001), network component analysis (S. Shuster et al., 2000; Liao et al., 2003), C-metabolic flux analysis (Siddiquee et al., 2004;
Toya et al., 2010), dynamic modelling (Chassagnole et al., 2002; Usuda et al., 2010), metabolic analysis design (Simon and David, 1996), Metabolic control analysis (Diana and Joseph, 2002) and the steady-state of the model (Barbara et al., 1992). In order to simulate the kinetic parameters in a model, there is the need to consider the mathematical equations as simple as possible so that the implementation will become easy.

If the modeling can be effectively simulated, it can be of a great help at in answering some specific questions such as the accuracy of the model outputs. These models are however declared using simulation and represented by specific or some part of metabolic pathways (Chassagnole et al., 2002; Yugi et al., 2005; Ishii et al., 2007; Kremling et al., 2007; Nishio et al., 2008; Kadir et al., op cit). After the model is build, there would be need for sensitivity analysis in order to optimize the model.

1.1.2 Sensitivity analysis

Engineering and science are often studied with the aid of mathematical models designed to simulate the complex physical process (Gangelosi and Parisi, 2001). One of the steps in mathematical model development is the determination of the most effective parameter in the model outputs. A “sensitive analysis” of these parameters is not only definite to model validation, but also it can lead to future research. Sensitivity analysis is often referred to as either local or global. The local analysis addresses sensitivity relative to point estimates of parameter values while global analysis examines sensitivity with regard to the entire parameter distribution. Sensitive analysis can help the researcher to determine which parameter enables the very effectiveness of the model’s result (Saltelli, 2000).

The sensitive analysis method can be classified in a variety of ways: statistical, mathematical or graphical. The statistical method involves running a simulation in which an input is assigned some probability distributions, and later the assessment of the effect of variance on the input is done to identify the output distribution. Also, it can allow one input to identify the effects of the interaction among multiple inputs (Griensven et al., 2006). The mathematical method is the sensitivity of a model output