

# Modeling of CHO Metabolism and Krebs Cycle Using Petri-Nets (PN)

Isaac Barjis, Sidi Berri, Nwayigwe Okpa, Jennifer Tan, & Idline Agustin  
New York City College of Technology of the City University of New York, 300 Jay St., Brooklyn, NY 11201

## ABSTRACT

Metabolism is a highly complex biochemical network whose functions are tightly coordinated and regulated by feedback mechanisms to meet the physiological demands of living organisms. One approach to understanding those complex metabolic reactions is to use mathematical methods and computational tools to model, simulate and analyze each metabolic network. Unfortunately, most publications on modeling present only the final products without describing the details as to how they were developed and tested. In this paper, we use Petri nets as a modeling tool to model, simulate and analyze the process of carbohydrate metabolism, and in particular, the Krebs cycle. This paper will show both the compact model (which presents only the final product) and detailed model of Krebs cycle.

## INTRODUCTION

Due to the increasing volume of biological data and advances in biological sciences, it has become clear that biologists need mathematical methods and computational tools to model, analyze, simulate, validate, execute and organize those data. As a result, more and more biologists and biochemists have grown interested in using mathematical and computational approaches for their work.

The complexity of phenomena ranging from wave propagation in random media to genome expression data processing and modeling of biological systems, however, makes everyone agree on the need for large parallel work around the symbolic notation of biological processes and data. This is particularly true in network biology (metabolic networks, extra and intracellular networks, networks of genetic regulation), which we explain in this paper.

Modeling of metabolic networks helps us understand the dynamics of metabolism (real-world processes), by using the computer to mimic the actual forces that are known or assumed to result in the process of metabolism (system's behavior). This will open new perspectives to biological entities and processes that are often not accessible by available "wet" methods or in an acceptable time frame. Therefore, one would not only save time and money, but also use models and simulation for educational institutions to teach specific processes, as the students would observe what actually happens in each step of the reaction throughout the process [Barjis et al 2001].

In order to construct any kind of model that could simulate and analyze a metabolic system, we must first encode the relevant information in a way which can be represented as simply as possible in the computer's memory [Regev et al 2001].

One approach to the representation of concurrent systems is based on a mathematical concept called a *Petri Net*, which was developed in the early 1960s by Carl Adam Petri and has subsequently been adapted and extended in many directions [Murata 1989].

As an ongoing research, the authors of this paper invested their efforts in the study of carbohydrate metabolism, from a computing point of view, and in the task of modeling a biological process named Krebs cycle using Petri nets. This research shows how Petri-net modeling techniques and methodologies are used to represent biological processes in a graphical language. Graphical language of any process is the most crucial

and important step in developing software application or simulating dynamic behavior.

The content of this paper is divided into two sections: a compact model and a detailed model. In section one, a compact model of the carbohydrate metabolism is developed. Part two presents a detailed model of the Krebs cycle. Each section consists of two subsections; the first one describes reactions and molecular events that occur during the process of protein production, while the second subsection develops compact and detailed notations. Conclusions, followed by suggestions for future works are then given at the end of this paper.

## PETRI-NETS (PNS)

Petri net (PNs) is an instrument for studying systems. It is a formalism and a graphical language for the design, specification, simulation and verification of systems [Peterson, 1981; Jenson, 1997]. The theory of PNs is based on the application of PNs in the modeling and design of a system [Reisig, 1985]. This modeling methodology is very useful as it allows us to model concurrency and parallelism and to combine easily subsystems [Barjis, I 2005, Kurt Jensen, 1997].

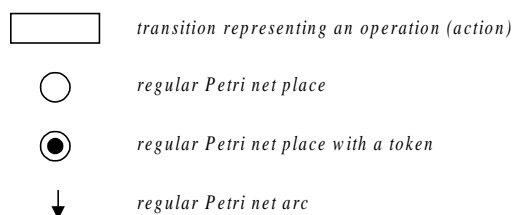
The Petri net structure consists of places and transitions. Its graph has two types of nodes: place and transition. Place/state is shown graphically as a circle and transition or event (operation) is shown as a rectangle (see figure 1).

Let's see how we can apply Petri net model to carbohydrate metabolism and how we can construct a detailed model of glycolysis using Petri net.

## METABOLISM

Metabolism is a collective term for all the chemical processes that take place in the body. Metabolic pathways can be viewed as series of enzyme-catalyzed reactions where product of one reaction becomes substrate for the next reaction. The process of metabolism is divided into catabolism and anabolism. In catabolic process a complex substance is broken down into smaller ones, usually with the release of energy. In an anabolic process, a complex substance is build from simpler ones, usually with the consumption of energy. These pathways can be branched and interconnected via shared substrates. Computer simulation of biochemical processes is a means to augment the knowledge about the control

Figure 1. Legend of Petri nets



mechanisms of such processes in particular organisms. This knowledge can be helpful for the goal-oriented design of drugs. Before we develop the Petri-net model of Krebs Cycle, let's explain the process of carbohydrate metabolism.

### CARBOHYDRATE METABOLISM

Dietary carbohydrates such as disaccharides or polysaccharides (lactose, sucrose, maltose, and starch) are digested into simple sugars (glucose, galactose, fructose) before they could be absorbed into the circulation. After the process of digestion monosaccharides (principally glucose) are then absorbed through the intestinal wall and into blood stream for distribution throughout the body. Some of the glucose is used immediately by cells and metabolized in a series of biochemical reactions (glycolysis, citric acid cycle) to generate energy. The excess glucose is conveyed to the liver, muscle and fat cells where it is converted into glycogen and fat for storage. When more energy is required, this glycogen is converted back to glucose, which reenters the blood stream for distribution around the body (see figure 3).

Figure 2. Carbohydrate digestion to monosaccharide by digestive enzyme amylase. Once the carbohydrate has been broken into monosaccharide than the monosaccharide is absorbed by the intestine and transported to the liver and muscle for metabolism.

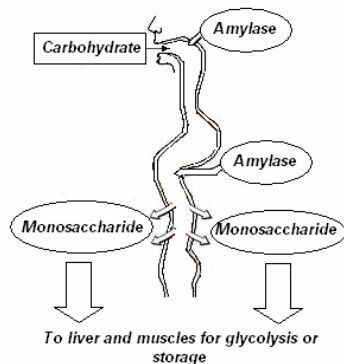
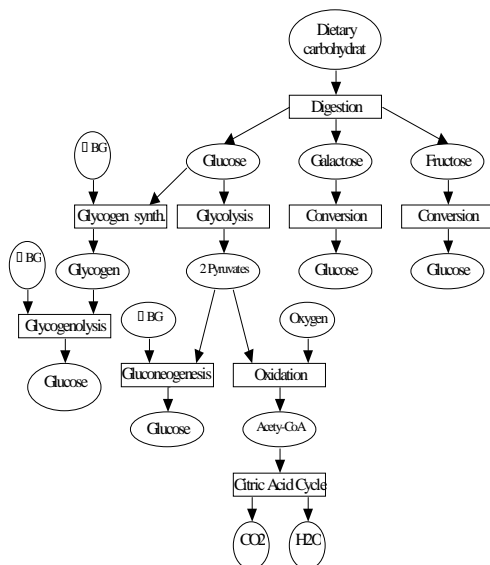


Figure 3. A compact Petri net model of carbohydrate process: BG-blood glucose,  $\uparrow$ -high,  $\downarrow$ -low.



From the above description of carbohydrate metabolism, we can assert that this process is a dynamic one that changes its state after each operation. Furthermore there are some conditional and optional processes taken place throughout the process of carbohydrate metabolism. For instance if energy is required by the body, glucose would undergo process of glycolysis and generate energy, however if the body do not utilize the glucose as an immediate energy, then glucose would undergo process of glycogen synthesis to produce glycogen. So, based on the above information, we could construct a Petri net model of carbohydrate process.

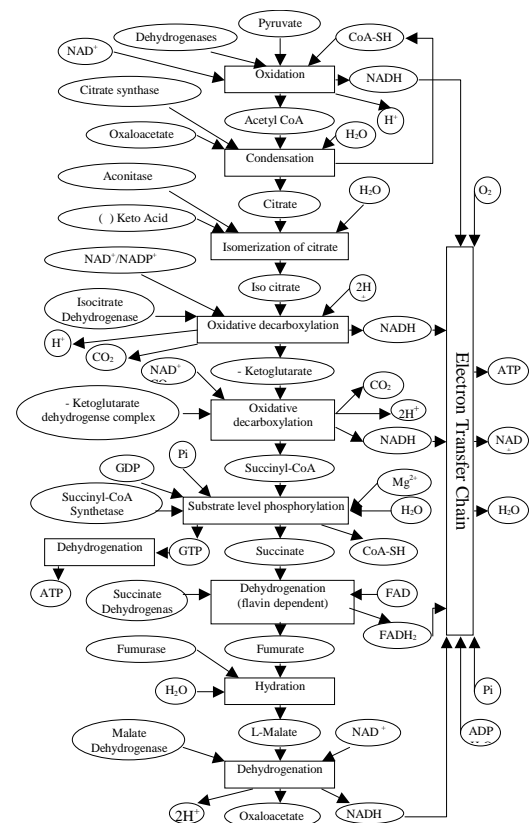
As we can see from the above model in Figure 3, it is clear that the carbohydrate process can be both static and a dynamic process. The above model is a very compact model of carbohydrate process, and it does not show all steps, enzymes, hormones, cofactors, substrates products and conditions involved in this process. The process of glycolysis alone consists of more than 100 places and transitions (Barjis et.al. 2001 ). In this paper we will construct a compact model for the last transition of the above Petri net model known as Citric Acid Cycle (krebs cycle)

### CITRIC ACID CYCLE

Before we develop the Petri net model of the citric acid cycle, first we will look at some of the chemical reactions that take place during the process of citric acid cycle.

The citric acid cycle, also commonly known as the Krebs cycle or tricarboxylic acid cycle (TCA), consists of 8 successive reaction steps [Stryer,L., 1995]. Where in each step molecular and biochemical reactions occur. All the biochemical reactions in the process of krebs cycle is shown in the Petrinet Model below.

Figure 4. A detailed model of Citric Acid Cycle



As we can see from the above description of the Petri net model of the Citric Acid Cycle it is clear that the Citric Acid Cycle process represents:

- A parallel processes - when the enabled transition fires, it enables two other transitions in parallel e.g. substrate level phosphorylation (transition) enables dehydrogenation (transition) of GTP (place) to ATP (place) and also it enables dehydration (transition) of succinate (place) to fumarate (place).
- An alternative process - only one of the two processes, for which the condition is true, will be undertaken e.g. pyruvate will only enter the mitochondria in the presence of oxygen. So if the condition is true (oxygen is present) pyruvate will enter mitochondria and if the condition is not true (oxygen is not present) then pyruvate will not enter the mitochondria.
- Synchronization or AND-join processes - there is necessary to finish both processes completely before starting the following one e.g. in order for the pyruvate to undergo through the process of condensation it would need dehydrogenase, CoA-SH, oxygen, NAD<sup>+</sup>

## CONCLUSION

The main purpose of this paper was to develop a modeling methodology for the process of krebs cycle using Petri nets. The model represents an abstract description of dynamic system (in this case the process of krebs cycle). Simulation of a modeled process allows decisions to be pre-tested before implementation. Further more real-life laboratory experimentation or standard analysis of a system or process is often too complex or/and expensive. Modeled biological processes would allow researchers to be in control of the experiment. They would be able to pre-test their laboratory experiment by touch of few buttons, without spending time and material in laboratory. Educational institutions would be able to use this modeling techniques and simulation to replace the dry text. Students would better digest the subject if they observe the biological process of krebs cycle visually rather than reading a dry text about what would happen to glucose once in the body. This could be a very useful tool for

educational institutions in teaching the biological processes, as it would allow them to simulate the process and students would visually observe what happens in each step of a reaction and what are the involved substrates or cofactors. They would see how the reaction could not be completed if not all the necessary substrates and cofactors present (in case of synchronization process, e.g. glycolysis).

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