

# MODELING AND SIMULATION OF CARBOHYDRATE METABOLISM USING PETRI NET

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## ABSTRACT

In this paper, we present discrete-event simulation modeling of biological process. Carbohydrate metabolism, which plays an important role in the regulation of the glucose concentration in the blood, is modeled using Petri nets. In particular, we study application of Petri nets to model the processes of carbohydrate catabolism in a compact notation. The model does not show all the molecular and biochemical reaction that take place in each step. The breakdown of carbohydrate occurs in a series of steps and the final outcome of the carbohydrate anabolism is generation of ATP, water and carbon dioxide as it is shown in figure ?. During this process some of the potential energy stored in the hexose structure is released and used to derive the synthesis of ATP from ADP. There will be give an overview of the carbohydrate metabolism and a Petri net model would be constructed for the carbohydrate metabolism, which will show all the involved pathways in carbohydrate metabolism. However since the emphasis of this paper is on application of Petri net rather than the underlying molecular aspects, the molecular and biological events and reactions are not covered in depth. Only the most important reactions and processes of the carbohydrate metabolism, that are needed as an input data for building a Petri net model, are described.

The Petri net model is developed using Petri net tools which allows graphical editing, analysis and simulation of Petri net models.

**KEYWORDS:** Petri net, Discrete simulation, Carbohydrate, Modeling in Biology

## 1 INTRODUCTION

Metabolism refers to all the chemical reactions of the body. In this paper we will use Petri nets to model and simulate the process of carbohydrate metabolism. Modeling and simulating the structure of

Biological molecules and processes are critical for understanding how these structures and processes perform their function. Simulation is a tool which is used to study the behavior of complex systems. The first step in simulation is *modeling*. The development of a theory of PNs is based on the application of PNs in the modeling and design of systems (Reisig, 1985). The ability to model concurrency, parallelism and to combine easily subsystems modeled as PNs makes the PN model very useful for modeling complex processes such as biological processes.

The modeled biological process can be used for designing compounds to modify or enhance the functions of biological molecules for medical or industrial purpose, or just to simulate a biological process for teaching purpose. Real life laboratory experiments are expensive and time consuming business, and not always the researchers get the desired results. Using computational approaches to model and simulate a real life laboratory experiment or process would allow us to pre test the decisions and observe the outcome of the experiment before implementation or real laboratory experiment. This would not only save time and money, but would be a great help for educational institutions to teach the particular process, as the students would observe what actually happens in each step of the reaction throughout the process. These models would allow educational institutions to teach a biological process using modeling and simulation instead of dry text. Analysts could get the outcome of their experiment by touch of few buttons, rather then spending weeks or even months in a laboratory and not always getting the desired/expected results. Computational biology would help researchers to use models of biological processes or experiments, and be more in control of the experiment. Using the model would enable them to make any changes in the condition of the experiment or change the precursors of the reaction within the biological process and observe the outcome with matter of minutes instead of spending time and material in the laboratory. Therefore more and more biologist and biochemists become increasingly interested in using computational

approaches for their work. So as an ongoing research the authors of this paper put their efforts to study the process of carbohydrate metabolism from computing point of view and to model a biological process named carbohydrate anabolism, using Petri nets.

## 2 PETRI NETS

Petri net (PNs) is an instrument for study of system. 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 system (Reisig, 1985). This modeling methodology is very useful as it allows us to model concurrency, parallelism and to combine easily subsystems.

Although PNs were first introduced to model and analyze communication systems, but they have been applied extensively to other areas as well, because they are able to describe many of the common characteristics of discrete dynamic system. The Petri net structure consists of places and transitions, and Petri net 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 rectangle (see figure 1).

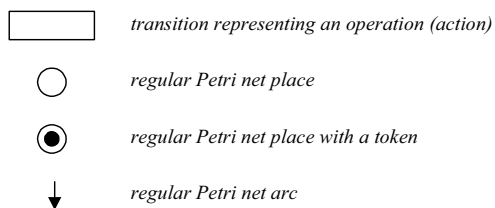


Figure 1. Legend of Petri nets

In a graph representation of Petri net model arcs connect input places to transitions and transitions to output places. Now lets see how we can apply Petri net model to carbohydrate metabolism in general and then how can we construct a detailed model of glycolysis using Petri net. But before we construct any model lets look at the biological events that occur during the process of carbohydrate metabolism.

## 3 CARBOHYDRATE METABOLISM

Although the main purpose of this paper is to model and simulate the process of glycolysis, but first an overview of the entire process of carbohydrate metabolism will be done very briefly.

Metabolism is a collective term for all the chemical processes that take place in the body. It is divided into catabolism and anabolism. In catabolic process a complex substance is broken down into smaller ones, usually with the release of energy. A good example of catabolic process could be the burning of glucose in the body cell to produce energy

and the by-products carbon dioxide and water. In an anabolic process, a complex substance is build from simpler ones, usually with the consumption of energy as it is shown in figure 2 of Petri net model.

In carbohydrate metabolism the monosaccharides or simple sugars (glucose, galactose, fructose) are absorbed into the blood stream unchanged, however the disaccharides or polysaccharides (lactose, sucrose, maltose, and starch) have to be broken down to simple sugars first. So the disaccharides would undergo process of digestion as it is shown in the Petrin net model in figure 2.

The 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 (glycolosis, 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 2).

From the above description of the carbohydrate metabolism process we could draw a conclusion that this process is a dynamic process that changes its state after each operation. Further more there are some conditional, and optional processes take place throughout the process of carbohydrate metabolism. For instance if energy is required by the body glucose would undergo process of glycolosis and generate energy, however if body do not utilize the glucose as an immediate energy, then glucose would undergo process of glucogen synthesis to produce glycogen.

So based on the above information we could construct a Petri net model of carbohydrate process.

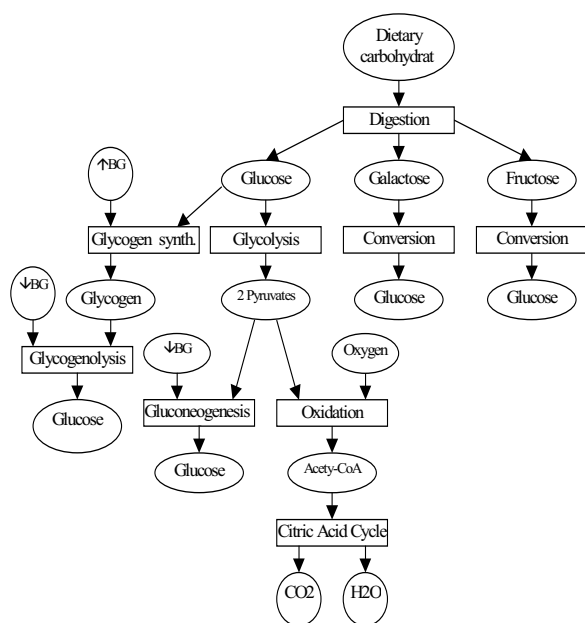


Figure 2. A compact Petri net model of carbohydrate process: BG- blood glucose, ↑-high, ↓-low.

As we can see from the above model in figure 2 it is clear that the carbohydrate process can be both static and dynamic process. For instance it is dynamic process because as we can see from the figure 2 above glucose is converted to pyrovate, and then if glucose level of the blood stream is low, pyruvate is converted back to glucose. Also one should note that unlike glucose, galactose and fructose cannot be used directly by the body's cells, therefore first they must be converted to glucose by the liver cells, and thereafter the glucose will enter the process of glycolysis (see figure 2 above). The above model is a very compact model of carbohydrate process, and it does not show all the reactions involved in this process. The process of glycolysis alone consists of 10 chemical reactions that are not shown in the compact model. But before we discuss glycolysis in some details and construct a detailed model of glycolysis, lets talk about glycolysis as a two-phase process.

#### 4 CARBOHYDRATE METABOLISM

Foods supply carbohydrates in three forms: starch, sugar, and cellulose (fiber). Starch and sugar are major and essential sources of energy for humans. A lack of carbohydrates in the diet would probably result in an insufficient number of calories in the diet. Cellulose furnishes bulk in the diet. Since the tissues of the body need glucose at all times, the diet must contain substances such as carbohydrates or substances which will yield glucose by digestion or metabolism. For the majority of the people in the world, more than half of the diet consists of carbohydrates from rice, wheat, bread, potatoes,

macaroni and so on. All the dietary carbohydrates are converted to glucose, galactose or fructose during the process of digestion as it is shown in figure 2 above. Both fructose and Galactose will be converted into Glucose for energy generation. The final product of glucose anabolism is ATP, water and carbon dioxide as it is shown in figure 3 below.

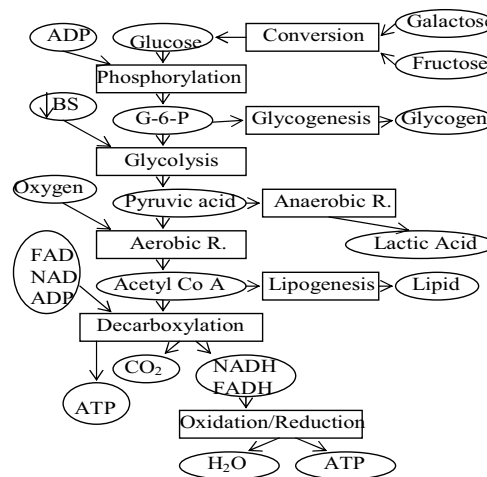


Figure 3: Compact model of carbohydrate metabolism. BS=Blood Sugar and the arrow indicate low level of BS. Anaerobic R=Anaerobic Respiration

The above model is in a very compact notation. Lets look at Glycolysis in some details.

#### 5 THE GLYCOLYSIS PROCESS

The generation of metabolic energy from carbohydrate begins with glycolysis. Glycolysis is the initial pathway in catabolism of carbohydrates. It is an appropriate point to begin a detailed study of metabolism. First, it was the earliest metabolic pathway to be understood in details. Secondly, the pathway is nearly universal in living cells. Third, the regulation of glycolysis is particularly well understood. Last, because it plays central metabolic role in carbohydrate metabolism in energy generation and as metabolic intermediate for other pathways. Glycolysis is a 10 step pathway that converts one molecule of glucose to two molecule of pyruvate as it is shown in figure 5 of Petri net model. The 10-reaction pathway in the process of glycolysis is described as energy investment phase and energy generation phase in section 4 of this paper. Each phase of the glycolysis process consist of 5 reaction, that is not shown in section 4 above. Now lets discuss the 10 steps of reactions that are involved in the process of glycolysis and then based on that information construct a detailed Petri net model of glycolysis

Lets consider in sequence the 10 reactions leading from glucose to pyruvate, numbering each reaction as '1-10'.

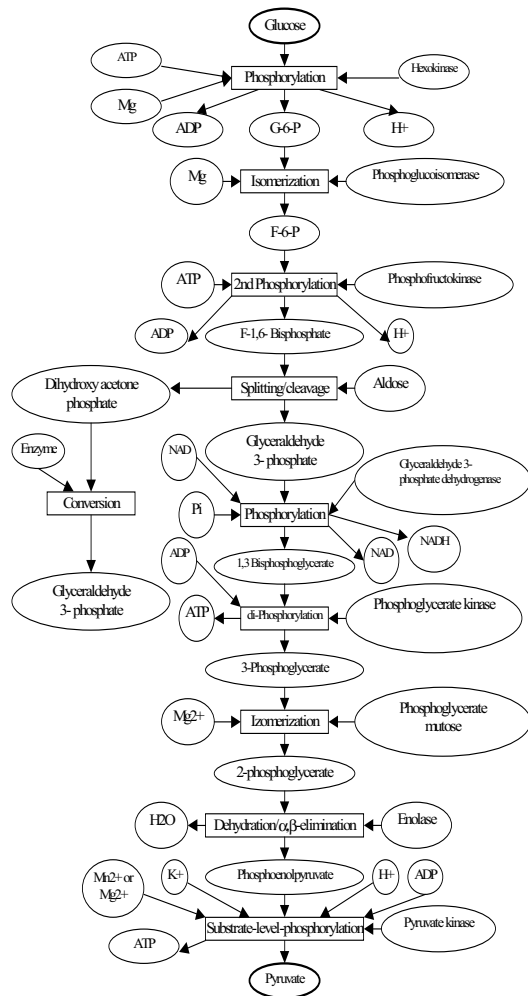


Figure 5. Detailed model of glycolysis.

Ninth reaction is the conversion of 2-Phosphoglycerate to Phosphoenolpyruvate. This reaction that is catalyzed by enolase, generate another super high-energy compound Phosphoenolpyruvate, which participates in the second substrate level phosphorylation of glycolysis. The enzyme in this reaction requires  $Mg^{2+}$  or  $Mn^{2+}$  and is inhibited by fluoride ions. Tenth reaction is the last reaction in the process of glycolysis. In this last reaction, phosphoenolpyruvate transfers its phosphate to ADP and generate ATP. The enzyme pyruvate kinase that requires  $K^{+}$  and either  $Mg^{2+}$  or  $Mn^{2+}$  converts phosphoenolpyruvate to pyruvate. Based in the above information one can see that the process of glycolysis is a dynamic process that changes its states (compound in this case) after each operation (reaction in this case). Also there are conditions for each operation. For instance lets look at the last

reaction; in order for the reaction to be completed an enzyme is required to catalyze the reaction, and the enzyme requires potassium and manganese as a cofactor. So we can say that this is a synchronization or AND-join process.

## 6 CONCLUSION

The main purpose of this paper was to develop a modeling methodology for the process of glycolysis using Petri nets. Why should we bother to model a biological process at the first place? Well, the answer is that: first to develop an abstract description of dynamic system (in this case the process of glycolysis); second simulation and modeling allows decisions to be pre-tested before implementation; and third real-life laboratory experimentation or standard analysis of a system or process is often too complex or/and expensive. So it 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 the observe the biological process of glycolysis visually rather than reading dry text 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 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 sychronization process, e.g. glycolysis).

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