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Simulation of Metabolic Pathway Model Using Petri Net Approach

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Abstract. A metabolic pathway consists of a series of metabolites which participate in more than one metabolic pathways, forming a complex network of reactions. The approach of Petri net is well suited for modeling metabolic networks as it analyzes the pathways both qualitatively and quantitatively. Hybrid Functional Petri net combines with software like Cell Illustrator to give a more intuitive and natural modeling method for complex metabolic pathways with both discrete and continuous properties. The purpose of this paper is to describe the application of HFPNe to construct pentose phosphate pathway and glycolytic pathway. This model using Cell illustrator determines the flow of the pathway and demonstrates the concentration-time data of metabolites.

Keywords: Petri net, biological pathways, simulation, modeling.

1. Introduction

Petri net theory can serve to model, analyze and simulate biological processes [2]. Petri nets have been proposed as a promising tool among the various methods for the modeling and analysis of molecular networks [3]. Petri nets are a network where tokens in the input places will initiate transitions which will result in the generation of new tokens in the output places [1]. The nodes in the Petri net are places which can represent metabolites, transitions can represent metabolic reactions, and values associated with transitions can represent rate constants, which describe the rates at which reactions proceed [4]. Quantitative and qualitative simulations are required for the better understanding of molecular behavior of biochemical reactions [6]. The initial model of Petri net has got many extensions so as to transform models into a more compact form.

The hybrid functional Petri net model (HFPN) is an extension of the discrete Petri net model as it can handle real numbers in a continuous way while keeping the good characteristics of discrete Petri net [5]. Furthermore, software tools for molecular biology modeling and simulation based on a Petri net architecture are being developed [1]. Simulations of the Hybrid Functional Petri net with extension (HFPNe) model are performed using the software package Cell illustrator [7, 9]. Cell Illustrator, which builds a GUI on top of HFPNe, is a pathway simulation tool for modeling and simulating structurally complex dynamic interactions and processes like metabolic pathways, signal transduction cascades [8, 14, and 15]. The pentose phosphate pathway or hexose monophosphate metabolism generates both NADPH and ribose-5-phosphate, which, along with its derivatives is a constituent of ATP, coenzyme A, NAD+, FAD+, RNA and DNA. Of the two phases in pentose phosphate pathway, the oxidative phase generates NADPH and the non-oxidative phase generates 5-carbon sugars [10]. The glycolytic pathway can use pentose phosphate pathway as a source for its initial metabolites. A method of qualitative analysis of metabolic pathways is presented in this article. The technique incorporates the use of software called Cell Illustrator which makes use of Hybrid Functional Petri net with extension (HFPNe) for the representation and analysis of metabolic reaction networks. This paper analyses using qualitative method like Petri net, how high-energy compounds ATP and NADH are produced in metabolic pathways. The derived model with pictures reflecting the biological entities and processes with graphical format has a close similarity with the normal pathway scheme that biologists are familiar with.

2. Methods and Results

The pentose phosphate pathway is a major source of reducing power and metabolic intermediates for biosynthetic processes like glycolytic pathway [11].

Table 1: Enzymes of Pentose Phosphate Pathway

(Oxidative Phase)	**(Nonoxidative Phase)**
Glucose 6-phosphate dehydrogenase	3- Epimerase
Gluconolactonase	Keto- isomerase
6-Phosphogluconate dehydrogenase	Transketolase
--	Transaldolase
--	Phosphofructokinase
--	Fructose-1,6-bisphosphatase

There are a variety of starting points for glycolysis, the most usual ones start with glucose or glycogen to produce glucose-6-phosphate.The intermediates between different points that enter and leave the glycolysis pathway are contributed by other processes [12]. The fructose-1, 6-bisphosphate of pentose phosphate pathway can contribute glyceraldehyde-3-phosphate which is an intermediate in glycolytic pathway. Phosphofructokinase is an obvious control point in glycolysis as it phosphorylates fructose-6-phospahte which eventually feeds glycolytic pathway [13]. Pyruvate molecules are formed before the glucose can be converted into ATP.

Table 2: Enzymes of Glycolytic Pathway

Glyceraldehyde 3- phosphate dehydrogenase
Phosphoglycerate kinase
Phosphoglycerate mutase
Enolase
Pyruvate kinase

For this work, we defined a modeling architecture known as the Hybrid Functional Petri net extension (HFPNe). By using Cell Illustrator Online 5.0 (trial version), we analyzed a model of pentose phosphate pathway and glycolytic pathway to illustrate how metabolites between different points enter and leave the glycolytic pathway.

This HFPNe model cannot represent equilibrium biochemical reactions as they serve the function of a boom but not of a regulator [13]. The derived model (Fig 1) contains three sections:

i. Oxidative phase of pentose phosphate pathway
ii. Non-oxidative phase of pentose phosphate pathway
iii. Glycolytic pathway

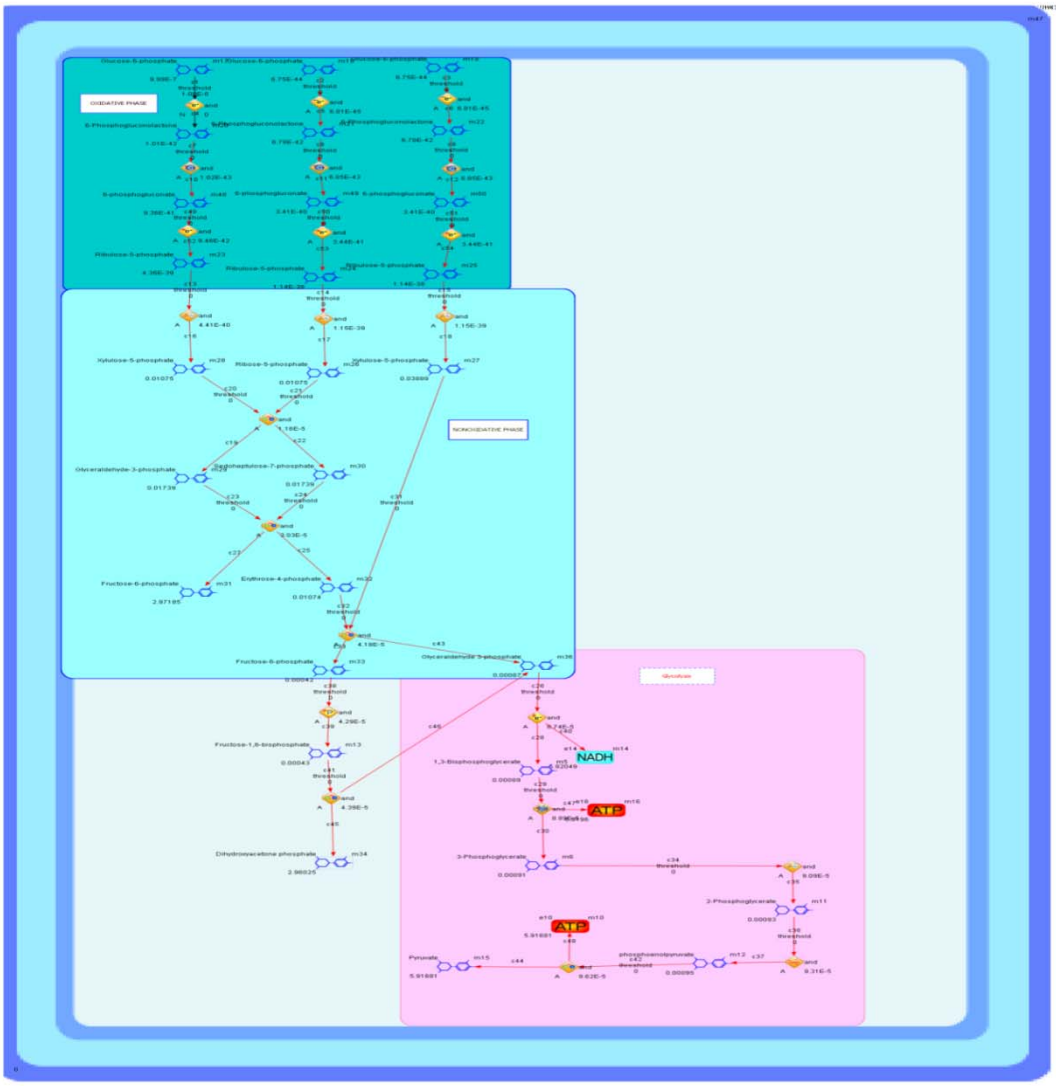


Fig 1: HFPNe model of Pentose Phosphate pathway and Glycolytic Pathway using Cell Illustrator 5.0

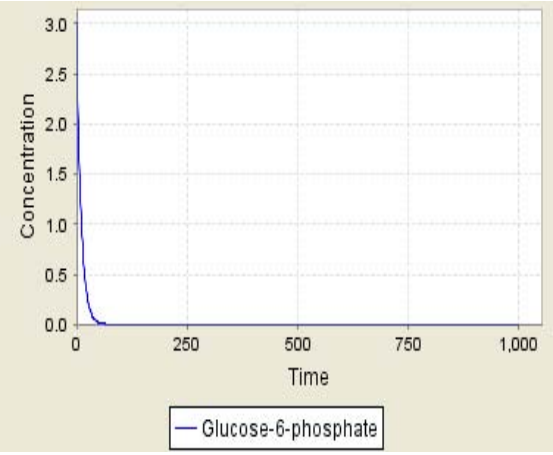


Fig 2: Time vs Concentration of Glucose-6-phosphate

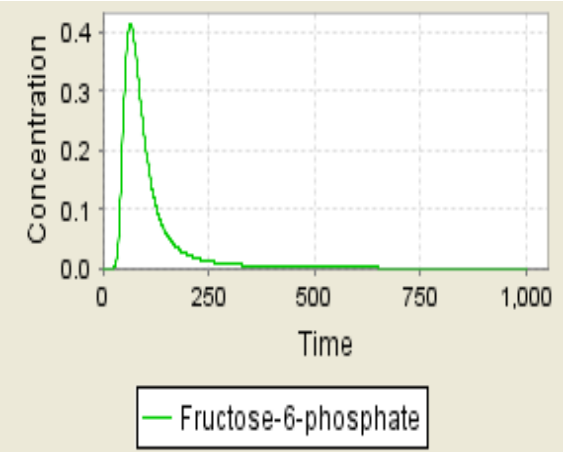
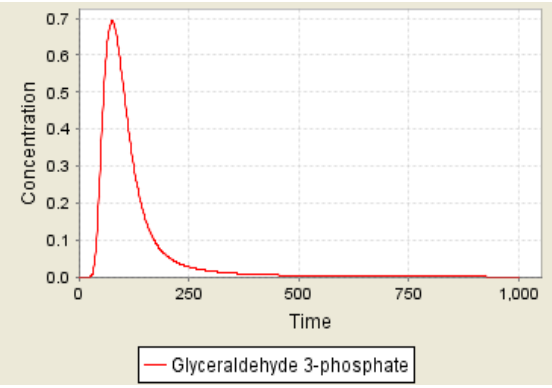


Fig 3: Time vs Concentration of Fructose-6-phosphate



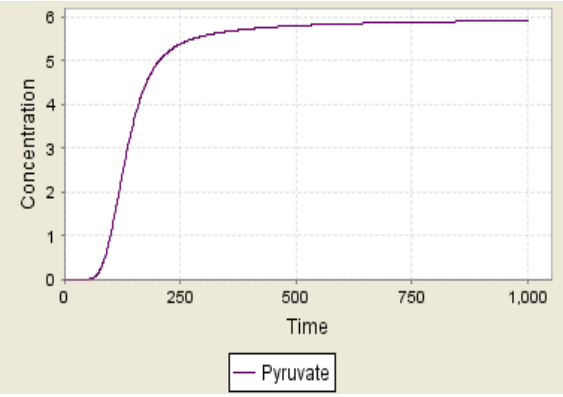


Fig 4: Time vs Concentration of Glyceraldehyde-3-phosphate Fig 5: Time vs Concentration of Pyruvate

Using Cell Illustrator, the graphs for initial molecule, intermediates as well as the final product of the pathway are produced. From these graphs it is clearly understood that the concentration of glucose-6-phosphate decreases (Fig 2) gradually as the outcome of the pathway, Pyruvate increases its concentration (Fig 5). The fructose-6-phosphate and glyceraldehyde-3-phosphate, which are produced in pentose phosphate pathway, are used as source for glycolytic pathway. In glycolytic pathway, these molecules are being used up to produce Pyruvate, which is the final molecule of the model. This model using Cell Illustrator determines the flow of the pathway and demonstrates the concentration-time data of metabolites.

3. Conclusion

We have proposed a Hybrid Functional Petri net with extension model using Cell Illustrator which seems to be a useful method for the fundamental representation and simulation of metabolic networks. The usage of Petri nets allows a stepwise extension of the biological network and to evaluate in detail the changes promoted in metabolic pathways. As a model system, we selected the glycolytic and pentose phosphate pathways, which are some of the best-studied metabolic pathways. Our simulation results indicated that the concentrations of metabolites vary according to time. We believe that in the future it will be possible to extend the model computationally using different Petri net approaches.

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5. References

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