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WORKFLOW NET MODELING USING WoPeD FOR THE EFFECTS OF INHIBITORS IN THE SYNTHESIS AND PROCESSING OF N-LINKED GLYCOPROTEIN

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Abstract- In order to understand and predict the behavior of any system, modeling is essential. Hence the research on modeling and simulation of complex biological system has drawn the attention of researchers in this direction. In this paper, we have determined the effects of inhibitors in the pathway of plasma membrane glycoprotein synthesis and processing through work flow net. Petri nets are widely used for modeling and analyzing workflows. To enhance the effectiveness of the bio pathway model, we have associated and visualized the process of Petri net model with the help of work flow net using WoPeD (Workflow Petri net Designer), a Java-based software tool to design and verify work flow models using Petri net.
Keywords- work flow net, inhibitors of plasma membrane glycoprotein, Petri net, WoPeD.

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Introduction

Petri Nets (PN) are a graphical tool for the formal description of the flow of activities in complex systems. Petri nets are a popular technique for modeling the control flow dimension of workflows. When modeling workflows, people tend to draw nodes that represent tasks or activities, and arrows between the nodes that represent sequencing of activities. The resulting diagrams look like Petri nets, and so Petri nets seem a natural technique for modeling work flows. Petri nets are highly useful in the analysis of complex biological systems integrating both the quantitative and qualitative studies. Work flow modeling and analysis have been studied for many years and by now, there have been many researches in this field. As methods of modeling and analyzing physical system, Petri nets have shown their abilities to deal with concurrence and conflict and have been widely used to model, analyze and verify work flow.

To understand workflow net, some basic concepts and definitions of work flow nets are used. Petri net is called a work flow net iff PN has two special places: ϵ and θ where ϵ is a source place: $\cdot\epsilon = \phi$ and θ is a sink place: $\theta\cdot = \phi$: where $\cdot\epsilon$ is a set of input places / transitions of the place ϵ and $\theta\cdot$ is the set of output places / transitions of the place θ.

If we add a new transition t to *PN* which connects θ with ϵ, namely, $\cdot t = \{\theta\}$, $t\cdot = \{\epsilon\}$, then the resulting extended net *PN* = (P, T, F), where $P = P$, $T = T \cup \{t\}$, and $F = F \cup \{(\theta, t), (t, \epsilon)\}$ is strongly connected. In a WF-net, building blocks such as And-split, And-join, OR-split, and OR-join are also used to model the structure.

Processing of N-Linked Glycoprotein

Proteins destined for secretion or incorporation into membranes or localization inside membranous organelles contain carbohydrates and are classified as glycoprotein. The polypeptide components of glycoprotein are ribosomally synthesized and entered into RER for glycosylation. Synthesis of N- linked oligosaccharides begin in the RER with the multistep formation of lipid linked precursor [4]. From this precursor, the oligosaccharide is transferred to an Asn (Asparagine amino acid) residue of a growing polypeptide chain by oligosaccharide transferring enzyme. This glycoprotein is partially trimmed and is transported to Cis Golgi complex via transition vesicles. Processing of glycoprotein is completed in Cis , medial and Trans GC cisternae , by the removal and addition of sugar units, catalyzed by specific enzymes. The completed N-linked glycoproteins are sorted in the Trans GC, according to the identities of their carbohydrate components for transport to their final destinations via transport vesicles. Three major types of N-linked oligosaccharides have been identified, high mannose type, hybrid type and complex type. Studies of glycoprotein have been facilitated by the use of inhibitors, which inhibit specific enzymes involved in the synthesis of glycoprotein and alter the carbohydrate structure. Since glycoproteins are involved in many areas of metabolism and turn over, inhibitors of these enzymes could have many kinds of beneficial effects as therapeutic agents of many diseases and disorders such as cancer [3,4,7].

For easy and intelligent computing, we have used a hybrid work flow net to model the effects of inhibitors in glycoprotein synthesis and processing and we are able to associate automata with it for verification and quantitative analysis of the model. The work flow model is called hybrid since it deals with three types of glycoprotein synthesis say, High mannose, hybrid and complex type.

Effects of Inhibitors

Studies of glycoprotein functions and structures are facilitated by the use of inhibitors. Ribosomally synthesized proteins enter rough endoplasmic reticulum for glycosylation. Introduction of Puromycin in ribosome inhibits protein synthesis. Synthesis of N-linked glycoprotein begins in RER and is processed both in RER and Golgi complex. In RER, an oligosaccharide chain is donated by dolichol - pyrophosphate - oligosaccharide (precursor) to the Asn to the residue of protein chain as it traverses the RER. Tunicamycin inhibitor prevents both the formation of the precursor and the transfer of oligosaccharide to protein from the precursor. Castenospermine prevents the function of ER-Glucosidases I and II enzymes and blocks the removal of 3 glucose units [3]. In normal cells the removal of glucoses occurs and the partially trimmed glycoprotein is transported to GC by transition vesicle.

In cis GC, mannosidase I enzyme removes three mannoses from the glycoprotein chain. The introduction of Deoxymannojirimycin inhibits the functions of this enzyme and prevents the removal of three mannose sugars. Presence of more mannoses forms the High Mannose type of glycoprotein. In medial GC, the glycosyl transferases enzymes add one GlcNac and one fucose sugar units to the glycoprotein. GC mannosidase II enzyme removes two more mannoses. If Swains nine inhibitor is introduced, it prevents the function of GC mannosidase II enzyme, there by inhibiting the removal of two mannose sugar units. It leads to the formation of hybrid type of glycoprotein. The removal of two mannoses leads to the formation of complex type of glycoprotein. The processing of glycoprotein is completed by the addition of terminal sugars in trans GC. Non - Clathrin coated transport vesicles transport the completely processed glycoprotein to the plasma membrane [4,7].

Activity Diagram for Modeling Work Flow

Work flow refers to automation of any processes, in whole or part, during which information or tasks are passed from one participant to another for action, according to a set of any procedural rules. A work flow is used to define, create and manage the execution of tasks. While designing a work flow, one describes which tasks have to be done and in what order. So process approach is given more importance

Activity diagram provides all the basic constructs needed. Major constructs for workflow modeling are sequence, parallel path, alternative path and iteration[5]. Activity diagram constructs, start, end, fork, decision. Start can be used to indicate beginning of a process where as end can be used to indicate end of a process. Fork can be used for splitting a process into several parallel execution paths. Decision can be used for providing alternative paths. An activity diagram can be mapped to a Petri net which includes all kinds of control flow. The Petri net model can be represented using Petri Net Markup Language (PNML). PNML is an XML based interchange format for Petri nets. Fig. 1 shows the Work flow net model for one activity without resources. Fig. 2 shows the activity diagram of N-Linked Glycoprotein and the list of activities associated with the synthesis and processing of Gp to model it and Fig. 3 shows the corresponding Petri net obtained after converting it.

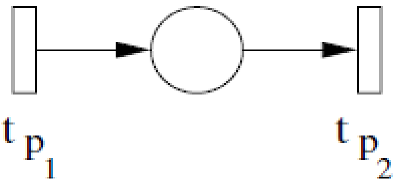

Fig. 1- Work flow net model for one activity without resources

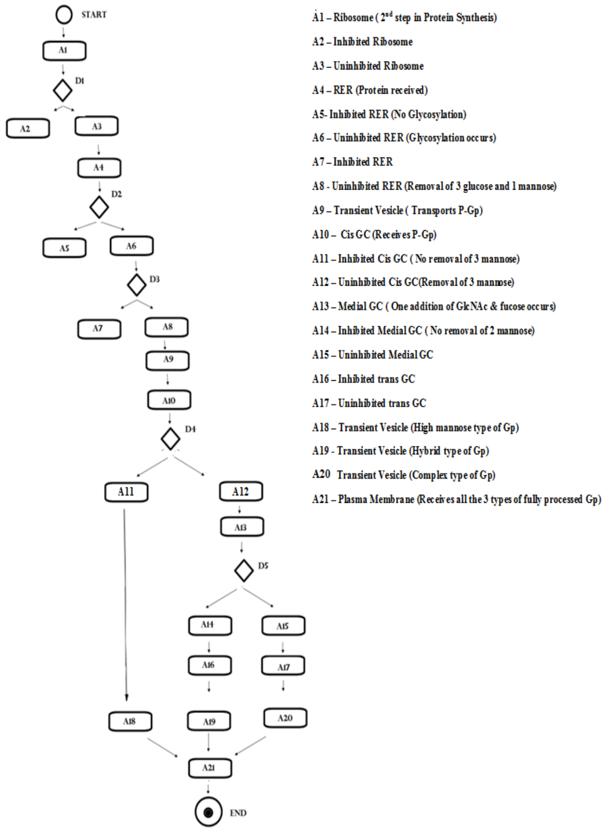

Fig. 2- Activity Diagram and the list of activities associated for the synthesis and processing of N-linked glycoprotein.

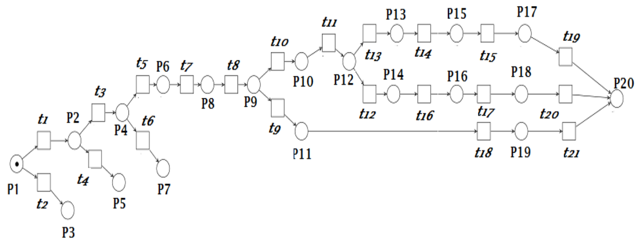

Fig. 3- The Petri net obtained from fig 2.

Places instead of transitions are used to represent the activities of the workflow $\forall\ p \in PA$, if $\exists\ tp1, tp2 \in T$ such that $t\ p1 = \cdot tp2 = \{p\}$, $tp1$ and $tp2$ mean the start and termination of activity p respectively. The presence of token in the place $pi \in PA$ implies that the activity associated with it is being processed. Each activity A_k ($1 \leq k \leq 21$) is associated with places.

Analysis Techniques

The success of any model depends on two factors: its modeling power and its decision power. Modeling power refers to the ability to correctly represent the system to be modeled; decision power refers to the ability to analyze the model and determine properties of the modeled system. The modeling power of PN has been examined in the previous sections, and in this section we take into consideration the analysis techniques of PNs [8].

Two major Petri net analysis Techniques have been suggested, and these techniques provide the solution mechanisms. The major technique which has been used with Petri nets is the reachability tree, the other technique involves matrix equations.

Analysis of Work Flow Net

We have implemented the mapping of an activity diagram to a Petri net which includes all kinds of work flow. We have modeled work flows using Activity diagrams and then analyze models. While performing analysis, the activity diagrams are first converted into their Petri nets representations which are analyzed and results reported back into the work flow domain

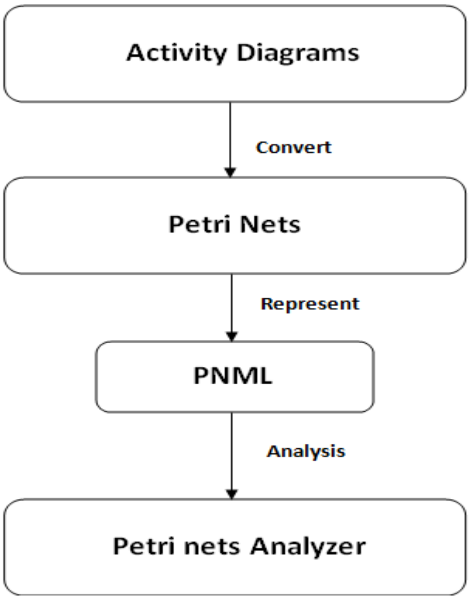

Fig. 4- Data flow of our tool

We generate the Petri nets into PNML format, which is a standardized XML based format for representing Petri Nets. WoPeD, a Java based Software tool uses the Petri Net Markup Language (PNML) as interchange format and is able to edit simulate and analyze workflow Petri nets(WF-nets) as originally introduced by Wil Van der Aalst. By representing the Petri nets in PNML we provide means for future extensions using new analysis methods for Petri Nets. Fig. 5 is the screen shot of the corresponding Petri net in PNML representation converted from the activity diagram using our tool WoPeD and Fig. 6 is the reachability graph of 20 vertices and 21 Edges respectively.

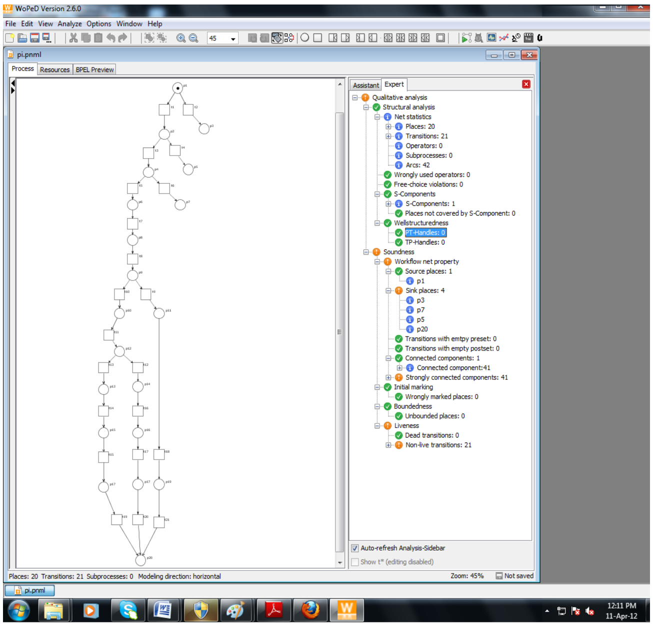

Fig. 5- Petri net conversion in PNML format using WoPeD

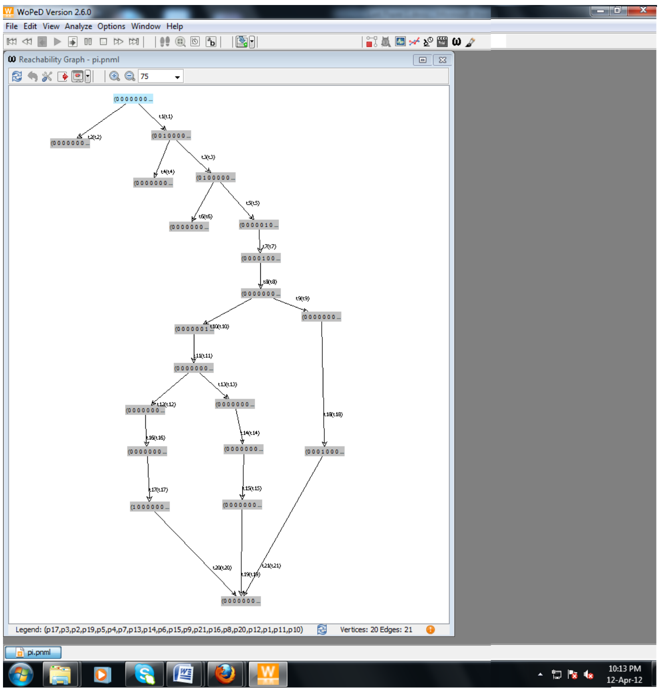

Fig. 6- Reachability Graph generated using WoPeD

It is not enough to only design a work flow. It is also necessary to analyze it. Petri Nets are used to analyze work flows. A huge amount of work has been done on Petri net so far and hence a huge number of results are available. One needs to find out a set of results which can help in analyzing work flows.

The Reachability Tree and Reachability Graph

Reachability is a fundamental basis for studying in the dynamic properties of any system. The firing of an enabled transition will change the token marking in a net according to the firing rule. A sequence of firings will result in a sequence of markings. A marking Mn is said to be reachable from a marking M0 if there exists a sequence of firings that transforms M0 to Mn. A firing sequence is denoted by $\sigma = M_0\ t_1\ M_1\ t_2\ M_2 \ldots t_n\ M_n$ or simply $\sigma = t_1 t_2 \ldots t_n$. In this case, Mn is reachable from M0 by σ and we write M0 [σ > Mn.] The set of all possible markings reachable from M0 in a net (N, M0) is denoted by R(N,M0) or simply R(M0) and the set of all possible firing sequence is denoted by L(N,M0) or simply L(M0).

Reachability Graph Algorithm

A reachability graph of a PN is a directed graph G = (V, E), where v Î V represents a class of reachable markings; e Î E represents a directed arc from a class of markings to the other class of markings. A reachability graph is also called occurrence graph or state space. The reachability graph demonstrates a better performance than the reachability tree. The Fig. shows the reachability graph generated for the Petri net using our tool. Table 1 shows the reachability set and the token distribution obtained from the reachability graph

Table 1- Reachability Set and the Token Distribution

m_i	Transition	Markings
m_0	$< t_0$	00000 00000 00000 00100
m_1	$< t_1$	00100 00000 00000 00000
m_2	$< t_2$	00000 00000 00100 00000
m_3	$< t_3$	01000 00000 00000 00000
m_4	$< t_4$	00000 00100 00000 00000
m_5	$< t_5$	00000 10000 00000 00000
m_6	$< t_6$	00000 00010 00000 00000
m_7	$< t_7$	00001 00000 00000 00000
m_8	$< t_8$	00000 00001 00000 00000
m_9	$< t_9$	00000 00000 10000 00000
m_{10}	$< t_{10}$	00000 01000 00000 00000
m_{11}	$< t_{11}$	00000 00000 00001 00000
m_{12}	$< t_{12}$	00000 00000 00000 01000
m_{13}	$< t_{13}$	00000 00000 01000 00000
m_{14}	$< t_{14}$	00000 00000 00000 00001
m_{15}	$< t_{15}$	00000 00000 00000 00010
m_{16}	$< t_{16}$	00000 00000 00010 00000
m_{17}	$< t_{17}$	10000 00000 00000 00000
m_{18}	$< t_{18}$	00010 00000 00000 00000
m_{19}	$< t_{19}, t_{20}, t_{21}$	00000 00000 00000 10000

The following Algorithm for the construction of a Reachability Graph (RGA) of a place transition nets general needs the boundedness of the net to terminate:

Step 1 Let N=(P,T,F,K,W,m0) a bounded PT-net.
G consists of a directed, labeled graph without an arrow and with m0 as its only node.
Step 2 a) Select a node m of G and a transition t ÎT such that the pair (m,t) was not considered in a proceeding step, and t is enabled in m using the strong firing rule.
b) Fire t and determine the marking m' after firing (m[t>m').If m' is already a node in G, then add the new arrow (m,t,m') to G and go to step 2a).
c) Add m' as a new node and (m,t,m') as a new arrow to G and go to step 2a)

Matrix Analysis

We present matrix equations to describe and analyze completely the dynamic behavior of Petri nets.

Incidence Matrix- For a Petri net PN with n transitions and m places, the incidence matrix A = $[a_{ij}]$ is an n × m matrix of integers and its typical entry is given by;

$a_{ij} = a_{ij}^{+} - a_{ij}^{-}$

where

a_{ij}^{+} = w(i, j) is the weight of the arc from transition i to its output place j and

a_{ij}^{-} = w(i, j) is the weight of the arc to transition i from its input place j.

Transition i is enabled at marking M iff $a_{ij} \leq M(j)$, j = 1, 2, . . . , m.

	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10	t11	t12	t13	t14	t15	t16	t17	t18	t19	t20	t21
P1	-1	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
P2	1	0	-1	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
P3	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
P4	0	0	1	0	-1	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
P5	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
P6	0	0	0	0	1	0	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
P7	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
P8	0	0	0	0	0	0	1	-1	0	0	0	0	0	0	0	0	0	0	0	0	0
P9	0	0	0	0	0	0	0	1	-1	-1	0	0	0	0	0	0	0	0	0	0	0
P10	0	0	0	0	0	0	0	0	0	1	-1	0	0	0	0	0	0	0	0	0	0
P11	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	-1	0	0
P12	0	0	0	0	0	0	0	0	0	0	1	-1	-1	0	0	0	0	0	0	0	0
P13	0	0	0	0	0	0	0	0	0	0	0	0	1	-1	0	0	0	0	0	0	0
P14	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	-1	0	0	0	0	0
P15	0	0	0	0	0	0	0	0	0	0	0	0	0	1	-1	0	0	0	0	0	0
P16	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	-1	0	0	0	0
P17	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	-1	0	0
P18	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	-1	0
P19	0	0	0	0	0	0	0	0	0	0	0	0	v0	0	0	0	0	1	0	0	-1
P20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1

Fig. 7- shows the incidence matrix for the PN with 21 transitions and 20 places

Van Der Aalst et al has proposed Petri nets for both modeling and analyzing workflows [5-8]. Petri nets have been enhanced with time, color and hierarch to enhance their modeling power [15]. However, there are not many theoretical results available with high-level Petri nets, which can be used for this kind of analysis [2]. Activity diagram has been argued by many as an alternative for modeling workflows. After Van Der Aalst et al identified workflow patterns [9], it has been shown that they can be modeled using Activity diagrams [10]. There have been efforts for defining semantics for activity diagram, so that execution of the workflow models can be done using Petri nets

Conclusion

We have proposed a new way of looking at analysis of workflow net. Modeling of workflows should be done in a language, which is easy and more intuitive to work with like Activity diagrams. But analysis has to be done in a more formal way like Petri nets. We demonstrate this by WoPeD (Workflow Petri net Designer), Java-based software tool to design and verify work flow models using Petri net which can model workflows using Activity diagrams, and then analyze the model using Petri nets. We have so far mentioned two analysis techniques of Petri nets, which are useful in commenting on workflow models. More such properties can be looked for and at the same time more constructs from activity diagrams can be added.

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