A Fuzzy Continuous Petri Net Model for Helper T cell Differentiation

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ABSTRACT: Helper T(Th) cells regulate immune response by producing various kinds of cytokines in response to antigen stimulation. The regulatory functions of Th cells are promoted by their differentiation into two distinct subsets, Th1 and Th2 cells. Th1 cells are involved in inducing cellular immune response by activating cytotoxic T cells. Th2 cells trigger B cells to produce antibodies, protective proteins used by the immune system to identify and neutralize foreign substances. Because cellular and humoral immune responses have quite different roles in protecting the host from foreign substances, Th cell differentiation is a crucial event in the immune response. The destiny of a naive Th cell is mainly controlled by cytokines such as IL-4, IL-12, and IFN-γ. To understand the mechanism of Th cell differentiation, many mathematical models have been proposed. One of the most difficult problems in mathematical modeling is to find appropriate kinetic parameters needed to complete a model. However, it is relatively easy to get qualitative or linguistic knowledge of a model dynamics. To incorporate such knowledge into a model, we propose a novel approach, fuzzy continuous Petri nets extending traditional continuous Petri net by adding new types of places and transitions called fuzzy places and fuzzy transitions. This extension makes it possible to perform fuzzy inference with fuzzy places and fuzzy transitions acting as kinetic parameters and fuzzy inference systems between input and output places, respectively.

1 INTRODUCTION

Two types of helper T(Th) cells, called Th1 and Th2, have been defined based on the profile of cytokines they produce and are differentiated from common Th cell precursors(Th0). These two subsets of Th cells have quite different roles in the immune response. Th1 cells induce cellular immune response by activating cytotoxic T cells, which defend a host against infectious intracellular microorganisms such as viruses and some types of bacteria by killing infected cells. Th2 cells lead to humoral immune response by activating B cells to produce antibodies, protective proteins used by the immune system to identify and neutralize foreign substances. The humoral immune response helps a host remove extracellular pathogens. Thus, Th1/Th2 cell differentiation from a naive Th cell is an important event in the immune response. Although there are many different factors affecting Th cell differentiation, it is mainly controlled by cytokines such as IL-4, IL-12, and IFN-γ [1]. To understand the mechanism of Th cell differentiation with cytokine network, many mathematical models have been developed[2, 3, 4]. One of the most difficult problems in mathematical modeling is to find appropriate kinetic parameters needed to complete a model. However, it is relatively easy to get linguistic, incomplete or qualitative knowledge of a model dynamics. For example, we can easily find sentences like 'IFN-γ and IL-12 promote Th1 differentiation' and 'IL-4 helps Th2 differentiation' using literature search. Linguistic knowledge can be very useful in modeling the immune system, but previous approaches do not use it. Here we present a novel approach based on Petri nets and fuzzy inference systems for incorporating qualitative knowledge when constructing a immune system model.

2 METHOD

2.1 Petri Nets

A Petri net is a graphical and mathematical modeling tool successfully used in a number of fields for concurrent, asynchronous, and parallel system modeling. Recently, Petri nets have been widely applied to represent biological pathways or processes. Following is the definition of basic Petri nets[5, 6].

Definition 1 *A Petri net is a 5-tuple $R = < P, T, F, W, M_0 >$ where $P = \{p_1, p_2, \cdots, p_n\}$ is a finite set of places, $T = \{t_1, t_2, \cdots, t_n\}$ is a finite set of transitions. The set of places and transitions are disjoint, $P \cap T = \emptyset$. $F \subseteq (P \times T) \cup (T \times P)$ is a set of arcs. $W : F \rightarrow \{1, 2, 3, \cdots\}$ is a weight function. And $M_0 : P \rightarrow \{0, 1, 2, 3, \cdots\}$ is the initial marking.*

The behavior of a Petri net is described in terms of changes of tokens in places according to the firing of transitions. If every input place of a transition has more tokens than the weight of the arc between the transition and the place, the transition is enabled. Of enabled transitions, only one transition can fire. After a transition is fired, as many tokens as the weights of the arc are removed from the input place and as many tokens are added to output places.

Because of its discrete nature, basic Petri net is not suitable for immune system modeling so that we used a continuous Petri net, an extension of basic Petri net, instead. The differences between the basic Petri net and the continuous Petri net are following: In the continuous Petri net, places can have real value marking and transitions fire continuously with some velocity. The velocity of a transition firing is affected by the marking of places. Shown below is the definition of continuous Petri nets[7].

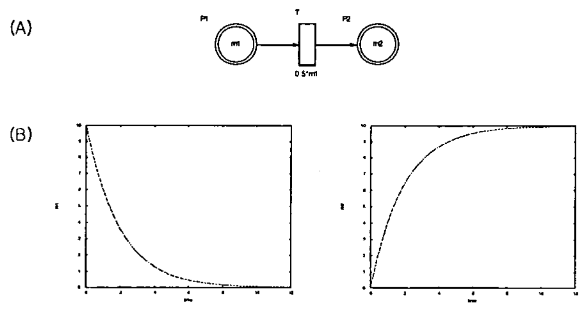


Figure 1: Continuous Petri net. In the graphical representation of the Petri net (A), a circle represents a place and a rectangle represents a transition. Two graph (B) show the changes of tokens of places with respect to time

Definition 2 *A continuous Petri net is a 6-tuple* $R = < P,T,V,F,W,M_0 >$ *where* P,T,F,W,M_0 *are identical to those of the basic Petri net.* $V : T \rightarrow V(p_1, p_2, p_3, \cdots) \in R^+$ *is the firing speed function.*

In our immune system model, places represent immune cells or external entities (e.g. antigen or virus) and transitions represent interactions (e.g. B cell activation by antigen).

2.2 Fuzzy Inference System

Fuzzy inference systems are reasoning systems based on fuzzy set theory, fuzzy if-then rules and fuzzy reasoning. The strength of fuzzy inference systems lies in their capability of handling uncertain linguistic concepts. They are composed of several parts; fuzzification interface, fuzzy rule base, fuzzy inference and defuzzification interface[8].

Fuzzy if-then rules are generally expressed in the form *'If x is A, then y is B'* where A and B are linguistic values defined by fuzzy sets on the universe of discourse $x \in X$ and $y \in Y$, respectively. For example,

If pressure is high, then volume is small.

where *pressure* and *volume* are fuzzy variables, *high* and *small* are linguistic values. By applying inference operation upon fuzzy rules, fuzzy inference systems can deduce consequences. Followings are the steps of fuzzy inference.

1. Compare the input variables with the membership functions on the premise part to obtain the membership values of each linguistic label. (This step is often called *fuzzification.*)
2. Combine the membership values on the premise part to get the firing strength of each rule.
3. Generate the qualified consequence of each rule depending on the firing strength.
4. Aggregate the qualified consequents to produce a crisp output. (This step is called *defuzzification.*)

There are many inference methods; Mamdani, Larsen, Tsukamoto and TSK.

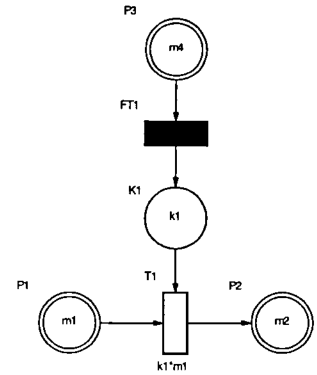


Figure 2: A fuzzy continuous Petri net. In the figure, a black transition represents a fuzzy transition and a single circle represents a fuzzy place. Fuzzy transition FT1 inferences k_1 value from fuzzy if-then rules given the value of input place P_3. And k_1 is used in the firing speed function of a continuous transition, T1.

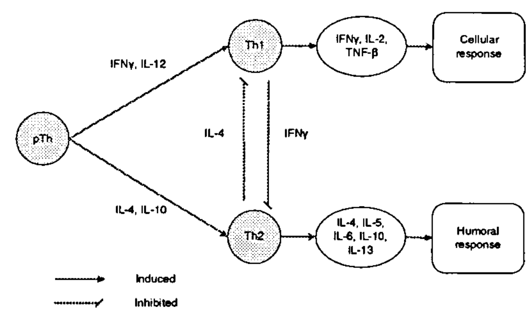


Figure 3: The schematic diagram of a cytokine network

2.3 Fuzzy Continuous Petri Nets

In mathematical modeling and simulation, we usually need appropriate kinetic parameters of a system. However, it is difficult to find parameter values of a system. Therefore, various methods are used to estimate unknown parameters. On the other hand, it is relatively easy to get linguistic or qualitative knowledge. To make use of linguistic and qualitative knowledge in the estimation of kinetic parameters, we employed fuzzy inference systems.

To include a functionality of fuzzy inference, we add new types of transitions and places so-called, fuzzy transitions and fuzzy places. The role of fuzzy transitions is to inference parameter from fuzzy if-then rules between input and output places. And only fuzzy places can be a output place of a fuzzy transition. Fuzzy places act as kinetic parameters of reactions represented by continuous transition. Fig. 2 shows a simple example of a fuzzy continuous Petri net.

3 Model

Dendritic cells are stimulated by recognizing antigens. Stimulated dendritic cells act as APC, antigen presenting cell, by presenting processed antigen fragments using MHC-II molecules and produce signals required for the proliferation and differentiation of naive Th cells. A naive Th cell differentiates into Th1 or Th2 cell upon interaction with MHC-peptide complex presented on the membrane of APC. The dynamics of interaction between naive Th cell and APC is affected by many factors such as the density of MHC-peptide complex and the strength of interaction[9]. APC produces cytokines such as IL-10 and IL-12 which affect naive Th cells differentiation.

Fig. 3 shows a schematic diagram of cytokine network of Th cell differentiation. IFN-γ and IL-12 induce Th1 differentiation. On the other hand, IL-4 and IL-10 promote Th2 differentiation. Activated Th1 produces such cytokines as IFN-γ, IL-2 and TNF-β which induce cellular immune response whereas activated Th2 produces such cytokines as IL-4, IL6 and IL-10, which induce humoral immune response. Besides, IL-4 and IFN-γ inhibit Th1 and Th2 differentiation, respectively.

In our fuzzy continuous Petri nets approach, we integrated signals affecting behaviors of immune cells by fuzzy inference, which simplifies rate equations. All the variables appearing in the reaction equations in continuous transitions are directly related to the reaction.

Fig. 4 and 5 show important reactions in the Th cell differentiation with cytokines. Listed below are examples of rules in fuzzy transitions depicted in Fig. 4.

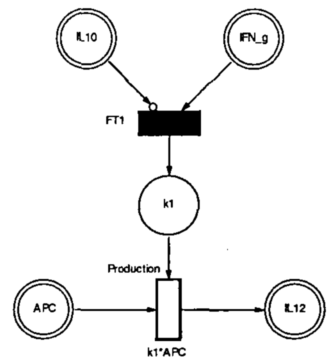
Example 1 *Th1 differentiation: FT2 in Fig. 4(b)*

- *The concentration of IL-12 is higher than* $0.5ng/ml$ *and that of IL-4 is lower than* $10ng/ml$ *, the differentiation rate is about* $4day^{-1}$.
- *The concentration of IL-4 is higher than* $10ng/ml$*, the differentiation rate is about* $2day^{-1}$.
- *The concentration of IL-4 is higher than* $100ng/ml$*, the differentiation rate is nearly 0.*

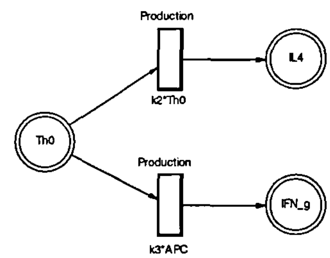
Example 2 *Th2 differentiation: FT3 in Fig. 4(b)*

- *The concentration of IL-4 is higher than* $100ng/ml$*, the differentiation rate is about* $6day^{-1}$.
- *The concentration of IL-4 is lower than* $10ng/ml$*, the differentiation rate is about* $1.2day^{-1}$.
- *The concentration of IL-4 is lower than* $10ng/ml$ *of IL-4 and that of IFN-γ is higher than than* $10ng/ml$ *of , the differentiation rate is nearly 0.*

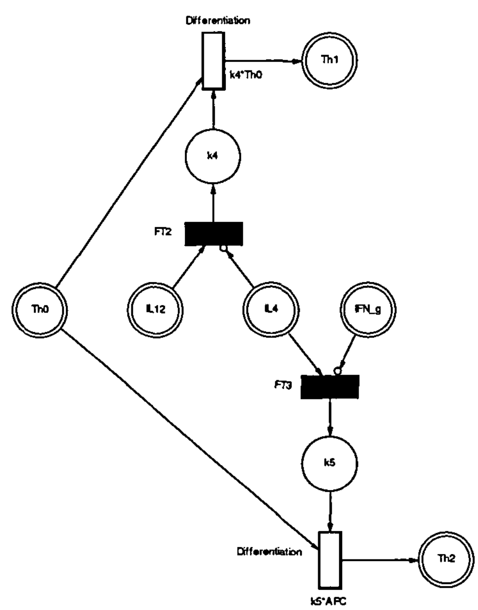
Even though we just have partial knowledge about a system being modelled, we can easily include the knowledge in the model. On top of that, newly discovered knowledge can be easily incorporated into the fuzzy rule based system[8].



(a) APC cytokines production



(b) Th0 cytokines production

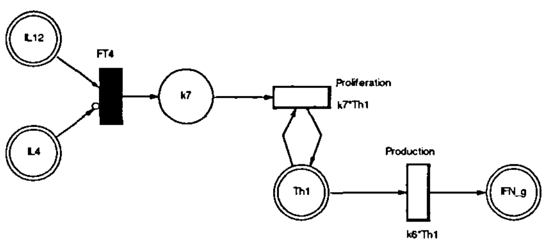


(c) Th1/Th2 differentiation

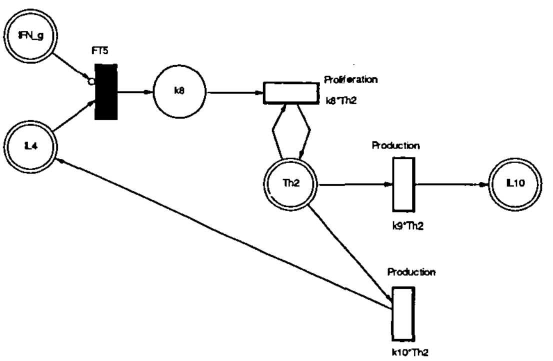
Figure 4: Important reactions of Th cell differentiation

4 Discussion

In conclusion, we propose a new approach to the immune system modeling, a fuzzy continuous Petri net. The advantage of the modeling method is that we can make use of qualitative or linguistic knowledge that are relatively easier to obtain



(a) Th1 proliferation and cytokine production



(b) Th2 proliferation and cytokine production

Figure 5: Important reactions of Th cell differentiation

than kinetic parameters. We show that fuzzy inference systems successfully used in expert systems in various domains can be also used in the immune system modeling. To make it more useful, we need to develop more robust methods for constructing fuzzy rules from immunological knowledge. Moreover, we have to develop analysis techniques such as reachability and boundedness for traditional Petri nets.

The challenge of recent research is how to integrate molecular transcriptional network and cellular communication via cytokines in the immune response[10]. Hierarchical Petri nets approach could be a good candidate formalism for integration of knowledge from different levels.

5 Acknowledgements

This work was supported by the National Research Laboratory Grant (2005- 01450) from the Ministry of Science and Technology. We would like to thank CHUNG Moon Soul Center for BioInformation and BioElectronics and the IBM SUR program for providing research and computing facilities..

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