Dependent shrink for Petri net models of signaling pathways

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Abstract. Retention-free Petri net has been used in modeling of signaling pathways, which is a timed Petri net such that total input and total output token flows are equivalent at any place. Previously we have investigated the dependency of transitions in retention-free Petri net. In this paper, we introduce a modeling method for signaling pathway by using Petri net, giving properties of retention-freeness by considering arc weight. Based on the obtained properties, we propose an algorithm to find shrinkable transitions and to shrink them into a single transition. This algorithm eventually provides a set of transitions whose firing frequencies are dependent. As an example, we apply the algorithm to IL-3 signaling pathway Petri net model to show the usefulness of our proposed algorithm.

Keywords: signaling pathway, Petri net, retention-free Petri net, dependent shrink

1 Introduction

Li et al. [1] have proposed a qualitative modeling method by paying attention to the molecular interactions and mechanisms using discrete Petri nets. Furthermore, Miwa et al. [2] modeled it with timed Petri net, which is an extended Petri net on the concept of time, proposing a method to have firing frequency conditional expressions based on its structure information. At the same time, they introduced "retention-free" Petri net for defining smooth signal flows in signaling pathways.

In Petri net model of signaling pathway, firing frequency of each transition should be measured by biological experiments. However, such biological data of reactions are very few. As a method to cope with this problem, Murakami et al. [3] proposed an approach to check the retention-freeness of a given Petri net based on firing frequencies of transitions of this Petri net. According to this method, Matsumoto et al. [4] formally described the concept of dependent shrink after giving formal definitions of dependent subnet. Dependent shrink is a concept to express a dependent subnet which is shrunk into a single transition.

Fig. 1. Elements of Petri nets

The advantage of this concept is that all the firing frequencies of transitions in the subnet can be computationally obtained from the firing frequency of that shrunk transition. Namely, by only getting the reaction speed of a reaction that corresponds to that shrunk transition, all other reaction speeds in dependent subnet can be estimated by the proposed procedure in this paper.

In this paper we propose an algorithm to do equivalent transformation for retention-free Petri nets. Concretely, we first classify dependent shrink pattern according to the patterns of input and output transitions of a place and then perform the dependent shrink operations of the patterns. Finally, we reconstruct the Petri net based on the dependent shrink result.

2 Basic Definitions and Properties

In this section, we briefly give the necessary definitions and properties of Petri nets. For detailed definitions the reader is suggested to refer to [5].

Definition 1. *A Petri net denoted as* $PN = (T, P, E, \alpha, \beta)$ *that is a bipartite graph, where* $E = E^+ \cup E^-$ *and*

- T*: a set of transitions* $\{t_1, t_2, \cdots, t_{|T|}\}$
- P*: a set of places* $\{p_1, p_2, \cdots, p_{|P|}\}$
- E^+*: a set of arcs from transitions to places* $e = (t, p)$
- E^-*: a set of arcs from places to transitions* $e = (p, t)$
- α_e*: is the weight of arc* $e = (p, t)$
- β_e*: is the weight of arc* $e = (t, p)$ □

Definition 2. *Let* PN *be a Petri net*

1. $^\bullet t$ $(t^\bullet)$ *is the set of input (or output) places of* t*, and* $^\bullet p$ $(p^\bullet)$ *is the set of input (or output) transitions of* p.
2. *A transition without input arc is called source transition and the set of source transitions are denoted by* $T_{sour} = \{t_1^{sour}, \cdots, t_a^{sour}\}(a \geq 1)$.
3. *A transition without output arc is called sink transition and the set of sink transitions is denoted by* $T_{sink} = \{t_1^{sink}, \cdots, t_b^{sink}\}(b \geq 1)$.
4. *A transition* t *is called* $P_s - synchronous$ *transition if there exists a set of input places* P_s *that for any* $p \in P_s$, $p^\bullet = \{t\}$ *holds, and is defined by* $T_{sync} = \{t_1^{sync}, \cdots, t_c^{sync}\}(c \geq 1)$.

5. *A place can hold a positive integer that represents a number of tokens. An assignment of tokens in places expressed in form of a vector M is called a marking, which varies during the execution of a Petri net. Given with an initial marking M_0, the Petri net is called Marked Petri net and denoted by $MPN = (PN, M_o)$.* □

Fig. 2 shows source(i) and sink(ii) transition and Fig. 3 shows synchronous transitions. Note that, we use discrete Petri nets in this paper.

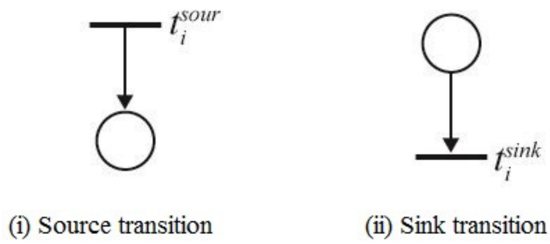

Fig. 2. Source and sink transition

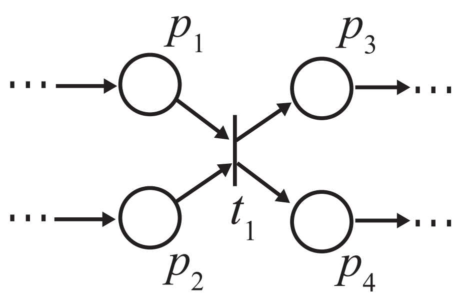

Fig. 3. Synchronous transition

2.1 Modeling rules

Li et al. [1] gave the following modeling rules for signaling pathways based on Petri net representation.

1. Places denote static elements including chemical compounds, conditions, states, substances, and cellular organelles participating in the biological pathways. Tokens indicate the presence of these elements. The number of

tokens can be regarded as a representation of the amount of chemical substances. Current assignment of tokens to the places is expressed in form of a vector, namely a *marking* as defined above.

2. Transitions denote active elements including chemical reactions, events, actions, conversions, and catalyzed reactions. A transition fires by taking off tokens from its individual input places and creating new tokens that are distributed to its output places if its input places has at least as many tokens in it as arc weight from the place to the transition.
3. Directed arcs connecting the places and the transitions represent the relations between corresponding static elements and active elements. Arc weights α and β (defined in Definition 1) describe the quantities of substances required before and after a reaction, respectively. Especially in case of modeling a chemical reaction, arc weights represent quantities given by stoichiometric equations of the reaction itself. Note that, weight of an arc is omitted if the weight is 1.
4. Since an enzyme itself plays a role of catalyzer in biological pathways and there occurs no consumption in biochemical reactions, an enzyme is exceptionally modeled in Definition 3 below.
5. An inhibition function in biological pathways is modeled by an inhibitor arc.

Definition 3. [1] *An enzyme in a biological pathway is modeled by a place, called enzyme place, as shown in Fig. 4.*

1. *Enzyme place p_i has a self-loop with the same weight connected from and to transition t_s. Once an enzyme place is occupied by a token, the token will return to the place again to keep the firable state, if the transition t_s is fired.*
2. *Let t_p and t_d denote a token provider of p_i and a sink output transition of p_i, respectively, where the firing of t_p represents an enzyme activation reaction and the firing of t_d implies a small natural degradation in a biological pathway. p_i holds up token(s) after firing transition t_p and the weights of the arcs satisfy $\alpha(p_i, t_d) \ll \alpha(p_i, t_s)$.* □

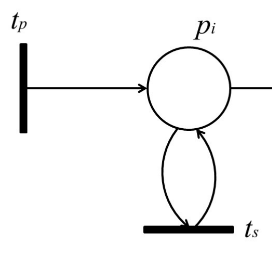

Fig. 4. An enzyme place in Petri net model

[Firing rule of Petri net] A transition t is firable if each input place p_I of PN has at least α_e tokens, where α_e denotes the weight of an arc $e = (p_I, t)$. Firing of a transition t removes α_e tokens from each input place p_I of t and deposit $\beta_e(e = (t, p_O))$ tokens to each output place p_O of t, where β_e denotes the weight of an arc $e = (t, p_O)$. A source transition is always firable.

Definition 4. *A timed Petri net TPN is defined by $TPN = (PN, D)$, where D is a set of positive number expressing firing delay times (or delay time for short) of transitions in T.* □

[Firing rule of timed Petri nets] (i) If the firing of a transition t_i is decided, tokens required for the firing are reserved. We call these tokens as reserved tokens. (ii) When the delay time d_i of t_i passed, t_i fires to remove the reserved tokens from the input places of t_i and put non-reserved tokens into the output places of t_i. In a timed Petri net, firing times of a transition t_i per unit time is called *firing frequency* f_i. $\overline{f_i}$ represents the maximum firing frequency of t_i. The delay time d_i of t_i is given by the reciprocal of $\overline{f_i}$.

Definition 5. [2] *With the firing of transition t_I, token amounts flowed into place p per unit time is called "input token-flow", and is denoted by $TF_{t_I,p}$. On the other hand, with the firing of transition t_O, token amounts flowed out of place p per unit time is called "output token-flow", and is denoted by TF_{p,t_O}. $TF_{t_I,p}$ and TF_{p,t_O} (shown in Fig. 5) are defined by following equations, respectively:*

$$TF_{t_I,p} = f_I \cdot \beta_I \tag{1}$$
$$TF_{p,t_O} = f_O \cdot \alpha_O, \tag{2}$$

where f_I and f_O are firing frequencies of t_I and t_O, respectively; β_I and α_O are the weights of $e = (t_I, p)$ and $e = (p, t_O)$, respectively. □

Based on this definition, the following equation hold.

Proposition 1. [2] *Let p be a place with input transitions $\{t_{I_i} | t_{I_i} \in {}^\bullet p\}$ and out put transitions $\{t_{O_j} | t_{O_j} \in p^\bullet\}$. Then $\sum_{i=1}^{m} TF_{t_{I_i},p}$ and $\sum_{j=1}^{n} TF_{p,t_{O_j}}$ are the total input token-flow and the total output token-flow for place p, respectively. Furthermore, when firing frequency f take the maximum firing rate $\overline{f}$, input token-flow $TF_{t_I,p}$ and output token flow TF_{p,t_O} become the maximum, $\overline{FT_{t_I,p}}$ and $\overline{FT_{p,t_O}}$, respectively. These maximum token-flows satisfy following equations.*

$$\sum_{i=1}^{m} TF_{t_{I_i},p} \leq \sum_{i=1}^{m} \overline{FT_{t_{I_i},p}} \tag{3}$$
$$\sum_{j=1}^{n} TF_{p,t_{O_j}} \leq \sum_{j=1}^{n} \overline{FT_{p,t_{O_j}}} \tag{4}$$

□

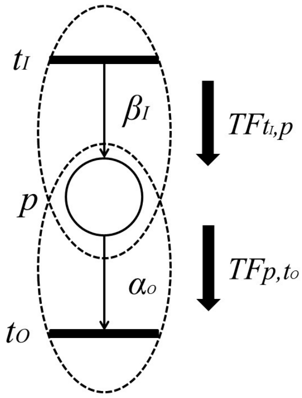

Fig. 5. Token flows

The following requirement is trivial.

Proposition 2. [2] *In a timed Petri net, a total output token-flow is not more than a total input token-flow for each place p:*

$$\sum_{i=1}^{m} TF_{t_{I_i},p} \geq \sum_{j=1}^{n} TF_{p,t_{O_j}}, \tag{5}$$

□

Definition 6. [2] *A timed Petri net TPN is called Retention-free Petri net (RFPN) (satisfying Proposition1) if a total input token-flow and a total output token-flow are equivalent at any place of TPN; that is,*

$$TF_{t_{I_i},p} = TF_{p,t_{O_j}} \tag{6}$$

□

Definition 7. [3] *Each unreserved token deposited to input place p is assigned to be reserved by the transition t_{O_j} that satisfies the following expression:*

$$\{(\frac{c_j}{\alpha_j})/\sum_{k=1}^{n}(\frac{c_k}{\alpha_k}) - s_j\} =$$

$$min\{(\frac{c_i}{\alpha_i})/\sum_{k=1}^{n}(\frac{c_k}{\alpha_k}) - s_i \mid i = 1, 2, \cdots, n\} \tag{7}$$

When the number of reserved tokens of t_{O_j} is not less than a required token number for the firing, the firing of t_{O_j} is decided. After the delay time d_{O_j} of t_{O_j} passed, t_{O_j} fires to remove the reserved tokens from the input place of t_{O_j} and deposit unreserved tokens into the output places of t_{O_j}. □

In the above expression (7), s_j is the firing probability of transition t_{O_j}, which represents the proportion of the firing frequency of each transition to the total firing frequencies of the transitions in conflict. A probability s_j is assigned to corresponding transition t_{O_j}, which is given as a constant in advance according to the event. A variable c is an accumulated number of tokens that t_{O_j} has been reserved so far, and thus $\lfloor \frac{c_j}{\alpha_j} \rfloor$ represents the number of firing times of transition t_{O_j} from the beginning.

Expression (7) is designed to reserve the token to such a transition t_i that has the largest difference between calculated firing probability $\frac{c_j}{\alpha_j} / \sum_{k=1}^{n} \frac{c_k}{\alpha_k}$ and given firing probability s_j among all the transitions in conflict.

Definition 8. [2] *If output transitions of p are in conflict, the maximum firing frequency of t_{O_j} must satisfy the following expression:*

$$\frac{s_j \cdot \alpha_j}{\sum_{k=1}^{n} s_k \cdot \alpha_k} \cdot \sum_{i=1}^{m} TF_{t_{I_i},p} = f_{O_j} \cdot \alpha_j, \tag{8}$$

where α_j is the weight of $e = (p, t_{O_j})$ and s_j is the firing probability of t_{O_j}. $\frac{s_j \cdot \alpha_j}{\sum_{k=1}^{n} s_k \cdot \alpha_k}$ represents the ratio of the token amount deposited to t_{O_j} to the total token-flow from p to each output transition $p^\bullet$. □

3 Shrink of Dependent Subnet

The equation (8) shows a relationship of firing frequency about input and output transitions, which are dependent each other. Based on this dependency, a set of transitions can be obtained, by which firing frequencies of all transitions in a Petri net model can be calculated. Note that the transitions in the set determined in this way correspond to the reactions whose speeds need to be measured by biological experiments.

3.1 Dependent subnet

Dependent subnet, obtained as follows, is a Petri net induced from a set of transitions which are dependent on each other.

Definition 9. [4] *If firing frequency of a transition t is determined by the firing frequency of transition α, this transition is called α-dependent transition. The subnet induced by the set of α-dependent transitions and transition α is called α-dependent subnet, denoted by PN_α.* □

Definition 10. [4] *For a given set A of transitions, A-dependent transition is a set of transitions whose firing frequencies are determined by the firing frequencies of transitions in A. The subnet induced by A-dependent transition and A is called A-dependent subnet, denoted by PN_A.* □

3.2 Dependent shrink

For a set of α-dependent transition T, dependent shrink is a procedure to substitute the set of α-dependent transition T to a single transition t.

Definition 11. [4] *If two transitions t_i and t_j exist are dependent each other, these two transitions can be shrunk into a single transition.* □

Note that the proofs of the following propositions are omitted to save the space of this paper.

Proposition 3. *As shown in Fig. 6, if a place p has one input transition t_I and one output transition t_O, these two transitions can be shrunk into a single transition t', where the weight of new input arc $\alpha' = \alpha_1$, and the weight of new output arc $\beta' = \beta_2 \cdot \frac{\beta_1}{\alpha_2}$.* □

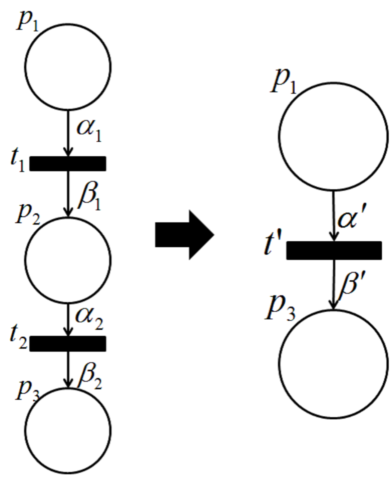

Fig. 6. Markgraph

Proposition 4. *As shown in Fig. 7, if place p has multiple output transitions $T_O = \{t_{O.1}, t_{O.2}, \cdots, t_{O.k}\}$, T_O can be shrink into a single transition t', where* *the weights of input arc α' and new output arc β' are defined by the following formulas;*

$$\alpha' = \frac{s_{O.1} \cdot \alpha_1 + s_{O.2} \cdot \alpha_2 + \cdots + s_{O.k} \cdot \alpha_k}{s_{O.1}} \tag{9}$$

$$\begin{aligned} \beta'_1 &= s_{O.1} \cdot \beta_1 \\ \beta'_2 &= s_{O.2} \cdot \beta_2 \\ &\vdots \\ \beta'_k &= s_{O.k} \cdot \beta_k \end{aligned} \tag{10}$$

□

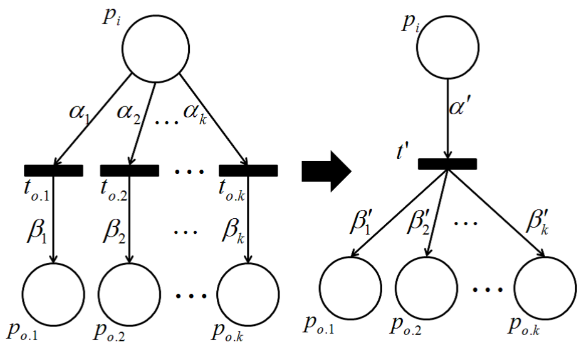

Fig. 7. Conflict structure

Proposition 5. *As shown is Fig. 8, if place p has multiple output transitions of two types, with self-loop $T_l = \{t_{l.1}, t_{l.2}, \cdots, t_{l.k}\}$ and without self-loop $T_O = \{t_{O.1}, t_{O.2}, \cdots, t_{O.k}\}$,$T_l$ and T_O can be shrunk into a single transition, where input arc α' and new output arc β' are defined by the following formulas;*

$$\begin{aligned} \alpha' = \Big(&(s_{O.1} \cdot \alpha_{O.1} + s_{O.2} \cdot \alpha_{O.2} + \cdots + s_{l.k2} \cdot \alpha_{l.k2}) \\ &-(s_{l.1} \cdot \beta_{l.1} + s_{l.2} \cdot \beta_{l.2} + \cdots + s_{l.k2} \cdot \beta_{l.k2})\Big)/s_{O.1} \end{aligned} \tag{11}$$

$$\begin{aligned} \beta'_1 &= s_{O.1} \cdot \beta_1 \\ \beta'_2 &= s_{O.2} \cdot \beta_2 \\ &\vdots \\ \beta'_{k2} &= s_{l.k2} \cdot \beta_{k2} \end{aligned} \tag{12}$$

Note that, in equation (11) $\alpha' > 0$ *should be held.* □

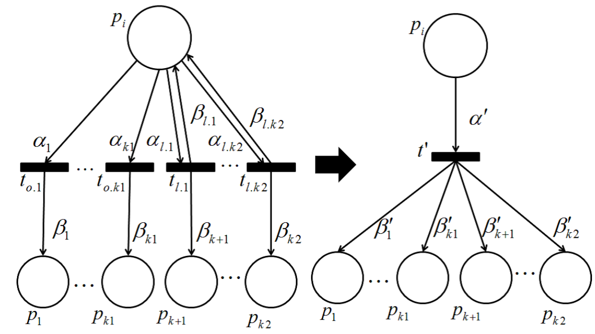

Fig. 8. Self-loop structure

4 Dependent Shrink Algorithm and an Example

In this section, we propose a dependent shrink algorithm based on the dependent shrink method. Furthermore, we apply this algorithm to IL-3 signaling pathway Petri net model (shown in Fig. 10), which is transformed from IL-3 phenomenon model (shown in Fig. 9) obtained from the website [10]. Note that IL-3 is a glycoprotein and is known to be involved in the immune response [6–9].

4.1 Outline of shrink process

The shrink process of dependent subnet can be briefly described as follows:

step1: *Shrink of self loop structure*
A place randomly selected from a Petri net is stored in a queue after the conversion of the self-loops and the structures of conflict of it.

step2: *Shrink of conflict structure*
If a place picked up from the queue has a self-loop or a transition of one-input and one-output, this place is shrunk.

step3: *Changing weight of the input arc*
If shrunk Petri net has a multiple input place, it re-stores to the queue, performing the above step2 again. This procedure is repeated until the queue becomes empty.

The variables used in the algorithm are as follows:

- PN_0 is a given signaling pathway Petri net model constituted by $T_0, P_0, and\ E_0$.
- N is a variable that stores Petri net after dependent shrink, constituted by $T, P, andE$.
- Q is a queue.
- X is a set of place initially set as a given place set P_0.
- f is a flag, by which dependent shrink pattern is determined.

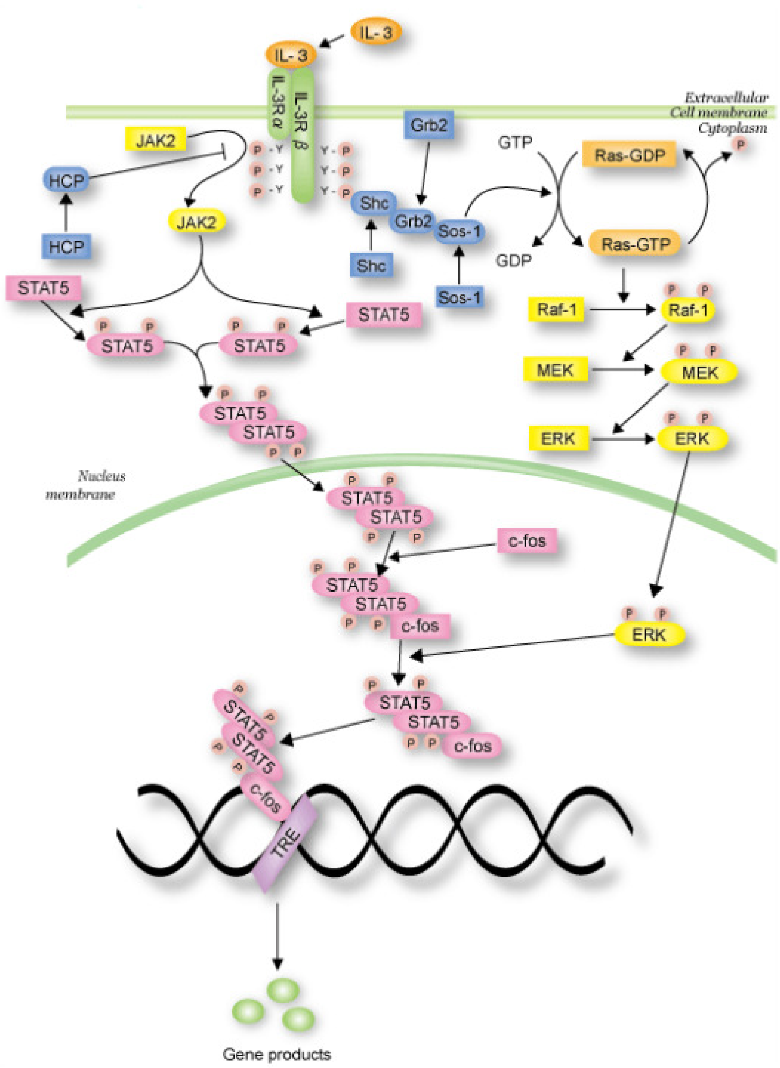

Fig. 9. IL-3 phenomenon model

4.2 Dependent shrink algorithm

The following algorithm is used to shrink dependent subnets into a single transition in order to find transitions with interdependent firing frequency.

Algorithm: Dependent shrink
Input: $PN_0 = (T_0, P_0, E_0)$
Output: Shrunk Petri net $N = (T, P, E)$

Main(PN_0)
1°$T \leftarrow T_0$, $P \leftarrow P_0$, $E \leftarrow E_0$, $N \leftarrow (T, P, E)$
2°$X \leftarrow P$, $Q \leftarrow \phi$
3°**while** $(X \neq \phi)$
  Pull an element x from $X(X \leftarrow X - \{x\})$
  Enqueue(Q, x)
  Shrink1(N, x)
4°**Shrink2**(N, Q)
Shrink1(N, x)
1°**if** $(|{}^{\bullet}x \cap x^{\bullet}| \geq 1)$ **then**
    $f \leftarrow 1$
    Arcweight(N, x, f)
2°**if** $(|x^{\bullet}| \geq 2)$ **then**
  $f \leftarrow 2$
  Arcweight(N, x, f)
Shrink2(N, Q)
1°**while** $(|Q| \geq 1)$
  $x \leftarrow$ **Dequeue**(Q)
    if $(|{}^{\bullet}x \cap x^{\bullet}| \geq 1)$ **then**
      $f \leftarrow 1$
      Enqueue(Q, x)
    else if $(|{}^{\bullet}x| = |x^{\bullet}| = 1)$ **then**
      $f \leftarrow 3$
    else if $(|{}^{\bullet}x| \geq 2)$ **then**
      $f \leftarrow 4$
      Enqueue(Q, x)
    if $(f \neq 4)$ **then**
      Arcweight(N, x, f)
Arcweight(N, x, f)
1°**if** $(f = 1)$ **then**
  $\forall t' \in {}^{\bullet}x \cap x^{\bullet}$
    $\alpha(x, t') = \alpha(x, t') - \beta(t', x)$
    if $(\alpha(x, t') < 0)$ **then**
      $\beta(t', x) = |\alpha(x, t')|$
      $E \leftarrow E - \{(x, t')\}$
    else if $(\alpha(x, t') > 0)$ **then**
      $E \leftarrow E - \{(t', x)\}$
    else if $(\alpha(x, t') = 0)$ **then**
      $E \leftarrow E - \{(t', x), (x, t')\}$
2°**else if** $(f = 2)$ **then**
  $T \leftarrow T \cup \{t'\}$
  $E \leftarrow E \cup \{(x, t')\} \cup \{(u, t') | u \in {}^{\bullet}z, z \in x^{\bullet}\} \cup \{(t', v) | v \in z^{\bullet}, z \in x^{\bullet}\}$
  Choose $z' \in x^{\bullet}$.
  $\forall z \in x^{\bullet} - \{t'\}$
    $\alpha(x, t') = \alpha(x, t') + s(z) * \alpha(x, z)$

$\forall v \in z^\bullet, z \in x^\bullet$
$\beta(t', v) = s(z) * \beta(z, v)$
$\forall u \in {}^\bullet z, z \in x^\bullet$
$\alpha(u, t') = s(z) * \alpha(u, z)/s(z')$
$\alpha(x, t') = \alpha(x, t')/s(z')$
$T \leftarrow T - \{z | z \in x^\bullet - \{t'\}\}$
3°**else if** $(f = 3)$ **then**
$T \leftarrow T \cup \{t'\}$
Let z_i, z_o be $\{z_i\} = {}^\bullet x$, $\{z_o\} = x^\bullet$ (due to $|{}^\bullet x| = |x^\bullet| = 1$).
$E \leftarrow E \cup \{(u, t') | u \in {}^\bullet z_i \cup {}^\bullet z_o\} \cup \{(t', v) | v \in z_i^\bullet \cup z_o^\bullet\}$
$\forall u \in {}^\bullet z_i$
$\alpha(u, t') = \alpha(u, z_i)$
$\forall u \in z_i{}^\bullet$
$\beta(t', u) = \beta(z_i, u)$
$\forall v \in {}^\bullet z_o$
$\alpha(v, t') = \beta(z_i, x) * \alpha(v, z_o)/\alpha(x, z_o)$
$\forall v \in z_o{}^\bullet$
$\beta(t', v) = \beta(z_i, x) * \beta(z_o, v)/\alpha(x, z_o)$
$T \leftarrow T - \{z_i | z_i \in {}^\bullet x\} - \{z_o | z_o \in x^\bullet\}$
$P \leftarrow X - \{x\}$

When the above algorithm is applied, a dependent subnet, say S, is transformed into a single transition, say t_S. Obviously S and t_S possess the same input and output places. As the result, for each input place, p, the tokens flowed out of p per unit time are the same before and after dependent shrink. Similarly, the tokens flowed into an output place per unit time are the same.

4.3 An Example for Signaling Pathway Petri Net Model

Here we give an example to show an application of our proposed algorithm. The algorithm is applied to dependent shrink for IL-3 Petri net model (see Fig.10 (a)), obtained from the website [10]. As the result, the original IL-3 Petri net model shown in Fig.10 (a) is shrunk into Fig.10 (c). This means that the firing frequency of all transition in Fig.10 (a) are denpendent each other. In the intermediate shrunk net (see Fig. 10 (b)), by assuming the firing frequency of the input transition f_I be 1, the weights of input and output arcs be $\frac{1}{2}$ and 1, respectively, then the firing frequency of output transition f_O is $\frac{1}{2}$. In this way, we can calculate all of the firing frequency of transitions in the IL-3 Petri net model from one firing frequency in this model.

5 Conclusion

In this paper, after giving basic definitions of Petri net and modeling method, we introduced dependent shrink method and its properties to find dependent subnet. Further, we designed an algorithm of dependent shrink and applied it to IL-3 signaling pathway Petri net model as an example.

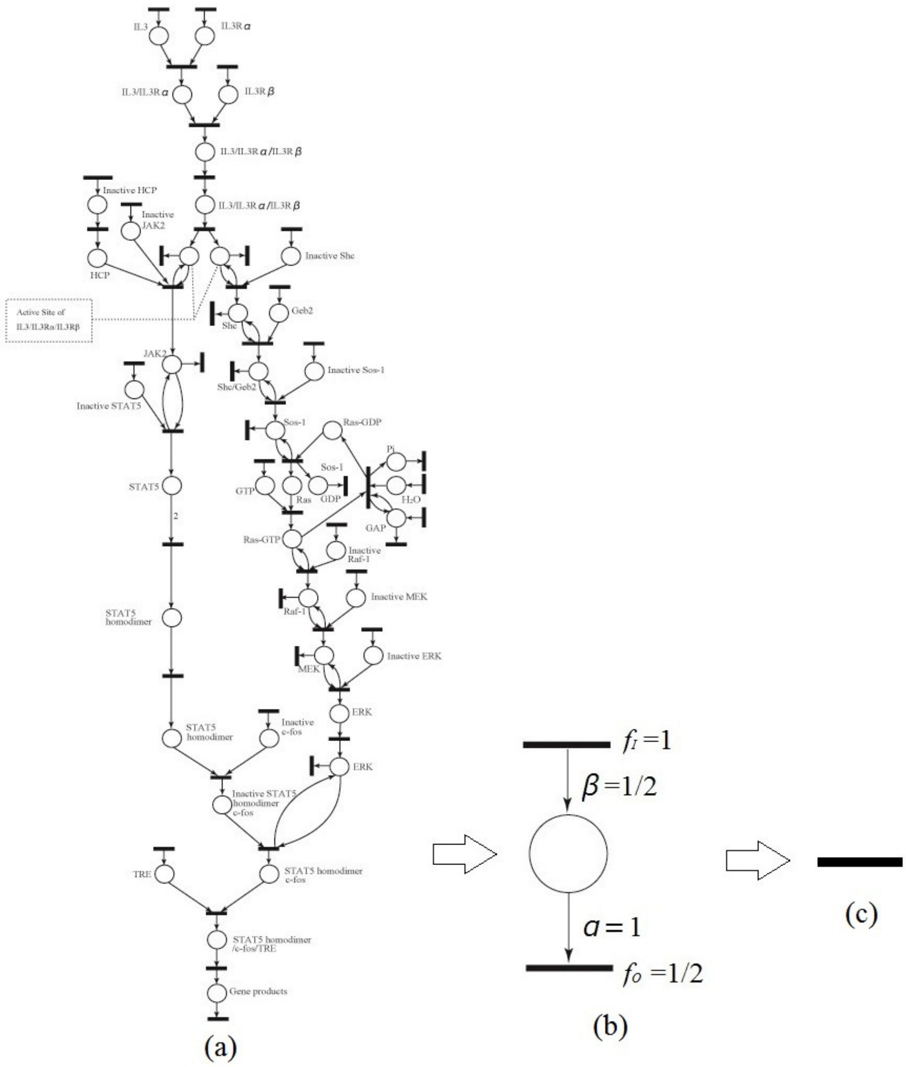

Fig. 10. Shrunk IL-3 Petri net model

By applying the dependent shrink algorithm, IL-3 Petri net model is converted to a simple model, with which we could find the transitions which are dependent each other.

This algorithm allows us to obtain firing frequencies of all transitions in a dependent subnet only by measuring reactions corresponding to the transitions by biological experiments in the simple model.

In this paper, we only discussed discrete Petri nets. By extending transitions to include firing speed, it is possible to extend our method to continuous Petri nets.

As a future work, we need to improve our algorithm so that it can indicate transitions corresponding to measurable reactions by biological experiment. Also the uniqueness of our algorithm needs to be investigated.

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