YAMAGUCHI UNIVERSITY

Dependent Shrink for Petri Net Model of Signaling Pathway

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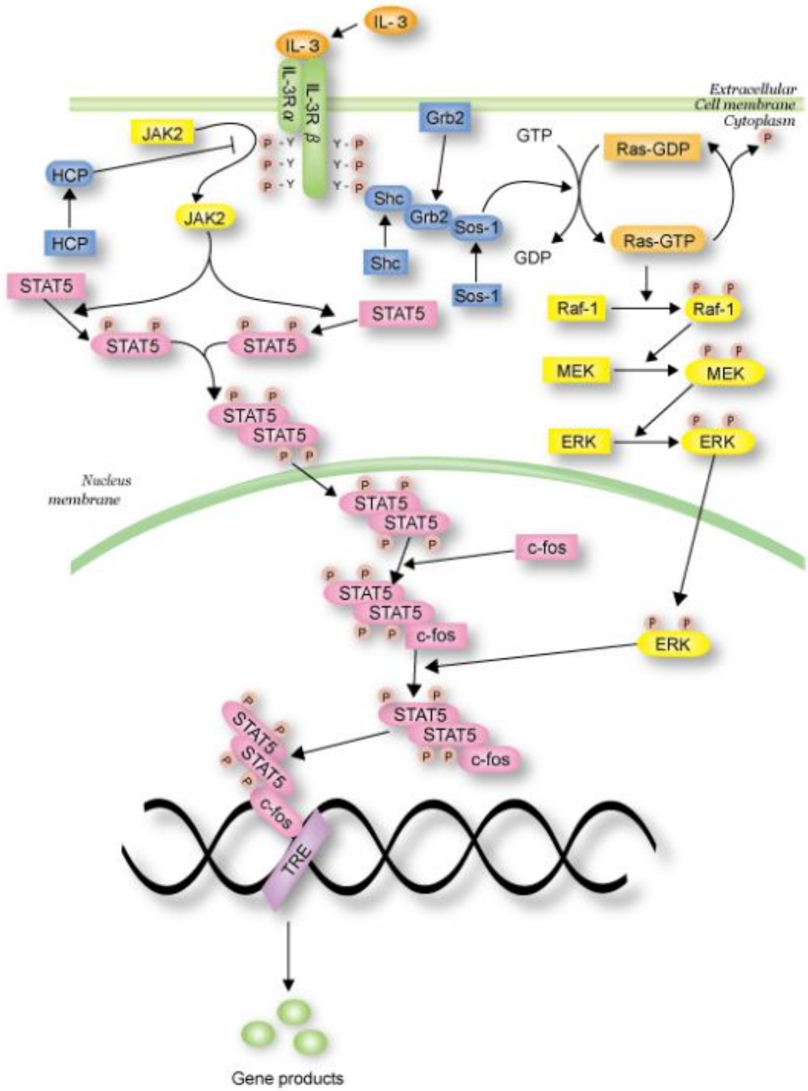
Signaling Pathway

- •Established by the biochemical interactions of proteins and molecules
- •Controls the cell proliferation, differentiation, survival and death
- •IL-3 is involved in the immune response

Structure is too large and complex to analyze by hand

Use signaling pathway modeled by Petri net and simulate it



“http://genome.ib.sci.yamaguchi-u.ac.jp/pnp/w_il3.html”

Modeling by Petri net

- Method of modeling was proposed by Li et al.[1]
- According to this method, we can simulate signaling pathway
- In a signaling pathway Petri net model, firing frequency of each transition should be determined by biological experiments

→However, experimental data is few

- As a method to cope with this problem, Murakami et al. [2] proposed an approach to check the retention-freeness of a given Petri net based on firing frequencies of transition of Petri net

[1]C. Li, S. Suzuki, Q.W. Ge, M. Nakata, H. Matsuno, S. Miyano, ``Structural modeling and analysis of signaling pathways based on Petri nets,'' *it Journal of Bioinformatics and Computational Biology*, Vol.4, No.5, pp.1119-1140, 2006.
[2]Y. Murakami, Q. W. Ge, H. Matsuno, ``Consideration on the token retention-free in timed Petri net model based on the signaling pathway characteristics”, Technical Report of IEICE, Vol. 111, No. 453, MSS 2011-77, pp.29-34, 2012 (In Japanese)

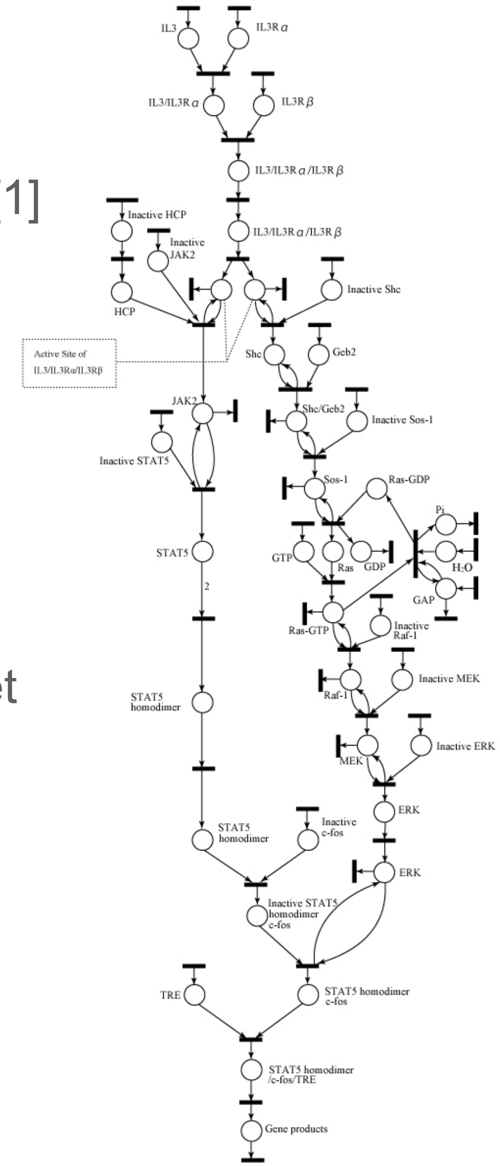


Fig: http://genome.ib.sci.yamaguchi-u.ac.jp/pnp/w_il3.html

Modeling by Petri net

•Matsumoto et al.[3] 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

- Give some properties of dependent shrink
- Propose a dependent shrink algorithm
- Apply the algorithm to IL-3 signaling pathway Petri net model

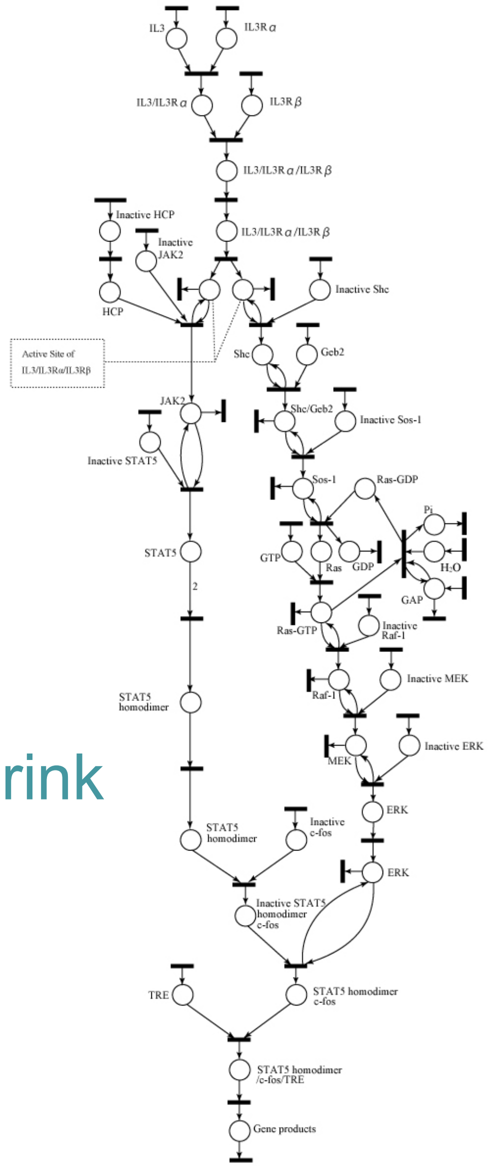


Fig: http://genome.ib.sci.yamaguchi-u.ac.jp/pnp/w_il3.html

[3] T. Matsumoto, Q.W. Ge, H. Matsuno, ``An algorithm for finding dependent subnets in a retention-free Petri net,'' Technical Report of IEICE, MSS2012-50, pp.27-32, 2013 (in Japanese).

2. Petri net

Basic definitions of Petri net

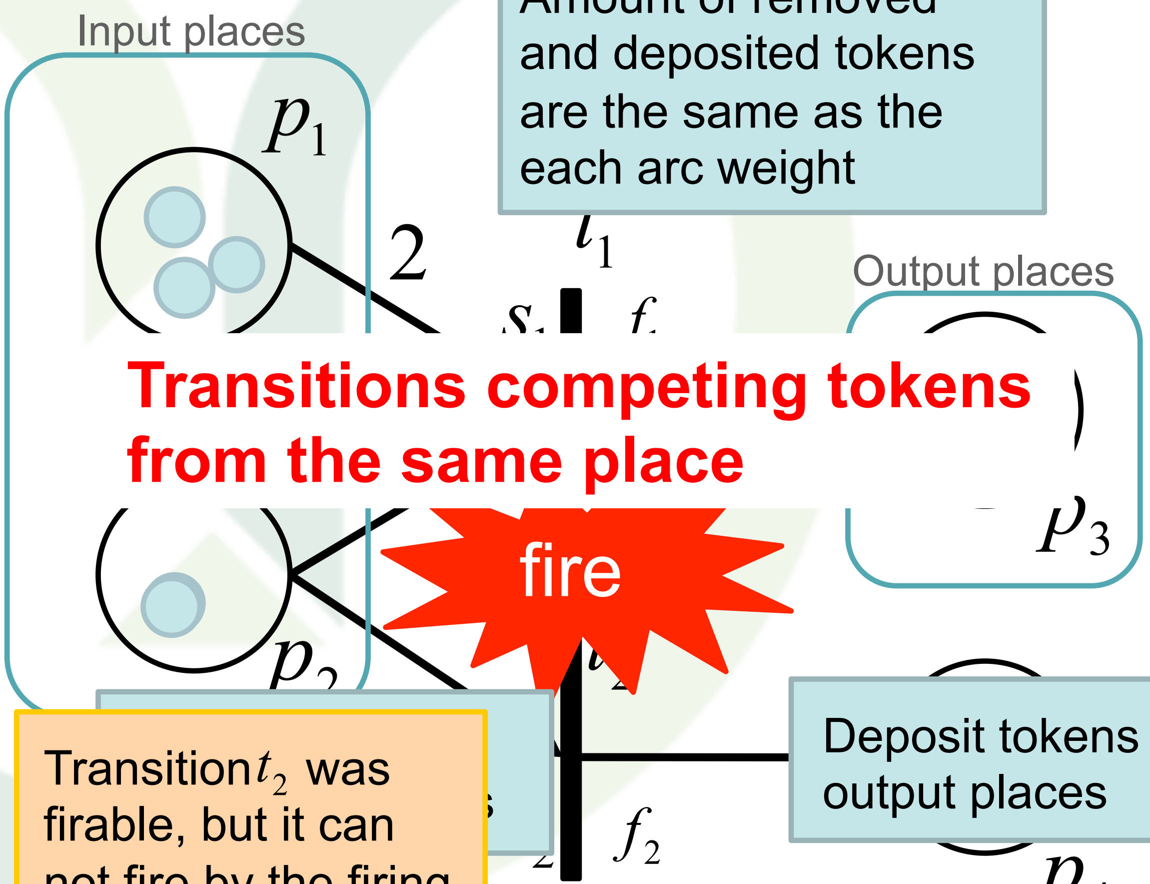
Petri net is bipartite directed graph

place(p)	○	Express the state and condition of system
transition(t)	▬	Express state transitions of system
arc	$\xrightarrow{\omega}$	express relations about connection of transition with place Has weight which express positive integer When the weight is 1, transcription is omitted
token	●	Drawn in place Express the status of each places

2. Petri net

State transition c… e of transition

Amount of removed and deposited tokens are the same as the each arc weight



Transitions competing tokens from the same place

Transition t_2 was firable, but it can not fire by the firing of other transition

Deposit tokens to output places

conflict

Fire times of transition per unit time

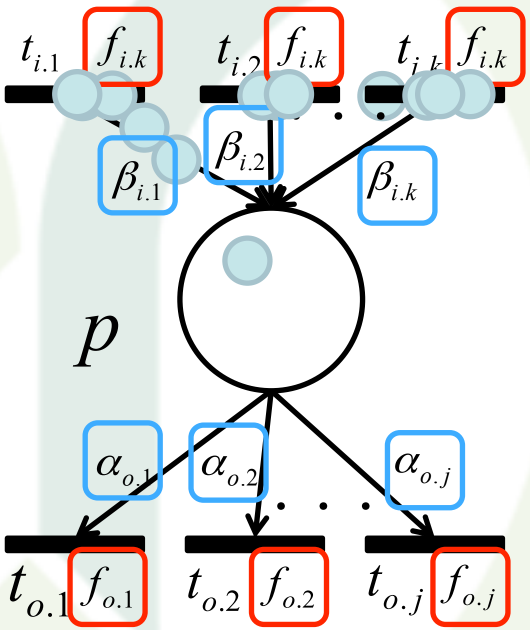
Firing frequency f_1

Firing probability s_1, s_2

$$s_1 : s_2 = f_1 : f_2$$

S is given to be the same as the ratio of the firing frequency

Token flow



Retention of the token to the place represent anomalous in the cell

In order for retention of the token not to be happen, the total input and output token flow must keep equal amounts at any place

Amount of input tokens per unit time

$$f_{i.k} \cdot \beta_{i.k}$$

Amount of output tokens per unit time

$$f_{o.j} \cdot \alpha_{o.j}$$

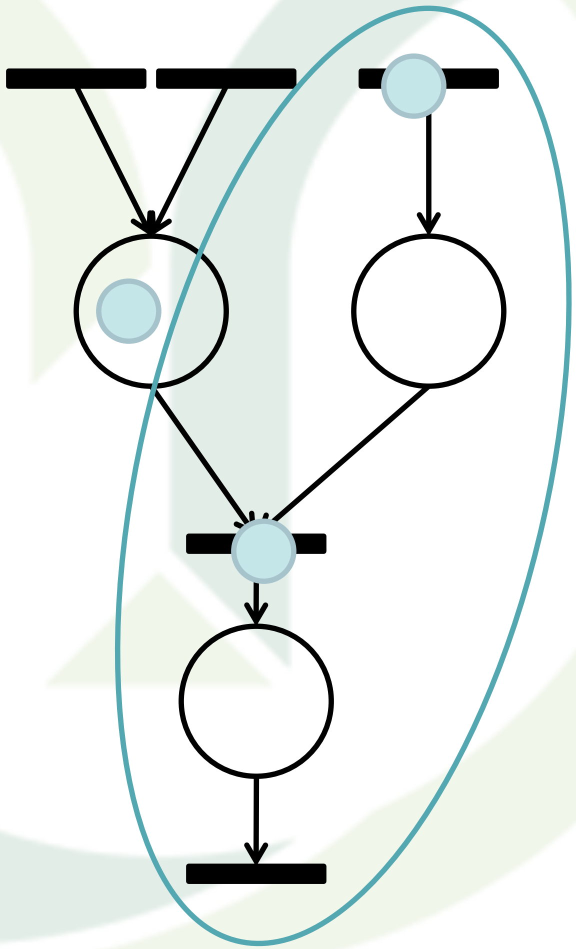
Total

$$\sum_{k=1}^{n} TF_{t_{i.k},p} = \sum_{j=1}^{m} TF_{p,t_{o.j}}$$

Keep equal

Retention-free Petri net

Dependent subnet



Dependent subnet

In retention–free Petri net

The net by which firing rate of all transition is decided uniquely by firing frequency of one transition

All of the transition in dependent subnet are dependent each other

3. Dependent shrink

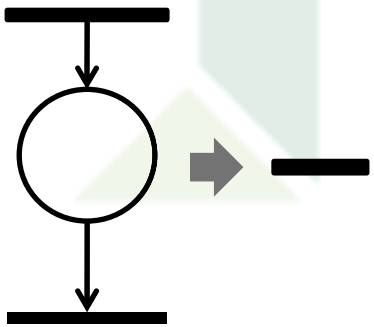
Dependent shrink is a method to find dependent subnet

Definition [3]

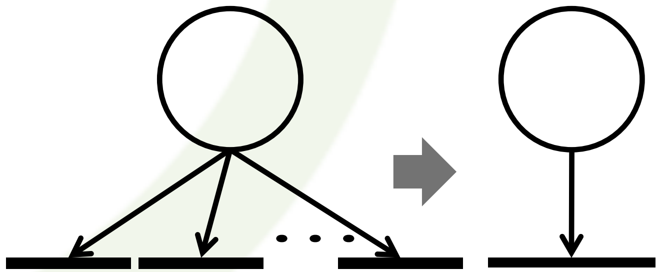
If two transitions t_1 and t_2 are dependent each other,
these two transitions can be shrunk into a single transition

Based on this definition, these three propositions are derived

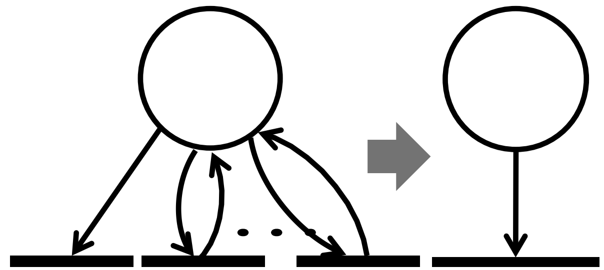
Proposition 1



Proposition 2

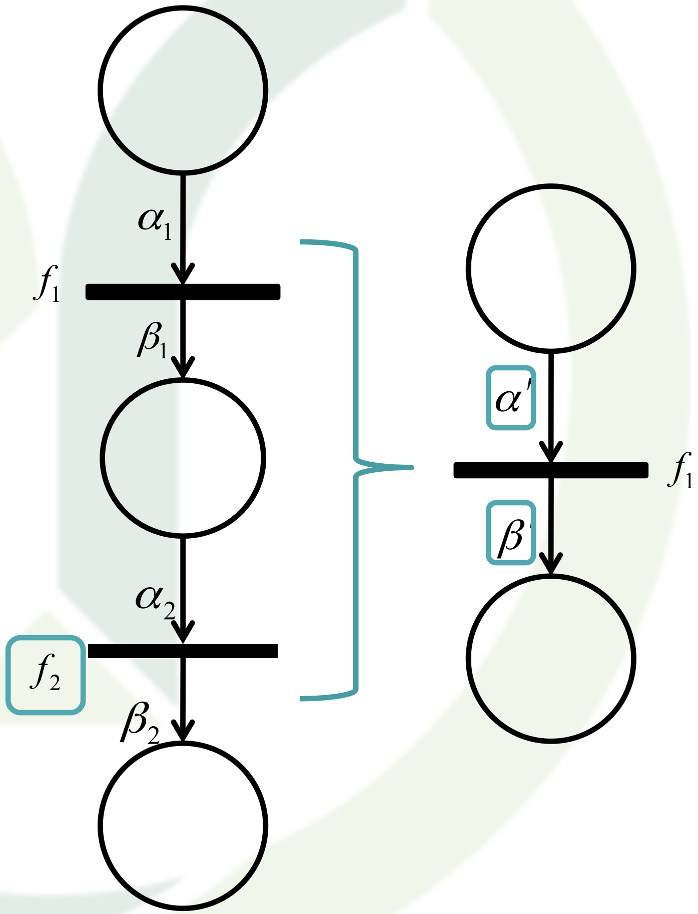


Proposition 3



[3] T. Matsumoto, Q.W. Ge, H. Matsuno, ``An algorithm for finding dependent subnets in a retention-free Petri net,'' Technical Report of IEICE, MSS2012-50, pp.27-32, 2013 (in Japanese).

Proposition 1. One-input one-output



Dependency of firing frequency

$$f_1 \cdot \beta_1 = f_2 \cdot \alpha_2$$

$$f_2 = \frac{\beta_1}{\alpha_2} f_1$$

Changed input arc weight

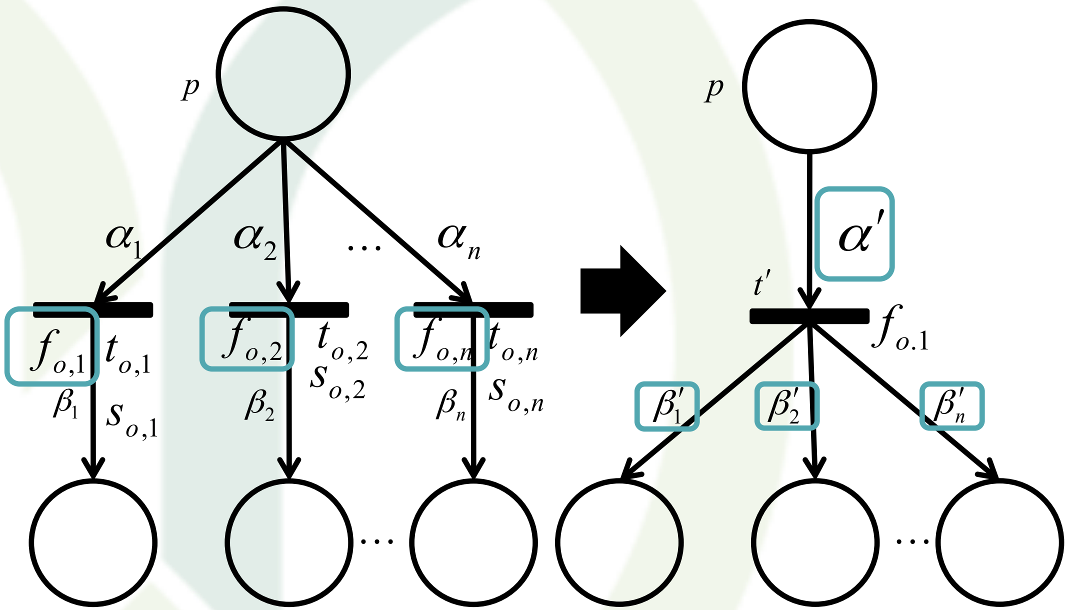
$$\alpha' = \alpha_1$$

Changed output arc weight

$$\beta' = \frac{\beta_1 \cdot \beta_2}{\alpha_2}$$

Proposition 2. Conflict

The firing frequency of each transition is represented by using f_1



Dependency of firing rate

$$f_{o.1}\cdot\frac{s_{o.2}}{s_{o.1}}=f_{o.2}$$

$$f_{o.1}\cdot\frac{s_{o.3}}{s_{o.1}}=f_{o.3}$$

$$\vdots$$

$$f_{o.1}\cdot\frac{s_{o.n}}{s_{o.1}}=f_{o.n}$$

Changed input arc weight

$$\alpha'=\frac{1}{s_{o.1}}(s_{o.1}\cdot\alpha_{o.1}+s_{o.2}\cdot\alpha_{o.2}+\cdots+s_{o.n}\alpha_{o.n})$$

Changed output arc weight

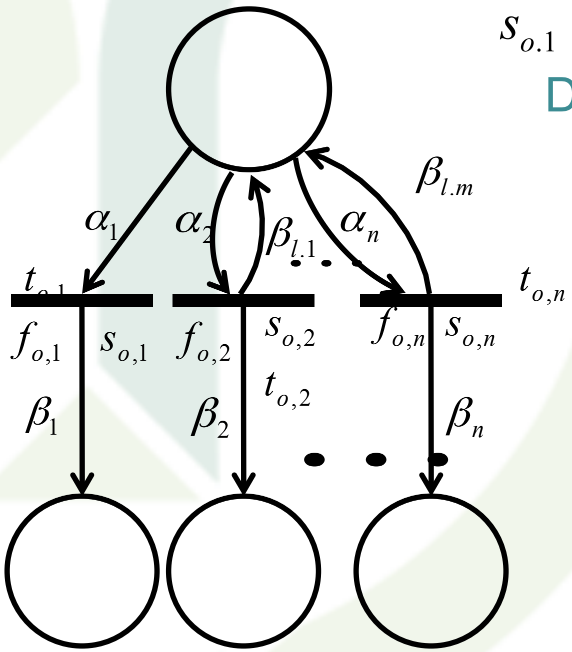
$$\beta_1'=s_{o.1}\cdot\beta_1$$

$$\beta_2'=s_{o.2}\cdot\beta_2$$

$$\vdots$$

$$\beta_n'=s_{o.n}\cdot\beta_n$$

Proposition 3 . Self-loop



Changed input arc weight

Tokens flow in to transitions — Token flowed out from transitions

$$\alpha' = \frac{1}{s_{o.1}}\left(s_{o.1}\cdot\alpha_1 + s_{o.2}\cdot\alpha_2 + \cdots + s_{o.n}\cdot\alpha_n - s_{o.2}\cdot\beta_{l.1} - \cdots - s_{o.n}\cdot\beta_{l.m}\right)$$

Dependency of firing rate

$$f_{o.1}\cdot\frac{s_{o.2}}{s_{o.1}} = f_{o.2}$$

$$f_{o.1}\cdot\frac{s_{o.3}}{s_{o.1}} = f_{o.3}$$

$$\vdots$$

$$f_{o.1}\cdot\frac{s_{o.n}}{s_{o.1}} = f_{o.n}$$

Changed output arc weight

$$\beta_1' = s_{o.1}\cdot\beta_1$$

$$\beta_2' = s_{o.2}\cdot\beta_2$$

$$\vdots$$

$$\beta_n' = s_{o.n}\cdot\beta_n$$

These are the same as proposition 2

Dependent shrink algorithm

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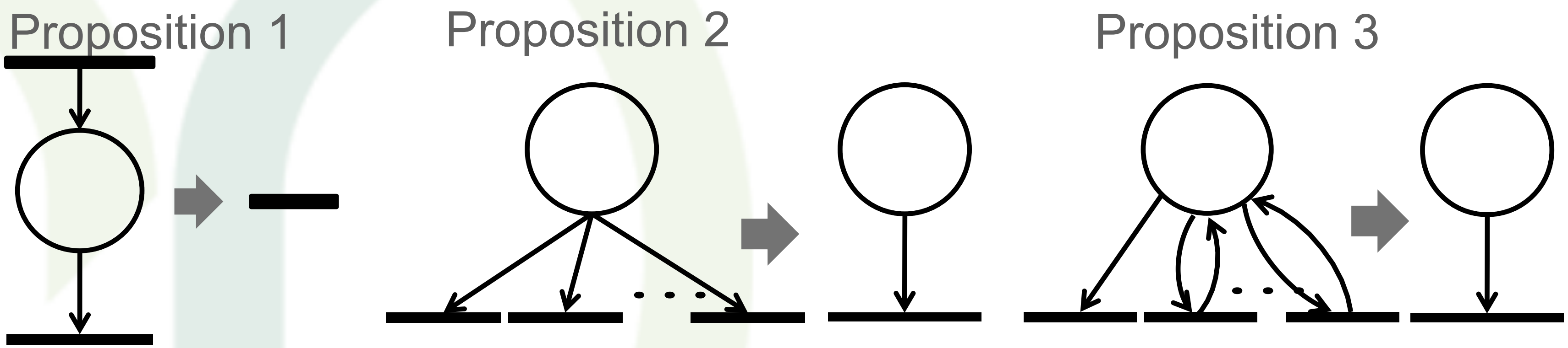
------------------------------------------------------------------------------------------
-
Algorithm: Dependent shrink
Input: PN0 = (T0, P0, E0)
Output: Shrunk Petri net N
------------------------------------------------------------------------------------------
-
Main(PN0)
   1, T ← T0, P ← P0, E ← E0, N ←(T, P, E)
   2, X ← P, Q ← φ
   3, while (X ≠ φ)
                 Pull an element x from X (X ← X – {x})
                 Enqueue(Q, x)
                 Shrink1(N, x)
   4, Shrink2(N, Q)

Shrink1(N, x)
   1, if (|•x ∩ x•|≧1) then
                 f ← 1
                 Arcweight(N, x, f)
   2, if (|x•|≧2) then
                 f ← 2
                 Arcweight(N, x, f)

Shrink2(N, Q)
   1, while (|Q|≧1)
                 x ← Dequeue(Q)
                 if (|•x ∩ x•|≧1) then
                    f ← 1
                    Enqueue(Q, x)
                 else if (|•x|=|x•|=1) then
                    f ← 3
                 else if (|•x|≧2) then
                    f ← 4
                    Enqueue(Q, x)
                 if (f ≠ 4) then
                    Arcweight(N, x, f)
```

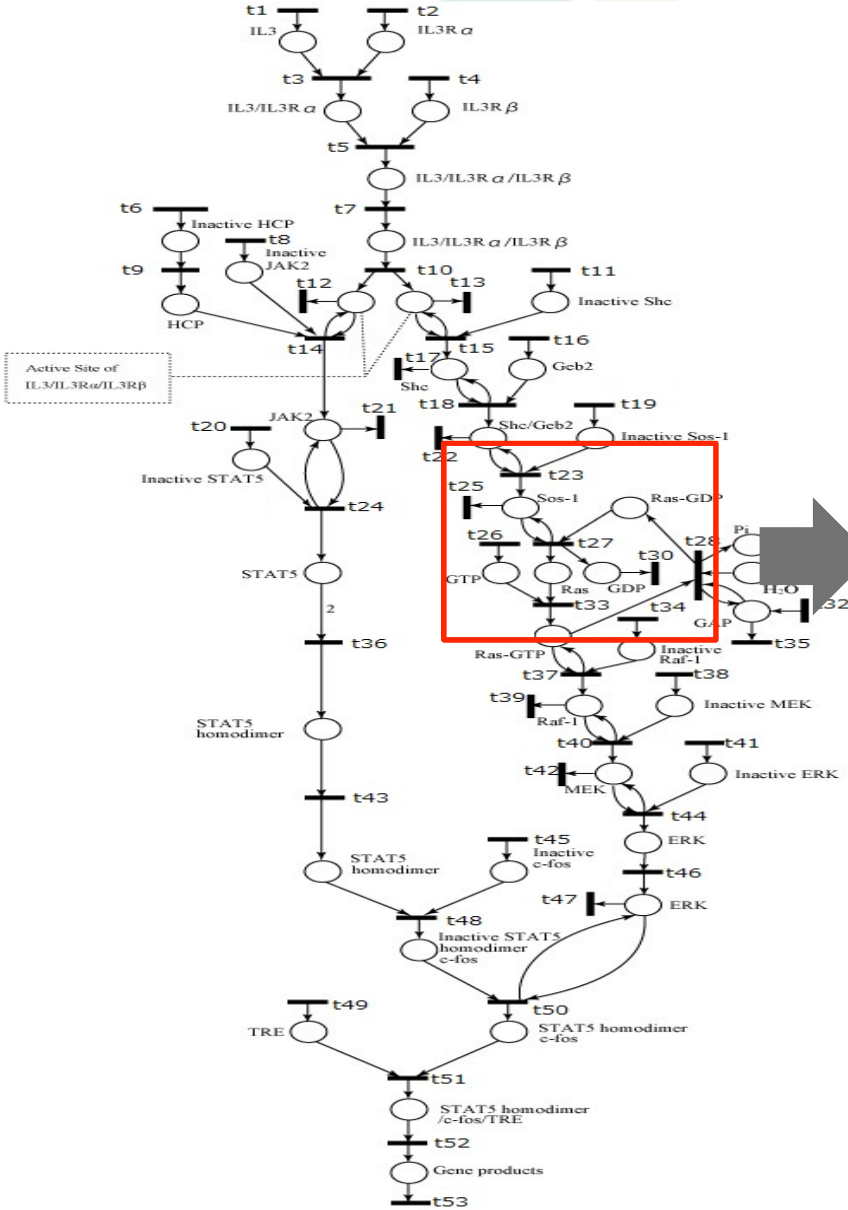
```
Arcweight(N, x, f)
   1, if (f = 1) then
      ∀t' ∈ •x ∩ x•
         α(x, t') = α(x, t') – β(t', x)
         if (α(x, t') < 0) then
            β(t', x) = |α(x, t')|
            E ← E – {(x, t')}
         else if (α(x, t') > 0) then
            E ← E – {(t', x)}
         else if (α(x, t') = 0) then
            E ← E – {(x, t'), (t', x)}
   2, else if (f = 2) then
      T ← T ∪ {t'}
      E ← E ∪ {(x, t') ∪ (u, t')|u ∈ •z, z ∈ x•} ∪ {(t', v)| v ∈ z•, z ∈ x•}
      Choose z' ∈ x•
      ∀z ∈ x• − {t'}
         α(x, t') = α(x, t') + s(z) * α(x, z)
         ∀v ∈ z•, z ∈ x•
            β(t', v) = s(z) * β(z, v)
         ∀u ∈ •z, z ∈ x•
            α(u, t') = s(z) * α(u, z) / s(z')
      α(x, t') = α(x, t') / s(z')
      T ← T – {z| ∀z ∈ x• − {t'}}
   3, else if (f = 3) then
      T ← T ∪ {t'}
      Let z_i, z_o be {z_i} = •x, {z_o} = x• (due to |•x|=|x•|=1).
      E ← E ∪ {(u, t')|u ∈ •z_i ∪ •z_o} ∪ {(t', v)|v ∈ z_i • ∪ z_o •}
      ∀u ∈ •z_i
         α(u, t') = α(u, z_i)
      ∀u ∈ z_i •
         β(t', u) = β(z_i , u)
      ∀v ∈ •z_o
         α(v, t') = β(z_i , x) * α(v, z_o)/ α(x, z_o)
      ∀v ∈ z_o •
         β(t', v) = β(z_i , x) * β(z_o, v)/ α(x, z_o)
      T ← T – {z_i |z_i ∈ •x} – {z_o |z_o ∈ x •}
      P ← X – {x}
```

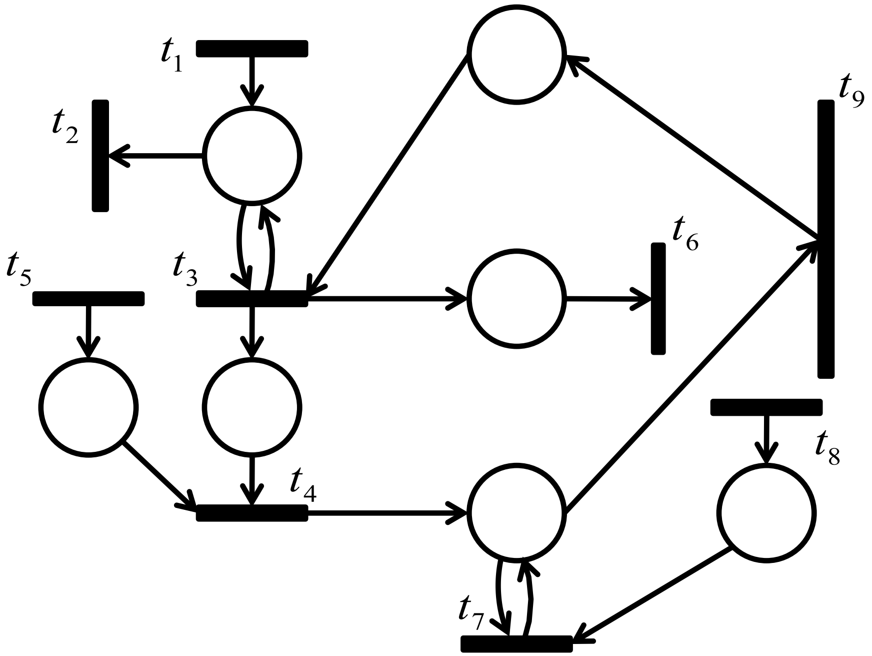
Dependent shrink algorithm



1. Change transitions which have self-loop structure in model
2. Shrink places which have conflict structure
3. Shrink places which have one-input one-output structure

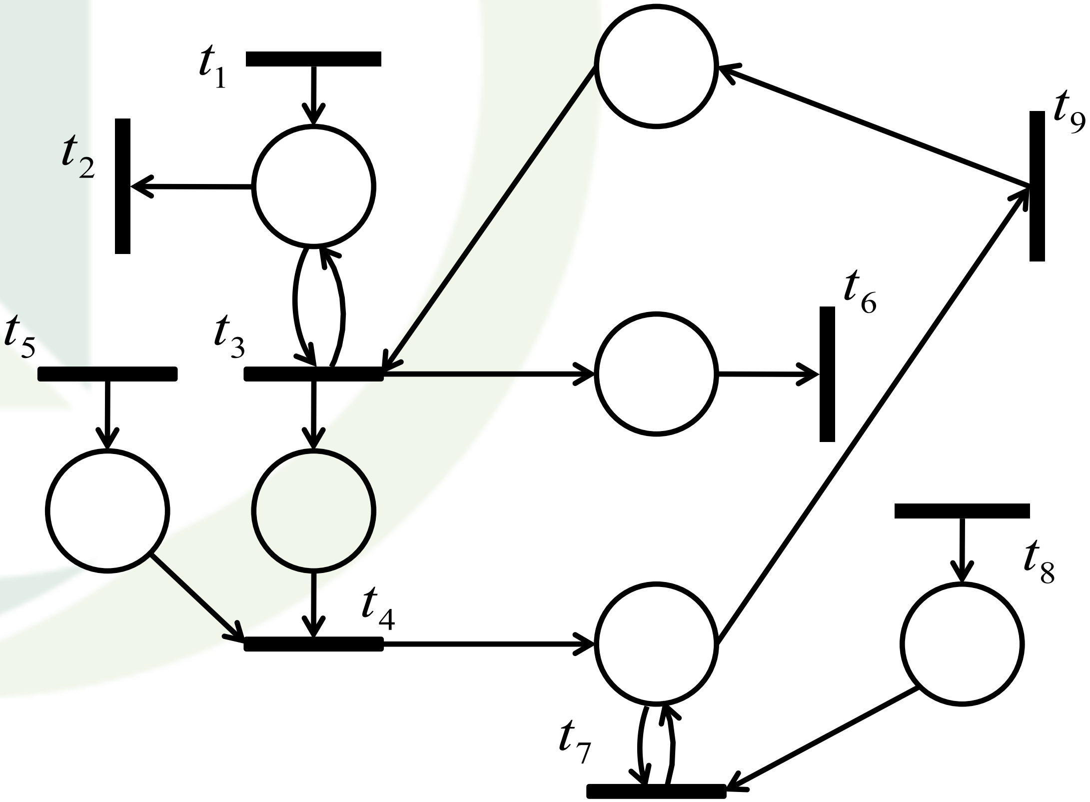
4. Appling to IL-3 Petri net model





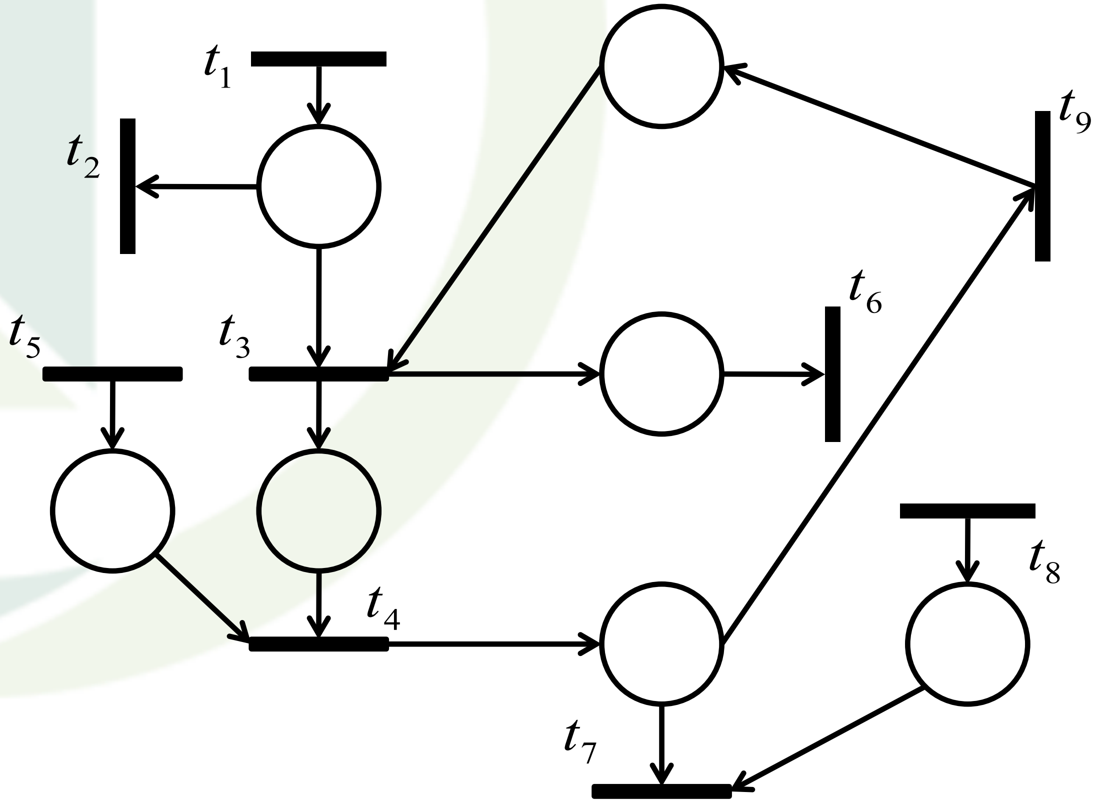
Appling to IL-3 Petri net model

1. Change transitions which have self-loop structure in model



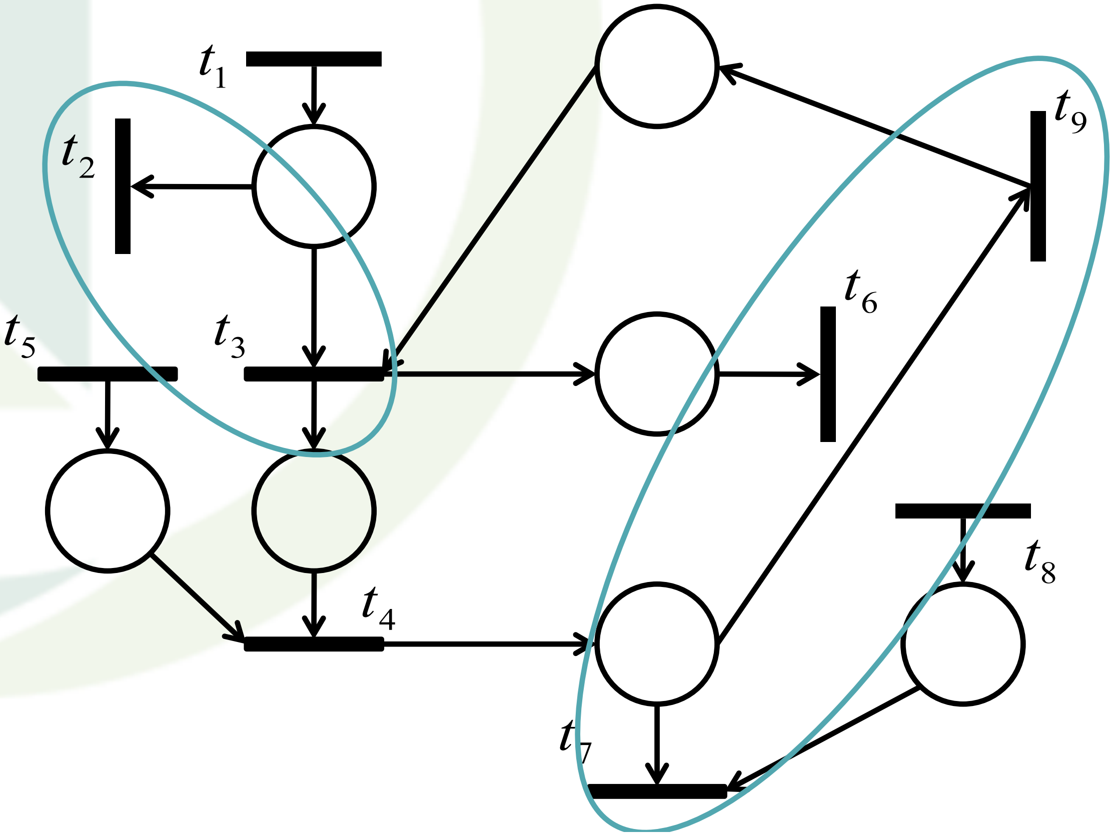
Appling to IL-3 Petri net model

1. Change transitions which have self-loop structure in model



Appling to IL-3 Petri net model

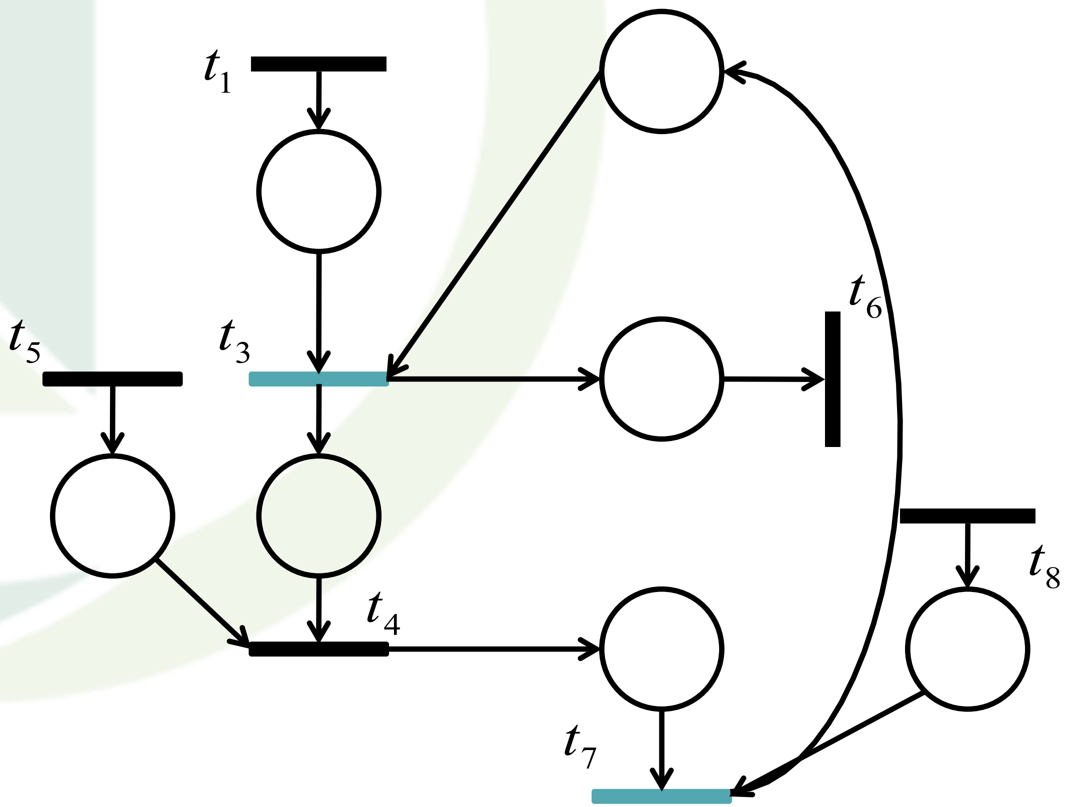
2. Shrink transitions which have conflict structure



$$s = \frac{1}{2}$$

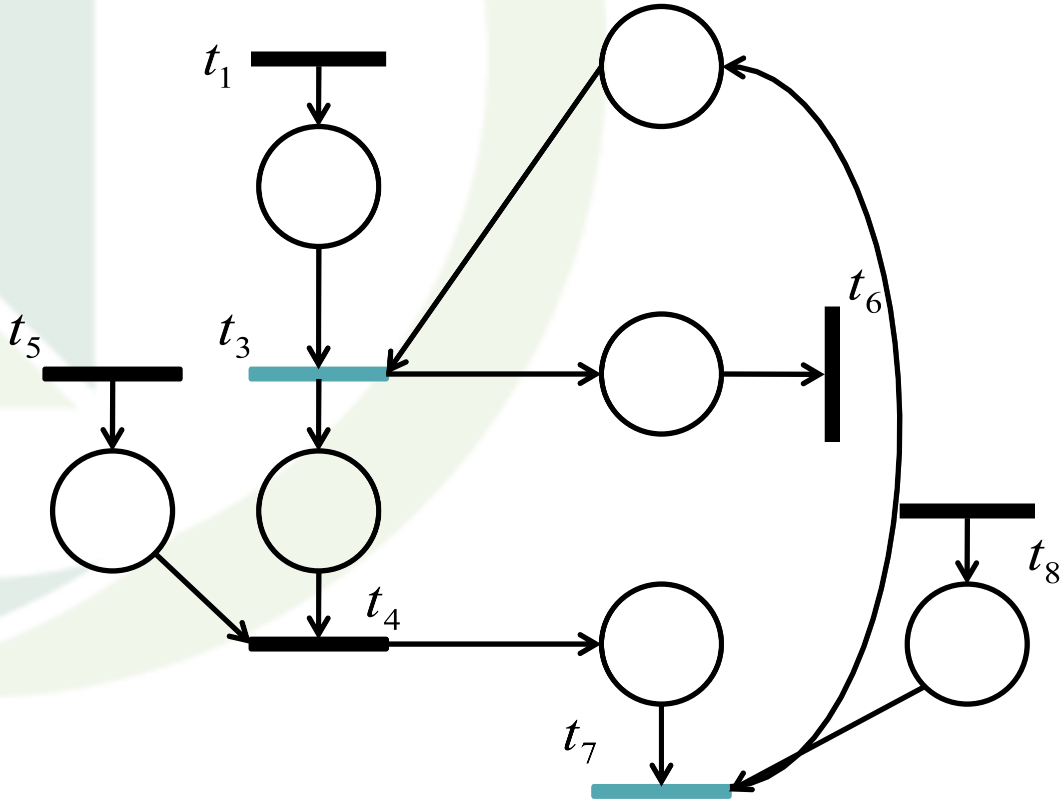
Appling to IL-3 Petri net model

2. Shrink transitions which have conflict structure



Appling to IL-3 Petri net model

3. Shrink transitions which have one-input one-output structure



Appling to IL-3 Petri net model

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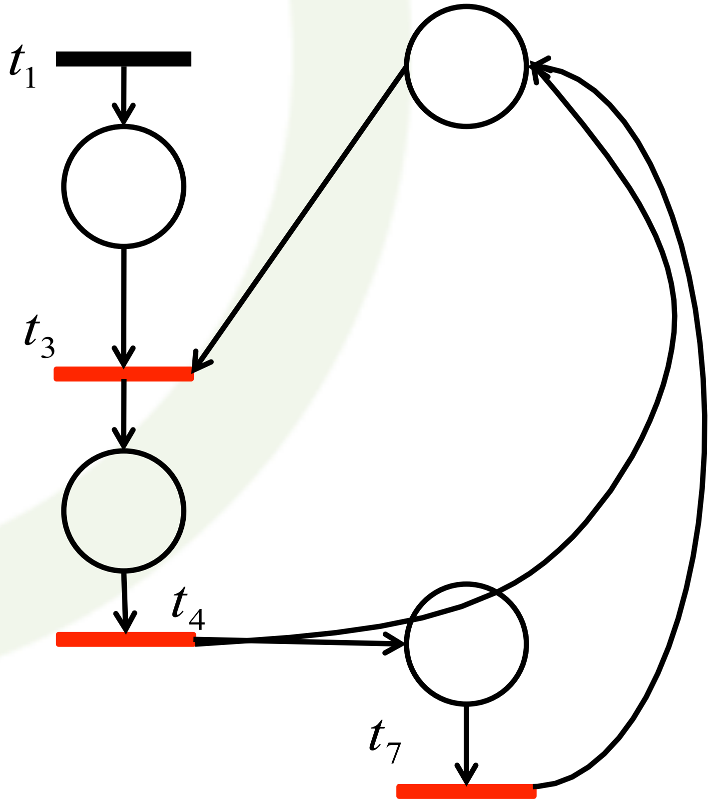
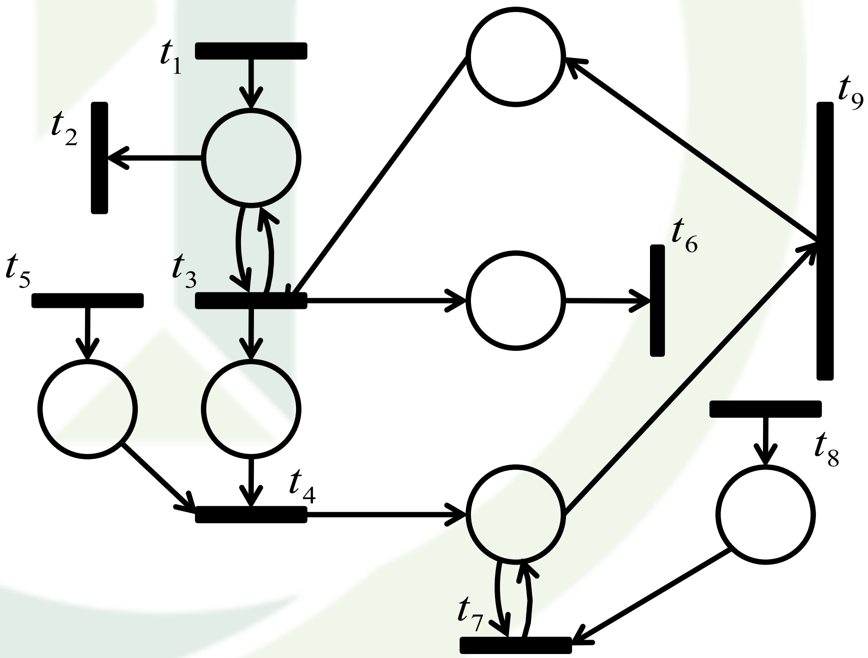
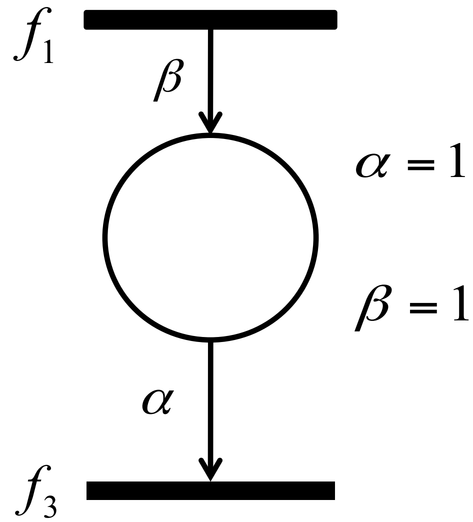


Appling to IL-3 Petri net model

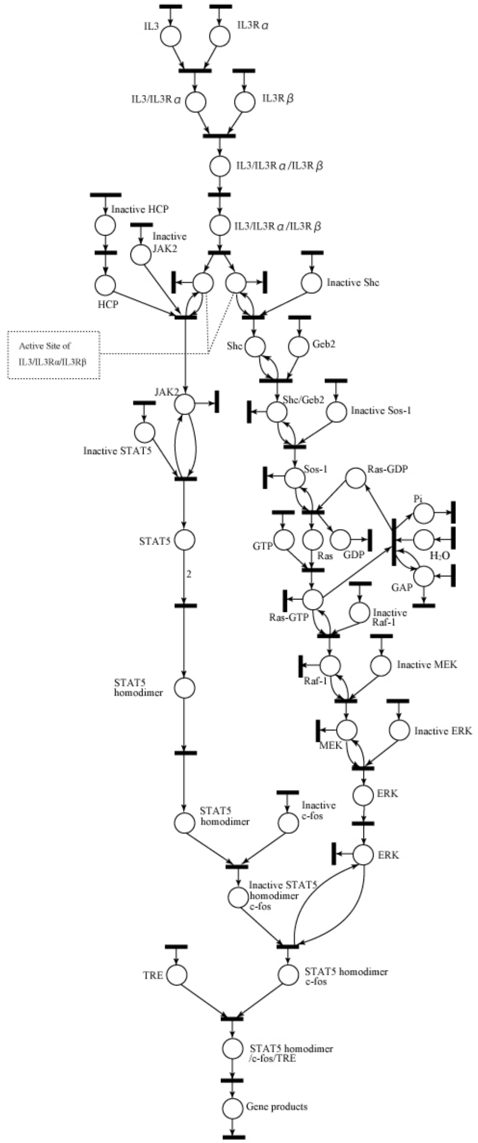
Present model

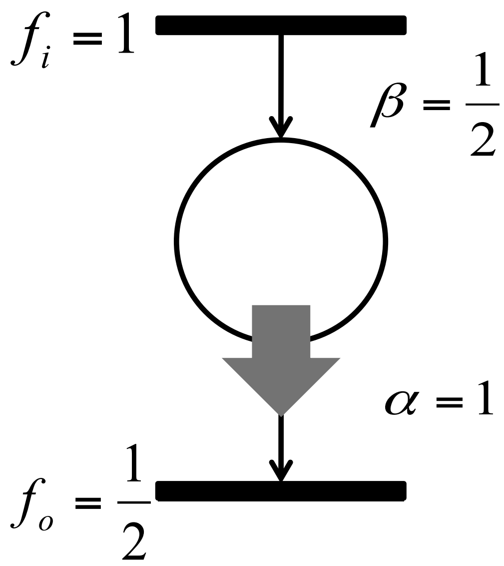


shrunk model



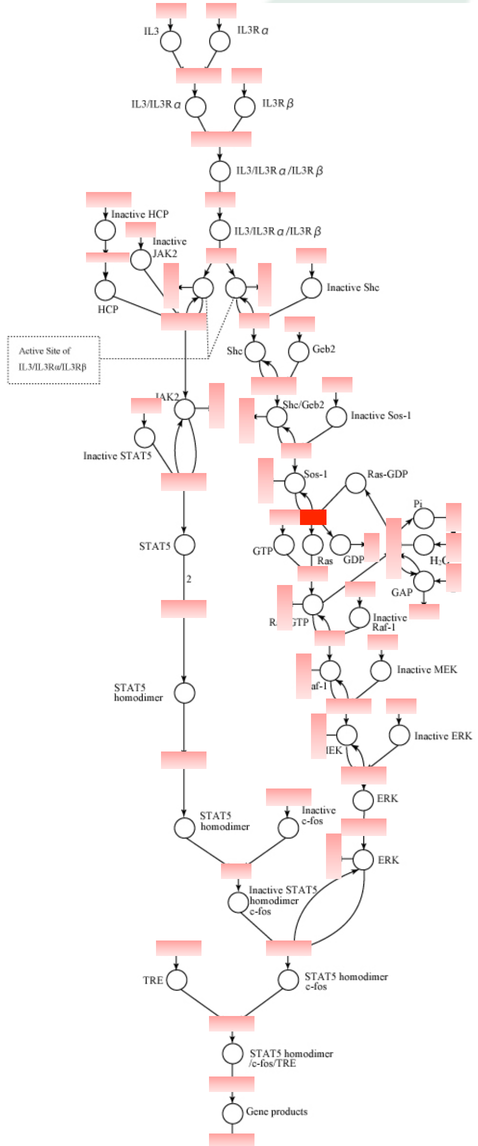
Appling to IL-3 Petri net model



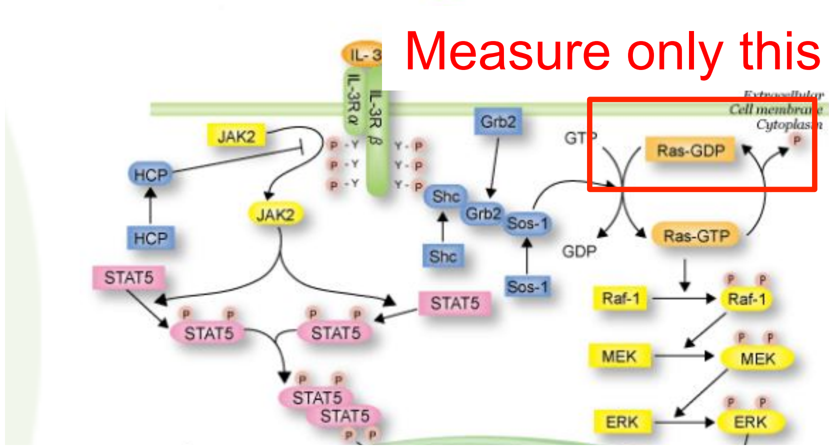


All of transitions in this model
was found to be included
in the same dependent subnet

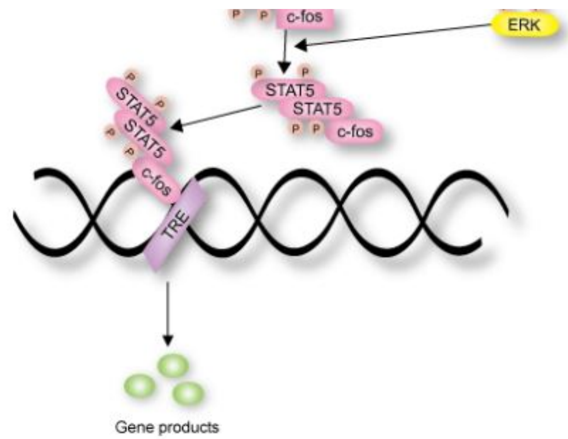
Appling to IL-3 Petri net model



Measure only this point



Firing frequency of all transitions
can be calculated from one firing frequency

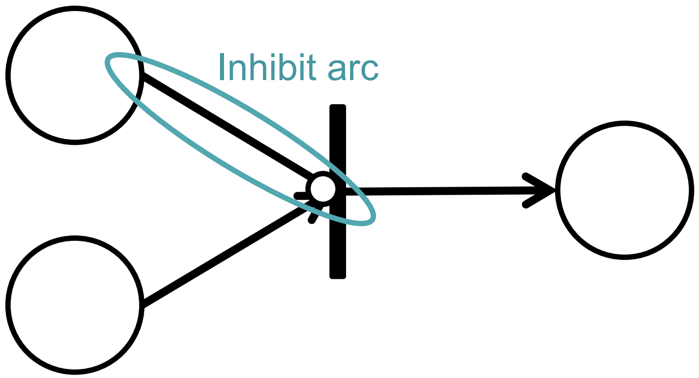


Conclusion

- We apply dependent shrink algorithm to IL-3 signaling pathway Petri net model
- We can shrink IL-3 signaling pathway Petri net model and watch the change of arcs
- We can find dependent subnet of IL-3 signaling pathway Petri net model

Future work

- Shrink expansion to inhibit arc
- Improve algorithm so that it can indicate transitions corresponding to measurable reactions by biological experiment
- Investigate the uniqueness of our algorithm



Thank you for attention