Petri nets

- proposed by Carl Adam Petri in the 60s
- simple graphical and mathematical formalism for modeling and analyzing distributed systems
- originally for qualitative models, but many extensions exist
- variety of applications, in particular molecular networks

Definition A Petri Net is a quadruple $\mathcal{N} = (P, T, g, m_0)$, where
P and T are finite, non-empty, disjoint sets,
and $g : (P \times T) \cup (T \times P) \to \mathbb{N}_0$ and $m_0 : P \to \mathbb{N}_0$ are functions.

Structure and state space

Structure

- $\mathcal{N}$ can be visualized as a bipartite graph, with vertex set $P \cup T$ and weighted directed arcs derived from g (network structure)
- vertices in P are called *places*, vertices in T *transitions*

State space

- places are marked with *tokens*, number of tokens in a place constitutes its component value
- a *marking* $m : P \to \mathbb{N}_0$ assigns each place a token count (states), can be written as vector of length $|P|$
- m_0 gives an initial marking (initial state)
- a priori: state space $\mathbb{N}_0^{|P|}$, but initial marking generally restricts the state space (e.g. boundedness)

Informally, places represent resources of the system, while transitions correspond to events influencing the resources

Dynamics

Firing given a marking $m \in \mathbb{N}_0^{|P|}$

- a transition t is *enabled* if $m(p) \geq g((p,t))$ for all places p with $g((p,t)) \neq 0$ (input places of t)
- enabled transitions may *fire* resulting in a new marking obtained by consuming tokens from input places and producing tokens according to arc weights in places p with $g((t,p)) \neq 0$ (output places of t)

Algebraic description

- arc weights expressed in *pre- and postcondition matrix*: $Pre, Post \in \mathbb{N}_0^{|P|\times|T|}$, where $Pre_{pt} := g((p,t))$ and $Post_{pt} := g((t,p))$ for all $p \in P$, $t \in T$
- *incidence matrix* $C := Post - Pre$ describes token balance of firings
- *state equation* $m' = m + C\sigma$, where entries of $\sigma \in \mathbb{N}_0^{|T|}$ represent number of transition occurrences:
  m' represents the marking resulting from firing a single transition t once, if σ is the t-th unit vector
  Remark: in general σ represents multiple transition firings, solvability of the state equation is limited (non-negativity of markings, non-determinism) and yields no information on sequence of events

Marking graph

Given a marking $m \in \mathbb{N}_0^{|P|}$

- any enabled transition t may fire: *state transition* from m to $m' := m + C\sigma$ with σ the t-th unit vector
- firing is non-deterministic
- marking graph $\mathcal{R}(m_0)$ of $\mathcal{N}$: vertices are markings m such that there exists a sequence of state transitions leading from initial marking m_0 to m, edges represent state transitions (state transition graph)

Properties

- *Boundedness:* number of tokens in each place is bounded (regardless of initial marking), $\mathcal{N}$ is k-bounded if no marking in $\mathcal{R}(m_0)$ has more than k tokens in a place,
  boundedness results in finite marking graphs
- *Reachability:* marking m is reachable from m_0 if there is a path from m_0 to m in $\mathcal{R}(m_0)$ (that is if m belongs to the vertex set of $\mathcal{R}(m_0)$)
- *Liveness:* every transition is in some state of the marking graph enabled

Remark: analysis using temporal logic and model checking techniques

Invariants

P-invariants

- solutions $x \in \mathbb{N}_0^{|P|}$ of $C^T x = 0$
- support of x: non-zero components of x
- satisfy $m^T x = m_0^T x$ for all markings m in $\mathcal{R}(m_0)$, i.e.,
  represent sets of places (support of x) with constant weighted sum for all markings in $\mathcal{R}(m_0)$ (conservation relations)

T-invariants

- solutions $y \in \mathbb{N}_0^{|T|}$ of $Cy = 0$, i.e.,
  firing sequences that reproduce a marking m
- correspondence to elementary modes in metabolic networks

Biological modeling

- models of metabolic, regulatory and signal transduction networks
- very different interpretation of places, transitions, tokens ...

Metabolic networks

Modeling

- places represent reactants, products, enzymes
- transitions represent biochemical reactions
- arc weights correspond to stoichiometric coefficients

  $\longrightarrow$ topology of metabolic network and petri net model match

- markings represent distribution of species molecules in the network

Analysis

- dynamic model (other than flux cone analysis)
  - simulation
  - reachability, liveness etc. (model checking techniques)
- stoichiometric matrix of the metabolic network corresponds to incidence matrix of the petri net, T-invariants correspond to elementary modes

Regulatory networks

Modeling Given a Boolean network $f : \{0,1\}^n \rightarrow \{0,1\}^n$

- places represent components
- transitions represent interactions
- tokens represent activity levels (on/off), markings represent states

  but translation is not straight forward

  - for each component α_i introduce complementary places α_i (component active) and $\overline{\alpha_i}$ (component inactive), state in $\{0,1\}^n$ corresponds to marking restricted to places α_i
    $\rightarrow$ guarantee sum of tokens in α_i and $\overline{\alpha_i}$ is 1
  - for each α_i let $Pred(\alpha_i)$ denote the predecessors of α_i in $G(f)$, i.e. f_i only depends on components in $Pred(\alpha_i)$, represent all states defining f_i by the states x^R, where $R \subseteq Pred(\alpha_i)$ and $x_j^R = 1$ for all $j \in R$, $x_j^R = 0$ for all $j \in \{1, \dots, n\} \setminus R$
  - for each $i \in \{1, \dots, n\}$ introduce transitions $t_{i,x^R} = t_{i,R}$ representing update of α_i to $f_i(x)$ in a state x coinciding with x^R in components of $Pred(\alpha_i)$

Mathematical description

Petri net model Given a Boolean network $f:\{0,1\}^n \to \{0,1\}^n$

- set of places $P := \{\alpha_1, \overline{\alpha_1}, \dots, \alpha_n, \overline{\alpha_n}\}$
- set of transitions $T := \{t_{i,R} \mid i \in \{1,\dots,n\}, R \subseteq Pred(\alpha_i)\}$
- define $g:(P\times T)\cup(T\times P)\to\{0,1\}$ as follows

In case $\alpha_i \notin Pred(\alpha_i)$,

with $x^R \in \{0,1\}^n$, $x_j^R = 1$ for $j \in R$, $x_j^R = 0$ for $j \in \{1,\dots,n\}\setminus R$

- $g(\alpha_i, t_{i,R}) = g(t_{i,R}, \overline{\alpha_i}) = 1 - f_i(x^R)$ and $g(\overline{\alpha_i}, t_{i,R}) = g(t_{i,R}, \alpha_i) = f_i(x^R)$
  $\to$ responsible for activity level change of component α_i, ensures token sum of α_i and $\overline{\alpha_i}$ remains 1
- $g(\alpha_j, t_{i,R}) = g(t_{i,R}, \alpha_j) = 1$ for all $\alpha_j \in R$
  $g(\overline{\alpha_j}, t_{i,R}) = g(t_{i,R}, \overline{\alpha_j}) = 1$ for all $\alpha_j \in Pred(\alpha_i)\setminus R$
  $\to$ enabling of $t_{i,R}$, if current marking corresponds to x^R, conservation of component markings
- in all other cases g is set to zero

Mathematical description

In case $\alpha_i \in Pred(\alpha_i)$,

with $x^R \in \{0,1\}^n$, $x^R_j = 1$ for $j \in R$, $x^R_j = 0$ for $j \in \{1,\dots,n\} \setminus R$

If $\alpha_i \in R$

- $g(\alpha_i, t_{i,R}) = g(t_{i,R}, \overline{\alpha_i}) = 1 - f_i(x^R)$,
  $\alpha_i \in R$ implies α_i carries a token, moving it to $\overline{\alpha_i}$ is only necessary if $f_i(x^R) = 0$
- $g(\alpha_j, t_{i,R}) = g(t_{i,R}, \alpha_j) = 1$ for all $\alpha_j \in R \setminus \{\alpha_i\}$
  $g(\overline{\alpha_j}, t_{i,R}) = g(t_{i,R}, \overline{\alpha_j}) = 1$ for all $\alpha_j \in Pred(\alpha_i) \setminus R$
  $\rightarrow$ corresponds to case $\alpha_i \notin R$

If $\alpha_i \notin R$

- $g(\overline{\alpha_i}, t_{i,R}) = g(t_{i,R}, \alpha_i) = f_i(x^R)$,
  $\alpha_i \notin R$ implies $\overline{\alpha_i}$ carries a token, moving it to α_i is only necessary if $f_i(x^R) = 1$
- $g(\alpha_j, t_{i,R}) = g(t_{i,R}, \alpha_j) = 1$ for all $\alpha_j \in R$
  $g(\overline{\alpha_j}, t_{i,R}) = g(t_{i,R}, \overline{\alpha_j}) = 1$ for all $\alpha_j \in Pred(\alpha_i) \setminus (R \cup \{\alpha_i\})$
  $\rightarrow$ corresponds to case $\alpha_i \notin R$
- in all other cases g is set to zero

Remarks

- mathematical description yields automated procedure for translating network description by Boolean function into petri nets
- similar translation for multi-valued models possible
- petri net topology carries information on structure and dynamics
- counting transitions, petri net model is exponential in size (simplifications possible)
- non-determinism of petri net dynamics results in asynchronous update for the regulatory network,
  it is possible to construct petri net models yielding synchronous dynamics
- simulation, algebraic methods and model checking techniques can be used for analysis
- treatment of signalling networks similar